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Current Theories for Multiple Sclerosis Pathogenesis and Treatment

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1. Introduction

Multiple Sclerosis (MS) is a chronic, progressive, immune mediated central nervous system (CNS) disorder that affects both adults and children. MS is characterized by the formation of multiple lesions along the nerve fibers in the brain, spinal cord and optic nerves (Bradl and Lassmann, 2009; Bruck, 2005; Bruck and Stadelmann, 2005; Chitnis *et al.*, 2009; Hafler, 2004; Holland, 2009; Mah and Thannhauser, 2010; Pohl *et al.*, 2007). The precise triggers of autoreactive T cell development remain to be fully understood, however, it is clear that myelin antigens are the major target (Grau-Lopez *et al.*, 2009). T cell activation results in cytokine release and recruitment of other immune cells that results in tissue damage not only to the myelin sheath but, over time and with repeated attacks, to the underlying axons as well. Demyelination and axonal damage impairs or interrupts nerve transmission, giving rise to clinical signs and symptoms.

Clinically, neurological symptoms in patients with MS vary from mild to severe and typically include one or more of the following: sensory symptoms (numbness, tingling, other abnormal sensations, visual disturbances, dizziness), motor symptoms (weakness, difficulty walking, tremor, bowel/bladder problems, poor coordination, and stiffness), and other symptoms such as heat sensitivity, fatigue, emotional changes, cognitive changes and sexual symptoms (Bronner *et al.*, 2010). While some persons have a limited number of “attacks” or “relapses” and remain fairly healthy for decades, others may deteriorate rapidly from the time of diagnosis, with poor quality of life and shortened lifespan. There is no way of knowing at the clinical onset what course the disease will take (Andersen, 2010; Bradl and Lassmann, 2009; Bruck, 2005).

In this chapter how the autoimmune process is triggered as well as current clinical options to try and reduce disease symptoms are addressed. While the induction of long-term durable antigen-specific T cell tolerance is the desired treatment option, such a therapy

remains to be clinically developed. Instead, once a diagnosis of MS is made, immune based treatment is generally begun, with numerous therapies aimed primarily at inactivating T cells and other immune functions.

2. Multiple Sclerosis triggers and animal models

The ability for the immune system to differentiate between self and non-self is critical for host preservation. Deficits in self-non-self discrimination can result in opportunistic infections or immunological over-reactivity resulting in immunopathology and autoimmunity. It is therefore, not surprising that multiple genetic factors that influence the sensitivity of the immune system are known to trigger autoimmune mediated diseases. However it is hypothesized that clinical symptom development may only manifest after exposure to certain environmental factors, including viral infection. The interplay of genetics and the environment in regards to the development of MS, and other autoimmune diseases, has not been completely elucidated. No matter what the potential switch that causes MS initiation the activation, proliferation and effector functions of auto-reactive CD4⁺ T cells appears to be critical for disease development and progression (Goverman, 2009; Miller and Eagar, 2001; Miller et al., 2001).

i. Predisposing genetic factors

The significantly higher concordance rates of MS in monozygotic twins compared to dizygotic twins (Hansen *et al.*, 2005; Islam *et al.*, 2006; Willer *et al.*, 2003), the 2-fold increased risk of disease development in siblings of affected individuals (Ebers *et al.*, 2004) as well as the observed increased susceptibility in offspring from two affected parents, compared to those with only one affected parent (Ebers *et al.*, 2000; Robertson *et al.*, 1997) all point to a strong genetic component in the pathogenesis of MS. However, like many other complex autoimmune diseases, MS is not transferred from parent to offspring via classic Mendelian genetics and the disease trait involves a large number of genes (Hoffjan and Akkad, 2010). Until recently, most gene variations associated with increased or decreased susceptibility were thought to be within the human leukocyte antigen (HLA) loci (Ramagopalan *et al.*, 2009). However, recent studies have also identified risk-conferring alleles within several non-HLA genes (Nischwitz *et al.*, 2011). Importantly, most of these genes are known to play important roles in T cell activation and function, which further supports the concept that a dysfunctional immune process is involved in the initiation and progression of MS (Nischwitz *et al.*, 2011).

