

Editorial

Secondary Progressive Multiple Sclerosis: What is in the Horizon?

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EDITORIAL

Multiple Sclerosis (MS) is an inflammatory disorder of the Central Nervous System (CNS) characterised by focal lymphocytic infiltration leading to myelin and axonal damage. The aetiology is unknown but believed to involve environmental and genetic factors [1]. There are four recognised types: a) Relapsing-remitting (RRMS): clearly defined relapses and full or partial recovery, b) Primary-Progressive (PPMS): progression from onset with or without transient minor improvements, c) Secondary-Progressive (SPMS): progression follows a relapsing-remitting course with or without occasional relapses, remissions, and plateaus, d) Relapsing-Progressive (RPMS): combination of relapses and progression [2]. Disease progression is defined as continuous worsening of neurological status over at least 6 or 12 months. If progression follows an initial relapsing-remitting course, this is referred to as SPMS [3].

First disease modifying therapies started in 1990s targeting relapse rate to reduce disability. After more than two decades, many injectable and oral agents are used worldwide [4]. Although reduction in relapse rate and MRI lesions was achieved by different therapies, effect on disease progression has been a major challenge due to the difference in the pathophysiological mechanisms between RRMS and SPMS. It is now believed that the progression phase of MS is caused by a neurodegenerative process with antero- and retro-grade degeneration of interconnected brain areas (including normal-appearing tissue) and grey matter damage playing crucial role in accumulating disability and cognitive dysfunction [5].

The European Trial in SPMS (EUSPMS) tested INF β -1b against placebo in 718 patients showing 22% reduction in the proportion of patients with three months confirmed disability progression. Reduction in clinical and MRI activity similar to that seen in pivotal RRMS trials was achieved. A subsequent North American study failed to support INF β -1b effect on progression. Further trials on INF β -1a demonstrated no benefit too. The MIMS trial tested mitoxantrone against placebo in 194 patients with worsening RRMS or SPMS. There was reduction in disability progression at three and six months (however less than 20% of cases progressed during the study and no separate statistical analysis done for SPMS cases which represented 50% of total) [5]. INF β -1b, INF β -1a, and mitoxantrone are approved in SPMS

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by the European Medicines Agency (EMA) while the US Food and Drug Administration (FDA) only approved mitoxantrone [6].

The monoclonal antibody daclizumab resulted in reduction in gadolinium enhanced lesions and relapse rate in RRMS and SPMS trials. Two studies showed positive effect on progression in small number of cases. Azathioprine, cyclophosphamide, glucocorticoids, intravenous immunoglobulins, and mycophenolate were tried with some benefit in SPMS patients but none is approved [6]. A phase II trial comparing simvastatin to placebo in 140 SPMS patients showed 43% reduction in the annualised rate of brain atrophy. A phase III trial with larger number of cases is needed, using clinical outcomes as primary endpoints [7]. Autologous mesenchymal stem cells used in ten SPMS patients with visual pathways involvement resulted in some improvement in visual endpoints suggestive of neuroprotection [8]. Alemtuzumab, cladribine, dirucotide, dronabinol, and lamotrigine were tested in trials with no effect on progression [5].

Rituximab, B cell-depleting anti-CD20 therapy, showed positive effect in RRMS trials [6]. A phase I trial is ongoing to evaluate the safety and effectiveness in SPMS. The aim is to find the most sensitive outcome measures and trial design for future phase II trials and investigate the mechanism of action on the human immune system [9].

Masitinib, a selective tyrosine kinase inhibitor, showed promising results in trials on Alzheimer's disease, rheumatoid arthritis, asthma, and mastocytosis. A phase 2b/3 study is in progress to compare efficacy and safety of the drug to placebo in the treatment of relapse-free SPMS or PPMS [10].

A biological agent, Tcelna (Imilecleucel-T), is being tried in a phase II study to measure its effect on brain atrophy. The drug is an autologous T-cell immunotherapy made from a pool of myelin-reactive T-cells isolated from patient's own peripheral blood mononuclear cells raised against selected peptides from myelin basic protein, myelin oligodendrocyte glycoprotein,

and proteolipid protein. The attenuated T-cells are injected subcutaneously triggering a therapeutic immune system response [11].

A phase 3 study evaluating Siponimod in SPMS is expected to finish in 2016. The primary outcome is the delay in time to confirmed disability progression. Siponimod is a selective sphingosine 1-phosphate (S1P)-1 and -5 receptor modulator administered once-daily orally. It reduces lymphocyte infiltration into the CNS. It crosses the blood-brain-barrier and modulates neurobiological processes via S1P₁ and S1P₅ receptors on astrocytes and oligodendrocytes. It has been shown that S1P receptor modulation reduces accumulation of neurological impairment and slows brain atrophy in relapsing MS [12].

Adrenocorticotrophic Hormone (ACTH) was the first immunosuppressant used in MS. Other steroids, like prednisone and methyl prednisone, have replaced ACTH. Steroids suppress cell-mediated immunity and to a less extent humoral immune response with marked suppression of inflammatory response including immunologic reactivity. Pulsed ACTH (Acthar Gel) is being tested in a phase 3 trial against placebo looking at the proportion of patients with progressive MS exhibiting 20% worsening in Timed 25 Foot Walk (T25FW) at 36 months [13].

Ibudilast, an anti-inflammatory drug used in asthma, has shown some effect on disease progression in RRMS patients. A phase 2 trial in progressive MS is in progress measuring its effect on brain atrophy over 96 weeks [14].

MS-SMART; a multi-arm phase IIb randomised, double blind, placebo-controlled trial is expected to start this year comparing the efficacy of Ibudilast, Amiloride, and Riluzole in SPMS patients. All of the three drugs have shown neuroprotective properties in previous studies. The primary outcome is to establish whether the studied drugs slow the brain volume loss using MRI-derived percentage brain volume change over 96 weeks [15].

The progress made in finding treatments for RRMS patients and the positive results in some SPMS studies make us hopeful of new therapies in the horizon. An important aspect for future consideration is to come up with specific markers which can reflect treatment efficacy. At present, axonal repair and remyelination are the obvious targets for emerging treatments. More understanding of the disease process will lead to more targeted therapies and better outcome.

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