Disease-Modifying Agents for Multiple Sclerosis
Recent Advances and Future Prospects

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Abstract

Multiple sclerosis (MS) is a chronic autoimmune disease of the CNS. Current-
ly, six medications are approved for immunmodulatory and immunosuppressive
treatment of the relapsing disease course and secondary-progressive MS. In the

first part of this review, the pathogenesis of MS and its current treatment options are discussed.

During the last decade, our understanding of autoimmunity and the pathogenesis of MS has advanced substantially. This has led to the development of a number of compounds, several of which are currently undergoing clinical testing in phase II and III studies. While current treatment options are only available for parenteral administration, several oral compounds are now in clinical trials, including the immunosuppressive agents cladribine and laquinimod. A novel mode of action has been described for fingolimod, another orally available agent, which inhibits egress of activated lymphocytes from draining lymph nodes. Dimethylfumarate exhibits immunomodulatory as well as immunosuppressive activity when given orally. All of these compounds have successfully shown efficacy, at least in regards to the surrogate marker contrast-enhancing lesions on magnetic resonance imaging.

Another class of agents that is highlighted in this review are biological agents, namely monoclonal antibodies (mAb) and recombinant fusion proteins. The humanized mAb daclizumab inhibits T-lymphocyte activation via blockade of the interleukin-2 receptor. Alemtuzumab and rituximab deplete leukocytes and B cells, respectively; the fusion protein atacicept inhibits specific B-cell growth factors resulting in reductions in B-cells and plasma cells. These compounds are currently being tested in phase II and III studies in patients with relapsing MS.

The concept of neuro-protection and -regeneration has not advanced to a level where specific compounds have entered clinical testing. However, several agents approved for conditions other than MS are highlighted. Finally, with the advent of these highly potent novel therapies, rare, but potentially serious adverse effects have been noted, namely infections and malignancies. These are critically reviewed and put into perspective.

Multiple sclerosis (MS) is a chronic disease confined to the CNS. Its pathological hallmarks are neuroinflammation, de- and remyelination, neurodegeneration and astrogliosis. To date, the aetiology of MS remains unknown; however, growing evidence supports an autoimmune pathogenesis triggered by environmental factors in genetically susceptible individuals. Perhaps not surprisingly, immunomodulatory therapies have been the mainstay of pharmacotherapy for many decades. Currently, clinicians have access to two distinct treatment strategies. In the past, our limited knowledge of MS pathogenesis allowed only general modulation or suppression of immune responses. During the last decade, several agents belonging to the class of immunomodulators were shown to be effective in clinical trials, and were approved. All of these agents have modest efficacy and good safety profiles. Over the past 10 years, specific anatomical, cellular and molecular targets have become the focus of drug development. A more in-depth understanding of the inflammatory cascade underlying MS disease activity will allow the development of increasingly specific, and hopefully safe and effective, pharmacological agents for all clinical MS phenotypes. As a consequence, future treatments will have to be designed to tackle the neurodegenerative processes inherent to MS.

On the basis of the current pathogenetic concepts of MS, we provide an overview of future compounds, describe the mechanisms by which they modulate the immune system in patients with MS, known adverse effects and their stages of clinical development. Publications were retrieved by searching PubMed Entrez provided by the National Center

for Biotechnology Information. The search strategy consisted of a combination of the following keywords: multiple sclerosis OR experimental autoimmune encephalomyelitis AND therapy, clinical trial(s), drug development, experimental, drug efficacy, drug safety. Latest search dates assessed were June 2008. The National Institute of Health's website and the website of the National Multiple Sclerosis Society (http://www.nationalmssociety. org/research/clinical-trials/index.aspx) have been utilized to screen for clinical trials of compounds related to MS.

1. Pathogenesis of Multiple Sclerosis (MS)

In order to highlight current advances in the treatment of MS, one must appreciate the current pathogenic concepts of the disease. Typically, MS becomes clinically apparent during early adulthood. The disease is more prevalent in females than males. It is very likely that in many patients, CNS inflammation starts many years before the onset of clinical signs and symptoms.[1] Despite tremendous progress in our understanding of the disease and in the development of specific therapies, MS remains one of the leading causes of neurological disability among young individuals, second only to trauma.[2-4] Following a period of monophasic disease, termed clinically isolated syndrome (CIS), the disease in the majority of patients enters a relapsing-remitting MS (RRMS) disease course. After another 10–15 years, the disease enters a chronic progressive phase in about 30–50% of patients, termed secondary-progressive MS (SPMS).[2,5] Approximately 10–20% are affected by a primary-progressive MS (PPMS) disease course[4] and a rather small group of patients (<5%) experience a progressive-relapsing disease course that most rapidly progresses, resulting in loss of ambulation in a median of 7 years.[6]

