Can the course of multiple sclerosis be modified?

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INTRODUCTION
In the conference hall, in an attractive foreign location, it is easy to be seduced into believing that our current licensed therapies for multiple sclerosis (MS) offer dramatic benefits to people with the disease. And patients who lived through the hullabaloo over the licensing, approval and funding of the interferons, are naturally inclined to have great expectations for their efficacy. But sitting in an MS clinic is a sobering experience. Interferons are seen to be as efficacious in controlling relapses as some of the minor antiepileptic drugs are in reducing seizures. More worryingly, the reasonable questions asked by patients are at present unanswerable: 'what are the chances that this drug will stop me from being in a wheelchair in 10 years time... keep me fit to look after my children until they leave home... allow me to continue in my work until retirement...?' Undoubtedly great indirect benefits have followed the introduction of the interferons. They have brought MS to the attention of the pharmaceutical world. It is depressing that many of the great UK and US drug companies had thought that MS was commercially unattractive, and unworthy of investment, until the last few years. Likewise, in the UK, the infrastructure created to support interferon prescribing, with the provision of MS specialist nurses, more neurologists, dedicated clinics and so on, may give greater value and last longer than the drugs themselves.

This article considers whether immunotherapies can influence the course of MS. It is not intended to be a catalogue of drugs, but rather an analysis of how susceptible the disease is to any type of immunotherapy. Nor does it touch on the role of neuroprotective treatments, such as sodium-channel blockers and cannabinoids, for which there are great hopes but as yet no clinical trial evidence (Pryce et al. 2003; Bechtold et al. 2004).

FLAWED PIVOTAL TRIALS IN RELAPSING-REMITTING MULTIPLE SCLEROSIS
The pivotal trials (Jacobs et al. 1996; Paty & Li 1993; Duquette et al. 1995; Johnson et al. 1995) showed that the interferons and glatiramer reduced the relapse frequency of MS by about one third (Fig. 1). From the results of extension studies, it has been claimed that this effect persists beyond two years of treatment (Fig. 2) (Duquette et al. 1995). However, a systematic review and meta-analysis of the interferon trials, using Cochrane methodology, makes sober reading (Filippini et al. 2003). The dataset was reasonably large: a total of seven trials including 1674 randomised patients, from which data were available on 1215. However, the variable quality of the trials reduced the power of this
Multiple sclerosis

**Figure 1.** Drugs that reduce relapse rate in relapsing-remitting MS. Data extracted from the pivotal trials. Error bars indicate 95% confidence intervals, which were not always available.

**Figure 2.** Interferon-beta may slow the progression of disability in relapsing-remitting MS. Data extracted from the pivotal trials. EDSS: expanded disability status scale NS: not significant.
meta-analysis considerably. For instance, the raw data for the primary outcome (the chance of continuing relapses over two years of treatment) suggested interferon beta had a significant beneficial effect. But this significance dissolved after a sensitivity analysis, where excluded cases were put back into the analysis and assumed to have done well or badly (Fig. 3). In the worst case scenario, the apparent treatment effect became insignificant. The fault for this lies largely with the Avonex trial which was stopped prematurely and only 57% of the randomised patients contributed two-year data (and one-year data were not published) (Jacobs et al. 1996). The single result that withstood the sensitivity analysis, but only just at $p = 0.04$, was that interferon reduced the number of patients who had relapses during the first year of treatment (relative risk 0.73, 95% CI 0.54–0.99). It would be wrong to conclude that the interferons only work for a year; rather the poor quality of the pivotal trials does not allow any further conclusions.

Naturally enough, the results of the pivotal trials mean more for people with a relatively high relapse rate (over 1 relapse/year) where the absolute reduction in relapse rate may be worth having (for example from 3 to 2 relapses in a year). But it is hard to imagine the interferons offering any useful benefit to those with much lower relapse rates. Hence the Association of British Neurologists (ABN) criteria (Table 1) for ‘at least two clinically significant relapses in the past two years’. Quite what constitutes ‘clinically significant’ is not clearly defined. The phrase is certainly an improvement on the previous requirement for ‘disabling relapses’ which is illogical, since the symptomatology of a plaque reflects the lottery of anatomy and having non-disabling relapses in the past is no guarantee they will be so in the future. In passing, the ABN naturally enough, the results of the pivotal trials mean more for people with a relatively high relapse rate (over 1 relapse/year) where the absolute reduction in relapse rate may be worth having (for example from 3 to 2 relapses in a year). But it is hard to imagine the interferons offering any useful benefit to those with much lower relapse rates. Hence the Association of British Neurologists (ABN) criteria (Table 1) for ‘at least two clinically significant relapses in the past two years’. Quite what constitutes ‘clinically significant’ is not clearly defined. The phrase is certainly an improvement on the previous requirement for ‘disabling relapses’ which is illogical, since the symptomatology of a plaque reflects the lottery of anatomy and having non-disabling relapses in the past is no guarantee they will be so in the future. In passing, the ABN

