Rituximab nella Sclerosi Multipla: Revisione Critica

Revisione congiunta della Società Italiana di Neurologia (SIN) e dell'Associazione Italiana Sclerosi Multipla (AISM)

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Obiettivi congiunti del Gruppo di Studio SIN & AISM

1 **Standardizzazione**

Standardizzare i percorsi terapeutici per la SM in Italia.

2 **Efficacia e Sicurezza**

Garantire terapie precoci, efficaci e sicure.

3 **EBM**

Applicare le regole della Medicina Basata sull'Evidenza.

Le criticità del Rituximab

L’inserimento del rituximab nell’elenco istituito con la Legge n.648/96**, con indicazione terapeutiche già previste per farmaci “on label”** pone delle criticità importanti nella gestione della scelta prescrittiva.

Sebbene il rituximab mostri una capacità di soppressione dell’infiammazione cerebrale comparabile a quella di altri farmaci anti-CD20 nel breve termine (in particolare sui parametri di RM), nessun dato sostiene l’uso di questo anticorpo monoclonale in protocolli terapeutici a lungo termine nella SM.

Ampia disponibilità di Farmaci

Oltre 15 farmaci disponibili per la SM testati mediante ampi trials clinici multicentrici di fase III.

Rituximab

Evidenze molto limitate in SM

Risultati non conclusivi

Studi Clinici su Rituximab: Revisione

Fase II

Studi di Fase II* limitati ed eterogenei per numero di pazienti (min 32, max 84), durata (talvolta < 12 mesi) ed endpoints eterogenei.

Doppio Cieco

Solo due studi in doppio cieco, uno per SMRR (HERMES: HauseR Sl N. Engl J Med 2008) e uno per SMPP (OLYMPUS: Hawker et al Ann Neurol 2009)).

Rifund-MS :Trial controllato randomizzato, in cieco parziale, di fase III

(Svenningsson et al Lancet Neurol 2022)

Registri

Swedish (Spelman T et al 2017) e MSBase registry and Danish MS Registry (Roos I et al. JAMA Neurol 2023)

Revisione Cochrane:

He D 2013 (Cochrane Database Syst Rev. 2013)

Filippini G. et al (Cochrane Database Syst Rev. 2021)

* Bar-Or et al., Ann Neurol, 2008; Naismith et al., Neurology, 2010; De Flon et al., Neurology, 2016; Honce et al., Neurology, 2019; Cheshmavar et al., Acta Neurol Scand, 2020

Lo Studio HERMES

1

Fase II

Trial in doppio cieco, controllato con placebo, 48 settimane.

Pazienti trattati con singolo ciclo di Rituximab

2

Risultati

Riduzione di lesioni Gd+ e nuove lesioni Gd+.

3

Limiti

Piccolo numero di pazienti (104 di cui 69 trattati con RTX e 35 placebo)

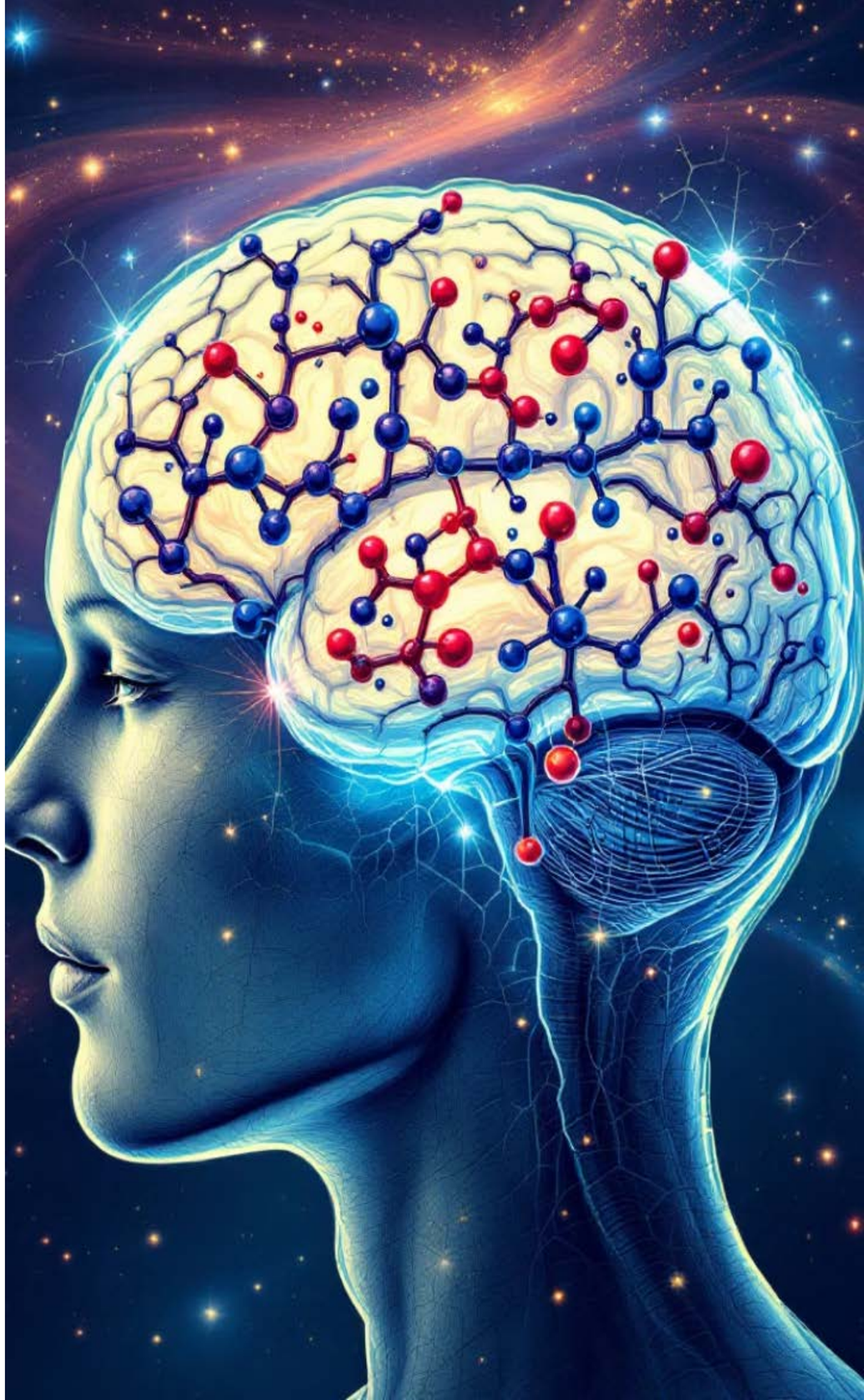
Breve follow-up (48 settimane)

