Tesis doctoral

EFECTIVIDAD Y EFICIENCIA DE LA TERAPIA BIOLÓGICA EN ARTRITIS REUMATOIDE EN LA PRÁTICA CLÍNICA HABITUAL

Tesis doctoral presentada por Manuel Jesús Cárdenas Aranzana,

Licenciado en Farmacia, por la que opta al grado de Doctor por la Universidad de Córdoba

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Prof Dr. Eduardo Collantes Estévez

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UNIVERSIDAD D CÓRDOBA

TITULO: *EFECTIVIDAD Y EFICIENCIA DE LA TERAPIA BIOLÓGICA EN ARTRITIS REUMATOIDE EN LA PRÁCTICA CLÍNICA HABITUAL*

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Memoria presentada por:

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Tesis doctoral realizada bajo la dirección del Profesor Dr.Eduardo Collantes Estévez y la Dra.Pilar Font Ugalde en el Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC)

Programa de Doctorado: Biomedicina

El doctorando

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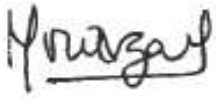

Dra. Pilar Font Ugalde

TÍTULO DE LA TESIS: Efectividad y eficiencia de la terapia biológica en artritis reumatoide en la práctica clínica habitual

DOCTORANDO/A: Don Manuel Jesús Cárdenas Aranzana

INFORME RAZONADO DEL/DE LOS DIRECTOR/ES DE LA TESIS

(se hará mención a la evolución y desarrollo de la tesis, así como a trabajos y publicaciones derivados de la misma).

D. Manuel Jesús Cárdenas Aranzana presenta un trabajo original en el que se han analizado en profundidad los resultados obtenidos con diferentes regímenes de dosificación/optimización de terapias biológicas en los pacientes con artritis reumatoide incluidos en la cohorte CREATE incluyendo el análisis farmacoeconómico de los mismos resultados.

Los trabajos conducentes a esta Tesis Doctoral son un ejemplo de lo que se puede conseguir mediante la colaboración y sinergia de dos especialidades hospitalarias: Reumatología y Farmacia.

Los resultados obtenidos en este trabajo han sido publicados en tres artículos, en una misma revista científica de reconocido prestigio internacional en el campo de la investigación en Reumatología: **Rheumatology International** Q3 y será defendidos en el sistema de Tesis por compendio de artículos, ya que estos artículos constituye una misma unidad temática de objetivos y resultados progresivos.

La tesis doctoral presentada se enmarca dentro de del proyecto de investigación de la Consejería de Salud de la Junta de Andalucía: APLICABILIDAD CLINICA DE UN PROTOCOLO DE DISMINUCION DE DOSIS ESTANDARIZADO EN PACIENTES EN REMISION CLINICA PERSISTENTE DIAGNOSTICADOS DE ARTRITIS REUMATOIDE Y TRATADOS CON ANTAGONISTAS DE TNF, cuya IP es la Codirectora de la Tesis Profesora PILAR FONT UGALDE .

Finalmente, cabe destacar la formación técnica y científica alcanzada por el doctorando que ha sido excelente.

El desarrollo de la tesis le ha permitido adquirir conocimientos teóricos y metodológicos que lo capacitan para desarrollar nuevas hipótesis y participar activamente en la redacción y coordinación de nuevos artículos científicos y proyectos de investigación.

Córdoba, 8 de Junio de 2017

Firma del/de los director/es

Fdo.: Eduardo Collantes Estévez

Fdo.: Pilar Font Ugalde

"Un primer paso no te llevará a la meta, pero te saca de donde estás"

Anónimo

"Confía en el tiempo, que suele dar dulces salidas a muchas amargas dificultades"

Miguel de Cervantes

Para Ana, mi amor

AGRADECIMIENTOS

Este trabajo no habría sido posible sin la colaboración de muchas personas, a quien les agradezco de corazón su tiempo y su ayuda.

En primer lugar tengo que mencionar a mis directores, el Dr.Collantes y la Dra.Font. Ellos han sido completamente imprescindibles desde el inicio hasta el final. Sin toda su dirección, revisión, análisis y consejos no hubiese llegado hasta aquí. Al Dr.Collantes le agradezco además que me hubiese abierto la puerta de la UGC Reumatología para trabajar conjuntamente ya en 2007, y que posteriormente me brindase la oportunidad de investigar y realizar mi tesis doctoral con ellos. A la Dra.Font quiero agradecerle de forma especial su apoyo continuo, estando siempre dispuesta para ayudarme, dando igual el día y la hora. A ambos les agradezco también el buen grado con el que siempre me han ayudado.

También quiero agradecer al Dr. Miguel Angel Casado su colaboración durante el primer año. Su orientación en el enfoque del proyecto de investigación fue esencial para el buen desarrollo del trabajo.

Quiero agradecer igualmente la ayuda recibida de Mª Dolores Aguilar. Para mí sus consejos e implicación en el trabajo han sido de gran valía.

Por supuesto tengo que mencionar a mi jefe, José Ramón del Prado, a quien agradezco que me animase a llevar a cabo este proyecto, buscando siempre que logre un desarrollo profesional lo más completo posible.

Gracias a la colaboración de mis compañeras de la UGC Reumatología y de Farmacia, con quienes he trabajado en el día a día para disponer del registro de pacientes y sus datos. Gracias a MªCarmen, Montse, Desiré y Soraya, siempre solícitas a cualquier petición, siempre dispuestas a hacerme el camino más fácil.

Quiero dar las gracias a mi familia. Mis padres y mis hermanas, de quienes he aprendido la necesidad de la perseverancia y la importancia del esfuerzo.

Y finalmente y de forma especial, quiero agradecer y dedicar este trabajo a mis hijos, Martina y Javier, y a mi amor, Ana, por su apoyo y confianza. Siempre convencida de lograrlo. Gracias por creer en mí, incluso más que yo mismo.

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Introducción

La Artritis Reumatoide (AR) es una enfermedad inflamatoria, sistémica, de etiología desconocida, que se caracteriza por dolor, inflamación crónica de múltiples articulaciones y vainas tendinosas de la membrana sinovial, destrucción articular, con deterioro progresivo. Aunque la sinovial es el foco principal de la lesión, en la AR se producen cambios sistémicos responsables de las manifestaciones extra articulares, como vasculitis, glomerulonefritis, pericarditis, pleuritis, escleritis, siendo los nódulos reumatoides la manifestación extra articular más frecuente. Además, los pacientes que padecen AR pueden sufrir comorbilidades (enfermedad cardiovascular, infecciones, neoplasias, osteoporosis y enfermedad gastrointestinal) con mayor frecuencia que la población general [1].

En España, según datos del estudio sobre prevalencia de las enfermedades reumáticas en la población española, EPISER, llevado a cabo entre 1998 y 1999, se estima que afecta al 0.5% de la población en España mayor de 20 años [2]. Es más frecuente en mujeres, en una proporción aproximada de 3:1 y, aunque puede ocurrir a cualquier edad, tiene un pico de incidencia entre los 40 y los 60 años.

Se sabe que la tendencia al desarrollo de AR puede ser heredada genéticamente. Se trata de una enfermedad heterogénea y está influenciada por variaciones en factores ambientales y por las características genéticas del individuo.

Distintos estudios han puesto de manifiesto una disminución de la esperanza de vida y un aumento de la mortalidad estandarizada en pacientes con AR, a pesar de los avances en el manejo de la enfermedad, y se ha establecido un acortamiento de la esperanza de vida de entre 5 y 10 años [3]. Por lo tanto son pacientes con un deterioro funcional, disminución de la calidad de vida y una mortalidad prematura [4-6].

En consecuencia, el objetivo del tratamiento de la AR comprende controlar del dolor y la inflamación, reducir al máximo el daño articular y la discapacidad, controlar las manifestaciones extra articulares, mejorar la calidad de vida de los pacientes y alcanzar la remisión de la enfermedad, o al menos lograr una baja actividad clínica sostenida [7,8].

El tratamiento de la AR ha experimentado avances muy importantes durante las dos últimas décadas, debido en gran medida a dos circunstancias principales:

1) El desarrollo de terapias biológicas (TB) como tratamientos alternativos a los fármacos inductores de remisión o modificadores de la enfermedad clásicos o sintéticos (DMARDs, o *disease modifying antirheumatic drugs*. Actualmente en España se disponen de 8 fármacos biológicos con distintos mecanismos de acción: infliximab, etanercept, adalimumab, golimumab y certolizumab pegol como bloqueantes del factor de necrosis tumoral alfa (antiTNF), rituximab como antiCD20, abatacept a nivel del linfocito T y tocilizumab como anti-interleukina 6. Todos estos fármacos han demostrado eficacia [9-18] y un perfil de efectos adversos que obliga a una estrecha monitorización.

Organismos como el Servicio Andaluz de Salud (SAS) y sociedades científicas han elaborado guías de consenso para el tratamiento en los pacientes con AR [19,20], con el objetivo de establecer recomendaciones para el manejo de los pacientes con AR, centrado en el papel de los DMARDs sintéticos y biológicos disponibles. La ausencia de estudios comparativos directos entre los tratamientos biológicos

dificulta la elección sobre qué fármaco que debe emplearse como terapia de inicio preferente por ser más eficaz, seguro o eficiente que el otro [7,21],

2) El desarrollo de una estrategia terapéutica más ambiciosa para conseguir la remisión de la enfermedad.

Actualmente existe una fuerte corriente que aboga por abordar el tratamiento de la AR mediante una estrategia de tratamiento basada en tratar por objetivos (treat to target, T2T). Los puntos clave del T2T suponen establecer objetivos concretos, seguimiento estrecho de los pacientes, monitorizar la actividad de la enfermedad y ajustar el tratamiento de acuerdo a protocolos establecidos [22,23]. Ensayos clínicos y estudios observacionales han demostrado que esta estrategia es más eficaz que un abordaje estándar para reducir la actividad de la enfermedad y en última instancia, lo más eficaz supondría plantear esta estrategia con el objetivo de alcanzar remisión clínica [23-25]. Esto supone una inversión adicional de recursos, pero se ha demostrado que puede resultar una medida costo-efectiva a partir del tercer año, frente a mantener una estrategia de tratamiento y revisión usual, cuando se aplica a pacientes con AR de inicio [26].

En pacientes con AR establecida y persistente tras el tratamiento con al menos dos fármacos modificadores de la enfermedad clásicos (DMARDs) y un valor de DAS28>5.1, se recomienda el uso de terapia biológica [27]. Sin embargo, debido a la ausencia de suficiente evidencia clínica, en esta población de pacientes no se han establecido acuerdos para puntos esenciales que implican al T2T, como son el tratamiento intensivo con terapia biológica o si el objetivo debe ser alcanzar remisión clínica, baja actividad de la enfermedad o control de la enfermedad.

Los datos disponibles de registros de tratamientos con fármacos biológicos en AR muestran que se alcanza la remisión clínica en el 19-39% de los pacientes [28-29]. Pese a los datos de eficacia y efectividad, las TB no están exentas de riesgos y potenciales efectos adversos, suponiendo además un elevado coste. Estos hechos han llevado a cuestionar qué hacer con las TB una vez el paciente ha conseguido entrar en remisión de forma sostenida en el tiempo [30].

Se dispone de ensayos clínicos y estudios en los que se ha observado que la discontinuación del tratamiento en pacientes con AR precoz presenta una tasa de recaídas de entre el 40 y el 75% [31-37]. Alternativamente, para pacientes con AR establecida, se ha planteado una reducción de dosis como posible estrategia eficiente de manejo [31, 38-39].

En esta línea, las Sociedades Españolas de Reumatología Clínica y Farmacia Hospitalaria han elaborado un documento de consenso con recomendaciones de manejo de pacientes en remisión clínica [40]. Este documento establece como posible una reducción de dosis de entre un 20-50% en pacientes con AR que alcanzan y mantienen su objetivo terapéutico durante más de seis meses. Además propone estrategias de manejo en el caso de recaídas, todo ello con el objetivo de disminuir la variabilidad clínica.

En resumen, el uso de estos fármacos biológicos ha supuesto un gran avance para el tratamiento de la AR, pero tiene un elevado impacto económico debido al coste *per se* de estos tratamientos y también a su

carácter crónico [41-42]. Existen trabajos que describen el uso de fármacos biológicos como una intervención coste-efectiva en diferentes escenarios [43], pero no determinan que fármaco resulta más eficiente, siendo necesario la incorporación de aspectos económicos en la realización de guías de práctica clínica [44].

De esta forma se están promoviendo la realización de estudios que avalen la relación coste-efectividad de los medicamentos biológicos en la práctica clínica habitual, al margen del conocimiento aportado por los ensayos clínicos disponibles [45], ya que éstos solamente representan a una parte de la población en general y no incluyen datos de coste ajustados a los recursos reales disponibles [46-48].

Por tanto, en general y aún más en el actual contexto de crisis y ajuste presupuestario de recursos en sanidad, se necesita conocer qué terapia y qué estrategia de tratamiento resulta más eficiente en la práctica clínica habitual, desde el punto de vista hospitalario. De esta forma se podrán optimizar los recursos disponibles para conseguir los mejores resultados en salud posibles en nuestros pacientes.

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Hipótesis y Objetivos

La hipótesis general del trabajo de investigación desarrollado es la siguiente: la eficiencia de las terapias biológicas y de la estrategia de tratar por objetivos a pacientes con artritis reumatoide establecida depende del fármaco administrado y del resultado clínico perseguido.

El objetivo principal fue comparar el coste-efectividad de los fármacos antiTNF-alfa empleados como terapia biológica de inicio (infliximab, etanercept o adalimumab), con un horizonte temporal de dos años, empleando la perspectiva del sistema sanitario.
Este objetivo se aborda en la primera de las publicaciones, junto con los siguientes objetivos operativos: contrastar la supervivencia de cada fármaco antiTNF-alfa e identificar posibles factores pronósticos de respuesta.

Los objetivos secundarios fueron los siguientes:
-Analizar la efectividad y el coste-efectividad en la práctica clínica real de la estrategia T2T para conseguir remisión clínica en pacientes con AR establecida, tras dos años de tratamiento con TB. Este objetivo se aborda en la segunda de las publicaciones que se presentan.
-Evaluar la efectividad y la eficiencia en la práctica clínica habitual de la reducción de dosis en pacientes con AR en remisión clínica sostenida e identificar variables predictivas de respuesta a la optimización. Este objetivo se aborda en la tercera y última de las publicaciones presentadas.

Rheumatol Int (2016) 36:231–241
DOI 10.1007/s00296-015-3374-2

Rheumatology INTERNATIONAL

ORIGINAL ARTICLE - HEALTH SERVICES RESEARCH

Real-world cost-effectiveness of infliximab, etanercept and adalimumab in rheumatoid arthritis patients: results of the CREATE registry

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El primer artículo del trabajo de investigación se publicó en Febrero de 2016 en Rheumatology International. En este estudio se analizó la cohorte de pacientes con AR que comenzó tratamiento con infliximab, etanercept o adalimumab entre 2007 y 2012 en el Hospital Universitario Reina Sofía de Córdoba.

El objetivo principal del estudio era comparar el coste efectividad de estos tres fármacos, considerando alcanzar remisión clínica (DAS28<2,6) , un horizonte temporal de dos años y empleando como perspectiva el sistema sanitario, por lo que se tuvieron en cuenta todos los posibles costes directos sanitarios.

Se llevaron a cabo además varios análisis de sensibilidad considerando por un lado el resultado de alcanzar baja actividad de la enfermedad y teniendo en cuenta por otro sólo el coste de adquisición directa del fármaco. Así resultaron diversos posible escenarios.

Se incluyeron 130 pacientes, de los que 55 se trataron con infliximab, 44 con adalimumab y 31 con etanercept, sin diferencias en las caraterísticas clínicas y demográficas basales.

Al cabo de dos años, el porcentaje de pacientes que lograro remisión clínica no fue diferente entre adalimumab e infliximab, siendo superior adalimumab a etanercept.

Considerando los costes directos sanitarios, adalimumab resultó ser más eficiente que infliximab y etanercept en alcanzar remisión clínica. Este resultado y las diferencias entre cada uno de los fármacos se repite prácticamente en los distintos escenarios y análisis de efectividad y de coste efectividad planteados, con ligeros cambios en algún caso.

Se encontró que el coste de adquisión del fármaco era el componente de mayor peso en los costes directos sanitarios.

Como conclusiones de este primer trabajo, adalimumab, en condiciones de práctica clínica habitual, resultó ser más eficiente que adalimumab y etanercept para alcanzar remisión clínica. Sin embargo, y dado que el coste de adquisición del fármaco resulta determinante, cambios relevantes en el mismo podrían modificar los resultados de coste-efectividad alcanzados.

ABSTRACT

Introduction

Biological drugs have proven efficacy and effectiveness in treatment of rheumatoid arthritis (RA), although none has been shown to be superior. Few studies have evaluated the cost-effectiveness of biological drugs in real-life clinical conditions. The objective of this study was to compare the cost-effectiveness of infliximab, etanercept and adalimumab in achieving clinical remission (DAS28 < 2.6) when used as initial biological therapy.

Methods

Patients were diagnosed with RA who began treatment with infliximab, etanercept or adalimumab in the Reina Sofia Hospital (Cordoba, Spain) between January 1, 2007, and December 31, 2012. Effectiveness was measured as the percentage of patients who achieved clinical remission after 2 years. The cost analysis considered the use of direct health resources (perspective of the healthcare system). Cost-effectiveness was calculated by dividing the total mean cost of each treatment by the percentage of patients who achieved remission.

Results

One hundred and thirty patients were included: 55 with infliximab, 44 with adalimumab and 31 with etanercept. After 2 years, 45.2 % of patients with adalimumab achieved clinical remission, versus 29.1 % with infliximab (p = 0.133) and 22.7 % with etanercept (p = 0.040), with no differences between etanercept and infliximab (p = 0.475). The average total cost at 2 years was €29,858, €25,329 and €23,309 for adalimumab, infliximab and etanercept, respectively, while the mean cost (95 %CI) to achieve remission was €66,057 (48,038–84,076), €87,040 (78,496–95,584) and €102,683 (94,559–110,807), respectively. Adalimumab was more efficient than etanercept (p < 0.001) and infliximab (p = 0.026), with no differences between etanercept and infliximab (p = 0.086).

Conclusion

Adalimumab was the most cost-effective treatment in achieving clinical remission in real-life clinical conditions in RA patients during the study period.

Keywords

Rheumatoid arthritis · Biological drugs ·Cost-effectiveness · Real-life clinical conditions

1 Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by pain, chronic inflammation, and joint destruction. In most cases the course is progressive and leads to irreversible joint damage, resulting in functional impairment, reduced quality of life and premature mortality [1-3]. Recently, however, the development of biological therapy has been an important advance in the treatment of this disease, which is helping to change its prognosis.

The goal of RA treatment is to control pain and inflammation, minimize joint damage and disability, control extra-articular manifestations, improve patients' quality of life, and achieve disease remission or at least sustained low clinical activity [4,5].

Eight biological drugs, with different mechanisms of action, are currently available in Spain: infliximab, etanercept, adalimumab, golimumab and certolizumab pegol, which are blockers of tumor necrosis factor alpha (anti-TNF); rituximab, an anti-CD20 monoclonal antibody; abatacept, a T-cell co-stimulation modulator; and tocilizumab, an interleukin-6 receptor inhibitor. All these drugs have proven efficacy [6-15], as well as an adverse effect profile that requires they be closely monitored, resulting in a major economic impact on the healthcare system.

Although the Andalusian Health Service has a protocol establishing the clinical criteria for initiation of biological therapy [16], and despite recommendations of the Spanish Society of Rheumatology (SER) and the European League Against Rheumatic Diseases (EULAR) [4,5] establishing the importance of adjusting treatment until remission is achieved, there is no evidence on the preferred drug for initial therapy given the lack of comparative studies to evaluate whether one is more efficacious, safe or efficient than the others [4,17]. This situation persists despite the major economic impact of these drugs [18,19] and the fact that it is now considered necessary to incorporate economic aspects when developing clinical practice guidelines [20].

Some studies have described the use of biological drugs as a cost-effective intervention in different scenarios [21], but they do not show which drug is most efficient. Studies are also needed on the cost-effectiveness ratio of biological medications, given that clinical trials [22] represent only part of the general population and do not include cost data adjusted to the actual resources available [23-25].

Given the current economic crisis and the need to adjust healthcare budgets, it is desirable to know which initial therapy is most efficient in clinical practice from the hospital point of view, in order to select the drug that can best fit the available budget while achieving the best possible health outcomes.

The main objective of this study was to compare the cost-effectiveness of three anti-TNF-alpha drugs used as initial biological therapy (infliximab, etanercept or adalimumab) over a 2-year period, from the perspective of the healthcare system. Secondary objectives were to compare drug survival (median time to treatment change), perform a multivariate analysis to identify possible predictive variables of response and, finally, to describe the main adverse effects registered.

2 Methods

2.1 Patients

The data for this study were taken from the registry of the multidisciplinary Team for Rheumatoid Arthritis in the Reina Sofia University Hospital, Córdoba, Spain (CREATE Registry). The CREATE registry is a prospective database that systematically includes each patient with inflammatory rheumatoid disease who begins treatment with biological therapy. For each patient diagnosed with RA, information is collected on demographics, disease characteristics, previous treatments used, their duration and reason for suspension, current treatment and its duration, data on disease activity [number of tender joints (NTJ), number of swollen joints (NSJ), erythrocyte sedimentation rate (ESR), C-reactive protein (PCR) and the Disease Activity Score (DAS28)], patient data that could influence treatment, biological drug chosen, and concomitant treatment. Each patient is followed up prospectively to monitor the clinical variables collected and any adverse effects that may occur.

From this registry we selected all patients diagnosed with RA who began biological treatment with infliximab, etanercept or adalimumab in our hospital between January 1, 2007 and December 31, 2012, with 2 years' follow-up per patient. The study was limited to this subgroup because these are the three drugs most frequently used as initial therapy in the CREATE registry, and are the only ones for which we had 2 years' follow-up data after treatment initiation.

RA is diagnosed in accordance with the 1987 ACR criteria, based on the medical history, physical examination, complementary tests (blood count, biochemistry, presence of antibodies), chest and joint radiography, and clinical assessment of disease activity using the DAS28.

All patients had to follow the Andalusian Health Service treatment protocol for biological therapies, based on the SER [5] and EULAR [4] recommendations. To begin biological treatment, patients had to have active RA despite treatment for at least 3 months with at least two of the following drugs at the maximum authorized doses: methotrexate, leflunomide or sulfasalazine. The initial biological treatment is selected based on the characteristics of each patient and drug, as well as the cost of each drug to the hospital. In the absence of any limiting constraints (inability to attend the day hospital or to self-administer treatment, or presence of intestinal inflammatory disease for which biological treatment with infliximab is indicated), the lowest cost drug was used.

