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Abstract:	

Paradigm shifts: Early initiation of high efficacy disease modifying treatment in Multiple Sclerosis

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Clinical development of disease modifying drugs for the treatment of MS has been exceedingly successful over the past three decades (1). This in part reflects advances in our knowledge of the pathogenetic underpinnings of the disease and improvement in trial design permitting more rapid translation. The available arsenal contains up to 18 drugs (depending on countries location and income,(2)) that differ in efficacy, route and timing of administration, side effects, risks and tolerability. Starting with the injectable interferons and glatiramer acetate, the introduction of the first monoclonal antibody curtailing lymphocyte invasion of the CNS, the first long-awaited oral agents and the high efficacy lymphocyte depleting monoclonal antibodies, many patients with the relapsing forms of MS and fewer with progressive disease clearly receive therapeutic benefit from these disease-modifying agents.

In the absence of a cure for this chronic disorder, timing and sequencing of treatments are of key importance in achieving optimal outcomes for individuals with MS.

Natural history studies, identification of prognostic factors, pathological and radiological recognition of early axonal damage, observation of aberrant immune responses broadening over time in autoantigenic scope with the build-up of immunoinflammatory cascades causing accumulating irreversible parenchymal damage provided the rationale in the late 1990s to explore the utility of early intervention with disease modifying agents. Randomized placebo-controlled trials of the first generation injectables and later teriflunomide and cladribine in clinically isolated syndrome examining time of conversion to definite MS supported the concept of early treatment commencement yielding better short-term outcomes. The advantages offered by early institution of disease modifying therapies were corroborated in open label extension studies of the first generation agents. Participants with delayed treatment initiation never caught up with those that received the intervention from trial start. Open label extension studies of short term randomized controlled trials cannot provide robust information on long-term effects of disease-modifying treatments (DMTs) in achieving the principal goal of MS management, slowing or halting disease progression. There are several reasons such as

duration of the observation, multiple sources of bias including informative censoring, selective dropout, and declining number of participants over time losing required statistical power.

Real world evidence, which defines treatment effectiveness and implementation in an environment beyond the strict confines of randomized drug trials, is collected from large data sets, health insurance databases, comprehensive national registries and international databases. Extremely useful information has been forthcoming when data are interrogated applying statistical methodology adopted from other fields, such as propensity scoring, marginal structural modelling and weighted cumulative exposure analysis (3,4).

The importance of early treatment initiation was the clear message from the Swedish STOP-MS project which adopted this approach. Kavaliunas et al, who recruited patients between 2001 and 2007, there examined data from 639 people with MS receiving DMTs for any period of time (5). These were mostly first generation injectables, natalizumab, fingolimod and rituximab. They compared patients who started DMTs after 3 years of disease onset with those who embarked on DMTs within one year of disease onset. Later DMT commencement carried a hazard ratio of 2,64. For each year of treatment delay the risk to reach EDSS4 increased by 7.4% These results were recently confirmed independently on a much larger patient cohort in the first report emanating from the Big Multiple Sclerosis Data (BMSD) network, a joint effort of the Danish, French, Italian, Swedish national registries and MSBase published in this issue of MSJ (6). Drawing on data from 11.871 patients, the authors determined four outcomes: three and 12-month confirmed disability worsening and assignment of irreversible EDSS 4 and EDSS 6. First, Cox regression models were used to estimate hazard ratios and confidence intervals of reaching the outcomes. Time from disease onset to commencement of DMT in quintiles was included. The propensity score matching was applied to pairwise comparisons of different time interval quintiles. The first DMT was almost exclusively interferonß or glatiramer acetate. Only 1.1% of patients received natalizumab, fingolimod or mitoxantrone as a first line treatment. Delayed first treatment was associated with an elevated risk to develop

three or 12-month confirmed disability worsening (18%, 31% respectively) and increased the risk of reaching EDSS 4 and EDSS 6 by 40% and 53%, respectively.

Kalincik and colleagues (7) from MSBase undertook a comparison of long-term disability outcomes during periods when patients were under treatment and those periods without treatment. Extracting data from a cohort of 14,717 patients followed prospectively for a median of 6 years receiving over time in the great majority first generation injectables (some 60%, with 5% receiving natalizumab), exposure to DMTs clearly diminished the frequency of relapses (hazard ratio 0.6), disability worsening (hazard ratio 0.56) and progress to the critical benchmark EDSS 6 (hazard ration 0.33). In a subset of patients for whom follow-up data over at least 15 years were available, the likelihood to have a relapse or worsening of disability was similarly lowered (hazard ratios of 0.59 and 0.81).

Another MSBase Study Group investigation of 1555 patients treated initially with first generation injectables had a lower risk to convert to SPMS than a matched untreated control group (hazard ratio 0.71, 5-year absolute risk 12% vs. 27%) (8). The fingolimod group had a hazard ratio of 0.37) and the 5-year absolute risk was 7% vs. 32%. The hazard ratio for natalizumab was 0.61 and the 5-year absolute risk 19% vs. 38%. The hazard ratio for alemtuzumab was 0.32 and the 5-year absolute risk 10% vs. 25%.

In aggregate, these and previous studies clearly underscore the greater benefits people with MS receive when DMTs are commenced early after disease onset.

