

Effectiveness of a rehabilitative programme in improving fatigue and function in rheumatoid arthritis patients treated with biologics: a pilot study

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ABSTRACT

Objective. To evaluate the effectiveness of a personalised rehabilitative programme in improving fatigue and function in rheumatoid arthritis (RA) female patients treated with biologic DMARDs.

Methods. Thirty-eight consecutive female RA in-patients treated with biologics, entered this prospective pilot study. All subjects were in high disease activity (DAS-28>5.1). After baseline (T0) evaluation, a personalised 4-weeks rehabilitative programme was added to standard biologic treatment and all patients were re-evaluated at the end of the rehabilitative treatment (T1), at 3 (T2), 6 (T3) and 9 (T4) month follow-up. Clinical rheumatologic assessment included the DAS-28, TJC, SJC, global health status, HAQ and FACIT.

Results. Subjects showed a mean age of 65±3.5 years and a 10±1.1 years mean disease duration. All clinical and laboratory outcomes significantly improved at the different follow-up times as compared to baseline. In particular, a significant improvement in function and fatigue indices (HAQ and FACIT) was found since T1 to T4 as compared to T0. During the follow-up, DAS-28 decreased. Accordingly, about 30% of subjects achieved a moderate disease activity (DAS-28<5.1).

Conclusion. A combined treatment biologics-rehabilitation is effective in improving function and fatigue in female patients with established RA. Fatigue results independent from disease activity.

Introduction

Rheumatoid arthritis (RA) represents a major cause of disability secondary to reduced muscle mass (rheumatoid cachexia), joint damage and increased adiposity (1). Muscle loss is associated with impaired immune and pulmonary function, osteoporosis, glucose intolerance and increased mortality (1). There is also extensive evidence that a series of variables influence RA-related fatigue (pain, functional status, gender and disease duration) (1). Interventions aimed to increase muscle mass in RA patients may improve physical performance and decrease morbidity and

mortality (2). Marcora *et al.* showed that a 12-weeks high-intensity resistance training significantly improved functional capacity in RA cachectic patients (3). Similarly, Hakkinen *et al.* found that combined strength and aerobic training increased thigh muscle mass and decreased thigh fat mass in female RA patients (4). Nowadays, many reports show that biologic agents, particularly tumor necrosis factor- α inhibitors, improve RA fatigue. However, conclusive data on the efficacy of a combined biologic agents-rehabilitation programme on fatigue and disease activity in subjects with established RA are currently lacking. Our study is aimed to evaluate the effectiveness of a personalised intensive rehabilitation in reducing fatigue in female RA patients in high disease activity and with function impairment, treated with biologic DMARDs. The secondary end-point is to assess the relationship disease activity-fatigue.

Methods

From December 2009 to November 2011, 38 consecutive female in-patients diagnosed with RA according to the ACR 1987 revised criteria (5) non responders to traditional therapies and treated with biologic DMARDs, referring to the Rheumatology and Rehabilitation Research Unit of the "Salvatore Maugeri" Foundation entered this prospective study. All subjects were in high disease activity according to the disease activity score (DAS-28>5.1) and had been treated with a biologic agent for at least 12 months. After informed consent was given, a baseline (T0) clinical evaluation was carried out by a trained staff, including the 28-joint Disease Activity Score (DAS-28) according to ESR, tender joint count (TJC), swollen joint count (SJC), global health status (GH) and measures of function and fatigue including the Health Assessment Questionnaire (HAQ), and FACIT (Functional Assessment of Chronic Illness Therapy). Subjects were classified according to established criteria for the functional loss into 4 classes (6). Functional class (FC) I includes individuals without difficulties in daily life, FC II includes

Competing interests: none declared.

those with symptoms but minor limitations only, FC III includes those who are partly dependent, and FC IV includes those who are totally dependent on other persons in daily life. Venous blood samples were collected to evaluate the erythrocyte sedimentation rate (ESR).

