Estimation of inflammation by Doppler ultrasound: quantitative changes after intra-articular treatment in rheumatoid arthritis

L Terslev, S Torp-Pedersen, E Qvistgaard, B Danneskiold-Samsoe, H Bliddal

Objective: To evaluate the use of ultrasound, including quantitative Doppler analysis of synovial vascularisation, before and after intra-articular treatment with glucocorticosteroids in patients with rheumatoid arthritis (RA).

Methods: 51 patients with RA were followed prospectively after an intra-articular glucocorticosteroid injection. Disease modifying anti-rheumatic drug treatment was kept unchanged and no further injections given in this observation period. At baseline, disease activity was estimated clinically by target joint pain on a 100 mm visual analogue scale, on which the target joint was scored 0–3 for swelling and tenderness, and by ultrasound measurements of grey scale pixels, colour Doppler pixels, and the spectral Doppler resistive index (RI) as indicators of synovial swelling and inflammation. After four weeks, the measurements were repeated on the same joint. An observer unaware of the sequence and patient number evaluated the ultrasound images.

Results: At one month follow up after the glucocorticosteroid injection, a marked decrease in the fraction of colour pixels was seen in 41/51 patients (Student’s t test p<0.001). Correspondingly, the RI increased indicating a diminished flow to the synovium (Student’s t test p<0.01). Both the fraction of colour pixels and the RI values corresponded with the clinical evaluation and with the subjective effect of the treatment. The synovial membrane volume estimated by total amount of pixels showed a significant decrease by 31% after treatment.

Conclusion: Ultrasound-Doppler seems to be a promising tool for the estimation of synovial activity in arthritis. After intra-articular glucocorticosteroid, changes in RI and fraction of colour pixels may both be used as quantitative measurements of the blood flow.

In rheumatological research non-invasive imaging methods such as magnetic resonance imaging (MRI) and ultrasound (US) have been proposed for the detection and grading of rheumatic inflammatory lesions as they have the potential to provide objective analysis of the disease without ionising radiation. Among the two imaging modalities, US has the potential of becoming a tool used in daily rheumatology practice as it is already accessible in many outpatient clinics, has no contraindications, and poses no problems of patient compliance. Studies have shown that US is comparable with MRI in detecting synovitis in rheumatoid arthritis (RA). Macroscopically the synovial membrane in RA joints is greatly increased and reflects vascular congestion, oedema and cellular infiltration as well as synovial lining hyperplasia and pannus tissue formation. US may visualise the vascularity in the pannus and the hyperaemic synovium by the use of Doppler, and several studies have indicated that power and colour Doppler ultrasonography can detect treatment response.

The evaluation of the degree of inflammation and the treatment response has in general been based on a semiobjective scoring system grading the disease activity—for example, from 0 to 3, while a more quantitative analysis of the amount of pixels with signs of vascular activity has been proposed.

With spectral Doppler it is possible to evaluate the type of flow in the synovium—that is, low peripheral resistance versus high peripheral resistance. The degree of peripheral resistance is expressed numerically by the resistive index (RI). In this way it is possible to obtain objective information on the quality of flow in the synovium as a supplement to the estimation of vascularisation by colour pixels. Preliminary data have indicated low resistance flow and low RI values in pannus in RA. The dramatic effect of intra-articular injections of glucocorticosteroid has been known since 1951, and as glucocorticosteroid treatment has previously been seen to diminish the power Doppler signal, it seems ideal to choose intra-articular treatment for an evaluation of the ability of a new measure to detect and quantify an anti-inflammatory effect.

This study aimed at evaluating the quantitative response to glucocorticosteroid treatment by both colour and spectral Doppler in the diagnosis of inflammatory joint involvement in patients with RA and comparing the treatment with clinical estimates of the disease activity.

PATIENTS AND METHODS

Patients

Fifty one patients with rheumatoid arthritis were included (11 men, 40 women; mean age 63, range (29–93); mean disease duration 12 years, range (1–42); 34 had positive rheumatoid factor). All the patients needed an intra-articular glucocorticosteroid injection to treat a single joint flare

Abbreviations: CDI, colour Doppler image; CRP, C reactive protein; DMARD, disease modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; RI, resistive index; ROI, region of interest; US, ultrasound; VAS, visual analogue scale

