

Effects of a Combination Treatment of an Intensive Rehabilitation Program and Etanercept in Patients with Ankylosing Spondylitis: A Pilot Study

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ABSTRACT. *Objective.* To determine the effects of a combination treatment including rehabilitation and etanercept versus rehabilitation only, on function, disability, and quality of life in a group of patients with active ankylosing spondylitis (AS).

Methods. Nineteen patients with AS consecutively admitted to a rehabilitation inpatient clinic were enrolled. Patients first participated in an intensive rehabilitation program and after a 6-month interval started etanercept therapy. After 3 weeks, they started a combination of rehabilitation and etanercept. The primary outcome measure was an improvement of the Bath Ankylosing Spondylitis Functional Index (BASFI) defined as the difference (Δ) between the 2 measurements (beginning and end). The difference between the 2 measurements for the first rehabilitation program was expressed as Δ_1 and for the second as Δ_2 ; the comparison between Δ_1 and Δ_2 for each outcome measure was taken into account. Secondary outcome measures included an improvement in the Revised Leeds Disability Questionnaire (LDQ), anthropometric measures, EuroQol (EQ-5D_{vas}), and the 6 minute walking test (6-MWT).

Results. A statistically significant improvement was observed both for BASFI ($\Delta_1 = -0.71 \pm 0.23$; $\Delta_2 = -1.19 \pm 0.36$, $p < 0.001$) and for LDQ ($\Delta_1 = -0.28 \pm 0.08$; $\Delta_2 = -0.46 \pm 0.17$, $p = 0.001$). All anthropometric measures as well as 6-MWT were statistically improved. Finally, EQ5D_{vas} showed a statistically significant difference ($\Delta_1 = 6.63 \pm 2.81$; $\Delta_2 = 20.26 \pm 4.89$, $p < 0.001$). No adverse effects were seen during treatment with etanercept.

Conclusion. This combination treatment seems to improve function, disability, and quality of life in patients with active AS. (J Rheumatol 2006;33:2029–34)

Key Indexing Terms:

ANKYLOSING SPONDYLITIS
DISABILITY

ETANERCEPT

QUALITY OF LIFE
REHABILITATION

Ankylosing spondylitis (AS) is a chronic inflammatory disease that, if untreated, may progress to total bony ankylosing of the spine. This disease can lead to severe damage of the spine with functional impairment, disability, and poor quality of life^{1,2}.

AS requires combined management (pharmacological and physical therapy) and advice from different health professionals. However, optimal management for AS remains unresolved. For many years, pharmacological therapy of AS has been based predominantly on nonsteroidal antiinflammatory drugs

(NSAID) and some disease modifying antirheumatic drugs (DMARD), including sulfasalazine and methotrexate (MTX), which have shown some therapeutic effect on peripheral arthritis but minimal effect on spinal involvement³⁻⁶ of AS.

Anti-tumor necrosis factor- α (TNF- α) agents seem to be a promising therapy for AS^{7,8}. Among these agents, etanercept is a fully human recombinant protein that specifically binds to and neutralizes TNF- α ; it has been shown to be an effective treatment for reducing clinical symptoms and signs of AS as well as disability, and for improving the quality of life^{9,10}. Physiotherapy interventions for AS have also been shown to be an important part of AS management, with a tendency to be more effective when carried out in a supervised outpatient group setting¹¹⁻¹³. Studies have shown that intensive inpatient rehabilitation is effective in inducing short-term improvement in spinal mobility¹⁴, but doubts remain about sustained improvement after long periods of time^{15,16}. Some data showed that patients with AS experienced progressive loss of movement independent of disease duration and reported frequency of unsupervised exercise¹⁷. These contradictory results may depend on methodological differences such as patient selection and physiotherapy regimen.

We hypothesized that etanercept, acting on inflammation

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Accepted for publication May 23, 2006.

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and fatigue reduction, may improve the efficacy of a rehabilitation program, resulting in better function and quality of life. We evaluated the effects of a combination treatment (etanercept and rehabilitation) compared to rehabilitation alone in the same group of patients with AS, consecutively admitted to an intensive rehabilitation inpatient clinic.

