Seminars in Arthritis and Rheumatism 44 (2015) 506–513

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Safety of disease-modifying antirheumatic drugs and biologic agents for rheumatoid arthritis patients in real-life conditions

Lydia Abasolo, MD, PhD[a], Leticia Leon, MS, PhD[a,b,*], Luis Rodriguez-Rodriguez, MD, PhD[a], Aurelio Tobias, MS, PhD[c], Zulema Rosales, MD[d], Jose Maria Leal, MI[a], Victor Castaño, MI[a], Cristina Vadillo, MD[d], Pilar Macarron, MD[d], Oscar Fontsere, MD[d], Juan Angel Jover, MD, PhD[d,e]

[a] Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IDISSC), Hospital Clínico San Carlos, Calle Martín Lagos, s/n, 28034 Madrid, Spain
[b] Universidad Camilo José Cela, Madrid, Spain
[c] Consejo Superior de Investigaciones Científicas, Barcelona, Spain
[d] Rheumatology Unit, Hospital Clínico San Carlos, Madrid, Spain
[e] Medicine Department, Universidad Complutense, Madrid, Spain

ARTICLE INFO

Keywords:
Adverse drug reactions
Rheumatoid arthritis
Incidence rates
Biological agents
Disease-modifying antirheumatic drugs

ABSTRACT

Objective: The aim of this study was to describe the incidence rate (IR) of adverse drug reactions (ADRs) in daily clinical practice, related to disease-modifying antirheumatic drugs (DMARDs) and biologic agents (BA) in rheumatoid arthritis (RA) patients, and to analyze factors causing discontinuation due to ADRs.
Methods: This was a prospective observational study (October 2010 to October 2011). RA patients who were attended in our hospital taking DMARDs or BA during the study period were included. ADRs were injuries related to these drugs and registered with a software system in routine visits. ADRs could be mild (lowering dosage), moderate (drug discontinuation), or severe (hospital admission). The IR of ADR per 100 patient-years was estimated using survival techniques. Cox regression models (HR; 95% confidence interval) were used to explore factors associated with discontinuation due to ADRs.
Results: In total, 1202 patients were analyzed, with 158 ADRs (IR = 15.2). Of all ADRs, 80.4% required drug discontinuation (IR = 12.2). Age, less disease and therapy duration, taking corticoids, and combined therapy versus monotherapy (HR = 3; 95% CI: 2.0–4.4) were the factors independently associated to discontinuation due to ADRs. We did not find statistical differences between the different monotherapy regimens. Regarding combinations, Methotrexate + BA had the lowest risk of discontinuation compared to the rest (HR = 0.24; 95% CI: 0.09–0.6).
Conclusions: We have estimated the incidence of ADRs related to DMARDs/BA in real-life conditions. We confirm the role of combined therapy in the development of discontinuations due to ADRs, except for BA + MTX, which did not show an increase of toxicity compared to monotherapy. This combination seems to be safer than others.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease, characterized by persistent synovitis and systemic inflammation. The prevalence varies between countries, ranging from 0.5% to 1% [1,2], and is associated with serious morbidity, impaired functional capacity in more than 50% of the patients, work disability [3], reduced quality of life, and increased mortality [4].

RA patients often require long-term management, with early treatment, and often keep combination of NSAIDs, corticosteroids, slow-acting drugs, immunosuppressants, and biologic therapies. Monitoring, which occupies about 50% of all subsequent visits and almost all of the nursing consultation, aims to maximize the number of remissions of the disease, while minimizing the impact of frequent adverse events.

In the last decades, the management of RA has changed dramatically, and therapies for RA focus on the disease remission

This work was partially supported by a grant from the "Fondo de Investigaciones Sanitarias" of the Spanish Ministry of Health, code FIS PI08/1205, included in RETICS Program RD12/0009/0011 (RIER) from Instituto de Salud Carlos III (ISCIII), Spain.

* Corresponding author at: Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IDISSC), Hospital Clínico San Carlos, Calle Martín Lagos, s/n, 28034 Madrid, Spain.
E-mail address: lleon.hcsc@salud.madrid.org (L. Leon).

http://dx.doi.org/10.1016/j.semarthrit.2014.11.003
0049-0172/

or, at the very least, a reduction in activity in order to reduce or prevent joint damage and disability [5–7]. This approach has been made possible largely by the emergence of a growing number of disease-modifying antirheumatic drugs (DMARDs) and biologic agents (BA) with very favorable profiles of safety and efficiency.

To inform about potential discrepancies between standard clinical practice and the results from randomized controlled trials [8,9], reports from many cohorts have been published, and several meta-analysis have been conducted in the last years. Nevertheless, the strength of evidence is still low when looking at the tolerability and discontinuation rates against studies comparing oral DMARD and BA either in combination or alone [10–14].

