Multiple Sclerosis Society

Time to Act – a consensus on early treatment

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Suzanne Crighton

Suzanne Crighton (pictured overleaf) was involved in the steering group which reached the conclusions in this report. She was diagnosed with MS in 1991, when disease modifying treatments were not available, and some years later she decided to begin treatment with a newly available DMT. However, during the seven month wait she had before beginning treatment, she had five relapses and her health deteriorated dramatically. Her relapses during this period still have an impact today, and early treatment could have made a huge difference to Suzanne.

Does early treatment with disease modifying therapies improve long-term outcomes for people with MS?

Introduction

In November 2014, the MS Society facilitated a consensus meeting with key members of the MS community to consider the balance of clinical evidence and emerging practice around whether early treatment with disease modifying therapies (DMTs) improves long-term outcomes for people with MS. It was attended by people with MS, neurologists, MS nurses, MS Society staff and MS Trust staff. This group of experts agreed that current evidence confirms the importance of treating with DMTs as close as possible to making a diagnosis of MS (consistent with people being able to make informed decisions). This paper outlines why early treatment is important for people with relapsing forms of MS and what has led to this conclusion.

Why is the question of early treatment important to people with MS?

Being diagnosed with relapsing forms of MS and trying to come to terms with having a chronic health condition can be an extremely challenging and distressing time. People are also faced with the difficulty of deciding when – if at all – to take a (DMT), and which DMT would be best for them.

Without clear guidance on whether there are time-related benefits to starting on DMTs as soon as possible, the decision to start or not start a long-term treatment – with potentially serious side effects and impacts on day-to-day quality of life – will remain a difficult one. This is particularly true if relapses and symptoms are mild.

Because of perceived uncertainties around efficacy, risk and tolerability, and limitations in prescribing guidelines that are, in part, determined by estimations of cost effectiveness, the treatment decision in the UK is quite often no treatment. There is a preference to "wait and see", with less frequent prescribing compared with other countries[1], particularly early in the disease course.

The key question, then, is whether this matters in terms of long-term outcomes for people with MS?

What are the long-term effects of MS?

MS is a highly individual condition with its consequences varying greatly from person to person and over time. Its impact is wide ranging, affecting physical, emotional and social aspects of people's lives.

Averages inevitably mask personal experience, both of the impact of disease and its treatment. Nevertheless, studies have shown that the long-term effects of MS are that the average person with MS

[1] MS Society. A lottery of treatment and care – MS Services across England at the UK, 2013 http://mslottery.mssociety.org.uk/wp-content/uploads/2013/04/UK-ms-lottery.pdf

[2] Miller D, Compston A. The differential diagnosis of multiple sclerosis. McAlpine's multiple sclerosis. 4th edition.London: Churchill Livingstone; 2005.

[3] Pfleger CCH et al. Social consequences of multiple sclerosis. Part 2. Divorce and separation: a historical prospective cohort study. Mult Scler July 2010 vol. 16 no. 7 878-882 http://msj.sagepub.com/content/16/7/878.short

will need to use a walking stick within 20 years of diagnosis and a wheelchair within 30 years.[2] People with MS have a greater risk of depression and suicide and are 40% more likely to separate, or divorce, and do so sooner than the general population.[3]

Why take a DMT?

There are 11 DMTs licensed for MS, all with different efficacies, side effects and methods of administration. As a general rule, the more effective treatments tend to have more severe potential side effects.

DMTs can decrease the number and severity of relapses,[4, 5] delay the progression of disability and slow the speed at which it happens.[6, 7, 8] Fortunately, this matches the treatment goals of people with MS.[9]

By preventing relapses and disability progression, people should be able to take greater control of their condition and their lives, directly and indirectly improving physical, emotional and social outcomes.

Why aren't more people taking a DMT?

Access to DMTs in the UK is low. Six of 10 people with relapsing forms of MS do not take a DMT[10] and the UK is ranked 25 of 27 European countries on the proportion using DMTs.[11]

Access to specialists and to information from them is crucial, with those who have recent access to an MS nurse and a neurologist and adequate information being ten times as likely to be taking a DMT compared with people who have no such access. But, in the employment of neurologists, the UK lags behind comparable European countries. For every neurologist in the UK, Germany and Spain have six and Italy has eight.[12]

It is no wonder that professionals and people with MS frequently complain that their appointments are too short to adequately address the complex options for treatment and care. In one study, one in three people with relapsing MS said that they had not even discussed treatment options with their clinician.[13]

