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Reply: Re: Layton et al. Comparison of the incidence rates of selected gastrointestinal events reported for patients prescribed rofecoxib and meloxicam in general practice in England using prescription-event monitoring data

Sir, Thank you for providing us with an opportunity to respond to recent communications sent to your journal about our studies [1,2]. We thank the authors for their support in the importance of providing evidence on the safety of new drugs in real prescribing settings. However, we feel that we need to respond to some of the points that they have included in their letter.

First, we agree that the unadjusted estimates of time to event were not statistically different for rofecoxib compared with meloxicam, or for celecoxib compared with meloxicam, as stated in the first publication of this series of retrospective studies. We did not provide annualized incidence rates in these manuscripts although the respondents have attempted to calculate such values. We would like to take the opportunity to point out that the incidence rate reported in both of these papers reflects the first event within each event group and not all events for each subject. Thus one should be careful about making such extrapolations. As indicated in the second paper which compares celecoxib with meloxicam, because of the similar nature of these retrospective comparisons one needs to refer to the first paper published in this series for a complete picture of the design and methodology of the study as well as the limitations which are described in full in the discussion [1].

With regard to the reported ‘difficulties’ with following our statistical analysis, our choices of risk factors were derived from those variables for which data were collected systematically from the prescription-event monitoring (PEM) studies of each drug and which had been originally identified as important risk factors possibly associated with the phenomenon of ‘channelling’ of patients with higher baseline risk of gastrointestinal (GI) events onto such new non-steroidal anti-inflammatory drugs (NSAIDs). Thus, information on these pre-specified potential confounding variables (history of upper GI problems and NSAIDS prescribed within 3 months of starting treatment) were obtained by a systematic approach to data collection from the additional questions included on the green form questionnaires for the rofecoxib, celecoxib and meloxicam PEM studies [3–5]. As highlighted in both papers in question, we also examined the answers to the additional questions requesting information on use of concomitant gastro-protective or gastro-irritant drugs, but subsequently found that we could not adjust for these variables because of the low response rate for these specific questions. The inclusion of each variable was then based on basic epidemiological methodological principles, where the relationship between each of these potential confounders with either the exposure or the outcome was assessed using univariate analysis (as described in full in the first paper). Those that satisfied the criteria as confounding variables were selected for inclusion in the regression model, as well as age and sex. The variable age squared was subsequently identified as being important since a non-linear relationship between age and event group was observed (as reported in the first paper). No other covariates were selected a priori for screening, although we did acknowledge the existence of other important confounders in the discussion.

We feel that the respondents have misinterpreted our sensitivity analysis. We first fitted an unadjusted model based on all 34 355 cases and then fitted an unadjusted model based on reduced cases excluding those cases with missing values for the adjusting
variables only (n = 24012), i.e. not all missing values for all variables, as stated in their letter. This gives an unadjusted analysis based on the same dataset as the final adjusted model estimating the relative rate. The unadjusted ‘reduced case’ model found no significant difference in the event group rate between the two drugs, whereas the adjusted model did. In both papers we only reported the sensitivity analysis where the final adjusted model predicting relative risk of the event found a significant difference, to show that our findings were not purely down to a reduction in cases due to missing values for the adjusting variables.

With regard to missing values, PEM attempts to minimize the effect of such bias in that all GP prescribers in England are invited to provide any information related to health that they have available to them from the medical records of patients who have been identified systematically according to the first prescription issued and dispensed to each individual patient for that new study drug. We believe that there is no evidence that selection bias exists in the inclusion of cases included in the final adjusted model based on non-random sample of missing variables.

The Drug Safety Research Unit (DSRU) is an independent charity which works in association with the University of Portsmouth. It receives unconditional donations from pharmaceutical companies. The companies have no control on the conduct or the publication of the studies conducted by the DSRU. The Unit has received such funds from some of the manufacturers of the products included in this article. Professor Shakir has received support from Pfizer to attend scientific conferences.

