REVIEW

OPEN

Interrogating large multiple sclerosis registries and databases: what information can be gained?

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Purpose of review
Although substantial progress has been made in understanding the natural history of multiple sclerosis (MS) and the development of new therapies, many questions concerning disease behavior and therapeutics remain to be answered. Data generated from real-world observational studies, based on large MS registries and databases and analyzed with advanced statistical methods, are offering the scientific community answers to some of these questions that are otherwise difficult or impossible to address. This review focuses on observational studies published in the last 2 years designed to compare the effectiveness of escalation vs. induction treatment strategies, to assess the effectiveness of treatment in pediatric-onset and late-onset MS, and to identify the clinical phenotype of secondary progressive (SP)MS.

Recent findings
The main findings originating from real-world studies suggest that MS patients who will qualify for high-efficacy disease-modifying therapies (DMTs) should be offered these as early as possible to prevent irreversible accumulation of neurological disability. Especially pediatric patients derive substantial benefits from early treatment. In patients with late-onset MS, sustained exposure to DMTs may result in more favorable outcomes. Data-driven definitions are more accurate in defining transition to SPMS than diagnosis based solely on neurologists' judgment.

Summary
Patients, physicians, industry, and policy-makers have all benefited from real-world evidence based on registry data, in answering questions of diagnostics, choice of treatment, and timing of treatment decisions.

Keywords
disease registries, induction vs. escalation strategies, multiple sclerosis, observational studies, pediatric multiple sclerosis, secondary progressive multiple sclerosis

INTRODUCTION

Comprehensive multiple sclerosis (MS) registries, cross-sectional and longitudinal databases, and cohorts have seen extraordinary growth worldwide in recent years. Real-world data, routinely acquired from these sources, are increasingly used in observational studies to address clinical questions related to diagnostics, burden of MS, natural history, prognostics, and long-term safety and effectiveness of treatments [1]. In parallel, the ongoing development and application of new statistical methods to minimize the impact of confounding, bias, and heterogeneity, is providing MS researchers with an evolving toolkit that enables more sophisticated and relevant analyses leading to improved validity and reliability of the generated evidence. To date, studies in both registries and cohorts have been instrumental in exploring potential prognostic markers of disease outcomes and in assessing comparative effectiveness of several MS disease-modifying therapies (DMTs) over the medium term and long term. The field is now expanding to interrogate different treatment strategies (i.e., escalation vs. induction therapy) in MS patients. Special attention is being paid to pediatric-onset (POMS) and late-onset (LOMS) forms of MS.

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KEY POINTS

- MS patients should be offered high-efficacy DMTs as early as possible to prevent irreversible accumulation of neurological disability.
- Early treatment is of paramount importance in the pediatric MS population.
- Beneficial effect of sustained exposure to DMTs may occur in late-onset MS subgroups.
- Data-driven definitions may help capture specific subgroups of patients with SPMS that could benefit most from DMTs.
- Further studies are needed to evaluate the effectiveness of more complex treatment strategies and individual treatment response.

Moreover, since new therapies are now available to slow down progression in secondary progressive MS (SPMS) [2], an early and accurate identification of transition to SPMS is needed.

In this review, we focus on observational studies, published in the last 2 years, designed to compare effectiveness of treatment strategies, assess the importance of proper treatments in the pediatric and elderly populations, and describe the clinical phenotype of SPMS. Next frontiers for research based on MS registries are also discussed.

COMPARATIVE EFFECTIVENESS OF TREATMENT STRATEGIES

With the increasing number of treatments available and the advent of more effective therapies, two different treatment strategies are being confronted, the escalation approach and the early use of high-efficacy immunotherapies (early intensive treatment – EIT) [3].

The preference toward an escalation approach is mainly driven by the favorable safety profile of the moderate-efficacy DMTs, and by the limited accessibility of high-efficacy DMTs for treatment-naïve patients, or those without highly active disease due to restrictions imposed by reimbursement bodies in many jurisdictions [4▪].

