WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 13, 67-87. Research Article ISSN 2277– 7105

ADVERSE EVENTS OF DRUG TREATMENT IN 547 PEDIATRIC PATIENTS WITH RHEUMATIC AUTOIMMUNE DISEASES: A RETROSPECTIVE COHORT IN A SINGLE CENTER

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Article Received on
12 May 2018,
Revised on 03 June 2018,
Accepted on 24 June 2018,
DOI: 10.20959/wjpr201813-12802

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SUMMARY

Introduction: Treatment of autoimmune rheumatic diseases (AIRDs) can cause adverse events (AEs) and the severity depends on different factors. **Objectives**: To describe the AEs of the medications used in the treatment of AIRDs and to report their severity, associated factors, procedures and the follow-up in patients with juvenile idiopathic arthritis (JIA), juvenile systemic lupus erythematosus (JSLE) and juvenile dermatomyositis (JDM). **Methods**: Retrospective descriptive and analytical study of a cohort of pediatric AIRDs. We evaluated all AEs and the aggravating factors for the AE. A regression logistic model and a multiple regression model of Poisson were set up. **Results**: 547 patients were included and 951 AEs were observed. MTX was the cause of the most AEs (63.3% of patients), followed by the GCs. Other immunosuppressive medications, biological agents and gammaglobulin also caused AEs. The risk of AEs to MTX and to GCs was higher in patients up to 16 years of age and who received MTX subcutaneously. In addition, the patients with JIA and JDM presented less risk of AEs to GCs than patients with JSLE. In the multiple regression model every additional month of use of GCs led to an increase of 0.5% in the mean of number of AEs. Two patients (0.2%) presented life

threatening AEs. Drug withdrawal occurred in 23.9% of cases. **Conclusion**: This study is unique because it is the largest retrospective study in the literature, which focuses on the AEs for medications used in the treatment of childhood AIRDs in a specialized center.

KEYWORDS: Autoimmune rheumatic diseases, adverse events, methotrexate, glucocorticoids, biological agents, childhood.

INTRODUCTION

Autoimmune rheumatic diseases (AIRDs) are inflammatory diseases arising from changes in the immune system, and their symptoms manifest with the involvement of joints and other organs and systems. The treatment includes anti-inflammatory and immunosuppressive drugs and biological agents.[1-3] These medications control AIRDs, however can cause several adverse events (AEs) of mild to severe intensity, with need for new medications to treat the AE, dose reduction or even withdrawal of the medication which caused the AE. AEs contribute to morbidity or even mortality in some cases.[4-5] The severity and frequency of AE depend on the dose, route of administration and length of use, in addition to the presence or not of other aggravating factors.[6,7]

Most studies that have approached the safety of medications were restricted to a few years follow up or performed in a transversal way. Registering the AEs and the factors associated with the occurrence of these events, particularly in chronic diseases, is essential for the health team, in order to select the best procedures, and to help the pharmacosurveillance. These notifications can be used to monitor the safety of the drugs and find solutions to minimize the AEs. A better understanding of the AEs of each medication used to control the chronic diseases leads to better treatment adherence and thereby better prognosis.

The objective of this study was to evaluate the frequency and factors associated with AEs of the medications used in the treatment of AIRDs and their severity, procedures taken and the follow up of these events during the treatment in a cohort of pediatric patients with juvenile idiopathic arthritis (JIA), juvenile systemic lupus erythematosus (JSLE) and juvenile dermatomyositis (JDM) in a tertiary center.

MATERIAL AND METHODS

A descriptive and retrospective study of a cohort of children and adolescents with JIA, JSLE and JDM diagnosed according to the classification criteria for their diseases[8-10] and followed in a tertiary center specialized in pediatric rheumatology was carried out. The medical records of all patients with JIA, JSLE and JDM in a total of 662 records (391 JIA, 162 JSLE and 69 JDM), who attended the unit since 1985 until 2016 for at least six months and who were aged at the disease onset up to 16 years for patients with JIA and up to 18 years for patients with JSLE and JDM, were evaluated.

Exclusion criteria were: patients without treatment or only treated with non-steroidal anti-inflammatory drugs (NSAIDs) or patients with more than an AIRD or with another associated non-rheumatic disease, that could present symptoms or complications which could interfere with the interpretation of the AE.

