and patient’s global assessments, and significant reductions in disease activity as assessed by objective laboratory measures (erythrocyte sedimentation rate and C-reactive protein level) (Table 1). Ornidazole was well tolerated. There were no dose-limiting toxic effects. The most frequently reported adverse events in the 1000- and 500-mg ornidazole treatment groups (seen in at least 5% of patients, and excluding worsening of RA) were headache (18.9 and 14.5%, respectively), dry mouth (16.7 and 12.3%, respectively) and nausea (13.2 and 9.1%, respectively).

The results of this randomized, double-blind trial show the clinical efficacy of ornidazole in patients with active RA. Treatment with ornidazole for 3 months was associated with a reduction in disease activity, as assessed by a number of clinical end-points, biochemical markers of disease and quality of life.

Ornidazole produced significant and sustained reductions in disease activity. The few adverse events noted—headache, dry mouth and nausea—were mild and easily managed.

Ornidazole, a synthetic nitroimidazole derivative, is used in the treatment of infections caused by periodontopathic bacteria. Porphyromonas gingivalis, Prevotella intermedia, Prevotella melaninogenica and Bacteroides forsythus are Gram-negative anaerobic bacteria and are considered to be directly responsible for the periodontitis (periodontopathic bacteria).

P. gingivalis has arginine- and lysine-specific proteinases. The citrullination or deamination of arginine residues in autoantigens (prolifaggrin/filaggrin, fibrinogen/fibrin, keratin and vimentin) creates epitopes that are targeted by rheumatoid autoantibodies [7]. Arginine is the most important of the amino acids associated with autoantigencity in proteins.

RA patients have significantly fewer galactose residues on their IgG Fc compared with age-matched healthy control subjects. A lack of terminal galactose residues early in disease is associated with a worse prognosis [8]. Prevotella melaninogenica, as a saccharolytic bacteria, disintegrates galactose. Consequently, P. melaninogenica causes this condition by binding to the Fc region of the IgG molecule and metabolizing galactose with its enzymes.

P. melaninogenica and P. intermedia heat shock proteins of approximately 70 kDa have been found in periodontal disease processes [9]. Hsp 70 antibodies have been detected in the synovial tissue of RA patients, and when the hsp 70 expression is induced with certain stress-stimulating factors, pro-inflammatory cytokines (TNF α, IL-1, IL-6) develop in the RA synovium [10].

Ornidazole treatment in RA is very economical compared with other treatments. It can be concluded from this study that ornidazole is an effective treatment for RA. The above evidence indicates that antibodies formed against oral anaerobic bacteria could be important in the aetio-pathogenesis of RA. However, further studies are needed to confirm this.

The authors have declared no conflicts of interest.

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Two- and three-dimensional Doppler sonographic evaluation of the effect of local cryotherapy on synovial perfusion in wrist arthritis

Sir. Physical treatment including local cold and heat application has been used since antiquity in patients with arthritis. Both methods are known to relieve pain and improve disability in different stages of various rheumatic diseases. An analgesic effect can be readily accomplished after 3 min of local cryotherapy by destimulating pain receptors, which are located in the subcutis. Antiphlogistic effects are obtained after cold application for 20 min and longer by vasoconstriction, by inhibiting the cellular metabolism in the inflammatory cells and by repressing the release of lysosomal enzymes [1, 2]. Whereas the effects of local cold treatment inside the cutis and subcutis have been investigated extensively, not much is known about the influence of cryotherapy inside the affected and inflamed joints themselves. In a study by Oosterveld and Rasker [3] in which a temperature probe was positioned inside the knee joint cavity of patients with rheumatoid arthritis (RA), a decrease in temperature not only in the skin and superficial tissues but also inside the joint cavity could be verified.

