Multiple Sclerosis: A Review of Disease Modifying Therapies

Sinead Doyle

INTRODUCTION

Multiple Sclerosis (MS) is an acquired primary demyelinating disease of the CNS, in which myelin is the target of an autoimmune inflammatory process. It is the commonest cause of non-traumatic, chronic neurological disability in young adults, with at least 50,000 cases in the UK and more than 1 million cases worldwide. The female to male ratio is 2:1 and the clinical manifestations usually appear between 20 and 40 years of age. The disease has a varied worldwide distribution, the prevalence being directly proportional to the distance from the equator. At latitudes of 50 to 60 degrees north, roughly from Southern England to Iceland, the prevalence is 50-120 per 100,000 people; at latitudes of less than 30 degrees north the prevalence is less than 10 per 100,000.

Multiple Sclerosis is rare at the equator.[1] Hence, it is clear that MS is place-related.

Epidemiological evidence has suggested that two factors are involved in causing MS: a genetically determined susceptibility and exposure to an environmental agent. Genetic studies have shown that there is not one single gene for MS. Instead multiple genes are thought to be

involved.[2] First degree relatives of a patient have an increased risk of developing MS, though there is no clear –cut pattern of inheritance. While there is a high degree of concordance of MS in identical twins, this never exceeds about 40 per cent, hence suggesting that non-genetic factors are also important. Prevalence studies for migrants from high to low risk areas, show that the age of adolescence is critical for risk retention: those migrating beyond the age of 15 are thought to retain the MS risk of their birthplace, whilst those migrating before the age of 15 acquire the lower

risk of their new homeland.[3] It has also been discovered that clustering of MS occurs in different countries throughout the world. Such clustering, in addition to the migrant data and the geographical distribution of MS, serve to define MS as an acquired, exogenous, environmental disease.

AETIOLOGY

It is widely assumed that the environmental agent that is responsible is infective, and is most likely to be of viral origin. Numerous viruses have been implicated, but the evidence has so far been inconclusive and only a minority of scientists believe that a single, unique virus is involved. It is not yet understood how the environmental agent and the predisposing genetic factors interact in order to establish disease.

CLINICAL COURSE AND SYMPTOMS

Multiple Sclerosis has two clinical hallmarks; the first is the temporal profile of symptoms and neurological deficits occurring in multiple episodes, designated as a relapse, followed by the disappearance of symptoms and/or the restoration of function, known as a remission. Disease progression may substitute or be associated with relapses and remissions, thus resulting in the different subtypes of disease. Such subtypes include relapsing-remitting (RR), relapsing progressive (RP), secondary progressive (SP), and primary progressive (PP). The second hallmark is the anatomical dissemination of lesions within the CNS. 70% of MS patients experience the prototypical relapsing-remitting pattern, and roughly 50% of these will have converted to a secondary progressive form of MS within 10 years. 15% of patients exhibit the

relapsing progressive pattern and 15% the primary progressive variety.[4] MS can also be classified according to clinical severity. Benign MS is defined as disease which allows patients to retain fully functional neurological systems 15yrs after its onset. Malignant MS is characterised by a rapid progressive course leading to significant neurological disability or death soon after the onset of disease. 20-40% of patients have benign MS. MS is generally not a fatal disease. The average

survival is 30 yrs from onset and 25 yrs from diagnosis.[5] The majority of deaths are due to complications that occur secondary to the MS, for e.g. pneumonia, pulmonary embolus and

aspiration.[6]

Multiple Sclerosis is a complex clinical disorder with highly variable signs and symptoms arising from CNS demyelination and the consequent disturbance of conduction in axons. Despite the fact that any part of the CNS can suffer from demyelination, the majority of patients usually have a limited number of initial symptoms (see Table 1). Negative signs or symptoms for e.g. loss of vision, loss of strength or sensation, are the usual presenting symptoms. At some stage throughout the disease-course, virtually all MS patients will have increased reflexes, spasticity, sensory loss and visual impairment. Bladder, bowel and sexual dysfunction are also common.

