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Editorial

More immunotherapy for multiple sclerosis

In the two years since we last reviewed the immunological treatment of multiple sclerosis,[1] argument has raged about the value of interferon-β and other promising drugs which have been subjected to trials and marketed in some countries. The argument exists because of the absence of accepted criteria which would command inclusion of a new treatment for multiple sclerosis in the international, national, or individual pharmacopoeia. Lack of such criteria has placed neurologists, patients, and healthcare purchasers at the mercy of the formidable advertising skills of the pharmaceutical industry.

Clinical outcome measures

The outcome measure most commonly used to test efficacy in treatment trials has been relapse frequency, but this is unsatisfactory as a criterion for acceptance in a pharmacopoeia. Relapses may have only transient, trivial effects on patients' lives: according to the usual definition, transient symptoms, which may be trivial to both patient and neurologist, would "count" as a relapse provided that they last more than 24 hours.[2] At the other extreme a relapse may cause permanent, devastating paralysis, blindness, or incoordination. Most relapses are intermediate in severity. In the best and most arduous trial designs, the protocol requires that investigators verify the presence of an "objective" neurological deficit before a reported episode is scored as a "relapse". In the first major trial of interferon-β-1b, a non-glysylated form prepared in *Escherichia coli*, the reported relapse rate was significantly less in the patients treated with low (1·6 MIU) and high (8 MIU) subcutaneous doses on alternate days than in the placebo treated group.[3] However, the proportion of patients remaining free of verified relapses was 34·8% on interferon-β-1b and 25% on placebo, a 9·8% difference which was not significant.[4–6] Such attempts to "harden" end point data are laudable but, even when achieved, their interpretation is still complicated by the subjectivity of both the patient's decision to report symptoms and the neurological examination itself. The usefulness of relapses as an end point would be enhanced if combined with a meaningful measure of the disability generated by each relapse. Relapse rate can only be a useful end point in relapsing-remitting multiple sclerosis. Even then reduction of relapse frequency may be a bad omen because it may be explained by the onset of the secondary progressive phase.

The impact of disease progression on the lives of patients would be a more meaningful and robust end point. Unfortunately no agreement has been reached on whether it is better to measure impairment, disability, handicap, or quality of life.[7] Measuring one of these dimensions without including at least one of the others is difficult. Visual "impairment", for instance, is traditionally assessed by measuring the "disability" in reading the Snellen chart. "Disability" due to fatigue is reflected in the amount of "handicap" caused in the patient's ability to work, study, and enjoy him or herself. Many measures of impairment, such as tendon reflexes, plantar responses, and vibration sense, do not relate meaningfully to ability or disability and are inappropriately used to assess the outcome of a new treatment. Handicap and quality of life measures are important in assessing the social and economic burden of disease on patients' and on their communities, but they are also very subjective and dependent on level of education, occupation, and socioeconomic status, and affected by adapting home or work environments. Measures of disability remain the most relevant and meaningful end points both to physicians and patients but none of the clinical rating scales currently used for multiple sclerosis is completely satisfactory.[8] The scale usually used, the Kurtzke expanded disability status scale,[9] incorporates both impairment and disability. It is heavily weighted for ambulation and has an interrater variability of at least 1·0 to 1·5 steps out of the 0–10 steps available.[10 11] The Scripps neurological rating score[12] converts the neurological examination into an ordinal impairment scale with an arbitrary weighting system and interrater variability of up to 19 of the 100 points.[13] More meaningful lower[14] and upper[15] limb impairment/disability scales only measure limited aspects of the wide range of disabilities encountered in multiple sclerosis. The need for a new, comprehensive, and meaningful clinical scoring system is recognised.[16]

