Persistent low grade synovitis without erosive progression in magnetic resonance imaging of rheumatoid arthritis patients treated with infliximab over 1 year

João Eurico Fonseca · Helena Canhão · Nuno Jalles Tavares · Margarida Cruz · Jaime Branco · Mario Viana Queiroz

Abstract Disease remission is only reached by a minority of rheumatoid arthritis (RA) patients treated with infliximab. Radiological assessment reported in clinical trials support the view that even under persistent inflammatory activity there is no further structural damage. Magnetic resonance imaging (MRI) allows a highly accurate detection of synovitis, bone edema, and erosions, constituting the ideal instrument for the evaluation of treatment response. The goal of this study was to evaluate MRI changes over 1 year in RA patients treated with infliximab. Four RA patients refractory to methotrexate (MTX) therapy were treated with infliximab 3 mg/kg 8/8 weeks and followed up for 1 year. Disease Activity Score (DAS28) was measured in the day of each infliximab administration. MRI was performed at baseline, 3 months, and 1 year. A simplified OMERACT RA MRI scoring (RAMRIS) was applied to the dominant wrist: synovitis (0–3) was measured in the intercarpal–carpometacarpal joints (CMTJ); bone edema (0–39) and erosions (0–130) in the base of the metacarpal and wrist bones. Baseline DAS28 was superior to 3.2 in all patients (ranging from 4.8 up to 6.2). At 14 weeks, DAS28 was still superior to 3.2 (ranging from 3.5 up to 4.6) and at 46 weeks all patients have responded, however without having achieved clinical remission, as DAS28 was still above 2.6 (ranging from 2.6 up to 3.4). MRI showed that synovitis was reduced in all patients to a score of 1, bone edema was slightly reduced (10% reduction), and erosive score was unchanged (baseline values ranging from 2 up to 20). Despite persistent low disease activity, these four RA patients treated with infliximab had stable simplified RAMRIS erosive scores over 1 year. These results support the view that there might be an uncoupling process between inflammation and bone erosions when tumor necrosis factor alpha is targeted in RA.

Keywords Erosions · Infliximab · Magnetic resonance imaging · Rheumatoid arthritis

Introduction

Clinical trials have shown that despite disease remission is only reached by a minority of rheumatoid arthritis (RA) patients treated with infliximab, radiological assessment showed arrest in structural damage progression even in patients who did not respond to therapy and still presented a persistent inflammatory activity [1]. However, conventional radiographs of the joints are a two-dimension evaluation method and are less sensitive to changes in joint damage than magnetic resonance imaging (MRI) [2]. In fact, MRI allows a highly accurate detection of synovitis, bone edema, and erosions, constituting the ideal tool for the evaluation of treatment response in RA patients [3]. The goal of this study was to evaluate MRI changes over 1 year.
in RA patients treated with infliximab, by performing MRI at baseline, 3 months, and 1 year after infliximab treatment was started.

Materials and methods

Patients included in this study fulfilled the criteria established by the American Rheumatism Association (ARA 1987) for RA and had to have a Disease Activity Score of the 28 joints (DAS28) superior to 3.2, despite treatment with the maximum tolerated dose of methotrexate (MTX) in a stable dose for more than 2 months. Patients were allowed to be treated with other concomitant disease-modifying anti-rheumatic drugs (DMARDs), as long as it had been administered in a stable dose during the 6 weeks preceding inclusion in the study. Exceptions for this rule were patients treated with cyclosporine and/or leflunomide who were excluded. Patients undergoing treatment with oral corticosteroids (maximum acceptable dose of prednisone or equivalent was 10 mg a day) or non-steroidal anti-inflammatory drugs (NSAIDs) must have been taking stable doses for at least 4 weeks before the screening. The doses of MTX, other DMARDs, NSAIDS, and corticosteroids were kept stable over the study period. All patients were treated with 3 mg/kg of infliximab in weeks 0, 2, and 6 and then every 8 weeks up to week 46. DAS28 was evaluated in every visit.

MRI was performed at baseline, week 14, and week 46. The MRI studies were performed in the dominant hand using 1.5 T (GE SIGNA), with a coil phase array of four

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Disease activity (DAS28 score) and synovitis, bone edema, and erosive MRI scores at baseline, 14 weeks, and 46 weeks after infliximab therapy</th>
<th>Baseline</th>
<th>14 weeks</th>
<th>46 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28</td>
<td>6.0 (4.8–6.2)</td>
<td>4.1 (3.5–4.6)</td>
<td>2.8 (2.6–3.4)</td>
<td></td>
</tr>
<tr>
<td>Synovitis score (0–3)</td>
<td>2 (1–2)</td>
<td>1 (1–2)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Bone edema score (0–39)</td>
<td>4 (0–22)</td>
<td>3 (0–21)</td>
<td>3 (0–22)</td>
<td></td>
</tr>
<tr>
<td>Erosive score (0–130)</td>
<td>17.5 (2–20)</td>
<td>18 (2–20)</td>
<td>17.5 (2–20)</td>
<td></td>
</tr>
</tbody>
</table>