The barriers to accessing treatment are complicated by several other factors. An MS Society survey of how people with MS make decisions about taking DMTs confirmed that neurologists and MS nurses are the most influential source of information.[14] However, factors such as the negative NICE (National Institute for Health and Care Excellence) technology appraisal of beta interferon and glatiramer acetate in 2002[15] and a lack of long-term safety and efficacy data for the newer DMTs has led to conservatism among some sections of the professional community and people with MS about initiating treatment with a DMT. The early data from the MS Risk Sharing Scheme, published in 2010, strengthened the argument made by some that use of DMTs in MS could not be justified.[16]

[4] PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. Lancet 1998; 352(9139): 1498-504. http://www.ncbi.nlm.nih.gov/pubmed/9820297

[5] Kappos L, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010; 362: 387-401. http://www.nejm.org/doi/full/10.1056/NEJMoa0909494

[6] Palace J, et al. Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK. Multiple Sclerosis Risk Sharing Scheme at 6 years: a clinical cohort study with natural history comparator. Lancet Neurol 2015 http://www.thelancet.com/journals/laneur/article/PIIS1474-4422%2815%2900018-6/abstract

[7] Coles AJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 2012; 380(9856): 1829-39. http://www.ncbi.nlm.nih.gov/pubmed/23122650

[8] Polman C, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006; 354: 899-910. http://www.nejm.org/doi/full/10.1056/NEJMoa044397

[9] Holloway E, Redford-Totts D (MS Society). Right Treatment, right time? How people with MS make decisions about disease modifying drugs http://www.treatmerightms.org.uk/wp-content/uploads/2014/04/Right-treatment-right-time.pdf

[10] MS Society. A lottery of treatment and care – MS Services across England at the UK, 2013 http://mslottery.mssociety.org.uk/wp-content/uploads/2013/04/UK-ms-lottery.pdf

[11] Kobelt G, KastenG F. The burden of multiple sclerosis and access to innovative treatments in Europe 2009. www.comparatorreports.se

[12] Multiple Sclerosis International Federation – Atlas of MS 2013, 2013 http://www.msif.org/about-us/advocacy/atlas/

[13] Holloway E, Redford-Totts D (MS Society). Right Treatment, right time? How people with MS make decisions about disease modifying drugs http://www.treatmerightms.org.uk/wp-content/uploads/2014/04/Right-treatment-right-time.pdf

The effect of this has been that some people with MS do not start treatment at all, while others have been encouraged to 'wait and see' how their MS develops before they make their decision.

The more recent data from the Risk Sharing Scheme, for years four and six (announced in 2014, but published in 2015), should reinforce new professional treatment guidance and help to change attitudes to and practice around the use of DMTs in the management of MS.

Our changing understanding of MS

Our understanding of the disease activity that underpins MS has developed significantly over the past 15 years. This can largely be attributed to improved use of MRI scanning, which provides a more sensitive tool for identifying inflammatory damage in MS.

Prior to using MRI in both research and clinical practice, neurologists were limited to identifying clinical relapses (a sudden manifestation of new and/or increased symptoms that may, for example, affect vision, balance, mobility and sensation) to diagnose people with active relapsing remitting MS and make treatment decisions.

MRI scanning has facilitated a greater understanding of the role of the immune system and inflammatory processes that cause damage to the myelin sheath and contribute to neurodegeneration. It has shown that new MRI lesions are a more sensitive and comprehensive indicator of inflammatory disease activity than clinical relapses, occurring up to ten times more frequently than clinically apparent relapses.[17,18] This has greatly improved our understanding of the damage that can be accrued without someone experiencing obvious relapses as well as during a more obvious attack.

This greater understanding has been reflected in the McDonald criteria (developed in 2001, updated in 2005 and 2010[19]), the diagnostic criteria for MS recommended by NICE and the Association for British Neurologists for use in clinical practice. The criteria support diagnosis on the basis of clinical and radiological evidence (spatial and temporal dispersion of MRI lesions), meaning that many people previously considered to have a first clinical episode (known as clinically isolated syndrome) can now be diagnosed with MS following MRI.

Coupled with the modified Rio criteria (2012 [20]), significant progress has been made in understanding how activity measured by MRI over 12 month intervals could inform treatment decisions, both early on and in ongoing management.[21] However, such regular use of MRI to monitor disease activity and treatment effect is still not common practice in the UK, though MRI is increasingly used as an outcome measure for clinical trials.

