Clinical and Experimental Rheumatology 2012; 30: 266-268.

Onset of action of etanercept in rheumatoid arthritis based on patient-reported outcomes

M. Dougados[1], M. Ripert[2], P. Hilliquin[3], O. Brocq[5], Y. Brault[2], I. Logeart[2]

[1]Department of Rheumatology B, Cochin Hospital, Paris, France;
[2]Pfizer SAS France, Paris, France;
[3]Department of Rheumatology, CH Sud Francilien, Corbeil-Essonnes, France;
[4]Department of Rheumatology, CH Princesse Grace, Monaco.

Maxime Dougados, MD
Mahaut Ripert, MD
Pascal Hilliquin, MD, PhD
Olivier Brocq, MD
Yves Brault, MSc
Isabelle Logeart, MD

Please address correspondence to:
Dr Maxime Dougados,
Service de Rhumatologie B,
Cochin Hospital,
27 rue du Faubourg Saint-Jacques,
75014 Paris, France.
E-mail: maxime.dougados@cch.aphp.fr

Received on June 23, 2011; accepted in revised form on October 26, 2011.

Key words: rheumatoid arthritis, etanercept, clinical trials, patient-reported outcomes, EULAR-RAID, onset of action

Funding: this study was conducted with the support of Pfizer, France, who participated in design of the trial, selection of investigators and the contract research organisation in charge of monitoring of the trial and data management.

Competing interests: M. Dougados has received research grants from Pfizer and has acted as consultant for Pfizer; M. Ripert, Y. Brault and I. Logeart are employees of Pfizer Inc.; O. Brocq has received honoraria for the Rainbow study; P. Hilliquin has delared no competing interests.

ABSTRACT

Background. *Onset of action is considered to be a key characteristic of the treatment of rheumatoid arthritis. The efficacy of TNF blockers is usually evaluated after 2 to 4 weeks of therapy. EULAR-RAID is a valid patient-reported outcome composite index.*

Objective. *To evaluate the onset of action of etanercept in rheumatoid arthritis patients according to the EULAR-RAID score.*

Methods. *An open-label, single-arm (etanercept 50 mg/week), 12-week study was carried out in patients with active rheumatoid arthritis. Patients were asked to fill in the RAID score questionnaire each day for the first 14 days of the study and at the 4-week and 12-week visits. Onset of action was evaluated by considering: a) changes over time of the EULAR-RAID score; b) the percentage of patients achieving an "acceptable" condition according to the EULAR-RAID score (e.g. a score ≤3.00).*

Results. *Of the 120 screened patients, 108 (female: 75%), age 54±13 years, disease duration 8±7 years) were enrolled. At baseline, patients had active rheumatoid arthritis (DAS: 5.4±0.8; CRP: 18.±30mg/l). Eleven patients dropped out of the study. A statistically significant decrease in the EULAR-RAID score was observed by day 1 of therapy. Kaplan-Meier estimates of the proportion of patients achieving an acceptable RAID score were 29.8 [% 95% C.I. 23.8–X42.6], 50 % [95% C.I. 41–60.9], 51.9% [95% C.I. 43.8–63.7], 56% [95% C.I. 49.5–69.1, after 1, 2, 4 and 12 weeks of therapy respectively. The median time to achieve an acceptable EULAR-RAID score was 14.5 days.*

Conclusion. *This open-label study suggests that patients can perceive a clinically relevant improvement by the first week of etanercept therapy.*

Introduction

The current objective of management of rheumatoid arthritis is to achieve an acceptable status as soon as possible and for as long as possible (1-5). From the patient's perspective, onset of action of a rheumatoid arthritis treatment is one of the key factors related to patient satisfaction (6). The concept of onset of action is therefore an important aspect to be taken into account and it has been recommended that onset of action should be included in the reports of all clinical trials based on rheumatoid arthritis disease activity (7).

TNF blockers are considered to be rapid-acting drugs compared to conventional disease-modifying anti-rheumatic drugs (DMARDs). This conclusion is mainly based on data observed after 2 to 4 weeks of therapy (8-11). However, to our knowledge, no information is available concerning changes in the patient's condition during the first 2 weeks of therapy (except for the one-week data reported with certolizumab (12)).

