Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: Baricitinib

Stand: November 2015

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Baricitinib zur Behandlung der moderaten bis schweren rheumatoiden Arthritis	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*siehe „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	„nicht angezeigt“
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	IQWiG-Beauftragung zu Biologika – Zweitlinientherapie bei rheumatoider Arthritis • Rituximab, Abatacept, Etanercept, Infliximab, Adalimumab, Certolizumab Pegol, Golimumab, Anakinra, Tocilizumab; IQWiG-Abschlussbericht A10-01 veröffentlicht am 26.08.2013 Therapiehinweise zu • Adalimumab, Infliximab, Etanercept, Celecoxib, Leflunomid
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Baricitinib	Geplante Indikation: Baricitinib ist zugelassen zur Behandlung der moderaten bis schweren aktiven Rheumatoiden Arthritis in erwachsenen Patienten, die Therapie-naiv sind, ein unzureichendes Ansprechen, oder eine Unverträglichkeit gegenüber Basistherapeutika (sowohl konventionelle, als auch biologische Basistherapeutika) gezeigt haben. Baricitnib kann als Monotherapie oder in Kombination mit konventionellen synthetischen Basistherapeutika eingesetzt werden.
Glukokortikoide	
Prednisolon H02AB06 Decortin H®	angezeigt zur Behandlung von Erkrankungen, die einer systemischen Therapie mit Glucocorticoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad (Dosierungsschemata (DS: s. Abschnitt 4.2. Dosierung): **Rheumatologie:** - […] - aktive rheumatoide Arthritis mit schweren progredienten Verlaufsformen, z. B. destruierend verlaufende Formen und/oder extraartikulären Manifestationen - andere entzündlich-rheumatische Arthritiden, sofern die Schwere des Krankheitsbildes es erfordert und nicht-steroidale Antirheumatika (NSARs) nicht angewandt werden können: o Spondarthritiden (Spondylitis ankylosans mit Beteiligung peripherer Gelenke, Arthritis psoriatica, enteropathische Arthropathie mit hoher Entzündungsaktivität, o Reaktive Arthritiden o Arthritis bei Sarkoidose - juvenile idiopathische Arthritis mit schwerer systemischer Verlaufsform - […] (Stand: Oktober 2014)
Methylprednisolon H02AB04 Urbason®	angezeigt zur Behandlung von Erkrankungen, die einer systemischen Therapie mit Glukokortikoiden bedürfen. Hierzu gehören je nach Erscheinungsform und Schweregrad zum Beispiel: **Rheumatische Erkrankungen**: - Aktive rheumatoide Arthritis mit schweren progredienten Verlaufsformen, z. B. schnell destruierend verlaufende Form und/oder extraartikuläre Manifestationen, - juvenile idiopathische Arthritis mit schwerer systemischer Verlaufsform […] (Stand: Februar 2013)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Konventionelle (synthetische) DMARDs (Basistherapeutika)	
Leflunomid L04AA13 Arava®	Leflunomid ist ein antirheumatisches Basistherapeutikum („disease modifying antirheumatic drug“ (DMARD)) zur Behandlung von Erwachsenen mit: • aktiver rheumatoider Arthritis, […] (Stand: September 2014)
Chloroquinphosphat P01BA01 Resochin®	[…] Chronische Polyarthritis (rheumatoide Arthritis) einschließlich juveniler chronischer Arthritis. […] (Stand: November 2013)
Hydrochloroquin-sulfat, P01BA02 Quensyl®	- Rheumatoide Arthritis. - Juvenile idiopathische Arthritis […] (Stand: März 2014)
MTX M01CX01 Lantarel®	Schwere Formen der aktiven rheumatoiden Arthritis (chronischen Polyarthritis) a) wenn eine Therapie mit anderen Basistherapeutika oder mit nicht-steroidalen Antiphlogistika (non-steroidal anti-inflammatory drugs, NSAIDs) nicht ausreichend wirksam ist oder nicht vertragen wird. b) bei primär besonders aggressiv verlaufenden („malignen“) Formen der rheumatoiden Arthritis (chronischen Polyarthritis) […] (Stand: Januar 2014)
Sulfasalazin M01CX02 Azulfidine RA®	- Behandlung der aktiven rheumatoiden Arthritis (chronische Polyarthritis) des Erwachsenen. - Behandlung der aktiven juvenilen idiopathischen Oligoarthritis (Enthesitis-assoziierte Arthritis) bei Kindern ab dem 6. Lebensjahr, die unzureichend auf nicht steroidale Antiphlogistika (non-steroidal anti-inflammatory drugs, NSAIDs) und/ oder lokale Glukokortikoidinjektionen angesprochen haben. - Behandlung der aktiven juvenilen idiopathischen Polyarthritis und polyarthritischen Spondylarthritis bei Kindern ab dem 6. Lebensjahr (Enthesitis-assoziierte Arthritis), die unzureichend auf nichtsteroidale Antiphlogistika (non-steroidal anti-inflammatory drugs, NSAIDs) angesprochen haben. (Stand: August 2013)
Sonstige	
Natriumaurothio-malat , M01CB01 Tauredon®	Chronische Polyarthritis (rheumatoide Arthritis) (Stand: November 2012)
Azathioprin L04AX01 Zytrim®	ist angezeigt in schweren Fällen der folgenden Erkrankungen bei Patienten, die Kortikosteroide nicht vertragen oder steroidabhängig sind und bei denen trotz hoher Dosen von Kortikosteroiden keine ausreichende therapeutische Wirkung erzielt werden kann: - schwere aktive rheumatoide Arthritis, die mit weniger toxischen antirheumatischen Basistherapeutika (disease modifying anti-rheumatic drugs (DMARDs) nicht kontrolliert werden kann […] (Stand: August 2013)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Ciclosporin L04AD01 Deximune®	[…] Behandlung der schweren, aktiven rheumatoiden Arthritis bei Erwachsenen, wenn sich eine konventionelle Therapie einschließlich mindestens eines hoch wirksamen antirheumatischen Basistherapeutikums (DMARD, z.B. niedrig dosiertes Methotrexat) als ungeeignet erwiesen hat. (Stand: April 2014)
Penicillamin M01CC01 Metalcaptase®	- Chronische Polyarthritis rheumatica […] (Stand: Juli 2009)
biologische DMARDs (inkl. Biosimilar)	
Abatacept L04AA24 Orencia®	ORENCIA ist in Kombination mit Methotrexat (MTX) indiziert zur Behandlung der mäßigen bis schweren aktiven Rheumatoiden Arthritis bei Erwachsenen, die unzureichend auf eine vorangegangene Behandlung mit einem oder mehreren krankheitsmodifizierenden Antirheumatika (DMARDs), einschließlich Methotrexat oder eines Tumornekrosefaktor (TNF)-alpha-Inhibitors ansprachen. Abatacept reduziert in Kombination mit Methotrexat die Progression der Gelenkschädigung und verbessert die körperliche Funktionsfähigkeit. (Stand: September 2014)
Anakinra L04AC03 Kineret®	- rheumatoider Arthritis: Kineret® ist zur Behandlung der Symptome der rheumatoiden Arthritis in Kombination mit Methotrexat bei Erwachsenen indiziert, die nur unzureichend auf Methotrexat allein ansprechen. - Cryopyrin-assoziierten periodischen Syndromen […] (Stand: November 2013)
Adalimumab L04AB04 Humira®	- rheumatoider Arthritis: ist in Kombination mit Methotrexat indiziert zur o Behandlung der mäßigen bis schweren aktiven rheumatoiden Arthritis bei erwachsenen Patienten, die nur unzureichend auf krankheitsmodifizierende Antirheumatika, einschließlich Methotrexat, angesprochen haben. o Behandlung der schweren, aktiven und progressiven rheumatoiden Arthritis bei Erwachsenen, die zuvor nicht mit Methotrexat behandelt worden sind. Humira® kann im Falle einer Unverträglichkeit gegenüber Methotrexat, oder wenn die weitere Behandlung mit Methotrexat nicht sinnvoll ist, als Monotherapie angewendet werden. Humira reduziert in Kombination mit Methotrexat das Fortschreiten der radiologisch nachweisbaren strukturellen Gelenkschädigungen und verbessert die körperliche Funktionsfähigkeit. - Axiale Spondyloarthritis […] - Ankylosierende Spondylitis (AS) […] - Polyartikuläre juvenile idiopathische Arthritis […] - Psoriasis-Arthritis […] - Psoriasis […] - Morbus Crohn […] - Colitis ulcerosa […] (Stand: September 2014)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Certolizumab Pegol L04AB05 Cimzia®	- rheumatoider Arthritis: Cimzia® ist in Kombination mit Methotrexat (MTX) für die Behandlung der mittelschweren bis schweren, aktiven rheumatoiden Arthritis (RA) bei erwachsenen Patienten angezeigt, wenn das Ansprechen auf langwirksame Antirheumatika (Disease-Modifying Antirheumatic Drugs [DMARDS]) einschließlich Methotrexat ungenügend war. In Fällen von Unverträglichkeit gegenüber Methotrexat oder wenn die Fortsetzung der Behandlung mit Methotrexat ungeeignet ist, kann Cimzia® als Monotherapie verabreicht werden. Für Cimzia wurde gezeigt, dass es bei gemeinsamer Verabreichung mit Methotrexat das Fortschreiten von radiologisch nachweisbaren Gelenkschäden reduziert und die körperliche Funktionsfähigkeit verbessert. - Axiale Spondyloarthritis […] - Psoriasis-Arthritis […] (Stand: Oktober 2014)
Etanercept L04AB01 Enbrel®	- Rheumatoide Arthritis Enbrel® ist in Kombination mit Methotrexat zur Behandlung der mittelschweren bis schweren aktiven rheumatoiden Arthritis bei Erwachsenen indiziert, wenn das Ansprechen auf Basistherapeutika, einschließlich Methotrexat (sofern nicht kontraindiziert), unzureichend ist. Enbrel® kann im Falle einer Unverträglichkeit gegenüber Methotrexat oder wenn eine Fortsetzung der Behandlung mit Methotrexat nicht möglich ist, als Monotherapie angewendet werden. Enbrel® ist ebenfalls indiziert zur Behandlung der schweren, aktiven und progressiven rheumatoiden Arthritis bei Erwachsenen, die zuvor nicht mit Methotrexat behandelt worden sind. Enbrel reduziert als Monotherapie oder in Kombination mit Methotrexat das Fortschreiten der radiologisch nachweisbaren strukturellen Gelenkschädigungen und verbessert die körperliche Funktionsfähigkeit. - Axiale Spondyloarthritis […] - Ankylosierende Spondylitis (AS) […] - juvenile idiopathische Arthritis […] - Psoriasis-Arthritis […] - Morbus Bechterew (Spondylitis ankylosans) - Plaque- Psoriasis […] (Stand: September 2014)
Golimumab L04AB06 Simponi®	- Rheumatoide Arthritis (RA) Simponi® ist in Kombination mit Methotrexat (MTX) indiziert zur: • Behandlung der mittelschweren bis schweren aktiven rheumatoiden Arthritis bei Erwachsenen, wenn das Ansprechen auf eine Therapie mit krankheitsmodifizierenden Antirheumatika (DMARDs), einschließlich MTX, unzureichend gewesen ist. • Behandlung der schweren, aktiven und progredienten rheumatoiden Arthritis bei Erwachsenen, die zuvor nicht mit MTX behandelt worden sind Es wurde gezeigt, dass Simponi in Kombination mit MTX die in Röntgenaufnahmen bestimmte Progressionsrate von Gelenkschäden verringert und die körperliche Funktionsfähigkeit verbessert. - Psoriasis-Arthritis (PsA)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	- […] - Ankylosierende Spondylitis (AS) - […] - Colitis ulcerosa (CU) - […] (Stand: September 2014)
Infliximab L04AB02 Remicade®	- Rheumatoide Arthritis Remicade® ist in Kombination mit Methotrexat indiziert zur: Reduktion der Symptomatik und Verbesserung der körperlichen Funktionsfähigkeit bei: • erwachsenen Patienten mit aktiver Erkrankung, die nur unzureichend auf krankheitsmodifizierende Anti-Rheumatika (DMARDs), einschließlich Methotrexat, angesprochen haben. • Methotrexat-naive, erwachsene Patienten oder erwachsene Patienten, die nicht mit anderen DMARDs vorbehandelt wurden, mit schwergradiger, aktiver und fortschreitender Erkrankung. Bei diesen Patienten wurde anhand von radiologischen Untersuchungen eine Reduktion der Progressionsrate der Gelenkschäden nachgewiesen (siehe Abschnitt 5.1). - Ankylosierende Spondylitis (AS) […] - Psoriasis-Arthritis […] - Psoriasis […] - Morbus Crohn […] - Colitis ulcerosa […] (Stand: Juli 2014)
Rituximab L01XC02 MabThera®	- rheumatoider Arthritis: MabThera® in Kombination mit Methotrexat ist für die Behandlung erwachsener Patienten mit schwerer, aktiver rheumatoider Arthritis angezeigt, die ungenügend auf andere krankheitsmodifizierende Antirheumatika (DMARDs) einschließlich einer oder mehrerer Therapien mit Tumornekrosefaktor(TNF)-Hemmern angesprochen oder diese nicht vertragen haben. Es konnte gezeigt werden, dass MabThera in Kombination mit Methotrexat das Fortschreiten der radiologisch nachweisbaren Gelenkschädigung vermindert und die körperliche Funktionsfähigkeit verbessert. - Non-Hodgkin-Lymphom (NHL) […] - Chronische lymphatische Leukämie (CLL) […] - Granulomatose mit Polyangiitis […] (Stand: Mai 2014)
Tocilizumab L04AC07 RoActemra®	- mäßiger bis schwerer aktiver rheumatoider Arthritis (RA) RoActemra ist, in Kombination mit Methotrexat (MTX), indiziert für: • die Behandlung der schweren, aktiven und progressiven rheumatoiden Arthritis (RA) bei Erwachsenen, die zuvor nicht mit Methotrexat behandelt worden sind. • die Behandlung erwachsener Patienten mit mäßiger bis schwerer aktiver rheumatoider Arthritis, die unzureichend auf eine

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	vorangegangene Behandlung mit einem oder mehreren krankheitsmodifizierenden Antirheumatika (DMARDs) oder Tumornekrosefaktor (TNF)-Inhibitoren angesprochen oder diese nicht vertragen haben. RoActemra® kann bei diesen Patienten als Monotherapie verabreicht werden, falls eine Methotrexat-Unverträglichkeit vorliegt oder eine Fortsetzung der Therapie mit Methotrexat unangemessen erscheint. RoActemra vermindert in Kombination mit Methotrexat das Fortschreiten der radiologisch nachweisbaren strukturellen Gelenkschädigungen und verbessert die körperliche Funktionsfähigkeit. - aktive systemische juvenile idiopathische Arthritis (sJIA) […] - polyartikuläre juvenile idiopathische Arthritis (pJIA) […] (Stand: September 2014)

Quellen: AMIS Datenbank, Fachinformationen

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Indikation für die Recherche bei Baricitinib:

Zur Behandlung der moderaten bis schweren Rheumatoiden Arthritis als:

a) Kombinationstherapie
- in Kombination mit MTX bei Patienten mit unzureichendem Ansprechen oder Unverträglichkeit gegenüber einer vorherigen Therapie mit einem oder mehreren konventionellen Basistherapeutika
- in Kombination mit konventionellen Basistherapeutika bei Patienten mit unzureichendem Ansprechen oder Unverträglichkeit gegenüber einer vorherigen Therapie mit einem oder mehreren konventionellen Basistherapeutika
- in Kombination konventionellen Basistherapeutika bei Patienten mit unzureichendem Ansprechen oder Unverträglichkeit gegenüber einer vorherigen Therapie mit einem oder mehreren Basistherapeutika
- in Kombination mit MTX bei Patienten, die zuvor nicht mit MTX behandelt worden sind
- Baricitinib in Kombination mit Methotrexat (MTX) oder andere konventionellen synthetischen DMARDs (disease-modifying anti-rheumatic drugs) ist zugelassen zur Behandlung von erwachsenen Patienten mit moderater bis schwere Rheumatoider Arthritis bei gleichzeitigem Vorliegen von ungünstigen Prognosefaktoren, die entweder unzureichend auf eine vorherige Therapie mit konventionellen synthetischen DMARDs (cDMARDs, inklusive MTX) oder Tumornekrosefaktor-α-Blockern (TNF-Blocker) angesprochen haben oder eine Unverträglichkeit gegenüber diesen Therapien besteht.

b) Monotherapie
- bei Patienten mit Unverträglichkeit gegenüber MTX oder bei denen eine Behandlung mit MTX nicht angemessen ist
- bei Patienten, die noch nicht mit MTX behandelt wurden.

- Baricitinib ist zugelassen zur Behandlung der moderaten bis schweren aktiven Rheumatoide Arthritis in erwachsenen Patienten, die Therapie-naiv sind, ein unzureichendes Ansprechen, oder eine Unverträglichkeit gegenüber Basistherapeutika (sowohl konventionelle, als auch biologische Basistherapeutika) gezeigt haben. Baricitinib kann als Monotherapie oder in Kombination mit konventionellen synthetischen Basistherapeutika eingesetzt werden.

Berücksichtigte Wirkstoffe/Therapien:

siehe Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation **„**Rheumatoide Arthritis**“** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 13.10.2015 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, G-BA, GIN, IQWiG, NGC, NICE, TRIP. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab **980** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies **51** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

ACR	American College of Rheumatology
AE	adverse event
AHRQ	Agency for Health Research and Quality
AIMS	Abatacept in Inadequate responders to Methotrexate
ATB	absolute treatment benefit
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AZQ	Arztliches Zentrum für Qualität in der Medizin
BSR	British Society for Rheumatology
BUC	bucillamine
CCT	controlled clinical trials
CDER	Center for Drug Evaluation and Research
CI	confidence intervall
CRP	C-reactive protein
CSA	cyclosporine
DAHTA	Deutsche Agentur für Health Technology Assessment
DAS	Disease Activity Score

DAS28	Disease Activity Score 28
DGHO	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie
DMARD	Disease modifying anti-rheumatic drug
EMS	early morning stiffness
ES	Erosion Score
ESMO	European Society for Medical Oncology
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HAQ	Health Assessment Questionnaire
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IR	inadaequate response
JSNS	Joint Space Narrowing Score
KI	Konfidenzintervall
KQ	key question
LEF	Leflunomid
MCMC	Markov chain Monte Carlo techniques
MRI	magnetic resonance imaging
MTC	Mixed-treatment comparisons
MTX	Methotrexate
NCCN	National Comprehensive Cancer Network
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NIHR HSC	National Institute for Health Research Horizon Scanning Centre
NSAID	non-steroidal anti-inflammatory drug
PARPR	percentage of the annual radiographic progression rate
PBO	Placebo
QALY	Quality Adjusted Life Years
RA	rheumatoid arthritis
RCT	Randomized controlled trial
RR	risk ratio
SAE	serious adverse event
SASP	Sulfasalazine
SD	standard deviation
SF-36	Short Form 36
SIGN	Scottish Intercollegiate Guidelines Network
SJC	swollen joint count
SSZ	sulfasalazine
TNF	tumour necrosis factor
TRIP	Turn Research into Practice Database
TSS	Total Sharp Score
VAS	Visual Analog Scale

IQWiG Berichte/ G-BA Beschlüsse

IQWiG, 2013 [17]. Biotechnologisch hergestellte Arzneimittel in der Zweitlinientherapie bei der rheumatoiden Arthritis.	**Fragestellung/Ziele:** Die Nutzenbewertung einer Behandlung mit biotechnologisch hergestellten Arzneimitteln im Vergleich untereinander, die Nutzenbewertung einer Behandlung mit biotechnologisch hergestellten Arzneimitteln im Vergleich zu einer Behandlung mit nicht biotechnologisch hergestellten Arzneimitteln, die Nutzenbewertung einer Behandlung mit biotechnologisch hergestellten Arzneimitteln im Vergleich zu einer Behandlung ohne Therapieerweiterung (mit oder ohne Placebo-Kontrolle), jeweils als **Zweitlinientherapie** bei Patienten mit RA. **Population:** Erwachsene mit RA ***Intervention:*** Biotechnologisch hergestellte Arzneimittel (bDMARDs) • Abatacept (Orencia®) • Adalimumab (Humira®) • Anakinra (Kineret®) • Certolizumab pegol (Cimzia®) • Etanercept (Enbrel®) • Golimumab (Simponi®) • Infliximab (Remicade®) • Rituximab (MabThera®) • Tocilizumab (RoActemra®) ***Kontrolle:*** Behandlung mit einem anderen bDMARD oder einem nicht biotechnologisch hergestellten Antirheumatikum oder die Behandlung ohne Therapieerweiterung (mit oder ohne Placebokontrolle) Die Anwendung der in den Studien eingesetzten Prüf- und Vergleichsinterventionen musste im Rahmen des für Deutschland gültigen Zulassungsstatus erfolgen. ***Endpunkte***: (siehe Anlage 1) • Remission • Symptomatik der RA (insbesondere Schmerz, Fatigue, Morgensteifigkeit) • Strukturelle Gelenkveränderungen (wie Deformitäten, Versteifungen, Kontrakturen) • Körperlicher Funktionsstatus einschließlich Aktivitäten des täglichen Lebens • Soziales Funktionsniveau (Teilhabe am beruflichen und sozialen Leben) • Gesundheitsbezogene Lebensqualität • Gesamtmortalität • unerwünschte Arzneimittelwirkungen ***Recherchezeitraum/Aktualität*** • Recherche bis 09/2010 Einschluss nur von RCT, mindestens 6 Monate Studiendauer, dabei auch Herstelleranfragen und Studienregister-Recherche **Ergebnis /Fazit:**

Tabelle 1: Paarweise Vergleiche der Interventionen mit Studien- und Patientenzahl

Intervention + MTX[a]	Kontrolle + MTX[a]	Anzahl der Studien	Anzahl der Patienten[b]
Abatacept	Placebo	6	2679
Adalimumab	Placebo	6	1508
Anakinra	Placebo	2	1653
Certolizumab pegol	Placebo	4	1286
Etanercept	Placebo	2	548
Etanercept[c] (MTX-Intoleranz)	Sulfasalazin[c]	1	71
Etanercept[c] (Patienten mit schwerer aktiver und progressiver RA)	MTX[c]	1	41
Golimumab (keine Vorbehandlung mit TNF-α-Inhibitoren)	Placebo	2	401
(Vorbehandlung mit TNF-α-Inhibitoren)	Placebo	1	205
Infliximab	Placebo	1	174
Rituximab (keine Vorbehandlung mit Rituximab)	Placebo	1	520
(nach fehlendem Ansprechen auf einen Zyklus Rituximab)	Placebo	1	475
Tocilizumab (mehrheitlich ohne Vorbehandlung mit TNF-α-Inhibitoren)	Placebo	5	2836
(Vorbehandlung mit TNF-α-Inhibitoren)	Placebo	1	335
Direktvergleich:			
Tocilizumab[c] (Patienten, die für eine Weiterbehandlung mit MTX nicht geeignet waren)	Adalimumab[c]	1	326
Summe:		35	13 058

a: wenn nicht anders angegeben
b: relevante Populationen für die vorliegende Bewertung
c: Monotherapie
MTX: Methotrexat, RA: rheumatoide Arthritis, TNF: Tumornekrosefaktor

Hinweis: Es wurden lediglich direkte Vergleiche extrahiert. Auf eine Darstellung der Placebovergleiche wurde verzichtet.

Anzahl relevanter Studien/Patienten: 3 (n= 438)

Abatacept; Adalimumab; Anakinra; Certolizumab pegol; Golimumab; Infliximab; Rituximab; Tocilizumab: *Ergebnisse nur im Vergleich gegen Placebo*

Etanercept
Ergebnisse im Vergleich gegen Placebo sowie:

Für Etanercept gibt es (im Vergleich zu Sulfasalazin) bei Patienten mit MTX-Intoleranz

- einen Anhaltspunkt für einen Zusatznutzen von Etanercept gegenüber Sulfasalazin hinsichtlich der Symptomatik der RA bezogen auf schmerzhafte Gelenke und geschwollene Gelenke, Schmerz, die globale Einschätzung der Krankheitsaktivität durch den Patienten und die allgemeine Gesundheit sowie hinsichtlich der Morgensteifigkeit und des körperlichen Funktionsstatus,
- keinen Beleg für einen Zusatznutzen hinsichtlich der Remission und hinsichtlich der strukturellen Gelenkveränderungen (wie Deformitäten, Versteifungen, Kontrakturen), des sozialen Funktionsniveaus und der gesundheitsbezogenen Lebensqualität aufgrund fehlender Daten
- keinen Beleg für einen geringeren oder größeren Schaden durch eine der beiden Prüfinterventionen im Hinblick auf die Gesamt-mortalität und im Hinblick auf schwerwiegende unerwünschte Ereignisse,

	Studienabbrüche aufgrund von unerwünschten Ereignissen, die Gesamtrate der unerwünschten Ereignisse, schwerwiegende Infektionen und die Gesamtrate der Infektionen. Für Etanercept gibt es (im Vergleich zu MTX) bei Patienten mit schwerer aktiver und progressiver RA • einen Anhaltspunkt für einen Zusatznutzen von Etanercept gegenüber MTX hinsichtlich der Remission, hinsichtlich der Symptomatik der RA bezogen auf schmerzhafte Gelenke, geschwollene Gelenke, Schmerz, die globale Einschätzung der Krankheitsaktivität durch den Patienten, die allgemeine Gesundheit sowie die Morgensteifigkeit, • keinen Beleg für einen Zusatznutzen hinsichtlich der strukturellen Gelenkveränderungen (wie Deformitäten, Versteifungen, Kontrakturen) aufgrund fehlender Daten, hinsichtlich des körperlichen Funktionsstatus, des sozialen Funktionsniveaus und der gesundheitsbezogenen Lebensqualität jeweils aufgrund fehlender Daten • keinen Beleg für einen geringeren oder größeren Schaden durch eine der beiden Prüfinterventionen im Hinblick auf die Gesamt-mortalität und im Hinblick auf schwerwiegende unerwünschte Ereignisse, Studienabbrüche aufgrund von unerwünschten Ereignissen, die Gesamtrate der unerwünschten Ereignisse, schwerwiegende Infektionen und die Gesamtrate der Infektionen. Für Tocilizumab im Vergleich zu Adalimumab bei Patienten, die für eine Weiterbehandlung mit MTX nicht geeignet waren, gibt es • einen Hinweis auf einen Zusatznutzen hinsichtlich der Remission, • keinen Beleg für einen Zusatznutzen hinsichtlich der Symptomatik der RA bezogen auf schmerzhafte Gelenke, geschwollene Gelenke, Schmerz, die globale Einschätzung der Krankheitsaktivität durch den Patienten und Fatigue, hinsichtlich des körperlichen Funktionsstatus und hinsichtlich der gesundheitsbezogenen Lebensqualität – für strukturelle Gelenkveränderungen (wie Deformitäten, Versteifungen, Kontrakturen) und für das soziale Funktionsniveau lagen keine Daten vor, • keinen Beleg für einen größeren bzw. geringeren Schaden im Hinblick auf die Gesamtmortalität, schwerwiegende unerwünschte Ereignisse, Studienabbrüche aufgrund von unerwünschten Ereignissen, die Gesamtrate der unerwünschten Ereignisse, schwerwiegende Infektionen und die Gesamtrate der Infektionen.
IQWiG, 2015 [18]. **(Vorbericht)** Systematische Leitlinienrecherche und -bewertung sowie Extraktion relevanter Empfehlungen für ein DMP Rheumatoide Arthritis	**Fragestellung/Ziele:** • Identifizierung aktueller, thematisch relevanter, evidenzbasierter Leitlinien • Extraktion der Empfehlungen und Kennzeichnung derjenigen Empfehlungen, die für die Versorgung von Patienten in einem DMP Rheumatoide Arthritis relevant sind. **Population:** Patienten mit rheumatoider Arthritis **Ergebnis /Fazit:** Bei der medikamentösen Therapie wurden zu den folgenden Teilbereichen Empfehlungen identifiziert: • medikamentenübergreifende Empfehlungen zur Überprüfung der Therapieziele Remission und Minderung der Krankheitsaktivität sowie zum regelmäßigen Monitoring der medikamentösen Therapie • Empfehlungen zu krankheitsmodifizierenden antirheumatischen Medikamenten (DMARD). Dargestellt sind Empfehlungen zur Verwendung von konventionellen DMARD (csDMARD) und sogenannten Biologika (bDMARD). Die Empfehlungen beziehen sich auf die Auswahl geeigneter Medikamente und Medikamenten-kombinationen in Abhängigkeit von der Krankheitsdauer, der Symptomatik, von vorangegangenen Therapieversuchen, vom klinischen Ansprechen und von der Verträglichkeit. Weitere Empfehlungen beziehen sich auf die Durchführung und das Monitoring der DMARD-Therapie. • […]

4.4.4.2.2 Krankheitsmodifizierende Medikamente

4.4.4.2.2.1 Initiale Therapie mit csDMARD

Monotherapie

5 Leitlinien empfehlen den Einsatz von csDMARD zur Initialtherapie bei rheumatoider Arthritis. Dabei wird Methotrexat[1] (MTX) als Mittel der ersten Wahl genannt. Bei MTX-Kontraindikationen oder Unverträglichkeiten werden alternativ auch Sulfasalazin oder Leflunomid zur Initialtherapie empfohlen (Empfehlungen DMP-relevant).

Eine Leitlinie empfiehlt zur Initialtherapie von DMARD-naiven Patienten generell den Einsatz von csDMARD unabhängig von einer zusätzlichen Glukokortikoidtherapie (Empfehlung potenziell DMP-relevant).

Eine Leitlinie gibt Empfehlungen zum Einsatz von Minocyclin[2] bei Patienten mit früher RA und niedriger, moderater beziehungsweise hoher Krankheitsaktivität und ohne ungünstige prognostische Faktoren (Empfehlungen potenziell DMP-relevant).

2 Leitlinien empfehlen bis zum Eintritt der Wirkung der Initialtherapie (Mono- oder in Kombination) die additive Gabe von Glukokortikoiden. In Abhängigkeit von der klinischen Symptomatik sollten die Glukokortikoide aber so schnell wie möglich wieder ausgeschlichen werden (Empfehlungen DMP-relevant).

Kombinationstherapie mehrerer csDMARD

2 Leitlinien empfehlen eine Kombinationstherapie[3] von csDMARD, wenn eine Monotherapie nicht zielführend ist. Eines der csDMARD sollte dabei Methotrexat1 sein, jedoch nur wenn keine Kontraindikationen vorliegen (Empfehlungen DMP-relevant).

Aufgrund der im Vergleich zu anderen Kombinationstherapien erhöhten Toxizität gibt eine Leitlinie eine negative Empfehlung für den Einsatz von Methotrexat1 in Kombination mit Leflunomid (Empfehlung potenziell DMP-relevant).

Eine Leitlinie gibt die Empfehlung im Falle einer Kombinationstherapie3 bei DMARD-naiven Patienten (unabhängig von einer Glukokortikoid-Therapie), csDMARD einzusetzen (Empfehlung potenziell DMP-relevant).

2 Leitlinien geben Empfehlungen, dass Patienten, die nach einer csDMARD-Monotherapie noch moderate beziehungsweise hohe Krankheitsaktivität (und Vorliegen ungünstiger prognostischer Faktoren) aufweisen, auf eine Kombinationstherapie[3] mit 2 oder 3 csDMARD wechseln sollten (Empfehlungen potenziell DMP-relevant).

Eine Leitlinie gibt bei Patienten, die nicht angemessen auf die Initialtherapie ansprechen, der Kombinationstherapie[3] mit csDMARD den Vorzug vor einer sequenziellen Monotherapie (Empfehlung potenziell DMP-relevant).

4.4.4.2.2.2 Kombinationstherapie csDMARD und bDMARD

Insgesamt 5 Leitlinien geben Empfehlungen zur Kombinationstherapie csDMARD und bDMARD.

4 Leitlinien empfehlen bei unzureichendem Ansprechen einer csDMARD-Therapie (Mono- oder Kombinationstherapie) eine Kombination[3] aus csDMARD und biologischen DMARD (bDMARD). Die Indikationsstellung sollte durch einen Rheumatologen erfolgen. 3 Leitlinien empfehlen explizit die Kombination[3] von Methotrexat[1] und einem Biologikum (Empfehlungen sind DMP-relevant).

