Disease modifying therapy in MS: clinical outcomes of escalation versus early intensive treatment strategies.

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Key Points

Question: How do 5-year disability outcomes compare between people with MS who have an early intensive approach to disease-modifying therapy (DMT) versus those who have an escalation approach?

Findings: In this cohort study including 592 people, those who received high-efficacy treatment initially had a smaller increase in Expanded Disability Status Scale (EDSS) score at 5 years versus those who first received moderate-efficacy DMT (+0.3 vs. +1.2, p=0.001).

Meaning: These findings suggest that real-world escalation approaches may be inadequate to prevent unfavourable long-term outcomes and support the need for a prospective clinical trial to compare DMT algorithms.

Abstract

Importance: Uncertainty remains about how aggressively to treat early MS. High-efficacy disease modifying therapies (DMTs) are often reserved for individuals expressing poor prognostic features at baseline.

Objective: This study explores long-term outcomes in a population-based cohort according to initial treatment strategy.

Design, Setting and Participants: Cohort study, data derived from 1998 to 2016, analysis performed 2017. From a total of 720 patients prescribed a DMT, 592 (82%) were included in analysis. Reasons for exclusion were: first treated elsewhere or privately (n=39), clinical trial participant (n=25), insufficient clinical data (n=45).

Exposure: Patients were classified according to first-line treatment strategy: high-efficacy (early intensive, EIT) or moderate-efficacy DMT (escalation, ESC).

Outcomes measures: Primary outcome was 5-year change in EDSS. Secondary outcome was time to sustained accumulation of disability (SAD). Models were adjusted for sex, age at treatment, year of starting DMT, and escalation to high-efficacy treatment in the ESC group.

Results: Mean age at symptom onset was 27.0 years. Mean 5-year change in EDSS score was lower in the EIT group than the ESC group (+0.3 versus +1.2); this remained significant after adjustment for relevant covariates. (β= -0.96, 95%CI -1.49 to -0.42, p=0.0006). Median time to SAD was 6.0 years for EIT and 3.1 years for ESC (p=0.05) but after adjustment for relevant covariates was not significantly different between the groups (adjusted hazard ratio 0.50, 95%CI 0.13 - 1.91, p=0.31).

Conclusions and Relevance: In a real-life setting, long-term outcomes were more favourable following first-line high-efficacy versus first-line moderate-efficacy DMT. These real-life data support the need for a prospective controlled trial.

Introduction

The introduction of disease modifying therapies (DMTs) for multiple sclerosis (MS) has been associated with little measurable improvement in long-term disability outcomes.[1–3] Despite increasingly effective control of relapses afforded by newer DMTs, the quantifiable impact of these drugs on long-term disability has been generally disappointing.[4,5] The reasons for this are complex and are likely to relate in part to the rapid evolution of the therapeutic landscape in MS and a lack of detailed, prospective population–based disability data with follow-up durations sufficient to capture long-term outcomes. However, it may also be that current treatment strategies are not optimised to deliver the best possible long-term outcomes.

Permanent disability in MS is thought to occur through a number of mechanisms including the sequelae of relapses, the insidious effects of subclinical inflammation and neurodegeneration. Current DMTs are primarily directed at the inflammatory phase of disease. The modest impact of MS DMTs on long-term disability has led to speculation that the neurodegenerative phase of MS may represent a separate, parallel pathology. However, DMTs have been most effective when aggressive treatments have been applied very early in the clinical course of MS.[6,7] It is possible that there exists anearly window of therapeutic opportunity, in which the biology of disease can be modified for longer-term benefit,[8] but that after a certain period of time, a threshold is crossed beyond which cumulative immune-mediated injury leads to sustained neurological disability.

Disease modifying therapies in MS can be broadly divided according to the efficacy with which they are observed to prevent MS relapses. The licensed DMTs with the highest efficacy are associated with more complex safety profiles, monitoring requirements and the need for hospital or day-unit admission. These factors tend to lead clinicians or treatment guidelines to recommend that they be reserved for use in individuals with the most aggressive or resistant forms of MS.[9] In those with moderately active MS, clinicians often adopt an escalation approach whereby a DMT is selected that is considered to be most safe, subsequently escalating to more efficacious therapies, with more complex safety profiles, in the event of continued disease activity. However, in light of current knowledge, it is possible that the inevitable delay imposed by escalation strategies may result in a lost therapeutic opportunity.