At the initiative of EULAR, a patient-reported outcome composite index called RAID (Rheumatoid Arthritis Impact Disease) has been proposed (13) and validated (14, 15). This composite index includes 7 domains (*e.g.* pain, function, fatigue, physical well-being, psychological well-being, sleep disturbances and coping); each item is evaluated by a single question using a 0–10 Numerical Rating Scale. In the rheumatology literature, a score below or equal to 3 on a 0–10 continuous scale has been proposed to define a patient in an "acceptable" condition (16).

In a recent trial evaluating etanercept in active RA (clinicaltrials.gov allocated number NCT00768053), we evaluated the onset of action of etanercept during the first weeks of therapy based on the patient's perspective using the EULAR-RAID score.

Patients and methods

Study design

This study was a 12-week, open-label, single-arm, prospective trial. Written consent was obtained from each patient according to the Declaration of Helsinki. The study was approved by the Institutional Review Board of Cochin Hospital, Paris, France.

Inclusion criteria

To be eligible for this study, patients had to present documented rheumatoid arthritis meeting the 1987 American College of Rheumatology Criteria (17). This disease had to be active according

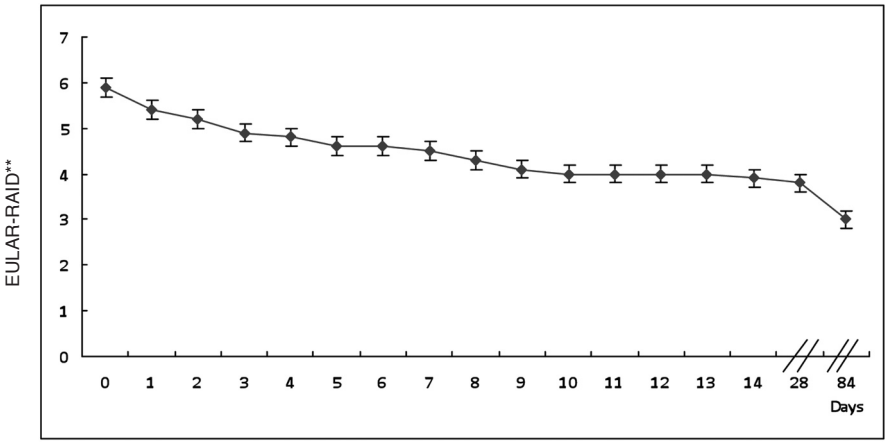

Fig. 1. EULAR-RAID score in response to etanercept therapy in 108 patients over time. Data expressed as mean ± SEM.

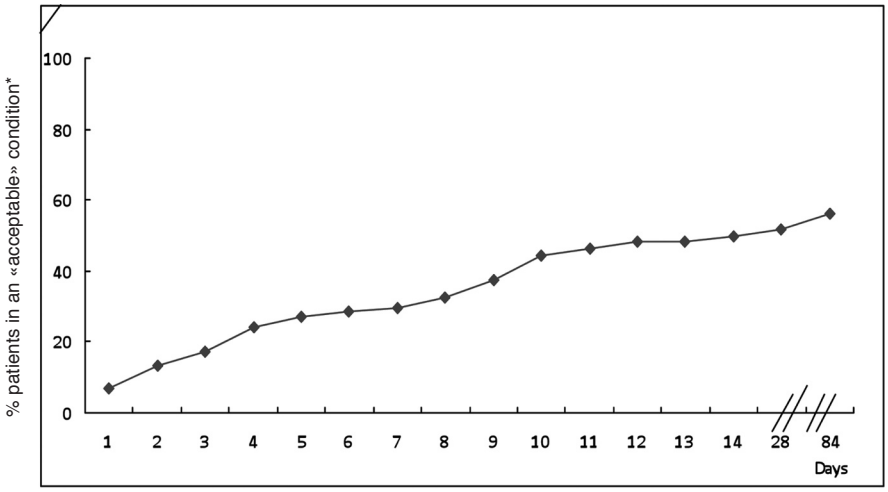

Fig. 2. Proportion of patients achieving an acceptable condition defined by a EULAR-RAID score ≤3.0 in X patients with a baseline EULAR-RAID score >3.0 and over the 12-week period of etanercept 50 mg weekly therapy (Kaplan-Meier estimate)
* Acceptable condition was defined by a EULAR-RAID score ≤3.0.

to the following definition: DAS28-ESR >3.2 and at least one of the following: ≥4 synovitis or CRP >10 mg/l or ESR >28 mm/1st hour and justifying TNF blocker therapy, as recommended by the French Society of Rheumatology (18).