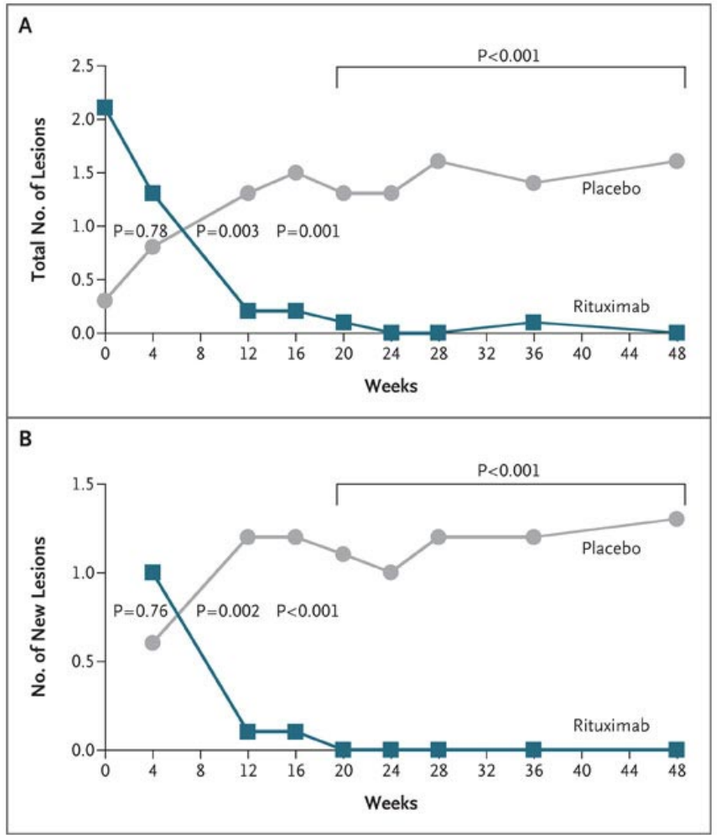
Efficacia induttiva sostanzialmente perduta entro 48 settimane

[ARR ridotta rispetto al gruppo placebo alla settimana 24 (p = 0.04),

ma non alla settimana 48 (p = 0.08)]

Hauser SL et al. N Engl J Med 2008





"…small 48-week trial […] not designed to assess long-term safety or to detect uncommon adverse events" e che "…rituximab may be an option for treating relapsing remitting multiple sclerosis, provided that efficacy and safety are sustained in larger and longer-term controlled trials".

Table 3. (Continued.)

End Point	Placebo (N=35)	Rituximab (N=69)	P Value
Clinical			
Relapses between wk 0 and wk 48 — no. of patients (%)			
0 relapses	21 (60.0)	55 (79.7)	
1 relapse	11 (31.4)	8 (11.6)	
2 relapses	1 (2.9)	5 (7.2)	
≥3 relapses	2 (5.7)	1 (1.4)	
Mean no. of relapses (range)	0.54±0.82 (0–3)	0.30±0.67 (0–3)	
Annualized rate of relapse from wk 0 to wk 24			
Total no. of relapses	13	11	
Total subject-years of follow-up	15.9	31.3	
Unadjusted rate	0.8	0.4	
Adjusted rate (90% CI)**	0.8 (0.53–1.31)	0.4 (0.23–0.60)	0.04††
Mean‡‡	0.8±1.20	0.3±0.86	
Median	0	0	
Annualized rate of relapse from wk 0 to wk 48			0.08††
Total no. of relapses	19	21	
Total subject-years of follow-up	27.2	59.7	
Unadjusted rate	0.7	0.4	
Adjusted rate (90% CI)**	0.7 (0.46–1.12)	0.4 (0.24–0.57)	
Mean‡‡	0.7±1.05	0.4±0.81	
Median	0	0	

Hauser SL et al. N Engl J Med 2008

Lo Studio OLYMPUS

1

Fase II/III

Trial in doppio cieco, controllato con placebo, 96 settimane.

sulle forme primariamente progressive

2

Risultati

Nessuna differenza significativa nell'endpoint primario rappresentato dalla progressione confermata della disabilità.

3

Sottogruppi

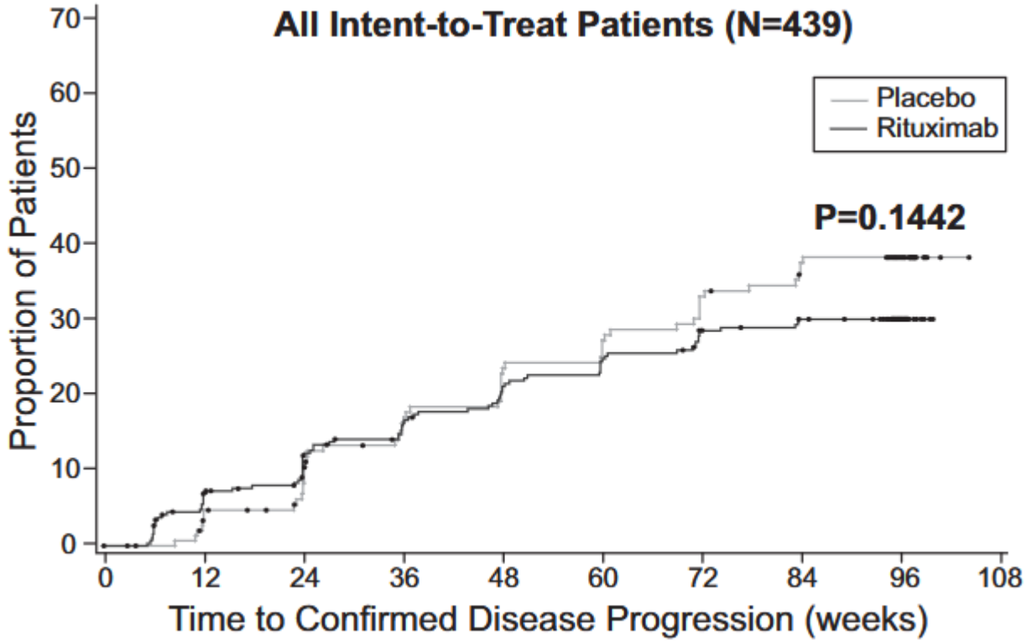
Effetti significativi solo in un piccolo sottogruppo di pazienti.

