

Original Article

Duration of Treatment With Etanercept and Motives for Discontinuation in a Cohort of Patients With Rheumatic Disease[☆]

José Miguel Senabre-Gallego,^{a,*} José Rosas-Gómez de Salazar,^a Gregorio Santos-Soler,^a Carlos Santos-Ramírez,^b Mabel Sánchez-Barrioluengo,^c Esteban Salas-Heredia,^a Xavier Barber-Vallés,^d Catalina Cano-Pérez,^e Núria Llahí-Vidal,^e Rosa Riestra-Juán^e

^a Reumatología, Hospital Marina Baixa, Villajoyosa, Alicante, Spain

^b Reumatología, Hospital Marina Salud, Denia, Alicante, Spain

^c INGENIO (CSIC-UPV), Universitat Politècnica de València, Valencia, Spain

^d CIO-UMH de Elche, Elche, Alicante, Spain

^e Enfermería de Reumatología, Hospital Marina Baixa, Villajoyosa, Alicante, Spain

ARTICLE INFO

Article history:

Received 17 February 2011

Accepted 28 June 2011

Available online 25 November 2011

Keywords:

Adverse event

Arthritis

Drug discontinuations

Etanercept

Survival

ABSTRACT

Objective: To evaluate the duration of etanercept (ETN) treatment and motives for discontinuation in our local cohort of patients with rheumatic pathology and compare them to the group with other biological treatments.

Patients and methods: Prospective observational cohort study. Disease diagnosis, start and end date and motive for discontinuation were recorded. Survival estimation was explored using Kaplan–Meier analysis with remaining patients censored at 1-year, 2-years and 5-years follow-up.

Results: Ninety-two (45%) out of 205 patients started ETN treatment. Disease diagnoses recorded were: 48% rheumatoid arthritis, 33% ankylosing spondylitis, 11% psoriatic arthritis, 8% others (juvenile idiopathic arthritis, inflammatory bowel disease related spondylitis, SAPHO syndrome). 52% of patients are still on the drug. The motives for discontinuation were: inefficacy (65%), adverse events (33%) and lack of compliance (2%). Two patients discontinued ETN due to prolonged disease control. Adverse events were: infection (4 patients), post-injection skin reaction (3), uveitis (3), neoplasia (2) and others (3). Using a Kaplan–Meier analysis, at 1-year 64% (CI_{95%} 54–74) of patients with ETN treatment had not experienced treatment failure, at 2-years, 59% (48–69) and at 5-years, 43% (30–52). With the rest of biologicals estimated survival was 61% (51–68), 47.5% (40–55), and 23% (10.5–32), respectively. Statistical analysis revealed significant differences (*log-rank*: $P=.024$; *Breslow*: $P=.068$; *Tarone-Ware*: $P=.040$).

Conclusions: In our cohort of patients treated with ETN the estimated survival was better than patients treated with other biological drugs at 1-year, 2-years and 5-years.

© 2011 Elsevier España, S.L. All rights reserved.

Duración del tratamiento con etanercept y razones de discontinuación en una cohorte de pacientes con patología reumática

RESUMEN

Objetivos: Evaluar la supervivencia del tratamiento con etanercept (ETN) y las causas de discontinuación en una cohorte local de pacientes en tratamiento biológico (TB). Comparar con la supervivencia general del resto de TB.

Pacientes y métodos: Estudio observacional prospectivo de cohortes. Se han analizado los datos de diagnóstico, fecha de inicio y fin de tratamiento, así como la causa de interrupción de nuestro registro de TB. Mediante el método de Kaplan–Meier se ha estimado la supervivencia de ETN al año, a los 2 años y a los 5 años.

Palabras clave:

Acontecimiento adverso

Artritis

Discontinuación

Etanercept

Supervivencia

Terapia biológica

[☆] Please cite this article as: Senabre-Gallego JM, et al. Duración del tratamiento con etanercept y razones de discontinuación en una cohorte de pacientes con patología reumática. Reumatol Clin. 2011;7(6):385–8.

* Corresponding author.

E-mail address: senabre@hotmail.es (J.M. Senabre-Gallego).