A pharmaceutical researcher (MAS) evaluated the medical records of the patients during the time of the AE. The data collection included: demographics, medications used for treatment of the disease (glucocorticoids - GCs, disease modified anti-rheumatic drugs - DMARDs, immunosuppressants, intravenous immune globulin – IVIG and biological agents) and data on dose, route of administration, length of treatment and medication associations. The data of the AEs have been compiled into a standard questionnaire for each disease and medication separately. An inter-observer evaluation was performed by a pediatric rheumatologist (MTT) in 10% of patient records.

The characterization of AE included type and its severity during the period of treatment. According to the literature, the severity of AE was classified as mild when an AE does not need an intervention; moderate to the AE which needs an intervention; serious for any AE who requires hospitalization or prolonged hospitalization, causing inability or limited daily activities; and AE life threatening, one that needs urgent intervention, and finally the AE related to death of the patient (CTCAE-Common Terminology Criteria for Adverse Events).[11]

All of the procedures to deal with the AEs were evaluated: medication withdrawal by the patient himself or by his physician, reduction of dose, change in the route of administration, association of other treatment for AE, or patient orientation.

All data base was stored in a spreadsheet format Microsoft Excel and clinical characteristics were described in absolute and relative frequency and mean or median. Categorical variables were compared between the diseases (JIA, JSLE and JDM) using the Pearson's Chi-square test or Fisher's exact test. The comparison of medians between two groups was held using the non-parametric test of Mann-Whitney due to non-normality in the data distribution. To evaluate the effect of sex, age, disease, and dose and route of administration of the medication on the occurrence of AEs, a logistic regression model to MTX and GCs was set. To evaluate the effect of the disease adjusted for the dose, treatment length and route of administration (MTX and GCs) to the number of AEs (dependent variable), we used the multiple regression model of Poisson, since the dependent variable corresponds to a count. Models were adjusted separately for each medication. The Poisson models were estimated using the STATA 12. For all other analyses the Statistical software SPSS 20.0 was used. For all statistical tests a significance level of 5% was set.

The study was approved by the Research Ethics Committee of the institution. As it was a retrospective study, the informed consent and assent were unnecessary. However, the confidentiality and anonimity of the information were guaranteed.

RESULTS

Medical reports of 622 patients were evaluated and 75 patients were excluded (JIA 57, 11 JSLE and 7 JDM) due to the presence of another associated disease such as Crohn’s disease, Hashimoto's thyroiditis, auto-immune hepatitis, multiple sclerosis, and nodular neoplasia of liver (a total of 26 patients); due the presence of gastritis prior to the use of medications for treatment of AIRD (5 patients); and due to the use of NSAIDs (44 patients). A total of 547 patients were evaluated (334 patients with JIA, 151 with JSLE and 62 with JDM). Of these, 389 (71.1%) patients presented AEs being 220 patients 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 951 AEs (mean 2.4 AEs per patient presenting AE). The patients had a mean age of 17.9 ± 1.5 years at evaluation and 7.9 ± 2.5 years at the disease onset and 72.6% were female. The mean time of disease follow-up was 8.0 ± 1.4 years.

Table 1: shows the AEs of glucocorticoids, disease-modifying antirheumatic drugs (DMARDs) and immunosuppressants in the treatment of patients with JIA, JSLE and JDM.

Table 1: Adverse events of glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs) and immunosuppressants in the treatment of patients with Juvenile Idiopathic Arthritis (N = 334), Juvenile Systemic Lupus Erythematosus (N = 151) and Juvenile Dermatomyositis (N = 62).

