Beginning of the end of two-stage theory purporting that inflammation then degeneration explains pathogenesis of progressive multiple sclerosis

Lawrence Steinman[a] *and Scott S. Zamvil*[b]

Purpose of review
The review discusses future directions in research on multiple sclerosis and neuromyelitis optica, as long-held beliefs about these diseases are undermined with data from recent clinical trials.

Recent findings
Results of clinical trials for registration (phase 3) were reported in the last year. Anti-inflammatory approaches, such as daclizumab high-yield process targeting IL-2 receptor, and ocrelizumab targeting CD20 B cells, confirmed a beneficial role of immune suppression in relapsing–remitting disease. And now for the first time achieving the primary end point in primary progressive multiple sclerosis was attained with ocrelizumab.

Summary
The results in the past year challenge the long-held belief that relapsing–remitting disease is inflammatory, whereas progressive forms of the disease are 'less inflammatory' and more 'degenerative.'

Keywords
multiple sclerosis, neurodegeneration, neuroinflammation, neuromyelitis optica

INTRODUCTION

A prevalent idea over the past 20 years is that the pathogenesis of progressive forms of multiple sclerosis (MS) is distinct from the inflammatory aspects of relapsing–remitting MS (RRMS). Much of the foundation for this theory came from the repeated successes of therapies that interfere with inflammation in RRMS. The success of all the approved drugs can be attributed in part to their known mechanisms of action in interfering with aspects of inflammation, including inhibition of monocyte and lymphocyte migration. The success of sphingosine phosphate modulators like fingolimod and natalizumab in RRMS, exemplifies the success in reducing relapses, via therapeutics that impede lymphocyte traffic [1,2].

ARE THERE TWO STAGES IN MULTIPLE SCLEROSIS, INFLAMMATORY THEN NEURODEGENERATIVE?

One of the authors of this review wrote 15 years ago that 'The pathogenesis of multiple sclerosis consists of an inflammatory and neurodegenerative phase' [3]. This concept was withstanding the test of time until the final quarter of 2015. Trials of highly efficacious drugs like fingolimod in primary progressive MS (PPMS) (https://www.novartis.com/news/media-releases/novartis-provides-update-fingolimod-phase-iii-trial-primary-progressive-ms-ppms) and natalizumab in secondary progressive MS (SPMS) (http://www.businesswire.com/news/home/20151021005273/en/Biogen-Reports-Top-Line-Results-Phase-3-Study) failed to achieve their primary end points. But after first reporting that the anti-CD20 antibody ocrelizumab (OCR) had met its primary end points in RRMS (http://www.gene.com/media/press-releases/

[a]Department of Neurology and Neurologic Sciences, Interdepartmental Program in Immunology, Stanford University, Stanford and [b]Department of Neurology and Program in Immunology, University of California, San Francisco, California, USA

Correspondence to Lawrence Steinman, MD, Department of Neurology and Neurologic Sciences, Interdepartmental Program in Immunology, Stanford University, Stanford, CA 94305, USA.
E-mail: steinman@stanford.edu

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KEY POINTS

- An approach that targets B lymphocytes achieved its primary end point in a trial of primary progressive MS, thus challenging the concept that MS is a two-stage disease, inflammatory then degenerative. A key component of the immune system, the CD20 B cell, therefore, is involved in progressive aspects of the disease.
- Not all immune approaches work in progressive forms of disease. Two more approved therapies for RRMS failed in phase 3 trials for primary progressive (fingolimod) and secondary progressive MS (natalizumab).
- Further stratification of subtypes of disease may allow appropriate choice of therapeutics.
- Meta-analyses indicate that some treatments are better than others at preventing relapse, but effects on disease progression between the approved drugs are unclear.
- If NEDA, 'no evidence of disease activity', is to be useful, a better understanding of the concept and comparisons between approved therapies will be necessary.

14597/2015–06–29/genentechs-ocrelizumab-significantly-red), investigators reported meeting the primary end points in a phase 3 trial of the same antibody in PPMS (http://www.gene.com/media/press-releases/14608/2015–09–27/genentechs-ocrelizumab-first-investigati).

