Rehabilitation Treatment in Patients with Ankylosing Spondylitis Stabilized with Tumor Necrosis Factor Inhibitor Therapy. A Randomized Controlled Trial

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ABSTRACT. ***Objective.*** To assess the 2- (T1) and 6-month (T2) followup effects on pain, spine mobility, physical function, and disability outcome of a rehabilitation intervention in patients with ankylosing spondylitis (AS) stabilized with tumor necrosis factor (TNF) inhibitor therapy.

Methods. Sixty-two outpatients (49 men, 13 women, mean age 47.5 ± 10.6 yrs) were randomized to rehabilitation plus an educational-behavioral (n = 20) program, to an educational-behavioral program only (n = 20), or to a control group (n = 22). The educational-behavioral program included 2 educational meetings and 12 rehabilitation exercise sessions (stretching, strengthening, chest and spine/hip joint flexibility exercises), which patients then performed at home. Outcome assessment at the end of rehabilitation training (T1) and at T2 was based on spinal pain intensity in the previous 4 weeks by self-report visual analog scale (VAS; 100 mm: 0 = no pain, 100 = maximum pain), BASMI, BASFI, BASDAI, and on chest expansion and the active range of motion of the cervical and lumbar spine measured by a pocket goniometer.

Results. The 3 groups were comparable at baseline. On intragroup comparison at T1, the rehabilitation group showed significant improvement in the BASMI and BASDAI, in chest expansion, and in most spinal active range of motion measurements. BASFI and cervical and lumbar VAS scores improved in both the rehabilitation and educational-behavioral groups. The positive results achieved in the rehabilitation group were maintained at the 6-month followup.

Conclusion. Combining intensive group exercise with an educational-behavioral program can provide promising results in the management of patients with clinically stabilized AS on TNF inhibitor treatment. (J Rheumatol First Release April 1 2011; doi:10.3899/jrheum.100987)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS
ACTIVITY INDEX
FUNCTIONAL INDEX
METROLOGY INDEX

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that primarily affects the sacroiliac joints and spine, although it may involve entheses, peripheral joints, and extraarticular organs, with functional impairment, disability and poor quality of life[1]. Assessment in AS (ASAS)/EULAR guidelines recommend combining pharmacological and nonpharmacological therapy in the management of patients with AS[2]. Among the pharmacological treatments, tumor necrosis factor (TNF) inhibitor therapy with 4 currently approved agents — infliximab, etanercept, adalimumab, and more recently golimumab — has been shown to improve signs and symptoms, function, and spinal mobility in the short term[3,4,5,6,7] but also in the long term by up to 5 years[8,9,10]. The ASAS/EULAR working group[2] suggested that nonpharmacological therapy could encompass education, exercise, and physiotherapy, which were recommended for all phases of the disease. Exercise seems to play an important role in management, particularly when performed in a supervised outpatient group or intensively in inpatients who show short-term improvement[11,12,13]. Since the introduction of TNF inhibitor therapy, the role of rehabilitation and the type of exercises performed by treated patients have only rarely been studied. Lubrano, *et al*[14] showed that etanercept and intensive inpatient rehabilitation had a synergistic effect on the management of active AS. Spadaro, *et al*[15] reported that associating occupational treatment with TNF inhibitor treatment produced positive benefits on pain, function, and disability. Dubey, *et al*[16] showed that motivation levels and time spent on physical therapy improved in AS patients on TNF inhibitor treatment. To date, however, optimal management of patients with AS has not been determined.

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Accepted for publication February 3, 2011.

In patients with stabilized AS, we hypothesized that by reducing inflammation, pain, and fatigue, TNF inhibitors may improve the efficacy of and compliance with a rehabilitation program, resulting in better function and less disability. The primary outcome was to compare the effects of combined TNF inhibitor and rehabilitation treatment with TNF inhibitors alone at 2 and 6 months' followup in patients with stabilized AS. Secondary outcome included evaluating the effects of an educational program in the same groups.

MATERIALS AND METHODS

Subjects. The study protocol considered a recruitment period from September 1, 2006, to December 31, 2007. During this period, 81 patients with AS (65 men, 16 women), classified according to the modified New York criteria[17] and treated with TNF inhibitors, were consecutively enrolled into the study. The patients, recruited via invitations to participate, were outpatients in our hospital rheumatology department. Patients were eligible to participate in the trial if (1) they had been on treatment with a standard dose of infliximab (5 mg/kg every 6 weeks) or etanercept (25 mg twice/week) or adalimumab (40 mg every 2 weeks) for at least 9 months; the patients did not require continuous intake of nonsteroidal antiinflammatory drugs; (2) they presented with a stable clinical picture, i.e., with a change in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of no more than ± 1/10 units in the previous 3 months; (3) they were aged between 18 and 65 years; (4) they did not present severe disability seriously affecting independence in activities of daily living (dressing, walking, moving, etc.); and (5) they presented no other osteoarticular diseases (e.g., rheumatoid arthritis, osteoporosis, osteoarthritis, or hip prosthesis implant).

