Diagnosis and disease modifying treatments in multiple sclerosis

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Multiple sclerosis (MS) refers to scattered areas of hardening found on sectioning central nervous system tissue of affected people, usually after many years of illness. It rarely causes early death but is the commonest cause of neurological disability among young people. Overall results from controlled trials over the past 50 years have been rather disappointing but the comparatively recent licensing of drugs such as interferon beta and glatiramer acetate has led to a reappraisal of many aspects of MS. There are now new diagnostic criteria, which encompass developments in magnetic resonance imaging. Older clinical methods of measuring disease impact are now being re-evaluated to facilitate clinical trials of the approximate 150 new products currently being developed as potential disease modifying agents. The success and failure of agents that should be effective on theoretical grounds, together with advances in neuropathology, have led to fundamental questions regarding our basic understanding of disease pathogenesis being re-addressed.

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Multiple sclerosis (MS) has a prevalence of around 1 in 800 across most of the UK, Northern Europe, and North America. Some parts of Scotland have reported levels as high as 1 in 500, whereas levels are considerably lower in tropical regions and most of Asia. It is about twice as common in women than men and has a peak age of incidence around 30 years of age. Evidence from twin studies suggests that monozygotic twin concordance is around 25%–30%, compared with 3%–5% in dizygotic twins. Although this is consistent with a significant genetic component to susceptibility, compatible with a number of susceptibility genes being involved, to date, despite considerable efforts in genome screening, particular genes have not yet been identified. Evidence from an analysis of population migration studies suggests that monozygotic twin concordance is around 25%–30%, compared with 3%–5% in dizygotic twins.

Most cases of MS will start with a single episode of neurological dysfunction, most commonly in the optic nerve (optic neuritis), spinal cord (transverse myelitis), or brain stem. These episodes reflect inflammation at the relevant site within the central nervous system (CNS), and can usually be identified by areas of gadolinium contrast enhancement on magnetic resonance imaging (MRI), reflecting disruption in the normally integral blood-brain barrier, with ingress of inflammatory cells. When these episodes occur, it is not possible to predict with certainty whether further episodes will occur in the future. The initial episode is therefore termed a clinically isolated syndrome (CIS), which may or may not develop into MS at a later date. If further episodes of neurological dysfunction occur, then a diagnosis of MS may be made (see diagnostic criteria below), and each episode is termed a relapse. Most people will make some recovery after each relapse, although this may be incomplete. Recovery is thought to reflect a combination of recovery in the integrity of the blood-brain barrier, a resolution of the inflammation, and repair of the disrupted myelin sheath. MS is generally considered as being an autoimmune condition, with the insulating myelin sheath being the focus of immune attack.

Unfortunately, the capacity for repair in the CNS is usually limited, and episodes of relapsing remitting MS (RR-MS), are all too often associated with a degree of permanent disability, which may become progressive with the passage of time. Although most people with MS will present with RR-MS, the bulk of this population will develop secondary progressive disease after a number of years. About 15% of people will present with a primary progressive clinical phenotype, usually at a slightly older age and with a more equal sex distribution. We now know that even very early episodes of inflammation can be associated with significant disruption, not only to the myelin sheath and the myelin producing oligodendrocyte, but also to the underlying axons. This axonal loss, together with a degree of astrocyte scarring probably underlies the progressive nature of most MS. It is probable that neurons can only sustain a limited amount of inflammatory abuse, and incomplete myelin repair may remove important growth factor trophic support, and lead to a gradual loss of nerve cells, with consequent CNS atrophy measurable using MRI.

The bulk of evidence would support these suppositions, which themselves carry significant implications. For example, if correct, then very early and aggressive anti-inflammatory treatment, with ongoing immune suppression, should prevent the development of secondary...
progressive disease. There is currently no proof to substantiate this hypothesis. Furthermore, in primary progressive disease, where comparatively little cerebral inflammation is apparent, anti-inflammatory treatments seem to be ineffective. Some people have gone so far as to question whether MS related inflammation is in fact a secondary, rather than a primary phenomenon. In other words, could some forms of MS be due to primary axonal or oligodendrocyte degeneration?

