Multiple Sclerosis: A Review of Existing Therapy and Future Prospects

Pages with reference to book, From 20 To 24

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Multiple sclerosis (MS) is an incurable neurological illness that frequently causes chronic disability. Neurologists broach the diagnosis with dread. "I"II end up in a wheel chair' is the anguished cry of the newly diagnosed and mostly young patients. The past decade has improved our understanding of the immunopathogenesis ofMS enormously. This has led to a plethora of clinical trials and the resultant emergence of several, new drugs in. various stages of development. In 1993, Food and Drug Administration (FDA) approvedBetaseronfor the treatment of MS. Todate, this is the only drug approved by the FDA, specifically for the treatment of MS. However, it would not be too long before several other drugs are approved, leaving the neurologist bewildered having gone from a state of practically little to offer to a state of several options to choose from. This review discusses the status of current and future therapy in the treatment of MS.

Multiple sclerosis EMS) is the most common demyelinating disease of the human central nervous system (CNS). Medline includes over 13000 articles on MS since 1966 that exclude book chapters and other references. MS typically affects the youth and women more than men, between the ages of twenty and forty. Clinically, the illness is characterized into a relapsing-remitting (RR) or chronic progressive (CP) stage although more precisely defined stages exist for research purposes. It tends to follow a highly unpredictable course leading to chronic and sometimes devastating disability. More recently, follow up data suggested that the disease may fall into a pattern after several years[1].

Despite decades of hectic research and better understanding of immunological mechanisms involving human CNS disease, the cause of MS remains unknown. However, it is widely believed that MS is the result of an- autoimmune disorder in a genetically susceptible individual, mediated by autoreactive T cells that migrate into the CNS and initiate the inflammatory deniyelinating lesion[2-4]. Regardless of the plausibility of this theory and without going into details, several aspects of immune mediated pathology of MS remain unexplained. This is an attempt to review the status of current therapy and future prospects in the treatment ofMS.

Established treatment of exacerbations of MS

Exacerbations or acute attacks of MS are usually treated with corticosteroids (CS) or adrenocorticotrophic hormone (ACTH). This widely practised treatment is based upon the anti-infiaiurnatoiy and immunosuppressive propertied of CS and ACTH. Of the two, CS are generally preferred over.

ACTh. High dose intravenous (My methyIprednisolone (IV MP; 500 to 1000 mg a day for three to seven days) has shown not only to reduce the severity and duration of relapses[5,6], but also decrease the numberof contrast enhancing lesions seenon brain magnetic resonance image (MRI)[7]. Furthermore, a large randomized trial in the treatment of acute optic neuritis showed that IVMP delayed the development of MS in the first two years of treatment[8], although that effect seemed to have reduced to the level of the placebo group at three years after treatment[9]. The decision to pursue treatment with steroids for an acute exacerbation of MS lies strictly with the clinician and the patient although there seems little doubt regarding the efficacy of steroids in the treatment of anacüte exacerbation of MS.

Investigational therapies for acute exacerbations of MS

Two randomized clinical trials involving plasmapheresis and intravenous immunoglobulin (IVIG) are underway to investigate the effect of these therapies in the treatment of acute MS. There have been

reports of efficacy of plasmapheresis in the treatment of acute fulminantMS when conventional treatment with steroids had failed[10], yet the mechanism of its benefit in MS remains unclear. Similarly, anecdotal experience and a randomized clinical trial suggested the efficacy of IVIG in the treatment of RR type of MS warranting a larger phase III study[11]. The mechanism of action of IVIG in the treatment of acute MS is also poorly understood despite several indications in other immune mediated neurological disorders. In general plasmapheresis and IVIG are better used as second line therapies for the treatment of severely incapacitating attacks of MS when conventional Ireatment with high dose IVMP has failed.

Treatment primarily aimed at reducing the number of attacks in RRMS

A number of therapies have recently emerged ill the treatment of RRMS. In all likelihood, in the near future, the neurologist will have more than one option to exercise when deciding appropriate therapy for a patient with MS. This will be in striking contrast to the dismal outlook for MS patients in the not too distant past.

