Eur J Nucl Med Mol Imaging (2012) 39:1339–1347
DOI 10.1007/s00259-012-2133-9

ORIGINAL ARTICLE

Role of scintigraphy with ^{99m}Tc-infliximab in predicting the response of intraarticular infliximab treatment in patients with refractory monoarthritis

F. Conti · G. Malviya · F. Ceccarelli · R. Priori · A. Iagnocco · G. Valesini · A. Signore

Received: 3 November 2011 / Accepted: 28 March 2012 / Published online: 16 May 2012

Abstract
Purpose The rationale for the present study was to evaluate the predictive role of ^{99m}Tc-infliximab scintigraphy in therapy decision-making in patients with refractory monoarthritis and also candidates for intraarticular (IA) infliximab treatment.
Methods We studied 12 patients (5 with rheumatoid arthritis and 7 with spondyloarthropathy) with active monoarthritis (11 knees and 1 ankle) that had lasted for at least 3 months. Patients were evaluated clinically and ultrasonographically at baseline and 12 weeks after IA administration of infliximab. At the same time-points, ^{99m}Tc-infliximab scintigraphy was performed: planar anterior and posterior images of arthritic joints were acquired at 6 and 20 h after injection and target-to-background (T/B) ratios were calculated.
Results After treatment, a significant improvement in clinical and ultrasonographic parameters was recorded in six patients. Three patients had a partial response and three did not respond. Regarding scintigraphic evaluation, the T/B ratio analysis showed a significantly higher uptake in affected than in nonaffected joints before therapy (1.78±0.46 vs. 1.29±0.27, p=0.006 at 6 h; 2.05±0.50 vs. 1.41±0.36 at 20 h, p=0.002), and mean uptake at 20 h was also significantly higher than at 6 h (p=0.0004). Scintigraphy showed a significant decrease in posttherapy T/B ratios of the affected joints (p=0.0001 at 6 h and p=0.0001 at 20 h), indicating a reduction in TNF into the affected joints. Most importantly, responders showed a significantly higher percentage increase in pretherapy uptake from 6 h to 20 h in the affected joints than nonresponders (p=0.00001).
Conclusion The results of the present investigation suggest that ^{99m}Tc-infliximab scintigraphy could be a useful tool to predict the clinical response to IA infliximab treatment in patients with refractory monoarthritis.

Keywords Infliximab · Anti-TNFα monoclonal antibody · Rheumatoid arthritis · Molecular imaging · Therapy decision making

Introduction

TNFα has been identified as a key cytokine in inflammatory arthropathies with a pathophysiological role, promoting synovial inflammation and erosion of bone and cartilage [1, 2]. TNF antagonists have demonstrated good efficacy in the treatment of patients with rheumatoid arthritis (RA) and a spondyloarthropathy (SpA), such as psoriatic arthritis (PsA), leading to a significant clinical improvement in many patients resistant to conventional therapies [3]. In the last few years, some experience with intraarticular (IA) treatment with TNF antagonists in patients with refractory monoarthritis has been reported. The majority of these patients have been treated with infliximab, and only a few studies have evaluated the efficacy of etanercept and adalimumab IA treatment [4–15].

F. Conti and G. Malviya contributed equally to this work.

F. Conti · F. Ceccarelli · R. Priori · A. Iagnocco · G. Valesini
Rheumatology Unit, Faculty of Medicine and Dentistry,
"Sapienza" University of Rome,
Rome, Italy

G. Malviya · A. Signore (✉)
Nuclear Medicine Unit, Faculty of Medicine and Psychology,
"Sapienza" University of Rome,
Rome, Italy
e-mail: alberto.signore@uniroma1.it

G. Malviya · A. Signore
Department of Nuclear Medicine and Molecular Imaging,
University Medical Centre Groningen, University of Groningen,
Groningen, The Netherlands

Observational studies investigating the clinical efficacy of IA treatment with a TNF antagonist in terms of clinical, laboratory and imaging parameters have generally demonstrated good responses, even though two randomized double-blind studies did not show better efficacy than IA glucocorticoids [9, 14]. Therefore, IA administration of a TNF antagonist could be an effective treatment in some patients with refractory monoarthritis, but a method for selecting patients potentially responsive to this innovative treatment is not yet available.

We have previously reported prolonged remission of persistent knee monoarthritis in a patient with undifferentiated SpA after a single 100-mg dose of IA infliximab, monitoring response to treatment using scintigraphy with ^{99m}Tc-infliximab. Imaging before treatment showed intense uptake in the affected knee, indicating high levels of TNF, while the second scintigraphy performed after 4 months showed no accumulation of the radiopharmaceutical, indicating the absence of detectable levels of TNF and confirming the efficacy of the IA infliximab treatment [7].

In the present study, we evaluated the predictive role of ^{99m}Tc-infliximab scintigraphy for therapy decision-making in patients with refractory monoarthritis who were candidates for IA treatment with a TNF antagonist.

Materials and methods

Patients

We studied 12 patients (5 men and 7 women; mean age 40.6 ±10.1 years) with active monoarthritis (11 knees and 1 ankle; mean disease duration 8.2±6.9 years) enrolled in the Rheumatology Unit of Sapienza University of Rome, Italy. There were 5 patients with RA diagnosed according to the 1987 ACR criteria [16] and 7 patients with SpA diagnosed according to the ESSG criteria [17].

All patients had active monoarthritis that had lasted for at least 3 months and was refractory to treatment with disease-modifying antirheumatic drugs (DMARDs) and IA injection of glucocorticoids. Concomitant treatment with an anti-TNF drug other than infliximab was not considered an exclusion criterion; indeed the biological agent was stopped 2 weeks before and restarted 2 weeks after the IA procedure. The DMARD dose had to have been stable for at least 6 weeks before IA injection of infliximab, and IA glucocorticoid (methylprednisolone 40 mg) had to have been injected in all patients at least 6 weeks before the procedure.

