Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2016-B-143 Ocrelizumab

Datum: 15.11.2016

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß § 6 5. Kapitel VerfO G-BA	
OCRELIZUMAB zur Behandlung von erwachsenen Patienten mit Multipler Sklerose (RMS)	
Kriterien gemäß 5. Kapitel § 6 Absatz 3 Satz 2 VerfO	
1. Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Alemtuzumab: RRMS Azathioprin: RMS Dimethylfumarat: RRMS Daclizumab Fingolimod Glatiramerazetat: RRMS+ CIS Glucocorticoide: (nicht angezeigt; Akuttherapie bei Schub) Interferon beta-1a: RMS+ KIS und SPMS+Schubaktivität (Rebif®) Interferon beta-1b: RMS und SPMS+Schubaktivität Natalizumab: RRMS Mitoxantronhydrochlorid: SPMS mit und ohne Schubaktivität Teriflunomid: RRMS
2. Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Plasmapherese bei Multiplen Sklerose: nicht anerkannt 24.03.2003
3. Als Vergleichstherapie sollen bevorzugt Arzneimittel-anwendungen oder nicht-medikamentöse Behandlungen herangezogen werden, deren patientenrelevanter Nutzen durch den Gemeinsamen Bundesausschuss bereits festgestellt ist.	- Plasmapherese bei Multiplen Sklerose: nicht anerkannt 24.03.2003 - Azathioprin: Arzneimittelrichtlinie Anlage IV; Therapiehinweis vom 24.August.2001 - Natalizumab: Arzneimittelrichtlinie Anlage IV; Therapiehinweis vom 10. April 2009 - Alemtuzumab: Arzneimittelrichtlinie Anlage IV; Therapiehinweis vom 15. September 2016 - Extrakt aus Cannabis Sativa: Beschluss nach § 35a SGB V vom 21. Juni 2012 - Fampridin: Beschluss nach § 35a SGB V vom 02. August 2012 - Teriflunomid: Beschluss nach § 35a SGB V vom 20. März 2014 - Dimethylfumarat: Beschluss nach § 35a SGB V vom 16. Oktober 2014 - Fingolimod: Beschluss nach § 35a SGB V vom 1. Oktober 2015, 19. Mai 2016
4. 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 Beratungsanfrage)
Zu bewertendes Arzneimittel:	
Ocrelizumab	- Ocrelizumab ist angezeigt zur Behandlung von erwachsenen Patienten mit schubförmiger Multipler Sklerose (RMS) (siehe Abschnitt 5.1).
Azathioprin L04AX01 Imurek® und Generika	Imurek® ist angezeigt bei schubförmiger Multipler Sklerose, wenn eine immunmodulatorische Therapie angezeigt und eine Therapie mit Beta-Interferonen nicht möglich ist, oder unter einer bisherigen Therapie mit Azathioprin ein stabiler Verlauf erreicht wurde.
Alemtuzumab LEMTRADA®	LEMTRADA ist angezeigt zur Behandlung von erwachsenen Patienten mit schubförmig-remittierender Multipler Sklerose (RRMS) mit aktiver Erkrankung, definiert durch klinischen Befund oder Bildgebung (siehe Abschnitte 4.4 und 5.1)
Dimethylfumarat N07XX09 Tecfidera®	Tecfidera® wird zur Behandlung von erwachsenen Patienten mit schubförmig remittierender Multipler Sklerose angewendet (siehe Abschnitt 5.1 für wichtige Informationen über die Populationen, für die eine Wirksamkeit bestätigt wurde).
Fingolimod L04AA27 Gilenya®	Gilenya ist als krankheitsmodifizierende Monotherapie von hochaktiver schubförmig-remittierend verlaufender Multipler Sklerose bei folgenden Gruppen erwachsener Patienten angezeigt: – Patienten mit hochaktiver Erkrankung trotz Behandlung mit einem vollständigen und angemessenen Zyklus mit mindestens einer krankheitsmodifizierenden Therapie (Ausnahmen und Informationen zu Auswaschphasen siehe Abschnitte 4.4 und 5.1). oder – Patienten mit rasch fortschreitender schwerer schubförmig-remittierend verlaufender Multipler Sklerose, definiert durch zwei oder mehr Schübe mit Behinderungsprogression in einem Jahr, und mit einer oder mehr Gadolinium anreichernden Läsionen im MRT des Gehirns oder mit einer signifikanten Erhöhung der T2-Läsionen im Vergleich zu einer kürzlich durchgeführten MRT..(2016 Januar)
Glatiramer acetate® L03AX13,	Copaxone® ist angezeigt zur Behandlung von Patienten mit einer klar definierten ersten klinischen Episode und einem hohen Risiko, eine klinisch gesicherte Multiple Sklerose („clinically definite multiple sclerosis“, CDMS) zu entwickeln (siehe Abschnitt 5.1). Copaxone ist angezeigt zur Reduktion der Schubfrequenz bei ambulanten Patienten (d. h. solche, die ohne Hilfe gehfähig

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Copaxone ®	sind) mit schubförmig remittierender Multipler Sklerose (MS). In klinischen Studien war dies gekennzeichnet durch mindestens zwei Schübe mit neurologischen Funktionsstörungen während der letzten 2 Jahre (siehe Abschnitt 5.1). Copaxone ist nicht indiziert bei primär oder sekundär progredienter MS.
Glucocorticoide z.B.: Prednisolon H02AB06 Decortin®	Multiple Sklerose (zum oralen Ausschleichen nach hochdosierter parenteraler Glucocorticoidgabe im Rahmen eines akuten Schubes).
Interferon beta-1a , L03AB07 Avonex®	AVONEX® ist indiziert für die Behandlung von Patienten mit schubförmiger Multipler Sklerose (MS).In klinischen Studien war diese durch mindestens zwei akut auftretende Exazerbationen (Schübe) während der letzten drei Jahre gekennzeichnet ohne Hinweise auf ein kontinuierliches Fortschreiten der Erkrankung zwischen den Schüben. AVONEX verlangsamt das Fortschreiten der Behinderung und verringert die Häufigkeit von Schüben. Patienten nach einem einmaligen demyelinisierenden Ereignis mit entzündlichem Prozess, wenn dieses demyelinisierende Ereignis eine intravenöse Kortikosteroidtherapie rechtfertigt, alternative Diagnosen ausgeschlossen wurden und ein hohes Risiko für die Entwicklung einer klinisch sicheren Multiplen Sklerose besteht (siehe Abschnitt 5.1). AVONEX ist bei Patienten, die eine progrediente Form der MS entwickeln, abzusetzen.
Interferon beta-1a, L03AB07 Rebif®	Rebifi® wird zur Behandlung von Patienten mit schubförmiger Multipler Sklerose verwendet. In klinischen Studien wurde dies durch zwei oder mehr akute Schübe innerhalb der vorausgegangenen zwei Jahre charakterisiert (siehe Abschnitt 5.1). Bei Patienten mit sekundär progredienter Multipler Sklerose ohne vorhandene Schubaktivität konnte eine Wirksamkeit nicht nachgewiesen werden (siehe Abschnitt 5.1).
Interferon beta-1b 1 L03AB08 Betaferon®	Betaferon® ist indiziert zur Behandlung von - Patientenmit erstmaligem demyelisierendem Ereignis mit aktivem entzündlichem Prozess, wenn dieses Ereignis schwer genug ist, um eine intravenöse Kortikosteroidtherapie zu rechtfertigen, wenn mögliche Differentialdiagnosen ausgeschlossen wurden und wenn bei diesen Patienten der Beurteilung zufolge ein hohes Risiko für das Auftreten einer klinisch gesicherten Multiplen Sklerose besteht (siehe Abschnitt 5.1). -Patienten mit schubweise verlaufender Multipler Sklerose, die in den letzten zwei Jahren zwei oder mehr Schübe durchgemacht haben. - Patienten mit sekundär progredient verlaufender Multipler Sklerose, die sich in einem akuten Krankheitsstadium befinden, d.h. klinische Schübe erfahren.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Interferon beta-1b 1 L03AB08 Extavia®	Extavia® ist indiziert zur Behandlung von: • Patientenmit erstmaligem demyelisierendem Ereignis mit aktivem entzündlichem Prozess, wenn dieses Ereignis schwer genug ist, um eine intravenöse Kortikosteroidtherapie zu rechtfertigen, wenn mögliche Differenzialdiagnosen ausgeschlossen wurden und wenn bei diesen Patienten der Beurteilung zufolge ein hohes Risiko für das Auftreten einer klinisch gesicherten Multiplen Sklerose besteht (siehe Abschnitt 5.1). • Patienten mit schubweise verlaufender Multipler Sklerose, die in den letzten zwei Jahren zwei oder mehr Schübe durchgemacht haben. • Patienten mit sekundär progredient verlaufender Multipler Sklerose, die sich in einem akuten Krankheitsstadium befinden, d. h. klinische Schübe erfahren.
Mitoxantronhydrochlorid L01DB07 Ralenova®	Ralenova® ist indiziert für die Behandlung von nicht-rollstuhlpflichtigen Patienten mit sekundär-progredienter oder progressiv-schubförmiger Multipler Sklerose mit einem EDSS von 3 bis einschließlich 6 mit und ohne überlagernden Schüben bei Versagen oder Unverträglichkeit einer Vortherapie mit Immunmodulatoren, die sich in einem aktiven Krankheitsstadium, definiert durch zwei Schübe oder eine EDSS-Verschlechterung um mindestens einen Punkt in 18 Monaten, befinden. Anmerkung: ,,EDSS‘‘ (Kurtzke Expanded Disability Status Scale) ist eine multifaktorielle Bewertungsmethode, bei der die Beeinträchtigungen verschiedener neurologischer Funktionssysteme wie z. B. Sehen, Blase, Hirnstamm bewertet werden.
Natalizumab L04AA23 TYSABRI®	TYSABRI® ist für die krankheitsmodifizierende Monotherapie von hochaktiver, schubförmig remittierend verlaufender Multipler Sklerose (MS) bei folgenden Patientengruppen indiziert: - Patienten mit hoher Krankheitsaktivität trotz Behandlung mit einem Interferon beta, definiert als Patienten, die nicht auf einen vollständigen und angemessenen (normalerweise mindestens ein Jahr dauernden) Zyklus einer Interferon-beta Therapie angesprochen haben. Bei den Patienten sollte es während der Therapie im vorangegangenen Jahr zu mindestens einem Schub gekommen sein und sie sollten mindestens 9 T2-hyperintense Läsionen in der kranialen MRT oder mindestens 1 Gadolinium anreichernde Läsion aufweisen. Ein „Non-Responder“ ist zu definieren als ein Patient mit einer im Vergleich zum Vorjahr unveränderten oder vermehrten Schubrate oder anhaltend schweren Schüben. oder - Patienten mit rasch fortschreitender schubförmig remittierend verlaufender Multipler Sklerose, definiert durch 2 oder mehr Schübe mit Behinderungsprogression in einem Jahr, und mit 1 oder mehr Gadolinium anreichernden Läsionen in der MRT des Gehirns oder mit einer signifikanten Erhöhung der T2-Läsionen im Vergleich zu einer kürzlich durchgeführten MRT.
Teriflunomid AUBAGIO® L04AA31	AUBAGIO ist zur Behandlung erwachsener Patienten mit schubförmig-remittierender Multipler Sklerose (MS) angezeigt. Siehe Abschnitt 5.1 für weitere Informationen über die Patienten, bei denen die Wirksamkeit nachgewiesen wurde

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Daclizumab Zinbryta® L04AC01	Zinbryta wird zur Behandlung von erwachsenen Patienten mit schubförmiger Multipler Sklerose (RMS) angewendet (siehe Abschnitt 5.1). *(2016-07)*
Stand November 2016	
Zu bewertendes Arzneimittel:	
Ocrelizumab	- angezeigt zur Behandlung erwachsener Patienten mit früher primär progredienter Multipler Sklerose (PPMS)
zugelassene Arzneimittel	
für die primäre progrediente MS sind keine Arzeneimittel zugelassen	
Stand November 2016	

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

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation Multiple Sklerose durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 12.10.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 850 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 32 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Behandlung von erwachsenen Patienten mit schubförmiger multipler Sklerose

Berücksichtigte Wirkstoffe/Therapien:

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

Abkürzungen:

AE	adverse event
ARR	Annual relapse rate
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BID	twice daily
CoI	Conflict of interest
DAHTA	Deutsche Agentur für Health Technology Assessment
EDSS	Expanded Disability Status Scale
GA	Glatirameracetat
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HD	High dose
IFN-β	Beta-Interferone
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LD	Low dose
mcg	Mikrogramm
MS	Multiple Sklerose
NGC	National Guideline Clearinghouse
NHS	National Health System
NICE	National Institute for Health and Care Excellence
NIHR HSC	National Institute for Health Research Horizon Scanning Centre
ns	nicht signifikant (statistisch)
NTZ	Natalizumab
NTZ	Natalizumab
PRMS	progressive relapsing MS
pU	pharmazeutischer Unternehmer
Quality of Life	QoL
RRMS	Schubförmig verlaufende MS („relapsing-remitting“, RRMS),
RTI	respiratory tract infection
SF-36	Short Form-36
SPMS	secondary progressive MS

IQWiG-Berichte/G-BA-Beschlüsse

GBA, 2014 [10] und IQWIG, 2013 [20] Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Teriflunomid	Stand: 20. März 2014 **Zugelassenes Anwendungsgebiet** von Teriflunomid (Aubagio®) gemäß Fachinformation: AUBAGIO ist zur Behandlung erwachsener Patienten mit schubförmig-remittierender Multipler Sklerose (MS) angezeigt. **Zweckmäßige Vergleichstherapie** Die zweckmäßige Vergleichstherapie für die Behandlung von erwachsenen Patienten mit schubförmig-remittierender Multipler Sklerose (MS) ist Beta-Interferon (IFN ß) 1a oder IFN ß-1b oder Glatirameracetat unter Beachtung des jeweils zugelassenen Anwendungsgebietes. **Wahrscheinlichkeit und Ausmaß des Zusatznutzens** Der G-BA stuft den Zusatznutzen von Teriflunomid für Patienten mit schubförmig-remittierender MS auf Basis der Kriterien in § 5 Absatz 7 der AM-NutzenV unter Berücksichtigung des Schweregrades der Erkrankung und des therapeutischen Ziels bei der Behandlung der Erkrankung als nicht belegt ein.
GBA, 2014 [8] **GBA, 2016 [12]** **IQWIG, 2014 [15,16]** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Dimethylfumarat	Stand: 16. Oktober 2014 **Zugelassenes Anwendungsgebiet** von Dimethylfumarat (Tecfidera®) gemäß Fachinformation: Tecfidera wird zur Behandlung von erwachsenen Patienten mit schubförmig remittierender Multipler Sklerose (RRMS) angewendet. **Zweckmäßige Vergleichstherapie**: Die zweckmäßige Vergleichstherapie für Dimethylfumarat zur Behandlung von Patienten mit schubförmig remittierender Multiplen Sklerose (RRMS) ist: Interferon beta-1a oder Interferon beta-1b oder Glatirameracetat. **Wahrscheinlichkeit und Ausmaß des Zusatznutzens** Ein Zusatznutzen gegenüber Interferon beta-1a ist nicht belegt. **Beschluss vom 07.01.2016:** Um hämatologische Veränderungen rechtzeitig zu identifizieren, die das Risiko für opportunistische Infektionen und insbesondere die progressive multifokale Leukenzephalopathie (PML) erhöhen, sollte unmittelbar vor Beginn der Behandlung mit Dimethylfumarat das Blutbild (einschließlich des Differentialblutbildes sowie der Blutplättchenzahl) kontrolliert werden. Nach Beginn der Behandlung sollten die Kontrollen im 6 bis 8 wöchigem Abstand erfolgen.
G-BA, 2008 [11] Beschluss über eine Änderung der Arzneimittel-Richtlinie in Anlage 4: Therapiehinweis zu Natalizumab	**Fazit:** *Wirksamkeit* • Für die Zulassung wurde die Wirksamkeit und Sicherheit von Natalizumab in zwei großen multizentrischen randomisierten kontrollierten doppelblinden Phase-III-Studien geprüft. In beiden Studien wurden Patienten mit schubförmig verlaufender MS aufgenommen, die mindestens einen Schub im Jahr zuvor erlebt hatten. Die Diagnose einer MS war nach den Kriterien von Mc Donald et al. gesichert. Im MRT lagen mit einer MS vereinbare

	radiologische Veränderungen vor. Weitere Einschlusskriterien waren ein Alter zwischen 18 und 55 Jahren und ein Score von 0 – 5 auf der „Expanded Disability Status Scale“ (EDSS). Ausschluss-kriterien waren eine immunsuppressive Therapie innerhalb der letzten sechs Monate, ein entzündlicher Schub oder Gabe von Glucosteroiden in den letzten 50 Tagen sowie eine primär oder sekundär progressive Verlaufsform der MS. • Bei der AFFIRM-Studie (Polman et al.) handelte es sich um eine Natalizumab-Monotherapie-Studie mit Patienten, die innerhalb der letzten sechs Monate nicht mit Interferonen behandelt worden waren und auch insgesamt nicht länger als sechs Monate Interferone erhalten hatten. Die Patienten wurden im Verhältnis 2:1 randomisiert den Behandlungsarmen mit Natalizumab 300 mg (n = 627) bzw. Placebo (n = 315) alle vier Wochen zugeteilt. • Primäre Endpunkte waren die Schubrate nach einem Jahr und die Progression der Behinderung nach zwei Jahren, definiert als eine für mindestens 12 Wochen anhaltende Erhöhung um mindestens 1,0 auf der EDSS bei einem Ausgangs-EDSS >=1,0 oder eine Erhöhung um mindestens 1,5 auf der EDSS bei einem Ausgangs-EDSS = 0. Sekundäre Endpunkte waren der Anteil schubfreier Patienten sowie radiologische Veränderungen in der MRT. • Nach einem Jahr reduzierte sich die Schubrate unter Natalizumab signifikant auf 0,26 gegenüber 0,81 unter Placebo entsprechend einer relativen Risikoreduktion um 68 %. Diese Verminderung der Schubrate setzte sich im zweiten Behandlungsjahr fort. • Nach zwei Jahren sank das Risiko einer Progression der Behinderung signifikant um 12 %. Während es unter Placebo bei 29 % der Patienten zu einer Progression kam, waren es unter Natalizumab nur 17 %. Dies entspricht einer Number Needed to Treat (NNT) von 9 und einer relativen Risikoreduktion von 42 %. • Der Anteil schubfreier Patienten betrug unter Placebo 41 % und unter Natalizumab 67 %. Unter Natalizumab zeigten im MRT 97 % der Patienten keine Gadolinium-anreichernden Läsionen, unter Placebo waren es 72 %. Das Ausbleiben neuer hyperintenser T2-Läsionen wurde bei 57 % der Patienten unter Natalizumab und bei 15 % unter Placebo beobachtet. • Post-hoc-Subgruppenanalysen ergaben in der kleinen Gruppe von Patienten mit weniger als neun hyperintensen T2-Läsionen keine Veränderung der Progression der Behinderung. • In der Subgruppe von Patienten mit hochaktiver schubförmig remittierender MS, definiert durch mindestens zwei Schübe im vorangegangen Jahr und mindestens eine Gadolinium-gegenüber 1,5 (n=61) unter Placebo. Die relative Risikoreduktion für eine Behinderungs-progression betrug 64 %. • Die EMEA bewertet das Vorgehen einer nachträglichen Subgruppenanalyse durchaus kritisch. Der Therapieeffekt in der Subgruppe der Patienten mit hochaktiver schubförmig remittierender MS wurde jedoch als so hoch eingeschätzt, dass für diese Patientengruppe eine Zulassung auch ohne Vortherapie mit Immunmodulatoren erging. • Bei der SENTINEL-Studie (Rudick et al.) handelte es sich um eine Kombinationstherapie-Studie, in der Patienten, die trotz einer Behandlung mit Interferon Beta mindestens einen Schub im vorangegangenen Jahr erlitten hatten, zusätzlich Natalizumab erhielten. Hierunter traten zwei Fälle einer PML auf, sodass aus Sicherheitsgründen eine Zulassung für diese Kombination nicht erfolgte. Die Studie hatte die gleichen Endpunkte wie die AFFIRM

	Studie. • Das Risiko einer Behinderungsprogression wurde nach zwei Jahren ebenfalls signifikant – jedoch weniger stark – um 6 % gesenkt. Während es unter Monotherapie mit Interferon Beta bei 29 % der Patienten zu einer Progression kam, waren es unter Natalizumab in Kombination mit Interferon Beta nur 23 %. Dies entspricht einer NNT von 17 und einer relativen Risiko-reduktion von 24 %. • Nach Einschätzung der EMEA ist der Anteil, den Natalizumab an diesem Ergebnis hat, nicht bestimmbar, da ein Natalizumab-Monotherapiearm in der Studie fehlte. Dennoch war dieses Studienergebnis Grundlage der Zulassung als Monotherapie für Patienten mit nur einem Schub im vorangegangen Jahr unter Interferontherapie. *Empfehlungen zur wirtschaftlichen Verordnungsweise* • Es sollten deshalb nur solche Patienten mit Natalizumab behandelt werden, bei denen Kontraindikationen oder Unverträglichkeiten für Interferon (IFN) beta oder/und Glatirameracetat bestehen oder die im Verlauf eines Jahres auf Interferon Beta oder/und Glatirameracetat nicht ausreichend angesprochen haben und die für eine Eskalationstherapie mit Mitoxantron unter Berücksichtigung seiner Zulassung und Risiken nicht geeignet sind.
G-BA, 2016 [9] **IQWiG, 2015, 2016 [17,18,19]** Beschluss über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a des Fünften Buches Sozialgesetzbuch (SGB V) Fingolimod vom 29. März 2012	**Zugelassenes Anwendungsgebiet:** • Patienten mit rasch fortschreitender schwerer schubförmig-remittierend verlaufender Multipler Sklerose, definiert durch zwei oder mehr Schübe mit Behinderungsprogression in einem Jahr, und mit einer oder mehr Gadolinium anreichernden Läsionen im MRT des Gehirns oder mit einer signifikanten Erhöhung der T2-Läsionen im Vergleich zu einer kürzlich durchgeführten MRT • Gilenya ist als krankheitsmodifizierende Monotherapie von hochaktiver schubförmig-remittierend verlaufender Multipler Sklerose bei folgenden Gruppen erwachsener Patienten angezeigt: • Patienten mit hochaktiver Erkrankung trotz Behandlung mit einem vollständigen und angemessenen Zyklus mit mindestens einer krankheitsmodifizierenden Therapie (Ausnahmen und Informationen zu Auswaschphasen siehe Abschnitte 4.4 und 5.1 der Fachinformation). **Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** Patienten mit hochaktiver RRMS, die nicht auf einen vollständigen und angemessenen Zyklus mit mindestens einer krankheitsmodifizierenden Therapie angesprochen haben, a) für die in einer patientenindividuellen Bewertung unter Berücksichtigung der klinischen Gesamtsituation, insbesondere der Schwere der Schübe, eine Umstellung in Abhängigkeit von der Vortherapie oder ggf. eine Fortführung bzw. Anpassung der vorangegangenen Therapie in Frage kommt:

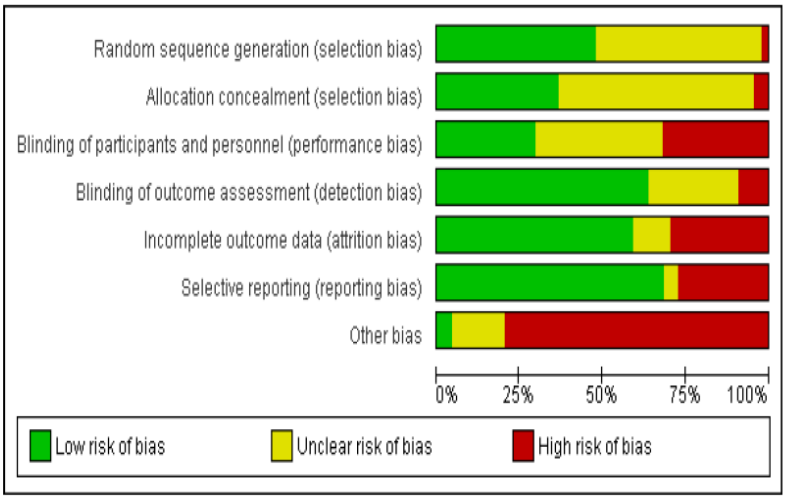
	Zweckmäßige Vergleichstherapie: • Glatirameracetat oder Interferon-beta (IFN-β) 1a oder 1b, Umstellung in Abhängigkeit von der Vortherapie, ggf. Fortführung bzw. Anpassung der vorangegangenen Therapie **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber IFN-β 1a:** Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [7]
Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage IV – Therapiehinweis Alemtuzumab, vom 15. September 2016
	Empfehlungen zur wirtschaftlichen Verordnungsweise
	• Direkte, aktiv kontrollierte Vergleichsstudien liegen für Alemtuzumab ausschließlich gegenüber Interferon (IFN) beta-1a vor. In den vergleichenden Phase-III-Studien zeigte sich gegenüber IFN beta-1a eine signifikante Verringerung der Schubrate. Ein Vorteil von Alemtuzumab bezüglich der Verminderung der Progression der Behinderung wurde bei vorbehandelten Patientinnen und Patienten gezeigt, aber nicht bei therapienaiven Patientinnen und Patienten.
	• Die Ergebnisse zur Behinderungsprogression sind aber bei den vorbehandelten Patientinnen und Patienten aufgrund der Erhebung von Ausgangswerten nach Randomisierung mit Unsicherheit behaftet.
	• Im Vergleich zur Therapie mit IFN zeigten sich vermehrt ihrer Art nach schwere, auch zeitverzögert nach der Behandlung auftretende, Nebenwirkungen, woraus sich die Notwendigkeit einer 48-monatigen Nachbeobachtung ergibt.
	• In der Gesamtbewertung ist die Verringerung der Schubrate abzuwägen gegen die häufigen und teilweise schweren Nebenwirkungen. Wegen dieser schweren, potentiell auch tödlich verlaufenden Nebenwirkungen insbesondere autoimmuner Art, die teilweise auch mit deutlicher zeitlicher Verzögerung nach der Gabe auftreten, ist bei der Abwägung der Therapieoptionen auch der individuelle Verlauf der Erkrankung der Patientinnen und Patienten und eine bereits bestehende Behinderung einzubeziehen. Bei nicht schweren Verläufen ist Alemtuzumab in der Regel nicht die Therapie der Wahl.
	• Die Anwendung von Alemtuzumab ist gemäß Zulassung auf 2 Behandlungsphasen in 2 Jahren begrenzt. Unklar bleibt dabei, wie Patientinnen und Patienten bei weiterhin aktiver Erkrankung weiterbehandelt werden können.
	• Der Einsatz von Alemtuzumab entspricht damit einer wirtschaftlichen Verordnungsweise bei Patientinnen und Patienten mit schweren Verläufen, d. h. insbesondere solchen
	  • die trotz des Einsatzes der zur Behandlung der RRMS zugelassenen Wirkstoffe IFN, Azathioprin, Dimethylfumarat, Glatirameracetat oder Teriflunomid mindestens 2 Schübe innerhalb von 2 Jahren erleiden und deren Behinderung progredient ist, definiert als Zunahme um mindestens 1 EDSS-Punkt bei einem Ausgangswert von ≤ 5,5 und von mindestens 0,5 bei einem Ausgangswert über 5,5, oder
	  • deren Erkrankung klinisch rasch progredient ist.

