Pan American Journal of Public Health

Adverse drug reactions associated with the use of disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis

Jorge Enrique Machado-Alba,[1] *Andrés Felipe Ruiz,*[2] *and Manuel Enrique Machado-Duque*[1]

Suggested citation Machado-Alba JE, Ruiz AF, Machado-Duque ME. Adverse drug reactions associated with the use of disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis. Rev Panam Salud Publica. 2014;36(6):396–401.

ABSTRACT *This study describes the adverse drug reactions (ADRs) and their incidence in patients with rheumatoid arthritis who were treated in the Colombian health system. A retrospective cohort study was conducted using information from all patients who were diagnosed with rheumatoid arthritis and attended specialized health care centers in the cities of Bogotá, Cali, Manizales, Medellin, and Pereira between 1 December 2009 and 30 August 2013. The ADRs were obtained from medical records and the pharmacovigilance system registry and sorted by frequency and affected tissue according to World Health Organization Adverse Reaction Terminology (WHO-ART). A total of 949 reports of ADRs were obtained from 419 patients (32.8 ADRs per 100 patient-years); these patients were from a cohort of 1 364 patients being treated for rheumatoid arthritis and followed up for an average of 23.8 months (± 12.9). The cohort was mostly female (366, 87.4%) and had a mean age of 52.7 years (± 13.1). The highest numbers of ADRs were reported following the use of tocilizumab, rituximab, and infliximab (28.8, 23.1, and 13.3 reports per 100 patient-years respectively). The most frequently reported ADRs were elevated transaminase levels and dyspepsia. Overall, 87.7% of ADRs were classified as type A, 36.6% as mild, 40.7% as moderate, and 22.7% as severe. As a result, 73.2% of patients who experienced an ADR stopped taking their drugs. The occurrence of ADRs in patients treated for rheumatoid arthritis is common, especially in those associated with the use of biotechnologically produced anti-rheumatic drugs. This outcome should be studied in future research and monitoring is needed to reduce the risks in these patients.*

Key words Arthritis, rheumatoid; drug-related side effects and adverse reactions; anti-inflammatory agents, non-steroidal; methotrexate; chloroquine; Colombia.

Adverse drug reactions (ADRs) are events that may seriously affect the health of people who use drugs for diagnostic, prophylactic, or therapeutic purposes. It is estimated that between 59% and 81% of ADRs are preventable or completely avoidable (1, 2). Between 0.34% and 23% of ADRs may end with hospitalization (3, 4). In addition to jeopardizing the health of individuals, ADRs generate unexpected costs that affect health system finances; early identification may help to prevent and resolve these issues (2, 5, 6). Rheumatoid arthritis is a chronic disease with an estimated prevalence of 0.8%–1.0% in the general population, but in Colombia was estimated at 0.5% (7, 8). The toxicity and tolerability of disease-modifying anti-rheumatic drugs (DMARDs)—biotechnologically made or not—is of concern to both health systems and patients because of the frequency in which the drug must be suspended or the type of treatment changed due to their association with significant adverse reactions (9).

In Colombia, several studies of ADRs have been conducted but there is very

[1] Grupo de Investigación en Farmacoepidemiología y Farmacovigilancia, Universidad Tecnológica de Pereira–Audifarma S.A., Pereira, Colombia. Send correspondence to: Jorge Enrique Machado-Alba, machado@utp.edu.co

[2] Pharmacoeconomics, Audifarma S.A., Bogotá, Colombia.

little information about these events in patients being treated for rheumatologic conditions (10). The aim of this study was to describe ADRs in patients diagnosed with rheumatoid arthritis who were being treated for the disease at specialized health care centers (*Instituciones prestadoras de salud–especializadas*, IPS-E) and were covered by Colombia's public health system (*Sistema General de Seguridad Social en Salud*, SGSSS).

RETROSPECTIVE COHORT STUDY

A retrospective cohort study was carried out that collected information on all rheumatoid arthritis patients of all ages and both genders who were being treated at an IPS-E run by Audifarma S.A., a private company providing health care services to people covered by the SGSSS in the cities of Bogotá, Cali, Manizales, Medellin, and Pereira. These patients received drug treatment between 1 December 2009 and 30 August 2013 (45 months) for seropositive and seronegative rheumatoid arthritis according to the International Classification of Diseases, 10th Revision (ICD-10) and the 2010 American College of Rheumatology (ACR) criteria.

