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Adverse drug reactions associated with treatment in patients with chronic rheumatic diseases in childhood: a retrospective real life review of a single center cohort

Manar Amanouil Said*, Liana Soido Teixeira e Silva, Aline Maria de Oliveira Rocha, Gustavo Guimarães Barreto Alves, Daniela Gerent Petry Piotto, Claudio Arnaldo Len and Maria Teresa Terreri

Abstract

Background: Adverse drug reactions (ADRs) are the sixth leading causes of death worldwide; monitoring them is fundamental, especially in patients with disorders like chronic rheumatic diseases (CRDs). The study aimed to describe the ADRs investigating their severity and associated factors and resulting interventions in pediatric patients with CRDs.

Methods: A retrospective, descriptive and analytical study was conducted on a cohort of children and adolescents with juvenile idiopathic arthritis (JIA), juvenile systemic lupus erythematosus (JSLE) and juvenile dermatomyositis (JDM). The study evaluated medical records of the patients to determine the causality and the management of ADRs. In order to investigate the risk factors that would increase the risk of ADRs, a logistic regression model was carried out on a group of patients treated with the main used drug.

Results: We observed 949 ADRs in 547 patients studied. Methotrexate (MTX) was the most frequently used medication and also the cause of the most ADRs, which occurred in 63.3% of patients, followed by glucocorticoids (GCs). Comparing synthetic disease-modifying anti-rheumatic drugs (sDMARDs) vs biologic disease-modifying anti-rheumatic drugs (bDMARDs), the ADRs attributed to the former were by far higher than the latter. In general, the severity of ADRs was moderate and manageable. Drug withdrawal occurred in almost a quarter of the cases. In terms of risk factors, most patients who experienced ADRs due to MTX, were 16 years old or younger and received MTX in doses equal or higher than 0.6 mg/kg/week. Patients with JIA and JDM had a lower risk of ADRs than patients with JSLE. In the multiple regression model, the use of GCs for over 6 months led to an increase of 0.5% in the number of ADRs.

Conclusions: Although the ADRs highly likely affect a wide range of children and adolescents with CRDs they were considered moderate and manageable cases mostly. However, triggers of ADRs need further investigations.

Keywords: Autoimmune rheumatic diseases, Pharmacosurveillance, Adverse drug reactions, Biological agents, Childhood

* Correspondence: manarmanar2@yahoo.com
Division of Pediatric Rheumatology, Department of Pediatrics, Federal University Sao Paulo (Unifesp), Rua Borges Lagoa, 802, Sao Paulo ZIP CODE: 04038-001, Brazil

Background

According to the World Health Organization (WHO), an adverse drug reaction (ADR) is any unfavorable and unintentional reaction due to the use of a medication in a normal dose used in humans for prophylaxis, diagnosis, or treatment of diseases or to modify a physiological function [1]. ADR is the sixth leading cause of death worldwide. Therefore, monitoring ADRs is vital to prevent their detrimental consequences among patients [1, 2].

Chronic rheumatic diseases (CRDs) are inflammatory diseases arising from changes in the immune system, and their symptoms involve joints and other organs. CRDs treatment includes synthetic or biological disease-modifying anti-rheumatic drugs (sDMARDs or bDMARDs) and these medications can cause several ADRs, ranging from mild to severe that may require other medications to treat the ADR, dose reductions or even suspending the suspected medication [3–5]. Severity and frequency of ADRs depend on the dose, route of administration and length of use, in addition to the presence or absence of other risk factors [6, 7].

Most studies that have examined the safety of medications were restricted to a few years of follow-up or were performed in a cross-sectional way. Registering ADRs and associated risk factors, particularly in chronic diseases, is essential for the health team to select the best procedures and to help with pharmacosurveillance. These data can be used to predict the ADRs in children and adolescents with CRDs. A better understanding of the ADRs of each medication used to control chronic diseases leads to better treatment adherence and thereby to a better prognosis.

The objective of this study was to evaluate the frequency, severity and associated factors of ADRs in children and adolescents with CRDs and to estimate the medical decisions made as a result of these events during treatment in a cohort of pediatric patients with juvenile idiopathic arthritis (JIA), juvenile systemic lupus erythematosus (JSLE) and juvenile dermatomyositis (JDM) at a tertiary medical center in Sao Paulo.

Methods

This was a descriptive and retrospective observational cohort that included children and adolescents with JIA, JSLE and JDM, who were diagnosed according to the classification criteria for their diseases [8–10]. This center serves approximately 2000 patients with rheumatic diseases a year. A total of 622 medical records were evaluated (391 JIA, 162 JSLE and 69 JDM).

Patients were included if they were up to 16 years old for patients with JIA and up to 18 years old for patients with JSLE or JDM at the first medical attendance in the center, according to the published criteria for the diseases [8–10]; if they were 21 years old or younger at the last follow-up visit; and if they had been seen in the pediatric unit for at least six months from January 1st 1985 until December 31st 2016.

The exclusion criteria were: patients taking higher doses of medication than prescribed; patients who were not treated or were only treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or analgesic drugs, due to the irregular length and dosis of use, making data difficult to evaluate; patients with more than one CRDs that could present symptoms or complications that could interfere with the data interpretation; and patients without enough data.