2.2 Effectiveness

The effectiveness of treatment in actual practice was evaluated by the DAS28 [26]. A value lower than 2.6 was considered clinical remission (CR), and less than 3.2 was considered a low disease activity state (LDAS). The percentage of patients who achieved CR and LDAS was determined.

In addition to the DAS28, we evaluated its components separately: NTJ, NSJ, ESR, CRP, and patient global assessment (PGA) on a visual analog scale.

Data were collected on patients' sociodemographic characteristics (age and sex), date of disease diagnosis, and clinical data including rheumatoid factor (RF+/-) and previous and concomitant treatments with disease modifying antirheumatic drugs (DMARDs). The demographic and clinical data on patients were obtained mainly from the CREATE registry and also from the database of the Andalusian Health Service.

2.3 Analysis of Resources and Costs

Two scenarios were considered. *Scenario 1:* The cost analysis was made from the perspective of the healthcare system, taking into consideration use of the following direct health resources: cost of purchasing the drug [ex-factory price (EFP)], consultations with specialists in rheumatology, use of emergency services, complementary tests performed, need for hospitalization, and use of the day hospital for intravenous drug administration. The use of resources includes consideration of the healthcare derived from the RA process as well as any adverse effects that may have occurred. *Scenario 2:* In this analysis, the only costs taken into account were the EFP costs.

Data on drug use were obtained from the databases of the Hospital Pharmacy Department. In the case of infliximab, which is dosed by weight, the cost was adjusted to the milligrams actually employed since individual doses are prepared in the Pharmacy Department, avoiding drug wastage. The remaining resources consumed were obtained from the database of the reports manager of th*e* Reina Sofia Hospital and from the Andalusian Health Service database for patients diagnosed with RA and treated with biological agents.

The cost of each drug was obtained using the official EFP, and the costs of the other resources were obtained from the price catalog of the Economics Directorate of the Reina Sofia Hospital (2014, in euros).

Periodically, the Hospital Pharmacy Department negotiates with laboratories discounts on the purchase price of these biologicals. In the absence of any clinical criteria or patient characteristic affecting the choice of anti-TNF (intestinal disease, impossibility of going to the day hospital, etc.), the drug with the lowest cost of acquisition for the hospital was chosen. This situation encouraged competition among laboratories in sales price and discounts to the hospital on the direct market cost of these drugs. An additional cost calculation was performed for scenario 2, using the negotiated purchase price of the drugs in the hospital, to quantify the savings achieved with this negotiation compared to the EFP.

2.4 Cost-Effectiveness

The cost-effectiveness of each drug was calculated by dividing the average total cost of each treatment by the percentage of patients who achieved CR. This value shows the cost per patient reaching CR with each drug and can identify the most efficient one in actual clinical practice for decision making.

The same analysis was also repeated for the effectiveness outcome "achieving LDAS" and considering as costs only the official purchase price of the drugs dispensed.

2.5 Statistical Analysis

A descriptive study was conducted, calculating the mean and standard deviation for quantitative variables, and absolute and relative frequencies for qualitative variables. An intention-to-treat analysis was made for each treatment branch.

The bivariate analysis of qualitative variables was made using the chi-square test or Fisher's test for 2x2 tables with any expected frequency less than 5. Quantitative variables were compared using Student's t-test for independent data, simple ANOVA test, and one-way ANOVA. Levene's test was used previously to test the homogeneity of variances and, depending on the results of this test, post-hoc comparisons were conducted using the Hochberg or Games-Howell tests. For data that were not normally distributed, we used the Mann-Whitney U test or the Kruskal-Wallis H test.

All comparisons were two-sided and were considered significant for values of $p<0.05$. The data were processed, tabulated and analyzed using SPSS v17 software.

Using the Kaplan-Meier Survival Analysis procedure, we examined the distribution of time to effect for the three different medications. The comparison tests showed there was no statistically significant difference among them.

We built a multiple logistic regression (MLR) model to identify the baseline clinical factors predictive of remission. We previously conducted univariate logistic regressions to establish the association between each of the potentially predictive variables and CR. The degree of association was estimated by the odds ratio (OR) and Cornfield´s 95% confidence interval. The variables that showed an association in the univariate analysis at $p<0.25$ (age in years, age at diagnosis, rheumatoid factor, NSJ at baseline, baseline DAS28, baseline ESR (mm/1h) and baseline CRP (mg/dL)) were introduced in the MLR model. Based on the Wald statistic, variables with $p>=0.15$ were eliminated one by one from the model (backward selection procedure). The scale of continuous variables was assessed by the Box-Tidwell test. Possible interactions between the variables were studied based on whether there was a significant change in the log-likelihood value after introducing the interaction in the model. Variables with $p>0.05$ were evaluated as possible confounding factors. Cooks' distance was used as the diagnostic test for outliers. The Hosmer-Lemeshow statistic was used to assess the goodness of fit.

The study was approved by the Ethical Committee of the Reina Sofia University Hospital.

3 Results

Between January 1, 2007 and December 31, 2012, a total of 130 patients in the CREATE registry who began treatment with biological therapy for the first time, were included in the study: 55 with infliximab, 44 with etanercept, and 31 with adalimumab. Baseline patient characteristics are shown in Table 1. No statistically significant differences were found between persons in the groups taking infliximab, etanercept or adalimumab.

Table 1. Patient characteristics at baseline

Baseline characteristics*	Total population (n=130)	Infliximab (n=55)	Etanercept (n=44)	Adalimumab (n=31)	P**
Sex (female)	82.3%	80%	81.81%	87.09%	NS
RF +	75.4 %	69.1%	79.5%	80.6%	NS
Age (years)	53.0 ± 13.6	51.5 ±12.7	55.1 ± 14.0	52.9 ± 14.7	NS
Weight (kg)	74.6 ± 15.8	74.8 ± 15.9	72.3 ± 19.6	72.0 ± 18.7	NS
Age at diagnosis (years)	44.0 ± 13.7	43.3 ± 11.4	45.9 ± 16.0	42.7 ± 14.3	NS
Time since diagnosis (years)	9.0 ± 7.1	8.0 ± 6.4	9.4 ± 7.3	10.2 ± 7.9	NS
Initial DAS28	5.7 ± 1.0	5.7 ± 1.1	5.8 +1.1	5.7 ± 0.9	NS
Initial NTJ 28	10.4 ± 6.4	9.6 ±6.3	11.2 ± 6.6	10.5 ± 6.4	NS
Initial NSJ28	7.1 ± 4.9	6.9 ± 5.0	7.7 ± 5.2	6.6 ± 4.2	NS
Initial ESR	33.2 ± 17.7	33.6 ± 18.2	33.9 ± 19.4	31.5 ± 14.4	NS
Initial CRP	19.2 ± 17.7	19.3 ± 17.2	21.3 ± 21.4	16.1 ± 12.0	NS
Initial PGH	69.9 ± 16.8	71.4 ± 49.6	69.6 ± 19.2	67.8 ± 16.4	NS

Abbreviations: CRP, C-reactive protein; DAS, Disease activity score; ESR: Erythrocyte sedimentation rate; NTJ, number of tender joints; NSJ, Number of swollen joints; NS, not significant; PGA, Patient global assessment; RF, Rheumatoid factor.

*Data expressed as percentage or mean ± standard deviation

**Statistical significance based on Chi-square test (sex and RF) and simple ANOVA test (rest of variables)

3.1 Effectiveness

Adalimumab was more effective than etanercept in attaining CR after 2 years, but was not significantly different from infliximab. There were no differences between infliximab and etanercept.

The percentage of patients who achieved LDAS at 2 years was higher with adalimumab than with 6-infliximab, with no differences for the rest of the possible comparisons. No differences were found for any of the secondary variables of effectiveness (Table 2).

Table 2. Comparative effectiveness at 2 years

	Total population	Infliximab (I)	Etanercept (E)	Adalimumab (A)	p**
Primary variables					
% patients with DAS28 <2.6 (CR)	30.8%	29.1%	22.7%	45.2%	A *vs.* E= 0.040 A *vs.* I= NS E *vs.* I= NS
% patients with DAS28 <3.2 (LDAS)	56.2%	47.3%	54.5%	74.2%	A *vs.* E= NS A *vs.* I= 0.015 E *vs.* I= NS
Secondary variables*					
DAS28	3.3 ± 1.1	3.4 ± 1.2	3.3 ± 1.0	2.9 ± 1.1	NS
NTJ28	1.9 ± 2.7	2.1 ± 3.2	1.7 ± 2.3	1.6 ± 2.3	NS
NSJ28	1.1 ± 2.0	1.2 ± 2.2	1.0 ± 1.8	0.8 ± 1.7	NS
ESR	22.5 ± 14.8	22.4 ± 14.4	25.4 ± 16.1	18.7 ± 13.0	NS
CRP	8.2 ± 11.3	8.9 ± 12.2	8.7 ± 11.8	5.9 ± 8.9	NS
PGA	42.6 ± 23.3	44. 5 ± 22.8	45.7 ± 22.8	34.7 ± 24.1	NS

Abbreviations:CR, clinical remission; CRP, C-reactive protein; DAS, Disease activity score; ESR, Erythrocyte sedimentation rate; LDAS, Low disease activity state; NPJ, Number of tender joints; NSJ, Number of swollen joints; NS, Not significant; PGA, Patient global assessment

* mean ± standard deviation

**Statistical significance based on Chi-square test (primary variables) and simple ANOVA test (secondary variables)

3.2 Analysis of Resources and Costs

No significant differences were found in the volume of non-drug resources used, except for a significantly higher use of Magnetic Resonance Imaging (MRI) with adalimumab than with infliximab, and greater use of the day hospital for infliximab compared with etanercept and adalimumab, due to its route of administration (Table 3).

Table 3. Comparison of resources used (mean number of units used per patient at 2 years ± standard deviation)

Non-drug resources*	Total population	Infliximab (I)	Etanercept (E)	Adalimumab (A)	P**
Consultations	13.5 ± 3.6	14.1 ±3.5	12.8 ± 3.4	13.6 ± 4.1	NS
Rheumatology	13.2 ± 3.3	13.8 ± 3.1	12.5 ± 3.3	13.2 ± 3.7	NS
Emergency services	0.3 ± 0.6	0.3 ± 0.7	0.3 ± 0.6	0.4 ± 0.6	NS
Complementary tests	23.1 ± 10.4	23.8 ± 11.2	20.5 ± 5.5	25.3 ± 13.5	NS
Laboratory	13.6 ± 4.8	14.2 ± 4.9	12.6 ± 3.3	14.0 ± 6.1	NS
Total CT	0.3 ± 0.9	0.3 ± 0.9	0.02 ± 0.15	0.5 ± 1.3	NS
MRI	0.2 ± 0.5	0.07 ± 0.32	0.1 ± 0.3	0.6 ± 0.7	ANOVA=0.021 A *vs.* I= 0.019 Rest NS
Radiological tests	8.8 ± 6.6	9.0 ± 6.8	7.5 ± 5.5	10.2 ± 7.3	NS
Ultrasound scans	0.3 ± 0.5	0.3 ± 0.6	0.2 ± 0.5	0.2 ± 0.4	NS
Days of hospitalization	2.6 ± 19.1	1.6 ± 6.8	0.1 ± 0.9	8.0 ± 38.0	NS
Day hospital	6.4 ± 7.2	13.0 ± 4.3	1.5 ± 4.7	1.6 ± 4.40	ANOVA <0.001 I *vs.* A <0.001 I *vs.* E <0.001 A *vs.* E= NS

Abbreviations: ANOVA, Analysis of variance; CT, Computed tomography; MRI, Magnetic resonance imaging; NS, Not significant

* mean ± standard deviation

** Statistical significance based on simple ANOVA test; if ANOVA <0.05 then the Hochberg test for multiple comparisons was calculated.

The same as with resources, no significant differences were found in the total cost or in any cost components, except for a higher cost of MRI in the adalimumab arm, and of the day hospital for infliximab (Table 4). The main cost component comes from the cost of purchasing the drugs, which averaged about 83% of the total cost.

Table 4. Comparative costs (€) at 2 years

Source of costs	Total Population Mean (95% CI)	% cost (%cum.)	Infliximab (I) Mean (95% CI)	% cost (%cum.)	Etanercept (E) Mean (95% CI)	% cost (%cum.)	Adalimumab (A) Mean (95% CI)	% cost (%cum.)	p*
Cost of consultations:	819.5 (780.4-858.7)	3.2% (3.2%)	847.6 (787.2-908.1)	3.3% (3.3%)	778.0 (716.9-839.1)	3.3% (3.3%)	828.7 (734.0-923.4)	2. 8% (2.8%)	NS
Rheumatology	779.6 (748.0-811.2)		810.8 (765.0-856.5)		740.6 (686.4-794.8)		779.6 (705.0-854.3)		NS
Emergency services	40.0 (25.4-54.2)		36.9 (13.4-60.3)		37.4 (13.1-61.8)		49.1 (20.5-77.6)		NS
Complementary Tests:	949.2 (883.5-1,015)	3.7% (6.9%)	983.4 (879.0-1,088)	3.9% (7.2%)	862.0 (802.3-921.6)	3.7% (7.0)	1012.6 (820.1-1,205)	3.4% (6.2%)	NS
Laboratory	850.9 (798.8-903.0)		884.5 (801.5-967.6)		790.2 (726.8-853.6)		877.4 (736.5-1,018)		NS
CT	16.7 (5.7-27.7)		22.0 (2.2-41.8)		1.9 (-1.9-5.7)		28.3 (-2.5-59.0)		NS
MRI	13.5 (6.8-20.2)		6.1 (-1.3-13.4)		11.4 (2.6-20.2)		29.4 (7.9-51.4)		ANOVA=0.021 A *vs.* I= 0.019 Rest= NS
Simple X-ray	61.1 (53.2-69.1)		62.6 (49.9-75.4)		52.2 (40.5-63.9)		71.0 (52.2-89.7)		NS
Ultrasound	7.1 (4.6-9.6)		8.1 (3.8-12.4)		6.3 (1.9-10.8)		6.3 (2.0-10.6)		NS
Cost of hospitalization	1,668.5 (421.6-3,759)	6.5% (13.4%)	1,020.3 (144.4-2,185)	4.0% (11.2%)	86.0 (87.4-259.4)	0.4% (7.4%)	5,064.7 (3,720-13,850)	17.0% (23.2%)	NS
Day hospital	801.2 (647.6-954.7)	3.1% (16.5%)	1,593.8 (1,429-1.759)	6.3% (17.5%)	249.8 (68.4-431.2)	1.1% (8.5%)	177.3 (17.9-336.8)	0.5% (23.7%)	ANOVA<0.001 A *vs.* I <0.001 E *vs.* I <0.001 Rest= NS
TOTAL non drug costs	4,238 (2,105-6,372)	16.5%	4,445 (3,228-5,662)	17.5%	1,976 (1,650-2,302)	8.5%	7,083 (1,871-16,037)	23.7%	NS
Drug cost at EFP	21,487 (20,232-22,742)	83.5%	20,884 (18,535-23,232)	82.5%	21,333 (19,532-23,135)	91.5%	22,774 (20,564-24,98)	76.3%	NS
TOTAL	**25,725 (23,473-27,978)**	**100%**	**25,329 (22,842-27,815)**	**100%**	**23,309 (21,465-25,153)**	**100%**	**29,858 (21,713-38,002)**	**100%**	**NS**

3.3 Cost-Effectiveness

3.3.1 Scenario 1: Direct Health Costs

The average cost per patient of reaching CR at 2 years of treatment, taking into account direct health costs, was €83,522.99 (95% CI: 76,209.84–90,836.43). The most efficient drug in achieving CR was adalimumab, which was significantly superior to both infliximab and etanercept. No differences were found between infliximab and etanercept.

When LDAS was considered as the effectiveness outcome, the most efficient drugs were adalimumab and etanercept, both of which were superior to infliximab, but not significantly different from each other (Table 5).

Table 5. Comparative cost-effectiveness at 2 years

Variable (95% CI) Value expressed in €	**Total population Mean (95% CI)**	**Infliximab (I) Mean (95% CI)**	**Etanercept (E) Mean (95% CI))**	**Adalimumab (A) Mean (95% CI)**	**p***
SCENARIO 1 (All direct health costs)					
Cost per patient in remission (DAS28<2.6)	83,523 (76,210-90,836)	87,040 (78,496-95,584)	102,683 (94,559-110,807)	66,057 (48,038-84,076)	ANOVA <0.001 A *vs.* E <0.001 A *vs.* I= 0.026 I *vs.* E= NS
Cost per patient in LDAS (DAS28<3.2)	45,774 (41,766-49,782)	53,549 (48,292-58,805)	42,769 (39,385-46,153)	40,240 (29,263-51,216)	ANOVA= 0.005 A *vs.* E= NS A *vs.* I= 0.013 I *vs.* E= 0.029
SCENARIO 2 (Considering as direct costs only the EFP of acquiring the drug)					
Cost per patient in remission (DAS28<2.6)	69,762 (65,688-73,836)	71,765 (63,694-79,835)	93,979 (86,044-101,915)	50,386 (45,497-55,275)	ANOVA <0.001 A *vs.* E= <0.001 A *vs.* I= <0.001 I *vs.* E= <0.001
Cost per patient in LDAS (DAS28<3.2)	38,233 (35,999-40,465)	44,151 (39,186-49,116)	39,144 (35,839-42,449)	30,693 (27,715-33,672)	ANOVA <0.001 A *vs*. E < 0.001 A *vs.* I <0.001 I *vs.* E= NS

Abbreviations: ANOVA, Analysis of variance; DAS, Disease activity score; LDAS, Low disease activity state; EFP, Ex factory price; NS, Not significant

*Statistical significance based on simple ANOVA test and for post-hoc tests: Hochberg test in scenario 1 and Games Howell in scenario 2

3.3.2 Scenario 2: Only Drug Costs

When cost-effectiveness was analyzed considering only the cost of purchasing the drugs as direct health costs, adalimumab was again statistically more efficient in achieving CR than either etanercept or infliximab, while infliximab was in turn more cost-effective than etanercept.

Considering LDAS as the effectiveness outcome, adalimumab was the most efficient of the three agents, with no differences between infliximab and etanercept (Table 5).

3.4 Savings to the Public Health System

The price negotiations between the Hospital Pharmacy Department and the drug manufacturers resulted in a savings to the public health system (in relation to the EFP) of €343,346, which represented 10.27% of the EFP.

3.5. Drug survival

Over 50% of the patients in each treatment branch maintained their initial treatment at the end of 2 years follow-up, (median exposure time for the three groups was 23.98 months). The discontinuation rates were very similar: 21.8% (for infliximab), 20.5% (for etanercept) and 22.6% (for adalimumab), with no significant differences among them (Chi-square test, p=0.974).

3.6 Multivariate analysis

The multivariate analysis of patient clinical and demographic variables identified sex and ESR value as factors predictive of remission. The rest of the potential variables considered were eliminated one by one from the analysis. For the same ESR, the probability of achieving remission was 3.6 times lower in women than in men [OR: 0.28 (95% CI: 0.08-0.98)]. For the same sex, the probability of achieving remission decreased 5% for each unit increase in the ESR value [OR: 0.95 (95% CI: 0.92-0.99) (Hosmer-Lemeshow test, p=0.477)].

3.7 Safety

The safety analysis took account of both the 130 patients included in the study and the fact that 17 of the 28 patients who changed treatment changed to one of the three anti-TNF in the study: 4 changed to infliximab, 10 to etanercept and 3 to adalimumab. This led us to modify the sample size for the descriptive analysis of safety, incorporating those patients who received another study anti-TNF as rescue therapy during the first 2 years.

About half of the patients reported some adverse effect of treatment, a proportion that was higher in the group that received etanercept, in which two-thirds of patients reported these effects. Of these, some 15% in the infliximab arm, 24% in the etanercept arm and nearly 12% in the adalimumab arm had to suspend treatment. The main reasons for suspension were infusion reactions and infections (7 and 2 patients, respectively) in the case of infliximab, and cutaneous reactions and infections (8 and 2 patients,

respectively), for etanercept. Four patients suspended adalimumab treatment, notably, one of them due to development of multiple sclerosis.

Overall, the most frequently reported adverse effect was infection, especially respiratory infections. Also commonly reported were infusion reactions with infliximab and cutaneous reactions, primarily with etanercept (Table 6).

Table 6. Description of adverse effects

Adverse effect (AE)	Total N	Infliximab N	Etanercept N	Adalimumab N
Patients with any AE	86 (66.2%)	34 (57.6%)	35 (64.8%)	17 (50%)
AE leading to suspension	26 (17.68%)	9 (15.2%)	13 (24.07%)	4 (11.7%)
Infections	53	28	18	7
Cutaneous reactions	17	3	10	4
Infusion reactions	10	10		
Cardiovascular events	7	3	3	1
Influenza-like illness	5	2	3	-
Abdominal pain	4	2	1	1
Dyspnea	1	-	-	1
Tiredness	1	-	1	-
Anemia	1	-	-	1
Lymphadenopathy	1	-	-	1
Depressive syndrome	1	-	1	-
Nausea	1	-	-	1
Neuropathy	1	1	-	-
Pulmonary nodules	1	1	-	-
Deep vein thrombosis	1	-	1	-
Hypertriglyceridemia	1	1	-	-
Kidney failure	1	1	-	-
Multiple sclerosis	1	-	-	1

4. Discussion

Our study suggests that adalimumab is the most cost-effective anti-TNF drug at 2 years of treatment for achieving CR and LDAS in patients with active RA despite combined treatment at the maximum possible doses with methotrexate, sulfasalazine, leflunomide and corticosteroids. This result is the same both when considering direct health costs and when considering only the official direct purchase price of the drug. The analysis of the components of cost-effectiveness in actual clinical practice shows differences that are favorable in effectiveness for adalimumab, with no overall differences in cost.

This study sought to deepen our knowledge of the effectiveness and efficiency of infliximab, etanercept and adalimumab in real-life clinical practice when used in RA patients who are naive to biological therapy. Its design has both limitations and advantages. One limitation is that, since it was observational, it was an open and non-randomized study. Despite the lack of randomization, however, it is important to note that each patient always received the most appropriate treatment for his or her situation, which was decided in a

joint session of the Rheumatology and Pharmacy Departments. If there was no patient characteristic that conditioned or advised against a specific biological, the one with the lowest cost to the hospital at the time was chosen. Another limitation is the small sample size, given that it was conducted in a single center, although proportionally and compared with other similar studies, the number of patients included per center is not low.

One of the study strengths derives from the database, the CREATE registry, which systematically includes all patients treated with biological therapy, with a prospective follow-up of all patients, in accordance with the recommendations of the SER and EULAR, and with standardized data collection. Patients are evaluated monthly by a multidisciplinary team of health professionals comprising rheumatologists, a pharmacist, a nurse and a statistician. Decisions on the initiation, maintenance or change of biological therapy are shared by the whole team. All of this makes the study more rigorous and exhaustive.

In this case, an observational design is recommended to advance our knowledge of actual cost-effectiveness [27], in contrast to other health economics studies that use models with numerous assumptions or data from clinical trials of highly selected patients. The cost data for the different health resources used were provided by the Pharmacy Department, and the statistical analysis was performed by an independent investigator, ensuring high-quality data collection and processing.

