Anti-TNF-α therapy itself does not trigger Guillain-Barré syndrome

Sirs,

We read with interest the article recently published by Manganelli *et al*. suggesting that Guillain-Barré syndrome (GBS) developed following monoclonal antibody treatment with the anti-tumour necrosis factor alpha (TNF-α) drug, Adalimumab (1). Over the past decade there have been a number of similar reports suggesting a possible association between TNF-α antagonists and the development of GBS. Given what is already know about the pathogenesis of GBS, we believe that inhibition of TNF-α does not cause GBS directly, but rather increases susceptibility to known infectious triggers.

In two-thirds of patients with GBS, a history of upper respiratory tract infection or diarrhea is observed 3 days to 6 weeks before the onset of limb weakness (2). In 30% of cases *Campylobacter jejuni* is identified as the infectious agent, although other microbial infections including; cytomegalovirus, Epstein-Barr virus, varicella-zoster virus and *Mycloplasma pneumoniae* also have well defined relationships with GBS. Direct causation has only been proven with respect to *C. jejuni*. Molecular mimicry between bacterial lipo-oligosaccharides and human nerve gangliosides results in the production of autoantibodies to peripheral nerves and the development of GBS. Median time interval between onset of diarrhoea secondary to infection with *C. jejuni* and development of GBS is approximately 10 days (3). The immunogenetic cascade leading to demyelination in GBS therefore advances over days, not months.

In the largest retrospective case series to date (4), information on timing was available in 11 of 15 patients and revealed that median interval between initial administration of anti-TNF-α therapy and GBS onset was 4 months, whereas in this case the time interval was over 5-years. Monoclonal antibodies against TNF-α have a rapid mechanism of action and a half-life, which can be measured in days. If time course is considered, direct involvement of Adalimumab or any other anti-TNF-α drug in the pathogenesis of autoantibody production in GBS therefore remains improbable. The authors do however correctly infer that an upper respiratory tract infection triggered GBS.

The association between anti-TNF-α therapy and increased susceptibility to infectious triggers of GBS therefore warrants discussion. Shin *et al*. noted that antecedent infections had occurred in 6 out of 15 cases and that all were characterised by upper respiratory tract symptoms (4). Inhibition of TNF-α, which plays an important role in the innate and adaptive immune responses against infection, has inevitable consequences, including the reactivation and dissemination of latent viruses (5) and increased risk of microbial infections (6). The second most commonly observed infection in GBS, after *C. jejuni*, is cytomegalovirus, which has been identified in up to 10% of cases (2). Life-long asymptomatic cytomegalovirus infection occurs in 40–90% of healthy humans, although reactivation can occur during periods of immunosuppression (7) and is frequently encountered in patients with collagen vascular diseases receiving intensive immunosuppressive treatment. In one large multicenter survey of 7377 patients with collagen vascular diseases, cytomegalovirus infection was noted in 151 and was more prevalent in patients receiving immunotherapy (8).

The postulated mechanism, noted by the authors, as an atypical immune response due to anti-TNF-α therapy is unlikely to be unique, in that development of GBS is well described in the presence of several systemic diseases associated with profound immune dysregulation, including; sarcoidosis, Hodgkin's lymphoma and human immunodeficiency syndrome (9). Development of GBS in immunocompromised patients and those receiving immunosuppressive therapies, including anti-TNF-α therapy, complicated by clinical or subclinical infections, is therefore predictable and the most robust mechanism in this case.

B.R. WAKERLEY, *PhD, MRCP*
N. YUKI, *MD, PhD*

Department of Medicine, National University Hospital, Singapore.

Address correspondence to:
Prof. Nobuhiro Yuki, Department of Medicine, National University of Singapore, Unit 09-01, Centre for Translational Medicine, 14 Medical Drive, Singapore 117599.
E-mail: mdcyuki@nus.edu.sg

This study was supported by the National Medical Research Council (IRG 10nov086 to N.Y.) in Singapore.

Competing interests: none declared.

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