Clinical and economic impact of the use of Adalimumab 40 mg every three weeks or once monthly, in rheumatoid arthritis, psoriatic arthropathy and ankylosing spondylitis patients

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Summary

Objective: To determine the clinical and economic impact of adalimumab 40 mg every three weeks (ADA21) and monthly (ADA28) on rheumatoid arthritis (RA), psoriatic arthropathy (PA) and ankylosing spondylitis (AS) patients in sustained clinical remission.
Methods: Observational, retrospective cohort study of adult patients treated with ADA 40 mg every two weeks (ADA14) who achieved and maintained clinical remission (DAS28 < 2.6 or BASDAI <2) over a period of 1 year were enrolled in an off-label program (January 2012 - July 2014) to switch from ADA14 to ADA21 or ADA28. Economic impact was assessed using Humira® official prices for Spain.
Results: From January 1, 2012 to July 1, 2014, 47 RA, 38 PA, and 33 AS patients were treated with ADA. 20 (17%) patients (10 women; ages 57±11 years; 7 RA, 8 PA, 5AS) received ADA in extended dose regimen: 17 ADA 21 and 3 ADA 28 for at least 6 months (1.6±0.5 years; range 0.7-2.4 years). At the end of follow up, 17 (85%) patients continued on ADA reduced dose (14 ADA21 and 3 ADA28). RA patients: 5 continued on ADA reduced dose, 2 patients discontinued use due to reactivation of RA (both switched back to ADA14 and achieved clinical remission). All PA patients continued on ADA optimized dose. AS patients: 4 patients continued on ADA reduced dose, 1 patient discontinued use due to reactivation of AS (switched back to ADA14, regaining clinical remission). The total savings associated with ADA21 and ADA28 over the 2.5 years observation period were €152,875, resulting in the ability to treat 9 additional patients with ADA14 for one year without increasing total ADA budget cost.
Conclusions: ADA extended dose regimen (ADA21 and ADA28) produces cost savings while maintaining clinical response in a high proportion of patients after at least 1 year under clinical remission with ADA14. At a time when the cost of therapy is an unavoidable component of Heath-care decisions, spacing the dosage of ADA could be a cost-effective option for selected RA, PA and AS patients.

Key Words: **Adalimumab, rheumatoid arthritis, tumor necrosis factor, pharmacoeconomics, psoriatic arthritis, ankylosing spondylitis.**

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Impacto clínico y económico del uso de adalimumab 40 mg cada tres semanas o una vez al mes, en artritis reumatoide, artropatía psoriásica y espondilitis anquilosante