Cochrane Reviews

Filippini G et al., 2013 [5] Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis	1. Fragestellung 1. to estimate the relative effectiveness and acceptability of immunomodulators and immunosuppressants for MS; 2. to provide a ranking of the treatments according to their effectiveness and acceptability to inform clinical practice.
	2. Methodik Population: Participants 18 years age or older with a diagnosis of MS were included. Only RCTs adopting the Poser (Poser 1983) or Mc-Donald diagnostic criteria (McDonald 2001; Polman 2005) were selected. We included all phenotypes: relapsing-remitting MS (RRMS); secondary progressive MS (SPMS); progressive-relapsing MS (PRMS); and primary progressive MS (PPMS), regardless of age, sex, degree of disability, and duration of the disease Intervention: Interferon ß-1b (IFNß-1b), IFNß-1a (Rebif, Avonex), glatiramer acetate, natalizumab, mitoxantrone, methotrexate, cyclophosphamide, azathioprine, immunoglobulins, and long-term corticosteroids Komparator: Placebo or another active agent Endpunkte: • Primäre Endpunkte: Clinical relapses; Disability progression; treatment discontinuation • Sekundäre Endpunkte: Adverse events (AE) Suchzeitraum (Aktualität der Recherche): We searched the Cochrane Database of Systematic Reviews, the Cochrane MS Group Trials Register, and the Food and Drug Administration (FDA) reports. The most recent search was run in February 2012. Qualitätsbeurteilung der Studien: We assessed the risk of bias of each included study using The Cochrane Collaboration criteria (Higgins 2011).
	3. Ergebnisdarstellung Anzahl eingeschlossene Studien/Patienten (Gesamt): Forty-four trials were included in this review, in which 17,401 participants had been randomised. Twenty-three trials included relapsing remitting MS (RRMS) (9096 participants, 52%), 18 trials included progressive MS (7726, 44%), and three trials included both RRMS and progressive MS (579, 3%). The majority of the included trials were short-term studies, with themedian duration being 24 months. The results originated mostly from 33 trials on IFNß, glatiramer acetate, and natalizumab that overall contributed outcome data for 9881 participants (66%). Anmerkung FB Med: Ergebnisse zu Studien, bei denen nicht eindeutig hervorgeht, dass nur RRMS behandelt wurde, wurden nicht aufgeführt.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Recurrence of relapses over 12 months (17 studies with 3581 participants)

- Natalizumab reduced the odds (OR 0.38, 95% CI 0.28 to 0.51), a 62% reduction in the number of participants who had relapses compared with placebo.
- Mitoxantrone probably reduced the odds (OR 0.14, 95% CI 0.04 to 0.48), an 86% reduction in the number of participants who had relapses compared with placebo, but the quality of evidence for this treatment was moderate.
- Azathioprine reduced slightly the odds (OR 0.63, 95% CI 0.44 to 0.89) when data across all trials that studied this agent were pooled, but meaningful odds estimates, specific for RRMS and progressive MS, were uncertain since there was only one small study for each of the two phenotypes (Ellison 1989; Goodkin 1991). The two studies (British and Dutch 1988; Milanese 1993) that included grouped data for participants with RRMS or progressive MS were excluded from the analysis.
- IFNß-1b (Betaseron), IFNß-1a (Avonex), IFNß-1a (Rebif) and long-term corticosteroids might have slightly reduced the odds (OR 0.60, 95% CI 0.10 to 3.49; OR 0.72, 95% CI 0.45 to 1.14; OR 0.66, 95% CI 0.25 to 1.78; OR 0.46, 95% CI 0.12 to 1.84) of the participants with RRMS, but the quality of evidence for all these treatments was low.
- There was uncertainty regarding the effect of glatiramer acetate and intravenous immunoglobulins for RRMS since the quality of the evidence for these two treatments was very low.

Recurrence of relapses over 24 months (20 studies with 4695 participants):

- Both natalizumab and IFNß-1a (Rebif) reduced the odds (OR 0.32, 95% CI 0.24 to 0.43; OR 0.45, 95% CI 0.28 to 0.71, respectively), a 68% and 55% reduction in the number of participants who had relapses over 24 months compared with placebo.
- IFNß-1b (Betaseron) and mitoxantrone probably decreased the odds

	(OR 0.55, 95% CI 0.31 to 0.99; OR 0.15, 95% CI 0.04 to 0.54, respectively) compared with placebo, but the quality of evidence for these treatments was moderate. • Azathioprine reduced the odds (OR 0.64, 95% CI 0.44 to 0.94) when all the included trials of azathioprine were aggregated, but this treatment was not statistically significantly different from control when data for RRMS and progressive MS were analysed separately. Azathioprine might have decreased slightly the odds of the participants with RRMS (OR 0.36, 95% CI 0.11 to 1.21). • Of the other five treatments (IFNß-1a (Avonex), glatiramer acetate, methotrexate, intravenous immunoglobulins, and long term corticosteroids), the numbers of RRMS participants experiencing new relapses were not statistically significantly different from the numbers in the placebo groups. Relapses over 36 months: This outcome was not reported in trials for RRMS. Disability progression over 36 months (This outcome was not reported in trials for RRMS.) Network meta-analysis (combination of direct and indirect comparisons) Relapses over 12, 24, and 36 months Participants with RRMS: a) Relapses over 12 months were provided in 16 trials (4817 participants, 32% of those included in this review) and nine treatments, IFNß-1b (Betaseron), IFNß-1a (Avonex), IFNß-1a (Rebif), glatiramer acetate, natalizumab, azathioprine, mitoxantrone, intravenous immunoglobulins, and long-term corticosteroids versus placebo. In the network meta-analysis there was no statistically significant effect of these treatments compared to the control groups. b) Relapses at 24 months were provided in 16 trials (7269, 48% of those included in this review) and nine treatments, IFNß-1b (Betaseron), IFNß-1a (Avonex), IFNß-1a (Rebif), glatiramer acetate, natalizumab, mitoxantrone, azathioprine, intravenous immunoglobulins, long-term corticosteroids, and placebo. Mitoxantrone was the most effective agent with a median OR of 0.14 (95% CrI 0.03 to 0.55; SUCRA = 92%) followed by natalizumab (median OR 0.31, 95% CrI 0.19 to 0.55; SUCRA = 75%), intravenous immunoglobulins (median OR 0.34, 95% CrI 0.13 to 0.69; SUCRA = 70%), azathioprine (medianOR 0.34, 95%CrI 0.08 to 1.30; SUCRA = 65%), IFNß-1a (Rebif) (median OR 0.46, 95% CrI 0.25 to 0.71; SUCRA = 53%), IFNß-1b (Betaseron) (median OR 0.50, 95% CrI 0.31 to 0.82; SUCRA = 45%), and glatiramer acetate (median OR 0.50, 95% CrI 0.29 to 0.77; SUCRA = 46%). The heterogeneity standard deviation was 0.17 (95% CrI 0.01 to 0.73). c) Progression at 24 months was provided in 15 two-arm studies (7444

	participants, 50%of those included in this review) and eight treatments, IFNß-1b (Betaseron), IFNß-1a (Avonex), IFNß-1a (Rebif), glatiramer acetate, natalizumab, mitoxantrone, azathioprine, intravenous immunoglobulins, and placebo. Mitoxantrone seemed to be the most effective agent in reducing the number of participants with disability progression at 24 months (median OR 0.11, 95% CrI 0.01 to 0.65; SUCRA = 96%), followed by glatiramer acetate (median OR 0.52, 95% CrI 0.28 to 0.88; SUCRA = 70%). The heterogeneity standard deviation was 0.29 (95% CrI 0.03 to 0.80). Acceptability of the interventions • No difference among treatments in the number of participants who dropped out (withdrawals or lost to follow-up) due to adverse events throughout the studies, up to 24 months. The heterogeneity standard deviation was 0.16 (95% CrI 0.01 to 0.46). No sensitivity to prior for heterogeneity was observed. Adverse Events: • Serious adverse events (SAEs): no statistically significant effect of the treatments compared to the placebo groups. • Withdrawals due to AEs: statistically significant effect of the treatments as a group compared to placebo (OR 2.41, 95%CI 1.92 to 3.03; P = 0.001) Agents associated with significantly increased odds of participants who were withdrawn due to AEs compared with placebo were interferons (OR 3.08, 95% CI 2.23 to 4.26; P < 0.001), glatiramer acetate (OR 3.48, 95% CI 1.55 to 7.84; P = 0.003), natalizumab (OR 1.36, 95% CI 0.99 to 1.85; P = 0.06), azathioprine (OR 6.35, 95%CI 2.50 to 16.11; P < 0.001), and intravenous immunoglobulins (OR 1.99, 95% CI 1.07 to 3.71; P = 0.03). No difference in withdrawals due to AEs was found for mitoxantrone, however only one study was included, which was likely to lead to type-II error. There were no significant differences in withdrawals in direct comparison trials of the interferons compared to each other or to glatiramer acetate. • Serious infections / Leukaemia, lymphoma, or any other type of cancer: No stat. significant differences.
	4. Fazit der Autoren: Our review should provide some guidance to clinicians and patients. On the basis of high quality evidence, natalizumab and IFNß-1a (Rebif) are superior to all other treatments for preventing clinical relapses in RRMS in the short-term (24 months) compared to placebo. Moderate quality evidence supports a protective effect of natalizumab and IFNß-1a (Rebif) against disability progression in RRMS in the short-term compared to placebo. These treatments are associated with long-term serious adverse events and their benefit-risk balance might be unfavourable. IFNß-1b (Betaseron) and mitoxantrone probably decreased the odds of the participants with RRMS having relapses, compared with placebo (moderate quality of evidence). The benefit-risk balance with azathioprine is uncertain; however this agent

	might be effective in decreasing the odds of the participants with RRMS having relapses and disability progression over 24 to 36 months, compared with placebo. The lack of convincing efficacy data shows that IFNß-1a (Avonex), has a favourable benefit-risk balance in RRMS. […] It is important to consider that the clinical effects beyond two years are uncertain, a relevant point for a disease of 30 to 40 years duration. Direct head-to-head comparison(s) between natalizumab and IFNß-1a (Rebif) or between azathioprine and IFNß-1a (Rebif) should be top priority on the research agenda and follow-up of the trial cohorts should be mandatory. 5.) Kommentar FB Med: • Da das Review alle Formen der MS behandelt, wurden nur Ergebnisse zur RMS extrahiert. • Neue Netzwerkanalyse von gleicher Arbeitsgruppe gibt ein anderes Urteil zu Interferon-beta ab, basierend auf einer neuen Beurteilung der Evidenz aus Netzwerkanalysen.
Tramacere I et al., 2015 [31] Immunomodulators and immune-suppressants for relapsing-remitting multiple sclerosis: a network meta-analysis	1. Fragestellung To compare the benefit and acceptability of interferon beta-1b, interferon beta-1a (Avonex, Rebif), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, pegylated interferon beta-1a, daclizumab, laquinimod, azathioprine and immunoglobulins for the treatment of people with RRMS
	2. Methodik Population We included participants 18 years of age or older with a diagnosis of RRMS according to Poser (Poser 1983) or McDonald (McDonald 2001; Polman 2005; Polman 2011) diagnostic criteria. Intervention Interferon beta-1b und 1a (Avonex, Rebif), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, pegylated interferon beta-1a, daclizumab, ocrelizumab, laquinimod, azathioprine, immunoglobulins We included regimens as defined in primary studies irrespective of their dose. Komparator: Placebo, above mentioned treatments Endpunkt Primary outcomes • **Relapses**: proportion of participants who experienced new relapses over 12, 24, or 36 months after randomisation or at the end of the

study (McDonald 2001; Polman 2005). A more stringent 48-hour criterion has been used in some RCTs.

- **Disability worsening**: proportion of participants who experienced disability worsening over 24 or 36 months after randomisation or at the end of the study. Worsening is defined as at least a 1-point Expanded Disability Status Scale (EDSS) increase or a 0.5-point increase if the baseline EDSS was greater than or equal to 5.5.
- **Acceptability:** We used treatment discontinuation due to adverse events to assess acceptability and we measured it by the number of participants who withdrew due to any adverse event over 12, 24, or 36 months after randomisation or at the end of the study out of the total number of participants randomly assigned to each treatment arm.

Secondary outcomes

The total number of serious adverse events (SAEs).

Suchzeitraum (Aktualität der Recherche): bis 30.09.2014
Anzahl eingeschlossene Studien/Patienten (Gesamt):
39 RCT/ 25113 Patienten
We applied no language restrictions to the search.

Qualitätsbeurteilung der Studien

We assessed the risk of bias of each included study using The Cochrane Collaboration criteria (Higgins 2011).

We provided estimates from the network meta-analysis based on the methodology developed from the GRADE Working Group (GRADE Working Group 2004, Salanti 2014).

3. Ergebnisdarstellung

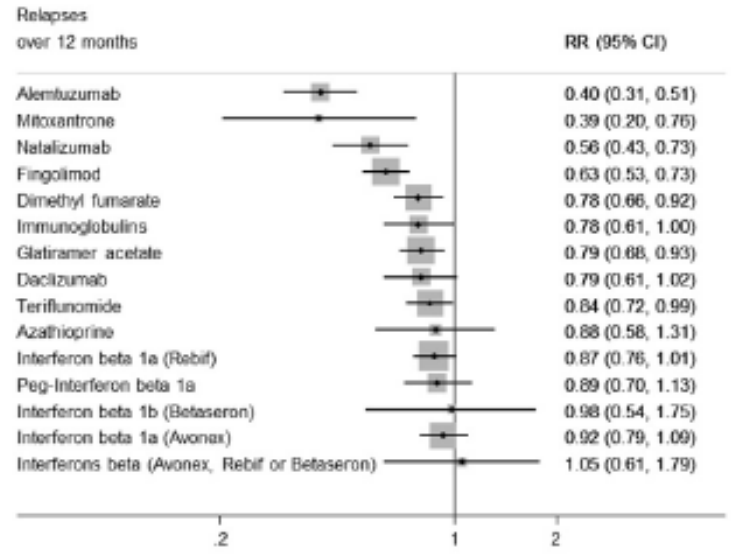
We included 39 studies involving 25,113 participants and published between 1987 and 2014 in this review. Median follow-up was 24 months (12-month follow-up from 12 studies, 24-month follow-up from 25 studies, and 36- month follow-up from two studies). Twenty-four (60%) were placebo-controlled and 15 (40%) were head-to-head studies.

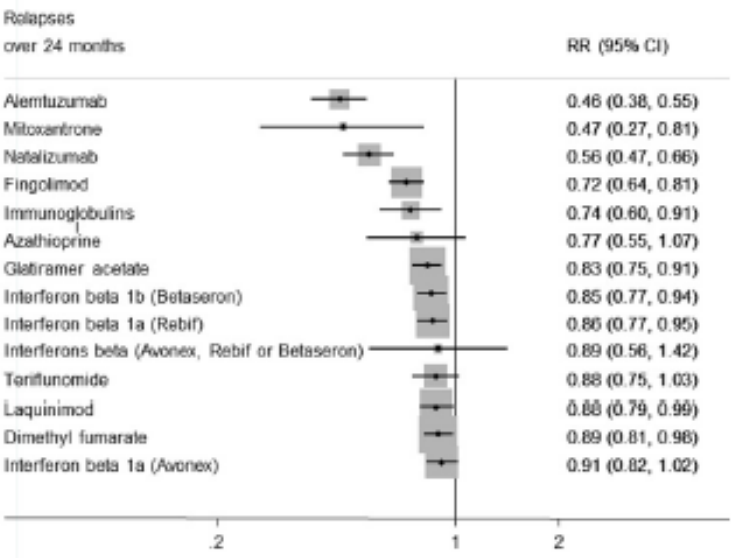
Anmerkung FB Med: Detaillierte Qualitätsbeurteilung siehe Anhang

- **Recurrence of relapses:** Network meta-analysis showed that, in terms of a protective effect against the recurrence of relapses in RRMS during the first 24 months of treatment, alemtuzumab,

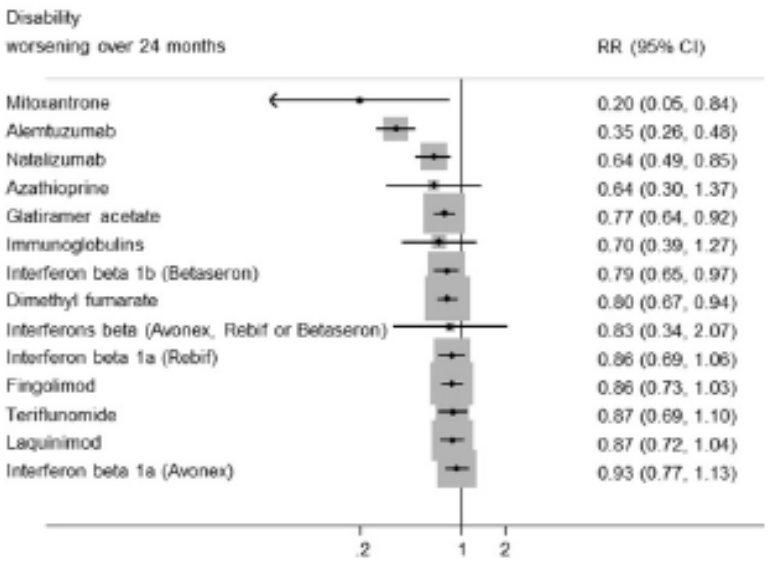
mitoxantrone, natalizumab, and fingolimod outperformed other drugs.

- The most effective drug was alemtuzumab (risk ratio (RR) versus placebo 0.46, 95%confidence interval (CI) 0.38 to 0.55; (SUCRA) 96%; moderate quality evidence), followed by mitoxantrone (RR 0.47, 95% CI 0.27 to 0.81; SUCRA 92%; very low quality evidence), natalizumab (RR 0.56, 95% CI 0.47 to 0.66; SUCRA 88%; high quality evidence), and fingolimod (RR 0.72, 95%CI 0.64 to 0.81; SUCRA 71%; moderate quality evidence).



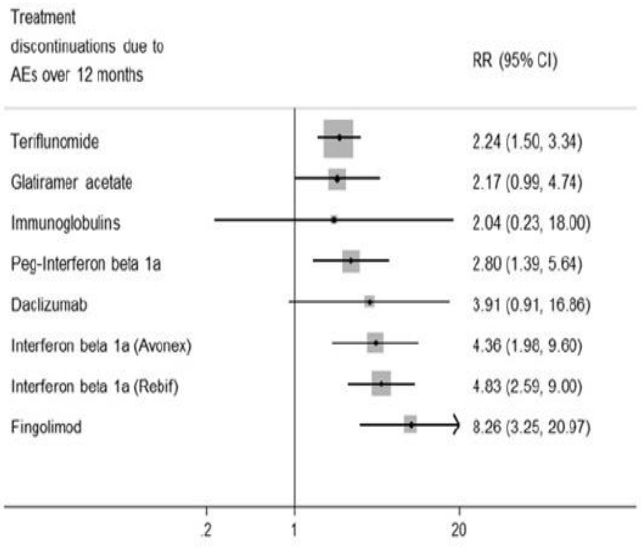


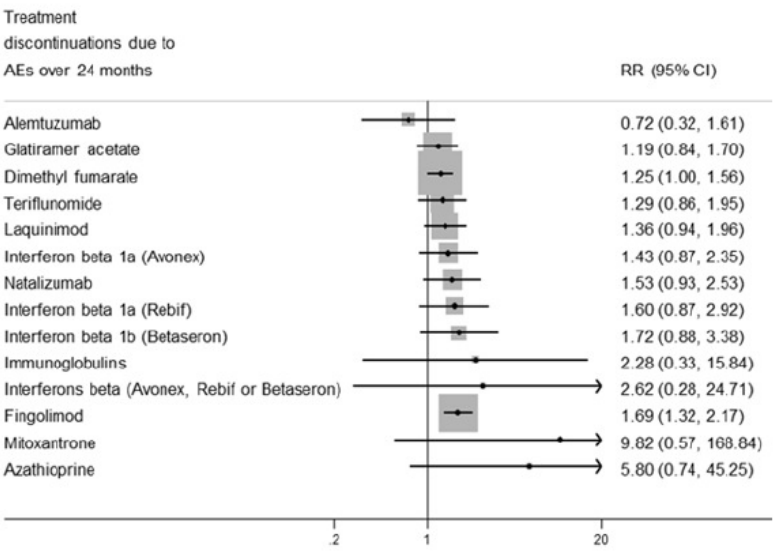
- **Disability worsening** was based on a surrogate marker, defined as irreversible worsening confirmed at three-month follow-up, measured during the first 24 months in the majority of included studies. Both direct and indirect comparisons revealed that the most effective treatments were mitoxantrone (RR versus placebo 0.20, 95% CI 0.05 to 0.84; SUCRA 96%; low quality evidence), alemtuzumab (RR 0.35, 95% CI 0.26 to 0.48; SUCRA 94%; low quality evidence), and natalizumab (RR 0.64, 95% CI 0.49 to 0.85; SUCRA 74%; moderate quality evidence).



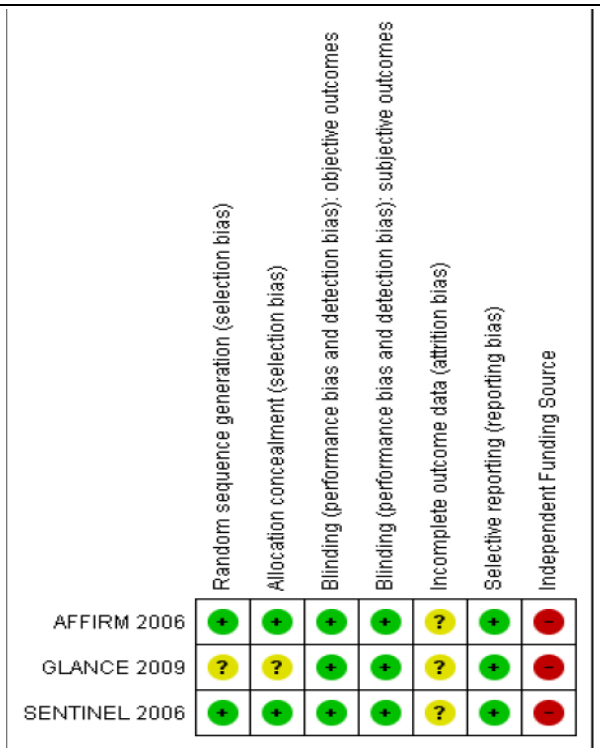
- Almost all of the agents included in this review were associated with a higher proportion of participants who withdrew due to **any adverse event** compared to placebo. Based on the network meta-analysis methodology, the corresponding RR estimates versus placebo over the first 24 months of follow-up were: mitoxantrone 9.92 (95% CI 0.54 to 168.84), fingolimod 1.69 (95% CI 1.32 to 2.17), natalizumab 1.53 (95% CI 0.93 to 2.53), and alemtuzumab 0.72 (95% CI 0.32 to 1.61).

Information **on serious adverse events (SAEs)** was scanty, characterised by heterogeneous results and based on a very low number of events observed during the short-term duration of the trials included in this review.



