

Review Article

Anti-CD20 Therapy and Disability Progression in Relapsing Multiple Sclerosis

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Abstract

Background: Anti-CD20 antibodies are now a dominant treatment class in relapsing multiple sclerosis (MS). Disability accumulation is increasingly understood as driven by relapse-independent progression, not relapses alone.

Objective: To review trial, mechanistic, comparative and safety evidence on anti-CD20 therapy and disability outcomes in relapsing MS.

Methods: Narrative review of randomised trials, extension studies, registries and mechanistic literature on rituximab, ocrelizumab, ofatumumab and ublituximab.

Findings: OPERA I/II, ASCLEPIOS I/II and ULTIMATE I/II each showed reduced relapse rate and confirmed disability progression versus active comparators. Pooled analyses show most disability accumulation in relapsing MS reflects progression independent of relapse activity (PIRA), which anti-CD20 therapy also reduces. Real-world Swedish cohorts and comparative registries broadly support efficacy across agents; long-term safety data highlight hypogammaglobulinemia and infection risk.

Conclusions: Anti-CD20 therapy slows both relapse-associated and relapse-independent progression, though agent selection, dosing intervals and long-term immune monitoring remain active areas of study.

Keywords: Anti-CD20 therapy; Multiple sclerosis; Disability progression; B-cell depletion; PIRA

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Background: Anti-CD20 antibodies are now a dominant treatment class in relapsing multiple sclerosis (MS). Disability accumulation is increasingly understood as driven by relapse-independent progression, not relapses alone. **Objective:** To review trial, mechanistic, comparative and safety evidence on anti-CD20 therapy and disability outcomes in relapsing MS. **Methods:** Narrative review of randomised trials, extension studies, registries and mechanistic literature on rituximab, ocrelizumab, ofatumumab and ublituximab. **Findings:** OPERA I/II, ASCLEPIOS I/II and ULTIMATE I/II each showed reduced relapse rate and confirmed disability progression versus active comparators. Pooled analyses show most disability accumulation in relapsing MS reflects progression independent of relapse activity (PIRA), which anti-CD20 therapy also reduces. Real-world Swedish cohorts and comparative registries broadly support efficacy across agents; long-term safety data highlight hypogammaglobulinemia and infection risk. **Conclusions:** Anti-CD20 therapy slows both relapse-associated and relapse-independent progression, though agent selection, dosing intervals and long-term immune monitoring remain active areas of study.

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Introduction

Relapsing multiple sclerosis (MS) is an immune-mediated demyelinating disease in which accumulating disability, rather than relapse frequency alone, determines long-term outcome. Over the past decade, monoclonal antibodies targeting CD20, a surface marker expressed on most B cells and a subset of T cells, have moved from experimental therapy to first-line options in many treatment algorithms [1]. Rituximab, a chimeric anti-CD20 antibody developed for lymphoma, was the first agent shown to reduce inflammatory activity in MS

[2,3]. It was followed by the humanised antibody ocrelizumab, the fully human antibody ofatumumab, and the glycoengineered antibody ublituximab, each tested in large randomised trials against active comparators rather than placebo [4,5,6].

A parallel conceptual shift has reframed how disability accumulation itself is understood. Confirmed disability progression, historically attributed largely to incomplete recovery from relapses, is now recognised as substantially driven by a relapse-independent process termed progression independent of relapse activity (PIRA), which can begin early in relapsing disease and continues even in patients free of overt relapses [7,8]. This distinction matters clinically because relapse rate has long served as the primary marker of treatment response and the principal outcome by which regulators and clinicians judge whether a disease-modifying therapy is working; if a substantial share of disability instead accrues silently, therapies must be evaluated not only for their effect on relapses but for whether they also modify this smouldering component of disease.

Anti-CD20 agents are of particular interest in this context because they achieve a depth and duration of peripheral immune suppression not matched by most other disease-modifying therapy classes, offering a natural test of whether more complete B-cell depletion translates into a measurable effect on relapse-independent disability. This review synthesises the mechanistic rationale for anti-CD20 therapy, the pivotal trial evidence for its effect on relapses and both categories of disability progression, comparative and real-world data across agents, and the safety considerations relevant to long-term treatment decisions. Because no single trial was designed from the outset to answer every one of these questions, the evidence base necessarily spans double-blind randomised trials, open-label extensions, national registries and a small but growing number of mechanistic and

head-to-head comparative studies, each contributing a different piece of the overall picture.

