Infliximab in Pediatric Rheumatology Patients: A Retrospective Analysis of Infusion Reactions and Severe Adverse Events During 2246 Infusions over 12 Years

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ABSTRACT. ***Objective.*** To describe infusion reactions (IR) and severe adverse events (SAE) associated with infliximab (IFX) in pediatric patients with rheumatologic and ocular inflammatory diseases in a real-world setting.

Methods. This is a retrospective chart review of all patients treated with IFX at the pediatric rheumatology division of a university hospital between October 2000 and December 2012.

Results. A total of 2446 IFX infusions were given to 82 patients (72% female). IR occurred in 46 infusions (2%) of 14 patients (17%) after a mean IFX treatment time of 340 days (range 41–780); 9/14 patients (64%) experienced repeated IR. IR were classified as mild (26%), moderate (74%), or severe (0%). Indications for IFX were arthritis (60%), uveitis (20%), arthritis and uveitis (13%), and other inflammatory diseases (5%). The most common clinical symptoms were respiratory signs (72%), cutaneous manifestations (69%), and malaise (61%). In 6/14 patients (43%) with IR, IFX was discontinued: 4 patients because of repeated IR and 2 patients wished to stop treatment immediately following a mild IR. The other 8/14 patients (57%) received premedication with high-dose antihistamine (100%), corticosteroids (75%), and IFX dose increase (75%) and continued IFX treatment for a mean followup period of 146 weeks (range 26–537) after the first IR. We observed severe infections in 5/82 patients (6%); other SAE were rare.

Conclusion. Mild and moderate IR occurred in 17% of our patients. Treatment with antihistamines and methylprednisolone, and increasing the IFX dose, allowed continued treatment despite IR in > 50% of patients. Other SAE were infrequent. (J Rheumatol First Release May 15 2014; doi:10.3899/jrheum.131231)

Key Indexing Terms:
INFLIXIMAB JUVENILE IDIOPATHIC ARTHRITIS UVEITIS INFUSION REACTIONS

Rheumatologic inflammatory diseases and inflammatory ocular diseases are quite common in children. The most frequent inflammatory rheumatologic disease in childhood is juvenile idiopathic arthritis (JIA), with an annual incidence of 5–20/100,000[1,2]; noninfectious uveitis has an incidence of 7–21/100,000 in children[3,4,5]. When JIA, uveitis, and other inflammatory diseases are refractory to standard treatment [e.g., corticosteroid injections, disease-modifying antirheumatic drugs (DMARD; such as methotrexate [MTX] or leflunomide)], tumor necrosis factor (TNF)-α inhibitors are indicated[6,7,8]. In the last decades, different new TNF-α inhibitors have been developed and approved to treat systemic inflammatory rheumatic and ocular diseases, especially in adults. In Switzerland, etanercept is still the only TNF-α inhibitor officially registered for the use in children. The use of any other TNF-α inhibitor in children is up to the judgment of the treating physician, with no legal difference between the use of infliximab (IFX) or adalimumab. Because IFX was available 3 years before etanercept was registered, IFX was used more frequently in patients with severe JIA or JIA uveitis, especially in the early years of TNF-α inhibitor therapy.

IFX is a monoclonal anti-TNF-α biologic agent consisting of a mouse-human chimeric immunoglobulin (Ig)G antibody[9] and is well described in adult patients[10,11].

IFX is administered by infusion and is usually well tolerated. However, in some cases, mild to severe reactions during the infusion have been observed. In adult patients

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with rheumatologic diseases, acute infusion reactions (IR) occur in 6% to 23% and are the most frequent therapy-limiting adverse event (AE)[10,12,13]. An acute IR is defined as any event occurring within 1 h of the IFX infusion[14] and commonly manifests with malaise, rash, respiratory symptoms (dyspnea, chest pain), gastrointestinal symptoms, and hypotonia. A link between IR and the presence of anti-drug antibodies has been described in different studies[15,16,17,18,19]. Ruperto, *et al*[20] found in a prospective clinical trial that lower IFX doses were associated with lower trough levels of IFX and a higher frequency of anti-drug antibodies and IR[17].

However, one can also assume the opposite causality, with the presence of anti-drug antibodies causing lower trough levels of IFX by formation of anti-drug antibody IFX complexes, which will then lead to an unsatisfactory treatment response.

