Review article

# Cost of disease modifying therapies for multiple sclerosis: Is front-loading the answer?

Lisa Batcheller*, David Baker

*Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom*

A B S T R A C T

There are now over a dozen disease modifying therapies (DMTs) available to treat multiple sclerosis (MS). They vary in efficacy and safety as well as in cost.

The literature on the cost effectiveness of these is often confusing and contradictory. There is a lack of quality evidence enabling the comparison of different DMTs. There are scarce randomized controlled trials which look at one DMT compared with another that is not IFN or GA. There is also a lack of systematic reviews comparing the efficacy and safety of different DMTs. This makes it difficult to perform good quality cost-effectiveness analyses (CEAs). Furthermore, CEAs in and of themselves are difficult to interpret or compare due to the variation in methods and cost estimations as well as the use of outcome measures which cannot be proven over a reasonable timeframe.

This review looks at the different DMTs available for MS and attempts to draw some conclusions on their cost-effectiveness. It also considers the costs and benefits of front loading the cost of treatment for MS by using more expensive and effective treatment earlier on.

## 1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune inflammatory condition of the central nervous system (CNS). It is a pathophysiological process of inflammation, demyelination and neurodegeneration [1]. It can cause severe disability as function of the CNS deteriorates [1]. Until the 1990s, treatment for MS consisted only of symptomatic control, usually a short course of high dose steroids during exacerbations of the disease [2]. Since then, a multitude of disease modifying therapies (DMTs) have been developed that can slow the course of the disease. These drugs (Table 1) are high-cost and not without their own risks, but are now widely used to treat relapsing-remitting forms of MS (RRMS). Several cost effectiveness analyses (CEAs) have now been published looking at DMTs for MS. These economic evaluations have aimed to inform decision makers on the costs and benefits of the DMTs. However these are often difficult to interpret. While CEA methods have become more standardised there is still little consensus between studies [3].

## 2. Pathogenesis and disease modification

There are several proposed mechanisms by which CNS autoimmunity may be initiated in MS. Molecular mimicry may initiate the process by which autoreactive T cells are stimulated by autoantigens [4]. By another proposed mechanism, antigens, such as glial or neural proteins may drain into cervical lymph nodes via the glymphatic drainage system [5,6]. Once in the cervical lymph nodes, these antigens are presented to autoreactive T cells by antigen presenting cells (APCs) [4]. DMTs act on various targets in the process of CNS autoimmunity. In MS, there seems to be a failure of regulatory T cells to suppress auto-reactive T cells upon activation by an autoantigen [7]. GA acts to promote apoptosis of autoreactive T cells by regulatory T cells (Table 1). These autoreactive T cells are able to extravasate into the CNS and they are then re-activated locally, causing the release of cytokines which promote recruitment of microglia and directly cause damage to myelin and axons [8]. Fingolimod acts on S1P receptors to inhibit the migration of lymphocytes out of the lymph glands (Table 1), and natalizumab inhibits the extravasation of lymphocytes across the BBB (Table 1). Autoreactive T cells will also activate B cells and a humoral response will further add to inflammatory cell recruitment and contribute to damage to myelin and axons [9]. Alternatively, it may be that memory B cells are the major driving force behind the inflammatory phase in MS and present antigens to T cells or directly damage the CNS via toxic molecules or stimulate the innate immune response [10,11]. Alemtuzumab depletes both T and B cells by binding to CD52 (Table 1). Cladribine rapidly depletes both T and B cells by incorporating into DNA and inhibiting DNA repair causing cell death (Table 1). Ocrelizumab binds to CD20 causing depletion of B cells (Table 1). Nearly all DMTs seem to deplete memory B cells, and the degree of depletion can be correlated to the efficacy of the drug

---

* Corresponding author at: Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, 4 Newark Street, London E1 2AT, United Kingdom.
  *E-mail address:* lisa.batcheller@nhs.net (L. Batcheller).

**Table 1**
Characteristics of disease modifying therapies for multiple sclerosis.

| DMT | Dose | Pivotal trial efficacy | MoA | Side effects | Monitoring | Annual cost (UK)[a] | Cost (US) (year 1 WAC) | EMA licensing |
|---|---|---|---|---|---|---|---|---|
| IFNb-1a (Rebif s.c. injection) (Avonex i.m. injection) | Weekly i.m. injection (30 μg) Or thrice weekly s.c. injection (20 or 44 μg) | s.c.: PRISMS – 27% and 33% reduction in ARR compared to placebo for the 22 μg and 44 μg dose groups respectively, Increased time to SAD compared to placebo [18] i.m.: 18% reduction in ARR compared to placebo, 37% reduction in SAD vs placebo [19] | The are several proposed mechanisms of action for beta-interferons, including inhibition of immune cell proliferation, inhibition of B and T cell activation [20,21], increasing anti-inflammatory cytokines [22], increasing apoptosis of autoreactive T cells [23] and limiting T cell-endothelial adhesion [24,25] | Injection site reactions, hepatic impairment, depression, flu-like symptoms. Rarer side effects include anaemia, thrombocytopenia, lymphopenia and thrombotic microangiopathy [26,27]. There is an association with capillary leak syndrome in undiagnosed monoclonal gammopathy, which is why the Association of British Neurologists recommend that protein electrophoresis should be carried out prior to commencing therapy [28,29]. | FBC, LFT, renal function, blood pressure at baseline and every 3–6 months Protein electrophoresis at baseline [29,30] | Rebif: 20/44 μg £9088/£12,068 (€10,613 /€14,093) Avonex: £9061 (€10,581) | Rebif: $86,416 (€76,134) Avonex: $81,965 (€72,213) | RRMS |
| IFNb-1b (Betaseron or Extavia) | s.c. injection every other day (250 μg) | 34% reduction in ARR compared to placebo, no significant effect on SAD [31] | | | | Betaseron And Extavia: £7264 (€8483) | Betaseron: $86,659 (€76,348) Extavia: $72,359 (€63,750) | RRMS |
| Pegylated IFNb-1a (Plegidy) | s.c. injection every two weeks (125 μg) | ADVANCE – 35% reduction in ARR and a 39% reduction in 3-month SAD compared to placebo [32] | | Flu like symptoms, headache, injection site reactions, raised liver enzymes and depression are common side effects Rarer side effects include hypersensitivity reactions, seizures, injection site reactions, renal damage [33] | Regular monitoring of FBC, LFT, TFT, blood pressure and renal function [33] | £8500 (€9926) | $81,956 (€72,205) | |
| Glatiramer Acetate (GA) (Copaxone or Glatopa (generic)) | Daily s.c. injection (20 mg) Or thrice weekly s.c. injection (40 mg) | 29% reduction in ARR vs placebo, no significant difference in SAD [34] | GA promotes apoptosis of autoreactive cells by increasing levels of a strongly suppressive subset of regulatory T cells (PD1-Treg cells) [23]. Furthermore GA is thought to interfere with antigen presentation and T cell activation, as well as increasing anti-inflammatory cytokines [35,36] | Injection site reactions, Symptoms mimicking cardiac ischaemia – chest tightness, shortness of breath, palpitations, anxiety [27] | No additional monitoring required | £6700 (€7824) | 20 mg: $86,554 (€76,256) 40 mg: $76,024 (€66,979) 20 mg Glatopa (generic): $63,193 (€55,675) | RRMS |
| Fingolimod (Gilenya) | Daily oral tablet (0.5 mg) | FREEDOMS – 48% reduction in ARR compared to placebo, no significant reduction in SAD [37] TRANSFORMS – 52% reduction in ARR compared to i.m. IFNb1a, no significant difference in SAD [38] | Fingolimod is a sphingoside-1-phosphate (S1P) receptor antagonist. S1P receptors are expressed in a variety of cells including lymphocytes, neurons and astroglia. Binding of S1P to S1P receptors mediates lymphocyte migration out of lymph glands, and this process is disrupted by fingolimod as it is an S1P analogue. This mainly affects central memory T cells and naïve T cells as these are | First dose bradycardia, First and second degree atrioventricular block, Macular oedema, Lymphopenia, Infections, Elevated liver enzymes, Hypertension [30,37] Rarely PML [40] | MRI, ECG, VZV IgG serology, pregnancy test, ophthalmology testing, FBC, LFT and blood pressure at baseline Regular 3-monhtly FBC, LFT and ophthalmology during therapy [30,40,41] | £19,169 (€22,385) | $82,043 (€72,282) | 2nd line in HARRMS, or 1st line in RESMS |