1.1 Genetic and Environmental Factors

The aetiology of MS remains unknown. However, there is strong evidence emerging that suggests a complex interplay of multiple genes and environmental factors.[7-9] The identification of specific sus-

ceptibility genes has been difficult. Until recently, the only strong and consistent linkage identified has been at chromosome 6p21, the location of the major histocompatibility complex (MHC).[10-13] For patients with MS of Northern European ethnicity, there is widespread consensus on the role of one common HLA allele: DRB1*1501. One allele of this gene increases the disease risk by an odds ratio of about 3.[14,15] More recently, it was shown by an international collaborative efforts that predominantly single nucleotide polymorphisms in the genes that encode parts of the interleukin (IL)-2 and -7 receptors appear to be associated with an increased risk of developing MS.[16,17] Interestingly, these genes play a critical role in inflammatory immune responses and neurodevelopment. In addition, a number of microbial agents, bacterial and viral, have been implicated in the pathogenesis of MS, of which Epstein-Barr virus, human herpesvirus (HHV)[6] and varicella zoster virus are currently being extensively studied.[18-22]

It is conceivable that in an individual carrying such disease susceptibility genes, an infection or sequential infections may eventually lead to an aberrant response of the immune system against self-antigens.[23,24]

1.2 Activation and Migration of Immune Cells

Both the innate and the adaptive immune systems play a role in the pathogenesis of MS. Structural homology of microbial antigens with CNS epitopes may lead to chronic activation of the immune system against self-antigens. This phenomenon is termed molecular mimicry. Animal studies have demonstrated that acquired immune responses to CNS antigens are initiated in the lymph nodes and spleen, where antigen-specific T and B cells become activated and clonally expand.[25] Activation enables these cells to cross biological membranes, including the blood-brain barrier (BBB). This is essential to physiological immune surveillance, including the CNS.[26] Unfortunately, it leads to autoimmunity if the antigen recognized in the lymph nodes resembles an autoantigen in the CNS. During the early

phase of MS, microglia activation and an amplification of immune cell infiltration into the brain and spinal cord are seen.[27] The physiologically tightly sealed BBB likely becomes compromised, and the transmigration of additional immune cells, including macrophages and dendritic cells, is facilitated.

Cell migration from the periphery into the CNS involves a complex sequential interaction of adhesion molecules, matrix metalloproteinases (MMPs) and chemokines.[28] Namely, the firm contact between leukocytes destined to enter the CNS and endothelial cells of the BBB activated by cytokines is, amongst others, mediated by α4-integrins on leukocytes and vascular cell adhesion molecule-1 (VCAM-1) on endothelial cells.[29] Other potentially relevant adhesion molecules and chemokine receptors are also expressed by lymphoid and myeloid cells.[30]

1.3 Lesion Formation

It was demonstrated by several investigators that macrophages and T cells (both CD4+ and CD8+) infiltrate the CNS parenchyma in MS.[31-33] In addition, clonotypic CD8+ T cells were also detected in cerebrospinal fluid (CSF).[31,32] CD4+ T cells and B cells appear to be more prominent in the perivascular spaces adjacent to lesions.[27] Macrophages and T cells within the lesion secrete a wide range of molecules toxic to the myelin sheath, including proteases, reactive oxygen species, nitric oxide derivatives and cytokines, that orchestrate the inflammatory damage.[34] Whereas some studies suggested a pro-inflammatory T helper (T$_h$)-1 and T$_h$17 cytokine signature in MS lesions,[33,35,36] other investigators demonstrated that both T$_h$1 and T$_h$2 cytokines, and their receptors are up-regulated in the CNS of MS patients.[37] More recently, it has also been discussed whether cytokines may be an essential component of CNS repair mechanisms, for example, remyelination after an acute attack.[38] In addition, it was proposed that the inflammatory milieu itself may support neuroprotection.[39] B cells in the CSF and MS plaques are oligoclonally expanded, expressing somatically mutated B-cell receptor genes that are compatible with an antigen-driven expan-

sion.[40-43] Some of these maturation steps may also take place in the CNS within lymphoid follicle-like structures found in late stages of MS.[44-46] The ultimate target specificities of these B cells still remain enigmatic.[47] Subsets of memory B cells and plasmablasts, which are attracted to the intrathecal space and parenchymal lesions,[48] produce antibodies that are detectable in MS lesions and are likely to be the cause of demyelination via complement activation in most MS patients.[49,50]

There is emerging evidence that in the progressive stages of MS, immune responses are further compartmentalized (see earlier in this section[44-46]) and locally sustained,[51] thus impeding the access of a number of immunoactive therapeutic compounds to the lesion site, including monoclonal antibodies, neurotrophic and gliotrophic factors, and cell therapies.