The exclusion criteria included: (1) complete ankylosis of the spine; (2) participation in rehabilitation treatment in the previous 6 months or rehabilitation treatments other than the one envisaged by our trial; (3) failure to take part in the study; and (4) variations in standard biological therapy regimens during the study. Seven eligible patients (6 men, 1 woman) declined to participate in the trial and 5 (4 men, 1 woman) did not fulfil the inclusion criteria.

Sixty-nine patients (55 men, 14 women) were randomly allocated to attend either rehabilitation therapy, including educational-behavioral training associated with an exercise program (Rehabilitation Group, RG), or an educational-behavioral program only (Educational Group, EG), or no rehabilitation (Control Group, CG). Casual randomization using a statistical program was carried out by a rheumatologist not involved in the study evaluation or rehabilitation intervention. The study was approved by the Ethical Committee of Padova University Hospital. Informed consent was obtained from all the participants.

Interventions. The protocol rehabilitation treatment started with 2 educational-behavioral meetings followed by 10 exercise training meetings prepared by the interdisciplinary team comprising a physiatrist, a rheumatologist, a physiotherapist, and a psychologist. The educational-behavioral program addressed to the RG and EG was based on approximately 3-hour sessions, every 2 weeks, for groups of 8–12 patients at a time (the patients were encouraged to bring a partner or other family member) (Appendix 1). The educational methods used were group discussion, problem solving, guided practice, and lectures designed to facilitate program comprehension. An illustrated brochure on the program meeting with a home guide was distributed at the end of the intervention.

The exercises illustrated in Appendix 2 consisted of 12 twice-weekly sessions lasting 60 minutes each, with groups of 4–6 subjects, supervised by an experienced physiotherapist. The protocol included analytic flexibility and muscle stretching exercises for the spine and limbs, proprioceptive training, and exercises to expand the chest and control abdominal and diaphragmatic breathing. Patients were taught how to perform the programmed exercises and encouraged to perform them at home at least 3 to 4 times per week in order to comply with the study. At the end of each meeting patients received an illustrated brochure on the program meeting with a home guide. At the start of each session, feedback was provided and problems with home practice were discussed.

The education and exercise sessions were recorded with a video camera. At the end of the rehabilitation programme, a DVD containing the complete exercise program and educational meeting was distributed to all participants. In addition, to facilitate compliance with a regular exercise regimen at home, a member of our team telephoned the RG patients on a monthly basis to check that they were doing the recommended exercises and to encourage them to follow recommendations.

Measurements. Sociodemographic characteristics including age, sex, employment status, and disease characteristics [duration of complaint (years), time since diagnosis (years)] were recorded at baseline. Disease activity at baseline was measured by the erythrocyte sedimentation rate (ESR; mm/h) and C-reactive protein (CRP; mg/l) levels. Other assessments included the following 6 factors: (1) cervical and lumbar pain intensity in the previous 4 weeks, measured by a 100 mm self-report visual analog scale (VAS; 0 = no pain, 100 = maximum pain); (2) chest expansion (cm) measured with a tape measure at xiphisternum level, with clothing removed, hands on head and arms flexed in the frontal plane; (3) the Bath Ankylosing Spondylitis Metrology Index (BASMI)[18], an index that includes assessment of (a) cervical rotation, (b) tragus-to-wall distance, (c) lateral lumbar flexion, (d) the modified Schober's test, and (e) intermalleolar distance. Each parameter was assigned an increasing severity score between 0 and 2. The total BASMI score therefore ranges from 0 to 10 (the higher the BASMI score the more severe the limitation of movement); (4) the BASDAI[19], composed of 6 questions related to 5 symptoms during the previous week: fatigue, spinal pain, joint pain, tenderness, and morning stiffness. A higher score on the BASDAI reflects greater disease activity. We also considered the BASDAI items fatigue and level of morning stiffness (at the time of awakening) individually; (5) the Bath Ankylosing Spondylitis Functional Index (BASFI)[20], which analyses functional ability to perform daily activities. The higher the score on the BASFI the higher the impairment; (6) measurement of the spinal active range of motion (A-ROM) by a gravity-dependent, compass-needle pocket goniometer (IncliMed®, University of Padova), developed to measure spine mobility[21]. A-ROM measurements (degrees) were made in 2 different regions: (1) cervical: flexion-extension, rotation, and lateral inclination movements; and (2) thoracic-lumbosacral: flexion-extension, rotation, and lateral inclination. The single cervical and thoracic-lumbosacral movements were then combined to produce 2 synthetic goniometric scales referred to as the total cervical scale and the total thoraco-lumbo-sacral scale. The A-ROM of the whole spine was evaluated by the same metrologist (LB) after training on how to use the Inclimed®[21]. The angular measurements of the spine were expressed in grades and then summarized. After baseline evaluation, the patients included in the trial were invited to return for assessment after 2 months (T1, corresponding to the end of the RG rehabilitation treatment) and 6 months (T2). All patient assessments were performed by the same clinician (LB), who was blind to patient allocation and not directly involved in the education or kinesiotherapy program.