Our results contrast with those of other studies in Spain. The PRAXIS study, conducted in 2007 in 41 hospitals in Spain, was also a retrospective observational study of cost-effectiveness [28]. Its objective was to analyze the use of healthcare resources and their associated costs, from the hospital perspective, in RA patients treated with etanercept, infliximab and adalimumab. The study concluded that in most of the scenarios analyzed, treatment of RA at 6 months with etanercept reduced the hospital costs as compared to infliximab and adalimumab. The 6-month time frame is an important limitation of the study. Other observational studies [29-30] conducted in Spain more recently in patients treated with adalimumab, etanercept or infliximab found similar effectiveness of the three drugs at 6 months, but with differences in the mean cost (including only the direct cost of purchase), due primarily to the different doses used as compared to conventional doses.

Our study differs from the aforementioned ones in several important aspects that could explain the different results. First, the time frame was 2 years, which is more appropriate for treatment of a chronic disease, as opposed to 6 or 12 months. Second, for patients in the CREATE registry there was no provision to escalate the drug dose in cases of incomplete response (DAS28 > 3.2) [31]. Finally, the main objective of treatment effectiveness was measured based on CR (DAS28<2.6) and not on LDAS (DAS28<3.2).

The current strategy in RA management is to “treat to target” (T2T), exerting all possible efforts to achieve CR [32-35]. On this basis, stringent treatment to achieve CR, or failing that, LDAS, allows better disease control over time, less joint damage, and dose optimization, making this the most efficient strategy to achieve a good health outcome.

In this regard, the results of the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry recently showed that the strategy of treating to the target of CR, as opposed to conventional care, became cost-effective after 3 years [36]. The percentage of patients who achieved the target effectiveness in the T2T arm of the DREAM registry was higher than in our study. In the CREATE registry, only patients treated with adalimumab had results close to those reported in the Dutch study. However, patients in the CREATE registry had slightly higher disease activity (baseline DAS28 5.71 ± 1.02 vs. 5.0 ± 1.1) and, since they had established RA, had received intensive treatment with combinations of classical DMARDs at the maximum tolerated doses, similar to patients in the Finnish cohort reported by Sokka et al. [37]. The results of the latter study support the efficacy of treatment with combinations of DMARDs to reach and maintain remission before using biological therapy.

Our cost analysis was made from the perspective of the healthcare system, which includes the costs of all healthcare resources involved in treating this disease. Nevertheless, some studies [38-44] have suggested the societal perspective as more appropriate for a study of RA costs. We decided to remain with the hospital perspective, however, for various reasons:

- First, the current economic crisis has made it necessary to assign a target budget to be met by each medical department. Accordingly, the proposed study objective was to analyze which drug was most efficient from the point of view of the payer – the hospital – which meant that indirect healthcare costs were not taken into account.

-Second, although an analysis from the societal perspective may be more complete, it is a more complex study that requires certain assumptions, since indirect and intangible costs are difficult to define and quantify [27,45-47]. The results of such a study would be somewhat theoretical, involving a level of uncertainty that would make them less valid and applicable; this is the exact opposite of the aim of our study: to find the most efficient drug in actual clinical practice. In any case, pharmacoeconomic analyses should always specify the study perspective and state the reasons why it was chosen in order to determine if the results can be extrapolated [27].

Finally, it is important to note that the cost-effectiveness results were calculated considering the EFP. The discounts on the EFP obtained by each country and hospital may change this result, since the main cost component is the purchase price of the drug. The arrival of biosimilars is key in this respect. The entry into the market of biosimilar infliximab may reduce the direct cost of the drug, making it more cost-effective. This could also indirectly affect the price of etanercept, adalimumab and other biological agents, which may be lowered to remain competitive.

5 Conclusions

Adalimumab was the most cost-effective drug in regular clinical practice for achieving both CR and LDAS in patients included in the CREATE registry. The actual negotiated price of acquiring these drugs is a key factor in the final analysis of cost-effectiveness.

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Rheumatol Int (2016) 36:1627–1632
DOI 10.1007/s00296-016-3583-3

Rheumatology INTERNATIONAL

PUBLIC HEALTH

Cost-effectiveness of clinical remission by treat to target strategy in established rheumatoid arthritis: results of the CREATE registry

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El segundo trabajo se publicó en la misma revista unos meses después. Se trata de una continuación del estudio anterior.

En este trabajo se incorporan a los pacientes con AR que se trataron de inicio no sólo con infliximab, etanercept o adalimumab, sino también con el resto de terapias biológicas. En esta ocasión, se trataba de analizar el coste efectividad de alcanzar remisión clínica. La estrategia de tratar a los pacientes con el objetivo de alcanzar remisión clínica se considera las más eficaz y en un ensayo clínico demostraba resultar coste-efectiva al cabo de tres años, en pacientes con AR tratados de forma precoz.

Sin embargo no se conocen sus resultados en condiciones de práctica clínica habitual y con pacientes con AR establecida. Este fue el objetivo de nuestro estudio.

Se estableció para ello nuevamente un horizonte temporal de dos años, y se empleó la perspectiva del sistema sanitario, teniendo en cuenta de nuevo todos los costes directos sanitarios posibles.

Se incluyeron en total 144 pacientes, de los que aproximadamente un tercio consiguieron remisión clínica a los dos años. El coste medio para alcanzarlo estaría en aproximadamente 80.000 euros.

Teniendo en cuenta los dinteles de eficiencia publicados y aceptados en otros países, este resultado pone en duda que la estrategia de tratar a pacientes con AR establecida deba tener el objetivo de alcanzar remisión clínica.

Sería necesario llevar a cabo estrategias adicionales para optimizar este resutado.

ABSTRACT

Introduction

To analyse the cost-effectiveness, in daily clinical practice, of the strategy of treating to the target of clinical remission (CR) in patients with established rheumatoid arthritis (RA), after 2 years of treatment with biological therapy.

Method

Adult patients with established RA were treated with biological therapy and followed up for 2 years by a multidisciplinary team responsible for their clinical management. Treatment effectiveness was evaluated by the DAS28 score. The direct costs incurred during this period were quantified from the perspective of the healthcare system. We calculated the cost-effectiveness of obtaining a DAS28<2.6, considered as CR.

Results

The study included 144 RA patients treated with biological therapies. After 2 years of treatment, 32.6% of patients achieved CR. The mean cost of achieving CR at 2 years was 79,681 ± 38,880 euros.

Conclusion

The strategy of treatment to the target of CR is considered the most effective, but in actual clinical practice in patients with established RA, it has a high cost.

Key words:

Rheumatoid arthritis, treat to target, clinical remission, cost-effectiveness, biological drugs, real clinical practice

1 Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterised by pain, chronic inflammation and joint destruction. In most cases, the progressive course of the disease leads to irreversible joint damage, functional impairment, reduced quality of life, and premature mortality. RA is estimated to affect 1% of the adult population [1-2].

The general objective of RA treatment consists of controlling pain and inflammation, minimising joint damage and disability, controlling extra-articular manifestations, improving patients' quality of life, and achieving disease remission, or at least sustained low clinical activity [3].

Nowadays a strong current of opinion advocates addressing RA management by a treatment strategy based on "treat to target" (T2T), whose key points are establishment of concrete objectives, close patient follow-up, monitoring of disease activity, and adjustment of treatment in accordance with established protocols [4,5].

Clinical trials and observational studies have shown that this strategy is more efficacious and effective than standard treatment to reduce disease activity and to achieve the target of clinical remission (CR) [5-7]. This strategy requires an additional investment of resources, but has been shown to be cost-effective beginning in the third year, as compared to maintaining a strategy of standard treatment and monitoring, when applied to patients with early RA [8]).

In patients with persistent established RA after treatment with at least two of the classic disease-modifying antirheumatic drugs (DMARDs) and a DAS28 value >5.1, the use of biological therapy is recommended [9]. However, due to the lack of sufficient clinical evidence, no agreements have been reached on essential points involved in T2T, such as intensive treatment with biological therapy or whether the objective should be to reach CR [10].

The objective of this study is to analyse the clinical effectiveness and cost-effectiveness of the T2T strategy in achieving CR in actual clinical practice in patients with established RA after 2 years of treatment with biological therapy, a further analysis of the Create registry [11].

2 Methods

2.1 Patients

The data for this study were taken from the cohort of patients included in the Córdoba Rheumatoid Arthritis Team (CREATE) registry [11], made up of patients diagnosed with established RA who began treatment with biologicals in the Reina Sofía University Hospital between 1 January 2007 and 31 December 2012, who had at least 2 years follow-up of their progress and no missing data.

The CREATE registry is a prospective database that systematically includes each patient with inflammatory rheumatoid disease who begins treatment with biological therapy. For each patient diagnosed with RA, information is collected on demographics, disease characteristics, previous treatments used, their duration and reason for suspension, current treatment and its duration, disease activity [number of tender joints (NTJ), number of swollen joints (NSJ), erythrocyte sedimentation rate (ESR), C-reactive protein (PCR) and the Disease Activity Score (DAS28)], patient data that could influence treatment, biological drug chosen, and concomitant treatment. Each patient is followed up prospectively to monitor the clinical variables collected and any adverse effects that may occur.

RA is diagnosed in accordance with the 1987/2010 ACR criteria, based on the medical history, physical examination, complementary tests, chest and joint radiography, and clinical assessment of disease activity using the DAS28.

All the patients had to fulfil the requirements of the treatment protocol developed jointly by the Departments of Clinical Rheumatology and Hospital Pharmacy and approved by Hospital Management. This protocol is based on the recommendations of the Spanish Society of Rheumatology (SER) [12] and the European League against Rheumatism (EULAR) [3], and approves beginning treatment with biological therapy for patients with active RA (DAS28>5.1) despite at least 3 months treatment with at least two of the following drugs at the maximum authorised doses: methotrexate, leflunomide or sulfasalazine.

2.2 Treatment decisions

The treatment decisions for these patients followed a model of clinical management based on efficiency, in which a multidisciplinary team of rheumatologists and clinical pharmacists share responsibilities related to the objectives of health costs and outcomes.

The multidisciplinary team meets monthly to review patients with established RA who are eligible to begin treatment with biologicals, and to monitor those in active treatment. The choice of biological treatment is based on patient characteristics and the evidence on the efficiency of each drug.

The T2T strategy of remission (DAS28<2.6) was applied to all patients. This involves application of standardised treatment protocols to achieve this objective, and review and follow-up of all patients at least every 2 months.

2.3 Outcome variable

The outcomes of the T2T strategy were evaluated based on the DAS28 score [13]. In accordance with this scale, treatment was considered to be effective if the patient achieved a DAS28 value of less than 2.6 and maintained it by the end of 2 years.

2.4 Variables of resources used and costs

For the cost analysis we considered the health system perspective, taking into account the use of the

following direct healthcare resources: cost of purchasing the drugs [ex-factory price (EFP)], specialist consultations in Rheumatology and other clinical Services, emergency care, complementary tests performed, need for hospitalisation, and use of the day hospital for intravenous drug administration.

Drug use was obtained from the databases of the Pharmacy Department. For drugs dosed based on weight (infliximab, abatacept and tocilizumab), the cost was adjusted to the milligrams actually used since individual doses were prepared in the Pharmacy Department, making it possible to avoid drug wastage. The remaining resources consumed were obtained from the database of the reports manager of the Reina Sofía University Hospital.

The cost of each drug was obtained using the official EFP, and the cost of the rest of the resources used was obtained from the price catalogue of the Economics Directorate of the Reina Sofía University Hospital (2014, in euros).

2.5 Cost-effectiveness analysis

To calculate cost effectiveness, the mean total cost for each patient was divided by the percentage of patients who achieved the outcome variable. The mean and standard deviation (SD) of this value were calculated to show the mean cost per patient to achieve CR.

A descriptive analysis was performed by calculating the absolute and relative frequencies for the qualitative variables, and the arithmetic mean and standard deviation for the quantitative variables.

2.6 Ethics

The study meets the standards of Good Clinical Practice, the principles of the Declaration of Helsinki and Order SAS 347/2009 of December 16, which develops guidelines on observational post-authorization studies for drugs used in humans in Spain. Patient data are coded to maintain anonymity in the study and to prevent their identification by third parties. The study was approved by the Et*hical Committee of the Reina Sofia University Hospital of Cordoba.

3 Results

During the study period, 144 patients met the inclusion criteria. Of these, 55 were treated with infliximab, 44 with etanercept, 31 with adalimumab, 4 with tocilizumab, 4 with golimumab, 3 with abatacept, 2 with certolizumab, and 1 with rituximab. The baseline characteristics of the patients for the overall sample are showed in table 1.

Table 1. Baseline characteristics of patients in the total sample and by DAS28 outcomes

Baseline characteristics	Total	DAS28 achieved and maintained at 2 years		P
		DAS28 ≤2.6	DAS28>2.6	
n (%)	144 (100%)	47 (32.6%)	97 (67.4%)	---
Sex (Female)	80.6%	70.2%	85.6%	0.085
RF + (%, n/N)	72.2% (104/144)	70.2% (33/47)	73.2% (71/97)	0.708
AntiCCP+ (%, n/N)	74.2% (72/97)	78.1% (25/32)	72.3% (47/65))	0.538
Age (years)*	53.43 ± 13.32	50.43 ± 13.77	54.88 ± 12.93	0.186
Weight (Kg)*	75.85 ± 15.96	76.76 ± 15.96	75.39 ± 16.14	0.751
Age at diagnosis (years)*	44.21 ± 13.35	40.79 ± 13.03	45.87 ± 13.25	0.085
Time since diagnosis (years)*	9.21 ± 7.50	9.15 ± 7.60	9.24 ± 7.49	0.948
Initial DAS28*	5.69 ± 1.00	5.50 ± 1.03	5.79 ± 0.98	0.107
Initial NTJ28*	10.32 ± 6.35	10.23 ± 6.25	10.36 ± 6.42	0.911
Initial NSJ28*	7.08 ± 4.92	7.32 ± 4.93	6.96 ± 4.93	0.682
Initial ESR*	33.01 ± 17.78	26.87 ± 17.20	36.07 ± 17.35	0.085
Initial CRP*	19.42 ± 17.94	18.03 ± 19.30	20.12 ± 17.28	0.517
Initial PGA*	69.91 ± 16.73	68.85 ± 14.78	70.43 ± 17.68	0.598

*Data expressed as mean ± standard deviation

Quantitative variables: Comparison of means by independent "t" Student test and Finner´s test ajusted p

Qualitative variables: Contingency table with significance according to Pearson's Chi-square and Finner´s test ajusted p

RF+: Positive rheumatoid factor

AntiCCP+: Positive anti-cyclic citrullinated peptide antibody

DAS28: Disease activity score on 28 joints

NTJ28: Number of tender joints on 28 joints

NSJ28: Number of swollen joints on 28 joints

ESR: Erythrocyte sedimentation rate

CRP: C-reactive protein

PGA: Patient Global Assesment

3.1 Effectiveness

After completing 2 years of treatment, 47 patients (32.6%) achieved and maintained CR. No differences in baseline characteristics were found between patients who did and did not achieve CR at 2 years. Mean±SD DAS28 at 2 years in patients achieving CR was 2.10±0.43 (95% CI=0.40-2.60), and was similar for each biological therapy used.

3.2 Use of resources and costs

Table 2 presents the data on resources consumed and costs. The second column contains the mean and standard deviation of the units of resources consumed per patient at the end of the 2 years of follow-up (mean number of consultations attended, mean number of laboratory tests performed, etc.). The third column shows the mean cost of each resource, considering the official EFP for the drugs and the hospital price catalogue for the other resources. Finally, the last column reflects the percentage of the total cost represented by each resource.

Table 2. Resources and costs at 2 years of biological therapy

	Units of resources consumed (mean ± SD)	**Cost of resources (euros) mean ± SD)**	**% of cost (cumulative)**
Drug cost, EFP	-	21,682.65 ± 7,125.65	83.47%
Consultations			
Rheumatology	13.31 ± 3.56	786.18 ± 194.03	
Emergency	0.33 ± 0.65	41.36 ± 81.84	
Total	13.64 ± 3.79	827.54 ± 231.44	3.19% (86.66%)
Complementary tests:	23.24 ± 10.39	962.01 ± 382.75	3.70% (90.36%)
Laboratory	13.78 ± 4.91	861.52 ± 307.16	
CT	0.28 ± 0.86	17.11 ± 61.17	
NMRI	0.19 ± 0.49	15.66 ± 40.69	
Simple X-ray	8.76 ± 6.49	60.95 ± 45.20	
USG	0.24 ± 0.51	6.77 ± 14.06	
Days of hospitalisation	2.73 ± 18.39	1,720.85 ± 11,596.47	6.62% (96.98%)
Day hospital for drug administration	6.90 ± 7.88	783.00 ± 866.62	3.02% (100%)
TOTAL	-	**25,976.05 ± 12,675.02**	**100%**

SD: Standard deviation

EFP: Ex-factory price

CT: Computed tomography scan

NMRI: Nuclear magnetic resonance imaging

USG: Ultrasonography

The mean cost of the direct healthcare resources at 2 years was € 25,976 (95% CI: 23,888-28,063). The main cost component was the drug, at 83.47% of the total.

3.3 Cost-effectiveness

After 2 years of treatment, the cost effectiveness of each CR achieved and maintained in our study was € 79,681 ± 38,880.

4 Discussion

The current tendency in RA management to treat patients by objectives (T2T) and to expend all possible efforts to achieve CR [4,10] may have a high cost, especially in patients with established AR when biologics are needed to achieve it, though Radner et al. [14] found that patients with CR showed better function and that, from a cost perspective, CR was also superior to achievement of low disease activity.

The results of the CREATE registry suggest that, in actual clinical practice, the strategy of treating to the target of CR is achieved in approximately one-third of patients with established RA after 2 years of biological therapy, albeit at a high cost.

Our study has limitations and advantages. One of its strengths lies in the registry database, which systematically includes all patients treated with biological therapy (CREATE registry), with prospective follow-up of all these patients by a multidisciplinary team for decision making and following standardised work protocols, in routine clinical practice conditions. These strengths support the rigor and exhaustiveness of the results. The cost data for the different health resources used were provided by the Pharmacy Department, and the statistical analysis was performed by an independent investigator, which ensures high-quality data collection and processing.

The observational design is recommended to advance our knowledge of actual cost-effectiveness [15], in contrast to other studies in health economics which use models with numerous assumptions or data from clinical trials with highly selected patients. However it has the limitation of being open and non random, although all patients received the best possible treatment according to the characteristics of each patient and drug. In the absence of any limiting constraints (inability to attend the day hospital or to self-administer treatment, compliance problems, presence of intestinal inflammatory disease, etc.), the drug with lowest cost to the hospital as advised by the pharmacist is used.

The cost analysis was made from the perspective of the health system, which includes the costs of all the health resources involved in this pathology, rather than from the societal perspective. This perspective was chosen to reflect real data and to avoid having to make estimates based on assumptions, given that indirect and intangible costs are difficult to quantify [15].

Our results are in line with other studies: Schoels et al. [16] found that most studies assessing early biologics reported cost effectiveness ratios of over $50,000. Van der Velde et al. [17] published a systematic study which found that, in patients who had no response to treatment with methotrexate in combination with leflunomide or sulfasalazine, the use of biologics was cost-effective in 14 out of 35 comparisons at a willingness-to-pay threshold of Can $100,000 per quality-adjusted life year.

In any event, considering the real direct costs to the healthcare system, achieving CR involves a high cost in established AR. Some options to optimize resources could be:

- Determination of the most efficient drug to achieve CR. Large observational studies or meta-analyses of published studies of cost effectiveness in actual clinical practice are needed.

-Once CR has been maintained over time, other options could be considered for these patients, such as reducing the dosage or therapeutic vacations [18]. This strategy has been shown to be efficient in the PRESERVE study [19] and is the basis for the current recommendations to optimise biological therapy in RA patients [20].

- Participation of clinical pharmacists in the treatment decisions can help to improve the efficiency of therapy.

5 Conclusions

The T2T strategy of CR is considered to be the most effective, but in daily clinical practice in patients with established RA it has a high cost. The development of clinical management based on efficiency may make it possible to optimise the most effective strategies so that they will also be the most efficient.

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Rheumatol Int
DOI 10.1007/s00296-017-3757-7

Rheumatology INTERNATIONAL

OBSERVATIONAL RESEARCH

Optimization of biological therapy in rheumatoid arthritis patients: outcomes from the CREATE registry after 2 years of follow-up

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Received: 27 January 2017 / Accepted: 2 June 2017

Finalmente, se presenta el tercero de los trabajos, aceptado para su publicación en la misma revista que los anteriores. Este trabajo explora los resultados de aplicar una estrategia de optimización de dosis en pacientes con AR que están en remisión clínica de forma estable en el tiempo. Como los anteriores, persigue conocer los resultados en salud y el coste de las intervenciones llevadas a cabo en la práctica clínica habitual, para emplear las más eficientes.

Se estudian los pacientes del registro CREATE que llevaban en remisión clínica al menos 6 meses a partir de noviembre de 2013 y a los que se les optimiza la dosis de la terapia biológica que recibían entre un 20% y un 50% de la misma, según un protocolo de actuación previsto en función de la respuesta conseguida. El objetivo del trabajo fue conocer la efectividad y la eficiencia de esta estrategia en el mundo real, así como identificar posibles variables predictoras de respuesta.

Así, en total, 68 pacientes optimizaron su dosis. 28 de ellos mantenían la optimización y la remisión clínica a los dos años, sin diferencias en cuanto al valor del DAS28.

De los 40 pacientes que necesitaron volver a dosis estándar, la mayor parte de los mismos consiguieron de nuevo la remisión clínica, o en su defecto una baja actividad de la enfermedad. Este hecho se refleja muy bien en los valores medios del DAS28. El DAS28 inicial y el DAS28 al año de este subgrupo de pacientes sí son diferentes, y sin embargo entre el basal y el de los dos años no hay diferencias.

El valor DAS28 inicial fue la única variable de las incluidas en el modelo construido que se asoció de forma significativa con la posibilidad de mantener remisión y dosis optimizada.

El ahorro conseguido estuvo en torno al 21% del coste estándar.

ABSTRACT

Introduction

The current strategy for managing rheumatoid arthritis (RA) focuses on achieving clinical remission. Once remission is achieved and sustained over time, the most efficient strategy is dose optimization. This work describes the results of dose optimization after 2 years of follow-up in patients with RA treated with biological therapy.

Methods

Cohort: Patients from the CREATE registry who, as of 1 November 2013, had been in clinical remission (DAS28≤2.6) for at least 6 months. Intervention: Dose optimization was 20-50% of the standard dose. Outcome measurement were effectiveness (percentage of patients who continued to meet criteria for clinical remission) and efficiency (dose reduction and mean savings).