[14] ibid

[15] NICE Technology Appraisal 32 https://www.nice.org.uk/guidance/ta32

[16] McCabe C, et al. Continuing the multiple sclerosis risk sharing scheme is unjustified BMJ 2010; 340: c1786 http://www.bmj.com/content/340/bmj.c1786

[17] Kappos et al. Magnetic resonance imaging in the evaluation of treatment in multiple sclerosis. Neuroradiology. 1988; 30(4): 299-302. http://www.ncbi.nlm.nih.gov/pubmed/3050587

[18] Isaac C, et al. Multiple sclerosis: a serial study using MRI in relapsing patients. Neurology. 1988; 38(10): 1511-15 http://www.ncbi.nlm.nih.gov/pubmed/3419593

[19] Polman CH, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. Annals of Neurology 2011; 69(2): 292-302. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3084507/

Does early treatment matter?

The greater understanding of disease activity, improved capacity to diagnose MS earlier, and increased range of treatment options have collectively opened an important question regarding the best time to begin treatment with a DMT. Significant evidence has emerged in recent years indicating the potential long-term benefits of taking a DMT early in the disease course, but questions have remained regarding whether this is sufficient to implement changes in policy and practice.

In November 2014, the MS Society facilitated a consensus meeting with key members of the MS community to consider the balance of clinical evidence and emerging practice around whether early treatment with disease modifying therapies improves long-term outcomes for people with MS. It was attended by people with MS, neurologists, MS nurses, MS Society staff and MS Trust staff (see appendix 1). The meeting was held within the following parameters:

- people with relapsing remitting MS as defined by the latest McDonald Criteria (therefore excluding people with clinically isolated syndrome)
- treatment with any DMT – type of treatment was not within the scope of this group.

The following evidence and practice was considered.

Evidence for early treatment

Long-term follow-up of the early pivotal interferon trials present interesting data, with the placebo group being switched to active treatment after three years. The 16 year data showed significantly improved physical and mental outcomes[22] for those receiving the treatment from the outset compared with those in the placebo group.

[20] Sormani et al. Scoring treatment response in patients with relapsing multiple sclerosis. Mult Scler. 2013; 19(5): 605-12.25 http://www.ncbi.nlm.nih.gov/pubmed/23012253

[21] Dobson et al. Assessing treatment response to interferon- : is there a role for MRI? Neurology. 2014; 82: 248-54.

[22] Goodin DS, et al.Relationship between early clinical characteristics and long term disability outcomes: 16 year cohort study (follow-up) of the pivotal interferon ß-1b trial in multiple sclerosis. Journal of Neurology, Neurosurgery and Psychiatry 2012; 83(3): 282-287. http://www.ncbi.nlm.nih.gov/pubmed/22193561

A further paper was published in 2012, showing an even more stark difference in outcomes between the two groups for the 21 year follow-up. It showed that people who were given beta-interferon in the original treatment group had a 50% reduction in mortality rates compared with people who started on the placebo and switched to interferon three years later.[23]

A six year study of patients taking glatiramer acetate concluded that early use of the treatment has a bearing on efficacy, with those taking treatment (rather than placebo) from the outset being less likely to be using a walking aid at six years.[24]

A seven year follow-up study of people taking alemtuzumab was published in early 2014. This showed that 68% of people on the treatment experienced an overall improvement or stabilisation in disability over seven years.[25] The alemtuzumab trial is especially valuable because people were consciously selected for early treatment. Crucially, the interferon arm also fared better than in previous trials, adding to the evidence around early treatment.[26]

Evidence presented at the ECTRIMS conference in 2014 (and published later that year) also suggested that early use of Plegridy led to improved outcomes compared with a later start,[27] though this was over a much shorter timescale than the pivotal 21 year study.

The five year results of a ten year observational study into the long-term efficacy and safety of natalizumab in clinical practice showed that patients who started natalizumab treatment when they were therapy naïve, or with lower baseline EDSS scores or relapse rates, or who had used fewer prior DMTs had lower on-therapy annualised relapse rates. This suggested the level of clinical disease activity may be lower when natalizumab treatment is initiated earlier in the disease course.[28]

In October 2014, a new study was published analysing observational data from 3,060 people with MS on the long-term risk of disability.[29] The researchers concluded DMTs delayed long-term disability in people with MS treated either in the early or, to a lesser extent, in the later phase of the disease. Thus, the window of therapeutic opportunity is relatively extended, assuming that early is better than late treatment, but late is better than never.

Several trials of DMTs in secondary progressive MS[30] showed a lack of effect of DMTs in treating progressive forms of the disease. Although there are ongoing questions over therapeutic lag and the need for longer follow-up, these studies have helped shape the therapeutic window for current DMTs as being earlier, relapsing forms of MS only.