Given the ever broadening armamentarium to treat MS and the appearance over time of more effective DMTs two fundamental management approaches have been developed and differentially adopted by neurologists but accumulating evidence may well shift the balance (9).

The escalation approach, long in favour, advocates use of a moderately or medium effective DMT initially and switching or escalating to other more efficacious and potentially higher risk agents should disease activity be insufficiently controlled. This would be judged e.g. by assessing NEDA (no evidence of – detectable – disease activity) status.

This philosophy is clearly dominated by safety concerns and the assumption that in many instances the disease may not run a severe course. However, reliably establishing the individual prognosis is not trivial and the unknown legacies of sequential drug administration in creating cumulative risks should not be taken lightly.

Early high efficacy or early intensive therapy is based on the idea that one should capitalize on a window of opportunity open for drugs to unfold their maximal anti-inflammatory actions when they are most likely to be most beneficial. Patients deemed to have a poorer prognosis with clinical and radiological evidence of high disease activity would receive high efficacy or intensive therapy. Natalizumab, alemtuzumab, rituximab, ocrelizumab, ofatumumab, cladribine, or mitoxantrone are considered to belong to his group. Most experts would include the sphingosine-1-phosphate receptor modulators in this category.

The assumptions underlying these two diverging management paradigms may now come into question.

Exploration of the relative merits of either strategy is best done using the gold standard of a randomized controlled trial. In fact, two such studies are currently underway: the Traditional versus Early Aggressive Therapy for MS (TREAT-MS) trial (NCT03500328) recruiting 900 participants is a pragmatic randomized single masked controlled study. The Determining the Effectiveness of earLY Intensive versus Escalation approaches for the treatment of Relapsing-remitting MS (DELIVER-MS) trial (NCT03535298) enrolling 800 patients is open label. Neither trial will read out before 2024 / 2026 .

In the meantime helpful information aiding in the differential therapeutic process has become available from a number of real world observational studies.

A study from Wales was conducted on a population-based cohort of 592 patients who were classified according to first line strategy: early high efficacy / intensive therapy or moderate efficacy DMT (escalation approach) (10). The mean change in EDSS at 5 years was lower in the former group (0.3 vs 1.2). The median time of developing sustained accumulation of disability was 6 years in the entire cohort for the early intensive therapy group compared with

3.1 years in the escalation group. Patients in the escalation group who were switched to a high efficacy agent as second line treatment strategy acquired sustained disability accumulation after a median of 3.3 years. They had higher baseline annualized relapse rates.

In a similar vein, patients from MSBase and the Swedish MS registry were compared in terms of the time when high efficacy treatment was instituted and subsequent disability outcome after 6-10 years. 51% of 544 patients received high efficacy DMT within 2 years of disease onset whereas 49% commenced treatment later. In the sixth year after disease onset, mean EDSS in the early treatment group was 2.2 and 2.9 in the late treatment group. The superiority of early treatment persisted each year of follow-up until year 10 (11).

A nationwide cohort study from Denmark provides further corroborative evidence (12). During the period 2001-2008, 194 patients who started on high efficacy DMTs were matched to 194 patients starting medium efficacy DMTs. After a follow-up of 4 years, the probabilities for 6-month confirmed disability progression were 16.7% for the high efficacy DMTs and 30.1% for the medium efficacy DMTs. These differences remained after covariate analysis of baseline disease activity, T2 lesion load or diagnosis after 2006.

The Welsh study referred to above also demonstrated that early therapy with high efficacy drugs delivered better outcomes than medium efficacy agents (interferonß, glatiramer acetate) since conversion to the secondary progressive disease stage was delayed (hazard ratio 0.66) (10). Further, when patients on interferonß or glatiramer acetate were escalated to fingolimod, natalizumab or alemtuzumab within 5 years compared to after 5 years, the risk to transition from relapsing remitting to secondary progressive MS was lower (hazard ratio 0.76).

Most recently, the Italian MS registry investigators determined long-term trajectories in people with relapsing MS who were treated with early intensive or escalation treatment strategies (13). Patients with a follow-up of at least 5 years, a first visit within 3 years of disease onset and at least 3 EDSS evaluations after the first DMT start were extracted from the database. These

patients were categorized according to early intensive treatment with natalizumab, alemtuzumab, mitoxantrone, fingolimod, cladribine, or ocrelizumab and the escalation treatment with interferonß, glatiramer acetate, teriflunomide, dimethylfumarate or azathioprine followed by switch to a high efficacy drug in case of lacking disease control. Each group included 363 individuals and were followed for a median of 8.5 years. Mean delta-EDSS scores were all higher in the escalation vs. early intensive treatment group. These differences increased from 0.1 at year 1 to 0.3 at year 5 and reached 0.67 at 10 years. The authors concluded that an early intensive treatment strategy is more effective than escalation treatment in controlling disease progression over time.

While it is now undisputable that early initiation of DMT generates greater benefit to patients both in the short- and long-term, deliberations are still ongoing as to whether the escalation approach commencing with medium efficacy DMTs should be superseded by the high efficacy / early intensive management approach. Given the large body of convergent evidence that has been accumulated recently through careful interrogation of large databases, there may now be sufficient evidence for the community to consider a new treatment paradigm now rather than waiting until the conclusion of the two ongoing controlled trials.

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