Regarding DMARD treatment, seven patients (58.3 %) were taking methotrexate (11.8±3.7 mg weekly, mean± SD), four patients (33.3 %) were taking sulfasalazine (Salazopyrin, 2±0.7 g daily), and one patient (8.3 %) was taking hydroxychloroquine (200 mg twice a day). Two patients had been previously treated with systemic adalimumab (40 mg every 2 weeks) and one patient with etanercept (50 mg weekly). The mean treatment period was 17±7.5 months. None of the patients were receiving concurrent systemic treatment with infliximab.

A tuberculin skin test and chest radiography were performed just before treatment in patients naive to anti-TNF therapy. After removing synovial fluid, IA infliximab was injected at concentration of 10 mg/ml (in sterile water for injection), according to the manufacturer's instructions. The doses of infliximab were 100 mg for the knee and 50 mg for the ankle. The local Ethics Committee approved the study and written informed consent was obtained from each enrolled patient.

Clinical assessment and ultrasonographic evaluation

Patients were evaluated at baseline, just before IA administration of infliximab, and after 12 weeks. The same rheumatologist performed a clinical examination evaluating pain using a visual analogue scale (VAS) that ranged from 0 to 100 according to the pain in the affected joint, and the degree of swelling and tenderness (no swelling or tenderness 0, mild 1, moderate 2, severe 3). As previously described, a total arthritis score (range 0–6) was obtained as the sum of the swelling and tenderness scores [13]. A complete response was defined as ≥70 % improvement in both total arthritis score and the VAS score for pain, and a partial response as ≥50 % improvement in at least either the total arthritis score or the VAS score for pain [13]. Erythrocyte sedimentation rate and C-reactive protein were also evaluated.

Ultrasonographic examination of the inflamed joint was performed by the same rheumatologist experienced in musculoskeletal ultrasonography, using a Philips/HP Image Point HX system with a 10-MHz linear probe. Power Doppler was used with a pulse repetition frequency of 1,000 Hz, a gain of 18–30 dB, and a low filter. The joints were examined according to EULAR guidelines for ultrasonography in rheumatology [14]. Patients were evaluated at baseline, and after 12 weeks. An arbitrary scoring system (range 0–6) for assessment of inflamed joints including synovial hypertrophy (range 0–3) and power Doppler evaluation (range 0–3) [11] was applied.

Antibody

Infliximab (Remicade) was provided by Centocor Ortho Biotech (Horsham, PA). Human nonspecific immunoglobulin (HIG, TechneScan) was provided by Mallinckrodt, Petten, The Netherlands.

Scintigraphic evaluation

Infliximab was radiolabelled with ^{99m}Tc using a direct method, as described previously [18]. Anterior and posterior planar whole-body images were acquired 6 h and 20 h after intravenous administration of 370–550 MBq (100–150 μg) of ^{99m}Tc-infliximab according to our previous experience [7]. Planar anterior and posterior images of specific joints (knee or ankle) were acquired with a Philips Sky-Light dual head gamma camera fitted with a high-resolution collimator. Whole-body planar images were acquired on a 1,024×1,024 pixel matrix at a scanning speed of 5 cm/min (at 6 h) or 10 cm/min (at 20 h). Joint-specific images (knee or ankle) were acquired on a 512×512 pixel matrix for 300 s (at 6 h) or 600 s (at 20 h).

Scintigraphy with ^{99m}Tc-infliximab was performed in all patients twice. The first scan was performed at the time of patient recruitment (about 1–2 weeks before IA therapy) and the second scan was performed 12 weeks after IA administration of a therapeutic dose of infliximab. For quantitative analysis, OSIRIS software (University Hospital of Geneva, Switzerland) was used to draw regions of interest (ROI) for evaluation of the target-to-background (T/B) ratio. For the target, a circular ROI was drawn on the affected joint, and for the background a rectangular ROI was drawn approximately 5 cm below the knee or above the ankle. Both pre- and posttherapy images were evaluated together using the same ROIs. The activity in the ROIs was normalized to the area of the ROI and divided by the background activity to obtain the T/B ratio for each joint. The T/B ratio was calculated for affected and nonaffected joints, in images acquired at 6 h (T/B_{6h}) and at 20 h (T/B_{20h}). The T/B ratio increase over time ($T/B_{20h\text{-}6h}$) was also calculated as an index of specific ^{99m}Tc-infliximab binding to TNF in the joints and expressed in absolute values and as the percentage increase at 20 h with respect to 6 h ($\%T/B_{20h/6h}$).

In addition, two patients were also studied with ^{99m}Tc-HIG, and therefore four ^{99m}Tc-HIG scans were performed. Before therapy a ^{99m}Tc-HIG was performed and a ^{99m}Tc-infliximab scan was performed within a week (typically the ^{99m}Tc-HIG scan was on Monday or Tuesday and the ^{99m}Tc-infliximab scan was on Wednesday or Thursday or on Thursday or Friday). The scans were performed again within a week 12 weeks after IA infliximab therapy. HIG was radiolabelled with ^{99m}Tc according to the manufacturer's instructions. Whole-body and joint-specific scintigraphic images were acquired using the same settings as for ^{99m}Tc-infliximab at 6 h and 20 h after intravenous administration of 370–550 MBq (500 μg) of ^{99m}Tc-HIG.

Statistical analysis

Wilcoxon's paired test was used to compare quantitative variables in the same group. Spearman's test was used for correlation analysis. Student's *t*-test was used for analysis of the T/B ratios from the scintigraphic images since the data were normally distributed.