Results

Sixty-eight patients with RA were optimized, with initial mean DAS28 of 2.2±0.7. After 2 years of follow-up, the mean DAS28 was 2.4±0.7, a non-statistically significant difference. Twenty-eight patients (41.2%) continued in clinical remission with dose optimization after 2 years. Mean survival time was 14.2 months (95% CI: 12.0-16.5).

Of the 40 patients who needed to return to a standard dose, 57.5% managed to achieve remission again at 2 years.

Dose optimization represented a mean savings at 2 years of €5,576 ± 5,099 per patient and a 21.17% mean savings in pharmacological cost per patient.

Conclusions

In actual clinical practice, over 40% of patients with established RA who had been in sustained clinical remission managed to continue in remission 2 years after receiving optimized doses. The savings achieved was about 21% of the actual direct health costs for patients in the CREATE registry.

Key words:

Rheumatoid arthritis

Clinical Remission

Biological therapy

Optimization

Efficiency strategies

Cost-effectiveness

Real clinical practice

1 Introduction

Biological therapy (BT) is the most important recent advance in the treatment of rheumatoid arthritis (RA) and is helping to modify its prognosis. RA treatment aims to control pain and inflammation, reduce joint damage and disability to the extent possible, control extra-articular manifestations, improve patients' quality of life, and achieve disease remission, or at least sustained low disease activity [1,2]. The data available from registries of treatment with biological drugs in RA show that clinical remission is achieved in 19-39% of patients [3,4].

Despite evidence of its efficacy and effectiveness, BT is costly and is not without risks and potential adverse effects. These facts have led to questions about how to manage this type of treatment once the patient has achieved sustained remission over time [5].

Data available from clinical trials and other studies have shown that discontinuing treatment in patients with early RA results in relapse rates of 40-75% [6-12]. Alternatively, for patients with established RA, dose reduction has been suggested as a potentially efficient management strategy [6,13-14].

In this regard, the Spanish Societies of Clinical Rheumatology and Hospital Pharmacy have developed a consensus document with recommendations for the management of patients in clinical remission [15]. This document suggests that a 20-50% dose reduction is possible in patients with RA who reach and maintain their therapeutic goal for more than 6 months. It also proposes strategies for managing relapses, all with the objective of reducing variability in clinical practice.

The objective of this study was to evaluate the effectiveness and efficiency in routine clinical practice of dose reduction in RA patients in sustained clinical remission. The secondary objectives were to identify predictive variables of response to optimization.

2 Methods

2.1 Patients

The data for this study were taken from the registry of the Multidisciplinary Team for RA in Cordoba (CREATE registry) [16] and included patients diagnosed with RA according to 1987/2010 criteria of the American College of Rheumatology. All patients were evaluated by conducting a clinical history, physical examination, complementary laboratory tests (hemogram, biochemistry, presence of antibodies), and radiographs of the chest, hands and feet. Disease activity was assessed by the clinician using the Disease Activity Index on 28 joints (DAS28). The CREATE Registry is a database which systematically and prospectively includes all patients with inflammatory rheumatic disease who begin treatment with BT. All patients must follow the Andalusian Health Service treatment protocol for BT, based on the recommendations of the Spanish Society of Rheumatology [1] and the European League Against Rheumatism [2]. Patients beginning BT had to have active RA despite treatment for at least 3 months with at least two of the following drugs at the maximum authorized doses: methotrexate, leflunomide or

sulfasalazine. The initial BT is selected based on the characteristics of each patient and drug, as well as the cost of each drug to the hospital. In the absence of any limiting constraints (inability to attend the day hospital or to self-administer treatment, or presence of intestinal inflammatory disease for which biological treatment with infliximab, adalimumab or golimumab is indicated), the lowest cost drug was used.

For each patient included, data are collected on demographics, disease characteristics, previous treatments used, duration and reason for withdrawal, current treatment and its duration, disease activity [number of tender joints (NTJ), number of swollen joints (NSJ), erythrocyte sedimentation rate (ESR) (mm/1h) and C-reactive protein (CRP) (mg/L)], DAS28, patient-related information that could condition treatment, biological drug chosen and concomitant treatment. Each patient included is followed prospectively, with information on the evolution of the clinical variables registered at 6 months and then annually thereafter.
From this CREATE registry, we selected for the study the subpopulation of patients treated with any TNF antagonist, tocilizumab and abatacept, who on 1 November 2013 had been in sustained clinical remission (DAS28≤2.6) for at least 6 months; exceptionally, patients with DAS28>2.6 were included if they were assessed by the physician as being in clinical remission and agreed to participate (this occurred in some cases with DAS28>2.6 resulting from an elevated score on the visual analogue scale, ESR or CRP due to diseases other than RA, but after sustained reduction of the number of painful and swollen joints to zero). All patients were followed prospectively for 2 years.

Decisions on treatment and dose reduction of BT were made by a multidisciplinary team comprised of rheumatologists and clinical pharmacists in a tertiary level hospital. This involved the application of protocols and patient follow-up at least every 2 months. In accordance with the consensus of the Spanish Societies of Rheumatology and Hospital Pharmacy, dose optimization refers to reduction of 20% to 50% of the dosage by lengthening the interval between doses of BT. This criterion was applied in accordance with the BT used and the response achieved (Table 1). Concomitant treatment was maintained.

Table 1: Dose optimization by drug

Drug	Standard dose	Optimization 1	Optimization 2
Infliximab	3mg/kg/8 weeks	3mg/kg/9 weeks	3mg/kg/10weeks
Etanercept	50mg/7 days	50mg/10 days	50mg/14 days
Adalimumab	40mg/2 weeks	40mg/3 weeks	40mg/4 weeks
Golimumab	50mg/month	50mg/5 weeks	50mg/6 weeks
Tocilizumab	8mg/kg/4 weeks	4mg/kg/5 weeks	4mg/kg/6weeks
Abatacept	(Dosage by weight: 500mg/750mg/1g)/4 weeks	(Dosage by weight: 500mg/750mg/1g)/5 weeks	(Dosage by weight: 500mg/750mg/1g)/6 weeks
Certolizumab Pegol	200mg/2 weeks	200mg/3 weeks	200mg/4 weeks

If the DAS28 exceeded 2.6 during follow-up, and with the patients' consent, they returned to the treatment regimen that immediately preceded this change.

2.2 Effectiveness

The effectiveness of treatment in actual clinical practice was evaluated by the DAS28 [17]. A value lower than 2.6 was considered clinical remission. We evaluated the outcome after 2 years of dose optimization, taking into account the DAS28 after the first year and the percentage of patients who remained in clinical remission. We also evaluated the time to relapse (failure of dose optimization).

2.3 Costs

The cost analysis was made from the perspective of the healthcare system, considering the cost of purchasing the drug, using the official ex-factory price (EFP).

Drug use was obtained from the databases of the Pharmacy Service. In the cases of infliximab, tocilizumab and abatacept, which are dosed by weight, the cost was adjusted to the milligrams actually used since the fact that they are prepared in the Pharmacy Service makes it possible to avoid drug wastage.

2.4 Efficiency

To estimate the savings in doses, we quantified the total dose actually received per year and divided it by the annual overall dose that would have been used according to the standard guidelines in the product specifications.

Efficiency was estimated by considering the effectiveness (percentage of patients who remained in clinical remission after the first year) and the cost savings based on the dose reduction achieved.

2.5 Statistical analysis

A descriptive study was conducted, calculating the mean and standard deviation for quantitative variables, and absolute and relative frequencies for qualitative variables. An intention-to-treat analysis was made for each treatment branch.

The bivariate analysis of quantitative variables was made using the one-way ANOVA test and mixed ANOVA. Post hoc comparisons were conducted using the Hochberg or Games–Howell tests. We used the log-rank test to compare the survival curves for the different drugs optimized.

Different univariate logistic regression analyses were made considering as the main variable relapse after one year of optimization (no/yes), and as potentially predictive variables: initial DAS28, anti tumour necrosis factor (TNF) (no, yes), use of disease-modifying antirheumatic drugs (DMARDs) (no, yes), previous BT (no, yes) and previous time in remission (<12 months, ≥12 months). The degree of association was estimated by the odds ratio (OR) and Cornfield's 95% confidence interval.

We also conducted univariate Cox regression analyses taking as the main variable the time to relapse (months). The degree of association was estimated by the hazard ratio (HR) and Cornfield's 95% confidence interval.

All comparisons were two-sided and were considered significant for values of $p<0.05$. The data were processed, tabulated and analysed using SPSS v17 software.

The study meets the requirements of the WHO Guidelines for Good Clinical Practice, the principles of the Declaration of Helsinki, and SAS Order 347/2009 of 16 December, which develops guidelines for observational post-authorization studies for medicinal products for human use in Spain.
Patient data were coded to maintain their anonymity in the study and to protect their identity from third parties. The study was approved by the Ethics Committee of the Reina Sofiá University Hospital of Córdoba.

3 Results

This observational prospective study included a total of 68 patients with RA who, on 1 November 2013, had been in clinical remission for at least 6 months. The baseline characteristics of these patients are shown in Table 2. Mean DAS28 of these patients at the beginning of optimization was 2.2 ± 0.7. Prednisone daily mean dose received was 5.56 ± 1.44mg.

Table 2: Baseline patient characteristics (n=68)

Characteristics	N (%) or mean ± SD
Sex (female)	56 (82.4)
RF +	43/62 (69,4)
Age at optimization (years)	57,04 ± 13,92
Weight (kg)	82,14 ± 19,68
Age at diagnosis (years)	43,54 ± 12,26
Time since diagnosis (years)	13,76 ± 8,20
Initial DAS28	2,23 ± 0,72
Initial NTJ 28	0,94± 1,40
Initial NSJ28	0,32± 0,85
Initial ESR (mm/1ªh)	14,91± 12,68
Initial CRP (mg/L)	4,00± 6,46
Initial PGA (cm)	35,91± 18,21
Mean time of BT treatment (years)	3,73± 2,75
Mean time of remission at baseline (months)	18,39 ± 18,75
Type of biological drug:	
TNF antagonists n(%)	
Infliximab	10 (14,7)
Etanercept	25 (36,8)
Adalimumab	10 (14,7)
Golimumab	3 (4,4)
Certolizumab	1 (1,5)
Abatacept	7 (10,3)
Tocilizumab	12 (17,6)
Concomitant treatment	
Methotrexate	26 (38,2)
Leflunomide	25 (36.8)
Corticosteroids	53 (77,9)
Sulfasalazine	4 (5,9)
Number of previous biological treatments	
None	48 (70,6)
One	12 (17,6)
Two	4 (5,9)
More than two	4 (5,9)

BT: Biological therapy; CRP: C-reactive protein; DAS: Disease activity index; ESR: Erythrocyte sedimentation rate; NST: Number of swollen joints; NTJ: Number of tender joints; PGA: Patient Global assessment; RF: Rheumatoid factor; TNF: Tumour necrosis factor

3.1 Effectiveness

Considering all the patients included, two years after beginning dose optimization, no significant difference was found between initial mean DAS28 (2.23 ± 0.72) and mean DAS28 at 2 years (2.43 ± 0.72). However, the mean DAS28 after the first year was significantly higher than the baseline value (Table 3).

These results were similar for the subgroup of patients who relapsed and returned to standard dose. In this subgroup of patients, the mean DAS28 after the first year was also significantly higher than the baseline value, even> 2.6 (2.80 ±0.13), though returned to 2.6 at the second year.

Nevertheless no significant differences between DAS28 at baseline and the score at the first or second year were seen in the subgroup of patients who did not relapse.

Table 3. Effectiveness at 2 years according to DAS28

Population	Initial DAS28 (mean±SD)	DAS28 at 1 year (mean±SD)	DAS28 at 2 years (mean±SD)	Difference at 2 years (mean±SD)	P
Total (n=68) All optimized patients	2.23±0.72	2.55±0.86	2.43±0.72	Initial vs. 1 year: -0.32±0.82	0.006
				Initial vs. 2 years: -0.20±0.82	0.146
				1 year vs. 2 years: 0.12±0.82	0.592
No relapse (n=28) Remission maintained	1.93±0.12	2.21±0.15	2.19±0.13	Initial vs. 1 year: -0.28±1.32	0.235
				Initial vs. 2 years: -0.26±1.32	0.268
				1 year vs. 2 years: 0.014±1.40	1.000
Relapsed (n=40) Remission not maintained: returned to standard dose	2.44±0.11	2.80±0.13	2.60±0.11	Initial vs. 1 year: -0.36±1.07	0.027
				Initial vs. 2 years: -0.15±1.07	0.568
				1 year vs. 2 years: 0.203±1.15	0.411

DAS: Disease activity index; SD: Standard deviation

Two years after beginning dose optimization, 28 patients (41.2%) continued with optimized doses.

The mean survival time was 14.2 months (95% CI: 12.0-16.5) and median survival time was 14.3 months (95% CI: 4.5-24.0)

As seen in Figure 1, no significant differences were seen among the survival curves for each drug [(Log Rank test (Mantel-Cox), p=0.20].

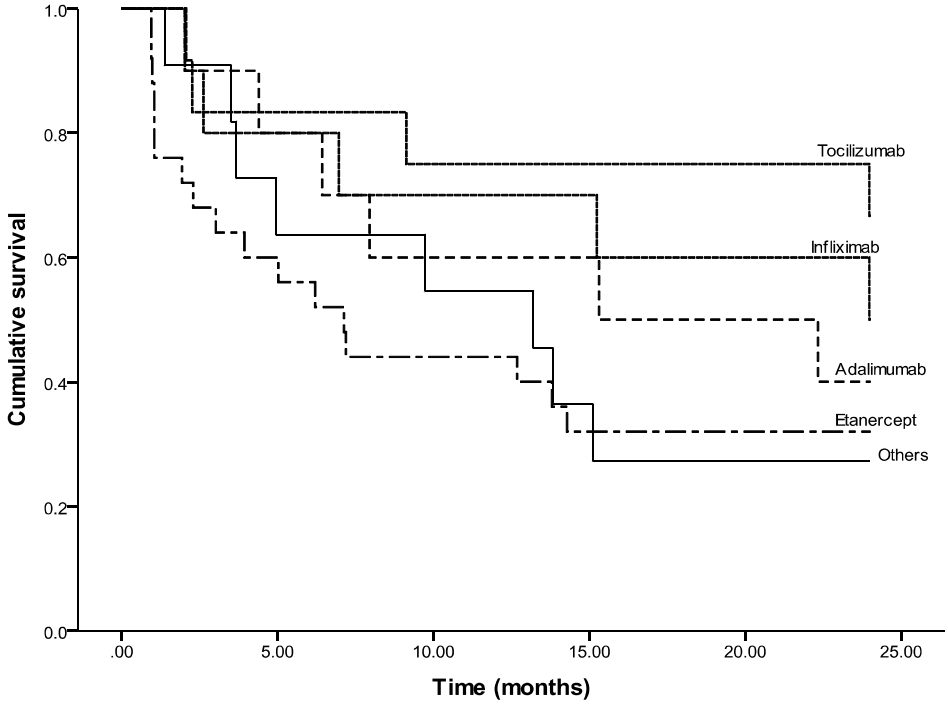

Fig. 1 Survival curves for each drug

Of the 40 patients who needed to return to a standard dose before the second year, 23 of them (57.5%) again reached remission, and 13 more achieved at least low disease activity. Thus, 36/40 of the patients, (90%) achieved either remission or at least low disease activity after returning to a standard dose (Figure 2).

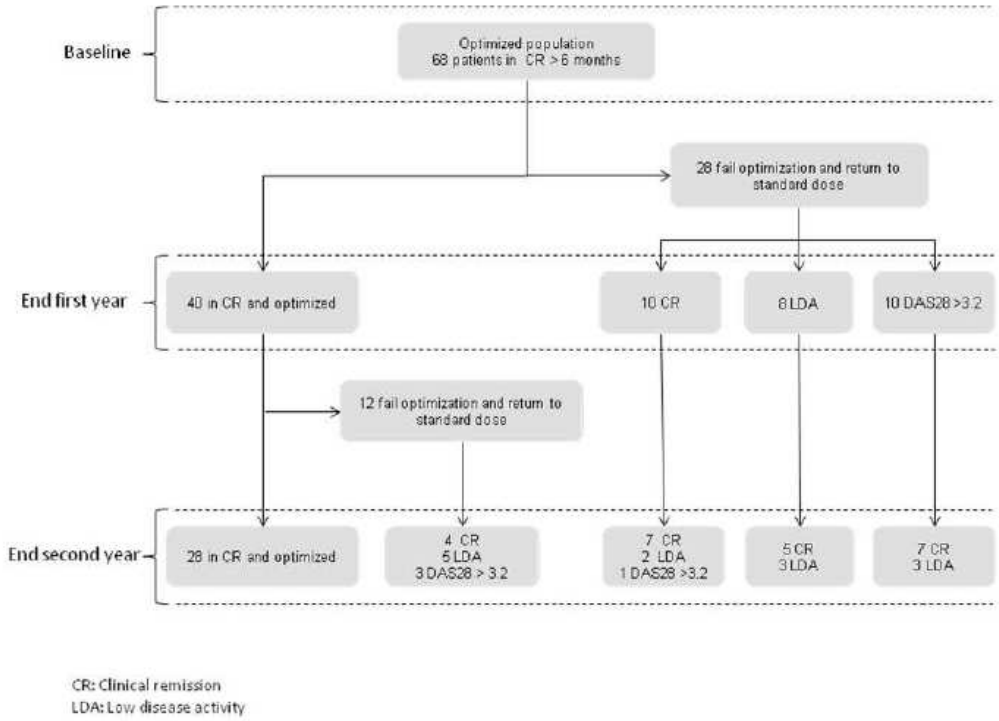

Fig.2 Effectiveness flowchart

3.2 Efficiency

Table 4 presents the variables for overall effectiveness and efficiency by optimized drug. Taking into account that patients who failed BT returned to a standard dose, the overall mean dose reduction of BT at 2 years and so, the mean savings obtained was 21.17%. Mean savings per patient at 2 years was €5,576 ± 5,099.

Table 4: Comparison of effectiveness and efficiency outcomes

	Total	Infliximab	Etanercept	Adalimumab	Tocilizumab	Others*
N	68	10	25	10	12	11
N (%) patients optimized at 1 year	39 (57.4)	7 (70)	11 (44)	6 (60)	9 (75)	6 (54.6)
N (%) patients optimized at 2 years	28 (41.2)	5 (50)	8 (32)	4 (40)	8 (66.7)	3 (27.3)
Mean time of optimization (months, 95% CI)	14.2 (12.0-16.5)	17.1 (11.5-22.7)	11.0 (7.2-14.8)	15.5 (10.0-90.9)	19.1 (14.3-24.0)	12.5 (7.6-17.4)
Mean savings first year (euros) (mean±SD)	3,348 ± 2,790	1,359 ± 980	3,457 ± 2,892	4,937 ± 1,859	3,889 ± 2,660	2,861 ± 3,631
Mean savings second year (euros) (mean±SD)	2,228 ± 2,877	841 ± 989	1,970 ± 3,060	4,407 ± 3,816	3,084 ± 2,497	1,163 ± 1,782
Mean savings at 2 years (euros) (mean±SD)	5,576± 5,099	2,201 ± 1,420	5,427 ± 5,369	9,344 ± 4,721	6,984 ± 4,916	4,024 ± 5,089
% savings on cost at 2 years (mean±SD)	21.17±18.28	11.45±6.46	22.43±22.42	33.52±15.56	22.22±13.23	14.75±16.96

*Others: golimumab, abatacept and certolizumab

SD: Standard deviation

In comparing the results shown in Table 4, it can be observed that in the first year, the mean difference in savings is statistically significant for adalimumab over infliximab (€3,577 ± 1,195; p=0.038). In the second year , no differences were found among drugs. Overall at 2 years, significant differences were found again in mean savings in favour of adalimumab over infliximab (€7,143 ± 2,134; p=0.014), with no differences seen in the baseline clinical or demographic characteristics in these groups of drugs.

Patients were analysed in two groups based on the type of optimized drug: antiTNF drug (infliximab, etanercept, adalimumab, golimumab and certolizumab pegol) and non-antiTNF drug (tocilizumab, abatacept). No statistically significant differences were found in the comparison of either the baseline clinical-demographic characteristics or in the variables of effectiveness or efficiency described.

Lastly, results of the logistic regression shows that DAS28 was the only predictive factor of relapse at 2 years (OR= 2.96; IC95%= 1.34-6.52), p=0,007. Similar results were obtained from the univariate Cox

regression analyses, wich also shows that DAS28 as the only predictive factor of time to relapse at 2 years (HR 2.03; IC95% 1.254-3.31), p=0,004. It was not possible to adjust a significant univariate model in either of the two types of analysis.

4 Discussion

In this study of patients with established RA, we evaluated the effectiveness and efficiency of a strategy of dose optimization, lengthening the interval between doses of BT in patients in clinical remission for at least 6 months. Different strategies have been considered for the management of these patients. In the case of patients with established RA, data from published studies indicate that suspension of the biologic leads to relapses in 50-90% within a year, therefore the option of reducing the dose or lengthening the interval between doses may be more effective and efficient [18,19].

Our results suggest that remission can be maintained at 2 years with an optimized dose in 40% of patients. Some 32.5% of those who go back to a standard dose achieve remission in 1 year. Another 50% of patients do not achieve remission but do achieve at least low disease activity.

These results are similar to those published by van Vollehoven et al. [20] in patients with established RA treated with etanercept. In that study, conducted in the framework of a clinical trial and after having achieved at least low disease activity, patients were randomized to maintain their dosage, reduce it by half (optimized dose) or receive placebo, always in association with methotrexate. At week 48, 44% of patients in the optimized dose arm had not failed optimization. In our work, the etanercept group showed a similar result at one year, although our initial guideline for optimization was etanercept at 50mg/10 days, changing to etanercept 50mg/2 weeks, depending on the outcome obtained. However, our results differ from the optimization results in the DRESS study [21], in which both etanercept and adalimumab achieved better outcomes at 18 months with dose optimization in a population apparently similar to those in the CREATE registry.

This study has several limitations. First, since it was observational, it was an open and non-randomized study. Another limitation is that it was conducted in only one centre, thus the sample size was not large. However, the fact that it was a single centre has some advantages, such as homogeneity in the application of the protocols established in the optimization strategy, as well as its database, the CREATE registry. Furthermore, an observational design is the type of study recommended to advance our knowledge of real-life cost-effectiveness [22].

The difference between the mean initial and final DAS28 in the total population was similar at 2 years, between 1 and 2 years, as was also the case in the patient subgroups that did and did not relapse.
Nevertheless, there was a significant difference between the mean DAS28 at baseline and at 1 year in the total population and in the subgroup of patients that relapsed, although it was not significant between baseline and 2 years, nor between 1 and 2 years. This indicates that clinical improvement is achieved by returning to the standard dose, and most patients regained clinical remission or at least achieved low disease activity in the period analysed by returning to standard dose. These data confirm this strategy would be a more suitable alternative than withdrawal the drug to manage patients in clinical remission with established rheumatoid arthritis. A longer follow-up period would make it possible to know how many finally achieve clinical remission.