Resultados: De un total de 205 pacientes que recibieron TB, 92 (45%) iniciaron tratamiento con ETN. En el 48% el diagnóstico fue artritis reumatoide, 33% espondilitis anquilosante, 11% artritis psoriásica y 8% otros diagnósticos (artritis idiopática juvenil, espondiloartritis asociada a enfermedad inflamatoria intestinal y síndrome SAPHO). Continúan con ETN 48 pacientes (52%). Las causas de discontinuación fueron: ineficacia (65%), acontecimiento adverso (33%), pérdida de seguimiento (2%). En 2 pacientes el tratamiento se retiró por remisión clínica. Los acontecimientos adversos fueron: infección (4 pacientes), reacción cutánea post-inyección (3), uveítis (3), neoplasia (2) y otros (3). La supervivencia estimada de ETN al año de tratamiento fue del 64% (IC del 95%, 54–74), a los dos años del 59% (48–69) y a los 5 años del 43% (30–52), y la del resto de TB fue del 61% (51–68), el 47,5% (40–55) y el 23% (10,5–32), respectivamente. Los tests estadísticos revelaron diferencias significativas (*log-rank*: $p=0,024$; Breslow: $p=0,068$; Tarone-Ware: $p=0,040$).

Conclusiones: En nuestra cohorte de pacientes la supervivencia estimada de ETN en el primero, segundo y quinto de año de tratamiento es superior a la obtenida con el resto de TB, siendo la diferencia significativa a los 5 años.

© 2011 Elsevier España, S.L. Todos los derechos reservados.

Introduction

Biological therapy (TB) was launched by inhibitors of tumor necrosis factor alpha (TNF- α), infliximab (INF), adalimumab (ADA) and etanercept (ETN), and has radically changed the treatment of certain rheumatic diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS) or psoriatic arthritis (PsA). The effectiveness of these anti-TNF drugs has been demonstrated in numerous clinical trials, but there are no comparative clinical trials and meta-analysis studies that demonstrate superiority between them.^{1,2}

Recent studies based on national registries of patients with RA and biological therapy have reported lower rates of discontinuation with ETN than with ADA and INF.^{3–6} Patients with PsA have reported higher compliance rates for ETN and ADA than with INF,⁷ a fact that has not been confirmed in later studies.⁸

The aim of our study is to evaluate the duration of treatment with etanercept (ETN) and the causes of its discontinuation in a cohort of patients with biological treatment in an actual clinical practice situation and overall compliance compared with the rest of biological drugs.

Methods

We performed a prospective, observational cohort study using data from a registry of patients with biological therapy of the section of rheumatology at the Hospital Marina Baixa. This registry began in 2001 to assess the safety and long-term management of these drugs in actual clinical practice and compare it with records from other populations. It includes obtaining informed consent prior to access to medical records of any patient who has received at least one dose of any biological drug prescribed by the section of rheumatology. This was an observational study in a real clinical practice setting, without interference in the selection, initiation or discontinuation of biological treatment.

Patient data were collected by the rheumatologists of the unit in a computer spreadsheet (Microsoft Excel 2003[®] TM), access to which was restricted in order to comply with the Data Protection Act currently in force.

The study protocol was approved by the local ethics committees and followed the guidelines of the Declaration of Helsinki.

Study Variables

These included: epidemiological characteristics (age, gender), primary diagnosis, year of diagnosis and result of Mantoux and booster tests. Rheumatoid factor (RF; U/ml) and citrullinated peptide antibodies (anti-CCP) using a second-generation ELISA technique were determined in patients with RA, JIA and PsA. Patients with spondyloarthritis were analyzed for the presence of histocompatibility antigen HLA-B27.

For each biological agent used we collected the type of drug and start and end dates (and thus the time of treatment). The causes of discontinuation were classified as: inefficiency, complication, clinical remission and loss to follow up.

The different treatments were followed prospectively for each patient, since the start of therapy. In those patients who had previously initiated treatment, for example in another facility, data were included retrospectively.

Statistical Analysis

We used Kaplan–Meier estimated survival function curves plotted for treatments with ETN and for other biological as a whole. To check for differences between the two groups we used a log-rank, Breslow, and Tarone-Ware tests using the statistical software package SPSS 18[®].

