Intra-articular infliximab in DMARD-resistant knee monoarthritis: clinical and ultrasound responses

Aim: Intra-articular (ia.) injection of steroid and systemic DMARD therapy are standard treatments for inflammatory knee monoarthritis. Reports suggest that ia. infliximab (INF) may be beneficial in refractory cases. We aimed to investigate the optimum use of this therapy. **Materials & methods:** A total of 14 patients with knee monoarthritis, despite DMARD and NSAID treatment, were treated with up to three ia. injections of INF. Clinical and ultrasound measures were recorded for up to 1 year. The primary response was an improvement in composite knee score by at least two points within 12 weeks and deemed clinically useful if maintained for more than 8 weeks. Pretreatment with ia. methylprednisolone was utilized in some cases, to try to prolong duration of response to INF. **Results:** All patients responded to the first INF injection and 11 (78.6%) achieved a clinically useful response. Three out of 14 remained in remission at 1 year, 11 of the 14 relapsed and were retreated. Of these, all achieved the primary response, 70% a clinically useful response and one remained in remission at 1 year. A total of 90% relapsed and seven received a third INF injection. Of these, 86% achieved the primary response, 50% a clinically useful response and all seven relapsed. A total of 11 ia. INF injections were preceded by methylprednisolone, but this did not improve duration of response. Ultrasound measures mirrored clinical scores in most patients and preceded clinical signs of relapse overall in 37% (synovial thickness) and 18.5% (power Doppler) by a median of 2–4 weeks. **Conclusion:** Repeated ia. INF appears to be an effective treatment in DMARD-resistant knee monoarthritis and remission up to 1 year was achieved in 29% of patients.

KEYWORDS: infliximab ■ psoriatic arthritis ■ spondyloarthropathy ■ ultrasonography

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Inflammatory monoarthritis of the knee is a condition that predominantly affects young men, who are usually rheumatoid factor negative and otherwise well. It is considered to be an undifferentiated variant of the seronegative spondyloarthropathies (SpA), although in some cases neither psoriasis, colitis, axial nor other manifestations of peripheral arthropathy ever develop.

Management is often difficult as repeated aspiration and administration of intra-articular (ia.) corticosteroid typically leads to short-term benefit, with re-accumulating knee effusion, swelling and disability recurring within a few weeks. Chemical (osmic acid), radiation (yttrium) or surgical synovectomy may lead to prolonged benefit but are invasive and potentially harmful. In many cases the disease escapes control and ultimately relapses. In such circumstances an alternative therapeutic approach is systemic immune suppression with DMARDs. These may be beneficial, but the patient (and physician) is often reluctant to take potentially toxic agents for the sake of one inflamed joint. Invariably the rheumatologist is faced with a young patient with disabling and painful synovitis of the knee, which has not responded in the long term to a variety of ia. or systemic therapies. In such cases there is a reluctance to perform knee arthroplasty (on the basis of a lack of cartilage damage and young age) but nevertheless quality of life is poor and ultimately knee damage and secondary osteoarthritis are likely to occur.

A role for TNF-α has been established in the pathogenesis of the seronegative SpA [1,2] and treatment with anti-TNF-α agents has led to dramatic clinical responses with respect to axial and peripheral joint manifestations [3–6]. With the exception of an increased incidence of opportunistic infections, these agents appear to have a favorable toxicity profile. However, in the UK current NICE treatment guidelines do not permit their use for monoarthritis [101]. There are increasing reports of the efficacy of ia. administration of anti-TNF-α therapies for rheumatoid arthritis (RA), undifferentiated SpA and psoriatic arthritis (PsA) [7–14]. This is an attractive option as it delivers therapy locally rather than systemically to the inflamed joint, thereby minimizing the total anti-TNF-α dose given, cost and possibly toxicity. Whilst these reports support the efficacy of the use of ia. anti-TNF-α, they do not provide long-term efficacy data from which to develop treatment protocols and ultimately assess cost–effectiveness.

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This prospective observational cohort study assesses the clinical, ultrasound (US) and serological response over 1 year to repeated ia. infliximab (INF), with and without preceding ia. corticosteroid, given to DMARD-treated patients with inflammatory monoarthritis of the knee. US has been utilized because it provides information relating to synovial thickness, and power Doppler (PD) sonography in the knee has been shown to be sensitive to changes following ia. steroid treatment in RA and SpA [15–17].

