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FOCUSED REVIEW

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Disease-modifying therapies in multiple sclerosis: A focused review of rituximab

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Abstract

Background: Treatment for multiple sclerosis (MS), a chronic inflammatory disease of the central nervous system, has changed drastically in the last 30 years. Several different disease-modifying therapies are now available, with off-label use of the B-cell-depleting antibody rituximab becoming an increasingly popular choice, as more and more studies report on its effectiveness.

Objectives: The objective of this study was to summarize the current state of evidence for rituximab as a treatment for relapsing-remitting MS (RRMS).

Methods: A structured literature search was conducted in PubMed, focusing on peer-reviewed studies of adult populations with RRMS. Ongoing trials with rituximab in MS were identified through Clinicaltrials.gov and additional references were identified through review articles.

Findings: Despite promising results for rituximab as a treatment of MS, the market-authorization holder switched focus from rituximab and discontinued the industry-sponsored trials programme. However, several observational studies, smaller clinical trials and one large investigator-initiated randomized-controlled trial have continued to report fewer clinical relapses, fewer contrast-enhancing lesions on magnetic resonance imaging and better drug survival with rituximab, compared with MS-approved alternatives.

Conclusions: Rituximab should be considered as both a first- and second-line therapy option for most MS patients with active, non-progressive disease. However, as an off-label therapy for MS, regulatory approval remains a barrier for wider adoption in many countries.

KEYWORDS
disease-modifying therapy, multiple sclerosis, review, rituximab

1 | INTRODUCTION

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system, resulting in the accumulation of demyelinating lesions and neurological disability.[1,2] The most common type of MS at diagnosis, relapsing-remitting MS (RRMS), is characterized by recurring bouts of inflammatory activity followed by periods of no disease activity and full or partial recovery of symptoms.[3] Eventually, with age, relapses become rarer while neurological

disability continues to worsen progressively, which is called secondary progressive MS (SPMS).[4] A minority of patients have a progressive disease course from the start, primary progressive MS (PPMS).

The aetiology of MS is not yet clearly understood. Both genetic and environmental factors have important roles,[5] and infection with Epstein–Barr Virus (EBV) has recently been identified as a leading cause of MS, increasing the risk of MS 32-fold after infection.[6] The pathophysiology of MS is also incompletely understood, but the inflammatory lesions in the central nervous system have a central role and is thought to be mediated through autoimmune processes.[7] Dysfunctional CD4+ and CD8+ T cells with specificity for the myelin protein have long been suspected to be the main drivers of the central nervous system inflammation. These T cells are thought to be primed in the periphery, possibly through molecular mimicry between EBV epitopes and neuroglial antigens, cross the blood–brain barrier, and contribute to the development of new inflammatory lesions.[7,8] However, new research, together with the success of several anti-CD20 therapies, have shown that B cells also play an important role. Possible mechanisms include high-capacity secretion of cytokines and the presentation of antigens to T cells.[7,9,10] Additionally, EBV establishes itself as a chronic latent infection in the memory B cell pool after primary infection, possibly further explaining the effectiveness of anti-B cell therapy in MS.

2 | DISEASE-MODIFYING THERAPIES

Treatment of MS has changed drastically in the last 30 years; from no available disease-modifying therapies (DMTs), to the several different types accessible today. The first DMTs to become available were the injectable therapies, interferon-beta and glatiramer acetate, followed by newer-generation oral synthetic and parenteral biologic drugs. Table 1 lists the currently available DMTs for MS. As few therapies have any proven effect for progressive MS (SPMS/PPMS), most DMTs are only approved for use in patients with RRMS.

TABLE 1 Currently available disease-modifying therapies for multiple sclerosis.

