

Pharmacotherapy Safety Assessment in Patients with Rheumatoid Arthritis Treated in a Regional Health Bahia

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Abstract— Rheumatoid arthritis is an autoimmune disease characterized by affect the joints causing chronic inflammation and premature death in the same. The present study is descriptive / observational and analytical, following a cross-sectional study of the association between a medical conditions (rheumatoid arthritis) of patients treated with synthetic and biological. The invitation to participate in the study was done in the following ways: in person, that is, by approaching the individual at the Regional Health Center of the Southwest Regional Health Center and by telephone, using a list of patients receiving the medicines for treatment of RA in the Specialized Component of Pharmaceutical Care in the NRS-S pharmacy. After the arrival of the individuals, they were referred to a particular room, where explanations were made of every procedure that would be performed and guidelines necessary for their participation in the research. The guests who agreed to participate signed the Free and Informed Consent Form. It was observed that of the 54 patients, only (5.7%) presented alteration in the OGT exam and (7.5%) in the CGT. Regarding the GGT analysis, 52 patients were used because of a loss that occurred during the analytical process, identifying the presence of lesions in 10 individuals, representing (19.2%) of this sample. In summary, (1.9%) of the studied population had creatinine and urea exams above the reference value, that is, characterizing a probable nephrotoxicity. In relation to the hematological cells, it was reported that (9.3%) of the population obtained erythrocytes below the reference value, as well as a decrease in leukocytes in (5.6%) of the population. And finally, the platelets were within the reference value.

According to data obtained in the study, it was possible to identify, in a general way, changes in laboratory tests, independent of the treatments used. Thus, the presence of these reactions' compromises patient safety, providing health risk factors for individuals.

Keywords— Arthritis Rheumatoid, Drug Utilization, Pharmacy.

I. INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by affect the joints causing chronic inflammation and premature death in the same (Oliveira, LM et al., 2015). According to the progression of RA, the evolution of bone erosion, joint deformities, cartilage tissue death, as well as involvement with other extra articular pathologies is noticed. According to data provided by the Brazilian Society of Rheumatology, the estimate of global prevalence for the development of the disease is about 1% of the population, affecting the female sex 2 to 3 times greater than the male (Ribas et al., 2016).

The exact cause that causes the body to develop RA is still not well understood. After studying, it was allowed to expose the risk factors of the development of RA such as: environmental, smoking, alcohol consumption, among other factors (Thakur, S. et al., 2018). Early diagnosis of rheumatoid arthritis is not a very common fact. However, this identification will determine the outcome of this chronic disease, thus resulting in less damage to the body, as well as lower costs in relation to medications that will be used during treatment (Guo, Q. et al., 2018).

The choice of the treatment that will be used by patients with autoimmune diseases is performed through the disease progression profile, which will provide a better choice, promoting therapeutic adherence. With the possibility of innovations of these drugs present in the market, doctors choose the treatment not only observing in costs and benefits, but also in the safety of the individual during the treatment (Mota, H.M.L. et al., 2010).

Gradually, over the years, the improvement of the contributions of the treatment with the use of pharmaceutical immunobiologicals was perceptible. However, it is necessary to observe and analyze the possibilities of the undesirable effects that these drugs can cause to the organism. With the need to promote safety during treatment, the Brazilian Society of Rematology has prepared a document based on review studies, which will provide a more appropriate choice for treatment that will be adopted (Shiratori, A.P. et al., 2013). Pharmacological therapy for RA treatment may include non-steroidal anti-inflammatory drugs (NSAIDs); corticosteroids, disease course modifiers (DMARDS) and biological (Fauci, et al., 2013).

In general, the drug that is recommended in the initial phase of the treatment RA is methotrexate, because according to systematic reviews it is considered safe and effective after the diagnosis of the disease, besides having similarity to the drug leflunomide and superior to other drugs with the same action. (Imm, L. et al., 2018). However, with the complexity of the disease, the use of methotrexate alone does not guarantee an effective clinical response when compared to individuals using combinations of synthetic or biological DMARDS, such as adalimumab, infliximab, golimumab, etanercept and certolizumab (anti- TNF) (Costa, et al., 2015).