Exercise intervention

After baseline assessment, all subjects underwent a 4-week-lasting twice/daily comprehensive rehabilitation, defined as systematic multidisciplinary treatment given by physicians, occupational therapist, psychologist, bio-engineer and exercise physiologists. The rehabilitation programmes included physical therapy with exercise aiming at improve aerobic fitness, muscle strength, mobility and balance, virtual reality rehabilitation, occupational therapy and self-management programmes. At discharge, subjects were instructed to maintain their habitual physical activity and diet during the experimental period.

Exclusion criteria were age <18 years, RA functional class <II, intolerance to exercise, cognitive impairment, unstable anti-inflammatory and/or anti-rheumatic therapy during the follow-up, cachexia related to other diseases (cancer or HIV infection), instable medical conditions, pregnancy.

Corticosteroids dosages were maintained on <10 mg/day when possible and, in order to avoid any confounding factors, anti-inflammatory drugs (NSAIDs) schedule was maintained as reported within 3 months before enrollment (Cox-2 inhibitors about twice/week). The treatment schedule was adapted when needed and any modifications were recorded. Clinical and laboratory assessments were re-evaluated in all subjects at the end of the rehabilitative treatment (T1) and after 3 (T2), 6 (T3) and 9 (T4) months.

Results

Because of intolerance to the exercise, 6 patients were excluded from the study, thus 32 subjects (mean age: 62.63 ± 13.35 years; mean disease duration: 14.87 ± 6.37 years) concluded the 4-weeks rehabilitation programme. All

Table I. Clinical and laboratory outcomes at different follow-up times.

	T0	T1	T2	T3	T4
TJC	18.63 ± 3.4	11.84 ± 3	11.56 ± 3.07	11.88 ± 3.2	11.69 ± 3.47
SJC	13.13 ± 3.96	7.34 ± 2.44	6.84 ± 2.5	6.88 ± 2.55	6.94 ± 2.9
VES	29.66 ± 23.9	18.16 ± 14.4	19.84 ± 15.15	$21.47 \pm 15.97^*$	$21.38 \pm 14.54^*$
GH	29.44 ± 9.08	47 ± 8.7	50.38 ± 7.21	49.75 ± 7.14	48.39 ± 6.3
DAS-28	5.98 ± 0.5	5.20 ± 0.55	5.15 ± 0.87	5.21 ± 0.83	5.3 ± 0.69
HAQ	2.42 ± 0.43	2.13 ± 0.42	2.13 ± 0.42	2.18 ± 0.42	2.19 ± 0.38
FACIT	16.75 ± 9	33 ± 9.06	33.63 ± 11.75	32.53 ± 12.9	29.22 ± 10.52

p vs. T0 always <0.001. **p* vs. T0 >0.05.

