Rare side effects of alemtuzumab remind us of the need for postmarketing surveillance

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Current therapeutics for multiple sclerosis (MS) include powerful agents targeting mediators of inflammation. Among them, the pan-lymphocyte–depleting anti-CD52 monoclonal antibody alemtuzumab is licensed to treat relapsing forms of MS on the basis of trial results demonstrating its efficacy compared to interferon β-1a and acceptable safety,1,2 despite the frequent occurrence (30%–35% of patients) of secondary autoimmunity. These clinical trials, alongside single-center, long-term follow-up cohorts3,4 have likely captured most of the major adverse effects in those patient groups. However, rare and late adverse events are often identified only during postmarketing surveillance.

Marketing authorization is typically paired with public authority-directed pharmacovigilance programs. For example, in the United States, the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is a database with information on adverse event reports submitted to the FDA. The database supports the FDA’s postmarketing safety surveillance program for drug and therapeutic biological products (open.fda.gov/data/faers/). In Europe, European Union law requires each marketing authorization holder, national competent authority, and the European Medicinal Agency to operate a pharmacovigilance system. In the United Kingdom (UK), the national authority MHRA (Medicines and Healthcare Products Regulatory Agency) runs the voluntary “Yellow Card” system, a database of adverse events, which provides interactive Drug Analysis Profiles for all licensed drugs (yellowcard.mhra.gov.uk/iDAP/). However, these pharmacosurveillance systems do not necessarily include mechanisms to alert clinicians of rare adverse events. Therefore, pharmacosurveillance programs need to interconnect with effective communication strategies.

Hence, publication of newly recognized adverse events in medical journals is valuable. In this issue of Neurology®, Croteau and federal regulatory colleagues5 reviewed the FAERS database and report 8 cases of acute acalculous cholecystitis (AAC) in patients with MS treated with alemtuzumab. The FAERS data include the previously published cases reported in Germany.6 Seven of the 8 patients developed AAC during or shortly after alemtuzumab treatment, and the authors speculate that the underlying mechanism may be similar to infusion-associated reactions mediated by a systemic inflammatory response. The German contribution to the FAERS highlights the value of integrating global surveillance efforts. There are likely more cases outside of United States and Germany, and better integration would expand our understanding of rare events such as AAC. Although surveillance programs can identify rare events, they have limited ability to identify the frequency of these events. Despite certain underreporting of the event and only estimated utilization of the therapy, the authors estimate the frequency of AAC at approximately 0.2%, which is similar to that observed in controlled clinical studies. It is of interest that Croteau et al.5 note that, because of the low frequency of AAC (alemtuzumab 2/919 and control 0/496) and uncertain causal association, initial product labeling for alemtuzumab for relapsing-remitting multiple sclerosis (Lemtrada; Genzyme Corp., Cambridge, MA) did not include AAC. However, AAC can be a life-threatening condition, and, in light of the 6 additional postmarketing cases, the FDA product label for alemtuzumab for relapsing-remitting multiple sclerosis (Lemtrada) was modified in October 2017 to include AAC in Warnings and
Precautions (Lemtrada Label. Available at: accessdata.fda.gov/drugsatfda_docs/label/2017/103948s5188lbl.pdf).

Saarela et al. report 2 cases of hemophagocytic lymphohistiocytosis (HLH) in patients with MS after alemtuzumab treatment. HLH following alemtuzumab treatment for leukemia has been previously reported, but it has not been associated with MS. In contrast to the early post-alemtuzumab treatment occurrence of AAC, presentation of HLH was delayed and similar to the time of development of secondary autoimmunity. The authors speculate that secondary autoimmunity could be the underlying mechanism, but this needs further study. Alternatively, HLH can lead to liver failure and has been previously associated with AAC due to endothelial damage possibly caused by a cytokine storm. Indeed, 1 of the 2 patients died of fulminant hepatic encephalopathy and coagulopathy, and autopsy showed mild AAC.

In this issue of Neurology, Ferraro et al. report a young, otherwise healthy woman with MS who developed cardiac ischemia midway through an alemtuzumab infusion. The close temporal association of the adverse event with the infusion suggested “probable” causation. The mechanism remains speculative, although the authors hypothesize that alemtuzumab may increase endothelial and myocyte membrane permeability and vasodilation via a cytokine-release syndrome, which in turn could lead to supply/demand ischemia of the myocardium (“type 2” myocardial ischemia). The need for preinfusion ECG is currently unknown, but routine and rigorous monitoring of vital signs, and vigilance regarding potential cardiac events during and immediately following alemtuzumab, seems prudent.

In other reports from postmarketing experience, the potential importance of uncommon infectious complications is emerging. Particularly prominent is listeriosis, especially meningitis, with a crudely estimated prevalence (with the same postmarketing caveats outlined above) of 0.26%. Listeria appears within days of alemtuzumab treatment, making it amenable to antibiotic prophylaxis—particularly given the limitations of dietary exclusion advice. Preventive sulfamethoxazole-trimethoprim treatment is now advocated in the UK.

These cases highlight the challenges of balancing high efficacy with potentially fatal complications with MS therapies. Alemtuzumab is an effective drug and the risks should be fully understood and considered by patients and clinicians. Finally, we applaud regulatory representatives contributing reports to the medical literature. Everyone who recognizes rare or delayed adverse events that may be related to medications is encouraged to publish their experience. A better understanding of the risks will be important in guiding clinicians and patients to make informed treatment decisions that balance the benefits and risks of novel medications.

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**References**

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