		Medications							
	GCs	**MTX**	**LEF**	**ANTIMAL**	**CSA**	**MMF**	**AZA**	**CFA**	**TOTAL**
N.P. on MED	339	398	86	271	92	29	115	75	-
N.P. with AE	151	252	18	30	31	5	17	34	-
N.P. on MED with AE (%)	(44.5%)	(63.3%)	(20.9%)	(11.1%)	(33.7%)	(17.2%)	(14.8%)	(45.3%)	-
N AE	295	439	22	36	43	6	23	51	917
Nausea \ vomiting	10	199	4	6	17	-	2	28	266
Epigastralgia \ abdominal pain	7	73	2	2	6	-	2	1	93
Chronic headache\dizziness\discomfort	8	32	0	1	-	2	-	4	47
Diarreia	-	8	-	1	-	2	-	-	11
Hiporexia	-	7	-	-	1	-	-	-	8
Constipation	-	1	-	-	-	-	-	1	2
⬆liverenzymes	2	68	7	1	1	-	5	1	85
Hepaticsteatosis	1	-	-	-	-	-	-	-	1
Oral ulcers	-	3	1	-	-	-	-	-	4
Infections	9	20	-	2	3	2	5	2	43
MAS	-	-	1	-	-	-	-	-	1
Osteoporosis	51	9	-	-	-	-	-	-	60
Cushingsyndrome	122	-	-	-	-	-	-	-	122
Striae	3	-	-	-	-	-	-	-	3
Obesity	3	-	-	-	-	-	-	-	3
Glaucoma	2	-	-	-	-	-	-	-	2
Cataract	19	-	-	-	-	-	-	-	19

Ocular toxicity	-	-	-	16	-	-	-	-	16
Visual blurring	-	1	-	-	-		-	-	1
Arterial hypertension	42	-	-	-	3	-	-	-	45
Arrhythmia	-	-	-	1	-	-	1	-	2
Edema	4	-	-	-	-	-	-	-	4
⬆muscleenzymes	-	-	-	1	-	-	-	-	1
Myositis	-	-	-	1	-	-	-	-	1
Myalgia	3	-	-	-	-	-	-	-	3
Allergicreactions	4	5	1	2	2	-	-	-	16
Infusionreactions and pain	3	4	-	-	-	-	-	-	7
Atopicdermatitis	-	-	-	1	-	-	-	-	1
Jaundice	-	-	1	1	-	-	-	-	2
Alopecia	-	5	4	-	-	-	1	10	20
Persistent anemia	-	1	-	-	-	-	-	-	1
Mucositis	-	3	-	-	-	-	-	-	3
Leukopenia\ Lymphopenia	-	-	-	-	-	-	6	4	10
Pancytopenia \ Neutropenia	-	-	-	-	-	-	1	-	1
Hypertrichosis	-	-	-	-	7	-	-	-	7
Pseudotumorcerebri	2	-	-	-	-	-	-	-	2
⬇convulsivethreshold	-	-	1	-	-	-	-	-	1
Gingivalhyperplasia	-	-	-	-	2	-	-	-	2
⬆urea	-	-	-	-	1	-	-	-	1

N - Number of patients. MED - Medication. N. P. on MED - number of patients who used the medication. N. P. with AE - number of patients who used the medication and presented adverse event. N.P.on MED with AE (%) -percentage of patients who used the medication and presented adverse event. AE - adverse event of medication.⬆liver enzymes- increased liver enzymes. MAS – macrophagicactivation syndrome. ⬆muscle enzymes - increased muscle enzymes. ⬇convulsive threshold – reduction of the convulsive threshold. ⬆urea - increased 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 mofetila (median dose –32.2 mg/kg/day and median length of treatment - 19.8 months). ANTIMAL - antimalarials (median dose-5.5 mg/kg/day and median length of treatment - 30.7 months for hydroxychloroquine and median dose- 4.7 mg/kg/day and median length of treatment - 28.3 months for diphosphate chloroquine). CFA - 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).

Allergic reactions occurred in 2 cases among 27 patients treated with IVIG during infusion and with a mean dose of 2 g/kg/dose monthly.

Table 2: Shows all AEs of biological medications in treatment of patients with JIA, JSLE and JDM.

Table 2: Adverse events of biological medications in the treatment of patients with juvenile idiopathic arthritis (N = 334), Systemic Lupus Erythematosus (N = 151) and Juvenile Dermatomyositis (N = 62).

			Medications				
	ETN	**ADA**	**IFX**	**TCZ**	**ABA**	**RTX**	**TOTAL**
N.P on MED	54	49	36	9	7	10	165
N.P with AE	10	6	11	2	-	1	30
N.P on MED with AE (%)	(18.5%)	(12.2%)	(30.5%)	(22.2%)	-	(10%)	18.2%
N.AE	12	8	11	2	-	1	34
Anaphylaxis	-	-	2	-	-	-	2
Allergicreactions	-	-	3	1	-	-	4
Localreactions and pain	5	1	2	-	-	-	8
Nausea / vomiting	2	3	1	-	-	-	6
Epigastralgia	-	1	-	-	-	-	1