All values are medians and ranges

Fig. 1 The MRI studies were performed at baseline (a, b), 14 weeks (c), and 46 weeks (d) after infliximab therapy. Synovitis score was reduced from 2 to 1 and the edema score decreased from 4 to 3. Erosions were stabilized
channels and 12 in. and the whole-body MRI system with imaging. A circular linear surface antenna was placed on the back of the hand with the patient lying face down with her arm extended. Five sequences were used for all the patients: multiple T1-weighted spin-echo coronal and axial sequences (SE) (T1 SE), multiple T2-weighted (T2 TSE FS), fat-suppressed turbo spin-echo coronal sequences, post-gadolinium axial sequences—DTPA in T1 SE (Gd-DTPA), and post-Gd-DTPA gadolinium coronal sequences in T1 FS. The evaluation parameters for the T1-weighted axial images were: TR 485 ms, TE 20 ms, matrix 256×256 (3 Nex), field of vision (FOV) 10 cm, thickness of slice 1.5 mm, interval 0.2 mm, 16 slices. The coronal SE T1 parameters were similar. The T1 FSE post-gadolinium coronal parameters were: TR 485 ms, TE 20 ms, matrix 256×256 (4 Nex), thickness of slice 2 mm, interval 0.2 mm, FOV 10 cm. The T1 post-gadolinium axial parameters were: TR 485 ms, TE 20 ms, matrix 256×256 (3 Nex), thickness of slice 1.5 mm, spacing 0.2 mm, 16 slices, FOV 10 cm. The T2 FS TSE acquisition parameters were as follows: TR 2,000 ms, TE 100 ms, matrix 256×256, field of vision (FOV) 10 cm, thickness of slice 1.5 mm, interval 0.2 mm, 16 slices. The coronal SE T1 parameters were similar. The T1 FSE post-gadolinium coronal parameters were: TR 450 ms, TE 20 ms, matrix 256×256 (4 Nex), thickness of slice 2 mm, interval 0.2 mm, FOV 10 cm. The T1 post-gadolinium axial parameters were: TR 450 ms, TE 20 ms, matrix 256×256 (3 Nex), thickness of slice 1.5 mm, spacing 0.2 mm, 16 slices, FOV 10 cm. The T2 FS TSE acquisition parameters were as follows: TR 2,000 ms, TE 100 ms, matrix 256×256 (4 Nex), FOV 10 cm, slice thickness 2 mm, spacing 0.2 mm.

A simplified OMERACT RA MRI scoring (RAMRIS) [4] was applied to the dominant wrist: synovitis (0–3) was measured in the intercarpal–carpometacarpal joints (CMTJ); bone edema (0–39) and erosions (0–130) in the base of the metacarpal and wrist bones. The study was approved by Santa Maria Hospital and Egas Moniz Hospital Ethics Committee and all patients signed an informed consent prior to any protocol-specific procedures.

Results

Five female RA patients were included in the study but one interrupted the first MRI due to claustrophobia and was excluded from the study. The four remaining patients had a median age of 46.5 (ranging from 31 to 62) and a median disease duration of 10 (4–20) years. All were treated concomitantly with MTX (median dose 17.5 mg/week, range 10–20 mg/week), prednisone (8.75 mg/day; 5–10 mg/day), and NSAIDs. No other concomitant DMARD was used. As can be observed in Table 1, baseline DAS28 was superior to 3.2 in all patients (ranging from 4.8 up to 6.2). At 14 weeks, DAS28 was still superior to 3.2 (ranging from 3.5 up to 4.6) and at 46 weeks, prior to the last MRI, it was ranging from 2.6 up to 3.4. Baseline median synovitis score was 2 (1–2) (Fig. 1a) and at final evaluation all patients had a synovitis score of 1 (Fig. 1c); baseline median edema score was 4 (0–22) and at final evaluation was 3 (0–22); baseline and final median erosive scores were 17.5 (2–20) (Fig. 1b and d). Therefore, synovitis was reduced in all patients to a score of 1, bone edema was slightly reduced (10% reduction), and erosive score was unchanged (baseline values ranging from 2 up to 20).

Discussion

All patients have clinically responded to infliximab; however, remission was not achieved. Despite persistent low disease activity, these four RA patients treated with infliximab had stable simplified RAMRIS erosive scores over 1 year. We did not have a control group treated only with conventional DMARDs, but data from other studies that have analyzed DMARD-treated patients, like McQueen et al. [5], are in contrast with our results. In fact, they have reported a progression of erosions assessed by MRI in a cohort of RA patients treated with several conventional DMARDs who had shown clinical improvement. However, in accordance with our results, Dohn et al., in a study with five RA patients treated with etanercept, documented no erosive progression evaluated by MRI, even in patients with sustained clinical activity [6].

Taken together, these previous observations and our study support the view that conventional DMARDs are not able to completely arrest joint destruction, even in patients with a clinical response, while tumor necrosis factor alpha antagonist therapies are able to stop this process in a more extensive way. Moreover, arguments from our results and from Dohn et al. [6] study favor the view that in RA there might be an uncoupling process between inflammation and bone erosions and that different mechanisms can be targeted when tumor necrosis factor alpha is antagonized.

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Disclosures None.

References