All reports were prepared by either a rheumatology specialist or a pharmacist responsible for a pharmacovigilance program. Information was collected from ADR notification reports from the Audifarma–IPS-E pharmacovigilance programs and patient medical records by four doctors trained in collecting this type of data, and validated. Four types of variables were recorded: 1) sociodemographic (age, gender, and city); 2) clinical (rheumatic disease diagnosis); 3) pharmacological (information about the DMARDs, divided into two main groups of medicines, non-biological (chloroquine; glucocorticoids such as prednisone, deflazacort, etc.; hydroxychloroquine; leflunomide; methotrexate; and sulfasalazine) and biological (abatacept, adalimumab, etanercept, infliximab, rituximab, tocilizumab, etc.)); and 4) reported ADRs (classified by frequency and affected organ or tissue) standardized according to World Health Organization Adverse Reaction Terminology (WHO-ART). In cases where patients took more than one drug, the one that was the main suspect for the ADR, according to the Naranjo causality algorithm, which has 10 criteria to define drugs as definite, probable, or possible cause, was recorded. The ADRs were classified as type A (dose-dependent or predictable (i.e., resulting from the drug's primary pharmacological effect)) or type B (dose-independent and unpredictable) and by severity of the event, in accordance with the WHO classification.

Data analysis was carried out using IBM® SPSS® Statistics version 22 (IBM Corporation, Chicago, Illinois, United States), and averages, frequencies, and percentages were employed to obtain the incidence per 100 patient-years of the most common ADRs.

Ethics approval

This research was classified as "without risk" according to Ministry of Health of Colombia Resolution No. 8430 (1993), which establishes the norms for research on humans following requirements in the Declaration of Helsinki. This study was approved by the Universidad Tecnológica de Pereira Bioethics Committee without the requirement for individual informed consent.

RESULTS

A total of 949 ADR reports were obtained from 419 patients from a cohort of 1 364 patients diagnosed with and treated for rheumatoid arthritis (i.e., more than one unintended effect per drug), resulting in an overall incidence of 32.8 ADRs per 100 patient-years. The average patient follow-up period was 23.8 months (± 12.9). The city with the most patients was Bogotá (271 patients or 64.7%), followed by Manizales (39 patients or 9.4%), Medellin (37 patients or 8.9%), Cali (36 patients or 8.6%) and Pereira (36 patients or 8.4%). The patients were predominantly female (366 or 87.4%) with a mean age of 52.7 years (± 13.1) (range: 3–90; median: 53). Only six patients were under 18 years old. The mean time to establish DMARD treatment was 2.2 years after the onset of symptoms, and 91.1% of patients were receiving combined therapy with two or more DMARDs.

Of the 15 drugs associated with an ADR, nine were non-biological DMARDs and six were biological DMARDs. Table 1 shows the number of patients who received each of the 15 different drugs; the number of ADR reports per drug; and the ADR incidence per 100 patient-years. The most widely used non-biological DMARD was methotrexate, which was associated with 6.6 ADRs per 100 patient-years, followed by prednisolone and leflunomide. Some of the biological DMARDs (e.g., infliximab, rituximab, and tocilizumab) were associated with more ADRs than other drugs. There was a notable difference in ADR incidence between patients who received etanercept in the innovative

TABLE 1. Frequency of use of disease-modifying anti-rheumatic drugs (DMARDs) and adverse drug reaction (ADR) incidence per drug in a cohort of rheumatoid arthritis patients, Colombia, 2009–2013

DMARD	Number of patients who received the drug	% use of each DMARD	Number of ADR reports	ADR incidence per 100 patient-years
Non-biological				
Sulfasalazine	515	37.7	115	10.1
Methotrexate	1343	98.5	202	6.6
Leflunomide	979	71.8	102	4.9
Chloroquine	657	48.2	75	4.8
Hydroxychloroquine	113	8.3	10	3.9
Azathioprine	9	0.7	1	3.9
Prednisolone	1246	91.3	60	2.5
Methylprednisolone	70	5.1	2	1.3
Deflazacort	288	21.1	9	11
Biological				
Tocilizumab	51	3.7	40	28.8
Rituximab	110	8.1	66	23.1
Infliximab	58	4. 3	21	13.3
Etanercept				
Biosimilar	13	1.0	3	11.4
Innovative	120	8.8	15	6.2
Adalimumab	68	4.9	15	8.4
Abatacept	79	5.8	10	4.7