Headache/dizziness\dyspnea	-	-	1	-	-	-	1
⬆liverenzymes	-	-	-	1	-	-	1
Atopicdermatitis	1	-	-	-	-	-	1
Psoriasis	-	1	-	-	-	-	1
Uveitis	2	1	-	-	-	-	3
Cataract	1	-	-	-	-	-	1
Infection	-	-	1	-	-	1	2
Nephritis	1	-	-	-	-	-	1
Hematuria	-	1	-	-	-	-	1
Plaquetopenia	-	-	1	-	-	-	1

N - Number of patients. MED - Medication. N. P. on MED - number of patients who used the medication. N.P.with AE - number of patients who used the medication and presented adverse event. N.P on MED with AE (%) - percentage of patients who used the medication and presented adverse event. AE - adverse event of medication.⬆liver enzymes- increased 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 – abatacepte (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).

Severity of AEs

MTX and GCs were the medications that caused the most AEs. MTX was responsible for 29.4% of moderate AEs, 12.5% of mild and 0.6% of severe with 42.5% of the total AEs. The GCs caused 18.2% of moderate AEs, 15.1% of mild and 0.7% of severe, with 34% of the total AEs.

Figure 1: shows the frequency and severity of AEs ofmedication. In total, there were 35 serious events, 604 moderate and 310 mild events. In addition, there were two cases (0.2%) of life threatening anaphylaxis after using infliximab.

Figure 1: Frequency and severity of AEs of medication used in the treatment of patients with Juvenile Idiopathic Arthritis (N = 334), Juvenile Systemic Lupus Erythematosus (N = 151) and Juvenile Dermatomyositis (N = 62)

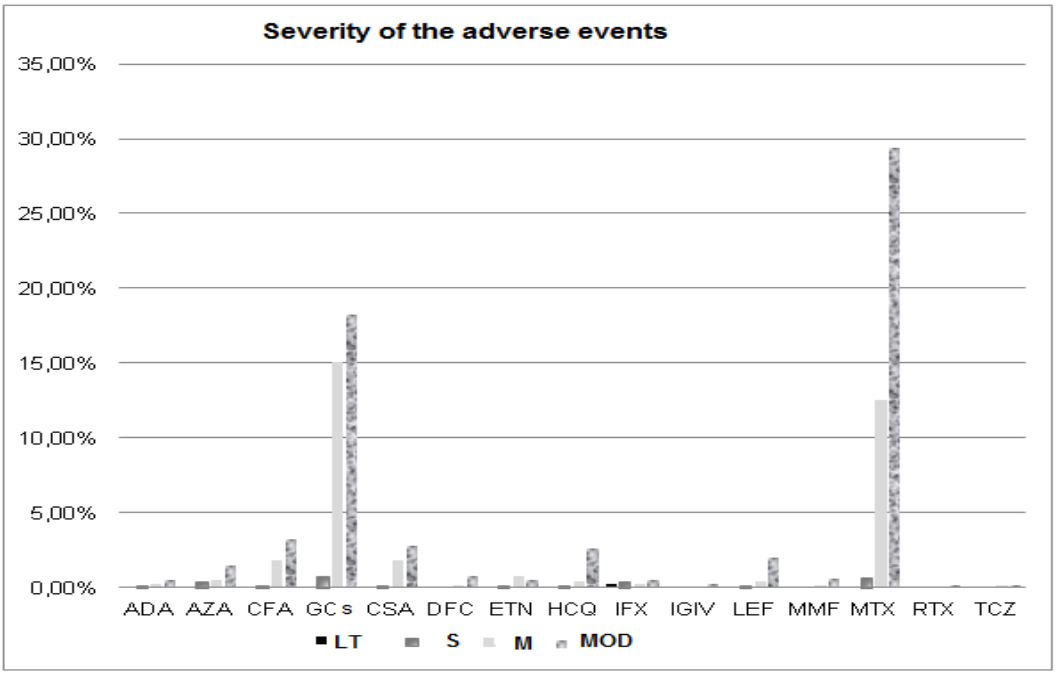

Figure 1: The vertical axis shows the percentage of adverse events of each medication.