MATERIALS AND METHODS

Study design. The study protocol considered a recruitment period from January 1, 2004, to March 31, 2004. During that period, 37 patients with AS, satisfying the modified New York classification criteria¹⁸, were consecutively admitted to our outpatient rehabilitation clinic; 19 were considered active and eligible for our study. Initiation of etanercept was based on the Assessment in Ankylosing Spondylitis (ASAS) working group recommendations^{19,20}. The 18 patients excluded from the study did not differ from the study patients in terms of sex, age, disease duration, and B27-positive antigen, but only in activity status (see below).

Exclusion criteria were presence of complete ankylosis (fusion) of the spine; previous usage of anti TNF- α inhibitors including etanercept; use of DMARD other than sulfasalazine or MTX within 4 weeks before enrollment; use of more than 10 mg prednisone daily; variation of NSAID or prednisone dose within 2 weeks before enrollment; and positive screening for tuberculosis. None of the 19 patients with active AS fulfilled any exclusion criteria. All patients gave their written informed consent and the study protocol was approved by the local Ethics Committee.

Recruited patients with active AS, after an initial outcome assessment (Time 1), carried out a 3-week intensive inpatient rehabilitation program. At discharge (Time 2) the patients did not receive any daily home exercise program. After 6 months, the patients had a reassessment of outcome measures and started etanercept treatment (25 mg twice/wk) (Time 3). After 3 weeks of etanercept therapy they were readmitted to the rehabilitation clinic. There, after a reassessment of outcome measures (Time 4), they received etanercept therapy and the same 3-week intensive inpatient treatment program previously undertaken. At the end of the second rehabilitation program the same outcome assessments were carried out (Time 5).

The difference between Time 2 and Time 1 assessments was expressed as $\Delta 1$; the difference between Time 5 and Time 3 as $\Delta 2$; $\Delta 1$ and $\Delta 2$ were compared for each outcome measure to determine the efficacy of the combination treatment versus rehabilitation only.

We also measured the differences between Time 5 and Time 4 (expressed as $\Delta 3$) and between Time 4 and Time 3 (expressed as $\Delta 4$). Comparisons between $\Delta 1$ and $\Delta 3$ (the 2 periods of rehabilitation) and $\Delta 3$ and $\Delta 4$ (rehabilitation vs etanercept only) were also carried out.

Disease activity assessment. Disease was considered active following recommendations of the ASAS working group^{19,20}. On the basis of these recommendations patients were enrolled if disease was not controlled by NSAID and at least 3 of the following conditions were present: (1) patient's global assessment ≥ 40 mm on a visual analog scale (VAS) rated from 0 (none) to 100 mm (most severe); (2) inflammatory pain (100 mm VAS) ≥ 40 mm; (3) Bath Ankylosing Spondylitis Functional Index (BASFI)²¹ value ≥ 40 mm; (4) erythrocyte sedimentation rate (ESR) > 28 mm/h or raised C-reactive protein (CRP).

As an additional measure of disease activity, a value ≥ 4 (0–10) on the Bath AS Disease Activity Index (BASDAI)²² was also taken into account.

Interventions. All participants participated in an intensive standardized exercise program, twice daily, under the supervision of a senior physiotherapist. Each session of the exercise program included (1) a warmup followed by 30 minutes of strengthening exercises of all limbs with active and passive mobility, performed in a supine or seated position, consisting of maximal isometric pain-free contractions and dynamic (concentric-eccentric) contractions against gravity; (2) stretching exercises, also using progressive neuromotor facilitation for 15 minutes; (3) endurance exercises of a progressive duration based on the patient's functional capacity and disease severity; generally the

program included 15 minutes of cycling (low speed, without resistance), 10 minutes on the treadmill (low speed, without resistance), and 10 minutes of walking; and (4) respiratory exercises for 15 minutes.

At the onset of the exercise program, for the first 5 days participants tried to reach 60% of their predicted heart rate at maximal exercise. This was progressively increased to a maximum of 80% of the predicted rate after the 5th day and until the end of the program.

After 3 weeks of intensive rehabilitation all patients were discharged.

Etanercept was self-administered by patients as a 25 mg dose subcutaneously twice weekly, starting the therapy at home and then continuing during the 3 weeks of intensive inpatient rehabilitation.