ATC	Generic name	Brand name/s	MAH/s	First approved EMA/FDA	Trials
L03AB08	Interferon-beta-1b	Betaferon/Extavia	Bayer/Novartis	1995/1993	11–18
L03AB07	Interferon-beta-1a	Avonex/Rebif	Biogen/Merck	1997/1996	19–23
L03AX13	Glatiramer acetate	Copaxone	Teva	—[a]/1997	24
L04AA23	Natalizumab	Tysabri	Biogen	2006/2004	25–28
L04AA27	Fingolimod	Gilenya	Novartis	2011/2010	29–34
L04AA31	Teriflunomide	Aubagio	Sanofi	2013/2012	35–38
L04AA34	Alemtuzumab	Lemtrada	Sanofi	2013/2014	39–41
L04AX07	Dimethyl fumarate	Tecfidera	Biogen	2014/2013	42–44
L03AB13	Peginterferon-beta-1a	Plegidry	Biogen	2014/2014	45,46
L01DB07	Mitoxantrone	Novantrone	Meda	2016/2000	47–50
L04AC01	Daclizumab	Zinbryta	Biogen	~~2016~~[b]	51–53
L04AA40	Cladribine	Mavenclad	Merck	2017/2019	54–57
L04AA36	Ocrelizumab	Ocrevus	Roche	2018/2017	58–60
L04AA42	Siponimod	Mayzent	Novartis	2020/2019	61–64
L04AA38	Ozanimod	Zeposia	Celgene	2020/2020	65,66
L04AX09	Diroximel fumarate	Vumerity	Biogen	2021/2019	67
L04AA52	Ofatumumab	Kesimpta	Novartis	2021/2020	60,68–70
L04AA50	Ponesimod	Ponvory	Janssen	2021/2021	71,72
L01XC02	Rituximab	MabThera/Rituxan	Roche	—[c]	73–77

Abbreviations: ATC, anatomical therapeutic chemical classification; EMA, European medicines agency; FDA, US Food and Drug Administration; MAH, market authorization holder.

[a]Glatiramer acetate is nationally authorized in Sweden since 2001.

[b]Daclizumab was voluntarily withdrawn in 2018 by its MAH.

[c]Rituximab are used off-label for multiple sclerosis in some countries.

The prevailing treatment strategy for MS has so far been one of escalation, where patients are started on less effective, often first-generation therapies.[78] These therapies exert less potent effects on the immune system and are therefore considered safer. Common first-line therapies include the older injectable therapies, and more recently also the oral therapies dimethyl fumarate and teriflunomide. In many cases, this initial treatment is insufficient and patients will have to switch to more effective treatment alternatives.[79] For patients where the disease is clearly aggressive already at diagnosis, a more potent therapy is often considered already from the start.

Choice of second-line therapy differs between countries and even treatment centres, but in Sweden, the most commonly used drugs are currently dimethyl fumarate, fingolimod, natalizumab and off-label rituximab (Figure 1). Third-line treatment options, reserved for patients with a very severe disease, include alemtuzumab and autologous haematopoietic stem cell transplantation (AHSCT).

However, this strategy of treatment escalation has recently come into question, as the neurological damage that accumulates while patients stay on less effective treatment for longer or move from one therapy to the next is debilitating and, at least in part, irreversible. Studies have shown that more aggressive treatment strategies positively affect disability outcomes,[79–83] and there is now enough clinical experience with the more potent DMTs for them to be used safely and effectively also early in the disease course. As a result, there is now a trend to use more effective therapy options earlier in the disease course. Notably, rituximab has seen a drastic increase in use since the initial reports from the clinical trials programme that showed it to be effective in MS, and it is now the most commonly used MS DMT in Sweden (Figure 1).

3 | RITUXIMAB

Rituximab is a monoclonal, chimeric IgG1 antibody targeting the CD20 antigen on B cells, resulting in B-cell depletion.[84] CD20 is a transmembrane protein located on pre-B and mature B lymphocytes, but not on stem cells, pro-B cells, normal plasma cells, other normal tissues or free in the circulation.[85] CD20 regulates cell cycle initiation and differentiation, and binding with rituximab (or another anti-CD20 antibody) quickly triggers cell death through complement-mediated cytotoxicity, antibody-dependent cell-mediated cytotoxicity or induction of apoptosis.[85] The half-life of rituximab has been measured to 18 to 23 days (in patients with rheumatoid arthritis).[86] A high degree of anti-drug antibodies (ADAs) have been observed in MS patients treated with rituximab (26%–37% of patients), but although there was correlation with efficacy of B-cell depletion, the clinical relevance is uncertain.[87]

Rituximab is approved for treatment of B-cell lymphoma and leukaemia, systemic vasculitis and rheumatoid arthritis but has a history of off-label use to treat several neuroimmunological conditions, such as MS. It is given as an infusion, usually every 6 months in doses between 500 and 2000 mg. In Sweden, a low-dose regimen has been adopted for the treatment of MS, with the most common dose being 500 mg every 6 months. Although, longer intervals between infusions are currently being investigated.