Data collection

The study included all the ADRs attributed to the listed drugs in the selected patients, whether or not reported to the Brazilian Health Surveillance Notification System (NOTIVISA). The data were collected at the baseline: sex, age at disease onset, the incidence of ADRs, last follow-up visit and last consultation, medications utilized to treatment besides their dose, route of administration, length of treatment, previous and current drugs at the occurrence of ADR.

The ADRs registered by the specialized physicians during the routine medical appointments and observed in the medical record were coded and analyzed with the causative drug. The data were compiled into a standard questionnaire for each disease and each medication separately.

ADRs definitions and characterizations

This study adopted the cited WHO definition of adverse drug event. The causality of ADRs was defined as "the connection between the appearance of ADRs and the drug utilization. It requires solid medical judgment based on observations of its onset and patient's status" [1].

The analysis adopted the expert judgment made by a panel of pediatric rheumatologists at that center [11, 12]. In addition, the majority of the patients used various medications combined together to control the disease. To attribute an ADR to a specific drug the following roles were used: if the ADR appeared after using the drug, lasted as long as the drug was used; were no longer observed after if that drug was withdrawn. In case of use of more than one drug, the causality of ADRs was based on previous knowledge from the literature and the judgement of the attending physician.

According to the CTCAE (Common Terminology Criteria for Adverse Events), the severity of ADRs was classified as mild when patients did not need an intervention; moderate when patients needed an intervention; serious when patients required hospitalization or caused an inability or limited ability to perform daily

activities; life-threatening when patients needed immediate intervention; and fatal if they resulted in the death of the patient directly or indirectly [13].

All of the procedures to address ADRs were evaluated: medication withdrawal by the patient or by his (her) physician, a reduction in the dose, change in the route of administration, an introduction of another treatment for the ADR or patient education.

The study was approved by the Research Ethics Committee of the Federal University of Sao Paulo. As it was a retrospective observational study, the requirement for informed consent and assent was waived. However, the confidentiality and anonymity of the patients were guaranteed once the name and other personal data in the records were sheltered.

Statistical methods

Initially, all the data were stored in Excel into two tables: conventional treatments with sDMARDs and bDMARDs. To detect risk factors associated with the ADRs, the statistical analysis concerned a main used drug and the most causative of ADRs as well. For categorical variables, absolute and relative frequencies were presented and for numerical variables, measures (mean, minimum, maximum and standard deviation) or median were used. The existence of association between two categorical variables was verified using the Chi-square test and Fisher's exact test in cases of small samples. The comparison of means between two groups was performed using the nonparametric Mann-Whitney test.

Only methotrexate (MTX) and glucocorticoids (GCs) were analyzed separately. To evaluate the effect of sex, age, disease type, dosage and administration route on the occurrence of ADRs due to MTX use, a logistic regression model was applied. To access the effect of disease (JIA, JDM, JSLE) adjusted by dose, time of use and the form of application of the medications (MTX and GCs) on the number of ADRs attributed to them (dependent variable) we used the model of Poisson multiple regression. Models were adjusted separately for each medication. For all analysis, the statistical software SPSS 20.0 was used; for all statistical tests, a significance level of 5% was adopted.

Results

Patients characteristics

After applying the exclusion criteria, a total of 547 patients were evaluated (334 patients with JIA, 151 with JSLE and 62 with JDM). Of these patients, 389 (71.1%) experienced ADRs, including 220 with JIA (65.9% of JIA), 131 with JSLE (86.7% of JSLE) and 38 with JDM (61.3% of JDM), with a total of 949 ADRs (mean 1.7 ADRs per patient).

The patients mean age was 7.9 ± 2.5 years at disease onset and 17.9 ± 1.5 years at last evaluation; the mean disease duration at follow-up was 8.0 ± 1.4 years, and 72.6% were females.

A minority (7.6%) of the patients was treated in monotherapy with MTX, GC or HCQ. The majority was treated with at least two drugs.

ADR characteristics

In total, there were 33 serious events, 604 moderate events and 310 mild events. In addition, there were two cases (0.2%) of life-threatening anaphylaxis after using infliximab (IFX). Allergic skin reactions occurred in 2 of 27 patients treated with intravenous immunoglobulin (IVIG) during infusion.

MTX was responsible for 29.4% of moderate ADRs, 12.5 and 0.6% of mild and severe cases, respectively. GCs caused 18.2, 15.1 and 0.7%, of moderate, mild and severe ADRs, respectively. The Fig. 1 illustrates the severity of ADRs of the medications.

MTX and GCs were the main used drugs among the patients. According to Table 1, more than 60% of the patients who utilized MTX suffered from ADRs; followed by GCs as a second used drug and causative drug of ADRs as well, especially Cushing Syndrome. One JDM patient presented vertebral fracture and one JIA patient presented osteonecrosis. In terms of cyclophosphamide (CPA), notwithstanding it was used by a few patients, it caused ADRs in approximately 40% of them.

Out of 165 patients (with JIA, JDM and SJLE patients) treated with bDMARDs, 30 (18.2%) suffered from ADRs. Among 33 cases of ADRs, 33.3% were caused by etanercept (ETN); 33.3% by infliximab (IFX) and 24.2% by adalimumab (ADA). The principal ADR was pain/local reaction due to the injection of the bDMARDs. Table 2 shows all ADRs of the bDMARDs.

