Letters to the Editor

Comment on: Sarcoid-like granulomatosis in patients treated with tumour necrosis factor blockers: 10 cases: reply

Sr, We appreciated the comments by Massara et al. [1] about our article [2] in a recent issue of this Journal. The two cases reported by Massara et al. [1] confirm that sarcoid-like granulomatosis can occur in patients treated for either RA or SpAs, at any time (the delays ranging from 1 to 67 months in the cases published thus far). In the literature, including those cases, 12 patients were treated with mAbs (seven with infliximab, five with adalimumab) and 17 with soluble receptor format, showing that the occurrence of granulomatosis is directly dependent on TNF blocker therapy, regardless of the type of drug. The cytokinin changes induced by the treatments seem to prevail upon the anti-granulomatous effect of the mAbs during granuloma formation.

Massara et al. [1] speculated that granulomas could be due to an allergic type hypersensitive lung injury. Granulomas can be induced by either a Th1 or a Th2 response. For example, mycobacterial and schistosomal antigens can induce granulomas in mice, after a type 1 and a type 2 reaction, respectively [3]. It is not known whether TNF blockers promote a Th1 or a Th2 response in the lungs. Some authors found an enhancement of Th2 cytokines (IL-10) in peripheral blood after TNF blockers [4]. Conversely, several reports showed an enhancement of Th1 response after treatment [5–6]. It was also found in CIA models that an increase in lymph nodes and a decrease in joints of Th1 cells [7] occurred. Moreover, anti-TNF drugs have been suggested for treatment of severe asthma [8] and atopic eczema [9], although evidence of their efficiency in those diseases is lacking. In order to know whether sarcoid-like granulomatosis is due to a Th1 or Th2 response, cytokines and cells should be measured in blood and bronchoalveolar fluid in patients with granulomas before and after the anti-TNF discontinuation.

Massara et al. [1] report two cases for 600 patients treated with anti-TNF drugs, which represents an incidence of at least 0.3% over ~9 years of follow-up. Thus, this condition has certainly been under-diagnosed up to now and we think it should be known by rheumatologists.

Disclosure statement: The authors have declared no conflicts of interest.

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Accepted 7 January 2010

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Letters to the Editor

Comment on: An analysis of MRI and ultrasound imaging in patients with gout who have normal plain radiographs

Sir, We read with interest the article by Carter et al. [1] on the use of MRI and ultrasound (US) in patients with gout and normal radiographs. Several findings reported in the article contradict our clinical experience as well as previous literature, and we would like to raise a few concerns.

With regard to their US methods, the authors report only a use of colour Doppler US to assess their index joints. While colour Doppler is an important tool for assessment of inflammation in rheumatic conditions, the primary and secondary end-points in this study did not include US assessment of inflammation. Optimal Doppler sonography and grey scale imaging have conflicting requirements, and therefore US was unnecessarily handicapped. As they note, transducer frequency (8 MHz) may have further obscured the true potential of US. While such a transducer frequency was standard in musculoskeletal US 10–20 years ago [2], transducer frequencies of 10–18 MHz are now recommended for assessment of hands or feet [3]. The authors report that they assessed first MTP joints. They show one (grey scale) image that they describe as an MTP joint with an erosion at the metatarsal head, which is labelled ‘2nd TARS MED’. Since a stand-off pad is apparently used, one wonders how a medial view of a second metatarsal head could be obtained.

With regard to the detection of erosions, Carter et al. [1] report that while 56% of index joints demonstrated erosions by MRI, an erosion was found by US in only 4% of the index joints. In our experience, and in recent literature, around two-thirds of the patients with clinical gout will demonstrate erosions on US, even when radiographic erosions were absent [4, 5]. While MRI was not investigated in the aforementioned studies, RA may be a valid comparator for assessing the detection of erosions. In a recent study of RA, MRI and US demonstrated similar sensitivities for the detection of erosion (using quantitative CT as a gold standard), when joints easily accessible to the transducer were evaluated [6].

The methodological concerns noted above may have contributed to the paucity of erosions visualized with US, but this is not likely to completely explain the discrepancy. In particular, we would like to know if the static images of the MTP joints reviewed by the radiologists included a complete assessment of the medial metatarsal head, where most erosions (and tophi) are found [4, 5]. Also, we would like to know whether the technician or radiologist obtaining the static scans is well versed in using US to assess gout.

With regard to soft tissue signs of gout, Carter et al. [1] report that neither modality appeared beneficial in this study. In our experience and in the literature, changes of gout such as the double-contour sign or tophi are seen in the majority of joints affected when using US. Although the authors did not attempt to visualize double-contour findings, they did look for tophi with both MRI and US. In the two previously mentioned studies of US and gout, 50% [4] and 100% [5] of clinically involved joints demonstrated tophi using US. MRI and US have not truly been compared for evaluating gout in the literature, but a study attempting to measure tophi using both techniques found that US identified 90% of MRI-identified tophi (missing apparently those outside of acoustic windows), whereas MRI only identified 81% of US-identified tophi (apparently missing the smallest tophi) [7]. In our experience as well, US is at least as sensitive in detecting tophi as MRI, and may identify clear evidence of gout when MRI cannot [8, 9].

Given that the majority of clinically affected joints have demonstrable tophi in previous papers using advanced imaging, how do the authors account for their finding only one tophus with US and none with MRI? Disease severity and duration are unlikely explanations for the lack of imaged tophi in the current study, as studies suggest that around one-third of even clinically unaffected joints of patients with gout or asymptomatic hyperuricaemia will have demonstrable tophi by US [4, 10]. Also, the authors note that the average number of gout attacks in the index joint was 6.2 and the average duration of disease was 6.8 years, suggesting that the patients had fairly chronic gout. Previously noted methodological concerns may play a role, but we would like to know what criteria were used to define synovitis and tophus using both MRI and US. In particular, it is not clear how they determined the difference between synovial hypertrophy and tophi. Also, it is not clear whether outcome measures in rheumatology (OMERACT) or other criteria were used to define sonographic synovitis.

In sum, we think that the report by Carter et al. [1] is a valuable contribution, particularly with respect to the

References