Materials & methods

Inclusion & exclusion criteria

Patients were recruited with symptomatic inflammatory knee monoarthritis, including undifferentiated SpA, psoriatic, enteropathic, juvenile and rheumatoid arthritis, despite concomitant treatment with DMARDs such as sulphsalazine (SSZ) and methotrexate, for at least 2 months, with no dose change within this time. Patients were excluded if they were unable to tolerate DMARD therapy or within the preceding 3 months had received systemic or ia. anti-TNF-α or any other ia. knee therapy or procedure.

The study was approved by the Charing Cross Research Ethics Committee and written informed consent was obtained from all patients. The study was registered with the EU Clinical Trials database, EUDRACT Number 2006-001448-29. The British Society for Rheumatology guidelines for detecting and treating active or latent tuberculosis prior to anti-TNF-α therapy were followed [102].

Clinical assessment

A clinical composite knee score (CKS) [18] was calculated (score: 0–6) for the affected knee (Table 1). A lower extremity function questionnaire (score: 0–80) [19] and pain visual analog scores (VAS: 0–10 cm) for walking slowly on the flat and either up or down stairs were also recorded.

US assessment

Ultrasound assessment of the knee was performed by experienced musculoskeletal radiologists (James Pilcher and Christine Heron) using a Philips HDI 5000 (Philips Medical Systems Andover, MA, USA) with a L12–5 MHz transducer. For each examination the depth and focal zones were adjusted to maximize visualization of the joint capsule and synovium. For the PD studies, the Doppler settings were optimized to 'low flow', with a medium wall filter (to minimize flash artefact) and a pulse repetition frequency of 700 Hz. The color gain was adjusted to just below the noise floor and remained at this level throughout the scanning protocol. Each knee was scanned in extension, with an anterior approach in both longitudinal section (LS) and transverse section (TS). Using a modified technique to that described by Rubaltelli *et al.*, five regions of the knee joint were assessed for maximum synovial thickness, appearance and PD activity [20]. A midline longitudinal image through the suprapatellar pouch was used to measure effusion depth in milimeters in addition to the parameters mentioned above. The medial and lateral suprapatella recess was then identified by scanning in TS and LS both medially and laterally to the initial midline position. Finally, the medial and lateral parapatellar recesses were scanned in TS, using the vertical border of the patella as an anatomical landmark. The worst area of synovial thickening, as determined by the operator, was measured in each of the five areas, and a mean score calculated. Grayscale synovial appearance was categorized as flat (score 1), heaped (score 2) or villous (score 3) and the mean score from these five areas was calculated. PD appearances were scored subjectively (0–3) in each of the five areas (0 = no flow seen; 1 = flow seen in <25% of synovium; 2 = flow seen in <50% of synovium; and 3 = flow seen in >50%) and an overall mean score calculated. A subjective overall global PD score (0–3) was also recorded.

The first ten examinations in the study were carried out by the two operators together to ensure agreement in their technique, after which scans were performed by only one of the operators. Although no formal measure of interobserver agreement was performed in this study, the approach was similar to that described by Karim *et al.*, who demonstrated good interobsever agreement between two independent operators [21]. Examples of the different categories of synovial appearance are presented in Figure 1.

Treatment protocol

Clinical and US assessments of the affected knee and serum full blood count, erythrocyte sedimentation rate and C-reactive protein, were measured at baseline. Immediately following this the knee was aspirated to dryness from a medial or lateral subpatellar approach, using an aseptic technique and then injected through the same needle with 100 mg INF reconstituted in 10 ml water for injection. If no joint aspirate was present the INF was injected with US guidance. The patient was provided with crutches to

enable them to be non-weight bearing through the injected knee for 24 h after the procedure. Stable therapy with DMARD, oral corticosteroid and anti-inflammatory drugs (NSAIDs) was continued. Clinical and US assessments of knee synovitis and serum acute-phase markers were repeated at 2, 4, 8 and 12 weeks and thereafter 8-weekly for 1 year.

