Available online at
ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EM|consulte
www.em-consulte.com

Multiple Sclerosis on behalf SFSEP

Treatment of progressive multiple sclerosis: Challenges and promising perspectives

E. Maillart

Department of neurology, Pitié-Salpêtrière hospital, AP–HP, 47-83, boulevard de l'Hôpital, 75013 Paris, France

INFO ARTICLE

Article history:
Received 22 November 2017
Accepted 4 January 2018
Available online xxx

Keywords:
Progressive multiple sclerosis
Therapy
Design
Treatment
Symptomatic

ABSTRACT

Management of progressive multiple sclerosis (MS) is one of the main challenges of the new century. Based on our knowledge of pathophysiology, three therapeutic strategies are proposed: anti-inflammatory (ocrelizumab, siponimod...); remyelinating (opicinumab); and neuroprotective (high-dose biotin, ibudilast, simvastatin...). Nevertheless, despite recent promising positive clinical trials, new methodological approaches for therapeutic protocols with adaptable outcomes to assess progression are still needed.

1. Introduction

Management of progressive multiple sclerosis (MS) is one of the challenges of the new century. Indeed, the following fundamental issues have been highlighted by the International Progressive Multiple Sclerosis Alliance [1]: understanding the mechanisms underlying progression; designing therapeutic trials with adaptable outcomes; and improving symptomatic treatment.

More than one million people, meaning more than half the population affected by MS worldwide, are living with a progressive form of the disease [2]. Lublin et al. [3] proposed defining progressive MS with or without activity [clinical relapse and/or changes on magnetic resonance imaging (MRI)] as MS with or without activity progression as assessed by at least annual Expanded Disability Status Scale (EDSS) monitoring [4]. This definition refers to the combined population of patients with primary progressive MS (PPMS), the 10% of MS patients with gradual neurological worsening with no relapse, and those with secondary progressive MS (SPMS), the evolution of MS after 15–20 years of relapsing–remitting MS (RRMS).

2. Therapeutic strategies

Based on our current knowledge of MS pathophysiology (Fig. 1), the three following therapeutic strategies have been proposed.

2.1. *Anti-inflammatory therapy*

Compared with success in developing treatments for RRMS, the story of progressive MS therapy was disappointing until 2016, when two clinical trials reported positive results (Table 1) that were milestones in progressive MS treatment.

E-mail address: elisabeth.maillart@aphp.fr.
https://doi.org/10.1016/j.neurol.2018.01.370
0035-3787/

Please cite this article in press as: Maillart E. Treatment of progressive multiple sclerosis: Challenges and promising perspectives. Revue neurologique (2018), https://doi.org/10.1016/j.neurol.2018.01.370

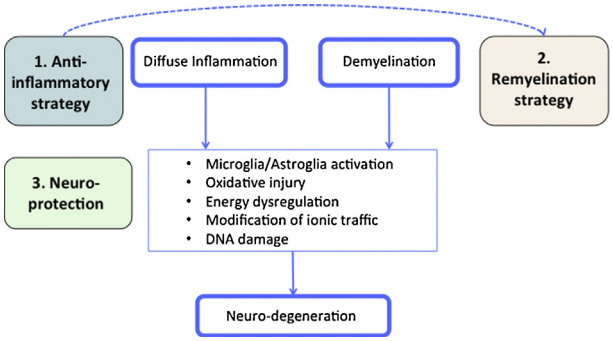

Fig. 1 – Therapeutic strategies for progressive multiple sclerosis.

First of all, ocrelizumab, a humanized monoclonal anti-CD20 antibody [5], proved successful in the phase-III ORATORIO trial of PPMS. With 732 patients included and randomized into two groups (ocrelizumab vs. placebo at 2:1), the risk of 12-week confirmed disability progression decreased by 24% at 2 years. The different disease evolution in the two groups was seen within the first 6 months of treatment (most likely because of the strong anti-inflammatory effect of ocrelizumab) and then remained stable for the rest of the study. Activity on MRI scans was a secondary outcome in this trial: there was no significant difference between patients with and patients without enhancing lesions at inclusion. However, this trial was probably insufficiently powered to find any differences between these two groups.