Several consensus working groups in MS,[9–11] have highlighted the need for further research to establish optimum treatment and monitoring strategies in MS. In this study, we report long-term, real-life clinical outcomes in a large, well-characterised cohort of patients with MS, according to whether they were treated initially with high-efficacy or moderate-efficacy DMT.

Methods

Patients and data collection

This study was undertaken on a population-based cohort of patients with MS in south east Wales, United Kingdom, which has a total population of 1.4 million from the cities of Cardiff and Newport and the surrounding

communities. Data collection for this population has been conducted by means of a cross-sectional epidemiological study in 1985, [12] with periodic updates thereafter.[13,14] Since 1999 longitudinal data has been gathered prospectively on this population, and is estimated to have captured over 97% of the MS cases in this region,[15] with a total of more than 3,000 patients. At each encounter data is gathered including relapse history and DMT prescription. Patients undergo a comprehensive clinical assessment at least annually. Disability is measured using the Expanded Disability Status Scale (EDSS).[16]

Data storage is within a secure NHS hosted web-based departmental database, registered under the Data Protection Act. Written consent is obtained from all patients. The study is approved by the South East Wales Research Ethics Committee (ref no.05/WSE03/111).

Inclusion and exclusion criteria

All patients who had ever been prescribed a licensed DMT for MS, while living within the region and who had comprehensive long-term follow-up data were included. Patients in whom a DMT had been commenced outside of area, with insufficient data or as part of an externally sponsored clinical trial, were excluded from analysis.

DMTs were classified as follows: monoclonal antibodies (alemtuzumab and natalizumab) were categorised as high-efficacy and all other DMTs as moderate-efficacy (interferons, glatiramer acetate, dimethyl fumarate,

fingolimod and teriflunomide).[9] Patients' initial treatment strategy was classified according to whether their first-line treatment was high-efficacy (early intensive treatment [EIT] group) or moderate-efficacy (escalation [ESC] group). Individuals who received EIT were selected on the basis of poor prognostic factors including higher relapse rates and radiological evidence of recent MS activity. Those individuals who embarked on an ESC strategy with a first-line moderate-efficacy DMT had regular clinical and radiological monitoring, and if required could escalate to a high-efficacy agent.

Prospectively recorded data on dates of starting and stopping DMTs (if not current) were used for analysis. Treatment discontinuation was defined as a period off treatment of 90 days or more.[17] Where the same treatment was restarted within 90 days of discontinuation, DMT prescriptions were amalgamated. Alemtuzumab was an exception since a standard regime consists of two short courses one year apart and no further treatment if patients remain clinically and radiologically stable. Indication and reasons for discontinuation of DMTs were analysed, noting that more than one discontinuation reason may be classified per event. Systematic review of clinical records of all individuals was performed to validate the dataset. Final data capture was performed on 3rd January 2017.

Statistical analysis

Following patient classification, demographic details were compared between EIT and ESC groups using Student's t-test or Mann-Whitney U test (if data was not normally distributed) and chi-squared test for categorical data.

Annualised relapse rates before and after treatment were compared using Mann-Whitney U test.

Primary outcome was change in EDSS at 5 years. Baseline EDSS was defined as that closest to starting DMT, and final EDSS score was measured five years later both ± 1 year). The change in EDSS from baseline to 5 years' follow-up was compared between EIT and ESC groups using a linear regression model. The secondary outcome was sustained accumulation of disability (SAD), defined as an increase in EDSS score of 1.5 if baseline was 0, an increase of 1.0 if baseline was 1.0 - 5.5, or an increase of 0.5 if baseline was ≥ 5.5, sustained for at least 6 months.[18] Cox proportional hazards regression modelling was used to compare the hazard of SAD in the EIT and ESC groups. All models were performed both without any adjustment for confounders, and also adjusted *a priori* for known confounders of outcome: sex and age at first starting DMT, as well as calendar year of starting DMT (to address whether secular trends in treatment may have affected the results given the long standby period). Escalation to a high-efficacy DMT for those in the ESC group was included in the linear regression model for change in EDSS as a binary variable, and in the Cox proportional hazards regression model for hazard of SAD as a time-dependent variable.

Two sensitivity analyses were performed. First, we recognize that dichotomising treatments into two levels of efficacy is somewhat arbitrary but it is not without precedent.[9] In recognition of the fact that a switch from injectables to fingolimod might be regarded as escalation, we classified

fingolimod as a high-efficacy treatment and analysed the data accordingly. Second, an analysis including only those patients treated since 2005 was performed; this is the date from which high-efficacy treatment was freely available in Cardiff, so that a choice between high and moderate-efficacy DMT at disease onset or diagnosis was always possible. Prior to that date, patients received high-efficacy treatment mainly by referral to another specialist centre.