Another important point is that obtaining accurate information on side effects and duration of therapy in clinical practice is extremely difficult in the traditional information systems, typically reduced as open questions, affecting the reporting of these events. This environment would require a process of improvement, in order to increase the quality and safety of care in rheumatology patients in general and in RA patients in particular.

Thus, in order to improve the quality of use of the most useful drugs in the treatment of RA, we have conducted a prospective study to evaluate the incidence rate of adverse events related to DMARDs and BA in the daily clinical rheumatology practice setting by implementing a software system Reporting and Analysis for Incident Learning and Adverse Events (SNAIEA). Afterwards, bearing in mind that at the present time rheumatologists have a wide range of therapeutic possibilities in the management of RA, we want to analyze which factors could potentially influence the discontinuation rate due to adverse drug reactions (ADRs), paying special attention to the different therapies (DMARDs/BA) and regimens used (either as in monotherapy or in combination).

Methods

Setting

In Spain, the Public Health system covers approximately 90% of the population. This study was carried out in one of the public Hospitals of the Community of Madrid (Hospital Clínico San Carlos). It is a tertiary hospital covering a catchment area of approximately 600,000 people, and our Rheumatology Service provides care to this population. Patients are referred from primary care physicians and from other specialists to a rheumatologist if needed. A rheumatologist's clinical activity is mainly carried out in the ambulatory setting.

Design

A prospective observational study was conducted from October 1, 2010, to October 1, 2011.

Subjects

The catchment area comprised all patients with clinical diagnosis of RA, who were attended at our outpatient rheumatology care, who were older than 16 years, and who were managed with DMARDs and/or BA during the study period.

Variables and data sources

Case definition: ADR

It was defined as an injury related to medical management [15] in RA patients attended during the study period. These medications included the following drugs: methotrexate (MTX), sulfasalazine (SLZ), antimalarials (AM), leflunomide (LEF) and BA, adalimumab (ADA), infliximab (IFX), etanercept (ETN), rituximab (RTX), and abatacept (ABA). ADR was defined as mild (lowering dosage or doing nothing), moderate (when required discontinuation of the drug), or severe (when the patient discontinues the drug and requires hospitalization or when the patient dies as a result of the ADR).

Covariables

We registered gender; age; marital status; educational level (no education, primary, secondary, and university); clinical characteristics of the patients [disease duration and disease activity, measured by the average ESR per patient, during the study period (at least four different measurements)]; and quality of life measured by mean Rosser index during the study period (at least four different measurements), categorized as slight (1–0.973), moderate (0.973–0.935), or severe (0.935–0) [16]. In relation to AE, we also collected the causal relationship between the event and the drug—unlikely, possible, probable, or certain (WHO-UMC system for standardized case causality assessment)—and the types of ADRs. Finally, we also registered the therapy used during the study period as follows: specific types, duration (starting during the study period (<1 year) or before), and regimen (alone or in combination) of DMARDs/BA, corticoids (yes: ≥ 5 mg/day at least for three months), and NSAIDs (yes: at least for three months).

Data sources

(1) Rheumatology patients' clinical and sociodemographic data has been registered in the Departmental Electronic Health Record (HCE) (MediLOG, 2006), which is a web services-based system used in our outpatient clinic, which codes and integrates the information collected and easily registers in a structured manner during routine consultation by rheumatologists.
(2) A software system Reporting and Analysis for Incident Learning and Adverse Events (SNAIEA). It is a web platform, integrated and connected to MediLOG. All information related to ADRs will be identified and transferred to SNAIEA, where it is analyzed, revised, and confirmed by an expert evaluator (pharmacologist). Afterwards, the completed information is sent back to the HCE [17].

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices and was approved by the HCSC Ethics Committee.

Statistical analyses

A description of the characteristics of patients was included, and the causes of ADRs were explored with frequency distribution and the mean and standard deviation. To estimate the incidence rate (IR) of any ADR we used survival techniques (allowing for multiple-failure data), expressing per 100 patient-years with their respective 95% confidence interval (95% CI). Kaplan–Meier curves were set to account for ADRs discontinuation. Time of observation comprised the elapsed time between October 1, 2010 and lost to follow-up or end of the study period (October 1, 2011). To analyze the effect DMARDs/BA in ADRs, time of observation was subsequently divided into successive periods, each of them defined by a particular type of therapy management, either alone or in combination. Factors associated with the dependent variable or discontinuation due to ADRs (moderate/severe adverse drug reactions) were analyzed by Cox bivariate and multivariate regression models, expressing the results in hazard ratio (HR) with the