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Letter to the editor

Giant cell arteritis – can we decrease its relapsing course with less toxic therapy?

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We read with great interest the excellent review article "Giant cell arteritis-a changing entity" by Kesten et al. [1]. As the authors note, glucocorticoids are still the mainstay of therapy in patients with giant cell arteritis (CGA). However, relapses often occur during corticosteroid tapering and adverse effects are frequent, especially in the elderly population. At present, methotrexate is used as a corticosteroid-sparing drug, which is not devoid of toxicity. Thus, an effective and safe corticosteroid-sparing drug would be desirable. As Kesten and colleagues [1] mention, at least two distinct CD4+ T-cell subsets, namely Th17 and Th1 cells, promote vascular inflammation in GCA. Th17 cells are explicitly corticosteroid-sensitive. However, Th1 cells are corticosteroid-resistant and abnormal Th1 responses continue, unaffected by corticosteroids, identifying GCA as a long-term, chronic immune-mediated disease. Interferon-γ is the signature cytokine produced by the Th1 cell lineage. Weyand et al. [2] observed that temporal artery biopsies obtained from patients with biopsy-proven GCA who experienced ischaemic complications expressed high amounts of IFN-γ messenger RNA. Thus, at present, the major therapeutic challenge in controlling GCA disease activity lies in persistent Th1 responses. We wonder whether with certain strategies that could be easily applied, it could change the course of this relapsing disease . Several studies have shown that pentoxifylline potently suppresses production of IL-12 in a concentration-dependent manner [3] and this methylxanthine derivative might have a role in immunological disorders characterised by inappropriate type-1 immune responses [4]. On the other hand, patients with giant cell arteritis are treated with calcium, vitamin D and, if indicated based on DEXA examination, with bisphosphonate for prevention of osteoporosis. Vitamin D3 and D2, produced by photo-synthesis in the skin or ingested, are transported to the liver and metabolised to 25-hydroxyvitamin D, the major circulating form. Further hydroxylation occurs in the kidney to form the highly biologically active 1,25-dihydroxyvitamin D. In contrast to the abundant availability of hepatic 25-hydroxylase, the renal capacity for 1- alfa-hydroxylation is limited. Already with a creatinine clearance of less than 65 ml/min it is significantly reduced [5]. Impairment of renal function is very frequent in the elderly and may be overlooked because normal serum creatinine levels in most patients. D-hormone preparations, as alfacalcidol, possess immunoregulatory effects in vitro and in vivo by inhibiting the cytokines IL-1, IL-6, TNF-alpha and particularly IL-12. At the cellular level, D-hormone reduces the expression of Th1 helper cells directly or indirectly by inhibition of IL-12 from monocytes [6]. Zold et al. [7] investigated the effects of alfacalcidol to modify the regulatory T cell functions in patients with undifferentiated connective disease and found that alfacalcidol could decrease the elevated levels of IFN-γ. Considering the results of these studies, we believe that it would be of interest to study whether pentoxifylline [8] and alfacalcidol, well-known and relatively non-toxic drugs, might have a role as adjuvant therapy for patients with GCA. Finally, studies in human temporal artery-mouse chimeras have shown that the transplanted vasculitis requires glucocorticoid doses up 4–40 times higher than those used as standard treatment for GCA in human patients [9]. Mazlumzadeh et al. [10] evaluated the initial use of intravenous methylprednisolone (1 g/d for 3 consecutive days) followed by prednisone in an attempt to decrease the glucocorticoid requirement. A higher proportion of patients achieved a daily dose of prednisone less than or equal to 5 mg/d by week 36, a significantly lower median daily prednisone dose at week 78, and a higher percentage of patients in sustained remission after the discontinuation of prednisone. The cumulative dose of prednisone was lower in the patients treated with methylprednisolone if the initial 3 g loading dose was excluded. To our knowledge, this protocol has not been studied in larger patient series.

To some extent, this study demonstrates that glucocorticoids, as methylprednisolone pulses, would be the best steroid-sparing agent. We believe it would also be interesting to assess the possibility of treating relapses with a short course of methylprednisolone in high doses (for example, 500 mg to 1 g for 2 or 3 days), maintaining the same dose of prednisone oral that the patient had at the time of relapse.

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