Statistical analysis. Since the sample size was quite small and the number of variables was larger than the sample size, the authors preferred to adopt a robust nonparametric approach, i.e., to use permutation tests to perform the multivariate correlation analysis[22]. Since most variables were ordinal, a Spearman permutation test was performed; a Pearson test was run for continuous data. The Bonferroni-Holm method for multiple tests was adopted to control for multiplicity, since several analyses were applied to the same variables. The cutoff significance level was set at $p < 0.05$. All statistical procedures were performed with SAS, version 9 (SAS Institute Inc., Cary, NC, USA).

To measure A-ROM we used a simple, reliable goniometric method. To test goniometric reliability (i.e., errors in measurement between 2 repeated

measurements), 31 healthy asymptomatic subjects (20 men, 11 women, mean age 25.8 yrs, SD 10.5) were randomly recruited at the university hospital where the study was conducted. All subjects underwent goniometric measurement with the same method used in the test subjects. After an average period of 35 ± 10 days, the same investigator repeated the assessment, in the same way, in the same subjects. (This investigator also took the goniometric measurements in the trial subjects.) Spearman's rho ranged from a minimum of rho = 0.90 to a maximum of rho = 0.98, while Kendall's coefficient of concordance ranged from 0.90 to 0.99.

RESULTS

Baseline evaluation. Of 69 patients randomized at the start of the study, 62 completed the trial (Figure 1). The demographic characteristics were not statistically different, and the 3 groups were matched for age, medication, disease duration, and disease severity and activity as measured by BASMI, BASDAI, BASFI, ESR, and CRP (Table 1). Table 1 also shows data relating to the start of TNF inhibitor treatment for BASMI, BASDAI, and BASFI. Spine mobility evaluated by the goniometer did not differ significantly among the 3 groups, as shown in Table 1.

Effects of rehabilitation treatment. At followup analysis at 2 and 6 months, the ESR and CRP values remained at < 27 mm/h and < 6.5 mg/l, respectively, in all patients. The intragroup comparison between preintervention and 2- and 6-month followup (i.e., at T1 and T2) is shown in Tables 2 and 3. In the RG, pain intensity ratings on the VAS at T1 were significantly reduced in the cervical ($p = 0.050$) and lumbar ($p = 0.026$) regions compared to the CG, but not to the EG ($p = 0.242$ and $p = 0.434$, respectively); similar