**Table 1** (*continued*)

| Drug | Dose | Efficacy | Mechanism | Side effects | Monitoring | Cost (UK/EU) | Cost (US/EU) | Indication |
|---|---|---|---|---|---|---|---|---|
| Teriflunomide (Aubagio) | Daily oral tablet (14 mg) | TOWER – 36.3% reduction in ARR compared to placebo, reduced risk of SAD by 31.5% [42] TEMSO – Reduced ARR by 31.5% compared to placebo, Reduced risk of SAD by 29.8% [43] TENERE – No difference in ARR compared to s.c. IFNb1a [44] | more likely to re-circulate through lymph glands [39] Teriflunomide is thought to inhibit proliferation of activated T cells by inhibiting pyrimidine synthesis by the enzyme DHODH (dihydroorotate dehydrogenase) [45]. | Elevated liver enzymes, Hair thinning, Nausea, Diarrhoea, Hypertension, Peripheral neuropathy [30,4] | Baseline FBC, LFT, pregnancy test, TB, blood pressure First 6 months of therapy: monthly FBC, LFT After 6 months: FBC and LFT every 6 months [30] | £13,529 (€15,799). | $76,612 (€67,497) | RRMS |
| Dimethyl fumarate (Tecfidera) | 120 mg twice daily oral tablet; increased to 240 mg twice daily after 7 days | DEFINE – 53% reduction in ARR compared to placebo, 38% reduction in risk of SAD [46] CONFIRM – 44% reduction in ARR compared to placebo, Significant reduction in ARR compared to GA, No reduction in SAD [47] | Dimethyl fumarate has anti-inflammatory effects, by affecting cytokine release and immune cell differentiation [48–52]. It may also have neuroprotective antioxidant effects via Nrf2 (nuclear (erythroid-derived 2) related factor) pathways. In vitro studies showed that dimethyl fumarate protected neurones and glial cells against oxidative stress [53], and that this effect was lost in Nrf2 deficient cells [54]. In vivo studies in EAE mice showed raised levels of Nrf2 and improved neuronal survival which was not seen in Nrf2 deficient mice [53] | Nausea, Diarrhoea, Flushing [55], Rarely PML [56] | Baseline FBC and LFT [30] Baseline MRI [56] Monthly FBC [57,58] | £17,898 (€20,901) | $82,977 (€73,105) | RRMS |
| Natalizumab (Tysabri) | 300 mg i.v. infusion every 4 weeks | AFFIRM – 68% reduction in ARR compared to placebo, and a 42% reduction in risk of SAD [59] | Natalizumab is a monoclonal antibody directed against α4β1 integrin, an adhesion molecule involved in the extravasation of leukocytes across the BBB | Mild infusion associated symptoms – headache and fever, Hypersensitivity reaction requiring discontinuation of infusion [30], Cases of hepatic injury have been reported [33] The risk of PML after two years of therapy is 1 in 100 in JCV seropositive patients who have received prior immunosuppressive treatment [60], Neutralizing antibodies causing delayed hypersensitivity and reduced efficacy [61] | MRI at baseline, then every 3–12 months during therapy based on risk followed by one 3–6 months post-therapy [62] JCV serology every 6 months [62] Consider anti-natalizumab antibody testing after 6 months [61] | £14,730 annually (€17,202) | $78,214 (€68,908) | 2nd line for HARRMS or 1st line for RESMS |
| Alemtuzumab (Lemtrada) | First annual course is 60 mg via i.v. infusion over 5 days Second annual course is 36 mg via i.v. infusion over 3 days | CARE MS I – (Alemtuzumab as 1st line therapy) 54.9% reduction in ARR and a 30% reduction in risk of SAD compared to 44 μg s.c. IFNb1a [63] CARE MS II – (Alemtuzumab as 2nd line therapy) 49.4% reduction in ARR and a 42% reduction in risk of SAD | Alemtuzumab is a mAb targeting CD52, a surface marker on lymphocytes and monocytes Alemtuzumab treatment depletes lymphocytes and monocytes which subsequently replete over a period of time, at different rates – CD4+ T cells take more than 5 years to reach pre-treatment levels [65]. B cells replete over three months and | Infusion related reactions (90%) - may warrant pre-treatment with steroid, antihistamine and paracetamol [67], Infections, Secondary autoimmune conditions develop in up to 50% of patients after 2 years of therapy [66], Neutralizing antibodies occur in up to 80% of cases after second annual course [64] | Monthly blood tests including FBC, TFT, LFT Consider testing for neutralizing antibodies [67] | £56,360 for full two year course (€65,817) | $103,749 (€91,405) | Active RRMS |

*(continued on next page)*

**Table 1** (continued)

| Drug (Trade name) | Dose/administration | Mechanism | Efficacy (trial) | Side effects | Monitoring | Cost | WAC | Indication |
|---|---|---|---|---|---|---|---|---|
| | | then rise beyond pre-treatment levels, and this is thought to contribute to the secondary autoimmune complications which frequently follow alemtuzumab therapy [65,66] | compared with 44 µg s.c. IFNb1a [64] | | | | | |
| Ocrelizumab (Ocrevus) | 600 mg i.v. infusion every 6 months | Ocrelizumab targets CD20, a B cell progenitor antigen, and thereby depletes B cells [10] | OPERA 1 and II– 46% -47% reduction in ARR and 40% reduction in risk of SAD compared to IFNb [68] ORATORIO – 24% and 25% reduction in risk of SAD at 12 and 24 weeks respectively compared to placebo [69] | Infusion-related reactions, Infections [68] | FBC [70] | £19,160 (£4790 per 300 mg) (€22,375) | $65,000 (€57,267) | RRMS PPMS |
| Cladribine (Mavenclad) | 1 or 2 10 mg oral tablet once per day for four or five days of 2 treatment weeks each year for a total dose of 3.5 mg/kg over 2 years | Cladribine is an analogue of deoxyadenosine, which is metabolised to an active compound which causes cell death by incorporating into DNA and inhibiting DNA repair. It rapidly depletes T and B cells [72] | CLARITY – 57.6% and 54.5% reduction in ARR compared to placebo for the 3.5 mg/kg and the 5.25 mg/kg groups respectively. 33% and 31% reduction in risk of SAD for the 3.5 mg/kg and 5.25 mg/kg groups respectively compared to placebo [71] | lymphopenia, infections – notably herpes zoster infections [73] | FBC Screen for HIV, TB and Hepatitis before commencing treatment [74] | £2047.24 per 10 mg tablet: Total cost of £50,157 for the 2 year course for a 70 kg person (€58,573) | $99,500 (€88,149) | HARRMS |

WAC = wholesale acquisition cost; s.c. = subcutaneous; i.m. = intramuscular; i.v. = intravenous; FBC = full blood count; LFT = liver function tests; TFT = thyroid function tests; PML = progressive multifocal leukoencephalopathy; JCV = John Cunningham virus; VZV = varicella zoster virus; TB = tuberculosis; RRMS = relapsing-remitting multiple sclerosis; HARRMS = highly active relapsing remitting multiple sclerosis; RESMS = rapidly evolving severe multiple sclerosis; ARR = Annualised Relapse Rate, Relapses are usually defined as worsening of neurological signs and symptoms lasting at least 24 or 48 h, not associated with fever or infection, on a background of at least 30 days clinical stability; EDSS = (Kurtzke) Expanded Disability Status Scale; SAD = Sustained Accumulation of Disability, usually defined as 1 or more point increase in EDSS sustained for at least 3 or 6 months, or 0.5 point increase if baseline EDSS is over 5.5.

a These are list prices, actual prices may be lower.

[10,11].

## 3. Impact

MS carries a huge burden for those afflicted with the disease and those close to them. People with MS experience a decreased quality of life, and life in the most severe stages of MS can be considered to be worse than death [12,13]. People with MS are more likely to suffer from anxiety and depression than the general population, and they are also more likely to commit suicide [14,15].

MS has an effect on the ability of people to work full-time and in most cases eventually leads to unemployment. A cost-of-illness study carried out in 2017 looking at data from 16,808 people with MS across 16 European countries found that overall average unemployment was 68% [16]. This represents a significant cost to society as the vast majority of people with MS are of working age [16].