However, like any other drug that may cause adverse effects, it is not different from the medicines used to treat RA, so it is necessary to consider the possibilities of developing adverse drug reactions (ADRs) (Mota, LMH et al., 2014). Unfortunately, the pharmacotherapy adopted for regression and control of RA may present adverse reactions idiosyncratic during treatment, causing alterations in liver enzymes and hematological cells, as well as renal failure. The main manifestations are: hepatotoxicity, nephrotoxicity, myelotoxicity, among others (Mota, H.M.L et al., 2013).

Patient safety is a key consideration in the choice of treatment (Kivitz, AJ et al., 2018). Even with all the technology and innovations present in immunobiologicals, the presence of ADRs becomes an unavoidable situation, and an increase in liver enzyme levels may occur; about 1.4% of patients may develop

pancytopenia alone, 0-5% of whom need to stop therapy due to this reaction, as well as altered renal function (Neves, C. et al. 2009). According to the literature, biological drugs are considered safer when compared to synthetic use. (Kivitz, A. et al., 2018) It

is therefore necessary to observe and perform laboratory tests to prevent and control the damages that can cause to the human organism, verifying if treatment is being safe (Mota, L.M.H et al., 2012), since several factors can develop ADRs in individuals, such as: gender, age, gender, people using multiple medications, among others. Depending on the organism the reaction may trigger more discreetly the more aggressive (Bagatini, F. et al., 2011). Therefore, this study aims to evaluate the safety of pharmacotherapy used by patients with RA, through the evaluation of laboratory tests that assess renal, hepatic and hematological function, correlating with the type of treatment (synthetic and biological DMARDS) of patients with arthritis rheumatoid.

II. METHOD

The present study is descriptive / observational and analytical, following a cross-sectional study of the association between a medical condition (rheumatoid arthritis) of patients treated with synthetic and biological DMARDS.

Bahia has nine Regional Health Centers (NRS), whose purpose is to monitor the activities of regulation, sanitary surveillance and dispensing of medicines, among others. The NRS-Southwest, has a seat in the city victory of the Conquest, which has the responsibility and duty to serve 74 municipalities, serving about 1,812,416 inhabitants. The headquarters of the NRS-Southwest meets the demands of the Pharmaceutical Assistance that are the responsibility of the State, referring to the 19 municipalities that make up the micro-region of Vitória da Conquista (669,396 inhabitants). The population to be studied are patients with RA, who receive their pharmacotherapy through the specialized component of pharmaceutical care (CEAF) in this region.

The invitation to participate in the study was done in the following ways: in person, that is, by approaching the individual at the Regional Health Center of the Southwest Regional Health Center (NRS-S) and by telephone, using a list of patients receiving the medicines for treatment of RA in the Specialized Component of Pharmaceutical Care (CEAF) in the NRS-S pharmacy. After the arrival of the individuals, they were referred to a particular room, where explanations were made of every procedure that would be performed and guidelines necessary for their participation in the research. The

guests who agreed to participate signed the Free and Informed Consent Form.

The collection was carried out through the application of questionnaires, in which the volunteers answered two questionnaires, the first one that addressed more personal issues, such as: habits; frequency of medication use; how the therapy was administered, and the other about rheumatology questions. Afterwards, these participants were referred to the Central Laboratory of Vitória da Conquista, where the laboratory tests were performed, as well as the volunteers were submitted to a dental consultation in a specialized center. The research was evaluated in the year 2017 in the period from November to December.

The study was carried out with 54 patients who were enrolled in the (NRS-southwest), aged over 18 years; individuals of both sexes; diagnosed with RA (CIDs M05.0, M05.3, M05.8, M06.0, M06.8, M05.1, M05.2 and M08.0). The exclusion criteria used were bedridden individuals; hospitalized and aprisonado 15 used a therapy with biological DMARDs and 37 used synthetic DMARDs.

The data provided were taken from the project "Evaluation of the effect of treatment with biological or synthetic DMARDs on the periodontal condition in patients with rheumatoid arthritis." The project was approved by the Ethics Committee of the Faculdade Independente do Nordeste-FAINOR and by the consent of the Regional Center of the Southwest, presentations 466/12, 580/18 of the National Health Council for research on human beings (Brazil, 2012). Approved by Opinion No. 1,362,253, CAAE: 72679117.5.0000.5578.