Resumen

Objetivo: Determinar el impacto clínico y económico de la reducción de la dosis de adalimumab a 40 mg cada 3 semanas (ADA21) y mensual (ADA28) en pacientes con artritis reumatoide (AR), artropatía psoriásica (AP) y espondilitis anquilosante (EA) en remisión clínica sostenida.
Métodos: Estudio de cohorte, observacional y retrospectivo, de pacientes en un programa fuera de indicación, que recibieron ADA21 o ADA28 al menos durante 6 meses entre enero 2012 y enero 2014. Criterio de inclusión: pacientes tratados con adalimumab 40 mg cada 2 semanas (ADA14) que alcanzan y mantienen la remisión clínica sostenida (DAS28<2.6 o BASDAI <2) durante 1 año fueron seleccionados para reducir la dosis estándar de ADA14 a ADA21 o ADA28. Se recogieron datos sobre la edad, sexo, indicación, duración (en años) de ADA14 durante el periodo de estudio. En estos pacientes simulamos el coste del tratamiento con adalimumab si hubieran recibido ADA14 durante su periodo con ADA21 o ADA28. El impacto económico fue evaluado usando los precios oficiales de adalimumab en España.
Resultados: Desde enero 2012 hasta julio 2014, 47 AR, 38 AP, and 33 EA pacientes recibieron ADA. 20 (17%) pacientes (10 mujeres; edad 57±11 años; 7 RA, 8 PA, 5 AS) recibieron ADA en un régimen de dosis extendida: 17 ADA 21 y 3 ADA 28 durante al menos 6 meses (1,6±0,5 años; rango 0,7-2,4 años). Al final del estudio, 17 (85%) pacientes continuaron en remisión clínica con dosis reducida de adalimumab (14 ADA21 y 3 ADA28). 5 pacientes con RA continuaron con ADA a dosis reducidas, 2 pacientes lo suspendieron por reactivación de la AR (cambio a ADA14 alcanzando la remisión clínica). Todos los pacientes con ESP continuaron con ADA a dosis optimizadas. 4 pacientes con AP continuaron con ADA a dosis reducidas. 1 paciente lo suspendió por reactivación de la AP (cambio a ADA14 alcanzando la remisión clínica). Los costes totales asociados a la estrategia de reducción de dosis durante el periodo de observación fueron de €152.875. Esta reducción del coste, lograda con el régimen de dosis extendida de adalimumab, nos permitiría tratar a 9 pacientes más con AR, AP o EA por un año sin incrementar el coste total de la terapia con ADA.
Conclusión: El régimen de dosis extendida de adalimumab produce una importante disminución de costes cuando es usado en pacientes que mantienen la remisión clínica con ADA14 al menos durante 1 año. Esta estrategia en pacientes seleccionados mejora la relación de coste-efectividad del tratamiento y permite tratar más pacientes con el mismo presupuesto.

Palabras clave: **Adalimumab, artritis reumatoide, factor de necrosis tumoral, farmacoeconomía, artritis psoriásica, espondilitis anquilosante.**

Introduction

Adalimumab (ADA) is a soluble tumor necrosis factor alpha receptor antagonist approved for the treatment of patients with moderate-to-severe rheumatoid arthritis (RA), polyarticular juvenile RA, psoriatic arthropathy (PA), plaque psoriasis and ankylosing spondylitis (AS)[1]. In adults, ADA is administered as a subcutaneous injection, 40 mg every other week[1]. The aim of treatment with ADA is to substantially improve the patient's condition without increasing the risk of severe side effects. The efficacy, safety and potential toxicity of this agent are well documented, and we now have more than 10 years' treatment experience in immune mediated inflammatory disease[2]. The most common side effects of ADA are injection site reactions, headaches, and mild upper respiratory tract infections[3].

ADA 40 mg every two weeks (ADA14) has demonstrated significant rates of clinical remission in patients with RA, PA and AS, maintained over the long term in clinical practice[4]. However, in certain patients who achieve and maintain clinical response, and in whom structural damage is controlled, ADA dose reduction is clearly desirable from both a clinical and a cost perspective[5].

Therefore, in certain patients who remain in clinical remission with a standard dose of ADA, a reduction in dose to ADA 40 mg every three weeks (ADA21) or monthly (ADA28) may prevent adverse drug reactions and reduce the cost of therapy with no worsening of patient quality of life.

The aim of this study was to determine the clinical and economic impact of the use of ADA21 and ADA28 on RA, PA and AS patients with at least 1 year of ongoing clinical and radiological remission in a 2.5-year clinical practice scenario.

Patients and methods

We performed an observational, retrospective cohort study of patients in an off-label program taking ADA21 and ADA28 for at least 6 months between January 1, 2012 and July 1, 2014, based on data from the rheumatology department and outpatient pharmacy of the Hospital de Sagunto, a 250-bed regional acute-care hospital belonging to the Spanish National Health System.

Patients with RA, PA and AS, defined by ACR criteria[6] and the modified New York criteria[7], respectively, who began ADA14 therapy between December 1, 2004 and December 30, 2011, were included in the study.

Inclusion Criteria: adult patients treated with ADA14 who achieved and maintained clinical remission (Disease Activity Score (DAS28) <2.6 or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) <2) for a period of at least 1 year were selected to have their standard dose switched from ADA14 to ADA21 or ADA28. Only patients treated with ADA extended dose regimen for at least 6 months were included in the study.