Infections were present in 45 cases among all the patients of the study; almost 45% were using MTX, 51% using other sDMARDs and two patients treated with the bDMARDs. The most of those infections were upper respiratory tract infections, herpes-zoster and cellulitis. Table 3 illustrates data on the ADRs as a dependent variable; age, dose, admissions and the use of MTX were screened into multivariate analysis. The median length of MTX use in patients who had ADRs was 35.5 months. There was no predicted time for the incidence of ADRs due to the use of MTX. The significant factors associated with the incidence of ADRs were the younger age, higher dose and the disease type.

Regarding the GCs, the median length of GCs use in patients who had ADRs was 28.0 months. ADRs due to GCs appeared after a median of 6.5 months. We observed that the dose of GCs was higher in patients with

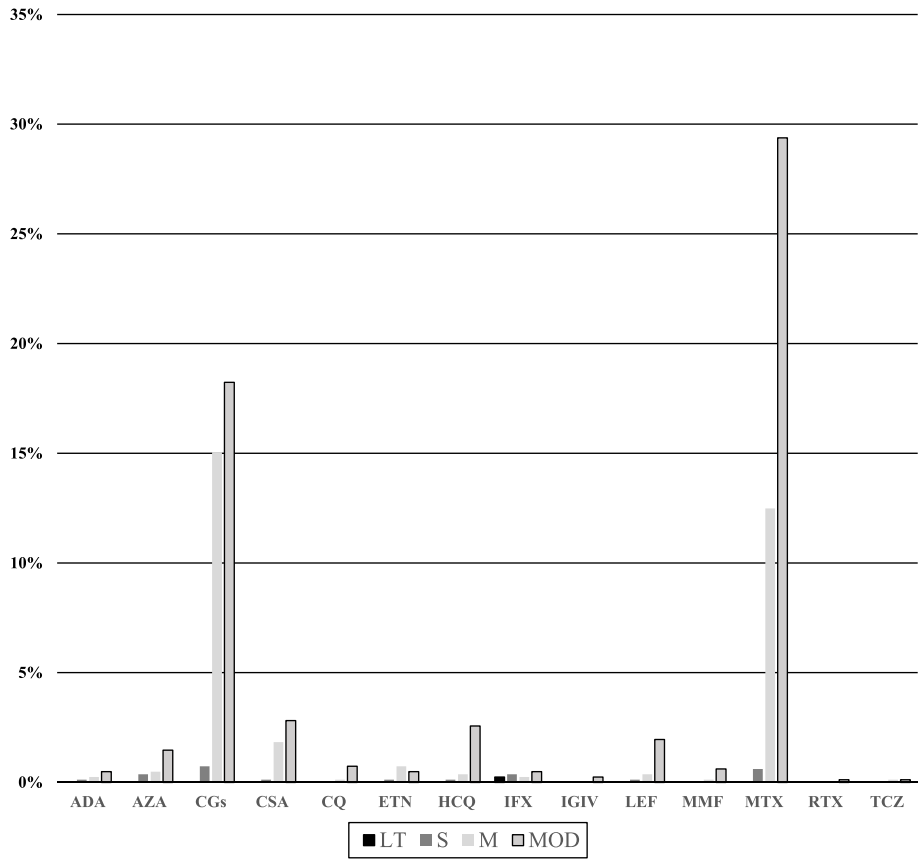

Fig. 1 Frequency and severity of adverse drug reaction. Frequency and severity of ADRs of medication used in patients with JIA, JSLE, and JDM. The vertical axis shows the percentage of adverse drug reactions of each medication. The horizontal axis shows the degree of severity of adverse drug reaction. ADR – adverse drug reaction. JIA – juvenile idiopathic arthritis. JSLE – juvenile systemic lupus erythematosus. JDM – juvenile dermatomyositis. LT – life threatening adverse event; S – severe adverse drug reaction; M – mild adverse drug reaction; MOD – moderate adverse drug reaction. % - percentage. ADA – adalimumab. AZA – azathioprine. CPA – cyclophosphamide. GCs – glucocorticoids. CSA – cyclosporine. CQ – diphosphate chloroquine. ETN – etanercept. HCQ – hydroxychloroquine. IFX – infliximab. IVIG – intravenous immunoglobulin. LEF – leflunomide. MMF – mycophenolate mofetil. MTX – methotrexate. RTX – rituximab. TCZ – tocilizumab

JDM than in patients with JSLE and JIA ($p = 0.001$). The patients with JSLE used GCs longer than patients with JIA ($p = 0.042$). Table 4 shows the characteristics of patients presented ADRs attributed to GCs. Females, younger age, patients with JSLE who used high doses of GCs demonstrated more ADRs.

Table 5 illustrates data on the risk factors associated with the ADRs. We observed that the odds ratio for experiencing an ADR in response to MTX in patients who were 16 years old or younger was 9.7-times higher than that in older patients. Additionally, patients who received MTX subcutaneously showed an odds ratio for experiencing an ADR that was 2.1 times higher than those who received MTX only orally. Higher doses of MTX were associated with the use of subcutaneous administration and with JIA. In addition, patients with JDM showed an odds ratio for experience an ADR that was 60% lower than patients with JIA; no differences in the odds ratio among patients with JSLE and JIA were observed.

Patients with JIA and JDM showed odds ratios for experiencing an ADR that was 97 and 95% lower, respectively than patients with JSLE. In detail, the covariate analysis was multiple regression. There was no association between the number of ADRs in response to MTX ($p = 0.441$) and GCs ($p = 0.718$) and the diseases.