Table 1 Association of British Neurologists criteria for prescribing interferon and glatiramer acetate

<table>
<thead>
<tr>
<th>Starting criteria in relapsing/remitting MS for interferon beta or glatiramer acetate:</th>
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<tr>
<td>• can walk 100 m or more without assistance</td>
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<tr>
<td>• has had at least two clinically significant relapses in the past 2 years</td>
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<tr>
<td>• aged 18 years or older</td>
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<tr>
<td>• no contraindications (uncontrolled epilepsy, severe depression)</td>
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<tr>
<th>Starting criteria in secondary progressive MS for interferon beta-1-b (the only interferon licensed for this use):</th>
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<tr>
<td>• can walk 10 m or more with or without assistance</td>
</tr>
<tr>
<td>• has had at least two disabling relapses in the past 2 years</td>
</tr>
<tr>
<td>• minimal increase in disability due to gradual progression over the past 2 years</td>
</tr>
<tr>
<td>• aged over 18 years</td>
</tr>
<tr>
<td>• no contraindications</td>
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<tr>
<th>Stopping criteria for interferon beta or glatiramer acetate, discussed and agreed before starting treatment:</th>
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<tr>
<td>• intolerable adverse effects</td>
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<tr>
<td>• becoming or trying to become pregnant</td>
</tr>
<tr>
<td>• occurrence of two disabling relapses within a 12-month period</td>
</tr>
<tr>
<td>• loss of ability to walk, with or without assistance, that has persisted for longer than 6 months</td>
</tr>
<tr>
<td>• development of secondary progressive MS (or in the case of those on interferon-beta-1b: secondary progression with an observable increase in disability over a 6-month period)</td>
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For further details see Health Service Circular 2002/004 (www.doh.gov.uk/pricare/drugsmultiplesclerosis.htm)
criteria for stopping interferon beta treatment are unhelpful: two disabling relapses in a year may represent a real treatment effect if the pre-treatment relapse rate was 4 or 5 a year!

Much of the reputation of the interferons is built upon their effect on relapse rate and MRI surrogates of cerebral inflammation. The unspoken assumption of many patients and their doctors is that these effects will inevitably translate into a beneficial impact on disability in the long term - but is this true?

DOES REDUCING RELAPSES PREVENT DISABILITY?

The same systematic review of the interferons did not show benefit on the acquisition of disability in relapsing-remitting MS (Filippini et al. 2003) even though a positive effect had been claimed in two out of the three pivotal studies (Fig. 2). Once again, these data did not allow an analysis that incorporated the many excluded cases and, again, this must be interpreted as a failure of trial execution rather than necessarily of the interferons. Two further points emerge from a close study of the PRISMS trial. First, at two years the survival curves for disability acquisition seem to be converging (Fig. 4A), fuelling the speculation that the effect of interferons on disability might not be maintained. In the four-year extension study of PRISMS, PRISMS-4, the original placebo cohort were randomised to active treatment and compared to the original active arm, which was maintained on interferon (2001). The trialists’ conclusions from the converging survival plots were that late interferon treatment did reduce the risk of disability acquisition but that this did not catch up with the benefit seen in the always-treated group. In the four-year extension study of PRISMS, PRISMS-4, the original placebo cohort were randomised to active treatment and compared to the original active arm, which was maintained on interferon (2001). The trialists’ conclusions from the converging survival plots were that late interferon treatment did reduce the risk of disability acquisition but that this did not catch up with the benefit seen in the always-treated group.

The trialists’ conclusions from the converging survival plots were that late interferon treatment did reduce the risk of disability acquisition but that this did not catch up with the benefit seen in the always-treated group. An alternative possibility is that the efficacy of the interferons was waning; this resonates with an earlier trial of sulphasalazine in MS which showed a benefit in terms of disability at two years which disappeared at four years (Noseworthy 1998).