[23] Goodin DS, et al. Cause of death in MS: long-term follow-up of a randomised cohort, 21 years after the start of the pivotal IFN -1b study. BMJ Open. 2012; 2(6). pii: e001972 http://www.ncbi.nlm.nih.gov/pubmed/23204140

[24] Rovaris M, et al. Long-term follow-up of patients treated with glatiramer acetate: a multicentre, multinational extension of the European/Canadian double-blind, placebo-controlled, MRI-monitored trial
Mult Scler. 2007; 13(4): 502-8 http://www.ncbi.nlm.nih.gov/pubmed/17483532

[25] Tuohy O, et al. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy
J Neurol Neurosurg Psychiatry doi:10.1136/jnnp-2014-307721 http://jnnp.bmj.com/content/early/2014/05/21/jnnp-2014-307721.abstract

[26] Cohen JA, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012; 380(9856): 1819-28. http://www.ncbi.nlm.nih.gov/pubmed/23122652

[27] Arnold DL, et al. Effect of peginterferon beta-1a on MRI measures and achieving no evidence of disease activity: results from a randomized controlled trial in relapsing-remitting multiple sclerosis. BMC Neurol. 2014; 14(1): 1058. http://www.ncbi.nlm.nih.gov/pubmed/25551571

[28] Butzkueven H, et al. Efficacy and safety of natalizumab in multiple sclerosis: interim observational programme results J Neurol Neurosurg Psychiatry 2014; 85: 1190-1197. http://jnnp.bmj.com/content/85/11/1190.long

[29] Cocco et al. Influence of treatments in multiple sclerosis disability: A cohort study.
Mult Scler. 2014. pii: 1352458514546788 http://www.ncbi.nlm.nih.gov/pubmed/25257611

[30] Kappos L. Effect of drugs in secondary disease progression in patients with multiple sclerosis. Mult Scler. 2004; 10 Suppl 1: S46-54; discussion S54-5. http://www.ncbi.nlm.nih.gov/pubmed/15218809

There have been several studies into treatment of clinically isolated syndrome with a DMT. A study into the effect of treatment with interferon beta-1b in clinically isolated syndrome showed that early treatment reduced the risk of conversion to clinically definite MS by 37% compared with delayed treatment. However, in this study a delay in treatment by up to two years did not significantly affect disability outcomes at five years.[31]

A study looking to asses the efficacy and safety of teriflunomide in people with a first clinical episode suggestive of MS showed that the treatment reduced the likelihood of converting to clinically definite MS and the number of new MRI lesions compared with placebo.[32]

A study into the effect of DMTs on cognition in patients with clinically isolated syndrome showed that treatment helped preserve the brain's grey matter and cognitive function.[33]

Evidence questioning the benefits of early treatment

A study looking at the effect of early treatment on various outcomes (including EuroQoL-5D [EQ5D], Patient Health Questionnaire-9 [PHQ9], Multiple Sclerosis Performance Scales [MSPS], and the timed 25-foot walk [T25FW]) showed that early treatment was only beneficial to certain subgroups of the MS population and its effect is modest.[34]

A follow-up study of people who had presented with a clinically isolated syndrome suggestive of MS 20 years earlier showed that 67 of 107 patients went on to develop clinically definite MS. Of those with clinically definite MS, 39% had an EDSS score of 3 or less at 20 years. 82% of those with an abnormal MRI went on to convert to clinically definite MS.[35]

Although other studies show that taking a DMT can reduce the risk of converting to clinically definite MS, DMTs also carry a risk of long-term side effects. Some of these side effects are particularly serious, such as thyroid problems or progressive multifocal leukoencephalopathy. Neurologists can struggle to predict who will go on to develop significant disability and who will not, so it is difficult for people with MS to make long-term decisions about the best treatment option for them. Treating people whose symptoms will remain mild with a DMT that could endanger their long-term wellbeing should be avoided.

Newer DMTs like alemtuzumab, dimethyl fumarate and teriflunomide have only been approved for use on the NHS in the past year by the UK's Health Technology Appraisal bodies; the phase 2 and 3 trials happened in the past decade. While follow up data from the alemtuzumab trials has shown very encouraging results at seven years with the majority of people on the treatment experiencing an overall improvement or stabilisation in disability, the long-term effect of these treatments will not be truly known for another 10 or so years. Further evidence of long-term early treatment effect would provide greater clarity.

[31] Kappos L, et al. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial.

