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Multiple Sclerosis

Dimitrios Karussis, Hebrew University, Jerusalem, Israel; and Hadassah Medical Center, Jerusalem, Israel

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Epidemiology

The overall prevalence of the disease varies in different regions of the globe, ranging from 15/100 000 to 250/100 000 (Kingwell et al., 2013; Rosati, 2001). According to WHO, it is estimated that more than 2 million people worldwide suffer from multiple sclerosis (MS) and the disease is one of the most common causes of neurological disability in young adults. Some have suggested that this variability follows a certain pattern greatly depended on the latitude of each country (Figure 1). However, epidemiological data depict that the disease varies greatly between areas of similar latitude (Ebers and Sadovnick, 1993). Nevertheless, MS prevalence is higher in Northern than in Southern Europe, as it is in the Americas (Table 1). This is most likely due to differences in the ethnicity of the populations: MS is much more frequent in people of Scandinavian (either direct or indirect) descent including Americans in the northern states. On the other hand, the prevalence is high in 'southern' countries, such as Croatia, Israel, Kuwait, and South Africa. There is a great difference in MS prevalence between geographically close areas, such as Malta and Sicilia or Sardinia. The disease is extremely rare in Hindus living in Mumbai, but not uncommon in Parsis living in the same city. Almost no cases of MS have been reported in North or South American Indians, in Samis (Lapps), Eskimos, Australian Aborigines, Maoris, Melanesians, Micronesians, or Polynesians. MS is also extremely rare in black Africans. Israel is a good paradigm to evaluate the variable incidence of MS in subpopulations at the same geographical region and under similar environmental conditions, since there are distinct and well-distinguished ethnic groups living in the country and new immigrants arriving from countries in which the prevalence of MS is variable. The prevalence of MS is three times higher in the Jewish than in the Arab

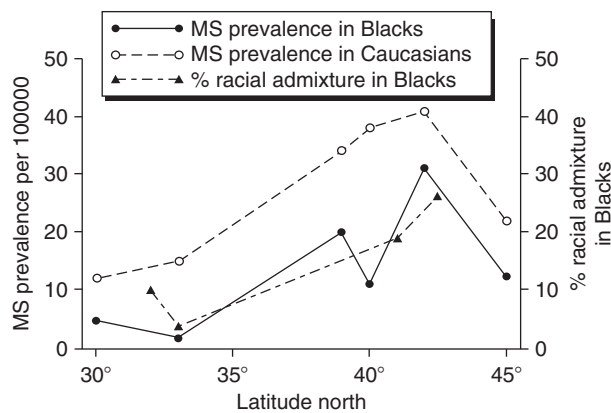


Figure 1 Prevalence of multiple sclerosis (MS) in African-Americans. The percentage of racial admixture based on blood group studies parallels the increase in latitude. Reprinted with permission from Poser, C., 1998. An Atlas of Multiple Sclerosis. Parthenon Publishing Group, London. Fig. 11, p. 52.

population. The disease is also three times more frequent in Askenazy Jews as compared to those of Sefaradic origin (Alter et al., 2006).

Arab populations in the region have MS at low to medium rates and the prevalence rates in Christian Arabs are thrice as high as for Muslim Arabs, suggesting that different risk factors operate in these two subethnic groups (Alter et al., 2006; Milo and Kahana, 2010; Siegel et al., 2012; Kami et al., 2003).

Etiopathogenesis

MS has been described as a disease of unknown etiology, implying the involvement of several factors and not a single cause. These include a genetic background, infectious agents, and hormonal and environmental factors. All these, in a complex interplay, give rise to an immune-mediated attack of the myelin sheath.

Table 1 Prevalence and incidence of MS around the world

Country	Latitude	Prevalence (per 100 000)	Incidence (per 100 000 year ⁻¹)
Europe			
Austria	46.27–49.00° N	98	
Baltic Republics, Belarus, Ukraine	44.20–59.33° N	25–55	
Belgium	49.30–51.30° N	74	
Bulgaria	41.15–44.10° N	45	
Croatia	42.24–46.31° N	28–122	5.9
Cyprus	34.34–35.41° N	39	
Czech Republic	48.33–51.00° N	89	
Denmark	54.34–57.44° N	112	4.6
England, Wales	49.57–55.48° N	74–140	4.7
Finland	59.47–70.03° N	54–110	1.8–5.2
France	42.27–51.00° N	25–58	
Germany	47.15–54.42° N	54–150	1.9–4.6
Greece	35.00–41.41° N	10–39	1.8
Hungary	45.45–48.33° N	32–79	0.8–7
		(Gypsies: 5–98)	
Iceland	63.22–66.30° N	120	4.1
Ireland	51.25–55.23° N	190	
Italy	36.38–47.03° N	33–81	1.1–4.2
Sardinia	38.51–41.18° N	157	6.6
Macedonia	40.51–42.22° N	16	
Malta	35.48–36.04° N	4	
The Netherlands	50.45–53.33° N	76	5.9
Norway	57.58–71.10° N	21–132	3.2–8.7
Orkney Islands	58.40–59.23° N	287	
Poland	49.00–54.50° N	43–62	
Portugal	36.57–42.08° N	47	

(Continued)

Table 1 Prevalence and incidence of MS around the world—cont'd

Country	Latitude	Prevalence (per 100 000)	Incidence (per 100 000 year ⁻¹)
Romania	43.37–48.13° N	26	
Russia–European	41.14–76.59° N	24–55	
Scotland	54.37–58.40° N	145–200	7.2
Serbia	42.14–46.10° N	42	
Slovenia	45.25–46.51° N	83	2.9
Spain	36.00–43.47° N	32–75	2.1–4.6
Sweden	55.20–69.03° N	96–154	4.2–4.8
Switzerland	45.49–47.48° N	110	
North America			
Canada	41.43–83.04° N	55–248	
USA	24.31–49.00° N	22–177	2.7–7.5
Central and South America			
Mexico	14.32–32.42° N	5	
Venezuela	00.39–12.11° N	2	
Brazil	33.45° S–05.15° N	4	
Peru	18.20–00.02° S	4	
Uruguay	34.58–30.05° S	30	
Argentina	55.03–21.47° S	18	
Asia			
China	18.10–53.33° N	1	
India	08.04–35.58° N	1–26	
Japan	24.02–45.31° N	2–9	
Malaysia	00.51–07.20° N	2	
Siberia	49.06–81.15° N	12–41	
Southern former Soviet Union	35.08–55.25° N	1–19	
Taiwan	21.53–25.17° N	2	
Middle East			
Iran	25.03–39.46° N	44	3.6
Israel	29.29–33.19° N	Jews: 19–68 Arabs: 14	1.3–3.1 0.7
Jordan	21.53–29.11° N	7	
Kuwait	28.31–30.05° N	6–31	2.6
Saudi Arabia	16.22–32.08° N	8	
Africa			
Libya	19.31–33.09° N	6–9	
Morocco	27.40–35.55° N	17	
South Africa	34.50–22.07° S	3	
Tunisia	30.15–37.20° N	10	
Australasia			
Australia	43.38–09.13° S	11–74	2.4
New Zealand	47.17–37.07° S	24–77	2.7–6.4

Genetics

The striking differences in prevalence in similar environments strongly suggest an important role of genetic factors. There is a familial occurrence rate of about 10–15%. The age-adjusted risk is higher in siblings (3%), children (1–2% risk in each child when one parent suffers from MS and 7% when both of them suffer from MS), than in second- and third-degree relatives. There is only a 25–35% concordance in monozygotic twins. Adopted offspring or other nonbiological relatives have no increased risk (Sadovnick, 1994).

Because of these indications, numerous studies of genetic markers have been carried out (International Multiple Sclerosis Genetics Consortium et al., 2011), but to date only few secure

candidates or regions have been identified and the associations are rather weak (Dyment et al., 1997; Ebers, 1996; Sawcer et al., 1997).

The strongest genetic association in MS patients has been with the class II major histocompatibility complex (MHC), and specifically the alleles of the human leukocyte antigen (HLA) system DR15 and DQ6 (DRB1*1501 and DBQ2*0602) and the gene for tissue necrosis factor encoded within the same linkage group. A specifically different association (with DR4 and its DRB1*O405-DQA1*0301-DQB1*0302 genotype) is seen in Mediterranean populations, primarily Sardinians. The haplotype DRB1*1501, DQA1*0102, DQB1*0602 was found to be associated with MS among both Ashkenazi and non-Ashkenazi patient (Karni et al., 1999; Kwon et al., 1999).

In general it seems that the existing data support the theory that MS is a polygenic disease, similarly to other autoimmune diseases, and that immune system-related genes (especially at the HLA region) largely contribute to the risk to develop the disease.

Infectious Agents

A number of infectious agents have been reported as potential etiological agents (Ascherio and Munger, 2007; Gilden, 2005; Steelman, 2015). They include the varicella zoster (Sotelo et al., 2007, 2008), corona viruses, measles, Epstein–Barr, herpes simplex type 6, and canine distemper viruses; the human T-cell lymphotropic virus (HTLV)-I, an ‘MS-associated agent’; and, most recently, Chlamydia. None of these has been confirmed, but the idea is mainly based on the mechanism of molecular mimicry, that is, the molecular similarities between antigens on the surface of bacteria or viruses and self-myelin proteins, leading therefore to a false response against myelin, in genetically susceptible individuals. The seasonal variations in MS exacerbations and the somehow increased incidence following vaccinations may also support the infectious theory (Sibley and Foley, 1965; Goodkin and Hertsgaard, 1989; Andersen et al., 1993; Kriesel et al., 2004; Kriesel and Sibley, 2005; Kneider et al., 2009; De Keyser et al., 1998; Sibley et al., 1985; Correale et al., 2006; Banwell et al., 2007; Edwards et al., 1998; Pohl et al., 2006; Alotaibi et al., 2004; Buljevac et al., 2005, 2003; Horakova et al., 2013; Kvistad et al., 2014; Lindsey et al., 2009; Ordonez et al., 2004; Burgoon et al., 2009; Leibovitch and Jacobson, 2014; Mulvey et al., 2011; Karussis and Petrou, 2014; Simpson et al., 2014). In the latter case (of bystander activation of the immune system, due to adjuvants that are used in the preparation of vaccines.

Hormones

The putative time of acquisition of MS has been generally accepted as being at puberty in most if not all patients. This was deduced from the study of MS in English immigrants to South Africa, noting that the disease rarely developed in those who had immigrated before the age of 15, compared to the number that would have developed it in England (Dean and Kurtzke, 1971). Similar studies confirmed this

observation. In support of this concept is that the secretion of female sex hormones, which play an important role in enhancing immune responses, significantly increases at puberty (Poser, 2006).

In addition to the fact that first MS signs appear often during puberty or shortly after it, data indicating changes in the activity of MS during the phases of menstrual cycle (Pozzilli et al., 1999) further support a role of the hormonal milieu as an additional risk factor for the disease. The rate of relapses of MS declines during pregnancy, especially in the third trimester, and increases during the first 3 months postpartum before returning to the prepregnancy rate (Korn-Lubetzki et al., 1984; Confavreux et al., 1998; Coyle, 2014; Runmarker and Andersen, 1995).

In support to the previous, treatment with high-dose gynecological hormones (such as in IVF) was shown to be associated with a higher risk for MS onset or for a relapse of the disease (Michel et al., 2012). Other investigators, however, failed to find significant correlation between pregnancy and MS activity (Sadovnick et al., 1994).

Other Environmental Factors

Since genetics alone cannot explain the variability in MS prevalence, it is likely that some environmental factors also influence the acquisition of the disease. Many studies of an enormous variety of possible agents and factors that could influence the acquisition or development of the disease have been carried out in various countries, with controversial results. Usually these factors are related to the clinical onset rather than the acquisition of MS (Ebers, 2008; Ascherio, 2013).

The influence of environmental factors is most apparent in considering the effects of migration on prevalence and incidence rates. Frenchmen living in Africa have a considerably lower prevalence rate than those living in France. The children of West Indian and Asian immigrants to the United Kingdom have the same incidence and prevalence rates as native-born Englishmen, and the Israel-born children of both Ashkenazi and Sephardic Jews also have the same prevalence rates, although their parents' rates are quite different. On the other hand, Jewish immigrants coming from Northern European countries carry a much higher risk for MS but only when they arrive in Israel after the age of 5–13 years, depending on both the length of 'exposure' and the stage/level of maturation of the immune system (Milo and Kahana, 2010; Kahana et al., 1994; Alter et al., 1978).

Most Martinican Blacks who developed MS had spent significant periods of time in metropolitan France before acquiring the disease. The situation in Hawaii illustrates what appears to be a unique, contradictory situation in which the presumably same environment exerts opposite effects on different ethnic groups (Alter et al., 1971). For persons of Japanese extraction living in Hawaii or in California there is an increased risk of MS compared with those living in Japan (6.5 vs 2.1); for Caucasians raised in Hawaii it appears to offer some protection against MS (10.5 vs 34.4). It is difficult to conceive of environmental factors having such a disparate effect unless the genetic makeup of the individual also plays a role in the equation. The existence of a premorbid genetic marker such as the MS 'trait' could provide an explanation.

Epidemiological studies have demonstrated the primary importance of genetic factors modified by an as yet unrecognized environmental one.

Among the environmental factors that may possibly include toxic substances' exposure, air pollution, irradiation, stress, and sunlight exposure (and they may be responsible for the growing incidence of MS and autoimmunity in general in the 'Western' world), vitamin D, seems to play an important role (James et al., 2013; Smolders et al., 2009; Salzer et al., 2012, 2014).

Variation in MS incidence among individuals born at certain seasons of the year may also indicate that sunlight exposure (and possibly vitamin D levels) of the mother may increase or decrease the risk for MS in the newborns. Children born in April or May were found to be of higher risk to develop MS (Sadovnick and Yee, 1994; Willer et al., 2005; Dobson et al., 2013).

Summarizing the pathogenetic model on the basis of the above-described available data, it seems that MS is the result – in a genetically susceptible subject – of the activation of the immune system by different infectious agents, which initiates a pathogenetic cascade that is not fully understood and which eventually leads to the destruction of the myelin and the axons.

The rather low rate of concordance of MS in monozygotic twins has never been fully explained, but it supports the possibility of multiple factors (and not only genetics) involved in disease pathogenesis; genetically susceptible individuals may develop MS only if and when an external trigger (infectious? environmental?) will trigger the onset. Poser (2006) has suggested a status that he defined as MS 'trait' which is different from asymptomatic MS and may never develop into the disease. It results from the action of an antigenic challenge to the immune system of a genetically vulnerable person that does not cause damage to the nervous parenchyma. A subsequent environmental viral-antigenic event in some MS 'trait' 'carriers' can change the trait into the disease. This event could be an infection, which need not be symptomatic, or a vaccination. The MS may become symptomatic, remain asymptomatic, or be manifested only by lesions visible by MRI (RIS). It is likely that the development of the MS 'trait,' defined as 'activation,' occurs early in life, whereas the transition from MS trait to MS (i.e., 'acquisition') takes place at puberty in most patients, when the immune system is made more vulnerable by the outpouring of female sex hormones.

Pathology

The pattern of destruction of myelin is unique to MS as compared to the other demyelinating (e.g., acute disseminated encephalomyelitis, ADEM) or dysmyelinating (e.g., metachromatic or adrenoleukodystrophy), diseases: it consists of plaques that are sharply demarcated from the normal white matter surrounding them (Figure 2). They have been aptly described as 'cut out with a cookie cutter.' In contrast, the inflammatory lesions in ADEM are almost invariably perivascular and often become confluent. Unless the pathognomonic sharp edge of the MS lesion is captured by the biopsy, it is sometimes impossible to clearly differentiate it from ADEM.



Figure 2

Plaques are most commonly seen in the optic nerves and chiasm, the periventricular centrum semiovale, the brain stem, the cerebellar hemispheres, and the cervical spinal cord. Although most plaques are seen in the white matter, they may involve the subcortical U-fibers and extend into the gray matter. The cortex, thalamus, the basal ganglia, and the dentate nuclei may all be affected. Lesions of the sensory nucleus of the trigeminal nerve, the intraparenchymal portion of the facial, and some of the connections of the acoustic nerve are frequently involved, but peripheral nerves are spared. Asymmetry of the lesions is the rule.

