

# Duration of remission after halving of the etanercept dose in patients with ankylosing spondylitis: a randomized, prospective, long-term, follow-up study

Fabrizio Cantini  
Laura Niccoli  
Emanuele Cassarà  
Olga Kaloudi  
Carlotta Nannini

Division of Rheumatology,  
Misericordia e Dolce Hospital,  
Prato, Italy

**Background:** The aim of this study was to evaluate the proportion of patients with ankylosing spondylitis maintaining clinical remission after reduction of their subcutaneous etanercept dose to 50 mg every other week compared with that in patients receiving etanercept 50 mg weekly.

**Methods:** In the first phase of this randomized, prospective, follow-up study, all biologic-naïve patients identified between January 2005 and December 2009 as satisfying the modified New York clinical criteria for ankylosing spondylitis treated with etanercept 50 mg weekly were evaluated for disease remission in January 2010. In the second phase, patients meeting the criteria for remission were randomized to receive subcutaneous etanercept as either 50 mg weekly or 50 mg every other week. The randomization allocation was 1:1. Remission was defined as Bath Ankylosing Spondylitis Disease Activity Index < 4, no extra-axial manifestations of peripheral arthritis, dactylitis, tenosynovitis, or iridocyclitis, and normal acute-phase reactants. The patients were assessed at baseline, at weeks 4 and 12, and every 12 weeks thereafter. The last visit constituted the end of the follow-up.

**Results:** During the first phase, 78 patients with ankylosing spondylitis (57 males and 21 females, median age 38 years, median disease duration 12 years) were recruited. In January 2010, after a mean follow-up of  $25 \pm 11$  months, 43 (55.1%) patients achieving clinical remission were randomized to one of the two treatment arms. Twenty-two patients received etanercept 50 mg every other week (group 1) and 21 received etanercept 50 mg weekly (group 2). At the end of follow-up, 19 of 22 (86.3%) subjects in group 1 and 19 of 21 (90.4%) in group 2 were still in remission, with no significant difference between the two groups. The mean follow-up duration in group 1 and group 2 was  $22 \pm 1$  months and  $21 \pm 1.6$  months, respectively.

**Conclusion:** Remission of ankylosing spondylitis is possible in at least 50% of patients treated with etanercept 50 mg weekly. After halving of the etanercept dose, remission is maintained in a high percentage of patients during long-term follow-up, with important economic implications.

**Keywords:** ankylosing spondylitis, anti-tumor necrosis factor, etanercept, remission, dose reduction

## Introduction

Ankylosing spondylitis is a chronic inflammatory disorder that occurs mainly in HLA B27-positive individuals, and is characterized by enthesal and synovial involvement, with progressive damage and ankylosis of the spine in the majority of patients.<sup>1</sup> The disease is characterized by impaired production of Th1 cytokines, with a sustained inflammatory response characterized by elevated serum levels of tumor necrosis

Correspondence: Fabrizio Cantini  
Rheumatology Division, Ospedale  
Misericordia e Dolce, Piazza Ospedale 1,  
59100 Prato, Italy  
Tel +39 0574 434572  
Fax +39 0574 434421  
Email fbrzcantini@gmail.com

factor alpha (TNF $\alpha$ ) and interleukin-6, and abundant TNF $\alpha$  mRNA in the sacroiliac joints.<sup>2,3</sup> These immunopathological data provided the basis for studies evaluating the efficacy of anti-TNF $\alpha$  agents in ankylosing spondylitis.<sup>4</sup>

The clinical response in patients with ankylosing spondylitis has been assessed by evaluating reduction in disease activity using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),<sup>5</sup> mobility using the Bath Ankylosing Spondylitis Metrology Index (BASMI),<sup>6</sup> and functional status by the Bath Ankylosing Spondylitis Functional Index (BASFI),<sup>7</sup> and more recently by the Assessments in Ankylosing Spondylitis Working Group (ASAS) improvement criteria<sup>8</sup> and the Ankylosing Spondylitis Disease Activity Score.<sup>9</sup> All these sets of response criteria evaluate the best response in terms of low BASDAI score (<4),<sup>5</sup> ASAS 70 partial response,<sup>8</sup> and Ankylosing Spondylitis Disease Activity Score inactive disease (<1.3).<sup>9</sup>