Outcome assessment. The primary outcome measure was an improvement of the BASFI. The composite score of the 10 VAS items of this validated scale were administered at the beginning (Time 1 and Time 4) and at the end of each rehabilitation program (Time 2 and Time 5), as well as at the beginning of etanercept treatment (Time 3).

As secondary outcome measures, we applied at the same timepoints (1) the Italian version of the revised Leeds Disability Questionnaire (LDQ) to assess function and disability²³; (2) anthropometric measures²⁴ including tragus to wall distance, measured as mean distance between right and left sides; chest expansion, measured with the patient's clothing removed, hands on head and arms flexed in the frontal plane, with a tape measure at the level of xiphisternum; and modified Schober's test, using distraction of marks 15 cm apart, the upper 10 cm above and the lower 5 cm below the lumbosacral junction; (3) the self-rating VAS scale (0–100) of the European quality of life (EuroQol)²⁵ questionnaire (EQ-5D_{vas}) because it is a quantitative measure of patients' evaluation of their own global health status²⁶; and (4) the 6-minute walking test (6-MWT)²⁷ as a quick measure of functional status and cardiovascular capacity in patients with chronic conditions, such as rheumatoid arthritis and AS^{28,29}. It was carried out on a level hallway and was supervised by a physician. Patients were instructed to cover the greatest distance possible during the allotted time, at a self-administered walking speed, pausing to rest as needed. The total distance in meters during the 6-MWT was recorded.

Involvement of peripheral joints, eyes, and skin and detection of HLA-B27 antigen were also assessed.

Statistical analysis. Statistical analysis was carried out using the SPSS package (version 11.5). Comparisons between baseline and after-treatment values were performed using Wilcoxon signed-rank test. Descriptive data were expressed, if not otherwise specified, as mean \pm standard deviation (SD). Statistical significance was accepted at $p < 0.05$.

RESULTS

Descriptive data. All descriptive data are summarized in Table 1. Of the 19 enrolled patients, there were 16 men and 3 women; mean age was 41.3 ± 8.6 years and disease duration was 9.3 ± 6.0 years. Sixteen of the 19 patients (84%) were HLA-B27-positive. Ten patients (53%) were receiving MTX during the study and 11 (58%) were receiving steroids. No patient was taking sulfasalazine. All patients were taking NSAID.

Five patients (26%) showed clinical hip involvement; only 1 showed shoulder involvement (5%). Psoriasis was recorded in 1 patient (5%) and eye involvement was found in 1 patient (5%).

Finally, patients showed limited peripheral joint involvement; given the paucity of information, no meaningful results on peripheral joints were obtained.

No patient dropped out of the study.

Changes in the outcome measures. Data obtained from the 5-point assessments for each outcome measure are shown in

Table 1. Demographic and clinical data of patients.

No. of patients (M/F)	19 (16/3)
Mean age, yrs \pm SD	41.3 \pm 8.6
Mean disease duration, yrs \pm SD	9.3 \pm 6.0
Peripheral hip involvement, n (%)	5 (26)
Peripheral shoulder involvement, n (%)	1 (5)
Skin involvement, n (%)	1 (5)
Eye involvement, n (%)	1 (5)
HLA-B27-positive, n (%)	16 (84)
Patients receiving steroids, n (%)	11 (58)
Patients receiving MTX, n (%)	10 (53)

MTX: methotrexate.

Figures 1 and 2. ESR was raised in all patients at study onset (Time 1), with a mean value of 35.8 ± 5.5 mm/h. Before starting etanercept (Time 3) the mean value of the ESR was 36.9 ± 8.5 and only one patient showed an ESR < 28 . ESR decreased at Time 5, reaching a mean value of 14.2 ± 6.5 . CRP was raised in all patients at Time 1 (14.1 ± 2.7 mg/dl), continuing to be raised at Time 3 (13.8 ± 2.0), and decreasing by Time 5 (5.0 ± 2.2).