The primary outcome measure of response was an improvement in CKS by at least two points from baseline within 12 weeks of INF injection. A clinically useful response was defined as suppression of CKS by at least two points from baseline, without return to baseline for more than 8 weeks. A second or third injection of INF was offered to patients who had achieved the primary outcome measure of response but then demonstrated clinical relapse, defined as a return in CKS to baseline or higher no sooner than 8 weeks after the preceding ia. INF injection. Second and third INF injections followed the same protocol as the baseline INF injection with the exception that on some occasions patients were pretreated with 80-mg ia. methylprednisolone (Depo-Medrone®; Pharmacia) into the same knee 1 week prior to ia. INF. Patients were permitted a maximum of three INF injections following the same response and relapse criteria. No further injections of INF were permitted if clinical relapse occurred less than 8 weeks after the preceding INF injection.

Statistical analyses

Data were analyzed using Graph Pad Prism software version 4.03 (GraphPad Software, San Diego, CA, USA). Significance was defined as a p-value less than 0.05.

Results

Clinical characteristics

A total of 14 patients (eight male, six female) with inflammatory knee monoarthritis were recruited. All had failed to respond to at least one DMARD and a median of five ia. steroid injections. Demographic, diagnosis and treatment characteristics are shown in Table 2. In those patients classified as having an oligoarthritis, the treated knee was the only symptomatic joint at enrollment into the study. All 14 patients received the first i.a INF injection, followed by a second INF injection in 11 and a third INF injection in seven patients. US guidance was required for eight INF injections, most usually when the knee had been aspirated and injected with Depo-Medrone a week earlier. All patients were treated according to protocol, except one, in whom a subsequent INF injection was given despite clinical relapse occurring at less than 8 weeks following primary response to the preceding INF injection. In this case a combination of unexpected trauma and discontinuation of DMARD were felt to be important factors in early relapse, supported by a period of 20 weeks clinical benefit following the subsequent INF injection and recommencement of DMARD therapy. One patient developed transient nausea and faintness during US-guided INF injection, thought to be a vasovagal response to the procedure rather than INF itself. This patient's treated knee then remained in remission for 1 year. No other adverse effects to either ia. INF or steroid were recorded.

Table 1. Composite knee score.

	Score	
	0	***1***
Increased warmth	Absent	Present
Effusion	Absent/not tense	Moderate–marked/tense
Synovial thickening	Absent	Present
Joint line tenderness	0–1	2–3
Early morning stiffness	<1 h	≥1 h
Inactivity stiffness	<15 min	≥15 min

A single point is assigned for each of the clinically determined parameters present, giving a maximum score of 6.
Adapted with permission from BMJ Publishing Group Ltd [18].

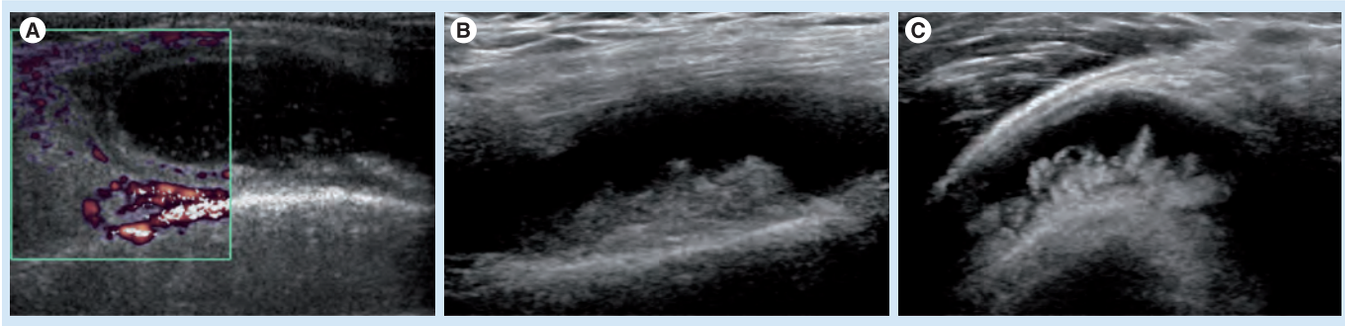

Figure 1. Examples of grayscale appearances of knee synovium. (A) Flat; **(B)** heaped; and **(C)** villous.

Table 2. Demographics, treatment and disease characteristics.