With regard to efficiency, the response to optimization was not similar in all drugs. Quantitatively, and after 2 years, tocilizumab appears to be the most efficient means of optimization in actual clinical practice. The number of patients treated with an optimized dose declined over time in all the drugs studied. The effect on savings differed due to the various possible ways to correct optimized doses.

In our case, the only significant difference for savings at 2 years was between adalimumab and infliximab. Adalimumab was also shown to be the most effective and efficient in achieving clinical remission at 2 years in another observational study of patients in the CREATE registry [23].

The only significant association in the statistical analysis was between the initial DAS28 value and relapse at 1 year. The results for the rest of the variables analysed did not reach statistical significance; for this reason, whether or not an antiTNF is used does not appear to be a decisive factor in achieving optimization. However, the small sample size limits our ability to reach conclusions on this point. Likewise, no differences were found when considering patients with 12 months previous remission, which would support current recommendations [14] that 6 months is the minimum time needed to begin dose optimization.

5 Conclusions

Dose optimization of BT in patients with established RA who achieve clinical remission is an efficient strategy in clinical practice, with clinical remission maintained in 40% of patients who received optimized doses after 2 years. Most patients who need to return to a standard dose again achieve clinical remission or at least low disease activity. Initial DAS28 is associated with maintenance of the optimized dose over time.

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Conclusiones

Las principales conclusiones que se pueden extraer de este trabajo son las siguientes:

- En pacientes con artritis reumatoide establecida y en la práctica clínica real, la estrategia más eficiente es la de tratar por el objetivo de alcanzar baja actividad de la enfermedad, y no la remisión de la misma (conclusión extraída del segundo de los artículos presentados).
- El coste efectividad de los fármacos antiTNF-alfa está muy influenciado por el coste de adquisición de cada uno de ellos, ya que supone más del 80% del total del coste y puede cambiar el resultado del coste-efectividad. La introducción en el mercado de los biosimilares puede ser clave en la elección del más eficiente (conclusión extraída del primero de los trabajos).
- Se considera necesario disponer del coste actualizado de los fármacos antiTNF-alfa para recalcular la eficiencia de cada uno de ellos. La participación del farmacéutico dentro del equipo multidisciplinar que debe tomar las decisiones farmacoterapéuticas es importante y se aconseja su incorporación al mismo (conclusión extraída de los 3 trabajos).
- Es necesario profundizar en estrategias de eficiencia. En este sentido, la optimización de dosis de terapia biológica en pacientes con AR establecida que alcanzan remisión clínica es una estrategia eficiente en la práctica clínica real, manteniendo la remisión clínica y la dosis optimizada de fármaco un 40% de los pacientes tras dos años de seguimiento (extraído del tercer artículo).
- La mayoría de los pacientes que requieren de nuevo la administración de dosis estándar del tratamiento biológico vuelven a alcanzar remisión clínica o al menos baja actividad de la enfermedad (extraído del tercer artículo).
- El valor del DAS28 antes de iniciar la optimización de la TB está inversamente relacionado con el mantenimiento de la dosis optiizada de fármaco (extraído del tercer artículo).
- Esta estrategia supone una reducción media aproximada de un 21% del coste medio a dos años en los pacientes del registro CREATE (extraído del tercer artículo).

Resumen

INTRODUCCIÓN

La artritis reumatoide (AR) es una enfermedad sistémica autoinmune caracterizada por dolor, inflamación crónica y destrucción articular. En la mayoría de los casos, el curso es progresivo y conduce a daño articular irreversible, lo que tiene como consecuencia un deterioro funcional, disminución de la calidad de vida y una mortalidad prematura en los pacientes. El objetivo del tratamiento de la AR comprende controlar del dolor y la inflamación, reducir al máximo el daño articular y la discapacidad, controlar las manifestaciones extraarticulares, mejorar la calidad de vida de los pacientes y alcanzar la remisión de la enfermedad, o al menos lograr una baja actividad clínica sostenida.

Sin embargo, en los últimos años el desarrollo de la terapia biológica (TB) ha supuesto un importante avance en el tratamiento de esta enfermedad, lo que está contribuyendo a modificar su pronóstico.

Actualmente en España se disponen de 8 fármacos biológicos con distintos mecanismos de acción: infliximab, etanercept, adalimumab, golimumab y certolizumab pegol como bloqueantes del factor de necrosis tumoral alfa (antiTNF), rituximab como antiCD20, abatacept a nivel del linfocito T y tocilizumab como anti-interleukina 6. Todos estos fármacos han demostrado eficacia y un perfil de efectos adversos que obliga a una estrecha monitorización, suponiendo un elevado impacto económico en el sistema sanitario. Sin embargo, no se conoce qué fármaco de ellos es el más eficaz o efectivo ya que no existen estudios comparativos directos entre ellos.

Por otra parte, existe una fuerte corriente que aboga por abordar el tratamiento de la AR mediante una estrategia de tratamiento basada en tratar por objetivos (treat to target, T2T). Esta estrategia supone una inversión adicional de recursos que ha resultado ser coste-eficaz en pacientes con AR precoz a los tres años. En pacientes con AR establecida y persistente tras el tratamiento con al menos dos fármacos modificadores de la enfermedad clásicos (DMARDs) y un valor de DAS28>5.1, se recomienda el uso de TB. Sin embargo, debido a la ausencia de suficiente evidencia clínica, no se han establecido acuerdos para puntos esenciales que implican al T2T, como son el tratamiento intensivo con TB o si el objetivo debe ser alcanzar remisión clínica, baja actividad de la enfermedad o control de la enfermedad.

Por último, se conoce que la administración de TB no está exenta de riesgos y potenciales efectos adversos, suponiendo además un elevado coste lo que ha llevado a cuestionar qué hacer con el mantenimiento de la administración de la TB una vez el paciente ha conseguido entrar en remisión de forma sostenida en el tiempo. En pacientes con AR establecida, se ha planteado una reducción de dosis como posible estrategia eficiente de manejo disponiendo de documento de consenso entre sociedades científicas para llevarlo a cabo, con estrategias de manejo en el caso de recaídas, todo ello con el objetivo de disminuir la variabilidad clínica.

En resumen: en el actual contexto de crisis y ajuste presupuestario de recursos en sanidad, se necesita conocer qué terapia y estrategias son más eficientes en la práctica clínica desde el punto de vista hospitalario, para implementarlas y alcanzar los mejores resultados en salud posibles de forma eficiente.

OBJETIVOS

El objetivo principal fue comparar el coste-efectividad de los fármacos antiTNF-alfa empleados como terapia biológica de inicio (infliximab, etanercept o adalimumab), con un horizonte temporal de dos años, empleando la perspectiva del sistema sanitario.

Como objetivos secundarios, los siguientes:

-Analizar la efectividad y el coste-efectividad en la práctica clínica real de la estrategia T2T para conseguir remisión clínica en pacientes con AR establecida, tras dos años de tratamiento con TB.

-Evaluar la efectividad y la eficiencia en la práctica clínica habitual de la reducción de dosis en pacientes con AR en remisión clínica sostenida e identificar variables predictivas de respuesta a la optimización.

MÉTODOS

Los datos de este estudio proceden del registro del Equipo Multidisciplinar de Artritis Reumatoide de Córdoba (CREATE registry). Este registro lo componen todos los pacientes diagnosticados de AR que iniciaron TB como tratamiento en el Hospital Reina Sofía de Córdoba entre el 1 de enero de 2007 y el 31 de diciembre de 2012 con un seguimiento de 2 años por paciente.

Todos los pacientes debían cumplir el protocolo de tratamiento de TB del Servicio Andaluz de Salud, basado en las recomendaciones de la Sociedad Española de Reumatología (SER) y de la Liga Europea contra las Enfermedades Reumatológicas (EULAR). Para iniciar TB, los pacientes debían presentar AR activa pese al tratamiento durante un mínimo de 3 meses con al menos 2 de los siguientes fármacos a dosis máximas autorizadas: metotrexato, leflunomida o sulfasalazina. La elección del tratamiento biológico de inicio tiene en cuenta las características de los pacientes y de cada medicamento, así como el coste que supone cada fármaco para el hospital. En caso de no haber ningún condicionante, se empleaba el de menor coste.

En una segunda fase, de este registro CREATE se seleccionaron para el estudio la subpoblación formada por todos los pacientes que a 1 de noviembre de 2013 estaban en remisión clínica, con un tiempo de al menos 6 meses de remisión mantenida. Se siguió prospectivamente a todos los pacientes durante dos años. La toma de decisiones sobre el tratamiento y la reducción de dosis se llevó a cabo por un equipo multidisciplinar.

Efectividad

La efectividad del tratamiento en la práctica real se evaluó a través del DAS28 . Un valor inferior a 2,6 se consideró remisión clínica (CR), e inferior a 3,2 se consideró baja actividad de la enfermedad (LDAS). Se determinó el porcentaje de pacientes que alcanzaron CR y LDA.

Además del DAS28 se evaluaron sus componentes por separado: número de articulaciones dolorosas (NAD), número de articulaciones inflamadas (NAI), velocidad de sedimentación glomerular (VSG), proteína C reactiva (PCR) y valoración global del paciente a través de una escala visual analógica.

Los pacientes se caracterizaron con los datos sociodemográficos de edad, sexo y fecha del diagnóstico de la enfermedad y con datos clínicos como factor reumatoide (FR +/-) y los tratamientos previos y

concomitantes de fármacos modificadores de la enfermedad. Los datos demográficos y clínicos de los pacientes se han obtenido de una base de datos del Servicio Andaluz de Salud.

Análisis de recursos y coste.

Para el análisis del coste se consideró la perspectiva del sistema sanitario, por lo que se tuvo en cuenta el consumo de los recursos sanitarios directos siguientes: coste de adquisición de fármacos (PVL), asistencia a consultas de especialista en Reumatología, asistencia a Urgencias, pruebas complementarias realizadas, necesidad de hospitalización y utilización de hospital de día para la administración de fármacos intravenosos.

RESULTADOS

144 pacientes cumplieron los criterios de inclusión previstos. 55 pacientes recibieron tratamiento con infliximab, 44 con etanercept, 31 con adalimumab, 4 con tocilizumab, 4 con golimumab, 3 con abatacept, 2 con certolizumab y 1 con rituximab.

En una comparación inicial entre adalimumab, etanercept e infliximab, adalimumab fue más efectivo que etanercept para alcanzar remisión clínica al cabo de dos años, sin diferencias con infliximab. No hubo diferencias entre infliximab y etanercept.

El porcentaje de pacientes que lograron LDAS a los dos años fue superior en adalimumab frente a infliximab, sin diferencias en el resto de las comparaciones posibles.

No se encontraron diferencias significativas en el coste total y en ninguno de sus componentes, salvo un mayor coste medio en RMN en el grupo tratado con adalimumab y un mayor coste asociado al uso del hospital de día para la administración de infliximab. El principal componente del coste viene dado por el coste de adquisición de los fármacos, suponiendo una media de aproximadamente un 83% sobre el total.

El fármaco más eficiente para alcanzar la remisión clínica fue adalimumab, con diferencias estadísticamente significativas sobre infliximab y etanercept. No hubo diferencias significativas entre infliximab y etanercept.

Cuando se consideró como resultado de efectividad conseguir un bajo nivel de actividad (DAS28 inferior a 3,2), los fármacos más eficientes fueron adalimumab y etanercept, sin diferencias entre ellos y superiores a infliximab.

El coste medio de los recursos sanitarios directos que supuso alcanzar remisión clínica en los 144 pacientes incluidos, estuvo en torno a los 80.000 euros, lo que está por encima de los límites aceptados en otros estudios y países.

68 pacientes en remisión clínica sostenida optimizaron su dosis.Tras dos años del inicio de dosis optimizada, 28 pacientes (41,17%) continuaban con dosis optimizadas.

El DAS28 medio a los dos años de inicio de la dosis optimizada fue de 2,43±0,72. La diferencia respecto al DAS28 antes de iniciar la pauta optimizada fue 0,29±0,86, y no fue estadísticamente significativa (p=0,146).

Tampoco se encontraron diferencias significativas en los valores medios del DAS28 al estratificar por la TB

recibida.

De los 40 pacientes que necesitaron volver a dosis estándar antes de los dos años, 23 de ellos alcanzaron de nuevo la remisión y 13 más alcanzaron al menos LDA. Por tanto 36/40 de los pacientes, es decir, el 90% consiguió o bien remisión de le enfermedad o al menos LDA al volver a dosis estándar.

La optimización de la dosis de la TB a los dos años reportó un ahorro medio de un 21,21% sobre el total de coste directo sanitario.

CONCLUSIONES

- Adalimumab resultó ser el fármaco más costo-efectivo en la práctica clínica real en los pacientes incluidos en el CREATE registry, tanto para lograr remisión clínica como para alcanzar baja actividad de la enfermedad. No obstante el coste real de adquisición de los fármacos puede resultar determinante en el análisis final de coste-efectividad.
- La estrategia T2T de remisión clínica es considerada la más efectiva, pero no resulta coste-efectiva en la práctica real en pacientes con AR establecida.
- Tras dos años de seguimiento, el 40% de los pacientes a los que se les optimizó la dosis de TB mantuvieron la remisión clínica. Por tanto la optimización de dosis de TB en pacientes con AR establecida que alcanzan RC es una estrategia eficiente en la práctica clínica real.
- La mayor parte de los pacientes que requieren de nuevo la administración de dosis estándar de TB vuelven a alcanzar remisión clínica o al menos baja actividad de la enfermedad.
- El DAS28 antes de la optimización está asociado con el mantenimiento de la dosis optimizada en el tiempo.
- Esta estrategia supone una reducción media aproximada de un 21% del coste medio a dos años en los pacientes del registro CREATE.

Summary

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by pain, chronic inflammation, and joint destruction. In most cases the course is progressive and leads to irreversible joint damage, resulting in functional impairment, reduced quality of life and premature mortality. The goal of RA treatment is to control pain and inflammation, minimize joint damage and disability, control extra-articular manifestations, improve patients' quality of life, and achieve disease remission or at least sustained low clinical activity.

Recently, however, the development of biological therapy (BT) has been an important advance in the treatment of this disease, which is helping to change its prognosis.

Eight biological drugs, with different mechanisms of action, are currently available in Spain: infliximab, etanercept, adalimumab, golimumab and certolizumab pegol, which are blockers of tumor necrosis factor alpha (anti-TNF); rituximab, an anti-CD20 monoclonal antibody; abatacept, a T-cell co-stimulation modulator; and tocilizumab, an interleukin-6 receptor inhibitor. All these drugs have proven efficacy, as well as an adverse effect profile that requires they be closely monitored, resulting in a major economic impact on the healthcare system.

However there is no evidence on the most efficacious or effective drug given the lack of direct comparative studies among them.

Nowadays a strong current of opinion advocates addressing RA management by a treatment strategy based on "treat to target" (T2T). This strategy requires an additional investment of resources, but has been shown to be cost-effective beginning in the third year, as compared to maintaining a strategy of standard treatment and monitoring, when applied to patients with early RA. In patients with persistent established RA after treatment with at least two of the classic disease-modifying antirheumatic drugs (DMARDs) and a DAS28 value >5.1, the use of biological therapy is recommended. However, due to the lack of sufficient clinical evidence, no agreements have been reached on essential points involved in T2T, such as intensive treatment with biological therapy or whether the objective should be to reach clinical remission (CR), low disease activity (LDA) or disease control.

Finally, BT administration is costly and is not without risks and potential adverse effects. These facts have led to questions about how to manage the maintenance of this type of treatment once the patient has achieved sustained remission over time. In patients with established RA, dose reduction has been suggested as a potentially efficient management strategy, having available a consensus document of scientist societies to do it, with strategies for managing relapses, all with the objective of reducing variability in clinical practice.

In summary, given the current economic crisis and the need to adjust healthcare budgets, it is desirable to know which therapy and strategy is the most efficient in clinical practice from the hospital point of view, in order to implement measures to achieve the best possible and efficient health outcomes.

OBJECTIVES

The main objective of this study was to compare the cost-effectiveness of the different antiTNF-alfa used ias initial BT (infliximab, etanercept or adalimumab) with a time frame of two years, and using the healthcare system perspective.

As secondary objectives:

- To analyse the clinical effectiveness and cost-effectiveness of the T2T strategy in achieving CR in actual clinical practice in patients with established RA after 2 years of treatment with BT
- To evaluate the effectiveness and efficiency in routine clinical practice of dose reduction in RA patients in sustained clinical remission and to identify predictive variables of response to optimization.

METHODS

The data for this study were taken from the registry of the multidisciplinary Team for Rheumatoid Arthritis in the Reina Sofia University Hospital, Córdoba, Spain (CREATE Registry). The CREATE registry includes each patient diagnosed with RA, who began biological treatment in our hospital between January 1, 2007 and December 31, 2012, with 2 years' follow-up per patient.

All patients had to follow the Andalusian Health Service treatment protocol for BT, based on the Spanish Society of Rheumatology (SER) and the European League Against Rheumatic Diseases (EULAR) recommendations. To begin BT, patients had to have active RA despite treatment for at least 3 months with at least two of the following drugs at the maximum authorized doses: methotrexate, leflunomide or sulfasalazine. The initial biological treatment is selected based on the characteristics of each patient and drug, as well as the cost of each drug to the hospital. In the absence of any limiting constraints, the lowest cost drug was used.

In a second phase, from this registry, we selected for the study the subpopulation of all patients who on 1 November 2013 had been in sustained clinical remission (DAS28≤2.6) for at least 6 months. All patients were followed prospectively for 2 years. Decisions on treatment and dose reduction of BT were made by a multidisciplinary team.

Effectiveness.

The effectiveness of treatment in actual practice was evaluated by the DAS28. A value lower than 2.6 was considered clinical remission (CR), and less than 3.2 was considered a low disease activity state (LDAS). The percentage of patients who achieved CR and LDAS was determined.

In addition to the DAS28, we evaluated its components separately: number of tender joints (NTJ), number of swollen joints (NSJ), erythrocyte sedimentation rate (ESR), C-reactive protein (PCR), and patient global assessment (PGA) on a visual analog scale.

Data were collected on patients' sociodemographic characteristics (age and sex), date of disease diagnosis, and clinical data including rheumatoid factor (RF+/-) and previous and concomitant treatments with disease modifying antirheumatic drugs (DMARDs). The demographic and clinical data on patients were obtained mainly from the CREATE registry and also from the database of the Andalusian Health Service.

Analysis of Resources and Costs.

The cost analysis was made from the perspective of the healthcare system, taking into consideration use of the following direct health resources: cost of purchasing the drug [ex-factory price (EFP)], consultations with specialists in rheumatology, use of emergency services, complementary tests performed, need for hospitalization, and use of the day hospital for intravenous drug administration

RESULTS

During the study period, 144 patients met the inclusion criteria. Of these, 55 were treated with infliximab, 44 with etanercept, 31 with adalimumab, 4 with tocilizumab, 4 with golimumab, 3 with abatacept, 2 with certolizumab, and 1 with rituximab. In an initial comparison among adalimumab, etanercept and infliximab, adalimumab was more effective than etanercept in attaining CR after 2 years, but was not significantly different from infliximab. There were no differences between infliximab and etanercept.

The percentage of patients who achieved LDAS at 2 years was higher with adalimumab than with -infliximab, with no differences for the rest of the possible comparisons.

No significant differences were found in the total cost or in any cost components, except for a higher mean cost of MRI in patients treated with adalimumab and of the day hospital for administration of infliximab. The main cost component comes from the cost of purchasing the drugs, which averaged about 83% of the total cost.

The most efficient drug in achieving CR was adalimumab, which was significantly superior to both infliximab and etanercept. No significant differences were found between infliximab and etanercept.

When LDAS was considered as the effectiveness outcome, the most efficient drugs were adalimumab and etanercept, both of which were superior to infliximab, but not significantly different from each other.

The mean cost of the direct healthcare resources at 2 years to achieve a clinical remission was about € 80,000, above the accepted threshold in other studies and countries.

A total of 68 patients in clinical remission for at least 6 months optimized their dose. Two years after beginning dose optimization, 28 patients (41.2%) continued with optimized doses.

Mean DAS28 after two years since optimization dose was 2.43 ± 0.72. Difference respect to DAS28 score before starting optimization was of 0.3 ± 0.9, wich was not significant ($p=0.146$). No significant differences were found among mean DAS28 score after stratification by BT received.

Of the 40 patients who needed to return to a standard dose before the second year, 23 of them again reached remission, and 13 more achieved at least low disease activity. Thus, 36/40 of the patients, (90%) achieved either remission or at least low disease activity after returning to a standard dose.
Efficiency by optimized BT dose at 2 years saved a 21.21% of the total direct health cost.

CONCLUSIONS

- Adalimumab was the most cost-effective drug in regular clinical practice for achieving both CR and LDAS in patients included in the CREATE registry. The actual negotiated price of acquiring these drugs is a key factor in the final analysis of cost-effectiveness.
- The T2T strategy of CR is considered to be the most effective, but in daily clinical practice in patients with established RA it is not cost-effective.
- After two years of follow-up, 40% of patients who received optimized doses maintained clinical remission. So dose optimization of BT in patients with established RA who achieve clinical remission is an efficient strategy in real-world clinical practice.
- Most patients who need to return to a standard dose again achieve clinical remission or at least low disease activity.
- DAS28 score before optimization dose, is associated with maintenance of the optimized dose over time.
- This strategy reports about 21% of total mean cost at 2 years of patients in the CREATE registry.

Otras aportaciones científicas

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March 2015 Volume 22 Supplement 1

European Journal of
Hospital
Pharmacy
SCIENCE AND PRACTICE

Volume 22 Supplement 1 Pages A1–A230

EUROPEAN JOURNAL OF HOSPITAL PHARMACY

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20th Congress of the EAHP

25-27 March 2015, Hamburg, Germany

March 2015

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from the outpatient unit of our pharmacy department (PD). The information collected was: age, sex, current drug treatment (obtained from PD program) and glucose, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, VL, CD4 count (obtained from the hospital's clinical laboratory program). The results were analysed using SPSS version 15.0.

Results 85 patients were included; 47 (55.3%) were Christians and the rest Muslims. 59 (69.4%) were men, of whom 23 (39%) belonged to the Muslim ethnic and 36 (61%) to Christian ethnic. Of the 26 women, 15 (57.7%) were Muslim and 11 (42.3%) Christian. The mean age of patients was 47.8 years (SD: 10.1). We found 19 different pharmacological treatments and the most prescribed were: efavirenz/emtricitabine/tenofovir (32.9%), lopinavir/ritonavir monotherapy (29.4%) and lopinavir/ritonavir + emtricitabine/tenofovir (9.4%). 24 Christian and 11 Muslim patients had hypertriglyceridemia (value >150 mg/dL) with statistically significant differences (p = 0.039). 21 Christian patients had CD4 counts below 450/mmc; this number of patients was statistically significant (p = 0.044). No statistical significance was found in the other laboratory test values.

