Letters to the Editor

Giant Cell Arteritis: Multiple Pathogenic Mechanisms and Potential Treatments

We read with interest the excellent article "Giant cell arteritis" by Smith and Swanson.[1] The authors note several factors that have putative roles in the pathogenesis of giant cell arteritis (GCA). In this regard, we would like to mention an additional point. Recently, several cases of polymyalgia rheumatica/GCA occurring in patients who received ipilimumab were reported.[2,3] Ipilimumab is an immunomodulating agent approved for the treatment of metastatic melanoma. This drug works by inhibiting cytotoxic T-lymphocyte antigen 4 (CTLA4) expressed on the surface of activated T cells and, by blocking CTLA4, ipilimumab disinhibits T cells and potentiates immune responses. As a result of the upregulation of the immune system, numerous immune-mediated adverse events have been reported including enterocolitis, dermatitis, hepatitis, hypophysitis, and polymyalgia rheumatica/GCA.[2-4] Thus, there should be a lower threshold for suspecting polymyalgia rheumatica and GCA in patients with compatible symptoms, if they have previously been treated with ipilimumab. In this respect, ipilimumab appears to be unique because no other drug has clearly been implicated as an inciting trigger in the development of polymyalgia rheumatica/GCA. The publication of these cases is important because they represent a stimulus for the study of pathogenic mechanisms and potential treatments. It would be interesting to evaluate ipilimumab in experimental models and assess whether this immunomodulatory agent can induce GCA. This would allow an improved experimental model to better understand certain aspects of the pathogenesis and to test the effectiveness of different drugs. In this context, abatacept is included in the list of potential drugs. Abatacept is a fusion protein that consists of the extracellular domain of CTLA4 and the Fc portion of immunoglobulin G 1. CTLA4-Ig binds cluster of differentiation (CD)80 (B7-1) and CD86 (B7-2) on antigen presenting cells, thereby acting as a competitive inhibitor of the CD28-B7 costimulatory interaction, and it prevents the second activation signal received by T cells via CD28. Currently, a clinical trial on the effectiveness of this drug in treating GCA and Takayasu's arteritis is underway (ClinicalTrials.gov Identifier: NCT00556439).

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Medication Overuse Headache: Inaccurate and Overdiagnosed

The article "Medication Overuse Headache"[1] is an excellent review. However, the entity "medication overuse headache" (MOH), as defined in the article, is misleading and inaccurate. Current diagnostic criteria for MOH only require abortive medication use on 10 or 15 days/month (depending upon the drug).[2] What is not needed is any evidence that the abortive actually causes an increase in headache. Medication overuse (MO) often occurs among people with frequent headaches. However, MO does not

necessarily lead to increased headache. Diagnosing MOH is not an easy task. MOH diagnosis must require an individualized assessment of the patient's medication and headache history. The epidemiologic studies of MOH are not valid, as they do not differentiate MO from MOH.

A number of years ago, all abortives, including nonsteroidal anti-inflammatories (NSAIDs), were implicated in MOH. We now realize that certain drugs (NSAIDs and triptans) are less likely to cause MOH than others. Opioids and butalbital compounds are the worst offenders. Although simple NSAIDs usually do not contribute to MOH, they continue to be included in the MOH criteria.

Patients often are given the label of MOH simply because they admit to regularly consuming over-the-counter analgesics or a triptan. Many patients who frequently use these medications do not suffer from MOH. There are a number of variables, including genetics, age, type of drug, and so on, that help to explain why one patient suffers from MOH, whereas the next patient does not.

For many patients with frequent headaches, behavioral techniques and preventive medications (including Botox) are inadequate. Our current preventives often provide little relief and frequently cause unacceptable side effects. We do not have any preventives that were initially developed for headache. One long-term study indicated that only about half of migraineurs found any preventive helpful for longer than 6 months.[3,4] Declining efficacy and increased side effects often lead to discontinuation of the preventive. Many physicians are quick to blame the patient for causing MOH. The patients are told that they are suffering from MOH because of a particular medication, even though (1) they have only been taking that drug for a short time, (2) the headaches did not increase once they began the medication, or (3) drug withdrawal did not lead to a lessening of the headaches.

Physicians often instruct the patient to only use the abortive 2 days/week. The patient usually responds, "that is fine, but what do I do the other 5 days? I have to function." Many headache specialists and neurologists maintain a rigid posture, refusing to allow more than a bare minimum of abortive medication. The patient either suffers or drifts elsewhere.

Much of what is written about MO and MOH is confusing, with little basis in fact. These are arbitrary terms without scientific validation. Of course we must try to minimize abortives. Patients on frequent abortive medication should be withdrawn for a period of time, which is easier said than done. However, many refractory patients would have zero quality of life without their (frequently used) abortives.

The current criteria conflates MO with MOH. As a result, MOH is wildly overdiagnosed. An inaccurate label of MOH may harm the patient. Patients with the MOH diagnosis often are denied the only medication that is helpful. We could redefine MOH using scientifically validated criteria. Alternatively, we could drop the term MOH altogether.

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