

# Freedom from disease activity in multiple sclerosis

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## ABSTRACT

**Background:** Multiple sclerosis (MS) shares many pathologic features with other immune-mediated inflammatory diseases, such as rheumatoid arthritis, Crohn disease, and psoriasis. The development of effective biologic agents for rheumatoid arthritis has resulted in a treatment paradigm shift such that disease remission is now an explicit goal.

**Expert Clinical Opinion:** The traditional immunomodulatory disease-modifying therapies for MS (interferon beta and glatiramer acetate) delay disease progression and reduce activity on brain MRI to varying degrees; however, they have not been demonstrated to induce disease remission. Therefore, the concept of disease remission or freedom from disease activity in MS has received little attention from the neurology community. We discuss some potential definitions of disease remission in MS and whether freedom from disease activity can become an increasingly useful measure of therapeutic response.

**Future Directions:** Future research should be directed at determining the long-term significance of freedom from disease activity during a short-term clinical trial in relapsing-remitting MS.

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## GLOSSARY

**ACR** = American College of Rheumatology; **DAS** = Disease Activity Score; **DMT** = disease-modifying therapy; **Gd+** = gadolinium enhancing; **IFN** = interferon; **IM** = intramuscular; **IMID** = immune-mediated inflammatory disease; **MS** = multiple sclerosis; **RA** = rheumatoid arthritis; **SC** = subcutaneous; **TNF** = tumor necrosis factor.

**INTRODUCTION** Multiple sclerosis (MS) is an immune-mediated inflammatory disease (IMID). Other IMIDs include rheumatoid arthritis (RA), Crohn disease, and psoriasis. These disorders generally develop in genetically susceptible individuals, and auto-immune mechanisms are central to their pathogenesis.<sup>1</sup> In MS, the transmigration of activated T lymphocytes across the blood-brain barrier into the CNS may ultimately result in the overproduction of inflammatory cytokines and toxic radicals, demyelination, and axonal injury that characterize the disorder.<sup>2,3</sup>

Conventional disease-modifying therapies (DMTs) for the treatment of patients with RA, such as methotrexate and sulfasalazine, have been limited by poor control of inflammation and tissue destruction, and low tolerability. Therefore, achieving long-lasting remission was a difficult goal for these patients.<sup>4</sup> However, since the early 1990s, improvements in DMTs

have revolutionized the treatment of IMIDs.<sup>1</sup> The latest generation of DMTs are immunomodulatory agents, the majority of which are humanized antibodies or other hybrid protein constructs. Among these DMTs, 3 tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) inhibitors (infliximab, etanercept, and adalimumab) have been approved for the treatment of RA, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis and juvenile idiopathic arthritis (etanercept and adalimumab), Crohn disease (infliximab and adalimumab), and ulcerative colitis (infliximab).<sup>5-7</sup> These agents inhibit TNF $\alpha$ -mediated inflammatory reactions and prevent tissue damage.<sup>8</sup> Two newer biologic agents also approved for the treatment of IMIDs are rituximab (chimeric anti-CD20 monoclonal antibody; RA)<sup>9</sup> and abatacept (CTLA4Ig fusion molecule; RA and juvenile idiopathic arthritis).<sup>10</sup> These agents act by depleting B cells<sup>11</sup>

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(rituximab) and inhibiting activation of T cells<sup>12</sup> (abatacept).

Many patients with RA achieve disease remission when treated with an immunomodulatory biologic DMT. This has resulted in a shift in the RA treatment paradigm, such that expectations for disease control with the new biologic DMTs are much greater than they were for earlier RA therapies. In this article, we consider how the treatment paradigm for RA has evolved and discuss the potential for a similar paradigm shift in the treatment of relapsing-remitting MS as new, more effective therapies become available.

### EVOLUTION OF THE TREATMENT PARADIGM FOR RA

Achieving remission or freedom from disease activity is the ultimate goal of therapy for patients with an IMID. Generally, disease freedom is defined as a complete suppression of disease activity. However, treatment outcomes may vary according to the criteria for freedom from disease activity that are applied.