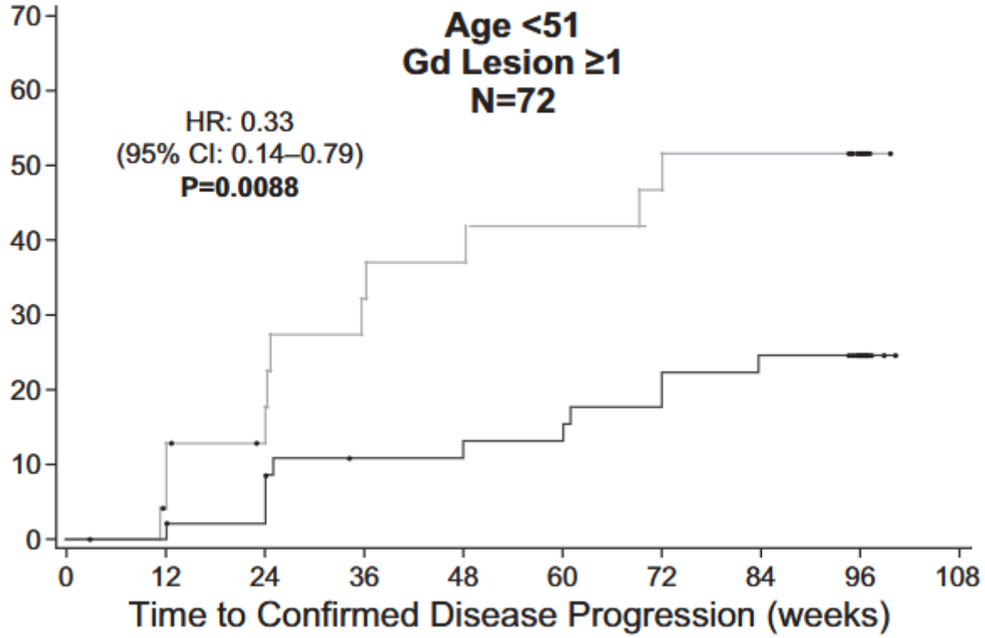
“ …. Rituximab may be an option for treating MS, provided that efficacy and safety are sustained in larger and longer-term controlled trials”.

Hawker K et al. Ann Neurol 2009

Table 1. **Patient Baseline Demographic Characteristics**

Demographic	Placebo, n=147	Rituximab, n=292	Total, N=439
Age, mean yr (SD)	49.6 (8.7)	50.1 (9.0)	49.9 (8.9)
Gender, No. (%)			
Male	66 (44.9)	152 (52.1)	218 (49.7)
Female	81 (55.1)	140 (47.9)	221 (50.3)
Ethnicity, No. (%)			
White	134 (91.2)	268 (91.8)	402 (91.6)
Other	13 (8.8)	24 (8.2)	37 (8.4)
Disease duration, mean yr (SD)			
Since onset	9.0 (6.8)	9.2 (6.4)	9.1 (6.6)
Since diagnosis	3.8 (4.2)	4.1 (4.2)	4.0 (4.2)
Prior MS treatment with IFN-beta or glatiramer acetate, No. (%)			
No prior MS therapies	96 (65.3)	189 (64.7)	285 (64.9)
Ended >90 days before trial entry	45 (30.6)	87 (29.8)	132 (30.1)
Ended ≤90 days before trial entry	6 (4.1)	16 (5.5)	22 (5.0)
EDSS score			
Median (min, max)	4.5 (2.0, 6.5)	5.0 (2.0, 6.5)	5.0 (2.0, 6.5)
Mean (SD)	4.7 (1.4)	4.8 (1.4)	4.8 (1.4)