Results

At the time of data extraction, there were 2568 registered MS patients, with complete clinical data from disease onset. Of 720 patients prescribed a DMT before January 2017, 109 were excluded from the analysis (45 had insufficient clinical data, 25 were treated in a clinical trial, 38 were first treated out of area, and 1 was treated via private prescription), leaving 592 were eligible for inclusion in the current analysis (23.1% of the total cohort and 82% of those prescribed a DMT). One hundred and four patients had been prescribed a high-efficacy DMT as first-line (EIT), whilst 488 patients had commenced DMT with a moderate-efficacy agent (ESC). Individuals who received EIT were most likely to receive alemtuzumab than natalizumab (67% vs. 33%), while individuals who received high-efficacy therapy second-line (as part of an escalation algorithm) were most likely to receive natalizumab than alemtuzumab (74% vs. 26%).

Of those 488 patients who initially embarked on moderate-efficacy treatment, 58 (11.9%) patients subsequently went on to receive a high-efficacy DMT

(see figure 1). The reason for escalation was clinical disease activity (relapses) in 52 cases; mean ARR in the 12 months before escalation in those individuals was 2.2 (SD 1.1). In 5 cases, escalation occurred in response to subclinical radiological evidence of disease activity during the preceding 12 months. One case had no evidence of clinical or radiological evidence of disease activity during the 12 months before escalation.

Median time spent on any single disease-modifying drug was 2.0 years (95% CI 1.8 – 2.4). In those patients from the ESC group who later escalated to a high-efficacy DMT the median time to escalation was 2.4 years (2.1 – 3.5). Reasons for discontinuation of DMTs in the group as a whole were: side effects 58%, relapse frequency or severity not improved 25%, radiological evolution 10%, disability progression 10%, patient choice 10%, pregnancy planning 7% and drug holiday 5%.

61 individuals received fingolimod in our cohort, and in the sensitivity analysis were reclassified to EIT (n=2) and escalation from moderate- to high-efficacy DMT (n=59) respectively.

Comparison of treatment strategies: demographics and relapse rates

The baseline characteristics of the two groups are shown in table 1. There was no difference in the sex ratio (p=0.37), mean age at symptom onset (p=0.73), median baseline EDSS score (p=0.55) or median follow-up time (p=0.30) between the EIT and ESC groups. As expected, the pre-treatment annualised relapse rate (ARR) was higher in the EIT group (1.7, interquartile

range, IQR 0.9 – 2.8) than the ESC group (0.7, IQR 0.4 – 1.3; p<0.0001). In retrospect, those who commenced a moderate-efficacy DMT but subsequently escalated to a high-efficacy agent had a pre-treatment ARR of 1.2 (IQR 0.7 – 2.1), as compared to 0.7 (IQR 0.4 – 1.2) in those who remained on moderate-efficacy DMT (p<0.0001).

The ARR fell in all groups following the introduction of a DMT (table 1). Following DMT the ARR was 0.16 (IQR 0 – 0.5) in the ESC group and 0 (0 – 0.3) in the EIT group (p=0.02). Within the ESC group, the ARR following initial DMT was 0.9 (IQR 0.7 – 1.5) in those patients who later escalated to high-efficacy treatment; ARR was 0 (IQR 0 – 0.2) in that group following escalation to high-efficacy DMT. The ARR was 0.11 (IQR 0 – 0.4) in the group who remained on moderate-efficacy DMTs (p=0.01).

Comparison of treatment strategies: change in EDSS over five years

179 patients (EIT n = 41; ESC n = 138) had EDSS scores available both at baseline and at five years follow-up. Mean baseline EDSS was 4.2 in the EIT group (standard deviation, SD 1.7) and 3.5 in the ESC group (SD 1.7). Median baseline EDSS was 4.5 in the EIT group (interquartile range, IQR 3.0 – 5.5), and 3.5 in the ESC group (IQR 2.0 – 4.5). Mean change in EDSS at 5 years was +1.2 in the ESC group, and +0.3 in the EIT group (t = 3.41, p = 0.001). After adjustment for relevant covariates, the EIT group had a significantly lower change in EDSS score at 5 years compared to the ESC group (β = -0.96, 95% confidence intervals: [CI] -1.49 to -0.42, p = 0.0006).