Imaging procedures such as high resolution grey-scale ultrasound and power Doppler ultrasonography (PDUS) including three-dimensional (3D) mode have enlarged the diagnostic spectrum by direct visualization of pathomorphologic synovial changes in rheumatic diseases [4, 5]. PDUS had already been used to assess a decrease of synovial vascularity during anti-inflammatory therapy with TNF-α inhibitors or after intra-articular steroid injection [6, 7]. In a small pilot study, we analysed the possibility to
visualize changes in synovial perfusion due to local cryotherapy in acute wrist arthritis by means of 2D and 3D PDUS. Wrists of 13 patients with RA, with clinically active arthritis as determined by soft-tissue swelling and tenderness, were examined by ultrasound (Table 1). Ultrasonography was carried out by a linear array transducer with variable frequency from 5 to 12 MHz (L12-5/38, HDI 5000 ATL/Philips, Bothell, WA, USA). Vascularity adjacent to, and inside, the joint capsule was visualized by PDUS. Doppler settings were standardized with a pulse repetition frequency (PRF) of 700–1000 Hz and the gain was set as suggested by Rubin et al. [8]. In a region with high-power Doppler signal intensity (region of interest, ROI), a 3D volume was acquired by a free-hand sweep. The online 3D power Doppler software (3D CPA6) provided by the HDI 5000 was used to generate a 3D image of a peri- and intra-articular blood vessel tree, in which the grey-scale information of the surrounding tissue had already been subtracted. After the first sonographic examination, a cold pack (TMP Tüshaus Type 12 ×29 cm) was put for 20 min on the inflamed wrist. Temperature of the cutis decreased from 33°C to 5.5°C after 20 min cold application. Immediately after removal of the cold pack, sonographic re-examination was performed by the same investigator. One of the two experienced ultrasound investigators (J.S. or K.S.) performed sonographic examination under supervision of the other. One representative 2D and 3D image of each patient, before and after local cryotherapy, were additionally reviewed by two blinded readers (P.K. and A.S.). The two investigators and the two blinded readers analysed the degree of vascularity by means of 2D and 3D power Doppler images before and after the application of local cold, using a semiquantitative grading system from 0 to 3 (0 = no flow, 1 = mild flow, 2 = moderate flow, 3 = intense flow). Informed consent was obtained from each patient.

An increased peri- and intra-articular microvascular power Doppler flow indicating arthritic activity could be found in all the examined joints (Fig. 1). In all patients, the ROI was identified at the second examination after 20 min of cryotherapy, so that the blinded readers could match the respective images. The rate of exact agreement in scoring between the two ultrasound investigators was 0.67 for all assessments before and after cryotherapy, compared with a rate of 0.65 between the two blinded readers. Median grading scores were calculated, which were based on the 2D and 3D scores of the four different assessors. A significant reduction of vascular signal, which was determined as a decrease of at least one grading level, was found in seven out of 13 patients (54%) after the application of local cold pack (Table 1). Five out of these seven patients (71%), who showed a temporary decrease of synovial blood flow, mentioned clinical symptoms of wrist arthritis for a period of no longer than 8 weeks. The discrimination between patients who showed a temporary reduction of synovial perfusion after local cold application and those who did not show a reaction of synovial blood vessels may reflect an underlying disturbance of normal vasoregulatory function, which possibly depends at least partially on the amount of the newly formed blood vessels (angiogenesis) [9, 10]. The 2D and 3D PDUS are able to detect and visualize changes in synovial perfusion, indicating that these methods are useful tools in the assessment of disease activity and response to different treatments in arthritis patients.