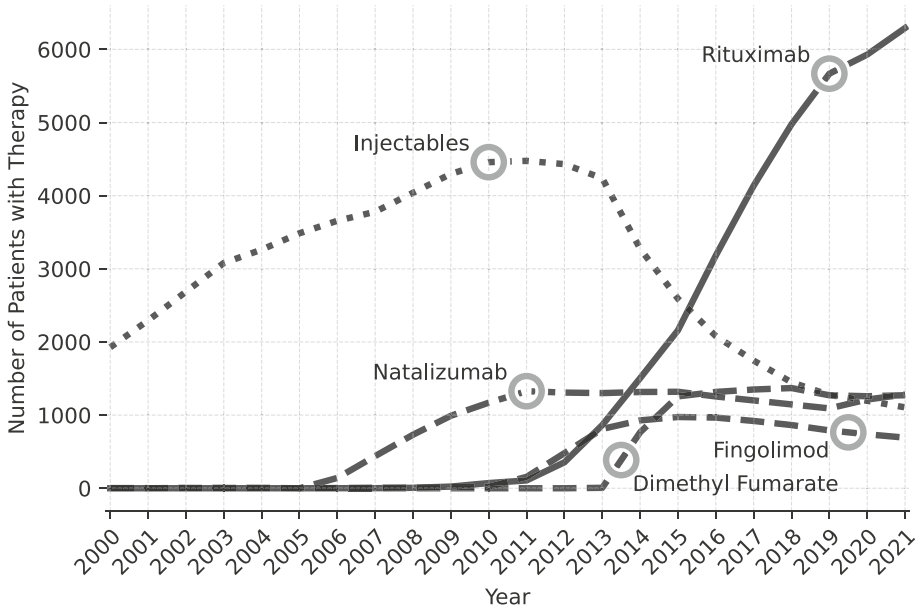

FIGURE 1 Disease-modifying therapies for multiple sclerosis in Sweden over time. Number of patients with ongoing therapy (vertical axis) by the end of the year (horizontal axis), for the four most common therapies in Sweden and injectables as a group consisting of interferon-beta, glatiramer acetate and peginterferon-beta.

Initial industry-sponsored clinical trials showed promising results for rituximab in active MS. However, before rituximab could be approved for MS, the market authorization holder shifted its focus to the newer anti-CD20 antibody ocrelizumab. Since then, investigator-initiated clinical trials and observational studies have continued to report positive results for rituximab in the treatment of active MS.

To summarize the current state of the evidence for rituximab as a treatment for MS, a structured literature search was conducted in PubMed, with the query "rituximab" [MeSH Terms] AND "multiple sclerosis" [MeSH Terms]. The focus was on studies of adults with RRMS, as this is the most common type of MS and the type that most readily responds to disease-modifying treatment. Ongoing trials with rituximab in MS were identified through Clinicaltrials.gov and additional references were identified through review articles. Only peer-reviewed publications were included.

3.1 | Clinical trials

The first industry-sponsored (Biogen and Genentech) trials with rituximab as a treatment for MS (one Phase I, one Phase II and one Phase II/III) were reported in 2008/2009.[73,74,88]

The initial small, open-label, uncontrolled Phase I trial of 26 RRMS patients, reported that 2000 mg rituximab, divided in two doses 2 weeks apart, every 6 months was associated with mild to moderate infectious and infusion-related adverse events.[88] However, no serious adverse events were reported. The study also found a reduction in relapses and lesions found on (magnetic resonance imaging) MRI from week 4 to week 72, compared with the year before treatment start.

The HERMES trial was a Phase II, double-blind, randomized, placebo-controlled trial of 104 RRMS patients.[73] It found that 2000 mg rituximab, divided in two doses 2 weeks apart, resulted in fewer contrast-enhancing lesions and a lower proportion with relapses, throughout the study period. However, more patients in the rituximab group reported mild to moderate infusion-related adverse events.

Finally, the OLYMPUS trial, a Phase II/III, double-blind, randomized, placebo-controlled trial of 439 PPMS patients, found no clear difference in confirmed disease progression or brain volume change between the control group and 2000 mg rituximab, divided in two doses 2 weeks apart, every 24 weeks.[74] However, the rituximab group had a smaller increase in T2-lesion volume and a subgroup analysis of younger patients with more active disease found a delay in time to confirmed disease progression. Also in this study, more patients in the rituximab group reported infections and mild to moderate infusion-related adverse events.

