Shortening infusion times for infliximab administration

Sir, Infliximab is generally administered over 2 h with further 2 h of monitoring, making its management expensive, with major utilization of hospital resources. The risk of infusion reactions remains a concern. This study’s aims (in accordance with our local ethics committee guidelines) were to determine: (i) the frequency of reactions and their relation to concomitant therapy; (ii) when reactions occurred; (iii) the consequences of infusion events; (iv) the incidence of adverse events in the monitoring period; and (v) the possibility of shortening infusion times incrementally. This study was performed in accordance with the guidelines of our local ethics committee, which has approved the recording and reporting of safety and clinical data of patients on biological therapies; specific patient consent was not required.

As part of this units’ protocol, the first four infliximab infusions [3 mg/kg in rheumatoid arthritis (RA) and 5 mg/kg in seronegative spondyloarthropathy] are administered over 2 h and patients are monitored for a further 2 h. If tolerated, infusions 5–10 are given over 1 h with 1 h post-infusion monitoring; the 11th and subsequent infusions are administered over half an hour with half an hour of monitoring. Infusion reactions are described as acute (during the infusion) or delayed (after completion of infusion and post-infusion observation). Severe reactions constitute a drop in systolic blood pressure (SBP) to ≤80 mmHg with or without bronchospasm and with or without rash, warranting cessation of the infusion. Cessation is usually managed by stopping the infusion and administering intravenous (i.v.) hydrocortisone 100 mg, i.v. chlorpheniramine 10 mg and, if indicated, nebulized salbutamol 2.5–5 mg. Mild reactions are defined as SBP falling below baseline but remaining above 80 mmHg with or without nausea and with or without other non-specific symptoms (e.g. headache) that clinically justify only a temporary stop of the infusion. The infusion is stopped for 30 min and restarted with i.v. hydrocortisone and chlorpheniramine administered as above. Subsequent infusions in this mild reaction group are premedicated with i.v. hydrocortisone 100 mg stat and chlorpheniramine 10 mg stat indefinitely.

From December 1999 to December 2003, a total of 2166 infusions have been administered (2–28 infusions/person) to a total of 234 patients (age 22–77, 164 female, 70 male). Two hundred and eight were being treated for RA [161 on concomitant methotrexate (MTX) 7.5–25 mg weekly, and 47 on leflunomide 10 or 20 mg daily]. Twenty patients with ankylosing spondylitis (AS) and six with psoriatic arthritis (PsA) were on concomitant MTX.

Fifteen of the RA patients had been on the ATTRACT study [1]; all flared on completing the study (mean time to flare 13.5–20 weeks for the four dosage regimens of the study) [2] and were re-established on infliximab, including the initial loading dose. Findings are summarized in Table 1.

Of the 234 patients who received infliximab at the usual rate of 2 h, 6% (n = 13) ceased treatment due to a severe infusion reaction (all between infusions 2 and 4). Of these 13, 62% (n = 8) patients were in the RA/leflunomide group (19% of this group) and 38% (n = 5) patients were in the RA/MTX group (3% of this group; included one anaphylactic and one delayed reaction). Application of the χ² test with (Yates’) continuity correction determined this to be a significant difference between patients on leflunomide and those on MTX (P = 0.002). No patients in the AS or PsA group developed a severe reaction. The total number of infusions administered to the 234 patients over 2 h was 845; reactions therefore occurred in 1.5% of all 2 h infusions.

Six per cent (n = 11) of patients who received infliximab at the usual rate over 2 h suffered a mild, acute reaction. Of these 11, 46% (n = 5) were in the RA/MTX group (3% of this group) and 27% (n = 3) in the RA/leflunomide group (6% of this group), 36% (n = 4) were in the AS group (20% of this group) and 18% (n = 2) in the PsA group (33% of this group) (no significant difference). This constituted 1.3% of all 2 h infusions. All patients continued with premedication for subsequent infusions and were able to follow the protocol of reduced infusion duration.

Of the 221 patients who had completed the first four infusions, 171 went on to receive further infusions at a rate of 1 h. One patient (0.6%) (RA/leflunomide group) suffered a serious acute infusion reaction (total of 796 infusions administered over 1 h; reaction in 0.1% of all 1 h infusions). Two patients (1.2%) (RA/leflunomide group) suffered a mild, acute reaction (0.2% of all 1 h infusions) and continued with premedication (no significant difference).

Eighty-nine patients received infusions 5–10 over 1 h and progressed to half-hour infusions. No infusion reactions were observed during these infusions (total of 525 infusions over half an hour).

Of the 15 patients reinfused with infliximab following completion of the ATTRACT study, none sustained an infusion reaction. Outcome with regard to efficacy was comparable, as has been described previously [2].

Of all the severe reactions observed, none warranted intra-muscular adrenaline or hospitalization. No patients sustaining severe reactions received further infliximab.

No differences in disease characteristics or serology were associated with the development of an infusion reaction. It may be relevant to note, however, that a separate study by Bingham et al. [3] assessing the efficacy and tolerability of infliximab and leflunomide revealed a higher rate of induction of ANA and double-stranded DNA antibodies (although this was observed in the response group as opposed to the toxicity group, possibly due to a longer time on therapy for this former group).