Inflammatory cellular infiltrates and edema are almost invariably seen in the walls of small blood vessels and the surrounding parenchyma at the edges of the plaques. Similar changes in the walls of capillaries and venules can also be seen in the so-called 'normally appearing white matter' (NAWM) in MS CNS. One of the earliest changes is separation of the myelin lamellae by vesicular edema, fragmentation of the sheath, invasion by macrophages that engulf the myelin debris, and eventual denudation of the axon. Most of the plaques show periaxial demyelination, the axon appearing intact, but older lesions clearly show axonal and neuronal degeneration. Clumps of large abnormal gemistocytic astrocytes may be seen near the lesions; these are occasionally mistaken for astrocytomas.

The MS variants, Marburg's acute MS, Balo's concentric sclerosis, and Schilder's 1912 type diffuse sclerosis, exhibit similar but also distinct pathological features (Poser and Brinar, 2004a,b).

Perivenular inflammatory lesions involving infiltrating mononuclear cells are evident in the earlier phases of the disease (Compston and Coles, 2008; Frohman et al., 2006; Steinman, 2001). This inflammation leads to damage or loss of oligodendrocytes and demyelination with resulting disruption of the conduction of neuronal signals in the affected regions. In the initial stages of MS, compensatory pathways (such as the upregulation of ion-channels in the affected areas) may partially restore conduction and reverse the neurological dysfunction. As the disease progresses, significant axonal loss

and eventually neuronal damage occurs (Trapp et al., 1998) and the lost function becomes permanent and nonreversible (Steinman, 2001; Trapp et al., 1998; Grigoriadis et al., 2004).

Immunopathogenesis

It is widely accepted that the inflammatory process in MS is caused or propagated by an autoimmune cascade (Figure 3a), involving mainly T cells that target myelin self-antigens (Zhang et al., 1994; Allegretta et al., 1990), possibly through mechanisms known as molecular mimicry (cross-reactive antigens expressed by viruses or other microorganisms and myelin components) (Wucherpfennig and Strominger, 1995). The 'autoimmune hypothesis' is also supported by the finding of increased incidence of other autoimmune diseases in patients with MS and their first-degree relatives (Barcellos et al., 2006; Ramagopalan et al., 2007).

An alternative hypothesis is that myelin-specific T cells that are present 'naturally' may expand to critical pathogenic quantities (Venken et al., 2010) due to malfunctioning immunoregulatory mechanisms (such as those involving the Th2, Th3, and CD8 T cells and the regulatory T cells: Tr1 and Treg).

Although the autoimmune hypothesis is attractive and supported by concrete data (including the efficacy of immunomodulatory treatments in MS), the initial insult which initiates the whole immune-mediated cascade is still obscure. Environmental, genetic, and infectious factors seem to play an important role in MS pathogenesis, but it seems that the role of any putative infectious agent is to trigger/drive the autoimmune process (Venken et al., 2010), rather than to serve as the primary target of infiltrating cells. In any case, T cells of the Th1 and Th17 phenotype specific for myelin antigenic epitopes seem to represent the common final pathogenetic effector pathway, regardless of the initial insult of the disease (Tesmer et al., 2008; Korn et al., 2009; Kebir et al., 2007). Following the initial damage of myelin, the blood-brain barrier opens and myelin-related antigens are released in the peripheral blood causing further activation of the anti-

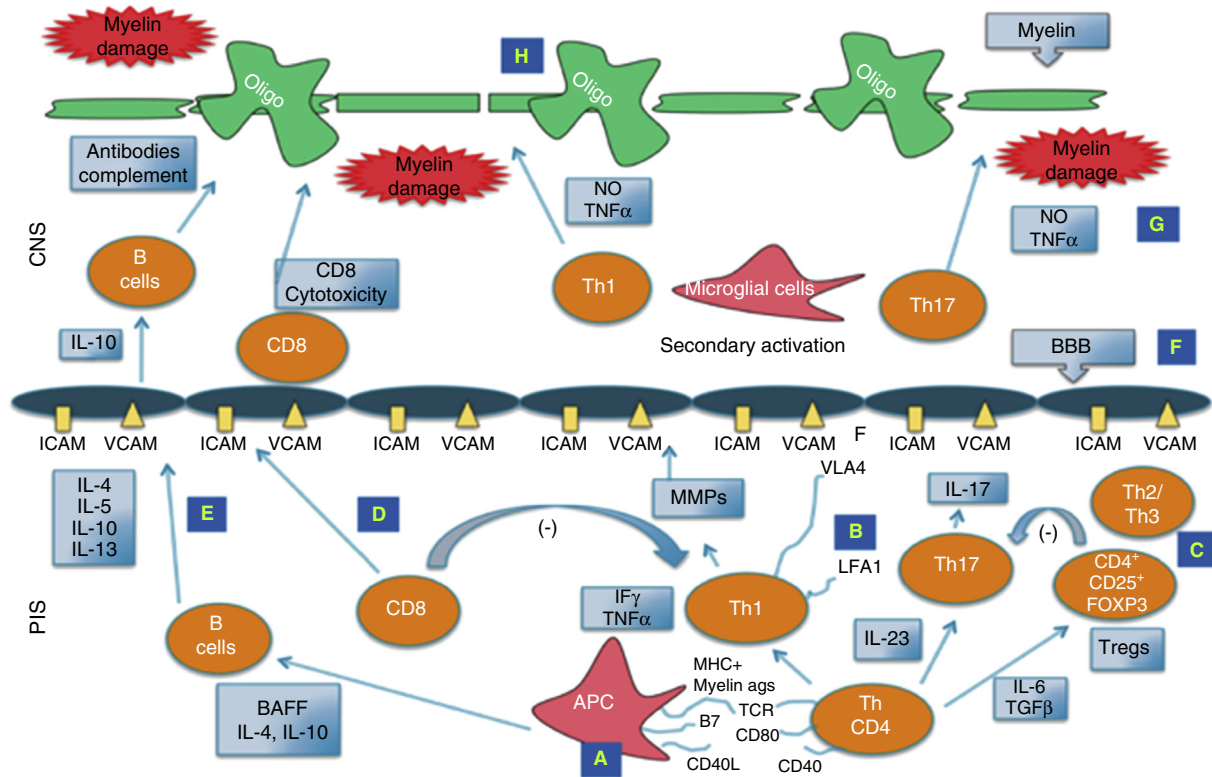


Figure 3a Multiple sclerosis (MS) immunopathogenesis.

myelin autoreactivity and production of new anti-myelin lymphocytes with a profile of T-cell receptor recognition that probably changes during the course of the disease (epitope spreading) (Vanderlugt and Miller, 1996, 2002; Quintana et al., 2014).

However, MS is not a homogenous disease and it is now increasingly recognized that it has several distinct immunopathological profiles, including prominent humoral immune mechanisms in some MS patients (Lucchinetti et al., 2000).

The initial stages of the autoimmune cascade in MS are probably initiated in the peripheral immune system. Following activation by the macrophages and dendritic cells (antigen-presenting cells: APC), Th1 and Th17 lymphocytes, which express the antigens specific for myelin, T-cell receptors (TCR), proliferate and begin to express on their membranes, adhesion molecules, and chemokine receptors that enhance their ability to extravasate to the site of inflammation in the CNS (Sharief et al., 1993a,b; Tsukada et al., 1993a,b,c; Washington et al., 1994) (and to produce interleukin (IL)-2, IL-17, tumor necrosis factor- α (TNF α) and interferon- γ (IFN γ) (pro-inflammatory cytokines)). This migration possibly follows 'damage signals' from the CNS tissue or is due to an opening/destruction of the blood-brain barrier. Adhesion molecules such as VLA4 are crucially important for this process and their blockage may prevent the extravasation of the lymphocytes through the blood vessels' endothelium (Yednock et al., 1992; Polman et al., 2006). Interestingly, the best existing evidence that MS is indeed an autoimmune disease and that the whole process is initiated in the periphery comes from the reported evidence of high efficacy in MS (and

the 'rebound' of MS activity following their discontinuation) of medications that specifically block the migration of the lymphocytes into the CNS (such as natalizumab which targets the CD40L molecule) (Polman et al., 2006).

The innate immunity has also shown to play an important role in MS pathogenesis and the inflammatory immune cascade (Gandhi et al., 2010) and especially the dendritic cells, as well as the NK cells, mast cells, $\gamma\delta$ T cells, and microglial cells (Mayo et al., 2012). Specifically the role of NK cells has been controversial.

The involvement of NK cells in the pathophysiology of autoimmune diseases has been studied for many years (Matsumoto et al., 1998; Zhang et al., 1997), but their actual role of NK cells in CNS autoimmunity is still not clear (Morandi et al., 2008). *In vitro* NK cells show cytotoxic activity toward oligodendrocytes and other glial cells, such as astrocytes and microglial cells during inflammation.

NK cells may also play a role in CNS protection and repair, as these cells have the ability to produce neurotrophic factors (Hammarberg et al., 2000). Several studies described a beneficial role of NK cells in mouse or rat EAE (Matsumoto et al., 1998; Zhang et al., 1997; Galazka et al., 2007; Huang et al., 2006; Xu et al., 2005).

In humans, a decreased cytotoxic activity of circulating NK cells has been described during clinical relapses of MS (Kastrukoff et al., 1998, 2003), whereas an increase of the 'NK2' NK cell subpopulation was observed during the remission phase (Takahashi et al., 2001).

Upregulation of the CD56^{bright} NK cell subset by immunomodulatory therapies, such as daclizumab (Bielekova et al.,

2006), IFN β (Saraste et al., 2007), and cyclophosphamide may contribute to the beneficial clinical effects of these medications (Bielekova et al., 2006).

B cells have traditionally been considered to play a secondary, producing antibodies that may promote tissue destruction by recruiting macrophages and through activation of the complement pathway (Hawker, 2008). Additionally, activated B cells can act as antigen-specific APCs for T cells and produce costimulatory molecules that influence the differentiation of T cells into Th1 or Th2 cells (Zouali, 2008). Patients with MS have increased B-cell numbers in the CNS, mainly memory cells and short-lived plasmablasts (Cepok et al., 2005). Plasmablasts persist in the cerebrospinal fluid (CSF) throughout the course of MS, and the numbers of these cells correlate with intrathecal immunoglobulin G (IgG) synthesis (oligoclonal antibodies, one of the hallmarks of MS diagnosis) and with active inflammatory disease (Cepok et al., 2005; Owens et al., 2006). Moreover, B cells, plasma cells, autoantibodies, and complement have been detected in MS lesions (Prineas and Graham, 1981; Archelos et al., 2000), indicating their implication in demyelination. Additional indications for antibody-mediated mechanisms in MS come from the presence of ectopic lymphoid follicles in the CNS of patients with MS (Cepok et al., 2005; Serafini et al., 2004; Krumbholz et al., 2006; Magliozzi et al., 2007), especially those with progressive disease. It appears, therefore, that as the disease evolves into the progressive stage, the inflammation becomes compartmentalized and predominantly mediated by B cells. Additional findings that may explain progression of MS and its correlation with 'slow' *in situ* inflammation come from reports showing significant meningeal, cortical, and deep gray matter inflammatory lesions predominant in progressive MS or in patients with advanced disability and represent a bad prognostic factor (Serafini et al., 2004; Magliozzi et al., 2007; Ruggieri et al., 2015; Haider et al., 2014; Cappellani et al., 2014; Daams et al., 2013; Calabrese et al., 2011; Ceccarelli et al., 2010; Neema et al., 2009; Geurts et al., 2005; Popescu and Lucchinetti, 2012; Popescu et al., 2013; Lucchinetti et al., 2011; Kutzelnigg and Lassmann, 2006; Romme Christensen et al., 2013).

Further support for the role of B cells in the immunopathology of MS is provided by the data of the efficacy of B-cell- and antibody-directed therapies (i.e., plasmapheresis and anti-CD20 monoclonal antibodies), in subgroups of MS patients (Hemmer and Hartung, 2007; Weinshenker et al., 1999; Kappos et al., 2011; Hauser et al., 2008). The involvement of antibody-mediated pathogenetic mechanisms is particularly pronounced in variants of CNS demyelinating disease, such as neuromyelitic types of MS (neuromyelitis optica (NMO) spectrum of disorders) associated with anti-aquaporin antibodies and long magnetic resonance imaging (MRI) lesions in the cervical spine.

Physiology

Normal motor and sensory function depend upon the rapid propagation of the nerve impulse along myelinated nerve fibers, measured in milliseconds. The myelin sheath is interrupted at regular intervals by the nodes of Ranvier, where the axon

is denuded. Because the axon has a high resistance to the electrical impulse, which makes the speed of conduction too slow, an alternative mechanism takes over. It is called 'saltatory conduction,' in which the electrical impulse jumps from one node of Ranvier to the next while achieving the required conduction velocity. However, if the distance between the available nodes is too great because of destruction of some myelin segments, the impulse cannot bridge the gap, and saltatory conduction is no longer possible. The electrical impulse must then travel via the slow axonal route (Figure 3b). Once the axon itself is destroyed, conduction is obviously no longer possible and the deficit, if any, becomes permanent. In some MS patients, signs or symptoms appear because nerve conduction slows when body temperature is elevated as a result of either ambient heat or fever. The latter is a common cause of pseudo-exacerbations. A body temperature increase of as little as 1 °C may be sufficient to cause such signs and symptoms, which disappear upon cooling. In the past, this was used diagnostically by means of the hot bath test.

Clinical Course

Several clinical types have been recognized: relapsing–remitting, primary, and secondary progressive (RRMS, PPMS, and SPMS, respectively) (Karussis, 2014; Lublin, 2014).

Some investigators believe that these clinical types represent different diseases or genetic variants of MS, but it is much more likely that the differences in evolution indicate the aggressivity of the disease process, the patient's susceptibility, and the accumulation of lesions in eloquent areas of the CNS. Many MS lesions remain silent, and a number of routine autopsy series have shown that asymptomatic MS may be as common as the diagnosed condition, with a putative prevalence of 100/100 000.

It is frequently perceived that PPMS is less 'inflammatory' and progresses slower (Miller and Leary, 2007). However, epidemiological data show that when RR disease turns to progressive disease (i.e., SPMS), which usually takes a median of two decades from onset (Tremlett et al., 2008), the rate of progression does not differ substantially from that of PPMS (Koch et al., 2009, 2015; Harding et al., 2015; Confavreux and Vukusic, 2006).

It is more acceptable nowadays that there is no clear demarcation between relapsing and progressive disease and there are also mixed courses of relapsing–progressive MS (RPMS). It will be more accurate to define progressive disease as either active/'inflammatory' (i.e., with evidence of relapses or changes in the MRI) or nonactive/'degenerative' (Lublin, 2014).

In general, negative prognostic factors for MS predicting progression to higher levels of disability, include: the early transformation to SPMS, a higher relapse rate and disability in the first 5 years, a shorter interval between the first and the second relapse, and the early involvement of more neurological systems (Degenhardt et al., 2009; Vukusic and Confavreux, 2007).