Some re-appraisal of the traditional homogenous nature of MS has occurred after recent neuropathological studies. The problem with much of the older MS literature has been that it is based on tissue from advanced cases. Once the inflammatory process has been occurring for many years, it is probable that many secondary and tertiary reactions are taking place. Trying to disentangle primary disease under these circumstances is extremely difficult. More recently there have been concerted attempts at analysing MS tissue from people very early in the disease process such as after sudden death from an unrelated cause, or where a biopsy has been performed in cases of diagnostic uncertainty. Results from such studies have suggested that MS pathology may not be the same in all cases. Four major disease types have been described, types I and II being largely inflammatory and immune mediated, whereas types III and IV seem to be more typical of primary cell death, rather than immunologically driven. Interestingly, all lesions from any individual patient seem to take the same form, but people differ in their disease subtype. There has also been a suggestion that apoptotic cell death of oligodendrocytes may underlie all early lesions, so phagocytosis of disrupted myelin may be a secondary event. If these results can be applied more widely, they will have profound implications for our understanding of MS. Rather than accepting everyone has the same basic disease process, we may need to direct specific treatments to particular disease subtypes, as well as investigating ways of influencing the cell death programmes of oligodendrocytes.

**CRITERIA FOR MAKING THE DIAGNOSIS OF MS**

There is no single diagnostic test that is specific to MS, and making a diagnosis still rests on confirmation of dissemination of CNS inflammation, both in time and position within the CNS. The important change in diagnostic criteria is the inclusion of MRI as a means of assisting in the identification of new lesions, rather than just relying on clinical evidence for lesion dissemination. In other words, to make a diagnosis of MS without objective evidence of a second lesion is extremely difficult. More recently there have been concerted attempts at analysing MS tissue from people very early in the disease process such as after sudden death from an unrelated cause, or where a biopsy has been performed in cases of diagnostic uncertainty. Results from such studies have suggested that MS pathology may not be the same in all cases. Four major disease types have been described, types I and II being largely inflammatory and immune mediated, whereas types III and IV seem to be more typical of primary cell death, rather than immunologically driven. Interestingly, all lesions from any individual patient seem to take the same form, but people differ in their disease subtype. There has also been a suggestion that apoptotic cell death of oligodendrocytes may underlie all early lesions, so phagocytosis of disrupted myelin may be a secondary event. If these results can be applied more widely, they will have profound implications for our understanding of MS. Rather than accepting everyone has the same basic disease process, we may need to direct specific treatments to particular disease subtypes, as well as investigating ways of influencing the cell death programmes of oligodendrocytes.

**CHANGING THE DISEASE COURSE IN MS**

One of the few predictable features of MS is that it is unpredictable, particularly early in the condition. To ascertain whether any treatment is having an impact on any patient’s MS, ideally we would be able to predict what would happen with and without that particular treatment. Current treatment options are a long way from this goal, and although certain drugs have been labelled as being disease modifying (a term used particularly by the pharmaceutical industry), there are no long term studies that show a reduction in the incidence of secondary progression. Other terms may be more appropriately used, such as immunomodulatory or neuroprotective, but only where the data support such terminology.

Most clinical trials have been designed using data derived from large natural history cohorts using a measurement scale known as the expanded disability status scale (EDSS). These data can also be used to advise patients in generic terms about prognosis. So, for example, being a woman, with few relapses, mainly sensory and optic nerve symptoms, little to find on examination, and with no coordination problems, are all good prognostic factors. Conversely, being male, with a mainly progressive pattern, with motor and coordination problems, and persistent abnormalities on neurological examination at an early stage of the condition, are all poorer prognostic factors. Attempting to individualise population or large trial data is fraught with problems, but none the less a necessary requirement in trying to tailor treatment for individual patients and in counselling people about treatment options.

It is often difficult for clinicians outside of a particular disease area to appreciate the complexities and idiosyncrasies of any particular measurement tool. The EDSS is disease specific and ranges from 0 (normal on examination) to 10 (dead). The first four points are based on neurological examination findings, scores from 4–7 based on mobility, and
scores above this based on degree of dependence. The scale is not linear, and changes of one point at lower levels on the scale do not equate to single point changes at higher scores. Patients spend different amounts of time at each level, there is no measurement of cognition (which unfortunately is commonly affected in MS), and overall the scale is very insensitive. Despite these shortcomings (and there are others), it is this scale that is the basis of virtually all trials of potential disease modification in MS. Better measurement tools have been developed, and we all look forward to the day that generic scales of physical disability, psychological and social wellbeing can be used across all medical conditions.