After these initial promising results and the discontinuation of the trial programme by the market authorization holder, several smaller, investigator-initiated trials followed. Most of which were uncontrolled and/or open-label. In summary, these smaller trials found rituximab to reduce the number of contrast-enhancing lesions and new/enlarged T2 lesions, lower levels of neurofilament (a marker of neurological damage) in cerebrospinal fluid, and improve Multiple Sclerosis Functional Composite (MSFC) scores and treatment satisfaction, while Expanded Disability Status Scale (EDSS) scores remained mostly stable.[9,89–91] However, the effects of treatment were less clear in patients with SPMS.[76] De-escalation from 1000 to 500 mg rituximab, every 6 months, did not appear to lower the effectiveness and could possibly increase safety by lowering the risk of infection.[92] Rituximab was also evaluated as an induction therapy in combination with glatiramer acetate, reducing disease activity and occurrence of new lesions on MRI over 3 years.[75] Although, the effectiveness appeared to fade within the study period.

It was not until 2022 that a new, large, randomized controlled trial of rituximab for MS was reported, the investigator-initiated RIFUND-MS Phase III trial.[77] In 200 RRMS patients, followed over 24 months, 1000/500 mg rituximab (first dose/subsequent doses) every 6 months was compared with dimethyl fumarate. Patients in the rituximab group experienced fewer relapses, but a greater a number of mild to moderate infusion-related adverse events. No major safety concerns were reported.

For a summary of the clinical trials of rituximab in MS, see Table 2.

3.2 | Observational studies

As the clinical use of rituximab in MS has increased, several observational studies have been conducted. Although not considered the same gold-standard as a well-made randomized controlled trial, observational studies excel at assessing real-world patient populations and investigating rare safety outcomes.

In 2016, a Swedish multi-centre, retrospective/register study (Salzer et al.) evaluated the effectiveness and safety of rituximab in 822 MS patients (557 RRMS), over an average follow-up of 23 months.[93] This study found that after starting treatment with rituximab, annualized relapse rates were low and few patients had contrast-enhancing lesions on MRI. EDSS remained stable for the patients with RRMS. Mild infusion-related reactions were

TABLE 2 Trials of rituximab in multiple sclerosis.

Year	Author (study)	Sponsor	Allocation	Blinding	Control	Participants	Follow-up (months)	ARR	Note	Ref.
2008	Bar-Or	Biogen/ Genentech	-	Open-Label	-	26 RRMS	18	0.18	Clinical Trials Programme	88
2008	Hauser (HERMES)	Biogen/ Genentech	Randomized	Double-Blind	Placebo	104 RRMS	12	0.4	Clinical Trials Programme	73
2009	Hawker (OLYMPUS)	Biogen/ Genentech	Randomized	Double-Blind	Placebo	439 PPMS	24/31	-	Clinical Trials Programme	74
2010	Naismith/Piccio	-	-	MRI-Blinded	-	30 RRMS	5/13	0.23	RTX as add-on therapy	9,89
2016/2017	de Flon	-	-	Open-Label	-	75 RRMS	24	-		90,91
2019	Honce (GATEWAYII)	-	Randomized	Double-Blind	Placebo/ GA	55 RRMS	36	0.155	RTX induction combined with GA	75
2021	Cheshmavar	-	Randomized	Open-Label	GA	84 SPMS	12	0.41		76
2021	Disanto	-	-	Open-Label	-	37 RRMS/22 SPMS	12	0	RTX de-escalation	92
2022	Svenningsson (RIFUND-MS)	-	Randomized	Rater-Blinded	DMF	200 RRMS	24	0.015		77

Note: The ARR is the reported ARR for the rituximab group at the end of the study period.
Abbreviations: ARR, annualized relapse rate; DMF, dimethyl fumarate; GA, glatiramer acetate; RTX, rituximab.

common, but no severe adverse events or cases of PML were reported.

Another 2016 Swedish, multi-centre, retrospective/register study (Alping et al.) of 256 RRMS patients switching from natalizumab, compared the effectiveness of rituximab (114) and fingolimod (142), over an average follow-up of 15–22 months.[94] Within 1.5 years after starting the new treatment, the rituximab group had less clinical relapses, fewer lesions on MRI and better drug survival, compared with fingolimod, adjusted for possible confounding.

A 2017 Swedish, nationwide, register study (Spelman et al.) of 1383 RRMS patients compared the effectiveness of rituximab (461) to the injectable therapies interferon-beta and glatiramer acetate (922), over an average follow-up of 26–34 months.[95] Patients in the rituximab group had lower relapse rates, better drug survival and a slight reduction in EDSS, compared with the matched injectables group.

