The efficacy of rehabilitation for patients with rheumatoid arthritis: comparison between a 4-week rehabilitation programme in a warm and a cold climate

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The efficacy of rehabilitation for patients with rheumatoid arthritis: comparison between a 4-week rehabilitation programme in a warm and a cold climate

YA Staalesen Strumse 1, B-Y Nordvåg 2, JK Stanghelle 3, M Reisland 4, A Winther 5, P-A Pajunen 4, T Garen 4, B Flatø 6

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Objectives: To investigate the long-term effect (week 16) of a 4-week rehabilitation programme for patients with rheumatoid arthritis (RA) and to compare the effect of this intervention given in a Mediterranean or a Norwegian climate.

Methods: A randomized, controlled, parallel group design, where 124 RA patients applying for rehabilitation were randomized to a rehabilitation programme either in Norway or in a Mediterranean climate. The participants were examined clinically immediately before (week 0) and after (week 4) the rehabilitation period as well as in week 16 and answered a mailed questionnaire in week 28. The 28-Joint Disease Activity Score (DAS28), American College of Rheumatology (ACR) response and physical tests were used to measure clinical response.

Results: The baseline DAS28 value 4.45 (1.16) was reduced by −0.95 (1.05) in the Mediterranean climate and the baseline DAS28 value 4.18 (1.17) was reduced by −0.37 (0.92) in the Norwegian climate at week 16 (p = 0.003). An ACR20 improvement was achieved in 25% of the patients treated in the Mediterranean climate and in 15% of those treated in the Norwegian climate. Sustained improvement in all ACR core components at week 16 and in patient’s assessment of health status at week 28 was found in the patients treated in the Mediterranean climate only. Tests of physical function, the 6-Minute Walk Test (6MWT) and the Timed Up and Go (TUG), showed comparable improvements in patients treated in both climates.

Conclusions: RA patients showed immediate positive effects with regard to disease activity, physical function, and symptoms during a 4-week rehabilitation programme. The effects on disease activity and symptoms were larger and better maintained at least 3 months after rehabilitation in a warm rather than in a cold climate.

Patients with rheumatoid arthritis (RA) profit from regular physical exercise and physiotherapy (1–9). Intensive inpatient multidisciplinary treatment of arthritis patients has been shown to be even more effective (10–13). Some studies have found a correlation between weather parameters and symptoms such as pain and rigidity in RA patients (14–16). Local heat or cold therapy has been reported to reduce pain and improve joint mobility and grip strength (17). High doses of ultraviolet radiation may induce immunosuppression (18–20). Thus, climatic factors might have an influence on the effect of a rehabilitation programme for RA patients.

The only reported controlled study of the outcome of a rehabilitation programme in a warm climate for RA patients showed that physiotherapy in a warm climate was superior to outpatient treatment in Sweden immediately after the treatment period, whereas the long-term effect was uncertain (21). Some uncontrolled studies of physiotherapy in a warm climate have reported sustained improvements in patients’ self-reports after 3 to 6 months (22–24). Hashkes found a beneficial effect of climatic therapy on inflammatory arthritis according to the American College of Rheumatology (ACR) response definition (25), but his study did not include any long-term follow-up.

The current study was conducted to investigate the long-term effect of a 4-week rehabilitation programme.
for RA patients, using internationally accepted core sets for disease activity and improvement and objective physical tests of endurance and functional capacity. Long-term effect was defined as a sustained effect for at least 3 months. The study was designed as a randomized, controlled, parallel group trial to compare the effect of therapy in a Norwegian and a Mediterranean climate.

Materials and methods

Eligibility

The 124 participants of this study were recruited from the population of adult patients with rheumatic diseases who applied for a 4-week rehabilitation programme either in a Mediterranean country through the Section of Treatment Abroad at Rikshospitalet in Oslo or at the North Norway Rehabilitation Centre (RNNK) in Tromsø during 2003. The main inclusion criteria were a diagnosis of RA (verified by a rheumatologist), need for rehabilitation (documented by the applying doctor), objective signs of arthritis such as swollen or deformed joints, age below 70 years, and reduced physical functioning. Eligible patients should not have attended a similar rehabilitation programme within the past 9–12 months before the intervention. Patients with concomitant diseases that might have influenced the effect of the rehabilitation programme were excluded. The inclusion of patients was according to the doctors’ application and enclosed medical records.