Randomized controlled trials have provided consistent evidence of the efficacy of the anti-TNF $\alpha$  agents, including infliximab, etanercept, and adalimumab, in the treatment of ankylosing spondylitis, with a 50% reduction in disease activity in around 60%–70% of patients.<sup>4</sup> Four randomized controlled trials have provided evidence of the efficacy and safety of subcutaneous etanercept 25 mg twice weekly in the treatment of active ankylosing spondylitis,<sup>10–13</sup> with 60%–80% of patients achieving an ASAS 20 response. Durability of the efficacy and tolerability of etanercept has recently been reported, with 81% of patients maintaining their ASAS 20 score after 192 weeks of treatment.<sup>14</sup> Notably, in the same long-term evaluation, 44% of patients maintained remission, as assessed by an ASAS 70 partial response.

A 12-week randomized controlled trial in ankylosing spondylitis in which etanercept was administered either as 50 mg once weekly or 25 mg twice weekly<sup>15–17</sup> demonstrated efficacy and safety results comparable with those observed in rheumatoid arthritis.<sup>18</sup> Like other biologics, etanercept is an expensive therapy with a heavy economic burden for health care systems in many countries. Consequently, we believed that any effective ethical strategy to reduce the cost with no worsening of patient quality of life would be of great value. Therefore, we designed this two-phase, randomized, prospective follow-up study to evaluate the proportion of patients with ankylosing spondylitis maintaining clinical remission after reduction of their etanercept dose to 50 mg subcutaneously every other week.

## Materials and methods

In the first phase of this study, all biologic-naïve patients treated between January 2005 and December 2009 who met

the modified New York criteria for ankylosing spondylitis<sup>19</sup> were given etanercept 50 mg weekly and evaluated for disease remission in January 2010. In the second phase, patients who satisfied the criteria for disease remission were randomized to one of the following two subcutaneous treatment arms: etanercept 50 mg weekly or etanercept 50 mg every other week. Randomization allocation was 1:1 and treatment was continued until disease flare-up. The local ethics committee reviewed and approved the study protocol. Before entering the trial, each patient was informed of the nature, duration, and purpose of the study, as well as all the potential benefits and drawbacks that could be expected. All participants gave their written informed consent.

## Definitions

- Disease remission: patients were considered to be in remission if they had a BASDAI score < 4, no extra-axial manifestations of peripheral arthritis, dactylitis, tenosynovitis, or anterior uveitis, and a normal erythrocyte sedimentation rate and C-reactive protein levels
- Disease flare-up: patients presenting at follow-up visits with BASDAI > 4 or any of the other above-mentioned peripheral articular and extra-articular manifestations independently of elevation of acute-phase reactants
- Dactylitis: diffuse tenderness and swelling of the entire digit with a sausage-like appearance
- Enthesitis: tenderness and swelling at sites of tendon, ligament, and joint capsule insertion into bone, assessed by the Maastricht Ankylosing Spondylitis Enthesitis score<sup>20</sup>
- Inflammatory spinal pain: patients were defined as having inflammatory spinal pain if they met the Calin's criteria for this clinical feature.<sup>21</sup>

## Primary and secondary endpoints

The primary endpoint was the proportion of patients with ankylosing spondylitis maintaining clinical remission after reduction of the etanercept dose to 50 mg every other week compared with those continuing to receive etanercept 50 mg weekly. Secondary endpoints were the proportion of patients with ankylosing spondylitis who achieved clinical remission, the duration of remission after halving the etanercept dose, time to relapse, and the frequency of adverse events.

