LETTER TO THE EDITOR

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Author response to comment on: Alopecia in multiple sclerosis patients treated with disease modifying therapies

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Dear Editor

We thank Goischke for the valuable comments, interest and discussions of alopecia, multiple sclerosis, vitamin D, and alemtuzumab. The correspondence entitled "Alemtuzumab-Induced Secondary Autoimmune Diseases in Multiple Sclerosis Therapy –Target of Vitamin D Supplementation?" provides insights into a possible risk mitigation strategy for immune mediated alopecia.[1]

Vitamin D's role in autoimmunity is certainly a topic of great scientific interest. The role of vitamin D insufficiency, mainly in childhood, is heavily studied as a risk factor for developing multiple sclerosis (MS).[2] Several mechanisms have been proposed, including the interaction with other risk factors, such as Epstein Barr Virus (EBV) infection.[2,3] In contrast, the role of vitamin D in MS progression and relapses is controversial. Several studies have failed to show favorable effects of vitamin D supplementation on MS progression or relapse reduction while others suggested a possible inverse association with MS disability.[4,5] However, many of these studies are classified as "low evidence" studies due to limitations in study design, including short study durations, small sample sizes, insensitive assessment tools, and poor control for confounding factors. However, an association between lower seasonally adjusted, serum vitamin D and higher disability was detected when a study with a longer follow-up duration (10 years) was pursued.[6]

The association between vitamin D and the immune system is indisputable. Several lines of evidence support the benefits of vitamin D to the health of the immune system, and many lines of evidence support the notion that vitamin D insufficiency is a major risk factor for autoimmune diseases, including MS.[2,7]

Alemtuzumab is an antiCD52 monoclonal antibody that received FDA approval to treat relapsing forms of MS in November of 2014.[8] Alemtuzumab is considered a highly effective treatment for relapsing MS, but because of its safety profile, it is generally reserved for patients who failed two or more disease-modifying therapies.[8] One of the major safety concerns with alemtuzumab is the development of secondary autoimmunity. Examples may include alopecia and other autoimmune disorders, some of which are potentially fatal such as thyroid disease (e.g., Graves' disease), immune cytopenia, and anti-glomerular basement membrane disease.[8] In the correspondence letter, Goischke suggests and advocates for vitamin D supplementation as a risk mitigation strategy for alemtuzumab-induced autoimmunity.[1] The theoretical concept is of interest, but supporting evidence is lacking from clinical studies. However, does the absence of evidence equal evidence of absence? In one prospective study, investigators failed to observe an association between vitamin D insufficiency and alemtuzumab-induced autoimmunity.[9] The authors found that the female sex was the only associated risk factor with alemtuzumab-induced autoimmunity in their cohort.[9] Apart from anecdotes, no other studies to our knowledge specifically examined this potential association. While there are no clinical studies that proved the role of vitamin D supplementation in preventing secondary autoimmunity in alemtuzumab-treated MS patients, we agree with Goischke that vitamin D supplementation is generally safe and accessible to patients. Also, we advocate for vitamin D supplementation in general for people with MS including those treated with alemtuzumab.

Another area of interest but scarce research is the approach of administering rituximab or other B cell depleting agents in close timing following alemtuzumab infusion to prevent secondary autoimmunity. In a small pilot study, the investigators administered low doses of rituximab when B cell percentage recovered to 40-50% of baseline following alemtuzumab treatment.[10] A total of 10 patients were studied, and none developed secondary autoimmunity.[10] However, a single-arm study with small sample size is insufficient to provide evidence to guide clinical practice. The rationale was based on the

immune dynamics of the B cells following depletion by an antiCD52 agent, where a rebound (overshoot) of B cells was observed and correlated with developing secondary autoimmunity following alemtuzumab treatment.

Finally, we agree with Goischke that mitigation strategies for alemtuzumab-induced secondary autoimmunity are lacking, and further studies of high dose vitamin D supplementation or subsequent B cell depleting agent administration are needed. Alemtuzumab is considered a highly effective agent for treating relapsing forms of MS, and its use is limited by safety concerns, primarily the potential for developing secondary autoimmunity. Effective and proven risk mitigation strategies are needed, and we share Goischke's comment on calling for further research and implementation of relatively safe potential strategies.

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