Table 2 shows the mean changes expressed as Δ for each outcome measure. Four measures, the BASFI ($\Delta 1: -0.71 \pm 0.23$; $\Delta 2: -1.19 \pm 0.36$, $p < 0.001$), the LDQ ($\Delta 1: -0.28 \pm 0.08$; $\Delta 2: -0.46 \pm 0.17$, $p = 0.001$), the EQ-5D_{vas} ($\Delta 1: 6.6 \pm 2.8$; $\Delta 2: 20.3 \pm 4.9$, $p < 0.001$), and the BASDAI ($\Delta 1: -0.71 \pm 0.40$;

$\Delta 2: -1.15 \pm 0.62$, $p = 0.002$), were all significantly different comparing timepoints 1 and 2.

All anthropometric measures showed a significant improvement: tragus to wall distance ($\Delta 1: -2.74 \pm 1.11$ cm vs $\Delta 2: -4.47 \pm 1.93$ cm, $p = 0.001$); chest expansion ($\Delta 1: 0.68 \pm 0.38$ cm vs $\Delta 2: 1.05 \pm 0.23$ cm, $p = 0.003$); modified Schober's test ($\Delta 1: 0.48 \pm 0.17$ cm vs $\Delta 2: 0.74 \pm 0.16$ cm, $p = 0.002$). A statistically significant difference in 6-MWT was observed between $\Delta 1$ (76 ± 34 m) and $\Delta 2$ (192 ± 98 m, $p < 0.001$), suggesting that the introduction of etanercept might increase endurance. Comparison of acute phase reactants also showed significant differences: $\Delta 1$ ESR: 0.4 ± 3.2 mm/h; $\Delta 2: -22.7 \pm 8.3$, $p < 0.001$; $\Delta 1$ CRP: 1.05 ± 2.53 mg/dl; $\Delta 2: -8.84 \pm 3.32$, $p < 0.001$.

Comparison of $\Delta 1$ and $\Delta 3$ was also carried out to determine if there was any difference in the 2 single periods of rehabilitation. No significant differences were found other than for the EQ-5D_{vas} ($\Delta 1: 6.63 \pm 2.81$; $\Delta 3: 9.63 \pm 4.28$, $p = 0.006$). The BASFI showed a positive trend without reaching statistical significance ($\Delta 1: -0.71 \pm 0.23$; $\Delta 3: -0.89 \pm 0.39$, $p = 0.06$) (Table 2).

Finally, when $\Delta 3$ and $\Delta 4$ were compared, a significant difference was found for the BASFI ($\Delta 3: -0.89 \pm 0.39$; $\Delta 4: -0.29 \pm 0.22$, $p = 0.001$). All anthropometric measurements showed a significant difference between $\Delta 3$ and $\Delta 4$. LDQ showed a positive trend without reaching significance ($\Delta 3: -0.30 \pm$