The results of the linear regression model are shown in table 2. There was no change in this finding for either of the sensitivity analyses (data not shown).

Comparison of treatment strategies: sustained accumulation of disability

In the total cohort, median time to SAD was 6.0 years (95% CI 3.4 – 8.2) for the EIT group, and 3.1 (95% CI 2.8 – 4.0) for the ESC group (log-rank test p=0.05). For those within the ESC group who escalated to high-efficacy DMT as second-line treatment, median time to SAD was 3.3 years (1.8 – 5.6; compared to EIT group log-rank test p = 0.08), and 60% of this group reached SAD while on initial moderate-efficacy treatment, before escalation of treatment. For those who remained on moderate-efficacy DMT median time to SAD was 3.1 years (2.6 – 4.0; compared to EIT group log-rank test p = 0.07). Treatment strategy was not associated with hazard of SAD either analysed alone (hazard ratio [HR] 0.72, 95% CI 0.52 - 1.01, p=0.05) or after adjustment for relevant covariates (HR 0.50, 95% CI 0.13 - 1.91, p=0.31). Neither unadjusted nor adjusted model violated the proportional hazards assumption. The results of the Cox proportional hazards regression models are shown in table 3. Again, this finding was unchanged in both sensitivity analyses (data not shown).

Safety

Adverse event data on patients receiving alemtuzumab within this cohort has been published previously: 87% developed infusion-related adverse events,

47% developed autoimmunity (51 different autoimmune diseases: 35 thyroid, 3 immune thrombocytopenic purpura and 13 other) but no serious infections and no treatment related deaths.[19] In patients receiving natalizumab there were no serious adverse events (SAEs), no cases of progressive multifocal leukoencephalopathy and no treatment-related deaths. In patients receiving moderate-efficacy DMTs there were no treatment-related deaths but 7 SAEs (1.4%): 3 cases of necrotic skin reactions and 1 case of anaphylaxis on injectable DMTs, and 3 severe infections on fingolimod.

Discussion

The concept of escalation versus early intensive treatment strategies has arisen largely as a result of concerns over the complex safety profiles of the high-efficacy DMTs. Contemporary treatment algorithms often suggest reserving first-line, high-efficacy treatments for individuals considered at highest risk of accumulating disability, usually those who meet an arbitrarily high level of clinical or radiological MS activity. For an escalation approach to be successful in the remaining cases, it is necessary that adequate procedure is in place to detect and respond to “failure” of first-line moderate-efficacy DMTs, without the individual accumulating permanent disability in the interim, and that any delay in escalation does not diminish the efficacy of subsequent DMTs. These assumptions have not been tested in a controlled trial. The benefit of reserving high-efficacy interventions for those patients perceived to have the most active disease therefore remains unclear.

In this study of a ‘real life’ cohort for which detailed clinical data from disease onset are available, we have compared long-term outcomes in patients who were started on EIT with a high-efficacy DMT versus those commenced on an ESC strategy. We found that although patients who received EIT were selected on the basis of poor prognostic factors including higher relapse rates and radiological evidence of recent MS activity, it was this patient group that had the better long-term outcomes. In patients starting on an ESC treatment strategy there was a mean increase in EDSS of +1.2 over 5 years despite clinical surveillance and targeted escalation, compared to only +0.3 in the EIT group. Time to SAD appeared delayed in those receiving EIT (6.0 years) compared to those who had an escalation approach (3.1 years) but the hazard of reaching SAD did not remain statistically significant after adjustment for potential confounders.

There could be a number of reasons for the difference in EDSS outcome identified between EIT and ESC approaches in this study. While it is possible that compliance (time spent on treatment) may have been lower in those on moderate-efficacy DMTs, the data points toward several other contributors. Firstly, those individuals who embarked on an escalation approach but subsequently required escalation to a high-efficacy agent, had a higher baseline annualised relapse rate (1.2) than those who remained on moderate-efficacy therapy (0.7). These data suggest that existing thresholds for using an EIT approach (e.g. rapidly evolving severe MS), may be too high. Secondly, it seems plausible that the majority of disability accumulation in the escalation group occurred while these individuals were receiving moderate-

efficacy therapies -60% of those who escalated had sustained accumulation of disability while on moderate-efficacy treatment, before escalation to high-efficacy DMT. This would imply that contemporary methods of clinical and MRI surveillance were insufficiently responsive to trigger escalation. Meanwhile, the reduction in relapse rate experienced after high-efficacy therapy appeared to be similarly great whether it was given as first-line or as escalation therapy. This suggests that the therapeutic benefit of high-efficacy therapy on relapse rate does not diminish after a mean delay of 2.4 years. Another possibility for the difference uncovered in this study relates to the underlying pathology of MS; a more robust therapeutic approach early during the course of the disease may confer prompt biological modification of inflammatory processes that propagate axonal degeneration.[20]