Signs and Symptoms

The symptoms of MS at onset in six series, in three of which the diagnosis was confirmed at autopsy. The disease is almost twice

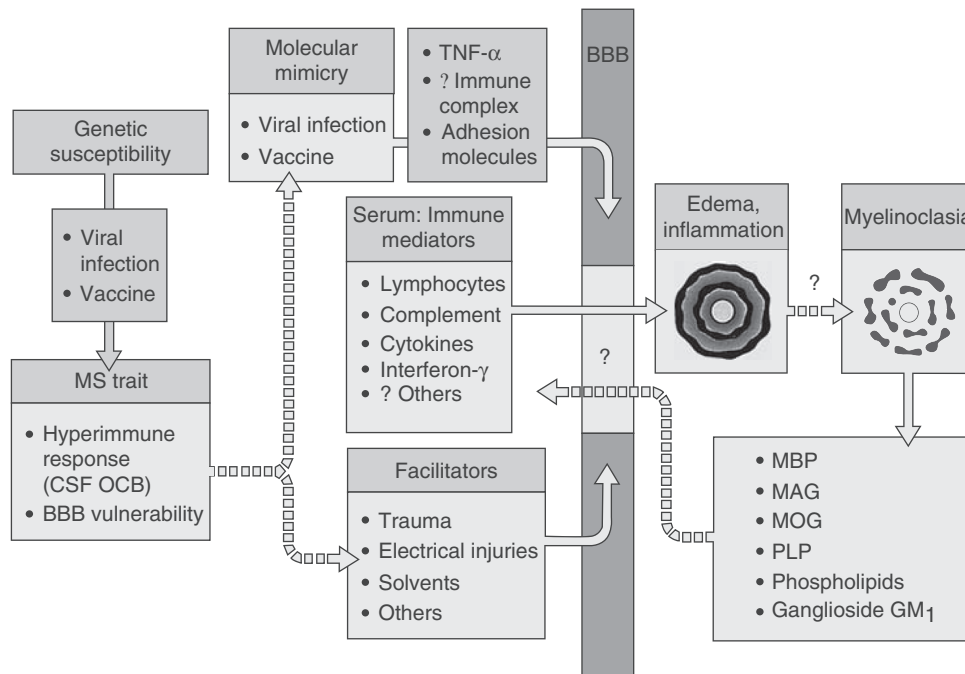


Figure 3b The pathogenesis of multiple sclerosis (MS). BBB, blood–brain barrier; TNF, tumor necrosis factor; OCB, oligoclonal bands; MBP, myelin basic protein; MAG, myelin-associated glycoprotein; MOG, myelin-oligodendroglia protein; PLP, proteolipid protein. Reprinted with permission from Poser, C., 1998. *An Atlas of Multiple Sclerosis*. Parthenon Publishing Group, London. Fig. 14, p. 53.

as common in women as in men, and the clinical onset is most frequent in the third and fourth decades. Certain neurological complaints in a person under the age of 40 are tantamount to making the diagnosis of MS: a Lhermitte symptom (tingling going down the back when flexing the neck), trigeminal neuralgia, hemifacial spasms, unilateral intention tremor, or binocular diplopia. Similarly, certain abnormalities of the neurological examination of a young person are also common enough in MS to be of diagnostic value: temporal pallor of the optic disk, unilateral hyperreflexia and a Babinski sign, a significant decrease in position and/or vibratory sensation at the ankles, or some dysmetria on finger-to-nose testing and internuclear ophthalmoplegia. MS patients may also experience rarer symptoms such as headaches, positional vertigo, seizures, back and neck pain, and significant cognitive decline. The latter was thought to be very rare since the disease does not affect the gray matter. However, it is now well documented that there is significant involvement of the gray matter in MS, and cognitive impairment is frequent even at the early stages of the disease (DeLuca et al., 2015; Langdon, 2011; Chiaravalloti and DeLuca, 2008; Cardoso et al., 2015) but often overseen/underdiagnosed. Patients with the so-called ‘benign’ MS (representing less than 10% of the patients, and defined by the absence of relapses or progression of disability for more than 10 years) actually do have significant silent activity and cognitive impairment (usually affecting concentration and memory in up to 50%) (Gajofatto et al., 2015; Correale et al., 2012; Amato et al., 2006; Sayao et al., 2011; Rovaris et al., 2008) and structural brain damage, similar to the nonbenign MS.

The diverse and variable clinical expressions and signs of MS are quantified by using scales of disability, the most universally

accepted over years, being the expanded disability status scale (EDSS) initially proposed by Kurtzke (1983) and revised over the years. EDSS steps 1.0–4.5 refer to people with MS who are able to walk without any aid and are based on measures of impairment in eight functional systems (FS). EDSS steps 5.0–9.5 are defined by the impairment to walking. The scale is criticized for its reliance on walking as the main measure of disability and the lack of linearity.

The Multiple Sclerosis Functional Composite (MSFC) is a newer measurement system. It is sensitive to changes other than mobility, and it is based mainly on three parameters: walking speed, using a timed 25-foot walk, arm and hand dexterity, using a nine-hole peg test and cognitive function, and using the Paced Auditory Serial Additions Test (PASAT) (Rudick et al., 2002). A wide range of other measures is used to assess MS disability. In many cases, these are simple questionnaires, such as the MS Quality of Life and the fatigue scale questionnaires.

True exacerbations/relapses appear spontaneously or may follow some kind of viral infection but must be differentiated from pseudo-exacerbations that result from fever, elevated ambient temperature, or some metabolic derangement.

The correlation between the number, site, and size of MS lesions, as revealed by neuroimaging and at autopsy, and clinical manifestations is poor. Many plaques involve the so-called ‘silent’ areas of the brain. Furthermore, the disease process must impair conduction in a critical number of fibers in order to produce neurological dysfunction. The available fibers in the affected tract above this number constitute the safety factor. If the signs and symptoms are due to inflammation and edema only, which is almost always the case at the onset of a bout,

they will be reversible; it is only when the safety factor is breached, that is, when the number of demyelinated or destroyed fibers exceeds the required minimum, that signs and symptoms become permanent.

Clinical Presentations

Several variants of MS (and CNS demyelinating syndromes in general) have been nowadays defined (Karussis, 2014) in an effort to increase the diagnostic accuracy, to identify the unique immunopathogenic profile (Table 2), and to tailor treatment. These include the initial events of demyelination defined as clinically or radiologically isolated syndromes (CIS and RIS, respectively) (Okuda et al., 2009; Miller et al., 2005a,b), ADEM (Brinar and Habek, 2010; Menge et al., 2007) and its variants (acute hemorrhagic leukoencephalitis – AHL, Marburg variant, and Balo’s (Brinar and Habek, 2010) concentric sclerosis) (Zettl et al., 2012; Kuperan et al., 2003; Mader et al., 2004; Susac and Daroff, 2005), Schilder’s sclerosis (Zettl et al., 2012) and transverse myelitis (Poser et al., 1986), neuromyelitis optica (NMO and NMO spectrum of diseases) (Wingerchuk and Weinshenker, 2013), recurrent isolated optic neuritis (Zettl et al., 2012), and tumefactive demyelination (Lucchinetti et al., 2008) (a large, tumor-like demyelinating lesion with surrounding edema) (Table 2). The differentiation between them is not only a terminological matter but has important implications on their management. For instance, patients with type-II MS immunopathogenesis (according to Lucchinetti’s classification (Lucchinetti et al., 2000), where autoantibodies seem to be more involved than T cells, or with the neuromyelitic variants of demyelination (NMO spectrum of diseases, associated with anti-aquaporin antibodies) (Wingerchuk and Weinshenker, 2013; Wingerchuk et al., 2006, 2007; Wingerchuk, 2010; McKay et al., 2006), may not only not respond well but also even deteriorate under some of the first-line treatments for MS (such as IFNs) (Bomprezzi et al., 2011). The unique clinical and neuroradiological features (Table 2), along with the use of immunological biomarkers (such as anti-AQP4 antibodies), help to distinguish these cases from classical MS. The use of such immunological and imaging biomarkers will not only improve the accuracy of diagnosis but also contribute to the identification of the patients with CIS or RIS, who are at greater risk for disability progression (worse prognosis) or, on the contrary, will have a more benign course.

Diagnosis and Diagnostic Criteria of MS

The original diagnostic criteria for MS were based on clinical features suggestive of CNS demyelination. The oldest Schumacher criteria called for two clinical relapses separated in time and space in patients aged 10–50 years and with no better explanation for their signs and symptoms (Schumacker et al., 1965). The subsequent Poser criteria added to the Schumacher definition laboratory/paraclinical parameters for the diagnosis (the presence of oligoclonal bands – OCBs – in the CSF and of abnormal/delayed responses of the visual and auditory-evoked potentials) (Poser et al., 1983; Table 3). The crucial request in both criteria, in order to definitely diagnose MS, was

the need for clinical (or laboratory) evidence of dissemination in time and space (DIT/DIS), that is, the presence of symptoms affecting more than one discrete CNS region and at more than one time point during the course of the disease. Patients were accordingly subclassified as clinically definite (CDMS) or probable and laboratory-supported definite or probable MS (Table 3).

With the advance of neuroradiological techniques (MRI), the need for clinical evidence of DIT and DIS was partially replaced by the radiological evidence of such dissemination. Based on this principle, a committee headed by McDonald defined the new proposed criteria (McDonald et al., 2001), which were later revised (Polman et al., 2011).

In general, the McDonald criteria focus on the integration of clinical, laboratory, and radiographic data to establish a diagnosis of MS. Similar to the Poser criteria, the 2001 McDonald diagnostic criteria require two clinical attacks varying in time and space to establish a definite diagnosis of MS. DIT could be fulfilled by either gadolinium (Gd)-enhancing lesion, or a new T2 lesion detected on repeat MRI scanning performed 3 or more months after the baseline study. DIT required either meeting the Barkhof/Tintore MRI criteria (3 of the 4 criteria: ≥ 1 Gd-enhancing or 9 T2 lesions, ≥ 1 juxtacortical, ≥ 1 infratentorial, and ≥ 3 periventricular lesions) (Barkhof et al., 1997; Tintore et al., 2003) or the presence of two silent T2-weighted brain lesions and OCBs in the CSF. The sensitivity and specificity of the 2001 McDonald criteria for prediction of conversion to MS in 1–3 years were high and could therefore establish the diagnosis of MS after CIS earlier than the Poser criteria, more than doubling the rate of MS diagnosis within the first year of disease (Tintore et al., 2003; Dalton et al., 2002). The revised 2005 criteria better underlined the significance of spinal cord lesions for DIS criteria and allowed new T2-weighted lesions on brain MRI after 30 days (rather than the previous time frame of 3 months) following the baseline MRI to establish DIT (Polman et al., 2005). These updated criteria led to an improvement in sensitivity compared with the 2001 criteria (60% vs 47%), while retaining good specificity (88% vs 91%) (Swanton et al., 2007).

The McDonald criteria were revised in 2010 with the intent of further simplification (Polman et al., 2011), requiring fewer MRI scans to establish the diagnosis of definite MS. To meet the criteria for DIS, a patient must have two clinical attacks in different CNS sites or one clinical attack accompanied by fulfillment of Swanton’s radiographic criteria. Symptomatic MRI lesions in the brain stem or spinal cord are excluded from the lesion count for these MRI criteria. Gd enhancement is not necessary for DIS. According to the 2010 criteria, DIT requires a new T2- or Gd-enhancing lesion on subsequent MRI (regardless of timing from baseline scan) or the presence of both asymptomatic Gd-enhancing lesions and nonenhancing lesions on the baseline MRI (Table 3). Thus, the diagnosis of MS after one clinical attack may now be established even based solely on the baseline MRI (if both enhancing and nonenhancing lesions coexist). CSF findings do not replace the radiographic requirements for DIS according to the McDonald 2010 criteria. These revised criteria are considered to have increased diagnostic sensitivity without compromising specificity.

Table 2 MS and MS variants

<i>Clinical syndrome</i>	<i>Definition</i>	<i>Additional characteristics and diagnostic criteria</i>
RIS	Incidentally detected MRI T2-bright foci suggestive of demyelination in the absence of clinical symptoms (Okuda et al., 2009).	<p><i>RIS criteria</i> (Okuda et al., 2009):</p> <p>Presence of incidentally identified CNS white matter anomalies meeting the following MRI criteria:</p> <ol style="list-style-type: none"> 1. Ovoid, well-circumscribed, and homogeneous foci with or without involvement of corpus callosum 2. T2 hyperintensities measuring >3 mm and fulfilling the Barkhof criteria (at least three of four) for dissemination in space 3. CNS white matter anomalies inconsistent with vascular pattern <ol style="list-style-type: none"> a. No historical accounts of remitting clinical symptoms consistent with neurological dysfunction b. MRI anomalies do not account for clinically apparent impairments in social, occupational, or generalized areas of function c. MRI anomalies not due to direct physiological effects of substances (recreational drug abuse, toxic exposure) or medical condition d. Exclusion of individuals with MRI phenotypes suggestive of leukoaraiosis or extensive white matter pathology lacking involvement of corpus callosum e. The CNS MRI anomalies are not better accounted for by other disease processes
CIS	First clinical CNS demyelinating event lasting ≥ 24 h, and consistent with MS but isolated in time; may or may not be isolated in space (Miller et al., 2005b).	In 85% involves the optic nerves, brain stem, or spinal cord. Multifocal brain lesions are present on MRI in many patients with CIS; some have additional abnormalities on quantitative MRI in otherwise normal appearing white and gray matter that suggest an extensive pathological process (Miller et al., 2005b).
MS	Chronic, multifocal demyelinating disease of the CNS with clinical and/or radiological evidence of dissemination in time and space.	Usually relapsing course (RRMS); in 60–80% of the cases the course becomes progressive with time (SPMS). Primary progressive (prevalence 10%), relapsing-progressive, and benign forms also exist. The median time from diagnosis of RRMS to SPMS is 10 years, and the time from disease onset to requiring a cane to walk is 15–25 years. More than 80% of the patients (40–50% in the first year of the disease) have oligoclonal antibodies in the CSF (which is typically acellular and with normal protein levels). Brain MRI pathological in 95% of the patients. Visual and/or brain stem-evoked potentials pathological in 60–70%.
ADEM	A first ever clinical event with presumed inflammatory or demyelinating cause, with an acute or subacute onset affecting multifocal areas of the CNS. This is usually polysymptomatic and includes encephalopathy, more common in children (Menge et al., 2007; Caldemeyer et al., 1994; Dale et al., 2000; Mikaeloff et al., 2007; Murthy et al., 2002; Tardieu and Mikaeloff, 2004).	<p>Presence of focal/multifocal lesion(s) predominantly affecting the white (but also the gray) matter, without evidence of previous destructive white matter changes, the occurrence of clinical/radiological improvement (although there may be residual deficits), and the absence of other etiology that could explain the event. New or fluctuating symptoms, signs, or MRI findings occurring within 3 months are considered part of the initial acute event.</p> <p>Lack of oligoclonal antibodies and the presence of several lymphocytes in the CSF; early involvement of CNS gray matter areas; lack of significant dissemination in space (in the case of relapsing ADEM; usually only expansion of previously existing lesions occurs); presence of fever, confusion, and headache (Menge et al., 2007).</p>
Tumefactive MS	Presents with at least one large (>2 cm) acute demyelinating lesion, with accompanying edema, mass effect, and ring enhancement. Clinical presentations vary by size and location of the lesion and often include headache, confusion, aphasia, apraxia, and seizures (which are atypical of CIS/MS) (Lucchinetti et al., 2008).	

(Continued)

Table 2 MS and MS variants—cont'd

<i>Clinical syndrome</i>	<i>Definition</i>	<i>Additional characteristics and diagnostic criteria</i>
Marburg type and Balo concentric sclerosis	Considered variants of tumefactive MS, characterized by severe (often lethal), rapidly evolving course, atypical neuropathological changes, and distinct radiographic changes (Zettl et al., 2012; Susac and Daroff, 2005).	<i>Marburg</i> : Numerous large multifocal demyelinating lesions in deep white matter. <i>Balo</i> : Concentric layers of partial demyelination alternating with bands of demyelination. Alternating isointense and hypointense concentric rings on T1-weighted images in MRI, partial enhancement limited to T1-hypointense areas.
Schilder's disease	Myelinoclastic diffuse sclerosis, usually characterized by a single or two symmetrically arranged lesions measuring at least 2 × 3 cm with involvement of the centrum semiovale in setting of symptoms unusual for MS (Zettl et al., 2012; Poser et al., 1986).	Absence of OCBs in CSF.
Acute hemorrhagic leukoencephalitis (AHL), acute hemorrhagic leukoencephalomyelitis (AHEM), and Hurst acute necrotizing hemorrhagic leukoencephalitis (ANHLE) Neuromyelitis optica (NMO)	Rare, severe, rapidly progressive inflammatory and hemorrhagic demyelinating disorders of the CNS, considered variants of ADEM (Kuperan et al., 2003; Mader et al., 2004; Rosman et al., 1997; Wong et al., 2006). Episodes of optic neuritis (often severe and bilateral leading to fixed visual loss) and acute myelitis are the major criteria for diagnosis and a contiguous spinal MRI lesion extending over ≥3 vertebral segments or NMO-IgG seropositive are secondary criteria for diagnosis. According to the modified criteria, brain lesions may also be present in NMO. CSF can show pleocytosis of >50 WBCs. The longitudinally extensive myelopathy usually affects the central part of the cord, and intractable hiccups, nausea, or vomiting may be reported as a result of a periaqueductal medullary lesion (Wingerchuk and Weinschenker, 2013; Wingerchuk et al., 2006; McKeon et al., 2009).	White matter lesions on MRI tending to be large and diffuse, with edema and mass effect, as well as restricted diffusion in affected areas of the brain. CSF typically demonstrates elevations in WBCs, red blood cells, and protein. <i>Revised NMO criteria</i> (Wingerchuk et al., 2006) 1. Optic neuritis 2. Acute myelitis 3. At least two of the following three supportive criteria: a. Contiguous spinal cord MRI lesion extending over at least three vertebral segments b. Onset brain MRI not meeting the diagnostic criteria for MS c. NMO-IgG seropositivity status
NMO spectrum (NMOS)	Includes classical NMO and limited forms of NMO: 1. Idiopathic single or recurrent events of longitudinally extensive myelitis (extending to ≥3 vertebral segments on spinal MRI) 2. Optic neuritis: Recurrent or simultaneous bilateral a. Asian optic-spinal MS b. Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease c. Optic neuritis or myelitis associated with brain lesions typical of NMO (hypothalamic, corpus callosum, periventricular, or brain stem) (Wingerchuk, 2010; Wingerchuk et al., 2007)	
Chronic relapsing isolated optic neuropathy (CRION)	An immune-mediated optic neuropathy considered distinct from CIS/MS. CRION, manifesting as recurrent or chronic unilateral or bilateral vision loss (Zettl et al., 2012).	Differs from MS-related optic neuropathy in that patients often experience more severe degree of visual loss, persistence of pain after onset of visual loss, and relapsing and steroid-dependent course of symptoms. MRI does not show additional CNS lesions. May, infrequently, develop into NMO or MS.
Transverse myelitis	Inflammation and demyelination across both sides of one level, or segment, of the spinal cord resulting in symptoms of neurological disconnection and dysfunction below the level of the demyelinating area (Greenberg et al., 2013).	It is mostly caused by infectious agents such as syphilis, measles, Lyme disease, varicella zoster, herpes simplex, cytomegalovirus, Epstein-Barr, influenza, echovirus, human immunodeficiency virus (HIV), hepatitis A, rubella, and <i>mycoplasma</i> , either directly or as a postinfectious autoimmune process. It may be also induced by various vaccinations or be idiopathic. The latter may occasionally represent one (or the initial) attack of MS or NMO. In MS, transverse myelitis is usually partial and does not affect the whole extent of the spinal cord segment.