In this study, the laboratory test was considered as a dependent variable, and the results were compared with the reference values available in the Manual of Support to the SUS Managers: Organization of the Network of Clinical Laboratories (BRASIL, 2002) and the explanatory variables were used the sociodemographic characteristics, being evaluated as follows: gender, age,

marital status, occupation, type of treatment used by the individuals, ie whether it was synthetic or biological DMARDs, in which an assessment will be made for check which one promotes greater security.

In this study, hepatotoxicity was considered when patients presented values higher than 40 IU / L in the AST exams/ TGO and ALT / TGP and as well as values above 51 IU / L for the GGT examination. Already for the occurrence of nephrotoxicity, the urea would have to present values above 51 IU / L and the creatinine above 1.3 mg / dL. For the eventuality of myelotoxicity, the blood count would have to present the leucopenia, thrombocytopenia and anemia, that is, the values of references below normal. Hemocytes below 3.9 million / μ L for women, 4.2 million / μ L for men; leukocytes below 4000 μ L and platelets below 140,000 μ L; for both sexes.

For the statistical analysis, an electronic spreadsheet was used in Excel, in the 2010 Microsoft® version, in which all the data referring to the questionnaire as well as the laboratory results were added. Subsequently, for the descriptive analysis, frequency comparison and Chi-square test, all data for the statistical Epi-Info program using version 7.1.5.2 were adopted, adopting a 5% level of significance. The univariate analysis was then performed.

III. RESULTS AND DISCUSSION

Table 1 shows the sociodemographic characteristics, and it was observed that individuals with RA have a prevalence of 83.3% in the female sex, with the age group from 19 to 84 years old, the corresponding average being 50.8 years; with predominance of brown color (50.0%); (44.4%) of the respondents had the highest percentage of incomplete elementary education, (79.6%) of the participants living in urban areas, (63.4%) with salary income of up to one salary, most interviewees were married individuals (64.8%); (51.9%) have worked and are no longer working.

Table 1: Descriptive analysis of the population studied to evaluate the safety of pharmacotherapy in patients with rheumatoid arthritis treated in a health region of Bahia, Brazil, 2017.

Variables	Nº	(%)	Variables	Nº	(%)
Sex			HigherEducationCompleteness	2	3.7
Male	9	16.0	HigherEducationIncomplete	1	1.9
Female	45	83.3	TechnicalEducation	2	3.7
Age			NotLiterated	3	5.6
19-29	2	3.8	Do notknow	1	1.9
30-39	4	7.6	Income²		
40-49	12	22.4	Upto 1 salary	34	63.4
50-59	26	48.2	More than 1 salary	20	36.6
> = 60	10	18.5	Occupation		

Marital status			Already worked but no longer working	28	51,9
Married	35	64.8	Neverworked	9	16.7
Divorced	4	7.4	Currentlyworking	14	25.9
Single	10	18.5	Not working, butnotcurrently	3	5.6
Widowed (a)	5	9.3	Participants' background		
Color¹			Rural area	43	79.6
White	21	38.9	Urbanarea	11	20.4
Black	5	9.3	Smoking		
Yellow	0	0	I do not smoke now	50	92.6
Brown	27	50.0	Yes, daily	4	7.4
Indigenous	0	0	Practice of physical activity ca		
Notanswered	1	1,9	Notpractical	31	57,4
Levelofeducation			Yes	23	42,6
Complete ElementarySchool	3	5,6	Treatment		
ElementarySchoolIncomplete	24	44.4	Synthetic	37	68,5
High School Complete	9	16.7	Biological	15	31.5
SecondaryEducationIncomplet	9	16.7			
e					

Source: Research data (2017).

- 1- Standard used according to IBGE.
- 2- Minimum wage equivalent to the year 2019.

This result is confirmed by other studies, affecting about three to four times the female sex, a fact explained by the hormonal issues (Azevedo, et al., 2015). Since it can affect adult life well in the productive phase, which can cause serious consequences, since normally after 10 years of illness, these carriers will be unable to carry out the work. (Silva, J. R.C., 2015). Since, aging is a major risk factor for the development of RA (Thakur, S. et al., 2018)

According to data presented in the table (92.6%) of the participants denied the act of smoking and (57,4%) do not practice physical activity. Thus, it prevents disease progression since the smoking act is considered a risk factor for the development of RA, its long-term use causes complications to the organism in the carriers of this disease (Thakur, S. et al., 2018). In relation to the lack of physical exercises is explained due to the progression of the disease, since it causes strong joint pains, redness, swelling, as well as limiting amplitude of movements (Guo, Q. et al., 2018).