Table 1. Multiple Sclerosis: symptoms commonly found at presentation and throughout the course

of the disease.[7]

Deficit	At Presentation	Throughout course of disease
Visual/Occulomotor	49[a]	100
Paresis	43	88
Paraesthesias	41	87
Incoordination	23	82
Genito-urinary/Bowel	10	63
Cerebral	4	39

[a] Expressed as a percentage.
Note: some patients had >1 symptom hence the total is >100%

PATHOPHYSIOLOGY

The widespread belief, although yet unproved, is that MS is an organ-specific autoimmune disease, orchestrated by auto-reactive T Lymphocytes. It is thought that the auto-reactive cells are activated systemically, with their subsequent passage through the blood-brain-barrier. This ultimately leads to multi-focal areas of peri-vascular cuffing of lymphocytes and the destruction of myelin within the CNS. It is suspected that the T cell-mediated autoimmune mechanism, and the resulting demyelination, might be triggered by earlier viral infection and/or other factors in those that have a genetic predisposition to the development of MS. This concept of MS as being an autoimmune disease stemmed, in part, from studies which reported the occurrence of Experimental Allergic Encephalomyelitis (EAE) in animals that had been inoculated with neural

tissue and also from the discovery of an increased immunoglobulin level in patients with MS.[8]

DIAGNOSIS

The diagnosis of MS involves the identification of the dissemination of lesions in time and space. The former relates to the clinical history of the patient and the latter will only be evident after further investigations have been carried out. MRI of the brain and spinal cord, where available, is

the first line of investigation. Brain MRI demonstrates multi-focal white matter abnormalities in

greater than 95% of patients with clinically definite MS.[9] The typical findings are of multiple white matter lesions, principally in the peri-ventricular region, brainstem and cervical cord. With diagnostic Magnetic Resonance Images and a compatible clinical picture, examination of the CSF is often unnecessary. The CSF picture in MS is typified by a raised mononuclear cell count and the presence of oligoclonal IgG bands. Evoked potentials might also be assessed in the diagnosis of MS. Delay in the visual-evoked response (VER) follows optic neuropathy. Brainstem and somatosensory evoked potentials also become delayed when these pathways have been damaged.

TREATMENT OF ACUTE RELAPSE

The treatment of relapse encompasses those which might occur in patients with relapsing-remitting or secondary progressive disease. Corticosteroids are most commonly used for this indication. Several studies have demonstrated the superiority of steroids over placebo in shortening recovery from relapses. In one of the first controlled trials of ACTH for the treatment of relapses, there was found to be a significant improvement in 11 of 22 patients in the treated group

by the end of the 3-week trial period, compared to 4 of 18 in the control group.[10] A similar result

was reported from a subsequent study of 197 MS patients.[11] In the mid-1980s intravenous methylprednisolone (IVMP) was shown to be as effective as ACTH in the treatment of relapses and subsequently replaced ACTH for this indication. One trial that compared the efficacy of ACTH

and IVMP, reported no difference in outcome between the two treatment groups.[12] However, fewer adverse effects were observed with IV methylprednisolone. Despite a lack of evidence of its superiority, an intravenous, rather than an oral course of methylprednisolone is often prescribed for treating acute relapses in MS. In an attempt to discover if any such superiority exists, Barnes et al (1997) carried out a study of 80 patients, who received either IVMP (1g for 5 days) or oral

MP (48mg for 7 days, 24mg for 7 days or 12mg for 7 days).[13] None of the outcome measures exhibited any significant benefit of either regimen over the other at any time interval. Despite these significant findings, and the fact that oral MP is cheaper to prescribe and more convenient to administer, the majority of neurologists still use IVMP as the steroid of choice, the most common regimen used being 1g daily for 3 days or 0.5g daily for 5 days.

It has been suggested that steroids might also have a role in the treatment of chronic progressive MS. In 1998, the results from a Phase 2 dose comparison trial of cyclical pulses of IV methylprednisolone in secondary progressive MS, demonstrated a modest treatment effect in

favour of the high-dose treatment option.[14]

Hence, corticosteroids are effective in hastening recovery from clinical relapse. They do not, however, benefit eventual outcome, either in terms of degree of disability or subsequent disease activity.

DISEASE MODIFYING AGENTS

The management of MS not only involves the treatment of symptoms, acute relapses, and rehabilitation, but also aims to reduce the frequency and severity of such relapses and to prevent or postpone the onset of the progressive phase of the disease. Over the last decade, disease modifying drugs for MS have finally emerged, which are believed to be partially effective in altering the natural history of the disease. Such disease modifying therapies include interferon b (IFN-b), glatiramer acetate, immunoglobulins and azathioprine.