Conclusion Our results show that ethnic Christians had a higher rate of hypertriglyceridemia and low levels of CD4. However other studies would be needed to confirm these findings, which could contribute to a better selection of antiretroviral therapy.

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No conflict of interest.

CP-061 LONG-TERM COST-EFFECTIVENESS ANALYSIS OF INFLIXIMAB, ETANERCEPT AND ADALIMUMAB IN RHEUMATOID ARTHRITIS PATIENTS IN REAL-LIFE CLINICAL PRACTICE

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10.1136/ejhpharm-2015-000639.60

Background Anti-tumour necrosis factor-α agents are very effective in the management of rheumatoid arthritis (RA) patients, but superiority among them has not been established. Also, long-term pharmacoeconomic studies examining the cost-effectiveness of biological agents in real-life clinical practice are scarce.

Purpose To assess the efficiency, in terms of cost, of achieving clinical remission (CR), of infliximab, etanercept and adalimumab in a real clinical setting after two years of treatment.

Material and methods All patients diagnosed with RA in a tertiary referral hospital referred through an interdisciplinary consensus protocol who started treatment with infliximab, etanercept or adalimumab between January 2007 and December 2012 were included. Data examined included demographic and clinical variables and use of health-care resources.

Effectiveness was measured as the proportion of patients achieving CR after two years of treatment (DAS28 value <2, 6).

Costs were assessed from the hospital perspective including the Spanish official drug acquisition costs and costs for diagnostic tests and different medical services, obtained from the Hospital's financial management database.

Cost-effectiveness was calculated dividing total health direct costs by percentage of patients achieving clinical remission.

Results 130 patients were included (55 on infliximab, 44 on etanercept and 31 on adalimumab).

45.20% of patients on adalimumab achieved clinical remission after two years, versus 29.1% on infliximab (p = 0.133) and 22.7% on etanercept (p = 0.04), with no significant differences between etanercept and adalimumab (p = 0.475).

Mean total health direct costs at two years were €29,857.67, €25,328.60 and €23,309.09 for adalimumab, infliximab and etanercept respectively.

The mean costs (IC95%) of achieving CR after two years with adalimumab, infliximab and etanercept were €66,057 (48,038–84,076), €87,040 (78,496–95,584) and €102,683 (94,559–110,807) respectively.

Adalimumab was more efficient than etanercept (p < 0.001) and infliximab (p = 0.026), without statistically significant differences between etanercept and infliximab (p = 0.086).

Conclusion Adalimumab was shown to be the most efficient treatment in achieving clinical remission in real-life clinical practice in our hospital.

REFERENCES AND/OR ACKNOWLEDGEMENTS

No conflict of interest.

CP-062 COST IMPACT OF BELIMUMAB IN A HOSPITAL SETTING

[1]N Chouaou*, [1]J Fontan, [2]O Fain, [1]S Kabiche. *[1]Hôpital Jean Verdier APHP, Pharmacie, Bondy, France; [2]Hôpital Saint Antoine APHP, Médecine Interne, Paris, France*

10.1136/ejhpharm-2015-000639.61

Background Belimumab is a monoclonal antibody indicated as add-on treatment in adult patients with active systemic lupus erythematosus (SLE) despite standard treatment. Given its modest efficacy and the lack of data for severe forms, the improvement in actual benefit (IAB) of belimumab was assessed to be minor. Thus, Health Authorities approved the hospital use of belimumab but its administration in hospital settings is not supported by health insurance.

Purpose To assess the cost impact of belimumab treatment in adult patients with SLE in our hospital.

Material and methods Data available from the SLE population in the Internal Medicine Department was used as input in the model. An Excel model was adopted for the analysis, which was performed from our hospital perspective. The recommended dose regimen was 10 mg/kg on days 0, 14 and 28 and at 4-week intervals thereafter. Patients received their treatment as part of a day hospital admission. Total charges and costs details were obtained from the National Tariffs Databases.

Results A retrospective analysis was conducted on a dataset of 12 female patients followed over a period of 15 months (from January 2013 to May 2014).

Based on a cost of €162.65 for a 120 mg vial and €542.15 for a 400 mg vial, the cost of belimumab per course and per patient was estimated at €972.5 whereas only €30 (drug-related reimbursement in the total hospital daily costs) were refunded to the hospital. 113 courses of treatment were recorded during this period. Therefore, a total of €106,504 remained chargeable to the hospital.

Conclusion Despite some evidence of its clinical effectiveness, the health benefits could be outweighed by the significant costs associated with belimumab. It is important to target patients most likely to benefit from belimumab, to establish well-defined

POSTER AWARD NOMINEES

Presentations on Wednesday, 25 March, 14:00 to 15:30, Hall D

Time	Poster number	Poster nominee oral presentations	Author(s)
14:00	PKP-001	Current vancomycin dosing recommendations for paediatric patients: a pharmacokinetic evaluation	N Rasouli
14:15	PP-002	Compatibility and stability of hyoscine N-butyl bromide and furosemide admixtures for use in palliative care	C Bosch-Ojeda
14:30	PS-042	Parenteral nutrition in premature infants: risk analysis after redesigning a production process	C Salazar
14:45	PS-046	Evaluation of a systematic tool to reduce inappropriate prescribing (STRIP) in adults with intellectual disability: a pilot study	R Zaal
15:00	CP-061	Long-term cost-effectiveness analysis of infliximab, etanercept and adalimumab in rheumatoid arthritis patients in real-life clinical practice	I Viguera-Guerra
15:15	DI-040	Long-term effect of an individualised medication plan with drug administration recommendations on the patients' drug knowledge	AFJ Send

Presentations on Thursday, 26 March, 09:00 to 10:30, Hall D

Time	Poster number	Poster nominee oral presentations	Author(s)
09:00	CP-136	Inappropriate prescribing in older patients: assessment of a screening tool based on the stopp and start criteria	A-L Sennesael
09:15	CP-143	Involvement of microbial flora in aetiology of surgical site infections	D Calina
09:30	PP-028	Long-term stability of diluted solutions of the monoclonal antibody infliximab	N Navas
09:45	PS-116	Exposure to anticholinergic and sedative drugs: relationship between drug burden index, anticholinergic risk scales and falls in elderly hospitalised patients	E Jean-Bart

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LONG-TERM COST-EFFECTIVENESS ANALYSIS OF INFLIXIMAB, ETANERCEPT AND ADALIMUMAB IN RHEUMATOID ARTHRITIS PATIENTS IN REAL-LIFE CLINICAL PRACTICE

at the EAHP 20th Annual Congress in Hamburg, Germany
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OPTIMISATION OF BIOLOGICAL THERAPY IN ESTABLISHED RHEUMATOID ARTHRITIS PATIENTS IN REAL LIFE CLINICAL PRACTICE

at the EAHP 21st Annual Congress in Vienna, Austria
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June 2015 Volume 74 Supplement 2

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was performed by two independent assessors, the same day as all laboratory tests. US of boths hands (dorsal wrist, 2nd to 5th volar metacarpophalangeal and 2nd to 4th volar proximal interphalangeal) was performed with an ESAOTE MY LAB70 machine using a linear probe of 15 MHz. Synovial hypertrophy and power Doppler (PD) signal were scored (grades 0–3). Synovial hypertrophy >2 plus power Doppler signal was classified as active synovitis. Serum drug level was measured just before the next iv infusion or sq injection by ELISA Kit Promonitor®, Progenika SA for ETA, ADL, IFX. All patients were divided in two groups according to the detectable or undetectable serum drug level. Statistical analysis was performed using IBM SPSS v20.0.

Results: All of the patients included had the biologic associated to DMARD, 80.8% were females, mean age 60.44 (11.39), mean disease duration 13.08 (7.05). 53.8% (28) patients were treated with ETN, 34.6% (18) with ADL and 11.5% (9) with IFX. All ETN patients, 61.11% ADL and 57.14% IFX patients had dosable drug level. No statistical significant difference between dosable and undosable drug level was found regarding age, disease duration, rheumatoid factor or ACPA positivity. The presence of dosable drug level negativelly correlated with markers of inflammation, ESR (p=0.030, r-0.357) C reactive protein (p=0.016, r-0.394), physician global assessement (PGA p=0.034, r-0.349). Regarding US parameters (see table) the only significant correlation was found between the number of PD joints and undetectable drug level. There were no statistically significant differences between anti TNF antagonists used.

	Undosable drug level	Dosable drug level	p
Grey Scale Joint No	6.00 (3.83)	6.02 (2.44)	0.980
Power Doppler Joint No	2.02 (1.53)	0.7 (0.82)	0.012
Total Grey Scale score	10.30 (8.87)	9.10 (3.75)	0.683
Total Power Doppler score	2.5 (2.03)	1.60 (2.22)	0.223

Conclusions: Drug serum levels of TNF antagonists correlates with markers of inflammation, number of power Doppler joints but not with total power Doppler score or total Grey scale score.

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Acknowledgements: This paper is partially supported by the Sectoral Operational Programme Human Resources Development (SOP HRD), financed from the European Social Fund POSDRU/159/1.5/S/137390.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2015-eular.2844

SAT0144 A PHASE I PHARMACOKINETIC STUDY COMPARING SB2, AN INFLIXIMAB BIOSIMILAR, AND INFLIXIMAB REFERENCE PRODUCT (REMICADE®) IN HEALTHY SUBJECTS

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Background: SB2, a biosimilar to infliximab reference product (INF), has an identical amino acid sequence and similar physicochemical and *in vitro* functional properties to its reference drug.

Objectives: The primary objective of this study was to demonstrate pharmacokinetic (PK) equivalence between SB2 and EU sourced INF (EU-INF), SB2 and US sourced INF (US-INF), and between EU-INF and US-INF. Safety, tolerability, and immunogenicity were investigated as secondary objectives.

Methods: This study was a randomised, single-blind, 3-arm, parallel group study in 159 healthy subjects. In each arm, all subjects received a single 5 mg/kg dose of SB2, EU-INF, or US-INF by intravenous infusion on Day 1 and then were observed for 71 days during which the PK, safety, tolerability, and immunogenicity measurements were made. The serum concentration of infliximab was measured using an enzyme-linked immunosorbent assay (ELISA). The primary PK parameters were area under the concentration-time curve from time zero to infinity (AUC_{inf}), area under the concentration-time curve from time zero to the last quantifiable concentration (AUC_{last}), and maximum concentration (C_{max}). Equivalence for the primary PK parameters was to be concluded if the 90% confidence intervals (CIs) for the ratio of geometric least squares means (LSMeans) of the groups compared were completely contained within the pre-defined equivalence margin of 0.8 to 1.25 using an analysis of variance (ANOVA).

Results: All of the 90% CIs for the geometric LSMeans ratios of primary PK parameters for SB2 and EU-INF comparison, SB2 and US-INF comparison, and EU-INF and US-INF comparison were within the pre-defined equivalence margin of 0.8 to 1.25 (Table). The proportion of subjects who experienced treatment-emergent adverse events (TEAEs) was comparable between the SB2, EU-INF, and US-INF groups. The most frequent TEAEs were nasopharyngitis and headache. The majority of TEAEs were mild to moderate in severity. Three serious adverse events (SAEs) were reported in two subjects from SB2 group where one SAE was assessed to be related to the study drug: one subject had a Borrelia infection which resolved without sequelae. There were no statistically significant differences in the incidence of post-dose anti-drug antibodies between the three groups.

Table 1. Comparison of primary PK parameters between the treatments

Comparison	PK parameters	Ratio	90% CI
SB2 vs EU-INF	AUC_{inf} (µg·h/mL)	0.986	0.897; 1.083
	AUC_{last} (µg·h/mL)	0.994	0.915; 1.079
	C_{max} (µg/mL)	1.007	0.964; 1.052
SB2 vs US-INF	AUC_{inf} (µg·h/mL)	0.979	0.894; 1.072
	AUC_{last} (µg·h/mL)	0.981	0.904; 1.064
	C_{max} (µg/mL)	0.985	0.942; 1.030
EU-INF vs US-INF	AUC_{inf} (µg·h/mL)	0.993	0.908; 1.086
	AUC_{last} (µg·h/mL)	0.987	0.913; 1.067
	C_{max} (µg/mL)	0.978	0.935; 1.024

Conclusions: This study demonstrated PK equivalence between SB2 and EU-INF, SB2 and US-INF, and between EU-INF and US-INF in healthy subjects. All three infliximab products were generally well tolerated with similar safety profiles.

Disclosure of Interest: D. Shin Employee of: Samsung Bioepis, Y. Kim Employee of: Samsung Bioepis, Y. S. Kim Employee of: Samsung Bioepis, R. Fuhr Grant/research support from: Samsung Bioepis, T. Körnicke Grant/research support from: Samsung Bioepis

DOI: 10.1136/annrheumdis-2015-eular.1265

SAT0145 LONG-TERM COST-EFFECTIVENESS ANALYSIS OF THE TREATMENT WITH INFLIXIMAB, ETANERCEPT AND ADALIMUMAB IN RHEUMATOID ARTHRITIS PATIENTS IN REAL-LIFE CLINICAL PRACTICE

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Background: Anti-tumour necrosis factor-α agents are effective in the management of rheumatoid arthritis (RA) patients, but superiority among them has not been established. Also, long-term pharmacoeconomic studies examining the cost-effectiveness of biological agents in real-life clinical practice are scarce.

Objectives: To assess the efficiency, in terms of cost to achieve clinical remission (CR: DAS28 value<2.6), of the treatment with infliximab, etanercept and adalimumab in a real clinical setting after two years of treatment.

Methods: All patients diagnosed of RA in a tertiary referral hospital attended through an interdisciplinary consensus protocol who started treatment with infliximab, etanercept or adalimumab between January 2007 and December 2012 were included. Data examined included demographic and clinical variables and use of direct health-care resources.

Effectiveness was measured as the proportion of patients achieving CR after two years of treatment (DAS28 value<2,6).

Costs were assessed from the hospital perspective including the official drug acquisition costs and costs for diagnostic tests and different medical services, obtained from the Hospital's economic management database.

Cost-effectiveness was calculated dividing total direct healthcare costs by percentage of patients achieving clinical remission.

Results: 130 patients were included (55 on infliximab, 44 on etanercept and 31 on adalimumab).

45.20% of patients on adalimumab achieved clinical remission after two years, versus 29.1% on infliximab (p=0.133) and 22.7% on etanercept (p=0.040), with no significant differences between etanercept and adalimumab (p=0.475).

Mean total health direct costs at two years were 29,857.67 €, 25,328.60 € and 23,309.09 € for adalimumab, infliximab and etanercept, respectively.

The mean cost (IC95%) to achieve CR after two years with adalimumab, infliximab and etanercept were 66,057€ (48,038-84,076), 87,040 € (78,496-95,584) and 102,683€ (94,559-110,807) respectively. Adalimumab resulted more efficient than etanercept (p<0,001) and infliximab (p=0,026), without statistically significant differences between etanercept and infliximab (p=0.086).

Conclusions: Adalimumab resulted the most efficient treatment to achieve clinical remission in patients with rheumatoid arthritis in real-life clinical practice conditions in our hospital during the period examined.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2015-eular.2900

a US real-world setting. Safety reasons are more commonly responsible for drug discontinuation early after initiation of therapy and become less common later in therapy. An opposite pattern was observed for discontinuations due to decreased efficacy. There were no significant differences in reasons for discontinuation by prior biologic use or for treatment as monotherapy vs combination therapy.

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Acknowledgements: The Corrona CERTAIN study is sponsored by Corrona, LLC, with support from Genentech, Eli Lilly, Momenta Pharmaceuticals and Pfizer.

Disclosure of Interest: D. Pappas Employee of: Corrona, LLC, Paid instructor for: Novartis, A. John Employee of: Genentech, Inc, J. Curtis Grant/research support from: AbbVie, Amgen, BMS, Corrona, Crescendo, Janssen, Pfizer, Roche/Genentech and UCB, Consultant for: AbbVie, Amgen, BMS, Corrona, Crescendo, Janssen, Pfizer, Roche/Genentech and UCB, Speakers bureau: AbbVie, Amgen, BMS, Corrona, Crescendo, Janssen, Pfizer, Roche/Genentech and UCB, C. Etzel Employee of: Corrona, LLC, C. Karki Employee of: Corrona, LLC, J. Ssemakula Employee of: Corrona, LLC, J. Kremer Shareholder of: Corrona, LLC, Grant/research support from: Genentech, Inc, Consultant for: Genentech, Inc, Employee of: Corrona, LLC, A. Shewade Employee of: Genentech, Inc, J. Greenberg Shareholder of: Corrona, LLC, Consultant for: AstraZeneca, Celgene, Novartis and Pfizer, Employee of: Corrona, LLC

DOI: 10.1136/annrheumdis-2015-eular.1867

AB0448 BASELINE CHARACTERISTICS AND CHANGES IN DISEASE ACTIVITY AT 12 MONTHS IN PATIENTS TREATED WITH ABATACEPT VERSUS OTHER BIOLOGIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS IN CLINICAL PRACTICE SETTING – RESULTS FROM THE BRASS REGISTRY

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Background: The advent and use of biologic DMARDs (bDMARDs) have advanced the standard of care in RA, reducing unmet needs and increasing remission rates. Abatacept (ABA), a selective T-cell co-stimulatory modulator, is approved for the management of moderate-to-severe RA. In clinical trial settings, ABA showed efficacy similar to TNFi.[1] In clinical practice, TNFi are the predominantly used bDMARDs in the management of RA; however, there are limited data comparing ABA to bDMARDs in clinical practice.

Objectives: The primary objective was to assess baseline characteristics of RA patients receiving ABA or other bDMARDs in clinical practice. The secondary objective was to evaluate changes from baseline to 12 months in RA disease activity measures (DAS28 [CRP], CDAI and SDAI), as well as patient-reported outcomes (PROs; physical functioning [modified Health Assessment Questionnaire (mHAQ)], quality of life [EQ-5D] and arthritis active/pain today) in RA patients receiving ABA or other bDMARDs in clinical practice.

Methods: Data from patients enrolled in the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) registry, established in 2003, were analysed to address the study objectives. The registry comprises mostly patients with established RA who were evaluated annually on clinical measures and semi-annually on multiple clinical PROs and resource utilization parameters. The current analysis is based on patients who had exposure to bDMARDs and had data on at least one disease activity measure available during 12-month follow-up in the registry. Descriptive statistics were used to summarize the baseline differences in demographics, disease activity measures and laboratory measurements between RA-patients prescribed ABA vs other bDMARDs. Mean change from baseline to 12 months in disease activity measures and PROs were assessed using univariate and multivariate regression analyses that controlled for baseline covariates, including baseline ABA vs bDMARD treatments.

Results: A total of 748 patients were included in the analysis; of these, 102 (13.6%) received ABA and 646 (86.4%) received other bDMARDs; the majority (83%) of ABA patients had prior exposure to bDMARDs. At baseline, ABA patients (vs other bDMARD patients) were older (mean [SD] age: 59.5 [10.7] vs 54.8 [14.2] yrs; p=0.0015), with higher CRP levels (17.09 [41.5] vs 8.1 [19.2] mg/L; p=0.0004), higher DAS28 (CRP) (4.42 [1.58] vs 3.68 [1.65]; p≤0.001), higher mHAQ (0.59 [0.52] vs 0.37 [0.47]; p≤0.001) and lower EQ-5D (0.71 [0.15] vs 0.80 [0.17]; p≤0.001). After controlling for baseline covariates, the mean changes from baseline to 12 months in disease activity measures and PROs were comparable in ABA and other bDMARD patients (Table).

Table: Change from baseline to 12 months between ABA vs bDMARD on disease activity and patient-reported outcomes*

	bDMARD patients	ABA patients	p-value
	Mean (95% CI)	Mean (95% CI)	
DAS28 (CRP)	−0.915 (−1.276, −0.554)	−0.606 (−1.123, −0.090)	0.147
CDAI	−8.406 (−11.819, −4.992)	−5.098 (−10.238, 0.042)	0.119
SDAI	−8.673 (−12.353, −4.994)	−7.004 (−12.348, −1.659)	0.299
mHAQ	−0.023 (−0.085, 0.039)	−0.038 (−0.137, 0.062)	0.239
EQ-5D	0.003 (−0.022, 0.028)	0.022 (−0.018, 0.063)	0.231
Arthritis active today	−0.285 (−0.708, 0.138)	−0.709 (−1.357, −0.061)	0.904
Arthritis pain today	−0.199 (−0.585, 0.187)	−0.595 (−1.187, −0.003)	0.944

*Negative values indicate a reduction in disease activity and improvement in patient-reported outcomes except for EQ-5D, where positive values indicate an improvement

Conclusions: RA patients prescribed abatacept (vs other bDMARDs) in clinical practice tend to be older, with longer disease duration, higher disease activity scores, higher acute-phase reactant and the majority had prior bDMARD exposure. Despite this, mean changes from baseline to 12 months in disease activity measures and PROs in patients on abatacept and other biologic therapies were comparable.

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[1] Schiff M, et al. Ann Rheum Dis 2014;73:86–94.

Disclosure of Interest: E. Alemao Shareholder of: Bristol-Myers Squibb, Employee of: Bristol-Myers Squibb, S. Joo Shareholder of: Bristol-Myers Squibb, Employee of: Bristol-Myers Squibb, M. Frits: None declared, C. Iannaccone: None declared, N. Shadick Grant/research support from: Bristol-Myers Squibb, Crescendo Bioscience, Amgen, UCB, AbbVie, M. Weinblatt Grant/research support from: Bristol-Myers Squibb, Crescendo Bioscience, UCB, Consultant for: Bristol-Myers Squibb, Crescendo Bioscience, UCB, Abbvie, Roche, Janssen, Pfizer, Lilly, Amgen

DOI: 10.1136/annrheumdis-2015-eular.1665

AB0449 IS COST-EFFECTIVE TREATING TO TARGET OF REMISSION IN ESTABLISHED RHEUMATOID ARTHRITIS? RESULTS OF THE CREATE REGISTRY

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Background: Treating to target (T2T) of remission has proven to be the most efficacy strategy to achieve clinical remission in patients with early rheumatoid arthritis (RA), resulting cost-effective after three years. It involves monitoring disease activity, adjusting drugs to approved protocol and aiming at a predefined target. However there is not enough clinical evidence in established and persistent RA and it has not been established the target treatment strategy.

Objectives: The objective was to estimate the cost-effectiveness of three strategies in real-life conditions from the Health Service perspective. T2T of remission versus achievement of low disease activity (LDA) and versus satisfactory disease control (SDC) after two years of treatment

Methods: All patients diagnosed of RA according to the American College of Rheumatology who started biologic therapy between January 2007 and December 2012 were included in the Create registry.

A multidisciplinary care team composed by rheumatologists, hospital pharmacists, nurse and statistical personal from a tertiary hospital was the responsible for making the decision about the treatment-choice.

A T2T strategy aiming at remission (DAS28<2,6) was applied to all patients. This included standardised and protocolised treatment adjustment. Patients were followed up and evaluated at least every two months.