In the RRMS phase 3 trials known as OPERA 1 and OPERA 2 (http://www.roche.com/media/store/releases/med-cor-2015–10–08.htm):
'…ocrelizumab (OCR) significantly reduced the annualized relapse rate – the primary end point of both studies – by nearly 50% compared with INF β-1a over the 2-year period. Additionally, OCR met secondary end points of the study, significantly delaying confirmed disability progression (loss of physical abilities, measured by the Expanded Disability Status Scale, or EDSS) by approximately 40% sustained for both 12 and 24 weeks compared with INF β-1a in prespecified, pooled analyses of the two studies ($P = 0.0006$ and $P = 0.0025$, respectively). OCR also significantly reduced acute MS-related inflammation and brain injury (total number of T1 gadolinium-enhancing lesions measured by MRI) at 24, 48, and 96 weeks by more than 90% and the emergence of more chronic or growing areas of MS-related brain injury (T2 hyperintense lesions) at 24, 48, and 96 weeks by around 80% compared with INF β-1a.'

What was truly new and unexpected was the first time any investigational drug had met its primary end points in a phase 3 trial in PPMS. The investigators reported (http://www.roche. com/media/store/releases/med-cor-2015–10–08.htm) that OCR 'met its primary end point, showing treatment with OCR significantly reduced the risk of progression of clinical disability sustained for at least 12 weeks by 24% compared with placebo, as measured by the EDSS ($P = 0.0321$). Additionally, OCR was superior to placebo in significantly reducing the risk of progression of clinical disability for at least 24 weeks by 25% ($P = 0.0365$) and the time required to walk 25 feet (timed 25-foot walk) over 120 weeks by 29% ($P = 0.0404$). OCR decreased the volume of hyperintense T2 lesions by 3.4% over 120 weeks, compared with placebo, which increased T2 volume by 7.4% ($P < 0.0001$). OCR reduced the rate of whole brain volume loss over 120 weeks by 17.5% compared with placebo ($P = 0.0206$).' Preliminary reports of safety in both the trials in RRMS and PPMS indicated that other than infusion reactions, there was no increase in adverse events in these trials.

The mechanism whereby anti-CD20 exerts its beneficial effects in RRMS and PPMS is not well understood. A detailed history of the development of anti-CD20 in MS with a description of some of its plausible mechanisms of actions is described in [4▪▪]. Hauser emphasizes that CD20 is not expressed on antibody-producing plasmablasts, and that anti-CD20 targets primarily the circulating CD20 positive B-cell population comprising only a few percent of the total B-cell pool. Independent to serving as a source of antibody-producing plasmablasts and plasma cells, B cells have an important role in antigen presentation to T cells *in vivo* [5]. Further, the rapidity of action in reducing gadolinium lesions in MS makes the potential effect of OCR on antibody production quite unlikely as its primary mechanism of action [4▪▪,6].

Perhaps neuropathologic studies may have been a harbinger for the success here with OCR in both RRMS and PPMS. Inflammation is present in both the relapsing and progressive phases of disease [7]: 'T and B-cell infiltrates correlated with the activity of demyelinating lesions, whereas plasma cell infiltrates were most pronounced in patients with SPMS and PPMS.'

The success of OCR in RRMS is perhaps less than surprising given the success seen with rituxan, another anti-CD20 in trials performed nearly a decade ago [4▪▪]. The delay of about a decade in bringing an anti-CD20 to the market for MS patients, as an approved pharmaceutical for RRMS, is a story that is worthy of scrutiny. In his essay following the award

of the Charcot prize, Hauser [4▪▪] is rather direct on the reasons for the decade long delay: 'it took 18 months for the rituximab (RTX) data to find their way into final print, one and by this time, to the surprise and disappointment of many, the prospects for advancing to phase 3 clinical trials of RTX were dead. The reasons for this were multiple but included complex governance of the RTX franchise between the two participating pharmaceutical companies, Biogen/Idec and Genentech; the development of a new fully humanized anti-CD20 monoclonal antibody, OCR by Genentech; and Roche's acquisition of Genentech in 2009. A plan was put forward to no longer pursue RTX but instead to initiate an OCR phase 2B trial.' Even though one might argue that 'all's well that ends well,' for individuals with RRMS the delay of a decade might be viewed differently.