Currently, two forms of recombinant IFN- b, IFN-b-1a and IFN- b-1b have been approved by US and European regulatory authorities for the treatment of relapsing-remitting MS. IFN- b is the

most commonly used disease modifying agent in relapsing-remitting MS. IFN-b 1a (Avonex, Rebif), is a glycosylated, recombinant product from mammalian cells, which is identical to the human protein. IFN- b-1b (Betaferon, Betaseron), is a non-glycosylated recombinant product from bacterial cells, which differs from the human protein by one serine residue. IFN-b has a wide range of effects that are both immunomodulatory and antiviral. IFN- b-1b has been shown to reduce the annual exacerbation rate in relapsing-remitting MS, by approximately one-third

(p=0.001).[15] The same multicentre, randomized, double-blind, placebo-controlled trial of IFN-b-1b, also looked at the proportion of patients who were exacerbation free. During the 1st 2 years-16% in the placebo group, as opposed to 31% in the high-dose treated group (p=0.007). Also, the time to the first relapse was doubled (p=0.015) in the treatment group. This study also showed a

significant treatment-related difference in serial MRI activity.[16] Those in the placebo group showed a 17.1% increase in mean lesion area over 3 yrs Vs a 6.2% decrease in the high-dosage interferon group (p=0.002). A subgroup of 52 patients underwent serial MRI examinations every 6 wks for 2 years- a 75% reduction in the rate of new lesion formation was reported in the high-dose treatment group compared to placebo. The number of new lesions observed on the proton density scan is very important, because the number of lesions that are evident at the onset of clinical symptoms and the rate of formation of lesions at 5 yrs, will predict the clinical severity of MS at 5

and 10 year follow up.[17]

IFN-b-1b has also been shown to be effective in treating secondary progressive disease.[18] The results of a randomised, double- blind, placebo- controlled trial of IFN-b-1b for the treatment of secondary progressive MS were published in 1998. The study involved 718 patients, who were given either subcutaneous injections of 8 Miu IFN-b-1b every other day (n=360), or placebo
(n=358). The trial showed a highly significant difference in the time to confirmed progression of disability in favour of IFN-b-1b (p=0.0008).

IFN-b-1a has also been shown to have a positive treatment effect in relapsing-remitting MS. It has been shown to reduce exacerbation frequency, the accumulation of permanent physical disability and disease activity as estimated by gadolinium-enhanced lesions on brain Magnetic Resonance

Images. [19]

Hence, both IFN-b-1b and IFN-b-1a are believed to be effective disease modifying agents for the management of relapsing-remitting MS, whilst IFN-b-1b has also been proven to have an additional role in the treatment of secondary progressive disease. Side effects of the treatments are similar and include injection site reactions and flu-like symptoms or fever. Neutralising antibodies to IFN-b-1b are also detected in some patients. Patients would probably find IFN-b-1a to be a more attractive therapy than IFN-b-1b. INF-b-1a is administered by intramuscular (IM) injection once a week instead of by subcutaneous injection every other day. Also, painful injection-site reactions occur less frequently with IFN-b-1a, and there are also concerns regarding the possible loss of efficacy in those who form neutralising antibodies to IFN-b-1b.

Glatiramer Acetate (Copaxone, Copolymer 1), is another disease modifying agent that is used in the management of MS. It is a synthetic copolymer, whose structure is similar to that of myelin basic protein, one of the major constituents of myelin and the presumed autoantigen in MS. Work began to create such a copolymer after it was discovered that EAE (the animal model for MS), could be induced by immunisation using myelin basic protein. Hence, it was then theorised that a polypeptide similar in structure to myelin basic protein, might induce immune tolerance for myelin basic protein. The results of a pivotal Phase 3 multi-centre clinical trial of copolymer 1 in patients with relapsing-remitting MS, were reported in July 1995. In this trial 251 patients with ambulatory relapsing-remitting MS were randomly assigned 20mg of daily subcutaneous copolymer 1 or placebo for 2 years. The primary outcome measure was difference in MS relapse rate. The mean number of relapses was reduced 27% by glatiramer (1.19 +/- 0.13 glatiramer Vs 1.68 +/- 0.13 placebo, (p=0.007)). Significantly more patients receiving copolymer 1 were improved and more

receiving placebo worsened (p=0.037). Such change in performance were measured by a change of one step (>0.5 points) in the Kurtzke Expanded Disability Status Scale (EDSS). Glatiramer Acetate was found to be well tolerated, the most common adverse effect being an injection-site