Mechanism of B-Cell Depletion

Anti-CD20 antibodies bind CD20 on the surface of pre-B and mature B cells, triggering depletion through antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity and direct apoptosis, while sparing CD20-negative plasma cells and haematopoietic stem cells [1]. Although B cells were long considered secondary to T cells in MS pathogenesis, the efficacy of B-cell depletion redirected attention to their roles as antigen-presenting cells, cytokine producers and, in meningeal aggregates, potential drivers of compartmentalised inflammation associated with cortical injury and progression.

Memory B cells appear to be the principal therapeutic target: their depletion correlates with treatment response, and their repopulation kinetics inform dosing strategies, including extended-interval regimens [9]. This memory B-cell hypothesis also helps explain why re-treatment can often be delayed well beyond the point of naive B-cell repopulation without loss of clinical control, since memory B cells repopulate more slowly and their return correlates more closely with recurrent disease activity than total CD19+ or CD20+ B-cell counts.

CD20 is also expressed on a small subset of pro-inflammatory T cells, and both rituximab and ocrelizumab measurably deplete this population, suggesting anti-CD20 therapy's benefit may not be attributable to B-cell depletion alone [10,11]. This dual B-cell and CD20+ T-cell effect offers one plausible explanation for why anti-CD20 agents outperform therapies that spare T cells more selectively, and for why depletion in cerebrospinal fluid, not only blood, was demonstrated in the earliest pilot studies [2]. Whether this CD20+ T-cell effect contributes meaningfully to the

reduction in PIRA discussed below, as opposed to relapse suppression alone, remains an open mechanistic question, since compartmentalised T-cell-driven inflammation behind an intact blood-brain barrier is more difficult for a peripherally administered antibody to reach than actively enhancing lesions.

Pivotal Trial Evidence

The phase 2 ocrelizumab trial first established a dose-dependent reduction in gadolinium-enhancing lesions and annualised relapse rate compared with placebo, providing proof of concept for phase 3 development [12]. The twin phase 3 OPERA I and OPERA II trials then compared ocrelizumab with subcutaneous interferon beta-1a in relapsing MS, demonstrating approximately 46-47% relative reductions in annualised relapse rate and significantly lower proportions of patients with 12- and 24-week confirmed disability progression over 96 weeks [4]. The companion ORATORIO trial extended ocrelizumab to primary progressive MS, showing a significant reduction in confirmed disability progression versus placebo, the first positive phase 3 result in that population [13].

Ofatumumab was subsequently tested in the ASCLEPIOS I and II trials against teriflunomide, again showing superior relapse-rate reduction and, notably, significant reductions in both 3-month and 6-month confirmed disability progression alongside near-complete suppression of new MRI lesion activity [5]. Subcutaneous self-administration and monthly dosing distinguished ofatumumab's development pathway; the preceding phase 2 APLIOS study established that this route achieved B-cell depletion as rapid and sustained as intravenous regimens, supporting the phase 3 design [14]. Ublituximab, a glycoengineered chimeric antibody, was evaluated in the ULTIMATE I and II trials, again against teriflunomide, confirming the class effect of superior relapse-rate and MRI-activity reduction, with a numerically favourable

disability trend [6]. Across all three head-to-head comparator programmes, no trial has directly compared two anti-CD20 agents against each other in a blinded fashion, leaving relative efficacy between agents inferred rather than proven.