It was this lack of clarity on the sustained efficacy of interferons that led the National Institute of Clinical Excellence in the UK to declare that the cost of interferon and glatiramer acetate treatment of MS (about £10 000 per patient per year at the time) did not represent value for money. These drugs are currently being prescribed under a unique ‘Risk Sharing Scheme’ between the National Health Service and the pharmaceutical companies, who have had to put their money where their press releases are because their future income from interferon sales will depend on the demonstration of a long-term benefit on disability, albeit in a non-randomised group of patients (Sudlow & Counsell 2003).

A second important and neglected issue was touched on in the PRISMS trial. The reduction in the acquisition of disability was greater in those with least fixed disability at the time of treatment; patients with an EDSS score greater than 3.5 did not seem to benefit from the lower dose of Rebif at all (Fig. 4B). However, the numbers of patients in this analysis are too small to be confident of this result. But it does resonate with the finding from a large epidemiological study of a threshold disability (EDSS 4.0) after which the trajectory of disability progression is uniform, whatever the prior history of relapses or treatment (Confavreux et al. 2003).

Epidemiologically, the relationship between relapse rate and disability is complex. The relapse rate during the progressive phase of multiple sclerosis does not alter disability outcomes (Confavreux et al. 2000). However, the relapse rate early in the course of the disease is associated with time to reach fixed disability milestones (Weinshenker et al. 1989; Confavreux et al. 2003). A real, but poor correlation of 0.5
or so has also been reported between the load of early inflammatory lesions on brain MRI and subsequent clinical disability (Brex & Ciccarelli 2002) and cerebral atrophy (Chard et al. 2003). So the tacit assumption, that reducing relapses will translate into a reduction in the accumulation of disability in the long term, remains to be proven. It is most likely to be true for treatment of those with least fixed disability.

WORSENING RELAPSING AND PROGRESSIVE MULTIPLE SCLEROSIS
Some insight into the processes underlying worsening relapsing and progressive MS has come from the re-discovery of axonal injury, well known to those who studied the disease in the late 19th century. Axons in acute lesions may be acutely transected (Ferguson et al. 1997; Trapp et al. 1998) and the extent of acute axonal injury is correlated with the degree of inflammation (specifically CD8+ and microglial numbers) (Kuhlmann et al. 2002). This axonal injury will result in persistent deficits after relapses. Chronic lesions, by contrast, are characterized by a lack of inflammation and considerably fewer axons (Trapp et al. 1998) suggesting that there may have been continued attrition of the axons long after inflammation had resolved. This 'axonal degeneration' probably accounts for the secondary progressive form of multiple sclerosis (Coles et al. 1999). So disability may be acquired in two separate ways: from axonal injury (and persistent demyelination) directly attributable to a relapse, and from axonal degeneration, which is expressed clinically as progressive deficits outside of the context of relapses. The phrase 'progression of disability', used in most trials, is confusing in this respect. What is actually measured is the accumulation of disability, sustained over 3 or 6 months. This might arise from either relapses or progression. This is illustrated nicely by trials of drugs in secondary progressive MS.

The interferons
There have been three trials of interferon-beta in secondary progressive MS. The first, a European trial of interferon beta-1b (Betferon), showed a positive effect on disability and the drug was rapidly licensed for this form of MS (European study group on beta-IFN in secondary progressive MS. 1998). The regulators might have regretted that decision when two other trials of interferons in secondary progressive MS proved negative; one tested the same interferon, but in the US (Panitch et al. 2004), the other was a trial of Rebif (SPECTRIMS 2001).

The different outcomes between these three large trials seems to be explained by the high relapse rate of a large proportion of the European study cohort compared to the other trials (Table 2) suggesting that their reduced acquisition of disability arose from a reduction in relapses rather than the underlying progression. The MRI demonstration that there was no change in the progression of brain atrophy (a surrogate perhaps of axonal degeneration) between the groups would support this view (Molyneux et al. 2000). This tallies with a close analysis of the IFN beta-1a trial in secondary progressive multiple sclerosis (SPECTRIMS 2001), where an effect on disability was seen in the small group who had relapses prior to the Rebif treatment. Overall, though, the SPECTRIMS trial was negative, prompting the concluding understatement, which somehow got past the reviewers, that 'IFN-β-1a is much less effective in slowing disability progression in secondary progressive MS than it is in relapsing remitting MS'!

Other immunotherapies
There have been several small trials of more potent immunotherapies than interferon beta in secondary progressive MS, with similar conclusions. For instance both Campath-1H (Coles et al. 1999) and cladribine (Filippi et al. 2000; Rice et al. 2000) significantly reduced relapse

Table 2 Immunotherapy trials in secondary progressive multiple sclerosis.