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Disease measures in evaluating the effect of anti-TNF therapy and predicting clinical outcome

Sir, We read with great interest the recent review by Scott et al. [1] concerning the routine use of tender and swollen joint counts in clinical practice and the regular assessment of rheumatoid inflammation. The recent introduction of biological agents has created substantial interest in methods to assess the effectiveness of therapy because of their unique properties, such as quick response rates after institution of therapy. However, rheumatologists face the paradigm of how to best evaluate disease activity in clinical setting. It has not yet been established which disease activity measures are ideal for use in the clinical setting.

At our hospital rheumatology clinic, the medical charts of 21 patients with either rheumatoid arthritis (n = 17) or psoriatic arthritis (n = 4), who had been recently begun tumour necrosis factor (TNF) inhibitor therapy, were reviewed over a 4-week period in order to evaluate how disease activity measurements correlated in assessing the response to anti-TNF therapy. Data collected at each visit prior to and following initiation of TNF therapy included tender and swollen joint scores, erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP), Health Assessment Questionnaire (HAQ) (0–3), pain [10-cm visual analogue scale (VAS)], duration of morning stiffness, fatigue (10-cm VAS) and global disease severity (10-cm VAS). At baseline the mean HAQ score was 1.07, and the mean Disease Activity Score (DAS28) was 5.03.

Despite efforts to obtain complete data sets, a DAS28 could not be calculated both prior to and post treatment for 4 patients (19%), typically because of missing laboratory values. Of the 13 RA patients for whom pre- and post-treatment DAS28 scores were calculated, 9 were DAS responders (5 good and 4 moderate). Looking at the 4 DAS 28 non-responders, there was marked heterogeneity among other individual outcome measures (Table 1). Of note, among 3 of 4 DAS28 non-responders, there was typically substantial improvement in other measures. Among the DAS28 good responders, HAQ and fatigue score showed the highest heterogeneity (Table 2).

Overall, looking at data from all patients, the pain score and the duration of morning stiffness seemed to be most markedly affected by anti-TNF therapy. In 7 cases (33.3%), there was a 100% improvement in duration of morning stiffness, and there was a greater than 80% improvement in pain scores in 6 cases (30%). Interestingly, fatigue was the parameter that has improved the least and, fatigue scores generally did not correlate with other measures. For example, one patient had a 6.25% worsening in his fatigue score while improving 80% in his pain score. Global assessment seemed to correlate more with pain scores than other measures, although there were disparities. One patient

Table 1. Changes in individual disease activity measures in DAS28 non-responders to TNF blocking agents. The numbers in parenthesis show the percentage change from baseline

<table>
<thead>
<tr>
<th>DAS28</th>
<th>HAQ (0–3)</th>
<th>Pain (0–10 cm VAS)</th>
<th>Fatigue (0–10 cm VAS)</th>
<th>Morning stiffness (h)</th>
<th>Global assessment (0–10 cm VAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.11–3.93</td>
<td>0.6–0.1 (83%)</td>
<td>4.7–1.9 (53%)</td>
<td>5.9–3.6 (39%)</td>
<td>0.75–0.5 (33%)</td>
<td>5.4–3.6 (33%)</td>
</tr>
<tr>
<td>4.80–5.34</td>
<td>1.1–1.1 (0%)</td>
<td>6.3–5.1 (19%)</td>
<td>6.7–8.0 (19%)</td>
<td>0.5–0.3 (33%)</td>
<td>5.1–7.2 (41%)</td>
</tr>
<tr>
<td>8.45–6.46</td>
<td>1.4–0.8 (43%)</td>
<td>8.5–2.2 (74%)</td>
<td>8.0–1.4 (83%)</td>
<td>5.0–2.0 (60%)</td>
<td>8.0–4.0 (50%)</td>
</tr>
<tr>
<td>7.29–5.53</td>
<td>1.7–1.0 (41%)</td>
<td>7.0–1.9 (73%)</td>
<td>7.2–1.1 (85%)</td>
<td>3.5–0.5 (86%)</td>
<td>6.2–1.0 (84%)</td>
</tr>
</tbody>
</table>