A 2018 Swedish, multi-centre, register study (Granqvist et al.) of 494 newly diagnosed RRMS patients starting their first DMT evaluated effectiveness and drug survival of several different MS therapies (rituximab, 120; natalizumab, 50; fingolimod, 17; dimethyl fumarate, 86; injectables, 215; others, 6), over an average follow-up of 11–19 months.[96] Treatment with rituximab was associated with fewer relapses and fewer lesions on MRI, compared with injectables and dimethyl fumarate, adjusted for possible confounding. These effects were also present, but less noticeable, when comparing rituximab to natalizumab and fingolimod. Drug survival was better for rituximab than any of the other groups.

A 2018 Swiss, single-centre, retrospective study (Scotti et al.) of 165 MS patients (126 RRMS) evaluated effectiveness and safety of rituximab (82) compared natalizumab (83), over an average follow-up of 18–28 months.[97] Time to first evidence of disease activity was similar between the treatment groups, although with wide confidence intervals. A third of the rituximab-treated patients suffered infectious adverse events, of which six required therapy discontinuation.

A 2019 Spanish, multi-centre, retrospective study (Alcalá et al.) of 55 RRMS patients, evaluated effectiveness and safety in patients switching from fingolimod to either rituximab (27) or alemtuzumab (28), over an average follow-up of 29 months.[98] After switching, patients in both groups showed similar reductions in annualized relapse rates and EDSS. Additionally, the number of patients with no evidence of disease activity and the occurrence of infusion-related adverse events were similar between the groups.

A 2019 Swedish, multi-centre, retrospective/register study (Boremalm et al.) of 241 RRMS patients, evaluated effectiveness and drug survival in patients switching from injectables to a second line therapy (rituximab 48, natalizumab 105, fingolimod 88) due to disease breakthrough, over an average follow-up of 31–34 months.[99] Patients switching to rituximab had a similar risk of relapse as those switching to natalizumab, and lower than patients switching to fingolimod. Rituximab had better drug survival than both comparators.

Another 2019 Swedish, nationwide, register study (Luna et al.) of 8600 therapy starts (in 6421 RRMS patients) evaluated the risk of infection with four MS DMTs (rituximab, 3260; natalizumab, 1588; fingolimod, 1535; injectables, 2217) and a general population reference cohort, over an average follow-up of 24–32 months.[100] The risk of infection was generally increased for MS patients compared with the general population, but also varied with treatment. Older injectable therapies had the lowest rate of infection, while rituximab had the highest among the newer DMTs, adjusted for possible confounding. However, the use of antiherpetic drugs was lower for rituximab compared with the newer MS-approved alternatives. Importantly, no deadly infections were reported in any of the groups and only one case of PML was recorded in the rituximab group (and one in the fingolimod group), which was consistent with carry-over disease from previous natalizumab treatment.

A 2020 Swedish, nationwide, register study (Alping et al.) of 7477 therapy starts (6302 in patients with RMMS, from a total of 6136 unique MS patients) assessed the risk of cancer with three MS DMTs (rituximab, 4187; fingolimod, 1620; natalizumab, 1670) and a general population reference cohort, over an average follow-up of 28–48 months.[101] There was no increased risk of invasive cancer with rituximab or natalizumab, compared with the general population. However, the fingolimod group had a slight increased cancer risk compared with both rituximab and the general population. The study had insufficient power to link this increased risk to any specific cancer type.

A 2020 US, single-centre, retrospective study (Vollmer et al.) of 1246 MS patients (1004 RRMS) evaluated the effectiveness of four MS DMTs (rituximab, 182; natalizumab, 451; fingolimod, 271; dimethyl fumarate, 342), with follow-up up to 24 months.[102] Patients on rituximab had less disease activity (measured by a composite score) and better drug survival, compared with patients on fingolimod and dimethyl fumarate, and compared with patients on natalizumab during Months 6–24.

A 2021 US, single-centre, register study (Hou et al.) of 319 MS patients (unknown proportion with RRMS) evaluated effectiveness of rituximab (115) compared with natalizumab (204), over an average follow-up of 44–61 months.[103] Rituximab was associated with fewer

relapses compared with natalizumab, adjusted for possible confounding.