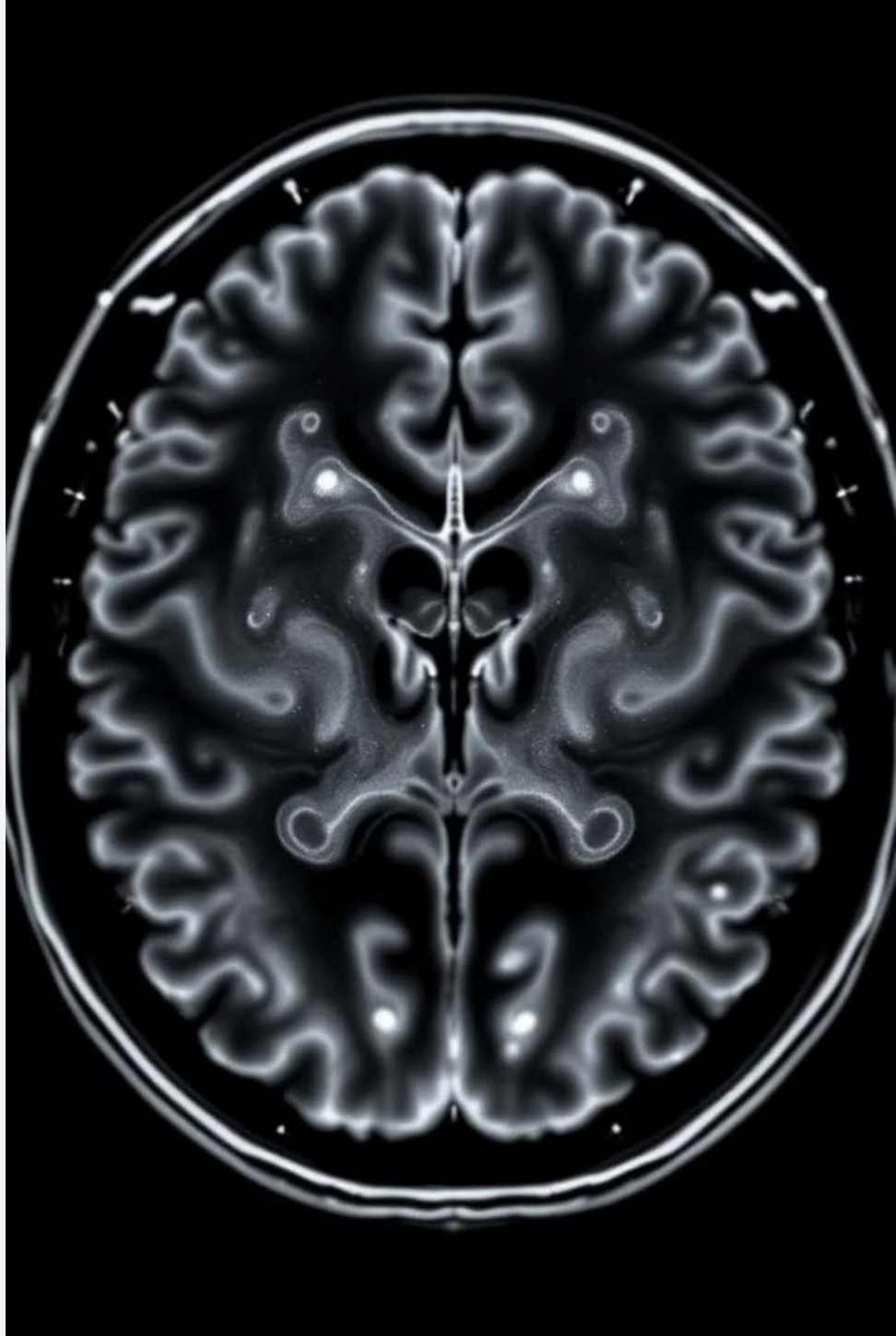


Hawker K et al. Ann Neurol 2009

Studio RIFUND-MS: Rituximab vs Dimetilfumarato nella Sclerosi Multipla

Safety and efficacy of rituximab versus dimethyl fumarate in patients with relapsing-remitting multiple sclerosis or clinically isolated syndrome in Sweden: a rater-blinded, phase 3, randomised controlled trial

Anders Svenningsson, Thomas Frisell, Joachim Burman, Jonatan Salzer, Katharina Fink, Susanna Hallberg, Joakim Hambraeus, Markus Axelsson, Faiez Al Nimer, Peter Sundström, Martin Gunnarsson, Rune Johansson, Johan Mellergård, Igal Rosenstein, Ahmad Ayad, Irina Sjöblom, Anette Risedal, Pierre de Flon, Eric Gilland, Jonas Lindeberg, Fadi Shawket, Fredrik Piehl, Jan Lycke



Svenningsson et al. Lancet Neurology 2022

Metodi e Risultati Principali

1 Disegno dello Studio

Trial multicentrico, randomizzato, i**n cieco per il valutatore**, della durata di 24 mesi**.** I pazienti **(99) hanno ricevuto rituximab** endovena (1000 mg seguito da 500 mg ogni 6 mesi) **o dimetilfumarato orale (98 pz)** (240 mg due volte al giorno).

2 Endpoint Primario

La proporzione di pazienti con almeno una recidiva definita dal protocollo

3 Endpoint secondari

- Pazienti con nuova attività di malattia alla risonanza magnetica
- Pazienti con peggioramento della disabilità confermata alla EDSS
- Variazione dello score alla EDDS

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Baseline patient characteristics

	Rituximab (n=99)	Dimethyl fumarate (n=98)
Age, years	33·5 (7·7)	33·4 (7·7)
Sex		
Female	67 (68%)	64 (65%)
Male	32 (32%)	34 (35%)
Diagnosis		
Multiple sclerosis according to McDonald criteria	97 (98%)	95 (97%)
Clinically isolated syndrome	2 (2%)	3 (3%)
Multiple sclerosis duration, years from symptom onset	1·6 (3·2)	1·8 (2·6)
Treatment naive	97 (98%)	93 (95%)
Interferon beta treatment before study (within past 3 months)	1 (1%)	4 (4%)
EDSS score		
Mean	1·6 (1·2)	1·7 (1·0)
Median	1·5 (1·0–2·5)	2·0 (1·0–2·0)
Relapses in the past year		
0	23 (23%)	30 (31%)
1	54 (55%)	58 (59%)
>1	22 (22%)	10 (10%)
Relapses in the past 2 years		
0	22 (22%)	27 (28%)
1	53 (54%)	56 (57%)
>1	24 (24%)	15 (15%)
MRI brain lesions		
0	1 (1%)*	3 (3%)*
1–9	45 (46%)	37 (40%)
10–20	21 (22%)	29 (31%)
>20	30 (31%)	24 (26%)
Missing data	2 (2%)	5 (5%)
Total number of contrast-enhancing lesions		
0	54 (57%)	59 (66%)
1	27 (29%)	17 (19%)
2	5 (5%)	5 (6%)
≥3	8 (9%)	9 (10%)

Primary and secondary endpoints

	Rituximab (n=98)	Dimethyl fumarate (n=97)	p value*	Risk ratio† (95% CI)
Primary outcome				
Patients with any protocol-defined relapse	3 (3%)	16 (16%)	0·0060	0·19 (0·06–0·62)
Secondary outcomes				
Patients with any new T2 lesion or contrast-enhancing lesion	21 (21%)	36 (37%)	0·019	0·58 (0·36–0·91)
Patients with confirmed EDSS score worsening	10 (10%)	5 (5%)	0·20	1·98 (0·70–5·58)
Mean change in EDSS score‡	−0·4 (1·1)	−0·3 (1·1)	0·68	NA
Patients who did not maintain NEDA-2	24 (25%)	42 (43%)	0·0072	0·57 (0·37–0·86)
Patients who did not maintain NEDA-3	31 (32%)	45 (46%)	0·038	0·68 (0·48–0·98)
Post-hoc outcome				
Patients who discontinued drug	3 (3%)	48 (49%)	<0·0001	0·06 (0·02–0·19)

Data are n (%) or mean (SD) except where otherwise stated. EDSS=Expanded Disability Status Scale. NA=not applicable. NEDA=No Evidence of Disease Activity. *p value from log-binomial regression for binary variables and Kruskal-Wallis test for continuous variables. †Risk ratio from log-binomial regression. ‡Missing data, rituximab two patients and dimethyl fumarate four patients.

Table 2: **Primary, secondary, and post-hoc outcomes other than time-to-event outcomes**

Limiti dello studio

1. «The RIFUND-MS trial had several limitations. The study was small for a phase 3 trial in patients with multiple sclerosis. The size was based on feasibility to recruit patients to an academic trial held in one country.

2. «A rater-blinded rather than double-blinded trial design was chosen because we were unable to obtain placebo capsules identical to dimethyl fumarate. However, even with placebo capsules, effective masking would have been difficult owing to the common side-effects associated with dimethyl fumarate».

3. «Conducting a clinical trial using two well known medical products poses specific challenges. First, recruitment of patients might be hampered by patient perceptions of relative efficacy of the drugs. Second, there could be expectation biases regarding interpretation of new neurological symptoms being more likely to be regarded as relapse-related »

4. «The evaluation of MRI investigations was done at the local sites rather than at a central reading centre»

5. «A further limitation of RIFUND-MS is that we did not collect data on ethnic background, meaning that we do not know the generalisability of our findings to different ethnic groups».