ADRs managements

In terms of the treatments for the ADRs, in 26.1% of the patients, other medications were introduced to minimize the ADRs, such as omeprazole, ranitidine, ondansetron and metoclopramide. Additionally, antibiotics and antiviral agents were indicated in cases of bacterial and viral infections, respectively.

Table 1 ADRs of glucocorticoids and synthetic DMARDs in patients with JIA, JSLE and JDM

Medications									
	GCs	**MTX**	**LEF**	**HCQ/CQ**	**CSA**	**MMF**	**AZA**	**CPA**	**TOTAL**
Patients on MED	339	398	86	271	92	29	115	75	1405
Patients on MED with ADR	151	252	18	30	31	5	17	34	538
Patients on MED with ADR(%)	(44.5)	(63.3)	(20.9)	(11.1)	(33.7)	(17.2)	(14.8)	(45.3)	(38,3)
Infections	9	20	–	2	3	2	5	2	43
Blood and lymphatic system disorders:									
- Persistent anemia	–	1	–	–	–	–	–	–	1
- Leukopenia/Lymphopenia	–	–	–	–	–	–	6	4	10
- Pancytopenia/Neutropenia	–	–	–	–	–	–	1	–	1
Immune system disorders:									
- MAS	–	–	1	–	–	–	–	–	1
Endocrine disorders:									
- Cushing syndrome	122	–	–	–	–	–	–	–	122
- Obesity	3	–	–	–	–	–	–	–	3
Metabolism and nutrition disorders:									
-Osteoporosis*/ Low bone mineral density	51	9	–	–	–	–	–	–	60
Nervous system disorders:									
- Chronic headache/dizziness/discomfort	8	32	0	1	–	2	–	4	47
- Pseudotumor cerebri	2	–	–	–	–	–	–	–	2
-↓ convulsive threshold	–	–	1	–	–	–	–	–	1
Eye disorders:									
- Glaucoma	2	–	–	–	–	–	–	–	2
- Cataract	19	–	–	–	–	–	–	–	19
- Maculopathy	–	–	–	16	–	–	–	–	16
- Blurred vision	–	1	–	–	–		–	–	1
Cardiovascular disorders:									
- Arterial hypertension	42	–	–	–	3	–	–	–	45
- Arrhythmia	–	–	–	1	–	–	1	–	2
- Edema	4	–	–	–	–	–	–	–	4
Gastrointestinal disorders:									
- Nausea/vomiting	10	199	4	6	17	–	2	28	266
- Epigastric/abdominal pain	7	73	2	2	6	–	2	1	93
- Diarrhea	–	8	–	1	–	2	–	–	11
- Hyporexia	–	7	–	–	1	–	–	–	8
- Constipation	–	1	–	–	–	–	–	1	2
Hepatobiliary disorders:									
- ↑ liver enzymes	2	68	7	1	1	–	5	1	85
- Hepatic steatosis	1	–	–	–	–	–	–	–	1
- Jaundice	–	–	1	1	–	–	–	–	2
Oral disorders:									
- Mouth ulcers	–	3	1	–	–	–	–	–	4
- Mucositis	–	3	–	–	–	–	–	–	3
- Gingival hyperplasia	–	–	–	–	2	–	–	–	2
Skin and subcutaneous tissue disorders:									

Table 1 ADRs of glucocorticoids and synthetic DMARDs in patients with JIA, JSLE and JDM *(Continued)*

Medications									
	GCs	**MTX**	**LEF**	**HCQ/CQ**	**CSA**	**MMF**	**AZA**	**CPA**	**TOTAL**
- Striae	3	–	–	–	–	–	–	–	3
- Atopic dermatitis	–	–	–	1	–	–	–	–	1
- Alopecia	–	5	4	–	–	–	1	10	20
- Hypertrichosis	–	–	–	–	7	–	–	–	7
- Urticaria	4	5	1	2	2	–	–	–	14
Musculoskeletal and connective tissue disorders:									
-↑ muscle enzymes	–	–	–	1	–	–	–	–	1
- Myositis	–	–	–	1	–	–	–	–	1
- Myalgia	3	–	–	–	–	–	–	–	3
Renal and urinary disorders:									
-↑ urea	–	–	–	–	1	–	–	–	1
General disorders and administration site conditions:									
- Infusion reactions and pain	3	4	–	–	–	–	–	–	7
Total number of ADRs	295	439	22	36	43	6	23	51	915