Results

Since 2001, a total of 205 patients started biologic therapy, 92 (45%) patients received ETN (51% as the first biologic drug, 42% as the second drug, 7% as a third drug, and 2% as the fourth drug).

The diagnoses of patients who received ETN were: RA 48%, SA 33%, PsA 11%, and other diagnosis 8% (JIA, spondylitis associated with inflammatory bowel disease and SAPHO syndrome). Currently 48 patients are continuing treatment with ETN (52%).

Causes of Discontinuation

The causes of discontinuation of ETN were as follows (Table 1) ineffectiveness in 30 patients (65%), adverse event in 15 patients (33%) and loss to follow up in 1 case (2%). In 2 patients the treatment was withdrawn after prolonged clinical remission.

Table 1
Causes for ETN Discontinuation.

| Cause for Discontinuation | No. of Patients | Percentage |
|---|-----------------|------------|
| Inefficacy | 30 | 65% |
| Adverse event | 15 | 33% |
| Infection (3 gastroenteritis and 1 pneumonia) | 4 | 9% |
| Post injection skin reaction | 3 | 6,5% |
| Neoplasia (1 prostate cancer and 1 melanoma) | 2 | 4% |
| Others (1 psoriasis, 1 respiratory insufficiency, 3 uveítis and 1 dermatome localized pain) | 6 | 13% |
| Loss to follow up | 1 | 2% |
| Withdrawal due to clinical remission | 2 | |
| Total (not counting remission) | 46 | 100% |

Table 2
Estimated Survival Times at Different Points in Time.

| Years of Treatment | Etanercept | | Other Biologics | |
|--------------------|------------|-------------|-----------------|-------------|
| | Estimate | 95% CI | Estimate | 95% CI |
| 1 year | 63.9% | 53.7%–74.1% | 61.2% | 51.2%–68.0% |
| 2 years | 58.7% | 48.1%–69.3% | 47.5% | 40.3%–54.7% |
| 5 years | 42.6% | 30.0%–55.2% | 22.9% | 10.5%–31.9% |

Adverse events reported were: infection in 4 patients, post-injection skin reaction in 3 patients, malignancy in 2 patients and other causes in 6 patients.

Of the total group of patients with biologic therapy, 7 (3%) interrupted their treatment due to prolonged clinical remission as evaluated by the rheumatologist. Of these, 4 patients resumed the same treatment due to worsening and were counted as “continuation” for the calculation of survival.

In 6 patients treatment was discontinued due to other causes (pregnancy, headache with numbness, nasopharyngeal granulomatosis, myocardial infarction, unstable angina and unknown causes) and was later restarted. These cases were also counted as “continuation” of treatment. Discontinuations due to infection were recorded as ‘discontinued’, although treatment was restarted a few months later.

Two patients dropped out for personal reasons and subsequently restarted the same biologic drug and were counted as “discontinuation” and then as starting new treatment.

Duration of Treatment and Estimated Survival

The mean duration of treatment with ETN was 53 months (mean of 44 months) and for the rest of biologics it was 43 months (mean 23 months). We estimated survival at 1, 2 and 5 years (Table 2). The Kaplan–Meier duration curve for ETN was greater than for all other biological treatments together (Fig. 1). Statistical tests of comparison between the two groups revealed significant differences (log-rank: $P=.024$, Breslow $P=.068$, Tarone-Ware $P=.040$).

Comparing duration between genders using ETN, there were no significant differences. No differences were found when comparing the diagnoses of RA and SA (results not shown).

Discussion

Clinical trials are the gold standard of clinical evidence, but have certain limitations. They often include a limited number of patients, and have strict selection criteria such as exclusion of comorbidities, and short follow-up periods.⁹ However, observational registries offer a real and ongoing assessment of the drugs studied and lead to a greater knowledge on their effectiveness and long-term safety. Local registries of drugs offer a detailed look at what happens in the daily follow up. In clinical practice, adverse events, lack of primary response and secondary lack of efficiency are common problems. Even first time use of ETN did not reach a satisfactory response in 40%–50% of patients with RA and is often without effectiveness over time.¹⁰

ETN is a fully human soluble TNF receptor, whereas INF and ADA are monoclonal antibodies against TNF (INF is chimeric and ADA fully human). Its pharmacokinetics is different in some respects. Specifically, the elimination half-life is lower and ETN neutralizing antibody formation is rare.¹¹ In addition, ETN has demonstrated efficacy in the treatment of inflammatory bowel disease whereas anti-TNF monoclonal antibodies have not done so.^{12,13} Furthermore, it appears that there is less incidence of TB with ETN than INF and ADA.^{14–17} This makes it likely that the efficacy and safety data are not identical between the three anti-TNF agents.