Conclusioni

1. «In summary, findings from the RIFUND-MS trial suggest that initiation of rituximab is superior to dimethyl fumarate for remaining free of relapse over 24 months in a population of patients with RRMS»

2. «However, further studies, including larger populations and formal health-economic evaluations, are needed to position rituximab properly in the treatment scheme of multiple sclerosis»

3. «However, further studies in larger and more diverse patient populations are needed to confirm the treatment efficacy of rituximab in early relapsing-remitting multiple sclerosis, and long-term safety of rituximab in this disease needs to be further explored».

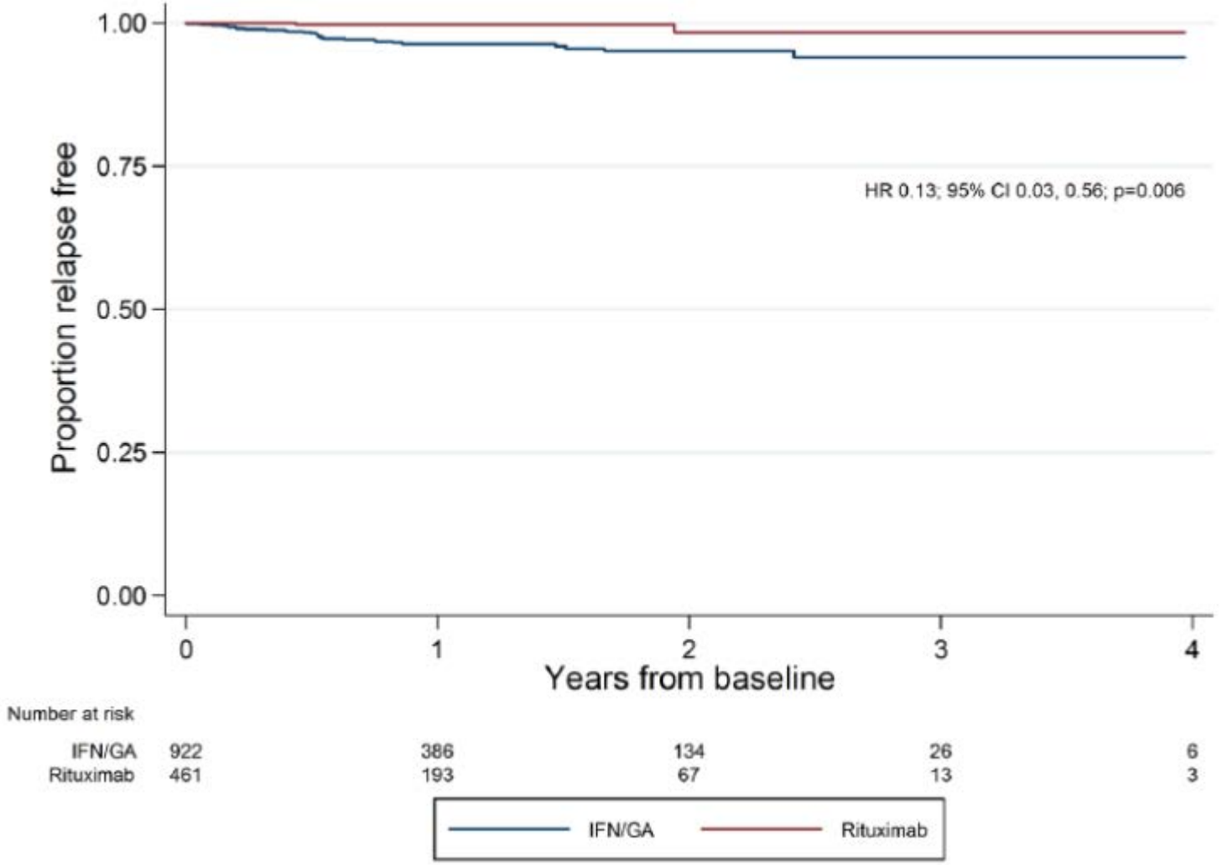
Svenningsson et al. Lancet Neurology 2022

