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The future of multiple sclerosis treatment

Jeffrey A. Cohen*

Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic Foundation, Cleveland, OH, USA

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ABSTRACT

Recent years have seen considerable evolution and increasing sophistication of our concepts of the pathophysiology of multiple sclerosis. These new notions include the increased recognition of the importance of extralesional pathology, of the interplay between inflammation and neurodegenerative changes, pathophysiological heterogeneity and additional immune cell populations contributing to disease. These advances have driven the development and evaluation of new therapeutic strategies and outcome measures for clinical trials. A sizeable number of new immunomodulatory and immunosuppressive agents are under development and attracting great attention. These may offer potential advantages over existing treatments in terms of convenience and efficacy, but certain agents may raise safety concerns. In addition, neuroprotective and repair strategies are beginning to be considered. Not all of these agents will eventually be marketed but they will all help us gain insight into the pathophysiology of multiple sclerosis and decipher the mechanisms that underlie its heterogeneity. The place that these therapies will come to occupy in future years will depend on their relative benefits and risks.

1. Introduction

Multiple sclerosis (MS) is a chronic disabling disease with many implications for patients and society. Advances in magnetic resonance imaging (MRI) and the availability of disease-modifying therapies have considerably changed the way MS is handled in clinical practice. However, the currently-approved standard medications to treat relapsing–remitting disease (interferon-β and glatiramer acetate), while safe and generally well-tolerated, are only partially effective. Mitoxantrone and natalizumab are potent but have the potential for rare but serious adverse events. In addition, all of these medications are administered by injection. For these reasons, new therapeutic options are needed. Advances in our understanding of the underlying pathogenesis of MS help identify potentially promising avenues of research for novel therapies with original mechanisms of action. This review will cover the background and current status of emerging therapies in MS and discuss the broader issues raised by their development.

2. Evolving disease concepts

The traditional view of the pathogenesis of MS has considered the disease process to start from a specific immune trigger in the periphery, whereby antigens related to myelin are processed by dendritic cells in the lymphoid system and presented to T-cells, leading to activation and clonal proliferation of antigen-specific T-cells. These T-cells cross the blood–brain barrier and enter the central nervous system, where they are reactivated by the target antigen on myelin. This leads to release of inflammatory cytokines and recruitment of phagocytic microglial cells. This inflammatory response leads to local destruction of myelin, resulting in the sclerotic plaque characteristic of the disease. In addition, the loss of the myelin sheath exposes underlying axons to toxic factors in their environment. The resulting axonal damage or loss is believed to be responsible for progressive irreversible accumulation of neurological disability.

However, this rather linear concept of the pathogenesis of MS has been enriched over recent years with a number of new ideas which suggest that the disease process may in fact be considerably more complex. These new ideas include the involvement of other immune cell types, the notion that the disease process may involve different pathological mechanisms in different individuals, the relationship between axonal damage and demyelination, the importance of pathology outside inflammatory foci and outside white matter, and the identification of compensatory and repair mechanisms.

With respect to other immune cell types, B-cells may potentially intervene in many aspects of the disease process. They can enter the nervous system and release antibodies

* *E-mail address:* cohenj@ccf.org (J.A. Cohen).

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directed against myelin epitopes, release cytokines that can amplify activation of T-cells and recruitment of microglia and also have a direct antigen-presenting capacity in their own right [1]. The potential involvement of B-cells in the development of pathology is supported by the observation of meningeal follicles of B-cells in autopsy samples from patients with MS [2]. These follicles were found adjacent to large subpial cortical lesions, suggesting that soluble factors diffusing from these structures may play a role in lesion development. Findings from a recent clinical trial of rituximab, a monoclonal antibody targeted to the CD20 surface protein on B-cells which selectively depletes these immune cells, support a critical role for B-cells in the development of inflammatory brain lesions [3]. This double-blind, 48-week trial in 104 patients with relapsing–remitting MS showed that patients treated with a single course of rituximab presented a reduced number of gadolinium-enhancing lesions at every time-point evaluated and experienced significantly fewer relapses. The rapidity of the clinical response (reduction in lesion number observable at twelve weeks) probably excludes an effect on antibody production as the sole explanation of the therapeutic effect observed.