In RA, several criteria for disease freedom, or remission, have been developed; they are summarized in table 1.<sup>4</sup> Before the advent of the biologic DMTs for treating RA, the American College of Rheumatology (ACR) developed 6 consensus-based criteria for defining remission, 5 of which were required.<sup>13,14</sup> In addition, the European League Against Rheumatism developed criteria for remission based on improvement in the Disease Activity Score (DAS) index<sup>15</sup> and the abbreviated DAS in-

dex (DAS28).<sup>16</sup> The most stringent criteria for remission of RA are those set forth by the US Food and Drug Administration. Patients must meet the ACR criteria for remission and have no radiographic progression for 6 consecutive months while off all antirheumatic therapies.<sup>17</sup>

The traditional antirheumatic agents, such as gold, penicillamine, and sulfasalazine, generally have been associated with low rates of remission according to the ACR criteria (7%–19%),<sup>18–20</sup> and the remissions were generally short (median of 10 months).<sup>20</sup> Although combination therapy with sulfasalazine, methotrexate, hydroxychloroquine, and prednisolone significantly increased the proportion of patients who achieved remission after 2 years compared with sulfasalazine monotherapy (40% vs 18%,  $p < 0.009$ ), the difference became nonsignificant after 5 years of treatment (28% vs 22%,  $p = 0.41$ ).<sup>19</sup> Furthermore, another study showed that remission rates for combination therapy and monotherapy were not significantly different after 3 years.<sup>18</sup>

The advent of TNF $\alpha$  antagonists for the treatment of RA led to increased reports of remission as a clinical study outcome. In randomized clinical studies, treatment with these agents in combination with methotrexate significantly improved remission rates according to the DAS28 criteria compared with methotrexate alone (etanercept, 54% vs 26%,  $p < 0.01$  at 2 years; infliximab, 31% vs 15%,  $p < 0.001$  at 1 year; adalimumab, 49% vs 25%,  $p < 0.001$  at 2 years) or the TNF $\alpha$  antagonists alone (etanercept, 54% vs 30%,  $p < 0.01$  at 2 years; adalimumab, 49% vs 25%,  $p < 0.001$  at 2 years).<sup>21–23</sup>

Thus, the TNF $\alpha$  antagonists and other biologics have made disease remission a more achievable outcome of treatment in patients with RA.<sup>4</sup> In contrast, disease remission in MS has been thought of as a difficult goal to achieve with the traditional DMTs. However, as new and more effective therapies for MS become available, the treatment paradigm for this disorder can also be expected to shift, such that freedom from disease activity becomes an achievable goal. As in RA, the principle criteria for freedom from disease activity in MS should be based on the major clinical and radiologic outcomes used in clinical studies, namely relapses, disability progression, and brain lesions detected by MRI.

### TRADITIONAL DMTs AND MEASURES OF DISEASE ACTIVITY IN MS

Since the mid 1990s, immunomodulatory agents have been the mainstay therapy for patients with relapsing-remitting MS. The first immunomodulatory agents available (the “traditional DMTs”) were the interferon-beta (IFN $\beta$ ) products (intramuscular [IM] IFN $\beta$ -1a,

**Table 1** Remission criteria in the treatment of rheumatoid arthritis

Remission criteria	Definition
American College of Rheumatology (ACR)	Morning stiffness <15 min; no fatigue; no joint pain by history; no joint tenderness or pain on motion; no soft tissue swelling in joints or tendon sheaths; and Westergren ESR <30 mm/h after 1 h in women or <20 mm/h in men.
ACR <sup>13</sup>	Fulfillment of at least 5 of the 6 criteria for at least 2 consecutive months.
Modified ACR <sup>14</sup>	Omission of fatigue and fulfillment of 4 of the remaining 5 criteria lasting at least 2 mo.
<b>Disease Activity Score (DAS)</b>	
DAS <sup>15</sup>	DAS <1.6, which is a composite index of Ritchie articular index of tender joints; 44 swollen joint count; Westergren ESR; and patient's global assessment.
DAS28 <sup>16</sup>	DAS28 <2.6, which is a composite index of an abbreviated 28-joint count for tender and swollen joints (omitting the feet); Westergren ESR; and patient's global assessment.
Food and Drug Administration (FDA) <sup>17</sup>	Complete clinical response: Achieving ACR remission criteria and radiographic arrest over a continuous 6-mo period while continuing antirheumatic therapy.
	Remission: Achieving ACR remission criteria and radiographic arrest over a continuous 6-mo period while off all antirheumatic therapy.