Relapses can be disabling for people with MS and costly for healthcare systems. In the 2017 European study, 13% of people had experienced a relapse and 7.5% had been admitted to hospital as an inpatient in the last 3 months [16]. Overall, 57% of people were using DMTs, with usage varying by country from 26 to 79% [16].

The 2017 study found that in the UK the annual per patient cost to society ranged from £11,400 (€12,800) for mild disease (EDSS 0–3) to £22,700 (€25,400) for the moderate disease group (EDSS 4–6.5) and £36,500 (€40,900) for the severe disease group (EDSS 7–9) [17]. Overall, the average annual cost by disease severity across Europe was €22,800, €37,100 and €57,500 for mild, moderate and severe disease [16]. For less severe disease, the majority of direct costs were due to health care usage, whereas informal care costs accounted for most of the direct costs in more severe disease [16]. Production losses accounted for 39%, 45% and 33% of total costs for mild, moderate and severe disease groups respectively [16].

## 4. Methods

This review has looked at CEAs for DMTs for MS and the issues associated with these. To select papers, a MEDLINE (PubMed) search was performed using search terms: "multiple sclerosis cost effectiveness". Studies from years 2014–2019 were included. Excluded were any studies that did not look at the cost effectiveness of DMTs, systematic reviews, studies that did not compare one DMT with at least one other DMT and those that were not available in full text. The following aspects of papers were assessed: data sources for cost, utility, efficacy, adverse events incidence, adverse event costs and natural history of disease, if there was a sponsor for the paper, whether a payer's perspective or societal perspective was used, the time horizon, the outcome measures used, the outcome of the analysis, if sensitivity analysis was performed and if so were variables specified and whether limits were acknowledged.

## 5. First-line therapies

First line injectable therapies were the first DMTs developed for MS, and are still the most commonly used. They are favoured as they have a good safety profile (see Table 1) and have been in clinical use the longest. However, they are less effective than most newer DMTs (Table 1) [18,19,31,34]. Of course, there are issues in simply comparing outcome figures across different trials – with varying methods, patient characteristics, outcome definitions, trial lengths performed, safety profiles and trials performed at different times over recent history. A meta-analysis showed that although IFN and GA were generally among the least effective DMTs when looking at Annualised Relapse Rate (ARR) and 3-month Sustained Accumulation of Disability (SAD), IFNb1b came out as the most effective in reducing the risk of 6-month SAD, and pegylated IFNb1a was third on the list for reducing 6-month SAD [75]. Still, cost-effectiveness models consistently show fewer

QALYs gained with IFN and GA compared to other DMTs, even though these models generally take into account both ARR and SAD [76–80].

These drugs were initially deemed by the National Institute for Clinical Excellence (NICE), within the UK, to not meet their cost-benefit threshold, but were provided by the NHS under the risk-sharing scheme (RSS), in which the drug would be approved by NICE for use in the NHS if it was found to be cost-effective in a 20-year model based off of 10 years of follow-up data, and if not the price of the drugs for these patients would be discounted by the manufacturer [81]. The outcome of the re-evaluation by NICE in early 2018 further concluded glatarimer acetate and all the beta interferons except Betaferon are recommended for use in people with RRMS but only if provided with a discount under commercial agreement with suppliers [82]. Betaferon was not considered to be cost-effective [82].

First line oral DMTs include terflunomide and dimethyl fumarate. These have the advantage of not being injected, however do require regular blood test monitoring (Table 1). Teriflunomide was cost effective over first line injectables and dimethyl fumarate in some CEAs [78,83]. However there were also CEAs which found dimethyl fumarate to be more cost effective than teriflunomide and first line injectable DMTs [84–86]. It is hard to tell which of the first line DMTs is more cost-effective, however they are all generally dominated by second line therapies when these are included in CEAs [87–91].

## 6. Second-line therapies

Fingolimod was found to be as effective as first line treatments in a meta-analysis however this was based on two placebo controlled RCTs of which only one showed a significant effect on SAD [75]. In terms of cost effectiveness, fingolimod performs generally worse than other second line therapies in CEAs [76,92–94].

Natalizumab was the first monoclonal antibody licensed for use in MS. Whilst natalizumab was found to be one of the most effective treatments in a meta-analysis when looking at SAD, this was based on the results of one RCT from 2006 which compared only to placebo [59,75]. At £14,730 annually, it is one of the less expensive DMTs for MS. However, this is not taking into account the cost for any additional monitoring required. Indeed, for one CEA the price per QALY gained went from 38,000 EUR (£32,000) when looking only at direct healthcare costs, to 59,000 EUR (£50,000) when taking into account the extra monitoring required due to the risk of progressive multifocal leukoencephalopathy (PML) [95]. This does not take into account the potential cost of an actual case of PML, which would be a considerable cost in light of care needs and loss of productivity as well as the impact on QoL.

PML is associated with immunosuppression and a low white cell count [96]. Currently, the only treatment is to terminate immunosuppressive therapy in order to minimise disease progression. It has a high mortality rate, approximately 20–25% at 6 months [97,98]. This is a rare occurrence with fingolimod and even more rarely with dimethyl fumarate therapy [40,99]. Though no cases have yet been reported with ocrelizumab therapy (unless following natalizumab therapy [100]), PML has been known to occur with anti-CD20 antibodies [101]. The greatest risk of PML reported so far occurs with natalizumab therapy. Although this risk is minimal in John Cunningham virus (JCV) seronegative patients, seroconversion can occur during treatment [102]. The risk of PML after two years of therapy is about 1 in 100 in JCV seropositive patients who have received prior immunosuppressive treatment [60]. Therefore, natalizumab therapy requires MRI monitoring and JC virus serology status is monitored at 6-monthly intervals whilst on therapy [103].

Alemtuzumab is another monoclonal antibody that is currently licensed for RRMS. According to one meta-analysis, it is the most effective treatment for RRMS when looking at outcomes such as ARR improvement and preventing disability progression [75]. However, it is worth bearing in mind that disease progression is not always defined by

the same criteria in different studies, and people in the pivotal alemtuzumab trials had a shorter disease course and therefore perhaps more neurological reserve to respond to therapy [75]. Significant monitoring is needed as the risk for secondary autoimmunity is as high as 50% of those treated with two annual courses [66]. The cost of these potential complications is high as they include thyroid autoimmunity, ITP (immune thrombocytopaenic purpura) and renal anti-glomerular basement membrane disease [66]. These are costly to manage and can lead to severe disability and death [66]. Furthermore, binding antibodies occur in up to 30% of patients following the first course [64]. This incidence increases to 80% after the second annual course [64]. Of these patients, over 90% had developed neutralizing antibodies [104]. It has been suggested that these antibodies can lead to poor lymphocyte depletion in some cases [105]. However, it remains to be seen what impact these antibodies have on the clinical efficacy of the drug. In many cases antibody levels decrease over the year between treatment courses, but in some cases they persist [64]. Repeated courses past two years may not be necessary though as effects can last up to 6 years and possibly beyond [106–109].

Two phase III trials were conducted with ocrelizumab for RRMS, and one for PPMS [68,69]. Its efficacy data in these pivotal trials was comparable to current most effective DMTs. SAEs occurred at a similar rate as with IFN treatment or placebo, making it relatively safe compared to most other DMTs [68,69]. However, development of ocrelizumab was halted for rheumatoid arthritis and lupus due to deaths from infection [110,111]. It remains to be seen what the long-term safety profile of this drug will be like. Currently, it is administered every 6 months, however the phase II extension study suggests that like alemtuzumab and oral cladribine, that ocrelizumab may have induction therapy potential with long-term benefit from short courses of therapy [10,11]. However, currently it is still administered every 6 months, and cost-effectiveness will therefore be affected when compared to DMTs with sustained effect after induction therapy such as alemtuzumab and cladribine. Although the cost-benefit value of ocrelizumab is accepted, this agent has yet to be seen as sufficiently cost-effective for treatment of PPMS. The manufacturers had offered supply to the NHS at a lower price than for use in relapsing MS variants, however NICE has yet to entertain this model [112].

Oral cladribine is arguably the most effective of the oral agents for MS [73]. In a recent cost effective analysis (CEA), cladribine was found to be more cost-effective than alemtuzumab and natalizumab [113]. This may in part account for the relatively rapid approval of oral cladribine by NICE and availability to the NHS shortly following approval by the European Medicines agency.