The horizontal axis shows the degree of severity of adverse events. LT- life threatening adverse event; S- severe adverse event; M- mild adverse event; MOD-moderate adverse event. % HCQ - hydroxychloroquine. IFX -infliximab. IVIG - intravenous immunoglobulin. LEF - leflunomide. MM F - mycophenolate mofetil. MTX - methotrexate. RTX -rituximab. TCZ tocilizumab.

The median length of use of MTX in patients who presented AEs was 35.5 months. AEs due to MTX occurred after a median use of one year. We observed that the dose of the MTX was higher and the length of use of MTX was longer in patients with JDM than in patients with JSLE ($p < 0.001$, respectively). Similar results occurred in patients with JIA compared to patients with JSLE ($p < 0.001$, respectively). The JIA group was not different to the JDM group.

Table 3 shows the characteristics of patients who used MTX and presented AEs. An association between AEs of MTX and younger patients, use of both oral and subcutaneous routes of administration, higher doses of MTX and the presence of JIA was found.

Table 3: Characteristics of patients who used methotrexate (MTX) and presented adverse events (AEs).

Variable	Adverse events of MTX (N=398)		
	Yes	No	*ρ**
	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)	<0.001
Oral Oral / Subcutaneous**	85 (46.4) 127 (84.1)	98 (53.6) 24 (15.9)	
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

*Chi Pearson square or Fisher exact. P < 0.05.

**Oral /subcutaneous indicates patients treated with MTX and who presented AEs by the oral route and continued the AEs by subcutaneous route.

The median length of use of GC in patients who presented AEs was 28.0 months. AEs due to GC appeared after a median of 6.5 months. We observed that the dose of the GCs was higher in patients with JDM compared to 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 who used GC and presented AEs. An association between the GC and female gender, younger age of the patients, use of oral medication, higher doses and presence of JSLE was observed.

Table 4: Characteristics of patients who used glucocorticoid (GC) and presented adverse events (AE).

Variable	Adverse events of GC (N=339)		
	Yes n (151)	No n (188)	*ρ**
Sex (%)			
Female	122 (48.2)	131(51.8)	0.019
Male	29 (33.7)	57 (66.3)	
Age			
≤ 16	135 (56.3)	105(43.8)	<0.001
> 16 years	16 (16.2)	83(83.8)	
Route of administration of GC			
Pulse therapy	3 (12.5)	21(87.5)	<0.001
Oral	71(100)	0 (0.0)	
Oral\Pulse therapy**	77 (31.6)	167(68.4)	
Dose of GC (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 GC

*Chi Pearson square or Fisher exact P < 0.05.

**Oral and pulse therapy indicates patients treated with GC and who presented AEs during the use of both oral and pulse therapy together. Three patients with AE and 21 patients of the group without AE did not use of GC orally but used pulse therapy only. The dose of 30 mg/kg/dose of pulse therapy was not added to the calculation.

In table 5, we observed that the odds ratio for AE to MTX in patients of age up to 16 years was 9.7 times higher than in the older patients. Additionally, patients who received MTX subcutaneously presented odds ratio for AE 2.1 times higher than those who received just orally. The odds ratio was 6.1 times higher in patients receiving MTX by both routes. Higher doses of MTX were associated with the use of subcutaneous administration or oral and subcutaneous routes and with JIA. In addition, patients with JDM presented odds ratio for AE 60% lower than patients with JIA; no differences in odds ratio among patients with JSLE and JIA were observed.

Also in table 5, we found that the odds ratio for AE to GC in patients of age up to 16 years was 9.9 times higher than in older patients. More frequent use of pulse therapy and use of

lower doses were associated with patients with JIA. In addition, patients with JIA and JDM presented odds ratio for AE, respectively, 97% and 95% lower than patients with JSLE.

Table 5: Risk of adverse events to methotrexate (MTX) and glucocorticoid (GC) through logistic regression.

	Logisticregressiontomethotrexate			
Variable	**OR brutal**		**OR adjusted**	
	Estimate (IC95%)	**P**	Estimate (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 MTX (ref- oral)				
Subcutaneous	1.92 (1.07-3.44)	0.028	2.10 (1.05-4.20)	0.036
Oral \Subcutaneous	6.10 (3.61-10.3)	<0.001	6.17 (3.36-11.33)	<0.001
Dose	5.14 (2.14-12.36)	<0.001	1.21 (0.4-3.68)	0.737
Dose of MTX ≥ 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
	Logisticregressiontoglucocorticoid			
Variable	**OR brutal**		**OR adjusted**	
	Estimate (IC95%)	**P**	Estimate (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 GC (oral)	5.63 (2,88-11,00)	<0,001	-	-
Dose of GC (oral) ≥ 0.5 mg\kg\day (ref. = lessthan 0.5)	2.51 (1.59-3.95)	<0.001	1.88 (0.96-3.69)	0.067
30mg/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

OR - odds ratio, 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 - miligrama per kilogram, GC - glucocorticoid.