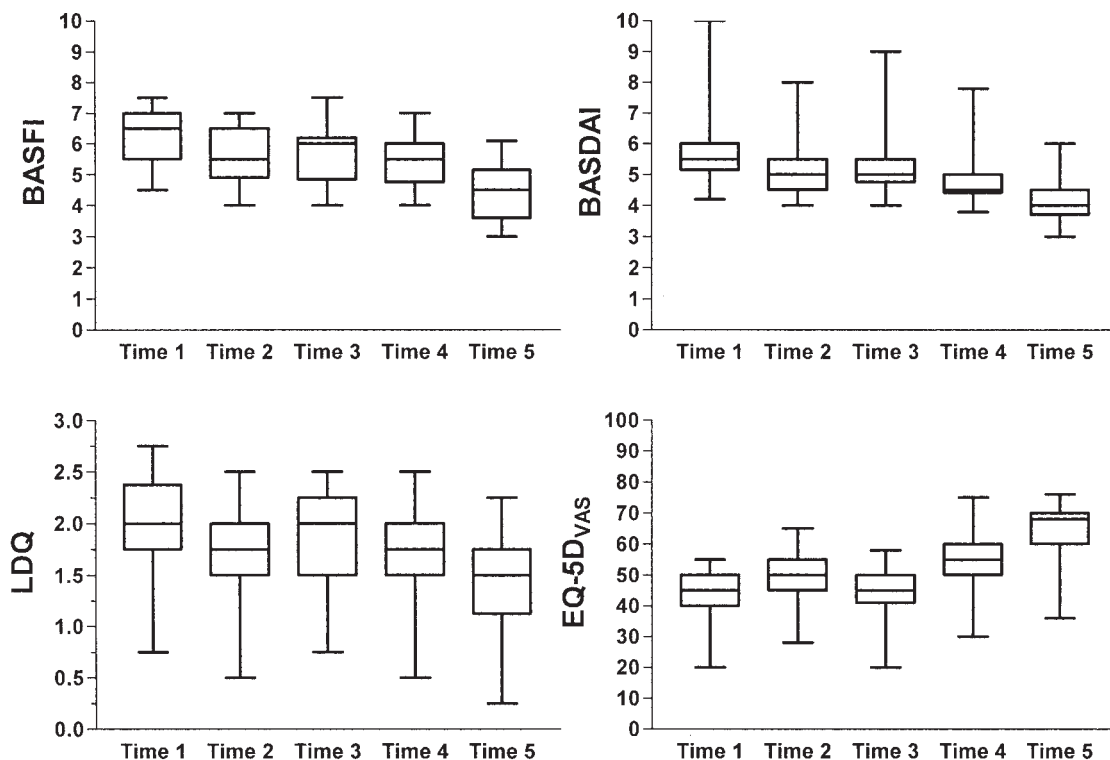


Figure 1. Changes, at the 5 timepoint assessments, of the primary and some secondary endpoints. Boxes show 25th to 75th percentile and median (the 50th percentile). Whiskers show highest and lowest values of the series.

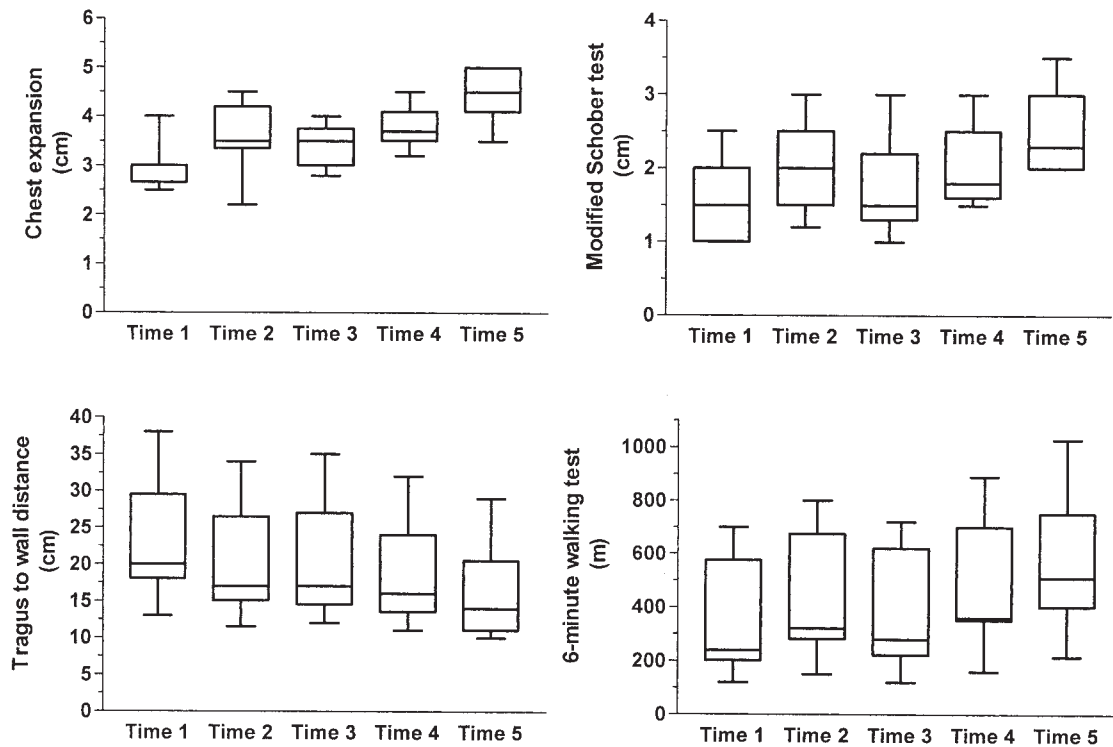


Figure 2. Changes, at the 5 timepoint assessments, of the main anthropometric measures and the 6-minute walking test. Boxes show 25th to 75th percentile and median (the 50th percentile). Whiskers show highest and lowest values of the series.