TABLE 2. Incidence of most common adverse drug reactions (ADRs) reported in a cohort of patients (*n* = 1 346) receiving rheumatoid arthritis treatment, Colombia, 2009–2013

ADR	Frequency	ADR incidence per 100 patient-years
Elevated transaminase levels	147	8.3
Dyspepsia	145	8.2
Nausea/vomiting	65	3.9
Dermatological reactions	45	3.3
Leukopenia	50	3.2
Retinopathy	54	3.1
Neutropenia	30	2.0
Infusion reactions	25	1.8
Dizziness/vertigo	27	1.6
Headache	24	1.5
Cushing's syndrome	24	1.5
Alopecia	23	1.4
Diarrhea	20	1.3
Osteoporosis	20	1.3
Urinary infections	14	0.8
Latent tuberculosis	13	0.8

molecular regime and those treated with biosimilars. Table 2 shows the most commonly reported ADRs and the incidence per 100 patient-years for each.

Of all ADRs reported, 832 (87.7%) were type A (70.2% from non-biological DMARDs and 17.5% from biological DMARDs) and the remaining 117 (12.3%) were type B (8.1% from non-biological DMARDs and 4.2% from biological DMARDs); this second type of ADR was common among hypersensitivity reactions (not shown). Of the ADRs that could be classified by severity, 36.6% were mild (30.9% from non-biological DMARDs and 5.7% from biological DMARDs); 40.7% were moderate (28.5% and 12.2% for the two types of drugs respectively); and 22.7% were severe (18.9% and 3.8% respectively) (not shown). There were no fatalities. A behavior trend was found in which monitoring of ADRs and ADR severity by doctors led to the suspension of the drug (for 507 out of 693 ADRs or 73.2%) or reduced doses (47 ADRs or 6.8%). For 90 patients (13.0%), it was possible to continue with the same drug at the same dose; for 49 patients (7.1%), there was a switch to another drug of the same group. Among all methotrexate users, 10.9% had to discontinue therapy. Discontinuation of therapy also occurred in 8.3% of patients taking leflunomide and 3.0% of those who were using prednisolone. This percentage increased to 17.3% among sulfasalazine users. Among patients taking biological drugs, 47.1% of those using tocilizumab, 31.0% of those using infliximab, and 14.5% of those receiving rituximab stopped taking their drugs due to adverse reactions (not shown).

The main ADRs associated with the use of methotrexate were elevated transaminase levels (83 patients or 41.1% of those using this drug) and dyspepsia (49 patients or 24.3%). Prednisolone was found to cause Cushing's syndrome (21 patients or 33.4%) and osteoporosis (20 patients or 33.3%), while the main ADRs for leflunomide were elevated transaminase levels (34 patients or 23.8%) and dyspepsia (19 or 13.3%). For sulfasalazine, the main ADR was dyspepsia (62 patients or 53.9%); for chloroquine, it was retinopathy (37 patients or 41.1%). For biological DMARDs, the main ADRs were as follows: for tocilizumab, leukopenia (six patients or 11.7%) and elevated transaminase levels (five patients or 9.8%); for infliximab, infections such as urinary infections and tuberculosis (eight patients or 24.2%), and reactions during infusion (six patients or 18.2%); for rituximab, infusion reactions (17 patients or 25.8%), infections (16 patients or 24.2%), and leukopenia (13 patients or 19.7%) (not shown).

DISCUSSION

Rheumatoid arthritis remains a disease that causes disability, morbidity, and a significantly increased mortality rate; therefore, management of this disease should focus on reducing complications with the remission of symptoms and functional disabilities (11). However, ADRs associated with biological and non-biological DMARDs can cause problems with patient therapies, as shown in the study reported here—the first in Colombia on the frequency and types of adverse reactions experienced among patients receiving treatment for this disease.