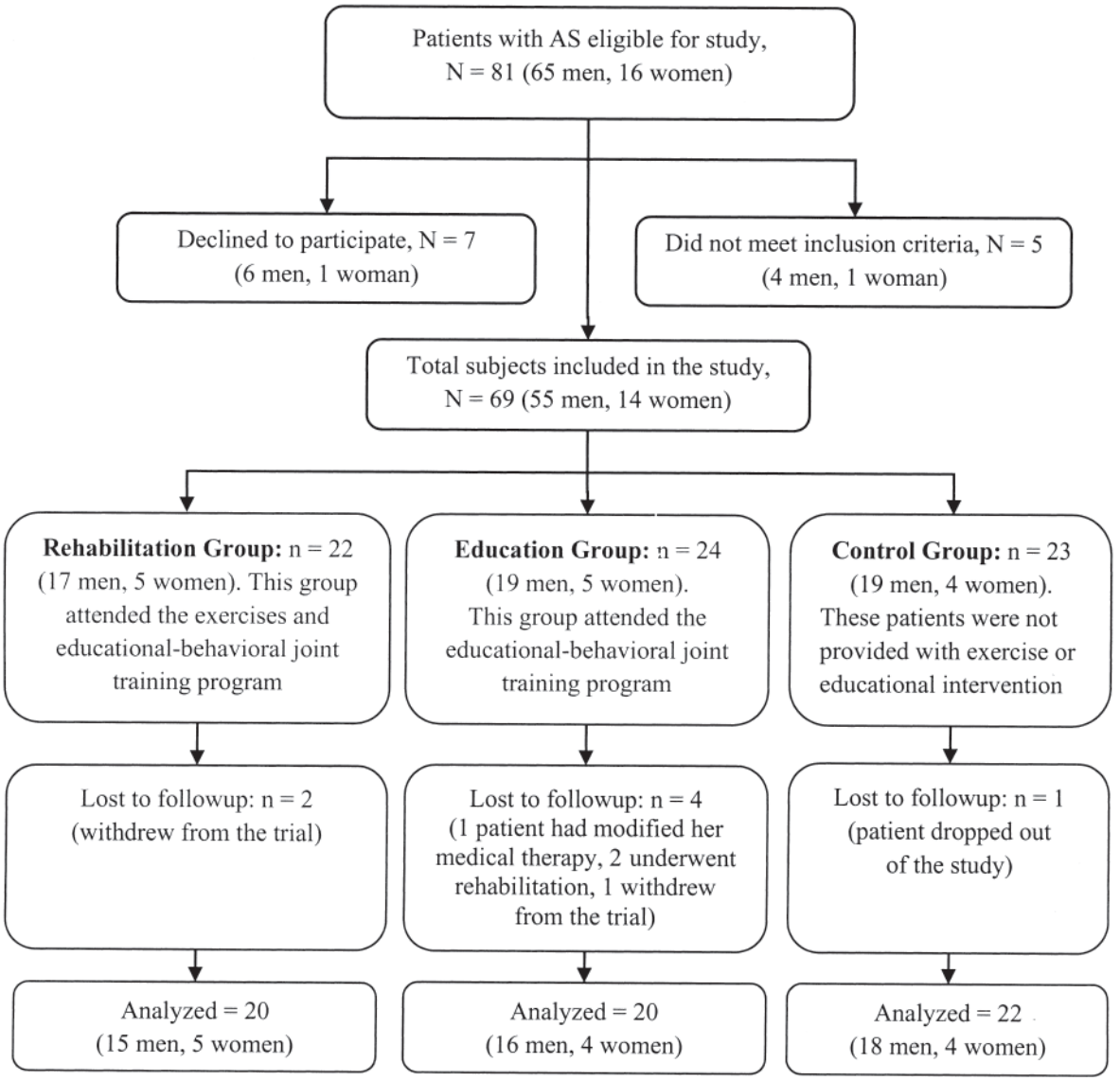

Figure 1. Subjects' participation in the trial.

Table 1. Demographic and baseline evaluation in the study patients, expressed as medians (25th-75th percentile). Fatigue and level of morning stiffness are BASDAI items.