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up. The joints included 30 wrists, 9 elbows, 5 proximal interphalangeal joints, 2 metacarpophalangeal joints, 1 metatarsophalangeal joint, 3 talocural joints, and 1 sternoclavicular joint. For at least three months before the study all patients were receiving stable disease modifying anti-rheumatic drug (DMARD) and non-steroidal anti-inflammatory drug (NSAID) treatment. During the observation period of four weeks their drugs were unchanged and no further injections were given. None of the patients received oral glucocorticosteroid treatment in doses larger than 7.5 mg daily. The patients fulfilled the 1987 American College of Rheumatology criteria for RA.12

Clinical evaluation included pain in the target joint on a 100 mm visual analogue scale (VAS), Health Assessment Questionnaire (HAQ), morning stiffness in minutes, and the degree of swelling and tenderness of the target joint graded from 0 to 3. Blood samples were obtained for the determination of erythrocyte sedimentation rate (ESR) and C reactive protein (CRP).

### Table 1 Changes in clinical and ultrasound parameters during the observation period

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline</th>
<th>4 Weeks</th>
<th>Mean change and significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pixel fraction</td>
<td>0.21 (0.16)</td>
<td>0.10 (0.13)</td>
<td>+0.11 (0.19)**</td>
</tr>
<tr>
<td>Total pixels</td>
<td>14721.5 (12043.5)</td>
<td>10169.9 (7567.2)</td>
<td>+4515.6 (9389.67)**</td>
</tr>
<tr>
<td>RI mean</td>
<td>0.71 (0.12)</td>
<td>0.79 (0.17)</td>
<td>+0.08 (0.2)**</td>
</tr>
<tr>
<td>VAS (target joint)</td>
<td>53.9 (28.0)</td>
<td>35.2 (26.2)</td>
<td>+18.7 (25.7)***</td>
</tr>
<tr>
<td>HAQ</td>
<td>16.1 (8.3)</td>
<td>13.7 (9.3)</td>
<td>+2.4 (5.4)**</td>
</tr>
<tr>
<td>ESR</td>
<td>19.4 (14.7)</td>
<td>18.8 (15.9)</td>
<td>+0.5 (12.8)**</td>
</tr>
<tr>
<td>CRP</td>
<td>21.2 (21.6)</td>
<td>16.2 (16.4)</td>
<td>+5.0 (15.7)**</td>
</tr>
<tr>
<td>Morning stiffness</td>
<td>30 (0–300)</td>
<td>5 (0–300)</td>
<td>25*</td>
</tr>
<tr>
<td>Patient’s global</td>
<td>3 (2–4)</td>
<td>3 (1–4)</td>
<td>0*</td>
</tr>
<tr>
<td>Tenderness of the</td>
<td>2 (0–3)</td>
<td>1 (0–3)</td>
<td>1**</td>
</tr>
<tr>
<td>Swelling of the</td>
<td>2 (0–3)</td>
<td>1 (0–3)</td>
<td>1***</td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.01; ***p<0.001.
Results are shown as mean (SD) unless indicated otherwise.
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arteries to be the same as in extrasynovial musculoskeletal tissue. The synovium was noted as non-inflamed when no pixels were present in the ROI.

After four weeks the measurements were repeated on the same joint using the predefined positioning of the probe.

Injections

All injections were carried out guided by ultrasound. The ultrasound probe was held just outside the disinfected area but with a clear view of the area of interest. Using the "no-touch" technique, the needle was then inserted into the joint cavity visualised on ultrasound to ensure correct placement of the needle. The injection site was determined from the ultrasound image as the area with the most pronounced Doppler activity. The following injection with 40 mg methylprednisolone was monitored and the injected fluid was seen distributing in the joint cavity. In some of the finger joints it was impossible to inject all 40 mg of methylprednisolone because of lack of space. In these situation as much as possible was injected (>20 mg).

Statistics

Statistical analysis was performed using the SPSS 10.0 program. Student's t test for paired samples was used for continuous data, which include ESR, CRP, the pixel fraction, the total number of pixels, and mean RI. We also chose to regard HAQ and VAS as continuous data in this study. As model control the difference between the baseline and follow up visits was tested for normality (1-sample Kolmogorov-Smirnoff test). The CRP had a borderline normal distribution, but the choice of test had no influence on the statistical result. Wilcoxon signed rank sum test was used for categorical data, including morning stiffness and assessment for tender and swollen joints. For the correlation between the US parameters and the clinical evaluation Pearson's test was used.

For statistical reasons we needed a value for RI even when no vessels were detectable in the synovium and we defined it as 1.00 in those situations. Level of significance was chosen at p ≤ 0.05.