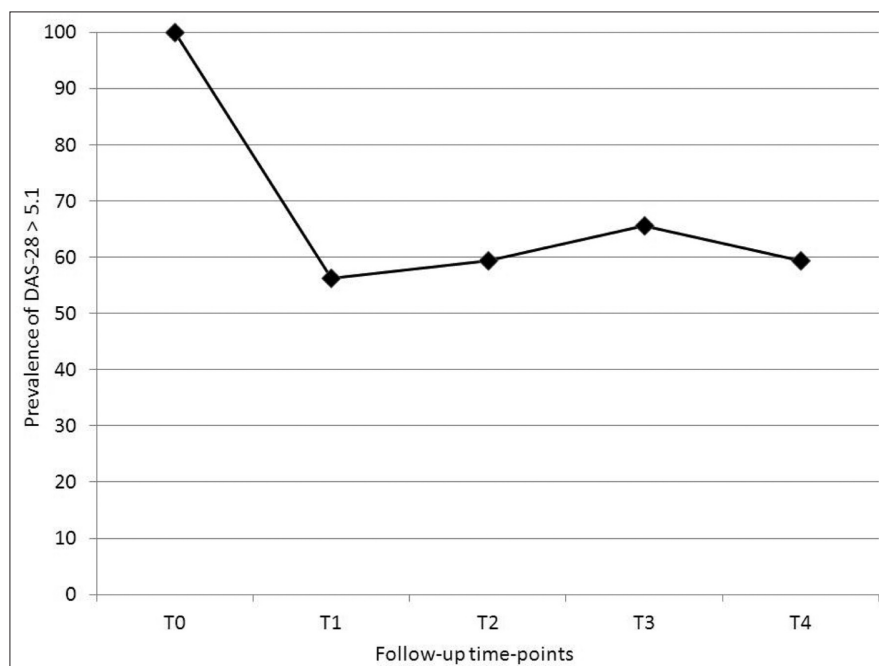


Fig. 1. Trend of DAS-28 at different follow-up times.

subjects were receiving a second biologic agent from a 16 ± 3 months mean period. More in detail, 2 subjects were receiving etanercept, 3 adalimumab, 2 infliximab plus methotrexate (15 mg/week), 3 abatacept, 9 tocilizumab, 9 rituximab plus methotrexate (15 mg/week), 6 golimumab plus methotrexate (15 mg/week) and 6 certolizumab. Among the study population, 7 (21.9%), 15 (46.9%) and 10 (31.3%) resulted in II, III and IV FC respectively. As shown in Table I, all the clinical outcomes significantly improved at the different follow-up times as compared to baseline, while a significant ESR reduction was found until T2. In particular, since T1, a significant improvement in function and fatigue indices was found. Despite a slight worsening of these values up to T4, the statistical

difference was maintained significant as compared to T0 (*p* always <0.001). Of interest, as shown in Figure 1, also DAS-28 improved during follow-up. Stratifying according to age (over- or under- 60 years of age), no significant differences in $\Delta\%$ were found for all clinical and laboratory outcomes at the different follow up times (*p* always >0.005). Of interest, at T4, the $\Delta\%$ FACIT directly correlated with $\Delta\%$ TJC and $\Delta\%$ SJC (*p*<0.005). Moreover, Pearson's correlation showed that $\Delta\%$ FACIT at T1 directly correlated with $\Delta\%$ FACIT at T2, T3 and T4 (*p* always <0.001). In addition, linear regression analysis showed that $\Delta\%$ FACIT at T1 results predictor of $\Delta\%$ FACIT at T4 ($\beta=0.883$, *p*<0.001). A direct correlation among disease duration and $\Delta\%$ ESR ($r=0.455$, *p*<0.001), $\Delta\%$ DAS-

28 ($r=0.513$, $p<0.001$) and $\Delta\%$ HAQ ($r=0.452$; $p<0.001$) at T4 was found. Stratifying according to FC, no statistical significance was found in $\Delta\%$ of all variables evaluated (p always >0.05). As to the secondary endpoint, at T4, the prevalence of DAS-28 >5.1 resulted similar in the population stratified according to T0-T4 $\Delta\%$ FACIT tertiles (1st tertile: 63.6%; 2nd tertile: 63.6%; 3th tertile: 50.0%; p for trend 0.767). No NSAIDs or corticosteroids modification was needed.