Sex (M:F)	8:6
Mean age (range); years	36 (25–65)
Underlying diagnosis	5 seronegative monoarthritis 4 seronegative oligoarthritis 3 psoriatic monoarthritis 1 enteropathic arthritis 1 rheumatoid arthritis
DMARD treatment	6 SSZ monotherapy 3 MTX monotherapy 3 MTX + SSZ combination 1 MTX + HCQ combination 1 SSZ + HCQ combination 2 oral prednisolone†
Mean duration of disease (range); years	10.2 (1–24)
Median number of ia. steroid injections	5
Mean number of previous DMARDs	2 (1–3)
Previous ia. therapies	3 arthroscopic lavage 2 osmic acid synovectomy 3 arthroscopic surgical synovectomy

Seronegative monoarthritis/psoriatic monoarthritis/enteropathic arthritis/rheumatoid arthritis: other joints all controlled on existing DMARD, leaving monoarthritis of one knee.
†Both patients also receiving DMARD.
F: Female; HCQ: Hydroxychloroquine; ia.: Intra-articular; M: Male; MTX: Methotrexate; SSZ: Sulfasalazine.

Clinical scores

Table 3 details the proportion of patients and time intervals for the primary response, a clinically useful response, CKS scores, remission at 1 year and relapse rates and time intervals after each of the three INF injections. One patient withdrew from the study after the second INF injection as he moved away.

Clinical improvement was sustained at 1 year in four patients, in each of whom the CKS was 0 or 1 and other clinical and US parameters of synovial disease were also normal throughout follow-up.

The proportion achieving a clinically useful response dropped from 78.6% following the first INF injection to 70 and 50% following the second and third INF injections, respectively (nonsignificant vs first injection, Fisher's exact test).

The median time to relapse was 12 weeks after the first INF injection and 9 weeks after the second and third injections (nonsignificant vs first injection, Fisher's exact).

The VAS scores for knee pain on the flat and on stairs and the lower extremity function scores all changed in parallel with the CKS scores, but did not add any additional information to that represented by the CKS scores. The erythrocyte sedimentation rate and C-reactive protein were elevated in some patients, but did not necessarily rise or fall with changes in the clinical scores.

US scores

In general, US parameters of synovial disease paralleled clinical changes of improvement and relapse and in a proportion of patients preceded clinical signs of relapse. The most sensitive index to change was mean synovial thickness taken from five knee regions. At baseline the cohort (n = 14) mean thickness was 4.34 mm (range: 2–6.62 mm; median: 3.42). Following the first INF injection mean synovial thickness fell in all patients, overall by a mean of 2.78 mm. All patients demonstrated a reduction in mean synovial thickness by at least 1 mm and this occurred in ten patients (71%) at the first assessment, within 2 weeks. In the 11 patients who relapsed, mean synovial thickness rose by at least 1 mm in nine cases (82%), occurring synchronously with the clinical signs of relapse in five and in the other four cases a median of 3 weeks (range: 2–16 weeks) earlier (36% of all who relapsed). In no case did synovial thickness rise without being accompanied or followed by a clinical relapse.

Of the ten patients who received a second INF injection, mean synovial thickness fell by more than 1 mm in eight (80%), at the time of INF injection in four out of five cases where patients had received steroids a week earlier and in the other four cases within 2 weeks of the INF injection. Of the nine patients who relapsed after the second INF injection, mean synovial thickness increased in seven by at least 1 mm, occurring synchronously with clinical relapse in three cases and in the other four cases a median of 4 weeks (range: 3–17 weeks) earlier (44% of all who relapsed). Similarly in the seven patients who received a third INF injection, mean synovial thickness fell within 2 weeks in the majority (six out of seven) and rose again synchronously with clinical relapse in five cases and 3–4 weeks earlier in two cases (28% of all who relapsed; Table 4).

The grayscale appearance score (flat, heaped or villous) in general decreased following INF injection and increased synchronously or a few weeks before clinical relapse. This score was less sensitive to change than the synovial thickness measurements, with no change occurring at the time of clinical relapse on 37% of occasions. Similarly, the PD appearances, recorded as either a mean score from each of five measured regions or an overall subjective score, also changed in parallel with the clinical state, but not as closely as mean synovial thickness. Mean PD scores from each of the five regions are shown in Table 4. This score

Table 3. Clinical composite knee score response to intra-articular infliximab.