Study design

The study was a randomized, controlled, parallel group trial. All eligible patients were invited to participate. Those accepting the invitation were randomly assigned to a 4-week rehabilitation programme either in a Mediterranean country through the Section of Treatment Abroad at Rikshospitalet in Oslo or at the North Norway Rehabilitation Centre (RNNK) in Tromsø during 2003. The main inclusion criteria were a diagnosis of RA (verified by a rheumatologist), need for rehabilitation (documented by the applying doctor), objective signs of arthritis such as swollen or deformed joints, age below 70 years, and reduced physical functioning. Eligible patients should not have attended a similar rehabilitation programme within the past 9–12 months before the intervention. Patients with concomitant diseases that might have influenced the effect of the rehabilitation programme were excluded. The inclusion of patients was according to the doctors’ application and enclosed medical records.

Intervention

The participants followed the regular rehabilitation programme given to RA patients at the centres. The main components of the therapy offered were individualized physiotherapy with exercises, group exercises, passive therapy, relaxation, and patient education.

Active physiotherapy. This included both individualized physiotherapy with exercises and group exercises. The individualized physiotherapy was given once a day; either on the couch, in the fitness department using specially constructed equipment, or in the pool. The group training (eight to 15 patients) was given twice a day; in the gym and in a temperature-controlled swimming pool. During 1 week the patients had a total of 12–15 obligatory sessions, active physiotherapy of 20–45-min duration in the Mediterranean climate and 15–16 sessions of 30–60-min duration in Norway. The exercise therapy aimed at increasing endurance, mobility, and strength. While the Norwegian programme included more endurance training, the Mediterranean programme had more focus on mobility. At all treatment centres the patients had different opportunities for additional, voluntary, physical activities either in groups or individually.

Passive therapy. This therapy comprised physiotherapy, massage, and electrotherapy. At both rehabilitation centres in the warm climate (thermo-) mineral water was used in the swimming pools, bubble baths, and for underwater massage, hence balneotherapy was part of the programme. Two passive treatments of 10–15 min a day were usually given to each patient here, whereas the patients in Norway only received passive therapy when they had a special need for it.

The programme included classes in relaxation, organized as 30–45-min supervised relaxation two to four times a week at Lillehammer, Tromsø and Balcova. At Institute Igalo activities such as yoga and tai chi were offered.

Patient education. Disease-specific lectures about RA were given at all four centres, focusing on diet, physical activity, self-efficacy, coping techniques, and advice related to general health.

To avoid interference with medication changes, we aimed to keep the DMARD medication constant both during the intervention and the follow-up.

Daylight and climate

The study period in the warm climate was in May–June in Igalo and September–October in Balcova. Both centres are located by the Mediterranean Sea and have a subtropical Mediterranean climate. Mean daylight time was 14 h 59 min in Igalo and 11 h 51 min in Balcova (computed using the National Mapping Division’s sunrisenset program, version 2.2; www.ga.gov.au/bin/astro/sunrisenset). The mean
morning temperature (measured at 0800/0730 h at the Therapy Centre in Igalo/Balcova) was 24.4°C (range 15.6–30.4°C) in Igalo and 20.1°C (range 15.0–26.0°C) in Balcova. Igalo had 2 days and Balcova 1 day with precipitation at 1.0 mm or more in average during each 4-week rehabilitation period.

The study period in Norway lasted from March to June and from August to December. Mean daylight time was 11 h 38 min in Lillehammer and 13 h 37 min in Tromso. The mean morning temperature (measured at 0700 h at the Norwegian Meteorological Institute) was 1.2°C in Lillehammer (range −9.3°C to 11.8°C) and 5.8°C in Tromso (range −6.0°C to 13.0°C). Lillehammer had an average of 8.8 days and Tromso 12.7 days with precipitation above 1.0 mm during each 4-week rehabilitation period.