Eine Leitlinie empfiehlt bei Patienten mit früher RA, hoher Krankheitsaktivität und gleich-zeitigem Vorliegen ungünstiger prognostischer Faktoren eine Initialtherapie mit Infliximab und Methotrexat[1] (Empfehlung potenziell DMP-

	relevant). **4.4.4.2.2.3 Therapie mit bDMARD** Insgesamt 8 Leitlinien geben Empfehlungen zur Therapie mit bDMARD. Eine Leitlinie gibt eine negative Empfehlung für eine Therapie mit TNF-α-Antagonisten bei Patienten mit schwerer, aktiv-entzündlicher und etablierter RA, wenn zuvor nicht mit Methotrexat[1] oder anderen csDMARD behandelt wurde (Empfehlung potenziell DMP-relevant). Eine Leitlinie empfiehlt, Patienten mit Unverträglichkeit von Methotrexat und mit moderater bis schwerer RA zur Kontrolle der Krankheitsaktivität mit intravenös appliziertem Tocilizumab zu behandeln. Dagegen sollten Patienten, die nicht ausreichend auf Methotrexat[1] ansprechen, aber keine Unverträglichkeitsreaktion zeigen, weiter mit Methotrexat[1] behandelt werden (Empfehlungen potenziell DMP-relevant). Eine Leitlinie empfiehlt, für DMARD-naive Patienten mit hoher Krankheitsaktivität und Vorliegen ungünstiger prognostischer Faktoren eine Therapie mit TNF-α-Antagonisten in Erwägung zu ziehen (Empfehlung potenziell DMP-relevant). 3 Leitlinien empfehlen, die Therapie von TNF-α-Antagonisten auf Biologika mit anderen Wirkmechanismen oder andere TNF-α-Antagonisten umzustellen, wenn die Wirksamkeit ausbleibt oder die Behandlung wegen Nebenwirkungen abgebrochen werden muss (Empfehlungen potenziell DMP-relevant). 3 Leitlinien empfehlen zum Wechsel von Nicht-TNF-α-Antagonisten Biologika auf TNF-α-Antagonisten, sollte die gewünschte klinische Wirkung ausbleiben oder wenn die Therapie wegen Nebenwirkungen abgebrochen werden muss (Empfehlungen potenziell DMP-relevant). Eine Leitlinie empfiehlt den Einsatz von Tofacitinib[4] bei Patienten mit RA, wenn alle Behandlungsversuche mit bDMARD ausgeschöpft wurden und trotzdem keine Verbesserung zu verzeichnen ist (Empfehlung potenziell DMP-relevant). 2 Leitlinien geben Empfehlungen zur Behandlung mit Rituximab[5]. Rituximab wird für Patienten mit Kontraindikationen gegen TNF-α-Antagonisten und für Patienten mit hoher Krankheitsaktivität, bei denen die Behandlung mit einem oder mehreren Biologika erfolglos geblieben ist, empfohlen. Eine Leitlinie weist auf die besondere Effektivität von Rituximab bei Patienten mit positivem Rheumafaktor oder positivem Anti-CCP-Ak-Wert hin (Empfehlungen DMP-relevant). [1] Nicht alle Methotrexat-Präparate haben eine Zulassung zur Behandlung von RA bzw. es sind nicht alle Darreichungsformen für die Indikation rheumatoide Arthritis zugelassen. [2] Gemäß Fachinformation ist Minocyclin in Deutschland nicht für den Anwendungsbereich rheumatoide Arthritis zugelassen [3] Es ist im Einzelfall zu prüfen, ob die Medikamente auch für die in den Leitlinien jeweils genannten Kombinationstherapien zugelassen sind. [4] Tofacitinib ist in Deutschland nicht für den Anwendungsbereich rheumatoide Arthritis [5] Gemäß Fachinformation ist Rituximab in Deutschland nur in der intravenösen Darreichungsform für den Anwendungsbereich rheumatoide Arthritis zugelassen
G-BA, 2007 [12]. Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie in Anlage 4: Therapiehinweis zu Leflunomid.	**Wirkstoff: Leflunomid (Arava®)** **Indikation: Rheumatoide Arthritis** • In fortgeschritteneren Krankheitsstadien hat sich Leflunomid als ähnlich wirksam erwiesen wie MTX oder SSZ. Unter wirtschaftlichen Gesichtspunkten bietet es sich als Mittel der zweiten oder dritten Wahl an. Bei therapierefraktären Verläufen kann sein Einsatz erwogen werden bevor auf einen TNF Alpha Blocker umgestellt wird. Die Überlegenheit einer Kombination von Leflunomid mit einem Tumornekrosefaktor (TNF) Alpha Blocker gegenüber einer TNF Alpha Blocker Monotherapie ist durch randomisierte kontrollierte Studien nicht belegt. Vergleichende

	Studien zur Kombination von TNF Alpha Blockern mit MTX gibt es nicht. Es ist bisher kein TNF Alpha Blocker explizit für eine Kombinationstherapie mit Leflunomid zugelassen. • Bei ungesichertem Nutzen und erhöhtem Risiko für toxische Nebenwirkungen ist eine Kombinationstherapie von Leflunomid mit TNF Alpha Blockern in der Regel unwirtschaftlich. Für den Fall einer Unverträglichkeit von MTX auch in niedrigeren Dosierungen bzw. Vorliegen von Kontraindikationen, die den Einsatz von MTX ausschließen, sind die TNF Alpha Inhibitoren Adalimumabund Etanercept auch als Monotherapie zugelassen. Bei Versagen einer Therapie mit TNF Alpha Blockern stehen für diese Situation zugelassene Biologicals wie Abatacept oder Rituximab zur Verfügung.
G-BA, 2007 [13]. Bekanntmachung eines Beschlusses des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie/AMR in Anlage 4: Therapiehinweis zu Adalimumab	**Wirkstoff: Adalimumab (zum Beispiel Humira®)** **Indikation Rheumatoide Arthritis und Psoriasis-Arthritis** • Die Behandlung mit TNF-alpha-Hemmern stellt dabei eine Alternative zur Reduktion der Symptomatik und Verbesserung der körperlichen Funktionsfähigkeit bei Patienten mit aktiver Rheumatoider Arthritis oder Arthritis psoriatica dar, wenn eine Therapie mit allen individuell indizierten DMARDs und deren Kombinationen, mindestens jedoch 2 einschließlich Methotrexat (MTX) — soweit keine Kontraindikationen dafür vorliegen — bis zur individuell angezeigten Höchstdosis (in der Regel 20 bis 25 mg pro Woche, ggf. als Injektion und ggf. Folsäure- bzw. Folinsäurepräparate), erfolglos geblieben ist. Diese müssen lange genug (in der Regel je nach DMARD mindestens jeweils 3 bis 6 Monate) in adäquater Dosis und unter fachlich kompetenter Überwachung eingesetzt worden sein. • Für einen breiten Einsatz von Adalimumab als erstes DMARD bei neu diagnostizierter Rheumatoider Arthritis fehlen derzeit u. a. evaluierte prädiktive Faktoren für den Krankheitsverlauf, die eine ausreichend sichere Auswahl der Patienten mit schwerer progressiver Arthritis in frühen Krankheitsstadien ermöglichen würde. In der Regel ist die Primäranwendung daher bei der derzeitigen Studienlage nicht angezeigt. Bei seltenen individuellen Besonderheiten (Kontraindikationen gegen alle DMARDs oder hohe Krankheitsprogression) kann ein frühzeitiger Einsatz von TNF-alpha-Hemmern angemessen sein. • Bei der Wahl eines TNF-alpha-Hemmers können aus medizinisch-therapeutischer Sicht aufgrund der derzeitigen Studienlage oder evidenzbasierter Leitlinien bei der Indikation Rheumatoide Arthritis keine allgemeinen Prioritäten gesetzt werden. • Bei der Indikation Psoriasis-Arthritis ist der unterschiedliche Zulassungsstatus bzgl. der Hautmanifestation der Psoriasis zu beachten, insbesondere da die Zulassung von Etanercept und Infliximab die Anwendung bei Arthritis psoriatica und bei therapieresistenter mittelschwerer bis schwerer Plaque psoriasis abdeckt. Die voraussichtlichen Therapiekosten für das ausgewählte Präparat stellen damit bei Beginn einer TNF-alpha- Therapie den wesentlichen Gesichtspunkt bei der Produktwahl dar. Davon kann abgewichen werden, wenn individuelle klinische Faktoren (z. B. Neben- und Wechselwirkungen) bzw. die spezifischen Eigenschaften oder die Anwendungsmodalitäten des Arzneimittels eine nachvollziehbare Kontraindikation darstellen oder die bevorzugte Anwendung im Einzelfall begründen. Auch die Praxisausstattung (z. B. Lagerungsmöglichkeit für Infusionen und Nachüberwachung beim Einsatz von Infliximab) begründet keine unwirtschaftliche Produktwahl. • Ein Ansprechen auf die Therapie ist bereits nach 1 bis 2 Wochen zu erwarten. Soweit auch nach 3 Monaten kein deutliches klinisches Ansprechen (klinische Symptomatik, DASScore, Labor) zu verzeichnen ist, ist die Therapie mit Adalimumab abzusetzen. • Eine Dosiserhöhung durch Verkürzung des Intervalls auf wöchentlich 40 mg bei Patienten mit einer Adalimumab-Monotherapie ist in der Regel unwirtschaftlich.
G-BA, 1999 [11]. Arzneimittel-	**Wirkstoff:** Etanercept (z.B. Enbrel®) **Wirksamkeit**

richtlinien: Etanercept	Etanercept wurde in mehreren klinischen Phase II und Phase III Studien an erwachsenen Patienten mit rheumatoider Arthritis allein oder in Kombination mit Methothrexat erprobt. Gegenüber Plazebo zeigte sich eine signifikante Verbesserung hinsichtlich der Entzündungsaktivität und der Funktionseinschränkungen. Die Wirksamkeit der Therapie zeigte sich nach ein bis zwei Wochen und war dosisabhängig. Nach Absetzen der Therapie kam es überwiegend innerhalb von 4 Wochen zu einem Wiederaufflammen der Symptome. Unter der Kombinationsbehandlung mit Etanercept und Methotrexat konnte eine klinische Besserung auch bei Patienten erreicht werden, die zuvor auf Methotrexat allein nicht oder unzureichend angesprochen hatten. Es liegen bisher keine Erfahrungen zur Langzeitbehandlung über mehr als 36 Monate vor. Weiterhin ist offen, ob es sich ausschließlich um eine kurzfristige symptomatische Therapie handelt oder ob Etanercept den natürlichen Krankheitsverlauf mit Destruktion der Gelenke aufhalten kann. **Empfehlungen zur wirtschaftlichen Verordnungsweise** Voraussetzung für den Einsatz von Etanercept als Behandlungsalternative ist das Versagen aller im individuellen therapeutischen Verlauf angemessenen Basismedikationen. Die Erfahrungen mit dem Präparat sind noch begrenzt. Aufgrund der Zytokinhemmung können Langzeitwirkungen bzw. Nebenwirkungen noch nicht abgeschätzt werden. Es ist zu empfehlen, vor Verordnung von Etanercept unter Einbeziehung rheumatologischen Sachverstandes eine strukturierte Zweitmeinung (z. B. Clearingstelle bei der KV) einzuholen.

Cochrane Reviews

Therapieerfahrene Patienten bzw. gemischte Patientenpopulation (therapienaiv und therapieerfahren)	
Lethaby A et al., 2013 [25]. Etanercept for the treatment of rheumatoid arthritis.	**1. Fragestellung** To update the previous Cochrane systematic review published in 2003 assessing the benefits and harms of etanercept for the treatment of RA. In addition, we also evaluated the benefits and harms of etanercept plus DMARD compared with DMARD monotherapy in those people with RA who are partial responders to methotrexate (MTX) or any other traditional DMARD.
	2. Methodik ***Population:*** Extraktion fokussiert auf Patienten die <u>vorbehandelt</u> sind → What happens to people with rheumatoid arthritis who take etanercept plus traditional DMARDs (methotrexate or sulphasalazine) after they have NOT improved with traditional DMARDs alone ***Intervention:*** Etanercept ***Vergleiche/Komparatoren:*** siehe Ergebnisteil ***Endpunkte*** <u>Primär</u>: The set of efficacy measures includes: 1) tender joint count; 2) swollen joint count; 3) patient assessment of pain using 10-cm visual analogue scale or Likert scale; 4) patient global assessment of disease activity; 5) physician global assessment of disease activity using 10-cm visual analogue scale or Likert scale; 6) patient assessment of functional ability as measured by a validated scale such as the Health Assessment Questionnaire (HAQ), which is a standardised, validated scale used in people with arthritis; 7) acute phase reactants such as ESR or CRP; 8) Radiographic bone changes are accepted as part of the core set of disease activity measures in studies of a minimum of 12 months' duration. <u>Sekundär</u>: • health-related quality of life (HRQoL) such as the Short Form (SF)-36, when available; • adverse events (AEs); • withdrawals from the study (total, due to lack of efficacy, due to AEs and death). ***Einschlusskriterien für Primärstudien*:** RCTs or controlled clinical trials (CCTs) (minimum 24 weeks' duration) ***Suchzeitraum***: 1966 bis 2003; 2003 bis 01/2012 (Update) ***Anzahl eingeschlossene Studien/Patienten (Gesamt)*:** 9 (n = 2800) ***Qualitätsbewertung der Studien:*** Cochrane Risk of Bias
	3. Ergebnisdarstellung <u>Allgemein</u>: The trials were **generally of moderate to low risk of bias**, the majority funded by pharmaceutical companies. Follow-up ranged from six months to 36 months.

	What happens to people with rheumatoid arthritis who take etanercept plus traditional DMARDs (methotrexate or sulphasalazine) after they have NOT improved with traditional DMARDs alone: ACR 50 (number of tender or swollen joints and other outcomes such as pain and disability) - 38 more people out of 100 had a 50% improvement in symptoms after six months to three years compared with people taking a DMARD alone (38% absolute improvement). 79 people out of 100 on etanercept plus DMARDs had a 50% improvement in symptoms. 41 people out of 100 on DMARDs alone had a 50% improvement in symptoms Disease activity - 22 more people out of 100 were considered to have low disease activity of their rheumatoid arthritis from six months to three years on etanercept with DMARDs (22% absolute improvement). - 46 people out of 100 on etanercept plus DMARDs were considered to have low disease activity of their rheumatoid arthritis. - 24 people out of 100 on DMARDs alone were considered to have low disease activity of their rheumatoid arthritis. Disability - People who took etanercept plus a DMARD rated the change in their disability to be 0.36 points lower on a scale of 0 to 3 after six months to three years compared with people who took a DMARD alone (12% absolute improvement). - People who took etanercept plus a DMARD rated the change in their disability to be between 0.51 and 1.08 on a scale of 0 to 3 after six months to three years. - People who took a DMARD alone rated the change in their disability to be between 0.15 and 0.72 on a scale of 0 to 3 after six months to three years. X-rays of the joints - When all people in all the studies were considered, joint damage improved slightly in those who received combined treatment with etanercept plus DMARD compared with DMARD or etanercept alone after 12 to 36months. Joint damage in people whom DMARDs were not working and received combined treatment with etanercept plus DMARD was similar to those given a DMARD alone, but this result might be due to low numbers of people in this group.
	4. Fazit der Autoren: Etanercept 25mg administered subcutaneously twice weekly together with MTX was more efficacious than either etanercept or MTX monotherapy for ACR50 and it slowed joint radiographic progression after up to three years of treatment for all participants (responders or not). There was no evidence of a difference in the rates of infections between groups.
Ruiz GV et al., 2014 [41]. Certolizumab pegol (CDP870) for rheumatoid arthritis in adults	**1. Fragestellung/Zielsetzung** To assess the clinical benefits and harms of certolizumab pegol (CDP870) in patients with RA who have not responded well to conventional disease-modifying anti-rheumatic drugs (DMARDs).
	2. Methodik **Population:** Adults (18 years of age and older) with RA who have persistent disease activity despite current or previous use of conventional DMARDs. **Intervention:** Certolizumab pegol (CDP870) at any dose **Komparator:** Placebo or any DMARD including other biologic agents used to treat RA **Endpunkte** *Major Endpoints:* • The proportion of patients achieving an ACR50 • Health-related quality of life, such as the Health Assessment Questionnaire

	(HAQ) or Short Form Health Survey (SF-36) • Disease Activity Score (DAS28 or other versions of DAS) • Radiological changes (erosion score (ES), modified total Sharp score, joint space narrowing) • Serious adverse events • All withdrawals • Withdrawals due to adverse events *Minor Endpoints:* • ACR20 and ACR70 • Frequency of adverse events **Suchzeitraum (Aktualität der Recherche):** We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library 2014, Issue 5), MEDLINE, EMBASE, Scopus, TOXLINE,Web of Knowledge; websites of the US Food and Drug Administration (FDA) and EuropeanMedicines Evaluation Agency (EMEA); reference lists of articles; and searched http/clinicaltrials.gov. The searches were updated from 2009 (date of last search for the original review) to 5 June 2014. **Anzahl eingeschlossener Studien/Patienten (Gesamt):** Eleven trials were included in this update. Ten (4324 patients) were included in the pooled analysis for benefits, five more than previously, and 10 (3711 patients) in the pooled analysis for harms, four more trials (1930 patients) than previously. The duration of follow-up varied from 12 to 52 weeks and the range of doses of certolizumab pegol varied from 50 to 400 mg given subcutaneously (sc). In phase III trials, the control was placebo plus MTX in five trials and placebo in four trials. **Qualitätsbewertung der Studien:** Cochrane Risk of Bias zur Bewertung des Verzerrungsrisikos auf Einzelstudienebene, GRADE zur Bewertung der overall quality of evidence
	3. Ergebnisdarstellung **Quality of Evidence** • The quality of the evidence found in the trials included in this review was high. Studies had high standards for treatment allocation, concealment and blinding, but there may have been a risk of attrition bias. • The risk of bias was low and the quality of evidence was downgraded to <u>moderate</u> because of high rates of dropouts (> 20%) in most of the trials. We did not find any problems with inconsistency, indirectness, imprecision or publication bias. **Wirksamkeit:** • Statistically significant improvements were observed at 24 weeks with the approved dose of 200 mg certolizumab pegol every other week, in 1) <u>American College of Rheumatology (ACR) 50% improvement</u>: 27% absolute improvement (95% CI 20% to 33%), risk ratio (RR) 3.80 (95% CI 2.42 to 5.95); moderate quality of evidence 2) <u>the Health Assessment Questionnaire (HAQ)</u>: -12% absolute improvement (95% CI -9% to -14%), mean difference (MD) - 0.35 (95% CI -0.43 to -0.26) (scale 0 to 3); moderate quality of evidence 3) <u>Disease Activity Score (DAS) remission improvement:</u> absolute improvement 11% (95% CI 8% to 15%), RR 8.47 (95% CI 4.15-17.28); 4) radiological changes: erosion score (ES) absolute improvement -0.29% (95% CI -0.42% to -0.17%), MD -0.67 (95% CI -0.96 to -0.38) (scale 0 to 230); moderate quality of evidence **Sicherheit:** • Serious adverse events were statistically significantly more frequent for certolizumab pegol (200 mg every other week) with an absolute rate difference of 4% (95% CI 2% to 6%), Peto odds ratio (OR) 1.77 (95% CI

	1.27 to 2.46).; moderate quality of evidence • There was a statistically significant increase in all withdrawals in the placebo groups (for all doses and all follow-ups) with an absolute rate difference of -34% (95% CI -18% to -50%), RR 0.42 (95% CI 0.36 to 0.50); moderate quality of evidence • There was a statistically significant increase in all withdrawals due to adverse events in the certolizumab groups (for all doses and all follow-up) with an absolute rate difference of 2% (95% CI 1% to 3%), Peto OR 1.66 (95% CI 1.15 to 2.37). moderate quality of evidence
	4. Fazit der Autoren: The results and conclusions did not change from the previous review. There is moderate-level evidence from randomised controlled trials that certolizumab pegol alone or combined with methotrexate is beneficial in the treatment of RA. Adverse events were more frequent with active treatment. We found a potential risk of serious adverse events.
Singh JA et al., 2010 [48]. Golimumab for rheumatoid arthritis	**1. Fragestellung** to compare the efficacy and safety of golimumab (alone or in combination with DMARDs or biologics) to placebo (alone or in combination with DMARDs or biologics) in randomized or quasi-randomized clinical trials in adults with RA.
	2. Methodik ***Population:*** Adults with RA ***Intervention:*** Golimumab alone or in combination with DMARDs or biologics ***Komparator:*** Placebo plus methotrexate or golimumab alone or in combination with DMARDs or biologics compared to other DMARDs or biologics. ***Endpunkte*** Primär: 1) ACR50 defined as 50% improvement in both tender and swollen joint counts and 50% improvement in three of the five following variables: patient global assessment, physician global assessments, pain scores, HAQ score, and acute phase reactants (Erythrocyte Sedimentation Rate (ESR) or C-Reactive Protein (CRP) 2) Safety: Safety as assessed by a) number and type of AEs and SAEs b) withdrawals: (*i*) Total, (*ii*) due to lack of efficacy, (*iii*) due to AEs c) death Sekundär: 1) ACR20 and ACR70 defined as 20% and 70% improvement in variables defined above under the primary outcome (Felson 1995). 2) Changes in either DAS, a composite index of tender and swollen joint counts, patient global assessment and ESR (van der Heijde 1993) or DAS28 score (Prevoo 1995). In an occasional case, where median was presented instead of mean, due to large sample size we used median to substitute for mean and calculated standard deviation from the interquartile range. 3) Proportion achieving a "good state": (a) good EULAR response – defined by a decrease in DAS or DAS28 of ≥ 1.2 from baseline with a final DAS < 2.4 (or DAS 28 < 3.2); (b) low disease activity defined by DAS < 2.4 or DAS28 ≤ 3.2; (c) remission defined as DAS < 1.6 or DAS28 < 2.6. We used good EULAR response based on ESR, where data were presented for both ESR- and CRP-based outcomes. 4) Quality of Life, measured by SF-36 and the proportion achieving minimally clinically important difference on HAQ ≥ 0.22. 5) Radiographic progression, as measured by Larsen/Sharp/ modified Sharp scores.

	Suchzeitraum (Aktualität der Recherche): Bis 04/2010 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 4 (n = 1231 in aktiven Armen, n = 483 in Placebo-Armen) ***Qualitätsbewertung der Studien:*** Cochrane Risk of Bias tool
	3. Ergebnisdarstellung Four RCTs with 1231 patients treated with golimumab and 483 patients treated with placebo were included. Of these, 436 were treated with the FDA-approved dose of golimumab 50 mg every four weeks. Compared to patients treated with placebo + MTX, patients treated with the FDA-approved dose of golimumab + MTX were 2.6 times more likely to reach ACR50 (95% CI 1.1, 95% CI 0.9 to 1.2; P=0.44), and 0.5 times as likely to have overall withdrawals (95% CI 0.3 to 0.8; P=0.005). Golimumab-treated patients were significantly more likely to achieve remission, low disease activity and improvement in functional ability compared to placebo (all statistically significant). No significant differences were noted between golimumab and placebo regarding SAEs, infections, serious infections, lung infections, tuberculosis, cancer, withdrawals due to AEs and inefficacy and deaths. No radiographic data were reported. **Concomitant methotrexate:** Since all 4 included studies had one or more arm with background methotrexate, we combined all doses of golimumab with concomitant methotrexate to obtain estimates for efficacy and safety of golimumab when used with concomitant methotrexate.We found that golimumab was statistically significantly more efficacious than control in all efficacy outcomes. For safety outcomes, we found that there was no statistically significant difference between golimumab and placebo, except in withdrawals where there was statistically significantly more total withdrawals in the placebo arm, because of statistically significantly more withdrawals due to inefficacy in the placebo group. Use in patients who have methotrexate-failure versus biologic failure: Only one study enrolled patients who had failed biologics (Smolen 2009). A detailed comparison was not done since there was only one study in patients with biologic-failure. Single biologic DAMRD agent versus combination biologic therapy: None of the studies included combination biologic therapy, therefore this comparison could not be done. DMARD-naive versus not naive: Only one study (Emery 2009) recruited methotrexate naive patients, therefore this comparison was not done.
	4. Anmerkungen/Fazit der Autoren Golimumab improves the number of tender or swollen joints and other outcomes such as pain and disability (ACR 50). Golimumab increases the number of people in remission. Slightly more people who take Golimumab will have minor side effects (such as a minor infection), but this may be the result of chance. There is no difference in the number of people who will have a SAE, compared to people who took a placebo. We do not have precise information about side effects and complications. This is particularly true for rare but serious side effects. Possible side effects may include a serious infection or upper respiratory infection. Rare complications may include certain types of cancer. **5. Hinweise FBMed:** Analysen beinhalten sowohl Patienten, die therapienaiv als auch vorbehandelt waren**.**
Singh JA et al., 2010 [47]. Tocilizumab for rheumatoid	**1. Fragestellung** To assess the efficacy and safety of tocilizumab in patients with RA using the data from published randomized or quasi-randomized controlled trials.
	2. Methodik

arthritis (Review)	***Population:*** Adult RA patients ***Intervention:*** Tocilizumab alone or in combination with DMARDs or biologics ***Komparator:*** Placebo or other DMARDs or biologics ***Endpunkte*** <u>Primär</u> 1) Major efficacy outcome (binary): ACR50 defined as 50% improvement in both tender and swollen joint counts and 50% improvement in three of the following five variables: patient's global assessment, physician's global assessment, pain scores, HAQ score and acute phase reactants (Erythrocyte Sedimentation Rate (ESR) or C-Reactive Protein (CRP). 2) Safety: as assessed by the number and type of AEs and SAEs, withdrawals due to lack of efficacy, withdrawals due to AEs, overall withdrawals and death. <u>Sekundär</u> 1) ACR20 and ACR70 defined as 20% and 70% improvement in variables defined above under primary outcome. 2) Continuous: changes in either DAS, a composite index of tender and swollen joint counts, patient global assessment and ESR (van der Heijde 1993) or DAS28 score. 3) Proportion achieving a 'good state': a) good EULAR response, defined by a decrease in the DAS or DAS 28 of > 1.2 from baseline with a final DAS < 2.4 (or DAS 28 < 3.2); b) low disease activity, defined by DAS < 2.4 or DAS28 <3.2; c) remission, defined as DAS < 1.6 or DAS28 < 2.6. 4) Quality of life measured by SF-36 (which has eight domain scores and two summary scores, physical and mental component summary; all continuous data) and function measured by HAQ score or modified HAQ calculated as score changes and the proportion achieving minimally clinically important difference on HAQ ≥ 0.22. 5) Radiographic progression, as measured by modified Sharp scores ***Suchzeitraum (Aktualität der Recherche)***: Bis 2009 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 8 (n = 3334). ***Qualitätsbewertung der eingeschlossenen Studien:*** Cochrane Risk of Bias und GRADE
	3. Ergebnisdarstellung Of the eight included studies, only <u>one included patients with prior TNF-biologic failure</u> (Emery 2008 (RADIATE); <u>all others included patients who had failed methotrexate or other traditional DMARDs</u>. 1 RCT im direkten Vergleich gegen DMARDs[1] relevant. **Best estimate of what happens to people with RA who have not improved with methotrexate alone, who take tocilizumab for rheumatoid arthritis:** <u>ACR50 (number of tender or swollen joints and other doctor or patient-assessed aspects of rheumatoid arthritis)</u> • 31 people out of 100 who took tocilizumab experienced improvement in the symptoms of their rheumatoid arthritis. • 10 people out of 100 who took placebo experienced improvement. • 11 more people experienced improvement with tocilizumab. <u>Side effects</u>

[1] Nishimoto 2007 (SAMURAI) *published data only.* Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an X ray reader-blinded randomised controlled trial of tocilizumab. Annals of the Rheumatic Diseases 2007; 66:1162–7.

	• 5 people out of 100 dropped out of studies of tocilizumab because of the side effects. • 3 people out of 100 who took placebo dropped out of the studies. • 2 more people had side effects with tocilizumab. Subgruppenanalysen: • Concomitant methotrexate versus no methotrexate: tocilizumab was significantly better than placebo in achieving ACR 20/50/70 rates by a factor of 2.5 to 5.9, in patients with and without methotrexate. • Use in patients who have methotrexate/DMARD failure versus biologic failure: tocilizumab seemed effective in both those who had failed methotrexate and those that failed biologics compared to placebo (See 'Data and analyses' 15). The relative risk ratios were much higher favoring tocilizumab in biologic failure compared to methotrexate/DMARD failure. • We were unable to perform two other pre-specified subgroup analyses in the absence of data: DMARD-naive versus not naive, and single versus multiple biologic. Comparison 15. Tocilizumab versus placebo (use in patients with MTX/DMARD failure versus biologic failure)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ACR20	7	3288	Risk Ratio (M-H, Random, 95% CI)	2.51 [1.99, 3.18]
1.1 MTX/DMARD failure	6	2790	Risk Ratio (M-H, Random, 95% CI)	2.35 [1.87, 2.95]
1.2 Biologic failure	1	498	Risk Ratio (M-H, Random, 95% CI)	4.05 [2.50, 6.57]
2 ACR50	7	3288	Risk Ratio (M-H, Random, 95% CI)	3.80 [2.37, 6.10]
2.1 MTX/DMARD failure	6	2790	Risk Ratio (M-H, Random, 95% CI)	3.56 [2.13, 5.95]
2.2 Biologic failure	1	498	Risk Ratio (M-H, Random, 95% CI)	6.07 [2.70, 13.64]
3 ACR70	7	3288	Risk Ratio (M-H, Random, 95% CI)	5.03 [2.32, 10.91]
3.1 MTX/DMARD failure	6	2790	Risk Ratio (M-H, Random, 95% CI)	4.83 [2.05, 11.40]
3.2 Biologic failure	1	498	Risk Ratio (M-H, Random, 95% CI)	7.10 [1.72, 29.35]

	4. **Fazit der Autoren:** Tocilizumab is beneficial in decreasing RA disease activity and improving function. Tocilizumab treatment was associated with significant increase in cholesterol levels and in total AEs. Larger safety studies are needed to address these safety concerns.
Katchamart W et al., 2010 [20]. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying antirheumatic drugs for rheumatoid arthritis.	**1. Fragestellung** To evaluate the efficacy and toxicity of MTX monotherapy compared to MTX combination with non-biologic DMARDs in adult with RA.
	2. Methodik ***Population:*** Erwachsene Patienten (≥ 18 Jahre) mit rheumatoider Arthritis, sowohl DMARD naiv als auch therapieerfahren ***Intervention:*** MTX kombiniert mit anderen nicht-biologischen DMARDs ***Komparator:*** MTX-Monotherapie oder MTX plus Placebo ***Endpunkt*** • Wirksamkeit: Anzahl schmerzempfindlicher/geschwollener Gelenke, Schmerzempfinden, ACR Ansprechen/Remission (20,50,70), VAS, DAS (28), EULAR Ansprechen • Sicherheit: Nebenwirkungen • Studienabbrüche: aufgrund mangelnder Wirksamkeit und/oder Nebenwirkungen ***Suchzeitraum*** (Aktualität der Recherche): up to 2009 ***Anzahl eingeschlossene Studien/Patienten*** (Gesamt): 19 (n=2025) ***Qualitätsbewertung der Studien:*** Cochrane Risk of Bias

3. Ergebnisdarstellung

Die Wirksamkeitsanalyse wurde in 3 Gruppen stratifiziert:

1. "DMARD naive, parallel strategy" (→refers to trials where patients who never received DMARDs (including MTX) were randomised to start MTX alone or MTX plus another DMARD): Basierend auf sechs Studien. Untersuchte Kombinationen: MTX+SSZ; MTX+CSA, MTX+doxycycline. Alle eingeschlossenen Patienten hatten eine frühe rheumatoide Arthritis mit einer Dauer von <1 Jahr.
2. "MTX inadequate response, step-up strategy" (→refers to trials where patients with inadequate response to MTX were randomised to continue the use of MTX alone or to add a second DMARD): Basierend auf 5 Studien in den Patienten mit MTX weiterbehandelt wurden (plus placebo) oder ein zweites DMARD hinzgefügt wurde: MTX + leflunomide (LEF), MTX+CSA, MTX+intramuscular gold, MTX + levofloxacin, oder MTX + zolendronic acid.
3. "Non-MTX DMARDs inadequate response, step-up strategy" (→refers to trials where patients with inadequate response to DMARDs (other than MTX) were randomly switched to MTX alone or MTX plus another DMARD): Basierend auf 8 Studien. Untersuchte Kombinationen (MTX + SSZ; MTX + azathioprine, MTX + chloroquine, MTX + SSZ + hydroxychloroquine, MTX + bucillamine, MTX + previous DMARDs inclusive: gold, D-penicillamine , BUC, and SSZ.

Hauptanalyse basierend auf Parameter ,,Studienabbrüche aufgrund mangelnder Wirksamkeit oder Nebenwirkungen''):

- Studienabbrüche aufgrund mangelnder Wirksamkeit oder Nebenwirkungen allgemein: Es zeigten sich keine stat. signifikanten Vorteile unter einer Kombinationstherapie gegenüber einer Monotherapie mit MTX, sowohl bei der gepoolten Analyse als auch bei den definierten Subgruppen (*Hinweis: Stat. signifikante Heterogenität bei der Gruppe Patienten die vorher auf eine DMARD Therapie angesprochen hatten*)
- **Ergebnisse zu der Subgruppe der DMARD-naiven Patienten:**
  - Informationen über Studienabbrüche aufgrund von fehlender Wirksamkeit lagen in 5 von 6 Studien vor (insgesamt 405 Patienten). Eine MTX Kombinationstherapie wies weniger Patienten auf die die Studie abbrachen, verglichen mit der MTX-Monotherapie, bei jedoch keiner stat. Signifikanz.