Measurements: Effectiveness was evaluated using the DAS28 value. Three different results were compared:

Strategy 1 (S1): Clinical Remission (CR). DAS28<2,6 at two years.

Strategy 2 (S2): Patients at CR or at least with LDA (DAS28<3,2) at two years.

Strategy 3 (S3): Patients from S2 and also those patients with a DAS28>3,2 at two years, but whose disease activity is judged by both the rheumatologist and patient to be low enough not to require switch of treatment (SDC).

Care and cost: Direct health care costs were assessed from the hospital perspective and included the official drug acquisition costs, diagnostic tests, rheumatologist visits, hospital admission and use of day-care facilities for intravenous drug administration. Data were retrieved from hospital information system and electronic case reports forms. Data of two year follow-up were analysed.

Cost-effectiveness: It was calculated dividing total direct healthcare mean costs by percentage of patients achieving the target clinical result for each strategy.

Results: 144 patients were included. After two years, 32,6% of patients achieved target for S1 (DAS28<2,6), 57,6% of patients reached at least DAS28 value<3,2 (S2) and 90,9% of patients reached a SDC (S3).

Direct health mean cost after two years was 25,976.05 € (IC95%:23,888.16-28,063.93).

T2T of remission was the least cost-effective strategy: 79,681.14€ per clinical remission (SD ±38,880.43€), versus 45,097€/LDA (±22,00.,24€) and 28,545.11€/SDC (±13,958.59€), (p<0,001 in both cases S1 vs S2 and S1 vs S3). Similarly, S2 was less cost-effective than S3 (p<0,001).

Conclusions: T2T of remission strategy with biologic therapy in established RA and in real-life conditions is less cost-effective than T2T of low disease activity or satisfactory disease control.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2015-eular.2588

contractor], Employee of: DOCS, C. Rauch Employee of: Bristol-Myers Squibb, M. Le Bars Shareholder of: Bristol-Myers Squibb, Employee of: Bristol-Myers Squibb
DOI: 10.1136/annrheumdis-2015-eular.1452

AB0478 OPTIMIZATION OF BIOLOGICAL THERAPY IN A COHORT OF PATIENTS WITH RHEUMATOID ARTHRITIS IN HURS, CÓRDOBA

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Background: Optimization of Biological Therapy (BT) in patients with Rheumatoid Arthritis (RA) in remission, is a strategy employed in rheumatology practice in recent years consisting in dose reduction or enlargement dose interval (1,2) Some published studies (3-6) and recommendations of RA (7) management guidelines suggest that patients in sustained remission, could get the same benefit with a lower dose (8) Recently, there has been a consensus document from the Spanish Society of Rheumatology and hospital pharmacy about the unification of criteria for dose optimization with BT in order to minimizing the variability among professionals, striving for the minimum effective dose for each patient, limiting the occurrence of adverse effects and promoting economic savings.
Objectives: To compare the clinical and laboratory characteristics that define the activity of RA patients in remission treated with BT at baseline and at one year after its optimization.
Methods: Observational prospective study of 40 patients followed during 12 months, from a cohort of patients with RA (ACR 1987 criteria) in BT treatment (Anti TNF, Abatacept or Tocilizumab).
After reaching sustained clinical remission according DAS28 (ESR) the patients were optimized using the following treatment regimen:etanercept: 50 mg/10 days (10%), 50 mg/14 days (17.5%), infliximab: 3 mg/9 weeks (10%),3 mg/10 weeks (5%), adalimumab: 40 mg/21 days (7.5%), 40 mg /30 days (7.5%),golimumab: 50 mg/ 5 weeks (5%), tocilizumab: 8 mg/kg/5 weeks (10%), 8 mg/kg/6 weeks (15%), abatacept: 750 mg/5 weeks (7.5%) and 750 mg /6 weeks (5%)
We compared the clinical and laboratory features at the beginning of optimization and at 12 month of follow-up.
Results: Of the 40 patients with RA who were optimized, 80% were women with a mean age of 55.25±14.05 years, a DAS28 at baseline optimization 2.1±0.91 and a mean duration of disease of 16.3±15.3 years. The most widely used drug with spacing pattern was etanercept (27.5%), followed by tocilizumab (25%), both infliximab and adalimumab with 15%, abatacept 12.5% and golimumab 5%. No statistically significant differences were found when contrasting clinical and laboratory parameters of activity at baseline and at 12 months, maintaining remission rates close to 100% at one year of follow-up (DAS28 medium at 12 months 2.30±0.77)
Conclusions: The optimization of BT is a routine clinical practice in our hospital, employing more frequently enlargement dose interval rather than reducing it, managing to maintain remission status one year after the optimization. The adequacy to the published consensus recommendations regarding therapeutic target compliance and the rate of dose reduction was excellent, so we can conclude that optimization can be a useful performance in patients who are in sustained remission.
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Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2015-eular.2606

AB0479 TREATMENT PERSISTENCE OF BIOLOGICAL THERAPY IN RHEUMATOID ARTHRITIS (RA) PATIENTS IN ROUTINE CLINICAL PRACTICE

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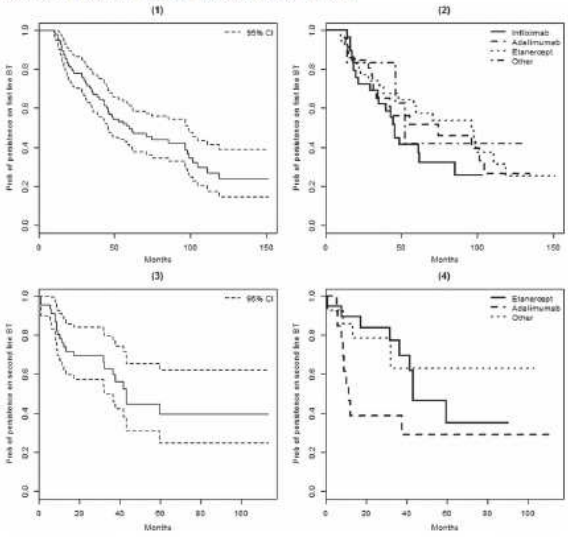
Background: The use of biological DMARDs to treat RA patients has increased over the past 15 years probably due to their efficacy and tolerability profile.
Objectives: Describe persistence (time between biological agent initiation and its discontinuation), the impact of biological therapy (BT) in clinical outcomes (DAS28) and the reasons for its discontinuation.
Methods: A retrospective study of RA patients (pts) followed at Hospital Garcia de Orta with 1st BT [abatacept (ABT), adalimumab (ADA), anakinra (ANA), etanercept (ETN), golimumab (GLM), infliximab (IFX), rituximab (RTX), and tocilizumab (TCZ)] starting between 1/1/2001 and 31/7/2014. Electronic clinical records (Reuma.pt database) were reviewed for all pts that have been treated at least 12 months previously to their recruitment. Available demographic, clinical and therapeutic data were collected. Survival methods were used to analyze time to an event.
Results: 97 RA pts with mean age at RA diagnosis of 45.4±13.4 years were included. 86% were women, 53% with erosive disease, 66% with positivity for rheumatoid factor and 70% with positivity for anti-CCP antibodies. The mean age at the beginning of BT was 53.0±12.7y. Concerning 1st BT, ETN was the most frequent one (36%), followed by IFX (30%), and ADA (27%). 61 pts discontinued their 1st BT, mainly due to secondary ineffectiveness (15 IFX, 10 ETN, 9 ADA, 2 ANA and 1 TCZ). The median time on 1st line was 59.6 months (plot 1). The treatment persistence was not significantly different between BT (p=0.6). Notwithstanding, ETN showed a higher median persistence (96.1 months) than the others (plot 2). Comparing with IFX, the adjusted risk of discontinuation was 42% and 33% inferior with ETN and ADA respectively, though statistical significance was not reached. More than 50% of pts discontinued 1st BT within first 5 years. 46 pts started a 2nd BT (19 ETN, 13 ADA, 5 IFX, 5 RTX and 4 others). Of these, 21 discontinued most due to secondary ineffectiveness (7 ADA, 3 IFX and 3 ETN). The median time on 2nd line was 43.2 months (plot 3). The differences between BT in persistence are fairly statistically significant (p=0.06). Again, ETN showed a higher median persistence (43.5 months) followed by ADA (11.5 months) (plot 4). ADA as 2nd BT presented an adjusted risk to discontinue almost 4 times higher than ETN (HR=3.98, p=0.02). 15 pts switched their 2nd BT (5 TCZ, 4 ABT, 4 RTX e 2 ETN). More than 50% of the pts discontinued their 2nd BT within 4 years after starting it. The adjusted risk for switching with ADA was 9 times higher than the risk for switching ETN (HR=9.06, p=0.004). Regarding evolution of DAS28 during 1st line, ETN presented the highest variation from the baseline at 3, 6, 12, 18 and 30 months compared with all other agents. Regarding 2nd BT, the longitudinal analysis revealed that all agents achieved response between 6 and 18 months after treatment initiation.



Conclusions: The analysis per BT suggests that ETN was the TNF antagonist with the highest persistence on treatment and efficacy profile. Comparing 1st and 2nd lines of biological therapy, there is a decrease of 16.4 months on persistence. Additionally, the probability of switch increases and the probability of end of treatment decreases from 1st to 2nd line.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2015-eular.3116

AB0480 CLINICAL EFFICACY OF TNF INHIBITORS AND ABATACEPT IN JAPANESE RHEUMATOID ARTHRITIS PATIENTS SWITCHING FROM TOCILIZUMAB

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Background: Tocilizumab, a humanized anti-interleukin-6 receptor monoclonal antibody, was approved in 2008 for use in clinical practice in Japan. The efficacy of tocilizumab in treating rheumatoid arthritis (RA) has been demonstrated in several clinical trials as well as in clinical practice. Given the high efficacy and safety,

ISSN:1699-258X

Reumatología Clínica

Volumen 11, Especial Congreso Mayo 2015

XLI Congreso Nacional de la Sociedad Española de Reumatología

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PÓSTERS EXHIBIDOS

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1.ª Sesión

Miércoles, 20 de mayo de 2015

1. ESTUDIO RENACER: EVALUACIÓN DE LA EFICACIA Y RESPUESTA A LOS 12-MESES DE 168 PACIENTES CON ARTRITIS REUMATOIDE TRATADOS CON CERTOLIZUMABPEG EN PRÁCTICA CLÍNICA. REGISTRO NACIONAL DE CERTOLIZUMAB

V. Torrente-Segarra, A. Urruticoechea, H. Corominas, A. Sánchez, J.V. Tovar, A. Muñoz, A. Martínez, J.A. González y M. Fernández, en nombre del Grupo de Estudio RENACER

Hospital Moisès Broggi. Barcelona. Hospital Can Misses. Baleares. Hospital Universitario Virgen del Rocío. Sevilla. Hospital de la Ribera. Alzira. Hospital Universitario de Guadalajara. Hospital General Universitario de Elche.

Introducción: Hay una escasa información de CertolizumabPEGol (CZP) en la práctica clínica Objetivo del estudio: evaluar la eficacia y la seguridad de CZP en pacientes con AR a los 3, 6,12 meses (m), y las variables clínicas serológicas que predicen respuesta clínica de CZP a los12 m.
Métodos: Estudio observacional retrospectivo de pacientes con AR (ACR 2010) en 35 centros en España Los pacientes en CZP ya sea tras otra terapia biológica (TB) o a fallo de otro anti-TNF. El estudio fue aprobado por un Comité Ético local. Variables de eficacia: reducciones en el recuento de articulaciones dolorosas (NAD) y recuento de articulaciones inflamadas (NAI), y DAS28 así como en la Repuesta EULAR, y SDAI, la dosis de esteroides, PCR, y VSG. Variables de seguridad: interrupción debido a efectos adversos. Análisis estadístico: SPSS v19.0 comparativo mediante pruebas Mann Whitney chi-cuadrado, y longitudinal: prueba de Friedman Cochran. Se realizó un análisis de regresión logística.
Resultados: 168 pacientes: 79,2% mujeres, 54,5 años (± 13,2) Media edad, tiempo medio de enfermedad de 7,5 (± 7,3) años, FAME previ (25,6% ninguno 32,1% 1 el 42,3% = 2) MTX 55,4% leflunomida 36,9% sales de oro 25,6% 11,3% SSZ HCQ 10,7%. Número medio FAME previo: 1,4 (± 1,2) TB previa (54,2% ninguno el 28,6% uno el 17,2% = 2): etanercept 23,8% 19,0% adalimumab infliximab 16,1% 6,5% rituximab tocilizumab 5,4% 4,2% abatacept golimumab 3,0%. Media nr antes BT 0,8 (± 1,1). Tiempo medio en CZP 9,8 meses (± 3,4), dosis de inducción 93,5%. Tratamiento concomitante: 11,9% esteroides orales el 24,4% DMARD, 50,0% FAME + esteroides (69,6% un FAME 4,8% 2 FAME). 19 pacientes tuvieron efectos secundarios leves 6 a los 3 m (1 reactivación varicela zoster) 8 a los 6 m (1 infección del tracto respiratorio) que motivó la retirada de CZP), 5 a los 12 m (1 otitis infecciosa). Un total de 48 tratamientos fueron retirados (28,6%): 31 por falta de eficacia, 15 intolerancia, 2 otros; 11,9% a los 3 m y 16,7% a los 6 m. Buscando respondedores frente a los no respondedores mediante respuesta DAS28 EULAR SDAI vimos algunos factores predictivos de respuesta ($p < 0,05$): menor número de FAME previos TB, mayor PCR, VSG NAD NAI DAS28 SDAI En cuanto al uso de monoterapia, no se encontraron diferencias en cuanto a tasa de respuesta entre aquellos que utilizaron TB previa o eran naïve para TB.
Conclusiones: CZP mostró un beneficio claro en pacientes con AR grave refractaria a BT/FAME con una reducción significativa en los niveles de PCR VSG NAD NAI y DAS28 El 75% de los pacientes alcanzaron buena/moderada respuesta EULAR, ya fueran pacientes RF/antiCCP (+) o (–) La respuesta a los 12 m presentó los siguientes factores predictivos: elevada puntuación NAD, NAI, DAS28, SDAI, PCR y VSG bajo número de FAME y TB previos. CZP fue bien tolerado, sin efectos secundarios graves. En la práctica clínica CZP mostró un claro beneficio en el 71% de los pacientes con AR grave y refractaria a los 12 m, incluso siendo un 45,8% no respondedores a antiTNF.

2. ANÁLISIS DE LA EFECTIVIDAD, SEGURIDAD Y COSTE DE DIFERENTES DOSIS DE RITUXIMAB EN UNA COHORTE DE PACIENTES CON ARTRITIS REUMATOIDE

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Objetivos: Evaluar la efectividad, el coste y la seguridad de rituximab en pacientes con artritis reumatoide (AR) dependiendo la dosis utilizada.
Métodos: Estudio observacional retrospectivo. Se incluyeron pacientes con AR tratados al menos con una dosis de rituximab y seguidos en el servicio de Reumatología del Hospital Carlos Haya de Málaga. Según las dosis utilizadas se obtuvieron 3 grupos de tratamiento: (1): Primer ciclo y siguientes consistentes en 2 infusiones de 1 g separadas entre sí por 15 días; (2): Primer ciclo consistente en 2 infusiones de 1 gramo seguido por ciclos de dos infusiones de

se asocia de forma significativa con la presencia de ECV. En AR de estadio inicial, los marcadores inflamatorios están elevados y los lípidos se afectan cuantitativamente (suelen estar disminuidos) y cualitativamente (alteración subfracciones). Navarro-Millán mostró que el uso de metotrexato (mtx) durante 24 semanas aumenta las concentraciones de lípidos, aunque su uso se asocia con una tendencia a la reducción de ECV y es por ello que se ha sugerido que presenta propiedades cardioprotectoras produciendo efectos sobre las características de los lípidos.
Objetivos: Valorar la influencia del uso de mtx en los niveles de colesterol (Col), triglicéridos (Tg) y hemoglobina (Hb) en una cohorte de pacientes con AR de reciente inicio durante 5 años de seguimiento, así como registrar la aparición o no de ECV.
Métodos: Estudio observacional longitudinal que incluye 50 pacientes con diagnóstico de AR (criterios ACR/EULAR 2010) de menos de 6 meses de evolución desde el inicio de los síntomas y que habían iniciado tratamiento con mtx o hidroxicloroquina (hcq). Se registró la presencia o no de ECV y se realizó control analítico basal (sin tratamiento), al año y a los 5 años de seguimiento. Se comparó en ambos grupos (mtx o hcq), la actividad clínica según índice DAS28 (VSG), así como los niveles de Hb, Col y Tg tras inicio del tratamiento.
Resultados: De los 50 pacientes 72% fueron mujeres con una edad media de 50,39 ± 16,13 años y un tiempo medio de evolución de enfermedad inferior a 6 meses. El 64% inició tratamiento con mtx con una dosis media de 9,08 ± 1,89 mg/semanal. La proporción de fumadores, hipertensos y diabéticos era escasa, aunque la carga inflamatoria era elevada con un DAS28 medio > 4. La media de Col y Tg basales fue de 199,18 ± 37,48 mg/dl y 95,60 ± 46,65 mg/dl respectivamente, estando ambos dentro de la normalidad, al igual que los niveles Hb (12,54 ± 1,81 g/dl). Durante el seguimiento no se registró ningún ECV en ninguno de los grupos. Cuando comparamos el cambio en los niveles de Col y Hb al año y a 5 años con respecto a los valores basales en relación a la toma de mtx, no encontramos diferencias significativas, manteniéndose los niveles séricos estables antes y después del tratamiento; si encontramos reducción de los niveles de Tg en el grupo de pacientes tratados con mtx respecto a hcq al año de seguimiento ($p < 0,05$) Durante el seguimiento también observamos una reducción significativa de la actividad clínica según DAS28 cuando lo comparamos con la situación basal, ocurriendo lo mismo en ambos grupos ($p < 0,01$).
Conclusiones: A la vista de nuestros resultados, podríamos concluir que la introducción de mtx en paciente con AR de reciente inicio mejora la actividad clínica y con ello la inflamación subyacente sin que se produzca un aumento en los niveles de Col total ni conlleve un aumento en la presencia de desarrollo de EVC; a su vez existe una disminución en los niveles de Tg de forma significativa si lo comparamos con el uso de hidroxicloroquina, lo cual corroboraría su perfil cardioprotector.

23. LA RIGIDEZ ARTERIAL SE INCREMENTA CON EL TIEMPO EN PACIENTES CON ARTRITIS REUMATOIDE. FACTORES RELACIONADOS CON EL CAMBIO

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Introducción: La artritis reumatoide (AR) está asociada a un mayor riesgo de padecer una enfermedad cardiovascular (CV). La medición de la rigidez arterial mediante la velocidad de la onda de pulso (VOP) refleja estadios precoces de la enfermedad CV. En personas sanas, la VOP aumenta de forma fisiológica con la edad. En pacientes con AR se ha observado una mejoría en distintos marcadores de daño vascular (entre ellos la VOP) tras intervención terapéutica pero no se ha valorado la evolución natural de la VOP en práctica clínica habitual.
Objetivos: Explorar la evolución natural de la VOP en pacientes con AR y los factores relacionados con estos cambios.
Métodos: Tipo de estudio: antes-después. De una cohorte de 237 pacientes con AR en los que se había investigado la existencia de enfermedad vascular subclínica, se reclutaron de forma consecutiva 90 pacientes, a los que se volvió a evaluar un año después. Se recogieron de nuevo datos demográficos (sexo, edad, IMC), clínicos y analíticos de la AR (FR, antiCCP, PCR media, tiempo de evolución de enfermedad), y factores clásicos de riesgo CV(HTA, DL, tabaquismo, índice aterogénico). Con estos datos, se estimó el SCORE modificado según recomendaciones EULAR Utilizamos el dispositivo validado Mobil O Graph® para medir la velocidad de onda de pulso (VOP), como marcador de rigidez vascular. Los pacientes se clasificaron en alto RCV si la VOP ≥ 10 m/s El estudio estadístico se realizó con el programa SPSS 17.0.
Resultados: Tras excluir a los pacientes con alto riesgo CV (evento CV previo, filtrado glomerular < 60 mg/dL, y/o diabetes mellitus tipo II o tipo I con lesión de órgano diana), se evaluaron finalmente al año un total de 70 pacientes: 74,3% mujeres, 20% fumadores, IMC medio 27,89, 31,4% con HTA, 51,4% con DL; 54,3% antiCCP positivo, 62,9% FR positivo. Se detectó una VOP patológica en un 32,4% de los pacientes, siendo la VOP media estadísticamente superior a la basal (0,07-0,32). El incremento de VOP se asoció con el SCORE modificado (p 0,048), y se correlacionó de forma moderada con la TAS (43,7%). El estudio de regresión lineal determinó una dependencia entre VOP y TAS [b (0,07-0,021), R2 0,191], controlado por tiempo de evolución de enfermedad, QIMT, IA, edad e IMC. En relación con otras variables(sexo, HTA, DL, tabaquismo, FR y antiCCP) sí se observaron diferencias, pero éstas no resultaron estadísticamente significativas.
Conclusiones: Al igual que en la población general, en pacientes con AR la VOP cambia con el tiempo en relación con la TAS, pero no con el tiempo de evolución de enfermedad. Se hace necesario un seguimiento más prolongado para poder determinar con certeza la posible relación entre diferentes factores de riesgo CV, clásicos y/o relacionado con la AR, y la progresión del daño vascular determinado por la VOP.

24. EFECTIVIDAD Y EFICIENCIA DE INFLIXIMAB, ETANERCEPT Y ADALIMUMAB EN PACIENTES CON ARTRITIS REUMATOIDE EN LA PRÁCTICA CLÍNICA REAL

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Introducción: Los fármacos contra el factor de necrosis tumoral alfa (anti TNF-a) son eficaces y efectivos en el tratamiento de pacientes con artritis reumatoide (AR), si bien no se ha establecido superioridad entre ellos. De igual forma, no se dispone de estudios de farmacoeconomía que evalúen el coste-efectividad de los fármacos biológicos en condiciones de práctica clínica real.
Objetivos: Comparar el coste-efectividad de infliximab, etanercept y adalimumab para alcanzar remisión clínica cuando se emplean como terapia biológica de inicio en pacientes de práctica clínica real, utilizando la perspectiva del sistema sanitario y con un horizonte temporal de 2 años.
Métodos: Se incluyeron todos los pacientes diagnosticados de AR que empezaron tratamiento con infliximab, etanercept o adalimumab entre el 1 de enero de 2007 y el 31 de diciembre de 2012. Los

pacientes fueron atendidos aplicando un protocolo de consenso multidisciplinar para el manejo de AR en un hospital de tercer nivel. Se analizaron variables clínicas, datos demográficos y consumo de recursos sanitarios directos. La efectividad se midió como el porcentaje de pacientes que alcanzaban remisión clínica (DAS28 < 2,6) a los 2 años de tratamiento. Para el análisis del coste se consideró la perspectiva del sistema sanitario, por lo que se tuvo en cuenta el consumo de los recursos sanitarios directos siguientes: coste de adquisición de fármacos (PVL), asistencia a consultas de especialista en Reumatología, asistencia a Urgencias, pruebas complementarias realizadas (laboratorio y pruebas de imagen), necesidad de hospitalización y utilización de hospital de día para la administración de fármacos intravenosos. El análisis coste-efectividad de cada fármaco se calculó dividiendo el coste medio total de cada uno a los dos años por el porcentaje de pacientes que alcanzaron remisión clínica. Esto dato nos indica el coste por paciente a dos años de cada fármaco para alcanzar remisión clínica.

