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Reason for hope: the advent of disease-modifying therapies in multiple sclerosis

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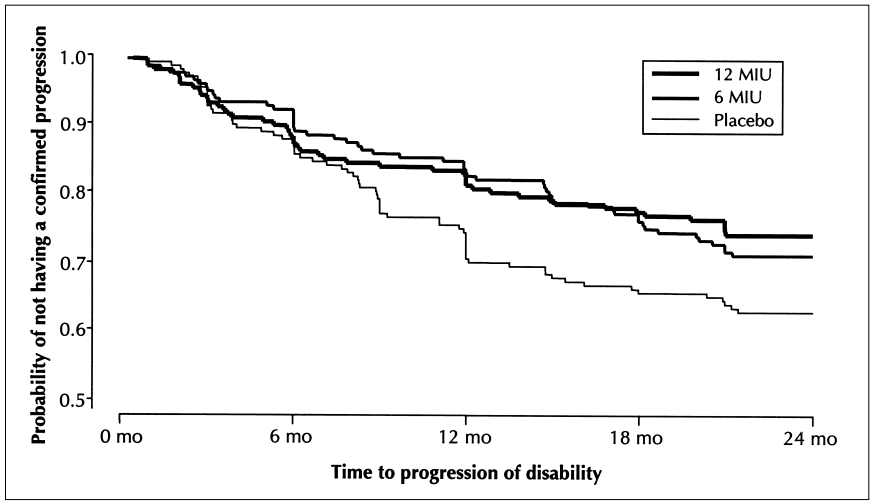
Technology: Cytokine- and antigen-based immunosuppressive therapies for multiple sclerosis.

Use: In the last decade partially effective disease-modifying drugs for multiple sclerosis (MS) have finally emerged. All require self-injection and include interferon-β (Betaseron, Avonex and Rebif) and glatiramer acetate (Copaxone). In general, these agents reduce the frequency of MS relapses by one-third and slow progression of disability, at least as shown in relatively short-term (2–3 years) clinical trials.

History: MS is the commonest disabling neurologic disorder of young Canadian adults, exacting a heavy toll on patients and their families. Pathophysiologically, inflammatory demyelination and axonal degeneration occur, with attendant neurologic symptoms and signs. Quality of life tends to be lowered,[1] unemployment frequent and the condition chronic, with median survival of about 30 years.[2] The prevalence of MS in Canada is particularly high, estimated at 1 in 1000 to 1 in 500.[3] In 85% of cases patients begin with the relapsing-remitting form of the disease, although half of such patients enter the debilitating secondary-progressive phase within 10 to 15 years.[4] Until the interferons appeared, treatment was purely symptomatic and largely empiric.

Interferon-β has a wide range of biologic effects that are both immunomodulatory and antiviral. Beta-interferon comes in 2 types: interferon beta-1a (Avonex and Rebif), which is identical to the human protein, and interferon beta-1b (Betaseron), which differs from the human protein by one serine residue. Glatiramer acetate is thought to induce immune tolerance for myelin basic protein, the presumed autoantigen in MS.The decision to try interferon-β in MS patients was largely inspired by their effectiveness in animal MS models. Interferon-β was first administered intrathecally by Jacobs in 1981.[5] There were many subsequent small trials using interferon-β, but not until 1993 was a large appropriately designed multicentre trial involving patients with relapsing-remitting MS completed and published.[6] Further trials of interferon-β in this patient population included the Multiple Sclerosis Clinical Research Group Trial, published in 1996,[7] and the PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study, published in 1998.[8] In late 1998 a mildly positive trial of Betaseron in the treatment of secondary-progressive MS was published, although results from a negative trial of Rebif in the same condition were presented in early 1999.[9,10] Positive results from a major multicentre trial of glatiramer acetate appeared in 1995.[11]