ii. HLA genes

Allelic variations within the major histocompatibility complex (MHC) exert the greatest individual effect on the risk of MS (Ramagopalan *et al.*, 2009). Initial studies published in 1972 identified the HLA Class I antigens *HLA-A*03* and *HLA-B*07* as risk-conferring alleles (Jersild *et al.*, 1972; Naito *et al.*, 1972). Between 1973 and 1976, several studies reported a significant link between the HLA Class II gene *HLA-DR2* and MS (Jersild *et al.*, 1973; Terasaki *et al.*, 1976; Winchester *et al.*, 1975). This has been further subtyped into a strong

and consistent association between the *HLA-DRB5*0101*, *HLA-DRB1*1501*, *HLA-DQA1*0102* and *HLA-DQB1*0602* extended haplotype and disease (Fogdell *et al.*, 1995). As these genes are tightly linked, early genetic studies failed to identify which of these alleles confers the greatest risk for MS (Hoppenbrouwers and Hintzen, 2011). However, statistically-powered studies conducted in the past decade, including several international genome-wide association studies (GWAS), have identified *HLA-DRB1*1501* as the major risk conferring gene for the development of MS (2007; 2009; Hafler *et al.*, 2007; Lincoln *et al.*, 2005; Oksenberg *et al.*, 2004; Sawcer *et al.*, 2011).

Other HLA-DR2 alleles that confer susceptibility in some populations include *HLA-DRB1*17* and *HLA-DRB1*08*, however the effects of these alleles are modest compared to *HLA-DRB1*1501* (Dyment *et al.*, 2005; Modin *et al.*, 2004). Some variants are also reported to confer protection from the development of MS, including *HLA-DRB1*14*, *HLA-DRB1*01*, *HLA-DRB1*10* and *HLA-DRB1*11* (Brynedal *et al.*, 2007; Dyment *et al.*, 2005; Ramagopalan *et al.*, 2007).

iii. Non-HLA genes

Early gene linkage studies failed to validate associations between non-HLA genes and the development of MS, potentially due to the small individual contribution of each gene to disease (Nischwitz *et al.*, 2011). However, in recent years, several GWAS have identified polymorphisms within a number of non-HLA genes that play an important role in the development of MS (Pravica *et al.*, 2012). These include genes that are involved in cytokine pathways, such as those encoding the IL-2, IL-7, IL-12 and TNF receptors, which are important for T cell development, homeostasis, proliferation and differentiation (2009; Baranzini *et al.*, 2009; Sawcer *et al.*, 2011).

Also, variations within genes coding for co-stimulatory molecules, such as CD40, CD58, CD80 and CD86, which promote the activation of T cells, were also implicated in susceptibility to MS (2009; Baranzini *et al.*, 2009; Sawcer *et al.*, 2011). Polymorphisms within genes encoding for molecules such as STAT3 and TYK2, which are involved in several signal transduction pathways including those that mediate T cell activation and Th17 differentiation, were also linked with the development of MS (2009; Baranzini *et al.*, 2009; Sawcer *et al.*, 2011).

Variations within other genes that can affect T cell functioning, including CD6, CLEC16A, and the vitamin D alpha hydroxylase gene CYP27B1 are also implicated in the pathogenesis of MS (2009; Baranzini *et al.*, 2009; Sawcer *et al.*, 2011). Although the individual contribution of each gene to the development of MS is modest, the identification of such genes is critical, as they will provide novel targets or approaches for therapeutic intervention in MS (Nischwitz *et al.*, 2011).

There is clearly further research to be performed to better understand the role of genetics and MS development. However the data clearly show that genes associated with T cell activation and other immune functions certainly highlight the importance of targeting immune factors when treating disease.

3. Environmental factors

Although it is clear that genetics play a key role in determining susceptibility to MS, concordance rates between monozygotic twins (*i.e.* with identical genomes) varies between 6 and 30 percent (Dyment *et al.*, 2004). This suggests that other non-inheritable factors play an important role in the initiation of the auto-reactive immune response. A number of infectious and non-infectious stimuli have been identified as key factors that increase the risk of MS development.

i. Infectious factors

For many years, underlying infections have been implicated in the induction of the autoreactive CD4⁺ T cell response that leads to MS (Kakalacheva and Lunemann, 2011). Roles for several pathogens, including Epstein Barr Virus (EBV), Human Herpes Virus-6 (HHV-6) and Varicella Zoster Virus (VZV) have been investigated. There is considerable evidence that links EBV with the initiation and progression of MS (Ascherio and Munger, 2007a, b; Dyment *et al.*, 2004). EBV infects over 90% of the world population and causes infectious mononucleosis (IM) in a large proportion of individuals, which is characterized by glandular fever and the massive expansion of virus-specific T cells (Vetsika and Callan, 2004). Pooled data from 18 clinical studies revealed a significant link between IM and an elevated risk of MS (Kakalacheva *et al.*, 2011).