Table 3 Various diagnostic criteria of MS

Schumacker committee criteria (1965)	<p>Clinical signs of problem in CNS</p> <p>Evidence of two or more areas of CNS involvement</p> <p>Evidence of white matter involvement</p> <p>One of these: Two or more relapses (each lasting ≥ 24 h and separated by at least 1 month) or progression (slow or stepwise)</p> <p>Patient should be between 10 and 50 years of age at the time of examination</p> <p>No better explanation for patient's symptoms and signs</p>										
Poser's criteria (1983)	<ol style="list-style-type: none"> 1. <i>CDMS</i> (clinically definite MS): Two or more attacks (relapses), with clinical (neurological dysfunction demonstrable by neurological examination) or paraclinical evidence. (Demonstrable by any test of the existence of a nonclinical lesion in the CNS); at least one event should be of clinical evidence 2. <i>LDMS</i> (laboratory-supported definite MS): At least one attack and oligoclonal bands. (1) Two attacks (occurrence of a symptom of neurological dysfunction for more than 24 h), and evidence (clinical or paraclinical) along one of the following lines; (2) one attack and two clinical manifestations; (3) one attack, one clinical, and one paraclinical manifestation 3. <i>CPMS</i> (clinically probable MS). One attack. (1) Two attacks and one clinical manifestation; (2) one attack and two clinical manifestations; (3) one attack, one clinical, and one paraclinical manifestation 4. <i>LSPMS</i> (laboratory-supported probable MS): Two attacks with no other evidence 										
McDonald criteria (2001)	<table border="0"> <thead> <tr> <th><i>Clinical presentation</i></th> <th><i>Additional data needed</i></th> </tr> </thead> <tbody> <tr> <td> <ul style="list-style-type: none"> ● Two or more attacks (relapses) ● Two or more objective clinical lesions ● Two or more attacks ● One objective clinical lesion </td> <td> <p>None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)</p> <p>Dissemination in space, demonstrated by:</p> <ul style="list-style-type: none"> ● MRI ● or a positive CSF and two or more MRI lesions consistent with MS ● or further clinical attack involving different site </td> </tr> <tr> <td> <ul style="list-style-type: none"> ● One attack ● Two or more objective clinical lesions </td> <td> <p>Dissemination in time, demonstrated by:</p> <ul style="list-style-type: none"> ● MRI ● or second clinical attack </td> </tr> <tr> <td> <ul style="list-style-type: none"> ● One attack ● One objective clinical lesion (monosymptomatic presentation) </td> <td> <p>Dissemination in space demonstrated by:</p> <ul style="list-style-type: none"> ● MRI ● or positive CSF and two or more MRI lesions consistent with MS <p>Dissemination in time demonstrated by:</p> <ul style="list-style-type: none"> ● MRI ● or second clinical attack </td> </tr> <tr> <td> <p>Insidious neurological progression suggestive of MS (primary progressive MS)</p> </td> <td> <p>One year of disease progression (retrospectively or prospectively determined) and two of the following:</p> <ol style="list-style-type: none"> a. Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP) b. Positive spinal cord MRI (two focal T2 lesions) c. Positive CSF </td> </tr> </tbody> </table>	<i>Clinical presentation</i>	<i>Additional data needed</i>	<ul style="list-style-type: none"> ● Two or more attacks (relapses) ● Two or more objective clinical lesions ● Two or more attacks ● One objective clinical lesion 	<p>None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)</p> <p>Dissemination in space, demonstrated by:</p> <ul style="list-style-type: none"> ● MRI ● or a positive CSF and two or more MRI lesions consistent with MS ● or further clinical attack involving different site 	<ul style="list-style-type: none"> ● One attack ● Two or more objective clinical lesions 	<p>Dissemination in time, demonstrated by:</p> <ul style="list-style-type: none"> ● MRI ● or second clinical attack 	<ul style="list-style-type: none"> ● One attack ● One objective clinical lesion (monosymptomatic presentation) 	<p>Dissemination in space demonstrated by:</p> <ul style="list-style-type: none"> ● MRI ● or positive CSF and two or more MRI lesions consistent with MS <p>Dissemination in time demonstrated by:</p> <ul style="list-style-type: none"> ● MRI ● or second clinical attack 	<p>Insidious neurological progression suggestive of MS (primary progressive MS)</p>	<p>One year of disease progression (retrospectively or prospectively determined) and two of the following:</p> <ol style="list-style-type: none"> a. Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP) b. Positive spinal cord MRI (two focal T2 lesions) c. Positive CSF
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<ul style="list-style-type: none"> ● Two or more attacks ● One objective clinical lesion 	<p>Dissemination in space, demonstrated by:</p> <ul style="list-style-type: none"> ● MRI ● or positive CSF and two or more MRI lesions consistent with MS ● or further clinical attack involving different site <p><i>New criteria:</i> Dissemination in space (DIS) can be demonstrated by presence of one or more T2 lesions in at least two out of four of the following areas of the CNS: Periventricular, juxtacortical, infratentorial, or spinal cord.</p>										
<ul style="list-style-type: none"> ● One attack ● Two or more objective clinical lesions 	<p>Dissemination in time (DIT), demonstrated by:</p> <ul style="list-style-type: none"> ● MRI ● or second clinical attack <p><i>New criteria:</i> No longer need to have separate MRIs run; dissemination in time, demonstrated by: simultaneous presence of asymptomatic gadolinium(Gd)-enhancing and nonenhancing lesions at any time; or new T2 and/or Gd-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to baseline scan; or await a second clinical attack. (This allows for quicker diagnosis without sacrificing specificity, while improving sensitivity.)</p>										
<ul style="list-style-type: none"> ● One attack ● One objective clinical lesion (clinically isolated syndrome) 	<p><i>New criteria:</i> Dissemination in space and time, demonstrated by:</p> <p>For DIS: one or more T2 lesions in at least two of four MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord); or await second clinical attack implicating a different CNS site. For DIT: Simultaneous presence of asymptomatic Gd-enhancing and nonenhancing lesions at any time; or new T2 and/or GD-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan; or await second clinical attack.</p>										
<p>Insidious neurological progression Suggestive of MS (primary progressive MS)</p>	<p><i>New criteria:</i> One year of disease progression (retrospectively or prospectively determined) and two or three of the following:</p> <ol style="list-style-type: none"> 1. Evidence of DIS in the brain based on one or more T2 lesions in the MS-characteristic regions (periventricular, juxtacortical, or infratentorial) 2. Evidence of DIS in the spinal cord based on two or more T2 lesions in the cord 3. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index) 										

Magnetic Resonance Imaging

MRI can support the investigation, diagnosis, and management of patients with MS, but the association between conventional neuroradiological markers and clinical disability of MS is weak, a phenomenon referred to as the clinico-radiological paradox (Miller et al., 1998). Reasons for this poor association include the emphasis of MRI protocols only on the detection of focal white matter pathology, the limited sensitivity of the EDSS score to detect small degrees of clinical deterioration, and the inability of the routine MRI techniques to provide an accurate estimation of degeneration, axonal damage, and compartmentalized inflammation (i.e., in the meninges or in the cortical and deep gray matter) (Ruggieri et al., 2015; Haider et al., 2014; Cappellani et al., 2014; Daams et al., 2013; Calabrese et al., 2011; Neema et al., 2009; Magliozzi et al., 2007; Ceccarelli et al., 2010; Geurts et al., 2005; Popescu and Lucchinetti, 2012; Popescu et al., 2013; Kutzelnigg and Lassmann, 2006; Serafini et al., 2004; Lucchinetti et al., 2011; Romme Christensen et al., 2013). T1 hypointense lesions ('black holes') seem to correlate better with measures of disability than T2 lesion number and volumes (Venken et al., 2010). Contrast-enhancing lesions indicate acute inflammation; such enhancement is transient, typically lasting about 6–8 weeks (Venken et al., 2010; Lucchinetti et al., 2000).

Another confounding factor for this clinico-radiological dissociation is the heterogeneity of lesions in MS and the involvement of the 'normally appearing white and gray matter.' Correlations between clinical parameters and imaging are improved with the use of novel neuroimaging techniques such as magnetization transfer imaging, functional MRI, or diffusion tensor MRI (Rovira et al., 2015; Wattjes et al., 2015), but these techniques still do not have a central role in monitoring disease evolution in the everyday practice.

The increasing use of such MR protocols may provide a better insight into the disease activity, which, in turn, can be used to inform prognosis and guide treatment decisions.

Nowadays, MRI is a critical tool for both the diagnosis of early MS (McDonald criteria) and the prediction of its future course. It can detect clinically silent activity of MS, better than the clinical history or neurological examination alone (Rudick and Cutter, 2013). Up to 70% of brain lesions (Jacobs et al., 1986; Ormerod et al., 1987) and 30% of spinal lesions (Dalton et al., 2004; O'Riordan et al., 1998) develop without clinical evidence of relapse. New silent lesions (that may be defined as 'radiological relapses') appear up to 10 times more frequently than lesions associated with clinical relapses (Wingerchuk et al., 2006; Isaac et al., 1988; Kappos et al., 1988). More than half of CIS patients show one or more clinically silent T2-bright abnormalities on their baseline brain MRI (Miller et al., 2005b; O'Riordan et al., 1998; Brex et al., 2002; Frohman et al., 2003), the presence and the number of which may predict the risk of development of MS in the next 5–14 years (O'Riordan et al., 1998; Kappos et al., 1988; Ghezzi et al., 1999; Miller et al., 1988; Morrissey et al., 1993).

The standard brain MRI protocol for MS includes a three-plane scout, sagittal fast FLAIR, axial fast spin echo proton density/T2, axial fast FLAIR, and axial Gd-enhanced T1, as recommended by the Consortium of Multiple Sclerosis Centers (CMSC) to evaluate patients presenting with possible CIS

(Simon et al., 2006). The CMSC guidelines also recommend spinal cord MRI in patients presenting with symptoms at the spinal cord level or in patients with focal neurological signs and an equivocal brain MRI.

The results of numerous studies assessing the risk of conversion from CIS to CDMS suggest that patients who have asymptomatic brain MRI lesions at the time of presentation of CIS have a 60–80% chance of developing CDMS within 10 years, whereas those without brain lesions carry a much lower risk (~20% risk) (Brex et al., 2002; Frohman et al., 2003; Beck et al., 2003; Minneboo et al., 2004; Scott et al., 2005). In general, the number of lesions seems to be well correlated with the risk of conversion to CDMS.

MRI parameters that may predict conversion to CDMS include:

1. The presence of multifocal homogenous or ring-enhancing white matter lesions.
2. T2-hyperintense lesions in the corpus callosum (Zivadinov and Cox, 2007).
3. T2-hyperintense lesions in the posterolateral compartment of the spinal cord (Cordonnier et al., 2003).
4. Positivity for Barkhof criteria (i.e., at least nine T2 lesions or at least one contrast-enhancing, the presence of an infratentorial lesion, the presence of a juxtacortical lesion, at least 3 periventricular; three out of four may suffice (Barkhof et al., 1997)).

However, particularly in the very early stages of MS, the sole use of MRI may introduce diagnostic errors due to low specificity. Hyperintense lesions in the white matter of the CNS (sometimes defined also as UBOs—unknown bright objects) can be detected in a plethora of pathological conditions (including migraine, microvascular disease, and various connective tissue diseases) or even in a small percentage of 'healthy' individuals (Kruit et al., 2004; Morris et al., 2009; Vernooij et al., 2007). This is the reason why the old diagnostic criterion introduced in the 1960s by Shumacker ('rule out other possible causes'), still appears in the 2010 revised criteria by McDonald (Polman et al., 2005) and in the recent criteria for RIS, stressing the need for analysis of the MRI data with care and performance of a thorough differential diagnosis.

Conventional 1.5 T imaging does not capture the entire extent of MS activity. For example, cortical lesions, that may exist in nearly 40% of patients with early MS (Roemer et al., 2011; Lucchinetti et al., 2011; Calabrese et al., 2010a), cannot be captured by conventional imaging but only with double inversion recovery imaging (Calabrese et al., 2007; Nelson et al., 2007) and/or using a 7 T MRI machine (Hasan and Narayana, 2009; Hammond et al., 2008; Kangarlu et al., 2007; Mainero et al., 2009). The presence of at least one cortical lesion in patients with CIS may help identify those at high risk for conversion to CDMS (Montalban et al., 2010; Calabrese et al., 2010b; Filippi et al., 2010).

Small studies using additional and more advanced MR techniques such as magnetic resonance spectroscopy (MRS) and magnetization transfer imaging (MTI) have shown that these methods can contribute to the prediction of conversion from CIS patients to CDMS (Wattjes et al., 2008a,b; Filippi et al., 2000; Iannucci et al., 2000). Standardization of protocols and improvements in technology (e.g., software) seem to be

essential in order that MRI will be used routinely to monitor time-based changes in brain volume (atrophy measure) (Venken et al., 2010; Lucchinetti et al., 2000).

Evoked Potentials

Visual-evoked potentials (VEPs) are abnormal in 30% of patients with CIS, regardless of clinical symptoms (Rot and Meseck, 2006) and in >50% of patients with MS (Bradley et al., 2008) who have no history or clinical evidence of optic nerve dysfunction. Somatosensory-evoked potentials (SSEPs) and brain stem auditory-evoked potentials (BAEPs) may also be used as evidence of demyelination that is nondetectable clinically or on MRI. It was shown (Pelayo et al., 2010) that if all three evoked potentials (VEP, SSEP, and BAEP) are abnormal at the time of CIS, there is an increased risk of developing moderate disability from MS that is independent of MRI findings.

