Dr. Mattey, *et al* reply

To the Editor:

Harty and Veale have confirmed our finding of higher tender joint counts and overall DAS scores in ever-smokers compared with never-smokers in patients with RA receiving anti-TNF therapy[1]. However, in contrast to our findings, they also suggest that ever-smokers have marginally higher mean swollen joint counts than never-smokers at both 3 and 12 months. Unfortunately, they do not show the standard deviations and p values, so it is difficult to assess the variability and significance of the data. In fact our own data suggested that the median swollen joint count was marginally higher in ever-smokers than never-smokers after 3 months on anti-TNF therapy, although the difference did not achieve significance (4.5 vs 4.0, respectively; $p = 0.2$). It is therefore quite likely that there is a small difference in swollen joint counts between ever-smokers and never-smokers receiving anti-TNF, but because of the small size of the effect and the variability in the data a large number of patients is needed to show a significant difference.

It would have been interesting for Harty and Veale to have shown the other components of the DAS, such as erythrocyte sedimentation rate (ESR) and patient global assessment (PGA), as well as the VAS pain score in their analysis. In line with the swollen joint count we found a marginally higher median ESR in ever-smokers than never-smokers after 3 months of anti-TNF therapy, but again the difference did not achieve significance (32.0 vs 27.0 mm/h, respectively; $p = 0.09$). The data are suggestive of a possible increased level of inflammation in the smokers. However, the variable showing by far the biggest difference between ever-smokers and never-smokers at 3 months was the PGA (38.0 vs 23.0; $p = 0.0004$). This variable also showed the strongest correlation with the VAS pain score in our patients (Spearman $r_s = 0.76$, $p < 0.0001$). The correlations of VAS pain with ESR and swollen joint count were much lower ($r_s = 0.29$, $p = 0.0002$, and $r_s = 0.24$, $p = 0.002$, respectively).

We agree with Harty and Veale that important questions remain with regard to the relationship between smoking and pain perception. A lower pain threshold in smokers may appear paradoxical given the analgesic nature of nicotine, but as pointed out this is only one of thousands of chemical constituents in tobacco smoke. It is also important to distinguish between immediate, short-term and cumulative, longterm effects of smoking. It is of particular note that after 3 months of anti-TNF therapy the ex-smokers among our patients had significantly higher VAS pain scores than never-smokers (45.0 vs 22.5, respectively; $p = 0.0006$). This suggests that the increased pain perception in this group is possibly linked to longterm damage associated with previous smoking, which may include general, and possibly irreversible, damage to musculoskeletal and neurological tissue through vasoconstriction, hypoxia, etc. Further, indirect evidence of a link between pain and cumulative smoking-related damage is provided by the smaller improvement in VAS pain score after 3 months' treatment in those patients with the highest number of pack-years.

The absence of a relationship between smoking and erosive disease is less clear than suggested by Harty and Veale. There is evidence from cross-sectional studies that smoking is associated with longterm erosive damage[2-5], although some longitudinal studies failed to find an association[6,7]. However, the longitudinal studies have been carried out mainly in patients with earlier disease. It is therefore not clear whether the differences are due to the design of the studies or differences in the effects of smoking on radiographic outcome in early and in well established RA. The data of Wolfe[3] indicated a nonlinear relationship, with no effect of smoking for smoking durations of 0–20 years, but a curvilinear effect thereafter, in which longer duration of smoking was associated with increased radiographic damage. Differences in the longterm response of smokers and nonsmokers to DMARD and (more recently) biologic therapies might partly explain differences in the results from studies on relatively early and late disease. However, further work is needed to investigate whether smoking is associated with a worse response to therapy in general, and what impact that might have on disease progression.

Although the association of smoking with erosive disease is still contentious, there is good evidence that smoking is associated with measures of more severe RA (nodules, rheumatoid factor, anti-cyclic citrullinated peptide antibody). Thus, although many patients may consider smoking cigarettes to offer respite from their suffering, the current evidence suggests otherwise. We are therefore in total agreement that advice on smoking cessation should be given to patients with RA in the interest of their general health and sense of well-being, as well as their rheumatoid disease.

DEREK L. MATTEY, PhD, Staffordshire Rheumatology Centre, University Hospital of North Staffordshire, Institute of Science and Technology in Medicine, Keele University; ANN BROWNFIELD, MSc; PETER T. DAWES, FRCP, Staffordshire Rheumatology Centre, University Hospital of North Staffordshire. Staffordshire, UK. Address correspondence to Dr. D.L. Mattey, Staffordshire Rheumatology Centre, Haywood Hospital, High Lane, Burslem, Stoke-on-Trent, Staffordshire, England, ST6 7AG. E-mail: Derek.Mattey@uhns.nhs.uk

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