Outcome measures

The medical examinations included swollen (SJC) and tender joint counts (TJC) (0–28), physician’s global assessment of disease activity [visual analogue scale (VAS), 0–10 cm], erythrocyte sedimentation rate (ESR, mm), medication, the 6-Minute Walk Test (6MWT) measuring exercise capacity (26), and the Timed Up and Go (TUG) measuring physical function (27). The same assessor performed the same medical examinations on the same patient throughout the whole study period.

The patient’s evaluation of health status included global assessment of disease activity, pain, and fatigue [all VAS scales 0–10 cm], 80% power, a minimum clinically significant difference (MCSD) at 0.9, and a standard deviation (SD) at 2.2, we needed 100 participants in each climate group to detect a difference between the two treatment groups. Randomization was performed with the Splus language for data analysis. Statistical analyses were undertaken with SPSS version 13.0.

Continual data are presented as mean and SD or median and 25th, 75th centiles according to whether the observations showed normal distribution.

To compare the non-participants with the participants and the two treatment groups we used the Pearson $\chi^2$ test, or Fisher’s exact test when appropriate, for categorical variables, independent samples t-test for continuous variables with normal distribution and the Mann–Whitney U-test for continuous variables without normal distribution. The clinical response is given as the mean difference from baseline with the corresponding SD. The paired samples t-test and independent samples t-test were used for within-group and between-group analyses, respectively. The one-sample $\chi^2$ test was used to analyse the change in percentage of patients on sick leave during the study. The chosen level of significance was probability (p) values $\leq 0.05$.

As Bonferroni correction of multiple comparisons presumes independency between the variables tested and the tests in this study were on the same subjects using highly correlated variables, Bonferroni correction was judged to be too conservative (33).

Results

Patient disposition

Three hundred and fifty-three eligible RA patients were invited to participate (Figure 1). One hundred and eighty-six patients were randomized for treatment in a Mediterranean country (n=91) or in Norway (n=95). One hundred and twenty-four patients completed the study, 72 in a Mediterranean country (44 in Turkey and 28 in Montenegro) and 52 in Norway (12 in Tromso and 40 in Lillehammer).

One hundred and sixty-seven persons chose not to participate. Additionally, 19 patients randomized to the Mediterranean climate group and 43 patients randomized to the Norwegian climate group withdrew or were excluded after randomization.

There were no significant sex and age differences between the participants (n=124) and the non-participants (n=167+19+43) of this study (data not shown). The patients who discontinued after randomization before treatment (n=12+29) were comparable to the completers (n=124) regarding age, sex, and use of DMARDs (data not shown). A higher number of patients completed the study among those randomized to the Mediterranean climate group.

Statistics

Sample size was calculated with the Sample power program. For patient’s assessment of pain (VAS; 0–10 cm), 80% power, a minimum clinically significant difference (MCSD) at 0.9, and a standard deviation (SD) at 2.2, we needed 100 participants in each climate group to detect a difference between the two treatment groups. Randomization was performed with the Splus language for data analysis. Statistical analyses were undertaken with SPSS version 13.0.

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353 Invited to participate

167 Patients would not participate or did not answer our request

186 Patients randomized

91 Assigned to treatment in Mediterranean climate

95 Assigned to treatment in Norway

19 Discontinued the study

- 12 Withdrawn after randomization before treatment
- 4 Lost to follow-up at control after 3 months
- 3 Were excluded from the study after completion *

43 Discontinued the study

- 29 Withdrawn after randomization before treatment
- 2 Lost to follow-up at control after 3 months
- 12 Were excluded from the study after completion *

72 (79% of the randomized)
Completed the study

52 (55% of the randomized)
Completed the study

Table 1. Baseline characteristics in RA patients receiving rehabilitation in a Mediterranean or Norwegian climate.