	1st Rx (n = 14; ia. steroid n = 0)	2nd Rx (n = 11 [1/11 no follow-up]; ia. steroid n = 5)	3rd Rx (n = 7; ia. steroid n = 6)
Primary response; n	14 (100%)	10 (100%)	6 (86%)
Clinically useful response; n	11 (78.6%)	7 (70%); NS†	3 (50%); NS†
Median time to primary response (range); weeks	2 (2–12)	2 (0–4)	1 (0–2)
Mean baseline CKS (range)	3.64 (2–6)	4.5 (3–6)	4.0 (2–6)
Mean maximum fall in CKS	2.86	3.0	2.7
Mean baseline VAS flat (range)	4.6 (1–10)	4.9 (0.3–9.2)	4.7 (1.5–8)
Mean minimum VAS flat (range)	1.1 (0–6.7)	1.6 (0–6.4)	0.4 (0–2.8)
Mean baseline VAS stairs (range)	6.1 (1–10)	5.9 (1.6–9.5)	5.5 (3.1–8.4)
Mean minimum VAS stairs (range)	1.5 (0–7.8)	2.4 (0–7.5)	1.2 (0–4.6)
Remission at 1 year; n	3 (21.4%)	1 (10%)	0
Relapse; n	11 (78.6%)	9 (90%)	7 (100%)
Median time to relapse (range); weeks	12 (8–21)	9 (4–19); NS‡	9 (4–20); NS‡

ia. steroid: 80 mg Depo-Medrone®, 1 week prior to infliximab. Primary response: drop in CKS score by 2 points from baseline. Clinically useful response: CKS suppressed below baseline for a duration of more than 8 weeks.
†Fisher's exact versus first infliximab injection.
‡Mann Whitney U versus first infliximab injection.
CKS: Composite knee score; ia.: Intra-articular; NS: Nonsignificant; Rx: Treatment; VAS: Visual analog score.

improved following INF in 74% cases and rose with or prior to relapse overall in 63% of cases. The subjective overall PD score improved following INF in 45% of cases and rose with or prior to relapse in 64% of cases.

In 22 out of 26 (85%) cases of clinical relapse synovial fluid was measured as recurring or increasing in volume, synchronously with clinical relapse in 13 cases (59%) or between 2 and 19 weeks earlier in nine cases (41%).

Pretreatment with ia. Depo-Medrone

Pretreatment with ia. steroid was used prior to the second INF injection in five patients and prior to the third INF injection in six patients. US data before and after ia. steroid injection demonstrate that eight out of 11 knees responded, with reduction in synovial hypertrophy and vascularity after 1 week (mean PD score prior to steroid: 1.13; mean poststeroid: 0.17), but this approach did not improve the duration of clinical response to INF; median duration with ia. steroid was 9 weeks compared with 12 weeks without (p = 0.49; Mann Whitney U test).

Comparison of patients achieving long-term remission versus short-term response

Table 5 summarizes the characteristics of patients who were in remission at 1 year (n = 4) compared with those who demonstrated relapse. Baseline

Table 4. Ultrasound response to intra-articular infliximab.

	Injection 1 (n = 14)	Injection 2 (n = 10)	Injection 3 (n = 7)
Mean synovial thickness			
Falls >1 mm post-ia. injection	14/14 (100%)	8/10 (80%)	7/7 (100%)
Rises >1 mm in patients with clinical relapse	9/11 (82%)	7/9 (78%)	7/7 (100%)
Rises >1 mm prior to clinical relapse	4/11 (36%)	4/9 (44%)	2/7 (29%)
Median time prior to clinical relapse (weeks)	3	4	3.5
Mean PD score			
Falls post-ia. injection	12/14 (86%)	6/10 (60%)	5/7 (71%)
Rises in patients with clinical relapse	7/11 (64%)	5/9 (55%)	5/7 (71%)
Rises prior to clinical relapse	2/11 (18%)	2/9 (22%)	1/7 (14%)
Median time prior to clinical relapse (weeks)	2	2	3

ia.: Intra-articular; PD: Power Doppler.