	
	4. Anmerkungen/Fazit der Autoren • The results of this review show that for preventing clinical relapses in the short term (24 months), alemtuzumab, natalizumab, and fingolimod are superior to several other treatments, on the basis of moderate to high quality evidence. • For preventing disability worsening in the short term (24 months) natalizumab is superior to placebo on the basis of moderate quality evidence only. • First, the benefit of all of these treatments beyond two years is uncertain and this is a relevant issue for a disease with a duration of 30 to 40 years. Second, short-term trials provide scanty and poorly reported safety data and do not provide useful evidence to obtain a reliable risk profile of treatments. • Finally, more than 70% of the studies included in this review were sponsored by pharmaceutical companies and this may have influenced the results. Anmerkung des Autors bezüglich Interferon beta 1a • We cannot confirm the previous results (Anmerkung FB Med: Filippini 2013) for interferon beta-1a (Rebif), which we now judge to be low or very low quality evidence. We have judged the evidence for interferon beta-1a (Rebif) versus placebo as low quality due to limitations of the studies. We found a similar scenario for relapses and disability worsening over 24 months. • In this new review we were able to assess the quality of the evidence using an adaptation of the standard GRADE approach to the results from network meta-analysis, which is now available (Salanti 2014).
Pucci E et al., 2011 [28] Natalizumab for relapsing remitting multiple sclerosis (Review)	1. Fragestellung Welche Wirksamkeit, Verträglichkeit und Sicherheit besteht für Menschen mit schubförmig verlaufender MS durch die Therapie mit Natalizumab (NTZ)?
	2. Methodik

	Population: Menschen mit RRMS, beide Geschlechter (Kriterien nach Poser – Poser 1983 oder McDonald – McDonald 2001, Polman 2005), > 17 Jahre alt Intervention: NTZ (Dosierung > 3 mg/kg i.v. Infusion alle 4 Wochen), auch als ergänzende („add on“) Therapie Kontrollintervention: Placebo oder andere Arzeimittel Endpunkte 1a) Anzahl der Menschen mit mindestens einem erneuten Schub nach 2 Jahren 1b) Anzahl der Menschen mit Progression nach 2 Jahren 1c) Mittlere Änderung in Short Form 36 (SF-36) Punktzahlen (körperlich/seelisch) nach 2 Jahren 1d) Anzahl der Menschen mit mindestens einem schweren unerwünschtem Ereignis während zweijähriger Therapie 1e) Anzahl der Menschen mit einem schweren unerwünschtem Ereignis (unabhängig von Behandlungsdauer und/oder Rückfälle ausgeschlossen) 2) 13 weitere sekundäre Endpunkte definiert (Beispiele: Wirksamkeit – Mittlere Veränderung im Wohlbefinden anhand VAS, Sicherheit – Anzahl an Personen bei denen mindestens eine unerwünschte Arzneimittelreaktion auftritt) Studientyp: 3 RCTs (942+110+1171 Patienten) Literaturauswahl ohne Spracheinschränkungen Suchzeitraum: 1966 bis 19.02.2010 Qualitätsbeurteilung der Studien The risk of bias assessment for RCTs and CCTs was performed as recommended by the Cochrane Handbook (Handbook 5 2008)
	3. Ergebnisdarstellung



eingeschlossene Studien (Review)

- eine placebo-kontrollierte Studie (n = 942) (AFFIRM 2006)
- zwei “add-on” placebo-kontrollierte Studien: eine plus GA (n = 110 – GLANCE 2009), eine plus IFN-β 1a (n = 1171 – SENTINEL 2006)

ausgeschlossene Studien (Synopse): AFFIRM 2006, da keine Menschen mit Vorbehandlung (IFN-ß, GA, Azathioprin) innerhalb der vergangenen 6 Monate oder mit IFN-ß- oder GA-Therapie über mehr al 6 Monate eingeschlossen

Ergebnisse

- SENTINEL 2006 als methodisch “gut” bewertet
- GLANCE 2009: unklares Risiko für „selection“ und „attrition bias“

1a) NTZ + IFN-β vs. IFN-β (n = 1 171) Risk Ratio (M-H, Random, 95% CI): 0.62 [0.55, 0.70] sign.

1b) NTZ + IFN-β vs. IFN-β (n = 1 171) Risk Ratio (M-H, Random, 95% CI): 0.80 [0.69, 0.93] sign.

1c körperlich) NTZ + IFN-β vs. IFN-β (n = 1 171) Mean Difference (IV, Random, 95% CI): 1.96 [0.79, 3.13] ns

1c seelisch) NTZ + IFN-β vs. IFN-β (n = 1 171) Mean Difference (IV, Random, 95% CI): 1.14 [-0.00, 2.28] ns

1d) NTZ + IFN-β vs. IFN-β (n = 1 171) Risk Ratio (M-H, Random, 95% CI): 0.95 [0.81, 1.10] ns

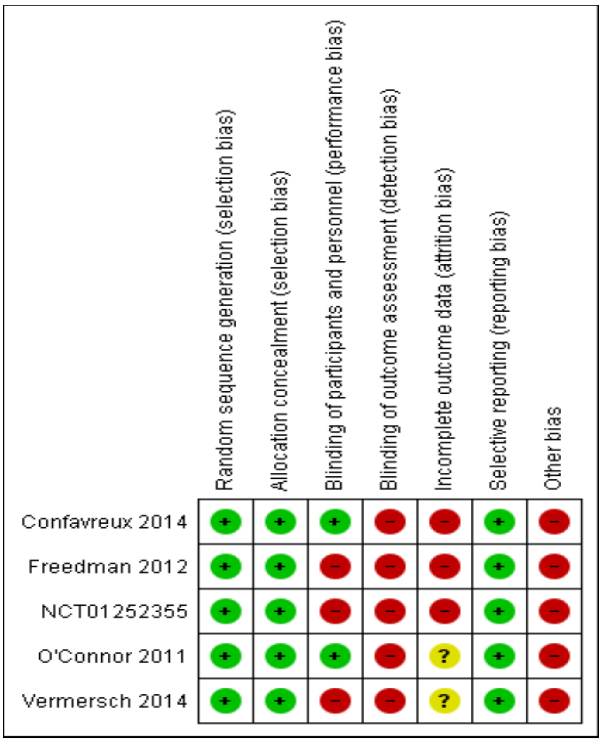
1e unabhängig von Behandlungsdauer) NTZ + IFN-β vs. IFN-β (n = 1 171) Risk Ratio (M-H, Random, 95% CI): 0.87 [0.69, 1.09] ns

1e unabhängig von Behandlungsdauer) NTZ + GA vs. GA (n = 110) Risk Ratio (M-H, Random, 95% CI): 0.5 [0.05, 5.36] ns

1e unabhängig von Behandlungsdauer – Rückfälle ausgeschlossen) NTZ + IFN-β vs. IFN-β (n = 1 171) Risk Ratio (M-H, Random, 95% CI): 1.10 [0.81, 1.49] ns

1e unabhängig von Behandlungsdauer – Rückfälle ausgeschlossen) NTZ + GA vs. GA (n = 110) Risk Ratio (M-H, Random, 95% CI): 1.0 [0.06, 15.59] ns

	4. Fazit der Autoren: Although one trial did not contribute to efficacy results due to its duration, we found robust evidence in favor of a reduction in relapses and disability at 2 years in RRMS patients treated with NTZ. The drug was well tolerated. There are current significant safety concerns due to reporting of an increasing number of PML cases in patients treated with NTZ. This review was unable to provide an up-to-date systematic assessment of the risk due to the maximum 2 year-duration of the trials included. An independent systematic review of the safety profile of NTZ is warranted. NTZ should be used only by skilled neurologists in MS centers under surveillance programs. All the data in this review came from trials supported by the Pharmaceutical Industry. In agreement with the Cochrane Collaboration policy, this may be considered a potential source of bias. 5. Hinweise durch FB Med • Wegen Ausschluss der AFFIRM 2006, keine gepoolten Ergebnisse extrahiert.
He D et al., 2016 [13] Teriflunomide for multiple sclerosis Update from 2012	1. Fragestellung: To explore the potential benefits of teriflunomide and so expand the available DMT options, the effectiveness and safety of teriflunomide, as monotherapy or combination therapy, were assessed versus placebo or approved DMDs (IFN-ß, glatiramer acetate, natalizumab, mitoxantrone, fingolimod, dimethylfumarate, alemtuzumab) for modifying disease in patients with MS.
	2. Methodik Population: Definite diagnoses of MS according to Poser's (Poser 1983) or Mc Donald's (McDonald 2001; Polman 2005; Polman 2011) criteria, any clinical phenotypes categorized according to the classification of Lublin and Reingold (Lublin 1996), and an Expanded Disability Status Scale (EDSS) scores of 6.0 or lower Intervention: Treatment with oral teriflunomide (7mg/14mg per day), as monotherapy or combination therapy Kontrollintervention: Placebo or other treatments (IFN-, glatiramer acetate, natalizumab, mitoxantrone, fingolimod dimethylfumarate, alemtuzumab) for MS. Endpunkte • Primäre Endpunkte: 1.) The rate of relapse at one year or two years 2.) The proportion of participants with disability progression as assessed by the EDSS (Kurtzke 1983) at one year or two years. • Sekundäre Endpunkte: 1.) The annualized relapse rate at one year or two years, defined as the mean number of confirmed relapses per participant adjusting for the duration of follow-up to annualize it.

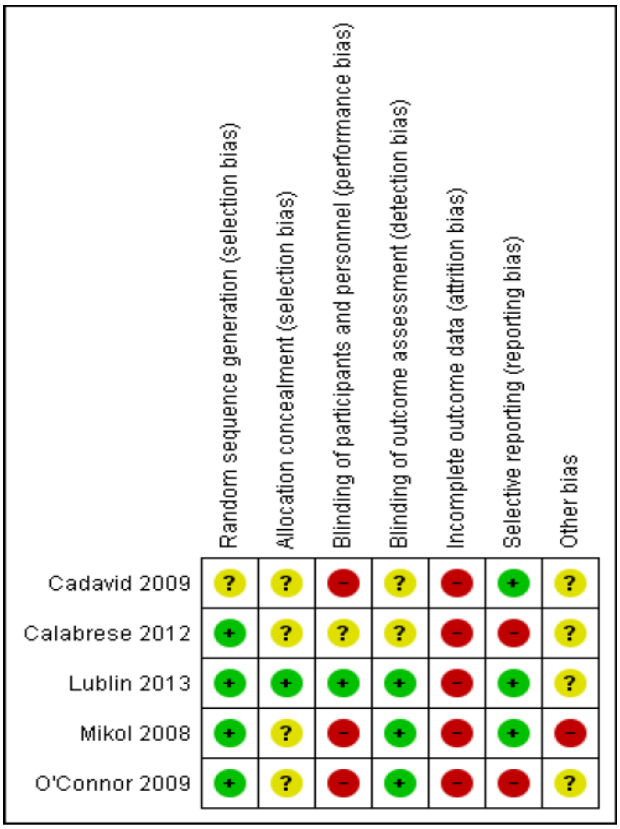
	2.) The number of gadolinium-enhancing T1-weighted lesions at one year or two years. Lesions that persisted for more than four weeks were counted more than once. 3.) The time to disability progression at one year or two years. 4.) Changes in T1 hypointensity or magnetization transfer 5.) Ratio of lesion damage at one year or two years. 6.) Mean change in HRQoL at one year or two years (questionnaires used: Short Form-36 (SF-36) scores, MSQoL-54 questionnaire scores, MSQLI or FAMS Suchzeitraum: 2004 bis September 2016 Anzahl eingeschlossener Studien: 5 RCTs including 3231 people Qualitätsbeurteilung The risk of bias assessment for RCTs and CCTs was performed as recommended by the Cochrane Handbook (Handbook 5 2008).
	3. Ergebnisdarstellung: • All participants had an entry score of 5.5 or lower on the EDSS and no relapse for at least 30 days before randomization (Confavreux 2014; O'Connor 2011, Freedman 2012; NCT01252355, Vermersch 2014) All participants had a diagnosis of definite MS according to Mc-Donald's diagnostic criteria and a relapsing clinical course with or without progression (RRMS, SPMS or PRMS).  • No meta-analyses was performed because of the high risk of bias and clinical diversities of the included studies. • All studies were sponsored by Sanofi-Aventis. In Confavreux 2014 and O'Connor 2011, the sponsor analysed the data and some co-

	authors were affiliated to Sanofi-Aventis. Ergebnisse: • Compared to placebo, administration of teriflunomide at a dose of 7mg/day or 14mg/day as monotherapy reduced the number of participants with relapse by one year or by two years, as well as the annualized relapse rate by two years. • However, only teriflunomide at a dose of 14 mg/day as monotherapy significantly reduced the number of participants with disability progression and delayed the progression of disability by one year and two years. • When compared to IFN ß-1a, low-dose teriflunomide was inferior to IFN ß-1a in respect of the annualized relapse rate and the number of participants with relapse, but there was no difference for high dose teriflunomide. • Neither doses of teriflunomide improved QoL measured by SF-36 scores by one year. • Overall, the risks for AEs and SAEs in participants receiving teriflunomide were similar to those in participants receiving placebo both at one year and two years of follow-up. However, the risks for study drug discontinuation due to AEs were increased by both doses of teriflunomide administration at one year of follow-up, but not at two years of follow-up. • The common adverse effects were diarrhoea, nausea, hair thinning, elevated alanine aminotransferase, neutropenia and lymphopenia. These adverse effects were mostly mild-to-moderate in severity, but had a dose-related effect.
	4. Fazit der Autoren: There was low-quality evidence to support that teriflunomide at a dose of 7mg and 14mg orally once daily as monotherapy by direct comparison with placebo reduced both the annualized relapse rate and the number of participants with a relapse over one year and two years of treatment. Only teriflunomide at a dose of 14 mg/day as monotherapy reduced the number of participants with disability progression and delayed the progression of disability over one year or two years, but the quality of the evidence was very low. The quality of available data was too low to evaluate the benefit of teriflunomide as monotherapy versus interferon beta-1a (IFN ß- 1a) or as combination therapy with interferon beta (IFN ß).
Xu Z et al., 2015 [32] Dimethyl fumarate for multiple sclerosis	1. Fragestellung To assess the absolute and comparative efficacy and safety of dimethyl fumarate as monotherapy or combination therapy versus placebo or other approved disease-modifying drugs (IFN-, glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, alemtuzumab) for patients with MS.
	2. Methodik Population: Diagnosis of MS as defined according to Poser's McDonald's criteria, any clinical phenotypes categorized according to the classification of Lublin and Reingold, and an Expanded Disability Status Scale (EDSS) (Kurtzke 1983) score of 6.0 or lower. Intervention: Dimethyl fumarate orally, as monotherapy or combination therapy (240 mg orally three times daily or twice daily)

	Komparator: Placebo Endpunkte Primäre Endpunkte: Benefit 1. The proportion of patients with at least one relapse at one year or two years. Confirmed relapse was defined as the occurrence of new or worsening of previously stable symptoms, not associated with fever or infection, occurring at least 30 days after the onset of a preceding relapse, lasting longer than 24 hours and that were accompanied by new objective neurological findings according to a neurologist's evaluation. 2. The proportion of patients with disability worsening as assessed by the EDSS at one year or two years. Safety The proportion of patients with at least one adverse event (AE), the proportion of patients with at least one SAE and the proportion of patients who discontinued the study drug because of AEs at one year and two years. Sekundäre Endpunkte: ARR at one year or two years, number (rate) of gadolinium-enhancing T1-weighted lesions at one year or two years, number (rate) of new or enlarging T2-weighted hyperintense lesions at one year or two years, percentage brain volume change at one year or two years, mean change in HRQoL from baseline to one year or two years. Suchzeitraum (Aktualität der Recherche): 2004 to June 2014. We also communicated with investigators participating in trials of dimethyl fumarate and the Biogen Idec Medical Information. Anzahl eingeschlossene Studien/Patienten (Gesamt): 2 RCTs (n=2667) Qualitätsbeurteilung der Studien:
	3. Ergebnisdarstellung • We included two RCTs in this review, involving 2667 adult patients with RRMS to mainly evaluate the benefit and safety of the dosages of dimethyl fumarate (240 mg orally three times daily or twice daily) by direct comparison with placebo. Patients with progressive forms of MS were excluded. Baseline demographic and disease characteristics were similar among the study groups (including the MRI cohort and the HRQoL cohort). • Qualitätsbewertung der Studien: Overall, there were no obvious clinical and methodological heterogeneities between the studies. Both studies had a high attrition bias, resulting in moderate-quality evidence for most primary outcomes. The results of disability worsening were additionally subjected to a serious indirectness of evidence because disability worsening was confirmed in less than six months in both studies. All these factors contributed to a low quality

	28ft he evidence for disability worsening. The quality of MRI data reported in the primary studies was poor. Ergebnisse • Meta-analyses showed that dimethyl fumarate both three times daily and twice daily reduced the number of patients with a relapse (risk ratio (RR) 0.57, 95% confidence interval (CI) 0.50 to 0.66, P < 0.00001 and 0.64, 95% CI 0.54 to 0.77, P < 0.00001, respectively) or disability worsening (RR 0.70, 95% CI 0.57 to 0.87, P = 0.0009 and 0.65, 95% CI 0.53 to 0.81, P = 0.0001, respectively) over two years, compared to placebo. • Data of active lesions on MRI scans were not combined because there was a high risk of selection bias for MRI outcomes and imprecision of MRI data in both studies, as well as an obvious heterogeneity between the studies. • In terms of safety profile, both dosages increased the risk for adverse events and the risk for drug discontinuation due to adverse events. The most common adverse events included flushing and gastrointestinal events (upper abdominal pain, nausea and diarrhoea). Uncommon adverse events included lymphopenia and leukopenia, but they were more likely to happen with dimethyl fumarate than with placebo (high dosage: RR 5.25, 95% CI 2.20 to 12.51, P = 0.0002 and 5.23, 95% CI 2.47 to 11.07, P < 0.0001, respectively; low dosage: RR 5.69, 95% CI 2.40 to 13.46, P < 0.0001 and 6.53, 95%CI 3.13 to 13.64, P < 0.00001, respectively). Both studies had a high attrition bias resulting from the unbalanced reasons for dropouts among groups.
	4. Fazit der Autoren: There is moderate-quality evidence to support that dimethyl fumarate at a dose of 240 mg orally three times daily or twice daily reduces both the number of patients with a relapse and the annualized relapse rate over two years of treatment in comparison with placebo. However, the quality of the evidence to support the benefit in reducing the number of patients with disability worsening is low. There is no high-quality data available to evaluate the benefit on MRI outcomes. The common adverse effects such as flushing and gastrointestinal events are mild-to-moderate for most patients. Lymphopenia and leukopenia are uncommon adverse events but significantly associated with dimethyl fumarate. Both dosages of dimethyl fumarate have similar benefit and safety profile, which supports the option of low-dose administration. New studies of high quality and long-term follow-up are needed to evaluate the benefit of dimethyl fumarate on prevention of disability worsening and to observe the long-term adverse effects including progressive multifocal leukoencephalopathy.
La Mantia L et al., 2014 [22] Interferons-beta versus glatiramer acetate for relapsing remitting multiple sclerosis	1. Fragestellung To assess whether IFNs-beta and GA differ in terms of efficacy and safety in the treatment of patients with RRMS.
	2. Methodik Population: Patients of any age, gender and race affected by RRMS according to Poser's (Poser 1983) or McDonald's (McDonald 2001; Polman 2005; Polman 2011) criteria were included. Intervention: We included trials in which participants received

	recombinant IFN-beta 1a (Rebif, Avonex) or IFN-beta 1b (Betaferon, Betaseron, Extavia) at any dose and by any route of administration in any setting. (Details siehe Ergebnisdarstellung) Komparator: GA at any dose, route of administration and setting. For trials comparing multiple groups of participants, only the following designs were considered. 1. IFN-beta 1a versus IFN-beta 1b versus GA. 2. GA (dose 1) versus GA (dose 2) versus IFNs-beta. 3. GA versus IFNs-beta (dose 1) versus IFNs-beta (dose 2). Endpunkte: Primäre Endpunkte: • Number of participants who experienced at least one relapse at 12 – 24 months and at the end of follow-up; • Number of participants whose condition worsened during the study; • number of participants who withdrew from or dropped out of the study because of adverse events (Aes), SAEs Sekundäre Endpunkte: • Frequency of relapse (number of relapses/patient-year: Annual relapse rate (ARR); no relapses no change in EDSS and no MRI changes (T1-T2); number of participants treated with steroids for relapse of MS; mean changes in quality of life (QOL) and MRI outcomes Suchzeitraum (Aktualität der Recherche): 29 October 2013 + and the reference lists of retrieved articles. We contacted trialists and pharmaceutical companies. Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 RCTs (n=2858) Qualitätsbewertung der Studien: CochraneHandbook for Systematic Reviews of Interventions (Higgins 2011).
	3. Ergebnisdarstellung • Five RCTs met our predefined selection criteria: Two studies compared the effects of GA versus IFN-beta 1b (Cadavid 2009; O'Connor 2009), and three compared GA versus IFN-beta 1a (Calabrese 2012; Lublin 2013;Mikol 2008), with one comparing GA versus IFN-beta 1a 44 mcg SC (Mikol 2008), one GA versus IFN-beta 1a 30 mcg IM (Lublin 2013) and one GA versus both IFN-beta 1a 44 mcg SC and IFN-beta 1a 30 mcg IM (Calabrese 2012). • Participants were randomly assigned to IFNs (1679) and GA (1179). The IFNs analyzed in comparison with GA were IFN-beta 1b 250 mcg (two trials, 933 participants), IFN-beta 1a 44 mcg (two trials, 441 participants) and IFN-beta 1a 30 mcg (two trials, 305 participants). Enrolled participants were affected by active RRMS. • The quality of evidence was moderate overall, although in terms of the safety profile, the quality of evidence was low. The risk for incomplete outcome data was found to be high, as some studies present

	incomplete reporting of adverse events and numbers of participants who dropped out.  Ergebnisse • Both therapies showed similar clinical efficacy at 24 months, given the primary outcome variables (number of participants with relapse. However at 36 months, evidence from a single study suggests that relapse rates were higher in the group given IFNs than in the GA group (RR 1.40, 95% CI 1.13 to 1.7, P= 0.002). • Secondary magnetic resonance imaging (MRI) outcomes analysis showed that effects on new or enlarging T2- or gadolinium (Gd) - enhancing lesions at 24 months were similar. However, the reduction in T2- and T1-weighted lesion volume was significantly greater in the groups given IFNs than in the GA groups (MD -0.58, 95% CI -0.99 to -0.18, P = 0.004, and MD -0.20, 95% CI -0.33 to -0.07, P = 0.003, respectively). • The number of participants who dropped out of the study because of adverse events was similar in the two groups
	4. Fazit der Autoren: The effects of IFNs-beta and GA in the treatment of patients with RRMS, including clinical (e.g. patients with relapse, risk to progression) and MRI (Gd-enhancing lesions) activity measures, seem to be similar or to show only small differences. When MRI lesion load accrual is considered, the effect of the two treatments differs, in that IFNs-beta were found to limit the increase in lesion burden as compared with GA. Evidence was insufficient for a comparison of the effects of the two treatments on patient-reported outcomes, such as quality of life measures. Hinweise durch Autoren:

	• High risk of attrition bias • Analysis of the safety profile was restricted to the number of participants who withdrew from or dropped out of the study; drug-related adverse effects (tolerability) were not considered.
La Mantia L et al., 2016 [23] Fingolimod for relapsing-remitting multiple sclerosis	1. Fragestellung To assess the safety and benefit of fingolimod versus placebo, or other disease-modifying drugs (DMDs), in reducing disease activity in people with relapsing-remitting multiple sclerosis (RRMS).
	2. Methodik Population: RRMS according to McDonald's diagnostic criteria Intervention: Fingolimod (0.5, 1.25, 5mg) without restriction of treatment duration Komparator 1. Placebo 2. Other approved DMDs (interferon beta 1a, i.m., interferon beta 1b, glatiramer acetate) Endpunkt **Primary outcomes** 1. Number of participants relapse-free at six,12 and 24 months after randomisation and at the end of follow-up. 2. Number of participants free from disability worsening at 12, 24 and 36 months after randomisation and at the end of follow up. Disability worsening is defined as at least one point Expanded Disability Status Scale (EDSS) (Kurtzke 1983) increase, or a 0.5 point increase if the baseline EDSS was > 5.5, confirmed during two subsequent neurological examinations separated by at least 6 months' interval free of relapses. We considered separately studies that reported disability worsening defined using different criteria. 3. Number of participants who withdrew from the study due to a) adverse events; b) serious adverse events, i.e. death, life-threatening, hospitalisation, disability or permanent damage, congenital anomaly/birth defect **Secondary outcomes** 4. Annualised relapse rate at six, 12 and 24 months after randomization and at the end of follow-up. 5. Number of participants free from MRI gadolinium-enhancing lesions at six, 12 and 24 months after randomisation and at the end of follow-up. 6. Mean change of total MRI T2 weighted lesion load at 12 and 24 months after randomisation and at the end of follow-up. 7. Quality of life measured by validated questionnaires such as MSQOL-

54 (Vickrey 1995).

Suchzeitraum (Aktualität der Recherche): bis 15.02.2016

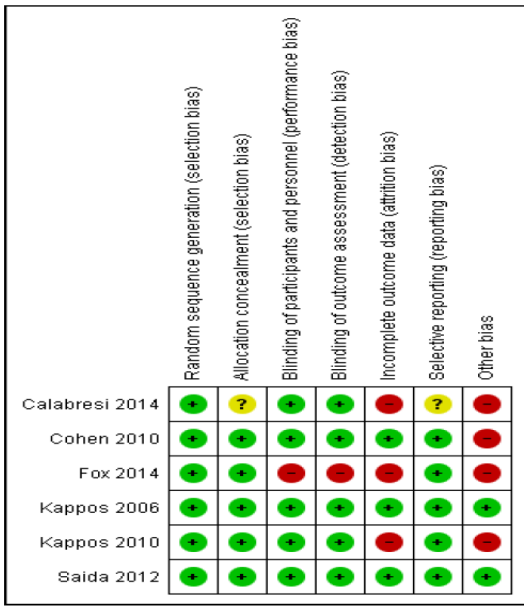
Keine Eingrenzung der Sprache.

Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 (n=5152)

Qualitätsbewertung der Studien:
Cochrane Handbook for Systematic Reviews of Interventions.