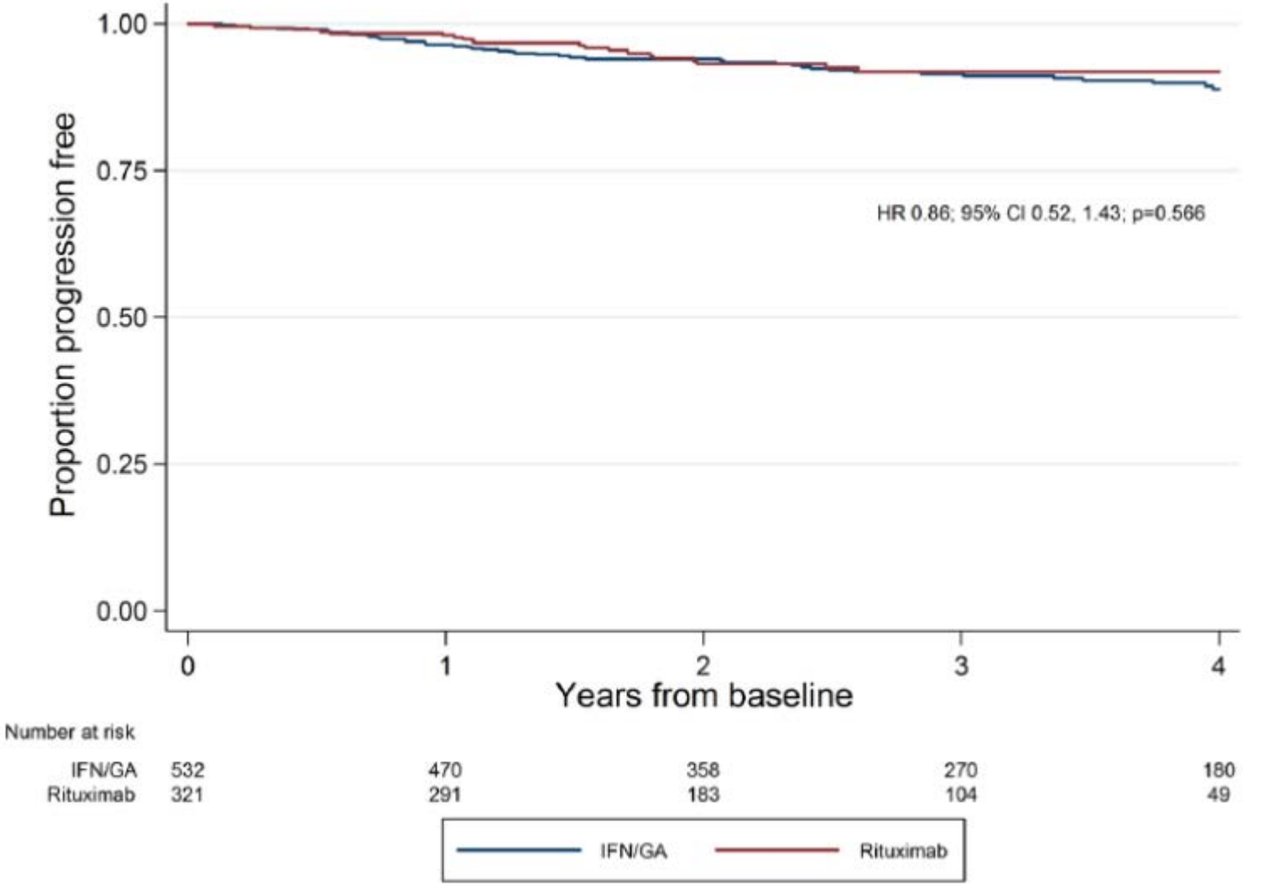
Dati del Registro Svedese

Studio su 461 pazienti SM trattati con rituximab e 922 trattati con IFNB/GA (propensity score match 1:2).

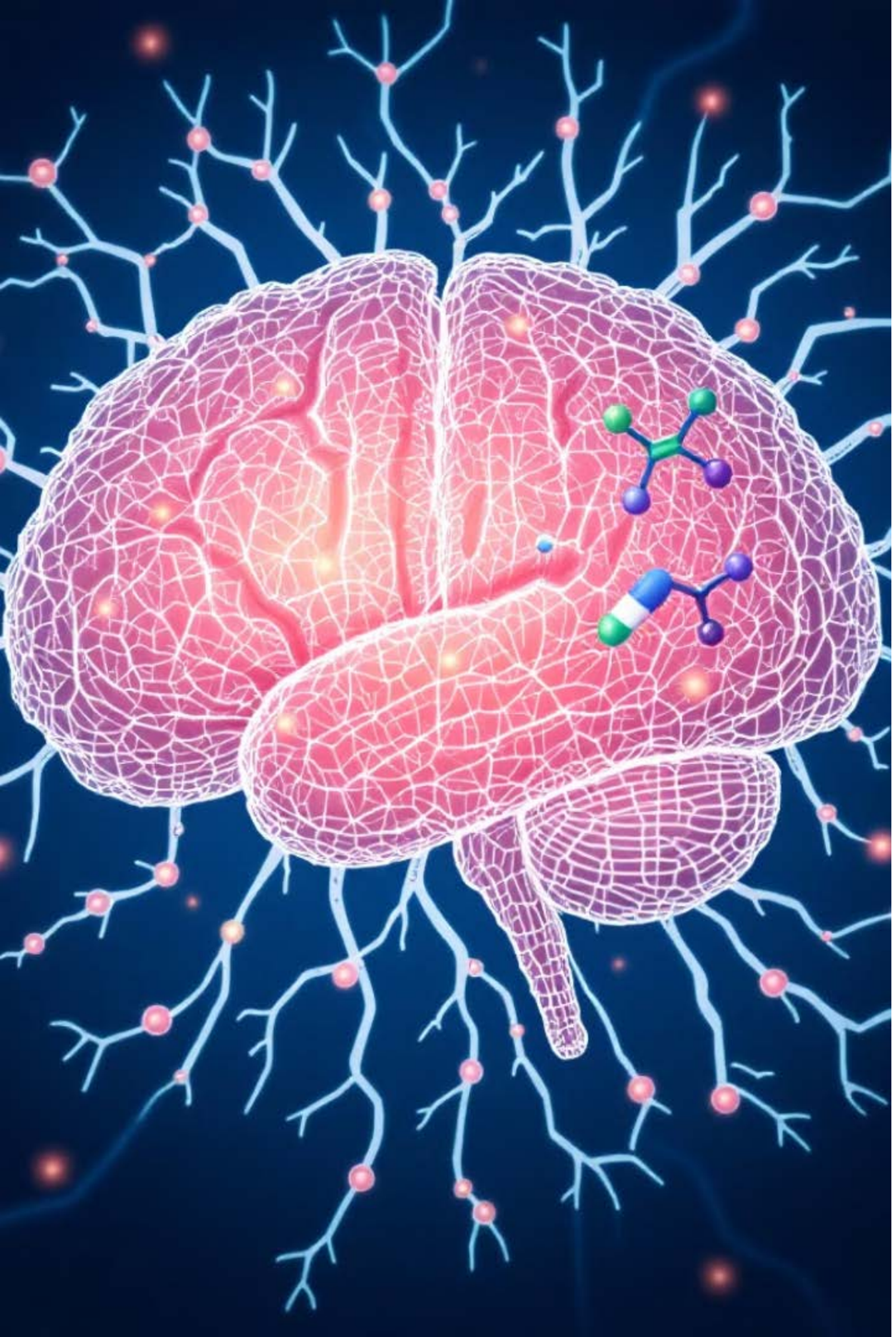
Riduzione dei parametri infiammatori, ma nessuna differenza significativa sulla progressione della disabilità.