Results

Clinical assessment and ultrasonographic evaluation

Table 1 shows the clinical, laboratory and ultrasonographic parameters before and 12 weeks after IA administration of infliximab. Significant reductions in the mean VAS scores for pain, the mean total arthritis scores and the ultrasonography scores were recorded. Of the 12 patients, 9 (75 %) showed a response to IA therapy (6 had a complete response, and 3 had a partial response) and 3 did not respond to therapy (nonresponders).

Table 1 Clinical, laboratory and ultrasonographic parameters before and 12 weeks after IA administration of infliximab. Values are means±SD

Parameter	All patients (n=12)			RA patients (n=5)			SpA patients (n=7)		
	Baseline	12 weeks	p value	Baseline	12 weeks	p value	Baseline	12 weeks	p value
VAS score for pain	62.4±25.7	19.1±16.2	0.0004	56±27.7	17.2±7.3	NS	67±25.3	16.8±15.4	0.03
Total arthritis score	5±1	1.7±2.6	0.0005	5±1	1.4±1.5	0.05	5±1.1	1.3±1.1	0.01
Erythrocyte sedimentation rate (mm/h)	17.3±8.5	17.4±5.1	NS	20.4±7.3	18.4±6.2	NS	15.1±9.1	13±6.5	NS
C-reactive protein (mg/dl)	8.1±6	6.4±2.8	NS	10.2±8.4	7.2±3.4	NS	6±2.9	11±11.2	NS
Ultrasonography score	5.4±1.4	1±1.3	0.00002	5.2±1.8	0.4±0.5	0.05	5.5±1.1	0.8±0.8	0.01

NS not significant

Scintigraphic evaluation

The labelling efficiency of ^{99m}Tc-infliximab was always >95 % with a negligible amount of colloids (<2 %). Quantitative analysis of the acquired images (T/B ratio) showed a higher uptake in the affected than in the nonaffected contralateral joints (1.78±0.46 vs. 1.29±0.27 at 6 h, p=0.006; 2.05±0.5 vs. 1.41±0.36 at 20 h, p=0.002; Fig. 1a, b). The mean uptake in the affected joints at 20 h was also significantly higher than at 6 h (p=0.0004). Most importantly, responders showed a significantly greater increase in uptake from 6 h to 20 h than nonresponders in the affected joints (%T/$B_{20h/6h}$ 20.37±2.9 % vs. 1.98±1.3 %, p=0.00001; T/B_{20h-6h} 0.43±1.3 vs. 0.04±0.02, p=0.0007). Partial responders showed a smaller increase than responders (%T/$B_{20h/6h}$ 11.73±3.9 %, vs. 20.37±2.9 % p=0.003; T/B_{20h-6h} 0.22±0.02 vs. 0.43±0.13, p=0.01) and a greater increase than nonresponders (%T/$B_{20h/6h}$ 11.73±3.9 vs. 1.98±1.3 %, p=0.008; T/B_{20h-6h} 0.22±0.02 vs. 0.04±0.02, p=0.0001), indicating that the more TNF is present in the lesion (and therefore detected by anti-TNF antibodies) the more is the therapeutic benefit of IA therapy with infliximab (Fig. 1c).