3. Ergebnisdarstellung

- These trials were published between 2006 and 2014. Four studies compared fingolimod to placebo (Calabresi 2014; Kappos 2006; Kappos 2010; Saida 2012), one to intramuscular interferon beta- 1a (Cohen 2010), and one to other DMDs (interferon beta-1a, interferon beta-1b, glatiramer acetate) (Fox 2014). Four studies used fingolimod at doses of 0.5 mg and 1.25 mg (Calabresi 2014; Cohen 2010; Kappos 2010; Saida 2012). One study used doses of 1.25mg and 5.0mg (Kappos 2006). One study evaluated only the dose of 0.5 mg (Fox 2014). Fingolimod was administered orally in all studies.
- The overall population included in the six trials was 5152 participants with 3531 treated with fingolimod; 2061 with 0.5 mg daily, 1376 with 1.25 mg daily, and 94 with 5.0 mg daily.
- The comparison population included 1621 participants; 923 treated with placebo and 698 with intramuscular interferon beta-1a or other DMDs. Enrolled participants were Caucasian, except in Saida 2012, which included Japanese participants. Participants were affected by relapsing-remitting multiple sclerosis (RRMS) in all studies, and secondary progressive multiple sclerosis (SPMS) in a small percentage in two studies; 11% in Kappos 2006 and 2.3% in Saida 2012

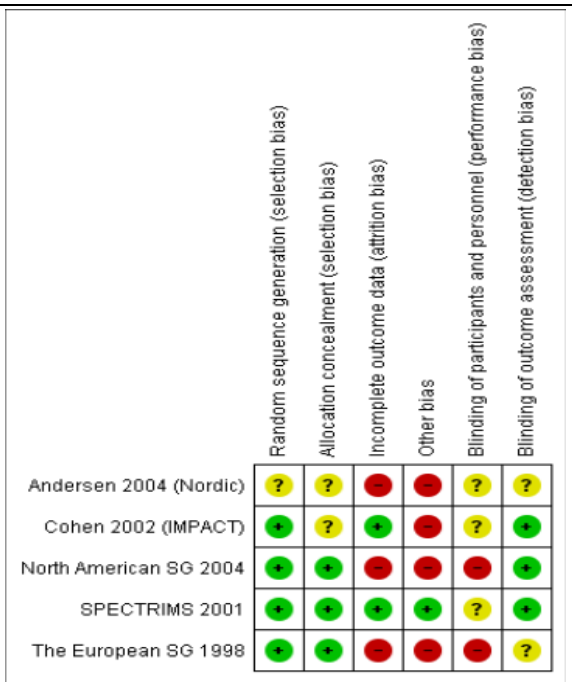


- Overall we gave a GRADE rating of moderate for relapses, low for disability progression, very low for withdrawals due to adverse events,

	and low for MRI gadolinium-enhancing lesions. Ergebnisse Comparison Fingolimod to placebo • Comparing fingolimod administered at the approved dose of 0.5 mg to placebo, we found that the drug at 24 months **increased the probability of being relapse-free (**risk ratio (RR) 1.44, 95% confidence interval (CI) (1.28 to 1.63); moderate quality of evidence), but it might lead to little or **no difference in preventing disability progression** (RR 1.07, 95% CI 1.02 to 1.11; primary clinical endpoints; low quality evidence). • Benefit was observed for other measures of inflammatory disease activity including clinical (**annualised relapse rate**): rate ratio 0.50, 95% CI 0.40 to 0.62; moderate quality evidence; and magnetic resonance imaging (MRI) activity (gadolinium enhancing lesions): RR of being free from (MRI) gadolinium-enhancing lesions: 1.36, 95% CI 1.27 to 1.45; low quality evidence. The mean change of MRI T2-weighted lesion load favoured fingolimod at 12 and 24 months. • No significant increased risk of discontinuation due to **adverse events** was observed for fingolimod 0.5 mg compared to placebo at six and 24 months. The risk of fingolimod discontinuation was significantly higher compared to placebo for the dose 1.25 mg at 24 months (RR 1.93, 95% CI 1.48 to 2.52). • No significant increased risk of discontinuation due to **serious adverse events** was observed for fingolimod 0.5 mg compared to placebo at six and 24 months. A significant increased risk of discontinuation due to serious adverse events was found for fingolimod 5.0 mg (RR 2.77, 95% CI 1.04 to 7.38) compared to placebo at six months. • Quality of life was improved in participants after switching from a different DMD to fingolimod at six months, but this effect was not found compared to placebo at 24 months. Comparison Fingolimod to interferon beta-1a • Comparing fingolimod 0.5 mg to intramuscular interferon beta-1a, we found moderate quality evidence that the drug at one year slightly increased the number of participants **free from relapse** (RR 1.18, 95% CI 1.09 to 1.27) or from gadolinium-enhancing lesions (RR 1.12, 95%CI 1.05 to 1.19), and decreased the relapse rate (rate ratio 0.48, 95%CI 0.34 to 0.70).We did not detect any advantage for preventing disability progression (RR 1.02, 95%CI 0.99 to 1.06; low quality evidence).We did not detect any significant difference for MRI T2-weighted lesion load change. • There was no significant difference for AEs versus interferon beta-1a at 12 months (RR 1.51, 95%CI 0.81 to 2.80; moderate quality evidence). A higher incidence of adverse events was suggestive of the lower tolerability rate of fingolimod compared to interferon-beta 1a. • We found a greater likelihood of participants discontinuing fingolimod, as compared to other DMDs (Studie Fox 2014), due to adverse events in the short-term (six months) (RR 3.21, 95% CI 1.16 to 8.86).
	4. Anmerkungen/Fazit der Autoren

	The results of this review showed that fingolimod is a useful treatment of people with RRMS, because of its efficacy in the prevention of disease activity compared to placebo, although the benefit in terms of preventing disability worsening remains unclear. The direct comparison with other approved first-line DMDs, in particular intramuscular interferon beta-1a, indicates a higher benefit of fingolimod in terms of relapse prevention, but a significant risk of discontinuation in the first months of treatment. A higher incidence of adverse events was found, suggesting lower tolerability for fingolimod versus interferon beta-1a, requiring careful monitoring over time. However, the data were inadequate, for the low number of head to-head RCTs and types of comparisons, with short follow-up duration. 5. Hinweise durch FB Med All Studies were sponsored by Novartis Pharma.
La Mantia L et al., 2012 [24] (assessed as up-to-date 2005) Interferon beta for secondary progressive multiple sclerosis	1. Fragestellung The main objective was to verify whether IFNs treatment in Secondary Progressive Multiple Sclerosis (SPMS) is more effective than placebo in reducing the number of patients who experience disability progression 2. Methodik Population: SPMS definied according to Poser (Poser 1983), Mc Donald (McDonald 2001) or Polman (Polman 2005) criteria. Intervention: Beta recombinant interferons (rIFNb) (IFN-ß-1b 250 ug and 160 ug/m2 and IFN-ß-1a: 60 µg intramuscular injections (i.m.)/22mg weekly/22mg or 44 mg subcutaneously/three times weekly) Komparator: Placebo Endpunkt Primary outcomes • Proportion of patients who had **disability progression or cognitive impairment after two and three years.** Progression of disability, was defined as a 6 month sustained increase in Expanded Disability Status Scale (EDSS) (Kurtzke 1983) of at least one point (0.5 point if baseline EDSS ≥5.5) recorded in a period without relapses. Less stringent criteria (sustained disability at 3 months without mention of intercurrent relapses) have been accepted. • **Safety** was evaluated in terms of: 1. patients with **serious adverse events (SAE),** defined as any untoward medical occurrence at any dose that results in death, requires patients hospitalisation (excluding hospitalisation for relapses), results in persistent or significant disability/incapacity or is life-threatening (WHO www.who-umc.org/umc.html); 2. **proportion of patients who withdrew or dropped out from the study because of adverse events (AE),** i.e. an adverse event for which the causal relation between treatment and the event is at least a reasonable possibility;

	3. **number** of patients with any AE. Secondary outcomes • **Proportion of patients who had one or more relapses** during the treatment and follow-up periods. Relapses were defined as newly developed or recently worsened neurological dysfunction symptoms that lasted more than 24 hours, with or without objective confirmation, and that stabilised or resolved either partially or completely. • **Quality of life (QOL)** measured by validated questionnaires such as the "Multiple Sclerosis Quality of Life-54 " (MSQOL-54), activities of daily living (ADL), psychological aspects measured by validated scales or other instruments for depression or anxiety • **The effect of treatment** on cerebral MRI findings, i.e. number and/or volume of enhancing T1 and new T2 lesions, and cerebral atrophy. Suchzeitraum (Aktualität der Recherche): 1995 – 15.02.2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 5 RCTs (n=3122: 1829 IFN and 1293 placebo) Keine Sprachenrestriktion während der systematischen Recherche. Qualitätsbewertung der Studien: Qualitätsbeurteilung: entsprechend dem Cochrane Handbook Version 5.1.0.
	5. Ergebnisdarstellung • Five trials were eligible (Andersen 2004 (Nordic); Cohen 2002 (IMPACT); North American SG 2004; SPECTRIMS 2001;The European SG 1998). • The baseline characteristics of the studied population were heterogeneous in terms of age, percentage of patients with superimposed relapses, pre-study number of relapse and duration of the disease. Furthermore, the adopted criteria for disability progression for patient inclusion and treatment effect were different. • We cannot exclude the fact that some patients classified as progressive might actually have experienced a prolonged relapse (transient treatment failure).



Ergebnisse

Primary outcomes

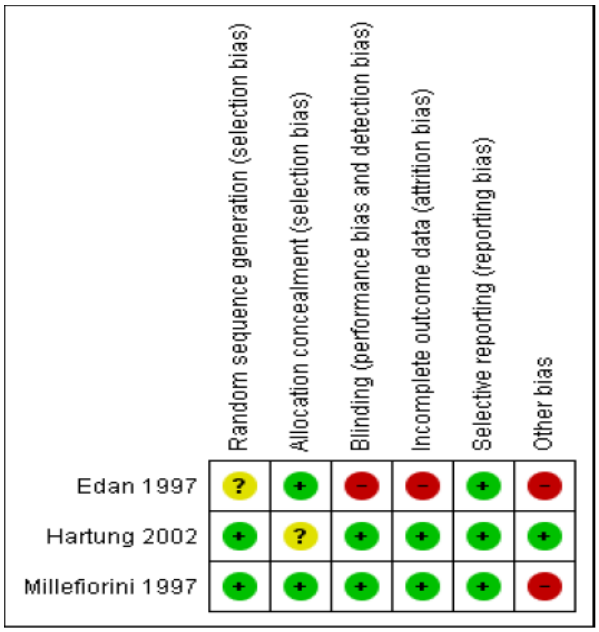
- **The number of patients who had a sustained disability progression**: IFN beta 1a and 1b did not decrease the risk of progression sustained at 6 months (RR, 95% CI: 0.98, [0.82-1.16]) after three years of treatment. A significant decrease of the risk of progression sustained at 3 months (RR, 95% CI: 0.88 [0.80, 0.97]) and of the risk of developing new relapses at three years (RR 0.91, [0.84-0.97]) were found.
- **The number of patients who had progression of cognitive impairment:** It was not possible to give a synthesis due to differences in timepoint reporting, used tests type of measures (PASAT's score and BRB-N). In the first study (North American SG 2004), BRB-N's score decrease over time appeared to be similar between treatment groups, while no significant changes in mean PASAT's score were found at the end of 24 month follow-up (Cohen 2002)
- **Safety:** The risk of experiencing a Serious Adverse Event (SAE) was not significantly increased (RR, (95% CI): 1.00 [0.83; 1.19]) in treatment group, while the number of patients withdrew or dropped out due to AEs were higher in the treated group (RR (95% CI): 2.62 [1.92, 3.57]).
- Sixteen deaths occurred in the treated group (4 suicide, 3 pulmonary embolism, 3 cardiac arrest, 1 cancer, 1 intracerebral haemorrhage, 2 brainstem infarction and urosepsis, 2 unknown) and seven in the control groups (1 subarachnoid haemorrhage, 2 suicide, 1 "arteriosclerosis", 1 pneumonia, 2 unknown).
- The following AEs were significantly related to the IFN treatment injection site reactions, cutaneous necrosis and influenza like syndrome. Among haematological AEs, only leukopenia was significantly related to treatment

Secondary outcomes:

	• **Risk to have relapses** during a three year follow-up: IFN-beta significantly reduces the risk: RR (95% CI): 0.91 [0.84,0.97] • **Relapse rate during follow-up**: We compared Betaseron® 250 ug versus placebo and Rebif® 44 ug versus. From these data the Mean Difference was -0.16 [-0.21, -0.10] • **Quality of life:** It may be described that a slight positive effect favouring the IFN group was found for the physical domain at 6 and 12 months and at last visit in The European SG 1998. To the contrary, no significant differences between treatment groups at any time point was found in health-related QOL measures in North American SG 2004. Significant benefit favouring IFNbeta-1a treatment was observed in MSQLI in the IMPACT study (Miller 2006). • **Depression and anxiety:** It may be described that patients on interferon beta 1b had no increased incidence of new or worsened depression, according to studies results (The European SG 1998; North American SG 2004; SPECTRIMS 2001). Depression was reported in 29% of patients receiving placebo, 32%receiving low-dose IFN, and 35% receiving high-dose IFN (SPECTRIMS 2001). • **Change in MRI markers of disease activity:** The risk of developing new active brain lesions decreased over time but this data was obtained from single studies on Magnetic Resonance Imaging (MRI), performed in subgroups of patients; in spite of no effect on progression, the radiological data supported an effect on MRI parameters.
	6. Anmerkungen/Fazit der Autoren This review defines the profile of therapeutic effects of IFN in SPMS; this therapy is able to prevent relapses, while the deterioration of the disease remains unresolved. The "window of therapeutic opportunity" for IFNs within the natural history of the disease is limited to the inflammatory phase, rIFNs not being useful in the secondary phase of the disease when the progression is established. 7. Hinweise durch FB Med: Vergleich der Studien bezüglich kognitive Beeinträchtigung, Lebensqualität, Depression, MRI Marker auf Grund der Heterogenität in den Erhebungsinstrumenten und Zeitpunkten nicht möglich.
Martinelli Boneschi F et al., 2013 [26] Mitoxantrone for multiple sclerosis	1. Fragestellung "The main objective was to assess the efficacy and safety of Mitoxantrone (MX) compared to a control group in relapsing-remitting (RRMS), progressive relapsing (PRMS) and secondary progressive (SPMS) MS participants."
	2. Methodik Population: Poser (Poser 1983) or McDonald criteria and further revisions. We excluded patients with primary progressive (PP) MS. Intervention: Mitoxantron (72-96 mg/m^2 Körperoberfläche) Steroide in Kombination mit Mitoxantron Komparator: Plazebo mit/ohne Steroide

	Endpunkte: Primary outcomes • Number of participants who had confirmed **disability progression at one year and after**, from the inclusion into the trial: increase of at least 1 point above the entry score if baseline score < 5.5, and of at least a half-point if baseline score > 5.5, of the Kurtzke Expanded Disability Status Scale (EDSS) • Number of participants who withdrew from the study because of **major side effects of the drug**, considered as those side effects causing death or hospitalisation of the participant. Secondary outcome: • mean change in **expanded disability status scale** (EDSS) in the allocated treatment groups at one year and longer; • patients with **no relapses** at six months or one year and after; • **annualised relapse rate** at six months or one year and after; • frequency of major (cardiotoxicity; major haematological abnormalities) and minor (nausea; vomiting; alopecia; urinary infections) side effects during the follow-up period; Suchzeitraum: Mai 2013 Keine Sprachrestriktion während der Literaturrecherche Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 RCTs (n=221) Qualitätsbewertung der Studien: Cochrane Handbook Version 5.1.0
	3. Ergebnisdarstellung • Three trials contributed to this review. They were published between 1997 and 2002: Edan 1997, Millefiorini 1997 and Hartung 2002. It is worth mentioning that Edan 1997 was published three years after the end of the recruitment period of the trial, Millefiorini 1997 four years later and Hartung 2002 seven years later. A total of 221 participants contributed to the present review, of whom 111 were assigned to MX and 110 to placebo; Hartung 2002 accounted for 58% of the total number of participants. • All studies recruited patients affected by definite MS (McDonald 2001; Poser 1983). The disease course and disability status inclusion criteria were different across studies. • Disability progression: At the time we assessed the data for this review, we realised that the definitions and measures of disability progression varied between the included trials. Therefore, we decided to perform additional analyses accepting the definitions of disability given in the original papers • In all the studies MX was the active drug, apart from the Edan 1997 study in which MX was given with steroid therapy. The placebo was a short course of steroids (1 g /month of intravenous methylprednisolone). However, different dosages and time schedules were used in the studies. • No major heterogeneity was found according to the statistical

methods used. meta-analysis.



Progression of disability

- MX reduced the progression of disability at two years follow-up (proportion of participants with six months confirmed progression of disability (OR 0.30, 95% CI 0.09 to 0.99 and MD - 0.36, 95% CI- 0.70 to -0.02; P = 0.04)
- Post-hoc-analysis:

a. with three or six month confirmed disability progression: at one year only data from Millefiorini 1997 were available for 51 participants (23% of the total) of whom eight progressed, two in the MX group and six in the placebo group, leading to an OR of 0.24 (95% CI 0.04 to 1.33; P = 0.1).
b. At two years, data from two trials (Hartung 2002; Millefiorini 1997) and 179 participants (81% of the total) were available for the analysis: 27 participants (12% of the total) progressed over two years (6 patients in the MX group and 21 in the placebo group). This corresponded to a sustained overall efficacy of the drug on the progression of disability (OR 0.23, 95% CI 0.09 to 0.59; P = 0.002).

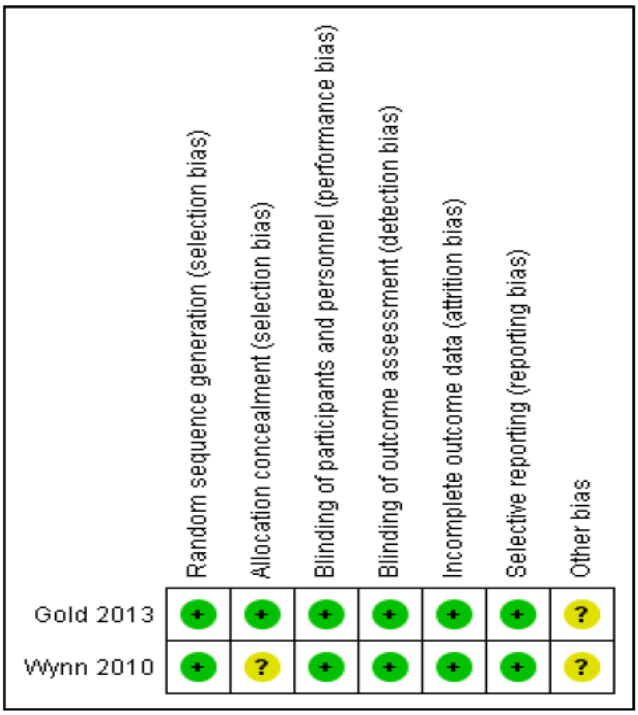
Patients with no relapses

- At six months or one year, 93 participants from Edan 1997 and Millefiorini 1997 were available. 45 participants did not experience any relapses at six months or one year follow-up (33 MX-treated and 13 placebo-treated participants). The OR of the two studies was 5.39 (95%CI 2.21 to 13.15; P = 0.0002) suggesting an important role of MX in relapse rate reduction.
- At two years, data from 179 participants (81% of the total) were provided by Millefiorini 1997 and Hartung 2002. Seventy-nine of them didn't have any relapse at the two year follow-up (51 MX-treated patients and 28 placebo-treated patients); the OR was 2.82 (95% CI 1.54 to 5.19; P = 0.0008)

	Mean change in Expanded Disability Status Scale • At six months or one year, a subgroup of participants enrolled in Millefiorini 1997 (11%of the total) were available for the analysis. The effect of treatment on the patients' disability was not statistically significant (MD -0.35, 95% CI -0.86 to 0.16). • At two years, 175 participants (79.2% of the total) enrolled in Hartung 2002 and Millefiorini 1997 were available for the outcome. The effect of treatment on the patients' disability was statistically significant (MD -0.36, 95% CI -0.7 to -0.02; P = 0.04) based on a single study as no dispersion measures were provided for Millefiorini 1997. **Annualised relapse rate** • For six months or one year, data from Millefiorini 1997 and 52 participants were used for the analysis, with a MD of -1.02 (95% CI -1.69 to -0.35; P = 0.003). • At two years, data from 206 participants were analysed, including Millefiorini 1997 and Hartung 2002. In both studies there was a reduction in the annualised relapse rate in MX-treated versus placebo-treated participants. However, as no dispersion measure was available for Hartung 2002, only Millefiorini 1997 contributed to the estimate of weighted mean difference (MD -0.85, 95% CI -1.47 to -0.23; P = 0.007). **Safety** Amenorrhea • MX-treated female participants had an OR of 22.3 (95% CI 4.03 to 123.47; P = 0.0004) of developing amenorrhoea compared with placebo-treated participants. Persistent amenorrhoea had an OR of 8.27 (95% CI 1.02 to 67.18; P = 0.05). Symptomatic cardiac events and cardiotoxicity (LVEF<50%) • 2 MX-treated participants showed a decrease in LVEF to below 50% at the 3 year follow-up which was not present at the end of the treatment and one interrupted the treatment after four doses of the drug because of decreased LVEF. An LVEF reduction, lower than 50%, was observed in 3/110 (2.7%)of MX-treated participants (Hartung 2002), resulting in discontinuation of therapy in three of them. Nausea and vomiting • It was reported by 62/110 MX-treated participants (56.3%) and by 13/109 (13%) of placebo-treated participants. Therefore, MX-treated participants had a risk which was 14.01 times greater (95% CI 6.36 to 30.85; P < 0.00001) than for placebo-treated participants of developing nausea and vomiting during the administration of the drug. Alopecia • It was reported by 50/110 MX-treated participants (45.5%) and by 20/109 (18.3%) placebo-treated participants. MX-treated participants had a 4.65 times greater risk (95% CI 2.37 to 9.12; P <0.0001) than placebo-treated participants of developing alopecia during the treatment period. Urinary tract infections

	• Twenty-seven of 110 MX-treated participants (24.5%) and nine of 109 (8.3%) placebo-treated participants experienced urinary tract infection during the trials (OR 3.76, 95% CI 1.67 to 8.46; P = 0.001). Respiratory tract infections • Forty of 110 MX-treated participants (36.4%) and 35/109 (32.1%) placebo-treated participants experienced respiratory tract infections during the trials. The difference between the two groups was not statistically significant (OR 1.34, 95%CI 0.72 to 2.50; P = 0.35). Headache • Headache was reported by 7/110 MX-treated participants (6.4%) and 5/109 (4.6%) placebo-treated participants. The difference was not statistically significant (OR 1.36, 95% CI 0.44 to 4.24; P = 0.59).
	4. Anmerkungen/Fazit der Autoren „We found a moderate effect of MX treatment in reducing disability progression and the frequency of exacerbations in patients affected by worsening RR, PR and SPMS in the short-term follow-up (two years). (…) Given the partial efficacy of MX and the increased reports in the literature of cardiotoxicity (~12% of risk of systolic dysfunction) and therapy-related leukemia events (0.8%) in MX-treated patients, MX should be limited to treating patients with worsening RR and SPMS with evidence of persistent inflammatory activity after a careful assessment of the individual patients' risk and benefit profiles, which should also consider the availability of alternative therapies with less severe adverse events."
Liu J et al., 2013 [25] First published 2010, previously updated 2012 Daclizumab for relapsing remitting multiple sclerosis	1. Fragestellung To assess the safety of daclizumab and its efficacy to prevent clinical worsening in patients with RRMS.
	2. Methodik Population: 5. Diagnosis of RRMS by the criteria of Poser (Poser 1983) or McDonald criteria 6. An Expanded Disability Status Scale (EDSS) score between 1.0 and 7.0 Intervention: Daclizumab intravenously or subcutaneously, alone or combined with interferon beta treatment (Wynn 2010: High-dose daclizumab was 2 mg/kg of subcutaneous daclizumab every 2 weeks for 11 doses. Low dose was 1mg/kg of subcutaneous daclizumab every 4 weeks for 6 doses on top of interferon beta regime. Gold 2013: s.c. injections of daclizumab HYP 150 mg/300mg). Komparator: placebo (Wynn:2010: + interferon beta therapy)

	Endpunkte Primary outcomes Efficacy 1. Increased disability change defined as a six months' sustained increase in EDSS of at least 1 to 2 points change (Kurtzke 1983). 2. Proportion of patients who had new clinical relapses. Safety 1. Number of patients who exhibited any type of adverse events. Secondary outcomes 1. Number of new or enlarged gadolinium contrast-enhancing lesions (Gd-CELs) on monthly brain MRIs collected; 2. Number of total Gd-CELs on monthly brain MRIs collected; 3. Immunological biomarker measurement outcomes, which were measured in the treatment phase and at the completion of treatment versus baseline; 4. Mean change in Neurologic Rating Scale (NRS). Suchzeitraum: Update bis Mai 2013 Anzahl eingeschlossene Studien/Patienten (Gesamt): 2 RCTs (n=851) Suche ohne Restriktion der Sprache. Qualitätsbewertung der Studien: • Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011)
	3. Ergebnisdarstellung • Both were multi-centre, double-blind, parallel RCTs. Wynn 2010: n=230 and Gold 2013: 621



- We were unable to undertake a meta-analysis because of lack of data and different time points of evaluation.
- The quality of the evidence was limited by the low number of included studies and different time points of evaluation, although both of them were of high quality.

Ergebnisse

- Wynn 2010:

Change in EDSS score at 24 weeks in n=230:

Interferon beta + placebo (n=77): 0 (range -2 to 3)

Interferon beta + low dose daclizumab (n=78): 0 (-2 to 4)

Interferon beta + high-dose daclizumab (n=75): 0 (-2 to 2)

The proportion of patients who had new clinical relapses and the annualised relapse rate were not significantly different in the interferon and placebo group, in the interferon beta and high-dose daclizumab group, and in the interferon beta and low-dose daclizumab group.

- Gold 2013:

Changes in EDSS score from baseline after52 weeks in n=621

Placebo group (n=204): 0.09 ± 0.71

Low dose daclizumab group (n=208): -0.08 ± 0.52 (p=0.01 versus placebo)

High dose daclizumab (n=209): 0.05 ± 0.61 (p=0.49)

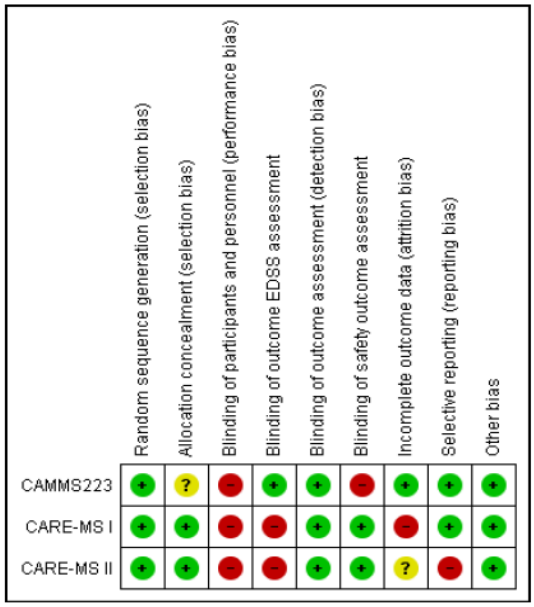
At 52 weeks, the annualised relapse rate was lower for patients in low-dose daclizumab (54% reduction, 95% CI 33% to 68%) or high-dose daclizumab (50% reduction, 95% CI 28% to 65%) than for those given placebo.