<table>
<thead>
<tr>
<th></th>
<th>Mediterranean climate (n=72)</th>
<th>Norwegian climate (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>56 (78)</td>
<td>41 (79)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>53 (9)</td>
<td>53 (10)</td>
</tr>
<tr>
<td>Married or living with a partner, n (%)</td>
<td>43 (60)</td>
<td>34 (67)</td>
</tr>
<tr>
<td>Years of education, mean (SD)</td>
<td>13 (3)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Employed full-time/part-time, n (%)</td>
<td>25 (35)/17 (24)</td>
<td>17 (33)/11 (22)</td>
</tr>
<tr>
<td>Once on sick leave during past 6 months, n (%)</td>
<td>18 (41)</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Days on sick leave past 6 months, median (25th, 75th centile)</td>
<td>25 (14, 60)</td>
<td>34 (10, 90)</td>
</tr>
<tr>
<td><strong>Disease characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration, years, median (25th, 75th centile)</td>
<td>9 (4, 16)</td>
<td>10 (3, 18)</td>
</tr>
<tr>
<td>Rheumatoid factor positive, n (%)</td>
<td>48 (67)</td>
<td>39 (75)</td>
</tr>
<tr>
<td><strong>Co-morbidity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>9 (13)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Metabolic disorders, n (%)</td>
<td>11 (15)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Asthma bronchiale, n (%)</td>
<td>5 (7)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Migraine, n (%)</td>
<td>3 (4)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Ulcus or dyspepsia, n (%)</td>
<td>1 (1)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Other diseases, n (%)*</td>
<td>6 (8)</td>
<td>9 (17)</td>
</tr>
<tr>
<td><strong>Baseline drugs (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs or coxibs daily/when needed, n (%)</td>
<td>45 (63)/15 (21)</td>
<td>30 (58)/10 (19)</td>
</tr>
<tr>
<td>Analgesics daily/when needed, n (%)</td>
<td>3 (4)/42 (62)</td>
<td>5 (11)/19 (41)</td>
</tr>
<tr>
<td>DMARDs, n (%)</td>
<td>54 (76)</td>
<td>39 (60)</td>
</tr>
<tr>
<td>Prednisolone, n (%)</td>
<td>22 (31)</td>
<td>15 (36)</td>
</tr>
<tr>
<td>Daily prednisolone dose, mg, mean (SD)</td>
<td>5 (2)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Biological treatment, n (%)†</td>
<td>11 (16)</td>
<td>14 (33)</td>
</tr>
</tbody>
</table>

NSAID, non-steroidal anti-inflammatory drug; DMARD, disease-modifying anti-rheumatic drug. *Osteoporosis n=4, Sjögren’s syndrome n=4, cancer n=4, coronary artery disease n=3. †p=0.036.
climate group (n=72) than to the Norway group (n=52) (p<0.001), but the completers of the two groups did not differ with regard to age, sex, and use of DMARDs (data not shown).

The known reasons for withdrawal after randomization before treatment were practical considerations of DMARDs (data not shown).

The known reasons for withdrawal after randomization before treatment were practical considerations (n=6), dissatisfaction with the randomization result (n=5), acute trauma/hospitalization (n=4), responsibility at home (n=4), elective therapies such as drug infusion and surgery (n=3), economic reasons (n=3), and improved condition with no need for rehabilitation (n=1). Fifteen patients withdrew without giving us any reason.

Baseline characteristics

The patient characteristics of the 72 patients treated in the Mediterranean climate [78% women, mean age 53 (range 27–69) years] were comparable to those of the 52 patients treated in the Norwegian climate [79% women, mean age 53 (range 34–69) years] (Table 1).

Efficacy

At the end of the rehabilitation programme (week 4), all disease variables except for ESR improved significantly in both patient groups treated in the Norwegian and Mediterranean climates (Table 2).

At follow-up in week 16, all assessments of disease activity (SJC, TJC, physician’s global assessment, ESR, and DAS28) showed significant improvements in patients treated in the Mediterranean climate but only DAS28 in those treated in the Norwegian climate. The tests of endurance (6MWT) and physical function (TUG) showed sustained improvements after 16 weeks in both patient groups. The improvements were larger in patients treated in the Mediterranean climate than those treated in the Norwegian climate for physician’s global assessment, ESR, and DAS28 (p<0.01).

The patient-evaluated components (patient’s global, pain, MHAQ, and fatigue) were significantly improved at weeks 16 and 28 only among patients in the Mediterranean group (Table 3).