## Treatment regimen

Patients received etanercept 50 mg in prefilled syringes for subcutaneous injection. Qualified personnel instructed all patients in correct injection technique and directly observed self-administration of the first dose. The drug was delivered

monthly to each patient in package containing four prefilled syringes, and all patients were instructed on how to store the drug protected from light at 2°C–6°C. Patients were advised to call the center for substitution of their drug package in the event of malfunction of their home refrigerator and consequent altered storage. In the event of relapse, patients reverted to using etanercept 50 mg weekly. Intra-articular and systemic corticosteroids and nonsteroidal anti-inflammatory drugs were not permitted during the study period. In the event of pain, the patients were allowed to take analgesics (acetaminophen or tramadol). None of the patients in either group received psychotherapy or physiotherapy.

## Outcome measures

The patients were evaluated for remission as the primary outcome measure at enrolment and at every follow-up visit. Secondary outcome measures were the proportion of patients achieving remission at the end of the first phase of the study, ie, ASAS 20, 50, and 70 responses, improvement in BASDAI, BASMI, and BASFI scores, chest expansion, finger-to-floor distance, tender and swollen joint counts, number of painful entheses, number of digits showing dactylitis, erythrocyte sedimentation rate and C-reactive protein levels, and number and severity of adverse events.

## Follow-up

Patients were followed by the same rheumatologist, and follow-up visits were scheduled at baseline, after one month, and every 3 months thereafter. Intervals between control visits were shortened in the event of urgent clinical problems, and all patients were instructed to call the center if there was any worsening of axial or peripheral symptoms, onset of extra-articular manifestations, or adverse events.

At every visit, patients had a complete physical examination including all previously listed outcome measures. Routine blood examinations, including erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, complete blood cell count with differential count, renal and liver function tests, and antinuclear antibodies were also carried out. All clinical and laboratory data were recorded in a computerized patient chart.

The date of the last visit constituted the end of follow-up, which was extended to December 2011.

## Adverse events

All patients were monitored for clinical and laboratory evidence of adverse events, defined as mild (transient and easily tolerated), moderate (subject discomfort with

interruption of usual activities), or severe (incapacitating or life-threatening).

## Statistical analysis

Descriptive statistics and statistical differences were calculated using the Statistical Package for Social Sciences version 11 for Windows (SPSS Inc, Chicago, IL). The Wilcoxon's matched-pairs signed rank test was used to measure changes from baseline, and the *t*-test for continuous variables and Chi-square test for nominal variables were used to calculate the differences between the two treatment arms. *P* values less than 0.05 were accepted as being statistically significant.

## Results

From January 2005 to December 2009, 78 patients with ankylosing spondylitis were treated with etanercept 50 mg weekly. Table 1 summarizes the patient demographic and clinical characteristics at baseline. Etanercept was discontinued in 12 (15.3%) patients, due to inefficacy in nine (11.5%) and adverse events in three (4%), including repeated urinary and upper airway infections, severe cutaneous reaction at the injection site, and pneumonitis in one patient each.

In January 2010, after a mean follow-up of  $25 \pm 11$  months, 43 (55.1%) patients were in clinical remission. Of these patients, 22 were randomized to receive etanercept 50 mg every other week and 21 to 50 mg weekly. The results are shown in Table 2. As expected, the two groups did not differ regarding their demographic and clinical characteristics. At the end of follow-up, 19 of 22 (86.3%) patients treated with etanercept 50 mg every other week and 19 of 21 (90.4%) receiving etanercept 50 mg weekly were still in remission, with no statistically significant difference between the two groups.

Disease relapse occurred after a mean interval of  $8 \pm 3.2$  months in the etanercept 50 mg every other week group and after  $10 \pm 1.1$  months in the etanercept 50 mg weekly group; this difference was not statistically significant. As dictated by the protocol, escalation of the etanercept dose to 50 mg weekly was prescribed for patients who relapsed on etanercept 50 mg every other week, and they entered remission again after a mean interval of  $5.1 \pm 2.4$  months. Two patients who had a disease flare-up on etanercept 50 mg weekly were switched to a different anti-TNF $\alpha$  agent.