In children, IFX has only been approved for the treatment of inflammatory bowel disease. However, it is regularly used in pediatric patients with inflammatory rheumatologic diseases and noninfectious uveitis owing to the form of application, the experience in JIA[6,20], and the positive effects on uveitis[21]. There are only a few publications that have studied adverse reactions toward IFX for these latter indications, including a total of 117 children with JIA and 48 cases with uveitis[18,20,21,22,23,24,25] showing incidences of IR between 6% and 36%. Therefore, the purpose of our study was to analyze the frequency and nature of severe adverse reactions to IFX infusions in children treated for refractory rheumatologic systemic inflammatory diseases and noninfectious uveitis in a real clinical setting, to discuss the results, and to compare to the available literature.

MATERIAL AND METHODS

This is a retrospective review of all consecutive patients treated with IFX from October 4, 2000, to December 31, 2012, at the Rheumatologic Department of the University Children's Hospital Zurich, Switzerland. The indication for IFX treatment included the different categories of JIA (diagnosed according to the diagnostic criteria of the International League of Associations for Rheumatology[26,27]), ocular inflammatory disease and other systemic inflammatory diseases. The indication for IFX was prior failure of standard therapy for the disease, e.g., corticosteroids and/or DMARD. Contraindications for IFX consisted of acute or recurrent infections, including tuberculosis, heart failure (New York Heart Association III or IV), and a patient or first-degree relative with a history of lymphoma. Prior to IFX initiation, patients were screened for tuberculosis by history and skin test. Patients were all treated at the Outpatient Day Clinic and were visited by a pediatric rheumatologist at every IFX administration. Two patients were treated within an international study conducted to evaluate the efficacy and safety of IFX and followed the study protocol for dosage and frequency of infusion[20]. Twenty-one of the 82 patients had previous biological treatment, but all were naive to IFX.

IFX dosage and monitoring. IFX was administered according to the manufacturer's instructions. The starting dose was 3–5 mg/kg when arthritis was the indication and 5–6 mg/kg when uveitis was the indication for IFX. The dose was adapted (rounding up or off) to the next 100-mg increment and given at weeks 0, 2, 6, and every 4 weeks thereafter. In case of a good clinical response, the interval between 2 consecutive infusions was subsequently increased, typically in 1-week increments after every third infusion. Thus, with good clinical response, IFX was tapered by extension of the infusion interval up to 12 weeks, when IFX was discontinued. Also, IFX dose was adapted depending on the observed clinical response, either by increasing infusion frequency or drug dose in 100-mg increments. Vital signs including temperature, pulse, blood pressure, and O_2 saturation were recorded before, during (every 30 min), and after the infusion (last recording 60 min postinfusion). When patients were treated for at least 1 year without an IR, the infusion protocol was shortened to 1 h with monitoring of vital signs 30 min postinfusion.

Acute IR were defined as any event occurring during IFX infusion or up until 1 h after IFX infusion. Severity of IR was assessed by the physician based on patient's signs and symptoms and classified as mild, moderate, or severe in accordance with the Cheifetz criteria[14] (Table 1).

According to hospital routine, all patients took an oral antihistamine (cetirizine) at least 1 h before commencing infusion or received clemastine intravenously 15 min prior to commencing infusion. Once an IR occurred in a patient, clemastine was prescribed as a premedication for subsequent infusions. In case of repeated IR, the clemastine premedication dose was increased stepwise (maximally 4-fold of the recommended dose) until good infusion tolerance was achieved. If this premedication was not successful, corticosteroids were added to the premedication schedule. Once the effective premedication dose for an individual patient was established, it was maintained for at least 3 consecutive infusions before it was then gradually reduced again, at the discretion of the treating physician. In addition to premedication, the infusion rate was decreased for the consecutive infusions after a first IR had occurred.

Following clinical routine, all patients treated with IFX received comedication with an immunosuppressive drug (e.g., MTX) to reduce the risk of anti-drug antibody formation[17,28,29]. MTX dose was 15 mg/m^2 body surface area at the start of IFX treatment in all patients. Once disease inactivity was achieved, MTX dose was reduced to 10 mg/m^2 in most patients.