<table>
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<tr>
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<th>SPECTRIMS</th>
<th>European Trial</th>
<th>North American</th>
<th>MIMS</th>
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<tr>
<td>N</td>
<td>618</td>
<td>718</td>
<td>939</td>
<td>194</td>
</tr>
<tr>
<td>Trial duration (years)</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Drug</td>
<td>Rebif</td>
<td>Befaeron</td>
<td>Betaseron</td>
<td>Mitoxantrone</td>
</tr>
<tr>
<td>% of patients with relapses before treatment</td>
<td>47</td>
<td>70</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>Annual relapse rate before treatment</td>
<td>0.9</td>
<td>1.74</td>
<td>0.82</td>
<td>1.3</td>
</tr>
<tr>
<td>Probability of a change in disability</td>
<td>0.15</td>
<td>0.0008</td>
<td>0.7</td>
<td>0.02</td>
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rate and MRI markers of cerebral inflammation, but had no effect on the accumulation of disability and progressive cerebral atrophy. From these, and the disappointing interferon trial data, has emerged the consensus that immunotherapies do not alter the course of secondary progressive MS. And it is little surprise that similar trials in primary progressive MS, where the inflammatory load is so much less, are negative also (Leary et al. 2003).

Mitoxantrone
Superficially, the exception to this rather negative conclusion seems to be mitoxantrone. This anthracyclinedione, which depletes neutrophils and lymphocytes, is licensed in the US (but not UK) for the treatment of ‘worsening multiple sclerosis’ on the basis of the MIMS trial (Har-tung et al. 2003). 194 patients with aggressive relapsing-remitting or secondary progressive multiple sclerosis, who had deteriorated by over one EDSS point in the previous 18 months, were followed for two years. The headline result was a mean increase in disability in the placebo arm by 0.23 EDSS points and an improvement in the treated arm by 0.13 EDSS points. The patients in this trial also had a higher relapse rate before treatment, which was suppressed to a greater extent in the mitoxantrone arm than by placebo, and the improvement in disability was entirely attributable to the subgroup of patients who were having relapses prior to treatment, a fact the authors seemed to want to bury rather than bring out. It is unusual to see patients’ disability improve following immunotherapy for multiple sclerosis. But such an effect was seen in a recent uncontrolled study of aggressive relapsing-remitting patients treated with Campath-1H (Coles et al. 2005). Presumably in patients with such active disease, part of the pretreatment disability is due to conduction block induced by inflammatory mediators (Redford et al. 1997) and this is released by potent anti-inflammatory treatments. In other words the patients are effectively in relapse at baseline. To avoid this, patients’ baseline disability should ideally be confirmed at an interval of several months before treatment to show it is a true reflection of persistent deficits. Patients who are deteriorating fast might not appreciate such a delay though.

A reasonable summary of these studies is that in patients with nonrelapsing progressive MS, no immunotherapy has been shown to be effective in reducing the acquisition of disability. However, in patients whose disability is worsening in part or in whole because of relapses, immunotherapies can marginally influence the acquisition of disability in the short term. But, as with interferon treatment of ordinary relapsing-remitting disease, it is not known if this translates into a long-term effect. Hence the ABN criteria for the treatment of MS with interferons allows for patients with secondary progressive MS to receive interferon beta-1b if they have had at least two ‘disabling’ relapses in the past 2 years (again, rather illogical), and minimal increase in disability due to gradual progression over the past 2 years (Table 1).

Of course, in dealing with an individual patient whose disability is rapidly deteriorating, it is often hard to distinguish on clinical grounds between secondary progression and multiple relapses. There is no evidence base to guide clinicians in this situation. On-going cerebral inflammation can be revealed in two ways. Firstly, through the number of gadolinium-enhancing MRI lesions on serial scans and, secondly, from the symptomatic response to a course of corticosteroids outside the context of an obvious relapse. A high inflammatory lesion load and a significant improvement with steroids is a logical – but unproven – indication that the patient might benefit from immunotherapy.

A DISEASE OF TWO HALVES AND THE NIGHTMARE SCENARIO
From such considerations has emerged a consensus that MS is a disease of two phases. At the outset the course is dominated by inflammation causing demyelination and expressed clinically as relapses with remissions. This phase can be influenced by immunotherapy. Subsequently, axonal degeneration is the predominant pathology, causing cerebral atrophy and progressive accumulation of disability, and this is not influenced by immunotherapy (Fig. 5). As the MIMS trial and other trials have shown, these phases may merge into each other rather than be clearly distinct.