A total of 30.7% of patients in this large cohort reported at least one ADR when taking DMARDs, a frequency within the range reported by other authors (19.0%–32.8%) (12–14). A higher proportion of women were found in this study versus previous studies (87.4% versus 65.0%), but the reasons for this difference are unclear (15, 16). The suspension of therapy due to undesirable effects was significantly higher (73.2% versus 34.0%) than that reported by McWilliams in his study in the United Kingdom in 2013, where a lower proportion of patients were forced to stop taking their drug, but this can probably be explained by better follow-up of individual cases (17).

For methotrexate, the most commonly used DMARD, ADR incidence was 6.6 per 100 patient-years, similar to what has been reported in the literature (13, 18, 19). A total of 10.9% of methotrexate users had to stop taking the drug because of ADRs—a percentage 19.7% less than that reported in Saudi Arabia (13). The ADRs most commonly associated with the use of prednisolone are weight gain, increased blood pressure, and gastrointestinal events, versus Cushing's disease and osteoporosis, the most common adverse effects found in this study. This difference may be related to the fact that the first three effects are undervalued by doctors in Colombia because of their frequency and reports are only made for the most serious and striking cases (20). The ADRs most commonly associated with the use of sulfasalazine are blood disorders; however, that was not the case in this study, which may reflect differences in the dosage and duration of use (21).

In this study, an incidence of 4.9 ADRs per 100 patient-years was found for the use of leflunomide, a much lower frequency than that reported in the literature (18, 22). In the cohort for this study, 8.3% of patients using leflunomide had to suspend therapy due to ADRs—a lower figure than that reported in Holland, which was close to 29.0% (22).

The causes of such differences must be established.

Biotechnology drugs are being used more frequently to control disease. These DMARDs potentially have higher costs and more adverse effects than non-biological DMARDs (11). In Colombia, a study was carried out between 2008 and 2009 that showed the patterns of use for these drugs; the most commonly used were adalimumab, etanercept, and infliximab, in order of frequency (10). This situation has changed since then in favor of etanercept, currently the most commonly used drug in this group, due to the fact that it was the only one included in the list of drugs covered by the SGSSS when the information for this study was compiled (23).

Based on the literature, the most commonly documented ADRs for tocilizumab are related to increased risk of urinary infections and latent tuberculosis, and elevated transaminase levels (24, 25); this does not coincide with what was found in this study. However, the ADRs most commonly associated with the use of rituximab (reactions during the infusion, and infections) were the same for both this study and a previous study of patients in Colombia (26).

In this study, infliximab was associated with an ADR in 13.3 per 100 patient-years, an incidence level that exceeded those reported by pharmacovigilance studies in Canada, Japan, and Spain (14, 27, 28). Infections of all types were the ADRs most frequently associated with the use of the drug in this study, at an incidence rate double that found in a study by Takeuchi in Japan (24.2% versus 12.5%). The occurrence of tuberculosis was also significantly higher in this study than that found in Japan, where only 1.0% of Japanese patients (versus 3.0% of Colombians) developed the disease. This finding is most likely related to the higher prevalence of infection from *Mycobacterium tuberculosis* in the Colombian population (28, 29). In addition, 31% of users in this study suspended their infliximab treatments—6.7% more than in a study in Spain by Pérez-Zafrilla, possibly due to the frequency of infusion reactions that may be associated with differences in the application technique used in each cohort (14).

In this study, the use of etanercept was particularly associated with local reactions at the site of application. Any use of etanercept was associated with urticaria in two other studies—Sweden (15.4%) (30), and Spain (6.5%) (31). The finding in this study that 21.8% of patients who used this drug had to cease treatment due to ADRs is higher than the levels recorded in both those studies (7.2% and 7.3% for Sweden and Spain, respectively) (30, 31), a difference that may be associated with the application technique but needs to be explored further to determine that with any certainty.

Despite the fact that non-biological DMARDs such as chloroquine, leflunomide, methotrexate, and prednisolone corticosteroid were the most commonly employed type of drug in this cohort, more ADRs were reported for the biological DMARDs. It was also observed that patients in this study treated with non-biological DMARDs were not required to suspend therapy as often as those taking biological DMARDs (13, 14, 22, 30–32).