Table 2. Comparisons of the change (Δ) in the primary and secondary endpoints. Data are mean (standard deviation).

	$\Delta 1$	$\Delta 2$	p ($\Delta 1-\Delta 2$)	$\Delta 3$	$\Delta 4$	p ($\Delta 1-\Delta 3$)	p ($\Delta 3-\Delta 4$)
BASFI	-0.71 (0.23)	-1.19 (0.36)	< 0.001	-0.89 (0.39)	-0.29 (0.22)	0.06	0.001
LDQ	-0.28 (0.08)	-0.46 (0.17)	0.001	-0.30 (0.20)	-0.16 (0.17)	NS	0.06
EQ-5D _{vas}	6.63 (2.81)	20.26 (4.89)	< 0.001	9.63 (4.28)	10.63 (4.41)	0.006	NS
BASDAI	-0.71 (0.40)	-1.15 (0.62)	0.002	-0.61 (0.42)	-0.55 (0.34)	NS	NS
Tragus to wall, cm	-2.74 (1.11)	-4.47 (1.93)	0.001	-2.61 (1.36)	-1.87 (1.00)	NS	0.04
Chest expansion, cm	0.68 (0.38)	1.05 (0.23)	0.003	0.64 (0.20)	0.41 (0.18)	NS	0.007
Modified Schober, cm	0.48 (0.17)	0.74 (0.16)	0.002	0.48 (0.05)	0.26 (0.15)	NS	< 0.001
6-MWT, m	76 (34)	192 (98)	< 0.001	96 (55)	96 (62)	NS	NS

See text for Δ abbreviations. NS: nonsignificant.

0.20; $\Delta 4$: -0.16 ± 0.17 , $p = 0.06$). No differences were found for the EQ-5D_{vas} and for 6-MWT (Table 2).

No adverse effects were seen during the treatment with etanercept.

DISCUSSION

The optimal management of AS remains unresolved. For a long time this disease has been considered treatable only with NSAID or more recently with cyclooxygenase 2 (COX 2) selective inhibitors³⁰, and rehabilitation³¹. There are no established DMARD for AS; sulfasalazine and MTX have been used in AS and have shown some therapeutical effects on peripheral arthritis but with minimal effect on spinal involvement³⁻⁶.

Recently, the introduction of anti-TNF- α agents has changed the treatment scenario of AS, showing some beneficial effects on various aspects of the disease². Nonpharmacological therapy (including education, exercise, and physiotherapy) has been recommended by ASAS/EULAR for the management of AS³².

There are no prior studies reporting the effects of combination therapy with anti-TNF- α agents and rehabilitation.

Our study assessed the effects of a combination of an intensive rehabilitation program and etanercept compared to a rehabilitation program previously performed in the same group of patients with AS. All patients had a "washout" of rehabilitation for 6 months in which no home exercise inter-

ventions were suggested. Our results showed that the combination treatment seemed to be more effective than a simple rehabilitation program. Indeed, all patients showed an improvement in the main (BASFI) and secondary outcome measures (LDQ, anthropometric measures). We also recorded an improvement in quality of life as measured by EQ-5D_{vas}, and results obtained from the 6-MWT showed an improvement in endurance. In particular, the improvement in quality of life could be related to etanercept therapy, confirming reports by others³³.

Our results favor this combination treatment strategy. A possible explanation for its success could be the strong effects of etanercept on inflammation and fatigue, playing a role as "overboost" in the physical performance of our patients. Indeed, during the combination treatment, our patients had a significant improvement of function as well as acute phase reactants, indicating that during the second rehabilitation program, patients coped better with all physical activities undertaken. A possible psychological effect due to initiating a new therapy might also explain the improvement in BASFI during the second rehabilitation program. However, anthropometric measurements and serological markers of activity showed that there was a physical improvement, excluding any potential psychological bias.