**INTERFERON BETA AND GLATIRAMER ACETATE**

There is now considerable clinical experience of using these drugs in routine clinical practice. We know from the pivotal studies that these compounds share similar levels of clinical efficacy, although there are two major types of interferon beta (1a and 1b), and three different interferon beta products— as well as glatiramer acetate. When used in ambulant patients with RR-MS, and a relapse rate of around one per year for the previous two to three years (the average relapse rate of RR-MS being one every two years), patients may expect a reduction in relapses of about 30%. Another way of putting this statistic is that if the treatment works and someone is having a relapse a year, over a three year period, a patient with RR-MS might expect two relapses instead of three. The evidence would suggest that these drugs do not work in progressive disease, unless there are concomitant relapses.

There is more controversy over the long term effects of these drugs and whether they truly have an impact on disability. A recent Cochrane review of interferon beta in MS identified seven trials that met the criteria of double blind, placebo controlled, randomised trials of RR-MS. Although 1215 patients were included in this review, only 919 (76%) contributed to the results concerning exacerbations and progression of the disease at two years. Specifically interferon significantly reduced the occurrence of exacerbations (RR = 0.80, 95% CI 0.73, 0.88, p <0.001) and progression of the disease (RR = 0.69, 95% CI 0.55, 0.87, p = 0.002) two years after randomisation. However, the clinical course and assignment of drop outs was essential to the demonstration of efficacy, most conspicuously concerning the effect of the drug on disease progression. Hence, if interferon treated patients who dropped out were deemed to have progressed (worst case scenario) the significance of these effects was lost (RR = 1.31, CI 0.60, 2.89, p = 0.5). A further recent Cochrane review of glatiramer acetate concluded that there was little evidence of any beneficial effect on the main outcome measures in MS (both disease progression and risk of clinical relapses). These drugs have been controversial mainly because of their cost in relation to the size of any beneficial effect. There is fierce global commercial competition for the available market, and publications should be interpreted on the basis of scientific content, with an understanding of the background interests. For example there is an ever-expanding literature on the significance of anti-interferon antibodies in relation to lack of clinical efficacy. This literature has generated more heat than light, and may serve to cloud interpretation of other, more important data. Part of the problem in the interpretation of data from immunomodulatory studies in MS is that the most studies have only been placebo controlled for two years. Lessons can be gleaned from the Mayo Clinic-Canadian cooperative study of sulfasalazine in MS here. This was a year three year study, which showed no significant treatment effects at three years, although there were effects at two years. Thus, if this study were only of two years duration, it would have been judged to be a successful treatment, which it is not. In the UK the Association of British Neurologists has produced guidelines on the use of interferon beta and glatiramer acetate, which are a useful summary of available evidence and recommended practice.

Two further points are worth mentioning. Firstly, although there have been two published studies of interferon beta in CIS, the results of both studies are consistent with previous information on reduction in relapse rate. It is not surprising that if these compounds reduce relapses, then we would expect to see a prolongation of time between CIS and development of MS in the treatment group. This is not powerful evidence for treating CIS at the earliest opportunity, and we desperately need longer term studies to establish whether early treatment really does have an impact on long term disease course. Secondly, these compounds (interferon beta much more than glatiramer acetate) do have large effects on aspects of MRI at follow up. The problem here is that the clinical correlation of disability with cranial MRI is not good, and if we are not careful, the tendency to treat scans rather than patients becomes manifest. If surrogate outcome measures are reliable and clinically well correlated, (for example, tumour mass in cancer treatment), then it is reasonable to accept surrogate measures of treatment effect. This is not yet the case in MS, and ultimately we need both better clinical measures and better surrogate measures that accurately reflect the most important clinical aspects of the condition from the patient and carer perspective.