Recommendations

Based on the results of this study, the authors recommend the following: 1) ongoing, timely, and complete recording of ADRs in rheumatologic patients; 2) active monitoring of the safety of all drugs used by rheumatoid arthritis patients; 3) evaluation of the risks involved in modifying a biological therapy, given the increased incidence of undesirable effects from these types of changes; and 4) more pharmacovigilance studies to update the incidence levels of new ADRs associated with the use of DMARDs. Given the reports of increased toxicity of some DMARDs in people of Hispanic ethnicity, this pharmacogenetic relationship should also be assessed (33, 34).

Limitations

This study had some limitations. First, the overall incidence of ADRs reported across the entire patient cohort for all drugs is not comparable with any previous study results because there are no other published reports on ADR incidence associated with multiple medicines across such a large patient cohort. Therefore, the results on ADR incidence are only comparable for each drug taken individually. Second, the research reported here was not a prospective study on ADRs; the results are based only on data reported by the treating physicians. This aspect of the study also provided an advantage, however, as it allowed for the use of information from a reliable database. Third, this research only includes data for the patients in the cohort who were treated and followed up at the IPS-E; no data were collected on untreated people who may have experienced an ADR. Fourth, the high incidence of ADRs associated with biological DMARDs may be attributable to the recent introduction of these drugs. However, the fact that these drugs were new also resulted in access to spontaneous ADR reports associated with their use, in addition to those obtained from patient monitoring and the pharmacovigilance registry, which may have strengthened the study results.

Conclusions

For treatment of rheumatoid arthritis in the cohort studied in the research reported here (patients covered by Colombia's SGSSS and treated at an IPS specialized in rheumatology), the most commonly used drugs are DMARDs, particularly chloroquine, corticosteroid prednisolone, leflunomide, methotrexate, and sulfasalazine, which are associated with an ADR incidence of between 2.5 and 10.1 per 100 patient-years. This incidence is lower than that for adverse effects in those receiving biological DMARDs as treatment, for which ADR incidence ranges from 6.2 to 28.8 per 100 patient-years. Some of the ADRs reported in this study are characteristic of these drugs, but the frequency was higher than that reported by other authors (e.g., elevated transaminase levels in patients using leflunomide and methotrexate). An explanation of the causes of these differences should be sought in future research. In addition, compared to the literature, this study found a higher number of ADRs associated with the use of biotechnology drugs, including reactions at the injection site or during infusion, and increased susceptibility to infections (particularly tuberculosis), most likely attributable to variations in drug administration techniques and a higher prevalence of tuberculosis in Colombian patients, respectively. For the reasons given above, the authors rec-

ommend implementation of an active pharmacovigilance system that allows for early detection of ADRs and timely interventions.

Acknowledgments. The authors thank Mónica Murillo; Vladimir Solano; and Álvaro Villalobos, for his role in collecting information.

Funding. This study received funding from the Universidad Tecnológica de Pereira–Audifarma S.A. and Pfizer Colombia.

Conflicts of interest. Pfizer Colombia financed the data collection from medical records. However, there was no intervention by Pfizer in any stage of processing, analyzing, or publishing the data.