Our experience of infliximab administration is comparable to that of other large centres and studies [1, 4, 5] and confirms the

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general tolerability of infusions. Furthermore, it demonstrates the possibility of shortening infusion times incrementally.

In this retrospective survey, 6% of patients (0.7% of all 2166 infusions) ceased treatment due to a severe reaction. Notably, 93% of the severe reactions occurred during infusions 2-4 and, strikingly, 64% of patients were on concomitant leflunomide therapy. Overall, for the 2166 infusions, only 1.2% resulted in either a severe or mild infusion reaction; most (89%) were during the first four infusions (none during half-hour infusions). Our approach of shortening infusion times is similar to the more limited experience outlined in a brief letter by van Vollenhoven et al. (440 infusions to 113 patients) [5].

We conclude that (i) administration of infliximab with concomitant leflunomide in patients with RA confers a significantly increased incidence of infusion-related reactions, (ii) greatest care should be taken during the first four infusions, (iii) infusion reactions are rarely associated with hospitalization and further sequelae, (iv) the monitoring period may not be necessary, (v) our incremental shortened infusion time does not seem to compromise safety if initial infusions are tolerated, and (vi) stopping and restarting infliximab (albeit in a small subgroup of patients) does not seem to confer greater toxicity risks, suggesting careful reintroduction of infliximab can be justified.

The authors have declared no conflicts of interest.

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Use of vitamin D supplements and vitamin D status in patients taking bisphosphonate drugs

Sir, Bisphosphonate drugs are widely used to treat and prevent osteoporosis. Following recent guidance from the National Institute for Clinical Excellence (NICE) on secondary fracture prevention [1], it is likely that bisphosphonate use will increase, particularly in older women. In the case of etidronate, the benefit of treatment may be attenuated by concomitant vitamin D deficiency [2]. In trials demonstrating fracture reduction with modern bisphosphonates, such as risedronate and alendronate, it was ensured that subjects were replete in calcium and vitamin D, so the effects of concomitant vitamin D deficiency are unknown. In order to replicate the results of these studies in practice, we should ensure that patients receiving bisphosphonates are replete in calcium and vitamin D.

Low vitamin D levels are common in people over the age of 65 yr without apparent risk factors for vitamin D deficiency [3]. High rates of vitamin D deficiency have been reported in women receiving treatment for osteoporosis: 52% of women with a mean age of 71 yr [4] and 17% of early postmenopausal women, mean age 56 yr [5]. Vitamin D deficiency is even more common in high-risk groups, such as falls patients (of whom 72% are deficient) [6], elderly hip fracture patients (80% deficient) [7] and middle-aged medical in-patients (57% deficient) [8]. Many of these patients will receive bisphosphonates for the treatment or prevention of osteoporosis.

It is our impression that vitamin D status is not being ascertained and supplements are not being appropriately given to patients receiving bisphosphonate drugs.

The aim of this study was to: (i) assess the proportion of people taking bisphosphonate drugs who are coprescribed a vitamin D supplement; and (ii) measure vitamin D levels and determine the prevalence of vitamin D deficiency in those people who take bisphosphonates without a vitamin D supplement. The study was approved by the research ethics committees of North Bristol NHS Trust and the primary care trusts.

Recruitment took place in two settings, primary care and secondary care, as we wanted to enrich the sample for subjects with comorbidity. It was anticipated that the clinical profile, demographic characteristics and therefore, vitamin D levels, would differ between the two groups so data were analysed separately for each group. No subject appeared in both groups, although some of the subjects recruited from primary care were attending hospital clinics elsewhere. Patients were recruited consecutively over 12 months in secondary care and 2 yr in primary care to minimize effects due to seasonal variation. A power calculation determined that a sample size of 100 vitamin D measurements in each population would provide an estimate of the true prevalence of vitamin D deficiency of 20% (95% confidence interval 11–29%) in primary care subjects and 50% (95% confidence interval 40–60%) in secondary care subjects.

General practices identified patients receiving prescriptions for bisphosphonate drugs using computerized records. Hospital in-patients taking bisphosphonates were identified by ward pharmacists during their daily drug chart reviews. A small number of subjects attending respiratory and rheumatology out-patient clinics were included in the secondary care sample.

Age, gender, indication for treatment, medications and duration of treatment were recorded. Subjects who were not taking vitamin D supplements were invited to give a blood sample for vitamin D levels. All subjects gave written informed consent according to the Declaration of Helsinki. Exclusion criteria were subjects who took bisphosphonate drugs for the treatment of malignancy or Paget’s disease, those aged under 20 and those who could not consent.

Serum 25-hydroxyvitamin D was measured (since this is the major circulating form and provides an integrated assessment of both intake and stores) using a radioimmunoassay (Diasorin 25-hydroxyvitamin D; Diasorin, Stillwater MN, USA). Vitamin D deficiency was defined as a level <30 nmol/l and vitamin D insufficiency as a level <50 nmol/l [9].