Cerebrospinal Fluid

About 60–70% of patients with CIS and up to 90% of those with MS have two or more immunoglobulin G (IgG) oligoclonal bands (OCBs) uniquely to the CSF (Miller et al., 2005b; Avasarala et al., 2001; Awad et al., 2010; Paolino et al., 1996; Polman et al., 2008; Sastre-Garriga et al., 2003; Tintore et al., 2001; Zipoli et al., 2009). CSF OCB testing must be run in parallel with sampling of serum obtained within 72 h of the lumbar puncture. The preferred method of analysis with the highest sensitivity and specificity for MS is isoelectric focusing on agarose gels, followed by immunodetection by blotting or fixation (Freedman et al., 2005). Some 70–90% of MS patients will have an elevated IgG index (Awad et al., 2010) and (Link and Huang, 2006), and this may be in conjunction with, or independent of, the presence of OCB in the CSF. The presence of ≥ 2 OCBs in the CSF has a positive predictive value of 97%, a negative predictive value of 84%, a sensitivity of 91%, and a specificity of 94% for developing relapsing–remitting MS (RRMS) after a CIS (Masjuan et al., 2006). The presence of OCBs within 3 months of CIS (Tintore et al., 2008) nearly doubles the risk of a second clinical attack over 4–6 years (Martino et al., 2005). On the other hand, CSF with >50 white blood cells (WBCs) mm^{-3} or >100 mg dl^{-1} protein is rarely observed in MS, and this should raise the possibility of an alternative diagnosis (McDonald et al., 2001; Trapp and Nave, 2008). It is also important to bear in mind that disorders other than MS may also be associated with the presence of OCB and a high IgG index. The differential diagnosis for the presence of OCBs in the CSF includes the Sjogren's syndrome (75–90% of patients with neurological involvement), neurosarcoidosis (40–70%), systemic lupus erythematosus (30–50%), Behcet disease (20–50%), paraneoplastic disorders (5–25%), antiglutamic acid decarboxylase antibody syndromes (40–70%), Vogt–Koyanagi–Harada syndrome (30–60%), Hashimoto's steroid-responsive encephalopathy (25–35%), subacute sclerosing panencephalitis (100%), rubella encephalitis (100%), neurosyphilis (90–95%), neuroborreliosis (80–90%), human immunodeficiency virus infection (60–80%), meningitis (5–50%), adrenoleukodystrophy

(100%), ataxia telangiectasia (50–60%), Leber hereditary optic atrophy (5–15%), CNS vascular disorders (5–25%), and CNS tumors (<5%) (Awad et al., 2010).

Additional Immunological Biomarkers

As MS pathogenesis involves mainly immune-mediated mechanisms, serum immune biomarkers are good candidates for the diagnosis and prognosis of the disease, reflecting the presence, nature, and intensity of certain immune responses (Hawa et al., 2004). Also, from a practical standpoint, tests for serum biomarkers could prove very useful, as blood is relatively simple to collect and the tests can be easily repeated as a monitoring strategy (Schwarz et al., 2006; Freedman et al., 2009; Brettschneider et al., 2009). Such biomarkers may also be identified in the CSF, which is in closer proximity to the lesions in the CNS.

Biomarkers in conjunction with other prognostic criteria, such as MRI, may help in the early identification of MS and stratify CIS patients according to their risk for progression to CDMS. Such classification rules may provide additional tools for the determination of the most appropriate treatment strategy for the individual patient (Rudick and Polman, 2009; Rudick et al., 1997; Jacobs et al., 2000; Kappos et al., 2007).

Antibodies targeting myelin antigens are, naturally, one of the most extensively studied serum biomarkers in MS. The presence of IgM, against the extracellular domain of myelin oligodendrocyte protein (MOG), together with antibodies specific for myelin basic protein (MBP), (which are two of the main immunogenic antigens in the CNS myelin sheath) in CIS patients, was shown to be highly predictive for CDMS (Berger et al., 2003; Tomassini et al., 2007). However, other studies testing the prognostic value of anti-MOG and anti-MBP antibodies revealed controversial results ranging from highly significant to totally insignificant (Berger et al., 2003; Tomassini et al., 2007; Kuhle et al., 2007a,b; Pelayo et al., 2007).

Antibodies targeting alpha glucose-based antigens were found to differentiate MS from other neurological diseases and to predict progression to a more severe disease phenotype (Schwarz et al., 2006; Freedman et al., 2009; Brettschneider et al., 2009). More recently antibodies against a novel astrocyte target, the potassium channel KIR4.1 protein, have been found to be associated with MS (Srivastava et al., 2012; Brill et al., 2015). However, such association has not been universally confirmed by additional groups and remains controversial (Brickshawana et al., 2014).

The B-cell chemoattractant chemokine CXCL13 was also shown to serve as a prognostic marker for conversion to CDMS in patients with CIS, especially when combined with the Barkhof MRI criteria (Festa et al., 2009; Alvarez et al., 2013; Ferraro et al., 2015; Khademi et al., 2011).

Additional novel biomarkers for MS include osteopontin, TNF α , various cytokines and chemokines, and a b-crystallin. Neurofilament protein subunits have been lately in the focus of interest as prognostic biomarkers. Their presence at high levels in the CSF may reflect acute axonal damage and imply a prognostic value for conversion from CIS to

CDMS (Teunissen and Khalil, 2012; Teunissen et al., 2009; Fialova et al., 2013a,b).

Therapy of MS

Logically, based on this widely accepted model for MS immunopathogenesis described previously (Tables 2 and 3; Figure 3a), the therapeutic approaches to the disease include modalities aimed at downregulating the various immune elements that are involved in the immunological cascade (Karussis, 2013). Since the introduction of IFNs in 1993, which were the first registered immunotherapies for MS, huge steps have been made in the field of MS immunotherapy. The novel, at that time, concept of 'immunomodulation' (referring to a specific downregulation of the pathogenic immune cells through induction of a shift of the immune response or enhancement of the intrinsic regulatory immune networks), as opposed to generalized immunosuppression, was initially introduced from the studies with IFNs and linomide, in the early 1990s (Abramsky et al., 1996; Karussis et al., 1993a, 1996).

During the last two decades, since the advent of IFN and Copaxone, more target-focused immunoactive drugs have been introduced and it appears that these new treatments are more efficacious (Figure 4). However, this seemingly increased efficacy of the new immunomodulatory drugs has to be carefully interpreted as the clinical trials during the last decade included MS patients with a lower relapse rate, and this fact complicates the comparisons between old and new generation drugs. In addition, more safety issues have arisen with these new immunomodulators (Figure 4).

Since, neurodegeneration evolves early and – probably – as a consequence of inflammation, early immune intervention is warranted to prevent not only the relapses of the disease but also the accumulation of disability and future irreversible damage. The use of neuroimaging (MRI) techniques that allow

the detection of silent inflammatory activity and neurodegeneration has provided an important tool for the substantiation of the clinical efficacy of treatments and the early diagnosis of MS. The introduction of new diagnostic criteria (McDonald et al., 2001) for CDMS does not necessitate – as in the past years – the occurrence of a second clinical relapse, but only the dissemination in time and space, reflected by MRI dynamic changes. This has paved the path to the concept of early immunotherapy in selected patients experiencing the first demyelinating episode (CIS), or even (theoretically) in individuals with a sole neuroradiological evidence of demyelination (RIS). However, the prognosis of MS is highly variable and therefore additional clinical, radiological, and immunological surrogate biomarkers should be used to define those cases with a bad prognosis in which early immunotherapy at the stage of CIS or RIS may be justified.

The immunotherapeutic modalities can be divided into two main groups: those affecting the acute phase (relapse) of the disease and the long-term preventive treatments. Immunomodulating treatments may also be classified according to the level of the 'immune axis' where they exert their main effect (Figure 3a; Tables 4 and 5).

Based on their molecular construction and their basic mechanism of action, immunotherapeutic agents may also be classified as (1) cytotoxic drugs; (2) synthetic immunomodulators; (3) monoclonal antibodies; (4) vaccines (T-cell vaccines, antigen vaccines); (5) oral tolerizing agents; (6) modalities that act as indirect immunosuppressants (plasmapheresis, intravenous immunoglobulins – IVIG); and (7) cellular therapies (stem cells, progenitors).

Treatment of Acute Deterioration/Relapses of MS

Corticosteroids

The most widely used treatment, during an acute MS relapse, is methylprednisolone or other corticosteroid preparations.

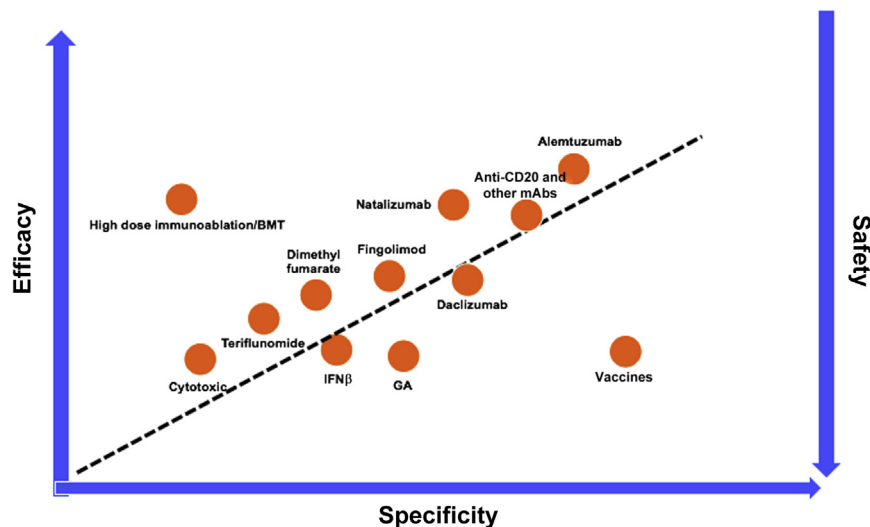


Figure 4 The spectrum of various immunotherapies in MS: Newer modalities have seemingly increased efficacy and specificity but also more safety issues. Reprinted with permission from Poser, C., 1998. *An Atlas of Multiple Sclerosis*. Parthenon Publishing Group, London. Fig. 44, p. 70.

Table 4 Description of the mechanisms of action of immunotherapeutic agents in MS and their Class evidence of efficacy

<i>Immuno-therapeutic agents</i>	<i>Basic mechanism of action</i>	<i>Class evidence of efficacy in MS</i>
Corticosteroids	<ul style="list-style-type: none"> ● Induction of lipocortin-1 (annexin-1) synthesis, with resulting diminished eicosanoid production ● Suppression of cyclooxygenase (COX-1 and COX-2) expression ● Inhibition of genes affecting production of cytokines Interleukin 1 (IL-1), IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IFNγ, TNFα, resulting in T-cell inhibition ● Down-regulation of antibody production ● Down-regulation of adhesion molecules expression ● Reduction of blood–brain barrier (BBB) permeability 	Class I–II (in attacks of MS) Class II–III (as long-term tx)
Interferon beta (IFN β)	<ul style="list-style-type: none"> ● Reduction of T-cell activation and proliferation ● Down-regulation of antigen presentation (reduction of MHC/HLA expression and blocking of co-stimulatory signals from antigen-presenting cells-APCs) ● Up-regulation of CCR7, TGFβ, and IL-10 and enhancement of regulatory cell function ● Induction of cytokine shift in favor of anti-inflammatory profile (Th1 to Th2 shift) ● Prevention of T-cell adhesion and extravasation across BBB (increased sVCAM and reduced metalloproteinase-MMP9 production) ● Induction of T-regulatory (Treg) cells ● Activation of B cells ● Neuroprotection (unknown) 	Class I in RRMS Class I–II in SPMS with relapses Class II–III in other SPMS None in PPMS
Glatiramer acetate (GA)	<ul style="list-style-type: none"> ● Blockage of lymphocyte sensitization to myelin basic protein (MBP) ● Down-regulation of antigen presentation (competitive inhibition for binding with MHC/HLA) ● Induction of a Th2 shift ● Induction of bystander suppression ● Induction of regulatory and CD8 suppressor GA-reactive cells ● Induction of a shift toward an M2 type of antigen-presenting cells (APCs) ● Neuroprotective effects (unknown) 	Class I in RRMS None in SPMS or PPMS
Fingolimod	<ul style="list-style-type: none"> ● Action as a super agonist of the S1P1 receptor on lymphocytes, inducing its uncoupling/internalization and intracellular lysosomal degradation, depriving CD4⁺ and CD8⁺ positive T-cells and B-cells of the obligatory signal to egress from lymphoid organs and recirculate to peripheral inflammatory tissues 	Class I in RRMS
Plasmapheresis (PLEX) Intravenous immunoglobulins (IVIG)	<p>Mechanical clearance of circulating antibodies</p> <ul style="list-style-type: none"> ● Formation of immune complexes and blockage of circulating antibodies ● Interaction with Fc receptors on dendritic cells, which then mediate anti-inflammatory effects ● Activation of complement ● Blockage of macrophages ● Direct suppression of T and B cells 	Class II in relapses of MS and NMO Class II in RRMS No evidence in progressive MS
Natalizumab	A humanized monoclonal antibody against cellular adhesion molecule α 4-integrin, which is crucial for lymphocyte migration to target organs prevents all activated lymphocytes from entering CNS through the BBB	Class I in RRMS
Rituximab	Genetically engineered chimeric murine/human IgG1 monoclonal antibody that targets the CD20 antigen, expressed only on pre-B and mature B cells Rituximab lyses B cells via complement and antibody-dependent cellular cytotoxicity	Class II in RRMS
Alemtuzumab	<ul style="list-style-type: none"> ● A recombinant humanized monoclonal antibody directed against cell surface glycoprotein CD52 ● Depletion (antibody-dependent lysis) of all B- and T-cells ● Reduction of the number of monocytes, macrophages, NK cells, and part of granulocytes 	Class I–II in RRMS
Daclizumab	<ul style="list-style-type: none"> ● A humanized monoclonal antibody (mAb) that blocks IL-2 receptor alpha subunit (CD25) expressed on activated T cells ● Inhibition of T-cell expansion ● Expansion of CD56 natural killer (NK) cells which, in turn, inhibit T-cell survival 	Class II in RRMS

(Continued)

Table 4 Description of the mechanisms of action of immunotherapeutic agents in MS and their Class evidence of efficacy—cont'd

<i>Immuno-therapeutic agents</i>	<i>Basic mechanism of action</i>	<i>Class evidence of efficacy in MS</i>
Cyclo-phosphamide	<ul style="list-style-type: none"> ● A nitrogen mustard alkylating agent from the oxazophorine group with broad cytotoxic and immunosuppressive effects; its main metabolite phosphoramidate mustard is only formed in cells with low aldehyde dehydrogenase (ALDH) levels. ● Formation of DNA crosslinks at guanine positions, leading to cell death ● Suppression mostly of B cells ● Suppression of T cells and IFNγ and IL-12 cytokine production ● Increase in IL-4 and IL-10 production and induction of a Th2 shift 	Class II–III in progressive cases
Azathioprine	<ul style="list-style-type: none"> ● Inhibition of the first step in <i>de novo</i> purine biosynthesis, with resulting prevention of mitosis and proliferation of fast dividing cells (especially lymphocytes), leading to decreased T-cell number and reduced antibody synthesis 	Class II in RRMS and SPMS
Mitoxantrone	<ul style="list-style-type: none"> ● A cytotoxic agent from anthracenedione family; acts by intercalating with DNA and inhibiting topoisomerase II ● Reduction of the number of B cells ● Inhibition of the T helper cells and the Th1-related cytokine production ● Augmentation of T-cell suppressor activity 	Class I in RRMS
Methotrexate	<ul style="list-style-type: none"> ● A folate antagonist; diminishes proliferation of immune cells by inhibiting <i>de novo</i> purine and pyrimidine synthesis ● Decrease of neutrophil leukotriene synthesis the adenosine-mediated inflammation ● Inhibits (AICAR transformylase, resulting in intracellular accumulation of AICAR, which promotes release of the antiinflammatory autocoid adenosine ● Suppression of antigen-dependent T-cell proliferation 	Class II–III in RRMS
Mycophenolate (MMF)	<ul style="list-style-type: none"> ● Inhibition of purine synthesis and noncompetitive inhibition of type II isomer of inosine monophosphate dehydrogenase ● Depletion of guanosine and deoxyguanosine nucleotides in T and B lymphocytes, inhibiting therefore their proliferation and immunoglobulin (Ig) production ● Suppression of dendritic cells maturation decreasing their capacity of antigen presentation to T lymphocytes 	Class III
Cyclosporine A	<ul style="list-style-type: none"> ● A calcineurin inhibitor that acts on IL-2 by inhibiting its production, leading to decreased T-lymphocyte proliferation 	Class III
Cladribine	<ul style="list-style-type: none"> ● A synthetic purine nucleoside that acts as antimetabolite, interfering with DNA synthesis and repair and with immunosuppressive effects (mainly causing lymphocyte depletion) ● Suppression mainly of the CD4⁺ and CD8⁺ T cells, and B cells ● Prevention of lymphocyte migration through BBB 	Class I in RRMS Class II in SPMS
Dimethyl fumarate (BG12)	<ul style="list-style-type: none"> ● Induction of anti-inflammatory effects ● Suppression of macrophages ● Activation of nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, the innate cellular phase 2 detoxifying pathway antioxidant ● Th1 to Th2 shift ● Neuroprotection 	Class I in RRMS
Laquinimod	<ul style="list-style-type: none"> ● A synthetic immunomodulator ● Down-regulation of antigen presentation ● Induction of a shift toward Th2 ● Neuroprotective effects (?) 	Class I–II in RRMS
Teriflunomide	<ul style="list-style-type: none"> ● An active metabolite of leflunomide ● Inhibition of dihydroorotate dehydrogenase, a key mitochondrial enzyme involved in new pyrimidine synthesis for DNA replication ● Reduction of T- and B-cell activation and proliferation 	Class I–II in RRMS

In high supraphysiological doses, glucocorticoids strongly downregulate inflammation. They suppress cellular immunity by inhibiting genes that affect the production of various cytokines and TNF α and by reducing the proliferative ability of T cells (Rose et al., 1970; Abbruzzese et al., 1983b; Barkhof et al., 1991; Beck et al., 1992; Miller et al.,

1991). Glucocorticoids also suppress humoral immunity, causing B cells to express smaller amounts of IL-2 and IL-2 receptors, thus diminishing their expansion and antibody production.