Lancet Neurol. 2009; 8(11): 987-97 http://www.ncbi.nlm.nih.gov/pubmed/19748319

[32] Miller AE, et al. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2014; 13(10): 977-86 http://www.ncbi.nlm.nih.gov/pubmed/25192851

[33] Uher T, et al. Relationship between gray matter volume and cognitive learning in CIS patients on disease-modifying treatment. J Neurol Sci 2014; 347(1-2): 229-34. http://www.ncbi.nlm.nih.gov/pubmed/25456460

Beyond the biomedical argument, there is a question of best use of resources. Limited NHS funds need to cover a broad range of treatment and care, so investment in DMTs needs to be considered alongside the relative importance of other interventions. Clearly, the cost of treatment goes beyond the actual cost of a DMT itself. Factored into the overall cost of the treatment include:

- the time spent with specialists to advise, prescribe and monitor patients
- the facilities in which DMT services take place
- monitoring of DMT efficacy and safety e.g. blood tests and/or MRI scans
- referrals or changes to treatment that need to be made as a result of suboptimal response or side effects.

Recommendations

✔ On the balance of evidence available, the group agreed that early treatment with a DMT can improve long-term outcomes for people with relapsing remitting MS, compared with a later initiation of treatment.

✔ However, there is a subgroup of people with MS who will not go on to develop significant disability or experience significant relapses. For this group, treatment with DMTs would not be optimal. While there are some prognostic indicators, it is very difficult to identify those who will experience this less active form of the MS over the long term and therefore a programme for monitoring disease activity must be in place to make and re-visit informed decisions regarding treatment.

✔ The group recommended that conversations regarding treatment should begin at diagnosis and be followed up during the following six months with a view to developing a treatment plan in this time period that includes a more considered initial treatment decision. The type of DMT, treatment strategy and treatment goal should be decided jointly between patient and neurologist.

✔ Then, as part of the comprehensive treatment and care review now recommended by NICE[36] to occur at least yearly, there should be ongoing MRI monitoring to detect any undercurrent of disease activity. Suboptimal responses to treatment should prompt further discussion about changes in treatment regime.

[34] Conway DS, et al. Long term benefit of multiple sclerosis treatment: an investigation using a novel data collection technique. Mult Scler. 2012; 18(11): 1617-24 http://www.ncbi.nlm.nih.gov/pubmed/22653659

[35] Fisniku LK et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. Brain. 2008; 131(Pt 3): 80817 http://www.ncbi.nlm.nih.gov/pubmed/18234696

[36] NICE guidelines [CG186] Multiple sclerosis: management of multiple sclerosis in primary and secondary care (2014) https://www.nice.org.uk/guidance/cg186

✔ To support conversations around initiating early treatment, it is crucial that clinicians and patients have access to up-to-date and dynamic information materials. While clinicians recognise their role in conveying this information, the group agreed that patient organisations such as the MS Society and MS Trust have an important role to play in providing supporting information to clinicians and people with MS to support shared decision making, including conveying the importance of early treatment.

✔ Further research is required to provide greater clarity in a number of areas:

- improving understanding of individual prognosis
- measuring the effectiveness of a more intense monitoring regime (with more frequent MRI)
- clarifying the risks and benefits around the early use of more aggressive therapies and the appetite of people with MS to take informed risk.

✔ Further consideration needs to be given to people with clinically or radiologically isolated syndrome and whether or not to recommend treatment with DMTs for these groups of people as well as what monitoring is appropriate.

Influencing policy and practice

While the MS Society endeavoured to draw together a representative group of people from the MS community to consider the evidence around early treatment, significant further work needs to be done to build consensus among wider stakeholders to change policy and practice.

Important changes in DMT prescribing policy and practice are set to happen in the coming year. The importance of early treatment should have an important bearing on the outcome of these policy and practice reviews. The developments include:

- The Association of British Neurologists prescribing guidelines for MS – influential guidelines that guide clinical practice throughout the UK
- A NICE multi-technology appraisal of DMTs (scope to be confirmed) – an assessment of the cost-effectiveness of the treatments which determines their availability through the NHS (with implications for all UK countries)
- An NHS England treatment algorithm for DMT prescribing – the commissioning policy which underpins how and where DMTs will be provided.

Appendix 1

Participants involved in consensus meeting in November 2014

Nick Rijke	MS Society
Sally Hughes	MS Society
Andrew Boaden	MS Society
Jo Chapman	MS Society
Dr Emma Gray	MS Society
Janice Sykes	MS Trust
Amy Bowen	MS Trust
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Dr Belinda Weller	Neurologist
Dr Matthew Craner	Neurologist
Dr Nikos Evangelou	Neurologist
Dr Waqar Rashid	Neurologist
Prof David Miller	Neurologist
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Carmel Wilkinson	MS Nurse
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Gail Clayton	MS Nurse
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