Apart from the above studies, several smaller observational studies and studies without any active comparator have been reported for rituximab in MS. The main results of these studies were:

- **Rommer 2016:** Mild infusion-related reactions were common, and infections were seen in three of the 56 patients, of which two were hospitalized.[104]
- **Barra 2016:** Three of the 107 patients had relapses or lesions on MRI despite undetectable B cell levels. Mild infusion-related reactions were common, and three patients were hospitalized with urinary tract infections.[105]
- **Alcalá 2018:** Reduced annualized relapse rates after starting rituximab and a small decrease in EDSS during the first year. Mild infusion-related reactions were common, and three thrombotic events were detected among the 90 patients.[106]
- **Alldredge 2018:** Most patients with RRMS had low annualized relapse rates and were reported to be stable on rituximab at the end of follow-up. Mild infusion-related reactions were common, and one of the 64 patients chose to stop rituximab treatment due to multiple adverse events.[107]
- **Yamout 2018:** Reduced annualized relapse rates and fewer lesions on MRI, while EDSS remained stable, compared with before start of rituximab. Mild infusion-related events were common, and two of the 89 patients experienced serious adverse events requiring surgical intervention (pyoderma gangrenosum vaginalis and increase in the size of a meningioma). No cases of PML were reported.[108]
- **Durozard 2019:** Reduced annualized relapse rates and fewer contrast-enhancing lesions on MRI, after switching to rituximab due to disease breakthrough on a previous DMT.[109]
- **Airas 2020:** Fewer relapses and contrast-enhancing lesions on MRI in the patients with RRMS, compared with before starting rituximab. No serious infusion-related reactions were reported, but one of the 72 patients had to discontinue treatment due to neutropenia.[110]
- **Bellinvia 2020:** Lower annualized relapse rate and less activity on MRI, compared with before starting rituximab.[111]
- **Mathew 2020:** Very few relapses and improved EDSS in the patients with RRMS, compared with before start of rituximab. No opportunistic infections or malignancies were reported.[112]
- **Mazdeh 2020:** Fewer relapses and stable EDSS, compared with before start of rituximab. Mild infusion-related reactions were common for the first infusion.[113]
- **Zecca 2020:** Reduced annualized relapse rates in the patients with RRMS, compared with before start of rituximab. After 3 years, the proportion with EDSS progression remained low and no major safety concerns were reported.[114]
- **Boremalm 2021:** No difference in annualized relapse rates or MRI activity after dose reduction or ending treatment with rituximab during a mean follow-up of 6.5 years.[115]
- **Perriguey 2022:** Reduced levels of immunoglobulin G after start of rituximab, which correlated with an increased risk of infection. During a median follow-up of 3.5 years, 13 severe infections were recorded among the 188 patients.[116]
- **Bribiesca-Contreras 2022:** Decreased annualized relapse rates, lesions on MRI and EDSS, compared with before start of rituximab. Two among the 85 patients experienced mild infusion-related reactions, and no serious adverse events were reported.[117]

For a summary of the observational studies of rituximab in MS, see Table 3.

3.2.1 | Ongoing research

Four investigator-initiated, randomized controlled trials of rituximab are registered at ClinicalTrials.gov and expected to report their findings in the coming years.

NOR-MS (NCT04121403) is an open-label, blinded-endpoint, randomized controlled trial, assessing non-inferiority of rituximab compared with cladribine, over 8 months, in patients with RRMS. Estimated enrolment of 264 participants. Main outcome is proportion of patients with no new or enlarging lesions on MRI from Week 12 to 96, with several secondary efficacy and safety endpoints. The study focuses on personalized MS care with specific blood and MRI biomarkers, as well as health-economic aspects of the two therapies. (Norway, estimated primary completion in July 2024).

OVERLORD-MS (NCT04578639) is a double-blind, randomized controlled trial, assessing non-inferiority of rituximab compared with ocrelizumab, over 30 months, in patients with RRMS. Estimated enrolment of 211 participants. Main outcome is proportion of patients with no new or enlarging lesions on MRI, between Months 6 and 24, with several secondary efficacy and safety endpoints. (Norway, estimated primary completion in February 2025).

DanNORMS (NCT04688788) is an open-label, blinded endpoint, randomized controlled trial, assessing non-inferiority of rituximab compared with ocrelizumab,

TABLE 3 Observational studies of rituximab in multiple sclerosis.