There was no association between the number of AEs to MTX (p = 0.441) and GC (p = 0.718) and the diseases.

According to table 6, in the multiple regression model, there was no effect of disease (p = 0.842) on the number of AEs adjusted by length of use, dose and route of administration of MTX. Also in table 6, there was no effect of disease (p = 0.913) on the number of AEs adjusted for length of use and dose of GC. However every additional month of use of GCs led to an increase of 0.5% in the mean of number of AEs (p = 0.006).

Table 6: Multiple Regression for adverse events to methotrexate (MTX) and glucocorticoid (GC).

Regression of Poisson for adverse events to methotrexate				
Variable	**Rate of brutal medium**		**Rate of adjustedmedium**	
	Estimate (IC95%)	p	Estimate (IC 95%)	p
Disease (ref.=JIA)				
JSLE	0.86 (0.59-1.25)	0.428	0.93 (0.63-1.38)	0.729
JDM	1.10 (0.81-1.49)	0.531	1.07 (0.79-1.45)	0.650
Length of use of MTX (months)	1.00 (1.00-1.00)	0.208	-	-
Length of use of MTX ≥ 12 months (ref-until 12 months)	1.23 (0.92-1.64)	0.169	1.18 (0.87-1.59)	0.282
Dose MTX	0.99 (0.67-1.46)	0.948	-	-
Dose MTX≥ 0.6 mg\kg\week (ref- less than 0.6)	1.03 (0.85-1.24)	0.790	0.95 (0.78-1.17)	0.655
Subcutaneousroute (ref- oral)	1.17 (0.96-1.41)	0.116	1.14 (0.93-1.41)	0.202
	Regression of Poisson for adverse events to glucocorticoid			
Variable	**Rate of brutal medium**		**Rate of adjustedmedium**	
	Estimate (IC 95%)	p	Estimate (IC 95%)	p
Disease (ref.=JSLE)				
JIA	0.86 (0.59-1.25)	0.421	0.95 (0.62-1.45)	0.814
JDM	0.96 (0.63-1.45)	0.836	0.92 (0.60-1.41)	0.711
Length of use of GC (months)	1.005 (1.001-1.008)	0.007	1.005 (1.001-1.008)	0.006
Length of use of GC ≥ 6 months (ref - until 6 months)	0.73 (0.36-1.48)	0.390	-	-
DoseGC	1.33 (0.97-1.82)	0.073	-	-
Dose GC ≥ 0.5 mg\kg\day (ref- less than 0.5)	1.23 (0.97-1.57)	0.090	1.29 (0.94-1.78)	0.120

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-miligrame per kilogram, GC-glucocorticoid.

Procedures taken against the AEs

In relation to the procedures taken against the AEs, 26.1% of the times other medications were introduced to minimize the AE such as omeprazol, ranitidine, ondansetron and metoclopramide. Additionally, antibiotics and antiviral agents were indicated in cases of bacterial and viral infections respectively.

The withdrawal of the drug which caused the AE occurred in 23.9% of the totality of the procedures taken by the medical staff or by the patient himself. Reduction of the dose of the medication was required in 8.6%. In 6.3% of cases, there was a change of route of administration. Other procedures (2.9%) included patient orientation such as taking the MTX separately from naproxen, or after breakfast or at night, or weekly dose administration at two different times on the same day. In 1.1% we spaced the interval between the doses. In 0.4% of cases we prevented increasing the dose of the medication, even if there was a need to increase the dose due to the disease activity.

Two patients (0.3%) presented pseudotumorcerebri caused by GCs that improved after liquor puncture and use of acetazolamide. No procedure was necessary in 30.4% of cases because the AEs were mild. Of the 951 AEs, 64.5% remitted, 35.4% remained and 0.1% worsened despite the procedure taken.