The key question is whether altering the relapse rate in the first phase of the disease, with drugs that suppress inflammation, has any effect at all on the axonal loss and hence progressive clinical deficits, in the second phase. Most clinical trials to date have shied away from answering that question for reasons partly of expense of time and money. This is understandable, for it takes roughly 10 years for 50% of patients with relapsing-remitting MS to enter the secondary progressive phase (90% after 25 years). Nonetheless, the
The ideal opportunity to address this question came with the two interferon trials of the first demyelinating episode (ETOMS and CHAMPS) (The CHAMPS Study Group. 2000; Comi et al. 2001). The subsequent relapse rate was slightly reduced by interferon, and hence the conversion to clinically definite MS was delayed: hardly a surprise. Much more informative, had the investigators chosen to collect and report the data, would have been the long-term disability data after several years of interferon treatment.

Few people are facing up to the ‘nightmare scenario’, consistent with available evidence, that axonal degeneration starts early in the course of MS and is uninfluenced by anti-inflammatory treatments: with the onset of progressive disability fixed from the outset. So that time spent suppressing relapses and MRI shadows is time wasted.

For what it is worth, which is a lot, there is good laboratory evidence that axonal loss may be due to altered patterns of electrical activity following demyelination (Smith K.J et al. 2001) and the loss of oligodendrocyte-derived growth factors (Wilkins et al. 2001). In which case, axonal loss may be a late consequence of demyelination and so, it follows, suppressing inflammation radically early in the course of MS just might prevent the progression of disability in the long term. To interrogate this, and to answer the questions of ‘how early?’ and ‘how radically?’ we need to expose people with early MS to potentially toxic drugs.

**MISTAKES OF THE PAST AND THE BALANCE OF RISKS AND BENEFITS**

**Immunosuppression with cyclophosphamide and cyclosporin**

Conventional immunosuppressants such as cyclophosphamide and cyclosporin are considered ineffective in MS; a claim repeated in the recent NICE guidelines. However, this view is based on the results of early trials in people with primary and secondary progressive MS (called ‘chronic progressive’ at the time) (Rudge et al. 1989; Steck et al. 1990; Noseworthy et al. 1991; Weiner et al. 1993). Now, we recognize that these forms of the disease are largely due to non-inflammatory degeneration. So we can only conclude that the trials were inappropriate tests of anti-inflammatory agents. It might well be time to reconsider them, but that would involve a change in our attitude to risk in the treatment of MS.

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**Figure 5** The clinical phases of relapse with recovery, relapse with persistent deficits and progression depend mainly on the effect of inflammation, demyelination and axonal degeneration, respectively. Disease activity is often presymptomatic and, later, not invariably expressed clinically. As inflammation wanes, brain volume reduces with accumulated axonal loss. Perivascular inflammation (panel 1) causes acute axonal transection (Trapp et al. 1998) (panel 2), and microglia-mediated removal of myelin (panel 3) with persistent demyelination despite some remyelination (panel 4); chronic lesions show further axonal loss (Wolswijk 1998) (panel 5) and gliosis (panel 6). The scheme does not depict primary progressive multiple sclerosis in which there is significant axonal degeneration with or without a preceding inflammatory phase.
The toxicity of conventional immunosuppressants is alarming to neurologists and patients, used to treating MS with nothing or only benign medications. But a renal physician, looking over our shoulders, might well conclude that his colleagues and patients are prepared to take more risks to save their kidneys than we and the MS community are to prevent irreversible brain damage.

Azathioprine

One exception to the view that traditional immunosuppressants are ‘ineffective’ in MS is azathioprine. Azathioprine has been tested in over 30 trials, the largest being of 354 patients over 3 years by the British and Dutch Multiple Sclerosis Azathioprine Group; no significant difference in disability or relapse rate was found compared to placebo (Hern et al. 1988). Indeed no single study has shown a significant treatment effect of azathioprine. However, a meta-analysis of all the trials has shown that three years of treatment results in a statistically significant improvement of 0.2 points on the Kurtzke scale (Yudkin et al. 1991). Perhaps azathioprine has equivalent efficacy to the interferons and deserves to be tested alongside them (Palace & Rothwell 1997; Sudlow & Counsell 2003). This optimism needs to be tempered with the fourfold increase in cancer risk after 10 years of azathioprine treatment in people with MS (Confavreux et al. 1996); of course we do not yet know the long-term risks of the interferons.