**THE UK RISK SHARING SCHEME**

The cost of interferon beta and glatiramer acetate treatment led to these drugs being early targets for the newly formed UK National Institute for Health and Clinical Excellence (NICE), whose role includes a cost effectiveness analysis of new treatments and interventions, to help decide whether treatments are effective and affordable to the UK NHS. Their report from 2002 concluded that these treatments were not cost effective and should not be used routinely in the NHS in England and Wales, unless costs could be reduced. Not surprisingly, the pharmaceutical industry, together with the vocal patient group argued strongly against this conclusion, which led to an exploration of alternative ways of reducing the cost and also the risk of these treatments not being cost effective. The UK “Risk Sharing Scheme” was essentially developed to enable patient access to treatment at reduced cost, with monitoring of patient disability over time, with the eventual aim of further adjusting prices, depending on data generated by the monitoring scheme. This innovative solution to the NICE report has been criticised, particularly for the lack of scientific rigour of the monitoring scheme, and the missed opportunity for conducting well designed independent clinical trials rather than simply monitoring patients without a control group. Rather than spending tens of millions of pounds on treatments with questionable long term benefit, a fraction of these costs could have generated...
is beyond the scope of this review, but some general points should be noted. Most compounds are immunomodulatory in some way, ranging from non-specific immunosuppressants such as azathioprine and mitoxantrone, through more specific monoclonal antibody treatments such as alemtuzumab (Campath 1H)\textsuperscript{27} and natalizumab (Antegren),\textsuperscript{28} to attempts at blocking antigen presentation at the immunomological trimolecular complex between T cells and antigen presenting cells.\textsuperscript{29} A full consideration of all compounds in development is beyond the scope of this review, but some general points are worth considering.

Some of the compounds currently being tested are extremely powerful, both on clinical and MRI parameters. However, none has yet proved to be without significant side effects. For example, alemtuzumab is very effective at abolishing new MRI activity and most clinical relapses, but has a 30% risk of thyrotoxicosis at the doses previously used. If these products are to make a useful transition from clinical trials to routine practice, they will almost certainly need to be targeted to those patients in whom they are most likely to be useful. This means that in patients likely to have a benign disease course, milder treatments with fewer side effects may be a more sensible option. On the other hand, patients destined for a catastrophic disease may warrant the most powerful treatment options. The difficulty comes in spotting which patients fall into each category, and we simply do not have accurate methods of predicting disease course with any certainty. Once again, treatment algorithms should be tested in clinical trials to provide clinicians with appropriate decision making tools.

Another issue relates to when to use these compounds. As described above, if we believe that MS is fundamentally an autoimmune disorder, with damage sufficient to trigger the processes necessary for secondary degeneration occurring early in the disease course, then strong treatment given early is the most logical step. We still need evidence to back up our theories, and in our present information vacuum, there is a strong argument for appropriating counselling patients about clinical risk. In a notoriously unpredictable disease, do they wish to wait and see what happens to them, by which time immune intervention therapies may have become ineffective, or do they wish to take a long term risk with comparatively untried treatments in a gamble that their disease is going to get worse?

A further issue revolves around how accurately we are able to predict the behaviour of the immune system if we target one component of it. Most of the animal and experimental data would suggest that tumour necrosis factor α (TNFα) is harmful in MS,\textsuperscript{23} yet a treatment aimed at blocking TNFα action (Lenercept) actually made the disease worse.\textsuperscript{24} Most treatments effective in animal models of MS have not made the transition to human use, perhaps illustrating the complexity of nature and our inadequate understanding of damage and repair mechanisms. There is also considerable redundancy in the immune system, so for example, there are several adhesion molecules and chemokines involved in migration of white cells across the blood-brain barrier into the CNS. Targeting any single molecule may fail if there are alternatives ready to step into the immunological breach when one molecule is blocked. Ultimately there is no substitute for good, preferable long term, clinical trials and until we have more evidence, it is very difficult to make recommendations for everyday practice. Consideration of which drug to use when and in whom is best made by a neurologist with expertise of using these drugs, after appropriate patient counselling.

Unfortunately, the lack of convincingly effective treatments, especially later in the disease course means that patients may become desperate for treatments based on the latest anecdotal information. The history of MS treatment is littered with treatment failures after huge initial enthusiasm. Recent results showing the size of placebo effects in MS trials only serve to illustrate this point.\textsuperscript{31} Such placebo responses, possibly improved by the increased care and attention given to participants in clinical trials, may persist for many months, if not years, and experienced clinicians learn to become immune to the power of anecdote.