The superior short-term effect of high-efficacy DMTs, including natalizumab, alemtuzumab, ocrelizumab, cladribrine, mitoxantrone, ofatumumab, or fingolimod, in reducing clinical and MRI disease activity in comparison with moderate-efficacy DMTs, such as IFN-β, glatiramer acetate or teriflunomide, have been consistently demonstrated by randomized clinical trials (RCTs) [5–9]. Evidence of a more beneficial effect of the EIT strategy vs. the escalation approach on disability outcomes over a medium-term to long-term has been provided by several observational studies conducted on data obtained from comprehensive national registries and international databases [10–13,14▪▪,15,16▪▪]. Most of these studies have been recently reported and discussed in an editorial by Hartung *et al.* [17▪▪]. The latest study published on October this year [18▪▪], based on data from the Swedish and Danish registries, investigated whether different national treatment recommendations and strategies, were associated with different disability outcomes in the medium-term (mean follow-up: 4.1 years). The study selected only patients who had started the first DMT between 2013 and 2016. Swedish neurologists were more likely to start treatment with high-efficacy DMTs in comparison to Danish neurologists (34.5 vs. 7.6%). The more aggressive treatment approach in Sweden was associated with a significant risk reduction of 6-month confirmed disability worsening and of reaching EDSS 3.0 and 4.0 (29, 24, and 25% relative risk reduction, respectively) in comparison to the Danish approach.

Overall, the evidence arising from these real-world studies highlights the need for a paradigm shift in the treatment of MS. Patients with MS should be offered high-efficacy DMTs as early as possible to prevent the irreversible accumulation of neurological disability. Further research is underway, investigating the benefits of early use of high-efficacy DMTs in pragmatic clinical trials, which will generate controlled and randomized data in the near future [19,20].

For the newer high-efficacy DMTs, the short-term and long-term risk/benefit ratios are yet to be established, with the latter requiring more clinical and real-world data.

TREATMENT RESPONSE IN PEDIATRIC-ONSET MULTIPLE SCLEROSIS

MS with pediatric-onset (before the age of 18) accounts for 2–10% of the entire MS population. The diagnosis in children is facilitated by refinement of accurate diagnostic criteria [21,22]. Almost universally, POMS follows a relapsing-remitting course, with a high rate of relapses and MRI lesions accrual [23▪]. Pediatric patients experience an improved recovery from relapses compared with their adult counterparts and rarely accrue significant physical disability in the first decade after disease onset [24▪▪]. However, they reach irreversible disability milestones at a younger age compared with adults [25]. Moreover, cognitive changes occur in approximately one-third of POMS patients [26]. Collectively, these considerations raise the issue of early and appropriate treatment intervention in these young patients. Until the recent few years, the literature

regarding the treatment of POMS has been largely restricted to retrospective studies of first-line injectable therapies, a few oral agents, and natalizumab. More recently, pediatric randomized trials resulted in the approval of two oral agents, fingolimod and teriflunomide in POMS [27,28▪▪]. Given the relative scarcity of POMS, systematic collection of data in registries and other large datasets have been fundamental to advance our understanding of prognostication and treatment strategies.

In a collaborative study of the Italian and MSBase registries, including a cohort of 770 pediatric patients with clinically isolated syndrome (CIS), DMT treatment before the second clinical attack was an independent protective factor against evolution to clinically definite MS [29]. After the diagnosis of MS, DMT exposure and onset before 15 years of age prolonged the time to confirmed disability progression [29]. Moreover, in an Italian cohort of 460 POMS patients the risk of 12-month confirmed disability worsening and of reaching EDSS 3.0 and 4.0, was significantly reduced in different quartiles of exposure to DMTs, seemingly in a dose-dependent manner [30▪▪]. Recent studies have tested in the pediatric population the emerging paradigm of early treatment with high-efficacy DMTs. The US network of pediatric MS Centers assessed treatment practices in the United States in 748 POMS and 271 pediatric CIS subjects, with a mean follow-up of 3.5 years [31]. The study showed that over the last 10 years the use of newer and more powerful drugs in pediatric patients has increased substantially and that in children these drugs have similar short-term safety, tolerability, and side effect profiles as in adults. The same Group analyzed the real-world effectiveness of initial DMT therapy in 741 MS children, of whom 197 were initiated with newer, more potent drugs and 544 with older injectables [32▪]. Those started on a newer DMT experienced a significantly lower relapse rate and rate of MRI activity than those on injectables, supporting greater effectiveness of the newer therapies [32▪]. Taking a different approach, a study in the Italian MS registry enrolled 3198 POMS individuals with a mean follow-up of 21.8 years and compared the time to disability milestones in four different diagnostic epochs (<1993, 1993–1999, 2000–2006, and 2007–2013). The cumulative probability of reaching EDSS 4.0 and 6.0 was found to decrease gradually over time. Of note, in later diagnostic epochs, a greater number of POMS patients were treated earlier with high-efficacy -DMTs, indicating that the prognostic improvement may owe to changing therapeutic standards [33▪▪].