Study design

All patients received etanercept 50 mg by weekly subcutaneous injection. Concerning the potential other RA medications, concomitant use of oral, intra-articular, intra-muscular corticosteroids, NSAIDs and analgesics were permitted at the discretion of the investigator but had to be stable between screening and baseline visits. Dose adjustments of concomitant corticosteroids were at the discretion of the investigator after the baseline visit.

Data collection

Patient (age, gender) and disease characteristics (duration, anti-CCP positive) were recorded at screening. At baseline and at the 4-week and 12-week visits to the rheumatology centre, the following outcome measures were recorded: DAS28-ESR, mHAQ and EULAR-RAID. At baseline, patients were also provided with a diary including the items of the EULAR-RAID questionnaire for the first 2 weeks of therapy.

Statistical analysis

Onset of action was evaluated using 2 approaches according to the EULAR-RAID variable (*e.g.* continuous or dichotomous variable).

For the continuous variable (*e.g.* a score ranging from 0 (best condition) to 10 (worst condition)), the mean changes (± standard error of the mean) were evaluated at each time point. The change from baseline was analysed using a one-way analysis of variance for repeated measures. Statistical testing was two-sided and at the 5% level of significance.

Data presented according to Intent-to-Treat analysis with the Last Observation Carried Forward (LOCF) technique for missing values.

For the dichotomous variable (*e.g.* a score below or equal to 3.0), a Kaplan-Meier method was used to evaluate the median time to reach this acceptable symptom state and to estimate the percentage of patients achieving this status over time, in subjects with a score higher than 3 at baseline.

Results

Of the 120 screened patients, 108 entered the study and received at least one etanercept injection. During the 12 weeks of the trial, 1 patient was lost to follow-up and 10 others withdrew from the study because of side effects.

The main characteristics of the 108 recruited patients were as follows: age: 54±13 years, 75% females, anti-CCP positive: 61%, disease duration: 8±7 years, CRP: 18±30 mg/l, DAS28-ESR 5.4±0.8).

At baseline, the EULAR-RAID score (5.9±1.7) ranged from 0.7 to 9.4.

Figure 1 illustrates the EULAR-RAID score (±SEM) over the 12 weeks of the study. The observed data suggest an improvement within the first days of therapy with a statistically significant difference compared to baseline observed as early as day 1.

Figure 2 illustrates the percentage of patients achieving an acceptable status defined as a EULAR-RAID score below or equal to 3.0. Since a EULAR-RAID score below or equal to 3.0 was observed at baseline in 3.7% of patients, this analysis was based on the group of patients with a baseline EULAR-RAID score greater than 3.0 (*e.g.* 104 patients) and showed an increase over time of patients considered to have an acceptable status to reach 57.9% of patients at week 12. The proportion of patients with an acceptable

status was estimated (Kaplan-Meier) to be 29.8 [% 95% C.I. 23.8–42.6], 50 % [95% C.I. 41–60.9], 51.9% [95% C.I. 43.8–63.7], 56% [95% C.I. 49.5–69.1], after 1, 2, 4 and 12 weeks of therapy, respectively. The median time to achieve an acceptable symptom state was estimated to be 14.5 days after initiation of etanercept therapy according to Kaplan-Meier analysis.

Discussion

This study confirms the efficacy of etanercept therapy after only a few weeks of therapy and suggests that this efficacy was not only detectable but also clinically relevant after a just few days from the patient's perspective.

The open-label design of the trial can be considered to be a weakness, On the other hand, this design can also be considered to be a strength, as it reflects daily practice. One of the strengths of this study is its prospective design, with daily completion of the questionnaire evaluating the patient's condition and use of a validated questionnaire evaluating the various domains considered to be the most important from the patient's perspective.

The two techniques used in this study to evaluate the concept of onset of action (*e.g.* mean changes in the outcome variable and percentage of patients achieving an acceptable condition over time) suggest that a relevant treatment effect can be observed by the first week of therapy in a non negligible percentage of patients.