- Wirksamkeit allgemein: Es zeigte sich eine stat. signifikante Schmerzreduktionen und eine Verbesserung der körperlichen Funktion unter der MTX Kombinationstherapie, aber nur bei Patienten die bei denen eine vorherige MTX Therapie versagt hatte (absolute RD: -9.72%, 95%KI: -14.7%; -4.75% für Schmerzen / MD: -0.28, 95%KI: -0.36; -0.21 für körperliche Funktion).
- **Ergebnisse zu der Subgruppe der DMARD-naiven Patienten:**
  - Keine stat. signifikanten Unterschiede hinsichtlich der Anzahl an schmerzempfindlichen/geschwollenen Gelenken, Schmerz, Patient global assessment, Erythrozytensedimentationsrate (ESR) und C-reaktives Protein (CRP).
  - Zum Endpunkt ACR Ansprechen lagen Informationen aus 3 der 6 Studien vor (insgesamt 287 Patienten). Keine stat. signifikanten Unterschiede zwischen MTX Monotherapie und einer Kombinationstherapie mit MTX, außer in einer Studie, die einen Vorteil der Kombinationstherapie mit CSA für den Endpunkt ACR 70 Ansprechen (RR: 2.41; 95% KI 1.07 - 5.44) aufwies.
  - Zum EULAR Ansprechen lagen in 3 Studien (insgesamt 368 Patienten) Informationen vor. Es zeigte sich kein stat. signifikanter Unterschied zwischen den Gruppen.
  - Stat. signifikanter Unterschied im HAQ Score zugunsten der Kombinationstherapie (WMD: 0.1; 95% KI 0.09 - 0.11; basierend auf 2

	Studien). o Kleine aber stat. signifikante Reduktion unter der Kombinationstherapie hinsichtlich der (radiografischen) Progression (WMD: -3.15; 95% KI:-5.85 bis -0.45; basierend auf 2 Studien). • Nebenwirkungen: Mehr Nebenwirkungen unter einer Kombinationstherapie verglichen mit MTX alleine.
	4. Anmerkungen/Fazit der Autoren 'Despite the introduction of new biologic therapies, methotrexate alone or in combination with other traditional DMARDs remains the recommended first line therapy for most patients with RA'. 'When the balance of efficacy and toxicity is taken into account, the moderate level of evidence from our systematic review showed no statistically significant advantage of the MTX combination versus monotherapy.' **5. Hinweise durch FB Med** • Die Kriterien für ein DMARD Versagen oder inadäquates Ansprechen waren unterschiedlich zwischen den Studien. • In einer Studie war der Einsatz vorheriger DMARDs unklar. • Spiegelt nicht die heutige Praxis wieder (Zu niedrige Dosierung von MTX) • Nur eine Studie zu der Kombination LEF+MTX
Maxwell LJ et al., 2010 [31]. Abatacept for rheumatoid arthritis	**1. Fragestellung** To assess the efficacy and safety of abatacept in reducing disease activity, pain, and improving function in people with RA.
	2. Methodik ***Population*** Patients at least 16 years of age meeting the ACR 1987 revised criteria for RA (Arnett 1988). ***Intervention*** Abatacept alone, or in combination with DMARDs or biologics ***Komparator*** Placebo or other DMARDs or biologics ***Endpunkte*** primary: ACR 50 response rate to treatment with abatacept as defined by the ACR (Felson 1995). The variables included in this definition are: • tender joint count, • swollen joint count, • patient's assessment of pain (visual analogue scale (VAS) or Likert scale), • patient and physician assessment of disease activity (VAS or Likert scale), • patient assessment of functional ability (HAQ, Arthritis Impact Measurement Scales (AIMS), McMaster Toronto Arthritis (MACTAR)), • laboratory parameters (i.e. acute phase reactants, such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). secondary • Individual ACR criteria and ACR 20 and 70 response criteria as outlined above. • Radiographic progression, as measured by the Sharp, modified Sharp or Larsen methods (also considered a primary outcome for studies longer than one year in duration). • EULAR criteria. Adverse events: Since RCTs are usually of limited duration, mainly short-term AEs were assessed. However, regulatory agency websites and long-term extensions

of included RCTs were also reviewed for potential longer-term AEs. Specific AE outcomes of interest were:

- AEs, including allergic reactions, and infections,
- SAEs, including serious infections, and lymphoma,
- withdrawals due to lack of efficacy, and AEs.

Suchzeitraum (Aktualität der Recherche)
1966 bis 12/2008

Anzahl eingeschlossene Studien/Patienten (Gesamt):
7 (n = 2908); nur RCTs

Qualtitätsbewertung der Studien: Cochrane Risk of Bias Tool

3. Ergebnisdarstellung

Abatacept (2 and 10mg/kg) + DMARDs/biologic versus placebo + DMARDs/biologic for rheumatoid arthritis

Patient or population: patients with rheumatoid arthritis
Settings:
Intervention: Abatacept (2 and 10mg/kg) + DMARDs/biologic
Comparison: Placebo + DMARDs/biologic

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo + DMARDs/biologic	Abatacept (2 and 10mg/kg) + DMARDs/biologic				
ACR 50% improvement Follow-up: 12 months	168 per 1000	371 per 1000 (291 to 474)	**RR 2.21** (1.73 to 2.82)	993 (3 studies)	⊕⊕⊕○ **moderate**[1,2,3]	**Absolute risk difference = 21% (16% to 27%)**. Relative percent change=121% (73% to 182%). NNT=5 (4 to 7)[4]
Pain measured at end of study on a 100 mm visual analog scale. Scale from: 0 (better) to 100 (worse). Follow-up: 12 months	The mean pain in the control groups was **49.24 mm**	The mean pain in the intervention groups was **10.71 lower** (12.97 to 8.45 lower)		1425 (1 study[5])	⊕⊕⊕○ **moderate**[2]	**Absolute risk difference=-11% (-13% to -8.5%)**. Relative percent change=-18% (-22% to -14%). NNT=5 (4 to 6)[4]
Improvement in physical function (HAQ: greater than 0.3 increase from baseline, 0-3 scale) Follow-up: 12 months	393 per 1000	637 per 1000 (531 to 766)	**RR 1.62** (1.35 to 1.95)	638 (1 study[6])	⊕⊕⊕○ **moderate**[1]	**Absolute risk difference = 24% (16% to 32%)**. Relative percent change= 62% (35% to 95%). NNT=5 (4 to 7)[4]

Achievement of low disease activity state (DAS 28 less than 3.2, scale 0-10) Follow-up: 12 months	**98 per 1000**	**424 per 1000** (278 to 646)	**RR 4.33** (2.84 to 6.59)	638 (1 study[6])	⊕⊕⊕○ **moderate**[1]	**Absolute risk difference=33% (26% to 39%).** Relative percent change=333% (184% to 559%). NNT=4 (3 to 5)[4]
Total serious adverse events Follow-up: 6 to 12 months	**121 per 1000**	**127 per 1000** (105 to 155)	**RR 1.05** (0.87 to 1.28)	3151 (6 studies)	⊕⊕⊕○ **moderate**[1,2,3,7]	**Absolute risk difference=1% (-2% to 3%).** Relative percent change=5% (-14% to 29%). NNT=n/a[4]
Change in radiographic progression measured by Genant-modified Sharp erosion score (increase in score means more joint damage). Scale from: 0 to 145. Follow-up: 12 months	The median change in radiographic progression in the control group was **0.27 units**	The median change in radiographic progression in the intervention group was **0 units**		586 (1 study[6])	⊕⊕⊕○ **moderate**[1,8]	Note there was no change in the abatacept group. MD -0.27 (-0.42, -0.12) . **Absolute RD=-0.2% (-0.3% to -0.08%).** Relative percent change=-1.2% (-1.9% to -0.6%). [9]
Long-term serious adverse events Follow-up: 2 years	See comment	See comment	Not estimable	950 (2 studies[11])	⊕⊕○○ **low**[10]	Number of patients with SAE: Genovese 2005: 103/357; 23.4 SAE/100 patient-years; 70% completed the LTE. Kremer 2006: 149/593; 16.3 SAE/100 patient-years; 90.5% completed the LTE

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

[1] Kremer 2006: Intention to treat analysis not performed. 9 patients in abatacept group and 5 in placebo group excluded from analysis.
[2] Weinblatt 2006: 15 people randomized were not treated and not included in analysis
[3] Kremer 2003: Risk of attrition bias - less than 80% completion rate in treatment group at 12 months
[4] NOTE: Number needed to treat (NNT)=n/a when result is not statistically significant. NNT for dichotomous outcomes calculated using Cates NNT calculator (http://www.nntonline.net/visualrx/). NNT for continuous outcomes calculated using Wells Calculator (CMSG editorial office).
[5] Outcome based on Weinblatt 2006
[6] Outcome based on Kremer 2006
[7] Weinblatt 2007: Risk of attrition bias - less than 80% completion rate in the treatment group at 12 months
[8] Radiographic data obtained for 90% of study participants
[9] RD=risk difference
[10] Long-term serious adverse events based on observational data. Two RCTs had a long-term extension (LTE) phase in which people in the placebo group during the RCT switched to abatacept for the LTE.
[11] Based on 2 long-term extension studies (LTE) of RCTs. Participants on placebo in the RCT switched to abatacept treatment.

4. Anmerkungen/Fazit der Autoren

There is moderate-level evidence that abatacept is efficacious and safe in the treatment of RA. Abatacept should not be used in combination with other biologics to treat RA. The withdrawal and toxicity profile appears acceptable at the present time but further long-term studies and post-

	marketing surveillance are required to assess harms and sustained efficacy. **5. Hinweise der FB Med** Patientenmerkmale als Einschlusskriterien in den Einzelstudien sehr unterschiedlich ausgeprägt, z.B. • active disease despite treatment with DMARDs (Kremer 2003, Kremer 2006, Moreland 2002, Schiff 2008) • inadequate response to three months of anti-TNF therapy (Genovese 2005) • must have received etanercept for more than three months and still have active disease (Weinblatt 2007) • inadequate response to DMARDs or biologics (Weinblatt 2006) • The average disease duration in most trials was between eight and 13 years, except in Moreland 2002 in which the average duration of disease was much shorter: only 3.4 years.
Lopez-Olivo MA et al., 2015 [27]. Rituximab for rheumatoid arthritis	**1. Fragestellung** To evaluate the benefits and harms of rituximab for the treatment of RA.
	2. Methodik ***Population*** adult RA patients ***Intervention:*** rituximab as monotherapy or in combination with any DMARDs (traditional or biologic) ***Komparator:*** placebo or other DMARDs (traditional or biologic) ***Endpunkte:*** response of RA defined by ACR, WHO and ILAR core set of disease activity measures • ACR50, ACR20, ACR70 • Disease remission • Functional status • Radiographic progression • QoL • Withdrawal due to AE • AE, SAE ***Suchzeitraum (Aktualität der Recherche):*** up to Jan 2014 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 8 (n=2720) ***Qualitätsbewertung der Studien*** Cochrane Risk of Bias
	3. Ergebnisdarstellung Study populations: • Patients intolerant to at least 1 TNF inhibitor: 1 study • Inadequate response to MTX/DMARDs: 5 studies • Previous MTX and either eta or ada: 1 study • No previous MTX/DMARD treatment:1 study The level of evidence ranged from low to high, but was rated as moderate for most outcomes <u>Rituximab + MTX vs MTX alone</u> (5 studies, 1664 patients) *At w24 (4 studies)* • ACR50: RR 3.3 (95% CI 2.3 to 4.6) • ACR20: RR 2.2 (95% CI 1.9 to 2.7) • ACR70: RR 3.9 (95% CI 1.8 to 8.3) • clinically meaningful improvement in the Health Assessment Questionnaire (HAQ) (>0.22): RR 1.6 (95%CI 1.2 to 2.1) *At w52*

	• ACR50: RR 2.2 (95%CI 1.3-4.0) • ACR20 RR 1.53 (95%CI 1.09 to 2.13) • ACR70 RR 1.95 (95%CI 1.53 to 2.49] • ACR90: RR 1.8 (95% CI 1.1 to 3.0) (1 study) • HAQ-MCID=-0.22: RR 1.57 (95%CI 0.71 to 3.44) • clinical remission (Disease Activity Score (DAS) 28 joints < 2.6): RR 2.4 (95%CI 1.7 to 3.5) • SF-36 o clinically meaningful improvement in the physical component score (SF-36 PCS ≥ 5): RR 2.0 (95% CI 1.1 to 3.4) o clinically meaningful improvement in the mental component score (SF-36 MCS ≥ 5): RR 1.4 (95% CI 1.1 to 1.9) • clinically meaningful improvement in the fatigue score (FACIT ≥ 4): RR 1.6 (95% CI 1.0 to 2.5) *at w104* • sig. superiority of combination based on ACR50, 70 and 90 response, HAQ but not on ACR20 ->**Superiority of combination therapy** Safety: • no statistically significant difference in the rates of withdrawals due to AE or for other reasons in either group. • However, statistically significantly more people receiving the control drug withdrew from the study compared to those receiving rituximab (two 1000 mg doses) in combination with methotrexate at all times (RR 0.40, 95% CI 0.32 to 0.50; RR 0.61, 95% CI 0.40 to 0.91; RR 0.48, 95% CI 0.28 to 0.82; RR 0.58, 95% CI 0.45 to 0.75, respectively). • A greater proportion of patients receiving rituximab (two 1000 mg doses) in combination with methotrexate developed AEs after their first infusion compared to those receiving methotrexate monotherapy and placebo infusions (RR 1.6, 95% CI 1.3 to 1.9); • no statistically significant differences in the rates of SAE <u>Rituximab monotherapy vs MTX monotherapy</u> Superiority of rituximab at w 24 based on ACR response: • ACR20: RR 1.7 (95% CI 1.1 to 2.8) • ACR50: RR 2.6 (95% CI 1.0 to 6.6) These statistically significant differences disappeared at 48 weeks and 104 weeks. In addition, no statistically significant differences between groups were observed on the ACR 70 response rates at 24, 48, and 104 weeks • significant difference in reduction from baseline in the DAS28 at 24weeks between rituximab alone and the methotrexate alone group (MD -0.90, 95% CI -1.47 to -0.33) • statistically significant improvement in HAQ scores with rituximab alone compared to methotrexate alone (MD of -0.40 (95% CI -0.65 • to -0.15)) at 24 weeks, but the statistically significant difference disappeared at 48 and 72 weeks
	4. Fazit der Autoren Evidence from eight studies suggests that rituximab (two 1000 mg doses) in combination with methotrexate is significantly more efficacious than methotrexate alone for improving the symptoms of RA and preventing disease progression **5. Hinweise FBMed** Heterogene Patientenpopulation (in Bezug auf Vortherapien) eingeschlossen

Systematische Reviews

Therapieerfahrene RA-Patienten bzw. gemischte Populationen	
Donahue KE, 2012 [10]. Drug Therapy for Rheumatoid Arthritis in Adults: An Update.	**1. Fragestellung** Compare the benefits and harms of corticosteroids, oral and biologic diseasemodifying antirheumatic drugs (DMARDs) for adults with RA. Key Questions (KQs): • KQ1: For patients with RA, do drug therapies differ in their ability to reduce disease activity, to slow or limit the progression of radiographic joint damage, or to maintain remission? • KQ2: For patients with RA, do drug therapies differ in their ability to improve patient reported symptoms, functional capacity, or quality of life? • KQ3: For patients with RA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects? • KQ4: What are the comparative benefits and harms of drug therapies for RA in subgroups of patients based on stage of disease, prior therapy, demographics, concomitant therapies, or comorbidities?
	2. Methodik ***Population:*** Patienten mit RA ***Intervention:*** Corticosteroids, oral DMARDs, and biologic DMARDs ***Kontrolle(n):*** Corticosteroids, oral DMARDs, and biologic DMARDs, placebo ***Endpunkte:*** <u>Efficacy/effectivness</u> • KQ 1: - Disease activity - Radiographic joint damage - Remission • KQ 2: - Functional capacity - Quality of life - Patient-reported symptoms • KQ 3: Harms, tolerability, adherence, adverse effects • KQ 4: Benefits and harms in subgroups based on stage, history of prior therapy, demographics, concomitant therapies, comorbidities ***Suchzeitraum (Aktualität der Recherche):*** 1980 – 02/2011 Nur RCTs, Beobachtungsstudien mit mehr als 100 Patienten, systematische Reviews ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 31 head-to-head RCTs 1 head-to-head nicht-randomisiert/kontrollierte Studie 44 Placebo-kontrollierte Studien 28 Metaanalysen oder systematische Reviews 107 Observationsstudien identifiziert Included articles by key question KQ1 TOTAL = 125 (62) KQ2 TOTAL = 80 (47) KQ3 TOTAL = 201 (101) KQ4 TOTAL = 6 (2) *Some articles were included for more than one KQ, The first number

listed includes all references identified in both the original and update reports

Qualitätsbewertung der Studien:
„To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the U.S. Preventive Services Task Force and the NHS Centre for Reviews and Dissemination. To assess the quality of observational studies, we used criteria outlined by Deeks et al., 2003 (graded the strength of evidence for the outcomes determined)."

Strength of Evidence:

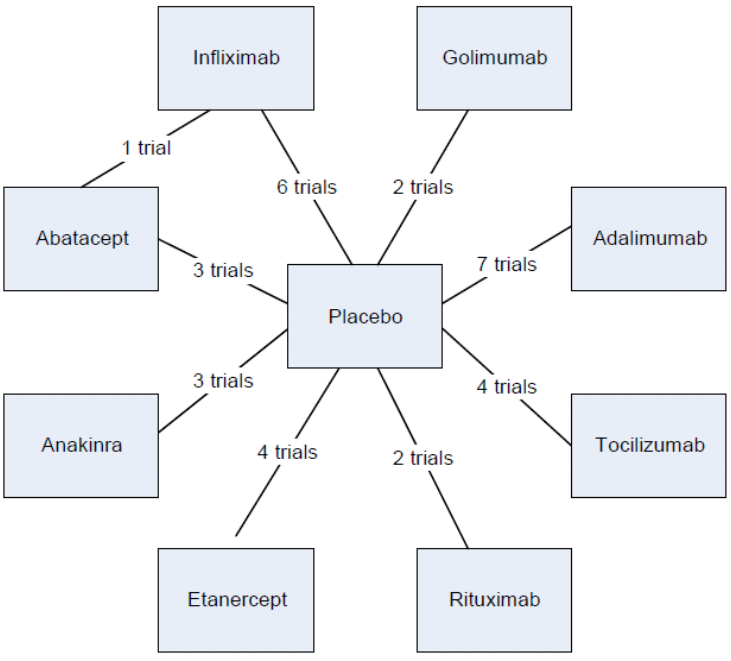
- ***High:*** Further research is very unlikely to change our confidence in the estimate of effect.
- ***Moderate:*** Further research may change our confidence in the estimate of effect and may change the estimate.
- ***Low:*** Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
- ***Insufficient***: Evidence either is unavailable or does not permit estimation of an effect.

3. Ergebnisdarstellung

Evidenzbewertung:
Auswertung der Evidenz nach:

- individual oral DMARD vs. oral DMARD,
- oral DMARD combinations (with or without corticosteroids) vs. oral DMARD combinations,
- biologic vs. biologic, biologic vs. oral DMARD,
- biologics plus oral DMARD vs. biologic,
- biologic plus oral DMARD vs. oral DMARD,
- early RA strategies.
-

Figure 2. Evidence network for ACR 50 mixed treatment comparisons



Note: The total number of trials does not appear to equal30 (the total number of studies included in the analysis) because some trials have multiple arms that were included.

Direkter Vergleich: Adatacept vs. Infliximab: kein Unterschied nach 1 Jahr[2]:

- We found one head-to-head RCT that compared one biologic DMARD

[2] Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheu-matoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2008 Aug; 67(8):1096-103. PMID: 18055472.

with another providing low strength of evidence that abatacept lessens disease activity at 1 year compared with infliximab. However, remission by DAS did not reach significance at 1 year.

Other existing direct head-to-head evidence is limited to a non-randomized, open-label effectiveness trial and six prospective cohort studies

Alle direkten und indirekten Vergleiche:

Table A. Summary of findings with strength of evidence

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Oral DMARD vs. Oral DMARD		
Leflunomide vs. MTX	No differences in ACR 20 or radiographic responses. **Low** No clinically significant difference for functional capacity. **Low** Greater improvement in health-related quality of life (SF-36 physical component) for leflunomide. **Low**	No consistent differences in tolerability and discontinuation rates. **Low** Mixed results for specific adverse events. **Insufficient**
Leflunomide vs. sulfasalazine	Mixed ACR response rates. **Insufficient** No differences in radiographic changes. **Low** Greater improvement in functional capacity for leflunomide **Low**	No differences in tolerability and discontinuation rates. **Low** Mixed results for specific adverse events. **Insufficient**
Sulfasalazine vs. MTX	No differences in ACR 20 response, disease activity scores and radiographic changes.† **Moderate** No differences for functional capacity.† **Moderate**	No differences in tolerability; more patients stayed on MTX long term. **Low** Mixed results for specific adverse events. **Insufficient**
Oral DMARD Combinations vs. Oral DMARD		
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy	In patients with early RA, no differences in ACR 20 response rates or radiographic changes. **Moderate** No differences in functional capacity. **Moderate**	Withdrawal rates attributable to adverse events higher with combination. **Low** Insufficient evidence for specific adverse events. **Insufficient**

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Oral DMARD plus prednisone vs. oral DMARD	Mixed results for disease activity. **Insufficient** Less radiographic progression in patients on DMARD plus prednisone. **Low** In patients with early RA, significantly lower radiographic progression and fewer eroded. joints **Low** Greater improvement in functional capacity for one oral DMARD plus prednisolone than for oral DMARD monotherapy. **Moderate** No difference in quality of life. **Low**	No differences in discontinuation rates; addition of corticosteroid may increase time to discontinuation of treatment. **Moderate** No differences in specific adverse events, except addition of corticosteroid may increase wound-healing complications. **Low**
Biologic DMARDs vs. Biologic DMARDs		
Abatacept vs. Infliximab	Greater improvement in disease activity for abatacept, but no difference in remission or functional capacity. Statistically significant difference between groups for quality of life (SF-36 PCS) that did not reach the minimal clinically important difference. **Low**	Discontinuation rates and severe adverse events higher with infliximab. **Low**

Biologic vs. biologic *(Mixed treatment comparisons)*	No significant differences in disease activity (ACR 50) in MTC analyses between abatacept, adalimumab, golimumab, infliximab, rituximab, and tocilizumab in patients resistant to MTX. **Low** Less improvement in disease activity (ACR 50) for anakinra compared with etanercept and compared with adalimumab in MTC analyses in patients resistant to MTX. Comparisons with abatacept, golimumab, infliximab, rituximab, and tocilizumab did not reach statistical significance. **Low**	Adjusted indirect comparisons found a more favorable withdrawal profile for certolizumab pegol than other biologic DMARDs. Also, etanercept and rituximab had a more favorable overall withdrawal profile than some other biologic DMARDs. Certolizumab pegol had fewer withdrawals due to lack of efficacy than adalimumab, anakinra, and infliximab. All but adalimumab, golimumab, and infliximab had fewer withdrawals than anakinra due to lack of efficacy. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab. **Low**
Biologic vs. biologic *(Mixed treatment comparisons)* (continued)	Greater improvement in disease activity (ACR 50) for etanercept compared with abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab in MTC analyses. No significant differences when compared with golimumab. **Low**	Risk for injection site reactions apparently highest with anakinra. **Low** Mixed results for specific adverse events. **Insufficient**
Biologic DMARDs vs. Oral DMARDs		
Anti-tumor necrosis factor drugs vs. MTX	In patients with early RA, no clinically significant differences in clinical response between adalimumab or etanercept and MTX; in patients on biologic DMARDs, better radiographic outcomes than in patients on oral DMARDs. **Moderate** No difference in functional capacity between adalimumab and MTX for MTX-naïve subjects with early RA; mixed results for etanercept vs. MTX. **Low**; **Insufficient** Faster improvement in quality of life with etanercept than MTX. **Low**	No differences in adverse events in efficacy studies. **Low** Insufficient evidence on differences in the risk for rare but severe adverse events. **Insufficient**
Key Comparisons	**Efficacy** **Strength of Evidence**	**Harms** **Strength of Evidence**
Biologic DMARD Combinations		
Biologic DMARD plus biologic DMARD vs. biologic DMARD	No additional benefit in disease activity or functional capacity from combination of etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy, but greater improvement in quality of life with etanercept plus abatacept vs. etanercept. **Low**	Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy. **Moderate**

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Biologic DMARDs plus MTX vs. biologic DMARDs	Better improvements in disease activity from combination therapy of biologic DMARDs (adalimumab, etanercept, infliximab, rituximab) plus MTX than from monotherapy with biologics. **Moderate** In MTX-naive patients with early aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression in the combination therapy group. **Low** In MTX-naïve subjects or those not recently on MTX, greater improvement in functional capacity (**Moderate**) and quality of life (**Low**) with combination therapy. In subjects with active RA despite treatment with MTX, no difference in functional capacity or quality of life. **Low**	No differences in adverse events in efficacy studies. **Low** Insufficient evidence on differences in the risk for rare but severe adverse events. **Insufficient**
Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs	No difference in clinical response rates, functional capacity, and quality of life between etanercept plus sulfasalazine and etanercept monotherapy. **Low**	No differences in adverse events in efficacy studies. **Low** Insufficient evidence on differences in the risk for rare but severe adverse events **Insufficient**
Biologic DMARD plus MTX vs. MTX	Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARDs and MTX than from MTX monotherapy. **High** for clinical response and functional capacity, **Moderate** for quality of life	Better tolerability profile for MTX plus abatacept, adalimumab, certolizumab, etanercept, and rituximab than for MTX monotherapy from meta-analysis. **Low** Mixed evidence on differences in the risk for rare but severe adverse events. **Insufficient**

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Strategies in Early RA		
Two oral DMARDs plus prednisone vs. oral DMARD	In patients on two oral DMARDs, improved ACR 50 response rates, disease activity scores, but no difference at 56 weeks. **Low** In patients with early RA, significantly lower radiographic progression and fewer eroded joints at 56 weeks. **Low** More rapid improvement in functional capacity by 28 weeks but no differences by 56 weeks. **Low**	No differences in discontinuation rates. **M**
Three oral DMARDs plus prednisone vs. one oral DMARD	In patients on three oral DMARDs, improved ACR 50 response rates, disease activity scores, and less work disability. **Low** In patients with early RA, significantly lower radiographic progression and fewer eroded joints **Low**	No differences in discontinuation rates. **M**
Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered high-dose prednisone vs. combination with infliximab	Less radiographic progression, lower disease activity scores, and better functional ability and health-related quality of life from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy. However no differences between groups for functional ability and quality of life by 2 years and no difference in remission at 4 years. **Low**	No differences in serious adverse events groups. **Low**

a. † at MTX doses ranging from 7.5-25 mg per week

4. Anmerkungen/Fazit der Autoren

Limited head-to-head comparative evidence does not support one therapy over another for adults with RA. Network meta-analyses from placebo-controlled trials of biologics suggest some differences, including higher odds of reaching ACR 50 response, but strength of evidence was low

5. Hinweise durch FB Med

- nicht immer eindeutige Angaben zur Vorbehandlung
- die meisten Studien waren von angemessener methodischer

	Qualität.
Machado MA et al., 2013 [29]. Adalimumab in rheumatoid arthritis treatment: a systematic review and meta-analysis of randomized clinical trials.	**1. Fragestellung** Systematic review and meta-analysis of randomized controlled trials to evaluate the efficacy and safety of Adalimumab in the treatment of RA.
	2. Methodik ***Population:*** Erwachsene mit RA (nicht spezifiziert). Laut Angaben des Reviews sind zwei Studien in der Analyse enthalten, welche Therapienaive Patienten beinhalteten (GUEPARD und PREMIER Studie) ***Interventionen, Kontrolle (Vergleiche):*** Adalimumab, etanercept, infliximab and rituximab ***Endpunkte***: Primär: ACR20 response defined by the ACR Sekundär: • ACR50 and ACR70 responses, • in which there are 50% and 70% improvement in the same parameters, • in addition to functionality, • measured by the HAQ scale, radiographic outcomes, loss to follow-up and safety ***Suchzeitraum (Aktualität der Recherche):*** Bis 06/2011 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 30 [Adalimumab: 11 (n = 3461); Infliximab: 10; Etanercept: 20; Rituximab: 14] ***Qualitätsbewertung der Studien:*** Quality assessment by the modified Jadad scale and risk of bias assessment proposed by the Cochrane Collaboration were employed.
	3. Ergebnisse • Eleven articles related to adalimumab were included and considered nine studies with 3461 patients. • 10 studies showed low risk of bias regarding the blinding of participants and personnel and blinding of outcome assessment. **Table 2 – Risk of bias proposed by the Cochrane Collaboration[11] and modified Jadad scale score10 of the methodological quality of the studies included in the systematic review.** Study | Random generation of allocation sequence (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data | Selective reporting of outcomes | Modified Jadad scale Van de Putte et al., 2004[24] | Low risk | Low risk | Low risk | Low risk | High risk | Uncertain | 6 PREMIER (Breedveld 2006; Kimel 2008)[18,20] | Uncertain | Uncertain | Low risk | Low risk | Low risk | Low risk | 5 DE019 (Keystone et al., 2004; Jamal et al.,2009)[21,22] | Uncertain | Uncertain | Low risk | Low risk | Low risk | Low risk | 5 Kim et al., 2007[27] | Uncertain | Uncertain | Low risk | Low risk | Low risk | Low risk | 5 ARMADA (Weinblatt et al., 2003)[16] | Uncertain | Uncertain | Low risk | Low risk | Low risk | Low risk | 5 CHANGE (Miyasaka et al., 2008)[28] | Uncertain | Uncertain | Low risk | Low risk | Low risk | Low risk | 5 Chen et al., 2009[23] | Uncertain | Uncertain | Low risk | Low risk | Low risk | Low risk | 4 STAR (Furst et al., 2003)[17] | Uncertain | Uncertain | Low risk | Low risk | Low risk | Uncertain | 4 GUEPARD (Soubrier et al., 2009)[19] | Uncertain | Uncertain | High risk | High risk | Low risk | Low risk | 3

Efficacy:
Patients who received the combination treatment of adalimumab and methotrexate showed better efficacy results and lower radiographic progression when compared to placebo + methotrexate in 24-104 weeks.

Meta-analysis of ACR20, ACR50 and ACR70 responses in up to 24 weeks. Adalimumab 40 mg every two weeks + DMARDs vs. placebo + DMARDs:

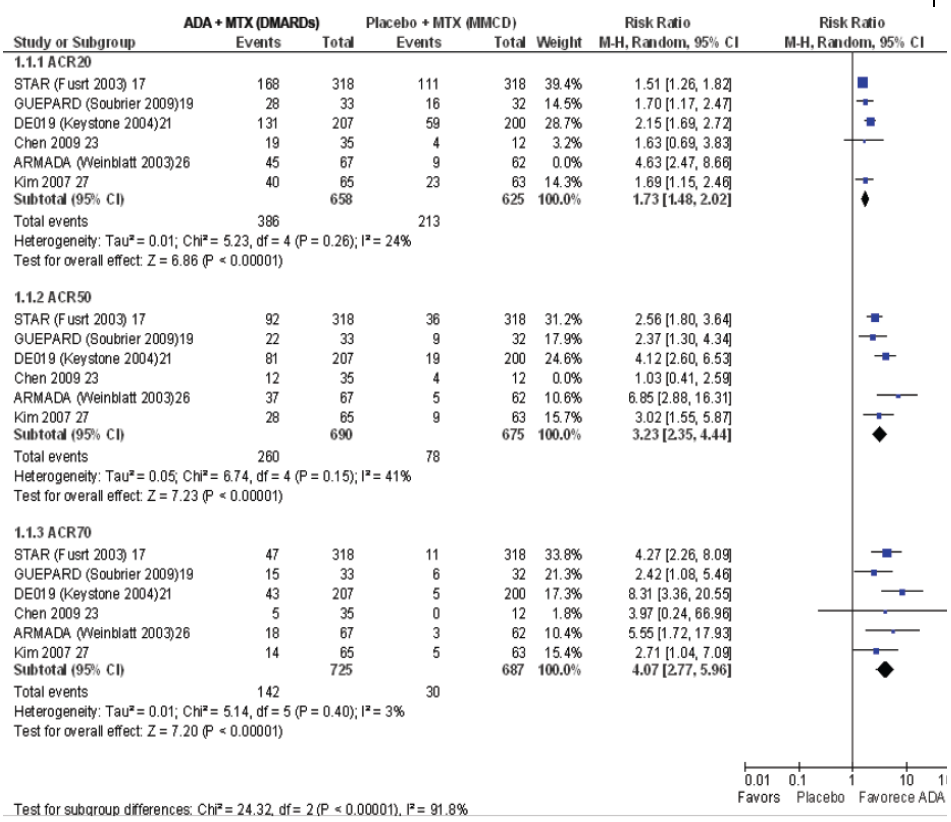


Fig. 2 – Meta-analysis of ACR20, ACR50 and ACR70 responses in up to 24 weeks. Adalimumab 40 mg every two weeks + DMARDs vs. placebo + DMARDs.
DMARDs, disease-modifying antirheumatic drugs; MTX, methotrexate. ADA, adalimumab.
Statistics I^2 >40% indicates statistical heterogeneity between the studies. A P value < 0.10 in the Chi-square test indicates heterogeneity.