Second, siponimod, an oral sphingosine 1-phophate (S1P) modulator receptor, was studied in the phase-III EXPAND trial of SPMS [6] in a large sample of 1651 patients (siponimod vs. placebo at 2:1). A significant effect was found in the treated group, with a 21% decrease in risk for 12-week confirmed disability progression at 2 years.

However, in summary, the results of both these studies were relatively modest despite the large sample size of recruited patients (Table 1). One possible explanation is the inclusion of young patients with progressive MS (with activity) as defined by Lublin et al. [3].

This same observation might also explain the effects found in a 1998 European trial of interferon (IFN) beta-1b in SPMS [7] in which 70% of patients had relapses in the 2 years preceding the study; the mitoxantrone trial [8] where a mean of 1.3 relapses was reported in the preceding 12 months and only 48% of patients with SPMS were followed; and a phase-II trial of autologous hemopoietic stem cell transplantation after immunoablation [9] in a small sample of 12 patients with aggressive SPMS.

Recently, in the French PROMESS trial [10], SPMS patients were randomized into two groups and treated respectively with monthly cyclophosphamide and methylprednisolone. This study was negative because of the limited number of recruited patients and large proportion of patients who stopped their follow-up in < 2 years. However, a secondary analysis revealed that, while patients in the cyclophosphamide group were significantly more likely to stop treatment, those who continued with the treatment had significantly less progression according to their EDSS scores at the end of the study.

Targeting mechanisms of inflammation is not enough, as many such studies were negative, and involved IFN beta-1a [11], recombinant IFN beta-1a (SPECTRIMS) [12], azathioprine [13], cyclosporine [14], sulfalazine [15], cladribine [16], linomide [17], intravenous immunoglobulins [18], glatiramer acetate [19] and, more recently, powerful drugs such as fingolimod [20] and natalizumab [21]. Also, in SPMS patients, when to stop a disease-modifying therapy (DMT) introduced during the relapsing–remitting phase remains an open question [22]. No randomized trial of DMT withdrawal in SPMS patients has so far been performed, and no guidelines have been provided to date.

2.2. *Remyelination therapy*

Remyelination is an ambitious goal in MS treatment. Opicinumab, a monoclonal anti-Lingo-1 antibody, has been identified as a potential remyelinating therapy to actively enhance oligodendrocyte differentiation and myelination. In one phase-II trial [23], 21% of the included patients had SPMS. Unfortunately, this study was negative. The primary outcome, based on improvement in a clinical composite score, based on the EDSS and/or one of the three Multiple Sclerosis Functional Composite (MSFC) components, was not reached.

Functional screening for compounds that promote remyelination have been developed using approaches such as micropillar arrays [24], and potential therapies such as clemastine fumarate, an antihistaminic and antimuscarinic drug, have been tested in MS clinical trials. In a recent double-blind randomized, placebo-controlled, crossover trial of clemastine fumarate vs. placebo [25], a positive result was reported with a significant reduction in P100 latency delay on the visual evoked potential (VEP) in RRMS patients with chronic demyelinating injury of the optic nerve.

Table 1 – Results of clinical trials of ocrelizumab and siponimod vs placebo in patients with progressive MS.

	ORATORIO		EXPAND	
	Primary progressive MS		Secondary progressive MS	
	Ocrelizumab	Placebo	Siponimod	Placebo
Duration of progressive disease, mean years	6.7 (SD 4)	6.1 (SD 3.6)	3.85 (SD 3.61)	3.56 (SD 3.28)
Patients with ≥ 1 relapse in the 2 years preceding the study	NA	NA	35.3%	37%
Patients with ≥ 1 active lesion on brain MRI at inclusion	27.5%	24.7%	21.4%	20.9%

MS: multiple sclerosis; SD: standard deviation; NA: not available; MRI: magnetic resonance imaging.

Please cite this article in press as: Maillart E. Treatment of progressive multiple sclerosis: Challenges and promising perspectives. Revue neurologique (2018), https://doi.org/10.1016/j.neurol.2018.01.370