Interferon beta-lb (Betaseron): In 1993 Food and Drug Administration (FDA) in the United States approved Interferon beta-lb (Betaseron) for the treatment of ambulatory RRMS patients. This decision was based upon the results of a large clinical.trial that showed that 8 million units (MU) of Interferon beta-lb given subcutaneously (SC), every other day reduced the number of attacks by 30%[12]. It also showed that treatment with this dose of interferon beta-lb reduced the total number of lesions as well as new and contrast enhancing lesions seen on brain MRI[13]. Interferon beta-lb acts by reducing interferon gamma (IFN-g) secretion by activated T lymphocytes as well as minimizing T cell lymphoproliferative responses and reducing tumor necrosis factor-alfa (TNF-a) secretion[14]. All three mechanisms are important in controlling immune mediated and cytokine induced damage in MS. This trial was an important study since we now know that MRI lesion load and enhancement bears a significant correlation with disease disability. Furthermore, the final outcome report of the five year follow-up trial withBetaserontends to support the results seen at two years of treatment with Betaseron[15].

Interferon beta-la: Another recently reported large randomized study showed that Interferon beta-la given at a dose of 6 MU intramuscularly once a week, reduced the number of attacks by about 30% and also reduced the lesion load on brain MRI[16]. However, the primaiy outcome of this stUdy was disease progression. Interferon beta-ia is the only agent reported todate that has clearly shown to slow down disease progression ma statistically significant manner in MS patients. The proposed mechanism of action is similar to interferon beta-lb and thus the effect on disease progression seen in this study (not seen with Interferon-beta Ib) may be the result of different clinical profiles of the patient population in the two studies. The drug is also being tested in Europe while it awaits FDA approval in the United States, anticipated in 1996.

Interferon-alfa: Interferon-aifa (IFN-a) was also evaluated in a randomized, double-blind placebo-controlled pilot trial[17]. Results from this small study are encouraging but need to be confirmed in a larger study.

Copolymer-I: A pilot study with Copolymer 1 (Cop-i) in i987 demonstrated a reduction in the relapse rate by about 50%[18]. Johnson et al recently reported in a large randomized, multicenter trial, the efficacy of copolymer-1 (Cop-i) in the treatment of RRMS[19]. The study showed that daily SC administration of 20mg of Cop-i reduced exacerbations of MS by approximately 30%. MRI data from this study is not available as yet. Cop-I is a synthetic polymer that is cross-reactive with myelin basic protein (MBP). While the precise mechanism of action of Cop-I is unknown, it may compete with MBP for major histocompatibility complex (MHC) class-Il binding sites and also induce suppressor cells[19]. Cop-i is pending approval by the FDA, anticipated in 1996.

Oral Myclin: Weiner et al. reported the results of a small pilot study that oral myelin was effective in reducing the relapse rate[20]. Surprisingly, the effect was seen predominantly in human leukocyte antigen

DR-2 (HLA DR-2) negative male patients. This led to a phase Iii, multicenter study with oral myclin that includes a large number of male HLA DR-2 negative patients. The study is expected to be completed in 1997. Oral myclin therapy is derived from the concept of "oral tolerance" which is based on the observationthat proteins, that pass through the gastrointestinal tract generate systemic "hyporesponsiveness". In recent years a great deal has been learned about oral tolerance[21]. Depending upon the amount of antigen fed, orally administered antigens result in the generation of regulatory T cells, TI-i-type 2 cells that secrete interleukin (1L)-4, IL-10 and transforming growth factor-beta (TGF-b); cytokines that help in suppressing inflammation and activation of T cells. Oral tolerance is also under investigation in human rheumatoid arthritis, uveitis and juvenile autoim— mane diabetes mellitus with encouraging results from initial pilot studies.

Treatment focused on progressive MS

More recently, there has been a lot of attention on attempts to halt or slow down the progression of disability in MS since a fairly large number of RRMS patients (50-70%) enter into a progressive phase at some point during the course of their illness. While a number of exciting therapies have emerged as potentially useful, on the dow'n side, toxicity and modest clinical benefits of these agents have been a limiting factor in tl)eir use.

Cyclosporine: Although there may be a potential benefit from this commonly used immunosuppressant for the prevention of transplant rejection, a high dropout rate ma large clinical trial and toxicity has limited its use in MS[22]. Few MS specialists are commonly using cyclosporine in treating progressive MS nowadays.

Cyclophospharnide: Cyclophosphamide is an alkylating agent and a commonly Used anti -neoplastic drug. There is some evidence that cyclophosphainide may stabilize disease progression for two to three years either alone or in conjunction with steroids. However, another study reported results to the contmry[23]. Nevertheless, cyclophosphamide remains a potentially effective therapeutic option in progressive MS specially those patients who may be rapidly progressing or may have become steroid dependent. It does require careful monitoring and follow up.