Table 5. Characteristics of patients with short-term response versus those in remission at 1-year evaluation.

	Remission	Short-term response
n	4	10
Sex (M:F)	1:3	7:3
Diagnosis	2 seronegative monoarthritis, 1 JCA monoarthritis, 1 seronegative oligoarthritis	2 seronegative monoarthritis, 3 seronegative oligoarthritis, 3 psoriatic monoarthritis, 1 enteropathic monoarthritis, 1 RA
DMARDs	3 SSZ monoarthritis, 1 MTX + SSZ	3 SSZ, 2 MTX, 3 MTX + SSZ, 1 MTX + HCQ, 1 SSZ + HCQ
Mean baseline CKS (1–6)	3 (median: 2; range: 2–6)	3.9 (median: 4; range: 2–6)
Mean baseline ESR	5.5 (median: 5; range: 4–10)	19 (median: 25; range: 7–33)
Mean baseline CRP	2.7 (median: 2.5; range: 0–6.1)	11.6 (median: 15.6; range: 5.2–26.2)
Mean baseline synovial thickness (mm)	3.41 (median: 2.78; range: 2–6.02)	4.72 (median: 3.58; range: 2.12–8.84)
Mean baseline PD	0.7 (median: 0.8; range: 0.2–1.4)	0.68 (median: 0.8; range: 0.2–1)

CKS: Composite knee score; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; F: Female; HCQ: Hydroxychloroquine; JCA: Juvenile chronic arthritis; M: Male; MTX: Methotrexate; PD: Power Doppler; RA: Rheumatoid arthritis; SSZ: Sulfasalazine.

CKS, acute-phase markers and synovial thickness were lower in the remission group. Owing to the small numbers no statistical analysis of this group was performed.

Discussion

This prospective cohort study has demonstrated the feasibility and good tolerability of up to three repeated ia. INF injections in conjunction with DMARD therapy for inflammatory knee monoarthritis. Long-term clinical and US remission was achieved in four out of 14 patients (28.6%) after one or two INF injections. In the remaining patients the primary clinical response was observed within a median of 2 weeks of the first INF injection and sustained for a clinically useful period of time (more than 8 weeks) in 78.6%. Repeat INF injection also showed a high rate of clinical response but for a statistically nonsignificant diminishing period of time, as judged by the proportion with a clinically useful response dropping to 70% and then 50% following second and third INF injections and the time to relapse shortening from a median of 12 weeks to 9 weeks with the second and third INF injections.

As it is documented that administration of ia. steroid to the knee can lead to beneficial effects in other joints and at other inflammatory sites [15,22], we postulated that the efficacy of ia. INF might be reduced by systemic spread. For this reason patients were provided with crutches to enable them to remain non-weight bearing through the injected knee for 24 h after INF injection. Complete bed rest was not practical in patients of working age range. A second strategy to diminish this effect was to use ia. steroid a week earlier, to attempt to reduce synovial vascularity and thus reduce systemic absorption of INF. A reduction in PD signal has been reported within days of steroid knee injection [15,17] and therefore a week's interval was utilized in our study. US confirmed that this strategy did diminish synovial thickness and PD signal in this time interval in eight out of 11 cases, but this did not lead to a prolongation of clinical response to INF injection. Although a reduction in vascularity might have increased ia. INF concentration, it also might have diminished the effectiveness of INF by reducing synovial TNF receptor expression. This would be interesting to explore with radiolabeled INF or synovial biopsies. Of additional interest, in two out of three cases where there was no US response to ia. steroid at 1 week, there was subsequently no clinical or US response to INF injection.

Our finding of a very rapid response to INF injection, with a median clinical response time of 2 weeks, is consistent with others, including Conti *et al.* who reported response rates 2 weeks after ia. INF of 90 and 85.7%, respectively, in RA and PsA patients treated with DMARDs and systemic anti-TNF therapies [23]. In this series PsA patients appeared to respond less well than RA patients, with only 57.1% of PsA patients continuing to respond after 12 weeks compared with 90% of the RA group. In our study population three out of 14 suffered from PsA, of whom none achieved long-term remission and despite good responses to the first two INF injections, two failed to have a clinically useful response after the third INF injection. By contrast, Niccoli *et al.* reported very good responses for up to 4 months following repeated ia. INF in three PsA patients (four treated knees) resistant to methotrexate and systemic INF [10].