Results of the meta-analyses for HAQ, AE and loss to follow-up for comparisons ADA 40 mg every two weeks+ DMARDs vs. placebo + DMARDs and ADA 40 mg every two weeks vs. placebo:

Outcome	Period (weeks)	Studies	Participants	Measure of effect (95%CI) *	I^2 (%)[a]	P value[b]
ADA 40 mg + MMCD vs. placebo + MMCD						
HAQ	Up to 24	4[19,21,26,27]	729	-0.32 (-0.40; -0.24)	0	0.99
HAQ	52	2[18,21]	932	-0.32 (-0.39; -0.24)	0	0.60
Loss due to lack of efficacy	Up to 104	4[17,18,21,27]	1696	0.31 (0.21; 0.45)	0	0.80
Loss due to adverse reaction	Up to 104	6[17,18,21,23,26,27]	1872	1.55 (1.08; 2.21)	0	0.61
Adverse reactions	Up to 104	5[17,18,21,23,27]	1955	1.03 (1.00; 1.05)	0	0.67
Severe adverse reactions	Up to 24	3[17,23,27]	811	0.84 (0.58; 1.20)	0	0.54
Infections	Up to 24	3[17,23,27]	1171	1.07 (0.93; 1.24)	0	0.59
Severe infections	Up to 104	6[17,18,21,23,26,27]	2014	1.73 (0.72; 4.14)	27	0.23
Reaction at the injection site	Up to 52	4[17,21,23,26]	1219	1.32 (1.02; 1.71)	2	0.38
Tuberculosis	Up to 104	5[17,18,21,23,27]	1743	2.25 (0.46; 11.02)	0	0.96
Cancer	Up to 104	6[17,18,21,23,26,27]	2226	1.02 (0.30; 3.47)	0	0.53
Death	Up to 104	5[17,18,21,23,27]	1743	2.38 (0.52; 10.84)	0	0.88
ADA 40 mg vs. placebo						
ACR20	24/26	2[24,28]	401	2.67 (1.89; 3.77)	0	0.45
HAQ	24/26	2[24,28]	401	-0.31 (-0.42; -0.19)	0	0.93
Loss due to adverse reaction	24/26	2[24,28]	401	3.34 (1.27; 8.80)	0	0.55
Severe adverse reactions	24/26	2[24,28]	401	1.24 (0.49; 3.13)	68	0.08
Reaction at the injection site	24/26	2[24,28]	401	12.45 (3.92; 39.52)	0	0.68

Safety:
The results of the meta-analyses of AEs were not statistically significant, except for reactions at the injection site, which favored the control group.

4. Anmerkungen/Fazit der Autoren

- Adalimumab efficacy was demonstrated in monotherapy and when associated to a DMARD, but the evidence for combined use is more robust.
- The results of the systematic review and meta-analysis showed that patients who were treated with ADA 40 mg every two weeks associated with MTX showed better efficacy results and lower radiographic progression when compared to patients receiving placebo + MTX. The risk of occurrence of loss to follow-up due to lack of efficacy was higher in the placebo + MTX group, while the loss due to adverse reactions was higher in the ADA + MTX group. However, these results are more robust for a follow-up of 24 weeks, as only two studies evaluated the patients for 52 and only one for 104 weeks
- There was no statistically significant difference regarding the efficacy and loss to follow-up due to lack of efficacy between the ADA monotherapy group with ADA 40 mg every two weeks and MTX monotherapy, whereas radiographic progression for the group that used ADA showed better results.
- The combination of ADA 40 mg every other week + MTX when compared to ADA 40 mg every two weeks as monotherapy showed better outcomes in ACR response and radiographic progression, whereas in the HAQ scale the result was statistically significant only at 52 weeks and also favorable to the combina-tion. The risk of loss to follow-up due to lack of efficacy was higher for the monotherapy. These comparisons were evaluated by only one trial.
- The results of the meta-analyses of AEs were not statistically significant, except for reactions at the injection site, which favored the control group. Adalimumab efficacy was demonstrated in monotherapy and when associated to a DMARD, but the evidence for combined use is more robust.

5. Hinweise der FB Med

- Schweregrad der Erkrankung spielte keine Rolle bei der Auswertung der Primärstudien.

Golicki D et al.,

1. Fragestellung

Evaluation der Wirksamkeit und Sicherheit von Leflunomid verglichen mit

2012 [14]. Leflunomide in monotherapy of rheumatoid arthritis: meta-analysis of randomized trials	Placebo, MTX, und Sulfasalazin in der Monotherapie. **2. Methodik** Population: Patienten mit RA Intervention: Leflunomid Komparator: Placebo or any other active treatment Endpunkte: • ACR Ansprechen • Lebensqualität • Schmerzempfinden • Krankheitsaktivität • Laborparameter • Nebenwirkungen Suchzeitraum (Aktualität der Recherche): up to Dec 2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 (n = 2861) Qualitätsbewertung der Studien: Jadad scale. **3. Ergebnisdarstellung** ***Anzahl relevanter Studien/Patienten:*** 7 (n = 2861) • 1432 Patienten unter Leflunomid • 312 Patienten unter Placebo • 922 unter MTX • 133 unter Sulfasalazin Studiencharakteristika: siehe Tab

TABLE 1 Characteristics of included trials

Trial	Number and localization of centers	Population size	Duration of follow-up (weeks)	Population	Type of intervention (n)	Comparator (n)	Trial design	Assessment of trial quality by Jadad (points)
Mladenovic et al.[23]	6 Yugoslavia, Croatia, Slovenia	402	24	RA, active phase	LEF 5 mg/d (95) LEF 10 mg/d (101) LEF 25 mg/d (104)	placebo (102)	RCT, DB	4 (2/1/1)[a]
Smolen et al.[24]	36 Europe, Australia, New Zealand, South Africa	358	104	RA, active phase	LEF 20 mg/d (133)	placebo (92) sulfasalazine (133)	RCT, DB	5 (2/2/1)
Strand et al.[25]	47 United States, Canada	482	104	RA, active phase	LEF 20 mg/d (182)	placebo (118) MTX 7.5–15 mg/w (182)	RCT, DB	5 (2/2/1)
Emery et al.[26]	117 Europe, South Africa	999	104	RA, active phase	LEF 20 mg/d (501)	MTX 10–15 mg/w (498)	RCT, DB	4 (1/2/1)
Kraan et al.[27]	2 The Netherlands, United Kingdom	39	16	RA, active phase, early phase	LEF 20 mg/d (18)	MTX 15 mg/w (21)	RCT, DB	3 (1/1/1)
Kraan et al.[28]	2 The Netherlands	15	52	RA, active phase	LEF 20 mg/d (7)	MTX 7.5–15 mg/w (8)	RCT, DB	2 (1/1/0)
Bao et al.[29]	9 China	566	12	RA, active phase	LEF 20 mg/d (323)	MTX 15 mg/w (243)	RCT, DB	4 (1/2/1)

a summary Jadad scale depends on 3 factors: randomization (0–2 points; 1st figure in parentheses), blinding (0–2 points; 2nd figure in parentheses), and description of patients excluded from the study (0–1 point; 3rd figure in parentheses).

Wirksamkeit

Leflunomid vs. MTX:

- keine stat. signifikanten Unterschiede hinsichtlich einer Reduktion in den meisten Anzeichen und Symptomen der RA; bei jedoch allgemein hoher Heterogenität zwischen den Studien.
- Leflunomid zeigte teilweise (nicht zu jedem Zeitpunkt) eine stat. signifikante Überlegenheit gegenüber MTX hinsichtlich der Endpunkte: Anzahl an Patienten mit einem ACR 50 und ACR 70 Ansprechen (jeweils nach einem Jahr), der durch den Arzt beur-teilten Krankheitsaktivität (nach 12-16 Wochen), der Reduktion des C-reaktiv Protein (CRP) Levels (nach 12-16 Wochen), und der Verbesserung der Lebensqualität (gemessen anhand HAQ; nach 1 Jahr knapp und nach 2 Jahren).
- In den verbleibenden Endpunkten zeigte sich kein Unterschied zwischen den Gruppen.

FIGURE 2 Meta-analysis of efficacy of leflunomide vs. placebo: ACR20 responders
Abbreviations: ACR – American College of Rheumatology, CI – confidence interval

Study or subgroup	Leflunomide events	Leflunomide total	Methotrexate events	Methotrexate total	Weight	Risk ratio M-H, fixed, 95% CI
1.1.1 ACR50 – after 4 months of treatment						
Kraan et al.[28]	3	7	2	8	100%	1.71 [0.39–7.48]
subtotal (95% CI)		**7**		**8**	**100%**	**1.71 [0.39–7.48]**
total events	3		2			
heterogeneity: not applicable						
test for overall effect: Z = 0.72 (*P* = 0.47)						
1.1.2 ACR50 – after 1 year of treatment						
Kraan et al.[28]	5	6	5	7	9.5	1.17 [0.65–2.10]
Strand et al.[25]	65	190	44	190	90.5%	1.48 [1.07–2.05]
subtotal (95% CI)		**196**		**197**	**100%**	**1.45 [1.07–1.96]**
total events	70		49			
heterogeneity: $\chi^2 = 0.53$, df = 1 (*P* = 0.47); $I^2 = 0\%$						
test for overall effect: Z = 2.40 (*P* = 0.02)						
1.1.3 ACR50 – after 2 years of treatment						
Strand et al.[28]	65	190	53	190	100%	1.23 [0.91–1.66]
subtotal (95% CI)		**190**		**190**		**1.23 [0.91–1.66]**
total events	65		53			
heterogeneity: not applicable						
test for overall effect: Z = 1.33 (*P* = 0.19)						

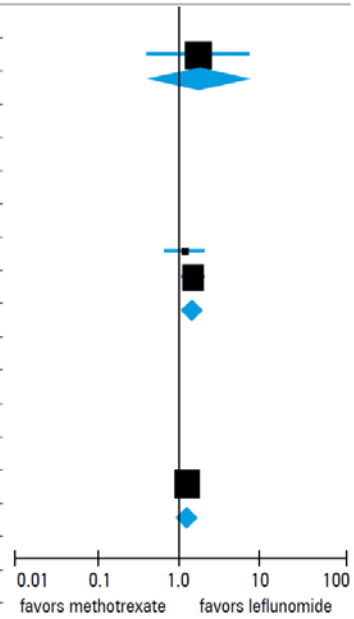


TABLE 3 Efficacy of leflunomide vs. methotrexate: summary of a meta-analysis

Endpoint	Number of trials	Number of patients	RR (95% CI)	Heterogeneity I^2
percentage of patients with ACR20 response				
– after 12–16 weeks	3[26,28,29]	558	1.04 (0.91–1.18)	0
– after 1 year	3[25,26,28]	1377	0.98 (0.73–1.32)	82.6
– after 2 years	2[25,26]	799	1.01 (0.77–1.32)	85.5
percentage of patients with ACR50 response				
– after 12–16 weeks	1[28]	15	1.71 (0.39–7.48)	–
– after 1 year	2[25,28]	393	1.45 (1.07–1.96)	0
– after 2 years	1[25]	380	1.23 (0.91–1.66)	–
percentage of patients with ACR70 response				
– after 1 year	1[25]	380	2.00 (1.20–3.34)	–
– after 2 years	1[25]	380	1.39 (0.85–2.29)	–
Endpoint	**Number of trials**	**Number of patients**	**WMD (95% CI)**	**Heterogeneity I^2**
reduction of tender joint count				
– after 12–16 weeks	2[27,29]	543	–1.42 (–3.96 to 1.12)	36.2
– after 1 year	2[25,26]	1346	0.21 (–2.24 to 2.66)	87.2
– after 2 years	2[25,26]	770	–0.16 (–1.87 to 1.54)	48.5
reduction of swollen joint count				
– after 12–16 weeks	2[27,29]	543	–0.40 (–1.17 to 0.38)	0
– after 1 year	2[25,26]	1346	0.99 (–1.46 to 3.44)	90.1
– after 2 years	2[25,26]	770	0.48 (–1.17 to 2.12)	57.8
patient's assessment of RA activity				
– after 12–16 weeks	2[27,29]	543	–0.23 (–0.72 to 0.27)	49.7
– after 1 year	2[25,26]	1346	0.03 (–1.15 to 1.20)	92.7
– after 2 years	2[25,26]	770	–0.30 (–1.37 to 0.78)	85.3
doctor's assessment of RA activity				
– after 12–16 weeks	2[27,29]	543	–0.35 (–0.67 to –0.02)	10.3
– after 1 year	2[25,26]	1346	0.13 (–0.84 to 1.11)	90.0
– after 2 years	2[25,26]	770	–0.01 (–1.28 to 1.26)	90.6
reduction in ESR				
– after 12–16 weeks	2[27,29]	543	1.60 (–6.42 to 9.62)	46.7
– after 1 year	2[25,26]	910	7.05 (–6.28 to 20.37)	95.0
– after 2 years	2[25,26]	747	7.51 (–3.74 to 18.76)	86.6
reduction in CRP levels				
– after 12–16 weeks	2[27,29]	543	–0.44 (–0.78 to –0.09)	0
– after 1 year	2[25,26]	907	0.03 (–0.37 to 0.44)	57.8
– after 2 years	2[25,26]	744	0.16 (–0.51 to 0.84)	28.3
patient's assessment of pain				
– after 12–16 weeks	2[27,29]	543	–0.38 (–0.74 to –0.01)	0
– after 1 year	2[25,26]	932	0.16 (–1.10 to 1.43)	91.9
– after 2 years	2[25,26]	769	–0.18 (–1.52 to 1.16)	89.5
duration of morning stiffness				
– after 12–16 weeks	2[27,29]	543	–16.59 (–43.99 to 10.80)	0
– after 1 year	2[25,26]	759	0.75 (–15.30 to 16.79)	66.8
– after 2 years	2[25,26]	759	8.28 (–8.72 to 25.28)	63.0
quality of life (HAQ) questionnaire				
– after 1 year	1[26]	530	0.06 (–0.02 to 0.14)	–
– after 2 years	1[26]	530	0.05 (–0.04 to 0.14)	–
quality of life (modified HAQ)				
– after 1 year	1[25]	362	–0.10 (–0.20 to 0.00)	–
– after 2 years	1[25]	199	–0.15 (–0.29 to –0.01)	–
progression of radiographic changes				
– after 1 year	2[25,26]	893	–0.03 (–0.85 to 0.78)	40.7
– after 2 years	1[25]	137	0.40 (–0.94 to 1.74)	–

Leflunomid vs. Sulfasalazin:
Es zeigte sich teilweise ein stat. signifikanter Vorteil unter Sulfasalazin hinsichtlich der Endpunkte: Reduktion der Erythrozyten-Sedimentationsrate (ESR) (nach einem halben Jahr); während Leflunomid stat. signifikant überlegen war hinsichtlich des ACR20 Ansprechen (nach 2 Jahren Krankheitsdauer) und ACR50 Ansprechen (nach 2 Jahren Behandlung), der Lebensqualität (gemessen anhand des HAQ; nach einem halben Jahr und nach 2 Jahren) und der CRP Level Reduktion (nach einem halben Jahr, einem Jahr und 2 Jahren).

TABLE 4 Efficacy of leflunomide vs. sulfasalazine: summary of the trial by Smolen et al.[24] and supporting publication – Scott et al.[35]

Endpoint	Number of patients	RR (95% CI)
percentage of patients with ACR20 response		
– after 0.5 year of treatment	262	0.99 (0.80–1.23)
– after 1 year of treatment	152	0.97 (0.78–1.20)
– after 2 years of treatment	117	1.37 (1.07–1.75)
percentage of patients with ACR50 response		
– after 0.5 year of treatment	262	0.98 (0.64–1.51)
– after 1 year of treatment	152	1.08 (0.74–1.59)
– after 2 years of treatment	117	2.10 (1.25–3.53)
percentage of patients with ACR70 response		
– after 0.5 year of treatment	262	1.52 (0.64–3.60)
– after 1 year of treatment	152	0.88 (0.44–1.75)
– after 2 years of treatment	117	1.43 (0.70–2.91)
Endpoint	**Number of patients**	**WMD (95% CI)**
reduction of tender joint count	262	–1.60 (–3.44 to 0.24)
reduction of swollen joint count	262	–13.40 (–14.89 to –11.91)
patient's assessment of RA activity	262	0.00 (–0.25 to 0.25)
doctor's assessment of RA activity	262	–0.10 (–0.32 to 0.12)
reduction in ESR		
– after 0.5 year of treatment	261	9.20 (3.47 to 14.93)
– after 1 year of treatment	150	8.10 (–0.13 to 16.33)
– after 2 years of treatment	114	–1.10 (–11.03 to 8.83)
reduction in CRP levels		
– after 0.5 year of treatment	260	–1.20 (–1.98 to –0.42)
– after 1 year of treatment	150	–1.10 (–2.17 to –0.03)
– after 2 years of treatment	111	–1.40 (–2.77 to –0.03)
patient's assessment of pain		
– after 0.5 year of treatment	262	–7.50 (–14.21 to –0.79)
– after 1 year of treatment	151	–11.40 (–20.35 to –2.45)
– after 2 years of treatment	117	–15.10 (–25.16 to –5.04)
duration of morning stiffness		
– after 0.5 year of treatment	262	–51.00 (–101.73 to –0.27)
– after 1 year of treatment	152	–76.00 (–135.49 to –16.51)
– after 2 years of treatment	165	–50.00 (–87.72 to –12.28)
quality of life (HAQ)		
– after 0.5 year of treatment	229	–0.21 (–0.34 to –0.08)
– after 1 year of treatment	128	–0.17 (–0.34 to 0.00)
– after 2 years of treatment	96	–0.29 (–0.49 to –0.09)
progression of radiographic changes		
– after 0.5 year of treatment	168	0.00 (–0.01 to 0.01)
– after 1 year of treatment	113	0.00 (–0.01 to 0.01)
– after 2 years of treatment	55	–0.04 (–0.19 to 0.11)

Sicherheit:

- **Leflunomid vs. MTX:**
  Verglichen mit MTX zeigte sich ein höheres Risiko unter Leflunomid hinsichtlich: Pruritus, Hypertension, Durchfall und Alopezie. Allerdings war das Risiko auf Schleimhautulzerationen und erhöhten Leberwerten geringer unter Leflunomide.
- **Leflunomid vs. Sulfasalazin:**

Höheres Risiko bei Rückenschmerzen und Durchfall unter Leflunomid verglichen mit Sulfasalazin.

TABLE 5 Summary of safety meta-analysis (only statistically significant comparisons showed)

Adverse event	Number of trials	Number of patients	RR (95% CI)	Heterogeneit I^2
leflunomide vs. placebo				
alopecia	3[23-25]	832	5.79 (2.09–16.08)	0
elevation of liver enzymes	2[23-25]	607	3.36 (1.71–6.63)	0
withdrawal due to adverse events	3[23-25]	832	2.69 (1.64–4.41)	0
diarrhea	2[24,25]	525	2,21 (1.48–3.32)	0
allergic reactions	1[25]	300	1.68 (1.01–2.79)	–
leflunomide vs. methotrexate				
pruritus	2[26,29]	1503	3.40 (1.72–6.74)	0
hypertension	2[25,26]	1363	2.75 (1.76–4.29)	0
diarrhea	3[25,26,29]	1867	2.01 (1.60–2.54)	0
alopecia	3[25,26,29]	1867	1.62 (1.21–2.17)	0
mouth ulceration	2[25,26]	1363	0.61 (0.38–0.96)	0
elevation of liver enzymes >3 × ULN	1[26]	999	0.26 (0.18–0.37)	–
leflunomide vs. sulfasalazine				
back pain	1[24]	266	3.67 (1.05–12.85)	–
diarrhea	1[24]	266	1.92 (1.00–3.69)	–

Abbreviations: UNL – upper normal limit, others – see TABLE 1

4. Fazit der Autoren:

There were no significant differences between the effects of treatment with leflunomide and methotrexate or sulfasalazine, but leflunomide monotherapy proved more effective than placebo in relieving symptoms and signs of RA.

5. Hinweise der FB Med

- Fazit weicht teilweise von der Ergebnisdarstellung ab
- Nur zwei Studien bei ACR50 gepoolt
- Dargestellte Ergebnisse (gepoolten ES) resultieren aus sehr wenigen Primärstudien

Aaltonen KJ et al., 2012 [1]. Systematic Review and Meta-Analysis of the Efficacy and Safety of Existing TNF Blocking Agents in Treatment of Rheumatoid Arthritis.

1. Fragestellung

The aim of our study is to estimate the efficacy and the safety of TNF blockers in the treatment of RA and indirectly compare all five currently available blockers by combining the results from included RCTs.

2. Methodik

Systematischer Review/ Metaanalyse von RCT

Population: Erwachsene mit RA

***Interventionen / Kontrolle*:** TNF-blockers vs. placebo, with or without concomitant MTX

Endpunkte: Efficacy data included ACR 20%, 50% and 70% improvements; safety

Suchzeitraum (Aktualität der Recherche): Bis 06/2010
Anzahl eingeschlossene Studien/Patienten (Gesamt): 26 (n = 9862)
Qualitätsbewertung der Studien: Cochrane Risk of Bias

3. Ergebnisse

- Most Studies with an unclear risk of bias
- Studienpopulationen: sowohl MTX-naïve als auch MTX erfahrene Patienten

Wirksamkeit

Kombination therapy

- Kombination (TNFi + MTX) signifikant besser als MTX Monotherapie bzgl. ACR20, ACR50, ACR70 zu verschiedenen Zeitpunkten (3, 6, 12 Monate)
- In a subanalysis of trials with patients who had previously used MTX, the results were similar. In comparison to MTX, golimumab

	combination therapy was still inferior in ACR 20 efficacy at 6 months to certolizumab combination therapy, with risk ratios of 2.14 (1.59–2.89) and 5.08 (3.46–7.48), respectively. • At six months patients previously naive to MTX are statistically significantly less likely to reach either ACR 20, 50 or 70 treatment responses compared to patients who had already been previously treated with MTX. Monotherapy • Monotherapie mit TNF-Blockern tendenziell besser als MTX-Monotherapie, aber Ergebnisse nicht statistisch signifikant., • Stratifying RTCs by previous exposure to MTX does not show any statistically significant differences in the treatment response to TNF-blocker monotherapy between these two groups ***Sicherheit***: • TNF-Blocker + MTX vs. MTX – mehr Nebenwirkungen bei Kombinationstherapie bzgl. Therapieabbruch und Infusions-/Injektions-Reaktionen • TNF-Blocker vs. MTX: mehr Nebenwirkungen bei TNF-Blocker bei Infusions-/Injektions-Reaktionen
	4. Fazit der Autoren: No single substance clearly rose above others in efficacy, but the results of the safety analyses suggest that etanercept might be the safest alternative. Interestingly, MTX performs nearly identically considering both efficacy and safety aspects with a margin of costs. **5. Hinweise der FB Med** • Schweregrad der Erkrankung spielte keine Rolle bei der Auswertung der Primärstudien
Orme ME et al., 2012 [39]. Systematic review and network meta-analysis of combination and monotherapy treatments in disease-modifying antirheumatic drug-experienced patients with rheumatoid arthritis	**1. Fragestellung** Wirksamkeit von EU licensed-dose Biologica-Kombinationen bei RA Patienten mit unzureichendem Ansprechen auf ein oder mehrere DMARDs
	2. Methodik SR/Metaanalyse/indirekter Vergleich (nach Bucher) von RCTs ***Population:*** Adult patients meeting the ACR classification criteria for RA, previously treated with MTX or other DMARD, <=15% of patients previously treated with TNF-α inhibitors ***Intervention*** Any bDMARD licensed in the EU Studies needed to include at least one treatment arm of bDMARD in combination with a DMARD or as a monotherapy ***Komparator*** (combination analysis) or placebo (monotherapy analysis) ***Endpunkte***: ACR 20/50/70 response rates Outcome reported between 12 and 30 weeks of follow-up ***Suchzeitraum (Aktualität der Recherche):*** Bis 05/2010 ***Anzahl* eingeschlossene Studien/Patienten *(Gesamt):*** Einschluss von 37 Studien (23 nur Kombi-Therapie, 8 nur Monotherapie, 6 beides) ***Qualitätsbewertung der Studien:*** Risk of bias was assessed using criteria set out in the National Institute for Health and Clinical Excellence (NICE) guidelines manual. For studies included in the meta-analysis, a formal assessment of publication bias was conducted via funnel plots with Egger's linear regression test of asymmetry.
	3. Ergebnisdarstellung:

Study characteristics/ quality of studies

- patients had active RA in spite of prior treatment with a DMARD; (moderate to severe disease)
- in most trials, the patient population was anti-TNFα inhibitor-naïve
- The definition of "active RA" was inconsistent across studies

- The risk of bias, as assessed by NICE criteria, was considered low for the majority of included studies. For five studies, the risk of bias was unclear, due to incomplete reporting. Only the study by van Riel et al47 was considered to have a high risk of bias, as there was no concealment of treatment allocation (and several other parameters were unclear).

Netzwerk-Meta-analyse zur Kombinationstherapie:

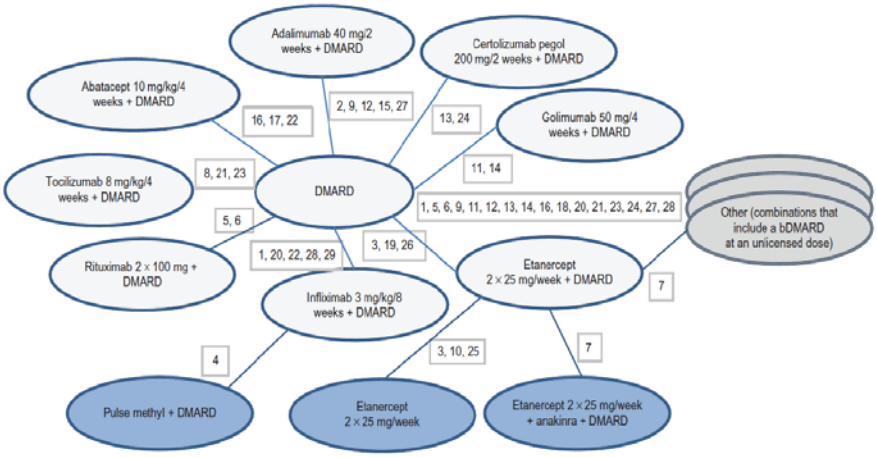


Figure 2 Network diagram for ACR20/50/70 outcomes for bDMARD combination therapies.
Notes: 1, Abe 2006; 2, Chen 2009; 3, Combe 2006; 4, Durez 2004; 5, Edwards 2004; 6, Emery 2010 (SERENE); 7, Genovese 2004; 8, Genovese 2008 (TOWARD); 9, Huang 2009; 10, Kameda 2010 (JESMR); 11, Kay 2008; 12, Keystone 2004 (DE019); 13, Keystone 2008 (RAPID 1); 14, Keystone 2009 (GO-FORWARD); 15, Kim 2007; 16, Kremer 2003; 17, Kremer 2006 (AIM); 18, Kremer 2010; 19, Lan 2004; 20, Maini 1999 (ATTRACT); 21, Maini 2006 (CHARISMA); 22, Schiff 2008 (ATTEST); 23, Smolen 2008 (OPTION); 24, Smolen 2009a (RAPID 2); 25, van Riel 2006 (ADORE); 26, Weinblatt 1999; 27, Weinblatt 2003 (ARMADA); 28, Westhovens 2006b (START); 29, Zhang 2006. DMARD 25 arms, 3039 patients; abatacept 10 mg/kg/4 weeks + DMARD 3 arms, 704 patients; adalimumab 40 mg/2 weeks + DMARD 5 arms, 495 patients; certolizumab pegol 200 mg/2 weeks + DMARD 2 arms, 639 patients; etanercept 2 × 25 mg/week + DMARD 6 arms, 500 patients; golimumab 50 mg/4 weeks + DMARD 2 arms, 124 patients; infliximab 3 mg/kg/8 weeks + DMARD 6 arms, 760 patients; rituximab 2 × 1000 mg + DMARD 2 arms, 212 patients; tocilizumab 8 mg/kg/4 weeks + DMARD 3 arms, 1058 patients.

Netzwerk-Meta-Analyse zur Monotherapie

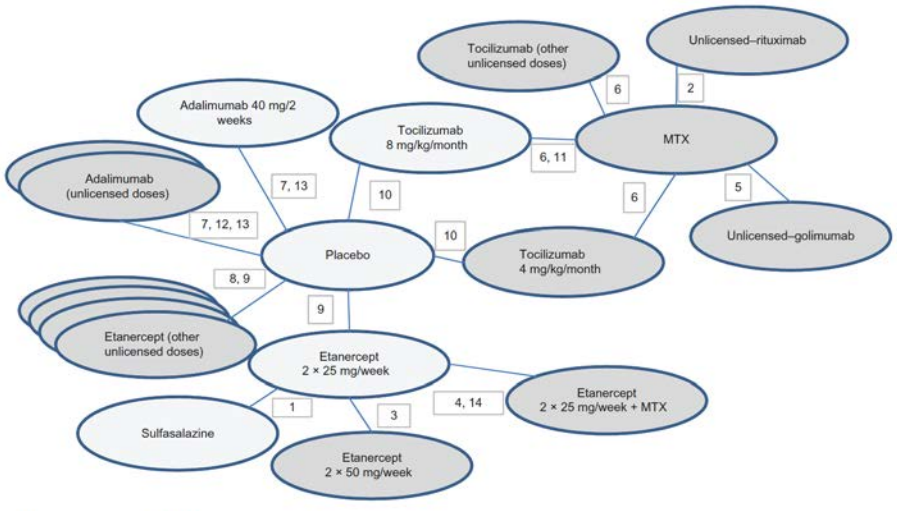


Figure 6 Network diagram for ACR20/50/70 outcomes for bDMARD monotherapy.
Notes: 1, Combe 2006; 2, Edwards 2004; 3, Johnsen 2006; 4, Kameda 2010 (JESMR); 5, Keystone 2009 (GO-FORWARD); 6, Maini 2006 (CHARISMA); 7, Miyasaka 2008 (Change); 8, Moreland 1997; 9, Moreland 1999; 10, Nishimoto 2004 (STREAM); 11, Nishimoto 2009 (SATORI); 12, van de Putte 2003; 13, van de Putte 2004; 14, van Riel 2006 (ADORE). Placebo 6 arms, 444 patients; MTX 4 arms, 488 patients; etanercept 2 × 25 mg/week, 5 arms, 441 patients; tocilizumab 8 mg/kg/4 weeks, 3 arms, 168 patients; adalimumab 40 mg/2 weeks, 2 arms, 204 patients; sulfasalazine 1 arm, 50 patients.