Data collection and analysis. The following clinical data were collected from the medical records of the patients: demographic data (age and sex), medical history and treatment, additional diagnoses and concurrent medication, as well as disease characteristics (e.g., current diagnosis, age at diagnosis, immunologic factors, associated diseases such as concurrent uveitis, and the indication for IFX treatment). Detailed information about each IFX infusion was documented in a standardized way including date of every infusion, IFX dose, patient's weight, occurrence of IR and other AE, arthritis, or uveitis at the time of infusion. Data about current or prior infections were collected at every patient visit. However, no structured interviews for AE other than severe AE (SAE) were conducted, and minor infections may therefore have been missed.

During the first years, when our patients were treated with IFX, anti-IFX-antibody testing was not available and at time of data examination the essential blood samples were incomplete for retrospective analysis of anti-drug antibody presence. Anti-IFX antibody results are available only for a few patients included in our study, which is why the results have not been considered for the purpose of our study.

Excel and SPSS were used for the statistical analysis (Microsoft Office Excel 2008 and SPSS Version 16 for Windows; IBM Co.). Comparisons between groups were made using chi-square. A p-value of < 0.05 was considered significant. The study was approved by the institutional ethics review board of the University Children's Hospital Zurich.

RESULTS

Patient's data. For summarized information on basic patient data and IFX infusions, see Table 2. There was no statistically significant difference in basic patient data between patients with and without IR.

IR. Of a total 2446 IFX infusions, 46 acute IR (2%) occurred

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Table 1. Definition of infusion reactions, in accordance with the Cheifetz criteria[14].

Severity of Infusion Reaction	Symptoms	Treatment
Mild	Hyperemia, malaise, or dizziness. Self-limited course	Reduction (to 10 ml/h) or stop infusion. Eventually clemastine IV (0.05 mg/kg). Monitoring of vital signs every few minutes until within normal limits. Restart of infusion after break of at least 30 min with slow infusion rate (10 ml/h), then gradual increase.
Moderate	Respiratory symptoms (e.g., dyspnea, chest tightness, stridor). Gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal pain). Urticaria	Stop infusion. Clemastine IV (0.05 mg/kg); methylprednisolone IV (2 mg/kg), and inhalation (albuterol, epinephrine) if necessary. Monitoring of vital signs every few minutes until within normal limits. Restart of infusion after break of at least 30 min.
Severe	Respiratory, gastrointestinal symptoms, and/or rash and tachycardia and hypotonia	Stop infusion. Clemastine IV (0.05 mg/kg); methylprednisolone IV (2 mg/kg), adrenalin (1:1000, 0.1 mg IM) in case of hypotonia. Monitoring of vital signs every few minutes until within normal limits.

IV: intravenously.

in 14 patients (17%). Of these 14 patients, 9 (64%) experienced more than 1 IR. The number of episodes of IR ranged from 1 to 9. Numerically, 5 patients experienced 1 IR, 1 patient 2, 3 patients 3, 1 patient 4, 2 patients 5, 1 patient 7 and 9 IR each. The first IR occurred between 41 and 1124 days (160 weeks) after IFX initiation, with a mean of 354 days (51 weeks).

In 12/14 patients, the first IR occurred during active disease. In 7 patients the first IR was preceded by a flare of previously quiet arthritis or uveitis. In these patients the IR was observed on average 569 days (21 months) after IFX treatment start (range 184–1675 days). The disease activity in the other 5 patients was never controlled before the first IR occurred (persistent arthritis or uveitis). In these patients the first IR manifested after a mean of 66 days after initiation of IFX treatment [in 4 patients the first IR occurred during the third IFX infusion (41–49 days after IFX treatment start), in 1 patient after 155 days]. Only in 2/14 patients (14%) did the first IR manifest without a preceding disease flare during an episode of well-controlled disease activity (after 420 and 1124 days, respectively). Following the IR, IFX infusion was restarted after an interruption of 30 min in 36/46 cases (78%).