However, OCR is a different molecule than RTX [4▪▪]. OCR is fully humanized, whereas RTX is a chimeric monoclonal antibody. OCR binds to different epitopes on CD20 than RTX [4▪▪]. There are different mechanisms of action for killing CD20 cells when comparing RTX and OCR: 'RTX has stronger complement-dependent cytotoxicity and less antibody-dependent cell-mediated cytotoxicity, whereas the converse is true for OCR' [4▪▪].

RTX failed to hit its primary end point differences in time to confirmed disease progression in a trial of 439 PPMS patients ($P < 0.14$) [8]. The OCR trial met its primary end point, 'the risk of progression of clinical disability' was 'sustained for at least 12 weeks by 24% compared with placebo, as measured by the EDSS ($P = 0.0321$).' Whether the differences in outcome in the trials of RTX versus OCR in PPMS were because of differences in trial design, differences in the characteristics of the anti-CD20 antibody, or simply that the phase 3 was more appropriately powered (732 in the OCR phase 3 versus 439 in the RTX phase 2, will be a topic of ongoing discussion. It will be interesting to see if there are subgroups of interest in the OCR study on PPMS as was seen in the trials of PPMS using RTX. Finally, and perhaps most importantly, as one of the authors of this opinion has commented in *Nature Biotechnology* [6], the results with OCR in PPMS are 'an absolute gift – it's the first time that anything's worked in the field.'

FURTHER PROMISING DEVELOPMENTS IN PROGRESSIVE FORMS OF MULTIPLE SCLEROSIS

In PPMS, phase 3 trial results were reported with high-dose biotin. A pilot study with 23 patients with both SPMS and PPMS were treated with high doses of biotin from 100 to 300 mg/day for 2–36 months [9]. Anecdotal results were described in [9]: 'in four patients with prominent visual impairment related to optic nerve injury, visual acuity improved significantly. Visual evoked potentials in two patients exhibited progressive reappearance of P100 waves, with normalization of latencies in one case. Proton magnetic resonance spectroscopy in one case showed a progressive normalization of the choline/creatine ratio. One patient with left homonymous hemianopia kept on improving from 2 to 16 months following treatment's onset. Sixteen patients out of 18 (89%) with prominent spinal cord involvement were considered as improved as confirmed by blinded review of videotaped clinical examination in nine cases. In all cases, improvement was delayed from 2 to 8 months following treatment's onset.'

Phase 3 results with high-dose biotin in a study of 154 patients have been reported at the 2015 meeting of the American Academy of Neurology. 'The primary end point was met ($P = 0.0051$, Fisher's exact test) in the intent to treat population with 12.6% of patients in the MD1003 arm showing an improvement of EDSS or a timed 25-foot walk at month 9, confirmed at month 12, compared with none of the patients (0%) in the placebo arm. The primary end point was supported by secondary analyses showing evidence for a decrease in the risk of disease progression. The mean change of EDSS between M0 and M12 decreased in the MD1003 group (−0.03) compared with progression in the placebo group (+0.13, $P = 0.015$). In the MD1003 arm, only 4% of patients treated with MD1003 exhibited EDSS progression at M9 confirmed at M12 versus 13% in the placebo group ($P = 0.07$), which equates to a 67% decreased risk of progression in the active arm within the studied period. The study was not prospectively powered to reach significance for this secondary endpoint.' (http://www.medday-pharma.com/news-and-events/medday-reports-positive-pivotal-phase-iii-study-results-with-md1003-in-patients-with-progressive-multiple-sclerosis/).