TREATMENTS FOR PROGRESSIVE DISEASE

Unfortunately there is no good evidence for any drug having an effect in progressive forms of MS in the absence of relapses. Many clinicians, often after heartfelt discussion with patients, have tried powerful immunotherapies at this stage of the illness, but with little, if any success. This is compatible with the hypothesis that if immunotherapies are going to work, they must be used early in the illness. There is mounting evidence from natural history studies that once walking starts to become affected in people with MS, there is a steady decline in physical functioning, which at present cannot be halted. A degree of optimism can be given to patients by telling them that most people with MS will not die from their disease, and disability does tend to stabilise over time, but it is impossible to predict at what point that will occur, or how disabled people will be when things settle down.

In this environment, there is now a massive swelling of interest in strategies aimed at slowing down progressive disease, so called neuroprotective therapies. Many compounds may have such a potential action, including drugs blocking the excitotoxic mechanisms of glutamate action, treatments to reduce free radical damage (including antioxidants), and trophic therapies designed to provide growth factors to damaged nerve cells. Once again lessons can be learnt from clinical trials in other disease areas. For example, the DATATOP study\textsuperscript{32} examining the use of selegiline in the treatment of Parkinson’s disease was confounded by the symptomatic effect of the drug. In other words people felt

<table>
<thead>
<tr>
<th>Available types of interferon beta for treating MS</th>
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<tbody>
<tr>
<td>• Interferon beta 1b (Betaseron)—for subcutaneous injection, 300 µg alternate days</td>
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<tr>
<td>• Interferon beta 1a (Avonex)—for intramuscular injection 30 µg once weekly</td>
</tr>
<tr>
<td>• Interferon beta 1a (Rebit)—for subcutaneous injection 22 or 44 µg three times/week</td>
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better receiving active medication because of a symptomatic, rather than a fundamental neuroprotective effect of the drug. This is a potentially significant problem with any treatment where a disability scale is used as a primary trial outcome, yet such measures are crucial to lending clinical credence to any positive results from surrogate measures such as a laboratory tests or MRI. The future lies in developing rating scales that are stable and linear, which can be used to disentangle the complex relation between symptoms and disability. Ideally surrogate measures will be used in parallel with such clinical scales and can also be used to illuminate pathological mechanisms in chronic disease.

**CONCLUSIONS**

This is an exciting time in MS care and research. A slow but steady array of drugs is becoming available that may be useful in the battle against this potentially disabling condition. Overall, the increased availability of drugs such as interferon beta and glatiramer acetate has increased resources and attention towards MS care. Yet there remain a significant number of challenges in future treatment strategies. Accurate diagnosis needs to be combined with some estimate of prognosis that should assist in making treatment decisions. Increasing availability of information needs to be combined with education of both health professionals and patients to the importance of developing research strategies to assist in answering the difficult questions. Finally, there must be a unity of purpose from everyone involved with MS, to ensure precious resources are directed at better treatments rather than commercial priorities.

**MULTIPLE CHOICE QUESTIONS (ANSWERS AT END OF REFERENCES)**

1. When a person presents with a clinically isolated syndrome, and has a normal cranial MRI, what is the 14 year risk of developing MS?
   - (A) 10%
   - (B) 20%
   - (C) 50%
   - (D) 60%
   - (E) 80%

2. Which of the following treatments are effective for primary progressive MS?
   - (A) glatiramer acetate
   - (B) interferon beta 1a high dose
   - (C) interferon beta 1a low dose
   - (D) mitoxantrone
   - (E) none of these.

3. What is the overall likelihood of relapse reduction using interferon beta if someone with MS had been having one relapse per year for the previous two years?
   - (A) 5%
   - (B) 10%
   - (C) 30%
   - (D) 50%
   - (E) 70%

4. What is the twin concordance rate for MS in monozygotic twins?
   - (A) 5%

5. What is the highest overall prevalence rate of MS in parts of Scotland?
   - (A) 1 in 200
   - (B) 1 in 300
   - (C) 1 in 800
   - (D) 1 in 300
   - (E) 1 in 1000

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**REFERENCES**


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ANSWERS
1. (B); 2. (E); 3. (C); 4. (C); 5. (D).