DISCUSSION

This study was the largest retrospective study in the scientific literature of pharmacosurveillance that focused on the AEs of all medications used to treat the AIRDs of 547 patients from a single center. It evaluated a great number of children and adolescents in their real life during 31 years of existence of the reference center. All AEs to the medications received during the treatment were evaluated and the procedures and the follow up were described. The study included the three most frequent AIRDs in infancy.

Over two thirds of the patients presented with at least an AE in a total of 951 AEs, with a mean of 2.4 AEs for each patient who presented AE. We observed that some patients presented up to 13 AEs. The patients treated with MTX, the medication of first choice in the treatment of JIA, had more AEs. The second drug most associated with AEs was the GC. However, when considering the number of patients who used the respective medication, the MTX and the CFA were the medications with more AE.

The gastrointestinal events such as nausea and\or vomiting and increased liver enzymes were the most common AEs to the MTX.[12] Transient hepatotoxicity occurred without permanent damage to the liver. Veld et al found increased liver enzymes in approximately 8% of patients with JIA treated with MTX for a year.[13] The different lengths of treatment may have directly influenced the prevalence of the studied AE. The routine laboratorial monitoring and the prompt withdrawal of MTX when the increase exceeds two fold the normal values or the reduction of the dose of the MTX in case that this rise is lower, explain why these patients are protected from irreversible damage. A study in adults with chronic arthritis showed a higher frequency of hepatic AEs, perhaps due to common comorbiditis and alcoholism in this age group.[14]

Infections, common in patients on immunosuppressants, occurred in 20 cases, mainly herpes zoster, whereas infections of the respiratory system, pneumonia and bacteremia or septicemia were specifically the main infections in hospitalized patients and most described in literature.[15] Although mucositis and oral ulcers are described during the use of MTX, we did not observe, very probably due to the prophylactic routine use of folic acid and due to the dose used in the AIRDs.

We observed an association between AE to MTX and the younger age of the patients, the use of subcutaneous route or use of both routes, and the presence of JIA. This was confirmed by the odds ratio for AE of about 2 to 10 times higher in these situations according to the logistic regression model. In our service and in the literature patients with JIA have indication of use of higher doses of MTX that are associated to the use of subcutaneous route or both, which may explain the association of this disease with a higher frequency of AEs.[16] Subcutaneous MTX has more bioavaliability and therefore can be more efficient.[17] Gastrointestinal intolerance and increased liver enzymes are also associated with the higher doses of MTX.[18,19] Moreover, patients with JDM presented odds ratio for fewer AEs than patients with JIA although they used statistically similar doses of MTX and for a similar length of time. This finding can raise a doubt on the interference of the autoimmune disease or its treatment with the occurrence of the AE. The eventual or continuous use of NSAIDs by JIA patients, for example, could exacerbate the AEs.[20]

Among the 339 patients treated with GC, approximately half presented AEs. These occurred mainly in patients with JSLE. Cushing's syndrome was the most observed AE in patients treated with GCs, followed by osteoporosis.[21,22] Other AEs such as cataract, arterial

hypertension and psychiatric symptoms occurred in a few cases in our study. Two patients developed cerebral pseudotumor, that is described associated with the use of GCs.[23] A patient with systemic JIA presented hepatic steatosis due to the necessity of high doses of the medication.

Although an association between AEs to GC and female sex, younger age of patients, oral use, higher doses and presence of JSLE has been observed, this was not confirmed in the logistic regression model where we only observed an association between AE to the GC and younger age of patients and presence of JSLE. This was confirmed by the odds ratio for AE of about 2 to 10 times greater in these situations. Higher frequency of use of pulse therapy and use of lower doses of GCs were associated with JIA patients, which could be the reason for presenting fewer AEs than in the population with JSLE.

Another study, however, showed that the administration of pulse therapy in association with oral doses of GCs is responsible for AEs in 70% of the treated patients.[24] A study emphasized that treatment with doses lower than 7.5 mg per day, showed to be safe during the time of use, whereas other studies showed that higher doses are associated with AEs.[25,26]

We observed that the dose of GCs was higher in the patients with JDM when compared with the JSLE and JIA patients, however this first group did not present higher frequency of AEs. The JSLE patients used GCs longer than JIA patients. In the multiple regression model every additional month of use of GCs led to an increase of 0.5% in the mean of number of AEs.