Spelman T et al. Mult Scler 2017





Spelman T et al. Mult Scler 2017

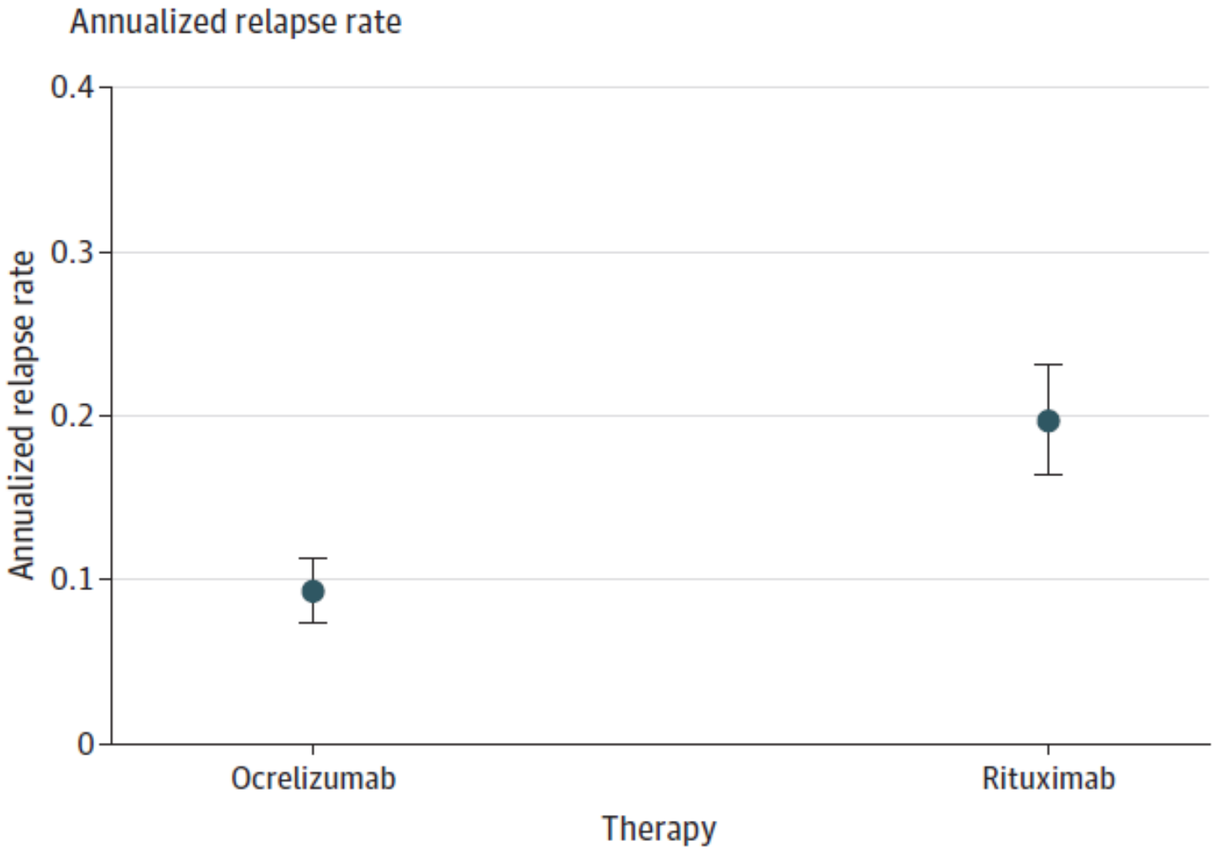


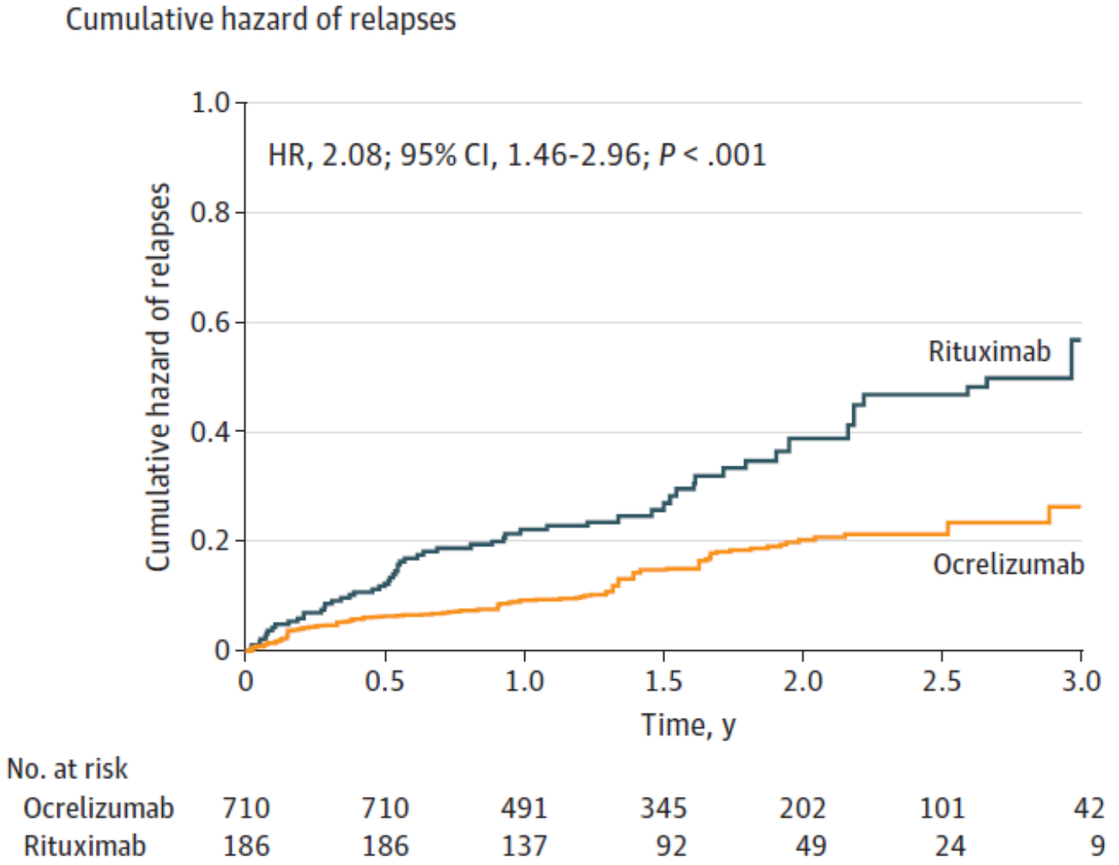
Dati del Registro Danese + MSBase

Studio su 710 pazienti SM trattati con ocrelizumab e 186 trattati con rituximab
(propensity score match 1:6).

Rituximab associato a maggiore relapse rate e rischio di ricaduta, nessuna differenza significativa sulla progressione della disabilità.