A higher proportion of patients treated in the Mediterranean group achieved an ACR20 and an ACR50 response at week 4 than in the Norwegian group (p<0.05), but the differences were not statistically significant at week 16 (Figure 2). Subanalyses including only those above median DAS28 level at baseline increased the percentage of patients having an immediate ACR20 improvement from 38 to 47 in the Mediterranean group and from 21 to 27 in the Norwegian group, whereas the corresponding percentages at week 16 were from 25 to 26 and from 15 to 18, respectively (data not shown).

When the participants were divided into two groups according to the median DAS28 value at baseline (=4.35), a low- and a high-baseline group were generated within each climate group (Figure 3). There were significant reductions in mean DAS28 scores at weeks 4 and 16 in both the low- and high-baseline groups in the Mediterranean climate, but only in the high-baseline group in the Norwegian climate (p<0.01). The reduction was significant higher in the Mediterranean climate than in the Norwegian climate both in low- and high-baseline participants at weeks 4 and 16 (p<0.05).

Medication

Seventeen (24%) of the 72 patients treated in the Mediterranean climate had reduced or ceased non-steroidal anti-inflammatory drug (NSAID) treatment during the 4-week period compared to four (8%) of the 52 patients in the Norwegian climate (p=0.020). Nine patients (13%) in the Mediterranean group had initiated or increased NSAID treatment between weeks 4 and 16 compared to no patients from the Norwegian group (p=0.008). Six patients (8%) had reduced or terminated use of analgesics between weeks 4 and 16 in the Mediterranean group compared with no patients in the Norwegian group (p=0.040).

Three (6%) participants in the Mediterranean and two (5%) in the Norwegian group had reduced or separated their DMARD medication and two (5%) of the participants in Norway had increased or initiated DMARD medication during the intervention period (week 4). The differences in changes in DMARD medication including biological drugs or prednisolone between the two groups were not statistically significance during the whole study period (week 0–28).

There were no differences in improvement between men and women or those using DMARDs or not according to the ACR20, ACR50, DAS28, or 6MWT (data not shown).

Other variables

The patients were asked how often they had been treated individually by a physiotherapist during the past few months. The median answer was ‘never or seldom’ in the Mediterranean climate group and between ‘never or seldom’ and ‘more than once a month’ in the Norwegian climate group at baseline, ‘never or seldom’ in both climate groups at week 16, and ‘more than once a week’ in both groups at week 28.

The patients in both treatment groups had a similar median exercise frequency of two to three times weekly at baseline. This did not change significantly during the study period (data not shown).
Table 2. Clinical responses of 4-week rehabilitation in physician's evaluations, ESR, DAS28, and physical tests at weeks 4 and 16.

<table>
<thead>
<tr>
<th>Physician's evaluations</th>
<th>Changes from baseline</th>
<th>Baseline values</th>
<th>Week 4</th>
<th>p-value</th>
<th>Week 16</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of swollen joints (SJC) (0–28), median (25th, 75th centile)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediterranean climate</td>
<td>3.0 (1.0, 5.0)</td>
<td>−1.2 (2.7)</td>
<td>0.001</td>
<td>−1.2 (3.0)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Norwegian climate</td>
<td>2.0 (0.0, 4.0)</td>
<td>−0.6 (1.9)</td>
<td>0.029</td>
<td>−0.6 (2.6)</td>
<td>0.117</td>
<td></td>
</tr>
<tr>
<td>Difference between the groups</td>
<td>p = 0.010</td>
<td>0.113</td>
<td>0.234</td>
<td></td>
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<tr>
<td><strong>Number of tender joints (TJC) (0–28), median (25th, 75th centile)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediterranean climate</td>
<td>5.0 (2.0, 11.0)</td>
<td>−3.6 (4.4)</td>
<td>0.001</td>
<td>−1.7 (4.8)</td>
<td>0.005</td>
<td></td>
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<tr>
<td>Norwegian climate</td>
<td>5.5 (2.3, 9.8)</td>
<td>−2.0 (4.2)</td>
<td>0.001</td>
<td>−1.3 (5.3)</td>
<td>0.088</td>
<td></td>
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<tr>
<td>Difference between the groups</td>
<td>0.047</td>
<td>0.659</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table 3. Clinical responses of 4-week rehabilitation in patients' evaluations at weeks 4, 16, and 28.