reaction.[20] A self-limiting systemic reaction was observed in 15.2% of actively treated and 3.2% of placebo treated patients. Glatiramer Acetate is also believed to significantly reduce MRI-measured disease activity and burden, the effect on the rate of accumulation of gadolinium-

enhanced lesions being evident as early as 2 months following initiation of treatment.[21] Glatiramer Acetate has been found to be well tolerated an is thought to have less side effects compared to IFN-b. However, it must be administered daily by injection and hence might be more cumbersome than IFN-b-1b (subcutaneous injection every other day) or IFN-b-1a (weekly injection). It has also been suggested that because of the differences in the presumed mechanism of action of IFN-b and glatiramer acetate, the combination of them might well have additive effects. Although in-vitro data supports this, data developed in mice has suggested that a

combination of them is ineffective in blocking the induction of EAE.[22,23] The early MRI signature of glatiramer's effect on the disease process also differs substantially from that reported for the beta interferons. Hence, the data suggests that glatiramer acetate can be expected to reduce the relapse rate by 1/3 over the first 2 yrs and that the protection from relapses may steadily increase thereafter. Despite such data and the fact that the indications for the use of glatiramer acetate are comparable to those for IFN-b, most clinicians consider it a second line treatment for relapsing-remitting MS.

Azathioprine has been used in the treatment of MS since the 1960s, although the degree of clinical benefit has been difficult to establish. Azathioprine is a purine analogue, designed as a "pro-drug" of the cytotoxic agent 6-mercaptopurine (6-MP). Although it has many effects, the exact mechanism of its immunomodulatory effect is not known. Although glatiramer acetate and IFN-beta have convincingly shown to be effective in the long-term management of MS, they also have limitations, for e.g. their high cost, inconvenience (parenteral administration) and modest effect on disease course. Such limitations have prompted many experts to urge the reconsideration of the use of azathioprine and other immunosuppressants in the management of MS. The relative probability of remaining exacerbation-free for 3 yrs while taking azathioprine,

compared to placebo is 1.97.[24] This benefit from azathioprine compares favourably with the

reduction in exacerbation rate reported with IFN-b-1b in relapsing-remitting MS.[15] However, azathioprine is similar to IFN-b-1b, in that it offers only a modest degree of protection against the progression of disability. This benefit only becomes evident after 2-3 years. Although the results of the azathioprine trials are less robust than those of the newer agents, one advantage of its use is the long-term experience of azathioprine and hence the extensive knowledge of its side-effect profile. Even though toxicity with azathioprine is quite common, cessation of therapy is necessary in less than 10% of MS patients. The incidence of malignancy associated with treatment is uncommon and treatment is usually stopped as a result of drug-related fever, rash or gastrointestinal intolerance. The fact that azathioprine is cheap, readily available and effective in reducing relapses has helped to establish it as one of the most commonly used immunosuppressants in MS. At present, however, the evidence for its effectiveness is somewhat weak, though it may well be as good as the newer treatments. Such lack of evidence, coupled with the possibility of such severe side-effects and the lack of convincing data for immunosuppressants from MRI (as opposed to IFN-b and glatiramer acetate), has probably contributed to their rather modest acceptance. These days, azathioprine is usually only administered to patients with moderately aggressive disease, for whom the newer disease modifying agents cannot be prescribed.

To date, 3 prospective, randomised, double-blind, placebo-controlled studies have shown a beneficial effect of Intravenous Immunoglobulin (IVIG) on disease activity and accumulation of

deficits in patients with relapsing-remitting MS.[25,26] These results , though modest, are

comparable to those that have been reported for other treatments, such as IFN beta and

glatiramer acetate.[15,16,19,20] However, the amount of supportive evidence for IVIG still lags far behind that for IFN-b. Also, the mechanism of action of IVIG in the treatment of MS is largely unknown; they are thought to act most probably through immunomodulation, and perhaps even by promoting remyelination. IVIG generally has few side effects, transient rash or fatigue, headache and low-grade fever being the most common, all of which resolve within hours. A possible long-lasting side effect of IVIG therapy is severe eczema, which resolves after discontinuation of the therapy. A huge advantage of IVIG, is that it only needs to be administered once a month, in comparison to IFN-b (every other day or once a week) and glatiramer acetate (once a day). Local painful reactions at the injection site can become a problem with the usage of IFN-b and glatiramer acetate. In such cases, IVIG could be considered as a further treatment option. Despite the uncertainties surrounding its efficacy and mechanism of action, the scientific evidence that is available for the use of IVIG in relapsing-remitting MS appears to be consistent enough to allow it to be used in a number of settings (see Table 2).

