Beta interferon and multiple sclerosis: why the fuss?

An unwelcome situation has developed in neurological out-patient practice recently, threatening to destroy the good relationships usually enjoyed by patients and their specialists. All neurologists accept that once they have made a diagnosis of an untreatable chronic disabling disease in a patient, they should continue to see that patient on an occasional out-patient basis, recognizing their role as a specialist who can offer advice, explanation and support. Neurological out-patient review may be the route of referral to physiotherapy departments, community nurse specialists, patient support groups and the source of medication to treat some or all of the complications of the underlying condition. Inevitably the patient and the neurologist build up a relationship of trust, and can generally share discussions about problems and new ideas for treatment. In many ways the patient and the neurologist act together as a team whose goal is the defeat, or at least the control, of the illness.

In a number of multiple sclerosis patients attending neurological out-patients during the past few months, this bond between patient and neurologist has been broken. The destructive force resulting in this deterioration in the neurologist-patient relationship is the arrival of beta interferon, an agent perceived either rightly or wrongly by patients as something which will significantly improve their condition, and perhaps even halt the disease in its tracks. The problem—as seen by the patient with multiple sclerosis—is that their neurologist seems unable or unwilling to prescribe the new drug for them. The converse is that the neurologist is—in general—yet to be convinced that the drug offers anything other than modest benefit to the patient, and moreover has an unproven safety record, so enthusiasm to prescribe the drug is lacking. To complicate matters, the cost of treatment of one individual with multiple sclerosis for one year is of the order of £10 000, and this price is known both by neurologist and patient. The patient infers from the doctor’s reluctance to prescribe that treatment is being denied on grounds of cost, and the result is often misery and acrimony unsettling a doctor–patient relationship which may have flourished over many years.

It seems probable that by the time of publication of this editorial, beta interferon-1-b (Betaseron, Schering) will have been granted a product licence in the UK. Consequently neurological units are bracing themselves for what they fear will be a barrage of patients with multiple sclerosis who will have increased expectations of receiving the drug. However, the granting of a licence will do nothing to increase the information available to neurologists regarding the efficacy of the drug and the decision whether or not to prescribe will be yet more difficult. The task will be to balance the expectations of patients with reality. At the time of writing, groups of neurologists in individual centres are trying to formulate their own policy for this difficult question, and it is possible that we shall see a situation with neurologists in one major centre announcing that they simply will not prescribe because they are not convinced of benefit, whereas another centre may offer a recommendation for treatment of all their local patients meeting the indications for the drug stated in the licence. Chaos will ensue.

The interferons are not really drugs at all, but naturally occurring substances which were first recognized in the 1950s as chemical messengers released by infected cells. A classification has evolved over the years, and presently this assigns interferons to three groups, alpha, beta (sometimes grouped together as the ‘type 1’ interferons) and gamma (‘type 2 interferon’). Alpha interferon has been shown to have a role in the treatment of some virus-associated malignancies and now has an established track record. Gamma interferon tends to augment immune function, and in the context of multiple sclerosis, seems to have a disease-exacerbating effect. Beta interferon appears to counteract some of the actions of gamma interferon, and for this reason alone could offer benefit in multiple sclerosis. But if we assume that multiple sclerosis occurs in genetically susceptible individuals as a result of a misdirected immune response to a component of myelin, then there are other theoretical reasons why beta interferon may be beneficial by suppressing abnormal immune activity. Possible mechanisms of benefit include suppression of abnormal T-lymphocyte activity, down-regulation of the expression of proteins of the major histocompatibility complex or enhancement of T-suppressor-cell function.
The precise mechanism of alleged benefit of beta interferon in multiple sclerosis is not known, but the theoretical arguments were strong enough to lead to preliminary trials in the early 1980s. Most of the early trials were hindered by small numbers of patients and lack of blinding, making meaningful analysis difficult. Often only very small quantities of beta interferon were available for study. Nevertheless initial studies suggested that in those patients who had a relapsing-remitting pattern of illness, the frequency of relapses in the treated group was reduced. Further small studies culminated in a major multicentre collaborative trial of beta interferon in patients with relapsing-remitting multiple sclerosis, and the results of this trial were published in April 1993. A total of 372 patients were randomly assigned to receive high-dose beta interferon, low-dose, or placebo. The interferon was given by subcutaneous injection on alternate days, and the patients were followed up for two years. The number of relapses experienced by patients in the high-dose group was reduced by one third in comparison to the number of relapses experienced by patients in the other two groups. The trial has been criticized for inadequate blinding, especially of the patients, many of whom experienced flu-like symptoms on the active agent, so raising concern that the reporting of relapses was biased. Moreover, there were a large number of patient drop-outs for assorted reasons, who were not included in the final analysis of the results. Subsequent observation of the patients who remained in the study for a total of five years has shown that the effect of beta interferon on relapse rate is maintained but this result has also been questioned, since the analysis was not made on an ‘intention-to-treat’ basis.

Whilst the outcome of this trial is of interest and encouraging, the positive result in terms of an effect on relapse rate is not the question which neurologists and their patients most want answered. Their main concern is whether or not the drug slows down the overall progression of the disease, in other words whether it can slow down the accumulation of disability. This question was addressed by the study, but the result was negative. Despite this disappointing finding, the authors of the study and the manufacturing company involved have made much of a reduction in the abnormal area seen on cranial magnetic resonance scans of the patients in the high-dose group. This was the secondary outcome measure of the study, and clearly showed a positive benefit in the so-called ‘lesion load’. In the placebo group after two years, the mean area of abnormality on the MRI scans had increased by 20%, but in the group treated with the high-dose active agent, the abnormal area had decreased by 0.1%. Exciting though this may be in theoretical terms, it is still not the result most needed by patients or their physicians, since whilst there may be some emerging association between the amount of abnormality on a scan and the severity of multiple sclerosis in a given patient, there is as yet no good correlation between the two.

