Reumatol Clin. 2016;12(3):139–145

Reumatología Clínica

www.reumatologiaclinica.org

Original Article

Eficiency of Different Doses of Rituximab in Rheumatoid Arthritis☆

Natalia Mena-Vázquez, Sara Manrique-Arija, Inmaculada Ureña-Garnica, Carmen M. Romero-Barco, Francisco G. Jiménez-Núñez, Virginia Coret, María Victoria Irigoyen-Oyarzábal, Antonio Fernández-Nebro*

Unidad de Gestión Clínica de Reumatología, Instituto de Investigación Biomédica de Málaga (IBIMA), Hospital Regional Universitario de Málaga, Universidad de Málaga, Málaga, Spain

ARTICLE INFO

Article history:
Received 4 April 2015
Accepted 3 July 2015
Available online 29 March 2016

Keywords:
Adult
Antibodies, monoclonal/administration and dosage
Antibodies, monoclonal/adverse effects
Antibodies, monoclonal/therapeutic use
Antibodies, monoclonal, murine-derived
Antirheumatic agents/administration and dosage
Antirheumatic agents/adverse effects
Antirheumatic agents/therapeutic use
Arthritis, rheumatoid/drug therapy
Arthritis, rheumatoid/immunology
Dose-response relationship, drug
Drug administration schedule
Humans
Rituximab
Treatment outcome

ABSTRACT

Objective: Evaluate the effectiveness, cost and safety of rituximab in patients with rheumatoid arthritis (RA) depending on the dose used.
Material and methods: Retrospective observational study conducted on 52 patients with RA treated with at least one dose of rituximab for 135.3 patient-years were included. Three treatment groups were obtained: (G1) First course and following two 1 g infusions separated by 15 days; (G2) First course 2 infusions of 1 g followed by 2 infusions of 500 mg; (G3) First course and followed by 2 infusions of 500 mg separated by 15 days. Re-treatments were administered on-demand according to the clinical activity. The retention time (Log-Rank), retreats and adverse events rates (incidence rate ratio) and treatment costs per patient-month of rituximab were analyzed by groups.
Results: Group 2 showed a better cost-effectiveness ratio than group 1, as it was associated with a longer retention of rituximab (mean [95% CI] 65.7 [60.8–70.7] months vs 33.5 [22.7–44.3]; *P*<.001) and a lower rate of severe adverse events with only a slight increase in the rate of retreatment (courses/patient-year [95% CI] 1.66 [1.39–1.93] vs 1.01 [0.69–1.34]; *P*=.005), and in the costs (median/patient-month, €484.89 vs €473.45). Although group 3 was €41.20/patient-month cheaper than group 2, it was associated with a higher rate of re-treatments and shorter retention of rituximab (*P*<.001).
Conclusions: The use of full-dose rituximab at onset, followed by reduced doses in successive courses administered on-demand retreatment may be the most cost-effective option.

Eficiencia de diferentes dosis de rituximab en la artritis reumatoide

Palabras clave:
Adulto
Anticuerpos, monoclonal/administración y dosis
Anticuerpos, monoclonal/efectos adversos
Anticuerpos, monoclonal/uso terapéutico
Anticuerpos, monoclonal, derivado-murino
Agentes antirreumáticos/administración y dosis
Agentes antirreumáticos/efectos adversos
Agentes antirreumáticos/uso terapéutico
Artritis, reumatoide/terapia farmacológica
Artritis, reumatoide/inmunología

RESUMEN

Objetivo: Evaluar la efectividad, seguridad y coste de rituximab en pacientes con artritis reumatoide (AR) dependiendo de la dosis utilizada.
Material y métodos: Estudio observacional retrospectivo. Se incluyó a 52 pacientes con AR tratados al menos con una dosis de rituximab durante 135,3 pacientes-año. Se obtuvieron 3 grupos de tratamiento: G1, primer curso y siguientes de 2 infusiones de 1 g separadas 15 días; G2, primer curso de 2 infusiones de 1 g seguido por cursos de 2 infusiones de 500 mg, y G3, primer curso y siguientes de 2 infusiones de 500 mg separadas por 15 días. Los retratamientos fueron a demanda según la clínica. Se analizaron por grupos: el tiempo retención (Log-Rank), las tasas de retratamientos y de eventos adversos (razón de tasas de incidencia) y los costes del tratamiento por paciente-mes de rituximab.
Resultados: El grupo 2 mostró una mejor relación coste-efectividad que el grupo 1 ya que se asoció a una mayor retención de rituximab (media [IC del 95%] 65,7 [60,8-70,7] meses vs 33,5 [22,7-44,3]; p < 0,001) y una menor tasa de eventos adversos graves, con solo un ligero incremento de la tasa de

☆ Please cite this article as: Mena-Vázquez N, Manrique-Arija S, Ureña-Garnica I, Romero-Barco CM, Jiménez-Núñez FG, Coret V, et al. Eficiencia de diferentes dosis de rituximab en la artritis reumatoide. Reumatol Clin. 2016;12:139–145.

* Corresponding author.
E-mail address: afernandezn@uma.es (A. Fernández-Nebro).