Resultados: Se incluyeron 130 pacientes, 55 con infliximab, 44 con etanercept y 31 con adalimumab. No se encontraron diferencias estadísticamente significativas entre las características basales de los 3 grupos. El 45,20% de los pacientes con adalimumab alcanzaron remisión clínica a los dos años, frente a un 29,1% con infliximab (p = 0,133) y 22,7% con etanercept (p = 0,040), sin diferencias entre etanercept y adalimumab (p = 0,475). El coste medio total de los recursos sanitarios directos empleados a los dos años fue de 29.857,67 €, 25.328,60 € y 23.309,09 € para adalimumab, infliximab y etanercept respectivamente (ns). Así, el coste medio (IC95%) para alcanzar remisión clínica a los dos años con adalimumab, infliximab y etanercept fue de 66.057€ (48.038-84.076), 87.040 € (78.496-95.584) y 102.683€ (94.559-110.807) respectivamente. Adalimumab resultó más eficiente que etanercept (p < 0,001) e infliximab (p = 0,026), sin encontrar diferencias entre etanercept e infliximab (p = 0,086).

Conclusiones: Adalimumab resultó el tratamiento más eficiente para alcanzar remisión clínica en condiciones de práctica clínica real en nuestro hospital durante el período examinado.

25. FACTORES PREDICTIVOS DE DISCONTINUACIÓN DE TERAPIA BIOLÓGICA POR REMISIÓN EN PACIENTES CON ARTRITIS REUMATOIDE. ANÁLISIS BASADO EN EL REGISTRO NACIONAL DE TERAPIAS BIOLÓGICAS BIOBADASER

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Introducción y objetivos: Actualmente, la remisión se considera un objetivo alcanzable en muchos pacientes afectados de artritis reumatoide (AR) tratados con terapia biológica. Sin embargo, aún existe poca información sobre los factores predictivos de discontinuación de terapia biológica por remisión en estos pacientes. Nuestros objetivos fueron analizar la frecuencia de discontinuación de terapia biológica por remisión en pacientes con AR tratados con fármacos biológicos e identificar aquellos factores predictivos de discontinuación en base a las características basales de los pacientes en el momento de inicio del tratamiento biológico.

Métodos: Estudio observacional, longitudinal, de cohortes de pacientes previamente incluidos en el registro nacional de terapias biológicas BIOBADASER 2.0. Se seleccionaron pacientes con AR que habían recibido tratamiento con el mismo fármaco biológico al menos durante 3 meses. No se incluyeron pacientes tratados con rituximab. El periodo de estudio incluyó todos los pacientes registrados en BIOBADASER 2.0 que habían recibido terapia biológica desde abril de 1998 hasta diciembre de 2013. El desenlace principal fue la discontinuación de fármaco biológico por remisión según criterio del médico responsable. Los datos censurados ocurrieron de forma administrativa (fin del registro de los datos), cuando los pacientes discontinuaron la terapia biológica por otras causas (efectos adversos, ineficacia o pérdida de eficacia, embarazo/deseo gestacional, entre otros) o por pérdida de seguimiento. Se utilizaron modelos multivariados de riesgos proporcionales (sub-distribution hazards (SHR)) para analizar la asociación entre los diversos factores predictivos y la discontinuación por remisión, considerando la falta de eficacia, la suspensión por efectos adversos, la pérdida de seguimiento, o la discontinuación por otras causas, como eventos competitivos.

Resultados: Se incluyeron 3.516 pacientes con AR de los que 3.161 habían recibido al menos 3 meses de terapia biológica. De ellos, 753 pacientes discontinuaron la terapia biológica por efectos adversos, 867 por ineficacia o pérdida de eficacia, 48 por embarazo o deseo gestacional, 143 por otros motivos, 101 fueron pérdidas de seguimiento, y en 15 casos el motivo de discontinuación no estaba

Tabla Póster 25

	No discontinuación por remisión* (n = 3,102)	Discontinuación por remisión (n = 59)	p
Edad (años, media ± DE)	53,9 ± 13,2	58,5 ± 12,4	0,007
Género (mujer %)	79,9	88,1	0,11
Duración de la enfermedad (años, media ± DE)	9,3 ± 8,7	7,0 ± 6,0	0,04
AR seropositiva (%)	89,3	89,8	0,89
Fumador actual	12,2	6,8	0,20
Enfermedad extraarticular (%)	20,1	15,3	0,35
AR nodular (%)	7,4	5,1	0,25
Índice DAS-28 (media ± DE)	3,75 ± 2,85	4,22 ± 2,47	0,21
Tratamiento con metotrexato (%)	56,7	62,7	0,35
Tratamiento con glucocorticoides (al inicio de biológico, %)	53,4	59,3	0,37
Tratamiento con FAMEs (al inicio del biológico, %)	71,2	71,2	0,99
Terapia anti-TNF (como primer biológico, %)	93,9	98,3	0,15

*Se incluyeron todos los pacientes que fueron censurados y los que continuaban recibiendo tratamiento con terapia biológica.

indicado. 1.175 pacientes continuaron recibiendo terapia biológica hasta el final del estudio. Sólo 59 pacientes (1,8%) discontinuaron terapia biológica por remisión. En la tabla se describen las características basales de los pacientes en el momento del inicio de la terapia biológica. En el análisis multivariado (sub-hazard ratio) el género (mujer) (SHR 2,81, IC95% (1,01-7,83)), la edad al inicio de la enfermedad (SHR 1,04, IC95% (1,01-1,07)) y la duración de la misma (SHR 0,94, IC95% (0,90-0,98)) fueron factores predictores de discontinuación por remisión, tras ajustar por el uso de metotrexato y glucocorticoides.

Conclusiones: Una pequeña proporción de pacientes con AR (< 2%) pudieron discontinuar la terapia biológica por remisión de la enfermedad. El género, la edad al inicio y la duración de la enfermedad fueron predictores de discontinuación. El pronóstico a largo plazo de los pacientes que han discontinuado biológico por remisión no es todavía bien conocido y serían necesarios futuros estudios para elucidar su evolución clínica.

26. OPTIMIZACIÓN DE TERAPIAS BIOLÓGICAS EN UNA COHORTE DE PACIENTES CON AR EN HURS CÓRDOBA

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Introducción: La optimización de dosis de terapia biológica (TB) en pacientes en remisión es una estrategia empleada en la práctica reumatológica en los últimos años consistente en la reducción de dosis o en la ampliación del intervalo de la misma. Algunos estudios publicados y recomendaciones en guías de manejo de artritis reumatoide (AR), sugieren que los pacientes en remisión sostenida podrían obtener el mismo beneficio con una dosis menor. Recientemente se ha presentado un Documento de Consenso entre la Sociedad Española de Reumatología y la de Farmacia Hospitalaria acerca de la unificación de criterios en la optimización de dosis con TB. Los objetivos de este documento se basan en minimizar la variabilidad entre profesionales en la optimización de estos fármacos, promoviendo la búsqueda de la dosis mínima efectiva para cada paciente, limitando la aparición de efectos adversos y promoviendo un ahorro económico.

Objetivos: Comparar las características clínico-analíticas que definen la actividad de los pacientes con AR en tratamiento con TB en remisión al inicio y al año de su optimización.

Métodos: Estudio observacional, prospectivo de 40 pacientes con un seguimiento de 12 meses, procedentes de una cohorte de pacientes con AR (criterios ACR 1987) en tratamiento con TB (anti TNF, abatacept o tocilizumab) que tras alcanzar remisión clínica sostenida según DAS28 (VSG) fueron optimizados siguiendo la siguiente pauta (tabla). Comparamos las características clínico-analíticas al inicio de su optimización y a los 12 meses de seguimiento.

Resultados: De los 40 pacientes con AR que fueron optimizados, 80% eran mujeres con una edad media de 55,25 ± 14,05 años, un DAS28 al inicio de la optimización de 2,1 ± 0,91 y un tiempo medio de evolución de la enfermedad de 16,3 ± 15,3 años. El fármaco más empleado con pauta de espaciamiento fue el etanercept (27,5%), seguido de tocilizumab (25%), infliximab y adalimumab ambos con un 15%, abatacept 12,5% y golimumab 5%. No se encontraron diferencias estadísticamente significativas al contrastar los parámetros clínico-analíticos de actividad basales y a los 12 meses, manteniéndose por tanto la tasa de remisión cercana al 100% al año de seguimiento (DAS28 medio a los 12 meses de 2,30 ± 0,77).

Tabla Póster 26

Fármacos	Pautas posológicas	N (%)
Etanercept	50 mg/10 días	4 (10)
	50 mg/14 días	7 (17,5)
Infliximab	3 mg/9 semanas	4 (10)
	3 mg/10 semanas	2 (5)
Adalimumab	40 mg/21 días	3 (7,5)
	40 mg/30 días	3 (7,5)
Golimumab	50 mg/5 semanas	2 (5)
Tocilizumab	8 mg/kg/5 semanas	4 (10)
	8 mg/kg/6 semanas	6 (15)
Abatacept	750 mg/5 semanas	3 (7,5)
	750 mg/6 semanas	2 (5)

Conclusiones: La optimización de dosis de fármacos biológicos es una práctica clínica habitual en nuestro hospital, empleando más frecuentemente el alargamiento de dosis en lugar de la reducción de la misma respecto a otros hospitales, consiguiendo mantener el estatus de remisión al año de la optimización. Por tanto el grado de adecuación a las recomendaciones del consenso publicado fue excelente respecto al cumplimiento del objetivo terapéutico y al porcentaje de reducción de dosis, por lo que podemos concluir que la optimización si puede ser una actuación útil en pacientes que se encuentran en remisión mantenida.

27. IMPACTO ECONÓMICO DEL ALARGAMIENTO DE DOSIS Y MONITORIZACIÓN DE LOS NIVELES SÉRICOS DE ADALIMUMAB Y ETANERCEPT EN PACIENTES CON ARTRITIS REUMATOIDE EN REMISIÓN CLÍNICA: ESTUDIO PRELIMINAR DE UNA UNIDAD LOCAL DE GESTIÓN DE TERAPIA BIOLÓGICA

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Objetivos: Evaluar el impacto económico del alargamiento de dosis y la monitorización de los niveles séricos de adalimumab (ADA) y etanercept (ETN), en pacientes con artritis reumatoide (AR), en remisión clínica, en seguimiento en la Unidad de Gestión de Terapia Biológica de Reumatología.

Métodos: Se determinaron en 2013-2014, los niveles séricos de ADA y ETN, y de anticuerpos anti-ADA y anti-ETN, con técnica de ELISA (Promonitor®-ADA/ETN, Progenika Biopharma, S.A., Grifols SA), en pacientes con AR en remisión, definida por alcanzar y mantener 6 meses consecutivos, un DAS28-VSG = 2,6. Los niveles séricos de corte para ADA y ETN fueron 0,024 mg/L y 0,035 mg/L y para Ac anti-ADA y anti-ETN: 3,5 UA/mL y 132 UA/mL. Las muestras se recogieron el día de administración de ADA y ETN, previo a la misma. Se recogieron características generales de los pacientes y de la AR: evolución de la AR, tiempo en tratamiento con ADA o ETN, causa de retirada o regreso a pauta previa, DAS28-VSG, índice de actividad ecográfica (señal Doppler) en 12 articulaciones, pauta administración basal (ADA: 14 días; ETN: 7 días) y en alargamiento de dosis (ADA: 18-21-28 días; ETN: 10-14 días). Se calculó el número de dosis evitadas anuales en pauta alargada con ADA (cada 18 días: 5,8 dosis; cada 21 días 8,7; cada 28 días: 13) y con ETN (cada 10 días: 15,5 dosis; cada 14 días: 26). Se calculó en euros el dinero ahorrado en los 2 años del estudio y el número teórico de pacientes tratados con dicho ahorro (coste dosis ETN: 250 € y ADA: 500 €).

Resultados: Durante 2013 y 2014, se incluyeron 94 determinaciones (ADA: 53, ETN: 41), de 45 pacientes con AR en remisión (ADA: 23, ETN: 18). El 87% son mujeres, edad media: 60,5 ± 18 años. El tiempo medio de evolución de AR: 15 ± 9,8 años y el tiempo medio en trata-

derado anormal). Se graduó la severidad de la PSAP a través de la señal de insuficiencia tricúspide en leve (30-39 mmHg), moderada (40-49 mmHg) y grave (= 50 mmHg).
Resultados: Se incluyeron 50 pacientes, con edad 59 ± 13 años siendo un 78% mujeres. El 72% eran hipertensos y 16% diabéticos. La mediana de evolución de la enfermedad fue de 12 [6-18] años. En cuanto a la relación E/A, el 74% de los pacientes presentaban un patrón diastólico compatible con la normalidad. En 7 pacientes (14%) existió patrón compatible con patrón pseudonormal (habiendo causa justificable en todos ellos: fibrilación auricular, cardiopatía isquémica y edad > 75 años). En cuanto a la relación E/e´, su valor medio fue de 10,2 ± 4,6 y un 20% tuvieron una relación E/e´ > 15. Estos pacientes eran significativamente más añosos (67,5 ± 8,1 vs 57,6 ± 13,9 años, p = 0,036) y presentaban mayores niveles de antiCCP (mediana 340 vs 31,5, p = 0,016) sin diferencias en el tiempo de evolución de la enfermedad (mediana 14,0 vs 11,0 años, p = 0,73) ni en otras características clínicas. Encontramos hipertensión pulmonar en el 42% de los pacientes, 86% de ellas de grado leve y sólo un 14% moderadas (3 pacientes, con cardiopatía isquémica asociada y/o edad > 70 años) con una presión máxima de 48 mmHg, no encontrando PSAP severa. La presencia de hipertensión pulmonar se asoció únicamente a la edad de los pacientes (65,5 ± 8,9 vs 57,2 ± 14,4 años, p = 0,05) y a los valores de E/e´ (12,9 vs 9,2, p = 0,011).
Conclusiones: En nuestra población la disfunción diastólica avanzada es poco frecuente y se asocia a la edad, comorbilidad y niveles más elevados de antiCCP mientras que la hipertensión pulmonar es frecuente, habitualmente ligera y reflejo de la edad y la disfunción diastólica inherente a la misma.

133. ¿ES EFICIENTE LA ESTRATEGIA DE TRATAR POR EL OBJETIVO DE REMISIÓN EN PACIENTES CON ARTRITIS REUMATOIDE ESTABLECIDA?

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Introducción: La estrategia de tratar por el objetivo (T2T) de remisión es la más eficaz para reducir la actividad de la enfermedad y alcanzar remisión clínica en pacientes con artritis reumatoide de inicio (ARi). Supone monitorizar la actividad de la enfermedad, ajustar el tratamiento según protocolos y fijar objetivos. Su implantación conlleva una inversión de recursos que puede ser coste-efectiva en ARi. En artritis reumatoide establecida y persistente (ARe) no hay suficiente evidencia clínica y no se ha establecido cuál debe ser el objetivo de la estrategia de tratamiento con biológicos (TB). Este trabajo compara el coste-efectividad en la práctica clínica real de la estrategia T2T de remisión, frente a la estrategia de alcanzar baja actividad de la enfermedad o el control satisfactorio de la enfermedad tras dos años de tratamiento y desde la perspectiva del sistema sanitario.
Métodos: Se incluyeron todos los pacientes diagnosticados de ARe de acuerdo con los criterios del American College of Rheumatology, y que iniciaron TB entre el 1 de enero de 2007 y el 31 de diciembre de 2012. Para la toma de decisiones sobre el tratamiento se contó con un equipo multidisciplinar formado por reumatólogos, farmacéuticos, una enfermera y un experto en estadística de un hospital de tercer nivel. Se aplicó a todos los pacientes la estrategia de T2T de remisión (DAS28 < 2,6). Esto suponía la aplicación de protocolos y revisión y seguimiento de los pacientes al menos cada dos meses. Efectividad: se evaluó a través del DAS28. Se compararon tres posibles resultados: Estrategia 1 (E1): Remisión (RC). Pacientes que alcanzaban un valor DAS28 < 2,6 a los dos años. Estrategia 2 (E2): Pacientes que alcanzaban RC o al menos un DAS28 < 3,2 (LDA). Estrategia 3 (E3): Los pacientes anteriores más aquellos que pese a tener un DAS28 > 3,2 se consideró que lograban un control satisfactorio de la enfermedad (CSE) a juicio del investigador. Recursos y coste: se consideraron los recursos sanitarios directos siguientes: coste de adquisición de fármacos (PVL), asistencia a consultas de especialista en Reumatología, asistencia a Urgencias, pruebas complementarias realizadas, necesidad de hospitalización y utilización de hospital de día para la administración de fármacos intravenosos. El horizonte temporal para cada paciente fue de dos años. El análisis coste-efectividad se calculó dividiendo el coste directo sanitario medio total por el porcentaje de pacientes que alcanzaron los objetivos de cada estrategia.
Resultados: Se incluyeron 144 pacientes y tras completar dos años de tratamiento, la estrategia 1 se alcanzó en un 32,6% de los pacientes. Un 57,6% de los pacientes alcanzaron al menos un valor de DAS28 < 3,2 (E2). Finalmente un 90,9% de los pacientes consiguió como mínimo un control satisfactorio de la enfermedad (E3). El coste medio de recursos sanitarios directos a los dos años fue de 25.976,05 € (IC95%: 23.888,16-28.063,93). La estrategia de tratar por el objetivo de remisión fue la menos costo-efectiva (79.681,14 ± 38.880,43 €/remisión), frente a E2 (45.097 ± 22.005,24 €/LDA) y E3 (28.545,11 ± 13.958,59 €/al menos CSE), (p < 0,001 en ambos casos). A su vez, la estrategia 2 es menos costo-efectiva que la estrategia 3 (p < 0,001).
Conclusiones: La estrategia de tratar por el objetivo de remisión en ARe, en la práctica real con terapia biológica es menos coste-efectiva que tratar para alcanzar baja actividad de la enfermedad o suficiente control de la enfermedad.

134. EFECTIVIDAD DE TOCILIZUMAB EN MONOTERAPIA A 2 AÑOS EN CONDICIONES DE PRÁCTICA CLÍNICA EN PACIENTES CON ARTRITIS REUMATOIDE

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Introducción: Recientemente, se ha demostrado la eficacia tocilizumab (TCZ) en monoterapia en el tratamiento de pacientes con artritis reumatoide (AR). Sin embargo, existen pocos datos de su eficacia en monoterapia en condiciones de práctica clínica.
Objetivos: Evaluar las características clínicas de pacientes con AR en tratamiento con TCZ en monoterapia y analizar la efectividad del tratamiento a medio/largo plazo en condiciones de práctica clínica habitual.
Métodos: Estudio observacional, retrospectivo, multicéntrico, a dos años. Se incluyeron los pacientes con AR en tratamiento con TCZ en monoterapia. Se analizaron las siguientes variables: de forma basal: datos demográficos (edad, género); datos clínicos (duración de la enfermedad, positividad para FR y anti-CCP, tratamientos previos al inicio de la monoterapia y motivo de su discontinuación); de forma basal y a los 3, 6, 9, 12, 18 y 24 meses: actividad de la AR (índice

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ISSN: 0172-8172

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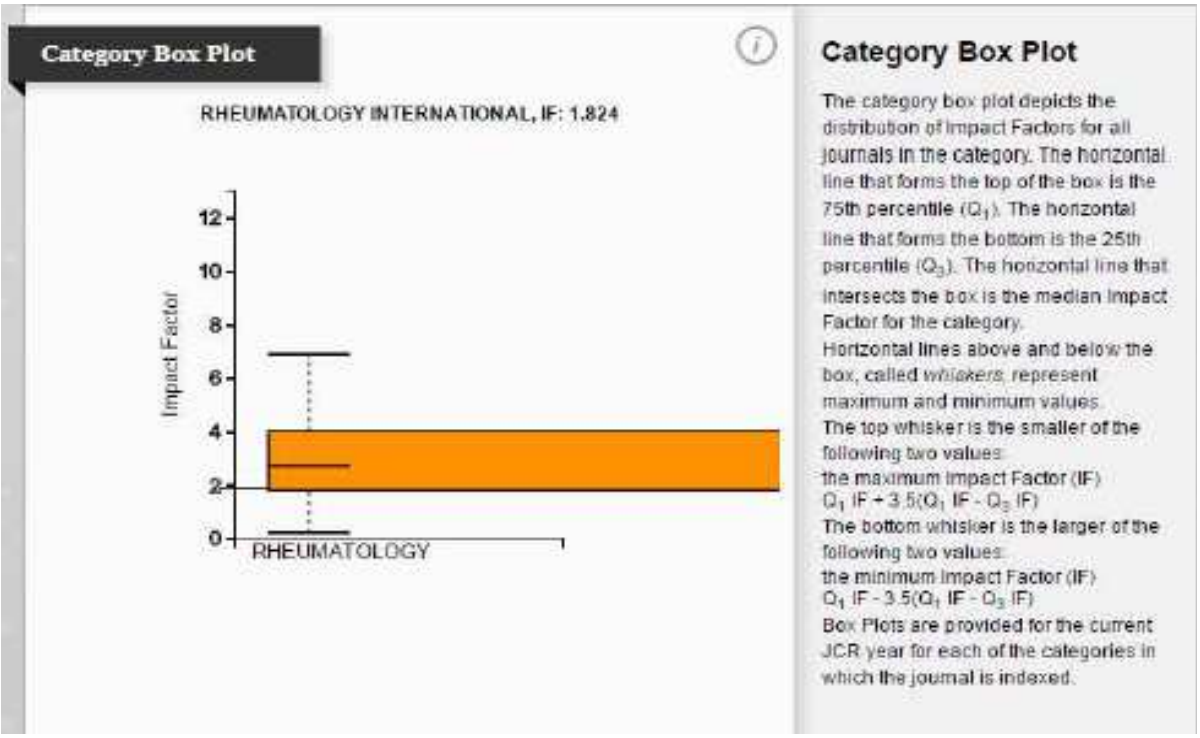

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Tras la aceptación del primer artículo, y dada la continuidad de resultados de nuestro estudio y del registro de pacientes, se optó por enviar los otros dos artículos a la misma revista.

El primero de los artículos posee tres citas.

El segundo de los artículos posee otras dos citas y fue calificado como de clínicamente relevante por los revisores asignados al mismo.

El tercer artículo acaba de ser publicado on line.