Magnetic resonance imaging

The difficulty in developing satisfactory measures of clinical outcome and the slow rate of progression of disability in multiple sclerosis have driven investigators to use surrogate laboratory markers which are objective and generate numerical data to which powerful statistical tests can legitimately be applied. Evoked potentials[17] have been replaced by MRI as the outcome measure of choice.[18] The sensitivity of MRI as a diagnostic tool and the greater frequency of new MRI lesions compared with clinical relapses led to

its use as a primary and secondary outcome measure in clinical trials. However, the lack of a consistent association between clinical relapses and activity detected by conventional MRI has been a major concern.[19] Cross sectional studies showed modest ($r = 0{\cdot}23$–$0{\cdot}26$)[18 20] or no[21] correlation between the T2 weighted lesion load and disability assessed by the EDSS. Longitudinal studies in patients presenting with isolated syndromes suggestive of multiple sclerosis showed that initial T2 weighted lesion load predicted subsequent disability and that the degree of disability after five years was strongly correlated ($r = 0{\cdot}75$) with the T2 weighted lesion load at that time.[22 23] However, longitudinal studies in patients with clinically definite multiple sclerosis have shown only modest correlation between the change in T2 weighted MRI lesion load and change in EDSS ($r = 0{\cdot}13$–$0{\cdot}23$).[20 24] This discrepancy is scarcely surprising as T2 weighted MRI of the head does not assess spinal cord pathology, which is more likely to be responsible for those aspects of impairment and disability measured by the EDSS,[25] and does not detect demyelination and axonal loss, which may be responsible for secondary progression.[26] A stronger correlation ($r = 0{\cdot}52$) has now been shown between mean gadolinium enhancing MRI lesion frequency and EDSS in patients with relapsing remitting multiple sclerosis.[27] This correlation was even greater in those patients with severe disability (EDSS $\geqslant 4{\cdot}0$). Other MRI acquisition methods such as T1 weighted imaging, magnetisation transfer ratio, and proton magnetic resonance spectroscopy may detect abnormalities which are more closely related to disability.[28] These modifications will enhance the usefulness of MRI in monitoring disease activity but it will remain a surrogate marker, subordinate to appropriate measures of clinical change.

Clinical trials

Against the background of these difficulties in outcome assessment, we must assess the latest information about interferon-β and other treatments. Since our last editorial on this subject,[1] the final outcome of the interferon-β-1b trial has been published.[20] Although the authors put a different gloss on their findings, the results of the follow up after five years are disappointing. Although there was a trend in favour of interferon-β-1b, the reduction in relapse frequency was not significantly less in the 8 MIU (high dose) group than in the placebo group in the past two years and there was no significant reduction in progression of disability after five years. It is possible that the effect of interferon-β-1b is masked by the development of neutralising antibodies in 38% of patients after three years. Interferon-β-1b has been released on the North American and some European markets, and has been met with varying levels of enthusiasm by neurologists and healthcare purchasers. In the United Kingdom strict guidelines have been issued, confining treatment to ambulant relapsing-remitting patients who would have fulfilled entry to the seminal trial,[3 18] and some health authorities have made available limited funds for its prescription. Many British neurologists remain unpersuaded of the value of the drug and are reluctant to prescribe it, emphasising the need for better evidence of efficacy.[29]