Roos I et al. JAMA Neurol 2023

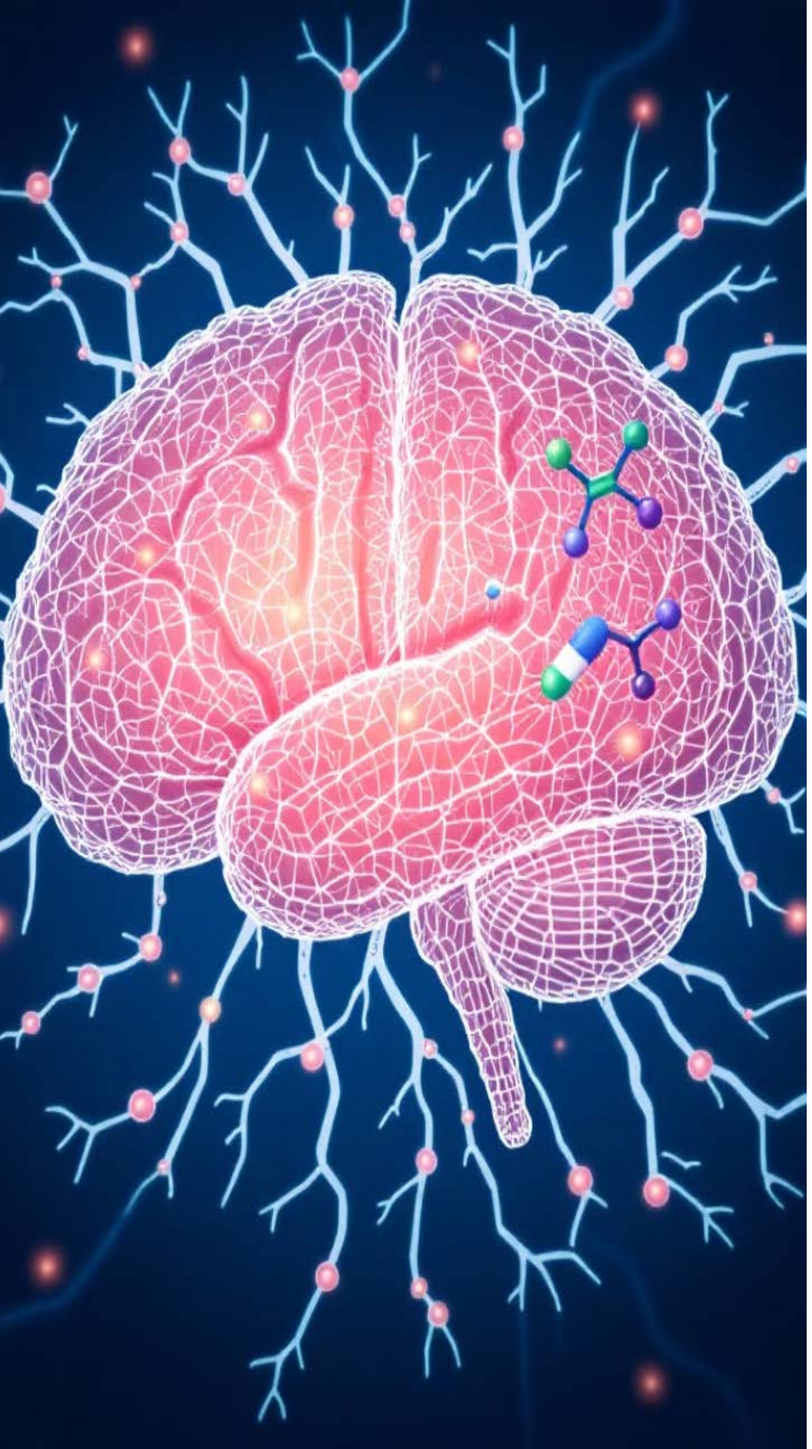




No. at risk

Ocrelizumab	710	710	491	345	202	101	42
Rituximab	186	186	137	92	49	24	9

Roos I et al. JAMA Neurol 2023



Revisione Cochrane

Dian He et al Cochrane Database Syst Rev 2013

Rituximab for RRMS

- **There is not sufficient evidence to support the use of Rituximab as a disease-modifyining therapy for RRMS** because only one RCT was included (Hermes study). The quality of the study was limited due to high attrition bias, the small number of partecipants and short follow-up. The beneficial effect of Rituximab for RRMS remain inconclusive.

- **The potential benefits of rituximab for treating RRMS need to be evaluated in large-scale studies that are of high quality along with long-term safety**

Filippini G et al. Cochrane Database Syst Rev. 2021

Rituximab for people with MS

- **A protective effect of rituximab against disability worsening is uncertain.** The evidence is uncertain about the effect of rituximab on SAEs

- **In the absence of randomized evidence, remaing uncertainties on beneficial and adverse effect of rituximab** for MS might be clarified by making larger real-word data available

Limitazioni del rituximab

1 Immunogenicità

Maggiore immunogenicità rispetto ad altri farmaci →

Più elevata probabilità dello sviluppo di anticorpi anti-farmaco.

2 Citotossicità

Maggiore citotossicità complemento-dipendente →

Più elevata probabilità di reazione infusionali.

Studi Clinici su rituximab: dosing regimens

Journal of Neurology (2022) 269:159–183
https://doi.org/10.1007/s00415-020-10362-z

REVIEW

Check for updates

Rituximab for the treatment of multiple sclerosis: a review

Clara Grazia Chisari[1] · Eleonora Sgarlata[1,2] · Sebastiano Arena[1] · Simona Toscano[1] · Maria Luca[1] · Francesco Patti[1]

Dosing regimen	Schedule	Interval	MS population
375 mg/m^2 i.v	Once weekly	Every 4 weeks	RRMS
500 mg i.v	Once weekly	2 weeks apart	RRMS
1000 mg i.v	Once weekly	2 weeks apart	RRMS
1000 mg i.v	Once weekly	2 weeks apart every 6 months	PMS
500 or 1000 mg i.v	Once	Every 6 months	RRMS
100 mg e.v. + 500 mg methylprednisolone	Once	Every 6 months	RRMS
10 mg IT	Once	2 months apart	RRMS
25 mg IT	Once weekly	Every week for 3 weeks	PMS

- Non esiste un consenso universale sulla dose iniziale ottimale, né sul protocollo di mantenimento (in alcuni casi stabilito ogni 6 mesi, in altri casi personalizzato in base ai livelli di cellule B CD19/CD20.
- Senza una dose standardizzata, non è possibile confrontare i risultati degli studi clinici e stabilire il profilo di sicurezza ottimale

(NHL) and RA, it is commonly used as off-label treatment for severe MS. However, due to the absence of formal head-to-head trials of therapy regimen comparisons for RTX in MS, there are neither consensus nor treatment guidelines on dosing regimens.

Conclusioni

Evidenze Scarse

Evidenze scientifiche limitate per l'uso del rituximab nella SM.

Alternative

Disponibilità di trattamenti specifici e di certa efficacia.

Consenso Informato

Acquisizione del consenso informato scritto del paziente.

Ulteriori Considerazioni

Responsabilità

Responsabilità del neurologo prescrittore per gli eventi avversi.

Principio di Continuità

Rischi di switch terapeutici che compromettono la continuità terapeutica.

Diritto alla Salute

Garantire il diritto alla salute di ogni paziente con SM.