Relación dosis-respuesta, fármaco
Pauta administración fármaco
Humanos
Rituximab
Tratamiento desenlace

retratamientos (cursos/paciente-año [IC del 95%] 1,66 [1,39-1,93] vs 1,01 [0,69.-1,34]; p = 0,005) y del coste (mediana/paciente-mes, 484,89 € vs 473,45 €). Aunque el grupo 3 fue 41,20 €/paciente-mes más económico que el grupo 2, se asoció a una mayor tasa de retratamientos y una menor retención de rituximab (p < 0,001).
Conclusiones: El uso de rituximab a dosis completa al inicio seguido de dosis reducida en los sucesivos cursos administrados a demanda parece la opción más coste-efectiva.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic synovial inflammation, joint destruction and functional disability.[1]

Rituximab is a chimeric, anti-CD20, B-cell-depleting monoclonal antibody composed of a human and a murine portion. It has been approved for use in combination with methotrexate in patients with moderately or highly active RA who have not responded satisfactorily to anti-tumor necrosis factor (anti-TNF) therapy.[1] A number of studies have demonstrated that changing to rituximab rather than to another anti-TNF agent may prove to be more effective.[2–4] Although biological treatments represent an important advance in the control of RA, their potential toxicity and high cost should be taken into account. Given both their elevated price and the costs of administration, monitoring, prophylaxis and treatment of the toxicity, they are cost-effective only in certain situations.[5–7] Although the price per dose of rituximab is higher than that of the anti-TNF agents, as the treatment with the former requires fewer courses, in the end, it is the less expensive of the two.

The authorized dose of rituximab is 2 infusions of 1000 mg separated by 15 days for each treatment course, and repeat treatments are administered every 6 months.[8] However, at the present time, patient management is being generalized by means of "tight control" and "treat to target" strategies. These strategies require frequent adjustments of the treatment intensity and have opened the door to modifications of the doses and regimens recommended in the specifications, depending on the clinical status of the patient. Moreover, the authorized rituximab doses have been found to be only slightly superior in the prevention of radiation damage, but there was no clear clinical superiority in the major phase 3 trials with rituximab.[9–16] As a consequence of these approaches, studies have been conducted in the attempt to determine whether the same therapeutic benefit is obtained in patients receiving rituximab at a dose of 500 mg, rather than the standard dose of 1 g.[14–16] The results suggest that, in some patients, the reduced dose can exhibit the same efficacy, as was observed in the DANCER study,[9] SERENE trial,[10] TAME study,[11] MIRROR trial[12] and IMAGE trial.[13]

On the other hand, in the clinical trials that evaluate the efficacy of rituximab for the treatment of RA, it has been observed that the most frequent adverse events are associated with reactions to infusion of the drug and the rate of infusion. This suggests that a reduction in the doses might also be accompanied by a lower incidence of adverse events.

Finally, it is not known whether or not a decrease in the dose of rituximab is associated with a higher frequency of retreatment when it is administered at the discretion of the treating physician. This datum is relevant as regards the efficacy of this drug, as a reduction in the dose could be accompanied by a reduced effectiveness and an even higher cost, should retreatment be required more frequently.

In short, clinical practice studies that evaluate the true efficacy of the use of rituximab in regimens of this type would be necessary.

Our objective was to investigate whether there were differences in efficacy in terms of effectiveness (measured by the treatment retention time and retreatment rates), safety and final cost among patients treated with different regimens and doses of rituximab.

Patients and Methods

Design and Study Setting

We performed a retrospective observational study based on the review of the medical records of RA patients treated with rituximab at the Hospital Regional Universitario de Málaga, Spain (a tertiary care center with a reference population of 628,912 inhabitants). The study was reviewed and approved by the hospital's clinical research ethics committee.

Patients

All the patients treated with rituximab between July 2006 and December 2012 were included in the study. The eligibility criteria were age ≥18 years, RA according to the 1987 American Rheumatism Association criteria,[17] and having been treated with at least 1 rituximab infusion. Patients who had been followed for less than 3 months after the first dose of rituximab were excluded.

Measurements and Variables

Main outcome measure

The main outcome of treatment effectiveness was measured by the rituximab treatment retention time in patient-years (including repeat courses).

Secondary Outcome Measures

1) Rates of retreatment adjusted for exposure time and incidence rate ratio (IRR) in the 3 study groups; *2)* treatment safety, based on the type, severity and incidence of serious and minor events throughout the entire study period, according to patient group; and *3)* costs of rituximab per patient-month associated with each treatment group, estimated by cost minimization from the care provider perspective.

Safety Variables

The presence or absence of serious and minor adverse events and their descriptions were recorded for all the patients at each visit. The safety profile was evaluated, first, by calculating the incidence rates of total and serious adverse events. This was done by dividing the total number of adverse events by the follow-up time of each patient in years (events/patient-year). Subsequently, the incidence rates in each group were calculated in the same way and compared using the IRR. The same operation was carried out taking only the serious adverse events.

Cost Calculation

The calculation of the costs associated with rituximab in each group was based on the purchase price of the drug corresponding to the latest tender of the procurement platform of the province of