The proportion of patients with new relapsing MS was significantly reduced in both daclizumab groups (19%in low-dose daclizumab group,

	20% in high-dose daclizumab group) compared with placebo group (36%) (P value < 0.0001 and P value = 0.00032, respectively) • Adverse events With regards to safety, no change in number of patients with any adverse events (RR 0.98, 95% CI 0.89 to 1.07) or serious adverse events (RR 1.15, 95% CI 0.29 to 4.54) was found in daclizumab groups compared with placebo group. Infections were the most frequent adverse events and were resolved with standard therapies.
	4. Anmerkungen/Fazit der Autoren There is insufficient evidence to determine whether daclizumab is more effective than placebo in patients affected by relapsing remitting multiple sclerosis (RRMS) both in terms of clinical and magnetic resonance imaging (MRI) measures of outcomes. The efficacy of daclizumab still needs to be further evaluated. Daclizumab appears to be relatively well tolerated. 5. Hinweise durch FB Med Studien wurden durch Facet Biotech und Biogen Idec sowie Biogen idec und Abbvie Biotherapeutics Inc finanziert.
Riera R et al., 2016 [29] Alemtuzumab for multiple sclerosis	1. Fragestellung To assess the safety and effectiveness of alemtuzumab used alone or associated with other treatments to decrease disease activity in people with any form of MS.
	2. Methodik Population We included adults diagnosed with MS according to the Mc- Donald criteria (McDonald 2001; Polman 2011), Poser criteria (Poser 1983): RRMS + SPMS Intervention: Alemtuzumab alone or associated with other medications at any dose and for any course duration (alemtuzumab 12 or 24mg). Komparator: Subcutaneous injection of interferon beta-1a 44µg three times weekly after dose titration. Endpunkt Primary outcomes (assessed after 12 and 24 months follow up) • Relapse-free survival. Relapse was defined as newly developed or recently worsened symptoms of neurological dysfunction, lasting longer than 24 hours and objectively confirmed. • Sustained disease progression-free survival, defined as a ≥ 1.0-point increase in the Expanded Disability Status Scale (EDSS) score (Kurtzke 1983) for participants with a baseline score ≤ 5.0 or a ≥ 0.5-point increase for participants with a baseline score ≥ 5.5 points confirmed at six months.

	Secondary outcomes (assessed after 12, 24 months and at the end of follow up) • Number of participants free of clinical disease activity, defined as no relapses and no sustained accumulation of disability. Sustained accumulation disability was defined as an increase of at least 1.5 points on the Expanded Disability Status Scale (EDSS) for patients with a baseline score of 0 and of at least 1.0 point for patients with a baseline score of 1.0 or more. • Quality of life as assessed by the Multiple Sclerosis Quality of Life scale (MSQOL)-54 (Vickrey 1995) or the Multiple Sclerosis Quality of Life Inventory (MSQLI) (Fischer 1999) + Change in disability as assessed by the EDSS (Kurtzke 1983). • Fatigue as assessed by the Fatigue Severity Scale or the Fatigue Index Scale (Krupp 1989). • Number of participants with new or enlarging T2- hyperintense lesions on magnetic resonance imaging (Li 1999). Suchzeitraum: bis 30. April 2015 Keine Sprachenrestriktion vorgenommen. Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 RCTs (n=1713) Qualitätsbeurteilung der Studien: Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).
	3. Ergebnisdarstellung • Participants were treatment-naive in the CARE-MS I and CAMMS223 studies. The CARE-MS II study included only participants with at least one relapse while being treated with interferon beta or glatiramer for at least six months. • CAMMS223 study, a phase II trial: alemtuzumab (either 12 mg per day or 24 mg per day) was given by intravenous infusion on five consecutive days during the first month and on three consecutive days at months 12 and 24 (CAMMS223). • CARE-MS I (or CAMMS323) study, a phase III trial: alemtuzumab (12 mg per day) was given by intravenous infusion on five consecutive days during the first month and on three consecutive days at month 12 (CARE-MS I). • CARE-MS II (or CAMMS324) study, a phase III trial: alemtuzumab (either 12 mg per day or 24 mg per day) was given by intravenous infusion on five consecutive days during the first month and on three consecutive days at month 12 (CARE-MS II). • The overall quality of the RCTs was low since in all of them we categorised at least one of the main domains (generation of allocation sequence, allocation concealment and blinding) as having a high risk of bias. In all studies, the participants and personnel were not blinded because the adverse effects related to each intervention preclude the masking. Additionally, in two studies the assessment of the EDSS scores could also be not blinded. • We noted no statistically significant heterogeneity among the studies for the co-primary outcomes. The quality of the evidence for dropouts

was impaired by the low number of events in the trials.



Alemtuzumab 12 mg (compared to s.c. interferon beta-1a) was associated with (3 RCTs):

• higher relapse-free survival at 24 months and 36 months;

• a lower number of participants with sustained disease progression-free survival;

• a slightly higher number of participants with at least one adverse event after 24 months;

• a higher improvement in Expanded Disability Status Scale (EDSS) scores after 36 months;

• a higher improvement in EDSS scores after 24 months (for patients previously treated with interferon or glatiramer acetate);

• a lower number of participants with new or enlarging T2- hyperintense lesions on magnetic resonance imaging;

Alemtuzumab 24 mg (compared to s.c. interferon beta-1a) was associated with (1 RCTs):

• higher relapse-free survival at 36 months;

• a lower number of participants with sustained disease progression-free survival at 36 months;

• no statistical difference in the number of participants with at least one adverse event at 24 and 36 months;

• a higher improvement in EDSS scores after 36 months;

• a lower number of dropouts at 24 months, but not at 36 months.

Adverse events:

- The higher number of participants with at least one adverse event was not associated with a higher dropout rate probably because most of

	these events were mild or moderate. • Data for severe adverse events were not provided separately by any of the included studies.
	4. Anmerkungen/Fazit der Autoren In patients with relapsing-remitting MS, alemtuzumab 12 mg was better than subcutaneous interferon beta-1a for the following outcomes assessed at 24 months: relapse-free survival, sustained disease progression-free survival, number of participants with at least one adverse event and number of participants with new or enlarging T2-hyperintense lesions on MRI. The quality of the evidence for these results was low to moderate. Alemtuzumab 24 mg seemed to be better than subcutaneous interferon beta-1a for relapse-free survival and sustained disease progression-free survival, at 36 months.

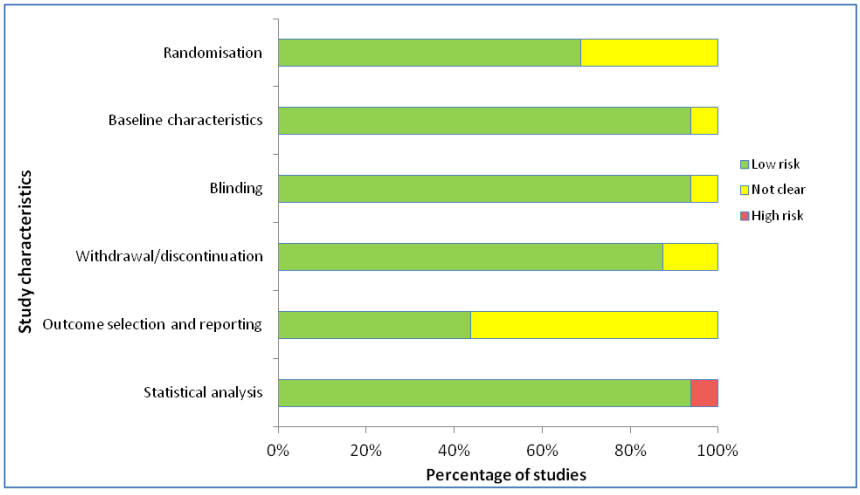
Systematische Reviews

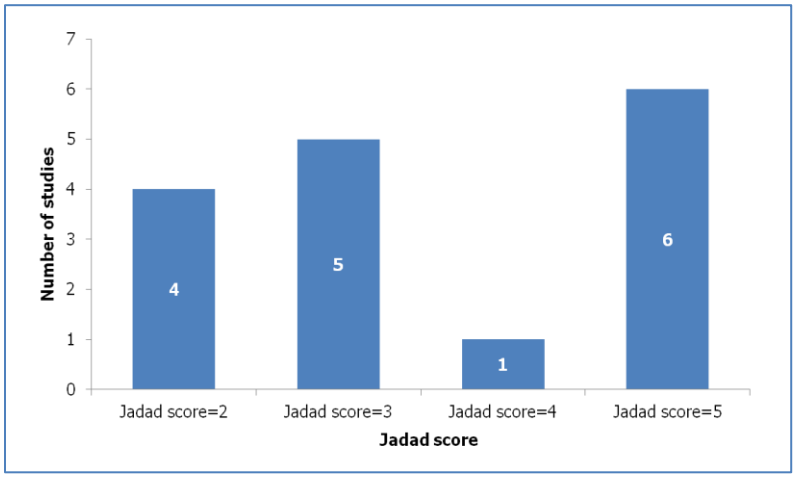
CADTH, 2014 [2] Comparative Clinical and Cost-Effectiveness of Drug Therapies for Relapsing-Remitting Multiple Sclerosis	1. Fragestellung • What is the comparative efficacy and safety between individual disease-modifying agents in RRMS? • What is the comparative efficacy and safety of combination therapy (two or more diseasemodifying agents compared with individual agents or other combinations) in RRMS?
	2. Methodik Population: Patients diagnosed with RRMS RCTs having a mixed population (i.e., persons with primary-progressive or secondary-progressive MS in addition to persons with RRMS will be included for completeness if the RRMS population is greater than 50% of the total population) Intervention und Komparator: Disease-modifying agents Currently available (formulations and doses approved and available in Canada only will be included) • Fingolimod - oral • Interferon beta-1 a - injectable • Interferon beta-1 b- injectable • Natalizumab - injectable • Glatiramer acetate – injectable • Teriflunomide - oral • Dimethyl fumarate - oral • Alemtuzumab – injectable • Placebo Endpunkte: • Relapse • Disability • MRI changes • Quality of life • Deaths • Serious adverse events • Discontinuation of treatment because of adverse events • Adverse events Suchzeitraum (Aktualität der Recherche): November 9th, 2012. Regular alerts were established to update the search until October 2013. Anzahl eingeschlossene Studien/Patienten (Gesamt): 30 unique studies. Twenty-seven trials provided monotherapy comparisons, and four trials provided comparisons between monotherapy and combination therapy. Qualitätsbewertung der Studien: Standardized table based on major items from the SIGN-50 instrument for intemal validity. Additional critical appraisal was performed based on input from clinical experts.

	3. Ergebnisdarstellung Evidence was available for the following drug therapies: alemtuzumab (three RCTs), dimethyl fumarate (two RCTs), fingolimod (three RCTs), glatiramer acetate (eight RCTs), interferon beta-1a subcutaneous (nine RCTs), interferon beta-1a intramuscular (nine RCTs), interferon beta-1b (five RCTs), natalizumab (one RCT), and teriflunomide (two RCTs). NMAs were conducted only for those outcomes for which sufficient data were available to allow for a stable network, ARR, and proportion of patients with sustained disability. For the remaining outcomes, direct pairwise results only are presented. Direct evidence • Compared with placebo, all active treatments (excepting alemtuzumab and interferon beta-1a 60 mcg, for which there were no placebo-controlled trials) resulted in statistically lower ARRs; rate ratios (95% confidence intervals [CI]) ranged from 0.32 (0.27, 0.37) for natalizumab to 0.81 (0.67, 0.96) for interferon beta-1a 30 mcg. Among active comparisons, ARRs were statistically lower for interferon beta-1b 250 mcg (0.69 [0.54 to 0.87]), interferon beta-1a 44 mcg (0.76 [0.59 to 0.98]), and fingolimod (0.49 [0.38 to 0.63]) compared with interferon beta-1a 30 mcg. In addition, ARRs were statistically lower for alemtuzumab at both 12 mg (0.44 [0.34 to 0.55]) and 24 mg (0.22 [0.14 to 0.35]) compared with interferon beta-1a 44 mcg, and for dimethyl fumarate (0.76 [0.62 to 0.93]) compared with glatiramer acetate. • Compared with placebo, all active treatments exhibited a numerically lower risk of sustained disability progression, but results were only statistically significant for interferon beta-1a (both 44 mcg and 30 mcg), natalizumab, fingolimod, teriflunomide 14 mg, and dimethyl fumarate; relative risk (95% CI) for these agents ranged from 0.59 (0.46 to 0.75) for natalizumab to 0.74 (0.57 to 0.96) for teriflunomide 14 mg. Among active comparisons, the risk of sustained disability progression was statistically lower for alemtuzumab at both 12 mg (0.59 [0.40 to 0.86]) and 24 mg (0.42 [0.21 to 0.84]) compared with interferon beta-1a 44 mcg, and for interferon beta-1b 250 mcg (0.44 [0.2 to, 0.80]) compared with interferon beta-1a 30 mcg. • Among active comparisons, MRI findings were more favourable for alemtuzumab compared with interferon beta-1a 44 mcg; and more favourable for all three of fingolimod, interferon beta-1b 250 mcg, and interferon beta-1a 44 mcg compared with interferon beta-1a 30 mcg. Compared with glatiramer acetate, dimethyl fumarate resulted in a statistically lower mean number of T2 lesions, but the mean number of gadolinium-enhancing (GdE) lesions was not statistically different between these two treatments. • Health-related quality of life findings were reported in only two trials, and the clinical significance of reported results was uncertain. • The incidence of serious adverse events and treatment discontinuation did not differ statistically between treatments in the majority of trials, excepting a higher incidence of treatment discontinuation for interferon beta-1a 44 mcg compared with both placebo and alemtuzumab 12 mg. Adverse events of note were treatment-specific and included influenza-like symptoms for interferons, injection site reactions and hypersensitivity for glatiramer acetate, cardiovascular disorders for fingolimod, infusion reactions

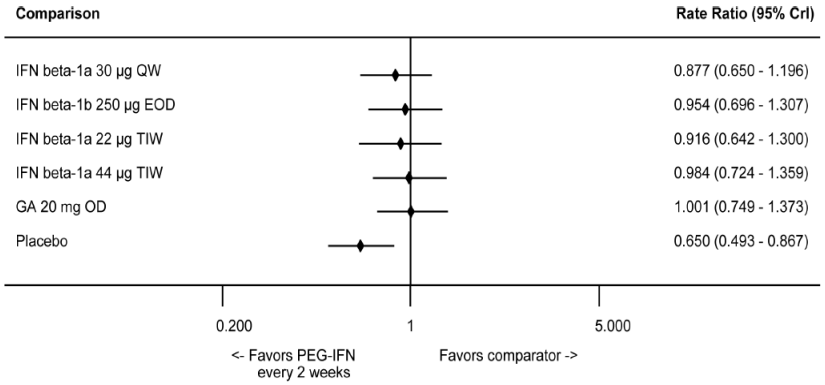
	and skin disorders for natalizumab, flushing for dimethyl fumarate, thyroid disorders for alemtuzumab, and alopecia for teriflunomide. Indirect evidence • There was considerable agreement between direct and indirect evidence for the outcome of ARR. Based on the NMA, alemtuzumab and natalizumab had the greatest activity, reducing the ARR by approximately 70% compared with placebo. Fingolimod and dimethyl fumarate had similar activity to each other, reducing the ARR by approximately 50% compared with placebo. Finally, subcutaneous interferons, glatiramer acetate, and teriflunomide appear to have similar activity to each other, reducing the ARR by approximately 30% compared with placebo. Intramuscular interferon beta-1a had the lowest activity of all active agents. • Compared with placebo, all treatments exhibited a trend toward a reduced risk of sustained disability progression. Estimated effect sizes were greatest for alemtuzumab and natalizumab, followed by dimethyl fumarate and interferon beta-1b, and lowest for interferon beta-1a, glatiramer acetate, and teriflunomide. However, credible intervals were wide and there was considerable overlap of credible intervals among all agents, resulting in unclear distinction between treatments. Combination Therapy Versus Monotherapy: One RCT provided evidence for each of the following comparisons in treatment-experienced patients: natalizumab plus interferon beta-1a 30 mcg versus interferon beta-1a 30 mcg, natalizumab plus glatiramer acetate versus glatiramer acetate, and teriflunomide plus interferon beta versus interferon beta. One additional RCT in treatment-naive patients compared interferon beta-1a 30 mcg plus glatiramer acetate to both agents alone. • Compared with interferon beta-1a 30 mcg alone, natalizumab plus interferon beta-1a 30 mcg resulted in a statistically lower ARR and a lower proportion of patients with sustained disability progression during the two-year trial. Two patients in this trial developed PML. • The two studies comparing natalizumab plus glatiramer acetate versus glatiramer acetate alone, and teriflunomide plus interferon beta versus interferon beta alone reported no improvements in measures of relapse or disability with combination therapy; however, both 24-week trials did report more favourable MRI findings with combination therapy. • The combination of glatiramer acetate plus interferon beta-1a 30 mcg was not superior to either agent alone for most outcomes over the three-year trial, with the exception of a lower ARR for patients treated with the combination compared with interferon beta-1a alone. • There were no apparent differences between combination therapy and monotherapy in the incidence of death, serious adverse events, and discontinuation of treatment because of adverse events in the reviewed trials.

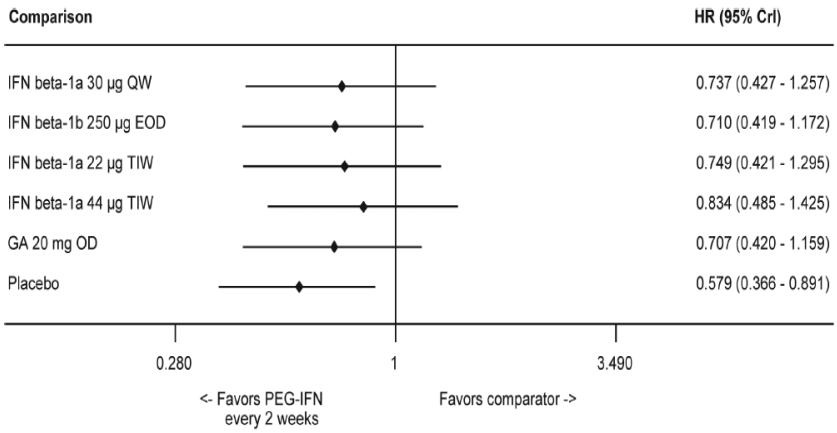
	4. Fazit der Autoren: Results from the systematic review and NMA suggest that all active treatments produce statistically significant reductions in the ARR compared with no treatment, and that there are clear between-treatment differences. Specifically, compared with no treatment, reductions in the ARR are approximately 70% for natalizumab or alemtuzumab; 50% for fingolimod or dimethyl fumarate; and 30% for subcutaneous interferons, glatiramer acetate, or teriflunomide. Between-treatment differences were less apparent regarding the risk of sustained disability progression. Given the wide credible intervals observed in the NMA, small between-treatment differences observed in the NMA should be interpreted with caution. Adverse events were treatment-specific and may be an important consideration in treatment selection. Given that the included studies were limited in their ability to identify infrequent or rare adverse events, decision-makers may consider that older agents such as the interferons and glatiramer acetate have the benefit of a longer post-market period. Anmerkungen der Autoren • None of the monotherapy trials explicitly included patients who had inadequate response or intolerance to prior treatment; thus, it is uncertain to what extent the results of the current review are applicable to this patient population. • In the three combination trials that enrolled patients previously treated with monotherapy, it was unclear to what extent patients could be considered to have had an inadequate response to treatment. In addition, these trials do not provide evidence that an add-on (combination) strategy is superior to a drug switch strategy. • There is a paucity of direct comparative evidence between treatments, given that the majority of trials compared active treatments with placebo. Indirect treatment comparisons via NMA of studies conducted over a 20-year time period were complicated by the heterogeneity of study and patient characteristics. • Relatively short duration of the included trials and the selection of primary outcome. Specifically, many trials selected short-term outcomes (e.g., relapse and MRI findings) as their primary outcome, which have an uncertain link to long-term disability.
Tolley K et al., 2015 [30] A Network Meta-Analysis of Efficacy and Evaluation of Safety of Subcutaneous Pegylated Interferon Beta-1a versus Other Injectable Therapies for the Treatment of Relapsing-Remitting Multiple Sclerosis	1. Fragestellung To evaluate the relative efficacy and safety of peginterferon beta-1a compared to other injectable DMTs approved for the treatment of RRMS
	2. Methodik Population: RRMS or a patient population with a subgroup composed of >80% of patients with RRMS Intervention peginterferon beta-1a 125 µg every 2 weeks Komparator IFN beta-1a 30 µg QW, IFN beta-1b 250 µg every other day (EOD), IFN beta-1a 22 µg three times a week (TIW), IFN beta-1a 44 µg TIW, GA 20mg OD or placebo Endpunkt ARR (measured at study endpoint), CDP3M and CDP6M (including onset of disability progression at the end of the randomized phase of the trials). Safety: most common AEs (≥5% incidence in any

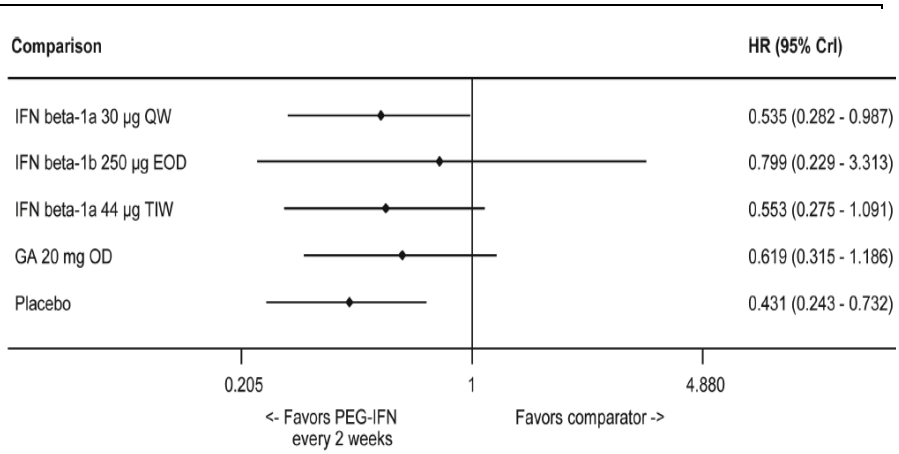
	treatment group), annual incidence of any AEs or serious AEs Suchzeitraum (Aktualität der Recherche): bis 2014 Articles were limited to those published in English. Anzahl eingeschlossene Studien/Patienten (Gesamt): 16 RCTs Qualitätsbewertung der Studien: Jadad Score
	3. Ergebnisdarstellung • In terms of quality assessment, all 16 trials were randomized, but only 11 trials reported the randomization method and treatment allocation concealment. The majority of trials (15 of 16) were blinded appropriately to avoid detection bias, and there were no major imbalances in the baseline characteristics of the treatment groups. All but one trial analyzed outcomes on an intention- to-treat basis. • Baseline patient characteristics were similar across trials and treatments. The mean age across trials ranged from 29–39 years, and the majority of participants were female and Caucasian. There were variations in the mean disease duration across trials, with values ranging from 1–8.3 years. • Similarly, there were variations in the definition of relapse across trials, particularly the duration of symptoms. • Of the 16 trials included in the analysis, nine defined relapse as the appearance of a new neurological symptom or worsening of an old symptom lasting at least 24 hours. Five trials required a duration lasting at least 48 hours, and two trials did not specify the duration. 


Number of studies
7
6
5
4
3
2
1
0
4
5
1
6
Jadad score=2
Jadad score=3
Jadad score=4
Jadad score=5
Jadad score

Ergebnisse


Comparison
Rate Ratio (95% CrI)
IFN beta-1a 30 µg QW
0.877 (0.650 - 1.196)
IFN beta-1b 250 µg EOD
0.954 (0.696 - 1.307)
IFN beta-1a 22 µg TIW
0.916 (0.642 - 1.300)
IFN beta-1a 44 µg TIW
0.984 (0.724 - 1.359)
GA 20 mg OD
1.001 (0.749 - 1.373)
Placebo
0.650 (0.493 - 0.867)
0.200
1
5.000
<- Favors PEG-IFN every 2 weeks
Favors comparator ->
Fig 5. Summary Plot Showing Relative ARR of Peginterferon Beta-1a vs Other Injectables (RR and 95% CrI). Effect size <1 indicates favorable efficacy of intervention. Abbreviations: ARR, annualized relapse rate; CrI, credible interval; EOD, every other day; GA, glatiramer acetate; IFN, interferon; OD, once daily; PEG, pegylated; QW, once a week; RR, rate ratio; TIW, 3 times a week.
doi:10.1371/journal.pone.0127960.g005


Comparison
HR (95% CrI)
IFN beta-1a 30 µg QW
0.737 (0.427 - 1.257)
IFN beta-1b 250 µg EOD
0.710 (0.419 - 1.172)
IFN beta-1a 22 µg TIW
0.749 (0.421 - 1.295)
IFN beta-1a 44 µg TIW
0.834 (0.485 - 1.425)
GA 20 mg OD
0.707 (0.420 - 1.159)
Placebo
0.579 (0.366 - 0.891)
0.280
1
3.490
<- Favors PEG-IFN every 2 weeks
Favors comparator ->
Fig 6. Summary Plot Showing the CDP3M for Peginterferon Beta-1a vs Comparators (HR and 95% CrI). Effect size <1 indicates favorable efficacy of intervention. Abbreviations: CDP3M, 3-month confirmed disability progression; CrI, credible interval; EOD, every other day; GA, glatiramer acetate; HR, hazard ratio; IFN, interferon; OD, once daily; PEG, pegylated; QW, once a week; TIW, 3 times a week.