High-quality, long-term treatment safety registries remain a key unmet need to advance the care of POMS patients, ensuring that the long-term risk–benefit balance of treatment during childhood is favorable. Prospective, long-term observational studies also hold promise of addressing complex issues in care of pediatric MS population, such as comparative effectiveness of treatments, treatment sequencing, response to treatment failure, and safety. Long-term sustained follow-up of this young population can pose unique challenges. The use of tele-health/remote visits, mobile devices to record patient-reported data and wearables, could be of particular help in maximizing participation in post-marketing extension and registry-based studies.

TREATMENT RESPONSE IN LATE-ONSET MULTIPLE SCLEROSIS

LOMS, commonly defined as disease onset after the age of 50, is considered a rare phenomenon with a reported prevalence between 4 and 9.6% of the total MS population. However, recent studies reported the peak age-specific prevalence in Europe and Northern America is shifting from 40 years toward an older age of around 60 years [34–36]. Therapeutic decision-making remains particularly challenging in elderly patients since most of RCTs of DMTs-excluded MS patients older than 50–55 years [37]. For instance, the age-induced immunosenescence may increase specific DMTs' risks, including infections and cancer [38,39,40▪], and comorbidities associated with age may influence the risk–benefit ratios of therapies and, as a result, lead to more frequent treatment discontinuation [41,42]. For all these reasons patients with LOMS are less frequently treated in comparison to adult-onset MS [43▪].

Considering the increasing prevalence of LOMS, observational studies from longitudinal MS registries or prospective cohort studies are both necessary and warranted. A recent multicenter, observational, retrospective Italian cohort study [30▪▪] assessed the treatment response to DMTs in three large cohorts of RRMS patients defined by age at onset: POMS (<18 years), adult-onset (18–49 years), and LOMS (≥50 years). All patients were followed for at least 5 years, including 3 EDSS scores and the first neurological evaluation within 3 years from onset. Multivariable Cox models were used to assess the risk of reaching a first 12-month confirmed disability worsening and reaching a sustained EDSS 4.0. The treatment effect was assessed with a time-dependent approach considering the total time a patient spent on treatment. The results from this real-world setting confirmed that sustained exposure to DMTs significantly decreases the risk of unfavorable outcomes in both POMS and adult-onset patients and demonstrated that this effect is still detectable in the LOMS subgroup.

Another Italian study comparing the effectiveness of injectable and oral first-line DMTs in a cohort of 302 LOMS patients with a median follow-up of 25.8 months did not report any difference between the two groups in terms of time to first relapse, first confirmed disability progression and to discontinuation [44]. This study further suggested that a potential effect of DMTs is sustained in elderly MS patients.

Presently, further dedicated research is needed to explore whether a hypothetical 'upper limit' of age for the response to DMTs exists and to characterize subgroups with a favorable risk–benefit ratio among older patients.

IDENTIFYING SECONDARY PROGRESSIVE PATIENTS

Although a growing amount of evidence suggests that the course of MS should be considered as a continuum [45,46], the clinical course descriptors – relapsing-remitting, secondary progressive, and primary progressive – are still in use [46]. Since new therapies are now available to slow down the progression in SPMS [2], an early and accurate identification of the secondary progressive transition has become even more needed.

A Swedish study proposed a nomogram to predict individual risk of conversion to SPMS at the time of disease onset [47]. The tool, utilizing several variables (sex, calendar year of birth, age at-recorded and first-recorded EDSS score, and age at disease onset), enabled prediction of risk of SPMS conversion at 10, 15, and 20 years with a good external validity [47]. More recently, the same group used several types of machine learning classification approaches to show that a decision tree based only on the most recently available EDSS score and current age allows accurate identification of disease phenotype as determined by a neurologist in 14 387 Swedish MS patients and in a validation cohort of 5431 patients from the British Columbia cohort [48▪].

Subsequently, an Italian MS Registry study [49▪] compared risk factors of SPMS transition by using two definitions based on the neurologist judgment and a slightly modified version of the MSBase algorithm [50]. The main risk and protective factors for SPMS did not differ between the two cohorts, but the data-driven algorithm identified older, more disabled, faster-progressing patients than the neurologists' definition [49▪].

The Danish MS registry provided a clinical description of SPMS patients identified by using the two different data-driven definitions, the MSBase algorithm [50] and one definition based on the EXPAND trial inclusion criteria [2].

In about 7000 patients, the EXPAND definition, applied to SPMS patients previously identified by the MSBase algorithm, captured patients who had converted to SPMS in a shorter time, with more active MS and more frequently treated with high-efficacy DMTs [51▪].

Finally, the real-word observational studies, which used a data-driven secondary progressive definition as the main outcome, support the possibility that exposure to DMTs can reduce the risk of transition to SPMS and improve disability outcomes, including the risk to become wheelchair-dependent, in patients with active SPMS [13,52▪▪].