ADR - adverse drug reaction, DMARDs - disease modifying antirheumatic drugs, JIA - juvenile idiopathic arthritis, JSLE - juvenile systemic lupus erythematosus, JDM - juvenile dermatomyositis, MED - Medication. Patients on MED- number of patients who used the medication. Patients on MED with ADR- number of patients who used the medication and experienced at least one adverse drug reaction. Patients on MED with ADR(%)- percentage of patients who used the medication and experienced at least one adverse drug reaction = N. P with ADR X 100/N.P on MED. ↑ liver enzymes - elevated liver enzymes. MAS - macrophagic activation syndrome. ↑ muscle enzymes - elevated muscle enzymes. ↓ convulsive threshold - reduction of the convulsive threshold. ↑ urea - elevated urea. MTX - methotrexate (median dose - 0.65 mg/kg/week and median length of treatment - 35.5 months). GCs - glucocorticoids (median dose - 0.64 mg/kg/day and median length of treatment - 28 months). CSA - cyclosporine (median dose - 4.2 mg/kg/day and median length of treatment - 35.3 months). LEF -leflunomide (median dose of 0.6 mg/kg/day and median length of treatment - 13.5 months). MMF - Mycophenolate mofetil (median dose - 32.2 mg/kg/day and median length of treatment - 19.8 months). HCQ-hydroxychloroquine (median dose - 5.5 mg/kg/day and median length of treatment - 30.7 months). CQ-diphosphate chloroquine (median dose - 4.7 mg/kg/day and median length of treatment - 28.3 months). CPA - cyclophosphamide (median dose of 734 mg/dose and median length of treatment - 5.9 months). AZA - azathioprine (median dose - 1.3 mg/kg/day and median length of treatment - 28.1 months). * one fracture

The withdrawal of the drug that caused the ADR (either by the medical staff or by the patient) occurred in 23.9% of the patients and 8.5% of the patients who used MTX had to interrupt the use. A reduction in the dose of the medication was required in 8.6% of all the patients and in 5.5% of patients who used MTX. In 6.3% of patients, there was a change in the route of administration.

Other procedures (2.9%) included patient education, such as taking MTX after breakfast or at night, or weekly dose administration at two different times on the same day. In 1.1% of the cases, we increased the interval between the doses of the medication. In 0.4% of cases, we did not increase the dose, even if there was a necessity due to disease activity.

Two patients (0.3%) suffered from pseudotumor cerebri caused by GCs that improved after lumbar puncture and the use of acetazolamide. No procedure was necessary in 30.4% of the patients because the ADRs were mild. Of the total of ADRs 64.5% remitted, 35.4% remained and 0.1% worsened despite treatment.

Discussion

More than two-thirds of the patients experienced at least one ADR, with a mean of 1.7 ADRs for each patient. We observed that some patients experienced up to 13 ADRs. Patients with JIA constituted the major group in the study and MTX was the drug of choice. In terms of the ADRs, MTX was the most causative of ADRs among approximately 60% of the patients treated with it; followed by GCs and CPA, respectively.

The ADRs due to MTX have been found more common in our research than in literature, most of them were attributed to gastrointestinal events such as nausea and/or vomiting and elevated liver enzymes [14, 15].

Our study recorded a 17% of patients with increase in liver enzymes with the use of MTX, while Veld et al. [16] found that 8% of patients with JIA treated with MTX for a year showed an elevation in liver enzymes. The different lengths of treatment may have directly influenced the prevalence of the studied ADRs. Reducing dosis (5.5%) or withdrawal of MTX (8.5%) and monitoring levels of liver enzymes were the selected managements and we did not find any irreversible liver damage.

Infections attributed to MTX occurred in 20 patients (5%) mainly herpes zoster infections. Whilst, infections of the respiratory system (pneumonia and bacteremia) or septicemia were the main infections in hospitalized patients; exactly as it was mentioned in the literature [17]. Although mucositis and oral ulcers have been described during the use of MTX, the small number of our cases is

Table 2 ADRs of bDMARDs in patients with JIA, JSLE and JDM

	Medications						
	ETN	**ADA**	**IFX**	**TCZ**	**ABA**	**RTX**	**TOTAL**
Patients on MED	54	49	36	9	7	10	165
Patients on MED with ADR	10	6	11	2	–	1	30
Patients on MED with ADR(%)	18.5	12.2	30.5	22.2	–	10	18.2
Infections	–	–	1	–	–	1	2
Blood and lymphatic system disorders:							
- Thrombocytopenia	–	–	1	–	–	–	1
Nervous system disorders:							
- Headache/dizziness/discomfort	–	–	1	–	–	–	1
Eye disorders:							
- Uveitis	2	1	–	–	–	–	3
Gastrointestinal disorders:							
- Nausea/vomiting	2	3	1	–	–	–	6
- Epigastric pain	–	1	–	–	–	–	1
Hepatobiliary disorders:							
-↑ liver enzymes	–	–	–	1	–	–	1
Skin and subcutaneous tissue disorders:							
- Atopic dermatitis	1	–	–	–	–	–	1
- Psoriasis	–	1	–	–	–	–	1
- Urticaria	–	–	3	1	–	–	4
Renal and urinary disorders:							
- Nephritis	1	–	–	–	–	–	1
- Hematuria	–	1	–	–	–	–	1
General disorders and administration site conditions:							
- Anaphylaxis	–	–	2	–	–	–	2
- Local reactions and pain	5	1	2	–	–	–	8
Total number of ADRs	11	8	11	2	–	1	33

ADR - adverse drug reaction, JIA - juvenile idiopathic arthritis, JSLE - juvenile systemic lupus erythematosus, JDM - juvenile dermatomyositis, MED - Medication. Patients on MED- number of patients who used the medication. Patients on MED with ADR- number of patients who used the medication and experienced at least one adverse drug reaction. Patients on MED with ADR(%)- percentage of patients who used the medication and experienced at least one adverse drug reaction = N. P with ADR X 100/N.P on MED. ↑ liver enzymes - elevated liver enzymes. ETN - etanercept (median dose - 1.1 mg/kg/week and median length of treatment - 8.4 months). ADA - adalimumab (median dose - 0.8 mg/kg/dose every 15 days and median length of treatment - 11 months). IFX - infliximab (median dose - 5.4 mg/kg/dose every 8 weeks and median length of treatment - 8.4 months). TCZ - tocilizumab (median dose - 9.7 mg/kg/dose monthly and median length of treatment - 7.5 months). ABA - abatacept (median dose - 10 mg/kg/dose monthly and median length of treatment - 12 months). RTX - rituximab (median dose 1 g/dose twice monthly every 6 months)

very likely due to the prophylactic routine use of folic acid and due to the MTX dose used to treat CRDs [18].