	 **Fig 7. Summary Plot Showing the CDP6M for Peginterferon Beta-1a vs Comparators (HR and 95% CrI).** Effect size <1 indicates favorable efficacy o intervention. Abbreviations: CDP6M, 6-month confirmed disability progression; CrI, credible interval; EOD, every other day; GA, glatiramer acetate; HR, hazard ratio; IFN, interferon; OD, once daily; PEG, pegylated; QW, once a week; TIW, 3 times a week. Adverse Events • Comparison of AEs was not possible within the NMA. However, based on a non-meta-analyzed comparison the safety and tolerability profile of peginterferon beta-1a 125 µg every 2weeks appears consistent with that of other evaluated treatments, with no evidence for additional AE burden. • The most frequently reported AE for peginterferon Beta-1a, is similar between peginterferon beta-1a and IFN beta-1a 44 µg TIW, and higher than those reported for other IFNs and GA. However, similar to IFNs and GA, the majority of patient-reported injection site reactions with peginterferon beta-1a were mild or moderate, with only 3% of patients reporting severe injection-site reactions over 2 years of treatment
	4. Anmerkungen/Fazit der Autoren Based on the evidence from the systematic literature review and NMA, peginterferon beta-1a demonstrated comparable efficacy compared to non-pegylated IFNs and GA in the treatment of RRMS. In addition, based on the descriptive analysis of relative safety data, peginterferon beta-1a is well-tolerated and has the potential to reduce the frequency of some of the more prevalent AEs associated with most injectable DMTs, such as flu-like symptoms and injection site reactions. The efficacy profile, the lower injection frequency, and a consistently more favorable safety profile of the peginterferon beta-1a 125 µg every 2 weeks regimen make it a suitable alternative to other approved injectable DMTs for the treatment of patients with RRMS. 5. Kommentar FB Med: Heterogenität der Studien bezüglich Definition „relapse of disease“ sowie der Krankheitsdauer.
Mendes D et al., 2016 [27] Benefit-Risk of Therapies for Relapsing-Remitting Multiple Sclerosis:	1. Fragestellung This study aimed to test the number needed to treat to benefit (NNTB) and to harm (NNTH), and the likelihood to be helped or harmed (LHH) when assessing benefits, risks, and benefit–risk ratios of disease-modifying treatments (DMTs) approved for relapsing–remitting multiple sclerosis (RRMS).

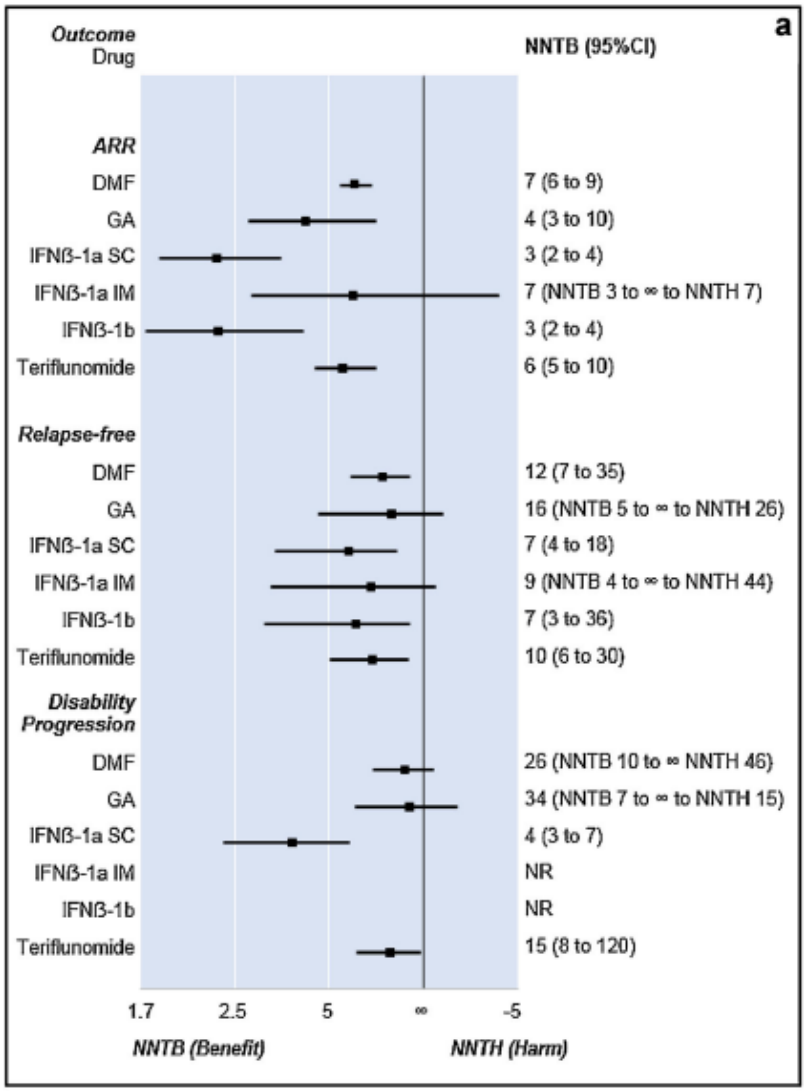
Testing the Number Needed to Treat to Benefit (NNTB), Number Needed to Treat to Harm (NNTH) and the Likelihood to be Helped or Harmed (LHH): A Systematic Review and Meta-Analysis.	2. Methodik Population: adult patients (aged ≥18 years old) with a confirmed diagnosis of RRMS, according to the McDonald criteria or the revised McDonald criteria Intervention: monotherapy with a currently approved DMT, namely alemtuzumab (12 mg/day intravenously [IV], for 2 treatment courses: the first for 5 consecutive days, and the second [12 months later] for 3 consecutive days), DMF (240 mg oral, twice daily), fingolimod (0.5 mg oral, once daily), GA (20 mg subcutaneous [SC], once daily), interferon[IFN]-β-1a (30 mcg intramuscular [IM], once weekly), IFN-β-1a (44 mcg SC, three times a week), IFN-β-1b (250 mcg SC, once every 2 days), natalizumab (300 mg IV, once every 4 weeks), peginterferon-β-1a (125 mcg SC, once every 2 weeks), and teriflunomide (14 mg oral, once daily); (iv) at least 100 patients randomized in every arm of the study Komparator: placebo or active comparators Endpunkt: • Annualized relapse rate (ARR), proportion of patients remaining relapse-free (PPRF), and proportion of patients remaining free of confirmed disability progression sustained for 3 months (PP-FCDPS3M), as measured at 2 years from study initiation • The main safety outcomes of interest were extracted based on 2-year data and included the following: (1) any serious adverse event (SAE); (2) any adverse event (AE) leading to discontinuation of study drug (AELD) Suchzeitraum (Aktualität der Recherche): PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched (until May 10, 2016) Anzahl eingeschlossene Studien/Patienten (Gesamt): 13 phase III RCTs, no information on total number of included patients Qualitätsbewertung der Studien: Cochrane risk of bias tool
	3. Ergebnisdarstellung One RCT compared GA with IFN-b-1b and two RCTs compared alemtuzumab with IFN-b-1a-SC. The remaining RCTs were controlled with placebo.

Study	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
AFFIRM 2006 [19]	+	+	+	+	+	+	−
BEYOND 2009 [20]	+	?	−	+	+	+	−
CARE-MS I 2012 [21]	+	+	−	?	−	+	−
CARE-MS II 2012 [22]	+	+	−	?	−	+	−
CONFIRM 2012 [23]	+	+	−	+	−	−	−
Copolymer 1 MS Group 1995 [24]	?	?	?	?	+	+	−
DEFINE 2012 [25]	+	+	?	+	−	−	−
FREEDOMS 2010 [26]	+	?	?	+	−	+	−
FREEDOMS II 2014 [27]	+	?	+	+	−	+	−
IFNB MS Group 1993 [28]	?	?	?	?	?	+	−
MSCRG 1996 [29-31]	?	?	?	?	+	+	−
PRISMS 1998 [32]	+	+	?	+	+	+	−
TEMSO 2011 [33]	+	+	+	−	?	−	−

+ Low risk of bias, ? Unclear risk of bias, − High risk of bias

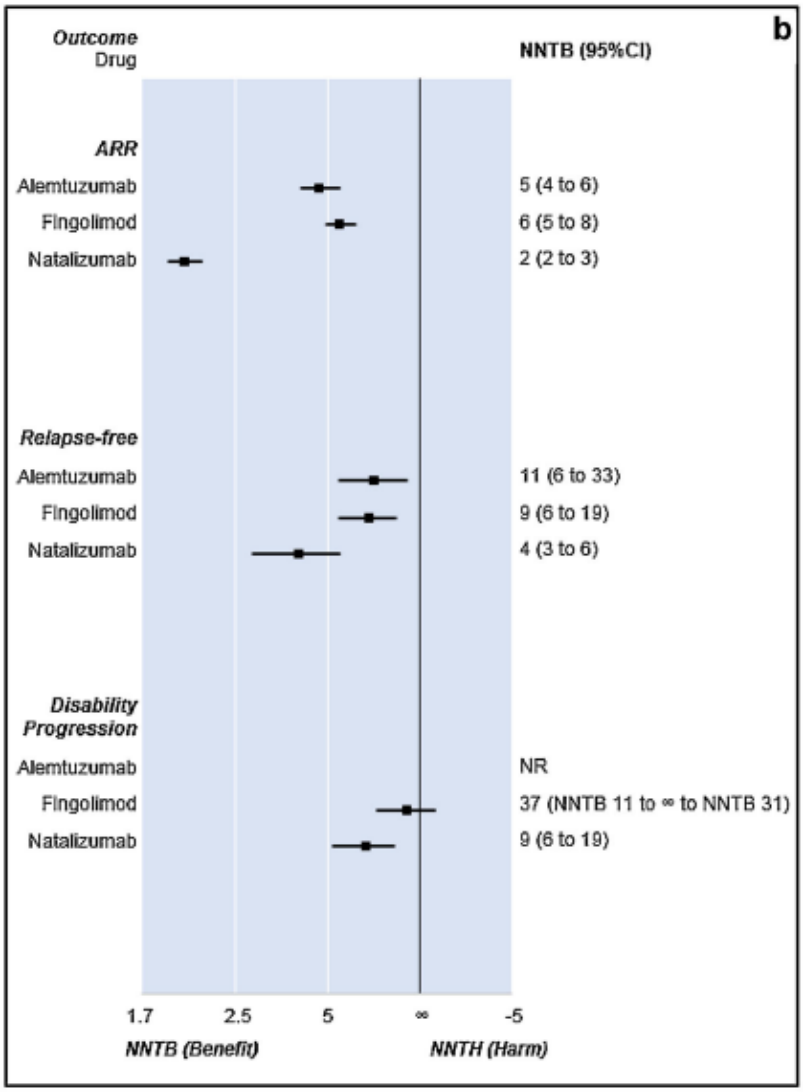
Efficacy

Numbers needed to treat (and 95 % confidence intervals) for efficacy outcomes with first-line disease-modifying therapies versus comparators (all interventions were compared with placebo)



ARR annualized relapse rate, CI confidence interval, DMF dimethyl fumarate, GA glatiramer acetate, IFN interferon, IM intramuscular, NNTB number needed to treat to benefit, NNTH number needed to treat to harm, NR not reported, SC subcutaneous

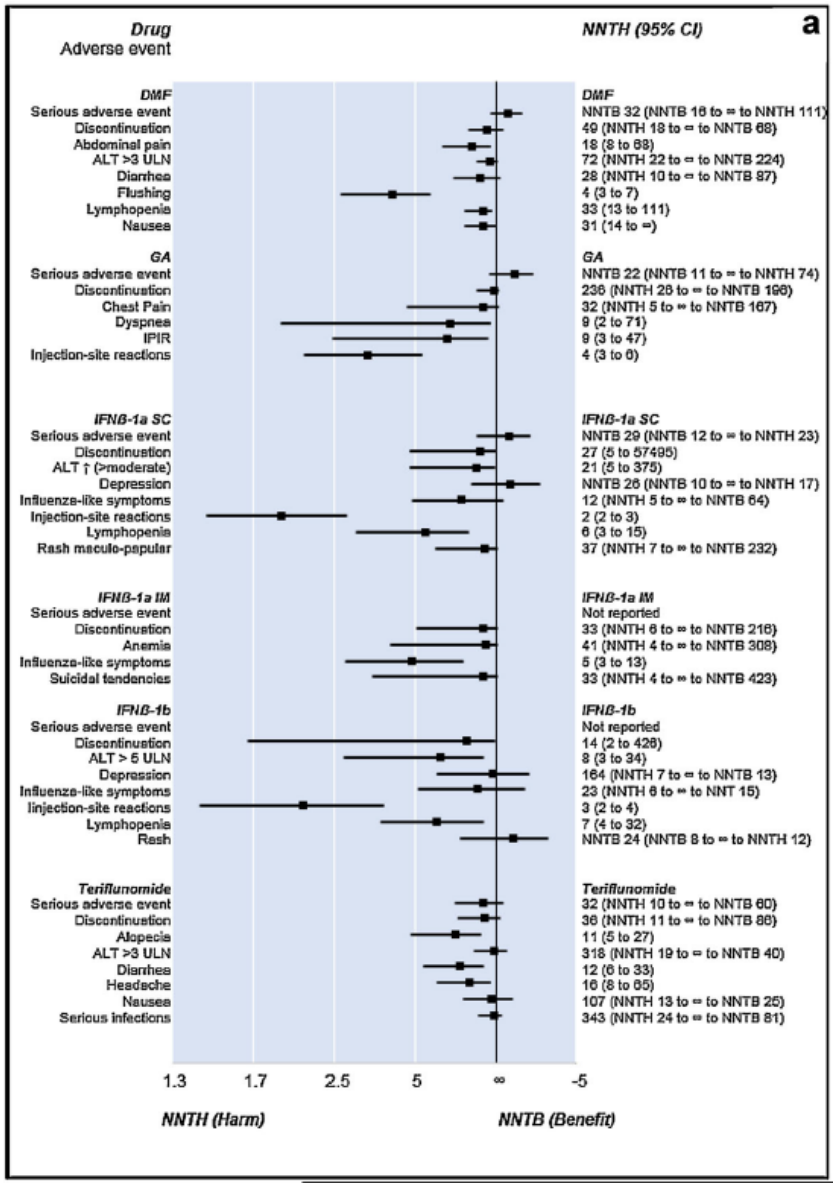
Numbers needed to treat (and 95 % confidence intervals) for efficacy outcomes with second-line disease-modifying therapies versus comparators (Alemtuzumab was compared with IFN-b-1a-SC; Fingolimod and Natalizumab were each compared with placebo)



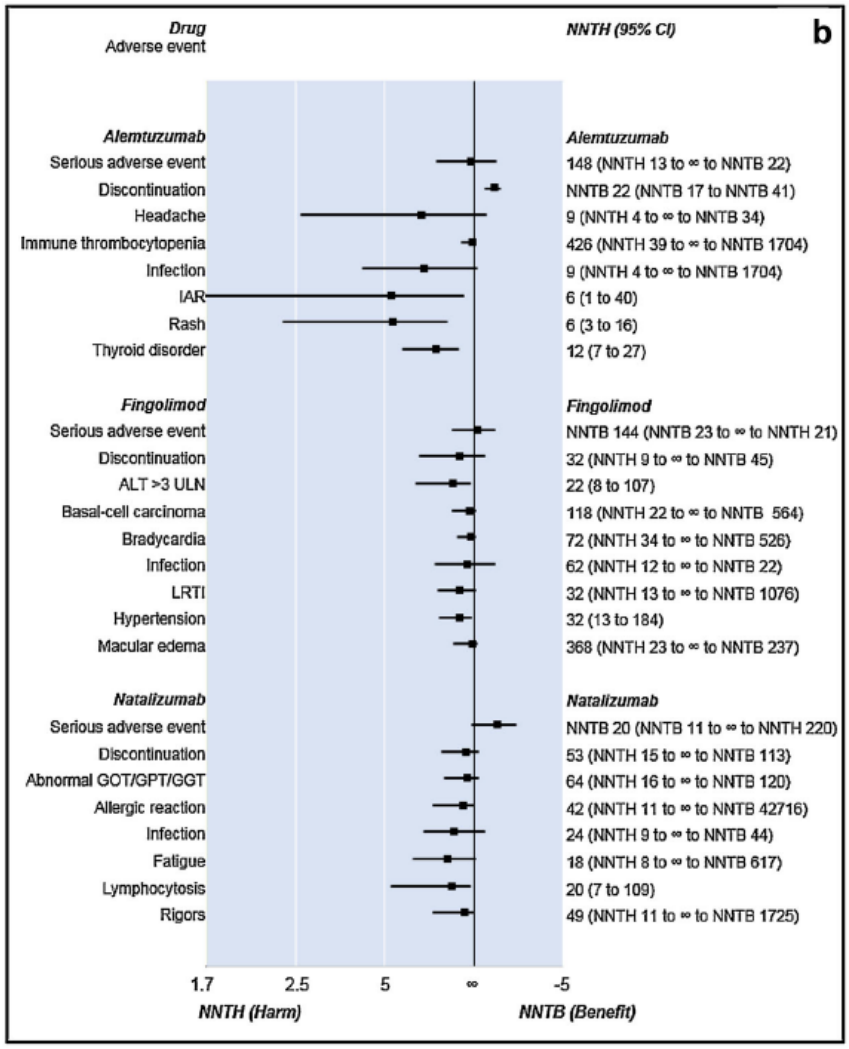
ARR annualized relapse rate, CI confidence interval, DMF dimethyl fumarate, GA glatiramer acetate, IFN interferon, IM intramuscular, NNTB number needed to treat to benefit, NNTH number needed to treat to harm, NR not reported, SC subcutaneous

Safety

Numbers needed to harm (and 95 % confidence intervals) for safety outcomes with first-line disease-modifying therapies versus comparators (all interventions were compared with placebo)



Numbers needed to harm (and 95 % confidence intervals) for safety outcomes with second-line disease-modifying therapies versus comparators (Alemtuzumab was compared with IFN-b-1a-SC; Fingolimod and Natalizumab were each compared with placebo)



4. Fazit der Autoren:

In conclusion, the overall results suggest that, as compared with placebo, IFN-b-1a-SC has the most favorable benefit–risk ratio among firstline treatment options for RRMS. Natalizumab was associated with better benefit–risk ratios than the other DMTs approved in second-line or in highly active RRMS. Continuous research needs to be carried out upon the production of new and/or updated evidence on efficacy and safety of DMTs.

5. Hinweis durch FB Med:

Die Einteilung in First- und Second-Line erfolgte in diesem Review gemäß den „European Summaries of Products Characteristics“. Die tatsächlich in die Primärstudien eingeschlossenen Patienten unterschieden sich bezüglich ihrer Therapielinien. Die obige Zuteilung zu First- und Second-line stimmt somit nicht unbedingt mit dem Patientenkollektiv der jeweiligen Primärstudie überein.

„Among second-line DMTs, natalizumab was consistently associated with lower NNTB values. However, alemtuzumab was compared with IFN-b-1a-SC instead of placebo, which may have contributed to higher NNTBs with alemtuzumab. Thus, caution is needed when interpreting these

	results.“ Die Berechnung der NNT ist nicht eindeutig beschrieben.
Hutchinson M et al., 2014 [14] Efficacy and safety of BG-12 (dimethyl fumarate) and other disease-modifying therapies for the treatment of relapsing–remitting multiple sclerosis: a systematic review and mixed treatment comparison	1. Fragestellung Currently, direct comparative evidence or head-to-head data between BG-12 (dimethyl fumarate) and other disease-modifying treatments (DMTs) is limited. This study is a systematic review and data synthesis of published randomized clinical trials comparing the efficacy and safety of existing DMTs to BG-12 for relapsing–remitting multiple sclerosis (RRMS)
	2. Methodik Population: Adults with RRMS Intervention: Dimethyl fumarate Komparator: DMTs (interferon [IFN] beta-1a, IFN beta-1b, glatiramer acetate [GA], fingolimod, natalizumab, and teriflunomide). Endpunkte: Annualized relapse rate (ARR), disability progression, and safety outcomes Suchzeitraum (Aktualität der Recherche): 1 January 1960 to 15 November 2012. Anzahl eingeschlossene Studien/Patienten (Gesamt): 27 RCTs Qualitätsbewertung der Studien: The extracted studies were assessed for quality by means of a study grade and Jadad score.
	3. Ergebnisdarstellung

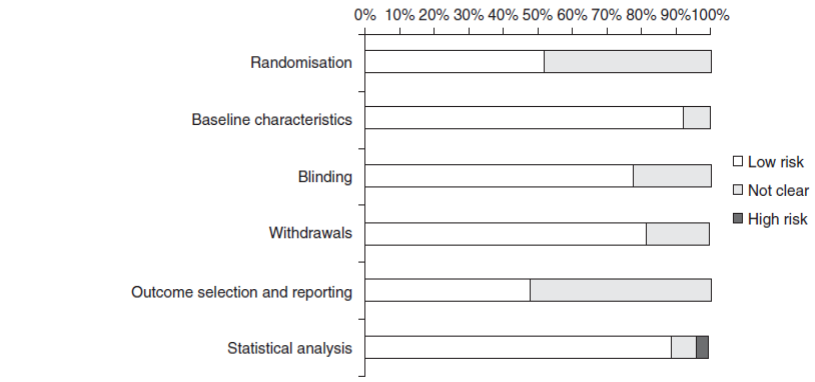
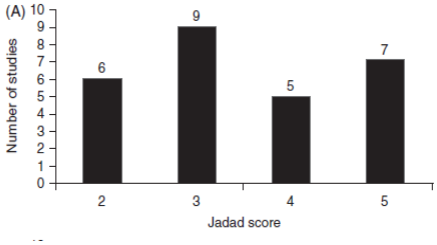


Figure S1. Percentage of studies presenting a risk of bias.



- Across all included RCTs, the patient population comprised adult patients with RRMS who had experienced at least one relapse within the preceding year or two relapses in the preceding 2 years, and had a mean EDSS score at baseline ranging from 1.9 to 3.

Indirekter Vergleich!
Annualized relapse rate:

- BG-12 240 mg BID significantly reduces ARR compared with pooled IFN treatments (rate ratio: 0.760 [95% CI: 0.639–0.904]), GA 20 mg once daily (QD) (rate ratio: 0.795 [95% CI: 0.668–0.947]), teriflunomide 7mg QD (rate ratio: 0.769 [95% CI: 0.610–0.970]), teriflunomide 14 mg QD (rate ratio: 0.775 [95% CI: 0.614–0.979]), and placebo (rate ratio: 0.529 [95% CI: 0.451–0.620]).
- Natalizumab 300 mg every 4 weeks (q4w) was the only therapy with a statistically significantly greater benefit in reducing ARR (54.1%) than BG-12 240 mg BID (rate ratio: 1.541 [95% CI: 1.234–1.924]).

Disability progression:

- BG-12 240 mg BID significantly reduced disability progression by 40.8% compared to placebo (HR: 0.592 [95% CI: 0.421–0.833]).
- Compared to other DMTs, BG-12 240 mg BID was numerically superior in terms of disability progression but statistical significance was not reached.
- As observed for ARR, natalizumab was numerically favorable when compared to BG-12 for disability progression which equated to a 7.0% improvement; however, this difference did not reach statistical significance.

Safety:

- BG-12 240 mg BID has a higher annual incidence rate for abdominal pain (5.14%), diarrhea (7.62%), and flushing (19.97%) when

	compared to at least one other agent. For the other nine AEs (injection site reactions, flu-like symptoms, headache, fatigue, depression, influenza, ALT increased, leukopenia, and lower respiratory tract infection [RTI]), at least one comparator had a higher annual incidence rate than BG-12 240 mg BID.
	4. Fazit der Autoren: Based on indirect comparison, BG-12 offers an effective oral treatment option for patients with RRMS with an overall promising efficacy and safety profile compared to currently approved DMTs. Key limitations of the systematic review were the large heterogeneity in patients enrolled and the variability in the definition of outcomes in included trials.
Kawalec P et al., 2014 [21] The Effectiveness of Dimethyl Fumarate Monotherapy in the Treatment of Relapsing-Remitting Multiple Sclerosis: A Systematic Review and Meta-Analysis	1. Fragestellung The aim of this systematic review with meta-analysis was to assess the efficacy and safety of BG-12 (Dimethyl fumarate) in the treatment of RRMS.
	2. Methodik Population: Adult patients (≥18 age) with RRMS as defined according to the McDonald criteria Intervention: BG-12 monotherapy (240 mg twice daily or 240 mg three times daily) Komparator: Placebo or active comparator (glatiramer acetate 2mg) Endpunkt: • Wirksamkeit: Efficacy evaluations were based on the annualized relapse rate (ARR) at 2 years, the proportion of patients who relapsed or had confirmed progression of disability by 2 years. We also assessed the change in the mean number of gadolinium-enhancing lesions on MRI at 2 years. • Sicherheit: The safety profile was evaluated on the basis of the proportion of patients who experienced any adverse events (AEs), any serious adverse events (SAEs) or discontinued the treatment due to adverse events or died from any cause. Suchzeitraum (Aktualität der Recherche): till 3rd November, 2013. Anzahl eingeschlossene Studien/Patienten (Gesamt): 3 RCTs described in 12 reference papers were included in qualitative synthesis (2907 patients), but only 2 RCTs (described in 10 full text articles) fulfilled the inclusion criteria for meta-analysis (2651 patients) Qualitätsbewertung der Studien: Jadad Score
	3. Ergebnisdarstellung • Two phase III RCTs (DEFINE and CONFIRM) evaluated the effectiveness of BG-12 monotherapy in adult patients with RRMS, in comparison with placebo. The starting dose was 120 mg two or three times daily for the first 7 days, followed by 240 mg two or three times daily.

- Additionally, in CONFIRM trial third group of patients received subcutaneous daily injections of glatiramer acetate at a dose of 20 mg. Duration of treatment in DEFINE and CONFIRM trials was 96 weeks. In phase IIb RCT adult patients with RRMS were given BG-12 at a dose of 120 mg once daily, 120 mg three times daily or 240 mg three times daily or placebo during 24 weeks of treatment, followed by additional 24 weeks for dose-blinded safety assessment.
- The included studies scored ≥3 points on the Jadad scale indicating good methodological quality (two studies scored 4 points, one study scored 3 points).