Characteristic	Rehabilitation Group, (n = 20)	Educational-Behavioral Group, (n = 20)	Control Group, (n = 22)	p
Age, yrs	47.5 (37.2–61.5)	44.0 (38.2–52.5)	47.5 (40.7–52.5)	0.265
Work (>sedentary/>orthostatism), n (%)	6 (30.0)/14 (70.0)	6 (30.0)/14 (70.0)	5 (22.7)/17 (77.3)	0.869
Male/female, n (%)	15 (75.0) / 5 (25.0)	16 (80.0) / 4 (20.0)	18 (81.8)/ 4 (18.2)	0.856
Duration of complaints, yrs	18.0 (11.0–28.0)	14.5 (10.0–21.5)	20.5 (10.5–28)	0.278
Time since diagnosis, yrs	9.5 (4.0–14.0)	6.5 (4.0–10.0)	9.0 (3.2–13.7)	0.424
Infliximab/etanercept/adalimubab	9/5/6	9/4/7	10/7/5	0.753
Erythrocyte sedimentation rate, mm/h	9.0 (7.0–17.5)	11.0 (5.0–18.0)	9.0 (3.2–13.7)	0.910
C-reactive protein, mg/l	0.9 (0.3–3.1)	0.5 (0.1–2.5)	1.7 (0.3–6.4)	0.820
VAS cervical (0–100)	29.0 (12.0–50.2)	22.5 (12.0–48.0)	24.0 (6.7–48.5)	0.587
VAS lumbar (0–100)	29.0 (10.0–60.5)	19.5 (10–50)	22.0 (6.0–41.5)	0.817
BASMI (0–10)**	5.2 (4.1–6.5)	4.6 (5.0–7.0)	4.9 (3.2–6.2)	0.831
BASMI (0–10)	4.4 (3.4–6.1)	3.6 (2.6–5.1)	3.8 (2.8–5.4)	0.092
BASFI (0–10)**	4.7 (1.9–6.3)	4.6 (2.5–7.0)	4.5 (3.0–4.8)	0.828
BASFI (0–10)	2.5 (1.8–4.9)	2.7 (1.2–3.5)	2.8 (1.2–4.0)	0.697
BASDAI (0–10)**	4.7 (3.4–6.4)	4.4 (2.4–7.4)	4.6 (2.3–6.4)	0.879
BASDAI (0–10)	3.6 (2.2–3.0)	3.0 (2.0–6.3)	3.2 (1.7–4.3)	0.390
Chest expansion, cm	3.0 (2.0–3.0)	4.0 (3.0–5.3)	3.4 (1.8–5.0)	0.020
Cervical flexion/extension**	60.0 (56.0–104.0)	78.0 (58.0–101.0)	82.0 (70.–93.0)	0.235
Cervical flexion/extension*	69.0 (60.5–100.5)	90.0 (80.0–102.0)	88.0 (63.0–110.0)	0.296
Cervical rotation**	75.0 (54.0–104.5)	90.0 (85.0–130.5)	85.0 (53.0–93.0)	0.335
Cervical rotation*	86.0 (56.5–103.5)	95.0 (68.0–128.0)	90.0 (63.5–109.5)	0.381
Cervical side flexion**	27.0 (14.0–42.0)	41.0 (22.5–47.5)	50.0 (42.0–58.0)	0.072
Cervical side flexion*	37.0 (21.0–47.5)	46.0 (26.5–63.5)	53.0 (27.5–72.5)	0.118
Lumbosacral flexion/extension**	75.0 (65.0–95.0)	82.0 (65.0–88.5)	78.0 (60.0–100.5)	0.219
Lumbosacral flexion/extension*	84.0 (72.0–103.5)	97.0 (79.0–106.5)	90.0 (72.0–106.0)	0.340
Thoraco-lumbar rotation**	47.0 (40.0–68.5)	47.0 (37.5–55.5)	55.0 (48.0–78.0)	0.211
Thoraco-lumbar rotation*	44.0 (40.0–48.0)	50.0 (40.0–79.5)	59.0 (34.5–73.0)	0.520
Thoraco-lumbar lateral flexion**	22.0 (15.5–33.5)	21.0 (13.5–37.0)	26.0 (19.0–39.0)	0.749
Thoraco-lumbar lateral flexion*	27.0 (16.5–31.0)	27.0 (18.0–49.5)	32.0 (13.0–47.0)	0.118
Cervical movements, total**	171.0 (95.0–203)	199.0 (154.5–283.5)	195.0 (178.5–259.0)	0.247
Cervical movements, total*	205.0 (147.5–255.0)	219.0 (200.0–260.0)	216.0 (166.0–267.5)	0.192
Thoraco-lumbo-sacral movements, total**	129.0 (111.0–196.0)	136.0 (116.0–157.0)	146.0 (144.5–156.0)	0.229
Thoraco-lumbo-sacral movements, total*	144.0 (130.5–173.5)	193.0 (150–198.0)	180.0 (129.0–213.0)	0.356
Fatigue (0–10)	5.0 (2.2–5.4)	4.5 (2.0–6.3)	3.0 (1.2–5.0)	0.356
Level of morning-stiffness (1–10)	2.7 (1.3–3.7)	2.9 (0.8–4.2)	1.8 (0.6–5.1)	0.960

* Spinal active range of motion measured by a pocket goniometer (degrees). ** Data relating to the start of tumor necrosis factor inhibitor treatment. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis Functional Index; VAS: visual analog scale.

results remained at the 6-month followup. Increased chest expansion was significantly greater in the RG compared to the EG (p = 0.000) and CG (p = 0.000), and similar results were observed at 6-month followup. BASDAI scores improved more in the RG than in the CG and EG. BASMI scores were significantly higher in the RG than in the CG and EG at both 2-month and 6-month followup, and the BASFI showed a greater increase in both the RG and EG compared to the CG at both 2- and 6-month followup. In the RG there were no significant differences between T1 and T2 in the BASMI, BASDAI, and BASFI in spine mobility and pain among the patients taking different TNF inhibitor therapies (p values from 0.073 to 0.952), or in age and years from diagnosis of AS (p values from 0.962 to 0.157).

Effects on spine mobility. At T1, the RG showed significant improvements in cervical spine A-ROM compared to the EG and CG with respect to rotation and lateral inclination but not flexion-extension, as indicated in Table 2. Table 2 also shows that, at the 2-month followup, rehabilitation in the RG brought about a significant improvement in the thoraco-lumbosacral region compared to the EG and CG in all evaluation planes, except the lateral inclination. In the RG, improved spine mobility measured by the goniometer at the 6-month followup was similar to that at the 2-month followup, with further improvements in absolute values, as shown in Table 3.

DISCUSSION

Our work shows that at 2-month and 6-month followup of a

Table 2. Two month followup evaluation (after rehabilitation treatment). Results are expressed as medians (25th-75th percentile).