## 7. Haematopoietic stem cell transplantation

A recent study showed total suppression of CNS inflammatory processes with autologous haematopoietic stem cell transplant (aHSCT), evidenced by a complete lack of relapses in any patients during a 7-year follow up period [114]. Disability progression was halted in 70% of patients [114]. This is similar to other studies looking at aHSCT for MS, but the total suppression of CNS immunity had not been seen before [115–118]. There is a high associated risk of mortality at around 5% [117], although this can be minimised in specialist centres to 1–2% [119]. For this reason, though effects seen have been dramatic, the procedure was initiallty reserved for last resort cases. However, more recently there is evidence to suggest that it is most effective when there is ongoing inflammation and there has been a movement towards consideration of HSCT for people with highly active disease who may not necessarily have had a long disease course [120]. If safety improvements can be made and high efficacy results continue to be seen, then the procedure may become more commonplace in the future.

## 8. Cost effectiveness and front-loading of costs

Recently, evidence is pointing towards the fact that front-loading of treatment costs in MS may be more cost-effective than paying for longer-term treatments, which are cheaper. It seems that drugs that are better at depleting memory B cells are more effective, and that induction of depletion may be all that is needed, without sustained treatment [10,72]. Furthermore, there is evidence to suggest that treating earlier in the disease course is more effective [121].

Second line therapies tend to dominate the CEAs they are included in, despite being more expensive and having a higher risk of serious adverse events. Alemtuzumab and ocrelizumab generally are found to be most cost-effective in the CEAs they are included in, with alemtuzumab also dominating ocrelizumab when both included – although there are few CEAs which included both [76,77,92,122,123]. Since being approved by the EMA, oral cladribine has also dominated in CEAs [113].

Currently, some of the more expensive and effective DMTs are showing promise as induction therapies with repeated courses after 1–2 years not being necessary, thus lowering the cost per QALY. Some of the best efficacy results have been seen with drugs such as alemtuzumab, ocrelizumab and oral cladribine, and there is evidence for all of these that treatment beyond the first couple of years may not be necessary [68,104–108,124]. This means that though these are among the most expensive DMTs for MS, the cost over a lifetime may actually be less than some of the cheaper DMTs that require longer periods of treatment [113,125–128]. Furthermore, treating aggressively early on in the disease to achieve NEDA may reduce hospital visits and admissions, further reducing the cost to healthcare systems and society [129]. Indeed, one retrospective cohort study looking at the relationship between healthcare costs and disease progression in Italy found that higher care spending was associated with reduced progression over a 14 year time period [130]. Long-term benefit from short treatment cycles means that the DMT are only present for short period and therefore may reduce problems of drug-drug interactions with the polypharmacopia of agents that will be needed to deal with symptomatic issues and neurorepair and protection. However, problems with these DMTs include the fact that they are new and long-term safety has not yet been determined. Furthermore, long-term efficacy has not been confirmed beyond a few years.

## 9. Cost effectivenes analyses: issues

CEAs for MS drugs use models to predict the long-term cost and benefit of drugs based on published trial data. There are various issues with this. CEAs can take on the societal or the third-party payers perspective. The third party payers perspective includes only the cost of the drug and the cost to healthcare providers, whereas societal perspective will include informal care costs and indirect costs, such as the cost of unemployment. Thus, changing the perspective will impact the cost-effectiveness of the drug. A societal perspective is arguably more useful and realistic, but also less reliable than the payers perspective. Indeed, methods for estimating costs to society can vary widely between CEAs [131]. Furthermore, cost estimates can vary even for the payer's perspective – in two recent US CEAs the year one admin cost for alemtuzumab was estimated as $634 in one study and $2038 in another (one paper citing "package inserts" and the other "package inserts and clinical experts" as their sources for these costs) [76,92].

Changing the length of time of the model can affect the outcome of CEAs [125], as can using different sources for utility values [132]. Some models do not account for non-drug care costs or the costs of complications and side effects of treatment. Many CEAs fail to transparently describe and justify their methods of cost estimation and the limitations of their studies, and sponsored CEAs tend to favour the drug of the sponsor [125,131]. Furthermore, as the payer threshold per QALY (quality adjusted life years) is known, health economic data may be

adapted to fit this threshold.

A CEA is only as good as the original trial data being used, therefore models using data from longer and larger trials with similar study populations are preferable. Head-to-head comparative randomized controlled trials (RCTs) are ideal but there is a near total dearth of RCTs comparing any DMT with any other DMT other than IFN or GA [75]. Yet there are a number of cost-effectiveness models comparing various DMTs with each other, using data from separate trials or from historical comparator populations [93,131]. However comparisons are emerging following comparisons of real life usage using registries such as NAR-COMS (North American) and MSBase [133].

The RCTs need to minimise the heterogeneity of outcome measures used. Defining SAD by 3 months instead of 6 may overestimate the rate of disability progression. Similarly, defining a relapse as lasting 24 verses 48 h can impact the results. Furthermore, as treatments become more effective these outcome measures become less relevant. There has been a move towards inclusion of other end points, notably that of the proportion of patients with no evidence of disease activity (NEDA). NEDA has been defined as "absence of new or enlarging T2 lesions or T1 gadolinium-enhancing lesions on MRI and no sustained EDSS score progression or clinical relapse" [134]. In light of the improving efficacy of therapies, NEDA has become an important end-point. However, current definitions of NEDA may not pick up slight changes in disability progression [135]. Furthermore, none of these outcome measures take into account the impact of MS and treatments on things like mental health, working status and quality of life, all of which may be more pertinent to look at as treatments are becoming more effective at suppressing disease activity as measured by relapses, MRI lesions and EDSS progression. As such NEDA evolves as new outcome measures form part of the definition such as brain atrophy and neurofilament levels [136].

A problem with long-term CEAs is that they cannot be challenged in a reasonable timeframe. There has been a call for manufacturers to support claims from CEAs with a protocol for empirical evaluation over a reasonable short-term timeframe, so that decision makers can confirm decisions on whether treatments shall be made available in their healthcare system [137]. Long-term CEAs are arguably more useful to estimate the overall cost-benefit of a drug, especially when looking at whether more expensive but effective drugs can be a more cost-effective option in the context of a lifetime. However, these predictions cannot be challenged or tested, and as such cannot provide any real evidence of cost-effectiveness. Using cost per relapse avoided or year of NEDA instead of QALYs gained provides outcomes that can be verified in short-term studies [81].

For the reasons outlined above, it is difficult to draw conclusions from CEAs about which DMT is most cost effective. There is a tendency for second-line therapies to be deemed more cost-effective, however to conclude which of these second line therapies is most cost-effective when looking at different CEAs is difficult. There has been a surge in CEAs on DMTs for MS in recent years. As the prices for DMTs continue to increase as new DMTs come to market, perhaps CEAs are a tool to be used to justify these soaring costs.

## 10. Conclusion

MS is a progressively disabling disease that has a significant impact on quality of life. This has implications for the individual with MS, for their families and for Society as people with MS are more likely to be unemployed causing a loss of productive life years and to require informal care from friends and family. This is in addition to the formal healthcare cost of managing the disease and the disability caused by it. Clearly there is a great need for treatments that can slow the progression of the disease and prevent disability.

First-line therapies are relatively safe and cheap but less effective compared to second-line therapies [75]. Currently, the drugs with the most benefit tend to be those that carry the most risk and highest price tag. Despite this CEAs support the idea that it may be worth using more

aggressive measures earlier on as front-loading the cost means the cost of long-term disability progression is reduced. It is difficult to say what the long term outcomes of different therapies may be as there is not enough long-term follow-up data. Cost-effectiveness models have aimed to compare DMTs with each other over long-term time horizons, but their results are often difficult to interpret or compare across analyses. Further head-to-head RCTs, RCT follow-up studies and CEAs are needed to answer these questions, and these need to take on board the recommendations that have been made for improving their quality. As patents expire notably on chemical small molecules that have low costs, the treatment landscape and cost-effectiveness requirements may change [138].