Year	Author	Country	Source	Design	Focus	Comparator/s	Participants (RRMS)	Avg. follow-up (months)	Note	Ref.
2016	Rommer	Germany	Nation	Register	Safety	-	56 (16)	10	Also included patients with NMO	104
2016	Barra	USA	Single	Retrospective	Effectiveness/ Safety	-	107 (54)	33		105
2016	Salzer	Sweden	Multi	Retrospective/ Register	Effectiveness/ Safety	-	822 (557)	23		93
2016	Alping	Sweden	Multi	Register	Effectiveness	FGL	256 (256)	15–22	Switch from natalizumab due to JCV+	94
2017	Spelman	Sweden	Nation	Register	Effectiveness	INJ	1383 (1383)	26–34		95
2018	Granqvist	Sweden	Multi	Register	Effectiveness	NTZ/FGL/DMF/ INJ	494 (494)	11–19	Newly diagnosed, first DMT	96
2018	Alcalá	Spain	Multi	Retrospective	Effectiveness/ Safety	-	90 (31)	30		106
2018	Alldredge	USA	Single	Retrospective	Effectiveness/ Safety	-	64 (23)	35	Also included patients with NMO	107
2018	Scotti	Switzerland	Single	Retrospective	Effectiveness/ Safety	NTZ	165 (126)	18–28		97
2018	Yamout	Lebanon	Single	Retrospective	Effectiveness/ Safety	-	89 (59)	22		108
2019	Durozard	France	Nation	Retrospective	Effectiveness	-	50 (50)	13	Switch after disease breakthrough on other DMT	109
2019	Alcalá	Spain	Multi	Retrospective	Effectiveness/ Safety	FGL/ALT	55 (55)	29	Switch from fingolimod	98
2019	Boremalm	Sweden	Multi	Retrospective/ Register	Effectiveness	NTZ/FGL	241 (241)	31–34	Switch after disease breakthrough on injectables	99

(Continues)

TABLE 3 (Continued)

Year	Author	Country	Source	Design	Focus	Comparator/s	Participants (RRMS)	Avg. follow-up (months)	Note	Ref.
2019	Luna	Sweden	Nation	Register	Safety - Infection	NTZ/FGL/INJ/GP	6421 (6421)	24–32		100
2020	Alping	Sweden	Nation	Register	Safety - Cancer	NTZ/FGL/GP	7477 (6302)[a]	28–48		101
2020	Vollmer	USA	Single	Retrospective	Effectiveness	NTZ/FGL/DMF	1246 (1004)	<24	Avg. follow-up not reported	102
2020	Airas	Finland	Single	Retrospective	Effectiveness/ Safety	-	72 (31)	23		110
2020	Bellinvia	Italy	Single	Retrospective	Effectiveness	-	69 (53)	16		111
2020	Mathew	India	Multi	Retrospective	Effectiveness	-	80 (58)	24	Experience from a developing country	112
2020	Mazdeh	Iran	Single	Retrospective/ Prospective	Effectiveness	-	70 (70)	18		113
2020	Zecca	Italy/Switzerland	Multi	Retrospective	Effectiveness/ Safety	-	355 (188)	23		114
2021	Boremalm	Sweden	Single	Retrospective	Effectiveness	-	225 (225)	78	Dose reduction/ Therapy discontinuation	115
2021	Hou	USA	Single	Register	Effectiveness	NTZ	319 (−)	44–61	Unknown proportion with RRMS	103
2022	Perriguey	France	Single	Retrospective	Safety - Infection	-	188 (151)	42		116
2022	Bribiesca-Contreras	Mexico	Single	Retrospective	Effectiveness	-	85 (73)	80		117

Abbreviations: ALT, alemtuzumab; DMF, dimethyl fumarate; FGL, fingolimod; GP, general population; INJ, injectables (interferons/glatiramer acetate); NMO, neuromyelitis optica; NTZ, Natalizumab; RRMS, relapsing remitting multiple sclerosis.

[a]Therapy episodes.

over 24 months (extension to 36 months), in patients with active MS. Estimated enrolment of 594 participants. Main outcome is proportion of patients with no new or enlarging lesions on MRI between Months 6 and 24, with several secondary efficacy and safety endpoints. (Denmark, estimated primary completion in April 2025).

RIDOSE-MS (NCT03979456) is a rater-blinded, randomized controlled trial, comparing rituximab 500 mg twice a year to 500 mg once a year, over 4 years, in patients with active MS. Estimated enrolment of 200 participants. Main outcome is proportion of patients with no evidence of disease activity (relapses, MRI lesions and EDSS progression) between Years 2 and 4, with several secondary efficacy and safety endpoints. (Sweden, estimated primary completion in June 2025).