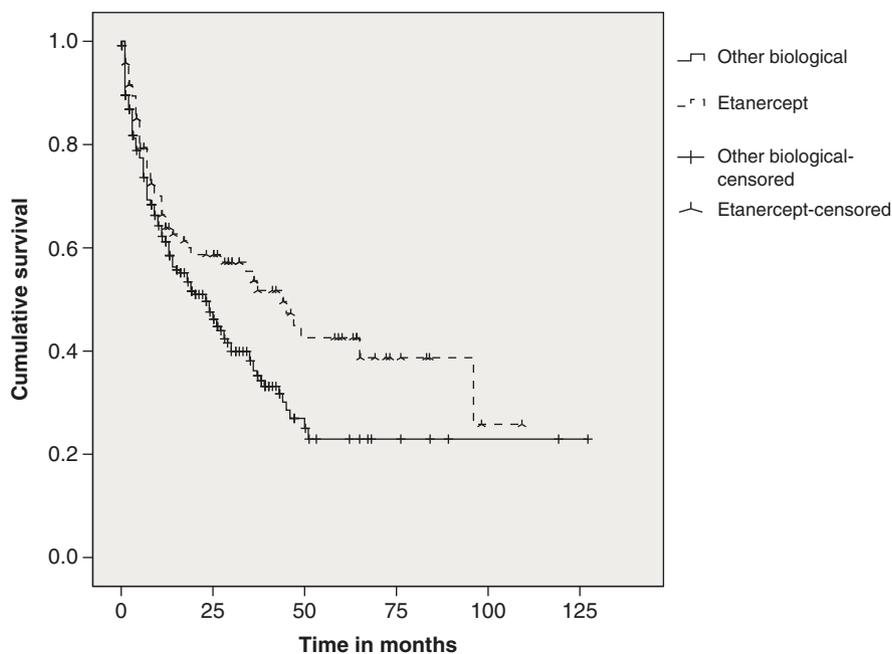


Fig. 1. Cumulative duration curve of treatment with etanercept and other biologics (Kaplan–Meier).

In our group of patients, treatment with ETN showed longer duration than the rest of biological therapy as a whole. This difference was significant from the second year of treatment onward, reaching statistical significance in the fifth year. These data are comparable with that reported by national RA registries in Germany⁵ (70% duration during the first year), Denmark³ (56% the second year), Italy, Lombardy¹⁸ (62.5% at 3 years) and differ from the Swedish registry⁴ (70% in the fifth year).

Our study found no duration differences in treatment with ETN or the rest of biologics by comparing patients with RA and AS. This differs from that reported by the Czech and BIOBADASER registries, describing increased duration of anti-TNF therapy compared with RA, although the Czech registry only includes patients who received biologics for the first time.^{19,20}

However, our study has limitations. The main one is the limited number of patients, which may influence its statistical power, in order to not to diminish the number, the treatments were included regardless of biologics used previously, and we know that this determines the effectiveness.²¹ Moreover, using data from a previous registry, we were unable to include variables of clinical activity, disease duration or previous drugs, which would have been desirable in order to compare the different drugs and avoid selection bias. In addition, our data is from patients with various diagnoses and the effectiveness of biologics may be different for each disease.²²

Our study, consistent with other registries, shows a lower discontinuation rate than the rest of ETN based biologic therapy. This could be due to a lower frequency of adverse events and / or better clinical efficacy. However, the study design is inappropriate to make direct comparisons and this may only be tested with randomized clinical trials.

Finally, in our case, the local registry has been useful to standardize the management of patients with biologic treatment and alert on the occurrence of adverse effects.

In summary, the data from our registry show a higher local duration of ETN treatment as compared with the rest of biologic therapy, similar to what is seen in other national registries.