Furthermore, in individuals that concurrently tested positive for IM and the HLA allele *HLA-DRB1*1501*, the risk of developing MS was increased by 7-fold (Kakalacheva and Lunemann, 2011). Also, an increased proportion of MS patients are seropositive for EBV, however, it is important to note that not all patients are seropositive which suggests that EBV infection is not critical for the development of disease (Kakalacheva and Lunemann, 2011; Kakalacheva *et al.*, 2011). Nevertheless, taken together these studies support the concept that EBV infection may at least increase the risk of MS development in genetically susceptible individuals. The mechanisms by which EBV infection trigger the autoreactive immune response are unclear, but some data suggest that CD4⁺ T cells in MS patients are specific for an increased range of EBV nuclear antigens, which frequently recognize myelin peptides (Lang *et al.*, 2002; Olson *et al.*, 2001). Further investigations into the role of infection in the development of disease are needed to show definitively the role of virus infection in the pathogenesis of MS.

ii. Non-infectious factors

Smoking and Vitamin D have been identified as the two primary non-infectious environmental factors that can contribute to MS susceptibility. Although the elevated risk of MS development in individuals who smoke was originally identified in a study in the 1960's (reviewed in (Wingerchuk, 2012)), it has become more prominent in recent years. Smoking is argued to increase the chance of MS development by a factor of 1.5 (Wingerchuk, 2012). In addition, patients that smoke increase the potential for rapid MS development. In a recent Belgium study, patients that smoked were more likely to develop a score of 6 on the Extended Disability Status Scale. This represents an increased potential to develop

intermittent or unilateral constant assistance (cane, crutch or brace) required to walk 100 meters without resting (D'Hooghe M *et al.*, 2012). The amount or timing of cigarette exposure to enhance MS risk remains to be defined, with linkage between smoking and MS remaining a predominately epidemiological observation. Further research is required to better define the role and process of smoking exposure in MS development and progression.

Vitamin D is a potent immunomodulatory molecule that has been shown to affect numbers and activity of regulatory T cells. Several epidemiological studies have identified a significant link between the incidence of MS and distance from the equator (Kurtzke *et al.*, 1979; Miller *et al.*, 1990; Vukusic *et al.*, 2007). Although MS occurred more frequently at high latitudes, this effect was negated in populations that consumed a vitamin D-rich diet (Agranoff and Goldberg, 1974; Swank *et al.*, 1952; Westlund, 1970). These findings are supported by a large study in which high serum levels of the vitamin D metabolite 25(OH)D were shown to correspond with a significantly decreased risk of MS (Munger *et al.*, 2006). In a separate study, low serum levels of 25(OH)D were associated with relapse and the degree of disability in MS patients (Smolders *et al.*, 2008a).

A possible explanation for these findings is the indirect immunomodulatory functions of vitamin D on T cells (Bartels *et al.*, 2010; Smolders *et al.*, 2008b). Also, T cells express vitamin D receptors (VDR), suggesting a direct vitamin D- T cell interaction resulting in T cell regulation (Cantorna, 2011). Indeed, a recent study using the EAE mouse model demonstrated that vitamin D could inhibit auto-reactive T cells, which express high levels of VDR, but did not affect numbers of regulatory T cells, which express low levels of VDR (Mayne *et al.*, 2011). An earlier study also showed that survival of EAE-induced mice could be prolonged with vitamin D injection (Hayes, 2000).