Regarding tolerability and safety, mild injection site reactions were documented in three of 22 (13.6%) patients in group 1 and four of 21 (19%) patients in group 2, along with urinary infections in two (9%) patients and one (4.7%) patient, upper airways infections in seven (31.8%) and five (23.8%),

**Table 1** Demographic and clinical characteristics of 78 patients with ankylosing spondylitis at baseline and at the end of follow-up in December 2009

| Patients  | Baseline    | End of follow-up | P      |
|---|-------------|------------------|--------|
| Total (n)   | 78          | 66               |        |
| Female (n, %)   | 21 (28%)    | 16 (24%)         |        |
| Male (n, %)   | 57 (72%)    | 50 (76%)         |        |
| Median age at study entry (years)                                 | 38          |                  |        |
| Mean disease duration (years)                                     | 12          |                  |        |
| ESR (mm/hour)   | 30.1 ± 16.3 | 12.3 ± 4.2       | <0.001 |
| CRP (mg/dL)   | 1.9 ± 1.1   | 0.34 ± 0.23      | <0.001 |
| Patients with elevated ESR (n, %)                                 | 36 (46.1%)  | 3 (4.5%)         |        |
| Patients with elevated CRP (n, %)                                 | 40 (51.2%)  | 5 (7.6%)         |        |
| B27+ (n, %)   | 72 (92.3%)  |                  |        |
| Peripheral arthritis (n, %)                                       | 15 (19.2%)  | 1 (1.5%)         |        |
| Enthesitis/dactylitis (n, %)                                      | 28 (35.8%)  | 7 (10.6%)        |        |
| Iridocyclitis at onset or complicating the clinical course (n, %) | 13 (16.6%)  |                  |        |
| BASDAI  | 6.9 ± 1.9   | 3.0 ± 1.6        | <0.001 |
| BASFI   | 5.5 ± 1.7   | 2.8 ± 1.3        | <0.001 |
| BASMI   | 4.8 ± 1.1   | 3.1 ± 1.5        | <0.001 |
| Modified Schober test (cm)  | 4.9 ± 1.56  | 3.1 ± 1.87       | <0.001 |
| Fingertip to floor distance (cm)                                  | 15.3 ± 6.6  | 7.6 ± 2.1        | <0.001 |
| Chest expansion (cm)  | 3.3 ± 0.28  | 3.96 ± 0.14      | <0.001 |
| Overall drug discontinuation and reason (n, %)                    |             | 12 (15.3%)       |        |
| No response   |             | 9 (11.5%)        |        |
| Adverse events*   |             | 3 (4.0%)         |        |
| ASAS 20 (n, %)  |             | 66 (100%)        |        |
| ASAS 50 (n, %)  |             | 48 (72.7)        |        |
| ASAS 70 (n, %)  |             | 43 (55.1)        |        |
| Remission (patients, n, %)  |             | 43 (55.1%)       |        |
| Time to remission (months)  |             | 9 ± 4.9          |        |
| Follow-up duration (months)                                       | 25 ± 11     |                  |        |

**Notes:** Data are expressed as the mean ± SD except where otherwise indicated. \*As reported in text.

**Abbreviations:** ASAS, Assessments in Ankylosing Spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; SD, standard deviation; ESR, erythrocyte sedimentation rate (Westergren); CRP, C-reactive protein.

slightly elevated liver enzymes in one (4.5%) and two (9.5%), in group 1 and group 2, respectively, with no severe adverse event requiring interruption of etanercept therapy. Antinuclear antibody positivity was observed in one (4.7%) patient in group 1 and two (9%) patients in group 2, but no patient developed signs or symptoms of lupus-like syndrome.

## Discussion

To the best of our knowledge, only three studies to date have focused on maintenance of clinical remission after reduction of the etanercept dose in patients with ankylosing spondylitis. In the first one,<sup>22</sup> reduction of the etanercept