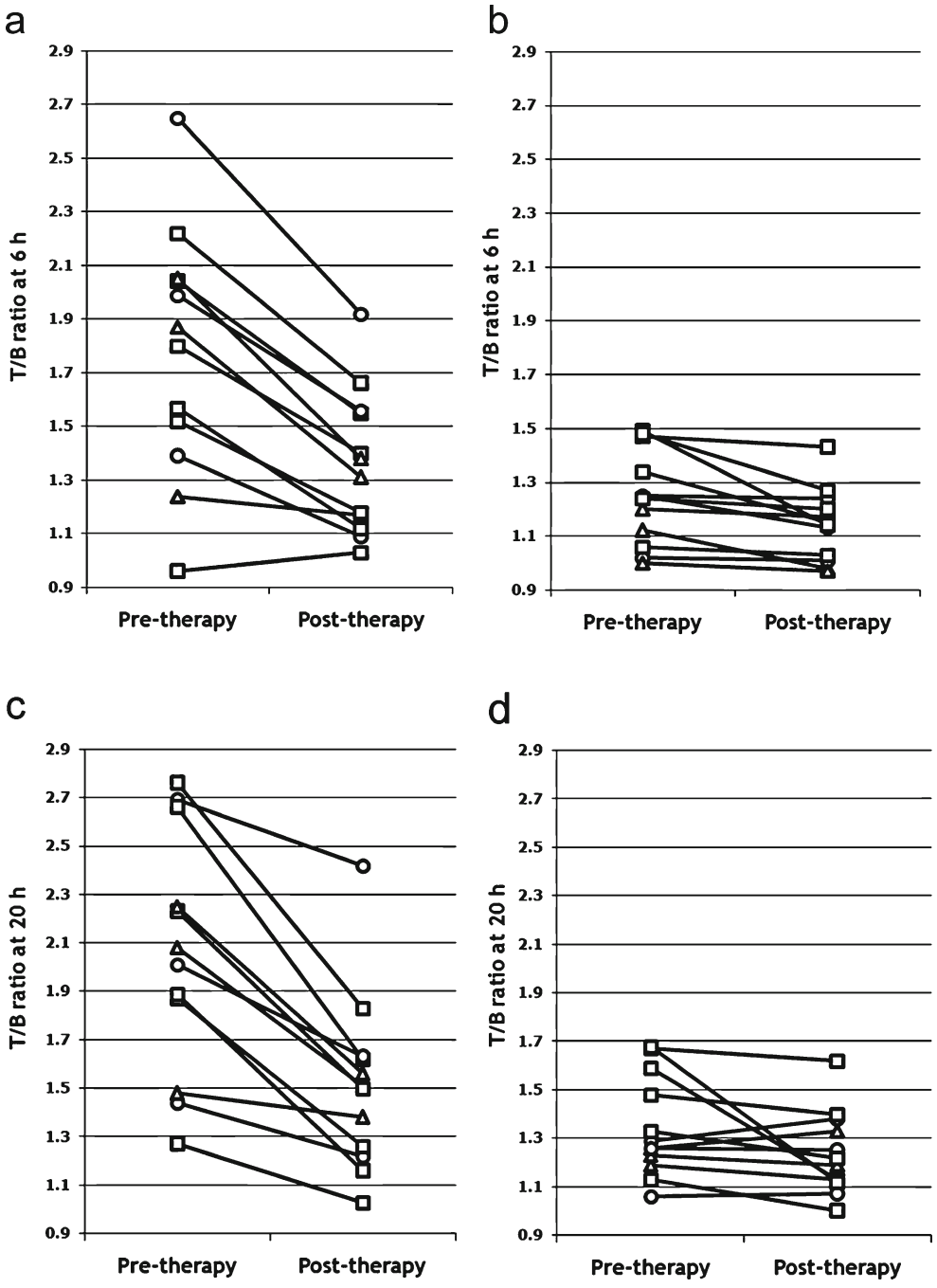

Fig. 1 **a**, **b** T/B_{6h} ratios determined by ^{99m}Tc-infliximab scintigraphy before and after IA infliximab therapy in (**a**) affected joints and (**b**) nonaffected joints. **c**, **d** T/B_{20h} ratios determined by ^{99m}Tc-infliximab scintigraphy before and after IA infliximab therapy in (**c**) affected joints and (**d**) nonaffected joints. **e** $\%T/B_{20h/6h}$ before and after therapy in affected joints. All responders (*squares*) showed a significant decrease in $\%T/B_{20h/6h}$ after therapy (p=0.000003), while nonresponders (*circles*) did not show a decrease. Indeed, all partial responders remained partial responders, suggesting they could be retreated with the same therapy. Of the nonresponders, one patient remained a nonresponder, one became a partial responder and one became a responder, suggesting that all patients could potentially become responders with time. **f** T/B_{20h-6h} before and after therapy in affected joints. Responders showed a significantly greater decrease in T/B_{20h-6h} after therapy in relation to before therapy in affected joints (p=0.00005), but partial responders showed a smaller decrease in T/B_{20h-6h} after therapy (p=0.125), while nonresponders did not show any decrease in T/B_{20h-6h} after therapy (p=0.109)

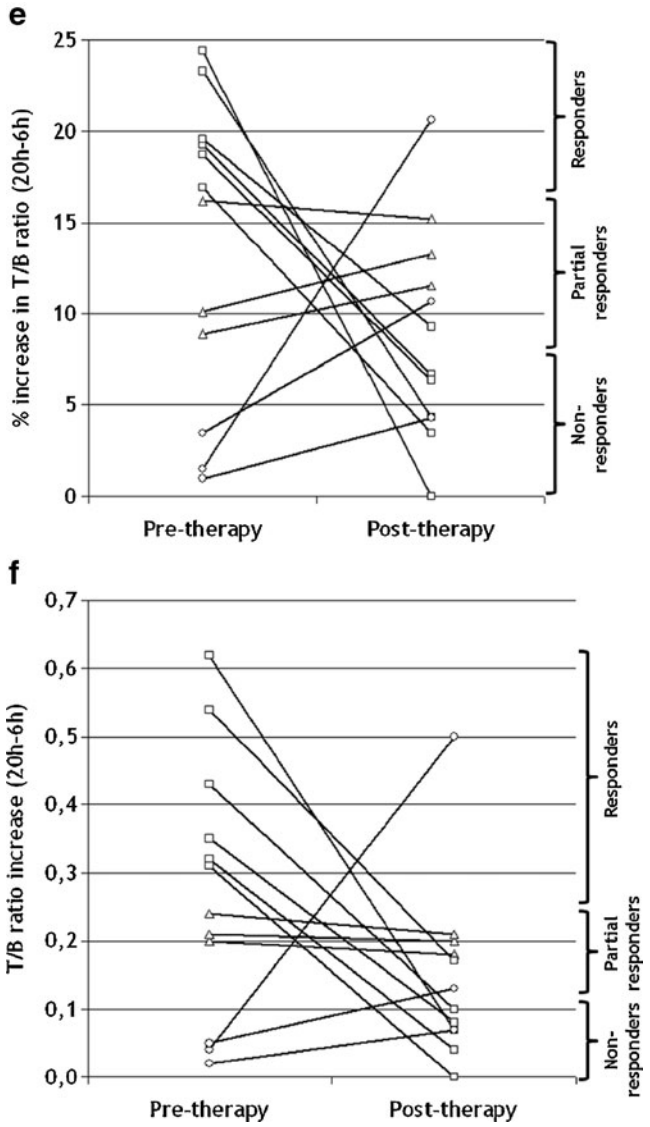

Fig. 1 (continued)

Scintigraphy showed a significant decrease in the T/B ratio of the affected joints 6 h (from 1.78±0.46 to 1.4±0.3; p=0.0001) and 20 h after therapy (from 2.05±0.5 to 1.5±0.4; p=0.0001), indicating a reduction in TNF in the joint after IA therapy, whereas nonaffected contralateral joints did not show marked differences in the T/B ratio at either 6 h (from 1.29±0.27 to 1.2±0.2; p=0.0074) or 20 h after therapy (from 1.41±0.36 to 1.3±0.3; p=0.08; Table 2).

Responders also showed a significant decrease in $T/B_{20h\text{-}6h}$ uptake after therapy in comparison with before therapy in the affected joint (0.43±1.3 vs. 0.08±0.06, p=0.00005), but partial responders showed a smaller decrease in $T/B_{20h\text{-}6h}$ uptake after therapy (0.22±0.02, vs. 0.20±0.02, p=0.125), and non-responders did not show any decrease in $T/B_{20h\text{-}6h}$ uptake after therapy (0.04±0.02 vs. 0.23±0.23, p=0.109; Fig. 1f).