The four patients who went into remission for at least 1 year had underlying diagnoses of seronegative oligoarthritis with solitary knee involvement, monoarticular juvenile inflammatory

arthritis and seronegative knee monoarthritis in the other two. Although the numbers are small, there is a suggestion that the remission group had less active disease at baseline. This may directly explain their better outcome and additionally we speculate that a less vascular synovium might have resulted in less systemic absorption and therefore more concentrated INF within the joint.

It is noteworthy that there are two studies [24,25] where a high rate of early relapse or no significant benefit to ia. INF is reported. These studies differ from our own and the many other beneficial case series, in that a large proportion of the patients were not taking DMARDs. This may be an important factor, as has been observed for the efficacy of systemic anti-TNF therapies in RA, where concomitant DMARD treatment confers benefit over anti-TNF monotherapy [26,27].

Interestingly, in our study one patient exhibited early relapse after discontinuing SSZ (of his own volition) and then responded for a long duration to a subsequent ia. INF injection with SSZ. These observations lead us to suggest that DMARDs be continued in patient receiving ia. INF, at least for the first year.

Ultrasound assessment allowed a study of synovial disease using both grayscale and PD appearances. This was noninvasive and relatively easy to perform and the additional information complemented the clinical scores. Of the different US scores, mean synovial thickness (taken from five regions) was the most sensitive measure of relapse, showing a rise on 85% of all occasions where there was a clinical relapse and this occurred before clinical features were apparent overall on 37% of occasions, an average of 5.9 weeks earlier (range: 2–17 weeks). The PD scores were less sensitive measures of clinical relapse, rising overall on 63% of occasions where there was a clinical relapse, and this preceded the clinical features of relapse on 18.5% of occasions, on average 2 weeks earlier. The difference in performance of the synovial thickness and PD scores may be a reflection of the subjective PD scoring system used, in having a narrow range of scores, rather than PD itself not being a useful measure. It is interesting that both the synovial thickness and PD scores changed very quickly after INF injection. This contrasts with the impact of systemic etanercept therapy on knee US appearances reported by Fiocco *et al*. where synovial thickness and pannus/cartilage interface PD scores showed no change at 3 months but were significantly diminished at 12 months [28]. We assume that the rapid changes recorded in our study reflect the high concentration of locally administered INF, despite concerns about systemic spread from the joint.

Based on our own and other investigators' findings, we conclude that ia. INF is well tolerated and appears to be effective and of clinical benefit in the management of resistant knee monoarthritis. We would suggest that optimal outcome requires continued DMARD treatment and that preinjection with ia. corticosteroid does not appear to prolong the duration of response to ia. INF. Although US provides interesting information about synovial disease, neither grayscale measures of thickness or appearance, nor subjective PD scores provide additional monitoring value over clinical indices of disease activity and in particular US does not predict relapse in the majority of cases. Patients with less aggressive knee inflammation may be more likely to respond for long periods (at least 1 year in our study) but regardless of baseline severity a clinically useful response of more than 8 weeks may be achieved with repeated INF injections. ia. INF therefore appears to be a useful therapy for this group of patients who are often resistant to ia. steroid, surgical or chemical synovectomy and traditional immune suppression with DMARDs.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent

has been obtained from the participants involved. Ethical approval has been secured for this study from the Charing Cross Research Ethics Committee (REC reference 06/Q0411/85) and the study has been registered with the European Union Clinical Trials database, EUDRACT number 2006–001448–29.

Executive summary

- Repeated intra-articular infliximab in addition to DMARD therapy appears to be an effective treatment of resistant inflammatory knee monoarthritis.
- The majority of patients demonstrate a clinically useful response of more than 8 weeks.
- Long-term remission at 1-year evaluation may occur, but only in a minority of patients.
- Patients with less aggressive knee inflammation may be more likely to respond for long periods.
- Pretreatment with intra-articular steroid does not lengthen the duration of response.
- Ultrasound measures of synovial disease mirror clinical signs and precede clinical relapse in a minority.
- Repeated intra-articular infliximab injections are well tolerated.

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- ▪ of interest
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