<table>
<thead>
<tr>
<th>Changes from baseline</th>
<th>Baseline values</th>
<th>Week 4</th>
<th>p-value</th>
<th>Week 16</th>
<th>p-value</th>
<th>Week 28</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient's global assessment of disease activity (VAS; 0–10 cm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediterranean climate</td>
<td>4.6 (2.5, 6.6)</td>
<td>−2.5 (1.8)</td>
<td>0.001</td>
<td>−1.9 (2.3)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norwegian climate</td>
<td>2.1 (1.4, 3.9)</td>
<td>−0.9 (1.2)</td>
<td>0.001</td>
<td>−0.5 (1.8)</td>
<td>0.055</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference between the groups</td>
<td>p &lt; 0.001</td>
<td>0.001</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ESR, mm, median (25th, 75th centile)**

| Mediterranean climate | 20.0 (12.0, 30.0) | −0.5 (9.3) | 0.629 | −8.9 (10.2) | 0.001 |
| Norwegian climate | 17.0 (10.0, 28.0) | −2.1 (7.4) | 0.054 | 0.1 (10.0) | 0.943 |
| Difference between the groups | 0.335 | 0.001 |

**DAS28 (2–10)**

| Mediterranean climate | 4.45 (1.16) | −1.14 (0.80) | 0.001 | −0.95 (1.05) | 0.001 |
| Norwegian climate | 4.18 (1.17) | −0.57 (0.76) | 0.001 | −0.37 (0.92) | 0.007 |
| Difference between the groups | 0.001 | 0.003 |

**Physical tests**

| Mediterranean climate | 550 (86) | 69.1 (38.2) | 0.001 | 58.4 (51.9) | 0.001 |
| Norwegian climate | 547 (85) | 53.7 (77.5) | 0.001 | 64.2 (52.8) | 0.001 |
| Difference between the groups | 0.151 | 0.559 |

**Fatigue (VAS; 0–10 cm)**

| Mediterranean climate | 5.1 (2.9) | −2.9 (2.7) | 0.001 | −1.8 (2.9) | 0.001 |
| Norwegian climate | 5.3 (2.3) | −1.9 (2.4) | 0.001 | −0.3 (2.4) | 0.003 |
| Difference between the groups | 0.048 | 0.044 |

**MHAQ disability index (0–3), median (25th, 75th centile)**

| Mediterranean climate | 0.38 (0.13, 0.63) | −0.29 (0.29) | 0.001 | −0.14 (0.26) | 0.001 |
| Norwegian climate | 0.60 (0.25, 0.88) | −0.24 (0.34) | 0.001 | −0.05 (0.32) | 0.256 |
| Difference between the groups | p = 0.030 | 0.378 | 0.981 | 0.566 |

**VAS, visual analogue scale; ESR, erythrocyte sedimentation rate; DAS28, 28-Joint Disease Activity Score. Baseline values are shown as mean (SD), unless stated otherwise. Changes from baseline are shown as mean difference from baseline (SD). Number of patients treated (n) was 72 in the Mediterranean climate and 52 in the Norwegian climate.**

Table 3. Clinical responses of 4-week rehabilitation in patients' evaluations at weeks 4, 16, and 28.

<table>
<thead>
<tr>
<th>Changes from baseline</th>
<th>Baseline values</th>
<th>Week 4</th>
<th>p-value</th>
<th>Week 16</th>
<th>p-value</th>
<th>Week 28</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient’s global assessment of disease activity (VAS; 0–10 cm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediterranean climate</td>
<td>4.7 (2.2)</td>
<td>−2.9 (2.0)</td>
<td>0.001</td>
<td>−1.8 (2.5)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norwegian climate</td>
<td>4.7 (2.1)</td>
<td>−1.5 (2.3)</td>
<td>0.001</td>
<td>−0.6 (2.2)</td>
<td>0.079</td>
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<td></td>
</tr>
<tr>
<td>Difference between the groups</td>
<td>0.001</td>
<td>0.008</td>
<td>0.250</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Patient’s assessment of pain (VAS; 0–10 cm)**

| Mediterranean climate | 4.2 (2.2) | −3.0 (2.2) | 0.001 | −1.6 (2.4) | 0.001 |
| Norwegian climate | 4.4 (2.2) | −1.7 (2.4) | 0.001 | −0.4 (2.2) | 0.197 |
| Difference between the groups | 0.002 | 0.005 | 0.113 |