Table 1: Pivotal randomised trials of anti-CD20 monoclonal antibodies in relapsing multiple sclerosis reviewed here [12,4,13,14,5,6,21].				
Trial	Agent	Comparator	Population	Key disability finding
Kappos 2011 (phase 2)	Ocrelizumab	Placebo	RRMS	Reduced MRI activity and ARR, dose-finding only
OPERA I/II	Ocrelizumab	Interferon beta-1a	RRMS	Lower 12- and 24-week CDP vs comparator
ORATORIO	Ocrelizumab	Placebo	PPMS	First positive phase 3 disability result in PPMS
APLIOS (phase 2)	Ofatumumab (SC)	IV ofatumumab	RMS	Rapid, sustained B-cell depletion, supported phase 3 design
ASCLEPIOS I/II	Ofatumumab	Teriflunomide	RMS	Lower 3- and 6-month CDP vs comparator
ULTIMATE I/II	Ublituximab	Teriflunomide	RMS	Favourable disability trend vs comparator
Torkildsen 2026	Rituximab vs ocrelizumab	Head-to-head	Newly diagnosed RMS	No significant difference between agents

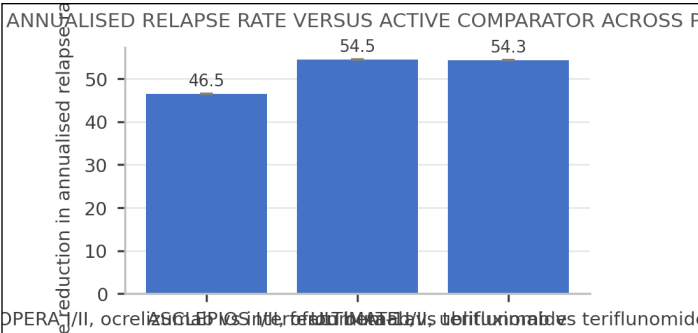


Figure 1: Relative reduction in annualised relapse rate versus active comparator across pivotal anti-CD20 phase 3 trials in relapsing multiple sclerosis [4,5,6].

Disability Progression Metrics: EDSS, PIRA and Relapse-Associated Worsening

Disability in these trials is measured predominantly using the Expanded Disability Status Scale (EDSS), a clinician-rated ordinal scale first described in 1983 that remains the regulatory standard despite recognised ceiling effects and inter-rater variability [15]. Confirmed disability progression is typically defined as a sustained EDSS increase confirmed at a subsequent visit, but this composite outcome conflates two biologically distinct processes: relapse-associated worsening (RAW), disability that follows incomplete recovery from a relapse, and PIRA, disability accumulation occurring independently of any recorded relapse.

A pooled analysis of the OPERA trials and related cohorts found that PIRA accounted for the majority of confirmed disability accumulation events even in this relapsing-remitting population, and that its relative contribution increased with age and disease duration [8]. This finding built on earlier observational work from the MS-EPIC cohort demonstrating "silent" progression detectable on detailed clinical and imaging assessment despite the absence of relapses or new MRI lesions, challenging the assumption that disease activity-free status equates to biological quiescence [7]. The imperfect correspondence between relapses, MRI lesion counts and

eventual disability, established in earlier meta-analytic work, provides context for why regulators and researchers increasingly report PIRA and RAW separately rather than relying on a single confirmed-progression endpoint [16].

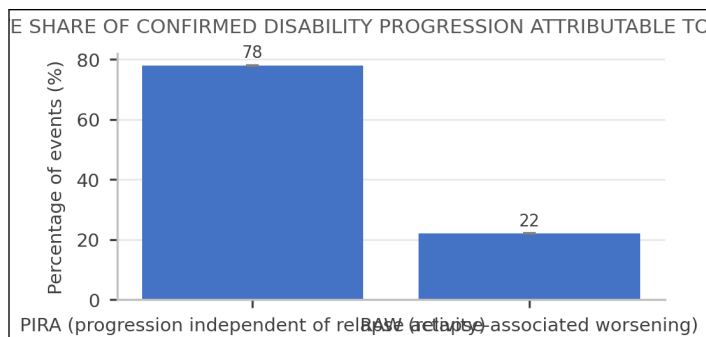


Figure 2: Approximate share of confirmed disability progression events attributable to progression independent of relapse activity (PIRA) versus relapse-associated worsening (RAW) in a pooled analysis of relapsing multiple sclerosis trial data [8].

Because anti-CD20 agents reduce both relapses and PIRA in the pivotal trials, their efficacy against the composite confirmed disability progression endpoint understates a mechanistically interesting finding: B-cell depletion appears to attenuate a slow, smouldering process previously assumed to be largely independent of peripheral immune activity. Epoch-based NEDA (no evidence of disease activity) analyses comparing ocrelizumab with interferon beta-1a showed a growing, sustained separation in the proportion of patients free of relapse, new MRI lesions and disability progression across successive six-month periods, consistent with an early and durable effect on both progression types [17].