Characteristic	Rehabilitation Group (RG)	Educational-Behavioral Group (EG)	Control Group (CG)	p, RG vs EG	p, RG vs CG	p, EG vs CG
VAS cervical (0–100)	11.0 (3.5–23.7)	20.0 (0.0–39.2)	22.0 (15.0–52.0)	0.242	0.050	0.410
VAS lumbar (0–100)	17.5 (2.5–29.7)	12.0 (0.0–40.0)	30.0 (7.5–40.0)	0.434	0.026	0.098
BASMI (0–10)	3.7 (2.6–4.7)	3.6 (2.6–4.7)	3.7 (3.1–5.4)	0.055	0.021	0.844
BASFI (0–10)	1.6 (1.0–2.9)	1.3 (0.6–4.0)	3.0 (1.3–3.8)	0.226	0.025	0.222
BASDAI (0–10)	2.4 (1.0–3.5)	2.7 (1.5–3.4)	2.7 (1.7–4.9)	0.045	0.050	0.444
Chest expansion, cm	4.5 (4.0–6.0)	4.0 (3.1–5.8)	4.0 (2.0–5.1)	0.004	0.003	0.754
Cervical flexion/extension*	80.0 (69.0–100.5)	90 (82.5–101.5)	72.0 (57.0–107.0)	0.428	0.080	0.380
Cervical rotation*	115.0 (82.5–71.5)	100.0 (88.5–113.0)	95.0 (72.0–116.0)	0.004	0.024	0.669
Cervical lateral inclination*	59.0 (32.0–71.5)	46.0 (40.5–58.0)	37.0 (26.0–62.5)	0.023	0.000	0.254
Lumbo-sacral flexion/ extension*	94.0 (74.0–113.5)	92.0 (78.0–108.5)	95.0 (71.0–104.0)	0.040	0.009	0.741
Thoraco-lumbar rotation*	66.0 (56.0–74.0)	44.0 (36.0–76.0)	62.0 (43.0–83.0)	0.008	0.014	0.689
Thoraco-lumbar lateral inclination*	34.0 (25.0–43.5)	30.0 (20.0–43.5)	29.0 (20.0–46.5)	0.006	0.036	0.838
Cervical movements, total*	226.0 (139.0–277.5)	212.0 (160.5–243.0)	160.0 (137–231.5)	0.000	0.014	0.848
Thoraco-lumbo-sacral movements, total*	190.0 (157.5–230.5)	186.0 (146.5–205.5)	178.0 (147.5–236.5)	0.000	0.000	0.980
Fatigue (0–10)	3.0 (1.6–4.0)	3.0 (1.0–6.0)	3.5 (2.0–6.0)	0.322	0.017	0.224
Level of morning stiffness (0–10)	1.2 (0.6–3.4)	3.6 (0.6–4.2)	1.2 (0.6–3.9)	0.055	0.027	0.800

*Active range of motion of spine measured by a pocket goniometer (degrees). BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis Functional Index; VAS: visual analog scale.

Table 3. Six month followup evaluation. Results are expressed as median (25th-75th percentile).

Characteristic	Rehabilitation Group (RG)	Educational Group (EG)	Control Group (CG)	p, RG vs EG	p, RG vs CG	p, EG vs CG
VAS cervical (0–100)	10 (0.0–13.0)	18 (0.0–30.0)	25.0 (20.0–40.0)	0.230	0.013	0.310
VAS lumbar (0–100)	7.5 (0.0–20.0)	25.0 (0.0–33.7)	34.5(20.0–41.5)	0.098	0.002	0.157
BASMI (0–10)	3.1(2.4–3.8)	3.6 (1.9–4.6)	4.3 (2.7–5.8)	0.033	0.000	0.375
BASFI (0–10)	1.1 (0.7–2.0)	1.3 (0.5–2.5)	2.7 (1.4–4.0)	0.426	0.000	0.002
BASDAI (0–10)	2.4 (0.5–3.0)	2.8 (1.3–4.1)	3.0 (1.8–5.1)	0.050	0.045	0.384
Chest expansion, cm	5.0 (3.7–6.7)	4.7 (3.1–5.8)	4.5 (3.0–6.1)	0.000	0.003	0.825
Cervical flexion/extension*	82.0 (68.5–107.5)	100.0 (86.5–114.5)	78.0 (49.0–105.0)	0.428	0.175	0.346
Cervical rotation*	122.0 (136.0–92.0)	100.0 (86.5–114.5)	79.0 (56.0–108.5)	0.004	0.000	0.575
Cervical lateral inclination*	58.0 (48.0–70.5)	51.0 (42.0–60.0)	43.0 (26.0–72.5)	0.020	0.000	0.254
Lumbosacral flexion/extension*	101.0 (82.0–114.0)	100.0 (76.0–107.0)	84.0 (69.5–98.5)	0.030	0.010	0.366
Thoraco-lumbar rotation*	66.0 (58.5–81.5)	41.0 (40.0–70.5)	52.0 (34.0–75.0)	0.005	0.000	0.984
Thoraco-lumbar lateral inclination*	37.0 (26.0–51.5)	28.0 (17.0–47.5)	20.0 (13.5–48.5)	0.003	0.017	0.730
Cervical movements, total*	236.0 (185.0–275.5)	218.0 (193.0–236.0)	179.0 (110.0–247.0)	0.000	0.000	0.481
Thoraco-lumbo-sacral movements, total*	190.0 (157.5–230.5)	186.0 (146.5–205.5)	178.0 (147.5–236.5)	0.000	0.000	0.801
Fatigue (0–10)	2.2 (1.0–3.0)	3.0 (2.0–5.1)	4.0 2.0–5.0)	0.035	0.000	0.069
Level of morning stiffness (0–10)	1.2 (0.6–3.4)	3.0 (0.6–3.6)	2.6 (0.6–4.2)	0.055	0.023	0.641