Promise: The advent of these disease-modifying therapies is a boon to patients and their physicians — gone is the therapeutic nihilism of the past. In relapsing-remitting MS, the early phase of the disease, these agents reduce the frequency of relapse and the progression of disability by about one-third (Fig. 1). Interestingly, they show much stronger effects in controlling the progression of disease as seen on brain MRI, particularly at higher doses. The recent Betaseron results in the treatment of the more challenging secondary-progressive form of the disease are also encouraging, although the observed treatment effect of slowing one-fifth of patients from progressing one disability level over 3 years is very modest indeed. For example, a 36-year-old woman with secondary-progressive MS who walks with a cane has a disability level of 6.0. With treatment for 3 years, her likelihood of progressing to the next disability level of 6.5 (requires 2 canes or a walker) falls from about 50% to 40%. With an observed absolute risk reduction for progression of about 10%, the number needed



PRISMS Study / Dr. G. Ebers

Fig. 1: Time to progression of disability in patients with multiple sclerosis receiving interferon beta-1a (6 or 12 million IU) or placebo in PRISMS Study.[8] Reprinted with permission from Serono Canada Inc.

to treat in order to slow one patient from progressing by one disability step in secondary-progressive MS over 3 years is 10.

In summary, the effectiveness of these agents in preventing relapses is well established. Whether they actually slow the progressive neurologic deterioration seen in secondary-progressive MS independent of their effect on relapse prevention remains debatable. The Health Protection Branch approved Betaseron treatment for secondary-progressive MS in 1999. Up until then, approval of these drugs had been restricted to use for relapsing-remitting MS.

Problems: However gratifying these developments, it is equally clear that these agents are only a first step in truly controlling MS. Interferon therapies are usually associated with flu-like side effects (myalgia, fever), particularly in the first 2 months of therapy. Glatiramer acetate causes fewer side effects but requires daily injections rather than injections every other day or weekly. Neutralizing antibodies that are of uncertain significance may occur with interferon therapies as well.

Even more problematic is the merely partial effectiveness of these treatments. They do not reverse neurologic deficits or even freeze the disease at its current status. Rather, they slow progression and are akin to transferring a passenger from a sinking ship to a life boat in the hope that a definitive rescue can be achieved in the not-too-distant future.

Complicating the use of interferons and glatiramer acetate are several medical, economic and political factors. Although effective in the clinical sense of the word, their effect on quality of life is unclear. These drugs are very expensive, costing between $12 000 and $20 000 annually. Showing that these drugs are cost-effective using short-term, conventional analytical methods is difficult. However, in the long run, slowing the progression of disability will likely lower the societal cost of this illness by reducing hospitalization, institutional and other costs.

Although these drugs are in use in Canada, provincial government rules for their funding differ across the country. The regulations are, however, invariably somewhat restrictive and administratively cumbersome, presumably to avoid casual drug prescription by the unfamiliar or use by the uncommitted.

Future prospects: There is no shortage of compounds currently undergoing clinical trial for the various forms of MS. Therapies being studied include cytokines, anticytokines, anti-adhesion molecules, matrix metalloprotease inhibitors, T-cell receptor peptides, myelin basic protein analogues, antiviral agents, insulin growth factors, immune globulin and antineoplastic agents. It is hoped that one or more of these agents will emerge as the true rescuers of MS patients. Even transplantation of bone marrow stem cells or oligodendrocyte precursors is being contemplated.

Studies of agents given orally, intravenously once a month, or even by inhalation are on the horizon. As in oncology, MS patients will probably receive treatment with multiple drugs. Costs associated with treating MS will remain high in terms of short-term treatment, but they will seem less so when viewed over the long term and in a broader societal perspective. In time, the economies of scale, technological innovation and patent expiration will bring down these costs.

The identification of effective technologies to treat MS has just begun. There is reason to hope that the ravages of this disease can be stopped and, dare I say, even reversed.

Competing interests: Dr. O'Connor has received speaker's fees and travel assistance to attend meetings from Berlex Inc., Teva-Marion Partners Inc. and Ares-Serono Inc.

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