Natalizumab

Until very recently, the expectation was that the interferons’ market would be taken over by natalizumab (Tysabri), a monoclonal antibody that blocks the adhesion molecule VLA-4. The FDA gave it expedited approval on the basis of unpublished one-year interim analyses from two phase III trials, in which it reduced relapse rate more than interferon-1a alone, and had additional benefit if combined with interferon-1a (Fig. 1). However, in March 2005, Biogen withdrew the drug from the market after two cases of progressive multifocal leukoencephalopathy (PML) were found in patients with MS treated with natalizumab and Avonex. A few weeks later the cause of death of a patient with inflammatory bowel disease, who had died during a previous natalizumab trial, was changed to PML. This withdrawal, amongst other considerations, was to shore up

CONCLUSIONS

- The interferons reduce the relapse rate of relapsing-remitting MS by about one third and are definitely effective for one year of treatment – beyond that, the trial evidence is not secure
- Unpublished data indicate that natalizumab, a drug now withdrawn, suppresses relapses to a greater extent than the interferons
- Reducing relapse frequency in relapsing-remitting multiple sclerosis may slow the acquisition of disability over 2–3 years, although the clinical trial evidence for this effect is not robust
- The effect of suppressing relapses on disability is greatest in those with least fixed disability at the time of treatment
- It is possible that patients who have reached a disability score of more than EDSS 4.0 may be destined to a fixed trajectory of progressive disability however they are treated
- Conflicting results of the effect of immunotherapies on secondary progressive MS are attributable to the varying relapse rate of the trial populations. Treating patients with a very high relapse rate in the secondary progressive phase may slow their acquisition of disability for 2–4 years, but the underlying axonal degeneration continues and it is doubtful (but not tested) that there would be any long-term benefit
- Deciding in an individual patient whether their worsening disability is due to inflammation (relapses) or axonal degeneration (progression) is sometimes very difficult but may be helped by assessing the MRI inflammatory load and the clinical response to corticosteroids
- The critical therapeutic issue in MS is whether giving immunotherapies early in the course of the illness prevents or slows entry to the secondary progressive phase. This has never been tested
Wall Street. The perception of the drug amongst financiers will be a major determinant of when and if natalizumab is ever returned to the market. The rush to market, which prompted the FDA to give expedited approval (a decision they now have the leisure to regret), was based on natalizumab having greater efficacy than the interferons and no significant adverse effects. Surely that is an unreasonable expectation? And surely it would have been more prudent for the FDA to insist Biogen complete their phase III trials and exposed the results to open peer review before licensing? That way, debate over the significance of an unexpected adverse effect would have been undertaken by physicians and researchers, rather than stock brokers and marketing gurus.

As a community – of physicians and patients with the disease - we need to ask ourselves what level of risk is reasonable for a treatment that alters the course of M S. Methotrexate and the anti-TNF-α treatments, accepted disease-modifying treatments for rheumatoid arthritis, have considerably more adverse effects than interferon beta. Should we conclude that joints are more important than brains? Or should we proceed with trials of novel agents even though they may well have significant toxicity? Perhaps a very low risk of death from PML is acceptable for a long-lasting improvement in the acquisition of disability. But how will we ever know if the drug is withdrawn?

THE IDEAL AND THE COMPROMISED TRIAL IN MULTIPLE SCLEROSIS

There is now a strong case for exposing a small cohort of people with early M S to powerful, if toxic, immunotherapy, and following them long enough to see if their entry to the secondary progressive phase is delayed or prevented. However, it is doubtful that any company will have the incentive to undertake such a trial, or that a non-commercial funding body will be able to afford one.

Our compromise has been to compare Campath-1H with interferon in 300 nondisabled (EDSS < 3.0) patients with early M S, with onset less than three years before treatment. The trial duration of three years is insufficient time to watch patients enter the secondary progressive phase, so we are using cerebral atrophy as a surrogate marker of axonal degeneration. This trial will report in 2007. In the future, perhaps we will look back on this trial as too simplistic. Perhaps, the pathological heterogeneity of M S (Lucchinetti C et al. 2000) underlies the varying responses to different treatments, and we will have to learn to discriminate these different forms in life and perhaps immunotherapies will have to be combined with neuro-protection strategies to prevent the onset of secondary progression.

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