Steroids reduce the permeability of the blood–brain barrier (Barkhof et al., 1991; Miller et al., 1992; Kesselring et al., 1989)

Table 5 Mechanisms of action of immunotherapeutic agents in MS

	Effects on T lymphocytes	Effects on antigen presentation	Effects on B lymphocytes and humoral immunity	Effects on cytokines and chemokines	Effects on migration/ BBB	Immune shift	Effects on regulatory cells	Levels of action on the immune cascade described in Figure 3a
Corticosteroids	++	++	+++	++	++	+	-	A, B, E, F, G
Interferon beta (IFN β)	+++	++	- (enhancement)	++	+	+++	++	A, B, C, F, G
Glatiramer acetate (GA)	++	+++	+	-	-	+++	-	A, C, D, G
Fingolimod	+++ (homing)	-	++	-	+++	-	-	B, D, E
Plasmapheresis	-	-	+++	++	-	-	-	E
IVIG	+	+	+++	+	-	+	+/-	A, E
Natalizumab	++ (homing)	-	++ (homing)	-	+++	-	-	D, E, F
Rituximab	-	-	+++	+	+	-	-	A, E
Alemtuzumab	+++	-	-	+	+	+/-	-	B, C, D, E, G
Daclizumab	+++	-	-	++	+	-	++	B, C, D
Cyclophosphamide (CFX)	++	+	+++	+++	+	++	++	A, B, C, D, E
Azathioprine	++	+	+++	++	+	+	+	A, B, C, D, E
Mitoxantrone	+++	+	+++	++	-	+	?	B, C, D, E
Methotrexate	++	?	++	+	-	-	?	A, B, C, D, E
Mycophenolate (MMF)	+++	++	+++	+/-	-	-	-	B, C, D, E
Cyclosporine A (CsA)	+++	-	+	+++	-	-	-	B, C, G
Cladribine	+++	-	++	+	++	-	-	B, C, D, E
BG12	++	++	?	++	?	++	?	A, B, G
Laquinimod	++	+++	?	++	++	++	++	A, B, C, D, E
Teriflunomide	+++	+++	++	++	-	-	-	B, C, D, E
Tarcolimus/Sirolimus	+++	-	+	+++	-	-	-	B, D, E, G

1. Level A: Antigen presentation to lymphocytes and early lymphocyte activation: glatiramer acetate (GA), interferon beta (IFN β), vaccines, laquinimod, steroids, rituximab, vaccinations.

2. Levels B and D: Activation and proliferation/expansion of the autoimmune, myelin reactive lymphocytes: Chemotherapeutic/cytotoxic agents (azathioprine, cyclophosphamide, methotrexate, cyclosporine, mycophenolate, cladribine, mitoxantrone, tarcolimus, teriflunomide); immunoablation and resetting of the immune system by hematopoietic stem cell transplantation; Lymphocyte depletion with monoclonal antibodies (alemtuzumab, rituximab, daclizumab); specific reduction of autoimmune myelin-responsive lymphocytes with vaccination techniques (i.e., T-cell vaccination, myelin peptides vaccination).

3. Levels C and D: Regulatory cells or immunological shift: IFN β , GA, laquinimod, fingolimod, alemtuzumab, teriflunomide, cyclophosphamide.

4. Level E: B cells and antibodies/humoral immunity: plasmapheresis, IVIG, anti-CD20 monoclonal antibodies, steroids, cytotoxic drugs (azathioprine, mycophenolate, cyclophosphamide), alemtuzumab.

5. Levels B and G: Cytokine production: various immunosuppressants, corticosteroids, IFN β , GA, fingolimod, teriflunomide, cyclosporine-A, laquinimod, cyclophosphamide, azathioprine, alemtuzumab.

6. Level F: Migration or homing of the lymphocytes and entrance through the blood-brain barrier: fingolimod, natalizumab, corticosteroids. ?, questionable effect; +, Mild effect; ++, moderate effect; +++, strong effect; -, negative effect; +/-, borderline effect.

as reflected by the reduction in gadolinium (Gd-DTPA) enhancement in the MRI.

Corticotropin (aka adrenocorticotrophic hormone, ACTH) hastens recovery at 1 month after treatment ([Rose et al., 1970](#)). Comparable or superior results were shown with methylprednisolone ([Abbruzzese et al., 1983a,b](#); [Barnes et al., 1985](#); [Thompson et al., 1989](#)). Data from the Optic Neuritis Treatment Trial showed that intravenous methylprednisolone is superior to oral prednisone for the treatment of acute optic neuritis ([Beck, 1988, 1995](#)). However, the long-term effect of both treatment regimens on the visual acuity was marginal and there was no significant 'protection' against later development of definite MS ([Beck et al., 1992, 1993](#)). A review of the trials with either intravenous methylprednisolone or ACTH showed a clear benefit of steroids in MS exacerbations ([Filippini et al., 2000](#)).

In patients with chronic progressive MS, steroids showed a milder effect. Two studies have shown a short-term improvement following high-dose intravenous methylprednisolone ([Cazzato et al., 1995](#)) or a long-term beneficial effect by 4-monthly intravenous methylprednisolone boosts which slowed the development of T1 black holes and delayed whole-brain atrophy and disability progression ([Zivadinov et al., 2001](#)).

Despite these data and the documented transient beneficial effect during the acute MS relapse, steroids do not seem to significantly alter the natural course of the disease and their chronic use does not seem justified. In addition, chronic steroid administration is associated with several adverse effects including osteoporosis, aseptic bone necrosis, hypertension, hyperglycemia, cataracts, and psychotic events.

Despite wide agreement on the efficacy of steroidal treatment in MS relapses, the optimal protocol for administration of the drug is still not settled. Current protocols (mostly empirical) include 3, 5, or even 10 days of 1–2 g intravenous methylprednisolone with or without oral tapering with prednisone. Oral administration of high-dose methylprednisolone appears to be equally efficient to intravenous administration ([Alam et al., 1993](#); [Sellebjerg et al., 1998](#); [Martinelli et al., 2009](#)). There are indications, not based on published studies in MS but on experience in other autoimmune diseases (such as systemic lupus erythematosus – SLE), that abrupt discontinuation of intravenous steroidal treatment in MS relapses may increase the risk of a recurrence of the symptoms. Therefore, a tapering-off protocol following high-dose intravenous methylprednisolone appears preferable.

Plasmapheresis

Plasmapheresis, also known as therapeutic plasma exchange (PLEX), is a procedure that separates the blood components, exchanging the plasma (typically with donor plasma or albumin), and returning the other components, primarily red blood cells, to the patient. PLEX is known to be effective in various autoimmune diseases.

Since the late 1980s, PLEX has been tried in several studies on MS patients, but with inconsistent effects. This may be related to (1) the small size of the studies, (2) the lack of homogeneity in the treatment protocols, (3) the use of PLEX as an adjuvant therapy to other immunomodulatory modalities, and (4) the patient populations and type/course of MS, which greatly varied among these studies (Khatri et al., 1991; The Canadian Cooperative Multiple Sclerosis Study Group, 1991; Noseworthy et al., 1991; Weiner et al., 1989).

In a more recent and randomized trial, which represented the revival of PLEX as a treatment modality for MS, PLEX was for the first time checked as a single modality in patients with various types of acute CNS demyelinating diseases (including acute disseminated encephalomyelitis and neuro-myelitic types of MS (NMO spectrum of disorders), either chronic or relapsing) (Weinshenker et al., 1999). Clinical improvement was noted in 42.1% PLEX-treated patients compared with 5.9% in the sham group. A follow-up study by Keegan et al. (2005) suggested that patients with myelitis and Pattern II immunopathogenesis (according to Lucchinetti et al., 2000, a predominantly antibody-mediated disease) had the best response to PLEX. A recent retrospective analysis of 153 patients treated with PLEX for a steroid-refractory CNS demyelinating episode showed that 59% exhibited moderate to marked functional neurological improvement within 6 months following treatment (Magana et al., 2011).

Logically, since NMO corresponds to the type-II histopathological phenotype of MS lesions, NMO patients are expected to have an optimal response to PLEX. Indeed two small open studies and a retrospective one in NMO patients during an acute attack of the disease showed an early and significant improvement following PLEX in most of the treated patients (Wang et al., 2011; Watanabe et al., 2007; Bonnan et al., 2009).

An American Academy of Neurology task committee, upon evaluating the neurological indications of PLEX, gave a level B recommendation for its use as second-line treatment of steroid-resistant exacerbations in relapsing forms of MS and of NMO (Cortese et al., 2011).

Preventive Long-Term Immunotherapy of MS

The First Generation: The 'Old Players'

Interferon Beta

The type-I IFNs (IFN α and IFN β) were first used in the 1970s on the grounds of their antiviral activity, which could possibly help in the elimination of the putative viral agents involved in MS pathogenesis. However, an initial trial with IFN γ (type II) showed that the treatment actually promoted relapses of MS (Panitch et al., 1987). IFN β , on the other

hand (intrathecally or subcutaneously), induced beneficial effects in patients with MS (Jacobs et al., 1981; Panitch et al., 2004).

IFN β was shown to inhibit T-cell activation, enhance suppressor cell activity, reduce IFN γ production and MHC-II expression, increase IL-10 production, downregulate antigen presentation, induce a Th1 to Th2 shift, and reduce the permeability of the blood-brain barrier (Dhib-Jalbut and Marks, 2010).

In the first pivotal double-blind trial, recombinant IFN β -1b (Betaferon, Schering/Bayer), given subcutaneously every other day, was reported to reduce the relapse rate by 31% but without significantly affecting the disability status (The IFNB Multiple Sclerosis Study Group, 1993). IFN β -treated patients had a significantly lower MRI T2 burden of disease and a 75–80% reduction in active scans (Paty and Li, 1993). The treatment was generally well tolerated with the exception of 'flu-like' symptoms (fever, chills, myalgias, and fatigue) that occurred in the majority (76%) of patients, but tended to decrease after the first months of treatment. Injection-site irritation was also very common.

In a second study, recombinant glycosylated IFN β -1a (Avonex, Biogen), at a dose of 6 MIU intramuscularly once per week, induced a reduction in relapse rate by a similar (to Betaferon) rate. The treatment also resulted in a decrease in the number and volume of Gd-DTPA-enhancing lesions in the MRI and delayed the sustained progression of disability by about 40% (Jacobs et al., 2000).

A third type of recombinant IFN β -1a (Rebif, Merk-Serono) (6 or 12 million IU subcutaneously every other day) (PRISMS Study Group, 1998) reduced the relapse risk by 27–33% and delayed the progression of disability and suppressed MRI activity (Li and Paty, 1999). These beneficial effects of IFN β were shown to be long-lasting (Freedman, 2011; PRISMS-4, 2001; Ebers et al., 2010).

Early treatment with IFN β in CIS patients showed to reduce the risk for conversion to CDMS over 2–3 years, by about 40% (Jacobs et al., 2000; Filippi et al., 2004; Kappos et al., 2006). In a comparative study, Comi et al. (2012a) showed that the cumulative probability of McDonald definite MS was significantly lower in all patients treated with IFN β -1a, with a stronger beneficial effect of the higher-frequency regimen (Rebif).

A systematic review of the efficacy of IFNs in MS concluded that there is evidence only for RRMS, and this is mainly in terms of a reduction in relapse frequency during the first (and less in the second) year of treatment, with no convincing efficacy thereafter and no effect on the accumulation of disability (Rice et al., 2001).

The data about the efficacy of IFN β in *progressive MS* are conflicting. One European study showed that Betaferon significantly increased (by 9–12 months) the time to confirmed disease progression and to becoming wheelchair bound compared with placebo in patients with SPMS (European Study Group, 1998).

On the other hand, the North American trial on SPMS failed to show any beneficial effect of the same medication (Betaferon) on disease progression (Panitch et al., 2004) but only benefits in secondary outcome measures. The differences found between the outcomes of these two studies remain puzzling (Kappos et al., 2004) and might be related to the different populations of MS patients included in these two trials.

In another trial that tested IFN β -1a in SPMS, there was no significant effect on disability progression but suppressed

superimposed relapses and MRI activity (PRISMS Study Group, 1998). Finally, in a study with the third type of commercial IFN (Avonex) in 436 patients with SPMS (Cohen et al., 2002), although no differences in EDSS were detected, there were significant beneficial effects on the Multiple Sclerosis Functional Composite (MSFC) scale and on the relapse-related parameters.

In PPMS, two randomized control trials failed to show beneficial effects of IFN β on disease progression (Rojas et al., 2010; Leary and Thompson, 2003; Montalban et al., 2009). Some differences favoring treatment were observed for the MSFC and in several secondary MRI parameters.

Three studies have compared the efficacy of the registered IFNs and reported greater efficacy of high-dose IFN β (Rebif or Betaferon) than the lower dose Avonex (IFN β -1a), but these trials were rather small and of short duration (Comi et al., 2012a; Panitch et al., 2002; Durelli et al., 2002). On the other hand, another trial (Cadavid et al., 2009) showed no significant differences between Betaferon and Avonex in all outcomes (Koch-Henriksen et al., 2006).

About 5–30% of IFN β -treated patients develop persistent neutralizing antibodies, usually in the first year of treatment and more commonly in those receiving IFN β -1b. Their presence is usually associated with a reduction in treatment effect (Malucchi et al., 2004; Francis et al., 2005; Hartung et al., 2011; Goodin et al., 2012; Pachner et al., 2009).

Glatiramer Acetate/Copaxone

Glatiramer acetate (GA; COP-1, Copaxone, Teva, Israel) is a synthetic co-polymer, composed of alanine; glutamine; lysine; and tyrosine, with some immunological similarities to the MBP molecule (and other myelin antigens), without itself being encephalitogenic. GA is presumed to block the MHC/TCR complex and to downregulate the antigen presentation to T cells (competitive inhibition) and/or induce regulatory cells (Racke et al., 2010). In a pilot controlled study (Bornstein et al., 1987), in 50 patients with RRMS, a great reduction in the number of relapses in the GA-treated group was reported. A later and larger pivotal, double-blind, trial (Johnson et al., 1995) showed that GA induced a 29% reduction in relapse rate, but without affecting the progression of disability at 2 years. MRI monitoring, performed in one of the centers, showed only marginal inhibition of the MRI activity. Adverse effects were usually mild, including mainly localized, injection-site reactions and a systemic reaction occurring within moments of GA administration (associated with chest pain, palpitations, or dyspnea) in 15% of the patients. In a separate randomized study treatment with GA led to a significant (10%) reduction in the total number of enhancing lesions compared with placebo (Comi et al., 2001); 57% of the patients treated for up to 22 years with GA maintained improved or unchanged EDSS scores and low annualized relapse rates (Miller et al., 2008; Karussis et al., 2010a). GA was also shown to reduce the risk of CIS patients to develop CDMS by 45% (Comi et al., 2009). A trial with GA in PPMS was terminated after an interim analysis that indicated no discernible treatment effect on primary outcome (Wolinsky et al., 2007; Sajja et al., 2008). An oral preparation of GA was shown ineffective evaluated in a later large trial including Filippi et al. (2006).

In two comparative trials between GA and IFN β , no differences in any clinical or MRI parameters were observed between

the treatment groups (Cadavid et al., 2009; O'Connor et al., 2009; Mikol et al., 2008).