Further results on a trial of MD1003 in patients with optic neuritis (ON) were reported in December of 2015. The trial included patients with progressive worsening visual loss who were given 300 mg/day of biotin for 24 weeks. 'The primary end point was the mean change, in the total study population, in 100% contrast visual acuity at 6 months from baseline of the diseased eye defined as the eye with the worst visual acuity and acute or progressive worsening within the 3 years prior to inclusion.' Results were reported showing that 'in

the subgroup of patients with progressive ON, 100% contrast visual acuity of the diseased eye improved by a mean of three letters in the active arm versus worsening by 1.5 letters in the placebo arm. The evolution of other important end points was consistent with the improvement of 100% contrast visual acuity.' The primary end point in the study did not reach statistical significance. (http://www.businesswire.com/news/home/20151130006379/en/MedDay-Update-MS-ON-Study-MD-1003).

SOME PROMISING DEVELOPMENTS IN SECONDARY PROGRESSIVE FORMS OF MULTIPLE SCLEROSIS

Chattaway and colleagues [10▪] reported on a 140 patient trial randomized 1 : 1 between placebo and simvastatin, 80 mg/day. 'The primary outcome was the annualized rate of whole-brain atrophy measured from serial volumetric MRI' [10▪]. The mean annualized rate of atrophy declined 43% and was significant ($P < 0.003$). The rate of adverse events was similar in the statin treated and control groups. Simvastatin is now being tested in a phase 3 trial in SPMS. Reflecting on the neuropathology studies of SPMS and PPMS [7] showing T-and B-cell accumulations in these progressive forms of disease, recent immunologic studies show that statins not only modulate Th1 immunity driven by IFN-γ [11], but also impact the other major inflammatory pathway known as Th17 [12].

CONCLUSION

New directions in RRMS

There were other advances in RRMS with successful completion of phase 3 trial involving 1841 patients for daclizumab high-yield process (HYP) in RRMS [13]. In this trial, the annualized relapse rate was 45% lower than a control group on IFN β-1a ($P < 0.001$). Results did not reach significance in the primary end point on disability: 'at week 144, the estimated incidence of disability progression confirmed at 12 weeks was 16% with daclizumab HYP and 20% with IFN β-1a ($P = 0.16$). Serious adverse reactions including rash and elevated liver transaminases were reported in the groups receiving daclizumab [13].

One of the major problems facing the neurologists in dealing with patients with relapsing–remitting disease is how to choose the optimal therapy from among the one dozen drugs now approved for this indication. Other than the comparisons already tested in phase 3 trials between type-1 interferon and many of the most efficacious drugs, such as alemtuzumab, daclizumab, or OCR, direct head-to-head comparison of the approved drugs are highly unlikely to be performed. As Sheridan quoting Prof. Mathews in [6] wrote, 'It's nearly impossible to imagine how a clinical trial could be designed to compare the relative effectiveness of the more effective agents – it's actually a crisis in MS now.'

To this date, no informative biomarker has been shown to predict outcome with any approved medicine. Many investigators, however, are probing the transcriptional profiles of existing drugs to search for differences with comparators. This approach has been used to compare how generic versions of glatiramer differ from generic versions [14]. Others have tried to stratify the entity known as RRMS, by high-throughput proteomic approaches. Multiplex analysis of the cytokine profile in patients with RRMS was shown to correlate with responsiveness to IFN-β [15]. Prediction of outcome to each of the approved medications for MS would help neurologists perform the 'risk versus benefit' assessment that is critical in deciding the optimal therapy for an individual with RRMS. For now, based on meta-analysis, alemtuzumab, natalizumab, and fingolimod are the most efficacious drugs in reducing relapse [16]. But these medications have their particular risk–benefit issues, like the risk of progressive multifocal leukoencephalopathy with natalizumab, and risk of additional autoimmune disease with alemtuzumab. It is an imperative to provide prescribing neurologists and our patients with guidance in selecting medicine. This guidance must be based on evidence from tests involving predictive biomarkers.

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Conflicts of interest

S.S.Z. serves as Deputy Editor of Neurology, Neuroimmunology, and Neuroniflammation and is a member of the advisory board for the International Society of Neuroimmunology. He has served as a consultant and received honoraria from Biogen-Idec, EMD-Serono, Genzyme, Novartis, Roche, and Teva Pharmaceuticals, Inc., and has served or serves on Data Safety Monitoring Boards for Lilly, BioMS, Teva, and Opexa Therapeutics.

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