EDITORIAL

Where are we Going with Drugs to Treat MS? Will Cost Continue to Increase?

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The article by Dalia Rotstein, Muhannad Mamdani and Paul O'Connor from St Michael's Hospital MS clinic published in this issue of the Canadian Journal of Neurological Sciences[1] is remarkable on two fronts: the finding that the use of Disease modifying drugs (DMD) in MS keeps growing and the fact that use of these drugs differs so much among the Provinces.

This is a retrospective cohort analysis study that examined changes of the rate and pattern of DMD prescription for MS and the subsequent changes in cost in the ten provinces of Canada from 2001 to 2007.

Based on CompuScript data coming from monitoring retail pharmacies over the entire country, Rotstein et al describe that prescriptions of the 4 DMDs used in MS (Beta-1a Interferon IM or Avonex®, Beta-1b Interferon or Betaseron®, Glatiramer Acetate or Copaxone® and Beta-1a Interferon S.Cu or Rebif®) increased by 50% over five years. Their cost jumped from 15 to 28 million dollars per year over that period. This occurred despite their limited efficacy, the frequency of the side effects and the fact that they are only available in an injectable form.

Indeed the DMDs are only very partially efficacious: they reduce relapse frequency by 30% or so, they retard the onset of the progressive phase but are not active on disability progression once the patient has reached the secondary progressive stage. They have numerous side effects which are not life-threatening but impact on quality of life: injection sites reactions, flue-like symptoms post injection. More rarely do they generate intractable headaches, blood cells maturation problems or liver enzyme increase. In fact these drugs have been remarkable for their absence of lethal complications[2]. A further draw back has been their route of administration as they are all injectable. Why do they keep being prescribed more and more out of proportion with a simple population effect?

Amazingly for such expensive medications, no stopping rules are in place in most provinces, in contrast guidelines have been introduced in Europe and Australia recommending to discontinue the medications in case of high levels of neutralizing antibodies - these are known to inhibit the drugs action. Further, efforts to delineate the possible benefits of the drugs have led to the extension of their indications to include first demyelinating episode, and even secondary progressive disease. One may wonder what will happen when new, more practical drugs will be allowed on the market.

Indeed we have now two medications which are more effective than the DMDs: Mitoxantrone or Novantrone® (not labeled for MS) and Natalizumab (or Tysabri®) Both reduce relapse rate more than DMDs; unfortunately they also exhibit rare but serious and possibly lethal side effects. Progressive Multifocal Leukoencephalopathy has been seen in 1/2000 patients treated with Tysabri® and leukemia in 1/1000 patient treated with Mitoxantrone. These complications will, probably, by the simple fact of their recognition, limit the use of these two drugs in MS. However further developments will appear when oral medications become available on the market and this time seems to get closer.

Fingolimod®, a once–a-day oral form just showed superior efficacy to Avonex®[3], and Cladribine®[4] showed marked benefit compared to Placebo. Both are oral medications and this could facilitate prescriptions. A distinct difference being that Cladribine can be taken as a once a year medication. It remains to be seen if the use of the DMD will be reduced, once these medications are approved and released to the market. This probably will depend on their cost. It should be noted that a third contender is still in phase III trials: Teriflunomide®. It appears that the safest way to curb the ascending cost of DMDs will be both to set stopping rules and to admit on the market oral drugs which are expected to be less expensive (if, and only if, they are less expensive). Still the frequency of their long term side effects is not clearly determined.

The second major contribution of this report to understanding the Canadian context is the unequal use of these DMDs among Provinces. According to their findings, the number of monthly doses sold per inhabitants in New Brunswick (9.9/1,000 inhabitants) is triple that in British Columbia (3.3). It is also high in Manitoba (9.0), Saskatchewan (7.3), and Quebec (7.0). It is lowest in Nova Scotia (2). The Canadian Health Act of 1984 and the Social Union Framework Agreement of 1999 enshrined the five principles to which Canada is committed: "comprehensiveness, universality, portability, public administration and accessibility"[5]. These findings of Rotstein et al[1] are obviously incompatible with three of these principles. The divergence comes probably from the fact that the different Provinces have set-up policies that differently restrict the prescription of those drugs. British Columbia, for example does not allow reimbursement of DMDs for initial demyelinating events, something that Quebec authorizes. Interestingly, the restrictions of prescription of drugs for heart failure are quite similar to the pattern recognized in Rotstein's paper[6]. Of note is that these Provincial differences are not seen in the prescription of sleep medication, indicating the weight of economic argument in the decision making of the politics[7]. Somehow it is difficult to admit that the reason for the indication to treat or not to treat a given patient with certain drugs is for at least 50% determined by economic factors.

As with other retrospective observational studies, there are limitations to this study. Data regarding changes in prevalence of MS over the years are very limited. This together with the fact that individual patients may have received multiple prescriptions made it impossible to calculate the percentage of MS patients who received DMD. It also rendered the calculations of the change of rate of drug prescription less accurate, although it is unlikely to have a major impact, since the 50% increase is way more than what is expected for the change in MS prevalence, the authors conclude.

This study is nevertheless very valuable for neurologists but also for health care system providers and planners alike. It casts some light on the possible mechanisms involved in shaping the pattern of prescription and attitude of the prescribing neurologists. This insight may prove helpful in further designing guidelines regarding whom to treat, when to treat, and what DMD to use. Furthermore, this study confirms the increasing financial burden of MS on the Canadian Health Care system, and would aid in further planning the allocation of resources. It also calls for the development of better medical plans for patients with MS.

Joel Oger, Mona AlKhawajah
Vancouver, British Columbia, Canada

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