**MHAQ disability index (0–3), median (25th, 75th centile)**

| Mediterranean climate | 0.38 (0.13, 0.63) | −0.29 (0.29) | 0.001 | −0.14 (0.26) | 0.001 |
| Norwegian climate | 0.60 (0.25, 0.88) | −0.24 (0.34) | 0.001 | −0.05 (0.32) | 0.256 |
| Difference between the groups | p = 0.030 | 0.378 | 0.981 | 0.566 |

**Fatigue (VAS; 0–10 cm)**

| Mediterranean climate | 5.1 (2.9) | −2.9 (2.7) | 0.001 | −1.8 (2.9) | 0.001 |
| Norwegian climate | 5.3 (2.3) | −1.9 (2.4) | 0.001 | −0.3 (2.4) | 0.003 |
| Difference between the groups | 0.048 | 0.044 |

**VAS, visual analogue scale; MHAQ, Modified Health Assessment Questionnaire. Baseline values are shown as mean (SD), unless stated otherwise. Changes from baseline are shown as mean difference from baseline (SD). Number of patients treated (n) was 72 in the Mediterranean climate and 52 in the Norwegian climate.**
Thirty-seven per cent of the employed patients in the Norwegian climate group and 44% in the Mediterranean climate group had been on sick leave once during the 6-month period preceding baseline. These percentages were reduced to 28% and 31% at week 28, respectively, a significant lower proportion than expected ($p < 0.016$ and $p < 0.014$, respectively).

There were no differences in the proportion of patients on sick leave between the groups at baseline or at week 28.

Discussion

In this study, RA patients had an improved physical function and exercise capacity lasting for at least 3 months after a 4-week rehabilitation programme in both the Mediterranean and the Norwegian climate. The changes in physical tests were comparable, while improvements in DAS28 score, ESR, physician's global assessment of disease activity, and patient's assessments of health status were larger in the warm than in the cold climate. The patient evaluations of health status remained improved after 3 and 6 months in the patients treated in the Mediterranean climate only. Our results are limited by some differences between the two groups regarding the number of dropouts, patient characteristics at baseline, treatment programmes, and levels of training of the physicians involved, as well as differences in both season and daylight time. However, because double-blinded, controlled studies of rehabilitation programmes are impossible to carry out, this randomized, controlled, open study may provide important information on the efficacy of rehabilitation for patients with RA.

Johansson and Sullivan found an immediate better effect of physiotherapy in a warm climate compared with outpatient treatment in Sweden (21). Our study confirms that there is also a difference in long-term efficacy, measured by the DAS28 score, ESR, physician and patient evaluations of disease activity, which showed larger improvements after therapy in a warm than in a cold climate.

Only the DAS28 improvement of the patients treated in the Mediterranean climate was clinically significant according to the European League Against Rheumatism (EULAR) response criteria’s definition of moderate improvement: $>0.6$ for moderate disease activity ($3.2–5.1$) and $>1.2$ for high disease activity ($>5.1$) at baseline (35). However, the difference in mean reduction from baseline to week 16 between the warm climate and cold climate therapy was just on the border of clinical importance.

Only a limited proportion of the study patients showed long-term ACR20 improvement, while immediate ACR20 improvement was achieved in 38% of the patients in the Mediterranean group and 21% in the Norwegian group. This is somewhat less improvement than shown in Hashkes’ uncontrolled study of climatic therapy in RA patients, concluding that the ‘short term effects of climatic therapy are not less than for most new medications’ (25). However, in the present study more patients with low levels of SJC and TJC at baseline were included, and a high proportion of patients with zero values made...
improvements according to the ACR criterion difficult to obtain. This is demonstrated by the increase in immediate ACR20 improvements in both groups when including those with baseline DAS28 score above median level only. Shorter disease duration and more active disease were associated with a greater response in RA patients according to Hashkes (25). The patients in our study had median disease duration of 9–10 years, and the baseline DAS28 score indicated a moderate disease activity (35). Thus, ACR improvement might not be the most appropriate response criterion in our study. The main goal of rehabilitation in RA patients is to improve the patients’ functional capacity and prevent further deterioration (36). Consequently, the positive effects obtained at the functional level should be emphasized.

