Disease modifying therapies and infection risks in multiple sclerosis—a decision-making conundrum

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Multiple sclerosis (MS) is a chronic immune-mediated demyelinating and neurodegenerative disorder of the central nervous system (CNS), its natural history being commonly characterized by relapses, infrequently progressive from onset, resulting in irreversible cumulative neurological disability and impairment of quality of life. With the goals to reduce the number and severity of these clinical and radiological relapses and more recently to halt the disease activity in mind, numerous disease-modifying therapies (DMTs) have been developed over the last more than two decades. Since the approval of interferon-β-1b (IFNβ-1b) by FDA in 1993 for treatment of relapsing-remitting multiple sclerosis (RRMS), several other DMTs for MS have been introduced comprising of more injectables, oral drugs, and monoclonal antibodies (1). Although the pharmacological armamentarium for MS has expanded and is still growing, the concerns of potentially increased infection risks associated with these DMTs will inexorably be present given their immunosuppressive or immunomodulatory effects (2). These risks will need to be taken into account during risk-benefit assessment of MS therapies, in addition to other multiple factors.

As the old adage goes, prevention is better than cure. In this regard, risk mitigation strategies (RMS) play a significant role. To have RMS in place, we first need to recognize the presence of specific DMT related infections and potential risk factors for their development. These risk factors could include, but not limited to, patients' age,

gender, concurrent co-morbidities, prior treatment such as chemotherapy and other immunotherapies, and body mass index, etc. In this context, the required data can be pooled from randomized controlled trials (RCTs), post-marketing surveillance (PMS), and real world evidence (RWE). RCTs are conducted in rigidly controlled settings involving highly selective population defined by strict inclusion and exclusion criteria as well as short period of follow-up. Consequentially, findings from RCTs may not be representative that of the actual entire population and potentially miss informing treatment related infection risks. As such, PMS and RWE play vital parts especially in identifying infections, which are inherently chronic and indolent and may not be observed during the typically fixed period of RCTs.

Findings from the study by Luna G *et al.*, published recently in the October 2019 issue of *JAMA Neurology*, are thus timely and most welcome (3). Using the nationwide MS register, linked to national health care and census registries, they reviewed and compared the infection risks among Swedish patients with MS who were treated with IFNβ, glatiramer (GA), fingolimod, natalizumab, or rituximab as well as among the general population. Data on 8,600 treatment episodes were retrieved from 6,421 patients and mean total treatment duration of IFNβ and GA was identified as 2.1 years, 2.7 years for fingolimod, 2.5 years for natalizumab, and 2.0 years for rituximab. The authors concluded that patients with MS who were treated with rituximab had the highest risk of serious infection,

defined as any infection requiring hospitalization, while the lowest rates were observed in patients with IFNβ and GA. Natalizumab and fingolimod usage was not associated with significantly higher rates of infection compared to the injectables after adjusting for confounders. These findings were to some extent differed with that published by Wijnands JMA *et al.*, whose cohort study among 6,793 patients with MS showed that higher infection risk was associated with fingolimod, dimethyl fumarate (DMF), and especially natalizumab as compared to treatment with IFNβ and GA. No patients on rituximab were included in this study (4).

Nevertheless, the findings have provided useful information regarding the relative risks of infection among the studied DMTs via utilization of RWE and it would be interesting to identify the reasons or factors for the increased infection risk associated with one drug compared to another. For example, previous reports related to rheumatoid arthritis and other non-neurological autoimmune diseases have suggested increased risk of infection and mortality rates with hypogammaglobulinemia after rituximab therapy (5). In addition, one study reported that prolonged treatment with rituximab in patients with neuromyelitis optica spectrum disorder was associated with hypogammaglobulinemia and possibly with risk of infection (6). Similar observation in MS patients treated with rituximab and ocrelizumab are also emerging (7-9). Yet, an observational report on long term safety of rituximab in rheumatoid arthritis over a period of 11 years suggested that serious infection events remained stable pre-, during, or post-development of hypogammaglobulinemia (10). As such, could hypogammaglobulinemia still be a contributing factor for the higher infection risk observed with rituximab in this study? Given the vast availability of real-world data in this study, analyzing the patients' immunoglobulin levels and delineating its correlation with rituximab as well as the associated infection risk (for instance, the lowest limit of immunoglobulin level as threshold for increased infection risk and as indicator for administration of immunoglobulin replacement therapy) may hopefully provide some answers and go a long way toward establishing RMS. This is particularly relevant and pertinent as anti-CD20 B cell-depleting therapies are likely to be increasingly used as long-term treatment in patients with RRMS (ocrelizumab and rituximab) and primary progressive MS (ocrelizumab), given their demonstrated efficacy in recent pivotal trials and likely increased treatment adherence in view of their administration in single or short-intermittent courses (11-13).