More ADRs attributed to MTX were found in younger patients. The need of high doses of MTX to control JIA may explain the association of this disease with a higher frequency of ADRs [19]. However, in the multiple regression model, the disease itself did not affect the number of ADRs, even with an adjusted using length, dose and route of administration of MTX. As also described in the literature, subcutaneous MTX has higher bioavailability and therefore can be more efficient [20]. Gastrointestinal intolerance and elevated liver enzymes are also associated with higher doses of MTX [21, 22] and the eventual or continuous use of NSAIDs by JIA patients could exacerbate the ADRs [23].

Interestingly, patients with JDM experienced fewer ADRs than the group with JIA, although these patients used statistically similar doses of MTX for a similar length of time. This is maybe due to the frequent or long use of NSAIDs by patients with JIA that may exacerbate the incidence of ADRs. The lack of the evaluation of the use of NSAIDs precludes more accurate conclusions, characterizing a probable bias.

Among the 339 patients treated with GCs, approximately half experienced ADRs. These occurred mainly in patients with JSLE. Cushing's syndrome was the most

Table 3 Characteristics of patients who used methotrexate (MTX) and presented adverse drug reactions (ADRs)

Variable	ADRs of MTX (*N* = 398)		
	Yes	No	*p**
	n = 252	*n* = 146	
Sex (%)			
Female	174 (63.3)	101 (36.7)	0.978
Male	78 (63.4)	45 (36.6)	
Age (years) – Cohort in median			
≤ 16	236 (72.6)	89 (27.4)	< 0.001
> 16	16 (21.9)	57 (78.1)	
Route of administration of MTX (%)			
Subcutaneous	40 (62.5)	24 (37.5)	0.882
Oral	212 (63.5)	122 (36.5)	
Dose of MTX (mg/kg/week)			
≥ 0.6	175 (69.7)	76 (30.3)	0.001
< 0.6	77 (52.4)	70 (47.6)	
Disease (%)			
JIA	207 (68.1)	97 (31.9)	0.001
JSLE	20 (57.1)	15 (42.9)	
JDM	25 (42.4)	34 (57.6)	

N - number of patients treated with MTX, JIA - juvenile idiopathic arthritis, JSLE - juvenile systemic lupus erythematosus, JDM - juvenile dermatomyositis
* Chi Pearson square or Fisher's exact. $P < 0.05$

Table 4 Characteristics of the patients who used glucocorticoids (GCs) and presented adverse drug reactions (ADRs)

Variable	ADRs of glucocorticoid (*N* = 339)		
	Yes *n* (151)	No *n* (188)	*p**
Sex (%)			
Female	122 (48.2)	131 (51.8)	0.019
Male	29 (33.7)	57 (66.3)	
Age			
≤ 16	135 (56.3)	105 (43.7)	< 0.001
> 16 years	16 (16.2)	83 (83.8)	
Type of glucocorticoid			
Methylprednisolone	3 (12.5)	21 (87.5)	< 0,001
Prednisone	71 (100)	0 (0.0)	
Prednisone / Methylprednisolone**	77 (31.6)	167 (68.4)	
Dose of prednisone (mg/kg/day) ***			
≥ 0,5	91 (58.1)	65 (41.9)	< 0.001
< 0,5	57 (35.8)	102 (64.2)	
Disease			
JIA	18 (12.8)	123 (87.2)	< 0.001
JSLE	120 (82.8)	25 (17.2)	
JDM	13 (24.5)	40 (75.5)	

N - number of patients treated with GCs, JIA - juvenile idiopathic arthritis, JSLE - juvenile systemic lupus erythematosus, JDM - juvenile dermatomyositis
* Chi Pearson square or Fisher's exact $P < 0.05$
** Prednisone (oral) / Methyprednisolone (pulse therapy) indicates patients treated with GCs and who presented ADRs during the use of combined oral and pulse therapy. Three patients with ADRs and 21 patients in the group without ADRs did not use GCs orally but used pulse therapy only
*** The dose of 30 mg/kg/dose of pulse therapy was not considered in the calculation

observed ADR in patients treated with GCs, followed by low bone mineral density [24, 25].

Cushing syndrome was observed in 80.8% of patients who had ADRs using GCs and is characterized by growth failure, central obesity, facial plethora, headaches, hypertension, hirsutism, amenorrhea, delayed sexual development, virilization in pubertal children, acne, violaceous striae, bruising, or acanthosis nigricans [26]. Obesity was observed in 1.9% of patients who had ADRs using GCs and 1.4% of total of patients with JSLE and JDM in our study. Obesity is defined by World Health Organization for children age 0–5 years as body mass index (BMI) or weight for length/ height > +3SD and for children age 5–19 years as BMI > + 2 SD [27].