Abbreviations: ACR = American College of Rheumatology; DAS = Disease Activity Score; ESR = erythrocyte sedimentation rate; FDA = Food and Drug Administration.

Adapted from Sesin CA, Bingham CO. Remission in rheumatoid arthritis: wishful thinking or clinical reality? *Semin Arthritis Rheum*; 35:185-196, Copyright 2005, with permission from Elsevier.

**Table 2** Efficacy of IFN $\beta$  and glatiramer acetate vs placebo over 2 years in pivotal clinical studies of patients with MS

	IM IFN $\beta$ -1a	SC IFN $\beta$ -1a (44- $\mu$ g dose)	IFN $\beta$ -1b (8-MIU dose)	Glatiramer acetate
Relapse rate: % reduction	32; $p = 0.002^{25}$	32; $p < 0.005^{27}$	34; $p = 0.0001^{24}$	29; $p = 0.007^{26}$
Relapse free: % of patients	38 vs 26; $p = 0.03^{25}$	32 vs 16; $p < 0.005^{27}$	31 vs 16; $p = 0.007^{24}$	34 vs 27; $p = 0.098^{26}$
Disability progression: % reduction	37; $p = 0.02^{25}$	31; $p < 0.05^{28,29}$	29; $p = NS^{24}$	12; $p = NS^{26}$
Number of Gd+ lesions: % reduction	52; $p = 0.05^{25}$	84; <sup>a</sup> $p < 0.001^{28,30}$	NR	29; <sup>a</sup> $p = 0.003^{31}$
Number of new or enlarging T2 lesions: % reduction	33; $p = 0.002^{33}$	78; $p < 0.0001^{30}$	83; $p = 0.009^{32}$	31; <sup>a</sup> $p < 0.003^{31}$

Abbreviations: Gd+ = gadolinium enhancing; IFN $\beta$  = interferon beta; IM = intramuscular; MS = multiple sclerosis; NR = not reported; NS = not statistically significant; SC = subcutaneous.

<sup>a</sup>Assessed at 9 mo.

subcutaneous [SC] IFN $\beta$ -1a, and IFN $\beta$ -1b) and glatiramer acetate.<sup>24-27</sup>

In pivotal clinical studies, the traditional DMTs have demonstrated moderate efficacy on clinical and radiologic outcomes after 2 years vs placebo. A summary of the efficacy results of these studies is provided in table 2, although it should be noted that these results are not directly comparable between studies. All the IFN $\beta$  products and glatiramer acetate significantly reduced relapse rate.<sup>24-27</sup> The proportion of relapse-free patients at 2 years was significantly increased with the IFN $\beta$  products<sup>24,25,27</sup> but not with glatiramer acetate.<sup>26</sup> IM IFN $\beta$ -1a and SC IFN $\beta$ -1a delayed progression of disability sustained for 6 months ( $p = 0.02$ ) and 3 months ( $p < 0.05$ ), respectively,<sup>25,28,29</sup> whereas IFN $\beta$ -1b and glatiramer acetate did not significantly affect this outcome.<sup>24,26</sup> The number of gadolinium-enhancing (Gd+) lesions was reduced in patients treated with IM IFN $\beta$ -1a ( $p = 0.05$ ),<sup>25</sup> SC IFN $\beta$ -1a ( $p < 0.001$ ; assessed at 9 months),<sup>28,30</sup> and glatiramer acetate ( $p = 0.003$ ; assessed at 9 months).<sup>31</sup> This outcome was not assessed in patients treated with IFN $\beta$ -1b.<sup>32</sup> The number of new or enlarging T2-hyperintense lesions was significantly reduced with all the traditional DMTs during the 9-month (glatiramer acetate) or 2-year (IM IFN $\beta$ -1a, SC IFN $\beta$ -1a, IFN $\beta$ -1b) study periods.<sup>30-33</sup>