4. Epitope spreading and disease progression

Multiple sclerosis is initiated by the activation of auto-reactive CD4⁺ T cells specific for a single or few myelin epitopes in the CNS (Vanderlugt and Miller, 2002). Inflammation caused by this initial response recruits and activates other CD4⁺ T cell clones specific for a range of other self-epitopes, a process which is referred to as "epitope spreading" (Lehmann *et al.*, 1992). This process occurs, within experimental settings, in a hierarchical fashion, likely the result of differential antigen liberation, processing and presentation by various antigen-presenting cell (APC) populations. In addition the availability of self-reactive CD4⁺ T cell clones throughout the course of disease is also important. Epitope spreading was originally described and characterized in the Experimental Autoimmune Encephalomyelitis (EAE) model of MS, but also occurs in Theiler's murine encephalomyelitis virus induced demyelinating disease (TMEV-IDD) (Lehmann *et al.*, 1992; Miller *et al.*, 2001; Miller *et al.*, 1997b; Vanderlugt *et al.*, 2000). Evidence has also accumulated supporting the existence of epitope spreading within the human context.

1. Epitope spreading in EAE

Experimental autoimmune encephalomyelitis is induced in susceptible murine strains by immunization with myelin peptides in conjunction with adjuvant (Miller *et al.*, 2010). This

disease initiation method, with a single and defined myelin peptide allows for the observation and measurement of changing T cell specificities over time (Vanderlugt and Miller, 2002). Using this model epitope spreading has been described as a hierarchical event, with a defined path through which T cells specific for certain epitopes emerge. Epitope spreading is a critical phenomenon in the SJL model of EAE, as it is responsible for the relapsing remitting pattern of disease (Vanderlugt and Miller, 2002).

The first study to demonstrate epitope spreading was reported in 1992 by Lehmann and colleagues (Lehmann *et al.*, 1992), in which susceptible (SJLxB10.PL) F_1 mice were immunized with guinea-pig MBP. T cell responses in the draining lymph node and spleen were measured 9 days after immunization. At this time point, T cells only responded to MBP_{Ac1-11}, and not MBP₃₅₋₄₇, MBP₈₁₋₁₀₀ or MBP₁₂₁₋₁₄₀. In comparison, T cells isolated from the spleen 40 days after immunization responded to all of these peptides. These findings demonstrate that epitopes that are initially hidden or sequestered during the initial phase of disease can become liberated as disease progresses (Lehmann *et al.*, 1992).

Studies in our laboratory have also characterized epitope spreading in EAE induced by immunization of SJL mice with the immunodominant PLP epitope PLP₁₃₉₋₁₅₁ (Vanderlugt *et al.*, 2000). In this model, T cell responses are initially specific for PLP₁₃₉₋₁₅₁. However, the first relapse, which occurs within 30-40 days after immunization, coincides with T cell responses against PLP₁₇₈₋₁₉₁. During the second relapse, which occurs between 50-70 days after immunization, T cells are also shown to respond to MBP₈₄₋₁₀₄. Understanding of the epitope spreading hierarchy has allowed for epitope specific therapeutic targeting in EAE. The induction of tolerance against relapse-associated peptides blocks the progression of disease, even though PLP₁₃₉₋₁₅₁ responses remain intact (Vanderlugt *et al.*, 2000). These observations highlight the role of changing T cell specificities in mediating chronic disease as well as the need for therapeutic strategies that address these specific T cells populations (Vanderlugt and Miller, 2002).

2. Epitope spreading in TMEV-IDD

Theiler's murine encephalomyelitis virus- induced demyelinating disease is induced by intracranial inoculation of SJL/J mice with TMEV, resulting in low-level chronic CNS infection that progresses into myelin-specific autoimmune disease (Getts *et al.*, 2010). The initial CD4⁺ T cell-mediated immune response against chronic TMEV infection of the CNS causes significant damage to myelin, which in turn results in the activation of myelin-specific T cell clones (Karpus *et al.*, 1995; Miller *et al.*, 1997a). Similar to EAE, this occurs in a hierarchical order, beginning with the immunodominant PLP₁₃₉₋₁₅₁ epitope (Miller *et al.*, 1997b). Subsequent T cell reactivity against other peptides, including PLP₁₇₈₋₁₉₁, PLP₅₆₋₇₀ and MOG₉₂₋₁₀₆ has been demonstrated as disease progresses (Miller *et al.*, 2001).

These findings correspond with antigen presentation by CNS APC. These cells present viral peptides but not myelin peptides up to day 40 post-immunization, at which time point there are still no clinical signs of disease and no evidence of myelin destruction (Katz-Levy *et al.*, 1999; Katz-Levy *et al.*, 2000). However, by day 90 post-infection, microglia and macrophages

isolated from the CNS present both viral and myelin antigens to T cells *in vitro* (Katz-Levy *et al.*, 1999; Katz-Levy *et al.*, 2000).