Discussion

Our findings highlight the contribution of exercise in improving fatigue and articular function in female RA patients treated with biologics, who experienced an inadequate response to therapies even because of joint damage. In order to avoid the inability to distinguish naturally occurring recovery from rehabilitation effects we enrolled only patients treated with biologic DMARDs since at least 12 months, maintaining corticosteroids and NSAIDs dosages stable during the study period. RA patients typically suffer from pain, reduced muscle strength and impaired physical function. Moreover, fatigue is common in this clinical setting being considered by patients a key determinant of their quality of life (7). Recent reports suggest that exercise should be carefully prescribed in these subjects (8). In addition, evidence is lacking for the effectiveness of exercise in patients of FC III and IV (9). Accordingly, in our knowledge this is the first study evaluating the effects of a rehabilitative programme in FC $\geq$ II subjects diagnosed with established RA undergoing biologics. It was initially thought that exercise might worsen the symptoms and cause additional damage. However, more recent reports have shown that physical activity plays a key role in RA (10). In line with these findings, our results show a significant improvement in all the variables evaluated. In detail, as shown by HAQ and FACIT variations, function and fatigue significantly improved in 4 weeks. FACIT at T1 directly related to $\Delta\%$ FACIT at T2, T3 and T4. In addition, $\Delta\%$ FACIT at T1 has been found to be a predictor of $\Delta\%$ FACIT at T4.

These results support the hypothesis that a greater functional recovery at T1 will lead to a greater functional improvement over time. At T1 a reduction of the percentage of subjects in high disease activity was found. This result was maintained up to T4, suggesting a positive effect of rehabilitation on disease activity. On the other hand, as shown by stratifying according to age and FC, older age and a severe functional status did not affect the likelihood of a good response to exercise. Of interest, whereas $\Delta\%$ FACIT correlates with $\Delta\%$ TJC and $\Delta\%$ SJC, no correlation was found with $\Delta\%$ DAS-28. This apparently contrasting result is likely to be explained by the composite nature of DAS-28. Indeed, at variance with TJC and SJC, other parameters relevant to define the disease activity (ESR and patient's global assessment of health) did not correlate with $\Delta\%$ FACIT.

These findings suggest that fatigue represents an independent RA clinical feature which, regardless of disease activity, should be investigated in all RA subjects. The latter is widely discussed. In particular, nowadays there is agreement about the positive effect of training on RA symptoms (9), but there is no evidence that exercise has detrimental effects on disease activity (6, 9). Further analyses of the impact of disease activity show that fatigue is mainly associated with pain and that SJC and the ESR have no significant associations. Accordingly, Huyser *et al.* found that the best predictors of fatigue were pain and depressive symptoms (11). In addition, less disease activity was associated with greater fatigue. Other studies concluded that pain and depression appear to be linked to higher fatigue but not disease activity (12). These differences could derive from the different clinical settings evaluated, such as early and established RA. In our setting, also ESR significantly reduced to T2. This is in line with previous reports showing the attitude of physical activity in improving inflammatory reactants in RA (13). Moreover, circulating cytokines reflect disease activity and may also play a role in the co-morbidities, such as vascular involvement (14, 15) and rheumatoid cachexia (13). Recent

reports assessed the effectiveness of a systematic multidisciplinary treatment in ameliorating fatigue, function and pain in subjects affected by different joint and muscle diseases (16, 17). In particular, Carbonell-Baeza *et al.* showed that a 3-month multidisciplinary intervention based on exercise and psychological therapy is effective in improving fatigue, stiffness, anxiety, depression and quality of life in women with fibromyalgia (18). Other groups evaluated the effectiveness of a combined rehabilitation and pharmacological treatment in subjects with severe osteoarthritis, founding that rehabilitation is effective in reducing pain, especially by adding appropriate pharmacological treatment (19) and that the implementation of multidisciplinary health care programmes is able to increase patients' satisfaction (20). Our study reveals some potential limitations such as the lack of a control group and a relatively small sample size. Being a rehabilitative centre we could not obtain a control group without training and by enrolling only female subjects, we tried to evaluate a homogeneous sample. Of interest, these patients who were affected by established disease were different from those in many of the fatigue clinical trials.

In conclusion, although many authors agree on the importance of exercise in RA, there is no specific therapy for rheumatoid cachexia and its major features. In this pilot study we showed that in RA patients in FC $\geq$ II undergoing biologics, a personalised training improves the RA features less responding to traditional therapies, fatigue and function. Larger studies assessing the drivers of fatigue in established RA are needed.

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