The physical tests showed sustained improvements after 16 weeks for both patient groups, and the improvements were comparable between the groups. The mean change in the 6MWT is judged to be of clinical significance when compared to other studies of patients with respiratory disease (37, 38). The improvements in TUG confirm that the patients had improved their walking pace.

Sustained improvement in all patient-evaluated components (patient’s global assessment of disease activity, pain, MHAQ, and fatigue) was found in the patients treated in the Mediterranean climate after both 16 and 28 weeks, but only at week 4 among those treated in Norway. This concurs with the earlier uncontrolled studies of physiotherapy in a warm climate revealing long-term efficacy in patients’ evaluations (22, 23, 24). The attained effects decline with time and it would have been interesting to know for how long they persisted.

More patients dropped out before the study started in the Norwegian group than in the Mediterranean group, even though we included the subjects who were willing to be randomized to both climate groups only. In fact, the Section of Treatment Abroad guaranteed rehabilitation in the warm climate the next year for the patients who agreed to stay in the study even though randomized to rehabilitation in Norway. We cannot ignore the possibility that the patients in the Norway group might have been disappointed about the randomization result and initiated their rehabilitation with less enthusiasm than the subjects in the Mediterranean group, and that it might have influenced the results.

The significantly higher baseline MHAQ score in the Norway group could indicate a lower functional level, and more frequent use of biological agents might indicate a more serious disease and simultaneous lower disease activity compared to the Mediterranean group. However, more baseline swollen joints and higher physician’s global assessment of disease activity in the patients treated in the Mediterranean climate could be a consequence of the fact that the medical examinations were performed by different physicians with differing levels of training in Mediterranean versus Norwegian climate patients. It has been shown that variation among observers is large for joint counts (39, 40). This emphasizes the importance of the fact that each study patient was examined by the same physician at all controls, and that the measured improvements within each group might be more reliable than the differences in improvements between the two groups in these parameters.

The climatic conditions were the main difference between the Mediterranean climate therapy and the Norwegian climate therapy given in this study. However, we still have some confounding variables that are difficult to control for. Differences in daily light exposure might influence disease activity in RA patients (41–43). The patients treated in the Mediterranean climate attended different centres during different seasons, which complicate a between-centre comparison. Factors associated with the change in environment and being far from home and daily duties might be of importance. We also cannot ignore the fact that the rehabilitation programmes had some differences even though the main components were similar. The main difference was the passive therapy, including balneotherapy, given in the Mediterranean climate centres only. Thus, our conclusion about the differences in efficacy in warm and cold climates must take into account more than just the relationship between climatic conditions and arthritis.

In a Cochrane review of balneotherapy in RA patients, Verhagen et al conclude that ‘the scientific evidence is insufficient . . . to give an answer about the apparent effectiveness of balneotherapy at this moment’ (44). However, for patients with ankylosing spondylitis, spa therapy has been shown to provide additional beneficial effect over standard treatment consisting of physical exercise and drug treatment alone (45–47).

The warm and stable climatic conditions are considered to enhance RA patients’ capacity to perform physical exercise (22). According to Hafström and Hallengren (22), the benefits of climate treatment could be due partly to the climate and partly to the change in environment as well as to the intense coordinated physiotherapy.

In conclusion, RA patients showed immediate positive effects with regard to disease activity, physical function, and symptoms during a 4-week rehabilitation programme, but the effects on disease activity and symptoms were larger and better maintained during the additional 3 months when the rehabilitation was performed in a Mediterranean rather than in a Norwegian climate. Further studies are needed to ascertain how much the rehabilitation programme, the climate, and the change in environment contribute to these differences.
Acknowledgements

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