dose to 25 mg weekly after a 12-week induction period with etanercept 50 mg weekly was effective for maintaining remission in 17 (94.4%) of 18 patients with ankylosing spondylitis over a 6-month follow-up period. Remission was defined as a 50% reduction in BASDAI score and normal levels of acute-phase reactants. In the second retrospective study, reported by the same group,<sup>23</sup> the clinical response at 21 months was maintained in 109 patients with ankylosing spondylitis despite progressive lengthening of the etanercept dosing interval to 12.1 ± 7.0 days. Finally, in a prospective study from Spain,<sup>24</sup> the etanercept dose was reduced in 16 (31.4%) of 51 patients with ankylosing spondylitis who were still in remission after a mean treatment duration of 17 ± 12 months. Remission was defined as a BASDAI score < 4 and normal C-reactive protein levels. The etanercept dose was reduced to 25 mg weekly in four (25%) patients, 25 mg every 10 days in one patient (6.3%), 25 mg every other week in two patients, 50 mg every 8 days in three patients (18.7%), and 50 mg every 10 days in the remaining six patients (37.5%). This treatment regimen was not changed and all patients maintained their remission through a mean follow-up of 26.1 ± 21 months.

Similar attempts to reduce the etanercept dose have also been reported in patients with ankylosing spondylitis treated with infliximab, with conflicting results. Reduction of the infliximab dose to 3 mg/kg was not effective in a clinical series of 12 patients with ankylosing spondylitis, 16 with axial psoriatic arthritis, and two with undifferentiated spondyloarthritis and prevalent axial involvement.<sup>25</sup> In keeping with a previous Canadian report,<sup>26</sup> a study from the United Kingdom reported that an infliximab dose of 3 mg/kg was effective in suppressing signs and symptoms of ankylosing spondylitis in 19 of 22 (86.3%) patients.<sup>27</sup> Discussing their results, the authors underscored the relevant economic implications of reduction of the infliximab dose in terms of both direct and indirect cost savings, including hospital attendance and nursing time.

Unlike in rheumatoid arthritis, anti-TNF therapy does not seem to inhibit radiographic progression of ankylosing spondylitis,<sup>28</sup> so clinical remission was defined in our study in terms of suppression of signs and symptoms of the disease, with 43 (55.1%) of 78 patients achieving this result on etanercept 50 mg weekly after a mean treatment duration of 9.0 ± 4.9 months.

Confirming the findings of other studies of reduction of the etanercept dose in ankylosing spondylitis,<sup>22-24</sup> no significant increase in disease flare-up was recorded in our randomized study of 43 patients treated with etanercept 50 mg every

**Table 2** Baseline and end of follow-up results in 22 patients with ankylosing spondylitis receiving etanercept 50 mg every other week and 21 patients receiving 50 mg weekly

| Clinical parameter               | Baseline                           |                                       | End of follow-up                   |                                       | P  |
|----------------------------------|------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|----|
|                                  | Group 1<br>Etanercept<br>50 mg eow | Group 2<br>Etanercept<br>50 mg weekly | Group 1<br>Etanercept<br>50 mg eow | Group 2<br>Etanercept<br>50 mg weekly |    |
| Patient (n)                      | 22                                 | 21                                    |                                    |                                       |    |
| Male (n, %)                      | 18 (81.8%)                         | 16 (76.1%)                            |                                    |                                       |    |
| Female (n, %)                    | 4 (18.1%)                          | 5 (23.8%)                             |                                    |                                       |    |
| Age (years, median)              | 37                                 | 38                                    |                                    |                                       |    |
| Disease duration (years, median) | 13                                 | 12                                    |                                    |                                       |    |
| ESR (mm/hour)                    | 11.8 ± 3.2                         | 10.6 ± 2.4                            | 10.2 ± 2.4                         | 11.1 ± 1.8                            | NS |
| CRP (mg/dL)                      | 0.28 ± 0.21                        | 0.32 ± 0.12                           | 0.38 ± 0.13                        | 0.26 ± 0.24                           | NS |
| BASDAI                           | 2.4 ± 0.3                          | 2.3 ± 0.4                             | 2.5 ± 0.7                          | 2.3 ± 0.87                            | NS |
| BASFI                            | 2.6 ± 1.4                          | 2.5 ± 1.3                             | 2.5 ± 1.1                          | 2.4 ± 0.9                             | NS |
| BASMI                            | 3.0 ± 1.2                          | 3.1 ± 0.8                             | 3.1 ± 1.1                          | 3.1 ± 1.2                             | NS |
| Modified Schober test (cm)       | 2.9 ± 1.65                         | 3.0 ± 1.23                            | 2.7 ± 1.96                         | 2.5 ± 1.57                            | NS |
| Fingertip to floor distance (cm) | 6.5 ± 3.2                          | 6.1 ± 2.5                             | 5.9 ± 2.8                          | 5.8 ± 2.1                             | NS |
| Chest expansion (cm)             | 4.1 ± 0.22                         | 4.0 ± 0.67                            | 4.2 ± 0.34                         | 4.2 ± 0.65                            | NS |
| Remission                        |                                    |                                       | 19 (86.3%)                         | 19 (90.4%)                            | NS |
| Relapse (n, %)                   |                                    |                                       | 3 (13.6%)                          | 2 (9.5%)                              | NS |
| Time to relapse (months)         |                                    |                                       | 8 ± 3.2                            | 10 ± 1.1                              | NS |
| Follow-up (months)               |                                    |                                       | 22 ± 1.1                           | 21 ± 1.6                              | NS |