We collected data from outpatient´s hospital pharmacy and medical records, regarding age, sex, indication, and duration (in years) of ADA21 or ADA28 during the study period (January 2012- July 2014). We also determined if ADA extended dose had been switched to ADA14 or suspended and replaced by another biological drug, and the reason for this change. The criteria for withdrawal of therapy was applied following EULAR recommendations[8-10].

ADA extended dose regimen was defined as a ≤25% decrease in the average daily dose for ADA during a single dispensing episode in comparison with the previous dose. The daily dose was calculated by dividing the total amount of drug dispensed (mg) by the time period (days) for the prescription as noted in the dosing instruction for each dispensing episode.

Concomitant medications such as non-steroidal anti-inflammatory drugs (NSAID), sulphasalazine, corticosteroids, cyclosporine, leflunomide, and methotrexate were allowed throughout the study.

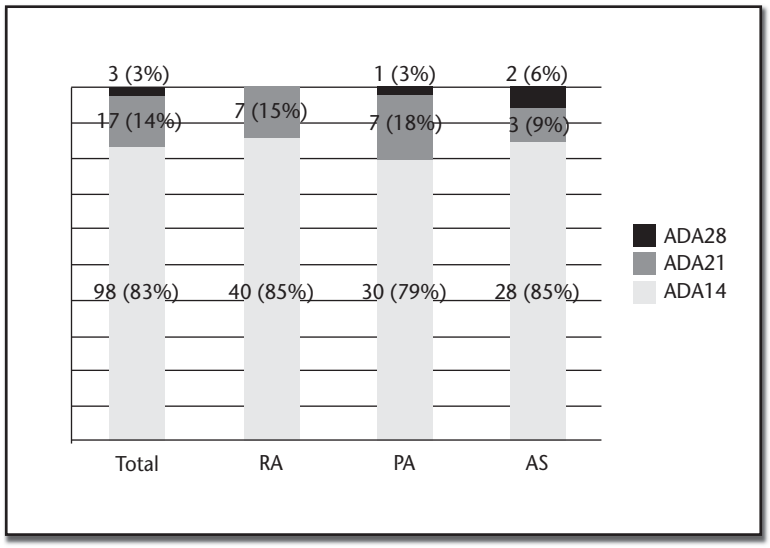
All patients gave their written informed consent for the dose reduction and the local ethics committee approved the procedure.

For these patients, we simulated the cost of treatment with ADA as if they had received ADA14 during their respective periods on ADA21 or ADA28. The price of Humira® 40 mg was taken from officially published price bulletins from the Spanish Medication Agency (Ex-Factory Price + VAT).

Results

From January 1, 2012 to July 1, 2014, 47 RA, 33 AS, and 38 PA patients were treated with ADA. During this period, a total of 20 patients (17%), 10 of whom were female, received ADA21 or ADA28 for at least 6 months: 7 RA patients (15%), 5 AS patients (15%) and 8 PA patients (21%) [Figure 1]. The mean number of years on ADA extended dose was 1.6±0.5 years (range 0.7 to 2.4 years). At the end of the study period, 85% of patients were still receiving ADA21 or ADA28. For these patients (17), the mean number of years on ADA extended dose was 1.6±0.5 years (range 0.7 to 2.4 years) and the time spent on ADA21 for the 3 patients for whom ADA21 was suspended was 1.5±0.6 years (range 0.8 to 1.9 years).

Figure 1
Distribution of patients treated with ADA throughout the study. ADA14: Adalimumab 40 mg every other week. ADA21: Adalimumab 40mg every three weeks. ADA28: Adalimumab 40mg once a month



Seven RA patients started ADA extended dose regimen. As of July 1, 2014, five patients (71%) were still receiving ADA21 with a median duration of 1.8±0.1 years. The remaining two patients (29%) discontinued ADA21 treatment: both patients due to a relapse of RA (DAS 28 >2.6). They switched back to ADA14, and achieved clinical remission again. These two patients had been treated with ADA21 for 1.3±0.8 years.