Table 2. The use of IVIG in the treatment of patients with relapsing-remitting disease: points to be considered.

Concerns about its use	Factors supporting its use
1. Relatively unknown mechanism of action	1. Found to be well tolerated
2. Dose-response relationship unclear	2. Administered once a month
3. Proven Efficacy in small populations only	3. Very few contraindications to its use
4. No available MRI data parallel to larger clinical trials	
5. Not widely available and significant cost	

Mitoxantrone (Novantrone), is a cytotoxic anthracenedione that is thought to have both immunosuppressive and immunomodulatory activity. Because of such activity, mitoxantrone has been studied in animal models of MS, as well as in phase 2 and phase 3 clinical trials for the treatment of relapsing-remitting and secondary progressive MS. Mitoxantrone has been found to reduce the annual relapse rate ($p<0.001$), and to improve or stabilise relapsing-remitting and/or secondary progressive MS patients, as assessed by a number of clinical scores (EDSS,

Ambulation Index, and Standard Neurological Status).[27,28] Evidence has also been found that

mitoxantrone profoundly reduces the number of gadolinium-enhancing lesions on MRI.[29] Overall, mitoxantrone is thought to be well tolerated. Common side-effects include predictable and reversible leucopenia, mild alopecia, nausea and menstrual disorders. There is also a risk of mitoxantrone-related cardiotoxicity, which is characterised by a decrease in the left ventricular ejection fraction (LVEF), and congestive heart failure. The risk of cardiac damage increases as the total dose increases. Despite its positive clinical impact on MS patients, there is clearly an unknown potential for long-term toxicity, particularly cardiotoxicity. At the moment, it is mandatory to perform cardiac monitoring (ECG and ECHO) before, during and after stopping treatment. Hence, there are undoubtedly a lot of important questions to be answered before considering the use of mitoxantrone in preference to IFN beta or glatiramer acetate for the routine treatment of relapsing-remitting and secondary progressive MS.

CONCLUSION

Hence, there is clearly no shortage of novel compounds undergoing clinical trial for the treatment of MS. Treatment strategies currently under investigation include the induction of immune tolerance, the use of cytokines, anti-cytokines, anti-adhesion molecules and metalloproteinase inhibitors, the administration of monoclonal antibodies, agents promoting remyelination and even

bone marrow transplantation.[30]

The identification of effective technologies to treat MS has undoubtedly just begun. The introduction of IFN-b and glatiramer acetate as drugs effective in modifying the natural course of MS, has vastly improved the management of this highly debilitating disease. Such drugs have given immense hope to all those suffering from MS, and have provided the tools to further unravel the mechanisms of this condition. The development of such disease modifying agents has ensured that, although still incurable, Multiple Sclerosis is, at present, no longer untreatable.

REFERENCES

1. Raine CS, McFarland HF, Tourtellotte WW. Multiple Sclerosis: Clinical and Pathogenetic basis. Chapman and Hall.1997
2. Oksenberg JR, Hauser SL. New insights into the immunogenetics of multiple sclerosis. Curr Opin Neurol 1997; 10:181-185.
3. Alter M, Leibowitz U, and Speer J. Risk of multiple sclerosis related to age at immigration to Israel. Arch. Neurol 1996; 15:234-7
4. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: A geographically-based study 1. Clinical course and disability. Brain 1989; 112:133-46.
5. Bronnum-Hansen H, Koch-Henriksen N and Hyllested K. Survival of patients with multiple sclerosis in Denmark: a nationwide, long-term epidemiologic survey. Neurology 1994; 44:1901-7.
6. Sadovnick AD, Eisen K, Ebers GC, et al. Cause of death in patients attending multiple sclerosis clinics. Neurology 1991; 41:1193-6.
7. Poser S, Wikstrom J and Bauer HJ. Clinical data and the identification of special forms of multiple sclerosis in 1271 cases studied with a standardized documentation system. J. Neurol. Sci 1979; 40:159-68.
8. Rivers TM and Schwentker FF. Encephalomyelitis accompanied by myelin destruction experimentally produced in monkeys. J. Exp. Med 1935; 61: 689-702.
9. Ormerod IEC, Miller DH, McDonald WI, et al. The role of NMR imaging in the assessment of multiple sclerosis and isolated neurological lesions: a qualitative study. Brain 1987; 110:1579-616.
10. Miller H, Newell DJ, and Ridley A. Multiple Sclerosis: treatment of acute exacerbations with corticotrophin (ACTH). Lancet 1961; 2:1120-22.