Azathioprine: Azathioprine is another immunosuppressant agent used in the treatment for the prevention of transplant rejection. Results of studies of azathioprine in progressive MS though, conflicting, but are indicative of some benefit[24,25]. It is at best beneficial for two to three years and requires cautious monitoring of patients. Howevex; because of the oral route, it remains a popular treatment in chronic progressive MS patients.

Methotrexate: A potent immunosuppressant and anti-in— flammatory best known for its use in rheumatoid arthritis, was recently reported to have some improvement in upper extremity function in a group of progressive MS patients in whom no other significant benefit was seen[26]. \\Vhile oral methotrexate may be safe and beneficial for the treatment of progressive MS, it needs to be tested in a larger study.

Mitoxantrone: Unfortunately an open label study with this anti- neoplastic drug did not show any significant benefit in the treatment of progressive MS[27]. However, a double-blind study is nearcompletioninEurope that may reveal more information regarding the efficacy ofmitoxantronefortreatingprogressive MS patients.

Colchicine: Coichicine, although better known for it& use in the treatment of gout, was studied in an open label trial in a small number of chronic progressive MS patients[28]. Like many uncontrolled open lable trials, the results of this study also suggested a favourable response. However, no larger, randomized controlled studies have been conducted to con-firm the benefit of colchicine in progressive MS.

Future prospects in the treatment of progressive MS

Several clinical trials are underway to examine the efficacy of promising agents in the treatment of progressive MS. They have largely stemmed from years of rigorous research and explosive expansion

in our understanding of immunological mechanisms involved in the pathogenesis of MS.

Linomide: Linomide is a novel immunomodulating drug that is being tested in neoplastic disorders as well as MS. Studies have confirmed the efficacy and safety of linornide in the treatment of progressive MS in humans as well as animal models of chronic relapsing MS[29,30]. A large multicenter phase III study is undenvay to confirm the results of the earlier trials and expected to be completed in 1998. Linomide has been shown to augment natural killer cell (NK cell) activity (usually depressed in MS patients) and also decrease interferon gamma released from activated T cells. However, the precise mechanism by which linornide may benefit MS is uncleat Given the oral route of administration and tolerable side effects, linomide holds alot of promise in the treatment of progressive MS.

Interferon beta-lb (Betaseron): Interferon beta-lb is now being tested in a clinical trial for the treatment of secondary progressive MS. This is a huge randomized study involving thirty centers in North America and expected to enroll 900 MS patients. This is also a three arm trial like the earlier study[14], with one being,placebo and two treatment arms to test 8 MU and 5.4 MU/m^2 of body surface area, given SC on alternate days respectively. Interestingly, a total of 10000 brain MRI scans are expected to be obtained during this study. This will be perhaps the first and the last time, that such a large number of MRI scans will be studied and certainly provide invaluable information about the natural history of the disease "imaged", both treated and untreated.

Interferon Consensus-i: Interferon consensus-i is a synthetic interferon sharing structural similarities with both interferons alpha and beta. A phase II study has been completed in the treatment of hepatitis C. A similar phase II study to test the efficacy and safety in MS is about to start and most likely lead to a larger phase III study. This interferon works in the same fashion as other recombinant interferons discussed previously, although data suggests that it may. be more efficacious and less toxic at higher doses[31].

Cladribine (2-Chlorodeoxyadenosine): Cladribine has been extensively used in the successful treatment of leukeinias and lymphomas. A recent study in progressive MS patients suggested that intravenous cladribine given on a monthly basis for one year reduced clinical disease progression and MRI activity[32]. A large multicenter phase III clinical trial is underway to confirm the earlier results in chronic progressive MS patients. Drug toxicity and route of administration are major concerns. Nevertheless, the phase II study results and anecdotal experience with cladribine in MS has been very encouraging.

Chimeric Monoclonal Antibodies to CD4: Chimeric monoclonal antibodies are composed of human "constaut region" coupled with a mouse "variable region". This allows for a more specific approach towards the target antigen without provoking an immunogenic response when used in humans. Monoclonal antibodies are being studied inMS patients based on the fact that T helper/inducer cells are thought to be pathogenic inMS (by attacking the immunodominant regions of the MBP) and causing the cascade of events leading to chronic demyelination. An open lable study in MS patients with intravenously administered monoclonal antibodies to CD4 demonstrated prompt and sustained depletion of CD4 T cells without serious toxicity[33]. The study was designed to assess safety only. Phase II studies are being conducted to test the efficacy of these monoclonal antibodies in MS.