## Declaration of Competing Interest

## References

[1] A. Compston, A. Coles, Multiple sclerosis, Lancet. 372 (2008) 1502–1517.
[2] A. Alonso, M.A. Hernan, Temporal trends in the incidence of multiple sclerosis: a systematic review, Neurology. 71 (2008) 129–135.
[3] L. Hernandez, M. O'Donnell, M. Postma, Modeling approaches in cost-effectiveness analysis of disease-modifying therapies for relapsing-remitting multiple sclerosis: An updated systematic review and recommendations for future economic evaluations, Pharmacoeconomics. 36 (2018) 1223–1252.
[4] A. Compston, A. Coles, Multiple sclerosis, Lancet. 359 (2002) 1221–1231.
[5] A.F. de Vos, M. van Meurs, H.P. Brok, L.A. Boven, R.Q. Hintzen, P. van der Valk, et al., Transfer of central nervous system autoantigens and presentation in secondary lymphoid organs, Journal of Immunology. 169 (2002) 5415–5423.
[6] M. van Zwam, R. Huizinga, M.J. Melief, A.F. Wierenga-Wolf, M. van Meurs, J.S. Voerman, et al., Brain antigens in functionally distinct antigen-presenting cell populations in cervical lymph nodes in MS and EAE, Journal of Molecular Medicine (Berl). 87 (2009) 273–286.
[7] V. Viglietta, C. Baecher-Allan, H.L. Weiner, D.A. Hafler, Loss of functional suppression by CD4 + CD25 + regulatory T cells in patients with multiple sclerosis, Journal of Experimental Medicine. 199 (2004) 971–979.
[8] I. Bartholomaus, N. Kawakami, F. Odoardi, C. Schlager, D. Miljkovic, J.W. Ellwart, et al., Effector T cell interactions with meningeal vascular structures in nascent autoimmune CNS lesions, Nature. 462 (2009) 94–98.
[9] R. Magliozzi, O. Howell, A. Vora, B. Serafini, R. Nicholas, M. Puopolo, et al., Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology, Brain. 130 (2007) 1089–1104.
[10] D. Baker, M. Marta, G. Pryce, G. Giovannoni, K. Schmierer, Memory B cells are major targets for effective immunotherapy in relapsing multiple sclerosis, EBioMedicine. 16 (2017) 41–50.
[11] D. Baker, G. Pryce, S. Amor, G. Giovannoni, K. Schmierer, Learning from other autoimmunities to understand targeting of B cells to control multiple sclerosis, Brain 141 (2018) 2834–2847.
[12] M. Orme, J. Kerrigan, D. Tyas, N. Russell, R. Nixon, The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK, Value Health. 10 (2007) 54–60.
[13] N. Murphy, C. Confavreux, J. Haas, N. Konig, E. Roullet, M. Sailer, et al., Quality of life in multiple sclerosis in France, Germany, and the United Kingdom, Journal of Neurology, Neurosurgery, and Psychiatry. 65 (1998) 460–466.
[14] N. Grytten Torkildsen, S.A. Lie, J.H. Aarseth, H. Nyland, K.M. Myhr, Survival and cause of death in multiple sclerosis: Results from a 50-year follow-up in Western Norway, Multiple Sclerosis. 14 (2008) 1191–1198.
[15] H. Hoang, B. Laursen, E.N. Stenager, E. Stenager, Psychiatric co-morbidity in multiple sclerosis: the risk of depression and anxiety before and after MS diagnosis, Multiple Sclerosis. 22 (2016) 347–353.
[16] G. Kobelt, A. Thompson, J. Berg, M. Gannedahl, J. Eriksson, New insights into the burden and costs of multiple sclerosis in Europe, Multiple Sclerosis. 23 (2017) 1123–1136.
[17] A. Thompson, G. Kobelt, J. Berg, D. Capsa, J. Eriksson, D. Miller, et al., New insights into the burden and costs of multiple sclerosis in Europe: results for the United Kingdom, Multiple Sclerosis. 23 (2017) 204–216.
[18] 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 352 (1998) 1498–1504.
[19] L.D. Jacobs, D.L. Cookfair, R.A. Rudick, R.M. Herndon, J.R. Richert, A.M. Salazar, et al., Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG), Annals of Neurology. 39 (1996) 285–294.
[20] H. Jiang, R. Milo, P. Swoveland, K.P. Johnson, H. Panitch, S. Dhib-Jalbut,

Interferon beta-1b reduces interferon gamma-induced antigen-presenting capacity of human glial and B cells, Journal of Neuroimmunology. 61 (1995) 17–25.

[21] N. Teleshova, W. Bao, P. Kivisakk, V. Ozenci, M. Mustafa, H. Link, Elevated CD40 ligand expressing blood T-cell levels in multiple sclerosis are reversed by interferon-beta treatment, Scandinavian Journal of Immunology. 51 (2000) 312–320.

[22] Z. Liu, C.M. Pelfrey, A. Cotleur, J.C. Lee, R.A. Rudick, Immunomodulatory effects of interferon beta-1a in multiple sclerosis, Journal of Neuroimmunology. 112 (2001) 153–162.

[23] M. Saresella, I. Marventano, R. Longhi, F. Lissoni, D. Trabattoni, L. Mendozzi, et al., CD4 + CD25 + FoxP3 + PD1- regulatory T cells in acute and stable relapsing-remitting multiple sclerosis and their modulation by therapy, The FASEB Journal. 22 (2008) 3500–3508.

[24] P.A. Muraro, L. Liberati, L. Bonanni, A. Pantalone, C.M. Caporale, C. Iarlori, et al., Decreased integrin gene expression in patients with MS responding to interferon-beta treatment, Journal of Neuroimmunology. 150 (2004) 123–131.

[25] P.A. Muraro, T. Leist, B. Bielekova, H.F. McFarland, VLA-4/CD49d downregulated on primed T lymphocytes during interferon-beta therapy in multiple sclerosis, Journal of Neuroimmunology. 111 (2000) 186–194.

[26] D. Hunt, D. Kavanagh, I. Drummond, B. Weller, C. Bellamy, J. Overell, et al., Thrombotic microangiopathy associated with interferon beta, New England Journal of Medicine. 370 (2014) 1270–1271.

[27] R. Vosoughi, M.S. Freedman, Therapy of MS, Clinical Neurology and Neurosurgery. 112 (2010) 365–385.

[28] S. Schmidt, H.J. Hertfelder, T. von Spiegel, R. Hering, M. Harzheim, H. Lassmann, et al., Lethal capillary leak syndrome after a single administration of interferon beta-1b, Neurology. 53 (1999) 220–222.

[29] Association of British Neurologists, http://www.theabn.org/media/docs/ABN %20publications/ABN_MS_Guidelines_2009_Final(1).pdf (Accessed 7/2/2017).

[30] A.H. Cross, R.T. Naismith, Established and novel disease-modifying treatments in multiple sclerosis, Journal of Internal Medicine. 275 (2014) 350–363.

[31] D.W. Paty, D.K. Li, Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group, Neurology 43 (1993) 662–667.

[32] P.A. Calabresi, B.C. Kieseier, D.L. Arnold, L.J. Balcer, A. Boyko, J. Pelletier, et al., Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study, Lancet Neurology. 13 (2014) 657–665.

[33] EMA, Plegridy - Summary of product characteristics, European Medicines Agency, 2014.

[34] K.P. Johnson, B.R. Brooks, J.A. Cohen, C.C. Ford, J. Goldstein, R.P. Lisak, et al., Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group, Neurology. 45 (1995) 1268–1276.

[35] A. Miller, S. Shapiro, R. Gershtein, A. Kinarty, H. Rawashdeh, S. Honigman, et al., Treatment of multiple sclerosis with copolymer-1 (Copaxone): implicating mechanisms of Th1 to Th2/Th3 immune-deviation, Journal of Neuroimmunology. 92 (1998) 113–121.

[36] M.K. Racke, R. Martin, H. McFarland, R.B. Fritz, Copolymer-1-induced inhibition of antigen-specific T cell activation: interference with antigen presentation, Journal of Neuroimmunology. 37 (1992) 75–84.

[37] P.A. Calabresi, E.W. Radue, D. Goodin, D. Jeffery, K.W. Rammohan, A.T. Reder, et al., Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial, Lancet Neurology. 13 (2014) 545–556.

[38] J.A. Cohen, F. Barkhof, G. Comi, H.P. Hartung, B.O. Khatri, X. Montalban, et al., Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis, New England Journal of Medicine. 362 (2010) 402–415.

[39] M. Mehling, L. Kappos, T. Derfuss, Fingolimod for multiple sclerosis: mechanism of action, clinical outcomes, and future directions, Current Neurology and Neuroscience Reports. 11 (2011) 492–497.