$T/B_{20h\text{-}6h}$ was also significantly correlated with the arthritis score (R^2=0.821, p=0.0004), swelling score (R^2=0.758, p=0.0002), tenderness score (R^2=0.758, p=0.001), ultrasonography score (R^2=0.417, p=0.00002) and VAS score for pain (R^2=0.034, p=0.0003; Fig. 2).

Figure 3 shows scintigraphic images in a representative patient with decreased uptake of ^{99m}Tc-infliximab in the affected joint at 12 weeks after therapy.

^{99m}Tc-HIG scan also showed higher joint uptake before therapy in affected knees (T/B ratios 2.14 and 1.61 at 6 h, and 2.22 and 1.7 at 20 h) than in nonaffected knees, but there was no significant increase in the uptake from 6 h to 20 h ($T/B_{20h\text{-}6h}$ 0.08 and 0.09), in contrast to the observations with ^{99m}Tc-infliximab ($T/B_{20h\text{-}6h}$ 0.43 and 0.58). ^{99m}Tc-HIG uptake in knees did not show any apparent relationship with clinical parameters in the two patients. The ^{99m}Tc-HIG scans after therapy failed to show significant decreases in uptake in either patient, in contrast to the observations with ^{99m}Tc-infliximab (Table 3).

No adverse events or infusion-related reactions were observed in patients undergoing ^{99m}Tc-infliximab or ^{99m}Tc-HIG scans.

Discussion

The results of the present investigation suggest that ^{99m}Tc-infliximab scintigraphy could be a useful tool for predicting the clinical response to IA infliximab treatment in patients with refractory monoarthritis. IA therapy is a frequently used procedure in the treatment of persistent inflammatory monooligoarthritis. When properly indicated and performed, it carries minimal risk for the patient. Several different compounds can be injected, among which glucocorticoids are the most commonly used.

In recent years some experience with IA administration of TNF-antagonists in patients with refractory monoarthritis has been reported with contrasting results. The first published studies, which included patients treated with IA infliximab, had important limitations including small sample sizes and short follow-up durations [4–7]. In 2008, we described the efficacy and safety of IA infliximab administration in a larger cohort of patients (17 patients. 10 with RA and 7 with PsA) evaluated clinically and ultrasonographically. In that study, a clinical response was seen 12 weeks after treatment in 90 % of RA patients and in 57.1 % of PsA patients. The ultrasonographic evaluation of synovial hypertrophy and the power Doppler signal showed significant decreases in joint inflammation [11]. This was the reason we selected the 12-week time-point for evaluating response to the IA infliximab therapy.

Different results were obtained in a more recent randomized clinical trial, which included a total of 41 IA injections (20 infliximab and 21 methylprednisolone) in 28 knees in 23 patients with recurrent knee monoarthritis despite previous

Table 2 Average scintigraphic scores for ^{99m}Tc-infliximab in all patients (n=12)

Joint	Before treatment			After treatment		
	T/B_{6h}	T/B_{20h}	T/B_{20h-6h} (%$T/B_{20h/6h}$)	T/B_{6h}	T/B_{20h}	T/B_{20h-6h} (%$T/B_{20h/6h}$)
Affected joint	1.78±0.46[a]	2.05±0.5[b]	0.28±0.19[c] (13.61±8.34)[n]	1.4±0.3[d]	1.5±0.4[e]	0.15±0.13[f] (8.81±5.8)[q]
Nonaffected contralateral joint	1.29±0.27[g]	1.41±0.36[h]	0.12±0.11[i] (7.86±5.43)[r]	1.2±0.2[j]	1.3±0.3[l]	0.11±0.10[m] (8.2±7.94)[s]

p values:
a: vs. b 0.0004, vs. d 0.0001, vs. g 0.006
b: vs. e 0.0001, vs. h 0.002
c: vs. f 0.120, vs. i 0.025
d: vs. e 0.002, vs. j 0.096
e: vs. l 0.108
f: vs. m 0.464
g: vs. h 0.0028, vs. j 0.0074
h: vs. l 0.08
i: vs. m 0.8
n: vs. q 0.11, vs. r 0.01
q: vs. s 0.8
r: vs. s 0.8

IA glucocorticoid therapy [14]. Patients were clinically evaluated using an arbitrary knee joint score, ranging from 0 to 7, encompassing knee tenderness and swelling and a VAS score for knee pain. In that study, all patients treated with IA infliximab were retreated within 6 months because of an insufficient response, while 54 % of initial IA glucocorticoid injections were effective without relapse during 6 months of follow-up [14].

These heterogeneous results indicate the need for prognostic factors able to identify patients who are potential candidates for IA treatment with TNF-antagonist drugs. In the present study we analysed the role of scintigraphy with ^{99m}Tc-infliximab in predicting the response to IA infliximab in patients with refractory monoarthritis, helping to select potential responders. The use of imaging with radiolabelled monoclonal antibodies and cytokine antagonists, such as the anti-TNF monoclonal antibody infliximab, is a new strategy that might provide the possibility to perform 'evidence-based biological therapy' of arthritis with a view to assessing whether an antibody will localize in an inflamed joint before using the same unlabelled antibody therapeutically [19, 20]. In a previous case study, the response to IA infliximab in a patient with SpA and persistent knee monoarthritis was monitored using ^{99m}Tc-infliximab scintigraphy. Clinical and laboratory improvement was associated with scintigraphy findings that showed the absence of ^{99m}Tc-infliximab accumulation in the affected knee 4 months after IA infliximab administration [7].