Acute IR led to immediate discontinuation of IFX treatment in 2/14 patients (14%). In both patients the indication for IFX was arthritis and they had experienced a flare of arthritis preceding the IR. IFX treatment was discontinued in a further 2 patients because of repeated IR without disease flare and in another 2 because of repeated IR with concomitant disease flare (flare of polyarthritis and of uveitis, respectively). Premedication with higher doses of antihistamines (8/8 patients, 100%), corticosteroids (6/8 patients, 75%), and an increase of IFX (reduction of interval or dose increase, 6/8 patients, 75%) allowed 8 patients (8/14, 57%) to continue IFX treatment after the first IR with a mean followup time of 146 (range 26–537) weeks. Only in 1 child did the second IR manifest with more severe symptoms (additional vomiting and abdominal pain), while the severity of repeated IR remained on a similar level for all other patients. IFX treatment was continued in 6/14 patients despite IR because no better treatment was available for 4 children with severe uveitis and in 2 patients after ineffective trials of etanercept and adalimumab prior to IFX treatment.

Severity and symptoms of acute IR. Twelve IR (26%) were classified as mild, 34 (74%) as moderate, and none as severe. During the acute IR most patients presented with more than 1 symptom. For detailed descriptions see Table 3.

Other adverse drug reactions. Three patients (3/82, 4%) developed psoriatic skin lesions during the course of IFX treatment; in all 3 cases IFX was eventually stopped (1.1 events per 100 patient-yrs). IFX was restarted in 1 patient after 19 weeks owing to unsatisfactory efficacy of adalimumab, which had been started after discontinuation of IFX. Overall, 50 patients (61%) experienced recurrent viral infections (mostly upper respiratory tract infections) or bacterial infections with need for antibiotic therapy. Four patients were hospitalized for severe infection (1 each with bacterial superinfection of varicella, septic shock without germ identification, fever of unknown origin, and perityphlitic abscess). Another patient treated with IFX and high-dose corticosteroids for unclear inflammatory syndrome died from meningococcal sepsis after 3 IFX infusions (1.8 severe infections per 100 patient-yrs).

Outcome during followup time. During the study period, IFX was discontinued in 22/82 patients (27%) after a mean treatment duration of 39 months (range 1–131 mos); in 4 patients (5%) because of insufficient efficacy, in 6 (7%) because of IR (3 of them simultaneously had a flare of polyarthritis, the main reason for discontinuation), in 2 (2%) owing to TNF-associated skin rashes, in 4 (5%) as a result of patient or parent wish, and in 6 (7%) for other reasons. Six of the 22 patients who discontinued the treatment had a good response to IFX, while the response was insufficient in the other 16 patients. Seven patients switched to adali-

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Table 2. Baseline characteristics of the patients.

Characteristics	All Patients, n = 82	Patients with Infusion Reactions, n = 14	Patients without Infusion Reactions, n = 68
Female, n (%)	59 (72)	12 (86)	47 (69)
Diagnosis, n (%)			
JIA	70 (85)	14 (100)	56 (81)
Persistent oligoarthritis/extended oligoarthritis	30	4	26
Polyarthritis (RF-negative)	24	7	17
Polyarthritis (RF-positive)	1	0	1
Enthesitis-related arthritis	3	0	3
Psoriatic arthritis	1	1	0
Systemic arthritis	5	1	4
Undifferentiated arthritis	6	1	5
Ocular inflammatory disease	10 (12)	0	10 (15)
Other inflammatory disease	2 (2)	0	2 (3)
Unclassified systemic inflammatory disease	1		1
Takayasu arteritis	1		1
Comorbid conditions, n (%)	16 (20)	3 (21)	13 (19)
Genetic diseases (e.g., trisomy 21, Williams-Beuren syndrome)	6	1	5
Autoimmune diseases (e.g., linear SSc, Crohn disease)	4	0	4
Other (e.g., osteochondritis dissecans, attention deficit disorder)	6	2	4
Indication for IFX (%)			
Arthritis	49 (60)	12 (86)	37 (54)
Uveitis	16 (20)	0	16 (24)
Arthritis and uveitis	13 (16)	2 (14)	11 (16)
Other	4 (5)	0	4 (6)
Crohn disease and JIA	1		1
Systemic JIA	1		1
Unclassified systemic inflammatory disease	1		1
Takayasu arteritis	1		1
Comedication, n (%)			
MTX	67 (82)	11 (79)	56 (82)
Leflunomide	8 (10)	2 (14)	6 (9)
MTX, then leflunomide	4 (5)	0	4 (6)
MTX, then azathioprine	0	1 (7)	0
Sulfasalazine	1 (1)	0	1 (1)
Azathioprine	1 (1)	0	1 (1)
Previous biologicals, n (%)	21 (26)	3 (21)	18 (26)
Age at IFX start, yrs, mean ± SD	10.1 ± 3.9	8.2 ± 4.2	10.5 ± 3.7
Range	2.3–17.0	2.3–16.9	3.7–17.0
Disease duration at IFX start, yrs, mean ± SD	3.9 ± 3.3	2.9 ± 2.2	4.1 ± 3.5
Range	0.2–14.7	0.7–7.0	0.2–14.7
Followup during study period, wks, mean ± SD	169 ± 136.6	173 ± 175.2	168.3 ± 128.8
Range	3–560	18–560	0–545.4
Number of infusions, mean ± SD	30 ± 20	30 ± 29	0
Range	2–114	6–114	
Dose of IFX, mg/kg/dose, mean ± SD	6.2 ± 1.5	5.5 ± 1.7*	6.3 ± 1.5
Range	3.5–10.4	3.5–8.5	3.5–10.4
Infusion interval of IFX, wks, mean ± SD	5.2 ± 1.3	5.0 ± 1.3*	5.3 ± 1.4
Range	2.2–15**	2.9 ± 7.0	2.2–15**