[40] New Recommendations to Minimise Risks of the Rare Brain Infection PML and a Type of Skin Cancer with Gilenya [press release]. EMA 2015.

[41] P.S. Rommer, U.K. Zettl, B. Kieseier, H.P. Hartung, T. Menge, E. Frohman, et al., Requirement for safety monitoring for approved multiple sclerosis therapies: an overview, Clinical and Experimental Immunology. 175 (2014) 397–407.

[42] C. Confavreux, P. O'Connor, G. Comi, M.S. Freedman, A.E. Miller, T.P. Olsson, et al., Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet Neurology. 13 (2014) 247–256.

[43] P. O'Connor, J.S. Wolinsky, C. Confavreux, G. Comi, L. Kappos, T.P. Olsson, et al., Randomized trial of oral teriflunomide for relapsing multiple sclerosis, New England Journal of Medicine. 365 (2011) 1293–1303.

[44] P. Vermersch, A. Czlonkowska, L.M. Grimaldi, C. Confavreux, G. Comi, L. Kappos, et al., Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial, Multiple Sclerosis. 20 (2014) 705–716.

[45] A. Bar-Or, A. Pachner, F. Menguy-Vacheron, J. Kaplan, H. Wiendl, Teriflunomide and its mechanism of action in multiple sclerosis, Drugs. 74 (2014) 659–674.

[46] R. Gold, L. Kappos, D.L. Arnold, A. Bar-Or, G. Giovannoni, K. Selmaj, et al., Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis, New England Journal of Medicine. 367 (2012) 1098–1107.

[47] R.J. Fox, D.H. Miller, J.T. Phillips, M. Hutchinson, E. Havrdova, M. Kita, et al., Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis, New England Journal of Medicine. 367 (2012) 1087–1097.

[48] K. Ghoreschi, J. Bruck, C. Kellerer, C. Deng, H. Peng, O. Rothfuss, et al., Fumarates improve psoriasis and multiple sclerosis by inducing type II dendritic cells, Journal of Experimental Medicine. 208 (2011) 2291–2303.

[49] N.H. Litjens, M. Rademaker, B. Ravensbergen, D. Rea, M.J. van der Plas, B. Thio, et al., Monomethylfumarate affects polarization of monocyte-derived dendritic cells resulting in down-regulated Th1 lymphocyte responses, European Journal of Immunology. 34 (2004) 565–575.

[50] R. de Jong, A.C. Bezemer, T.P. Zomerdijk, T. van de Pouw-Kraan, T.H. Ottenhoff, P.H. Nibbering, Selective stimulation of T helper 2 cytokine responses by the anti-psoriasis agent monomethylfumarate, European Journal of Immunology. 26 (1996) 2067–2074.

[51] K. Asadullah, H. Schmid, M. Friedrich, F. Randow, H.D. Volk, W. Sterry, et al., Influence of monomethylfumarate on monocytic cytokine formation–explanation for adverse and therapeutic effects in psoriasis? Archives of Dermatological Research. 289 (1997) 623–630.

[52] K. Zhu, U. Mrowietz, Inhibition of dendritic cell differentiation by fumaric acid esters, Journal of Investigative Dermatology. 116 (2001) 203–208.

[53] R.A. Linker, D.H. Lee, S. Ryan, A.M. van Dam, R. Conrad, P. Bista, et al., Fumaric acid esters exert neuroprotective effects in neuroinflammation via activation of the Nrf2 antioxidant pathway, Brain. 134 (2011) 678–692.

[54] R.H. Scannevin, S. Chollate, M.Y. Jung, M. Shackett, H. Patel, P. Bista, et al., Fumarates promote cytoprotection of central nervous system cells against oxidative stress via the nuclear factor (erythroid-derived 2)-like 2 pathway, Journal of Pharmacology and Experimental Therapeutics. 341 (2012) 274–284.

[55] R. Gold, G. Giovannoni, J.T. Phillips, R.J. Fox, A. Zhang, L. Meltzer, et al., Efficacy and safety of delayed-release dimethyl fumarate in patients newly diagnosed with relapsing-remitting multiple sclerosis (RRMS), Multiple Sclerosis. 21 (2015) 57–66.

[56] Updated Recommendations to Minimise the Risk of the Rare Brain Infection PML with Tecfidera [press release]. EMA2015.

[57] A. Salmen, R. Gold, Mode of action and clinical studies with fumarates in multiple sclerosis, Exp Neurol. 262 (2014) 52–56.

[58] R. Bomprezzi, Dimethyl fumarate in the treatment of relapsing-remitting multiple sclerosis: an overview, Ther Adv Neurol Disord. 8 (2015) 20–30.

[59] C.H. Polman, P.W. O'Connor, E. Havrdova, M. Hutchinson, L. Kappos, D.H. Miller, et al., A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis, N Engl J Med. 354 (2006) 899–910.

[60] G. Bloomgren, S. Richman, C. Hotermans, M. Subramanyam, S. Goelz, A. Natarajan, et al., Risk of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy, 366 (2012), pp. 1870–1880.

[61] P.A. Calabresi, G. Giovannoni, C. Confavreux, S.L. Galetta, E. Havrdova, M. Hutchinson, et al., The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL, Neurology. 69 (2007) 1391–1403.

[62] C. McGuigan, M. Craner, J. Guadagno, R. Kapoor, G. Mazibrada, P. Molyneux, et al., Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group, Journal of Neurology, Neurosurgery, and Psychiatry. 87 (2016) 117–125.

[63] J.A. Cohen, A.J. Coles, D.L. Arnold, C. Confavreux, E.J. Fox, H.P. Hartung, 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. 380 (9856) (2012) 1819–1828.

[64] Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. The Lancet.380:1829–39.

[65] A.J. Coles, A. Cox, E. Le Page, J. Jones, S.A. Trip, J. Deans, et al., The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy, Journal of Neurology. 253 (2006) 98–108.

[66] M.D. Willis, K.E. Harding, T.P. Pickersgill, M. Wardle, O.R. Pearson, N.J. Scolding, et al., Alemtuzumab for multiple sclerosis: Long term follow-up in a multi-centre cohort, Multiple Sclerosis. 22 (2016) 1215–1223.

[67] A.J. Coles, Alemtuzumab therapy for multiple sclerosis, Neurotherapeutics. 10 (2013) 29–33.

[68] S.L. Hauser, A. Bar-Or, G. Comi, G. Giovannoni, H.P. Hartung, B. Hemmer, et al., Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis, New England Journal of Medicine. 376 (2017) 221–234.

[69] X. Montalban, S.L. Hauser, L. Kappos, D.L. Arnold, A. Bar-Or, G. Comi, et al., Ocrelizumab versus placebo in primary progressive multiple sclerosis, New England Journal of Medicine. 376 (2017) 209–220.

[70] European Medicines Agency, Ocrevus - Summary of Product Characteristics, EMA, 2018.

[71] G. Giovannoni, G. Comi, S. Cook, K. Rammohan, P. Rieckmann, P. Soelberg Sorensen, et al., A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis, New England Journal of Medicine. 362 (2010) 416–426.

[72] B. Ceronie, B.M. Jacobs, D. Baker, N. Dubuisson, Z. Mao, F. Ammoscato, et al., Cladribine treatment of multiple sclerosis is associated with depletion of memory B cells, Journal of Neurology. 265 (2018) 1199–1209.

[73] S. Cook, P. Vermersch, G. Comi, G. Giovannoni, K. Rammohan, P. Rieckmann, et al., Safety and tolerability of cladribine tablets in multiple sclerosis: the CLARITY (CLAdRIbine Tablets treating multiple sclerosis orallY) study, Multiple Sclerosis. 17 (2011) 578–593.

[74] European Medicines Agency, Mavenclad - Summary of Product Characteristics, EMA, 2017.

[75] E. Fogarty, S. Schmitz, N. Tubridy, C. Walsh, M. Barry, Comparative efficacy of disease-modifying therapies for patients with relapsing remitting multiple sclerosis: systematic review and network meta-analysis, Multiple Sclerosis and Related Disorders. 9 (2016) 23–30.

[76] M. Zimmermann, E. Brouwer, J.A. Tice, M. Seidner, A.M. Loos, S. Liu, et al., Disease-modifying therapies for relapsing-remitting and primary progressive multiple sclerosis: a cost-utility analysis, CNS Drugs. 32 (2018) 1145–1157.