**Abbreviations:** BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; eow, every other week; ESR, erythrocyte sedimentation rate (Westergren); CRP, C-reactive protein.

other week versus etanercept 50 mg weekly over a mean long-term follow-up of 22 ± 1.1 months.

Beyond the potential advantages in terms of compliance with therapy and reduced drug exposure risk, data from other clinical series<sup>22–24</sup> along with our results seem to indicate a new therapeutic option for the management of patients with ankylosing spondylitis. Indeed, halving of the etanercept dose after achieving remission constitutes an ethical therapeutic strategy with relevant economic implications. As with other anti-TNF agents, etanercept is an expensive therapy, with an estimated yearly cost of around €15,000 per patient. Data from randomized clinical trials<sup>10–14</sup> show that around half of the patients with ankylosing spondylitis who are treated with etanercept 50 mg weekly achieve suppression of disease activity. Therefore, we suggest that reduction of the etanercept dose to 50 mg every other week in these patients would allow a consistent reduction of economic burden with no worsening of patient health status. As a direct consequence of our trial, we calculated a consistent cost saving of around €260,000 (€7500 per patient per year multiplied by 19 patients for 22 months).

## Conclusion

Our results indicate that suppression of disease activity is possible in more than 50% of patients with ankylosing

spondylitis treated with etanercept 50 mg weekly. Notably, after halving of the etanercept dose, a high percentage of patients maintain remission during long-term follow-up, with no significant differences from those continuing the standard etanercept dose. The sustained disease remission after reduction of the etanercept dose suggests that this therapeutic strategy can be applied in clinical practice, with important advantages in terms of drug exposure risk, patient compliance with therapy, and cost savings.

## Disclosure

The authors report no conflicts of interest in this work.

## References

1. Khan MA. Update on spondylarthropathies. *Ann Intern Med.* 2002;136:896–907.
2. Bal A, Unlu E, Bahar G, Aydog E, Eksioglu E, Yorgancioglu R. Comparison of serum IL-1 $\beta$ , sIL-2R, IL-6, and TNF- $\alpha$  levels with disease activity parameters in ankylosing spondylitis. *Clin Rheumatol.* 2007;26:211–215.
3. Braun J, Bollow M, Neure L, et al. Use of immunohistologic and in situ hybridization techniques in the examination of sacroiliac joint biopsy specimens from patients with ankylosing spondylitis. *Arthritis Rheum.* 1995;38:499–505.
4. Braun J, Baraliakos X, Brandt J, Sieper J. Therapy of ankylosing spondylitis. Part II: biological therapies in the spondyloarthritides. *Scand J Rheumatol.* 2005;34:178–190.
5. 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 Disease Activity Index. *J Rheumatol.* 1994;21:2286–2291.