1.4 Neurodegeneration

While demyelination is the hallmark characteristic of MS and occurs most prominently in areas of acute inflammation within the white matter, the neurodegenerative and neuroregenerative features of MS have only recently been rediscovered after their initial description by Charcot.[52-54] Damage to or even loss of axons occurs in early disease stages and appears to correlate with the degree of neurological disability.[55,56] Axonal injury is evident both at sites of inflammatory infiltrates and also in their conspicuous absence.[53] In the context of inflammation, the underlying mechanisms may be quite similar to those of demyelination: a direct attack on the axon by CD8+ T cells, complement-mediated antibody-dependent phagocytosis of axons after binding of antibodies to neuronal membrane antigens,[57] T-cell-dependent recruitment and activation of macrophages that express inflammatory mediators and toxic molecules all may lead to acute axonal transection. In contrast, the gradual loss of oligodendrocytes and axo-glial disconnection may eventually deprive axons of trophic support and further augment their insidious damage; once denuded, axons appear to be particularly vulnerable to noxious mediators, including nitric oxide metabolites and ex-

citotoxic molecules, and hence undergo degeneration.[58] In these denuded axons, the redistribution and enhanced activities of sodium channels can lead to mitochondrial energy failure and calcium overflow, ultimately activating proteases capable of disintegrating the axonal cytoskeleton.[57,59]

Up to 50% of all demyelinating lesions remyelinate spontaneously.[60] Remyelination occurs in all disease subtypes and takes place even late during the disease course.[61] It appears to be initiated by oligodendrocyte progenitor cells (OPCs), which proliferate within the lesion, differentiate into premyelinating oligodendrocytes and finally into mature oligodendrocytes. This orderly process requires an appropriately permissive microenvironment, such as growth factors and support of neurons.[62] Even in chronic MS lesions, premyelinating oligodendrocytes are present, but seem to be impaired in their remyelinating activity.[62,63] As yet, it remains enigmatic as to why remyelination occurs in some patients, but is absent or fails in other patients.[64,65] Possible mechanisms include ongoing destruction of OPCs, or the compromise of other glia cells and neurons that may support remyelination.[66,67]

Figure 1 illustrates the current concept of MS pathogenesis. Compounds that selectively interfere with certain pathogenic pathways are depicted in figure 1 to highlight their mode of action.

2. Testing the Efficacy of Pharmacological Agents in MS

Clinically, pathogenetically and histopathologically, MS is a complex and highly heterogeneous disease with an often unpredictable disease course.[4,49,50] Thus, clinical trials would have to enrol very large numbers of patients (and controls) and would have to last many years to attain meaningful results if they only relied on clinical outcomes. In the past two decades, disease surrogate markers on brain magnetic resonance images (MRIs) have been used to substitute for clinical outcomes. These paraclinical tests aim to capture subclinical disease activity. Conventional imaging sequences include T2 lesion load, contrast enhanc-

ing lesions on T1-weighted images, and the number of newly emerging lesions. However, there is a general notion that the use of these MRI disease makers may correlate insufficiently with histopathology and clinical disease progression; hence, MRI may never substitute for clinical outcome measures.[68] Biomarkers that unequivocally correlate to disease parameters have not yet been established.[69]

The animal model of MS, experimental autoimmune encephalomyelitis (EAE), has been extensively studied to investigate CNS autoimmunity, but does not faithfully reflect and model the heterogeneity and insidious onset of the human disease and its pathogenetic hallmarks.[70] EAE represents some of the characteristic features of MS (CNS damage mediated by CD4+ T cells and macrophages), while others are largely missing or incomplete (CNS damage mediated by CD8+ T cells and B cells, neurodegeneration in the absence of inflammation).[70-72] This may explain why compounds shown to be highly efficacious in EAE have failed in clinical trails.[73,74] Perhaps even more problematic is the fact that many pharmaceutical companies do not pursue drug development of compounds that fail to show a benefit in the EAE model.

Novel EAE models, including transgenic humanized models, have been generated to better replicate B-cell- and CD8+ T-cell-mediated demyelination and axonal damage, and may be applied to preclinical testing of novel compounds in the future.[72,75-80] Animal models of virus-induced autoimmunity or demyelination may add relevant information when evaluating pharmaceuticals for patients with MS.[23,70,71,81]

3. Current Treatment Regimens

Acute relapses are managed by intravenous corticosteroids: typically 3–5 days of methylprednisolone 1 g with or without oral tapering. This regimen was shown to shorten the duration of the relapse, mediated through a number of genomic and non-genomic actions.[82-84]

Two classes of agents are currently approved as first-line treatment for the prevention of clinical relapses. These drugs are considered first-line thera-

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