* Calculated from beginning of IFX treatment to first infusion reaction. ** Usually we discontinued treatment after maximum infusion interval of 12 weeks. The long interval of 15 weeks was due to retardation caused by viral illness. IFX: infliximab; RF: rheumatoid factor; SSc: systemic sclerosis; MTX: methotrexate.

mumab, 6 to tocilizumab, 3 to etanercept, 3 to golimumab, 1 to anakinra, and 1 to leflunomide. One patient interrupted IFX treatment and was lost to followup. Four patients (5%) were able to discontinue IFX treatment following disease remission after a mean treatment time of 36 months (range 23–59), but treatment had to be restarted in all 4 patients because of disease flare. In 3 patients IFX was restarted directly after a mean of 5 months (range 3–6). One patient started etanercept but had to change back to IFX as a result of an arthritis flare during etanercept treatment after 7.5 years. In 2 patients, IFX therapy was stopped following an adverse drug event (TNF-associated rash) and parents' wish

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Table 3. Characteristics of infusion reactions (IR).

Characteristics	All Patients, n = 82; All Infusions, n = 2446	All Patients with IR, n = 14	All Infusions, n = 2446
Patients with IR, n (%)	14 (17)	14 (100)	
No. patients with IR/100 patient-yrs		5.1	
IR, n (%)	46 (2)		46 (100)
IR/100 patient-yrs			16.9
Severity of IR, n (%)			
Mild	12 (26)	6 (43)	12 (26)
Moderate	34 (74)	11 (79)	34 (74)
Severe	0		0
Symptoms during IR, n (%)			
Respiratory	33 (72)	10 (71)	33 (72)
Dyspnea	22 (48)	7 (50)	22 (48)
Cough	19 (41)	7 (50)	19 (41)
Wheezing	5 (11)	4 (29)	5 (11)
Malaise	28 (61)	12 (86)	28 (61)
Cutaneous (flush, rash)	27 (59)	8 (57)	27 (59)
Gastrointestinal	6 (13)	5 (36)	6 (13)
Abdominal pain	1 (2)	1 (7)	1 (2)
Diarrhea and vomiting	5 (11)	4 (29)	5 (11)
Hypotonia/tachycardia	0	0	0
Treatment during IR, n (%)			
Antihistamine IV (clemastine)	39 (85)	13 (93)	39 (85)
Corticosteroid IV (methylprednisolone)	22 (48)	10 (71)	22 (48)
Epinephrine inhalation	6 (13)	2 (14)	6 (13)
Albuterol inhalation	1 (2)	1 (7)	1 (2)

IV: intravenous.

each, but was reinitiated in both cases because of arthritis flare (range until restart of IFX 14–390 wks = 7.5 yrs).