In further support of epitope spreading after TMEV inoculation, tolerance induction to multiple myelin epitopes using MP-4 during ongoing TMEV-IDD in SJL mice was shown to significantly attenuate disease progression, reduce demyelination and decrease CNS leukocyte infiltration (Neville *et al.*, 2002).

3. Epitope spreading in MS

Evidence of epitope spreading in human MS patients is growing, with a number of small studies at least supporting a potential for epitope spreading in human disease. A study by Tuohy and colleagues conducted over several years followed peripheral T cell responses to myelin epitopes in three patients with isolated monosymptomatic demyelinating syndrome (IMDS) (Tuohy *et al.*, 1997; Tuohy *et al.*, 1999a; Tuohy *et al.*, 1999b). T cell autoreactivity to several myelin epitopes was initially shown to be strong, waning with time. However, when two of these three patients progressed to clinically-defined MS, peripheral T cells isolated from these patients showed expanded reactivity to different myelin peptides than originally observed during the patients IMDS stage (Tuohy *et al.*, 1997; Tuohy *et al.*, 1999a; Tuohy *et al.*, 1999b). A separate study by Goebels and colleagues investigated MBP-specific responses of five MS patients over 6-7 years (Goebels *et al.*, 2000). Two of these patients showed a focused T cell response that broadened over the course of 6 years, thus providing evidence of epitope spreading in human disease. The pattern was non-consistent, however, with two patients showing a broad epitope response that fluctuated over time, with the other patient exhibiting a very focused response to a cluster of MBP epitopes. Together the data suggest that unlike the EAE model, patient T cell epitopes exhibit strong heterogeneity with the precise epitope spreading hierarchy likely to be variable between patients. Notwithstanding, the liberation of antigens and activation of novel T cell clones over time in MS patients supports the role of epitope spreading in human MS patients (Goebels *et al.*, 2000).

5. Current clinical strategies in Multiple Sclerosis to modify the course of disease

The pathologic role of T cells in driving MS has resulted in numerous therapies aimed at inactivating T cells and/or the induction of T cell tolerance. Tolerance induction in autoimmune disease refers to a reinstatement of sustained, specific non-responsiveness of the native immune system to self-antigen. Manipulation of T cell activation and differentiation pathways has been at the center of current tolerance induction theory, and the basis of tolerance induction utilizing current immunosuppressive agents. Over recent years, experimental models have shown that it is possible to exploit the mechanisms that normally maintain immune homeostasis and tolerance to self-antigens, as well as to reintroduce tolerance to self-antigen in an autoimmune setting (Getts *et al.*, 2011; Kohm *et al.*, 2005; Podojil *et al.*, 2008; Turley and Miller, 2007). However, in the clinical setting the utilization of co-stimulatory blockade, soluble peptide, altered peptide ligands among others have yielded disappointing results. As such while the induction of tolerance remains

the optimal future treatment for MS current therapies are focused on agents that are disease modifying.

Over the last three decades a number of broad acting immune modifying therapeutic options have been developed and introduced to treat MS patients. None of these therapeutic options is a cure, currently available therapies aim instead to prevent or at least reduce the frequency of relapsing inflammatory events, with the idea of reducing impact of disease on overall quality of life over time (Miller and Rhoades, 2012; Rio *et al.*, 2011). In addition to the clear efficacy requirement long-term safety is also paramount for any MS therapy, with typical MS patients requiring treatment for many decades. The available MS therapies may be divided based on function into “immune modulatory” or “disease modifying” drugs (DMFs) as well as classic immune suppressive substances. In addition, a third group has recently emerged, which includes monoclonal antibodies (biologics). These drugs act by direct interference with specific immune system functions or by broad immune subset depletion. DMFs are typically used early in the course of the disease, whereas immune suppressive drugs and biologics are mostly viewed as treatment options in those patients with abnormally high disease activity, a high risk of sustained disability and/or show poor response to the front line therapeutics (Table 1).