The frequent use of pulse therapy with GCs and longer time of use of oral GC is common in JSLE patients, where despite the therapeutic advances and ample use of imunossupressants, there is still an indication of GCs use in the disease flares and in the serious cases of vasculitis or visceral involvement. As we observed in our study, only 4% of patients with JSLE did not use GCs.

Although some studies in adults showed that females are more susceptible to have AEs, this finding was not found in this study.[27] What we observed was the occurrence of AEs in association with younger patients, which can be explained by different pharmakocinetic in the younger ages.

Other medications related to AEs presented fewer events and for this reason, they were not submitted to the statistical study. However, due to clinical relevance of these events they are described below in a descriptive way.

The cyclophosphamide (CFA) was the second medication that caused the most AEs taking into account the number of patients who used it. Half of patients presented AEs mainly nausea and/or vomiting and alopecia. We observed, in contrast to what was described in the literature, a small percentage of mielotoxicity manifested to leucopenia and/or linfopenia.[28] The routine use of 2-mercaptoethane sulfonate (Mesna) and hyperhydration probably prevented the occurrence of hemorrhagic cystitis. Although CFA is a potent immunosuppressant, infections directly associated with this drug occurred in only two patients.

The biological agents are medications indicated in the refractory cases with great effect and used in our service for about 15 years, however their AEs are potentially important mainly the infectious and possibly cancer.[29,30] The evaluation of immunogenicity and neoplasia associated to the biological agents was not objective of this study. About 20% of patients who used biological agents presented some AEs. However, between the AEs studied, reactions and pain at the infusion site, allergic reactions and/or anaphylaxis and gastrointestinal intolerance were predominant. Surprisingly we observed only few episodes of infections such as a bacterial abscess after IFX use and a case of tuberculosis after RTX use.

Interestingly, in relation to the ETN, a patient with JIA presented features of mixed renal syndrome (with hematuria and nephrotic levels of proteinuria) and needed hospitalization. The triggering of uveitis by the ETN was described in literature[31] and occurred in two patients from our study, while a case of uveitis was registered during treatment with ADA.

The IFX caused two cases of life threatening anaphylaxis and three serious cases of allergic reactions, as mentioned in other studies.[32] A patient with JIA presented a plaquetopenia while taking IFX, however the auto-antibodies for JSLE were negative.

Although the infections and their complications are the AEs most known related to the biological agents in some studies, in our study this occurrence was not frequent (about 1% of patients). By contrast, allergic reactions were the main AEs in those patients.[33]

We observed that the majority of the AEs were associated with the use of DMARDs, immunosuppressants and IVIG more than with biological medications (96.4% x 3.6%), showing that these medications although more recent on the market are safe. Also when considering the total use of DMARDs, immunosuppressants and IVIG (1432 uses of these medications) we observed 917 AEs (64% of the cases) whereas when considering the use of biological medications (165 uses of these medications) we observed 34 AEs (20.6% of the cases). However, the only two life threatening events were caused by biological agents.

As limitations of this study we can mention the retrospective nature with eventual omission of complaints or information by the patient or caregiver or even by the examiner when registering the file. The fact of not having evaluated the activity of the disease and the use of NSAIDs (due to the transient treatment with these medications and sometimes due to self medication by the patient) also must be considered as a limitation of this study. Moreover, study of some AEs in the long term such as neoplasia, teratogenicity or infertility, and AEs associated to the GCs as esteatosis, dislipidemia and diabetes mellitus were also not objectives of this study.

This study is unique and the largest study of pharmacosurveillance in the literature and has investigated the AEs in real life associated to the medical treatment in a large number of children and adolescents with AIRDs throughout their treatment. It provides a greater awareness in relation to the complications of the AEs as well as an orientation of the correct procedures. The interference of a particular disease on the occurrence of the AEs was observed in this study and should be studied deeper in the future to know if the AIRDs have some influence on the AEs.

CONCLUSION

We concluded that the AEs associated to the treatment of the AIRDS are frequent and need constant monitoring with pharmacosurveillance throughout treatment. The pharmaceutical professional must be included in the multiprofessional consultations, in order to assure the safety of medications, through the evaluation of the factors associated to the AE and through notification of serious and life threatening AEs.

ACKNOWLEDGEMENTS

We would like to thank Mitti Koyama for the statistical support.

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