When the 2 rehabilitation programs were compared, no major differences were found. Only the EQ-5D_{vas} showed a statistically significant difference in the 2 programs, suggesting that patients' improved well-being might have resulted in a better perception of global health status. However, when the BASFI was compared between the 2 rehabilitation programs, no statistically significant difference was found, only a positive trend towards an improvement in the second rehabilitation program. This could be related to a positive effect on function gained from the first rehabilitation program.

When we compared the treatment with etanercept alone to the combination treatment a significant difference was found for BASFI, anthropometric measurements, and acute phase reactants. No differences were found on LDQ, 6-MWT, and quality of life. Therefore it is possible that only the combination therapy allows an optimal multidimensional approach.

Our study could have potential bias in its design due to a comparison between 2 dissimilar periods of assessment, since $\Delta 1$ measured a 3-week intensive inpatient rehabilitation only, while $\Delta 2$ measured a period including 3 weeks of etanercept therapy plus 3 weeks of rehabilitation. This comparison could be biased from unknown biological variability. Indeed, comparing the same sample of patients at different periods of time induces bias that cannot be controlled, such as variability of the disease with time, disease flare, and remission periods. However, AS is a progressive disease in which a slow rate of change in spinal mobility is usually observed, and measures taken into account in our study are considered reliable and valid³⁴. In addition, the total number of patients enrolled did not allow for subgroup analysis (perhaps measured by disease

activity, e.g., BASDAI) to determine which types of patients benefitted the most from combination treatment. Further, our study did not consider health economic aspects, since the 2 interventions are expensive for the national health system in Italy. The rehabilitation program is considered a standard intensive inpatient treatment, with specific exercises only for patients with active AS, without using hydrotherapy. Our results seem to confirm that a possibly expensive treatment reduces disability and, in particular, improves quality of life. It would be interesting to find out if an outpatient rehabilitation program would show the same positive effects.

Our pilot study indicated that a combination treatment was beneficial for patients with active AS, with synergistic effects of the interventions on function and disability. A further controlled parallel study using 2 different groups of patients with AS is required to confirm our findings.

REFERENCES

1. Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A. Ankylosing spondylitis: an overview. *Ann Rheum Dis* 2002;61 Suppl 3:8-18.
2. Braun J, Sieper J. Therapy of ankylosing spondylitis and other spondyloarthropathy: established medical treatment, anti-TNF therapy and other novel approaches. *Arthritis Res* 2002;4:307-21.
3. Clegg DO, Reda DJ, Weisman MH, et al. Comparison of sulfasalazine and placebo in treatment of ankylosing spondylitis: a Departments of Veteran Affairs cooperative study. *Arthritis Rheum* 1996;39:2004-12.
4. Dougados M, van der Linden S, Leirisalo-Repo M, et al. Sulfasalazine in the treatment of spondyloarthropathy: a randomized, multicenter, double blind, placebo-controlled study. *Arthritis Rheum* 1995;38:618-27.
5. Biasi D, Carletto A, Caramaschi P, Pacor ML, Maleknia T, Barbara LM. Efficacy of methotrexate in the treatment of ankylosing spondylitis: a three year open study. *Clin Rheumatol* 2000;19:114-17.
6. Roychowdhury B, Bintley-Bagot, Bulgen DY, Thompson RN, Tunn EJ, Moots RJ. Is methotrexate effective in ankylosing spondylitis? [letter]. *Rheumatology Oxford* 2002;41:1330-2.
7. Gorman JD, Sack KE, Davis JC Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor α . *N Engl J Med* 2002;346:1349-56.
8. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. *Lancet* 2002;359:1187-93.
9. Calin A, Dijkmans BAC, Emery P, et al. Outcome of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. *Ann Rheum Dis* 2004;63:1594-600.
10. Davis JC. Understanding the role of tumor necrosis factor inhibition in ankylosing spondylitis. *Semin Arthritis Rheum* 2005;34:668-77.
11. Dagfinrud H, Kvien TK, Hagen KB. Physiotherapy interventions for ankylosing spondylitis. *Cochrane Database Syst Rev* 2004;Oct 18:CD002822.
12. van der Linden S, van Tubergen A, Hidding A. Physiotherapy in ankylosing spondylitis: what is the evidence? *Clin Exp Rheumatol* 2002;20 Suppl 28:S60-4.
13. Anay Y, Ozcan E, Karan A, Diracoglu D, Aydin R. The effectiveness of intensive group exercise on patients with ankylosing spondylitis. *Clin Rehabil* 2003;17:631-6.
14. Viitanen JV, Suni J, Kautiainen H, Liimatainen M, Takala H. Effect of physiotherapy on spinal mobility in ankylosing spondylitis. *Scand J Rheumatol* 1992;21:38-41.