<table>
<thead>
<tr>
<th>Patient No./sex/age</th>
<th>RF</th>
<th>CRP (mg/dl)</th>
<th>ESR (mm/h)</th>
<th>Duration of RA (yrs)</th>
<th>Duration of wrist arthritis (weeks)</th>
<th>Median grading level before CryoTh</th>
<th>Median grading level after CryoTh</th>
<th>Current medical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/45</td>
<td>+</td>
<td>0</td>
<td>18</td>
<td>11</td>
<td>6</td>
<td>3</td>
<td>1 (1)</td>
<td>Pred</td>
</tr>
<tr>
<td>2/F/39</td>
<td>+</td>
<td>4.3</td>
<td>78</td>
<td>5</td>
<td>32</td>
<td>2</td>
<td>2</td>
<td>Pred, NSAID, MTX</td>
</tr>
<tr>
<td>3/F/68</td>
<td>+</td>
<td>2</td>
<td>34</td>
<td>0</td>
<td>20</td>
<td>2.5</td>
<td>1 (1)</td>
<td>Pred</td>
</tr>
<tr>
<td>4/F/64</td>
<td>+</td>
<td>2.7</td>
<td>42</td>
<td>11</td>
<td>32</td>
<td>3</td>
<td>2 (1)</td>
<td>Pred, MTX</td>
</tr>
<tr>
<td>5/F/57</td>
<td>+</td>
<td>0.7</td>
<td>34</td>
<td>5</td>
<td>20</td>
<td>2</td>
<td>2.5</td>
<td>Pred, NSAID</td>
</tr>
<tr>
<td>6/F/73</td>
<td>+</td>
<td>8.2</td>
<td>75</td>
<td>16</td>
<td>6</td>
<td>2</td>
<td>1 (1)</td>
<td>Pred, etanercept, MTX</td>
</tr>
<tr>
<td>7/M/53</td>
<td>+</td>
<td>8.2</td>
<td>51</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>Pred, NSAID, MTX</td>
</tr>
<tr>
<td>8/F/45</td>
<td>+</td>
<td>1.1</td>
<td>54</td>
<td>13</td>
<td>4</td>
<td>3</td>
<td>1 (1)</td>
<td>NSAID, Lef</td>
</tr>
<tr>
<td>9/F/82</td>
<td>+</td>
<td>4.1</td>
<td>85</td>
<td>0</td>
<td>6</td>
<td>3</td>
<td>1.5 (1)</td>
<td>Pred</td>
</tr>
<tr>
<td>10/M/72</td>
<td>+</td>
<td>1.6</td>
<td>5</td>
<td>5</td>
<td>42</td>
<td>2.5</td>
<td>2</td>
<td>Pred, Lef</td>
</tr>
<tr>
<td>11/F/83</td>
<td>+</td>
<td>2.4</td>
<td>31</td>
<td>0.5</td>
<td>28</td>
<td>2.5</td>
<td>2</td>
<td>Pred, NSAID</td>
</tr>
<tr>
<td>12/F/59</td>
<td>+</td>
<td>1.4</td>
<td>23</td>
<td>6</td>
<td>8</td>
<td>3</td>
<td>1 (1)</td>
<td>Pred, Lef</td>
</tr>
<tr>
<td>13/F/47</td>
<td>+</td>
<td>1</td>
<td>17</td>
<td>11</td>
<td>32</td>
<td>2.5</td>
<td>2</td>
<td>NSAID, MTX</td>
</tr>
</tbody>
</table>

The median grading level, before and after local cryotherapy, resulted from all the scores of the two ultrasound investigators and the two blinded readers (0 = no flow, 1 = mild flow, 2 = moderate flow, 3 = intense flow). RF, rheumatoid factor; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RA, rheumatoid arthritis; CryoTh, cryotherapy (local application of a cold pack on an inflamed wrist for 20 min); Pred, prednisolone; NSAID, non-steroidal anti-inflammatory drug; MTX, methotrexate; Lef, leflunomide.

The 2D and 3D PDUS are helpful tools to evaluate different degrees of synovial perfusion under various conditions, which can be used as outcome measures in RA.

We are grateful for the help of Andrea Schlichting (A.S.) who read the ultrasound images under blinded conditions.