According to the analysis obtained, the most prevalent treatment was the use of synthetic DMARDs. Results are confirmed according to the obtained studies, in which the management of RA, monotherapy with MTX is recommended in the first months, but in case of failure the therapy is suggested a combination with other

DMARDs aiming to provide an adequate response to treatment when compared to using MTX alone(Weinbla, M.E et al., 1999).

If the organism cannot control the progression of the disease, an evaluation will be made to prescribe biological DMARDs. It is extremely important to start treatment with synthetic DMARDs, thus avoiding the unnecessary use of biologicals since they are more expensive, but also more effective. For the management responsible for this treatment takes into account the cost-effectiveness analysis (Romão, V.C et al., 2013).

In Table 2, it was observed that of the 54 patients, only (5.7%) presented alteration in the OGT exam and (7.5%) in the CGT. Regarding the GGT analysis, 52 patients were used because of a loss that occurred during the analytical process, identifying the presence of lesions in 10 individuals, representing (19.2%) of this sample. In summary, (1.9%) of the studied population had creatinine and urea exams above the reference value, that is, characterizing a probable nephrotoxicity. In relation to the hematological cells, it was reported that (9.3%) of the population obtained erythrocytes below the reference value, as well as a decrease in leukocytes in (5.6%) of the population. And finally, the platelets were within the reference value.

Table 2: Descriptive analysis of the type of lesion found to evaluate the safety of pharmacotherapy in patients with rheumatoid arthritis treated at a health center in Bahia Victoria achievement of Brazil, 2017.

Exam	No.	(%)	Exam	No.	(%)
AST			Urea		
Injury	3	5.7	Injury	1	1.9
Normal	50	94.3	Normal	52	98.1
SGPT			Erythrocytes		
Injury	4	7.5	Injury	5	9.3
Normal	49	92.5	Normal	49	90.7
GGT			Leukocytes		
Injury	10	19.2	Injury	3	5.6
Normal	42	80.8	Normal	51	94.4
Creatinine			Platelets		
Injury	1	1.9	Injury	0	0
Normal	53	98.1	Normal	54	100

Source: Research data (2017).

In order to assess the causality of liver damage due to the use of medications, it is necessary to make a consideration regarding the clinical evaluation as well as the chronological aspects regarding the treatment, since the TGO and GGT enzymes are normally present in several tissues, or (Larrey, D. et al, 2000). Therefore, if the TGO and GGT values are altered it does not mean that the treatment caused a hepatic injury, then it needs a clinical evaluation and the request of exams to investigate this change. However, when it comes to the increase in TGP, interpretation of this alteration is different, since this test is considered a specific marker of the liver, since the enzyme is found in this tissue (Tajiri, K. et al, 2008).

For the analysis of the occurrence of hepatotoxicity, it is essential to obtain an evaluation of the hepatic markers, in which they will be found higher than their reference values, therefore, that the occurrence of hepatotoxicity induced by pharmacotherapy was defined through the set of the alterations of the enzymes TGO, TGP and GGT. Taking into account the results of this research, it is noted that only one patient had alteration of these three enzymes, and one of the drugs used by this patient was DMARD methotrexate. According to Bittencourt (2011), the manifestations of hepatic lesions caused by the treatment is 12% for the use of MTX and unfortunately in Brazil no epidemiological data on the injuries caused by the use of drugs were found.

For Neves et al. (2009), it is considered that nephrotoxicity is another important point to be evaluated, since the treatment of RA can cause a renal toxicity, which can cause a reduction of the glomerular filtration rate, consequently increasing the levels of urea and creatinine in the organism. Therefore, elderly patients or those with some renal dysfunction need to have a greater therapeutic control, since they are more likely to have

nephrotoxicity. Comparing to this study, it is noticed that only one patient had altered creatinine and another individual had a change in the urea test, thus confirming with the literature, renal function alteration occurred, even though the result was statistically low.