4 | BIOSIMILARS

Generic preparations (of synthetic drugs) and biosimilars (of biologic drugs) become available as the original patents expire. These should have nearly identical pharmacokinetics and pharmacodynamics as the original preparations, although biosimilars might differ on a molecular level due to the production processes. In Sweden, the use of generics and biosimilars in MS has been limited. However, the patent for fingolimod recently expired (2022), resulting in an almost complete switch from Gilenya to the more affordable generic variants. Intravenous natalizumab is likely soon to follow. For rituximab, MabThera has begun to be replaced by the biosimilars Rixathon, Ritemvia and Truxima. There are few studies comparing these new biosimilars to MabThera in MS, but one study of Truxima reported equivalent effectiveness and safety.[118]

5 | OTHER B-CELL-DEPLETING THERAPIES

Newer B-cell-depleting therapies have been developed since the initial success of the rituximab trial programme, resulting in the recent approval of the anti-CD20 antibodies ocrelizumab (2017/2018) and ofatumumab (2020/2021). Both have been shown to be very effective in limiting MS inflammation.[58–60,68–70] However, it is unclear if these newer therapies provide any benefits over rituximab as the mechanism of action is identical. Studies comparing ocrelizumab and rituximab are currently ongoing (see above).

6 | CONCLUSIONS

The results from the first, industry-sponsored clinical trials of rituximab in MS were reported in 2008/2009. These studies demonstrated that rituximab was well tolerated and effective in limiting inflammation in patients with active MS, primarily RRMS, but with less impressive effects for progressive MS. Despite these positive results, the market authorization holder chose to shift their focus away from rituximab to the newer anti-CD20 antibody ocrelizumab, relegating rituximab to be used off-label for MS. Following this, several smaller trials, most of which were open-label and uncontrolled, continued to report positive findings for rituximab in active MS, even at lower doses. It would take more than a decade until another large randomized controlled Phase III trial for rituximab in MS was reported, RIFUND-MS. This time at the initiative of investigators, without industry sponsors. The trial showed that rituximab is an effective and safe treatment for patients with active MS, which by then was expected based on the available observational evidence.

This data came from the many observational studies conducted as rituximab started seeing increased off-label clinical use in MS, based on different populations and data sources. Many of these studies were small and often without an active comparator, but a few included large cohorts with an active-comparator design. Taken together, the observational data suggest that rituximab is an effective, safe and well tolerated treatment for active MS, primarily RRMS. Although, with some apparent effect also in patients with progressive disease with an active inflammatory component. Treatment with rituximab has been shown to be associated with fewer clinical relapses, fewer contrast-enhancing lesions on MRI and better drug survival, compared with MS-approved alternatives. The most commonly reported adverse events are mild infusion-related reactions that become less likely with additional infusions, but there is also an increased risk of infections, including severe infections requiring hospitalization. Importantly, there seems to be no significantly increased risk of PML, as seen with natalizumab. Compared with the MS-approved DMTs, rituximab has been reported to be more effective than interferons, glatiramer acetate, dimethyl fumarate and fingolimod, and have similar or slightly better effectiveness than natalizumab. The effects of rituximab appear to be mostly limited to preventing clinical relapses and the inflammatory lesions seen on MRI, while EDSS seems largely unaffected, at least in the short- to medium-term.

Further studies are needed to assess the comparative safety and effectiveness of rituximab and the newer, MS-approved, anti-CD20 therapies, ocrelizumab and ofatumumab. This becomes especially important when considering the vast difference in pricing between rituximab and the new B-cell-depleting therapies. It is also important to study the effects of using biosimilars of rituximab, instead of the original preparation, to assert similar effectiveness and safety.

Given the long experience with rituximab from its use in other conditions and the large amount of available evidence for it being effective, safe and well tolerated in MS, rituximab is an important addition to the treatment repertoire for neurologists and patients in their fight to limit the negative effects of MS. Rituximab should be considered as both a first- and second-line therapy option for most MS patients with active, non-progressive disease. However, as an off-label therapy for MS, regulatory approval remains a barrier for wider adoption in many countries.

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CONFLICT OF INTEREST STATEMENT

The author report no other conflicts of interest.

DATA AVAILABILITY STATEMENT

The data for the figure is available through the Swedish Multiple Sclerosis Register.

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