The most widely used disease modifying drugs are Interferon- β (IFN β) and glatiramer acetate (GLAT) (Johnson, 2012). Both drugs were approved after large phase III studies, which were conducted in the 1990s. These studies proved the efficacy of these drugs in relapsing remitting MS. IFN- β and GLAT reduce the relapse rate in relapsing remitting MS patients by up to 50% (Boster *et al.*, 2011; Johnson, 2012; Limmroth *et al.*, 2011). Furthermore, both agents significantly slowed the progression of disease and have an excellent safety profile allowing for long-term utilization. However, there remain a number of administration and efficacy issues with these drugs. Administration is required weekly at a minimum via subcutaneous or intramuscular injection, resulting in significant discomfort to patients. In addition, while IFN- β and GLAT have relatively comparable efficacy, there is some patient to patient variability. For example a patient that is not responsive to IFN- β may be responsive to GLAT and vice versa. Unfortunately no marker exists that may predict those populations that should be prescribed IFN- β over GLAT or GLAT over IFN- β . Currently trial and error serve as the best strategy for physicians to use when determining the optimal treatment regimen.

The exact mechanism(s) through which GLAT or IFN- β modify disease progression in MS patients are not completely defined, with multiple mechanisms likely to be involved. There is evidence suggesting IFN- β can inhibit T-cell co-stimulation and activation (Chen *et al.*, 2012). In an experimental setting, IFN- β inhibits immune-cell migration by increasing soluble Intercellular Adhesion Molecule 1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1), as well as by decreasing very late antigen-4 (VLA-4) on the cell surface of T cells. It has also been shown that IFN- β can stabilize the blood brain barrier by reducing matrix metalloproteinase-9, an important tissue degradation enzyme.

GLAT is a randomized mixture of synthetic polypeptides consisting of the amino acids l-alanine, l-lysine, l-glutamic acid and l-tyrosine. GLAT was originally designed to induce CNS

inflammation in animals by stimulating the myelin auto-antigen MBP, however, subsequent studies showed that the product appeared to be a protective immunomodulator. The ability for this drug to prevent relapses and disease progression is supported by large clinical studies. Mechanistically, GLAT may compete with myelin peptides for access to peptide binding cleft in MHC complex (Racke and Lovett-Racke, 2011). In addition to MHC binding, GLAT may stimulate a TH2 environment through its ability to modulate APC such as dendritic cells and monocytes (Miller *et al.*, 1998). Evidence for the ability of GLAT to induce a TH2 biased immune response includes the finding that GLAT promotes the expression of anti-inflammatory cytokines such as IL-10 and TGF- β in the CNS of MS patients (Neuhaus *et al.*, 2001). More recent studies revealed that GLAT elevates the levels of T-regulatory (Tregs) cells and reduces the levels of potentially harmful Th-17 cells (Lalive *et al.*, 2011).

It is difficult to establish the long-term efficacy of drugs in MS because the disease can be highly variable and unpredictable. Still, the available long-term observational data point toward a significant prevention and delay of disability in most MS patients treated with either GLAT or IFN- β over a long time. Furthermore, there is sparse evidence that the early treatment reduces the long-term mortality of MS patients (Goodin *et al.*, 2012).

More recently, new disease-modifying drugs have become or are expected to soon be available (Buck and Hemmer, 2011; Fox and Rhoades, 2012) (Table 1). These drugs include more convenient agents that can be applied orally and may have enhanced efficacy in regards to reducing patient disease activity relative to GLAT or IFN- β (Killestein *et al.*, 2011) (Hartung and Aktas, 2011). However, the long-term safety profiles of these substances remains questionable, with more time needed to adequately address the safety profile of these agents.

If front line disease modifying therapies fail to provide sufficient relief, therapeutic escalation to include more effective therapies has to be considered (Repovic and Lublin, 2011). The most effective currently available therapy for escalation is the monoclonal antibody Natalizumab (Tysabri®). Natalizumab acts via the blockade of the VLA-4 receptor, which plays a significant role in leukocyte migration into the brain parenchyma (Rudick and Sandrock, 2004). Clinical studies with Natalizumab have shown this drug to have high efficacy in terms of its ability to prevent disease relapses and progression (Chaudhuri and Behan, 2003; O'Connor *et al.*, 2004). However, this efficacy comes at the cost of some significant safety issues. For example severe JC-Virus mediated encephalitis called “progressive multifocal leukoencephalopathy” (PML) has been recorded in numerous patients receiving Natalizumab. This severe complication occurs in approximately 1:1000 patients. PML is severe, not only because it can potentiate MS symptoms, but because it can cause death (Berger and Koralnik, 2005; Langer-Gould *et al.*, 2005; Ransohoff, 2005). As a result of this treatment related risk, Natalizumab utilization is usually reserved for patients with highly active MS, who do not respond sufficiently to standard disease modifying therapies and subsequently likely to suffer rapid disease progression (Kappos *et al.*, 2011a; Keegan, 2011). Finally, Natalizumab must be given chronically for it to maximize its clinical effect. Patients that stop taking Natalizumab usually relapse, with patients developing symptoms similar to those experienced before Natalizumab therapy was initiated