15. Helliwell PS, Abbot CA, Chamberlain MA. A randomised trial of three different physiotherapy regimes in ankylosing spondylitis. *Physiotherapy* 1996;82:85-90.
16. Kraag G, Stokes B, Groh J, Helewa A, Goldsmith CH. The effects of comprehensive home physiotherapy and supervision on patients with ankylosing spondylitis: an 8-month followup. *J Rheumatol* 1994;21:261-3.
17. Lubrano E, Helliwell P. Deterioration in anthropometric measures over six years in patients with ankylosing spondylitis. An initial comparison with disease duration and reported exercise frequency. *Physiotherapy* 1999;85:138-43.
18. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.
19. Braun J, Pham T, Sieper J, et al. International ASAS consensus statement for the use of anti-tumor necrosis factor agents in patients with ankylosing spondylitis. *Ann Rheum Dis* 2003;62:817-24.
20. Pham T, van der Heijde D, Calin A, et al. Initiation of biological agents in patients with ankylosing spondylitis: results of a Delphi study by the ASAS Group. *Ann Rheum Dis* 2003;62:812-6.
21. Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis. The development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994;21:2281-5.
22. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: The Bath Ankylosing Spondylitis Activity Index. *J Rheumatol* 1994;21:2286-91.
23. Lubrano E, Sarzi Puttini P, Parsons WJ, et al. Validity and reliability of an Italian version of the revised Leeds disability questionnaire for patients with ankylosing spondylitis. *Rheumatology Oxford* 2005;44:666-9.
24. Helliwell PS, Moll JHM, Wright V. Measurement of spinal movement and function: In: Jayson MIV, editor. *The lumbar spine and back pain*. 4th ed. Edinburgh: Churchill Livingstone; 1992:173-206.
25. Hurst NP, Jobanputra P, Hunter M, Lambert M, Lochhead A, Brown H. Validity of EuroQol — a generic health status instrument — in patients with rheumatoid arthritis. Economic and Health Outcomes Research Group. *Br J Rheumatol* 1994;33:655-62.
26. Hurst NP, Kind P, Ruta D, Hunter M, Stubbings A. Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). *Br J Rheumatol* 1997;36:551-9.
27. Butlan RJA, Pang J, Gross ER, et al. Two, six, and 12 minute walking tests in respiratory disease. *BMJ* 1982;284:1607-8.
28. Enright P, McBurnie MA, Bittner V, et al. The 6-min walk test. A quick measure of functional status in elderly adults. *Chest* 2003;123:387-98.
29. Mengshoel AM, Jokstad K, Bjerkhoel F. Associations between walking time, quadriceps strength and cardiovascular capacity in patients with rheumatoid arthritis and ankylosing spondylitis. *Clin Rheumatol* 2004;23:299-305.
30. van der Heijde D, Baraf HS, Ramos-Remus CR, et al. Evaluation of the efficacy of etoricoxib in ankylosing spondylitis: result of a fifty-two-week, randomized, controlled study. *Arthritis Rheum* 2005;52:1205-15.
31. van Tubergen A, Landewe R, van der Heijde D, et al. Combined spa-exercise therapy is effective in patients with ankylosing spondylitis: a randomized controlled trial. *Arthritis Rheum* 2001;45:430-8.
32. Zochling J, van der Heijde D, Burgos Vargas R, et al. ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Ann Rheum Dis* 2006;65:442-52.
33. Davis JC, van der Heijde D, Dougados M, Woolley JM. Reductions in health-related quality of life in patients with ankylosing spondylitis and improvements with etanercept therapy. *Arthritis Rheum* 2005;53:494-501.
34. Haywood KL, Garratt AM, Jordan K, Dziedzic K, Dawes PT. Spinal mobility in ankylosing spondylitis: reliability, validity and responsiveness. *Rheumatology Oxford* 2004;43:750-7.