11. Rose AS, Kuzma JW, Kurtzkes JF et al. Co-operative study in the evaluation of therapy in multiple sclerosis: ACTH versus placebo: final report. Neurology 1970; 20:1-59.
12. Thompson AJ, Kennard C, Swash M, et al. Relative efficacy of IV methylprednisolone and ACTH in the treatment of acute relapses in multiple sclerosis. Neurology 1989; 39:969-71.
13. Barnes D, Hughes RAC, Morris RW, et al. Randomised trial of oral and intravenous methyprednisolone in acute relapses of multiple sclerosis. Lancet 1997; 349:902-6.
14. Goodkin DE, Kinkel RP, Weinstock-Guttman B, et al. A phase 2 study of IV methylprednisolone in secondary progressive multiple sclerosis. Neurology 1998; 51:239-45.
15. IFN beta Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis, 1. Clinical results of a multi-centre, randomised, double-blind, placebo-controlled trial. Neurology 1993; 43:655-61.
16. Paty DW, Li DKB, UBC MS/MRI Study Group and the IFN beta multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. MRI analysis results of a multi-centre, randomized, double-blind, placebo-controlled trial. Neurology 1993; 43:662-7.
17. O'Riordan JI, Thompson AJ, Kingsley DPE et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. Brain 1998; 121:495-503.

18. European Study Group on Interferon beta-1b in secondary progressive MS: placebo-controlled, multi-centre, randomised trial of interferon beta-1b in the treatment of secondary progressive multiple sclerosis. Lancet 1998; 352:1491-7.
19. Jacobs LD, Cookfair, DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing-remitting multiple sclerosis. Ann. Neurol. 1996; 39:285-94.
20. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer-1 reduces relapse rate and improves disability in relapsing-remitting MS: results of a phase 3 multi-centre, double-blind, placebo-controlled trial. Neurology 1995; 45:1268-76.
21. Comi G, Filippi M, Wolinsky JS. European/Canadian glatiramer acetate study group: multi-centre, double-blind, randomised, placebo-controlled study of the effects of glatiramer acetate on MRI-measured activity and burden in patients with relapsing-remitting multiple sclerosis. Ann. Neurol. 2001; 49:290-7.
22. Milo R, Panitch H. Additive effects of copolymer-1 and interferon beta-1b on the immune response to myelin basic protein. J. Neuroimmunol 1995; 61(2):185-93.
23. Brod SA, Lindsey JW and Wolinsky JS. Combined therapy with glatiramer acetate and a type 1 interferon (IFN alpha) does not improve experimental allergic encephalomyelitis. Ann. Neurol 2000; 47:127-31.
24. Yudkin PL, Ellison GW, Ghezzi A, et al. Overview of azathioprine treatment in multiple sclerosis. Lancet 1991; 338:1051-1055.
25. Fazekas F, Deisenhammer F, Strasser-Fuchs S, et al. Treatment effects of monthly intravenous immunoglobulin on patients with relapsing-remitting multiple sclerosis: further analysis of the Austrian Immunoglobulin in MS study. Multiple Sclerosis 1997; 3:37-42.
26. Edan G, Miller D, Clanet M, et al. Therapeutic effect of mitoxantrone combined with methyprednisolone in multiple sclerosis: a randomised, multi-centre study of active disease using MRI and clinical criteria. J. Neurol, Neurosurg, Psychiatr 1997; 62:112-18.
27. Millefiorini F, Gasperini C, Pozzilli C, et al. Randomised, placebo-controlled trial of mitoxantrone in relapsing-remitting MS: 24 month clinical and MRI outcome. J. Neurol 1997; 244:153-9.
28. Hartung HP, Gonsette RE and the MIMS study group. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, randomised, observer-blind European phase 3 multi-centre study. Clinical data. Multiple Sclerosis 1998; 4:325.
29. Sorensen PS, Wanscher B, Jensen CV, et al. IV immunoglobulin G reduces MRI activity in relapsing-remitting MS. Neurology 1998; 50:1273-81.
30. Hohlfeld R. Biotechnological agents for the immunotherapy of multiple sclerosis. Principles, problems and perspectives. Brain 1997; 120: 865-916.