Substance	Indication	Side-Effects	Comments
Interferon-β	Scheme 1. RR-MS, CIS	Scheme 2. Flu-like symptoms	Scheme 3. good safety profile, inconvenient administr., moderate efficacy (Sanford and Lyseng-Williamson, 2011)
Scheme 4. Glatirameracetate	Scheme 5. RR-MS, CIS	Scheme 6. Local irritation,	Scheme 7. good safety profile, inconvenient administr., moderate efficacy (Lalive <i>et al.</i> , 2011)
Scheme 8. Fingolimod	Scheme 9. RR-MS or escalation in RR-MS ¹	Scheme 10. Lymphopenia, arrhythmia, macular edema	Scheme 11. Increased relapse reduction compared to IFN-β (Singh <i>et al.</i> , 2011) (Jeffery <i>et al.</i> , 2011)
Scheme 12. Natalizumab	Scheme 13. Escalation in RR-MS	Scheme 14. Infections, hepatopathy, allergic response, PML	Scheme 15. Excellent efficacy, severe viral encephalitis as a dangerous side-effect (Keegan, 2011; Pucci <i>et al.</i> , 2011)
Scheme 16. Mitoxantrone	Scheme 17. Escalation in RR-MS, PP-MS, SP-MS, with fast progression	Scheme 18. Leukopenia, infections, cardiomyopathy, leukemia	Scheme 19. Immunosuppressive escalation option. Option in progressive MS courses (Rizvi <i>et al.</i> , 2004; Stuve <i>et al.</i> , 2004)
Scheme 20. Cyclophosphamide	Scheme 21. Escalation in RR-MS, PP-MS, SP-MS, with fast progression	Scheme 22. Leukopenia, infections	Scheme 23. Therapeutic option if other escalation therapies including mitoxantrone fail (Rinaldi <i>et al.</i> , 2009; Weiner <i>et al.</i> , 1984)
Scheme 24. Teriflunomide	Scheme 25. RR-MS? (phase-III trial ongoing)	Scheme 26. lymphopenia, hepatothopathy	Scheme 27. (Warnke <i>et al.</i> , 2009; Wood, 2011)
Scheme 28. BG-12 (fumaric acid)	Scheme 29. RR-MS? (phase-III trial ongoing)	Scheme 30. gastrointestinal complaints	Scheme 31. (Kappos <i>et al.</i> , 2008; Papadopoulou <i>et al.</i> , 2010)
Scheme 32. Laquinimode	Scheme 33. RR-MS? (phase-III trial ongoing)	Scheme 34. Hepatopathy, thrombosis?	Scheme 35. (Thone and Gold, 2011)
Scheme 36. Ocrelizumab	Scheme 37. Escalation therapy? (trials ongoing)	Scheme 38. Severe infections and sepsis possible, allergic response	Scheme 39. (Chaudhuri, 2012; Kappos <i>et al.</i> , 2011b)

Scheme 40. Daclizumab	Scheme 41. RR-MS, escalation? (trials ongoing)	Scheme 42. Cutaneous rash, infections	Scheme 43. Increased relapse reduction compared to IFN- β likely (Stuve and Greenberg, 2010)
Scheme 44. Alemtuzumab	Scheme 45. Escalation therapy? (trials ongoing)	Scheme 46. Induction of autoimmune diseases, infections (Cossburn <i>et al.</i> , 2011)	Scheme 47. Increased relapse reduction compared to IFN- β (Coles <i>et al.</i> , 2012; Klotz <i>et al.</i> , 2012)

RR-MS: relapsing remitting Multiple sclerosis, CIS: clinical isolated syndrome, PP-MS: primary progressive Multiple Sclerosis, SP-MS: secondary progressive Multiple Sclerosis, ¹: Fingolimod is recommended as a first-line treatment in the US but as an escalation therapy in the EU

Table 1.