Ergebnisse

Annualized Relapse Rate at 2 Years

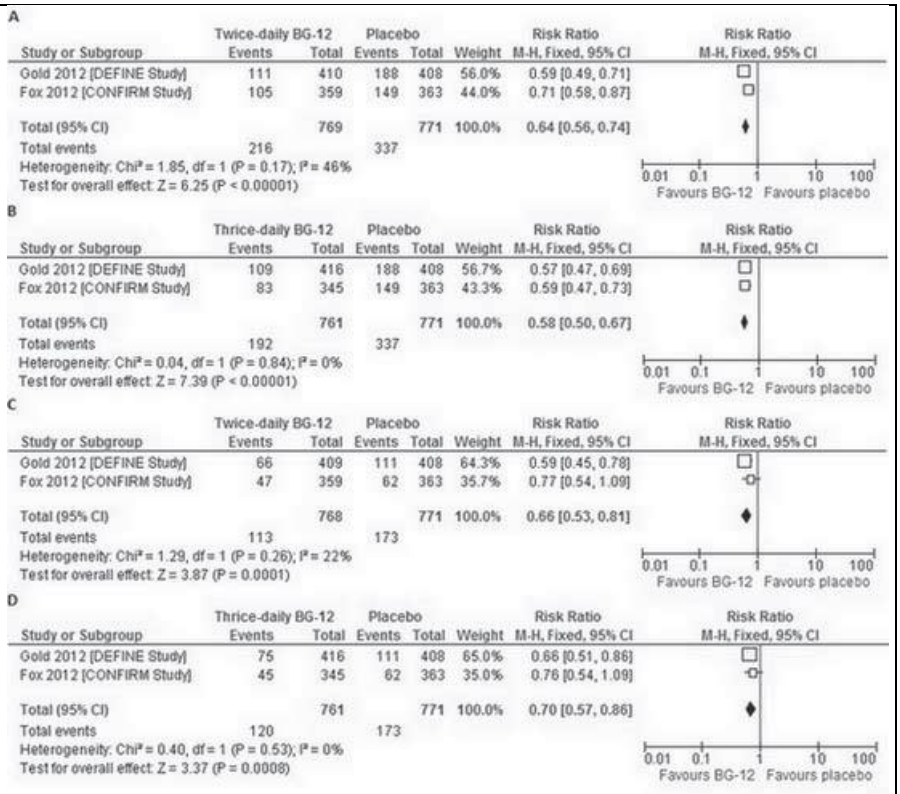
Comparison of the annualized relapse rate at 2 years (96 weeks of treatment)

Study, Year	Annualized Relapse Rate [95% CI]		Relative Rate Reduction or Rate Ratio [95% CI], p value
	BG-12 Twice Daily	Placebo	BG-12 vs. Placebo
Gold R., 2012 [15] (DEFINE Study)	ARR=0.17 [0.14-0.21]	ARR=0.36 [0.30-0.44]	RRR=53%; RR=0.47 [0.37-0.61], p<0.001
Fox R.J., 2012 [20] (CONFIRM Study)	ARR=0.22 [0.18-0.28]	ARR=0.40 [0.33-0.49]	RRR = 44.0% [26.0-57.7], p<0.001
Study, year	BG-12 twice daily	Glatiramer acetate	BG-12 vs. glatiramer acetate
Fox R.J., 2012 [20] (CONFIRM Study)	ARR=0.22 [0.18-0.28]	ARR=0.29 [0.23-0.35]	RR=0.78 [0.59-1.05]; p>0.05
Study, year	BG-12 three times daily	Placebo	BG-12 vs. placebo
Gold R., 2012 [15] (DEFINE Study)	ARR=0.19 [0.15-0.23]	ARR=0.36 [0.30-0.44]	RRR=48%; RR=0.52 [0.40-0.67], p<0.001,
Fox R.J., 2012 [20] (CONFIRM Study)	ARR=0.20 [0.16-0.25]	ARR=0.40 [0.33-0.49]	RRR=50.5% [33.8-63.1], p<0.001
Study, year	BG-12 three times daily	Glatiramer acetate	BG-12 vs. glatiramer acetate
Fox R.J., 2012 [20] (CONFIRM Study)	ARR=0.20 [0.16-0.25]	ARR=0.29 [0.23-0.35]	RR=0.69 [0.51-0.94]; p<0.05

ARR- annualized relapse rate; CI- confidential interval; RR - rate ratio; RRR- relative rate reduction (percentage ARR reduction vs. placebo).

The annualized relapse rate in group of patients who received BG-12 at a dose of 240 mg three times daily decreased by 32% during the first 24 weeks of treatment, nonetheless the difference between BG-12 and placebo was not significant.

Proportion of Patients with Relapse and the Rate of Disability Progression by 2 Years



Forest plot of the proportion of patients who had least one relapse ([a] BG-12 240 mg twice daily vs. placebo [b] BG-12 240 mg three times daily vs. placebo) or confirmed progression of disability ([c] BG-12 240 mg twice daily vs. placebo [d] BG-12 240 mg three times daily vs. placebo) over the 2-year study period. (96 weeks of treatment)

- A comparison between BG-12 three times daily and glatiramer acetate in CONFIRM study revealed a statistically significant difference in the proportion of patients who had a relapse in favour of BG-12 (RR=0.75 [95% CI: 0.59–0.96], p<0.05). However, the result of comparison between lower dosage of BG-12 (240 mg twice daily) and GA showed no statistically significant differences between groups (RR=0.91 [95% CI: 0.72–1.13], p>0.05). (96 weeks of treatment)
- There was no statistically significant difference between BG-12 at a dose of 240 mg three times daily and placebo in respect to the relative risk of relapse during 24 weeks of treatment (RR=0.77 [95% CI: 0.40–1.48], p>0.05). The rate of disability progression was not evaluated in this trial.
- The result of the comparison between each BG-12 regimen and glatiramer acetate did not reveal a statistically significant difference between analyzed groups in the proportion of patients who had confirmed progression of disability (for BG-12 twice daily and BG-12 three times daily RR=0.82 [95% CI: 0.57–1.17], p>0.05). (96 weeks of treatment)

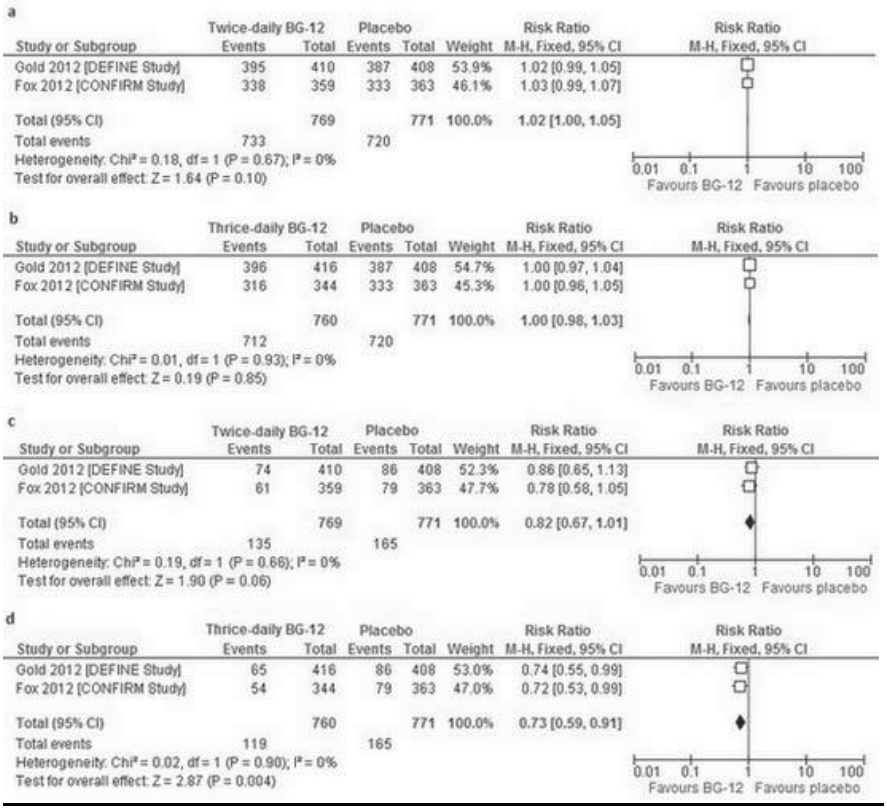
Gadolinium-Enhancing Lesions at 2 Years

- The treatment with BG-12 was also associated with the reduction in the mean number of gadolinium-enhancing lesions on MRI at 2 years in comparison with placebo. The differences between BG-12 and the placebo were statistically significant for both dosages of the study agent (for BG-12 twice daily WMD_{fixed}=-1.64 [95% CI: -2.17 – -1.10],

p<0.00001; for BG-12 three times daily WMD_{fixed}=-1.41 [95% CI: -1.96 – -0.85], p<0.00001). (96 weeks of treatment)

- The comparison between each BG-12 regimen and glatiramer acetate in CONFIRM trial did not reveal a statistically significant difference of the reduction in the mean number of gadolinium-enhancing lesions on MRI (for BG-12 twice daily MD=-0.20 [95% CI: -0.59–0.19], p>0.05; for BG-12 three times daily MD=-0.30 [95% CI: -0.64– 0.04], p>0.05). However, post hoc evaluation showed a significant treatment effects of BG-12 (both dosages) compared to glatiramer acetate for the number of new or enlarging T2 lesions on MRI. (96 weeks of treatment)
- Treatment with BG-12 at a dose of 240 mg three times daily was associated with significant reduction in the mean number of new gadolinium-enhancing lesions, when compared to placebo at weeks 12-24 (p<0.0001). (24 weeks of treatment)

Any adverse events and serious adverse events



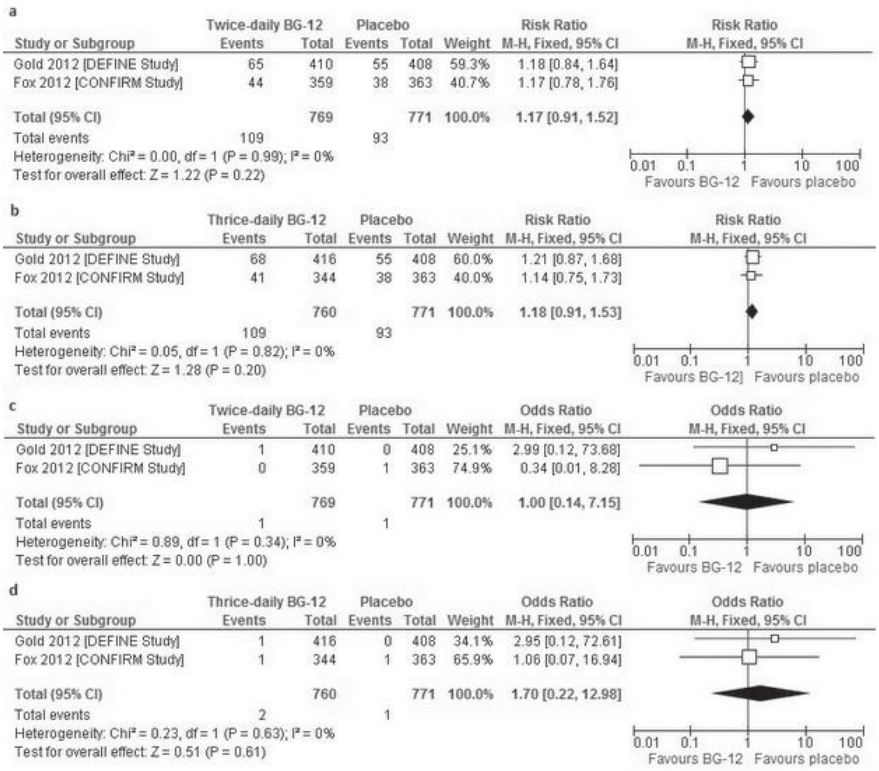
Forest plot of the incidence of adverse events ([a] BG-12 240 mg twice daily vs. placebo [b] BG-12 240 mg three times daily vs.placebo) and serious adverse events ([c] BG-12 240 mg twice daily vs. placebo [d] BG-12 240 mg three times daily vs. placebo) over the 2-year study period. (96 weeks of treatment)

- There was a significant difference in the risk of any AEs between BG-12 given at both dosages and glatiramer acetate in favor of glatiramer acetate (for BG-12 twice daily RR=1.09 [95% CI: 1.04–1.14], p<0.05; for BG-12 three times daily RR=1.06 [95% CI: 1.01–1.12], p<0.05). (96 weeks of treatment)
- Comparison between each BG-12 regimen and glatiramer acetate did not reveal a statistically significant difference

between groups in the risk of any SAEs (for BG-12 twice daily RR=0.99 [95% CI 0.72–1.38], p>0.05; for BG-12 three times daily RR=0.92 [95% CI: 0.66–1.29], p>0.05). (96 weeks of treatment)

- There were no statistically significant differences between BG-12 240 mg three times daily and placebo in the frequency of AEs (RR=1.16 [95% CI: 0.98–1.39], p>0.05) as well as in the risk of SAEs (RR=0.90 [95% CI: 0.36–2.26], p>0.05) during 24 weeks of treatment. (24 weeks of treatment)

Adverse Events Leading to a Discontinuation of the Study Drug and to Death from any cause



Forest plot of the incidence of adverse events leading to treatment discontinuation ([a] BG-12 240 mg twice daily vs. placebo [b] BG-12 240 mg three times daily vs. placebo) and deaths of any cause ([c] BG-12 240 mg twice daily vs. placebo [d] BG-12 240 mg three times daily vs. placebo) over the 2-year study period. (96 weeks of treatment)

- The comparison between each BG-12 regimen and glatiramer acetate in CONFIRM trial did not reveal a statistically significant difference in the risk of AEs leading to discontinuation (for BG-12 twice daily RR=1.23 [95% CI: 0.81–1.87], p>0.05; for BG-12 three times daily RR=1.20 [95% CI: 0.78–1.83], p>0.05). (96 weeks of treatment)
- The results of the analysis revealed no statistically significant differences between each BG-12 regimen and glatiramer acetate (for BG-12 twice daily OR=0.32 [95% CI: 0.01–8.00], p>0.05; for BG-12 three times daily RR=1.02 [95% CI: 0.06–16.25], p>0.05). (96 weeks of treatment)

	4. Fazit der Autoren: Despite limited RCTs data available, both analyzed BG-12 regimens showed their efficacy on clinical disease parameters and other measures of disease activity in RRMS. The safety profile of the study agent was acceptable. 5. Hinweis durch FB Med: Vorbehandlung der eingeschlossenen Patienten unklar.
Couto E et al., 2016 [3] Norwegian Institute of Public Health Medicines used for Multiple Sclerosis – A Health Technology Assessmen	1. Fragestellung The aim of this project was to compare the effect and cost-effectiveness of the disease modifying medicines used for multiple sclerosis in Norway.
	2. Methodik Population: RRMS CIS patients were not included in this report. We excluded studies with patients with primary progressive MS and radiologically isolated syndrome. Intervention: Alemtuzumab (nmber of studies: three) Dimethyl fumarate (two) Fingolimod (three) Glatiramer acetate (eight) Interferon beta-1a subcutaneous (nine) Interferon beta-1a intramuscular (nine) Interferon beta-1b (five) Natalizumab (one) Teriflunomide (two) Komparator: Placebo or the above mentioned interventions Endpunkt • annual relapse • disability progression • mortality • serious adverse events • withdrawal from the study due to adverse events Suchzeitraum (Aktualität der Recherche): 9/11/2015 Anzahl eingeschlossene Studien/Patienten (Gesamt): 37 RCT (n=75-1430) Qualitätsbewertung der Studien: GRADE

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

3. Ergebnisdarstellung

- Treatment histories varied, with 11 RCTs confined to treatment-naive patients, 4 included treatment experienced participants, 11 combined treatment naïve and treatment experienced patients, and treatment history was unclear in 9 studies.
- We had information for 39 comparisons including active treatments versus placebo, and active treatments compared with each other.
- We had evidence of high quality only for annual relapse rates and disability progression. This implies that results on other outcomes are less reliable.
- Many of the published studies did not examine medications separating first- and second- line treatments. We, therefore, present results for all MS treatments together (independent of them being used as first or second line treatments).

Ergebnisse

Annualized relapse rate: Treatment compared to placebo

- Fifteen treatments were compared to placebo. The highest effect against annual relapse was seen for alemtuzumab 12 mg IV q.d..
- The relative risk ranged between 0.29 (95% CI: 0.23; 0.35) for alemtuzumab 12 mg IV q.d and 0.86 (0.7 to 1.06) for interferon beta-1a 60 mcg IM q.w, compared to placebo.

Annualized relapse rate: Treatment compared with each other

- 24 head-to head comparisons Interferon beta-1a 44 mcg was less effective than alemtuzumab 12 mg (RR; 95% CI=2.21; 1.90 to 2.64).
- Fingolimod oral 0.5 mg and fingolimod oral 1.25 mg performed better than interferon beta-1a 30 mcg, with RRs (95% CI) of 0.57 (0.47 to 0.67) and 0.55 (0.47 to 0.66), respectively.
- Dimethyl fumarate 240 mg two times and three times daily were more effective than glatiramer acetate 20mg, with RRs of 0.77 (0.63 to 0.93) and 0.77 (0.64 to 0.93), respectively.

Disability progression: Treatment compared to placebo

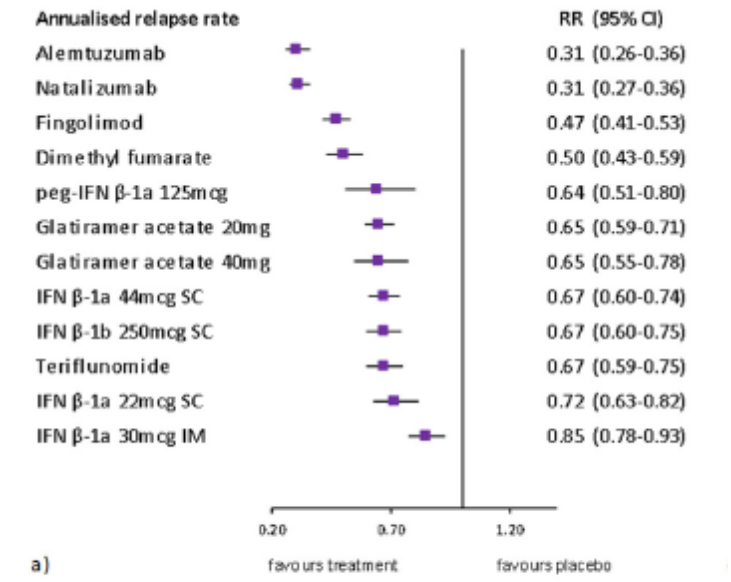
- Seventeen treatments were compared to placebo. The network meta-analysis RRs for disability progression were 0.65 (95% CI: 0.49; 0.85) for dimethyl fumarate 240 mg two times daily, 0.68 (0.52; 0.89) for dimethyl fumarate 240 mg three times daily, 0.71 (0.55; 0.90) for fingolimod oral 0.5 mg, and 0.71 (0.56; 0.90) for

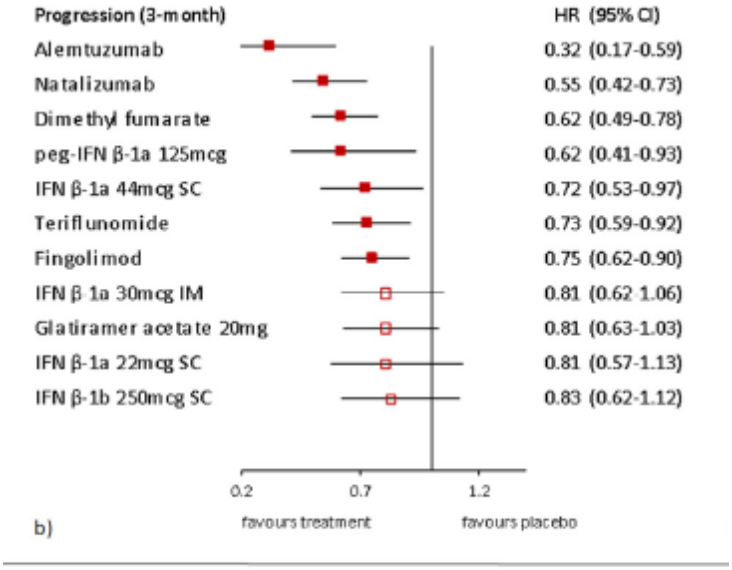
	fingolimod oral 1.25 mg. Disability progression: Treatment compared with each other • We had evidence of very low to moderate quality for two network meta-analysis • Interferon beta-1a 44 mcg was less effective against disability progression than alemtuzumab 12 mg and 24 mg, with RRs of 1.95 (95% CI: 1.45; 2.59) (evidence of moderate quality) and 2.15 (1.10; 4.55) (evidence of very low quality), respectively. Withdrawal due to adverse events: Treatment compared to placebo • We had evidence for 19 treatments versus placebo. The quality of the evidence considered for the whole network was of very low to moderate quality. • We found RRs for withdrawal due to adverse events of 2.20 (95% CI: 1.29-3.97) for interferon beta-1a 44 mcg (low quality evidence), of 2.21 (1.42; 3.58) for fingolimod oral 1.25 mg (moderate quality), and of 3.57 (1.27; 11.14) and 3.47 (1.25 to 10.9) for peg-interferon beta-1a 125 mcg once every 2 and 4 weeks, respectively (low quality evidence). Withdrawal due to adverse events: Treatment compared with each other • The quality of the evidence ranged from very low to moderate. • Patients withdrew more due to adverse events with interferon beta-1a 44 mcg than with alemtuzumab 12 and 24 mg (RRs of 3.6 (95% CI: 1.88; 7.33), and 4.08 (1.69; 11.42), respectively). Serious adverse events: Treatment compared to placebo • Through the network meta-analysis, we had information for 17 treatments. • Results from the “pairwise comparison method” showed that peg-interferon beta-1a 125 mcg once every 4 and 2 weeks were associated with more serious adverse events than placebo, with RRs of 1.55 (95% CI: 1.12-2.14) and 1.66 (1.21- 2.28), respectively. No statistical differences were found for network analysis. Change in Expanded Disability Scale: Treatment compared to placebo • We did not grade the quality of the evidence for this outcome • Twelve different treatments were compared to placebo in the network meta-analysis. • Four treatments were statistically significantly more effective than placebo against disability progression: alemtuzumab 24 mg (mean difference=-0.91 (95% CI:- 1.48; -0.4), alemtuzumab 12 mg (-06 (-1.02; -0.24)), interferon beta-1b 250 mcg every other day (-0.58 (-0.94; -0.22)), and interferon beta-1a 44 mcg three times a week (-0.28 (-0.58; -0.02). • When comparing results obtained through “network meta-analysis approach” and “pairwise comparison method”, we found a difference in the magnitude and statistical significance of the effect for the comparison interferon beta-1a 30 mcg versus placebo. The mean difference in change in EDSS score was -0.59 (-0.86 to -0.32) when considering pairwise comparisons, and -0.22 (-0.48 t0

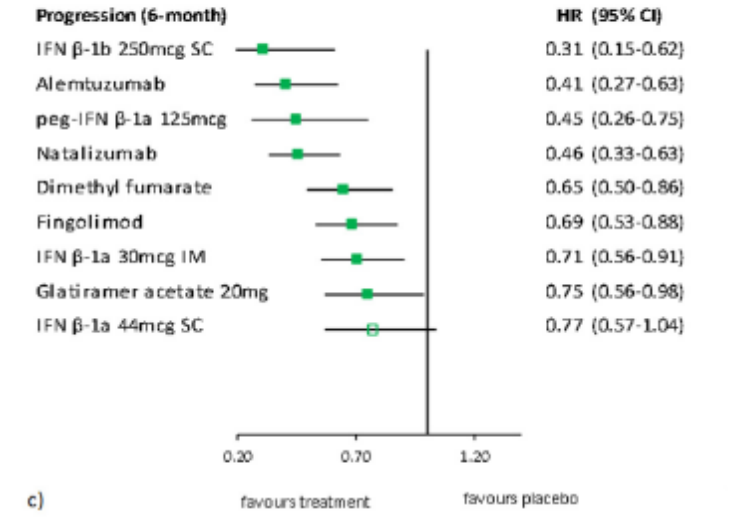
	0.02) for the network meta-analysis estimates. Mortality: Treatment compared to placebo • Results are available for nineteen treatments compared to placebo. • None of the examined treatments were associated with a higher risk for mortality than placebo.
	4. Anmerkungen/Fazit der Autoren • The quality of the available evidence ranged from very low to high. • Alemtuzumab 12 mg had the best effect on annual relapse (for medicines we had evidence of high quality). • Dimethyl fumarate 240 mg twice daily and fingolimod oral 0.5 mg were the most effective against disability progression (for medicines we had evidence of high quality). • Our results indicated that interferon beta-1a 44 mcg and peg-interferon beta-1a were associated with more withdrawal due to adverse events than placebo. The examined treatments had no effect on mortality compared to placebo. • Our health economic analysis, examining all multiple sclerosis treatment alternatives, indicated that alemtuzumab was more effective (in terms of quality-adjusted life-years (QALY)) and less costly than the other treatment alternatives.
Fogarty E et al., 2016 [6] Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: Systematic review and network meta-analysis	1. Fragestellung To perform a systematic review and network meta-analysis to evaluate the comparative efficacy of available therapies in reducing relapses and disability progression in RRMS.
	2. Methodik Population: Adult patients with RRMS. Intervention: Eleven DMTs met this criterion including interferon beta-1b (IFN β-1b) subcutaneous (SC) 250mcg, IFN β-1a SC 22 mcg and IFN β-1a SC 44mcg, IFN β-1a intramuscular (IM) 30mcg, pegylated IFN β-1a SC 125mcg, glatirameracetate 20mg, glatiramer acetate 40mg, natalizumab, alemtuzumab, fingolimod, teriflunomide, and dimethylfumarate Komparator: Placebo oder oben genannten AM Endpunkte • **Annualised relapse rate (ARR)** and confirmed disability progression were selected as the most commonly reported clinical outcomes in RRMS trials. ARR is defined as the mean number of confirmed relapses per patient adjusted for the duration of follow- up. • **Disability progression** varied between trials, but it was commonly defined as at least 1 point increase on the Expanded Disability Status Scale (EDSS, an ambulation -centred scale from 0 to 10), or a 0.5 point increase if the baseline EDSS was Z5.5, confirmed during two subsequent neurological examinations separated by an interval of at least three to six months free of relapses (Kurtzke,1983). Suchzeitraum (Aktualität der Recherche): März 2016

	Anzahl eingeschlossene Studien: 28 RCTs Qualitätsbewertung der Studien: Cochrane Collaboration's Risk of bias tool.