A recent systematic review about GCs use showed that the three most commonly observed ADRs associated with long-course oral corticosteroids in children were weight gain (ranging from 6 to 10%), growth retardation and cushingoid features, with respective incidence rates of 21.1, 18.1 and 19.4% of patients assessed for these ADRs [28]. The same review had found 21.5% of patients with decreased bone density [28].

Other ADRs, such as cataracts, arterial hypertension and psychiatric symptoms were observed in a few patients in our study. Two patients developed pseudotumor cerebri, which is associated with the use of GCs [29]. One patient with systemic JIA experienced hepatic steatosis, identified by ultrasonography, due to the need of high doses of the medication.

In terms of the risk factors associated with ADRs due to GCs, the ADRs occurred more frequently in females, younger age, oral use, higher doses and the presence of JSLE. Another study, however, showed that the administration of pulse therapy in association with oral doses of GCs is responsible for ADRs in 70% of treated patients [30]. A study emphasized that treatment with doses lower than 7.5 mg per day was safe during GC administration, whereas other studies showed that higher doses were associated with ADRs [31–33].

We observed that the dose of GCs was higher in patients with JDM than in JSLE and JIA patients. However, the JDM group did not show a higher frequency of

Table 5 Risk of ADRs in response to methotrexate (MTX) and glucocorticoids (GCs) based on logistic regression

Variable	Logistic regression to methotrexate			
	OR		Adjusted OR	
	(IC95%)	*p*	(IC95%)	*p*
Sex: male (ref-female)	1.01 (0.65–1.56)	0.978	1.04 (0.61–1.77)	0.882
Age (years)	0.84 (0.80–0.88)	< 0.001	–	–
Age ≤ 16 years (ref-more than 16 years)	9.45 (5.15–17.31)	< 0.001	9.68 (4.86–19.28)	< 0.001
Administration routes of methotrexate (ref-oral)				
Subcutaneous	1.92 (1.07–3.44)	0.028	2.10 (1.05–4.20)	0.036
Dose	5.14 (2.14–12.36)	< 0.001	1.21 (0.4–3.68)	0.737
Dose of methotrexate ≥ 0.6 mg/kg/week (ref-more than 0,6)	2.09 (1.37–3.19)	0.001	–	–
Disease (ref.- JIA)				
JSLE	0.62 (0.31–1.27)	0.195	2.4 (0.95–6.07)	0.064
JDM	0.34 (0.19–0.61)	< 0.001	0.40 (0.2–0.79)	0.008
	Logistic regression to glucocorticoid			
Variable	**OR**		**Adjusted OR**	
	(IC95%)	***p***	**(IC95%)**	***p***
Sex: male (ref.- female)	0.55 (0.33–0.91)	0.02	1.10 (0.50–2.38)	0.816
Age (years)	0.86 (0.81–0.91)	< 0.001	–	–
Age ≤ 16 years (ref.- more than 16 years)	6.67 (3.69–12.07)	< 0.001	9.92 (4.36–22.54)	< 0.001
Dose of glucocorticoid (oral)	5.63 (2,88-11,00)	< 0,001	–	–
Dose of glucocorticoid (oral) ≥ 0.5 mg/kg/day (ref.-less than 0.5)	2.51 (1.59–3.95)	< 0.001	1.88 (0.96–3.69)	0.067
30 mg/kg/dose (Pulse therapy)	0.26 (0.07–0.89)	0.033	0.54 (0.12–2.39)	0.42
Disease (ref.- JSLE)				
JIA	0.03 (0.02–0.06)	< 0.001	0.03 (0.01–0.06)	< 0.001
JDM	0.07 (0.03–0.14)	< 0.001	0.05 (0.02–0.11)	< 0.001

ADR - adverse drug reaction, OR - odds ratio, aOR - adjusted odd ratios, CI - confidence interval, *p* - probability of significance, *Ref* - reference, JIA - juvenile idiopathic arthritis, JSLE - juvenile systemic lupus erythematosus, JDM - juvenile dermatomyositis, MTX - methotrexate, mg/kg-milligrams per kilogram, GCs - glucocorticoids

ADRs; 14.5% of the JDM patients did not use GCs, because this was a mild disease with a favorable outcome. In the multiple regression model, every additional month of use of GCs led to an increase of 0.5% in the mean number of ADRs.

CPA was the medication that caused the second-most ADRs when the number of patients who used CPA was taken into account. Half of the patients experienced ADRs, which mainly included nausea and/or vomiting and alopecia. We observed, in contrast to what was described in the literature, a small percentage of myelotoxicity, which manifested as leukopenia and/or lymphopenia [34]. The routine use of 2-mercaptoethane sulfonate (Mesna) and hyperhydration probably prevented hemorrhagic cystitis. Although CPA is a potent immunosuppressant, infections directly associated with this drug occurred in only two JSLE patients.

The most frequent ADR related hydroxychloroquine (HCQ) / diphosphate chloroquine (CQ) was the maculopathy, that occurred in 5.9% of the patients in use. It was observed that median dose of HCQ was 5.5 mg/kg/d and the median length was 30.7 months. Previous study about toxic retinopathy related HCQ use showed that the overall prevalence of HCQ retinopathy was 7.5% although varied with daily intake and with duration of use [35]. For daily intake of 4.0 to 5.0 mg/kg, the prevalence of retinal toxicity remained less than 2% within the first 10 years of use and almost 20% after 20 years of use but is 2 to 3 times higher at use exceeding 5.0 mg/kg [35].