In the present study, we confirmed the clinical efficacy of IA infliximab treatment: after 12 weeks 75 % of treated patients showed a clinical response that was a complete response in 66.7 % of responders. The ultrasonographic features of synovitis significantly improved during follow-up and were correlated positively with the outcome measures. Moreover, the efficacy of IA infliximab was evaluated by ^{99m}Tc-infliximab scintigraphy, which showed 12 weeks after treatment a significant decrease in the T/B ratio of the affected joint at 6 h and 20 h. This response suggests a reduction in TNF in the affected joint and an improvement in the inflammatory status. However, the most interesting aspect was the baseline scan that predicted a response to treatment after 12 weeks.

In the pretherapy scan, responders showed significantly greater increases during the period 6 h to 20 h in than nonresponders. A possible explanation for the ^{99m}Tc-infliximab uptake in the early scan (6 h after injection) is the increased vascularity and joint swelling, particularly in those patients in whom the main complaint was oedema and/or pain. Retention of mAb in joints and its further accumulation at 20 h can be interpreted as the consequence of the specific binding of ^{99m}Tc-TNF mAb to the TNF expressed by different cell populations including macrophages, monocytes, neutrophils, T cells and NK cells, and/or to soluble TNF in inflamed joints. Partial responders showed a smaller increase in T/B ratio between 6 h and 20 h. We can hypothesise that in patients with lower expression of TNF in affected joints, ^{99m}Tc-TNF mAb can enter the joint at early time points due to inflammation, followed by little retention and washout due to the absence of specific binding sites. A similar phenomenon (i.e. the increase of joint uptake with time of a radiolabelled mAb in patients with severe

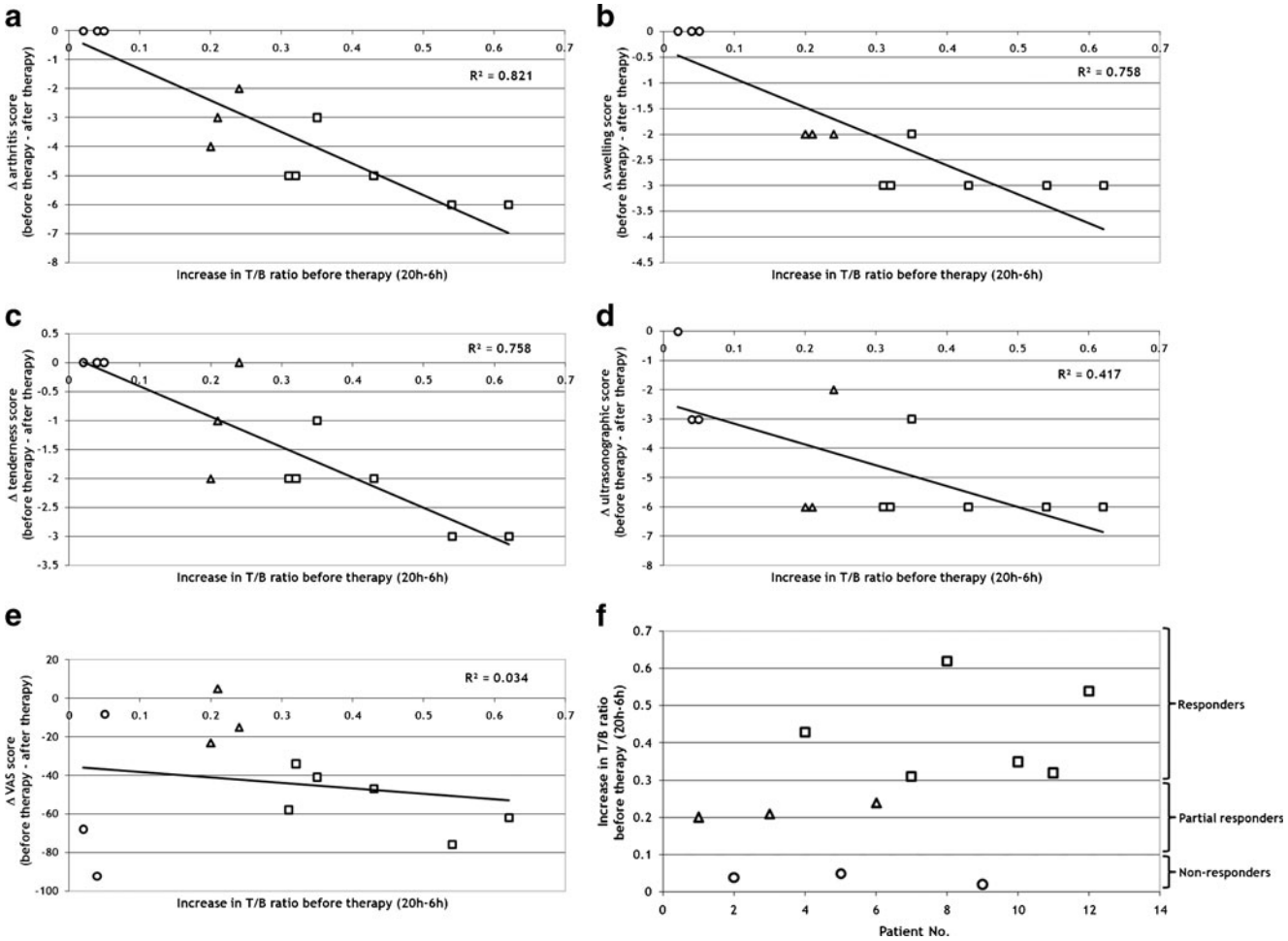

Fig. 2 **a**–**e** Correlations between increases in T/B ratio in affected joints from 6 h to 20 h and clinical parameters (**a** arthritis score, **b** swelling score, **c** tenderness score, **d** ultrasonographic score, **e** VAS score). **f** $T/B_{20h\text{-}6h}$ values before therapy in all patients (*squares* complete responders, *triangles* partial responders, *circles* nonresponders)

inflammation) has also previously been described in patients with RA using ^{99m}Tc-labelled anti-CD3 mAb [21]. In our study responders showed much higher $T/B_{20h\text{-}6h}$ in affected joints than nonresponders, whereas partial responders showed an intermediate $T/B_{20h\text{-}6h}$. $T/B_{20h\text{-}6h}$ in affected joints also correlated with several