	3. Ergebnisdarstellung
	
	• The systematic search identified 6086 potentially relevant publications, of which 28 trials met the inclusion criteria. Trials were published between 1993 and 2014, were of 1.75 years mean duration and comprised a total of 17,040 patients.
	• The overall risk of bias within included studies was judged to below in 14 studies (50%), medium in one study (4%) and high in 13 studies (46%). High risk of bias was predominantly due to the single-blind nature of many trials. All but one study employed outcome-assess or blinding but participants were not blinded to treatment allocation in a further 12 RCTs Incomplete outcome data due to loss to follow-up or imbalance in discontinuations across treatment groups was identified in three studies with high attrition bias identified in one study.
	  • Some studies, while specifying RRMS as an inclusion criterion, also recruited a small number of patients with progressive disease. In these cases, studies which included >10% progressive patients were excluded.
	  • Greater variation was observed in the mean number of relapses in the previous two years (1.7–3.5), mean duration of disease prior to recruitment (1.2–10.5years), and in the proportion of patients who had received prior treatment with a DMT (0–100%).
	
	Ergebnisse:
	
	• The magnitude of ARR reduction varied between15–36% for all IFN β products, glatiramer acetate andteriflunomide, and from 50 to 69%for alemtuzumab, dimethylfumarate, fingolimod and natalizumab.
	
	• The risk of disability progression confirmed after three months was reduced by 19–28% with IFN β products, glatirameracetate, fingolimod and teriflunomide, by38–45% forpegylatedIFN β, dimethylfumarate and natalizumab and by 68% with alemtuzumab. Superiority over placebo was less certain for IFN β_1a 30mcg, IFN β_1a 22mcg, IFN β_1b 250mcg and glatirameracetate 20mg compared with other therapies.
	• Ranking of treatments was affected by the definition of disability progression largely due to the conflicting results of IFN β_1b 250mcg,ranking as the most efficacious treatment for disability progression con-firmed after six months (92%) and as the least efficacious for dis ability progression confirmed after three months (30%).
	• Alemtuzumab and natalizuma bboth scored relatively highly for disability progression confirmed after six months. Notable variation in ranking across outcomes was observed for fingolimod (81%for ARR, 39–46% for the disability progression outcomes).


Annualised relapse rate
RR (95% CI)
Alemtuzumab
0.31 (0.26-0.36)
Natalizumab
0.31 (0.27-0.36)
Fingolimod
0.47 (0.41-0.53)
Dimethyl fumarate
0.50 (0.43-0.59)
peg-IFN β-1a 125mcg
0.64 (0.51-0.80)
Glatiramer acetate 20mg
0.65 (0.59-0.71)
Glatiramer acetate 40mg
0.65 (0.55-0.78)
IFN β-1a 44mcg SC
0.67 (0.60-0.74)
IFN β-1b 250mcg SC
0.67 (0.60-0.75)
Teriflunomide
0.67 (0.59-0.75)
IFN β-1a 22mcg SC
0.72 (0.63-0.82)
IFN β-1a 30mcg IM
0.85 (0.78-0.93)
0.20
0.70
1.20
a)
favours treatment
favours placebo


Progression (3-month)
HR (95% CI)
Alemtuzumab
0.32 (0.17-0.59)
Natalizumab
0.55 (0.42-0.73)
Dimethyl fumarate
0.62 (0.49-0.78)
peg-IFN β-1a 125mcg
0.62 (0.41-0.93)
IFN β-1a 44mcg SC
0.72 (0.53-0.97)
Teriflunomide
0.73 (0.59-0.92)
Fingolimod
0.75 (0.62-0.90)
IFN β 1a 30mcg IM
0.81 (0.62 1.06)
Glatiramer acetate 20mg
0.81 (0.63-1.03)
IFN β-1a 22mcg SC
0.81 (0.57-1.13)
IFN β-1b 250mcg SC
0.83 (0.62-1.12)
0.2
0.7
1.2
b)
favours treatment
favours placebo


Progression (6-month)
HR (95% CI)
IFN β-1b 250mcg SC
0.31 (0.15-0.62)
Alemtuzumab
0.41 (0.27-0.63)
peg-IFN β-1a 125mcg
0.45 (0.26-0.75)
Natalizumab
0.46 (0.33-0.63)
Dimethyl fumarate
0.65 (0.50-0.86)
Fingolimod
0.69 (0.53-0.88)
IFN β-1a 30mcg IM
0.71 (0.56-0.91)
Glatiramer acetate 20mg
0.75 (0.56-0.98)
IFN β-1a 44mcg SC
0.77 (0.57-1.04)
0.20
0.70
1.20
c)
favours treatment
favours placebo

	4. Anmerkungen/Fazit der Autoren Compared with placebo, clear reductions in ARR with disease-modifying therapies were accompanied by more uncertain changes in disability progression. The magnitude of the reduction and the uncertainty associated with treatment effects varied between DMTs. While natalizumab and alemtuzumab demonstrated consistently high ranking across outcomes, with older interferon-beta and glatiramer acetate products ranking lowest, variation in disability progression definitions lead to variation in the relative ranking of treatments. Rigorously conducted comparative studies are required to fully evaluate the comparative treatment effects of disease modifying therapies for RRMS.

Leitlinien

AIAQS, 2012 [1]

Clinical practice guideline on the management of people with multiple sclerosis

1. Fragestellung

TREATMENT OF PATIENTS WITH CONFIRMED MS

In patients with confirmed MS, what is the effect of disease-modifying drugs?

(The Agència d'Informació, Avaluació i Qualitat en Salut (AIAQS) is a founding member of the International Network of Agencies for Health Technology Assessment (INAHTA), a corporate member of the Health Technology Assessment International (HTAi), a member of the Guidelines International Network (G-I-N) and the CIBER of Epidemiology and Public Health (CIBERESP)

2. Methodik

Grundlage der Leitlinie

The guideline working group has been structured as a steering committee with a coordinating team, multidisciplinary clinical team, technical teatm and external reviewers.

- Suchzeitraum: August 2011 (fortnightly literature alerts were activated between July and September, 2012)
- Search for systematic reviews (SR), including randomised controlled trials (RCT), parallel clinical trials, open-label extension studies of RCTs and observational studies, available guidelines
- No language restrictions
- Cochrane Handbook for Systematic Reviews of Interventions criteria were applied for the RCTs and observational studies + AMSTAR instrument for SR

LoR: GRADE

GoR: GRADE

The recommendation categories suggested by GRADE are: strongly in favour ("We recommend doing"), weakly in favour ("We suggest to do"), weakly against ("We suggest NOT to do") and strongly against ("We recommend NOT to do").

3. Empfehlungen

Treatment of patients with confirmed MS

Interferon beta	
Strong	In patients with relapsing-remitting MS and clinical activity with attacks, treatment with interferon beta (1a or 1b) is recommended to reduce the frequency of these attacks.
Weak	In patients with relapsing-remitting MS and clinical activity with attacks, treatment with interferon beta (1a or 1b) is recommended to slow down disability progression.
Weak	In patients with secondary-progressive MS and clinical activity with attacks, subcutaneous treatment with interferon beta 1b or interferon beta 1a is recommended to reduce the frequency of attacks and slow down disability progression measured using the EDSS scale.
Strong	Treatment with interferon beta (1a or 1b) is NOT recommended in patients with primary-progressive MS.

Glatiramer acetate	
Strong	In patients with relapsing-remitting MS and clinical activity with relapses, treatment with glatiramer acetate is recommended to reduce the frequency these attacks.
Weak	In patients with relapsing-remitting MS and clinical activity with attacks, treatment with glatiramer acetate is recommended to slow down disability progression.
Strong	Treatment with glatiramer acetate is NOT recommended in patients with primary-progressive MS.

Natalizumab	
Strong	In patients with active relapsing-remitting MS that does not respond to interferon beta or glatiramer acetate, and in patients with aggressive relapsing-remitting forms of MS with no prior disease-modifying treatment, treatment with natalizumab is recommended to reduce the fre-

Fingolimod	
Strong	In patients with relapsing-remitting MS that does not respond to interferon beta or glatiramer acetate, and in patients with aggressive relapsing-remitting forms of MS with no prior disease-modifying treatment, treatment with fingolimod is recommended to reduce the frequency of attacks and slow down disability progression, provided the current indications established by health authorities are met.
√	Due to eventual heart rhythm involvement, the monitoring guidelines established by the European Medicines Agency must be followed after administration of the first dose of fingolimod.

Mitoxantrone	
Strong	Treatment with mitoxantrone is recommended for patients with aggressive relapsing-remitting MS or secondary-progressive MS with attacks that do not respond to appropriate medical therapy and show signs of active inflammation.
☑	Mitoxantrone must be administered in patients with a minimum ventricular ejection fraction of 50% and ultrasound monitoring of left ventricular function is required during treatment and subsequently for a period of several years.
☑	Patients treated with mitoxantrone must undergo periodic haematological controls during treatment and subsequently for a period of several years.

Azathioprine	
Weak	In patients with relapsing-remitting MS and certain clinical characteristics (for instance, associated systemic disease or neuromyelitis optica spectrum) treatment with azathioprine should be considered.

Interferon beta

Studies included into analysis: INFB MS 1993, MSCRG 1996, PRISMS 1998 and PRISMS4 2001 INFB MS 1993, MSCRG 1996, PRIMS 1998

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Mitoxantrone

Auswahl Referenzen

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Azathioprin

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4. FB Med Anmerkungen

Starke Heterogenität in den Studien zu Interferon beta und Glatirameracet beschrieben. Ein Großteil der Studien wurde vor 2000 (Interferon beta durchgeführt.

	Alemtuzumab wurde nicht untersucht.

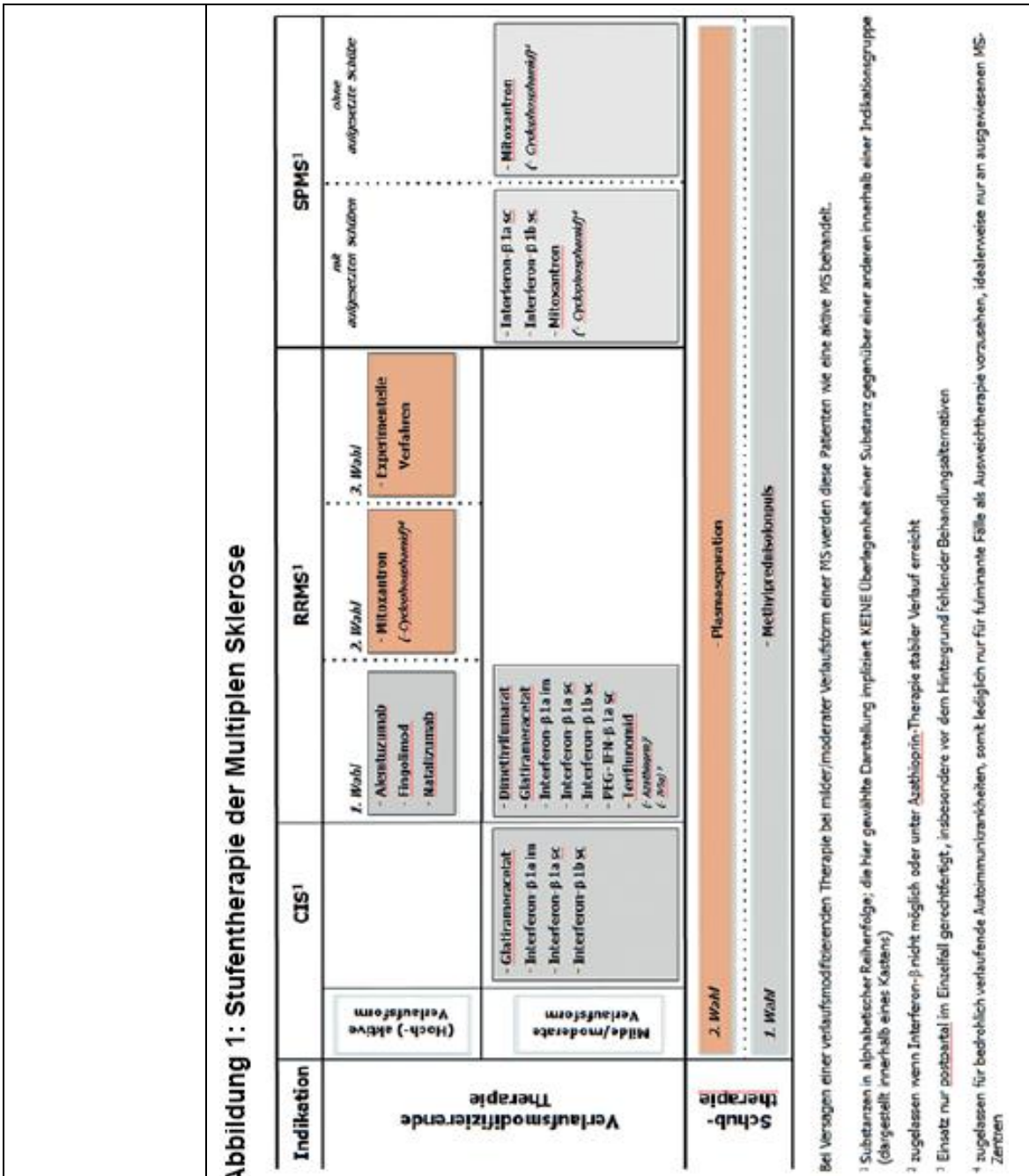
Ergänzende Dokumente

Deutsche Gesellschaft für Neurologie, 2012 [4] Leitlinie zur Diagnose und Therapie der Multiplen Sklerose (S2e). Stand: 12.04.2012 (mit redaktioneller Überarbeitung aus 08/2014), gültig bis 29.09.2017	1.2 Ziele der Leitlinie • Optimierung der Behandlung von Schüben und Symptomen der MS sowie der verlaufsmodifizierenden Sekundärprophylaxe • evidenzbasierte Leitlinie • Fortentwicklung der „Leitlinie der DGN 2008“ (Gold und Hartung 2008) und „Europäische MSTKG Empfehlungen“ (MSTKG 2008) • bezieht sich auf die modernen Therapieoptionen, genauso wie auf die Behandlung von MS in besonderen Lebenssituationen wie Schwangerschaft • Sicherheitsrisiken moderner MS-Therapien kritisch darstellen 1.3 Patientenzielgruppe • erwachsene Patienten mit schubförmigen oder progredienten Verlaufsformen einer MS 1.4 Versorgungsbereich • für alle Bereiche der MS-Versorgung (ambulant, §116 Versorgung, tagesklinisch, stationär) • Frühdiagnose, Immuntherapie, symptomatische Therapie 1.5 Adressaten der Leitlinie • Neurologen, Nervenärzte (ambulanter Sektor, Klinikbereich, Rehabilitationseinrichtungen)
	7. Methodik: • evidenzbasierte Leitlinie • kein formaler Prozess zur Formulierung/Graduierung der Empfehlungen Grundlage der Leitlinie: • systematische Recherchen zu folgenden Themen: 1. Aktuelle Bewertung der Interferon-beta-Präparate 2. Praktische Aspekte der Therapie mit Glatirameracetat 3. Eskalationstherapie mit Fingolimod oder Natalizumab 4. Unselektive Immunsuppressiva (Mitoxantron, Azathioprin, Cyclophosphamid, Methotrexat) 5. Verfügbare klinische Daten und Einsatzmöglichkeiten therapeutischer Antikörper (Rituximab und weitere anti-B Zellantikörper, Alemtuzumab, Daclizumab) Suchzeitraum • Zu 1: bis 10.07.2011 • Zu 2. Bis 31.07.2011 • Zu 3. Fingolimod bis 28.06.2011, Natalizumab bis 30.10.2011 • Zu 4. Azathioprin bis 30.04.2011 • Zu 5. Bis 30.04.2011 • Einschluß von deutschen und englischer Literatur Kommentar FB Med: • Keine Fleißdiagramme zu den Literaturauswahlprozessen • Bewertung der externen Evidenz unklar, keine Angabe von LoE • Angaben zu (Patienten)relevanten Endpunkten fehlen

	• Fazit/Empfehlungen im Text nicht hervorgehoben • scheinbar im Clinical Pathway mit Angabe zu GoR zusammengefasst (keine Erläuterung vorhanden)

	Relevante Inhalte (Hintergrundtexte):
	• Direkte, große Vergleichsstudien von Beta-Interferonen und Glatirameracetat bei schubförmiger MS liegen vor.
	• Sowohl im Vergleich von IFN-β1b (250 µg vs. 500 µg) vs. 20 mg Glatirameracetat (BEYOND) als auch bei der Head-to-Head- Studie REGARD mit IFN-β1a 3 × 44 µg s.c. vs. 20 mg Glatirameracetat s.c. ergaben sich im primären Studienendpunkt (Zeitraum bis zum Auftreten des nächsten Schubes) keine Unterschiede (Mikol et al. 2008, O'Connor et al. 2009).
	• Für das mögliche Umsetzen bei Nichtwirksamkeit eines Wirkprinzips auf das jeweils andere, also von Interferon auf Glatirameracetat und umgekehrt, ergibt sich formal die Empfehlungsstärke 0.
	• Es kann nicht ausgeschlossen werden, dass einzelne Patienten spezifischer auf das jeweils andere Basistherapeutikum reagieren.
	• Hierzu wären belastbare Prädiktoren und sog. Surrogatmarker des Therapieansprechens sinnvoll.
	• Bei leichten Schüben kann man eine solche Umstellung innerhalb der Basistherapie erwägen, bevor man eine Therapieeskalation durchführt.
	• In der bislang einzigen publizierten kontrollierten Studie waren 334 RRMS-Patienten eingeschlossen, die über 3 Jahre 1:1:1 randomisiert entweder IFN-β (44 mg IFN-β 1a s.c., 3 × wöchentlich), 12 mg oder 24 mg Alemtuzumab (jeweils über 5 Tage, d.h. kumulative Dosis 60 mg/Jahr oder 120 mg/Jahr) erhielten (CAMMS223-Trial-Investigators 2008).
	• In den primären Endpunkten ("time to sustained accumulation of disability and the rate of relapse" – Anm.d.Red. in der Leitlinie nicht beschrieben) war Alemtuzumab der IFN-β-Therapie deutlich überlegen.
	• Es wurden keine signifikanten Unterschiede zwischen den beiden Alemtuzumab-Dosierungen verzeichnet. Alemtuzumab reduzierte die Schubrate um 74 % und die Wahrscheinlichkeit der Behinderungsprogression um 71 % im Vergleich zu IFN-β (Coles et al. 2011).
	• Die Studie wurde abgebrochen, nachdem 3 Patienten unter Alemtuzumab eine Immunthrombozytopenie entwickelten, wobei ein Fall fatal verlief.
	
	Relevante Inhalte (Clinical Pathway – Verlaufsmodifizierende Therapie: Schubförmige Verlaufsform):
	• Basistherapie:
	  • Interferon-beta-Präparat oder Glatirameracetat ® (A)
	• Bei anderen Autoimmunerkrankungen, Kontraindikationen oder Ablehnung regelmäßiger Injektion:
	  • Azathioprin
	  • Intravenöse Immunglobuline nach Genehmigung in Ausnahmen, v.a. peripartal
	• Bei rasch fortschreitender schwerer schubförmig remittierender MS:
	  • Primärtherapie mit Fingolimod oder Natalizumab (Ausnahmeindikation, obwohl offiziell zugelassen)
	• Bei schweren lokalen Nebenwirkungen an der Haut nach Basistherapie:
	  • Umstellung auf i.m. Präparat (0)
	  • Weitere Möglichkeiten (0): Azathioprin, Natalizumab, Fingolimod
	• Bei anhaltender oder zunehmender Krankheitsaktivität:
	  • Bestimmung neutralisierender Antikörper, wenn 2x hochpositiv →Wechsel des Therapiekonzepts (A)

	• Umstellung auf Fingolimod oder Natalizumab (falls nicht schon als Primärtherapie) (B) Ergänzungen 2014: • Durch die Zulassung von zwei oralen Immuntherapeutika und einem monoklonalen Antikörper sind für die Basis- und Eskalationstherapie bzw. als Medikamente der 1., 2. Und 3. Wahl bei der MS deutlich mehr Optionen vorhanden. Mit Ausnahme von Alemtuzumab liegen für die neu eingeführten Medikamente keine wissenschaftlich belastbaren direkt vergleichenden (‚head-to-head') Daten zur Wirksamkeit im Vergleich mit etablierten Immuntherapeutika vor. Entweder waren die Vergleichsgruppen nicht ausreichend groß für statistische Vergleiche oder das Studiendesign war nicht doppelt geblindet. • Im neu gestalteten Stufenschema der MS Therapie unterscheiden wir nun zwischen milden/moderaten und (hoch)aktiven Verlaufsformen der MS. Dies trägt den regulatorischen Entscheidungen Rechnung, die schon frühzeitig die Einstellung auf oder Umstellung von Basistherapien auf aktive Immuntherapeutika ermöglichen. • Teriflunomid ist ein orales Basistherapeutikum, dessen Vorläufersubstanz Leflunomid bereits lange für die Therapie rheumatischer Erkrankungen eingesetzt wird. Vorteile sind hohe Adhärenz, gute Verträglichkeit sowie das relativ robuste Wissen um das Sicherheitsprofil. Nachteilig sind die lange enterohepatische Rezirkulation, reversible Haarwachstumsstörungen sowie potentielle Teratogenität. • Dimethylfumarat ist ebenfalls ein orales Basistherapeutikum, mit dessen Vorläufer gute Daten zur Langzeitsicherheit bei der Psoriasis vorliegen. Bei Therapiebeginn stellen sich häufig gastrointestinale Unverträglichkeit und Flush-Phänomene ein. Auch bei Langzeitgabe sollten regelmäßige Kontrollen des Differentialblutbilds erfolgen um opportunistische Infektionen zu vermeiden. • Mit Alemtuzumab wird ein hochaktiver monoklonaler Antikörper für die Therapie der aktiven MS eingeführt. Seine Bedeutung liegt bei Patienten, die nicht ausreichend mit Basistherapeutika stabilisiert bzw. primär hochaktiv sind. Das ursprünglich bei T-Zelllymphomen eingesetzte Alemtuzumab führt zu einer nachhaltigen und über Monate andauernden Elimination von T-und B-Zellanteilen des Immunsystems. Vorteile sind Behandlungszyklen mit 5 bzw. 3 Infusionen im 1. Bzw. 2. Jahr und ggf. im 3. Jahr und eine bei vielen Patienten sehr nachhaltige Wirkung auf die MS-Aktivität. Nachteile sind leichte Erhöhung der Infektneigung in den Monaten nach Infusion, die Entwicklung sekundärer, B-zellvermittelter Autoimmunitätsphänomene oder auch –krankheiten (Bildung von Autoantikörpern, ITP sowie Glomerulonephritis). Dies erfordert 48-monatige Labor- und Urinkontrollen im 4-Wochen-Zyklus nach der letzten Verabreichung von Alemtuzumab. • Alemtuzumab ist im Vergleich zu hochdosiertem Interferon-beta (Rebif®) getestet worden und in den meisten Endpunkten dieser Substanz signifikant überlegen. Die amerikanische FDA kritisierte als Einschränkung im Studiendesign, dass Patienten ihre Zuordnung zur Therapiegruppe potentiell vorab erfahren konnten, und damit die Einführung eines möglichen Bias während des Studienverlaufs.



Kommentar FB Med:

Da es in der Leitlinie um die Behandlungssituation in Deutschland geht, wurde diese in die Evidenzsynopse aufgenommen, obwohl es sich um nicht um eine S3-Leitlinie handelt.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) **am 11.10.2016**

#	Suchfrage
1	MeSH descriptor: [Multiple Sclerosis] explode all trees
2	(multiple next scleros*) or ms:ti,ab,kw (Word variations have been searched)
3	relapse* or relapsing or (secondary next progressive) or (chronic next progressive):ti,ab,kw (Word variations have been searched)
4	#2 and #3
5	#1 or #4
6	#1 or #4 Publication Year from 2011 to 2016, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 11.10.2016

#	Suchfrage
1	multiple sclerosis[MeSH Terms]
2	(multiple scleros*[Title/Abstract]) OR ms[Title/Abstract]
3	(((relapse*[Title/Abstract]) OR relapsing[Title/Abstract]) OR secondary progressive[Title/Abstract]) OR chronic progressive[Title/Abstract]
4	(#2) AND #3
5	(#1) OR #4
6	(Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
7	(((((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	(#5) AND #8
10	(#9) AND ("2011/10/01"[PDAT] : "2016/10/11"[PDAT])
11	(#10) NOT "The Cochrane database of systematic reviews"[Journal]

Leitlinien in Medline (PubMed) am 11.10.2016

#	Suchfrage
1	Multiple Sclerosis[MeSH Terms]
2	multiple scleros*[Title/Abstract]
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]) OR recommendation*[Title]
5	(#3) AND #4
6	(#5) AND ("2011/10/01"[PDAT] : "2016/10/11"[PDAT])

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8. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Dimethylfumarat, vom 16. Oktober 2014 [online]. Berlin (GER): G-BA; 2014. [Zugriff: 11.10.2016]. URL: https://www.g-ba.de/downloads/39-261-2075/2014-10-16_AM-RL-XII_Dimethylfumarat_2014-05-01-D-100_BAnz.pdf.

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ba.de/downloads/39-261-2578/2016-05-19_AM-RL-XII_Fingolimod_nAWG_D-198_BAnz.pdf.

10. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Teriflunomid, vom 20. März 2014 [online]. Berlin (GER): G-BA; 2014. [Zugriff: 11.10.2016]. URL: https://www.g-ba.de/downloads/39-261-1949/2014-03-20_AM-RL-XII_Teriflunomid_2013-10-01-D-078_BAnz.pdf.

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Band 387). URL: https://www.iqwig.de/download/A16-19_Fingolimod_Addendum-zum-Auftrag-A15-48_V1-1.pdf.

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Anhang

Figure 14. Study limitations distribution for each network estimate for pairwise comparisons versus placebo on relapses over 12 and 24 months and disability worsening over 24 months outcomes. Calculations are based on the contributions of direct evidence to the network estimates and the overall risks of bias considering our predefined criteria (allocation concealment, blinding of outcome assessor, and incomplete outcome data) within studies contributing to the direct evidence. The colours represent risk (green, low; yellow, moderate; red, high). The direct comparisons against placebo are described in the vertical axis.