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Fig. 1. 2D and 3D power Doppler sonographic images of three patients before and after local cryotherapy of the wrist (Patient 8, Patient 3 and Patient 11). A reduction of synovial blood vessels in size and number in Patients 8 and 3 is more obvious in a 3D mode compared with 2D PDUS, because 3D imaging visualizes the whole blood vessel tree in the region of interest.

Scleroderma is a rare connective tissue disease characterized by fibrosis and microvascular occlusion. The hallmark of scleroderma is tight, thickened skin brought about by excessive collagen deposition in the dermal and subdermal layers. Generalized scleroderma (systemic sclerosis) is associated with internal organ involvement, autoantibodies and a poor prognosis [1–4]. Patients with localized scleroderma also carry antibodies but their projected lifespan is not foreshortened because sclerotic involvement is largely confined to the skin and musculoskeletal systems.

Three variants of localized scleroderma exist: morphoea, generalized morphoea and linear scleroderma [4–7]. In linear scleroderma, sclerotic areas occur in a linear, band-like distribution, often crossing joint lines [3, 4]. The lesions follow the embryological lines of Blaschko. Local inflammation and fibrosis may affect the dermis, connective tissue, muscle and bone, giving rise to arthralgias, tenosynovitis, contracture, undergrowth of the limb, and nodulosis. There may be associated Raynaud’s phenomenon and carpal tunnel syndrome, but linear scleroderma usually affects the lower limbs of young females [2–4, 6, 7].

Linear scleroderma may cause substantial disability where one or more limbs are severely affected and there is the potential for marked cosmetic morbidity. Medical management may include non-steroidal anti-inflammatory drugs, penicillamine aimed at skin softening, and camouflage creams.

Local and systemic corticosteroids, methotrexate and interferon may also play a role [8]. Surgical intervention is rarely indicated and the outcome of surgery must be considered uncertain, given the patient’s predisposition to excessive local collagen deposition and that taut skin might significantly impair wound healing.

We present the case of a 19-yr-old, left-handed motor mechanic who complained of a 2-yr history of arthralgia involving the fingers of both hands. There was an ill-defined history of Raynaud’s phenomenon, but no symptoms of systemic disease. Examination revealed symmetrical, linear scleroderma arising around the mid-scapula region and radiating down the posterior aspect of the arms to the dorsum of the hands (Fig. 1). Anti-nuclear antibody was present at a titre of 1/160 IgG. Rheumatoid factor, ESR, anti-ScI70, anticentromere antibody and complement levels were normal or negative. The diagnosis of linear scleroderma was made.

Over the next 7 yr he continued to complain of palmar pain and swelling as well as ‘catching’ of his fingers with straightening, especially in the right hand. This interfered with his ability to grip tools and had a significant impact on his ability to work.

Examination revealed nodularity of the flexor tendons in the right hand proximal to the flexor retinaculum and within the palm, with palpable triggering of all digits as the fingers were actively flexed and extended. Similar findings were found in the left hand to a lesser degree. There were no signs or symptoms of carpal tunnel syndrome. Magnetic resonance imaging (MRI) demonstrated marked thickening around all flexor tendons.

The patient was managed with oral d-penicillamine and local corticosteroid injections, but his principal symptoms persisted unchanged. In view of his continuing intrusive symptoms, tenosynovectomy was considered as a means of reducing symptoms. In the absence of any information in the literature concerning the results of surgery in linear scleroderma, the patient was informed of the possibility of poor wound healing, and of recurrence and excessive fibrotic reaction.

Under a general anaesthetic and with tourniquet control, an approach from the distal forearm to the distal palmar crease was made. The median nerve was protected. There was nodular, fibrotic synovial thickening, most prominent around the profundus tendons. The synovial thickening extended from the musculo-tendinous junction to the entrance of the fibrous flexor sheath distally, confirming the findings on MRI.

A complete flexor tendon synovectomy was performed, combined with release of the A1 pulley of the index and middle finger (Fig. 2). Histological examination of the synovium showed minimal synovitis with marked fibrotic and fibrinoid changes,