(O'Connor *et al.*, 2011). The chronic treatment requirement increases patient risk and highlights the ongoing conundrum for all MS therapies, which is how to balance immune modulation efficacy with safety. The emergence of PML with Natalizumab is one striking example, however, more recent cardiac issues have been associated with the recently approved oral DMF, fingolimod (Gilenya), highlighting the point that all therapies focused on immune intervention require diligent safety studies.

The need for safer therapies, combined with animal data showing the ability for short course immune induction therapy (SCIIT) to induce long term disease remission, has supported a new approach to treating MS. SCIIT is a therapeutic strategy employing rapid, specific, short-term modulation of the immune system usually using a biologic therapeutic to induce long term T cell non-responsiveness. Alemtuzumab clinical studies are leading the way in employing this therapeutic concept. In this example, a one week dosing regimen with Alemtuzumab has been in phase 2 and 3 studies shown to have a long term dramatic impact on disease, reducing disease relapses for over a year (Coles *et al.*, 2008; Hauser, 2008; Moreau *et al.*, 1996). The ability for long lasting relapse prevention even after the treatment is discontinued is the primary objective of SCIIT. Unfortunately, from an immunological perspective, tolerance is the result of a number of T cell reprogramming pathways, not induced by Alemtuzumab. Alemtuzumab functions through long term whole scale immune cell depletion. While this drug may have great efficacy it comes with added consequences including the potential for JC-virus infection, cancer and up to 20% of patients may develop other autoimmune diseases (notably Thyroiditis). As such newer therapies are required that focus on immune reprogramming and less on immune depletion. Some potential candidates in development may include Daclizumab (Wynn *et al.*, 2010), Ocrelizumab (Chaudhuri, 2012; Kappos *et al.*, 2011b) or the anti-alpha beta T cell receptor antibody, TOL101 (Table 1).

In situations where all other avenues have been exhausted and disease continues to progress at an unusually rapid rate, physicians may prescribe the chemotherapy drugs mitoxantrone or cyclophosphamide (Neuhaus *et al.*, 2006; Perini *et al.*, 2006; Rinaldi *et al.*, 2009; Stuve *et al.*, 2004; Theys *et al.*, 1981). These drugs are often considered as final options due to their potent immunosuppressive and other serious effects. These drugs can suppress both cell-mediated and humoral immunity and often result in lymphopenia, increasing malignancy and

infection risk. Results from smaller clinical studies suggest, that treating with these immunosuppressive drugs at the very beginning of the disease and in addition to immune modulating drugs might have a beneficial impact on the course of the disease. However, the harmful side effects associated with these drugs means their use is usually restricted to patients that have failed other treatment options, such as Natalizumab.

6. Summary

Multiple Sclerosis (MS) is a chronic, progressive, immune mediated central nervous system disorder that affects both adults and children. The precise triggers of autoreactive T cell development remain to be fully understood, however, it appears that a host of genetic and environmental factors contribute to disease development. Disease initiation may be the result of a single myelin specific T cell clone being activated, however, animal models and preliminary human data suggest that epitope spreading which results in the activation of numerous myelin specific T cells is important for disease progression. Therapies capable of inducing T cell tolerance, thereby rendering these myelin specific T cells inactive remain to be developed for human use. Instead a number of disease modifying agents are available, with GLAT and IFN- β being the primary front line MS treatments. In those patients refractory to these therapies or who show a rapid disease progression, escalation to more broad acting therapies, such as Natalizumab may be considered. Unfortunately, while escalating therapies may have enhanced efficacy this comes with increases in safety concerns. In progressive MS patients whereby all other therapies have failed or no longer show efficacy more toxic chemotherapeutic agents are usually the last resort.

Currently within the field of MS treatment, reduction of relapse rates by around 50% is considered to be a success. As such even patients who are considered treatment successes suffer relapses. During these relapses CNS damage and epitope spreading continue to occur with further neurological impairment the result. Future therapies need to have a higher objective and bring the relapse rate down by 75-100%. This goal may not be out of reach with short course Alemtuzumab therapy shown to induce disease remission for an extended period of time. While the safety profile of this drug remains highly questionable, the observed efficacy certainly generates promise that safer more efficacious therapeutic options for MS treatment may soon be available.

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