A second major study of beta interferon in patients with multiple sclerosis is being much talked about. At the time of writing (October 1995), the results of this study frustratingly have not been published in any peer-reviewed form, but oral presentations of the data have been made at international conferences. This study used a marginally different form of interferon (Interferon-beta-1a, Biogen), and is important because the main outcome measure was disability, and the trial appeared to show a positive benefit. Again the study concentrated on patients with the relapsing-remitting form of multiple sclerosis and in this case the patients received either high-dose beta interferon or placebo as an intramuscular injection on a once-weekly basis. The main outcome measure was the time taken to progress by one point on the ‘expanded disability status scale’ (EDSS) devised by Dr John Kurtzke, which is widely used as a rating scale to describe the severity of multiple sclerosis in an individual. They recruited 301 patients into this trial, and amongst those who completed the study, there was a significant delay in the time taken to progress by one EDSS point in the group receiving active agent in comparison with the placebo group. Unfortunately, although the Kurtzke expanded disability status scale enjoys widespread usage, almost all authorities in the field of multiple sclerosis research have reservations about it, questioning its validity and applicability in the context of clinical trials, and in particular questioning whether a move between two points on the scale by one individual is a meaningful assessment of accumulation of disability.

Several other studies are currently underway both in Europe and North America. Some of these are concentrating on patients with relapsing-remitting multiple sclerosis, and others are looking at any effect on primary progressive and secondary progressive forms of the disease. The two major trials described above recruited only individuals with multiple sclerosis who were still able to walk unaided, so the study populations were not representative of the multiple sclerosis population as a whole, and current studies are looking for a benefit of beta interferon in more severely disabled individuals.

The problem faced by neurologists and their patients with multiple sclerosis is that great weight has been placed on the results of the two major studies described above. Few would argue that the Interferon-beta-1b study has shown that the agent has a modest effect on the frequency—but not necessarily the severity—of relapses, but this is not the result that the multiple sclerosis population needs. What is needed is a study which tells us whether or not beta interferon can usefully slow the progression of disability in multiple sclerosis patients. For the start
of an answer to this we can look at the Biogen study, but this must be substantiated by further large-scale trials, and neurologists will want to see a result more meaningful than a slight slowing of the time it takes for ambulant patients to progress by one point on a scale of questionable usefulness. We really need to know about differences in the speed of accumulation of major disability, probably over a trial period of some years. This approach to the question has been rather crudely referred to as a ‘count the wheelchairs’ sort of trial, that is, take a large number of patients, give beta interferon or placebo, and after a long trial period use a very simple outcome measure, such as how many patients need to use a wheelchair, to look for any benefit. If we could somehow confine the study population to those individuals who might be expected to show a rapid accumulation of disability, perhaps by scrutinizing rate of change on serial MRI scans in the pre-trial period, then the study could feasibly be done in just a few years in a relatively small number of patients. The granting of a licence to beta interferon at this stage in the acquisition of data may now mean that the performance of such a trial becomes impossible, both in ethical terms and in the ability to find patients willing to enter a study with only a 50% chance of receiving a treatment which will by then be perceived as having an official ‘stamp of approval’. Current development in the immunological sciences is bringing a wide range of other potential immune-modulating therapies for multiple sclerosis, many of which have stronger theoretical grounds to expect benefit, but some more sanguine observers have questioned whether it will ever be possible to perform placebo-controlled trials of these agents, or whether all future studies will be obliged to incorporate a beta-interferon arm.

Putting aside the question of how robust the current evidence is that beta interferon does any good, the other source of great anxiety is the cost of this agent. Estimates for the cost of treating one patient per year vary between about £7000 and £12 000. Even if the agent is prescribed for a relatively small percentage of the multiple sclerosis patients in the UK, we risk a situation where about 1% of this entire nation’s budget for health care might be spent on this drug alone. The figures involved are too huge to be borne by hospitals or purchasing authorities without special provision, and it may be that a unique source of funding at central government level will need to be established. It seems inconceivable that all the individuals with multiple sclerosis who request the drug will be able to have it. The licence is likely to suggest that the drug will be suitable only for ambulant patients with relapsing-remitting disease, and that the only licensed indication for prescription will be as an agent to reduce relapse frequency. This, however, is unlikely to match the perceptions of the patients, many of whom, even those with advanced disease, are already demanding that they be prescribed the drug regardless of the view of the neurologist or the ‘official indication’. If they have the ‘wrong sort’ of multiple sclerosis, disability which is too advanced, or simply a neurologist who is more sceptical about the data than others, then there will be yet more cries of ‘health care rationing’ added to the chorus of voices already raised in protest at perceived ‘meanness’ on the part of neurologists.

If beta interferon were as cheap as aspirin, and had an established safety record, then neurologists would almost certainly be willing to give it a try on the strength of the data currently available. Conversely, if it were the subject of a series of rigorous independent clinical trials with unequivocal evidence of effective slowing of disability accumulation, then neurologists would prescribe it, even at the current enormous cost. Unfortunately it is neither, hence the fuss.

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