Other studies using other designs and other drugs are necessary to more clearly evaluate the concept of onset of action of treatments used in the management of rheumatoid arthritis, particularly during the first days after treatment initiation.

Key messages

- EULAR-RAID is a valid instrument to evaluate rheumatoid arthritis disease activity from the patient's perspective.
- Etanercept efficacy is perceived by patients by the first week of therapy.

Acknowledgements

The authors would like to thank the patients and their rheumatologists for their participation in this study.

References

1. COMBE B, LANDEWÉ R, LUKAS C *et al*.: EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). *Ann Rheum Dis* 2007; 66: 34-45.
2. SMOLEN JS, ALETAHA D, BIJLSMA JW *et al*.; T2T Expert Committee: Treating rheumatoid arthritis to target: recommendations of an international task force *Ann Rheum Dis* 2010; 69: 631-7.
3. SMOLEN JS, LANDEWÉ R, BREEDVELD FC *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010; 69: 964-75.
4. FELSON DT, SMOLEN JS, WELLS G *et al*.: American College of Rheumatology / European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011; 70: 404-13.
5. KLARESKOG L, GAUBITZ M, RODRIGUEZ-VALVERDE V, MALAISE M, DOUGADOS M, WAJDULA J; ETANERCEPT STUDY 301 INVESTIGATORS: Assessment of long-term safety and efficacy etanercept in a 5-year extension study in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2011; 29: 238-47.
6. DOUGADOS M, SCHMIDELY N, LE BARS M *et al*.: Evaluation of different methods used to assess disease activity in rheumatoid arthritis: analyses of abatacept clinical trial data. *Ann Rheum Dis* 2009; 68: 484-9.
7. ALETAHA D, LANDEWÉ R, KARONITSCH T *et al*.: Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. *Ann Rheum Dis* 2008; 67: 1360-4.
8. EMERY P, BREEDVELD FC, HALL S *et al*.: Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008; 372: 375-82.
9. BREEDVELD FC, WEISMAN MH, KAVANAUGH AF *et al*.: The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006; 54: 26-37.
10. LIPSKY PE, VAN DER HEIJDE DM, ST CLAIR EW *et al*.: Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000; 343: 1594-602.
11. LAAS K, PELTOMAA R, PUOLAKKA K, KAUTIAINEN H, LEIRISALO-REPO M: Early improvement of health-related quality of life during treatment with etanercept and adalimumab in patients with rheumatoid arthritis in routine practice. *Clin Exp Rheumatol* 2009; 27: 315-20.
12. KEYSTONE E, HEIJDE D, MASON D JR. *et al*.: *Arthritis Rheum* 2008 Nov; 58: 3319-29. Erratum in: *Arthritis Rheum* 2009; 60: 1249.
13. GOSSEC L, DOUGADOS M, RINCHEVAL N *et al*.: Elaboration of the preliminary Rheumatoid Arthritis Impact of Disease (RAID) score: a EULAR initiative. *Ann Rheum Dis* 2009; 68: 1680-5.
14. GOSSEC L, PATERNOTTE S, AANERUD GJ *et al*.: Finalization and validation of the Rheumatoid Arthritis Impact of Disease (RAID) score, a patient-derived composite measure of impact of rheumatoid arthritis. A EULAR initiative. *Ann Rheum Dis* 2011; 70: 935-42.
15. HEIBERG T, AUSTAD C, KVIEN TK, UHLIG T: Performance of the Rheumatoid Arthritis Impact of Disease (RAID) score in relation to other patient-reported outcomes in a register of patients with rheumatoid arthritis. *Ann Rheum Dis* 2011; 70: 1080-2.
16. TUBACH F, RAVAUD P, BEATON D *et al*.: Minimal clinically important improvement and patient acceptable symptom state for subjective outcome measures in rheumatic disorders. *J Rheumatol* 2007; 34: 1188-93.
17. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
18. FAUTREL B, PHAM T, MOUTERDE G *et al*.: Club Rhumatismes et Inflammation; Société Française de Rhumatologie. Recommendations of the French Society for Rheumatology regarding TNF-alpha antagonist therapy in patients with rheumatoid arthritis. *Joint Bone Spine* 2007; 74: 627-37.