T cell vaccination: Innoculation of attenuated clones of T cells recognizing the inciting autoantigen can specifically prevent the induction of disease in animal models of autoimmune diseases[34,35]. This is based upon short lived anti-activated T cell responses and long-lived anti-clonotypic T cell responses, thus the tenn T cell vaccination. Furthermore, partial short term immunosuppression is also seen as evidenced by down regulation of subsequent stimulation via the CD2 pathway. Two phase I studies in MS patients have demonstrated the safety of autologous innoculation of T cells[36,37]. Further clinical trials are being planned to assess the efficacy of T cell vaccination in MS.

T cell Receptor Therapy: In a phase one study, MS patients were injected with immunogenic regions

of the T cell receptor that recognize inimunodominant regions of MBP[38]. This therapy is based upon the concept that T cell receptor usage by MBP reactive cells is restricted and such therapy will diminish T cell mediated immune responses to MBP. Further studies are underway to examine the efficacy of T cell receptor peptide therapy in MS.

Total Lymphoid Iriadiation (TLI): TLI has been used in Hodgkin's disease without significant toxicity. Besides having a profound immunosuppressive effect, TLI also generates "suppressor cells" that tend to regulate immune responses. Two studies have reported conflicting results of treatment with TLI in progressive MS patients[39,40]. The former study supported the use of TLI in the treatment of progressive MS, while the later study did not indicate any benefit. A larger double-blind randomized study is undenvay to study the efficacy of TLI in conjunction with steroids.

Arninopyridines: Aminopyridines arc mentioned in this sectioneven though they are not immunomodulating therapies and unlikely to affect the long term prognosis or outcome in MS. However, since the agents hold immense potential in improving the quality of lives in MS patients, a review onMS therapy without aminopyridines will be unfair.

Dernyelination leads to impaired nerve conduction and conduction blocks, which is widely regarded as the pathophysiologic mechanism for the clinicaldeficits seen in MS[41]. Aminopyridines aze agents that block potassium channels located on the exposed demyelinated axonal surface. It has been suggested that the conduction block in demyelinated fibers is partly due to the appearance of aminopyridine-sensitive potassium channels[43]. Thus blocking of the potassium channels improves nerve conduction, leading to symptomatic improvement. This led to years of research and clinical trials with aminopyridines. Two promising agents have thus far emerged as a result of these efforts and are being tested in various stages of development. 3,4-Diaminopyridine (DAP) and 4-Aminopyridine (4-AP) have been extensively studied in the symptomatic treatment of MS patients. DAP has been reported successfully in two studies[42,43] and 4-AP was also recently reported to be beneficial in reducing deficits in MS patients[44,45]. Both agents, especially 4-AP are in various stages of development and expected to enter phase III trials in 1996.

Emerging concepts in the treatment of multiple sclerosis

The evidence of an immune pathogenesis of MS is strong. After several years without effective treatment, we appear to be on the threshold of seeingan exponential increase in new therapies. This is happening because of better designed protocols, greater understanding of the pathogenesis of demyelination and the use of MRI as a major end point of efficacy. Furthermore, the acquisitionofrecombinanttechnology in the ~eighties" has made an immense difference in drug develOpment and production. Newer therapies can be expected, perhaps used incombinations, which will also alter the long term prognosis in MS, favourably. These new and exciting concepts emerging in the treatment of multiple sclerosis include recombinant myelin, basic protein as a more specific antigen to induce oral tolerance instead of oral myelin, protein growth factors to induce CNS remyelination, glial cell transplant therapy, blocking of T cell activation, suppression of TNF-a' induced inflammatory damage through TNF-a blocking agents or synthetic competitive TNF-a receptor proteins, and adhesion molecule therapy to block T cell migration into the CNS. Interestingly, several novel immuno-suppressive agents being developed for the treatment of transplant rejection and rheumatoid arthritis will also have therapeutic implications for MS treatment based onT cell and inflammatory cytokine regulatory mechanisms. Infact, the list merits a separate review to beware the interested reader of new' concepts that have implications not only for MS but autoimmune diseases in general.

Conclusion

For neurologists, having to choose among relatively non-toxic drugs that may alter the natural history

of MS is exciting and reassuring. Unfortunately none of these drugs provides a cure for the disease. Whether combination therapy will be additive remains to be seen. For the large number of individuals who are cuffently disabled, the more ambitious but realizable approach of glial repair holds the best hope for reversing persistent disabilities. The search for an effective therapy is compounded by the remarkable inter-patient variability in disease course. Nevertheless, additional therapies based on an ever improving knowledge of the disease process must be sought.

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