- Results
  - Kombination aus bDMARD + DMARD signifikant besser bzgl. ACR20/50/70 als DMARD allein (außer Rituximab bei ACR70)
  - Etanercept Kombination signifikant besser als Adalimumab, Infliximab, Abatacept Kombinationen bzgl. ACR20/50/70
  - keine signifikanten Unterschiede zwischen Etanercept-Kombination

und Certolizumab pergol oder Tocilizumab-Kombinationen
- Monotherapie mit Etanercept signifikant besser als Sulfasalazin bzgl. ACR 20/50/70

Table 6 American College of Rheumatology (ACR) criteria scores of 20, 50, and 70 network meta-analysis base case results for combination treatments in DMARD-experienced patients: licensed ETN combination versus other licensed biologic DMARD combination

Treatment	Control	Fixed effects OR v control (95% CrI)	Random effects OR v control (95% CrI)
ACR 20			
ETN 2 × 25 mg/week + DMARD	ABA 10 mg/kg/4 weeks + DMARD	2.715 (1.521, 4.956)‡	2.858 (1.306, 6.815)‡
ETN 2 × 25 mg/week + DMARD	ADA 40 mg/2 weeks + DMARD	2.53 (1.405, 4.742)‡	2.72 (1.235, 6.357)‡
ETN 2 × 25 mg/week + DMARD	CZP 200 mg/2 weeks + DMARD	0.836 (0.437, 1.613)	0.846 (0.341, 2.173)
ETN 2 × 25 mg/week + DMARD	GOL 50 mg/4 weeks + DMARD	2.546 (1.235, 5.249)‡	2.759 (1.066, 7.88)‡
ETN 2 × 25 mg/week + DMARD	INF 3 mg/kg/8 weeks + DMARD	2.651 (1.509, 4.791)‡	2.786 (1.299, 6.301)‡
ETN 2 × 25 mg/week + DMARD	RTX 2 × 1000 mg + DMARD	2.48 (1.278, 4.958)‡	2.521 (0.966, 6.711)
ETN 2 × 25 mg/week + DMARD	TOC 8 mg/kg/4 weeks + DMARD	1.987 (1.115, 3.602)‡	2.121 (0.959, 5.107)
ACR 50			
ETN 2 × 25 mg/week + DMARD	ABA 10 mg/kg/4 weeks + DMARD	2.871 (1.395, 6.523)‡	3.07 (1.161, 8.969)‡
ETN 2 × 25 mg/week + DMARD	ADA 40 mg/2 weeks + DMARD	2.625 (1.249, 6.101)‡	2.882 (1.082, 8.347)‡
ETN 2 × 25 mg/week + DMARD	CZP 200 mg/2 weeks + DMARD	1.144 (0.492, 2.847)‡	1.143 (0.358, 3.715)
ETN 2 × 25 mg/week + DMARD	GOL 50 mg/4 weeks + DMARD	2.264 (0.924, 5.999)‡	2.277 (0.672, 7.943)
ETN 2 × 25 mg/week + DMARD	INF 3 mg/kg/8 weeks + DMARD	2.896 (1.426, 6.583)‡	3.098 (1.186, 8.671)‡
ETN 2 × 25 mg/week + DMARD	RTX 2 × 1000 mg + DMARD	2.662 (1.109, 6.817)‡	2.714 (0.826, 9.174)
ETN 2 × 25 mg/week + DMARD	TOC 8 mg/kg/4 weeks + DMARD	1.759 (0.849, 4.018)	2.068 (0.766, 6.284)
ACR 70†			
ETN 2 × 25 mg/week + DMARD	ABA 10 mg/kg/4 weeks + DMARD	5.405 (1.348, 39.22)‡	5.278 (1.016, 46.3)‡
ETN 2 × 25 mg/week + DMARD	ADA 40 mg/2 weeks + DMARD	4.826 (1.171, 34.53)‡	5.45 (1.07, 45.914)‡
ETN 2 × 25 mg/week + DMARD	CZP 200 mg/2 weeks + DMARD	1.661 (0.329, 13.06)	1.636 (0.244, 14.84)
ETN 2 × 25 mg/week + DMARD	GOL 50 mg/4 weeks + DMARD	4.055 (0.796, 31.279)	4.312 (0.604, 48.757)
ETN 2 × 25 mg/week + DMARD	INF 3 mg/kg/8 weeks + DMARD	5.395 (1.358, 38.16)‡	5.642 (1.126, 48.13)‡
ETN 2 × 25 mg/week + DMARD	RTX 2 × 1000 mg + DMARD	7.924 (1.686, 59.453)‡	8.058 (1.225, 78.37)‡
ETN 2 × 25 mg/week + DMARD	TOC 8 mg/kg/4 weeks + DMARD	2.385 (0.593, 16.28)	2.766 (0.535, 25.2)

Notes: †ACR 70 data with continuity correction; ‡licensed ETN combination has significantly higher odds of ACR outcome compared to other licensed biologic DMARD combination (based on the 95% CrI).
Abbreviations: ABA, abatacept; ADA, adalimumab; ANA, anakinra; CrI, credible interval (Bayesian probability interval); CZP, certolizumab pegol; DMARD, disease-modifying antirheumatic drug (MTX or SUL); ETN, etanercept; exp, experienced; GOL, golimumab; INF, infliximab; MTX, methotrexate; OR, odds ratio; RTX, rituximab; SUL, sulfasalazine; TOC, tocilizumab.

4. Fazit der Autoren:
Licensed bDMARDs are efficacious in patients with an inadequate response to conventional therapy, but TNF-α inhibitor combination therapies are not equally effective.

5. Hinweise der FB Med
- Schweregrad der Erkrankung spielte keine Rolle bei der Auswertung der Primärstudien.

Lee YH et al., 2011 [24].
The efficacy and safety of rituximab for the treatment of active rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials.

1. Fragestellung
The aims of this study were to assess the efficacy and safety of rituximab in patients with active RA.

2. Methodik

Population: patients with active RA; intolerant or resistant to DMARD or TNF-blocker

Interventionen: Rituximab + MTX
Kontrolle: placebo + MTX
Endpunkte: ACR 20, 50, 70 – Ansprechrate

Suchzeitraum (Aktualität der Recherche): Bis 12/2009

Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 (n = 938 Pat.)

Qualitätsbewertung der Studien: assessment of concealment of treatment allocation, blinding, and adequacy of analyses

3. Ergebnisdarstellung

Studiencharakteristika:

Table 1 Characteristics of the studies included in the meta-analysis

Study	Country	Study design (name)	Patient number (intention to treat)	RF positivity (%)	Subjects	Treatments (numbers)	Follow-up period	ACR20, 50, 70 (%)
A								
Cohen et al. [11]	UK	RCT (REFLEX)	517 (499)	79	Active RA inadequate response or intolerant to anti-TNF	Rituximab +MTX (298) versus placebo + MTX (201)	24 weeks	51, 27, 12 versus 18, 5, 1
Emery et al. [12]	UK	RCT (DANCER)	341 (244)	82	Active RA, failure to DMARDs, biologic response modifiers	Rituximab +MTX (122) versus placebo + MTX (122)	24 weeks	54, 34, 20 versus 28, 13, 5
Edwards et al. [13]	UK	RCT	80 (80)	100	Active RA despite current MTX	Rituximab + MTX (40) versus placebo + MTX (40)	48 weeks	65, 35, 15 versus 20, 5, 0
Study		Concealment of allocation	Placebo control		Patient blinding	Intention-to-treat analysis	Patients randomly assigned	Duration of follow-up
B								
Cohen et al. [11]		Unclear	Adequate		Adequate	Adequate	Adequate	24 weeks
Emery et al. [12]		Unclear	Adequate		Adequate	Adequate	Adequate	24 weeks
Edwards et al. [13]		Unclear	Adequate		Adequate	Adequate	Adequate	48 weeks

RF rheumatoid factor, *RCT* randomized controlled trial, *REFLEX* randomized evaluation of long-term efficacy of rituximab, *DANCER* dose-ranging assessment international clinical evaluation of rituximab in rheumatoid arthritis, *TNF* tumor necrosis factor, *DMARD* disease modifying anti-rheumatic drug, *RA* rheumatoid arthritis, *MTX* methotrexate, *ACR20, 50, and 70* American College of Rheumatology 20, 50, and 70% response rates

- ACR20, ACR50, and ACR70 response rates were significantly higher for rituximab plus MTX-treated patients than for MTX plus placebo-treated patients (ACR50; RR 3.648, 95% CI 2.478–5.369)
- Regarding safety, rituximab was not found to be associated with any increase in AEs. Furthermore, no significant difference was observed between rituximab plus MTX and MTX plus placebo controls with respect to the proportions of patients that experienced at least one SAE.

4. Fazit der Autoren:

A single course of rituximab with concomitant MTX therapy was found to be effective in DMARD or TNF-blocker-resistant or intolerant patients with active RA.

5. Hinweise der FB Med

- Schweregrad der Erkrankung spielte keine Rolle bei der Auswertung der Primärstudien.
- nur 3 Primärstudien eingeschlossen
- keine Langzeitstudien
- beträchtliche qualitative und hohe quantitative Heterogenität zwischen den Primärstudien

An MM et al., 2010 [2]. The addition of tocilizumab to DMARD therapy for

1. Fragestellung

The purpose of this study was to evaluate the effect of adding tocilizumab to DMARD therapy for the treatment of RA.

2. Methodik

Population: Patients of all ages with RA (ACR 1987 revised criteria for RA).

rheumatoid arthritis: a meta-analysis of randomized controlled trials.	***Vergleich***: Tocilizumab in combination with DMARDs vs. DMARDs alone ***Endpunkte***: • *Primary*: Proportion of patients with a 20% improvement in RA signs and symptoms according to ACR criteria (ACR20 response) • *Secondary*: Proportion of patients with an ACR50 and ACR70 response and the proportion of patients with remission according to the Disease Activity Score ***Suchzeitraum (Aktualität der Recherche):*** Bis 08/2009 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 4 (n = 2701) ***Qualitätsbewertung der Studien:*** Jadad score
	3. Ergebnisdarstellung Bei drei der vier Studien handelt es sich um vorbehandelte Patienten. Bei der Studie von Genovese et al. fehlt eine derartige Angabe. *Study quality* All RCTs were assessed to be good in terms of methodology, with blinding protocols. A high Jadad score (two RCTs had a score of 5; two had a score of 4) also indicated the high quality of the RCTs included in the meta-analysis. We examined the funnel plot [standard error (SE) of log RR plotted against RRs) to estimate publication bias and obtained a symmetric inverse funnel distribution. *Results:* • The addition of tocilizumab to therapeutic regimens with DMARDs was associated both clinically and statistically with an increased number of patients achieving the ACR20 response [8 mg/kg, risk ratio (RR) 2.53, 95%; CI: 1.89–3.39; 4 mg/ kg, RR 1.96, 95% CI 1.40–2.73], as well as the ACR50 and ACR70 response, and showing remission according to the Disease Activity Score based on 28 joints. • However, the benefits were gained at the expense of the tendency of the patient to experience more adverse events (8 mg/kg, RR 1.12, 95% CI 1.03–1.20; 4 mg/kg, RR 1.08, 95% CI 1.00–1.17).
	4. Fazit der Autoren The superior efficacy of combined tocilizumab + DMARD therapy is associated with the tendency for the patient to have more AEs. Consequently, the benefits and disadvantages of such combined treatments should be carefully balanced against each other in RA therapy. We suggest that 8 mg/kg every 4 weeks should be the recommended dose of tocilizumab. **5. Hinweise der FB Med** Unklar ob die Patienten in der Studie von Genovese et al. vorbehandelt waren
Wiens A et al., 2010 [50]. A systematic review and meta-analysis of the efficacy and safety of adalimumab for treating rheumatoid arthritis	**1. Fragestellung** The aim of this study is to provide a systematic review and meta-analysis to assess the efficacy and safety of ADA treatment, relative to a placebo, in adult patients with RA, using or not concomitant MTX.
	2. Methodik ***Population:*** Patients with RA ***Intervention:*** Adalimumab oder adalimumab + MTX ***Kontrolle:*** Placebo oder Placebo + MTX ***Endpunkte:*** • *primär:* Response of RA to treatment with ADA by the ACR outcome

measures ACR20, 50 and 70
- *sekundär*: SAEs, serious infections, malignancy and deaths) and withdrawals from treatment due to lack of efficacy or AEs

Suchzeitraum (Aktualität der Recherche): *Nicht angegeben*

Anzahl eingeschlossener Studien/Patienten (Gesamt): 8 (n = 2692)
Qualitätsbewertung der Studien: Jadad Score;
Only studies with moderate or high quality were included in the meta-analysis.

3. Ergebnisdarstellung

Included studies

- Three studies compared ADA vs. placebo without concomitant MTX.
- Four other studies performed the comparison in which both groups received MTX.
- One study presented 83% of the patients using at least one DMARD during the comparison between ADA and placebo.

- All studies included patients with active disease, according to ACR criteria, except one, which included only patients with less than three years of RA. Five studies included patients with failure to at least one treatment with DMARD.

Table 1 Patients baseline characteristics of included RCTs

Study (Jadad's score) and interventions	*N*	Mean age (years)	Mean disease duration (years)	Mean no. of previous DMARDs	Mean no. of swollen joints	Mean no. of tender joints	% on steriods	% on NSAIDs	Mean baseline HAQ score
STAR [25] (5)									
Adalimumab 40 mg s.c. eow	318	55	9	>2.1	20	27	51	62	1.37
Placebo s.c. eow + DMCDs	318	56	12	>2.0	21	27	54	64	1.43
van de Putte et al. [13] (3)									
Adalimumab 20 mg s.c weekly	72	54	10	4.1	19.6	31.7	76	76	1.79
Placebo s.c. weekly	70	50	9	3.5	20.2	30.9	77	80	1.63
Weinblatt et al. [24] (4)									
Adalimumab 40 mg s.c. eow + methotrexate	67	57	12	2.9	17	28	46	NR	1.55
Placebo s.c. eow + methotrexate	62	56	11	3	16	28	58	NR	1.64
van de Putte et al. [20] (5)									
Adalimumab 20 mg s.c. weekly	112	54	11	3.6	19	35	68	75	1.88
Adalimumab 40 mg s.c. weekly	113	53	11	3.8	20	33	68	82	1.83
Placebo s.c. weekly	110	54	12	3.6	19	35	67	84	1.88
Keystone et al. [22] (4)									
Adalimumab 40 mg s.c. eow + methotrexate	207	56	11	2.4	19	27	44.9	NR	1.45
Adalimumab 20 mg s.c. weekly + methotrexate	212	57	11	2.4	19	27	–	NR	1.44
Placebo s.c. weekly + methotrexate	200	56	11	2.4	19	28	49.5	NR	1.48
Breedveld et al. [21] (5)									
Adalimumab 40 mg s.c. eow + methotrexate	268	51.9	0.7	0.4	21	31	36	NR	1.47
Placebo s.c. eow + methotrexate	257	52	0.8	0.4	22	32	35	NR	1.48
Kim et al. [23] (4)									
Adalimumab 40 mg s.c. eow + methotrexate	65	48.5	6.8	most: 2 a 3	12.2	19.2	NR	NR	1.4
Placebo w.c. eow + methotrexate	63	49.8	6.9	most: 2 a 3	12.8	20.3	NR	NR	1.3
Miyasaka [19] (4)									
Adalimumab 40 mg s.c. eow	91	56.9	9.9	at least one	19.1	24.4			1.64
Placebo s.c. eow	87	53.4	8.4		19.3	23.7	37.8	10.8	1.39

There is only one value from total of both groups

eow Every other week, *HAQ* health assessment questionnaire, *NSAIDs* non-steroidal anti-inflammatory drugs, *DMARDs* disease-modifying antirheumatic drugs, *NR* not reported, *NR* not reported, *N* participants

Results

Superiority of Adalimumab (+/- MTX) vs control (placebo +/- MTX) was shown based on ACR20, ACR50 and ACR70 from 6 months to 2 years of treatment

4. Anmerkungen/Fazit der Autoren
This meta-analysis shows a higher efficacy of ADA relative to placebo, but clinicians should be careful regarding adverse events in ADA-treated patients.

5. Hinweis der FB Med

- Jadad-Score allein als ergebnisdarstellungssteuerndes Qualitätsmerkmal ist problematisch, da Jadad-Score als

	Qualitätsbewertungssystem umstritten
Jansen JP et al., 2014 [19]. Comparative efficacy of biologics as monotherapy and in combination with methotrexate on patient reported outcomes (PROs) in rheumatoid arthritis patients with an inadequate response to conventional DMARDs – a systematic review and network meta-analysis.	**1. Fragestellung** To compare biologics as monotherapy or in combination with methotrexate (MTX) in terms of patient reported outcomes (PROs) in RA patients with an inadequate response to conventional DMARDs (DMARD-IR).
	2. Methodik ***Population:*** DMARD-IR RA patients ***Intervention:*** Tocilizumab, TNF-blockers, abatacept, and anakinra in their usual dose, alone and in combination with conventional DMARDs. Rituximab was not considered because its label is restricted to TNF-IR patients. Tofacitinib was not included because it was not approved at the time of this study ***Kontrolle:*** Placebo or one of the regimes described under interventions. Comparisons of different dosages of the same intervention only, or comparison of the same interventions with different background treatments were excluded ***Endpunkte:*** HAQ-DI, Pain, PGA, SF36, and fatigue ***Suchzeitraum (Aktualität der Recherche):*** Systematische Literaturrecherche bis 2012 ***Anzahl eingeschlossener Studien/Patienten (Gesamt):*** A total of 26 full text reports corresponding to 20 different RCTs. ***Qualität der Studien:*** Most of the trials were multi-centred and included patients predominantly from Europe and North America. The RCTs were generally considered to be good quality (Jadad score range 3–5).
	3. Ergebnisdarstellung In general: To synthesize the results of the included studies, Bayesian network meta-analysis models were used! → Ergebnisse basieren auf indirekter Evidenz! For the analysis we grouped the different aTNFs because previous analysis demonstrated that the different aTNFs are exchangeable **Monotherapy:** • Tocilizumab monotherapy showed greater improvements in pain (−11.1; 95% CrI −21.3, −0.1) than aTNF as monotherapy, and can be expected to be more efficacious in terms of PGA as well (−10.3, 95% CrI −20.4, 0.8; probability better = 97%). • Tocilizumab was at least as efficacious as aTNF agents in HAQ-DI improvements (−0.16; 95% CrI −0.37, 0.05; probability better = 94%) • Given the available studies, no comparison of SF36 for the biologics as monotherapy was possible. **Treatment in combination with methotrexate:** • aTNF (−17.9, −19.1), abatacept (−23.0, −13.6) and tocilizumab (−16.0, −15.1) in combination with MTX showed comparable reductions in pain and PGA relative to MTX in this DMARD-IR population. • These improvements over MTX are expected to be greater than the MCID. The reduction in pain and PGA with anakinra (−7.3, −8.7) was smaller. • Regarding HAQ-DI, the greatest improvements over MTX can be expected with aTNF (−0.30) and tocilizumab (−0.27), both clinically meaningful, followed by abatacept (−0.21) and anakinra (−0.11). Improvements in physical health according to the SF36-PCS with abatacept, aTNF and tocilizumab were comparable.

	Comparison of monotherapy and treatment in combination with methotrexate: • There is a 93% and 96% probability that aTNF in combination with MTX results in a greater reduction in pain (−12.4) and PGA (−16.1) than aTNF as monotherapy. These differences are expected to be greater than the MCID. • For HAQ-DI there is a 92% chance that aTNF with MTX is more efficacious than aTNF as monotherapy (−0.21). For tocilizumab however, the improvement in pain, PGA, and HAQ-DI with and without MTX was comparable at 24 weeks. • Efficacy of anakinra + MTX was much smaller as compared to other biologics. • The greatest improvements in HAQ-DI relative to MTX were observed with aTNF + MTX (−0.30 (−0.37, −0.22)) and tocilizumab + MTX (−0.27 (−0.42, −0.12)), followed by abatacept + MTX (−0.21 (−0.37, −0.05)) and anakinra + MTX (−0.11 (−0.26, 0.05)). • There is a >90% probability that aTNF +MTX results in a greater improvement in pain (−12.4), PGA (−16.1) and HAQ-DI (−0.21) than aTNF as monotherapy. • Efficacy of tocilizumab + MTX showed comparable improvements in PROs as tocilizumab monotherapy.
	4. Fazit der Autoren: Based on a network meta-analysis involving indirect comparison of trial findings, the following observations were made for DMARD-IR patients. In monotherapy, tocilizumab was associated with a greater improvement in pain and self-reported disease activity than aTNF, and was at least as efficacious regarding functional ability. The improvements in PROs with aTNF, abatacept and tocilizumab in combination with MTX were comparable. Improvements in PROs with tocilizumab as monotherapy were similar to that of tocilizumab +MTX, whereas aTNF as monotherapy was likely to be less efficacious than aTNF + MTX.
Scott DL et al., 2014 [43]. Randomised controlled trial of Tumour necrosis factor inhibitors Against Combination Intensive Therapy with conventional disease-modifying antirheumatic drugs in established rheumatoid arthritis: the TACIT trial and associated systematic reviews.	**1. Fragestellung** (HTA programme) We assessed whether or not combination DMARDs (cDMARDs) give equivalent clinical benefits at lower costs in RA patients eligible for TNFis. • We assessed whether or not RA patients eligible to receive TNFis achieve similar outcomes with cDMARDs in a head-to-head trial that compared both approaches [Tumour necrosis factor inhibitors Against Combination Intensive Therapy (TACIT)]. • We also systematically reviewed published trials that assessed the efficacy of cDMARDs, TNFis with methotrexate and both approaches in patients with active RA.
	2. Methodik des SR ***Population:*** Early and established RA patients • *Early RA:* disease duration was < 3 years • *Established RA:* patients were treatment resistant to at least one previous DMARD given for at least 3 months ***Intervention:*** • *Early RA:* one or other or both of cDMARDs and TNFi/MTX • *Established RA*: one or other or both of cDMARDs and TNFi/MTX; when more than one dosage of TNFi was used the treatment arm that mirrored clinical practice the closest was chosen ***Komparator:*** DMARD monotherapy ***Endpunkte:*** American College of Rheumatology responses, withdrawals (for inefficacy), diability (HAQ score)

	Suchzeitraum (Aktualität der Recherche): Ovid MEDLINE and EMBASE were searched from 1946 to 2013. ***Anzahl eingeschlossener Studien/Patienten (Gesamt):*** 32 für early RA; 19 für established RA ***Qualität der Studien:*** Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Methods Guide for Comparative Effectiveness Review. (AHRQ Publication) Heterogeneity: The cDMARD trials showed no evidence of heterogeneity in ACR20–70 scores. In contrast, the TNFi trials showed significant heterogeneity in ACR20 scores ($p < 0.00001$) and ACR50 scores ($p < 0.0002$) and borderline heterogeneity in ACR70 scores ($p = 0.06$).
	3. Ergebnisdarstellung **SR of early RA** • 19 trials compared cDMARDs with methotrexate • 10 trials compared TNFis/methotrexate with methotrexate monotherapy • 3 trials compared cDMARDs with TNFis/methotrexate *American College of Rheumatology responses and withdrawals for inefficacy* Indirect comparisons showed that in trials of DMARD combinations more patients achieved ACR20–70 responses with combination therapy (OR 1.76–2.81) and less patients withdrew because of inefficacy with combination therapy (OR 0.47, 95% CI 0.34 to 0.64). In trials of TNFi/methotrexate combinations more patients achieved ACR20–70 responses with combination therapy (OR 1.88–2.22) and fewer patients withdrew because of inefficacy with combination therapy (OR 0.44, 95% CI 0.22 to 0.85). Sensitivity analysis of trials using only methotrexate monotherapy showed similar results. Direct comparisons showed that there were no differences between DMARD combinations and TNFi/methotrexate with regard to ACR20 outcomes or patient withdrawals because of inefficacy. However, fewer patients achieved ACR50 and ACR70 responses using cDMARDs than using TNFi/methotrexate (ORs 0.54 and 0.53 respectively). Overall, there were small differences in favour of TNFi/methotrexate compared with cDMARDs at most time points but these were not always significant. There were also marked differences in response rates in the different trials. *Disability* In the indirect comparisons there were greater improvements in HAQ scores with both combination regimens when compared with DMARD monotherapy (OR −0.15, 95% CI −0.23 to −0.07) or methotrexate monotherapy (OR −0.17, 95% CI −0.33 to −0.01). No RCTs that made a direct comparison between cDMARDs and TNFi/methotrexate reported HAQ outcomes. *Toxicity* Indirect comparisons showed that more patients withdrew with DMARD combinations because of toxicity than with DMARD monotherapy (OR 1.50, 95% CI 1.11 to 2.03) or with methotrexate monotherapy (OR 2.69, 95% CI 1.49 to 4.83). There were no differences between TNFi/methotrexate and methotrexate monotherapy in terms of withdrawals because of toxicity. The direct comparisons showed no differences in patient withdrawal because of toxicity **SR of established RA:** • 10 trials compared cDMARDs with DMARD monotherapy, of which six used methotrexate monotherapy as the control arm, • Eight trials compared TNFi/methotrexate with methotrexate monotherapy,with one involving infliximab, two etanercept, one adalimumab, two golimumab and two certolizumab pegol.

	• one trial made a direct comparison between methotrexate/sulfasalazine/hydroxychloroquine and etanercept/methotrexate. Wirksamkeit *American College of Rheumatology responses and withdrawals for inefficacy* • In trials of DMARD combinations more patients achieved ACR20–70 responses with combination therapy (OR 2.75–5.07). • More patients withdrew with combination therapy (OR 1.51, 95% CI 1.02 to 2.25). • Sensitivity analysis of RCTs that included a methotrexate monotherapy arm showed that more patients achieved ACR20–70 responses with combination therapy (OR 3.55–4.74) but few patients withdrew because of inefficacy (OR 0.34, 95% CI 0.20 to 0.59). • In trials of TNFi/methotrexate combinations more patients achieved ACR20–70 responses with combination therapy (OR 5.32–8.13) • Fewer patients withdrew because of inefficacy with combination therapy (OR 0.12, 95% CI 0.06 to 0.25). • The trial comparing triple DMARD therapy with etanercept/MTX237 showed no statistical difference between groups in ACR20 (57% vs. 66%), ACR50 (35% vs. 43%) and ACR70 (18% vs. 26%). This study did not report patient withdrawals for inefficacy. *Disability* • Five randomised trials of cDMARDs reported change in HAQ scores • Only three of these trials reported both mean changes and SDs for these changes. • A combined analysis of these three trials' HAQ scores showed that, overall, there were greater improvements with cDMARDs than with DMARD monotherapy (WMD −0.19, 95% CI −0.27 to −0.10). • Only one of these RCTs used methotrexate as the monotherapy this trial also showed greater improvement with cDMARDs (WMD −0.30, 95% CI −0.42 to −0.18). • For TNFi/methotrexate combinations five trials reported change in HAQ scores • In all of these trials there was an improvement in HAQ score in the combination arm. • One trial reported mean (SD) change in HAQ score (WMD −0.35, 95% CI −0.56 to −0.14). • The trial that made a direct comparison between methotrexate/sulfasalazine/hydroxychloroquine and etanercept/methotrexate reported mean HAQ scores at 48 weeks. • There was no difference in HAQ scores between triple DMARD therapy (0.93 ± 0.85) and etanercept/methotrexate (0.83 ± 0.81). Sicherheit: • For cDMARDs, all 10 trials reported patient withdrawals because of toxicity. • The overall OR for withdrawal with combination therapy was 1.51 (95% CI 1.02 to 2.25). Seven of these studies used methotrexate as the monotherapy arm; the OR for withdrawal was 1.58 (95% CI 0.97 to 2.59). • For TNFi/methotrexate combinations, eight trials reported patient withdrawals because of toxicity. • There were no significant differences between treatments, with an OR of 0.94 (95% CI 0.62 to 1.41). • The direct comparison trial did not report patient withdrawals because of toxicity.
	4. Fazit und Anmerkungen der Autoren Systematic reviews of published trials in both early RA and established RA show equivalence of cDMARDs with TNFis. • Only three RCTs directly compared cDMARDs with TNFi/methotrexate combinations and all of these were in early RA. Although we have relied

	more on indirect comparisons, these are invariably less informative than direct comparisons. • There was diversity in the range of cDMARDs used and some are not commonly used in clinical practice, for example bucillamine and doxycycline.
Schoels M et al., 2012 [42]. Comparative effectiveness and safety of biological treatment options after tumour necrosis factor α inhibitor failure in rheumatoid arthritis: systematic review and indirect pairwise meta-analysis	**1. Fragestellung** Optimal treatment for RA after inadequate response (IR) to tumour necrosis factor (TNF) α inhibitors remains uncertain. Objective: To compare the efficacy and safety of biological agents after TNF α inhibitors IR.
	2. Methodik SR mit placebokontrollierten RCTs und indirektem Vergleich (Brückenkomparator: Placebo) ***Population:*** Adult RA populations with an inadequate therapeutic response to one or more TNF inhibitors ***Intervention***: a new biological treatment (combined with synthetic DMARD) ***Kontrolle:*** Placebo using synthetic DMARDs only ***Outcomes*** • Efficacy was defined as rates of ACR (20%, 50% and 70%) response, EULAR response criteria, or achieving remission (or a low disease activity state). • Safety outcomes extracted at the study level included any AEs, SAEs, serious infections and infusion- or injection-related reactions after a follow-up of ≥ 8 weeks. ***Suchzeitraum (Aktualität der Recherche):*** Bis 03/2011 ***Anzahl eingeschlossene Studien/Patienten (Gesamt):*** 4 (n = 1873) ***Qualitätsbewertung der Studien:*** Jadad Scale
	3. Ergebnisdarstellung *Studiencharakeristika:*

Table 1 Patient baseline characteristics

Treatment/study, year of publication	Co-medication (DMARD)	Patient (N)	Age (years)‡	Disease duration (years)	Female (%)	HAQ-DI‡	SJC‡	TJC‡	DAS28‡	Jadad score
ABA* Genovese ATTAIN; 2005	75% MTX*	393	53.4±12.4	12.2±8.5	77.1	1.8±0.6	22.3±10.2	31.2±13.0	6.5±0.9	3
GOL Smolen GO-AFTER 50 mg; 2009	†66% MTX	461 (all) (†304)	55.0 (46.0–63.0)§	9.6 (5.6–17.2)§	74	1.6 (1.1-2.0) (all) (†1.5 (1.1–1.9))§	14.0 (9.0–25.0)§	27.0 (16.0–42.0)§	6.3 (5.6–7.2)§	4
RTX Cohen REFLEX; 2006	MTX, 16.4± 8.8 mg weekly	520	52.2±12.2	12.1±8.3	81	1.9±0.5	23.4±11.8	33.9±15.1	6.9±1.0	5
TOC Emery RADIATE 8 mg; 2008	MTX (15.7±4.4 mg)	499	53.9±12.7	12.6±9.3	84	1.7±0.6	18.9±10.9		7.0±0.9	3

*Mixed population of patients receiving MTX (75%), and patients receiving monotherapy.
†Subgroup of patients receiving a combination of GOL and MTX.
‡Numbers are mean±SD if not indicated otherwise.
§Median (IQR).
ABA, abatacept; DAS, Disease Activity Score; DMARD, disease modifying drugs; GOL, golimumab; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; RTX, rituximab; SJC, swollen joint count; TJC, tender joint count; TOC, tocilizumab.

<u>Direct comparison:</u>

abatacept, golimumab, rituximab and tocilizumab vs. placebo:

- statistically significant mean ORs of 3.3-8.9 for ACR20, 5.5-10.2 for ACR50 and 4.1-13.5 for ACR70.
- Risks of AEs, SAEs and SIs vs. placebo were non-significant.

<u>Indirect pairwise comparisons</u>

Efficacy

- The four biological agents showed no significant differences in ACR50 and ACR70.
- Golimumab had a significantly lower OR (0.56-0.59) for ACR20 but significantly fewer AEs (RD 0.13-0.18).
- Efficacy after one vs. multiple TNF inhibitors failures did not differ significantly between the different biological agents.

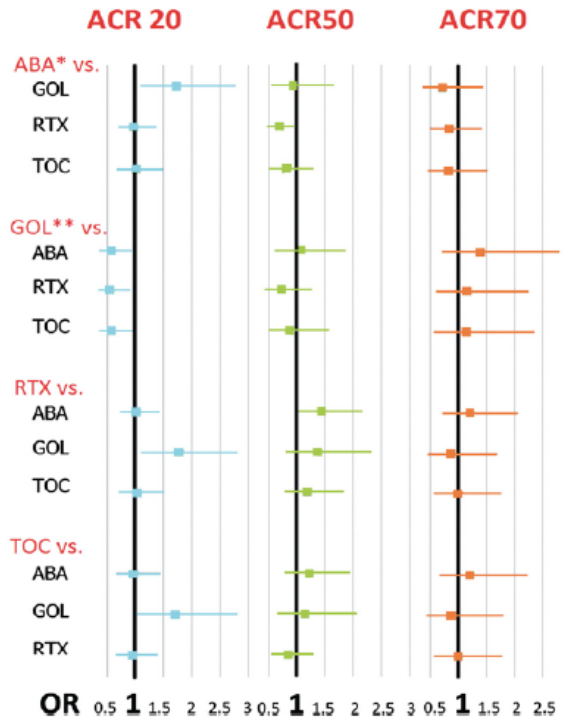


Figure 3 Efficacy in pairwise comparisons. similar success rates of abatacept (ABA), golimumab (GOL), rituximab (RTX), tocilizumab (TOC). Top to bottom: ABA is comparator versus GOL, RTX, TOC; GOL versus ABA, RTX, TOC; RTX versus ABA, GOL, TOC; TOC versus ABA, GOL, RTX. OR (95% CI) for American College of Rheumatology (ACR)20 (left column), ACR50 (middle column) and ACR70 (right column) are displayed in red. Black vertical lines indicate an OR of 1. ORs>1 (right of the black line) favour the comparator drug shown in red, ORs<1 (left of the black line) indicate poorer response rates than with the red comparator drug shown in red.