Detailed histopathological investigation of autopsy samples has demonstrated clearly that not all lesions found in the central nervous system of patients with MS are identical. From such observations, it has been proposed that lesion pathogenesis itself may be heterogeneous. Lucchinetti et al. [4] proposed that four fundamentally different patterns of demyelination (Types I–IV) may reflect four different underlying pathogenetic processes. In this classification, Types I and II represent typical autoimmune demyelination, staining for T-cell markers with (Type II) or without (Type I) complement activation. Types III and IV, on the other hand, are characterised by primary oligodendrocyte dystrophy and were proposed to arise primarily from gliopathy rather than from immune-mediated attack. However, the specific clinical and imaging correlates of these four subtypes are not clear, and it is not known whether they respond differently to treatment. Also, others have suggested that these different demyelination patterns may not correspond to discrete pathogenetic processes in individual patients, but rather to different stages of development of the disease [5].

Axonal pathology has traditionally been viewed as a late consequence of inflammatory activity in the nervous system. However, the presence of transected neurones in lesions is very common, and their number is correlated with the extent of inflammatory activity [6,7]. It is now recognised that the majority of axonal pathology occurs early in the disease process, although damage to neurones may persist in lesions after inflammation has ceased [8]. In addition, some neuronal loss can be demonstrated in areas of the nervous system without visible stigmata of demyelination [9]. Such observations suggest that axonal injury can proceed to some extent independently from inflammation. If this is the case, this has important consequences for therapy with agents directed solely against central inflammation, since axonal loss is considered to be the pathophysiological substrate of irreversible disability in MS.

Cortical involvement in the pathology of MS was under-recognised for a long time, in particular because lesions in grey matter are difficult to visualise using conventional MRI [10]. However, recent histopathological evaluation of autopsy samples has shown that cortical lesions account for around one quarter of total lesion load [10]. Although some of these lesions are observed at the boundary of the grey and white matter, others are contained entirely within the cortex, often associated with a cerebral blood vessel, and still others appear to extend into the cortex from the pial surface [11]. These latter lesions have been associated with adjacent follicles containing B-cells [2]. As well as showing different degrees of demyelination, cortical lesions contain a high density of transected neurones and apoptotic neurones [11]. Taken together with the observation that cortical pathology is only poorly correlated with focal lesion load, but is particularly common and extensive in progressive disease [12], these findings have suggested that damage to the cortex may be particularly important for the development of irreversible disability.

Another important new concept in MS is the notion that some degree of recovery from injury may be possible due to both remyelination and to plasticity involving recruitment of alternative neuronal pathways. Such mechanisms are particularly effective at compensating for damage early in the disease course, such that, between relapses, the disease remains clinically silent. Later in the course of the disease, as damage accumulates and the inherent safety reserve of the nervous system is exceeded, these mechanisms fail. Histopathological studies have demonstrated that extensive remyelination occurs in a substantial proportion of patients [13–15]. However, this process leads to the formation of relatively thin myelin sheaths. For this reason, the resulting remyelinated lesions can be distinguished from normal myelin in autopsy samples as 'shadow plaques' [16–19]. Remyelination is thought to be due to recruitment of oligodendrocyte precursor cells which infiltrate the lesion site and differentiate into mature myelin-producing oligodendrocytes. However, this mobilisation of oligodendrocyte precursor cells is relatively limited and depends on maintained axonal integrity in the lesion site [20]. It has been postulated that more generalised myelination is hindered by the presence of an inhibitory factor associated with myelin, or alternatively by the absence of a required trophic factor normally produced by healthy axons [13,21]. The mechanisms of remyelination in MS are discussed in more detail by Yong in this supplement [22].

Functional MRI provides useful information on brain plasticity in MS, and on how this may limit the clinical manifestations of the disease [23]. Such studies have provided evidence for altered recruitment of regions not normally devoted to the performance of tasks related to the visual, cognitive, and motor systems. These functional changes are observed not only after an acute relapse, but also in clinically stable patients. The relative importance of these compensatory mechanisms is correlated to the degree of brain injury, both in terms of lesion load visible on conventional MRI and of damage to normal-appearing white matter detected with techniques such as magnetisation transfer imaging.

All these evolving concepts in the pathogenesis of MS have led to a revision of the relatively simplistic traditional view of the disease process to a more dynamic model [24]. For example, it now seems likely that neurodegenerative changes do not just arise from inflammatory damage, but can also persist independently of inflammation and influence the immune response. This is consistent with the observation that immunomodulatory treatments are less effective in secondary