[77] A.A. Dashputre, K.M. Kamal, G. Pawar, Cost-effectiveness of peginterferon Beta-1a and alemtuzumab in relapsing-remitting multiple sclerosis, Journal of Managed Care & Specialty Pharmacy. 23 (2017) 666–676.

[78] E. Soini, J. Joutseno, M.L. Sumelahti, Cost-utility of first-line disease-modifying treatments for relapsing-remitting multiple sclerosis, Clinical Therapeutics. 39 (2017) 537–557.

[79] M.A. Frasco, T. Shih, D. Incerti, O. Diaz Espinosa, D.K. Vania, N. Thomas, Incremental net monetary benefit of ocrelizumab relative to subcutaneous inter-feron beta-1a, Journal of Medical Economics. 20 (2017) 1074–1082.

[80] D. Bozkaya, T. Livingston, K. Migliaccio-Walle, T. Odom, The cost-effectiveness of disease-modifying therapies for the treatment of relapsing-remitting multiple sclerosis, Journal of Medical Economics. 20 (2017) 297–302.

[81] M. Duddy, J. Palace, The UK risk-sharing scheme for interferon-beta and glatir-amer acetate in multiple sclerosis. Outcome of the year-6 analysis, Practical Neurology. 16 (2016) 4–6.

[82] National Institute for Health and Care Excellence, https://www.nice.org.uk/guidance/ta527 (Accessed 15/10/2018).

[83] Y. Xu, N. Mao, V. Chirikov, F. Du, Y.C. Yeh, L. Liu, et al., Cost-effectiveness of teriflunomide compared to interferon beta-1b for relapsing multiple sclerosis pa-tients in China, Clinical Drug Investigation. 39 (2019) 331–340.

[84] J. Chevalier, C. Chamoux, F. Hammes, A. Chicoye, Cost-effectiveness of treatments for relapsing remitting multiple sclerosis: a french societal perspective, PLoS One. 11 (2016) e0150703.

[85] X. Zhang, J.W. Hay, X. Niu, Cost effectiveness of fingolimod, teriflunomide, di-methyl fumarate and intramuscular interferon-beta1a in relapsing-remitting multiple sclerosis, CNS Drugs. 29 (2015) 71–81.

[86] W. Su, A. Kansal, C. Vicente, B. Deniz, S. Sarda, The cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing-remitting multiple sclerosis in Canada, Journal of Medical Economics. 19 (2016) 718–727.

[87] M.J. Maruszczak, S.M. Montgomery, M.J. Griffiths, N. Bergvall, N. Adlard, Cost-utility of fingolimod compared with dimethyl fumarate in highly active relapsing-remitting multiple sclerosis (RRMS) in England, Journal of Medical Economics. 18 (2015) 874–885.

[88] L. Hernandez, S. Guo, H. Toro-Diaz, S. Carroll, S.F. Syed Farooq, Peginterferon beta-1a versus other self-injectable disease-modifying therapies in the treatment of relapsing-remitting multiple sclerosis in Scotland: a cost-effectiveness analysis, Journal of Medical Economics. 20 (2017) 228–238.

[89] J. Darba, L. Kaskens, R. Sanchez-de la Rosa, Cost-effectiveness of glatiramer acetate and interferon beta-1a for relapsing-remitting multiple sclerosis, based on the CombiRx study, Journal of Medical Economics 17 (2014) 215–222.

[90] C. Dembek, L.A. White, J. Quach, A. Szkurhan, N. Rashid, M.R. Blasco, Cost-ef-fectiveness of injectable disease-modifying therapies for the treatment of relapsing forms of multiple sclerosis in Spain, European Journal of Health Economics. 15 (2014) 353–362.

[91] L. Hernandez, S. Guo, E. Kinter, M. Fay, Cost-effectiveness analysis of pe-ginterferon beta-1a compared with interferon beta-1a and glatiramer acetate in the treatment of relapsing-remitting multiple sclerosis in the United States, Journal of Medical Economics. 19 (2016) 684–695.

[92] V. Chirikov, I. Ma, N. Joshi, D. Patel, A. Smith, C. Giambrone, et al., Cost-effec-tiveness of alemtuzumab in the treatment of relapsing forms of multiple sclerosis in the United States, Value Health. 22 (2019) 168–176.

[93] K. O'Day, K. Meyer, D. Stafkey-Mailey, C. Watson, Cost-effectiveness of natali-zumab vs fingolimod for the treatment of relapsing-remitting multiple sclerosis: analyses in Sweden, Journal of Medical Economics. 18 (2015) 295–302.

[94] S.M. Montgomery, M.J. Maruszczak, D. Slater, J. Kusel, R. Nicholas, N. Adlard, A discrete event simulation to model the cost-utility of fingolimod and natalizumab in rapidly evolving severe relapsing-remitting multiple sclerosis in the UK, Journal of Medical Economics. 20 (2017) 474–482.

[95] G. Kobelt, J. Berg, P. Lindgren, B. Jonsson, L. Stawiarz, J. Hillert, Modeling the cost-effectiveness of a new treatment for MS (natalizumab) compared with current standard practice in Sweden, Multiple Sclerosis. 14 (2008) 679–690.

[96] D. Pavlovic, A.C. Patera, F. Nyberg, M. Gerber, M. Liu, Progressive multifocal leukoencephalopathy: current treatment options and future perspectives, Therapeutic Advances in Neurological Disorders. 8 (2015) 255–273.

[97] T. Dong-Si, S. Gheuens, A. Gangadharan, M. Wenten, J. Philip, J. McInnich, et al., Predictors of survival and functional outcomes in natalizumab-associated pro-gressive multifocal leukoencephalopathy, Journal of Neurovirology. 21 (2015) 637–644.

[98] K. Hellwig, R. Gold, Progressive multifocal leukoencephalopathy and natalizumab, Journal of Neurology. 258 (2011) 1920–1928.

[99] D. Balak, E. Hajdarbegovic, More on PML in patients treated with dimethyl fu-marate, New England Journal of Medicine. 374 (2016) 295.

[100] R. Kadish, D. Robertson, M. Sweeney, Fatal leukoencephalopathy in a patient with multiple sclerosis following treatment with ocrelizumab (P5.353), Neurology 90 (15 Supplement) (2018).

[101] P.S. Sorensen, M. Blinkenberg, The potential role for ocrelizumab in the treatment of multiple sclerosis: current evidence and future prospects, Therapeutic Advances in Neurological Disorders. 9 (2016) 44–52.

[102] A. Vennegoor, J.A. van Rossum, C. Leurs, M.P. Wattjes, T. Rispens, J.L. Murk, et al., High cumulative JC virus seroconversion rate during long-term use of na-talizumab, European Journal of Neurology. 23 (2016) 1079–1085.

[103] EMA Confirms Recommendations to Minimise Risk of Brain Infection PML with Tysabri [press release]. EMA2016.

[104] D. Baker, S.S. Herrod, C. Alvarez-Gonzalez, G. Giovannoni, K. Schmierer, Interpreting lymphocyte reconstitution data from the pivotal phase 3 trials of alemtuzumab, JAMA Neurology. 74 (2017) 961–969.

[105] N. Dubuisson, D. Baker, A.S. Kang, G. Pryce, M. Marta, L.H. Visser, et al., Alemtuzumab depletion failure can occur in multiple sclerosis, Immunology. 154 (2018) 253–260.

[106] S. Schippling, J. Cohen, A. Coles, D.A. Compston, E. Fox, M. Filippi, et al., Alemtuzumab-treated patients with RRMS demonstrate durable slowing of brain volume loss over 5 years despite most being treatment-free for 4 years: CARE-MS I and II extension study (S51.001), Neurology 86 (16 Supplement) (2016).

[107] V. Limmroth, G. Giovannoni, D. Arnold, J. Cohen, A. Coles, E. Fox, et al., Treatment-naive patients with active RRMS demonstrate durable improvements in relapse and disability following treatment with alemtuzumab: 5-year follow-up of the CARE-MS I study (S51.004), Neurology 86 (16 Supplement) (2016).

[108] A. Coles, D. Arnold, J. Cohen, E. Fox, G. Giovannoni, H.-P. Hartung, et al., Patients with active RRMS and an inadequate response to prior therapy demonstrate durable improvements in relapse and disability following treatment with alem-tuzumab: 5-year follow-up of the CARE-MS II study (P3.022), Neurology 86 (16 Supplement) (2016).