The eagerly awaited trial of interferon-β-1a, the glycosylated form prepared in Chinese hamster ovary cells, purports to show an effect on progression of disability,[30] but there are problems with the interpretation of this result. The primary outcome measure was sustained progression of disability of at least one point on the EDSS scale sustained for at least six months. Although 301 patients were randomised, the investigators unfortunately decided to terminate the study one year earlier than originally planned so that only 172 patients were followed up for two years. Although a Kaplan-Meier analysis of all the data showed that the curves defining the rates at which progression occurred differed significantly ($P = 0{\cdot}02$), the early termination meant that the actual proportions of patients seen to have progressed after two years were not significantly different (18/85 interferon-β-1a compared with 29/87 placebo recipients, $P = 0{\cdot}07$). Although the trial was designed to measure prevention of progression of "disability", the randomised patients had EDSS scores between 1·0 and 3·5, a part of the scale which measures impairment more than disability. The investigators are to be commended for their efforts to have each examination performed by the same rater for an individual patient, as 100% agreement in this part of the scale can only be achieved if agreement is defined as $\leqslant 1{\cdot}0$ points for intrarater and $\leqslant 1{\cdot}5$ points for interrater reliability.[10] Nevertheless, the very fact that the difference being sought in this trial is on the borderline of what two observers can reliably detect (and within the range in which patients fluctuate within a single day) indicates the small size of the effect of the drug so far demonstrated. The trial also documented significant reductions in relapse rate and in the number and volume of gadolinium enhanced lesions. Ironically—as this was one of the main arguments in favour of the efficacy of interferon-β-1b—the T2 MRI lesion load was not significantly reduced. The effect of interferon-β-1a in reducing the number of gadolinium enhanced lesions receives some support from the Italian study, published in this issue,[31] with a brand of interferon-β-1a manufactured by Ares-Serono. It is difficult to find a commentator in this field who is not in some way involved and we make no secret of the fact that our own centre is participating in trials of this particular brand of interferon. In this Italian trial 68 patients had an average of 3·0 (SD 4·3) gadolinium enhancing lesions/month during six months before treatment with 3 or 9 MIU interferon-β-1a subcutaneously three times a week and significantly less 1·3 (2·2) lesions/month during six months on treatment. However the absence of contemporary controls seriously reduces the strength of any conclusions which can be drawn from these data as the frequency of clinical relapses and of gadolinium enhancing lesions both diminish with the passage of time. In our view the results of the interferon-β-1a studies need to be confirmed with further studies showing more convincing evidence of efficacy in slowing disability before the drug is adopted in routine neurological practice. Such trials are in progress.[32 33]

Copolymer 1 is now competing with interferon-β since the publication of a phase III placebo controlled trial in which the relapse rate in 125 treated patients was reduced to 1·19 over two years compared with 1·68 in 126 placebo patients, a 29% reduction which was significant ($P = 0{\cdot}007$).[34] Copolymer 1 is a mixture of synthetic basic polypeptides which is known to suppress experimental autoimmune encephalitis in guinea pigs, a model with an unproved relation to human multiple sclerosis. It is given by daily subcutaneous injection and caused pain at the injection site in 64% and systemic reactions in 15% of recipients. Although blinding was not reported, these reactions were more common than in the placebo recipients and are likely to have unblinded the study. The patients randomised in this trial had an EDSS score between 1·0 and 5·0 and relapsing-remitting disease with two relapses in the previous two years. Progression of disability was a secondary outcome measure. There was a marginal reduction in the increase in EDSS from baseline in the copolymer 1 patients (mean $-0{\cdot}05$ (SD 1·13)) compared with the placebo patients (0·21 (0·99); P =

0·023) but no difference in the ambulation index. Unfortunately, when progression was defined more rigorously as a sustained increase of one or more EDSS steps, then there was no significant difference between the groups: 24·6% of the placebo and 21·6% of the copolymer 1 patients progressed. Previous, smaller, trials of copolymer 1 did not show a significant effect on progression of disability.[35 36] We consider that unequivocal evidence of reduction of progression of disability with copolymer 1 should also be provided before it is adopted in routine practice.

Other treatments

It is a very exciting, but also a very difficult time in the choice of treatment for patients with multiple sclerosis. Many other drugs are entering phase II or phase III trials. Some, such as anti-CD4 antibody have been disappointing.[37] Others, such as cladribine, an anti leukaemic agent,[38 39] deoxysparguline,[40] and mitoxantrone,[41 42] are still being investigated. Agents with entirely novel actions, such as matrix metalloproteinase inhibitors which inhibit proteases and the release of tumour necrosis factor-α, are being developed. More conventional immunosuppressant regimens of the type used in rheumatoid disease, such as methotrexate, deserve further attention.[43 44] Premature acceptance of interferon-β into routine practice would seriously hamper the eventual reduction of disease burden in patients with multiple sclerosis. We and our patients should avoid clutching at a drug which is hopeful but not proved, and should undertake the large trials which may turn hope into reality.

Possible conflicts of interest

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