* Active range of motion of spine measured by a pocket goniometer (degrees). BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis Functional Index; VAS: visual analog scale.

randomized trial, patients with clinically stabilized AS, who had started TNF inhibitor therapy at least 9 months previously, were able to further improve spine mobility and reduce pain, stiffness, and disability by rehabilitation therapy based on an educational-behavioral intervention and exercise training. On the basis of our unexpected results, we can also affirm that the rehabilitation treatment seems to work better than the previous anti-TNF treatment. Our exercise training protocol included a simple program that AS patients can easily perform at home (respiratory, stretching, proprioceptive, mobilization, and strengthening exercises for the lower and upper extremities and back muscles). Compliance with the home exercises was optimal even at the 6-month followup. No significant differences in the effects of the 3 types of TNF inhibitors used in our study were exhibited in the RG. Nevertheless, while the 4 currently approved TNF inhibitors infliximab, etanercept, adalimumab, and golimumab have transformed the standard of care for patients with AS by providing symptom relief, retarding spinal inflammation, and significantly improving quality of life, pharmacological therapy alone does not preclude the need for physical therapy or exercise[6,7,23,24]. In a recent review, Elyan, *et al*[25] maintained that current data do not address the role rehabilitation may play in patients with

AS in the era of TNF inhibitors. No comparisons are made, for example, between stabilized patients combining TNF inhibitor treatment with education and exercises, and patients on treatment with TNF inhibitors alone. In our study, changes in spine mobility (A-ROM), measured by a simple, repeatable, reliable goniometric method[22], refer to maximum single movements in the 3 spatial planes (cervical, thoracic, and lumbosacral) and global movement (given by the sum of movements for each individual region). At 2- and 6-month followup, the RG showed significant increases in A-ROM in both the cervical and thoraco-lumbosacral regions compared to the EG and CG. Muscle strength training exercises, which are not intensive but constant over time, are critical for keeping the back straight and mobile in AS[11]. These data corroborate the results of the BASMI index, classically used to express degree of global mobility in patients with AS. However, since goniometric measurement is also regional, the training exercises can be tailored to each patient. Despite its very good qualities, Jenkinson, *et al*[18] and Heikkila, *et al*[26] have reported that some measures in the BASMI index are sensitive while others are less so. Based on their analysis, the BASMI index has one highly sensitive (lumbar side flexion), 2 moderately sensitive (cervical rotation and intermalleolar distance), and 2 relatively poorly sensitive measures (Schober's test and tragus-to-wall distance). The BASMI index was adopted because it is the only validated index in the peer-reviewed literature (with established criterion validity and interobserver reliability) to assess the status of the axial skeleton in patients with AS. Widberg, *et al*[27] reported that 8 weeks of self- and manual mobilization treatment improved chest expansion, posture, and spine mobility at 4 months' followup. Fernandez de las Penas, *et al*[12,13] also recently demonstrated that AS patients treated with an exercise regimen based on the Global Posture Reeducation method, focused on specific strengthening and flexibility exercises for the muscle chains affected in AS, showed better functional and mobility outcomes and maintained a higher proportion of their clinical improvement at 12-month followup. None of these studies[12,13,27] included patients receiving TNF inhibitor treatment. The significant improvement in the BASDAI (an index of disease activity) and in 2 of its items in particular (fatigue and morning stiffness) is interesting because we believe that less fatigue and less morning stiffness may have helped enhance performance and compliance with exercises. Fatigue is a major symptom of AS and it appears to be associated with level of disease activity, functional ability, global well-being, and mental health status[28]. To explain the benefits obtained in functional status and quality of life in one study that used etanercept and intensive inpatient rehabilitation to manage active AS, Lubrano, *et al*[14] similarly hypothesized that reducing inflammation and fatigue with etanercept improved the efficacy of rehabilitation.