Eight PA patients started ADA21 or ADA28. By July 1st, 2014, all patients (100%) were still receiving ADA21 or ADA28 with a median duration of 1.3±0.5 years.

Five AS patients started ADA21 or ADA28. By July 1st, 2014, four patients (80%) were still receiving ADA extended dose with a median duration of 1.8±0.5 years. The remaining patient (20%) discontinued ADA21 treatment due to a relapse of AS (patient switched back to ADA14), and achieved clinical remission with the new dose. This patient had been treated with ADA21 for 1.9 years.

Pharmaco-economic analysis

During the study period, the total cost of the ADA extended dose regimen was € 247,477, taking into account direct costs only. If the patients had been treated with ADA14, the total cost of therapy would have been € 400,351. ADA21 and ADA28 produced cost savings of € 152,875 from January 1, 2012 to July 1 2014. 32% of the ADA extended dose cost savings were associated with RA patients, 32% with AS patients and 36% with PA patients. Figure 2 shows the ADA21/28 cost savings per indication.

Discussion

ADA is an effective therapy for RA, PA and AS. The recommended dosage is 40 mg every other week[1]. In this retrospective observational cohort study, we demonstrated that ADA21/28 can be effective in RA, PA and AS patients treated with ADA14 who achieve and maintain a score of DAS28 <2.6 or BASDAI<2 for at least one year. ADA21/28 maintained sustained relief of symptoms in 17 patients (85%) for more than 6 months. In July 1st, 2014, we were treating 118 patients with ADA. According to these data, 14% of the patients were on ADA21/ADA28 with good control of their disease. Interestingly, there were no flares among PA patients. All patients maintained their remission through a mean follow-up period of 1.3±0.5 years. Therefore, this regimen will be useful for clinically stable patients with PA.

Treatment had to be changed to ADA14 in 3 patients (15%) during the study with a rate of flare for RA patients of 29% and AS patients of 20%. Despite the discontinuation, these patients received the optimized dose for more than 7 months. Additionally, in all of these patients there was a reactivation of the disease, and the return to a standard dose of ADA was highly effective, as all of them regained clinical remission.

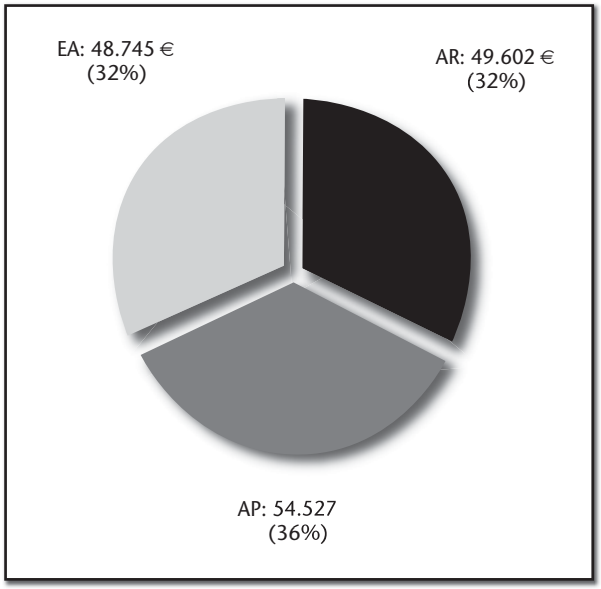
Available data about the discontinuation or dose reduction of ADA in RA, PA and AS patients are scarce. A few studies have focused on the optimization of anti-TNF agents in rheumatology disease patients who have achieved clinical remission.