REFERENCES

1. Pirmohamed M, James S, Meakin S, Green C, Scout AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329(7456):15–19.
2. Olivier P, Boulbès O, Tubery M, Carles P, Montastruc JL, Lapeyre-Mestre M. [Preventability of adverse effects in a medical emergency service]. Therapie. 2001;56(3):275–8.
3. Patel P, Zed PJ. Drug-related visits to the emergency department: how big is the problem? Pharmacotherapy. 2002;22(7):915–23.
4. Honigman B, Lee J, Rothschild J, Light P, Pulling R, Yu T, et al. Using computerized data to identify adverse drug events in outpatients. J Am Med Inform Assoc. 2001;8(3): 254–66.
5. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients—a meta-analysis of prospective studies. JAMA. 1998;279(15):1200–5.
6. Haerian K, Varn D, Vaidya S, Ena L, Chase HS, Friedman C. Detection of pharmacovigilance-related adverse events using electronic health records and automated methods. Clin Pharmacol Ther. 2012;92(2):228–34.
7. Wasserman AM. Diagnosis and management of rheumatoid arthritis. Am Fam Physician. 2011;84(11):1245–52.
8. Delgado-Vega AM, Martín J, Granados J, Anaya JM. Epidemiología genética de la artritis reumatoide: ¿qué esperar de América Latina? Biomedica. 2006;26(4):562–84.
9. Lobo MG, Pinheiro SM, Castro JG, Momenté VG, Pranchevicius MC. Adverse drug reaction monitoring: support for pharmacovigilance at a tertiary care hospital in Northern Brazil. BMC Pharmacol Toxicol. 2013; 14(1):5.
10. Machado J, Moncada JC, Pineda R. Perfil de utilización de los anti-factor de necrosis tumoral en pacientes de Colombia. Biomedica. 2011;31(2):250–7.
11. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet. 2010;376(9746):1094–108.
12. Sokka T, Toloza S, Cutolo M, Kautiainen H, Makinen H, Gogus F, et al. Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. Arthritis Res Ther. 2009;11(1):R7.
13. Al-Malaq HM, Al-Arfaj HF, Al-Arfaj AS. Adverse drug reactions caused by methotrexate in Saudi population. Saudi Pharm J. 2012;20(4):301–5.
14. Pérez-Zafrilla B, Angel Descalzo M, Carmona L; Grupo de Estudio BIOBADASER. Reacciones adversas relacionadas con la administración de inhibidores del TNF. Análisis de un registro de terapias biológicas. Reumatol Clin. 2008;4(3):90–5.
15. Duraj V, Tafaj A, Backa T. Epidemiology of rheumatoid arthritis in Tirana, Albania. Mater Sociomed. 2013;25(2):96–7.
16. Symmons D, Turner G, Webb R, Asten P, Barrett E, Lunt M, et al. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. Rheumatology (Oxford). 2002;41(7):793–800.
17. McWilliams DF, Kiely PD, Young A, Walsh DA. Baseline factors predicting change from the initial DMARD treatment during the first 2 years of rheumatoid arthritis: experience in the ERAN inception cohort. BMC Musculoskelet Disord. 2013;14(1):153.
18. Curtis JR, Beukelman T, Onofrei A, Cassell S, Greenberg JD, Kavanaugh A, et al. Elevated liver enzyme tests among patients with rheumatoid arthritis or psoriatic arthritis treated with methotrexate and/or leflunomide. Ann Rheum Dis. 2010;69(1):43–7.
19. Alves JA, Fialho SC, Morato EF, Castro GR, Zimmermann AF, Ribeiro GG, et al. Liver toxicity is rare in rheumatoid arthritis patients using combination therapy with leflunomide and methotrexate. Rev Bras Reumatol. 2011;51(2):141–4.
20. Kavanaugh A, Wells AF. Benefits and risks of low-dose glucocorticoid treatment in the patient with rheumatoid arthritis. Rheumatology (Oxford). 2014;10:1742–51. Epub 2014 Apr 10.
21. Grove ML, Hassell AB, Hay EM, Shadforth MF. Adverse reactions to disease-modifying anti-rheumatic drugs in clinical practice. QJM. 2001;94(6):309–19.
22. Van Roon EN, Jansen TL, Mourad L, Houtman PM, Bruyn GA, Griep EN, et al. Leflunomide in active rheumatoid arthritis: a prospective study in daily practice. Br J Clin Pharmacol. 2004;58(2):201–8.
23. Comisión de Regulación en Salud (CO). República de Colombia. Acuerdo #029 de 2011. Bogotá: CRS; 2011. Available from: http://www.minsalud.gov.co/Normatividad_Nuevo/ACUERDO%20CRES%200029%20DE%202011.pdf
24. Campbell L, Chen C, Bhagat SS, Parker RA, Östör AJ. Risk of adverse events including serious infections in rheumatoid arthritis patients treated with tocilizumab: a systematic literature review and meta-analysis of randomized controlled trials. Rheumatology (Oxford). 2011;50(3):552–62.
25. An MM, Zou Z, Shen H, Zhang JD, Cao YB, Jiang YY. The addition of tocilizumab to DMARD therapy for rheumatoid arthritis: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol. 2010;66(1):49–59.
26. Conti F, Ceccarelli F, Perricone C, Alessandri C, Conti V, Massaro L, et al. Rituximab infusion-related adverse event rates are lower in patients with systemic lupus erythematosus than in those with rheumatoid arthritis. Rheumatology (Oxford). 2011;50(6):1148–52.
27. Ducharme J, Pelletier C, Zacharias R. The safety of infliximab infusions in the community setting. Can J Gastroenterol. 2010;24(5): 307–11.
28. Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. Ann Rheum Dis. 2008;67(2):189–94.
29. World Health Organization. Global tuberculosis control: WHO report 2011. Geneva: WHO; 2011. Available from: http://whqlibdoc.who.int/publications/2011/9789241564380_eng.pdf
30. Feltelius N, Fored CM, Blomqvist P, Bertilsson L, Geborek P, Jacobsson LT, et al. Results from a nationwide postmarketing cohort study of patients in Sweden treated with etanercept. Ann Rheum Dis. 2005;64(2):246–52.
31. Senabre-Gallego JM, Rosas-Gómez de Salazar J, Santos-Soler G, Santos-Ramírez C, Sánchez-Barrioluengo M, Salas-Heredia E, et al. Duración del tratamiento con etanercept y razones de discontinuación en una cohorte de pacientes con patología reumática. Reumatol Clin. 2011;7(6):385–8.
32. Aaltonen KJ, Virkki LM, Malmivaara A, Konttinen YT, Nordström DC, Blom M. Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. PLoS One. 2012;14(1):e30275.
33. Ranganathan P, Culverhouse R, Marsh S, Mody A, Scott-Horton TJ, Brasington R, et al. Methotrexate (MTX) pathway gene polymorphisms and their effects on MTX toxicity in Caucasian and African American patients with rheumatoid arthritis. J Rheumatol. 2008;35(4):572–9.
34. Solomon DH, Tonner C, Lu B, Kim SC, Ayanian JZ, Brookhart MA, et al. Predictors of stopping and starting disease-modifying antirheumatic drugs for rheumatoid arthritis. Arthritis Care Res (Hoboken). 2014;66(8): 1152–8.