All these results consistently suggest that data-driven definitions help capture specific subgroups of SPMS that may most benefit from continued treatment with DMTs.

CONCLUSION AND NEXT FRONTIER FOR THE RESEARCH IN MULTIPLE SCLEROSIS REGISTRIES

The growing number of DMTs, used in increasingly specific clinical scenarios, has led to a high number of clinically plausible treatment pathways. As the next step, we will need to understand the effectiveness of more complex treatment strategies. For instance, treatment decisions after patients discontinued DMTs, due to either treatment failure of poor tolerance/toxicity, have become complex, in particular as a result of the broad spectrum of the mechanisms of action and duration of treatment effects of the available therapies. These complexities present not only clinicians but also researchers with design and analytical challenges that are yet to be answered. Considering the long-lasting biological effects of some of the presently used immunotherapies, research of the effect and tolerability of different approaches to treatment sequencing will require sophisticated statistical instruments in conjunction with consistent long-term clinical datasets. The methods such as propensity score weighting or matching (and to this end also randomization), are suited to compare small numbers of relatively simple treatment choices over a limited time. Complex treatment pathways, and questions around effective sequencing of therapies in particular, will require that researchers incorporate in their armamentarium methods of causal inference suited for dynamic treatment regimens, such as Robins' generalized methods (G-methods; Table 1) [53]. Further refinement of these methods is required to allow evaluation of immediate effects of present therapies and delayed/cumulative effects of previous therapies.

A number of prognostic factors are now known to be associated with future severity of MS among subgroups of patients. Such associations have been

Table 1. G-methods

G-methods provide consistent estimates of contrasts of potential outcomes of treatments in dynamic treatment regimens with time-varying confounding and treatment structure

identified early after first presentation of the disease, during established disease-modifying therapy, or preceding conversion to secondary progressive phase. Examples include intracranial lesion load, spinal cord lesions, intrathecal synthesis of antibodies, relapse frequency, tempo of disability worsening, and others [54▪,55,56,57▪,58]. However, only a very limited number of studies have translated group-level associations into individual predictions of risk [54▪,57▪,59▪,60,61]. The two key steps in such translation are external validation of the models and quantification of individual accuracy of the predictions.

Another frontier is a shift from general prognostics, corresponding to the prediction of disease severity in natural disease course, to prediction of outcomes conditional on future exposures to MS therapies – that is, individual treatment response. The first studies that personalized the prediction of treatment response used stratified modeling of on-treatment disease outcomes [61] or subtraction of models predicting magnitudes of treatment effectiveness [62,63]. More work is needed to eliminate treatment indication bias and improve generalizability of these models.

Progression of MS may occur at any stage of the disease. In fact, progression of disability independent from relapses is common not only in progressive but also in relapsing MS forms [64▪]. It is possible, that the overt progression, detected as objective deterioration of neurological function, may occur on the background of more sustained 'subclinical' or latent progression. A number of promising markers of such progression are emerging, such as global and segmented volumetric MRI changes, trajectory of serum neurofilament light chain concentration, or clinical assessment of cognitive performance. These markers were traditionally the domain of observational cohorts, but more recently, clinical registries have been developing strategies towards their incorporation into standard observational protocols, or at least define cohorts in which this information is recorded. The combined value of these markers for monitoring the tempo of subclinical progression is yet to be established. If successful, new instruments based on objective, quantitative, reproducible measures of subtle deterioration of the central nervous system structure and function have the potential to become not only diagnostic and monitoring tools, but also novel outcomes for trials of therapies to prevent progression in MS.

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Conflicts of interest

M.T. served on scientific advisory boards for Biogen, Novartis, Roche, Merck and Genzyme, BMS and Janssen; has received speaker honoraria from Biogen, Roche, Sanofi, Merck, Genzyme and Novartis; and has received research grants for her Institution from Biogen, Merck, Novartis and Roche.

T.K. served on scientific advisory boards for BMS, Roche, Janssen, Sanofi Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Eisai, Novartis, Biogen, Sanofi-Genzyme, Teva, BioCSL and Merck, received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck, and received research support from NHMRC, UK MS Society, MS Research Australia, Trish Foundation and EDMUS Foundation.

P.I. served on scientific advisory boards for Biogen, Novartis, Roche, Merck and Genzyme; has received speaker honoraria from Biogen, Roche, Sanofi, Merck, Genzyme and Novartis.

M.P.A. served on scientific advisory boards for and has received speaker honoraria and research support from Biogen Idec, Merck Serono, Bayer Schering Pharma, and Sanofi Aventis, and serves on the editorial board of BMC Neurology.

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