A case control study of 76 consecutive patients with early psoriatic arthritis were compared with 55 patients with rheumatoid arthritis and received the same treatment with ADA14. In the presence of clinical remission, ADA dose was reduced to ADA28 in both groups. 53 (69,7%) PA patients and 17 (30,9%) RA patients achieved remission after a mean time of 5,1±1,2 and 6, ±1,6 months respectively. After tapering the dose of ADA, 47 of 53 (88,6%) PA patients and 3 of 17 (17,6%) RA patients maintained remission over a period of 28,9±8,4 and 24,2±6,4 months, without occurring serious adverse events in either groups. Additionally ADA dose tapering permitted a marked cost-saving effect, with an estimated saving of more than 700,000 € for 47 patients in a period of 28 months.This study showed that clinical remission is possible in high percentage of patients with early PA receiving ADA. Such remission is maintained in a high proportion of subjects after ADA dose halving in PA patients, with relevant advantages in terms of patient compliance, drug exposure risk and economic burden[11].

An observational prospective study compared the clinical efficacy of ADA14 maintenance administration with ADA 28 in psoriasis patients. Clinical efficacy was evaluated by the proportion of patients who achieved PASI 75 (Psoriasis Area and Severity Index) at weeks 36, 48 and 60. After week 24, 10 of 17 patients treated previously with ADA 14 started with ADA28 while 7 continued with ADA14. At week 24, all the patients except for one in each group achieved PASI 75 and continued maintaining PASI 75 at week 60. Regarding two patients who did not achieve PASI 75 at week 24, one ADA14 treated patient experienced a gradual increase in therapeutic response while one ADA28 treated patients showed exacerbation after week 24. The study concluded that ADA28 seems to be a reasonable treatment option for patients who responded well to initial standard ADA treatment for 24 weeks[12].

A descriptive cross-sectional study which included 153 patients (82 RA; 29 AS; 20 PA; 22 miscellaneous) analyzed the frequency and characteristics of patients treated with low doses of biologics who achieved adequate control of the disease, comparing them with

Figure 2
ADA associated cost savings per indication over the course of the study period (January 2012 - July 2014)



those receiving standard doses. Mean time disease duration was 14,9±7,7 years. At the time of analysis, 70 patients (45,7%) were receiving low doses of biological therapy. Mean time dosage reduction was 17,4±17,5 months. The most common biological agents used in low dose were: Adalimumab, Etanercept and Tocilizumab in 57.6%, 54.9%, and 40% respectively, in patients with a reduced dose of biological therapy. The most employed reduced dose for ADA was ADA21 (78,9%) followed by ADA28 (21,1%). The study showed that patients at low dose of biological therapy compared with standard dose had similar mean disease duration, but received significantly less DMARDs, glucocorticoids and NSAIDs, and similar biological agent duration. It also concluded that 45,7% of the chronic arthritis patients received low dose of biological therapy, after achieving remission or low activity at standard doses, maintining a good control of the disease[13].

A cross-sectional study of 99 patients with chronic inflammatory arthritis treated with subcutaneous anti-TNF drugs showed that 23,2% of patients had dose optimization with 36% of ADA patients receiving an optimizated dose. The most commonly dosing regimen

used were ADA21 (34,8%) and Etanercept 50 mg/ 10 days (34,8%). ADA 30 was used in 4,3% of patients. The study concluded that there was a higher incidence of optimized doses for ADA and Golimumab compared with those described in recent published studies[14].

Considering the fact of the potential ADA cost–effectiveness, our study showed that the optimization in the ADA dose resulted in considerable cost savings. For a patient treated with ADA14, the weekly cost is € 247, whereas the weekly cost of ADA21 and ADA28 are € 164 and € 115 respectively. Thus, the total cost of ADA may be halved in selected patients. The total cost of the reduced-dose regimen during the study period was € 247,477, taking into account drug costs only. If the patients had been treated with ADA14, the total cost of therapy would have been € 400,351. Thus, implementation of the reduced-dose regimen saved € 152,875 from January 1, 2012 to July 1, 2014. Therefore, the cost reduction achieved with ADA21/28 could lead to savings in the hospital budget that would allow us to treat 9 additional patients with RA, PA or AS using ADA14 for 1 year, without increasing the total cost for biotreated patients. These cost savings have been reported in other studies published in literature[11].