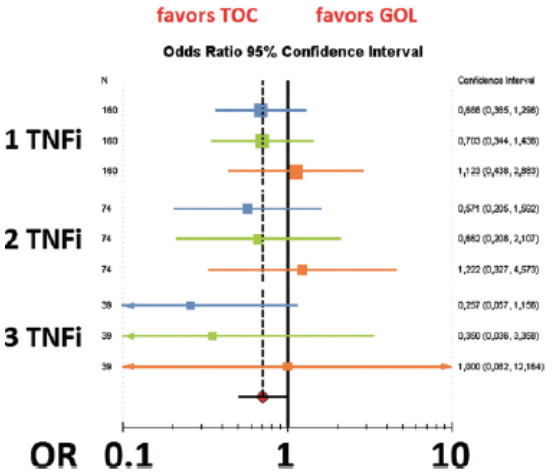


Figure 4 Efficacy after multiple tumour necrosis factor inhibitor (TNFi) failures. Response rates of golimumab (GOL) and tocilizumab (TOC). American College of Rheumatology (ACR)20 (blue lines), ACR50 (green lines) and ACR70 (orange lines) of patients for whom one (top), two (middle) and three (bottom) TNFi had previously failed.

Safety

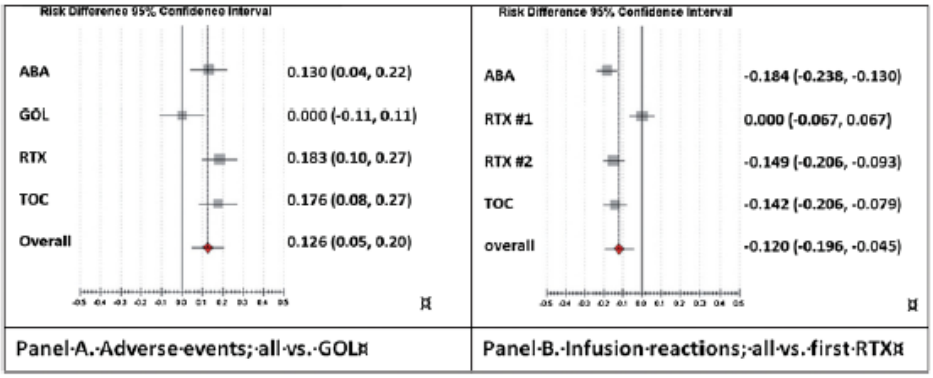


Figure 5 Drug safety. (A) Pairwise indirect comparison against golimumab (GOL): abatacept (ABA), rituximab (RTX) and tocilizuma higher general adverse event rates. (B) Infusion reactions within 24 h: pairwise indirect comparison against the first RTX infusion (RT higher risk than in TOC and ABA.

4. Fazit der Autoren:

In patients refractory to one or more TNF inhibitors, new biological agents provide significant improvement with good safety. Lacking head-to-head trials, indirect meta-analysis enables a comparison of effectiveness and safety of biological agents with each other and shows that all biological agents have similar effects.

In conclusion, in this patient group characterised by disease refractory to multiple previous treatments, significant improvement is possible with approved biological agents, which also show acceptable safety outcomes in the studied trial populations.

5. Hinweise der FB Med

nur 2 der eingeschlossenen Studien berichteten incomplete response

Malottki K et al., 2011 [30]. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation

1. Fragestellung

To assess the clinical effectiveness and cost-effectiveness of adalimumab, etanercept, infliximab, rituximab and abatacept when used in patients with RA who have tried conventional agents and have failed to improve after trying a first TNF inhibitor.

2. Methodik

Population: Patients with RA who have tried conventional agents and have failed to improve after trying a first TNF inhibitor

Interventionen, Kontrolle (Vergleiche): Adalimumab (ADA), etanercept (ETN), infliximab (IFX), rituximab (RTX), abatacept (ABT)

Endpunkt: clinical outcomes related to efficacy, safety or tolerability treatment withdrawal (and reasons for withdrawal)

Suchzeitraum (Aktualität der Recherche): Bis 2009

Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 RCTs,
1 comparative study
1 controlled study
28 uncontrolled studies

Weitere Einschlusskriterien:
- mindestens 12 Wochen Studiendauer
- for non-randomised studies – at least 20 patients in one arm

3. Ergebnisdarstellung

TABLE 2 Mapping of identified studies

Comparators	Interventions (newly initiated)					
	ADA	ETN	IFX	TNF inhibitors	RTX	ABT
None[a]	Bennett 2005[92] (*n* = 26, 52 weeks) Wick 2005[93] (*n* = 27, 24 weeks) Nikas 2006[94] (*n* = 24, 52 weeks) Bombardieri 2007[95,96] (*n* = 899, 12 weeks) van der Bijl 2008[97] (*n* = 41, 16 weeks)	Haraoui 2004[98] (*n* = 25, 12 weeks) Buch 2005[99] (*n* = 207, 12 weeks) Cohen 2005[100] (*n* = 24, 13 weeks) Buch 2007[101] (*n* = 95, 12 weeks) Iannone 2007[102] (*n* = 37, 24 weeks) Laas 2008[103] (*n* = 49, >36 weeks) Bingham 2009[104] (*n* = 201, 16 weeks)	Ang 2003[105] (*n* = 24, unclear) Hansen 2004[106] (*n* = 20, unclear) Yazici 2004[107] (*n* = 21, unclear)	Gomez-Reino 2006[108] (*n* = 488, 104 weeks) Solau-Gervais 2006[109] (*n* = 70, > 13 weeks) Hjardem 2007[110] (*n* = 235, 13 weeks) Duftner 2008[111] (*n* = 109, up to 208 weeks) Karlsson 2008[112] (*n* = 337, 13 weeks) Blom 2009[113] (*n* = 197, 48 weeks)	Bokarewa 2007[114] (*n* = 48, 52 weeks) Jois 2007[115] (*n* = 20, 26 weeks)[b] Keystone 2007[116] (*n* = 158, 24 weeks) Assous 2008[117] (*n* = 50, 26 weeks) Thurlings 2008[118] (*n* = 30, 24 weeks)	ATTAIN LTE[119] (*n* = 317, < 260 weeks) ARRIVE[120] (*n* = 1,046, 24 weeks)

Quantity and quality of evidence: No directly relevant head-to-head trial directly comparing any of the five technologies against each other or directly comparing any of the technologies against other biologics or previously untried, newly initiated DMARDs, was found.

Comparative effectiveness: No RCT provided evidence on genuine head-to-head comparisons between the technologies, other biologics and newly initiated, previously untried DMARDs.

<u>Evidence from randomised controlled trials</u>

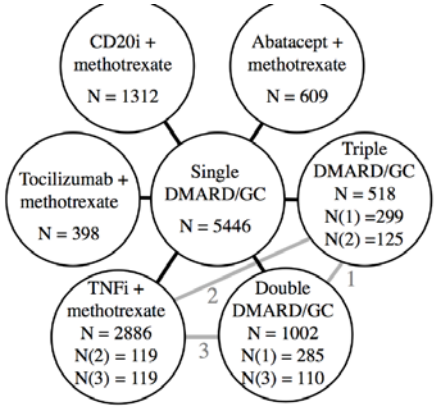
The effectiveness of RTX was demonstrated in a good-quality RCT (REFLEX). At 6 months, significantly more patients treated with RTX achieved American College of Rheumatology (ACR) 20 [relative risk (RR) = 2.85, 95% confidence interval (CI) 2.08 to 3.91] and ACR70 (RR = 12.14, 95% CI 2.96 to 49.86) compared with those treated with the placebo. Significant differences between groups in favour of RTX were observed at 6 months for mean change from baseline in Disease Activity Score 28 (DAS28) (mean difference –1.50, 95% CI –1.74 to –1.26) and mean change from baseline in Health Assessment Questionnaire (HAQ) score (mean difference –0.30, 95% CI –0.40 to –0.20).

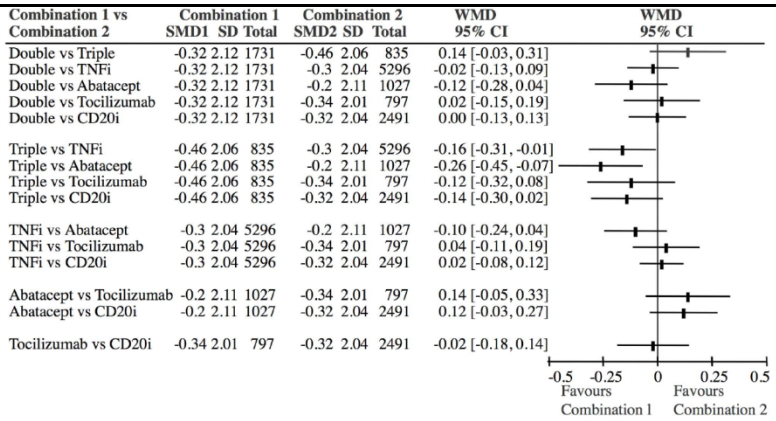
The effectiveness of ABT was demonstrated in a good-quality RCT (ATTAIN). At 6 months, significantly more patients treated with ABT achieved ACR20

	(RR = 2.56, 95% CI 1.77 to 3.69) and ACR70 (RR = 6.70, 95% CI 1.62 to 27.80) compared with those treated with the placebo. Significant differences between groups in favour of ABT were observed at 6 months for mean change from baseline in DAS28 score (mean difference –1.27, 95% CI –1.62 to –0.93) and mean change from baseline in HAQ score (mean difference –0.34, insufficient data for calculating 95% CI). One small RCT (OPPOSITE, n = 27) compared switching to IFX versus staying on ETN in patients who had incomplete response to ETN. The study population was not well defined and the comparator was considered inappropriate for this assessment. Two additional RCTs evaluated concurrent use of ABT and TNF inhibitor, which is not recommended in its licence. These studies were not further assessed.
	4. **Fazit der Autoren:** Evidence from RCTs suggests that RTX and ABT are more effective than supportive care. Data from observational studies suggest that the use of an alternative TNF inhibitor in patients who exhibit an inadequate response to a first TNF inhibitor may offer some benefit, but there remain uncertainties with regard to the magnitude of treatment effects and their cost-effectiveness. Future research should include head-to-head trials comparing the clinical effectiveness and cost-effectiveness of the technologies against each other and emerging biologics. Limitations: Paucity of evidence from RCTs for assessing the clinical effectiveness of TNF inhibitors and an absence of head-to-head trials comparing the five technologies.
Kim HL et al., 2014 [21]. Comparative effectiveness of cycling of tumor necrosis factor-α (TNF-α) inhibitors versus switching to non-TNF biologics in rheumatoid arthritis patients with inadequate response to TNF-α inhibitor using a Bayesian approach.	**1. Fragestellung** The objective of this study was to use Bayesian approach to compare the effectiveness of cycling TNF- α inhibitors versus switching to non-TNF biologics in TNF-IR patients.
	2. Methodik ***Population:*** Patients with RA who failed to respond to previous treatments with TNF-α inhibitors. ***Intervention:*** Cycling TNF-α inhibitors (means: after failure of the initial TNF-α treatment, an alternative TNF-α inhibitor will be given) ***Kontrolle:*** Switching to non-TNF biologics (means: after failure of the initial TNF- α treatment, an non-TNF biologic will be given) ***Endpunkte:*** ACR response 20/50/70, HAQ score change at six months ***Suchzeitraum (Aktualität der Recherche):*** A systematic review was conducted using MEDLINE and Cochrane Library until 2013. ***Anzahl eingeschlossener Studien/Patienten (Gesamt):*** 6 studies ***Qualität der Studien:*** Quality assessment performed using the Cochrane's risk of Bias, but no final evaluation of the quality described in the review.
	3. Ergebnisdarstellung • one study of golimumab, • one study of rituximab, • two studies of abatacept, • two studies of tocilizumab. All studies were conducted in samples of patients who failed initial TNF-α treatment and baseline characteristics were similar across all studies; no or unclear risk of bias . ACR response 20/50/70:

	• The proportion of patients who achieved **ACR20** was highest for tocilizumab (62,4%), followed by rituximab (47%), abatacept (43,7%) and golimumab (32,1%) and lowest for placebo (15,5%). • Similarly, the ACR50 effectiveness measure was highest for tocilizumab and lowest for placebo. • Rituximab had the highest proportion of patients who achieved ACR70. • ORs for non-TNF biologics in comparison to golimumab, a TNF-alfa inhibitor shows: For ACR20, abatacept had an OR of 1,639 (95% Crl 0,786-3,408; P(OR> 1)= 90,7%), rituximab 1,871 (95% Crl 0,937-3,725; P(OR>1)=96,2%), and tocilizumab 3,52 (95% Crl 1,567-7,946; P(OR>1)=99,9%). • The posterior probabilities of all non-TNF biologics were over 90%, suggesting that these agents were more effective. • For **ACR50**, ORs were: 1,623 (95% Crl 0,454-6,247; P(OR> 1)= 72,2%), 1,702 (95% Crl 0,558-5,087; P(OR>1)=83%), and 2,552 (95% Crl 0,752-9,1; P(OR>1)=93,3%) for abatacept, rituximab and tocilizumab, respectively. • For **ACR70**, ORs were: 2,048 (95% Crl 0,361-16,47; P(OR> 1)= 78,4%), 3,876 (95% Crl 0,685-35,37; P(OR>1)=93,5%), and 3,107 (95% Crl 0,532-25,49; P(OR>1)=89,2%) for abatacept, rituximab and tocilizumab, respectively. In this case, rituximab was shown tob e more effective than the TNF-alfa inhibitor based on the probability of OR>1. <u>HAQ score change:</u> • The median differences were -0,259 for abatacept, -0,160 for rituximab, and -0,200 for tocilizumab. • The probability of being the best among five treatments was highest for abatacept at 74.4%. • Comparisons of each bDMARD with placebo showed that the magnitude of the change was the highest for abatacept, followed by tocilizumab and tiruximab, and lowest for folimumab. Based on the posterior probabilities, non TNF biologics improved HAQ scores compared with then TNF-alfa inhibitor.
	4. Fazit der Autoren: *Switching to non-TNF biologics was more effective than cycling TNF-alfa inhibitor in TNF-IR patients.* **5. Anmerkungen der Autoren/FBMed:** • Limited clinical evidence (only one RCT available for each variable) • Duration of the studies too short to assess long-term benefits (vs. RA is a chronic disease) No head-to-head studies available; results based on indirect evidence/comparison
Zhou Q et al., 2014 [51]. The efficacy and safety of certolizumab pegol (CZP) in the treatment of active rheumatoid arthritis (RA): a meta-analysis from nine randomized controlled trials	**1. Fragestellung** To assess the efficacy and safety of CZP in the treatment of RA patients
	2. Methodik **Population:** adult patients with RA **Intervention**: CZP or CZP-based therapy (CZP+MTX) **Komparator**: placebo therapy (placebo or placebo+MTX) **Endpunkte:** ACR20, ACR50, ACR70, disease activity and PROs, and AEs **Suchzeitraum** (Aktualität der Recherche): up to June 14, 2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 9 (5228 patients) **Qualitätsbewertung der Studien:** Jadad scale.
	3. Ergebnisdarstellung • 3 trials with CZP vs placebo, • 6 trials with CZP plus MTX vs placebo+MTX

	• all of the nine studies had a high quality, and the median Jadad score was 4 (range from 4 to 5) *Results* • CZP (200 or 400 mg) combined with MTX associated with significantly higher ACR20, ACR50 and ACR70 response rates at week 12 and 24, and had amelioration in PROs, including HAQ-DI, arthritis pain, and fatigue, in the treatment of patients with active RA. • incidence of AEs (any intensity) between the CZP group and control group was not statistically significant difference
	4. Fazit der Autoren CZP 200 or 400 mg is clinically effective in the treatment of active RA patients. **5. Hinweise FBMed** • Keine Darstellung der Effektschätzer für CZP + MTX vs MTX, Effektschätzer nur über alle Studien angegeben • Studienpopulation: Patienten mit inadäquater Response gegenüber MTX bzw. DMARDs
Chen M et al., 2015 [6]. Efficacy of etanercept for treating the active rheumatoid arthritis: an updated meta-analysis	**1. Fragestellung** To evaluate the efficacy of etanercept (ETA) for treating active rheumatoid arthritis (RA) compared to placebo or methotrexate (MTX).
	2. Methodik **Population:** adult patients with RA **Intervention**: Etanercept **Komparator** placebo or/and MTX **Endpunkte:** u.a. ACR20, ACR50 and ACR70 **Suchzeitraum** (Aktualität der Recherche): Bis 05/2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 12 (n= 3878) **Qualitätsbewertung der Studien:** Cochrane Risk of Bias .
	3. Ergebnisdarstellung • 6 Studies with ETA vs MTX • 3 Studies with ETA + MTX vs placebo+MTX (or usual DMARD+MTX) • 3 Studies with ETA vs Placebo <u>ETA (25 mg twice weekly) vs MTX: mean change in total Sharp Score within 1–3 years (4 studies)</u> The MD of mean change in Sharp Score at 1, 2, 3 years were -3.07 (95% CI: -5.72 to -0.42, P = 0.02), -2.24 (95% CI: -4.61 to 0.13, P = 0.06) and -4.34 (95% CI: -7.56 to -1.12, P = 0.008), respectively → superiority of ETA at 1 and 3 years
	4. Anmerkungen/Fazit der Autoren In active RA patients treated with ETA, there was significantly higher efficacy compared to the treatment of placebo or MTX. High doses of ETA were more effective for active RA patients **5. Hinweise durch FB Med** • ACR-Response-Effektschätzer nur für alle Studien zusammendargestellt (mit sig. Vorteil für ETA, hier nicht dargestellt), nicht differenziert nach den unterschiedlichen Vergleichen • Studienpopulation: sowohl Studien mit MTX-naiven Patienten als auch

	mit Patienten mit inadäquater Response ggü. MTX/DMARDs
Graudal et al., 2014 [16] Effect of Combination Therapy on Joint Destruction in Rheumatoid Arthritis: A Network Meta-Analysis of Randomized Controlled Trials	**1. Fragestellung** Comparing combination treatment versus single DMARD treatment in RA
	2. Methodik Network Meta-analysis **Population:** patients with RA **Interventionen**: combination treatments of • methotrexate plus TNF inhibitors (etanercept (Et),infliximab (In), adalimumab (Ad), certolizumab (Cz), and golimumab(Go)), • methotrexate plus abatacept (Ab), • methotrexate plustocilizumab (Tz), and • methotrexate plus CD20 inhibitors (rituximab (Rt), ocrelizumab (Oc)) **Komparator:** single DMARD **Endpunkte:** change in radiographic erosion score **Suchzeitraum** (Aktualität der Recherche): Bis 07/2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 38 **Qualitätsbewertung der Studien:** Cochrane Risk of Bias Review protocol has been registered in PROSPERO.
	3. Ergebnisdarstellung Definition of 6 combination treatments vs single DMARD for the network MA (including 1 trial with direct comparison between TNFi, double and triple DMARD, and 2 trials with direct comparisons between double and triple DMARDs): siehe Abb.  **Figure 3. Star shaped network showing the 6 different combination treatments anchored on single treatment as the common comparator.** The loops (grey lines) with corresponding numbers (1, 2, 3) show the subgroups, which were directly compared in addition to being indirectly compared. N indicates the number of patients in the groups. doi:10.1371/journal.pone.0106408.g003 *Results* The indirect comparisons showed similar effects between combination treatments apart from triple DMARD being significantly better than abatacept plus methotrexate (-0.26 SMD (CI: -0.45, -0.07)) and TNFi plus methotrexate (-0.16 SMD (CI: -0.31, -0.01)) (Figure 10)

	 **Figure 10. Indirect comparisons of different combination treatments.** There is a trend towards triple treatment being superior to abatacept and TNFi. All other differences between the combination treatments are non-significant. Abbreviations: SMD: Standardized mean difference. WMD: Weighted mean difference (SMD1-SMD2). Heterogeneity analysis of the study effects was insignificant indicating similar results from study to study and direct and indirect comparisons were consistent when comparing treatment balanced data
	4. Anmerkungen/Fazit der Autoren Combination treatment of a biologic agent with 1 DMARD is not superior to 2–3 DMARDs including or excluding LDGC in preventing structural joint damage. Future randomized studies of biologic agents should be compared versus a combination of DMARDs. **5. Hinweise FBMed** Studienpopulation: Studien mit Patienten mit inadäquater Response ggü. DMARDs als auch ohne DMARD-IR
Graudal et al., 2015 [15] Combination therapy with and without tumor-necrosis factor inhibitors in rheumatoid arthritis.	**1. Fragestellung** To compared the effects of combination DMARD therapies with and without biologic agents as therapy for patients with rheumatoid arthritis.
	2. Methodik **Population:** patients with RA **Intervention**: combinations of different DMARDs **Komparator** TNF-alpha-inhibitors + DMARDs **Endpunkte:** • ACR20, ACR50 and ACR70 • Joint radiograph scores • disease activity score 28 (DAS28) • health assessment questionnaire (HAQ) scores **Suchzeitraum** (Aktualität der Recherche): Bis 09/2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 8 (n= 3878) **Qualitätsbewertung der Studien:** Cochrane Risk of Bias Review protocol has been registered in PROSPERO.
	3. Ergebnisdarstellung • infliximab and etanercept (combined with MTX) were identified as biologic drugs being compared with combinations of DMARDs • 3 studies with DMARD naïve patients; 5 studies with patients with inadequate response to DMARD *Results*

	• Change in joint radiographic progression score did not differ between the combination DMARD group and the TNFi group, neither during the second year (MD -0.09 [-0.61,0.44]) of treatment nor during the first two years (MD 0.66 [-0.12, 1.43]). • At 6 months, there were significant differences in radiographic progression score (MD 0.49 [0.15; 0.83]), ACR50 (RR 1.44 [1.01; 2.06]) and ACR70 (RR 1.90 [1.27;2.85]) in favor of TNFi but these differences were not present in patients treated with an initial steroid course and disappeared at 24 months irrespective of the use of steroids. • There was no difference in number of AEs. • Higher risk for drop-outs in the DMARD group than in the TNFi group (RR 1.47 [1.11;1.96])
	4. Anmerkungen/Fazit der Autoren The difference between DMARD combination treatments including or excluding TNF inhibitors is small. Due to the enormous cost-differences RA guidelines should recommend combination DMARD treatment before initiation of TNF inhibitors **5. Hinweise durch FB Med** • Ergebnisse nicht stratifiziert nach DMARD-Vorbehandlungsstatus dargestellt
Oliveira de Costa J et al., 2015 [8]. Infliximab, methotrexate and their combination for the treatment of rheumatoid arthritis: a systematic review and meta-analysis	**1. Fragestellung** To evaluate the efficacy and safety of infliximab + methotrexate (IFX + MTX) regimens versus MTX alone or in combination with other disease-modifying anti-rheumatic drugs (DMARDs).
	2. Methodik **Population:** RA patients regardless of disease duration **Intervention** IFX + MTX **Komparator** MTX as monotherapy or in combination with other synthetic DMARD **Endpunkt:** ACR20,ACR50, ACR70, clinical remission defined as DAS28, Patient's assessment of physical function **Suchzeitraum** (Aktualität der Recherche): until June/October 2012 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 9 **Qualitätsbewertung der Studien:** Jadad score and Cochrane Risk of Bias
	3. Ergebnisdarstellung *Study characteristics* Patients profile included individuals previously treated with DMARDs, not treated with MTX (2 studies) or those that had insufficient responses to MTX. *Methodological quality and risk of bias* Nine trials were classified as randomised, but only two of these studies reported the methods of randomisation. The Jadad scale score was generally good (ranging from moderate to high). The pharmaceutical industry funded six studies. We identified a potential source of bias in three trials, and only one study was classified as low risk of bias *Efficacy of infliximab vs control* Patients with insufficient response to MTX (6 studies): ACR20: RR1.77 (1.38 to 2.62); I2=74% ACR50: RR 2.13 (1.53; 2.97); I2=61%

	ACR70:RR 2.18 (1.43; 3.34, I2=43% MTX-naïve Patients (2 Studies) ACR20: RR 1.40 (0.84; 2.34); I2=64% ACR50: RR 1.44 (1.18; 1.76); I2=0% ACR70: RR 1.56 (1.19; 2.04); I2=0% *Safety* • no statistically significant differences between the IFX standard dose + MTX and DMARDgroups in the outcomes of infection, serious infections, serious adverse events, tumours and death. • Infusion reactions occurred more frequently in the IFX + MTX group (RR = 2.21[1.63; 2.99]) • serious infections and infusion reactions showed moderate heterogeneity. • Subgroup analysis revealed that MTX-naive patients who received IFX + MTX had more serious infections than the MTX group (2.80 [1.14; 6.84], 1 Study)
	4. Fazit The IFX + MTX combination is more effective than treatment with MTX alone or DMARDs combination. The IFX + MTX regimen presented good tolerability in patients previously treated with DMARDs, not treated with MTX or with insufficient responses to MTX. The efficacy of IFX + MTX is noted primarily during initial periods of treatment. High doses of IFX were as effective as the standard dose, but with possible higher risk of serious infections
Barra L et al., 2014 [3]. Efficacy of biologic agents in improving the Health Assessment Questionnaire (HAQ) score in established and early rheumatoid arthritis: a meta-analysis with indirect comparisons	**1. Fragestellung** To determine the comparative efficacy of biologic agents in improving HAQ in patients with established RA who failed DMARDs or anti-TNF agents and in early RA (ERA).
	2. Methodik MA + indirect comparison **Population:** patients > 15 years with RA; differentiation between: • (i) established RA patients failing DMARDs or • (ii) established RA patients failing anti-TNF at enrolment and • (iii) patients with ERA (as symptoms <2 years or <10% prior exposure to a biologic agent,) **Interventionen**: biologics for RA **Komparator:** single DMARD **Endpunkte:** improvement in HAQ **Suchzeitraum** (Aktualität der Recherche): Bis 08/2012 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 28 **Qualitätsbewertung der Studien:** Jadad score Indirect comparisons of the different drugs compared to the control group were conducted using the Q-test based on analysis of variance and reported as a p-value (p-value <0.05 was considered significant).
	3. Ergebnisdarstellung • 28 studies:

	o 17 trials on anti-TNF agents (7 adalimumab, 3 certolizumab, 4 etanercept,1 golimumab and 2 infliximab), o 4 trials on abatacept, o 3 trials on rituximab and o 4 trials on tocilizumab. • *Quality assessment:* jadad score of 4 trials = 3 (poor quality); majority of trials (n=19) had >20% cross-over from the control group to intervention groups and these studies used intention-to-treat analyses. *Efficacy of biologic agents at lowering HAQ in established RA patients failing DMARDs (19 studies,, n=8115)* • analysis of the different biologics revealed a significant difference in mean difference in change in HAQ (p<0.0001). o The $\Delta HAQ_{biologic}$-$\Delta HAQ_{control}$ for abatacept (-0.20; 95% CI:-0.28, -0.12; I2=0%), and infliximab (-0.11; 95% CI: -0.17, -0.05; I2=0%) were significantly lower than the other anti-TNF agents with $\Delta HAQ_{biologic}$-$\Delta HAQ_{control}$ of -0.32 to -0.35; I2=0% for all) (p<0.02) o $\Delta HAQ_{biologic}$-$\Delta HAQ_{control}$ for tocilizumab (-0.20; 95% CI:-0.24, -0.17; I2=0%) was lower compared to adalimumab and certolizumab (p<0.001) *Efficacy of biologic agents at lowering HAQ in established RA patients failing anti-TNF agents (4 studies, n=1694)* There were no significant differences in the efficacy of the different biologics at improving HAQ: $\Delta HAQ_{biologic}$-$\Delta HAQ_{control}$ was for • abatacept of -0.40; 95% CI:-0.51, -0.29), • rituximab (-0.37; 95% CI: -0.46, -0.27) and • tocilizumab (-0.36; 95% CI:-0.42, -0.30). *Efficacy of biologic agents at lowering HAQ in early RA (ERA) patients (5 studies, n=2492).* • 1 trial investigating infliximab with DMARD-naïve patients • 4 trials with MTX-naïve patients (subjects could have been exposed to other DMARDs previously There was no significant difference in HAQ improvement for the different biologic agents. The $\Delta HAQ_{biologic}$-$\Delta HAQ_{control}$ was for • adalimumab -0.20; 95%CI: -0.34, -0.06; • etanercept -0.3; 95%CI: -0.52, -0.07; • infliximab -0.2; 95%CI: -0.40, 0; and • rituximab -0.23; 95%CI: -0.32, -0.14)
	4. Fazit der Autoren Biologics improve physical function in established RA patients failing DMARDs and anti-TNF agents. In anti-TNF failures, the included biologics (abatacept, tocilizumab and rituximab) appeared equally efficacious. In DMARD-failures, there were differences in HAQ reduction for some biologics. These differences should be interpreted in the context of the doses used, the populations studied and the design of the included studies. **5. Hinweise FBMed** • Keine Informationen, welche Kontrollen in den Studien eingesetzt wurden
Hauptsächlich MTX naive Patienten	
Kuriya B et al., 2010 [23]. Efficacy of initial	**1. Fragestellung** This meta-analysis compared the efficacy of initial methotrexate monotherapy versus combination therapy (methotrexate plus biological agent) for clinical

methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission	remission and radiographic non-progression among ERA patients with minimal or no previous methotrexate exposure.
	2. Methodik **Population:** Frühe RA Patienten mit minimaler (≤4 w) oder keiner vorherigen MTX Therapie. **Intervention**: methotrexate plus biological agent **Komparator** MTX monotherapy **Endpunkte:** Anteil Patienten mit einer klinischen Remission, Anteil Patienten mit einer radiografisch nachweisbaren Krankheitsstabilität (Kein Progress) über eine Behandlungsdauer von mind. einem Jahr **Suchzeitraum** (Aktualität der Recherche): Bis 04/2009 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 7 (n=2763) **Qualitätsbewertung der Studien:** assessment of the following methodological features most relevant to the control of bias in RCT: randomisation, baseline comparability of the participants, blinding of care providers, patients and outcome assessors, handling of withdrawals and intention to- treat analyses.
	3. Ergebnisdarstellung (basierend auf 7 Studien; insgesamt 2763 Patienten): • The studied biological agents were abatacept, adalimumab, etanercept and infliximab. • All trials were judged to be of sufficiently high quality. • Die meisten Studien definierten eine klinische Remission als einen Score ≤2,6 auf der DAS28 Skala. • Keine Progression wurde meist als eine Veränderung um weniger als 0,5 Einheiten auf der modifizierten totalen Sharp Score (mtSS) definiert. • Alle Studien zeigten stat. signifikant vorteilhafte Effekte unter der Kombinationstherapie: o klinische Remission: gepoolte RR 1.74; 95% KI 1.54 bis 1.98; I2=0% o Abwesenheit einer Progression: RR 1.30; 95% KI 1.01 bis 1.68).; I2=94.7% -> stat. signifikante Heterogenität
	4. Anmerkungen/Fazit der Autoren The efficacy of combination therapy with a biological agent is superior to methotrexate monotherapy for remission. Combination therapy has a greater initial effect on clinical remission than radiographic non-progression. Uniform definitions of remission are needed and the proportion of subjects who achieve the combined endpoint of clinical and radiographic remission should be considered as a meaningful outcome in future studies of ERA. **5. Hinweise durch FB Med** • Heterogenität zwischen den Studien (z.B. unterschiedliche Definition der Endpunkte) • Studiendauer von einem Jahr zu kurz um eine Rückschlüsse auf eine dauerhafte Remission ziehen zu können • Nicht für alle biolog. DMARDs ausreichend Studien vorhanden
Ma MH et al., 2010 [28]. A systematic comparison of combination DMARD	**1. Fragestellung** To systematically reviewed the efficacy of combination treatment in early RA with both combination DMARDs and TNF inhibitors with MTX
	2. Methodik **Population:** RA patients with disease duration < 3 years **Intervention**: • combination DMARDs or

therapy and tumour necrosis inhibitor therapy with methotrexate in patients with early rheumatoid arthritis	• TNF/MTX combination (infliximab, adalimumab or etanercept with MTX) **Komparator** MTX monotherapy **Endpunkte:** ACR response, HAQ; x-ray progression **Suchzeitraum** (Aktualität der Recherche): Bis 2008 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 15 (n=4200) **Qualitätsbewertung der Studien:** Jadad scale

3. Ergebnisdarstellung

- The mean Jadad score was 3.9: four RCTs had maximum scores (5/5) and two RCTs were of poor quality (2/5).