Controversial or Less-Proven Preventive Immunotherapies

Intravenous Immunoglobulins

Data from an open pilot and a controlled study indicated that intravenous immunoglobulins (IVIG) had some efficacy in reducing the number of relapses and in the progression of disability in RRMS (Achiron et al., 1992; Fazekas et al., 1997a,b). However, two other trials failed to show any efficacy of this treatment in patients with RRMS or progressive MS (Cook et al., 1992; Francis et al., 1997). MRI monitoring in the latter trial did not reveal any effect of IVIG treatment in preventing the appearance of new lesions in the brain (Arnold et al., 1994).

In SPMS, two studies (Hommes et al., 2004; Pohlau et al., 2007) failed to show any beneficial effects. In PPMS, a single study reported significantly less patients with EDSS progression in the IVIG-treated group than in the placebo group, with a nonsignificant trend to a delay in time to disease progression (Pohlau et al., 2007).

MRI data reported in two RRMS studies (Lewanska et al., 2002; Fazekas et al., 2008) and in one on SPMS (Hommes et al., 2004) were conflicting and not convincing.

In an additional trial with clinical and MRI endpoints, significant differences were reported between the placebo and the IVIG-treatment groups (Sorensen et al., 1998). However, this study suffers from considerable methodological difficulties, particularly with respect to blinding and allocation concealment.

Two additional trials (Noseworthy et al., 2000; Achiron et al., 1998), of a rigorous methodological quality, were entirely negative across a wide range of clinical and paraclinical outcome measures.

Infusion-related side effects were reported in 4% of the participants treated with IVIG (Fazekas et al., 1997b; Hommes et al., 2004; Achiron et al., 1998). One study reported six participants with deep venous thrombosis, four of whom also developed pulmonary embolism in the treatment group. IVIG was poorly tolerated in one trial (Fazekas et al., 2008), with 11/21 (52%) experiencing severe cutaneous reactions. In the same study, there was one case with hepatitis C viral infection and one mortality from a pulmonary embolus (Fazekas et al., 1997a; Hommes et al., 2004; Pohlau et al., 2007; Achiron et al., 1998).

Immunosuppressants

Several immunosuppressive treatments have been tried in MS in the past decades, with variable efficacy.

Azathioprine, an antimetabolite with broad spectrum immunosuppressive effects and one of the main immunosuppressive cytotoxic substances available, is used extensively to control transplant rejection. By preventing the clonal expansion of lymphocytes it affects both cellular and humoral immunity. Azathioprine was tested in some pilot clinical trials (Achiron et al., 1998; British and Dutch Multiple Sclerosis Azathioprine Trial Group, 1988; Goodkin et al., 1991). In the British and Dutch Multiple Sclerosis Trial (1988) it was shown to reduce the rate of progression at 3 years.

In total, azathioprine was tested in five controlled trials (Achiron et al., 1998; British and Dutch Multiple Sclerosis Azathioprine Trial Group, 1988; Goodkin et al., 1991). Both relapsing and remitting MS patients and patients with progressive disease were included in these five trials. Almost half of the included patients suffered from progressive disease. Analysis of the cumulative data from 698 patients (from these five trials) showed that treatment with azathioprine caused a relative relapse risk reduction of 23% and 18% at 2 and 3 years, respectively (Casetta et al., 2009). The proportion of patients who progressed during 2–3 years of treatment was 42% lower in the azathioprine group.

In one small study (Massacesi et al., 2005), a reduction of 50% in gadolinium-enhancing lesions and T2 lesions was observed in patients treated with azathioprine.

The side effects of azathioprine include gastrointestinal discomfort or pain and a cutaneous rash (5% for each) and a 9% incidence of liver enzyme elevation. Macrocytic anemia occurred in 3% of the azathioprine-treated patients. There was a small but insignificant absolute increase of 3.4% in the risk for malignancies from a 3-year course of azathioprine and a slightly increased mortality rate in the azathioprine groups (Taylor et al., 2004).

Cyclophosphamide is an alkylating drug that binds to DNA and interferes with mitosis and cell replication, suppressing thus both cellular and humoral immunity. Cyclophosphamide is commonly used as an antineoplastic drug and for the treatment of severe systemic autoimmune disorders.

Initial pilot open studies back in the early 1970s showed some positive indications of the efficacy of cyclophosphamide in MS, but these trials were open and uncontrolled (Hommes et al., 1975).

Two large randomized trials reported conflicting results (Weiner et al., 1993a). The beneficial effect observed in the first was seen mainly in young patients and the difference in stabilization rates was small and disappeared by 36 months. In the latter (The Canadian Cooperative Multiple Sclerosis Study Group, 1991), there was no significant difference in the time to worsening in the EDSS.

Since the early 1990s there have been several trials and case reports with cyclophosphamide in patients with rapidly worsening or treatment-refractory MS, showing in general a moderate beneficial, clinical and neuroradiological effect on the activity of the disease (Hohol et al., 1999; Khan et al., 2001; Perini and Gallo, 2003; Zephir et al., 2004; de Bittencourt and Gomes-da-Silva, 2005; Gobbi et al., 1999).

The combination of cyclophosphamide and IFN β -1a reduced clinical disease activity and gadolinium-enhancing MRI lesions in the brain (Smith et al., 2005; Patti et al., 2004).

Cyclophosphamide can cause several side effects, including alopecia, nausea, vomiting, hemorrhagic cystitis, leukopenia, myocarditis, infertility, and pulmonary interstitial fibrosis.

Mitoxantrone is an anthracenedione antineoplastic drug that intercalates with DNA and inhibits both DNA and RNA synthesis. Mitoxantrone inhibits B-cell function, including antibody secretion, abates helper and cytotoxic T-cell activity, and decreases the secretion of Th1 cytokines such as IFN γ , TNF α , and IL-2 (Fox, 2004).

A first placebo-controlled trial of mitoxantrone showed a significant reduction in the annual relapse rate and an

increase in the proportion of patients who were relapse-free, but no differences in EDSS scores (Millefiorini et al., 1997). In the subsequent phase III trial, in 194 patients with worsening RRMS or SPMS (Hartung et al., 2002), the higher dose (12 mg m $^{-2}$ q 3 months) of mitoxantrone was significantly more effective in the combined clinical outcome measurement, consisting of five clinical parameters (change in EDSS, change in ambulation index, number of treated relapses, time to first-treated relapse, and change in neurological status).

Addition of mitoxantrone to IFN β -treated patients, decreased the mean frequency and volume of gadolinium-enhancing lesions, by 90%, and the relapse rate by 64% (Jeffery et al., 2005). Similar beneficial effects were observed also when mitoxantrone was added to GA (Ramtahal et al., 2006).

Mitoxantrone is the only licensed cytotoxic medication for MS (for patients with SPMS, progressive relapsing or worsening RRMS), but its use is confined to cases with sufficiently aggressive MS to justify its toxic effects. Mitoxantrone causes cardiotoxicity (the cumulative allowed dose should not exceed 120 mg m $^{-2}$) and acute leukemia (AML); the cumulative risk for both these adverse effects is 0.2%.

Methotrexate, a folic acid analog, is a potent immunosuppressant, whose mode of action is predominantly through inhibition of thymidine biosynthesis, although there are other anti-inflammatory effects, which do not rely upon this specific mechanism. By inhibiting purine and pyrimidine synthesis, methotrexate suppresses T-cell proliferation and promotion of adenosine-mediated inflammation. It is used in the treatment of autoimmune diseases and in transplantations.

In a placebo-controlled study, methotrexate, at a low dose, was reported to have a mild beneficial effect in a composite measure of EDSS, ambulation index, and two arm function tests, in progressive MS (Gray et al., 2006; Goodkin et al., 1995). The effect of methotrexate on MRI activity was also marginal. Another trial with methotrexate (Currier et al., 1993) did not show any difference in EDSS progression in the progressive group. A more recent study (Sadiq et al., 2010) investigated the intrathecal administration of methotrexate in 121 progressive MS patients. No serious adverse effects were noted during the study period. In 89% of the 87 SPMS patients, EDSS scores were stable or improved.

In general, methotrexate toxicity is usually low if treatment is paralleled by folate substitution. However, long-term methotrexate administration may be associated with serious side effects, including hepatotoxicity and hepatic fibrosis.

Cyclosporin-A, is a cyclic fungal peptide, that inhibits calcineurin, similar in this aspect to tacrolimus. It is one of the most widely administered immunosuppressive drugs.

Cyclosporin A was studied in a 2-year, multicenter, double-blind, clinical trial involving 547 progressive MS patients (The Multiple Sclerosis Study Group, 1990). The mean increase in EDSS was 0.39 ± 1.07 for the cyclosporine-treated patients and 0.65 ± 1.08 in the placebo group. Cyclosporin A delayed the time to becoming wheelchair bound (relative risk: 0.765), but there was no statistical significance on 'time to sustained progression.'

The high rate of hypertension and nephrotoxicity induced by this treatment limit its use along with an increased risk for malignancies and skin cancers.

Cladribine is a synthetic purine nucleoside analog that preferentially accumulates in lymphocytes, disturbing DNA synthesis and repair mechanisms, and resulting in lymphocyte depletion and long-lasting lymphopenia. Because cladribine can penetrate the CNS, it interacts with cells in both the peripheral circulation and in the CNS. It is used as first-line treatment for hairy cell leukemia.

Older studies in a total of 262 patients have shown the efficacy of parenteral cladribine in RRMS and progressive MS, both in clinical and MRI parameters (Sipe et al., 1994; Beutler et al., 1996). In a large and more recent phase III trial, a new preparation of oral cladribine (in two doses) and a new treatment scheme were tested in 1326 patients with RRMS (Giovannoni et al., 2010). There was a significantly lower annualized relapse rate in both cladribine groups compared with the placebo group (by about 50%), and a lower risk of 3-month sustained progression of disability, paralleled by a reduction in the number of brain lesions in the MRI. Adverse events included lymphocytopenia and herpes zoster infections. Neoplasms arose in 1.4% of the treated patients.

Mycophenolate mofetil (MMF) belongs to the antimetabolite drug class and is a pro-drug of its active metabolite, mycophenolic acid. It inhibits T- and B-cell proliferation and, hence, immunoglobulin (Ig) production. MMF also suppresses dendritic cell maturation, decreasing their capacity of antigen presentation to T lymphocytes. Small trials in progressive MS suggest some efficacy, of MMF and its administration appeared to be well tolerated (Frohman et al., 2004; Ahrens et al., 2001). Additionally, in an open-label trial, the combination of MMF with IFN β -1a exhibited superior efficacy, compared with IFN β -1a alone (Vermersch et al., 2007). In a retrospective trial, MMF was shown to prevent relapses in 24 NMO patients (Jacob et al., 2009). Adverse events include benign infectious diseases, insomnia and dizziness, nausea, and abdominal pains. There are still no controlled large studies with MMF in MS.

Tacrolimus/FK506 is a bacterial product that binds to the immunophilin FKBP1A. In this way, it prevents the cells from transitioning from the G0 to the G1 phase of the cell cycle. The drug, which is more potent than cyclosporin and has less pronounced side effects, is used primarily in transplantations. A pilot clinical trial (Lemster et al., 1994) with tacrolimus in chronic progressive MS showed that the overall degree of disability did not deteriorate significantly in the 19 patients studied over the 12 months of tacrolimus administration.

Combination Immunotherapy

The rationale for combination immunotherapy (reviewed in Conway and Cohen, 2010) comes from the reported synergistic effects and increased efficacy of such combinations of immunomodulatory agents in other autoimmune diseases (Breedveld et al., 2006). It is also justified by the acknowledged complexity of MS immunopathogenesis, which may necessitate the use of more than one drug to interfere with the various distinct immune elements involved at multiple levels of the immune axis, in order to maximize treatment efficacy (Figure 3a). However, owing to the complex interactions and the delicate balance between the various immune cells and cytokine/chemokine networks, unexpected or paradoxical effects may

occur when different drugs affecting the immune system are combined. Small-size open studies have provided some positive indications supporting the principle of combination treatments such as methotrexate or azathioprine plus IFN β (Calabresi et al., 2002; Pulicken et al., 2005). However, other larger controlled studies using IFN as basic therapy and methotrexate, steroids, or azathioprine as add-ons were negative (showing only some trends) (Havrdova et al., 2009; Cohen et al., 2009; Ravnborg et al., 2010), with the exception of one (Sorensen et al., 2009) which showed a benefit of combination of IFN with steroids. The combination of natalizumab with IFN β showed some additional benefits in reduction of the relapse rate, but this trial was terminated because of two cases of progressive multifocal leukoencephalopathy (PML) in the natalizumab-Avonex combination group (Goodman et al., 2009a). Addition of GA to natalizumab improved the neuro-radiological endpoints in this trial, but there was no additional benefit in terms of relapses and EDSS changes (Goodman et al., 200a).

A randomized, double-blind, placebo-controlled trial of cyclophosphamide as an add-on therapy to IFN β and a single-blind-controlled trial revealed a benefit of addition of cyclophosphamide (with or without steroids) to IFN β (Patti et al., 2004; Smith et al., 2005). Such treatment strategies entailing a rescue therapeutic scheme of strong immunosuppression (cyclophosphamide or mitoxantrone) followed by maintenance treatment with IFN or GA have been suggested and showed promising results (Smith et al., 2005; Patti et al., 2004; Jeffery et al., 2005; Ramtahal et al., 2006; Edan et al., 2011).

The combination of simvastatin, a cholesterol-lowering agent with putative immunomodulatory and neuroprotective properties, with IFN β -1a did not offer any additional beneficial effect (Sorensen et al., 2011).

New Generation of Immunotherapies

Monoclonal Antibodies

Monoclonal antibodies (mAb) are monospecific antibodies that are made by identical immune cells that are all clones of a unique parent cell, in contrast to polyclonal antibodies, which are made from several different immune cells. Monoclonal antibodies have monovalent affinity, in that they bind to the same antigenic epitope. Biologically synthesized mAbs can target precisely defined antigens like 'magic bullets' and represent a whole new category of immunotherapeutic drugs.

Natalizumab is targeting the VLA4 surface molecule which is crucial for the transmigration of lymphocytes through the BBB to the CNS. Monthly infusions of this antibody showed strong efficacy against placebo, reducing the relapse rate at 1 year by 68% and the chance of acquiring fixed disability over 2 years by 42% (Polman et al., 2006). Moreover, natalizumab-treated patients were free of any disease activity (relapses, progression of disability, and new MRI activity) by around 30%. Although this efficacy appears higher than that observed in the IFN and GA pivotal studies, such cross comparison between different studies (of different design and MS patients populations) is not scientifically sound. US and European authorities licensed natalizumab for relapsing MS, but the drug was later withdrawn from the market when two cases of PML (progressive multifocal

leucoencephalitis, an almost universally, lethal infection) were identified in a trial combining Avonex (IFN β -1a) with natalizumab (Rudick et al., 2006). As a result, natalizumab is now licensed as monotherapy only for severe RRMS, or as second-line immunotherapy for MS. Since licensing, many (more than 300) additional cases of PML have been identified, almost exclusively among the patients treated for more than 2 years with natalizumab. Three parameters have been identified as being related to an increased risk of PML: (1) duration of treatment; (2) previous exposure to cytotoxic medications; and (3) the presence of anti-JC (John Cunningham) virus antibodies (which are found in half of the MS patients and indicate previous exposure to the virus) (Sorensen et al., 2012). All reported cases of PML following natalizumab treatment were positive for the JC virus antibodies. Introduction of the test for these antibodies has helped in the selection of patients to be treated with natalizumab and those in whom the treatment should be discontinued due to a high risk (i.e., more than 1:1000 and in cases with all the above three risk factors, more than 1:100) of PML.

Alemtuzumab is a humanized monoclonal antibody targeting the CD52 antigen on T and B lymphocytes (Klotz et al., 2012) that produces rapid and sustained lymphocyte depletion. It is an approved therapy for B-cell chronic lymphocytic leukemia.

The first trial of alemtuzumab in RRMS (Coles et al., 2008) was suspended after immune thrombocytopenic purpura developed in three patients, one of whom died. In this study, alemtuzumab treatment reduced the relapse rate compared with IFN β -1a by up to 74%, and the chance of accumulating disability by up to 71%, over 3 years. MRI outcomes were also significant, favoring alemtuzumab. Adverse events in the alemtuzumab group included autoimmunity (thyroid disorders and immune thrombocytopenic purpura (3%)) and infections.