Conflict of Interest

The authors declare no conflicts of interest.

Acknowledgement

Thanks to Dr. Loreto Carmona for her cooperation in drafting the article; without her enthusiasm we would have been unable to disclose the results of our modest research.

References

- Gartlehner G, Hansen RA, Jonas BL, Thieda P, Lohr KN. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. *J Rheumatol.* 2006;33:2398–408.

- McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, et al. Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation. *Health Technol Assess.* 2007;11:1–158, iii–iv.
- Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, et al., Østergaard M. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry. *Arthritis Rheum.* 2010;62:22–32.
- Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden. *Arthritis Rheum.* 2006;54:600–6.
- Strangfeld A, Hierse F, Kekow J, Von Hinueber U, Tony HP, Dockhorn R, et al. Comparative effectiveness of tumour necrosis factor alpha inhibitors in combination with either methotrexate or leflunomide. *Ann Rheum Dis.* 2009;68:1856–62.
- Kristensen LE, Karlsson JA, Englund M, Petersson IF, Saxne T, Geborek P. Presence of peripheral arthritis and male sex predicting continuation of anti-tumor necrosis factor therapy in ankylosing spondylitis: an observational prospective cohort study from the South Swedish Arthritis Treatment Group Register. *Arthritis Care Res (Hoboken).* 2010;62:1362–9.
- Saad AA, Ashcroft DM, Watson KD, Symmons DP, Noyce PR, Hyrich KL, et al. Efficacy and safety of anti-TNF therapies in psoriatic arthritis: an observational study from the British Society for Rheumatology Biologics Register. *Rheumatology (Oxford).* 2010;49:697–705.
- Glintborg B, Østergaard M, Dreyer L, Krogh NS, Tarp U, Hansen MS, et al. Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor? therapy: results from the nationwide Danish DANBIO registry. *Arthritis Rheum.* 2011;2:382–90.
- Zink A, Askling J, Dixon WG, Klareskog L, Silman AJ, Symmons DP. European biologicals registers: methodology, selected results and perspectives. *Ann Rheum Dis.* 2009;68:1240–6.
- Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. *Lancet.* 2007;370:1861–74.
- Ficha técnica de Enbrel® (Pfizer).
- Ficha técnica de Remicade® (MSD).
- Ficha técnica de Humira® (Abbott).
- Mohan AK, Cote TR, Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. *Clin Infect Dis.* 2004;39:295–9.
- Gomez-Reino JJ, Carmona L, Angel Descalzo M. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis Rheum.* 2007;57:756–61.
- Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. *Arthritis Rheum.* 2003;48:2122–7.
- Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med.* 2001;345:1098–104.
- Marchesoni A, Zaccara E, Gorla R, Bazzani C, Sarzi-Puttini P, Atzeni F, et al. TNF-alpha antagonist survival rate in a cohort of rheumatoid arthritis patients observed under conditions of standard clinical practice. *Ann NY Acad Sci.* 2009;1173:837–46.
- Pavelka K, Forejtová S, Stolfa J, Chroust K, Buresová L, Mann H, et al. Anti-TNF therapy of ankylosing spondylitis in clinical practice. Results from the Czech national registry ATTRA. *Clin Exp Rheumatol.* 2009;27:958–63.
- Carmona L, Gómez-Reino JJ, BIOBADASER Group. Survival of TNF antagonists in spondylarthritis is better than in rheumatoid arthritis. Data from the Spanish registry BIOBADASER. *Arthritis Res Ther.* 2006;8:R72.
- Rémy A, Avouac J, Gossec L, Combe B. Clinical relevance of switching to a second tumour necrosis factor-alpha inhibitor after discontinuation of a first tumour necrosis factor-alpha inhibitor in rheumatoid arthritis: a systematic literature review and meta-analysis. *Clin Exp Rheumatol.* 2011;29:96–103.
- Heiberg MS, Nordvag BY, Mikkelsen K, Rødevand E, Kaufmann C, Mowinckel P, et al. The Comparative effectiveness of tumor necrosis factor-blocking agents in patients with rheumatoid arthritis and patients with ankylosing spondylitis: a six-month, longitudinal, observational, multicenter study. *Arthritis Rheum.* 2005;52:2506.