Our study is limited because it is a retrospective observation without a control group of patients who adhered to the standard dosing schedule and the study sample is small. The inherent limitation of our sample size could be reduced by supporting data from similar studies in larger institutions. Furthermore, only direct drug cost were accounted; for a complete vision indirect cost should be taken into account. Our results showed the advantages of ADA21/28 from a cost perspective. This regimen is expected to produce significant savings if used in patients with slow worsening of structural damage who maintain clinical remission of rheumatoid arthritis for at least 1 year using ADA14. This low dosage is probably not suitable for all patients, especially when the objective of therapy is to prevent structural damage. Thus, it still remains to be defined which patients could have received ADA21/28 instead of ADA14.

Conclusion

Optimizing the ADA dosage could make treatment more cost-effective and allow physicians to treat more patients on a fixed budget. At a time when the cost of therapy is an unavoidable component in health care treatment decisions, ADA 21 and ADA 28 could be a cost-effective option for selected patients with RA, PA and AS.

Conflicts of Interest: The authors have no affiliations with or financial interest in any company or organization that could conflict with the views expressed in this manuscript.
ener conflictos de intereses.

Blibliography

1. Abbvie Inc. Humira: summary of product characteristics.
2. Burmester GR, Mease P, Dijkmans BA, Gordon K, Lovell D, Panaccione R, et al. Adalimumab safety and mortality rates from global clinical trials of six immune-mediated inflammatory diseases. Ann Rheum Dis 2009;68(12):1863-9.
3. Schmeling H, Minden K, Foeldvari I, Ganser G, Hospach T, Horneff G. Efficacy and safety of Adalimumab as first and second used biologic agent in juvenile idiopathic arthritis - the German Biologics JIA Registry (BiKeR). Arthritis Rheumatol. 2014.
4. Hetland ML, Christensen IJ, Tarp U, Dreyer L, Hansen A, Hansen IT, et al. 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 Rheumatol 2010;62:22-32.
5. den Broeder AA, van Herwaarden N, van der Maas A, van den Hoogen FH, Bijlsma JW, van Vollenhoven RF, et al. Dose Reduction strategy of subcutaneous TNF inhibitors in rheumatoid arthritis: design of a pragmatic randomised non inferiority trial, the DRESS study. BMC Musculoskelet Disord 2013;14:299.

6. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
7. 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.
8. Nam JL, Winthrop KL, van Vollenhoven RF, Pavelka K, Valesini G, Hensor EM, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis 2010;69:976-86.
9. Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations forthe management of Ankylosing spondylitis. Ann Rheum Dis 2011;70:896-904.
10. Gossec L, Smolen JS, Gaujoux-Viala C, Ash Z, Marzo-Ortega H, van der Heijde D, et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. Ann Rheum Dis 2012;71:4-12.
11. Cantini F1, Niccoli L, Cassarà E, Kaloudi O, Nannini C. Sustained maintenance of clinical remission after adalimumab dose reduction in patients with early psoriatic arthritis: a long-term follow-up study. Biologics 2012;6:201-6.
12. Taniguchi T1, Noda S, Takahashi N, Yoshimura H, Mizuno K, Adachi M. An observational, prospective study of monthly adalimumab therapy for disease maintenance in psoriasis patients: a possible new therapeutic option for good responders to the initial induction treatment. J Eur Acad Dermatol Venereol 2013 Nov;27(11):1444-7.
13. Inciarte-Mundo J, Hernández MV, Rosario V, Ruiz-Esquide V, Cabrera-Villalba S, Ramírez J, et al. Reduction of Biological Agent Dose in Rheumatic Diseases: Descriptive Analysis of 153 Patients in Clinical Practice Conditions. Reumatol Clin. 2014;10(1):10-16
14. Sangrador Pèlluz C, Soler Company E, Fernandez Matilla M, Fernandez-Llanio Cornella N, Maiques Llacer FJ, Castellano Cuesta JA. Optimización de la terapia biológica en patologías reumáticas: grado de adecuación a las recomendaciones actuales. Rev O.F.I.L. 2014,24;1:10-16.