Letters to the Editor

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Do TNF-blockers reduce or induce uveitis?

Sir, Uveitis is a well-known manifestation of SpAs that may lead to functional impairment. TNF-blockers are effective for treating SpA-related uveitis flares [1], but recent retrospective studies support the possibility of differential TNF-blockers effectiveness, with infliximab or adalimumab showing a higher efficacy than etanercept in the treatment of uveitis [2–4]. In addition, Lim et al. [5] have recently published the finding that etanercept may induce new uveitis flares. During the last 2 years, we have conducted a study with the objective of investigating the impact of TNF-blockers on the appearance of new flares of uveitis in patients with SpAs who exhibit uveitis flares before beginning therapy for the rheumatic disease.

All clinical records of patients with SpAs with a previous acute anterior uveitis who received treatment with TNF-blockers in our department after January 1999 were reviewed. After the study began in October 2005, all data from new uveitis flares in patients with SpAs treated with TNF-blockers were registered prospectively in our database. Flares data were calculated by exposure time and compared both before and after the commence ment of therapy by a repeated measurements analysis of variance. The quantitative and qualitative variables were compared between groups with the Mann–Whitney U-test and Fisher’s exact test, respectively.

Out of 150 patients with SpAs on TNF-blockers therapy, 19 (12.7%) had uveitis flares prior to starting the treatment. Of these, 11 (58%) were women, 18 (94.7%) had HLA-B27, 10 were on etanercept and nine patients were on infliximab. One patient was switched from etanercept to infliximab because of the recurrence of uveitis and was analysed in both groups.

The types of SpAs were: 15 AS, two undifferentiated SpAs and two PsA. The patterns of uveitis were: 13 recurrent acute unilateral, five recurrent acute bilateral and one chronic bilateral. The mean age at the first flare of uveitis and at the diagnosis of the SpA was 38.15 ± 10.43 and 35.20 ± 11.5 yrs, respectively. The mean age at the onset of TNF-blockers therapy was 48.25 ± 11.1 yrs and the mean duration of the SpA at this time was 13.22 ± 10.18 yrs. The mean duration of the TNF-blockers treatment was 2.98 ± 1.7 yrs. The demographic characteristics of the different groups of treatment were comparable (data not shown).

The number of uveitis flares per patient in the exposure time before starting TNF-blockers was 0.61 ± 0.3 and 0.52 ± 0.4/yr for the infliximab and etanercept groups, respectively. These values changed to 0.05 ± 0.16 and 0.82 ± 0.99, respectively, during the therapy. We have not observed any uveitis flares in our patients treated with adalimumab since this drug was approved for SpAs in our country after starting this study. The incidence of uveitis in the infliximab group was 61.73 cases per 100 patient-years before treatment, and this number decreased to 2.64 after starting the therapy. In the etanercept group, the incidence changed from 34.29 before treatment to 60 cases per 100 patient-years after starting the therapy. This evolution of the uveitis flares was found to be significantly different between both groups (P = 0.041, Fig. 1).

Only one out of 10 patients developed a new uveitis flare during infliximab treatment. Six of the 10 patients on etanercept had new uveitis flares during the treatment.

Some studies seem to support the possibility of a differential effectiveness of etanercept, adalimumab and infliximab in the treatment of uveitis in favour of both mAbs [2, 6], and other studies suggest a poor effect of etanercept in treating uveitis [7, 8]. In addition, a review of patients with ocular inflammatory disease treated with etanercept found that 17 patients developed uveitis, scleritis and orbital myositis [9]. For this reason, an interesting question is whether etanercept would induce uveitis flares like others drugs such as bisphosphonates. With the intention to clarify this point, clinical trials in patients with AS treated with TNF-blockers or a placebo were reviewed in two articles [1, 10]. These studies showed a higher reduction of uveitis flares in patients treated with infliximab. Etanercept did not increase the number of uveitis cases with respect to placebo groups in the trials, and therefore, appears at least not to increase uveitis. In a recently published registry-based study [5], however, the communication of uveitis cases as an adverse effect associated with etanercept was significantly higher than with infliximab and adalimumab. The odds ratios of 5.375 (P < 0.001) and 8.6 (P < 0.01), respectively, suggest that etanercept can induce uveitis flares. Our findings may support this conclusion; furthermore, our data were collected prospectively, which strengthens our results. Other previous studies that have tried to address these questions either retrieved retrospective data [5, 6, 9] or collected data of AS patients with no specific previous episodes of uveitis [1, 10].

In conclusion, patients exhibiting SpAs show a greater improvement in the frequency of uveitis flares after treatment with infliximab than etanercept. The potential role of etanercept in causing uveitis flares requires further study.

**Rheumatology key message**

- Patients exhibiting SpAs show a greater improvement in the frequency of uveitis flares after treatment with infliximab than etanercept.

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Letters to the Editor

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Gout and nodal osteoarthritis: a case–control study

Sir, The characteristic pattern of joint involvement seen in gout has been attributed to the readiness of MSU crystals to form in osteoarthritic joints [1, 2]. In a recent community-based study, we found that joints that had been sites of acute attacks of gout are frequently also affected by OA [3] suggesting that OA predisposes to local MSU crystal deposition at individual joint sites. However, it is also possible that a general cartilage defect, such as may occur in nodal OA, increases the risk of developing gout. Using the same group of gout sufferers and a separate control group recruited from the same population, we undertook a case–control study to examine this possibility. Approval was gained from Nottingham Local Research Ethics Committee 2.