Results: compared to MTX monotherapy (Tab. 3)

- both combination DMARDs and TNF/MTX increased ACR20–70 responses, reduced withdrawals for inefficacy, reduced HAQ and reduced annual X-ray progression
- DMARD combinations increased withdrawals for toxicity
- The only head-to-head RCT showed comparable efficacy for combination DMARDs and TNF/MTX combinations

TABLE 3 Summary of meta-analysis of all outcomes: ACR response, patient withdrawals, HAQ and X-ray progression

Outcomes	Studies, *n*	Effects
Categorical outcomes		Random OR (95% CI)
ACR20		
DMARD combinations	6	2.02 (1.27, 3.20)
TNF/MTX	6	2.03 (1.63, 2.54)
ACR50		
DMARD combinations	5	1.64 (1.15, 2.34)
TNF/MTX	5	2.17 (1.78, 2.64)
ACR70		
DMARD combinations	5	1.84 (1.31, 2.57)
TNF/MTX	5	2.30 (1.89, 2.79)
Inefficacy withdrawals		
DMARD combinations	8	0.52 (0.33, 0. 82)
TNF/MTX	7	0.29 (0.19, 0.44)
Toxicity withdrawals		
DMARD combinations	8	2.69 (1.49, 4.83)
TNF/MTX	7	1.66 (0.83, 3.32)
Continuous outcomes		WMD random OR (95% CI)
Disability (HAQ)		
DMARD combinations	2	−0.17 (−0.33, −0.01)
TNF/MTX	2	−0.16 (−0.26, −0.04)
X-ray progression		
DMARD combinations	5	−1.20% (−1.36%, −1.04%)
TNF/MTX	4	−0.84% (−1.23%, −0.45%)

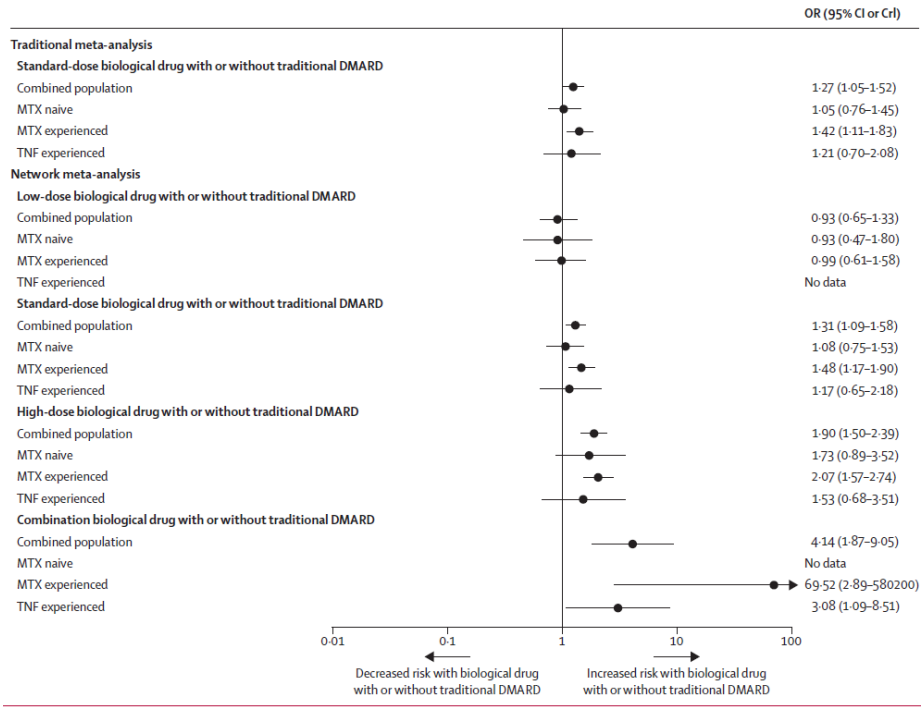
4. Fazit der Autoren

There is strong evidence in favour of combination treatment for RA but there is still uncertainty about which regimen is preferable

5. Hinweise FBMed

	• der größte Teil der Studien untersuchte MTX naive Patienten, mindestens jedoch 2 Studien mit MTX-vorbehandelten Patienten
SR zu Adverse Events	
Kourbeti IS et al., 2014 [22]. Biologic Therapies in Rheumatoid Arthritis and the Risk of Opportunistic Infections: A Meta-analysis	**1. Fragestellung** We aimed to review their association with opportunistic infections (OIs), including fungal, viral (with a focus on herpes virus related infections), tuberculosis and other mycobacterial infections.
	2. Methodik ***Population:*** Patients with RA ***Intervention:*** Any approved biologic agent ***Kontrolle:*** Included either placebo or disease-modifying antirheumatic drugs/conventional therapy) *Hinweis:* Low-dose corticosteroids (<10 mg equivalent to prednisolone) were permitted in all arms. ***Endpunkte:*** Opportunistic Infections (OIs) including fungal, viral (with a focus on herpesvirusrelated infections), tuberculosis and other mycobacterial infections ***Suchzeitraum (Aktualität der Recherche):*** We searched PubMed and EMBASE through June 24, 2013, and complemented the search with the reference lists of eligible articles. The analysis included randomized trials on RA that compared any approved biologic agent with controls and reported the risk of OIs. ***Anzahl eingeschlossener Studien/Patienten (Gesamt):*** 70 ***Qualitätsbewertung der Studien:*** GRADE approach
	3. Ergebnisdarstellung A total of 70 trials that included 32 504 patients (21 916 patients receiving biologic agents and 10 588 receiving placebo) included → Studies of patients with prior TNF exposure = 8! *Study quality* The majority of studies were considered high quality based on the criteria detailed in the methods section. More specifically, across eligible studies, 68 of 70 (97%) were doubleblinded, 62 of 70 (89%) included intention-to-treat analysis, 68 of 70 (97%) reported dropouts, and 67 of 70 (96%) provided institutional review board approval and informed consent. Most trials (67 of 70; 96%) were multicenter; allocation concealment was provided in 23 of 70 studies (33%) and was unclear in 47 (67%). *Summary of effects* • There was high quality of evidence that biologic agents are associated within increased risk of all OIs: patients receiving biologic agents were more likely to develop OIs than control patients (OR, 1.79; 95% CI, 1.17–2.74) • use of biologic agents was associated with increased risk of mycobacterial infections (OR, 3.73; 95% CI, 1.72–8.13;I2 = 0) and all viral OIs (OR, 1.91; 95% CI, 1.02–3.58; I2 = 0), • no stat. sig.differences for all fungal infections (OR, 1.31; 95% CI, 0.46–3.72), invasive fungal infections (OR, 2.85; 95% CI, 0.68–11.91), P. jirovecii pneumonia (OR, 1.77; 95% CI, 0.42–7.47), and VZV infections (OR, 1.51; 95% CI, 0.71–3.22), • combined effect of anti-TNF drugs was significant for OIs (OR, 2.10; 95% CI, 1.27–3.45; I2 = 0), as opposed to non–anti-TNF agents (OR,

	1.20; 95% CI, .54–2.68); this comparison of effects was not significant (P interaction= 0.18). • A difference that did not reach statistical significance was noted for patients without prior exposure to anti-TNF agents (OR, 2.05; 95% CI, 1.23–3.42; I2 = 0) compared with those with previous exposure to anti-TNF agents (OR, 1.33; 95% CI, 0.62–2.85; I^2= 31%; P interaction = .36). • There was no difference in OI-associated mortality
	4. Fazit der Autoren: Among patients with RA, biologic agents are associated with a small but significant risk of specific OIs. This increase is associated with mycobacterial diseases and does not seem to affect overall mortality. Because OIs are a relatively rare complication of biologic agents, large registries are needed to identify the exact effect in different OIs and to compare the different biologic agents
Singh JA et al., 2015 [45]. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis	**1. Fragestellung** To compare the risk of serious infections in rheumatoid arthritis between biological treatment and non-biological traditional treatment with DMARDs, and use network meta-analysis to compare subpopulations within rheumatoid arthritis, to synthesise data from RCTs
	2. Methodik Systematic review, meta-analysis, and Bayesian network meta-analysis **Population:** RA patients **Intervention**: biologics **Komparator** placebo, biologics, or traditional DMARDs or their combinations **Endpunkte:** malignancies **Suchzeitraum** (Aktualität der Recherche): 02/2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 106 (n=42330) **Qualitätsbewertung der Studien:** Cochrane Risk of Bias Tool
	3. Ergebnisdarstellung • Risk of bias ranged from low to high across the studies • results stratified by the following populations: (siehe Tab.1) o MTX-naïve (24 trials), o traditional DMARD-experienced (71 trials), and o anti-TNF biological drug-experienced (11 trials) pts All populations / Traditional DMARD-naive patients / Traditional DMARD-experienced patients / TNF-experienced patients Number of trials: 106 (100%) / 24 (23%) / 71 (67%) / 11 (10%) Number of patients in trials: 42 330 (100%) / 8375 (20%) / 29 167 (69%) / 4788 (11%) Number of patients with serious infection: 965 (100%) / 227 (24%) / 646 (67%) / 92 (10%) Median year of publication: 2008 (1992–2013) / 2006 (1992–2013) / 2008 (1994–2013) / 2008 (2005–2013) Number of treatment nodes: 10 / 5 / 10 / 6 Number of two-arm trials: 63 (100%) / 19 (30%) / 38 (60%) / 6 (10%) Number of multi-arm trials: 43 (100%) / 5 (12%) / 33 (77%) / 5 (12%) Mean follow-up duration (months): 9·0 (8·0, 1–60) / 13·1 (6·9, 3–24) / 8·0 (8·5, 1–60) / 6·3 (3·2, 2–12) Number of trials with duration ≥12 months: 33 (31%) / 17 (71%) / 18 (25%) / 2 (18%) Mean rheumatoid arthritis duration (years): 6·9 (4·0, 0·1–13·5) / 0·7 (0·7, 0·1–3·5) / 8·5 (2·3, 2·2–13·5) / 10·8 (2·0, 6·4–12·9) Mean annualised baseline risk of serious infection in traditional DMARDs arms*: 2% (2, 0–9%) / 2% (2, 0–9%) / 2% (2, 0–8%) / 2% (2, 0–5%) Data are n (%), year (range), mean (SD, range), or % (range). TNF=tumour necrosis factor. *Only included trials more than 6 months in duration for calculation. DMARD=disease-modifying antirheumatic drugs. *Table:* Characteristics of patients and studies *Serious infections*

	 *Figure 3:* **Traditional meta-analysis and network meta-analysis** Risk of serious infection among specified populations of patients compared with patients receiving traditional DMARD monotherapy. Data for the traditional meta-analysis are OR (95% CI) and data for the network meta-analysis are OR (95% CrI). OR=odds ratio. CrI=credible interval. DMARD=disease-modifying antirheumatic drugs. Traditional Meta-analysis: (siehe Figure 3) • significant increase in serious infections in patients receiving biological drugs (OR 1·27, 95% CI1·05–1·52, p=0·012 • risk of serious infections in patients treated with biological drugs varied depending on previous treatment experience o risk was significantly increased in MTX-experienced patients, o risk did not significantly differ in patients who were MTXnaive or anti-TNF-biological drug experienced Network MA: (siehe Figure 3) • standard-dose and high-dose biological drugs with or without traditional DMARD were associated with an increased risk of serious infection, low dose were not. • In MTX-naïve patients, standard-dose biological drugs with or without traditional DMARD and high-dose biological drugs with or without traditional DMARD were not associated with a significant increase in risk of serious infection • in MTX-experienced patients, standard-dose biological drugs with or without traditional DMARD and high-dose biological drugs with or without traditional DMARD were associated with an increased risk of serious infections. In MTX-experienced and anti-TNF biological drug experienced patients combination biological significantly increase serious with wider CI
	4. Fazit der Autoren Standard-dose and high-dose biological drugs (with or without traditional DMARDs) are associated with an increase in serious infections in rheumatoid arthritis compared with traditional DMARDs, although low-dose biological drugs are not.
Liu Y et al., 2014 [26]. Risk of Breast Cancer and Total Malignancies in	**1. Fragestellung** To analyze the risk of malignancies, especially breast cancer, in patients with RA enrolled in RCTs
	2. Methodik **Population:** adult RA patients **Intervention**: TNF-α antagonists (orTNF-α antagonists plus MTX)

Rheumatoid Arthritis Patients Undergoing TNF-α Antagonist Therapy: a Meta-analysis of Randomized Control Trials	**Komparator** placebo /MTX (or placebo plus MTX) **Endpunkte:** malignancies **Suchzeitraum** (Aktualität der Recherche): 07/2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 28 (n=11741) **Qualitätsbewertung der Studien:** Jadad scale
	3. Ergebnisdarstellung • Etanercept: 6 trials, • Infliximab: 5 trials, • certolizumab pegol: 4 trials, • adalimumab: 8 trials, • golimumab: 5 trials 71 malignancies were developed on TNF-α antagonists and 26 on placebo, and breast cancer was 10 *vs* 7. • No stat. sig. difference between groups for breast cancer (OR 0.65, 95%CI [0.22, 1.93] and for total malignancies (1.06, 95% CI 0.64, 1.75) • There were no significant differences among the five drugs at approved doses about risk of malignancies.
	4. Fazit der Autoren This study did not find a significantly increased risk of breast cancer and total malignancies in adults RA patients treated with TNF-α antagonists at approved doses. However, it cannot be ignored that more patients developed malignancies with TNF-α antagonists therapy compared with patients with placebo or MTX, in spite of the lack of statistical significance, so that more strict clinical trials and long-term follow-up are needed, and both mITT and PP analyses should be used in such safety analyses.
Michaud TL et al., 2014 [32]. The Comparative Safety of Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis: A Meta-analysis Update of 44 Trials	**1. Fragestellung** to evaluate and update the safety data from RCTs of TNF inhibitors in patients treated for rheumatoid arthritis
	2. Methodik **Population:** > 18 year old RA patients **Intervention**: TNF-α antagonists (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) **Komparator** placebo or DMARDs **Endpunkte:** • serious adverse events (any AE that resulted in death, was life threatening, resulted in hospitalization or prolongation of hospitalization, or caused persistent or substantial disability) • serious infection • malignancies **Suchzeitraum** (Aktualität der Recherche): 05/2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 44 (n= 11700)

	Qualitätsbewertung der Studien: Cochrane risk of bias, GRADE
	3. Ergebnisdarstellung o Etanercept: 12 trials, o Infliximab: 9 trials, o certolizumab pegol: 5 trials, o adalimumab: 11 trials, o golimumab: 7 trials Quality of evidence: moderate to high *Results:* • Overall serious AE: no sign. difference (OR, 1.11; 95% CI, 0.97-1.26). o The results were consistent across trials (I2 <50%) for all drugs except etanercept (I2 =64.8%) • Malignancy: no sign. difference (OR, 1.29; 95% CI, 0.85-1.97) • Serious Infection: higher risk with TNFi (OR, 1.42; 95% CI, 1.13-1.78) o adalimumab: OR 1.69, 95% CI 1.12-2.54 →sig. difference o certolizumab pegol: OR 1.98, 95%CI 0.99-3.96 → n.s. o infliximab: OR 1.63, 95%CI 1.07-2.47 →sig. difference o golimumab OR 1.55, 95% CI 0.76-3.17 → n.s. o etanercept: OR 0.73; 95% CI 0.45-1.20 → n.s. • treatment discontinuation due to AE: higher risk with TNFi (OR, 1.23; 95% CI, 1.06-1.43) o adalimumab: OR 1.38, 95%CI 1.00; 1.69 →sig. difference o certolizumab pegol: 1.67, 95%CI 1.09; 2.54 →sig. difference o infliximab 2.04, 95%CI 1.46; 2.84 →sig. difference o etanercept: decreased risk of discontinuation due to AE (OR, 0.72; 95% CI 0.55-0.93) →sig. difference o golimumab OR 1.43, 95%CI 0.88; 2.35 →n.s. • infliximab plus MTX was associated with a significantly increased risk of serious infection compared with the MTX (OR, 1.63; 95% CI, 1.08-2.48).
	4. Fazit der Autoren There is higher risk of serious infection associated with adalimumab, certolizumab pegol, and infliximab, which seems to contribute to higher rates of discontinuation. In contrast, etanercept use showed a lower rate of discontinuation. **5. Hinweise FBMed** siehe auch Anlage 6:Übersicht der Ergebnisse bisheriger MA zur Sicherheit von TNF
Poiroux L et al., 2015 [40]. All-cause Mortality Associated with TNF-a Inhibitors in Rheumatoid Arthritis: A Meta-Analysis	**1. Fragestellung** To compare mortality data obtained from RCTs for the 5 TNF-a inhibitors used in the treatment of rheumatoid arthritis.
	2. Methodik **Population:** adult RA patients **Intervention**: TNF-α antagonists (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab) **Komparator** placebo or DMARDs

of Randomized Controlled Trials	**Endpunkte:** all-cause mortality **Suchzeitraum** (Aktualität der Recherche): bis 10/2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 23 (n= 10048) **Qualitätsbewertung der Studien:** Jadad scale
	3. Ergebnisdarstellung • median study duration was 46 weeks (range: 24 to 104 weeks) • Most comparison analyses reached a high level of quality of evidence, with a mean Jadad score of 3.8±1.01 • risk of death with TNF-a inhibitors was not significantly different compared to control (OR]1.32; 95% CI 0.76-2.29), no differences between different TNFi • results were consistent across trials (P=0.99, I2 < 25%); type of comparator did not modify results; monotherapy and combination therapy
	4. Fazit der Autoren Treatment with TNF-a inhibitors is not associated with a higher risk of medium-term mortality of any cause in patients with rheumatoid arthritis. Further studies are warranted to assess the long-term effect of TNF-a inhibitors on mortality
Conway R et al., 2014 [7]. Methotrexate and Lung Disease in Rheumatoid Arthritis	**1. Fragestellung** To evaluate whether MTX is associated with an increased risk of lung disease in adults with RA based on RCTs
	2. **Methodik** **Population:** adult RA patients **Intervention**: MTX **Komparator** no MTX **Endpunkte:** respiratory side effects **Suchzeitraum** (Aktualität der Recherche): 02/2013 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 22 (n=8584) **Qualitätsbewertung der Studien:** Cochrane Risk of Bias
	3. Ergebnisdarstellung • Comparators in the studies: o DMARDs in 9 studies (1 of which had a placebo group), o biologic agents 9 studies, o chicken type II collagen in 2 studies, o a small molecule immune modulator in 1 study, and o a biologic agent plus cyclophosphamide in 1 study • data suggested a low risk of bias in the included studies *Results* • MTX increases risk of total adverse respiratory events (RR 1.10, 95% CI 1.02 -1.19, I2= 3%) • MTX increases risk of total infectious respiratory events (RR 1.11, 95% CI 1.02–1.21, I2= 0%)

	• no increased risk of total noninfectious respiratory events and death due to lung diseases subgroup analysis of studies in which pneumonitis was described revealed an increased risk associated with MTX (RR 7.81, 95% CI 1.76-34.72).
	4. Fazit der Autoren There is a small but significant increase in the risk of lung disease in patients with RA treated with methotrexate compared with other disease-modifying antirheumatic drugs and biologic agents.

Leitlinien

Smolen JS et al., 2013 [49]. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update	European League against Rheumatism (EULAR) **Fragestellung** Updating the 2010 EULAR recommendations for the management of RA.
	Methodik evidenz- und interdisziplinär (Rheumatologie, Patientenvertretung, Gesundheitsökonomie, Infektiologie) konsentierte Leitlinie ***Grundlage der Leitlinie:*** 4 systematische Übersichtsarbeiten und (teilanonym.) Konsensus-prozesse[3] ***Suchzeitraum:*** zu 1. „up to January 2009“, zu 2. “from 1962 to February 2009“, zu 3. “between 1962 and February 2009“, zu 4. „until January 2013“ ***Weitere Kriterien für die Qualität einer Leitlinie:*** Quellen im jeweiligen Hintergrundtext zu den Empfehlungen zitiert ***LoE/GoR:*** LoE and GoR are based on the recommendations of the Oxford Centre for Evidence-Based Medicine SoR=level of agreement (scale 0 to 10 with 0=no agreement at all; 10=full agreement), %=percent of votes for the respective items as worded ***Sonstige methodische Hinweise:*** • Competing interests: All participants have disclosed any conflicts of interest. After review by the EULAR Steering Committee, these potential conflicts have been considered as either absent or acceptable with this initiative. The individual declarations of conflicts are available on demand at the EULAR secretariat and are summarised below as remuneration for consultation and/or speaking engagements (‘R’), research funding (‘F’) or ‘none’. Funding: EULAR
	Empfehlungen • MTX should be part of the first treatment strategy in patients with active RA.(LoE 1a, GoR A, SoR 9.6±0.9, 100%) • In cases of MTX contraindications (or early intolerance), sulfasalazine or leflunomide should be considered as part of the (first) treatment strategy. (LoE 1a, GoR A, SoR 9.0±1.7, 87%) • In DMARD-naive patients, irrespective of the addition of glucocorticoids, csDMARD monotherapy or combination therapy of csDMARDs should be used. (LoE 1a, GoR A, SoR 9.5±0.8, 100%) • If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another csDMARD strategy should be considered; when poor

[3] Gaujoux-Viala C et al. Efficacy of conventional synthetic disease-modifying antirheumatic drugs, glucocorticoids and tofacitinib—a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis 2014;73:510–15.

Ramiro S, Gaujoux-Viala C, Nam JL, et al. Safety of synthetic and biological DMARDs—a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis 2013;73:529-35.

Nam JL, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis 2010;69:976–86.

Gorter SL, et al. Current evidence for the management of rheumatoid arthritis with glucocorticoids: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010;69: 1010–14.

	prognostic factors are present, addition of a bDMARD should be considered. (LoE 5, GoR D, SoR 8.9±1.3, 100%) • In patients responding insufficiently to MTX and/or other csDMARD strategies, with or without glucocorticoids, bDMARDs (TNF inhibitors*, abatacept or tocilizumab, and, under certain circumstances, rituximab†) should be commenced with MTX. (LoE 1b, GoR A, SoR 9.2±1.2, 90%) • If a first bDMARD has failed, patients should be treated with another bDMARD; if a first TNF inhibitor therapy has failed, patients may receive another TNF inhibitor* or a biological agent with another mode of action. (LoE 1a, GoR A, SoR 9.4±0.8, 97%) * TNF inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, biosimilars (as approved according to a thorough approval process, such as by EMA and/or FDA). † - The 'certain circumstances', which include history of lymphoma or a demyelinating disease, are detailed in the accompanying text: – Rituximab approved for use after patients have responded insufficiently to TNF blockers – trial data in patients who were naive for csDMARDs and those who had an inadequate response to csDMARDs published (level 1 evidence) – in presence of certain contraindications for other agents – such as recent history of lymphoma, latent tuberculosis (TB) with contraindications to the use of chemoprophylaxis, living in a TB-endemic region, or a previous history of demyelinating disease – rituximab may be considered as a first-line biological agent – some rheumatologists also prioritise this drug in patients with a recent history of any malignancy, because rituximab use is not associated with the occurrence of cancers – rituximab is the least expensive biological agent at present
Bykerk VP et al., 2012 [4]. Recommen-dations for Pharmacological Management of Rheumatoid Arthritis with Traditional and Biologic Disease-modifying Antirheumatic Drugs	Canadian Rheumatology Association (CRA) **Fragestellungen** <u>Treatment with traditional DMARD</u> • When should combination therapy with traditional DMARD be used? • Which traditional DMARD combinations are preferred? • Should leflunomide be used in combination with MTX? <u>Treatment with biologic DMARD</u> • In patients being considered for treatment with biologic DMARD, how should an inadequate response to traditional DMARD be defined? • Which investigations should be ordered prior to starting treatment with biologic DMARD? • Should MTX be coprescribed with biologic DMARD? • When should anti-TNF therapy be used in the treatment of patients with RA? • When should abatacept be used in the treatment of patients with RA? • When should rituximab be used in the treatment of patients with RA? • How should patients be retreated with rituximab? • When should tocilizumab be used in the treatment of patients with RA? • Which therapeutic strategy is recommended after failure of 1 anti-TNF? • Which therapeutic strategy is recommended after failure of 2 anti-TNFs? • Which therapeutic strategy is recommended after failure of abatacept, rituximab, or tocilizumab? • Should therapy be tapered or withdrawn in RA patients who achieve sustained remission?
	Methodik

	evidenz- und konsensbasierte Leitlinie ***Grundlage der Leitlinie**:* synthesis of international guidelines (according to ADAPTE), supporting evidence, and expert consensus of a national Canadian RA working group including clinical (rheumatology and primary care), methodo-logical (epidemiologists/health services researchers/information specialist), rheumatology research trainees, and patient consumers ***Suchzeitraum**:* 01/2000 – 06/2010 ***Weitere Kriterien für die Qualität einer Leitlinie**:* • Leitlinie mit AGREE überprüft (Ergebnisse: "Recommend" (R), "Recommend with Provisos" (R*), or "Would Not Recommend" (WNR)) • Aktualisierungsrecherchen durchgeführt • Quellen im jeweiligen Hintergrundtext zu den Empfehlungen zitiert ***LoE/GoR**:* we translated each guideline's grading system onto a custom system for assigning levels of evidence simplified from that developed by the Scottish Intercollegiate Guideline Network (SIGN) (siehe Anlage zu dieser Synopse) ***Sonstige methodische Hinweise:*** • Funded through the Canadian Institutes of Health Research (CIHR) and matched funds from the Canadian Rheumatology Association (CRA). • Potential conflicts for each working group member including industry funding, consultancies, commercial interests, and direct involvement in any guidelines included in the systematic review for the last 3 years are shown in Appendix 1.
	Empfehlungen <u>Treatment with MTX/DMARD</u> • Initial combination therapy with traditional DMARD should be con-sidered, particularly in patients with poor prognostic features, moderate-high disease activity, and in patients with recent-onset disease. Combination therapy should also be considered in patients who have an inadequate response to monotherapy (Level I; Strength B) 5 CPG and 3 CS (AGREE rating: R=4, R*=3, WNR=1) • When treating with combination therapy, MTX should be used as the anchor drug unless contraindicated. Combinations not including MTX can be considered on a case-by-case basis. (Level I; Strength A) 4 CPG and 2 CS (AGREE rating: R=2, R*=3, WNR=1) • Combination therapy with leflunomide and MTX should be used with caution as it is associated with higher toxicity, (gastrointestinal and liver) (I) and has no added benefit relative to other DMARD combinations (IV) (Level I, IV; Strength A) 1 CPG and 5 CS (AGREE rating: R=1, R*=5) <u>Treatment with biologics</u> • In patients being considered for biologic therapy, an inadequate response to DMARD (DMARD-IR) is defined as moderate to high disease activity despite treatment with at least 2 DMARD [including MTX unless contraindicated] in mono or combination therapy after 3 months at target dose. (Level IV; Strength D) 10 CPG and 7 CS (AGREE rating: R=3, R*=14) • MTX co-prescription with biologics is recommended for improved efficacy. (Level I; Strength A) 9 CPG and 4 CS (AGREE rating: R=4, R*=9) • Anti-TNF therapy is recommended for the treatment of patients with RA after an inadequate response to DMARD. In exceptional circumstances involving patients with DMARD contraindications or

	high disease activity and poor prognostic factors (particularly early disease), anti-TNF therapy may be an option after failure of DMARD monotherapy or in DMARD-naive patients. (Level I; Strength A) 8 CPG and 10 CS (AGREE rating: R=5, R*=12, WNR=1) • Abatacept is recommended for the treatment of patients with RA after an inadequate response to DMARD or anti-TNF therapy. (Level I; Strength A) 6 CPG and 1 CS (AGREE ratings: R=4, R*=3) • Rituximab is recommended for the treatment of patients with RF-positive RA after an inadequate response to DMARD or anti-TNF therapy. (Level I; Strength A) 7 CPG and 3 CS (AGREE rating: R=5, R*=5) • In patients who have failed treatment with 1 anti-TNF agent due to lack of efficacy or toxicity the following options are recommended: switch to another anti-TNF agent (I, II); switch to another biologic with a different mechanism of action [abatacept (ABAT), rituximab (RTX), tocilizumab (TCZ)] (I); or add MTX (or other DMARD) if the anti-TNF agent was used in monotherapy (II). (Level I, II; Strength B) 5 CPG (AGREE rating: R=2, R*=3) • In patients who have failed treatment with 2 anti-TNF agents a switch to another biologic with a different mechanism of action [abatacept (ABAT), rituximab (RTX), tocilizumab (TCZ)] is recommended. (Level II/IV; Strength C), no guideline • In the absence of data on therapeutic strategies after failure of abatacept (ABAT), rituximab (RTX), or tocilizumab (TCZ), the following options can be considered: switch to any biologic not previously tried and failed, add/switch to a traditional DMARD not previously tried and failed, or enroll the patient in a clinical trial with a new agent. (Level IV; Strength D), no guideline
Singh JA et al., 2012 [46]. 2012 Update of the 2008 Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis	American College of Rheumatology (ACR) **Fragestellungen** 1) indications for DMARDs and biologic agents 2) switching between DMARD and biologic therapies
	Methodik evidenz- und konsensbasierte Leitlinie ***Grundlage der Leitlinie:*** systematic literature review, development of clinical scenarios, rating the appropriateness of clinical scenarios, conversion of clinical scenarios to ACR RA treatment recommendations, peer review ***Suchzeitraum:*** February 26, 2010 for the efficacy and safety studies ***LoE und GoR:*** • Level of Evidence A: Data derived from multiple RCTs. • Level of Evidence B: Data derived from a single randomized trial, or nonrandomized studies. • Level of Evidence C: Only consensus opinion of experts, case studies, or standard-of-care. ***Sonstige methodische Hinweise:*** • Supported by a research grant from the ACR CoI declared
	Empfehlungen <u>Established RA:</u> <u>Initiating and switching among DMARDs</u> (…) 2) If after 3 months of methotrexate or methotrexate/DMARD combination, a patient still has moderate or high disease activity, then add another non-methotrexate DMARD or switch to a different non-

	methotrexate DMARD. Switching from DMARDs to biologic agents 3) If a patient has moderate or high disease activity after 3 months of methotrexate monotherapy or DMARD combination therapy, as an alternative to the DMARD recommendation just noted above, the panel recommends adding or switching to an anti-TNF biologic, abatacept, or rituximab (level of evidence A-C). If after 3 months of intensified DMARD combination therapy or after a second DMARD, a patient still has moderate or high disease activity, add or switch to an anti-TNF biologic (level of evidence C). Switching among biologic agents due to lack of benefit or loss of benefit. 4) If a patient still has moderate or high disease activity after 3 months of anti-TNF biologic therapy and this is due to a lack or loss of benefit, switching to another anti-TNF biologic or a non-TNF biologic is recommended. If a patient still has moderate or high disease activity after 6 months of a non-TNF biologic and the failure is due to a lack or loss of benefit, switch to another non-TNF biologic or an anti-TNF biologic (level of evidence B and C). Switching among biologic agents due to harms/adverse events. If a patient has moderate or high disease activity after failing an anti-TNF biologic because of a non-serious AE, switch to another anti-TNF biologic or a non-TNF biologic (level of evidence B and C). If a patient has moderate or high disease activity after failing a non-TNF biologic because of an AE (serious or non-serious), switch to another non-TNF biologic or an anti-TNF biologic (level of evidence C).
Leitlinien zur frühen RA	
AWMF, 2011 [9]. Management der frühen rheumatoiden Arthritis (S3)	AWMF Leitlinie (S3)
	Methodik ***Grundlage der Leitlinie***: – interdisziplinären Leitliniengruppe – Systematische Recherche, Auswahl und Bewertung der Literatur, Erstellung von Evidenztabellen – Formale Konsensfindung (nominaler Gruppenprozess ***Suchzeitraum***: bis 2009 ***LoE und GoR:*** ↑↑ Diesen Empfehlungen liegen Studien mit großer Ergebnissicherheit zugrunde, die einen eindeutigen Nutzen gegenüber Risiko belegen. ↑ Diesen Empfehlungen liegen Studien zugrunde mit eingeschränkter Ergebnissicherheit und/oder geringerem Nutzen gegenüber Risiko. Good Clinical Practice ist eine Empfehlung der Konsensgruppe
	Empfehlungen • Sorgen Sie dafür, dass Ihre Patienten von der Diagnosestellung an mit klassischen DMARDs behandelt werden, um eine Verzögerung der Krankheitsprogression zu erzielen und damit die Langzeitprognose zu verbessern. **(LoE: ↑↑)** **Wahl der Basistherapie** • Setzen Sie Methotrexat als Mittel der ersten Wahl als Monotherapie und als Kombinationspartner bei der Behandlung mit klassischen DMARD ein. (LoE: ↑↑) Erläuterung zur Wahl der Basistherapie: Die allgemeinen Daten zur Therapie

mit klassischen DMARDs belegen die Vorteile einer Methotrexat-Therapie aufgrund des relativ schnellen Ansprechens und der längerfristigen Kontrolle der Erkrankung (basierend auf 7 älteren Literaturangaben). Kann Methotrexat nicht verwendet werden (z.B. bei Unverträglichkeit oder Kontraindikationen), kann ein guter Therapieerfolg auch mit anderen klassischen DMARDs erreicht werden.

Weitere Erläuterungen aus Fazit bei 5.1.6 DMARD-Kombinationstherapie: In der Regel ist Methotrexat (meist in Kombination mit einem Glucocorticoid) als Ersttherapie der ERA empfohlen, in etwa 20–30 % kann damit bereits eine Remission erreicht werden. Bei nicht ausreichendem Ansprechen ist die Zugabe eines weiteren DMARD normalerweise der nächste Schritt. Biologika sind bei früher RA monotherapeutisch dem Methotrexat nicht überlegen, in Kombination mit Methotrexat jedoch deutlich besser wirksam als klassische DMARDs und deshalb bei DMARD-Versagen die nächste Option.