RESULTS

Table 1 shows the changes in clinical, biochemical, and ultrasound parameters during the observation period. There was a significant change in the global disease activity parameters such as CRP, morning stiffness and HAQ, after the intra-articular treatments, while the ESR remained stable. The local disease activity parameters such as synovial area, VAS, tender and swollen joint assessment of the target joint all showed significant changes after the treatment.

For the ultrasound parameters 41/51 had a significant decrease in colour fraction after the treatment, whereas only 32/51 had a significant increase in mean RI. The synovial volume assessed by the total amount of grey pixels decreased in 38/51.

The presence or absence of a positive rheumatoid factor had no impact on the treatment response. We found a significant correlation between the mean RI and the colour fraction (r = −0.32, p = 0.02), between the pixel fraction and the tender joint assessment of the target joint (r = 0.6, p = 0.02) and the ESR (r = 0.34, p = 0.02), and between mean RI and the VAS (r = −0.38, p = 0.02). No other significant correlations were found.

DISCUSSION

This study showed a significant effect of intra-articular glucocorticosteroid injections on the quantitative ultrasound measurements of synovial disease activity. The effect was demonstrated on both the synovial vascularity (as measured by the colour fraction) (fig 1) and in the flow profile indicated by the increasing RI values due to a higher peripheral resistance (fig 2). Our findings of a decrease in colour fraction are in accordance with those of other studies.4 5 Also the synovial volume expressed by the total amount of grey pixels decreased in 38/51.

The dramatic anti-inflammatory effect of intra-articular glucocorticosteroid injections has been known since 1951, when Hollander et al first injected hydrocortisone acetate intrasynovially into patients with RA and found that they acted quickly on pain and joint swelling in 90% of the
treated joints. Since then, intra-articular injections have become standard adjuvant treatment to normal NSAID and/or DMARD treatment of RA. One or several injections into the same joint may improve the patient’s condition significantly by decreasing joint pain and swelling, leading to improved function. The effect of intra-articular treatment varies from patient to patient, but may last for years. Intra-articular treatment has the advantage over oral glucocorticosteroid treatment in that the systemic effects of the drug used are minimal, though they may be seen in some patients.

Doppler US is a relatively new tool in the investigation of local inflammation. The Doppler signals are a reflection of the number of red blood cells that pass the transducer and the speed in which they pass. The colour pixels are therefore an estimate of the relative amount of moving blood in the investigated area. The appearance of colour pixels in a synovial membrane is a sign of an increase in the relative amount of moving blood, because colour pixels are rarely seen in normal joints. The number of vessels does not correspond with the number of colour pixels visualised by Doppler ultrasound but rather with the area of the already existing vessels. The colour pixels may therefore be interpreted as a sign of hyperaemia. Although Doppler ultrasonography does not depict hyperaemia itself, it depicts the increase in flow that is a part of the inflammatory process. Spectral as well as colour Doppler seems to offer an objective and easily obtainable estimate of the degree of synovial inflammation, which may be used both in clinical trials and in daily clinical practice. The RI (resistive index, resistance index, or Pourcelot index) is a numerical value of the amount of diastolic flow and is directly proportional to the peripheral vascular resistance. The RI has been used in obstetrics and in nephrology to give a numerical value for the diastolic component in the umbilical arteries and arteries of the transplanted kidney. In normal resting musculoskeletal tissue flow is seen with colour or power Doppler in muscles, connective tissue, seldom in joints, and never in tendons. When assessed by spectral Doppler, no diastolic flow is found in the resting tissues and, consequently, the RI is 1.00. In rheumatology low values of RI indicate disease, which has been observed in previous studies, although a definite cut off level for abnormality remains to be established.

Colour and power Doppler have been used to identify the hyperaemia associated with inflammation. The use of the colour fraction as an anti-inflammatory measure has in other studies been evaluated after treatment with glucocorticosteroids and has also been found to be comparable with other studies been evaluated after treatment with glucocorticosteroids. In an earlier study as 0.82–0.97 and 0.82, respectively. This may be due to differences in the general state of the disease and the local disease activity in, for example, a finger or a wrist joint. In our study, the US parameters (colour fraction and the mean RI) correlated with ESR, VAS, and tender joint assessment.

**CONCLUSION**

This study shows that the colour fraction can detect changes in the synovial vascularisation due to treatment. It also suggests that RI may be an objective measure of inflammation and treatment response in patients with RA. The RI measure may be used as an alternative or adjunct to the estimation of the colour fraction and has the advantage of being automated.

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