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Editorial

Emerging safety issues in alemtuzumab-treated MS patients

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Alemtuzumab is a very effective disease-modifying drug (DMD) for relapsing-remitting multiple sclerosis (RRMS).[1–3] Without the need of continued administration, its efficacy persists over many years. The use of the drug, however, has been limited by numerous adverse effects and even some potentially life-threating risks. Patients need to be stringently monitored during administration and for many years thereafter.

In this issue of *Multiple Sclerosis Journal*, Phelps et al.[4] report 16 well-documented alemtuzumab-associated nephropathies, among which are several cases of end-stage renal failure. Delayed diagnosis and inappropriate management increased the risk of losing renal function completely, emphasizing the need for stringent monitoring and early intervention. Importantly, all anti-glomerular basement membrane (anti-GBM) cases showed microscopic hematuria first. Microscopic hematuria, however, has low predictive value for anti-GBM disease as Phelps et al. discuss. Even though the incidence of autoimmune nephropathies is low (i.e. up to a maximum of 1 out of 300), the clinical consequences can be severe, thereby substantially contributing to the risk profile of the drug.

The rapidly expanding safety issues of this highly efficacious drug, in the context of the increasing number of highly effective alternative DMDs, is shifting the balance and makes alemtuzumab a less likely early treatment option to consider. It must be noted, however, that some of the alternative DMDs (e.g. ocrelizumab and cladribine) entered the market more recently and their long-term safety profiles have not yet had the time to take full shape. Importantly, the European Medicines Agency (EMA) recently announced a temporary measure while further reviewing the safety of alemtuzumab (article 20 procedure).[5] Alemtuzumab should only be started in adults with RRMS that is highly active despite treatment with at least two DMDs or where other DMDs cannot be used.[5] There will rarely be cases, however, where all other more effective DMDs will be contraindicated and alemtuzumab can still be used.

In addition to this restriction, EMA's safety committee (PRAC) has recommended an update of the product information in relation to cases of[5] (a) immune-mediated conditions, including autoimmune hepatitis and hemophagocytic lymphohistiocytosis;[6] (b) cardiovascular problems occurring within 1–3 days of receiving the medicine, including bleeding in the lungs, heart attack, stroke, and cervicocephalic arterial dissection;[7] and (c) severe neutropenia.[8,9]

The most frequently described autoimmune adverse events associated with alemtuzumab use include thyroid disease, of which Graves' disease is the commonest presentation. Thyroid autoimmune disease has been reported in more than 40% of multiple sclerosis (MS) patients after long-term follow-up, of whom the majority is relatively easy to manage, although chronic medication is often needed.[10] Apart from the nephropathies, other more serious autoimmune manifestations include immune thrombocytopenia. In addition, rare but serious alemtuzumab-related adverse effects are recognized and include hemolytic anemia, acute coronary syndrome, thrombotic microangiopathy, pneumonitis, hepatitis, encephalitis, meningitis, progressive multifocal leukoencephalopathy (PML), neutropenia, myasthenia gravis, Lambert–Eaton myasthenia, sarcoidosis, vitiligo, alopecia, diffuse alveolar hemorrhage, acquired hemophilia, myositis, and type 1 diabetes as recently summarized by Cree et al.[11] This long list of adverse effects occurred in little more than 22,000 alemtuzumab users worldwide.[11] In addition to the list of adverse effects described above, two cases of severely exacerbated central nervous system (CNS) inflammation after alemtuzumab in MS were reported.[12] Recovery after plasmapheresis and rituximab suggested a B-cell driven mechanism.[12] It was uncertain whether the observed disease activity was due to an MS exacerbation or the development of secondary CNS-directed autoimmunity.[12]

The miscellaneous assembly of alemtuzumab-associated adverse effects suggests that depletion of CD52 positive cells strongly alters immune tolerance. How alemtuzumab-induced lymphopenia leads to higher numbers of these potentially serious conditions in MS patients is incompletely understood. Secondary autoimmune disease may be generated by the pattern of T- and B-cell depletion and the swift re-population of immature B-cells. It has been proposed that regulating this B-cell subset "overshoot" may reduce the risk of secondary autoimmunity.[10,12,13] The reconstitution of T-cells may occur through thymopoiesis and proliferation of cells that have escaped depletion. An alternative explanation of the B-cell overshoot is that autoimmunity may be more likely when homeostatic proliferation predominates over thymic reconstitution.[10] However, additional work is definitely needed to further elucidate the cause of alemtuzumab-associated secondary autoimmunity, ideally leading to clinically useful tools of risk stratification before the start of treatment.[10]

Expanding alemtuzumab-associated autoimmune phenomena and other safety issues give rise to the debate as to whether EMA has taken a wise decision to initially approve the drug as a first line option in active MS (whereas the Food and Drug Administration (FDA) did not). Most autoimmune phenomena, however, are either rare or can be easily treated when recognized early. The recently acknowledged cardiovascular complications, including intracerebral hemorrhage during alemtuzumab administration,[7] may be of greater concern. A better understanding of hemodynamic alterations during and after alemtuzumab infusion is urgently warranted. Although these events seem to be rare, we will need to await the results of the EMA review process and to be very cautious in prescribing the drug in the meantime. Another crucial point is whether we should actively inform MS patients who received the drug already to discuss possible consequences of the update on safety issues and to increase their awareness, and help to motivate them to adhere to stringent monitoring.

Phelps and colleagues emphasize the importance of this close monitoring to avoid significant renal damage by identifying new cases early and of course all of us would agree. They conclude that their nephropathy report is important because treatment with alemtuzumab is expanding, having been judged to have a favorable benefit-risk profile in the majority of patients.[4] As long as we cannot clearly predict who will suffer from one of these diverse serious adverse effects and who will not, we believe—concerning the benefit-risk of alemtuzumab—the jury is still out.

Declaration of Conflicting Interests

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