Letters to the Editors

Anti-TNF scintigraphy to assess TNF-α-associated joint inflammation in rheumatoid arthritis and osteoarthritis

Sirs,

Tumour necrosis factor alpha (TNF-α) is a pivotal cytokine in rheumatoid arthritis (RA) since TNF-α amplifies and perpetuates synovitis and treatment with anti-TNF-α antibodies reduces disease activity and radiological progression of disease (1). Since ^{99m}Tc-labelled monoclonal TNF-α-antibodies can visualise TNF-α-expression, we compared joint-associated ^{99m}Tc-infliximab-uptake with clinical and imaging signs of synovitis in RA- and OA-patients (2-4).

Eleven TNF-inhibitor naive RA-patients (8 females; median age 61 (50–75) years; median disease duration 6 (1–29) years) and 11 patients with symptomatic OA (10 female; mean age 55 (11) years) underwent a physical examination including all peripheral joints and routine blood work to calculate serum CRP levels and the $DAS28_{CRP}$. Subsequently, patients underwent power Doppler ultrasonography (PDUS) of tender and/or swollen joints. Sonographic synovitis was diagnosed if either joint effusion or an enlarged hypo-echogenic and hypervascular synovium was visible. Thereafter, patients received a mean dose of 618 (range: 439-847) MBq ^{99m}Tc-infliximab intravenously over a period of 15 minutes. Planar whole body images and images of both hands were recorded and two experts in nuclear medicine read the ^{99m}Tc-infliximab scintigraphic results. A lesion-to-background ratio (L/B) ≥1.5 compared to unaffected joints was considered positive. Within 24 hours of scintigraphy seven RA-patients underwent gadolinium-enhanced MRI of the clinically more affected hand and two independent radiologists analysed the MRI images according to the OMERACT RA-MRI scoring system (5).

Ten RA-patients were on disease-modifying anti-rheumatic drug (DMARD) therapy (8 methotrexate, 1 chloroquine, 1 methotrexate and chloroquine); they had been treated with a median of 2 (1-9) DMARDs in the past. Six study-patients were on a stable dose of prednisolone (median, range 3, 2.5–10mg) for at least 4 weeks and only two patients received a daily dose of 10mg at the time of investigation. All patients had active disease with a mean (SD) $DAS28_{CRP}$ of 6.9 (1.2). Ten OA-patients presented with 9.5 (7.3) tender joints and one OA-patient had three swollen joints. Sonographic signs of synovitis were detected in two knees and one finger joint in two OA-patients.

Significant ^{99m}Tc-infliximab-uptake was detectable in 10 RA-patients and in two swollen joints of one OA-patient. Statistical analysis (Student's paired *t*-test, Wilcoxon matched-pairs signed rank test, Spearman's rank correlation coefficient, mean (SD), median (range)) revealed a significantly lower number of joints with ^{99m}Tc-infliximab-uptake compared to the median number of swollen joints [3 (0–23) *vs*. 12 (5–27), $p<0.005$], joints with sonographic signs [3(0–23) *vs*. 8(0–27), $p<0.05$] and with MR-tomographic signs [2(1–4) *vs*. 5(0–8), $p<0.01$] of synovitis. However, the number of joints with ^{99m}Tc-infliximab-uptake correlated highly significantly with serum CRP-levels (r=0.93, CI 0.74–0.98, $p<0.0001$) but not with the $DAS28_{CRP}$ score.

Table I. Correlation of ^{99m}Tc-infliximab-uptake on a single joint level with joint inflammation visualized clinically, sonographically, and on MRI in 11 RA patients.

	Joints with ^{99m}Tc-IFX-uptake (n)	Joints without ^{99m}Tc-IFX-uptake (n)	Spearman r	CI	*p*-value	Sensitivity (%)	Specificity (%)
SJ (n=175)	49	126	0.33	0.27-0.40	<0.001	64.5	82.9
PDUS (n=106)	42	64	0.46	0.40-0.52	<0.001	65.6	70.5
MRI (n=49)	19	30	0.36	0.15-0.53	<0.001	86.4	54.6

IFX: infliximab; SJ: clinically swollen joints; PDUS: synovitis visualised by power Doppler ultrasound in 281 joints; MRI: synovitis visualised by magnetic resonance imaging in 88 hand joints; CI: confidence interval.

On a single joint level, a significant correlation was found between joints with ^{99m}Tc-infliximab-uptake and clinical, sonographic, or MR-tomographic signs of synovitis (Table I). Sensitivity of ^{99m}Tc-infliximab-scintigraphy to detect TNF-α-expression was highest in joints with synovitis on MRI (86.4%).

Our study showed that joint-associated TNF-α-expression visualised by whole-body ^{99m}Tc-infliximab scintigraphy correlates with acute phase reactants and clinical and imaging signs of synovitis, indicating that this method has potential to assess TNF-α-associated synovitis. However, the sensitivity of this method visualising joint-associated TNF-α-expression was low, demonstrating that clinical, sonographic and MR-tomographic synovitis frequently occurs independently of TNF-α-expression. Our results are supported by work made by Roimicher and colleagues who also detected joint-associated TNF-α-expression in only about two-thirds of swollen joints (4). The reason for this is currently unclear. Experimental data have shown that synovial fluid TNF-α levels can vary substantially between individuals and are dependent on RA disease activity (6, 7). While the results of our study are limited by the small cohort size we could demonstrate that ^{99m}Tc-infliximab scintigraphy is able to determine TNF-α-associated synovitis. Everyday clinical use of this method is hampered by availability and limited sensitivity.

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References

1. LIPSKY PE, VAN DER HEIJDE DM, ST CLAIR EW *et al*.: Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000; 343: 1594-602.
2. ANNOVAZZI A, ALESSANDRIA C, CAPRILLI R *et al*.: Radiolabelling of monoclonal anti-TNF antibody with ^{99m}Tc: *in vitro* studies. *J Nucl Med* 2002; 46: 27 (abstract)
3. FURUZAWA-CARBALLEDA J, MACIP-RODRIGUEZ PM, CABRAL AR: Osteoarthritis and rheumatoid arthritis pannus have similar qualitative metabolic characteristics and pro-inflammatory cytokine response. *Clin Exp Rheumatol* 2008; 26: 554-60.
4. ROIMICHER L, LOPES FP, DE SOUZA SA *et al*.: ^{99m}Tc-anti-TNF-{alpha} scintigraphy in RA: a comparison pilot study with MRI and clinical examination. *Rheumatology* (Oxford) 2011; 50: 2044-50.
5. OSTERGAARD M, PETERFY C, CONAGHAN P *et al*.: OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. *J Rheumatol* 2003; 30: 1385-6.
6. TAKEUCHI T, MIYASAKA N, TATSUKI Y *et al*.: Baseline tumour necrosis factor alpha levels predict the necessity for dose escalation of infliximab therapy in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011; 70: 1208-15.
7. TETTA C, CAMUSSI G, MODENA V, DI VITTORIO C, BAGLIONI C: Tumour necrosis factor in serum and synovial fluid of patients with active and severe rheumatoid arthritis. *Ann Rheum Dis* 1990; 49: 665-7.
8. CECCARELLI F, PERRICONE C, TROTTA F *et al*.: Remission in early, aggressive rheumatoid arthritis: a multicentre prospective observational Italian study ARPA (Artrite Reumatoide Precoce Aggressiva). *Clin Exp Rheumatol* 2013; 31: 341-9.