Comparative and Real-World Evidence

Before regulatory approval of ocrelizumab, off-label rituximab use expanded rapidly in Sweden, and the resulting cohorts remain among the largest real-world anti-CD20 datasets in MS. An early nationwide cohort found low relapse rates and low discontinuation with rituximab in both relapsing and progressive MS [18], and a subsequent comparative-effectiveness study found rituximab associated with lower relapse rates and higher

treatment persistence than commonly used first-line injectable therapies [19]. More recent multinational registry data directly comparing rituximab and ocrelizumab found broadly similar effectiveness between the two agents, suggesting that molecule-specific differences may be less important than achieving consistent B-cell depletion [20]. This question has now also been addressed prospectively: a Norwegian randomised trial comparing rituximab and ocrelizumab head-to-head in newly diagnosed relapsing MS found no significant difference in disease activity between the two agents over the trial period [21], the first such direct comparison and a step toward resolving whether within-class agent selection meaningfully affects outcomes.

Long-term extension data further support durability of benefit: an open-label, single-arm study following patients with early-stage relapsing-remitting MS on ocrelizumab for four years reported sustained low relapse rates and disability outcomes comparable to those seen in the pivotal double-blind period [22].

Safety Considerations

Sustained B-cell depletion carries recognised infection and immunological risks that must be weighed against disability benefit. Pooled long-term ocrelizumab safety data across the pivotal trials and their open-label extensions showed serious infection rates that remained low but numerically higher than comparator arms, alongside surveillance for progressive multifocal leukoencephalopathy and malignancy signals that have not shown a clear excess to date [23]. Hypogammaglobulinemia, a predictable consequence of sustained B-cell suppression, has been documented with rituximab in a French cohort, where lower immunoglobulin G levels were associated with increased infection risk over extended treatment courses [24]. A comprehensive review of the ofatumumab trial and

post-marketing safety record found a similar pattern of modestly increased infection risk without a signal for opportunistic infection beyond that seen across the anti-CD20 class [25]. Most recently, a nationwide Swedish comparison found broadly comparable infection risk between ocrelizumab and rituximab, reinforcing that safety differences within the anti-CD20 class are, so far, modest relative to the shared class effect [26]. Collectively, these data support periodic immunoglobulin monitoring and individualised risk-benefit discussion, particularly for patients on long-duration therapy or with pre-existing risk factors for infection.

Table 2: Real-world and long-term safety data on anti-CD20 therapy in multiple sclerosis reviewed here [18,19,20,23,24,26].			
Study	Design	Agent(s)	Key finding
Salzer 2016	Swedish nationwide cohort	Rituximab	Low relapse rate, low discontinuation
Granqvist 2018	Swedish comparative cohort	Rituximab vs injectables	Rituximab outperformed first-line injectables
Roos 2023	Multinational registry	Rituximab vs ocrelizumab	Broadly similar effectiveness
Hauser 2021	Pooled trial + extension	Ocrelizumab	Low but non-zero serious infection rate
Perriguet 2022	French cohort	Rituximab	Hypogammaglobulinemia linked to infection risk
Frisell 2026	Swedish nationwide cohort	Ocrelizumab vs rituximab	Comparable infection risk between agents

Conclusion

Across five pivotal randomised trials, four anti-CD20 agents, and a growing body of registry, extension and head-to-head comparative data, anti-CD20 therapy consistently reduces relapse rate and confirmed disability progression in relapsing MS more effectively than the active comparators tested. Mechanistic work implicating memory B cells and CD20-expressing T cells, alongside pooled analyses showing a substantial PIRA contribution to disability that anti-CD20 therapy also attenuates, together suggest these agents act on both inflammatory

and smouldering components of MS pathology. Comparative and real-world data, culminating in the first randomised head-to-head trial between two agents, indicate that within-class differences in efficacy are modest, while safety data support ongoing vigilance for hypogammaglobulinemia and infection with prolonged use. Future work should refine PIRA-specific endpoints in trial design, clarify optimal dosing intervals for long-term B-cell suppression, and extend head-to-head comparisons across the full anti-CD20 class.

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