As reported previously [3, 4], a questionnaire survey was sent to all adults over 30 yrs of age registered with two general practices in Nottingham. Standard demographic information and details of gout were requested. Self-reported nodal OA [5], hallux valgus (HV) [6], knee [7] and big toe pain on most days for at least a month within the last year, joint replacement, diuretic use and previously diagnosed OA, RA or AS were assessed. The primary risk factor of interest was self-reported Heberden’s and Bouchard’s nodes (recognized central clinical markers of nodal OA): nodal OA was defined as the presence of nodes on at least two rays on each hand [8]. Subjects reporting a diagnosis of gout or acute attacks typical of crystal synovitis were invited to attend a clinical assessment where the diagnosis was confirmed on clinical grounds. A sample size of 326 cases and 1304 controls was required to detect an odds ratio (OR) of 1.4 for nodal OA between cases and controls (power 0.85, significance 0.05, cases: controls 1:4). Gout cases confirmed at the clinical assessment were each matched to four controls for age (£2yrs), gender and practice. Crude OR and 95% CI were calculated between gout and manifestations of OA. ORs (95% CI) were then adjusted for BMI (£30 kg/m2 or >30 kg/m2) and diuretic use using a conditional logistic regression model.

Four thousand two hundred and forty-nine completed questionnaire responses were received (adjusted response rate 32%). One hundred and sixty-four cases of gout were confirmed at clinical assessment. Characteristics of the cases have been reported previously [3, 4]. Mean ages of cases and controls were 63.4 yrs (s.d. 11.2) and 63.5 yrs (11.3), respectively. Both groups were predominantly male (81% both groups). Thirty-nine cases (24%) and 86 controls (13%) were obese (BMI >30 kg/m2) and 23 cases (14%) and 23 controls (4%) had taken diuretics prior to the age at which each index case experienced their first attack of gout. On univariate analysis, gout was associated with knee pain, HV and big toe pain but not nodal OA (Table 1). After adjustment for BMI and diuretic use, significant associations remained between gout and knee pain (OR 2.05; 95% CI 1.37, 3.06), HV (OR 2.10; 95% CI 1.39, 3.18) and big toe pain (OR 2.94; 95% CI 1.62, 5.34).

Although it may appear that this study is similar to our previous report [3], there are key methodological differences which provide interesting insights into the pathogenesis of gout. Participation in our previous analysis was limited to gout sufferers, the analysis comparing the presence of OA between joints which had and had not been the site of an acute attack of gout, and found a very strong association between sites of acute gout and the presence of OA. In the current patient-based case–control study, we compared self-reported manifestations of OA between gout cases and controls, with a particular focus on whether nodal OA is more common in gout sufferers than controls, and hence may be a risk factor for the development of gout. We were unable to find evidence of such an association although the study was significantly under-powered and therefore may be liable to a type II error. A further caveat is that the instruments used to assess self-reported OA have not been specifically validated in a gout population. The association of knee pain, HV and big toe pain with gout supports the hypothesis that OA at individual sites may predispose to MSU crystal deposition at that site as suggested by previous studies [3, 9]. These associations could equally reflect chronic joint damage from gout rather than OA. However, in our previous study [3], the association between gout and OA at individual joint sites was not influenced by the chronicity of gout, refuting this hypothesis. Further prospective radiographic clarification of this issue is not possible without a large prospective study.

Table 1. Crude and adjusted OR (95% CI) between gout cases and controls

<table>
<thead>
<tr>
<th>Case Groups</th>
<th>Controls</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodal OA (%)</td>
<td>12 (7)</td>
<td>38 (6)</td>
<td>1.28 (0.66, 2.52)</td>
<td>1.29 (0.64, 2.61)</td>
</tr>
<tr>
<td>Knee pain (%)</td>
<td>61 (37)</td>
<td>137 (21)</td>
<td>2.34 (1.59, 3.44)</td>
<td>2.05 (1.37, 3.06)</td>
</tr>
<tr>
<td>HV (%)</td>
<td>63 (41)</td>
<td>161 (25)</td>
<td>1.94 (1.31, 2.85)</td>
<td>2.10 (1.39, 3.18)</td>
</tr>
<tr>
<td>Big toe pain (%)</td>
<td>26 (16)</td>
<td>40 (6)</td>
<td>3.11 (1.78, 5.43)</td>
<td>2.94 (1.62, 5.34)</td>
</tr>
<tr>
<td>Knee replacement (%)</td>
<td>9 (1)</td>
<td>18 (3)</td>
<td>1.74 (0.54, 5.85)</td>
<td>1.78 (0.51, 6.16)</td>
</tr>
<tr>
<td>Hip replacement (%)</td>
<td>2 (1)</td>
<td>18 (3)</td>
<td>0.42 (0.10, 1.85)</td>
<td>0.35 (0.07, 1.65)</td>
</tr>
<tr>
<td>OA* (%)</td>
<td>29 (18)</td>
<td>111 (17)</td>
<td>1.05 (0.66, 1.67)</td>
<td>0.98 (0.60, 1.61)</td>
</tr>
</tbody>
</table>

*Adjusted for BMI and prior diuretic use. \( \times \) Self-reported OA or joint replacement in absence of RA or AS.

164) Controls (n=656)