BASFI scores, recommended by the ASAS group for evaluating physical function[29,30], revealed a significant improvement in both the RG and EG compared to the CG at both 2- and 6-month followup. This suggests that the education program also helped reduce disability in these patients. The usefulness of the education program, which probably improved disease management, is further confirmed by the positive effects on cervical and lumbar pain, which decreased in both the RG and EG. In the context of arthritis, self-efficacy through educational training means perceived ability to manage pain, fatigue, and physical functioning on a daily basis and has been shown to play a mediating role in the relationship between disease severity and adaptation, protecting the individual from the adverse effects of disease severity. Patient education may be one way of promoting arthritis self-efficacy among people with AS, thus enhancing psychological well-being and healthy behavior (e.g., exercise). In turn, the positive influence of the exercise program on daily life motivated AS patients to continue exercising at home through to followup. To facilitate compliance, we designed a simple exercise program that can be easily carried out at home; in addition, we believe that the TNF inhibitor may still have played a positive role to improve compliance. In this regard, Dubey, *et al*[16] showed that motivation levels and time spent on physical therapy can improve significantly in patients undergoing TNF inhibitor treatment. This result is interesting and may be partly attributable to reduced fatigue and morning stiffness and increased functional ability. Other authors[15] have also shown that a combination of TNF inhibitor and rehabilitation can improve the benefits perceived by AS patients when doing physiotherapy.

Our results suggest that combining exercise with an educational-behavioral program can provide promising results in the management of patients with clinically stabilized AS receiving TNF inhibitor treatment. According to Ton

APPENDIX 1. Educational-behavioral program.

Content of meeting	Descriptions
Information about AS	Pathophysiology of AS, physical structures involved, physiopathology and course; objective of medication today
Mechanisms and control of pain and stress	Information given about the relationships between pain, muscle tension, stress, and depression; cognitive methods of pain management were outlined. Extensive information given on relaxation as a method of pain management.
Importance of exercise training and strengthening and stretching exercises	Identification of barriers to exercise
Identification of problems during normal life (at home or at work)	Identification of problem-solving techniques to overcome barriers

APPENDIX 2. Exercise training program.

Type of Exercise	Characteristics	Sequences	Time
Respiratory exercises	(1) Deep breathing; (2) chest expansion; (3) thoracic breathless; (4) expiratory breathless; (5) abdominal control and diaphragmatic breathing exercises (6) exercises for scapular girdle muscle (shoulder elevation in combination with breathless	2 series of 10 repetitions each	10 min
Exercises to mobilize the vertebrae and limbs	(1) Cervical side: lateral flexion and rotation (left and right), flexion-extension; (2) thoraco-lumbar side: lateral-flexion, flexion-extension, rotation; (3) shoulder and upper limb side: ab/adduction, flexion, elevation, and circumduction; (4) coxofemoral, knee and ankle side: ab/adduction, rotation and flexo-extension	2 series of 10 repetitions each per mobilization. Exercises were performed lying and/or seated and/or standing and/or on all fours or walking pain-free. Spinal exercises were combined with respiratory exercises (i.e., deep breathing or expiratory breathless)	15 min
Balancing and proprioceptive exercises	Standing and walking	2 series of 10 repetitions each	10 min
Postural exercises and spinal and limb muscle stretching and strengthening	(1) Stretching exercises for the posterior (thoraco-lumbar and all erector spine group, etc.) and anterior (superior and inferior abdominal etc.) muscle chain of the spine; (2) stretching exercises for the anterior (psoas, hamstring etc.) and posterior pelvic girdle muscle chain; (3) stretching of anterior and posterior muscles of lower limbs	2 repetitions of an average of about 30/40 seconds each for stretching. All exercises could be performed both lying and seated or on all fours or in a standing position with active and passive mobility, pain-free	15 min
Endurance training	Endurance exercises for a progressive duration on the basis of the patient's functional capacity	Walking or treadmill or cycling (low speed, without resistance)	10 min

Nghiem, *et al*[31] and Elyan, *et al*[25], further research should aim to determine which exercise protocols to recommend in the management of patients with AS.

ACKNOWLEDGMENT

We acknowledge Prof. Luigi Salmaso for assistance in statistical calculations, Valentina Modesti, Rheumatologist Resident, and Alessandra Demontis, Physiatry Fellow, for their support in the clinical trial.

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