To date, there have been no investigations of the ability of the traditional DMTs to meet predefined criteria for freedom from disease activity in patients with MS, with the exception of the BEYOND study, which compared 2 doses of IFN $\beta$ -1b and glatiramer acetate over 2 years. In this study, the proportion of patients who were free from relapse and new Gd+ or T2 lesions at 2 years was the predefined secondary endpoint and considered to be indicative of freedom from disease activity. According to this criterion, the proportion of patients without disease activity was similar in all 3 treatment arms: 31.5% for IFN $\beta$ -1b 500  $\mu$ g, 25.6% for IFN $\beta$ -1b

250  $\mu$ g, and 25.7% for glatiramer acetate (a placebo group was not included).<sup>34</sup>

### NATALIZUMAB AND MEASURES OF DISEASE ACTIVITY IN MS

Natalizumab is a humanized monoclonal antibody that has demonstrated a high level of efficacy in patients with relapsing-remitting MS. In the 2-year AFFIRM study, natalizumab monotherapy significantly reduced the risk for disability progression sustained over 12 weeks by 42%, the frequency of relapse by 68%, the number of Gd+ lesions by 92%, and the number of new or enlarging T2-hyperintense lesions by 83% compared with placebo.<sup>35</sup>

Recently, a post hoc analysis of data from the AFFIRM study examined the ability of natalizumab to achieve freedom from disease activity. The analysis evaluated several measures of clinical and radiologic disease activity that are generally included in MS clinical trials. The individual measures included the proportions of patients who had no relapse, no progression of disability sustained for 12 weeks, no Gd+ lesions, and no new or enlarging T2-hyperintense lesions during the 2-year study period. Generally, the radiologic measures are considered to be more sensitive indicators of disease activity than the clinical measures. To further characterize the ability of natalizumab to achieve freedom from disease activity, its effects on several composite measures were also evaluated. Clinically disease-free patients were defined as those who had no relapse and no progression of disability sustained for 12 weeks during the 2-year study period. Radiologically disease-free patients were defined as those who had no Gd+ lesions and no new or enlarging T2-hyperintense lesions during the 2-year study period. Combined clinically and radiologically (the most stringent criterion) disease-free patients were defined as those who had no relapse, no progression of disability sustained for 12 weeks, no Gd+ lesions, and no new or enlarging T2-hyperintense lesions during the 2-year study period.

Natalizumab significantly increased the proportion of patients who were free of disease activity according to the clinical, radiologic, and combined clinical and radiologic criteria over 2 years compared with placebo.<sup>36</sup> Based on the composite of clinical and radiologic criteria, the proportion of patients who were free of disease activity over 2 years in the natalizumab group was 5-fold greater than that in the placebo group (37% vs 7%,  $p < 0.0001$ ).<sup>36</sup>

### WILL THE TREATMENT PARADIGM FOR MS SHIFT IN A MANNER SIMILAR TO THAT FOR RA?

Since their introduction in the early 1990s, the immunomodulatory biologic drugs have made remission an attainable goal for about 50% of patients with RA who are treated with these agents. Consequently, the treatment paradigm for this disease has shifted from an expectation of partial response to one of remission. It remains to be seen whether a similar expectation will eventually be reached for MS treatments. There are several obstacles to evaluating the relative abilities of MS therapies to achieve states of disease remission, and differences in how disease remission is defined and measured—together with the duration of remission—are important factors in this regard. However, currently, there is preliminary evidence that freedom from both clinical and radiologic disease activity is an attainable goal for approximately one third of patients treated with natalizumab. As new and increasingly effective treatments for MS are developed and made available, it can be anticipated that increasingly greater proportions of patients will become free of disease activity, the long-term duration of which will need to be evaluated. The use of these new and effective therapies will need to be balanced with a careful assessment of their potential risks.

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### DISCLOSURE

Prof. Havrdova has served on scientific advisory boards for Biogen Idec, Merck-Serono, Novartis Pharmaceuticals, and Teva; received compensation for travel/honoraria from Bayer, Biogen Idec, Genzyme, Merck-Serono, Sanofi-Aventis, and Teva; and received research funding/grants from Biogen Idec, GlaxoSmithKline, Merck-Serono, Novartis, Teva,

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