[109] D. Arnold, J. Cohen, A. Coles, D.A. Compston, E. Fox, H.-P. Hartung, et al., Treatment-naive patients with active RRMS who received alemtuzumab demon-strate durable suppression of new MRI lesion formation: 5-year follow-up of the CARE-MS I study (S51.002), Neurology 86 (16 Supplement) (2016).

[110] P. Emery, W. Rigby, P.P. Tak, E. Dörner, C. Martin, et al., Safety with ocrelizumab in rheumatoid arthritis: results from the ocrelizumab phase III pro-gram, PLoS One. 9 (2014).

[111] E.F. Mysler, A.J. Spindler, R. Guzman, M. Bijl, D. Jayne, R.A. Furie, et al., Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: results from a randomized, double-blind, phase III study, Arthritis Rheumatology. 65 (2013) 2368–2379.

[112] National Institute for Health and Care Excellence, https://www.nice.org.uk/guidance/indevelopment/gid-ta10153/documents (Accessed 15/10/2018).

[113] R. Hettle, G. Harty, S.L. Wong, Cost-effectiveness of cladribine tablets, alemtu-zumab, and natalizumab in the treatment of relapsing-remitting multiple sclerosis with high disease activity in England, Journla of Medical Economics. (2018) 1–11.

[114] H.L. Atkins, M. Bowman, D. Allan, G. Anstee, D.L. Arnold, A. Bar-Or, et al., Immunoablation and autologous haemopoietic stem-cell transplantation for ag-gressive multiple sclerosis: a multicentre single-group phase 2 trial, Lancet. 388 (2016) 576–585.

[115] R.A. Nash, G.J. Hutton, M.K. Racke, U. Popat, S.M. Devine, L.M. Griffith, et al., High-dose immunosuppressive therapy and autologous hematopoietic cell trans-plantation for relapsing multiple sclerosis (HALT-MS): a 3-year interim report, JAMA Neurology. 72 (2015) 159–169.

[116] J. Burman, E. Iacobaeus, A. Svenningsson, J. Lycke, M. Gunnarsson, P. Nilsson, et al., Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: the Swedish experience, Journal of Neurology, Neurosurgery, and Psychiatry. 85 (2014) 1116–1121.

[117] R.K. Burt, R. Balabanov, X. Han, B. Sharrack, A. Morgan, K. Quigley, et al., Association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability in patients with relapsing-remitting multiple sclerosis, Jama. 313 (2015) 275–284.

[118] J.A. Snowden, R.M. Pearce, J. Lee, K. Kirkland, M. Gilleece, P. Veys, et al., Haematopoietic stem cell transplantation (HSCT) in severe autoimmune diseases: analysis of UK outcomes from the British Society of Blood and Marrow Transplantation (BSBMT) data registry 1997–2009, British Journal of Haematology. 157 (2012) 742–746.

[119] G. Mancardi, R. Saccardi, Autologous haematopoietic stem-cell transplantation in multiple sclerosis, Lancet Neurology. 7 (2008) 626–636.

[120] J.A. Cohen, L.E. Baldassari, H. Atkins, J.D. Bowen, C. Bredeson, P.A. Carpenter, et al., Autologous hematopoietic cell transplantation for treatment-refractory re-lapsing multiple sclerosis: position statement from the American Society for Blood and Marrow Transplantation, Biology of Blood and Marrow Transplantation. 5 (2019) 845–854.

[121] C. Tur, X. Montalban, C. Tintore, J. Nos, J. Rio, F.X. Aymerich, et al., Interferon beta-1b for the treatment of primary progressive multiple sclerosis: five-year clinical trial follow-up, Archives of Neurology. 68 (2011) 1421–1427.

[122] S.M. Montgomery, J. Kusel, R. Nicholas, N. Adlard, Costs and effectiveness of fingolimod versus alemtuzumab in the treatment of highly active relapsing-re-mitting multiple sclerosis in the UK: re-treatment, discount, and disutility, Journal of Medical Economics. 20 (2017) 962–973.

[123] S. Taheri, M.A. Sahraian, N. Yousefi, Cost-effectiveness of alemtuzumab and na-talizumab for relapsing-remitting multiple sclerosis treatment in Iran: decision analysis based on an indirect comparison, Journal of Medical Economics. 22 (2019) 71–84.

[124] G. Comi, S. Cook, K. Rammohan, P. Soelberg Sorensen, P. Vermersch, A.K. Adeniji, et al., Long-term effects of cladribine tablets on MRI activity outcomes in patients with relapsing-remitting multiple sclerosis: the CLARITY extension study, Therapeutic Advances in Neurological Disorders. 11 (2018).

[125] D. Yamamoto, J.D. Campbell, Cost-effectiveness of multiple sclerosis disease-modifying therapies: a systematic review of the literature, Autoimmune Disorders. 2012 (2012) 784364.

[126] D. Ontaneda, O. Henry, Cost effectiveness of multiple sclerosis therapeutic stra-tegies for achieving no evidence of disease activity (P2.193), Neurology 86 (16 Supplement) (2016).

[127] A. Smith, L. Hashemi, I. Ma, Cost-utility analysis of alemtuzumab versus natali-zumab for the treatment of relapsing-remitting multiple sclerosis: us payer

perspective, Value in Health. 19 (2016).

[128] D. Rog, Salford Royal NHS Foundation Trust S, UK, Guo J, Sanofi C, MA, USA, Nucit A, Ividata L-P, France, et al., Alemtuzumab is the most cost-effective option in comparison to available therapies in the treatment of RRMS from the UK NHS perspective, Value in Health 20 (2017).

[129] J.J. Cerqueira, D.A.S. Compston, R. Geraldes, M.M. Rosa, K. Schmierer, A. Thompson, et al., Time matters in multiple sclerosis: can early treatment and long-term follow-up ensure everyone benefits from the latest advances in multiple sclerosis? Journal of Neurology, Neurosurgery, and Psychiatry. 89 (2018) 844–850.

[130] M. Moccia, R. Palladino, R. Lanzillo, A. Carotenuto, C.V. Russo, M. Triassi, et al., Healthcare costs for treating relapsing multiple sclerosis and the risk of progression: a retrospective italian cohort study from 2001 to 2015, PLoS One. 12 (2017).

[131] S. Guo, C. Pelligra, C. Saint-Laurent Thibault, L. Hernandez, A. Kansal, Cost-effectiveness analyses in multiple sclerosis: a review of modelling approaches, Pharmacoeconomics. 32 (2014) 559–572.

[132] M. Versteegh, Impact on the incremental cost-effectiveness ratio of using alternatives to EQ-5D in a Markov model for multiple sclerosis, Pharmacoeconomics. 34 (2016) 1133–1144.

[133] T. Kalincik, J.W.L. Brown, N. Robertson, M. Willis, N. Scolding, C.M. Rice, et al., Treatment effectiveness of alemtuzumab compared with natalizumab, fingolimod, and interferon beta in relapsing-remitting multiple sclerosis: a cohort study, Lancet Neurology. 16 (2017) 271–281.

[134] D.L. Rotstein, B.C. Healy, M.T. Malik, T. Chitnis, H.L. Weiner, Evaluation of no evidence of disease activity in a 7-year longitudinal multiple sclerosis cohort, JAMA Neurology. 72 (2015) 152–158.

[135] M. Stangel, I.K. Penner, B.A. Kallmann, C. Lukas, B.C. Kieseier, Towards the implementation of 'no evidence of disease activity' in multiple sclerosis treatment: the multiple sclerosis decision model, Therapeutic Advances in Neurological Disorders. 8 (2015) 3–13.

[136] I. Hakansson, A. Tisell, P. Cassel, K. Blennow, H. Zetterberg, P. Lundberg, et al., Neurofilament levels, disease activity and brain volume during follow-up in multiple sclerosis, Journal of Neuroinflammation. 15 (2018) 209.

[137] J.C. Schommer, A.M. Carlson, T.G. Rhee, Validating pharmaceutical product claims: questions a formulary committee should ask, Journal of Medical Economics. 18 (2015) 1000–1006.

[138] Z. Mao, C. Alvarez-Gonzalez, S. De Trane, O. Yildiz, C. Albor, G. Doctor, et al., Cladribine: off-label disease modification for people with multiple sclerosis in resource-poor settings? Multiple Sclerosis Journal – Experimental, Translational and Clinical. 4 (2018).