- Unterdrücken Sie bis zum Erreichen der Wirkung der Basistherapie die Krankheitsaktivität mit einer Glucocorticoid-Therapie. **(LoE: ↑↑)**
- Führen Sie zusätzlich zur Therapie mit klassischen DMARDs die Glucocorticoid-Therapie niedrig dosiert fort, um die radiologisch nachweisbare Gelenkzerstörung zu verzögern. **(LoE: ↑↑)**

SIGN, 2011 [44]. Management of early rheumatoid arthritis

Fragestellung

This guideline addresses the diagnosis of early RA, its pharmacological treatment including symptom relief and disease modification, and the role of the multidisciplinary team in improving the care of patients with RA.

Methodik

SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in SIGN 50: A Guideline Developer's handbook

Suchzeitraum: 2003-2009

LoE and GoR

LoE	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 -	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 -	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GoR	
A	At least one meta-analysis, systematic review, or RCT rated as 1++,and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
GOOD PRACTICE POINTS	Recommended best practice based on the clinical experience of the guideline development group

- Early initiation of treatment with DMARDs is recommended to control the symptoms and signs of RA as well as limiting radiological damage. **(LoE: B)**

DISEASE MODIFYING ANTI-RHEUMATIC DRUGS

- Methotrexate and sulfasalazine are the DMARDs of choice due to their more favorable efficacy and toxicity profiles. **(GoR: A)**
  A systematic review found leflunomide (LEF), methotrexate (MTX) and sulfasalazine (SASP) to have comparable efficacy. MTX has the most favourable efficacy/toxicity trade-off. **(LoE: 1++)**

- A combination DMARD strategy, rather than sequential monotherapy, should be considered in patients with an inadequate response to initial DMARD therapy **(GoR A)**
  A systematic review of three RCTs concluded that combination therapy is more effective than sequential monotherapy in improving the symptoms and signs, physical function, and reducing radiographic progression. Most combinations use MTX as an anchor drug. **(LoE 1++)**

Biologics

- A meta-analysis of seven RCTs involving 2,673 patients compared combination therapy with MTX and biologic (1,248 patients) to MTX alone (1,152). The biologics studied were infliximab, adalimumab, etanercept, and abatacept. The authors concluded that remission rates at one year were greater in the combination therapy groups, than MTX monotherapy. In the combination group significantly more achieved clinical remission but there was only a modest benefit on radiological non-progression. All of the biologic agents had a similar efficacy for clinical remission.(LoE 1++)
- In an RCT of a TNF-α inhibitor in patients with early moderate to severe RA (DAS28 ≥3.2), the addition of infliximab to those with an inadequate response (DAS28 ≥3.2) to MTX was found to achieve a good EULAR response in more patients than the addition of HCQ and SASP to MTX.73 This has yet to be shown to be cost effective (LoE 1++)
- Use of TNF-α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX or other DMARDs is not recommended (LoE 1++)

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Canadian Agency for Drugs and Technologies in Health (CADTH), 2013 [5]. Biologic Response Modifier Agents as First-line Treatment for Patients with Rheumatoid Arthritis: A Review of the Clinical Efficacy, Cost-effectiveness and Guidelines	KEY QUESTIONS • What is the clinical efficacy of using biologics as first-line therapy in the treatment of patients with rheumatoid arthritis? • What is the cost-effectiveness of using biologics as first-line therapy in the treatment of patients with rheumatoid arthritis? • Are evidence-based clinical practice guidelines recommending biologic response modifier agents as first-line therapy? METHODS • Literature search up to 02/2013 • Selection criteria: o *Population:* MTX-naïve or traditional DMARD naïve patients with: - early RA or established RA, any severity of disease (mild-severe) o *Intervention:* Biologic response modifier agents as first-line therapy (with or without combination MTX or DMARD): abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab o *Comparator:* MTX or traditional DMARD, combination DMARD therapy, placebo; Biologic vs. biologic o *Outcomes:* Clinical efficacy, safety, harms, cost-effectiveness, clinical practice guideline recommendations o *Study design:* Q1. HTA, meta-analysis, SR, RCT; Q2. Cost-effectiveness or cost-utility study; Q3. Evidence based clinical practice guidelines • Critical Appraisal of Literature (risk of bias, AGREE) KEY FINDINGS • First line treatment with biologic antirheumatic drugs in adults with rheumatoid arthritis (RA) was evaluated in 17 randomized controlled trials (RCTs) of moderate to good quality, published between 2000 and 2012. The biologic agents evaluated included adalimumab (5 RCTs), etanercept (3), golimumab (1), infliximab (5), abatacept (1), rituximab (1) and tocilizumab (1). Data from one RCT on rituximab (Tak 2009) was obtained from an abstract. No RCTs were identified that evaluated the efficacy of certolizumab or anakinra in RA patients who were MTX or DMARD naïve. • MTX or disease modifying antirheumatic drug (DMARD) naïve patients who received a biologic agent plus MTX were more likely to show a clinical improvement that met the American College of Rheumatology (ACR) 20, 50 or 70 criteria at six to 12 months, compared to those who received MTX alone. • Patients on biologic agents plus MTX were more likely to achieve clinical remission versus MTX alone, based on pooled data from seven RCTs, however studies published more recently have not shown a consistent advantage to early biologic therapy. • Most studies found that radiographic progression was less likely to occur for patients treated with biologic agents compared to DMARDs, although interpretation of these findings was difficult due to differences in how progression was defined. • The impact of first line biologic therapy on health related quality of life and work related outcomes were not consistent, and no conclusions can be drawn on the safety of biologic agents based on the data available. • The cost-effectiveness of first line biologic therapy exceeded commonly reported willingness to pay thresholds in six of eight economic evaluations conducted in countries other than Canada. • The recommendations from evidence-based guidelines were inconsistent on the use of biologics in RA patients who were DMARD naïve. Three guidelines from Canada, US and Europe recommended that TNF inhibitors may be used as first line mono- or combination therapy in early RA patients (defined as

	disease duration ≤ 6 months) who are DMARD naïve and have poor prognostic factors, high disease activity, or have structural damage. One guideline from Scotland recommended against the use of TNF inhibitors in adults not previously treated with DMARDs. Anmerkung FBMed: EULAR-LL wurde in der Zwischenzeit aktualisiert: Deletion of former recommendation No 14: '*DMARD-naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biological*'. In 2010 it was already stated that early use of a biological agent should only be considered in exceptional patients; however, as it stood, this statement could have been misinterpreted as advocating use of biological agents even before an initial csDMARD strategy had failed. With the current decision, the use of bDMARDs before trying a csDMARD approach is even more strongly discouraged than signified by the 2010 recommendation. The majority of the current Committee members felt that using a treat-to-target strategy that gave patients the initial opportunity to respond to treatment in line with items 4, 5 and 7 still provides the option of adding a biological agent within 6 months—and thus quite early in the disease course or therapeutic chronology—if the treatment target was not reached.
National Institute for Health and Clinical Excellence (NICE), 2013 [38]. Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying anti-rheumatic drugs (rapid review of technology appraisal guidance 234) NICE technology appraisal guidance 280	1) Abatacept in combination with methotrexate is recommended as an option for treating RA in adults whose disease has responded inadequately to 2 conventional DMARDs, including MTX, only if: • it is used in accordance with the recommendations for other biological DMARDs in adalimumab, etanercept and infliximab for the treatment of RA (NICE technology appraisal guidance 130) **and** • the manufacturer provides abatacept with the discount agreed in the patient access scheme. 2) People currently receiving abatacept whose disease does not meet the criteria in section 1) should be able to continue treatment until they and their clinician consider it appropriate to stop.
National Institute for Health and Clinical Excellence (NICE), 2010 [33]. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. NICE technology appraisal guidance 130	1) Rituximab in combination with MTX is recommended as an option for the treatment of adults with severe active RA who have had an inadequate response to, or are intolerant of, other DMARDs, including at least one TNF inhibitor. Treatment with rituximab should be given no more frequently than every 6 months. 2) Treatment with rituximab in combination with MTX should be continued only if there is an adequate response following initiation of therapy and if an adequate response is maintained following retreat-ment with a dosing interval of at least 6 months. An adequate response is defined as an improvement in DAS28 of 1.2 points or more. 3) Adalimumab, etanercept, infliximab and abatacept, each in combination with MTX, are recommended as treatment options only for adults with severe active RA who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an AE. 4) Adalimumab monotherapy and etanercept monotherapy are recommended as treatment options for adults with severe active RA who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to MTX, or when

	MTX is withdrawn because of an AE. 5) Treatment with adalimumab, etanercept, infliximab and abatacept should be continued only if there is an adequate response (as defined in 1.2) 6 months after initiation of therapy. Treatment should be monitored, with assessment of DAS28, at least every 6 months and continued only if an adequate response is maintained. 6) When using DAS28, healthcare professionals should take into account any physical, sensory or learning disabilities, communication difficulties, or disease characteristics that could adversely affect patient assessment and make any adjustments they consider appropriate. 7) A team experienced in the diagnosis and treatment of RA and working under the supervision of a rheumatologist should initiate, supervise and assess response to treatment with rituximab, adalimumab, etanercept, infliximab or abatacept.
National Institute for Health and Clinical Excellence (NICE), 2010 [34]. Certolizumab pegol for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 186	1) Certolizumab pegol is recommended as an option for the treatment of people with RA only if: • certolizumab pegol is used as described for other TNF inhibitor treatments in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 130) **and** • the manufacturer provides the first 12 weeks of certolizumab pegol (10 pre-loaded 200 mg syringes) free of charge to all patients starting treatment. 2) When using the DAS28 (as set out in NICE technology appraisal guidance 130), healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect a person's responses to the DAS28 and make any adjustments they consider appropriate.
National Institute for Health and Clinical Excellence (NICE), 2011 [35]. Golimumab for the treatment of methotrexate naive rheumatoid arthritis (terminated appraisal)	**Advice** NICE is unable to recommend the use in the NHS of golimumab for the treatment of methotrexate-naive RA because no evidence submission was received from the manufacturer or sponsor of the technology.
National Institute for Health and Clinical Excellence (NICE), 2011 [36]. Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs. NICE technology appraisal guidance 225	1) Golimumab in combination with methotrexate is recommended as an option for the treatment of RA in adults whose RA has responded in-adequately to conventional DMARDs only, including methotrexate, if: • it is used as described for other TNF inhibitor treatments in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 130), **and** • the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme. 2) Golimumab in combination with methotrexate is recommended as an option for the treatment of RA in adults whose RA has responded inadequately to other DMARDs, including a TNF inhibitor, if: • it is used as described for other TNF inhibitor treatments in 'Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor' (NICE technology appraisal guidance 195), **and** • the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme. 3) When using the DAS28, healthcare professionals should take into account any physical, sensory or learning disabilities, communication difficulties, or

	disease characteristics that could adversely affect patient assessment and make any adjustments they consider appropriate.
National Institute for Health and Clinical Excellence (NICE), 2012 [37]. Tocilizumab for the treatment of rheumatoid arthritis. NICE technology appraisal guidance 247	1) Tocilizumab in combination with methotrexate is recommended as an option for the treatment of RA in adults, if: • the disease has responded inadequately to DMARDs **and** it is used as described for TNF inhibitor treatments in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 130), specifically the recommendations on disease activity and choice of treatment **or** • the disease has responded inadequately to DMARDs and a TNF inhibitor and the person cannot receive rituximab because of a contraindication to rituximab, or because rituximab is withdrawn because of an AE, and tocilizumab is used as described for TNF inhibitor treatments in'Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of RA after the failure of a TNF inhibitor' (NICE technology appraisal guidance 195), specifically the recommendations on disease activity **or** • the disease has responded inadequately to one or more TNF inhibitor treatments and to rituximab **and** • the manufacturer provides tocilizumab with the discount agreed as part of the patient access scheme. 2) People currently receiving tocilizumab for the treatment of RA who do not meet the criteria in 1) should have the option to continue treat-ment until they and their clinicians consider it appropriate to stop.

Anlage 1

Patientenrelevante Endpunkte aus IQWiG 2013

Tabelle 15: Operationalisierung der Zielgrößen in den Einzelstudien

Patientenrelevante Endpunkte der Nutzenbewertung	Operationalisierung der Zielgrößen in den Studien[a]
Remission	▪ ACR 100 ▪ ACR Remission ▪ DAS 28 (CRP)[b] < 2,6, DAS 28 (BSG)[c] < 2,6 ▪ Pinals-Kriterien
Symptomatik der rheumatoiden Arthritis (insbesondere Schmerz, Fatigue, Morgensteifigkeit)	▪ schmerzhafte / empfindliche Gelenke[d] ▪ geschwollene Gelenke ▪ Schmerz (VAS) ▪ globale Erhebung der Krankheitsaktivität durch den Patienten ▪ allgemeiner Gesundheitszustand des Patienten (VAS) ▪ Morgensteifigkeit ▪ Fatigue (FACIT-F, VAS, FAS) ▪ Schlafqualität (MOS-Schlaf-Fragebogen)
Strukturelle Gelenkveränderungen (wie Deformitäten, Versteifungen, Kontrakturen)	Es konnten keine Zielgrößen der eingeschlossenen Studien diesem patientenrelevanten Endpunkt zugeordnet werden.
Körperlicher Funktionsstatus einschließlich Aktivitäten des täglichen Lebens	▪ HAQ ▪ HAQ-DI ▪ mHAQ ▪ MDHAQ
Soziales Funktionsniveau (Teilhabe am beruflichen und sozialen Leben)	▪ WPAI ▪ Fragen zum Arbeitsausfall, zur Arbeitsfähigkeit und zur Leistungsfähigkeit

Patientenrelevante Endpunkte der Nutzenbewertung	Operationalisierung der Zielgrößen in den Studien[a]
Gesundheitsbezogene Lebensqualität	▪ SF-36 ▪ SF-12 ▪ EQ-5D ▪ HUI
Gesamtmortalität	Todesfälle
Unerwünschte Arzneimittelwirkungen	▪ Gesamtrate unerwünschter Ereignisse ▪ Gesamtrate schwerwiegender unerwünschter Ereignisse ▪ Gesamtrate Studienabbrüche wegen unerwünschter Ereignisse ▪ Gesamtrate Infektionen ▪ Gesamtrate schwerwiegender Infektionen

a: Beschreibung der Instrument siehe Anhang E
b: DAS 28 unter Verwendung des Entzündungsparameters CRP. Im vorliegenden Bericht wird in den Ergebnistabellen vermerkt, welcher Entzündungsparameter verwendet wurde.
c: DAS 28 unter Verwendung des Entzündungsparameters BSG. Im vorliegenden Bericht wird in den Ergebnistabellen vermerkt, welcher Entzündungsparameter verwendet wurde.
d: im weiteren Verlauf des vorliegenden Berichts als „schmerzhaft“ benannt

ACR: American College of Rheumatology, DAS: Disease Activity Score, EQ-5D: EuroQol-5D, FACIT-F: Funtcional Assessment of Chronic Illness Therapy – Fatigue, FAS: Fatigue Assessment Scale, HAQ-DI: Health Assessment Questionnaire-Disability Index, HUI: Health Utility Index, mHAQ: modified Health Assessment Questionnaire, MDHAQ: multidimensionaler Health Assessment Questionnaire, MOS: Medical Outcomes Study, SF: Health Survey Short Form, VAS: visuelle Analogskala, WPAI: Work Productivity and Activity Impairment

Anlage 2

Evidenzklassifizierung aus *Bykerk 2012*

Table 2. Custom system for assigning level of evidence and strength of recommendation.

Levels of Evidence		Strength of Recommendation	
I	Metaanalyses, systematic reviews of RCT, or individual RCT	A	Strong recommendation: • Direct level I evidence
II	Metaanalysis, systematic reviews of observational studies (cohort/case control studies), or individual observational studies OR RCT subgroup/post-hoc analyses	B	Moderate recommendation: • Direct level II evidence or extrapolated level I evidence
III	Nonanalytic studies, e.g., case reports, case series	C	Weak recommendation • Direct level III evidence or extrapolated level II evidence
IV	Expert opinion	D	Consensus recommendation: • Expert opinion based on very limited evidence
NR	Recommendations are not linked to evidence		

RCT: randomized controlled trial; NR: not reported.

Anlage 3

Evidenzübersicht aus *National Collaborating Centre for Chronic Conditions 2009*

LoE	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

Anlage 4

Ergebnistabelle aus *Singh 2012*

Key Comparisons	Efficacy (Strength of Evidence)	Harms (Strength of Evidence)
Oral DMARD vs. Oral DMARD		
Leflunomide vs. MTX	No differences in ACR 20 or radiographic responses. **(Low)** No clinically significant difference for functional capacity. **(Low)** Greater improvement in health-related quality of life (SF-36 physical component) for leflunomide. **(Low)**	No consistent differences in tolerability and discontinuation rates. **(Low)** Mixed results for specific adverse events. **(Insufficient)**
Leflunomide vs. sulfasalazine	Mixed ACR response rates. **(Insufficient)** No differences in radiographic changes. **(Low)** Greater improvement in functional capacity for leflunomide. **(Low)**	No differences in tolerability and discontinuation rates. **(Low)** Mixed results for specific adverse events. **(Insufficient)**
Sulfasalazine vs. MTX	No differences in ACR 20 response, disease activity scores and radiographic changes.[a] **(Moderate)** No differences for functional capacity.[a] **(Moderate)**	No differences in tolerability; more patients stayed on MTX long term. **(Low)** Mixed results for specific adverse events. **(Insufficient)**
Oral DMARD Combinations vs. Oral DMARD		
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy	In patients with early RA, no differences in ACR 20 response rates or radiographic changes. **(Moderate)** No differences in functional capacity. **(Moderate)**	Withdrawal rates attributable to adverse events higher with combination. **(Low)** Insufficient evidence for specific adverse events. **(Insufficient)**
Oral DMARD plus prednisone vs. oral DMARD	Mixed results for disease activity. **(Insufficient)** Less radiographic progression in patients on DMARD plus prednisone. **(Low)** In patients with early RA, significantly lower radiographic progression and fewer eroded joints. **(Low)** Greater improvement in functional capacity for one oral DMARD plus prednisolone than for oral DMARD monotherapy. **(Moderate)** No difference in quality of life. **(Low)**	No differences in discontinuation rates; addition of corticosteroid may increase time to discontinuation of treatment. **(Moderate)** No differences in specific adverse events, except addition of corticosteroid may increase woundhealing complications. **(Low)**
Biologic DMARDs vs. Biologic DMARDs		
Abatacept vs. Infliximab	Greater improvement in disease activity for abatacept, but no difference in remission or functional capacity. Statistically significant difference between groups for quality of life (SF-36 PCS) that did not reach the minimal clinically important difference. **(Low)**	Discontinuation rates and severe adverse events higher with infliximab. **(Low)**
Biologic vs. biologic (*Mixed treatment comparisons*)	No significant differences in disease activity (ACR 50) in MTC analyses between abatacept, adalimumab, golimumab, infliximab, rituximab, and tocilizumab in patients resistant to MTX. **(Low)** Less improvement in disease activity (ACR 50) for anakinra compared with etanercept and compared with adalimumab in MTC analyses in patients resistant to MTX. Comparisons with abatacept, golimumab, infliximab, rituximab, and tocilizumab did not reach statistical significance. **(Low)** Greater improvement in disease activity (ACR 50) for etanercept compared with abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab in MTC analyses. No significant differences when compared with golimumab. **(Low)**	Adjusted indirect comparisons found a more favorable withdrawal profile for certolizumab pegol than other biologic DMARDs. Also, etanercept and rituximab had a more favorable overall withdrawal profile than some other biologic DMARDs. Certolizumab pegol had fewer withdrawals due to lack of efficacy than adalimumab, anakinra, and infliximab. All but adalimumab, golimumab, and infliximab had fewer withdrawals than anakinra due to lack of efficacy. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab. **(Low)** Risk for injection site reactions apparently highest with anakinra. **(Low)** Mixed results for specific adverse events. **(Insufficient)**
Anti-tumor necrosis factor drugs vs. MTX	In patients with early RA, no clinically significant differences in clinical response between adalimumab or etanercept and MTX; in patients on biologic DMARDs, better radiographic outcomes than in patients on oral DMARDs. **(Moderate)** No difference in functional capacity between adalimumab and MTX for MTX-naive subjects with early RA; mixed results for etanercept vs. MTX. **(Low; Insufficient)** Faster improvement in quality of life with etanercept than MTX. **(Low)**	No differences in adverse events in efficacy studies. **(Low)** Insufficient evidence on differences in the risk for rare but severe adverse events. **(Insufficient)**
Biologic DMARD plus biologic DMARD vs. biologic DMARD	No additional benefit in disease activity or functional capacity from combination of etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy, but greater improvement in quality of life with etanercept plus abatacept vs. etanercept. **(Low)**	Substantially higher rates of serious adverse events from combination of 2 biologic DMARDs than from monotherapy. **(Moderate)**

Key Comparisons	Efficacy (Strength of Evidence)	Harms (Strength of Evidence)
Biologic DMARDs plus MTX vs. biologic DMARDs	Better improvements in disease activity from combination therapy of biologic DMARDs (adalimumab, etanercept, infliximab, rituximab) plus MTX than from monotherapy with biologics. **(Moderate)** In MTX-naive patients with early aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression in the combination therapy group. **(Low)** In MTX-naive subjects or those not recently on MTX, greater improvement in functional capacity **(Moderate)** and quality of life. **(Low)** In subjects with active RA despite treatment with MTX, no difference in functional capacity or quality of life. **(Low)**	No differences in adverse events in efficacy studies. **(Low)** Insufficient evidence on differences in the risk for rare but severe adverse events. **(Insufficient)**
Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs	No difference in clinical response rates, functional capacity, and quality of life between etanercept plus sulfasalazine and etanercept monotherapy. **(Low)**	No differences in adverse events in efficacy studies. **(Low)** Insufficient evidence on differences in the risk for rare but severe adverse events. **(Insufficient)**
Biologic DMARD plus MTX vs. MTX	Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARDs and MTX than from MTX monotherapy. **(High)** for clinical response and functional capacity, **(Moderate)** for quality of life.	Better tolerability profile for MTX plus abatacept, adalimumab, certolizumab, etanercept, and rituximab than for MTX monotherapy from metaanalysis. **(Low)** Mixed evidence on differences in the risk for rare but severe adverse events. **(Insufficient)**
Strategies in Early RA		
2 oral DMARDs plus prednisone vs. oral DMARD	In patients on 2 oral DMARDs, improved ACR 50 response rates, disease activity scores, but no difference at 56 weeks. **(Low)** In patients with early RA, significantly lower radiographic progression and fewer eroded joints at 56 weeks. **(Low)** More rapid improvement in functional capacity by 28 weeks but no differences by 56 weeks. **(Low)**	No differences in discontinuation rates. **(Moderate)**
3 oral DMARDs plus prednisone vs. one oral DMARD	In patients on 3 oral DMARDs, improved ACR 50 response rates, disease activity scores, and less work disability. **(Low)** In patients with early RA, significantly lower radiographic progression and fewer eroded joints. **(Low)**	No differences in discontinuation rates. **(Moderate)**
Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered high-dose prednisone vs. combination with infliximab	Less radiographic progression, lower disease activity scores, and better functional ability and health-related quality of life from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy. However no differences between groups for functional ability and quality of life by 2 years and no difference in remission at 4 years. **(Low)**	No differences in serious adverse events between groups. **(Low)**

Source: Table A in Donahue KE, Jonas DE, Hansen RA, et al. Comparative effectiveness of drug therapy for rheumatoid arthritis in adults – an update. AHRQ Comparative effectiveness review No. 55. April 2012.[7]

[a]At MTX doses ranging from 7.5-25 mg per week.

Anlage 5

Therapiekaskaden (Abbildung aus *Singh 2012*)

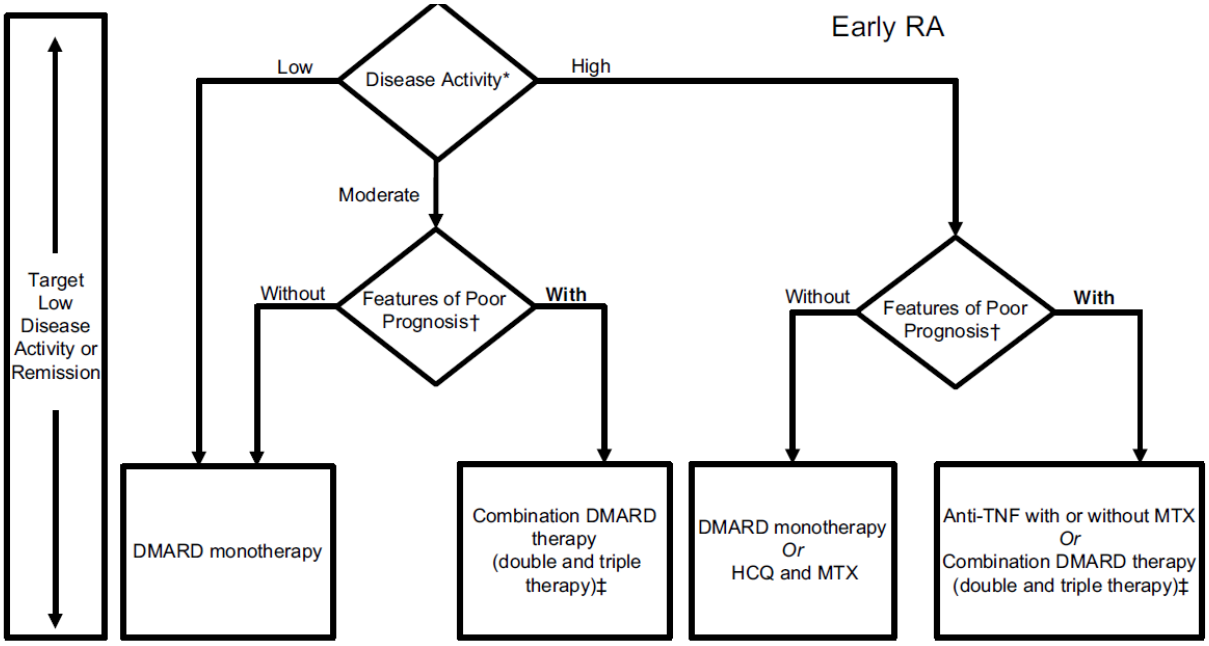


Figure 1. 2012 American College of Rheumatology recommendations update for the treatment of early rheumatoid arthritis (RA), defined as a disease duration <6 months. For the level of evidence supporting each recommendation, please see Supplementary Appendix 7 (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658). DMARD = disease-modifying antirheumatic drug (includes hydroxychloroquine [HCQ], leflunomide [LEF], methotrexate [MTX], minocycline, and sulfasalazine); anti-TNF = anti–tumor necrosis factor.

* Definitions of disease activity are discussed in Tables 2 and 3 and Supplementary Appendix 4 (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658) and were categorized as low, moderate, or high.

† Patients were categorized based on the presence or absence of 1 or more of the following poor prognostic features: functional limitation (e.g., Health Assessment Questionnaire score or similar valid tools), extraarticular disease (e.g., presence of rheumatoid nodules, RA vasculitis, Felty's syndrome), positive rheumatoid factor or anti–cyclic citrullinated peptide antibodies (33–37), and bony erosions by radiograph (38).

‡ Combination DMARD therapy with 2 DMARDs, which is most commonly MTX based, with some exceptions (e.g., MTX + HCQ, MTX + LEF, MTX + sulfasalazine, and sulfasalazine + HCQ), and triple therapy (MTX + HCQ + sulfasalazine) as defined in Table 2.

Anlage 6

Michaud et al. 2015: Übersicht der Ergebnisse bisheriger MA zur Sicherheit von TNF-Inhibitoren

Table 3 Summary of Previous Meta-Analyses on Serious Adverse Events Associated with Use of Biologics in Rheumatoid Arthritis

Author, Year	Interventions	Included Studies, N	Total Subjects	Study Design	Minimum Duration	SAE (Overall)	Malignancy	Serious Infection	Discontinuation due to AEs
Bongartz, 2006[2]	ADA, INF	9	5,005	RCT	> 12 wks	NA	↑ (RR=3.3)	↑(RR=2.0)	NA
Chen (NICE) , 2006[73]	ADA, ETN, INF	29	9,869	RCT	NA	↔	↔	↔ (overall) ↑ (INF)	↔ (overall) ↑ (INF)
Alonso-Ruiz, 2008[74]	ADA, ETN, INF	13	7,087	RCT	> 24 wks	↔	↔	↔ (overall) ↑ (INF)	↔ (overall) ↑ (ADA, INF) ↓ (ETN)
Bongartz, 2009[75]	ETN	9	3,316	RCT	> 12 wks	NA	↔	NA	NA
Leombruno, 2009[3]	ADA, ETN, INF	23 papers (18 RCTs)	8,808	RCT	> 10 wks	↔	↔	↔ (overall) ↑ (high dose 2x)	NA
Singh, 2009[76]	ADA, ETN, INF, ABT, ANK, RTX	31	NA	RCT	NA	NA	NA	NA	↔ (overall) ↑ (ADA, INF)
Wiens, 2009[77]	ETN	8	2,385	RCT	NA	↔	↔	↔	↔
Wiens, 2009[78]	INF	7	2,129	RCT	NA	↔	↔	↔	↑
Singh (CR), 2010[79]	GLM	4	1,714	RCT/ CCT	NA	↔	↔	↔	↔
Wiens, 2010[80]	ADA, ETN, INF	21	6,503	RCT	NA	↔	↔	↔	↔ (overall) ↑ (ADA, INF)
Askling, 2011[81]	ADA, ETN, INF	74	22,904	RCT	> 4 wks	NA	↔ (overall) ↑ (skin cancer)	NA	NA
Ruiz Garcia (CR), 2011[82]	CZP	5	2,094	RCT	NA	↑ (RR=2.02)	↔	↑ (RR>3)	↑ (RR=1.93)
Singh (CR), 2011*[5]	9 biologics†	160 RCTs, 46 OLEs	60,630	RCT, CCT, OLE	NA	↔	↔	↑ (OR = 1.55 in RA)	↔
Thompson, 2011[4]	ADA, CZP, ETN, GLM, INF	6 (early RA)	3,419	RCT	> 24 wks	NA	↔	↔	NA
Aaltonen, 2012[6]	ADA, CZP, ETN, GLM, INF	40 papers (26 RCTs)	9,862	RCT	NA	↔ (overall) ↑ (CZP)	NA	↔	↔ (overall) ↑ (ADA, CZP, INF) ↓ (ETN, RR = 0.71 compared with control)
Lopez-Olivo, 2012*[7]	9 biologics†	63	29,423	RCT	> 24 wks	NA	↔	NA	NA
Lethaby (CR), 2013[83]	ETN	9	2,842	RCT/CCTs	> 24 wks	↔	↔	↔	↓ (RR=0.53 for ETN + DMARDs vs. DMARD)
Current Study	**ADA, CZP, ETN, GLM, INF**	**44 papers (38 RCTs)**	**17,601**	**RCT**	**> 12 weeks**	**↔ ↑ (CZP)**	**↔**	**↑ (overall) ↑ (ADA, CZP, INF)**	**↑ (overall) ↑ (ADA, CZP, INF) ↓ (ETN, OR = 0.72)**

ADA = adalimumab; CZP = certolizumb pegol; ETN = etanercept; INF = infliximab; GLM = golimumab; ABT = abatacept; ANK = anakinra; RTX = rituximab; TCZ = tocilizumab; MTX = methotrexate; DMARD = disease-modifying antirheumatic drug; RR = relative risk; RD = risk difference; RCT = randomized controlled trial; CCT = controlled Clinical trial; OLE = open-label extension; SAE = serious adverse event; AEs = adverse events; NE = not estimable; NICE = National Institute for Clinical Excellence; CR = Cochrane Reviews.

*The results are based on all indications of the 9 biologics invested in that study, unless marked otherwise.

†ADA, CZP, ETN, GLM, INF, ABT, ANK, RTX and TCZ.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 09.10.2015**

#	Suchfrage
1	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
2	(rheumatoid arthritis):ti (Word variations have been searched)
3	#1 or #2
4	#3 Publication Year from 2010 to 2015

SR, HTAs in Medline (PubMed) am 08.10.2015

#	Suchfrage
1	"arthritis, rheumatoid/therapy"[MeSH Terms]
2	rheumatoid arthritis[Title]
3	((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR treat*[Title/Abstract]
4	(#2 AND #3)
5	(#1 OR #4)
6	(#5) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
7	(#5) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
8	(#6 OR #7)
9	(#8) AND ("2010/10/01"[PDAT] : "2015/10/08"[PDAT])

Leitlinien in Medline (PubMed) am 08.10.2015

#	Suchfrage
1	arthritis, rheumatoid[MeSH Terms]
2	rheumatoid arthritis[Title]
3	(#1 OR #2)
4	((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]
5	(#3 AND #4)
6	(#5) AND ("2010/10/01"[PDAT] : "2015/10/08"[PDAT])

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