Another data worth extracting from this study, if available,

and potentially contributing to more effective RMS would be lymphocyte counts. In a recent review of lymphopenia and DMTs in MS, the association between lymphopenia and opportunistic infections is not clear for most of the current DMTs (14). However, we are still concerned about the potential risk of infection conferred naturally by these immunosuppressive and immunomodulatory agents administered over time, especially in light of reports on DMF-associated prolonged lymphopenia and progressive multifocal leukoencephalopathy (PML) (15). Furthermore, observation from a retrospective review showed that nearly up to one-third of 41 fingolimod-treated patients with MS in Japan was found to have marked lymphopenia within a year of treatment (16). The role of lymphopenia in this context needs to be more well-defined given its implication in decision-making, especially when it influences the decision to cease treatment. For example, discontinuing fingolimod has been linked to the accounts of rebound worsening of disease (severely increased disability and presence of multiple new lesions on MRI) (17,18). Continuous monitoring of absolute lymphocyte counts from pre-commencement of therapy and beyond post-treatment hence should still be included in the RMS.

Future RMS may, not unexpectedly, incorporate genetic factors, in particular when prevalence of certain infections and their risk factors is plausibly associated with racial differences. An instance in mind concerns the reported findings of significantly higher seroprevalence of anti-John-Cunningham virus (JCV) antibodies and higher proportion of patients with elevated index among Asian (e.g., Japanese, Chinese, and Korean) patients with MS as compared to the Western cohorts (19-21). The exact reason for this apparent discrepancy is still not fully elucidated. Additionally, it appears that the prevalence of fingolimod-associated PML is significantly higher among the Japanese patients with MS (22). Further studies looking into the contribution of genetic factors in explaining these findings will be useful.

RWE such as those obtained in this study provides an opportunity to ascertain the role of increasing DMT dosages with cumulative infection risk over a long period of treatment exposure. The experience with natalizumab-related PML serves as a good example, with longer natalizumab therapy (especially >24 months) identified as a risk factor involved in development of PML, in addition to presence of serum anti-JCV antibodies and previous exposure to immunosuppressive agents (23). These findings subsequently led to establishment of extensive RMS for patients on natalizumab. In the same vein, RWE should

be continually looked into to enhance the detection of specific infections associated with specific DMT. While cryptococcal infections, varicella-zoster virus (VZV) related infection, and herpes simplex encephalitis (HSE) have been infrequently linked to fingolimod usage and only few patients on alemtuzumab have been found to develop listeriosis, tuberculosis (TB) (also observed particularly in patients treated with the anti-CD20 monoclonal antibodies), and *Pnuemocystis* pneumonia, it is still imperative for prescribing physicians to be aware of the possibility of these opportunistic infections arising from the specific DMTs. Targeted or specific screening for these infections can potentially result in cost-effective medical practice.

Comprehensive acquaintance with the specific treatment related infections, the extent of risk conferred by the specific drug to their development (reactivation in certain cases), and the potential risk factors for their occurrence, some of which have been discussed so far, facilitates preventative measures as part of the RMS. Appreciation of the epidemiology of infectious diseases where some infections are more prevalent in certain regions of the world would be essential e.g., screening for and treating latent TB infection prior to starting DMTs is especially suggested for patients residing in countries of high burden or high-risk populations. If required, infectious disease physicians are to be consulted. Practical guidelines on immunization of vaccine-preventable infections (influenza, hepatitis B, and VZV) have been made available recently. Vaccination should be considered during treatment discussion with patients and administered prior to initiation of DMTs, avoiding usage of live-attenuated vaccines while on DMTs and delaying them while patients are experiencing a relapse (24).

All in all, the efforts of Luna *et al.* in utilizing RWE in their analysis of infection risks related to different DMTs in patients with MS ought to be applauded. While questions remain regarding the roles of certain factors such as hypogammaglobulinemia, lymphopenia and perhaps even genetic predisposition in developing more specific infections with certain DMTs compared to others, future studies analyzing these and other specific factors via RWE are needed. Understanding these factors will hopefully gear us toward more effective RMS and optimize our decision making when it comes to benefit-risk ratio. Lest we forget, we shall first do no harm.

Footnote

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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