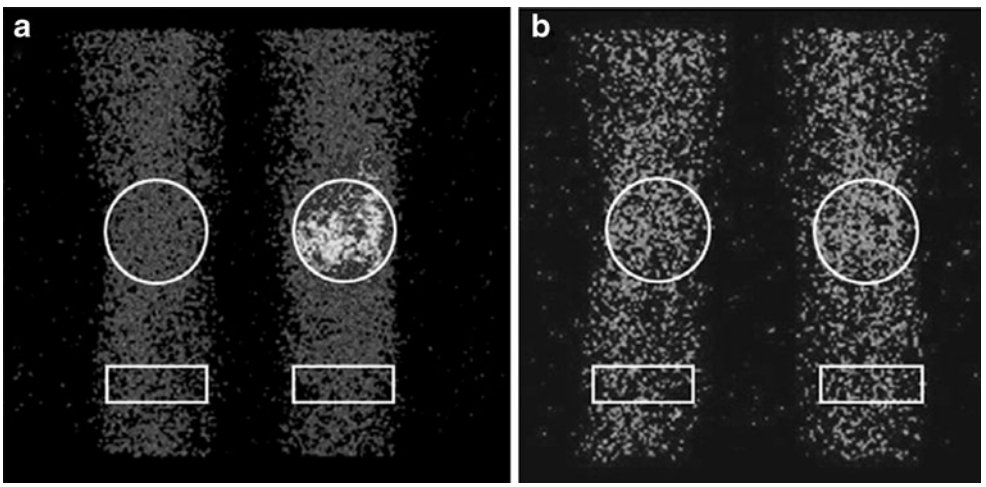

Fig. 3 Scintigraphic imaging with ^{99m}Tc-infliximab at 20 h (**a**) before and (**b**) 12 weeks after IA infliximab therapy. Higher uptake is seen in the left knee before therapy (**a**) and much lower uptake is seen in the left knee after therapy (**b**). Clinical evaluation confirmed that this patient responded to therapy. The ROIs for the target (*circles*) and background (*rectangles*) from which the T/B ratios were calculated are also shown

Table 3 Scintigraphic scores for ^{99m}Tc-infliximab and ^{99m}Tc-HIG scans in patients 4 and 12 who underwent both scans

Radiopharmaceutical	Before treatment						After treatment					
	Patient 4			Patient 12			Patient 4			Patient 12		
	T/B 6h	T/B 20h	T/B 20h-6h	T/B 6h	T/B 20h	T/B 20h-6h	T/B 6h	T/B 20h	T/B 20h-6h	T/B 6h	T/B 20h	T/B 20h-6h
^{99m}Tc-infliximab	1.8	2.23	0.43	1.32	1.90	0.58	1.4	1.5	0.1	1.14	1.31	0.17
^{99m}Tc-HIG	2.14	2.22	0.08	1.61	1.70	0.09	2.1	2.17	0.07	1.56	1.60	0.04

clinical parameters, indicating that this semiquantitative scintigraphic index can predict success of IA therapy.

IA infliximab was also efficacious in the three patients who had been receiving systemic TNF antagonists other than infliximab without any significant clinical benefit. We can speculate that changing the anti-TNF antibody for therapy and changing the route of administration may result in a good clinical response. Alternatively, patients who were not responders may become responders over time. Interestingly, no significant change in T/B ratio in nonaffected contralateral joints was observed, indicating that after IA therapy not enough infliximab escapes from the treated joint to affect the course of disease in other joints.

^{99m}Tc-HIG that has been proposed for imaging of inflammation in RA [22, 23] did not show any increase in T/B ratio at 20 h in the pretherapy scintigraphy with respect to the ratio at 6 h in either of the patients studied, and behaved differently from infliximab. This difference in behaviour of the two radiopharmaceuticals reflects the different uptake mechanisms involved in their accumulation process. Indeed, contrary to radiolabelled infliximab, the accumulation of radiolabelled HIG at the site of inflammation is mainly nonspecific and is related to the increase in vascularization, extracellular fluid volume, endothelial permeability and synovial fluid clearance in inflamed joints [24, 25]. Moreover, ^{99m}Tc-HIG was not able to demonstrate changes in disease activity after IA treatment with infliximab in the two patients, as confirmed by clinical evaluation, and consequently this radiopharmaceutical did not help therapy decision-making in these two patients.

Here we showed that scintigraphy with ^{99m}Tc-anti-TNF mAb can play a role in therapy decision-making, and in the selection of patients with RA as candidates for IA infliximab therapy. Lower TNF expression may suggest the use of a different therapy, directed towards other inflammatory targets. Therefore, in future, ^{99m}Tc-anti-TNF mAb scintigraphy could play a role in selecting the best therapeutic option for the individual patient, avoiding the extra cost burden of unnecessary anti-TNF therapies. However, a large prospective study is required to determine the predictive value of this technique. If we succeed in doing this, we will not only improve the clinical care of these patients but also provide a means to apply biological therapies in a cost-effective manner.

Conflicts of interest None.