Two consequent large phase III trials have been concluded in RRMS, showing a 49–55% reduction in relapse rate in the group treated with two annual cycles of alemtuzumab as compared with Rebif over 2 years and a 42% reduction of the risk of sustained accumulation of disability (Cohen et al., 2012; Coles et al., 2012).

The side effects of alemtuzumab include a high incidence of autoimmune diseases (22%), especially autoimmune thrombocytopenia and thyroiditis (up to 33%) (Cossburn et al., 2011).

Rituximab/ocrelizumab. The accumulating evidence on the involvement of B lymphocytes in the pathophysiology of MS paved the way for B-cell-directed therapies (Lassmann, 2007). B-cell depletion affects antibody production, cytokine networks, and B-cell-mediated antigen presentation and activation of T cells and macrophages. Rituximab is a genetically engineered, chimeric murine/human IgG1 monoclonal antibody that targets the CD20 antigen, expressed only by pre-B and mature B cells.

Rituximab has shown significant efficacy in the suppression of several autoimmune disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis.

Two pilot open studies, in 26 and 30 MS patients, tested the effect of two courses of rituximab 1000 mg, 6 months apart or with 375 mg m⁻² weekly for 4 weeks. No serious adverse events were noted, except mild-to-moderate infusion-associated

reactions. Fewer new gadolinium-enhancing or T2 lesions were seen in the rituximab-treated patients, associated with an apparent reduction in relapses (Bar-Or et al., 2008; Naismith et al., 2010).

In a randomized, phase II, double-blind, trial, treatment with rituximab 1000 mg, given once every 6 months, led to a significant reduction of 91% in gadolinium-enhancing lesions seen on MRI, and in T2-weighted lesion volume, compared with placebo. Patients in the rituximab group had 50% lower annualized rate of relapses (Hauser et al., 2008).

Rituximab treatment was also evaluated in 439 patients with PPMS (Hawker et al., 2009). The patients received two 1000 mg intravenous rituximab or placebo infusions every 24 weeks, through 96 weeks (4 courses). The differences between the two groups in terms of time to confirmed disease progression were not significant, although rituximab patients had a significantly lower increase in T2 lesion volume. Subgroup analysis showed significant differences in time to confirmed disease progression in patients aged <51 years and those with gadolinium-enhancing lesions, compared with placebo. Adverse events were comparable between groups. However, serious infections occurred in 4.5% of the rituximab and <1.0% of the placebo patients.

Another, totally humanized, anti-CD20 monoclonal antibody, ocrelizumab, was also tested recently (Kappos et al., 2011) in 220 patients with RRMS in a large multicenter, randomized, double-blind, placebo-controlled study. At week 24, the number of gadolinium-enhancing lesions was 89% lower in the 600 mg ocrelizumab group than in the placebo group, and 96% lower in the 2000 mg group, with similarly pronounced effects in secondary relapse-related outcomes. Recently presented data from two large double-blind trials have shown significant efficacy of treatment with ocrelizumab both in relapsing MS and in PPMS (the only medication by now having shown a significant efficacy in PPMS).

Daclizumab targets the cell surface IL-2a receptor (CD25) which is expressed only by activated T-lymphocytes. IL-2 is an important immune system regulator necessary for clone expansion and survival of activated T-lymphocytes. Daclizumab acts by binding the IL-2a receptor's α -chain, preventing the IL-2-induced clonal expansion of activated lymphocytes and shortening their survival. It is used in the prophylaxis of acute organ rejection after bilateral kidney transplantation, with only a few side effects.

Few pilot studies with daclizumab provided indications of efficacy in reducing gadolinium-enhancing lesions in MS patients (van Oosten et al., 1996; Wynn et al., 2010; Bielekova et al., 2011), accompanied by a significant expansion of natural killer (NK) cells in the peripheral blood and CSF.

In a first double-blind phase III trial against placebo, the annualized relapse rate was lower for patients given daclizumab HYP 150 mg subcutaneously every 4 weeks (54% reduction) or 300 mg (50% reduction) than for those given placebo. Slightly more patients in the daclizumab groups had serious adverse events excluding MS relapse (Gold et al., 2013).

In a recently reported phase III trial, patients treated with daclizumab had a significantly lower (40%) annualized relapse rate than those treated with IFN β -1a. The number of new or newly enlarged hyperintense lesions on MRI was also lower in the daclizumab group (Kappos et al., 2015).

New Oral Medications

Fingolimod (Gilenya, Novartis, Switzerland) modulates sphingosine-1-phosphate (S1P) receptors and has strong immunoregulatory properties since S1P1 receptor internalization appears to be a crucial step in the migration of lymphocytes. Neutralization of the S1P1 pathway inhibits the egress of T cells and B cells from the lymph nodes.

The results of two phase III studies in patients with RRMS (Kappos et al., 2010; Cohen et al., 2010) showed the efficacy of fingolimod over placebo, a clear superiority over IFN β -1a and an acceptable safety profile. ARR was reduced by 60% in the fingolimod 1.25 mg group compared to placebo and by 50% compared to IFN β 1a. Fingolimod also significantly reduced the cumulative probability of the 3-month confirmed disability progression and showed superiority in all secondary MRI-related endpoints. The FDA approved fingolimod as first-line treatment for RRMS, whereas the European Medicines Agency (EMA) restricted its use as a second-line treatment or a first-line treatment in patients with active disease.

Fingolimod treatment causes significant lymphopenia, but its effects on circulating lymphocytes are reversible, with cell counts returning to normal within 4–6 weeks after cessation of treatment. Other adverse events related to fingolimod include bradycardia and atrioventricular conduction block during the start of fingolimod administration, macular edema, elevated liver enzyme levels, lymphocytopenia, and hypertension (all relative rare). Long-term safety data are warranted.

Teriflunomide is the active metabolite of leflunomide, which is approved for use in patients with rheumatoid arthritis. It reduces the activity of the mitochondrial enzyme dihydroorotate dehydrogenase, which is crucial in pyrimidine synthesis. T-lymphocyte proliferation largely depends on pyrimidine synthesis.

In a randomized, controlled, phase III trial in patients with active RRMS (O'Connor et al., 2011), both teriflunomide doses (7 or 14 mg) significantly lowered (by 30%) the ARR and by a similar degree the rate of disability worsening. The superiority of the drug versus placebo was confirmed for a range of MRI endpoints. Both teriflunomide doses were well tolerated, although diarrhea, nausea, and liver enzyme elevation were recorded. Teriflunomide has been suggested to have teratogenic, hepatotoxic, and myelosuppressive effects.

Results from a head-to-head trial (Vermersch et al., 2014) revealed no statistical superiority between the Rebif and teriflunomide arms on risk of treatment failure, the primary composite endpoint of the study. The drug with the trade name Aubagio was licensed by the FDA and EMA.

Dimethyl fumarate (BG12) is an oral formulation of dimethyl fumarate that induces activation of the nuclear factor E2-related pathway, which protects against oxidative stress-related neuronal death and damage to myelin in the CNS. Several neuroprotective and anti-inflammatory mechanisms have been attributed to the drug, such as the expression of phase II detoxification enzymes in astroglial and microglial cells and a drug-induced shift toward a more anti-inflammatory cytokine profile.

In a pilot study in patients with RRMS, an oral formulation of fumaric acid (Fumaderm, Biogen Idec), approved in Germany for the treatment of psoriasis, reduced the number

of gadolinium-enhancing lesions in brain MRI scans (Schimrigk et al., 2006). Subsequently, a phase IIb study in RRMS (Kappos et al., 2008, 2012) showed that BG-12 at 240 mg three times daily reduced the number of gadolinium-enhancing, new T2 and T1 lesions by 69%.

A large phase III trial (Gold et al., 2012) showed that BG-12 at 240 mg twice or three times daily reduced by 53% the ARR and by 85–90%, the number of gadolinium-enhancing lesions and of new or enlarging T2 lesions compared with the placebo group. The cumulative probability of 3-month confirmed EDSS worsening was 38% lower. No new significant safety issues were reported (Gold et al., 2015).

In another phase III parallel/comparative trial (Fox et al., 2012) the annualized relapse rate was significantly lower in the BG-12 group and in the GA-treated arm than in the placebo group. Reductions in disability progression were not significant with either medication. BG-12 and GA had similar beneficial effects compared to placebo in terms of reducing the MRI activity. Adverse events associated with BG-12 include flushing and gastrointestinal events, such as diarrhea, nausea, and upper abdominal pain, as well as decreased lymphocyte counts and elevated liver enzyme levels. Lymphocyte counts tend to decrease with BG-12 and these chronically lymphopenic patients seem to have an increased risk for PML.

An additional, not yet approved, oral immunomodulatory drug is *laquinimod* (a derivative of linomide which effectively suppressed EAE and had a strong clinical effect in MS, which was shown in a phase III study (Comi et al., 2012b) to reduce by 23% the ARR, by 36% the EDSS worsening and by 33% the loss of brain volume over 2 years.

A second phase III study (Vollmer et al., 2014) failed to reveal a beneficial effect on relapse rate as compared to placebo but induced beneficial effects on EDSS progression and on brain volume loss.

More Experimental Treatment Approaches

T-cell Vaccination (TCV) was first introduced in 1981 in the EAE rat model, using activated and irradiated MBP-specific T-cell lines and clones (Ben-Nun et al., 1981). The rationale was that vaccination with attenuated myelin-responsive T cells should induce an immune response against those cells which are probably the ones responsible for the inflammation and demyelination in MS (Zhang et al., 1993).

Few small, phase II clinical trials with TCV at various stages of MS are already reported in the literature (Correale et al., 2000; Hermans et al., 1999, 2000; Medaer et al., 1995; Stinissen et al., 1996; Zhang, 2002; Vandebark and Abulafia-Lapid, 2008; Achiron and Mandel, 2004; Karussis et al., 2012). These studies showed a consistent reduction in MBP-specific T cells following TCV and revealed indications of clinical efficacy.

A similar approach is to vaccinate with only the relevant *anti-myelin antigen*-responsive (Bourdette et al., 2005) *T-cell receptor* (Vandebark et al., 1996) or using vaccines that contain altered myelin peptides (Kappos et al., 2000).

Another unique approach for specific downregulation of the myelin-reactive lymphocytes, which are considered the main responder cells for the induction of demyelination, is

utilizing oral tolerization techniques (Faria and Weiner, 2005). An initial small-scale double-blind trial with early RRMS patients showed a trend to better clinical outcomes, and a reduction in MBP-reactive T cells in myelin-treated patients, without any adverse effects (Weiner et al., 1993a; Hohol et al., 1996). However, the phase III trial did not confirm the efficacy of this therapy.

A slightly different approach, involving the administration of *synthetic peptides* derived from the sequence of MBP, by intrathecal and intravenous routes, was used in an attempt to tolerize patients (Warren and Catz, 1995, 2000; Warren et al., 1997; Goodkin et al., 2000).

Stem Cells Therapies

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) for MS (and autoimmune diseases in general) is based on the principle of radical suppression of the immune system to abrogate the inflammatory pathogenetic process in MS and subsequently reset the immune system from scratch. The autologous setting is usually used, where the immune system is reconstituted by the patient's own stem cells. The rationale for this type of therapeutic approach in MS derives from pivotal animal studies performed back in the early 1990s (Karussis et al., 1993a; 1992). Open, uncontrolled clinical trials have shown impressive effects on the suppression of inflammation, induction of remission, and stabilization of MS (Fassas et al., 1997; Curro et al., 2015; Nash et al., 2015; Burt et al., 2015; Mancardi et al., 2015).

Worldwide, more than 500 patients with MS have been treated with HSCT (reviewed by Karussis et al., 2013). The different conditioning protocols used in these studies complicate the uniform interpretation of the data. In general, an overall 85% 5-year survival rate and 43% progression-free survival have been recorded, with mean 100-day transplantation-related mortality ranging from 1% to 5%.

Other Stem Cells

Pivotal studies with neuronal stem cells have shown a significant beneficial clinical effect in mice with EAE (the animal model of MS) (Einstein et al., 2003; Ben-Hur et al., 2003; Pluchino et al., 2003). Subsequently, embryonic and other types of adult stem cells, especially mesenchymal stem cells (MSCs), were tested in various models of EAE (Nicoletti et al., 2005; Kassis et al., 2008; Aharonowicz et al., 2008). MSC injection, either intravenous or into the CSF, strongly suppressed the clinical and pathological signs of EAE and reversed disability. Most importantly, remyelination was evident in these MSC-treated animals, accompanied by impressive neuroprotection (Kassis et al., 2008).

The additional scientific rationale for using MSC in EAE and MS derives from the reported strong immunomodulatory effects of these cells (Nauta and Fibbe, 2007; Uccelli et al., 2006, 2007). Phase I/II safety studies with MSC or bone marrow-derived cells have been performed in MS (Karussis et al., 2010b; Yamout et al., 2010). Overall, MSCs given intravenously or intrathecally were well tolerated, with some

preliminary evidence of efficacy (Karussis et al., 2013; Connick et al., 2012).

Until 1993, no specific immunotherapy was registered for MS. Since the introduction of IFN β , huge steps have been made and increasingly more specific and efficacious (Figure 4) modalities have been introduced and registered. However, along with the seemingly increasing efficacy of the newly introduced and more targeted immunotherapies, more safety issues have arisen. The cumulative experience obtained from the numerous clinical trials in MS with various types of immunotherapies allows one to draw the conclusion that inflammation, most probably initiated in the peripheral immune system, is crucial for the formation of new demyelinating lesions and, with time, appears to be the main cause for the resulting axonal damage and neuronal tissue atrophy. Immunological therapies, ideally applied as early as possible, might prevent progression of disability if given before the cascade of events that lead to irreversible tissue loss. The reported lower efficacy of most of the known immunotherapies in patients with progressive forms of MS might be explained by the possibility that inflammation is less pronounced or only compartmentalized in the CNS at these stages of the disease. More effective modalities that exert strong local immunomodulation in the CNS might be more beneficial for progressive MS. The additional goals of future MS therapy should include neuroprotective modalities and techniques that may enhance neuroregeneration and remyelination. High expectations of this direction are focused on stem cell-related treatments, but these have to be substantiated in future controlled trials.

Finally, it is important to emphasize that MS is not a homogeneous disease and distinct types of immune pathogenesis seem to be involved in different subgroups (Lucchinetti et al., 2000). The use of neuroimaging and immunological biomarkers would help to tailor/personalize immunotherapy for each individual case.

Symptomatic Treatments

Management of symptoms in MS (Poser and Brinar, 2002) such as the spasticity, pains (usually neuralgic), sphincter abnormalities, fatigue, memory decline, depression, and walking difficulties has received less attention compared with disease-modifying treatments. However, the effect of these symptoms on quality of life can be profound. The interest in pharmacological treatment of symptoms in MS has increased in recent years, and several large randomized controlled trials have been reported.

Controlled trials have proven the efficacy of modafinil (Brioschi et al., 2009; Moller et al., 2011) and amantadine (Ledinek et al., 2013) on fatigue and of fampridine on improving walking ability (and other motor functions) and reducing spasticity (Allart et al., 2015; Goodman et al., 2009b; Keune et al., 2015). Medications used for control of pains (usually neuralgic pains, such as trigeminal neuralgia) include antiepileptic drugs (carbamazepine, lamotrigine, gabapentine, hydantoin, and so on) or antidepressive medications such as amitriptyline (Thompson et al., 2010; Zajicek and Apostu, 2011).

Baclophen, either orally or using an intrathecal pump, is the leading medication used to control spasticity, but also tizanidine; medical cannabis; or dantrolene have shown efficacy (United Kingdom Tizanidine Trial Group, 1994; Haselkorn et al., 2005; Lakhan and Rowland, 2009; Montalban, 2011; Rekan and Gronning, 2011; Schmidt et al., 1975; Stien et al., 1987; Vaney et al., 2004; Wade et al., 2006).

Urinary problems can be managed by various medications depending on the type of dysfunction (i.e., urinary detrusor overactivity, urinary retention, or dyssynergia of the bladder) that include anticholinergics (such as ditropan) or α -blockers or a combination of them.

Pharmacological strategies are a core component of the treatment of MS symptoms, but it is imperative to remember that a multidisciplinary rehabilitation approach is needed for effective management.

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See also: Autoimmune Diseases; Poliomyelitis; Poliomyelitis, Historical.

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