Thereby, the American Academy of Ophthalmology recommends that all patients using HCQ keep daily dosage less than 5.0 mg/kg and a baseline fundus examination should be performed to rule out preexisting maculopathy, followed by annual screening after 5 years for patients on acceptable doses and without major risk factors [36].

Biological DMARDs are medications indicated in refractory cases that have a great effect and have been

used in our service for approximately 15 years; however, their ADRs are potentially important, including infectious and the possibility of cancer [37–39]. The evaluation of immunogenicity and neoplasia associated with bDMARDs was not the objective of this study.

Approximately 20% of patients who used bDMARDs experienced some ADRs. However, among the ADRs studied, reactions and pain at the injection site, allergic reactions and/or anaphylaxis and gastrointestinal intolerance were the predominant ADRs. Although infections and their complications are the most known ADRs related to bDMARDs in some studies, in our study, fortunately, it was found in approximately 1% of patients. A bacterial abscess after IFX use and a case of tuberculosis after rituximab (RTX) use were described.

Interestingly, a patient with JIA, treated with ETN, experienced features of the mixed-renal syndrome (with hematuria and nephrotic levels of proteinuria) and needed hospitalization. Some series of cases reports in literature describe the nephropathy as an uncommon ADR related to anti-TNF-alpha agents that can present with a range of asymptomatic microscopic or macroscopic hematuria and varying degrees of proteinuria [40].

The triggering of uveitis by ETN occurred in two patients in our study, as it has been described in the literature [41], and one case of uveitis was registered during treatment with ADA. IFX caused two cases of life-threatening anaphylaxis and three serious cases of allergic skin reactions, as mentioned in other studies [42]. A patient with JIA experienced thrombocytopenia while taking IFX; however, autoantibodies for JSLE were negative.

The conventional drugs (GCs, sDMARD) caused much more ADRs than the bDMARDs (96.4% × 3.6%). Additionally, when considering the total use of sDMARDs medications (1405), we observed 915 ADRs (65.1% of the cases), whereas when considering the use of bDMARDs (165 uses of these medications), we observed 33 ADRs (20% of the cases). The fact that the use of bDMARDs is more recent and sometimes they are used in combination and with similar ADR must be taken into account. However, two life-threatening events were caused by bDMARDs.

The management of the ADRs was substantially based on the severity. The usual attitude of the physicians who were attending these patients at the referral medical center in front of an ADR was to stop the suspected medication, what occurred in roughly a quarter of the cases.

In regard to the limitations of this study, the retrospective nature and the eventual omission of complaints or information by the patient, caregiver or even by the examiner, when completing the file should be mentioned. The lack of the evaluation of the disease activity and of the use of NSAIDs (due to the transient treatment with these medications and sometimes due to self-medication by the patient) is also a limitation.

NSAIDs and analgesic drugs (such as paracetamol and dipyrone) were used as adjuvant medications in case of pain and not regularly. A total of 251 (45.8%) of patients have ever used NSAIDs, especially JIA patients (244), with the objective of controlling symptoms and supporting the main drug. In 72.5% of the patients who used NSAIDs, it was associated with MTX (data not shown). As we said before, these data couldn't be measured due to the large variability of the length and posology of the use. The ADRs presented were attributed to each medication due to previous knowledge based on the literature and the judgement of the attending physician.

Due to the need to control disease, drug combination was inevitable, which prevented the detection of ADR causality separately or even the use of associated drugs in multivariate analysis. In addition, the socioeconomic status and the health system in Brazil with consequent limited use of bDMARDs in patients with CRDs means that ADRs may be different in other countries due to different treatment practices. The lack of history of allergy of patients or ADRs prior to the listed drugs retains the study to detect the possibility of preventing ADRs. The lack of patients' history of allergy or previous ADRs to the listed drugs withholds the study to detect the preventability of ADRs.

This study is the largest in the literature in a real-life setting that investigated all ADRs associated with the medical treatment in a large number of children and adolescents with CRDs, based on a 30 years data from a reference center in Brazil and transferred information about the ADRs management made by pediatric rheumatologist. This study provides a greater awareness of about the necessity of pharmacovigilance to monitor and manage the ADRs in health care centers, which treat children with CRDs to avoid their detrimental complications and it can be in the future, a model for a long-term prospective study with the drugs used in children with CRDs.

Conclusions

A wide range of children and adolescents with CRDs might suffer from ADRs. Nonetheless, they were considered as a moderate and manageable. Triggers of ADRs need further investigation. This study was the first step towards the self-censorship in a health care center to monitor ADRs.

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Authors' contributions

MAS performed the sample collection and processing, data analysis and drafted the manuscript. MTT participated in the design of the study, helped to data analysis and in drafting of the manuscript. LSST, AMOR and GGBA helped to data analysis and in drafting of the manuscript. DGPP and CAL participated in the design of the study, helped to data analysis and in drafting of the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was approved by the protocol number 1.752.504 by Research Ethics Committee of the Federal University of Sao Paulo. As it was a descriptive and retrospective observational cohort, the requirement for informed consent and assent was waived.

Consent for publication
Not applicable.

Competing interests
The authors declared that they had no competing interests.

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