When it comes to the adverse effects of hematological cells, five patients were altered erythrocytes (9.3%) and three with leukocytes (5.6%) outside the reference value and only platelets were unchanged. Compared with the literature, the author Hernandez-Baldizon, S. (2012) reports that the alterations may vary according to each study, but normally in the treatment of RA, the leukocytes decrease in a discrete form, as well as erythrocytes and platelets, characterizing a pancytopenia. It is important to note that this pancytopenia can occur at any stage of treatment. According to the study, only platelets were within the reference value, this fact is explained due to the incidence of only 3% to 11% of the population (Neves, C. et al., 2009).

Table 3 shows the type of lesion found in patients using synthetic or biological treatment, through alterations in laboratory tests. When correlating the type of medication that used with the laboratory changes did not present statistically significant association since the value of p was greater than 0.05. With the evaluation of the data, it can be seen that both the synthetic and biological treatments present the same risks to develop lesions. However, when correlating the types of treatments there was no significant statistical result, that is, thinking about the safety of both the synthetic and the biological patients has the same chance of developing any lesion in the body of the individuals that make use of this pharmacotherapy.

Table 3: Univariate analysis to correlate lesion with synthetic and biological treatment in patients with rheumatoid arthritis treated at a health center in Bahia of Vitoria da Conquista, Brazil, 2017.

Variables	Synthetic	(%)	Biological	(%)	p -value
TGP					
Injury	3	8.3	1	5.9	0.40
Normal	33	91.7	16	94.1	
TGO					
Injury	2	5.6	1	5.9	0.46
Normal	34	94.4	16	94.1	
GGT					
Injury	6	16.7	4	25	0.25
Normal	30	83.3	12	75	
Creatinine					
Injury	1	2.7	0.	0	0.34
Normal	36	97.3	17	100	
Urea					
Injury	0	0	1	6.3	0.15
Normal	37	100	15	93.8	
Erythrocytes					
Injury	4	10.8	1	5.9	0.31
Normal	33	89.2	16	94.1	
Leukocytes					
Injury	3	8.1	0	0	0 , 15
Normal	34	91.9	17	100	
Platelet					
Injury	37	100	17	100	---
Normal	37	100	17	100	

* Association statistically significant ($p < 0.05$).

In general, the use of pharmacotherapy can cause serious damage to the body, which will compromise patient safety. With the evaluation of the prescriptions and the complementary tests can help in the identification of the ADRs coming from the treatment. It is important to point out that there are other factors that must be taken into account as the processes of transformation at both physiological and pharmacological levels (Taniguchi, C., 2014).

According to Bittencourt (2012), hepatotoxicity is one of the most common manifestations that occurs through the use of drugs, based on data from the World Health Organization, since 1963, more than three million cases have already been reported, this fact is characterized by the increase of the liver enzymes, among other manifestations. The adverse reactions that cause

hepatotoxicity are the most frequent causes for the suspension of new molecules made by the industries, but it is also the most common reason for the withdrawal of the drug from the market due to its adverse reactions.

In this study, patients who used synthetic DMARDs showed changes in liver enzymes, with alterations in (8.3%) in the TGP test, (5.6%) in the ORT and (16.7%) in the GGT study population, so this result may cause the risk of developing hepatotoxicity in individuals, this fact characterizes a common adverse reaction in this type of treatment. For this reason, it is recommended to monitor the serum levels of the TGO, GGT and TGP. According to the literature, the incidence of hepatotoxicity is found in 22% of the individuals who use this pharmacotherapy. Regarding the use of the biological drugs obtained in this study, it was observed

that the SGT and PGT exams occurred in only (5.9%) of the study sample and (25%) in GGT, thus, hepatotoxicity, on the other point of view, reports that treatment using biologicals is considered more rare, since GOT and GGT are not specific liver exams. Therefore, it is important to report that the majority of reports of hepatic changes in the use of biologicals have a higher frequency in the treatment using infliximab (Toscano, AE et al., 2009).

Regarding the liver enzyme alterations present in this study, it is considered a mild transaminitis, since the Upper Limit of Normality (LSN) was lower than 3 times when compared to other studies (Katchamart, W., 2009). Although not being evaluated in this study, it is important to note that the treatment discontinuation rates that cause hepatotoxicity are very small (Curtis Jr et al., 2010).