Manuscript received on 17 September 2014. Revised version accepted for publication on 26 December 2014.

Reacciones adversas a medicamentos asociadas con el uso de fármacos antirreumáticos modificadores de la enfermedad en pacientes con artritis reumatoide

RESUMEN

Este estudio describe las reacciones adversas a medicamentos (RAM) y su incidencia en pacientes con artritis reumatoide y tratados en el sistema de salud colombiano. Se llevó a cabo un estudio retrospectivo de cohortes utilizando la información correspondiente a todos los pacientes con diagnóstico de artritis reumatoide que acudieron a centros especializados de atención de salud de las ciudades de Bogotá, Cali, Manizales, Medellín y Pereira entre el 1 de diciembre del 2009 y el 30 de agosto del 2013. Los casos de RAM se obtuvieron de las historias clínicas y del registro del sistema de farmacovigilancia, y se clasificaron por su frecuencia y el tejido afectado, según la Terminología de Reacciones Adversas de la Organización Mundial de la Salud (WHO-ART). Se obtuvo un total de 949 informes de RAM en 419 pacientes (32,8 RAM por 100 pacientes-año); estos pacientes correspondían a una cohorte de 1 364 pacientes tratados por artritis reumatoide y seguidos durante un promedio de 23,8 meses (± 12,9). La cohorte estaba compuesta principalmente por mujeres (366, 87,4%) y la media de edad era de 52,7 años (± 13,1). El mayor número de casos de RAM se notificó tras el uso de tocilizumab, rituximab e infliximab (28,8, 23,1 y 13,3 notificaciones por 100 pacientes-año, respectivamente). Las RAM notificadas con mayor frecuencia fueron la elevación de los niveles de transaminasas y la dispepsia. En términos generales, 87,7% de las RAM se clasificaron como de tipo A, 36,6% como leves, 40,7% como moderadas y 22,7% como graves. Como consecuencia, 73,2% de los pacientes que presentaron una RAM dejaron de tomar sus medicamentos. La aparición de RAM en pacientes tratados por artritis reumatoide es frecuente, especialmente cuando se utilizan fármacos antirreumáticos de producción biotecnológica. Estos resultados deben ser objeto de estudio en futuras investigaciones y señalan la necesidad de actividades de vigilancia para reducir los riesgos en estos pacientes.

Palabras clave

Artritis reumatoide; efectos colaterales y reacciones adversas relacionados con medicamentos; antiinflamatorios no esteroideos; metotrexato; cloroquina; Colombia.