This study is subject to limitations that are common to population cohort data, such as a lack of uniformly acquired imaging or adverse event data compared with clinical trials. Various monitoring algorithms have been proposed to prompt escalation of DMT,[21–24] but none is universally accepted and some are not feasible in all real-world clinical settings.[10] We feel that this cohort is likely to represent the manner in which the majority of contemporary cohorts in developed countries were managed during the period. The data has practical relevance and may also provide a measure of the translatability of clinical trial results into general clinical practice, where resources tend to be more limited.

In spite of evidence from phase 3 trials that monoclonal antibodies are likely to have superior efficacy than more established DMTs,[25,26], the widespread

uptake of first-line, high-efficacy DMT has not emerged. Our study undermines the prevalent belief that an escalation approach represents a lower-risk strategy to MS treatment, and suggests that in the real world, an escalation approach to DMT may be inadequate to prevent unfavourable long-term outcomes. These data should prompt a more detailed study of whether refined selection and escalation criteria could negate the long-term risk of disability accumulation observed in this escalation cohort.

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Figure Legends

Figure 1. Flow chart showing treatment strategies and number of patients in each group

Figure 2: Kaplan-Meier curves showing time to sustained accumulation of disability by initial treatment strategy (adjusted hazard ratio 0.50, 95%CI 0.13 - 1.91, p=0.31).

EIT: early intensive treatment; ESC: escalation approach.

Table 1

Clinical and demographic features of the escalation (ESC) and early intensive treatment (EIT) cohorts.

	Early intensive treatment (EIT) n = 104	**Escalation treatment (ESC) n = 488**	**p value**
Sex ratio: number (%) female	79 (76%)	346 (71%)	0.37
Age at symptom onset (y)	29.8	30.2	0.73
Age at first DMT (y)	34.0	38.5	<0.001
Median EDSS at DMT onset	3.5	3.5	0.55
Median follow-up duration (y)	5.8	6.9	0.30
Baseline (pre-treatment) ARR (median, IQR)	1.7 (0.9 – 2.8)	0.7 (0.4 – 1.3)	< 0.001
Post-treatment ARR (median, IQR)	0 (0 – 0.3)	0.16 (0 – 0.5)	0.02
Median calendar year of first DMT	2010	2011	0.84

Table 2. The association of first-line DMT strategy (early intensive treatment, EIT: n=41 *versus* escalation approach, ESC: n=138) and change in EDSS at five years: adjusted linear regression model.

Covariate	**β estimate (95% confidence interval)**	**p value**
Unadjusted model:		
EIT treatment strategy	-0.92 (-1.45 - -0.41)	0.0006
Adjusted model:		
EIT treatment strategy	-0.96 (-1.49 - -0.42)	0.0006
Age at starting DMT	0.02 (-0.004 - 0.05)	0.10
Male sex	0.14 (-0.34 – 0.61)	0.57
Calendar year of starting DMT	0.05 (-0.02 - 0.11)	0.19
Escalation to high-efficacy DMT as second-line	-0.41 (-1.06 – 0.24)	0.22

EIT: early intensive treatment; ESC; escalation approach; EDSS: Expanded Disability Status Scale; DMT: disease-modifying therapy

Covariate	Hazard ratio (95% confidence interval)	p
Unadjusted model: EIT treatment strategy	0.72 (0.52 - 1.01)	0.05
Treatment strategy: EIT	–0.50 (0.13 – 1.91)	0.31
Age at starting DMT	1.02 (1.00 1.04)	0.04
Male sex	–0.89 (0.66 - 1.20)	0.44
Calendar year of starting DMT	1.02 (0.98 - 1.05)	0.42
Interaction term: treatment strategy and age at starting DMT	1.01 (0.97 - 1.05)	0.59
Escalation to high-efficacy DMT as second-line	0.57 (0.24 - 1.32)	0.19

Table 3. The association of treatment strategy (early intensive treatment, n=104, versus escalation approach, n=488) and hazard of sustained accumulation of disability: adjusted Cox proportional hazards regression model.
EIT: early intensive treatment. DMT: disease-modifying therapy