New treatment targets in multiple sclerosis therapy

A. Zanghì & E. D'Amico


To link to this article: https://doi.org/10.1080/23808993.2019.1627870
New treatment targets in multiple sclerosis therapy

A. Zanghì and E. D’Amico

Department "G.F. Ingrassia", MS center University of Catania, Catania, Italy

1. Introduction

The Multiple Sclerosis (MS) therapeutic scenario has radically changed in the last few years, due to new insights on disease pathogenesis and course. Although MS is considered a prototype of the central nervous system (CNS) diseases, the therapeutic possibilities are based primarily on immunomodulation and/or immunosuppression of peripheral immunotargets. Furthermore, communication between the immune system and the CNS is exemplified by crosstalk between glia and neurons, essential for maintaining homeostasis. Knowledge of the cross-talk between microglia and oligodendrocytes may continue to uncover novel pathways of immune regulation in the brain [1].

Classically MS was considered a T-cells mediated disease, but more recent evidence showed as B cells and other immune cells are actively involved [2,3]. Therefore, the deep use of immunotargets characterization before the beginning of any Disease Modifying Therapy (DMT) represents the future of MS therapy [4]. Treatment response has traditionally been based on clinical activity (relapse-rate), radiological activity/burden at Magnetic Resonance Imaging, and level of disability measured by Expanded Disability Status Scale. Larger longitudinal data sets have enabled the development of composite outcome measures and more stringent standards for disease control. Biomarkers, including neurofilament light chain, have potential as early surrogate markers of prognosis and treatment response but require further validation [5,6]. Overall, a personalized approach for MS which takes into account comorbidities and cognitive impairment is desirable but new researches are necessary to define it. Therapeutic algorithms that can classify patients according to their personal risk of disease progression should be developed.

2. Body

New insights into the function of B cells has shifted our understanding of the immunopathology of the disease. A conceptual turning point occurred in 2008, when a single course of rituximab – a monoclonal antibody that selectively targets and depletes CD20 + B cells – was shown to be highly effective in the suppression of new inflammatory MS activity [7]. Later, a larger amount of data on other anti-CD20 monoclonal antibodies for MS patients, as ocrelizumab and ofatumumab was obtained from several clinical trials assessing the safety and efficacy of such DMTs. However, no long-term trials evaluating the efficacy and safety of these anti-B-cell treatments for MS are currently available and the sample size in previous studies is small.

Recent studies are now also focusing on memory B-cells (CD19+ and CD27+) which could have a role in modulating disease activity [8]. Interestingly, DMTs classically considered acting via T cells (e.g. beta-interferons, glatiramer acetate, dimethyl fumarate, fingolimod, cladribine) were revealed to decrease the availability of B-cells to enter the CNS [8]. Furthermore, most B cells in MS lesions, meninges and ectopic B cell aggregates are CD27 antigen positive. These are cell populations that have been shown to co-express latent EBV proteins and support a role for EBV infection in B-cell activation in MS brain [9]. This will need to be elucidated further [10].

Such evidence should be considered at all stages of the DMTs’ choice process; MS requires life-long management and DMTs have to fit with the personal history of each patient. For example, natalizumab (NTZ), an anti-α-4 integrin antibody induces peripheral memory B cell elevation [11] but it is not associated with worsening of MS, and that could be due to the prevention of memory B cells entering the CNS [12,13]. Likewise, the enhanced levels of peripheral memory B cells may contribute to rapid disease rebound after NTZ is withdrawn [14].

Discontinuation of NTZ (usually for safety concerns, due to a high risk of progressive multifocal leukoencephalopathy) [15], is still a dramatic moment in MS therapeutic management and no guidelines exist about the ideal exit strategy. Therefore, the choice of CD20-depleting agents which reduce the high number of circulating B-cells could be useful. Data about treatment with rituximab post-NTZ revealed a lower relapse rates and also a reduced PML risk [16].

Another incoming issue is the choice of an induction therapeutic approach, which could be possible with the use of cladribine and alemtuzumab. Interesting lymphocyte phenotyping data, obtained from the trials CLARITY (for cladribine) and CARE-MS I (for alemtuzumab), revealed a substantial depletion of memory B cells with long term inhibition of disease activity. This indicates that induction therapies for MS may impact the B cells memory population [17]. During alemtuzumab treatment, lymphocytes repopulate over time, with B-cell recovery being usually complete within six months, whereas T-lymphocyte (included the regulatory T-cell subsets) counts rise more slowly and generally do not return to
baseline by 12 months post-treatment. Such different kinetics of T and B cell populations recovery (with B cells returning much earlier in peripheral blood) may trigger secondary autoimmunity [17].

The above-described phenomenon is not a feature of treatment with cladribine, which induces a marked and long-lasting CD19 B-cell depletion that did not reach baseline levels within the 12-month treatment cycle [17].

However, important safety alerts are coming out and the European Medicine Agency has started a review of alemtuzumab following new medical reports (hemophagocytic lymphohistiocytosis, bleeding in the lungs, heart attack, stroke, cervicocephalic arterial dissection, severe neutropenia). As a temporary measure while the review is ongoing, alemtuzumab should only be started in adults with MS highly active despite treatment with at least two DMTs or where other DMTs cannot be used (https://www.ema.europa.eu/en/news/use-multiple-sclerosis-medicine-limited-reserved-while-ema-review-ongoing).

Clinicians must consider what would be the right match of DMT for a specific patient, promoting therapeutic compliance and weighing the benefit/risk ratio and concerns regarding safety and tolerability. New DMTs that target CNS mechanisms, whether they’re neuro-inflammatory, or acting on astrocytes/microglia, on neurodegenerative component itself, or remyelination are important targets also for progressive MS. Regarding that, siponimod, a sphingosine 1-phosphate modulator, seems to have the focus for progressive forms of MS and it should be due to its biological mechanisms in the CNS. In vitro the investigators reported that siponimod reduced the release of IL-6 from activated microglial cells in addition to astrogliosis and microgliosis reduction. The potential neuroprotective effect of siponimod suggested by these studies could explain the benefit observed on disability progression in patients with secondary progressive MS treated with this drug [10,18].

Expert opinion

How to proceed after an induction strategy is still unclear, but de-escalation to a lower-risk DMT represent the most used approach. The advantage of an induction strategy should be balanced against the risks of this therapeutic strategy. For patients with a better prognostic profile, the escalating approach should be considered more appropriate than an induction scheme, considering also the role of lateral switch for safety concerns [19–21].

We hope that in the foreseeable future, the appropriate selection and prescription of DMTs in MS patients could be based also on the detailed knowledge of the direct and indirect immunological targets of each DMT. Moreover, it is mandatory to consider the phases of the long-lasting reshaping of the immune system which inevitably occur in patients with MS, who usually are exposed to different DMTs along MS’s course.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

ORCID

E. D’Amico http://orcid.org/0000-0001-7494-9057

References


• It provides algorithms for personalized therapy in MS scenario


• It provides interesting insights on new targets in MS therapy.