Although the increase in transaminases is the common theme in scientific research, it is important to note that the drugs used in RA also cause nephrotoxicity, causing serious damage to the human body. According to the data obtained, there is a small change in the analyzed samples in which the creatinine and urea tests were above the reference value. According to Martins, GA, (2004), the occurrence of nephrotoxicity is considered rare, since this reaction occurs in only 2% of all the population that treats with synthetic DMARDs. Confirming with the result found in the research, creatinine alteration was observed in (2.7%) of the study population.

Even though the possibility of an individual developing a renal lesion is small, this fact does not justify that this treatment is safe, since the high dosage of MTX results in renal insufficiency, such as nephrotoxicity of any degree. Thus, it is necessary to monitor renal function before and during treatment (Wiczer, T. et al., 2015). According to the study, it was noticed that in the use of biological tests, the urea test was predominant in (6.3%) of the studied sample and for the creatinine test, the results were within the reference value. Therefore, this low incidence of nephrotoxicity is confirmed by the literature because the biological drug etanercept has been considered the safest drug in the treatment of RA when renal toxicity is treated, since it has fewer adverse reactions when compared to other DMARDs (Sugioka, Y. et al., 2008)

According to the evaluation of the treatment, it was noticed that the synthetic DMARDs caused haematological alterations, observed through the hemogram. Five of the patients had anemia (10.8%) of the study population and (8.1%) had leukopenia. Regarding the amount of platelets were within the reference values. According to the literature, synthetic DMARDs, even using combinations with other medicinal products, remain causing small adverse effects, such as hematological and

hepatic abnormalities (Bird, P. et al., 2013). Certainly, the hemogram needs to be requested to monitor hematological changes (Lee, S.W et al., 2012).

According to Mota, LMH et al (2014), hematological alterations such as pancytopenia are rarely described in the use of biological DMARDs therapy. Although there are some recommendations of the Brazilian Society of Rheumatology for the evaluation of hematological levels during treatment. Leukopenia, is considered one of the abnormalities that are normally found during the treatment using biological, although in a low amount, the red blood cells and platelets are less common to evidence some alteration. Note that the literature is confirmed by the study evaluated, since only one patient had a change in the blood count.

Previous studies have shown evidence that using biological DMARDs are considered safer than using monotherapy such as methotrexate (Kivitz, A. et al., 2018). Thus, Burmester, G.R et al. (2017), demonstrated that MTX therapy combined with anti-TNF provides a better response to treatment and safety to individuals.

According to literature, comparing the use of synthetic and biological DMARDs has shown that the treatment provides a regression of the evolution of the disease, thus improving the quality of life of the individual (Mota; Laurindo; Santos Neto., 2010). Regarding safety, pharmacotherapy used in RA provides risk factors associated with the appearance of ADRs in rheumatologic patients, despite the therapeutic benefits (Chopra, A. et al., 2015).

This result made it possible to obtain data and information to evaluate the safety of the pharmacotherapy used. However, there was a considerable loss during the analysis of the research because many of the participants did not perform the laboratory tests, nor did they respond correctly to the forms.

IV. CONCLUSION

According to data obtained in the study, it was possible to identify, in a general way, changes in laboratory tests, independent of the treatments used (synthetic and biological DMARDs). Thus, the presence of these reactions compromises patient safety, providing health risk factors for individuals.

It is important to point out that there were limitations in this study, with a small sample of individuals belonging to the regional board of the interior of Bahia. It can be verified that there were no evolution or severity assessments regarding the disease in the study, being considered an important point to be analyzed, since the individuals that use pharmacotherapy for RA may have worsening of the disease since the treatment

promotes adverse reactions.

This study highlights results on the assessment of the safety of RA patients, through access to laboratory tests, as a tool in pharmacotherapy, as it can cause serious damage to the body, and the results of laboratory tests can be evaluated to aid in the identification of some pathology.

The data found indicate a need to develop new studies within this same alignment. However, the use of synthetic and biological DMARDs has demonstrated that the treatment provides the improvement of the disease. In view of this, it is believed that these laboratory indicators may be useful for other researchers and in clinical practice, in order to increase the safety of the treatments instituted.

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