6. Jenkinson TR, Mallorie PA, Whitelock H, Kennedy LG, Garrett S, Calin A. Defining spinal mobility in ankylosing spondylitis (AS): the Bath AS Metrology Index. *J Rheumatol*. 1994;21:1694–1698.
7. 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;21:2281–2285.
8. Anderson JJ, Baron G, van der Heijde D, Felson DT, Dougados M. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. *Arthritis Rheum*. 2001;44:1876–1886.
9. van der Heijde D, Lie E, Kvien TK, et al. ASDAS, a highly discriminatory ASAS endorsed disease activity score in patients with ankylosing spondylitis. *Ann Rheum Dis*. 2009;68:1811–1818.
10. Gorman JD, Sack KE, Davis JC. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor  $\alpha$ . *N Engl J Med*. 2002;346:1349–1356.
11. Brandt J, Khariouzov A, Listing J, et al. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis Rheum*. 2003;48:1667–1675.
12. Davis JC, van der Heijde D, Braun J, et al. Recombinant human tumor necrosis factor receptor (Etanercept) for treating ankylosing spondylitis. *Arthritis Rheum*. 2003;48:3230–3236.
13. Calin A, Dijkmans BAC, Emery P, et al. Outcomes of a multicentre randomised clinical trial of etanercept to treat ankylosing spondylitis. *Ann Rheum Dis*. 2004;63:1594–1600.
14. Davis JC, van der Heijde D, Braun J, et al. Efficacy and safety of up to 192 weeks of etanercept therapy in patients with ankylosing spondylitis. *Ann Rheum Dis*. 2008;67:346–352.
15. van der Heijde D, Da Silva JC, Dougados M, et al. Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis. *Ann Rheum Dis*. 2006;65:1572–1577.
16. Braun J, McHugh N, Singh A, Wajdula JS, Sato R. Improvement in patient-reported outcomes for patients with ankylosing spondylitis treated with etanercept 50 mg once-weekly and 25 mg twice-weekly. *Rheumatology (Oxford)*. 2007;46:999–1004.
17. Cantini F, Niccoli L, Benucci M, et al. Switching from infliximab to once-weekly administration of 50 mg etanercept in resistant or intolerant patients with ankylosing spondylitis: results of a fifty-four-week study. *Arthritis Rheum*. 2006;55:812–816.
18. Keystone EC, Schiff MH, Kremer JM, et al. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2004;50:353–363.
19. 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;27:361–368.
20. Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, et al. Assessment of enthesitis in ankylosing spondylitis. *Ann Rheum Dis*. 2003;62:127–132.
21. Calin A, Porta J, Fries JF, Schurman DJ. Clinical history as a screening test for ankylosing spondylitis. *JAMA*. 1977;237:2613–2614.
22. Lee SH, Lee YA, Hong SJ, Yang HI. Etanercept 25 mg/week is effective enough to maintain remission for ankylosing spondylitis among Korean patients. *Clin Rheumatol*. 2008;27:179–181.
23. Lee J, Noh JW, Hwang JW, et al. Extended dosing of etanercept 25 mg can be effective in patients with ankylosing spondylitis: a retrospective analysis. *Clin Rheumatol*. 2010;29:1149–1154.
24. Navarro-Compán V, Moreira V, Ariza-Ariza R, Hernández-Cruz B, Vargas-Ebrón C, Navarro-Sarabia F. Low doses of etanercept can be effective in ankylosing spondylitis patients who achieve remission of the disease. *Clin Rheumatol*. 2011;30:993–996.
25. Sidiropoulos P, Kritikos HD, Siakka P, et al. Low dose of infliximab is inadequate in most patients with spondylarthropathies. *Clin Exp Rheumatol*. 2005;23:513–516.
26. Maksymowych WP, Jhangri GS, Lambert RG, et al. Infliximab in ankylosing spondylitis: a prospective observational inception cohort analysis of efficacy and safety. *J Rheumatol*. 2002;29:959–965.
27. Jois RN, Leeder J, Gibb A, et al. Low-dose infliximab treatment for ankylosing spondylitis – clinically and cost-effective. *Rheumatology (Oxford)*. 2006;45:1566–1569.
28. Heldmann F, Dybowski F, Saracbası-Zender E, Fendler C, Braun J. Update on biologic therapy in the management of axial spondyloarthritis. *Curr Rheumatol Rep*. 2010;12:325–331.

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