References

1. Scott DL, Kingsley GH. Tumour necrosis factor inhibitors for rheumatoid arthritis. N Engl J Med. 2006;355:704–12.
2. Deleuran BW, Chu CQ, Field M, Brennan FM, Mitchell T, Feldmann M, et al. Localization of tumor necrosis factor receptors in the synovial tissue and cartilage-pannus junction in patients with rheumatoid arthritis. Implications for local actions of tumor necrosis factor alpha. Arthritis Rheum. 1992;35:1170–8.
3. Olsen NJ, Stein CM. New drugs for rheumatoid arthritis. N Engl J Med. 2004;350:2167–79.
4. Bokarewa M, Tarkowski A. Local infusion of infliximab for the treatment of acute joint inflammation. Ann Rheum Dis. 2003;62:783–4.
5. Nikas SN, Temekonidis TI, Zikou AK, Argyropoulou MI, Efremidis S, Drosos AA. Treatment of resistant rheumatoid arthritis by intraarticular infliximab injections: a pilot study. Ann Rheum Dis. 2004;63:102–3.
6. Schatteman L, Gyselbrecht L, De Clercq L, Mielants H. Treatment of refractory inflammatory monoarthritis in ankylosing spondylitis by intraarticular injection of infliximab. J Rheumatol. 2006;33:82–5.
7. Conti F, Priori R, Chimenti MS, Coari G, Annovazzi A, Valesini G, et al. Successful treatment with intraarticular infliximab for resistant knee monoarthritis in a patient with spondyloarthropathy. A role for scintigraphy with 99mTc-infliximab. Arthritis Rheum. 2005;52:1224–46.
8. Alstergren P, Larsson PT, Kopp S. Successful treatment with multiple intra-articular injections of infliximab in a patient with psoriatic arthritis. Scand J Rheumatol. 2008;37(2):155–7.
9. Bliddal H, Terslev L, Qvistgaard E, Recke P, Holm CC, Danneskiold-Samsoe B, et al. Safety of intra-articular injection of etanercept in small-joint arthritis: an uncontrolled, pilot-study with independent imaging assessment. Joint Bone Spine. 2006;73(6):714–7.
10. Boesen M, Boesen L, Jensen KE, Cimmino MA, Torp-Pedersen S, Terslev L, et al. Clinical outcome and imaging changes after intraarticular (IA) application of etanercept or methylprednisolone in rheumatoid arthritis: magnetic resonance imaging and ultrasound-Doppler show no effect of IA injections in the wrist after 4 weeks. J Rheumatol. 2008;35(4):584–91.
11. Conti F, Ceccarelli F, Priori R, Iagnocco A, Signore A, Valesini G. Intra-articular infliximab in patients with rheumatoid arthritis and psoriatic arthritis with monoarthritis resistant to local glucocorticoids.

Clinical efficacy extended to patients on systemic anti-tumour necrosis factor alpha. Ann Rheum Dis. 2008;67(12):1787–90.
12. Haroon M, O'Gradaigh D. Efficacy and safety of combining intra-articular methylprednisolone and anti-TNF agent to achieve prolonged remission in patients with recurrent inflammatory monoarthritis. Joint Bone Spine. 2010;77(3):232–4.
13. Fioravanti A, Fabbroni M, Cerase A, Galeazzi M. Treatment of erosive osteoarthritis of the hands by intra-articular infliximab injections: a pilot study. Rheumatol Int. 2009;29(8):961–5.
14. Backhaus M, Burmester GR, Gerber T, Grassi W, Machold KP, Swen WA, et al. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis 2001;60(7):641–9.
15. Fiocco U, Sfriso P, Oliviero F, Roux-Lombard P, Scagliori E, Cozzi L, et al. Synovial effusion and synovial fluid biomarkers in psoriatic arthritis to assess intraarticular tumor necrosis factor-α blockade in the knee joint. Arthritis Res Ther. 2010;12(4):R148.
16. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315–24.
17. Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. Arthritis Rheum. 1991;34:1218–27.
18. D'Alessandria C, Malviya G, Viscido A, Aratari A, Maccioni F, Amato A, et al. Use of a 99mTc labeled anti-TNFalpha monoclonal antibody in Crohn's disease: in vitro and in vivo studies. Q J Nucl Med Mol Imaging. 2007;51:1–9.
19. Chapman PT, Jamar F, Keelan ET, Peters AM, Haskard DO. Use of a radiolabeled monoclonal antibody against E-selectin for imaging of endothelial activation in rheumatoid arthritis. Arthritis Rheum. 1996;39:1371–5.
20. Jamar F, Chapman PT, Manicourt DH, Glass DM, Haskard DO, Peters AM. A comparison between 111In-anti-E-selectin mAb and 99mTc-labelled human non-specific immunoglobulin in radionuclide imaging of rheumatoid arthritis. Br J Radiol. 1997;70:473–81.
21. Lopes FP, de Azevedo MN, Marchiori E, da Fonseca LM, de Souza SA, Gutfilen B. Use of 99mTc-anti-CD3 scintigraphy in the differential diagnosis of rheumatic diseases. Rheumatology. 2010;49:933–9.
22. van der Lubbe PA, Arndt JW, Calame W, Ferreira TC, Pauwels EK, Breedveld FC. Measurement of synovial inflammation in rheumatoid arthritis with technetium-99m labelled human polyclonal immunoglobulin G. Eur J Nucl Med. 1991;18:119–23.
23. de Bois MH, Arndt JW, van der Velde EA, van der Lubbe PA, Westedt ML, Pauwels EK, et al. 99mTc human immunoglobulin scintigraphy – a reliable method to detect joint activity in rheumatoid arthritis. J Rheumatol. 1992;19:1371–6.
24. Signore A, Mather SJ, Piaggio G, Malviya G, Dierckx RA. Molecular imaging of inflammation/infection: nuclear medicine and optical imaging agents and methods. Chem Rev. 2010;110 (5):3112–45.
25. Malviya G, Galli F, Sonni I, Pacilio M, Signore A. Targeting T and B lymphocytes with radiolabelled antibodies for diagnostic and therapeutic applications. Q J Nucl Med Mol Imaging. 2010;54 (6):654–76.