DISCUSSION

We present a detailed description of the safety of IFX infusions in 82 children. The incidence of acute IR of 17% of patients treated with IFX is similar to data reported in cohorts of adult patients with rheumatoid arthritis[10,12] and children with JIA[20,30]. In patients treated with IFX for Crohn disease, IR occur variably (9.7% to 26%)[31,32,33,34]. The incidence of IR varies considerably within the different studies evaluating AE for IFX treatment. Because protocols for IFX premedication are not consistently mentioned and comedication is only partially prescribed, a detailed comparison of the incidence of IR as well as infusion protocols is not possible. A potential reason for the variability in incidence of IR could be the premedication with corticosteroids, which is more often used in patients with Crohn disease. Corticosteroids have been associated with fewer IR because of their antihistaminic effect[35]. In children, antihistamines are often used as a premedication and are usually well tolerated. In some cases, antihistamines were associated with AE such as malaise or respiratory (e.g., dyspnea) or gastrointestinal symptoms, which are similar to the symptoms observed during IR to IFX. However, because the symptoms in our patients always occurred during IFX infusion and resolved in many patients despite continuation or even increase of antihistamine dosage, we attributed the symptoms to the IFX treatment.

In accordance with other publications, most IR were classified as mild or moderate[20,21]. We did not observe any severe IR, suggesting that most IR are not anaphylactic, IgE-mediated reactions.

In our cohort, the first IR occurred after mean treatment duration of 51 weeks (range 41–160). In 50% of patients with IR, the first IR was preceded by a flare of arthritis or uveitis, and in 36% the patient's disease activity was not controlled before the first IR.

In different studies a clear relationship between the presence of anti-IFX antibodies and treatment failure has been demonstrated[15,28]. Bendtzen, *et al* showed that the degree of inflammation and disease activity at treatment initiation influences the serum levels of IFX[36]. Patients with higher pretreatment disease activity exhibited lower levels of IFX in plasma and were more prone to subsequent development of anti-IFX antibodies, leading to a non-response to IFX treatment and increased risk of IR. In that study, a substantial number of patients with low serum levels of IFX at an early timepoint of 1.5 months after treatment start experienced treatment failure. Further, early formation of anti-IFX antibodies (at 3 mos of treatment) was also associated with subsequent discontinuation of therapy due to treatment failure or IR. In our cohort, 5 patients with persistent baseline disease activity (persistent arthritis or

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uveitis) experienced the first IR after a mean of 66 days following initiation of IFX treatment. It may be hypothesized that a similar mechanism with low trough IFX levels and early anti-IFX antibody formation may also have occurred in these patients; however, serum IFX level and anti-IFX antibodies were not measured.

Eleven of 14 patients continued treatment despite the first IR, among them 8 patients (> 50%) who were able to continue IFX treatment with premedication (higher dose of antihistamines and in some cases additional corticosteroids) and increased IFX dose. Various studies have shown that higher dosages of IFX were associated with lower anti-IFX antibodies, suggesting induction of immune tolerance[15,20,37,38]. Ruperto, *et al* showed that patients treated with IFX 3 mg/kg/dose had a higher proportion of IR (35%) compared to patients treated with IFX 6 mg/kg/dose (17%)[20]. Our patients obtained a mean IFX dose of 6.2 mg/kg/dose and showed the same frequency of IR compared with patients treated with IFX 6 mg/kg/dose in the Ruperto, *et al* study[20]. Recently, Tambralli, *et al* published results of a retrospective study in which high doses of IFX (≥ 10 mg/kg) in the management of JIA were shown to be safe and associated with a low rate of IR (0.5%)[39]. Because IR are associated with anti-IFX antibodies[36,40], we hypothesize that the suppressive effect of higher IFX dosage on anti-IFX antibody formation leads to a reduction in the incidence of IR.

All patients continuing IFX treatment were able to stop the additional premedication after some time without recurrence of their symptoms. Based on our observation, we suggest continuing IFX treatment in case of a mild or moderate IR with the administration of additional premedication (antihistamines and corticosteroids as necessary) and an increase in IFX dose. The beneficial effect of premedication with antihistamines has already been shown by other groups[22]. The risk reduction of anti-drug antibody formation by comedication with an immunosuppressive drug has been shown in different studies[17,28,29]; there was no difference in the incidence of IR between the different comedication drugs in our patients. Overall, IFX was well tolerated regarding IR occurrence. Even though 61% of our patients treated with IFX had recurrent infections, serious infections occurred in only 6% of the patients and there was no report of opportunistic infection. However, 1 patient died from meningococcal sepsis during IFX treatment. This patient had a high disease activity and was concomitantly treated with high doses of systemic corticosteroids leading to an important additional immunosuppression. The observations on occurrence of infections are similar to the findings of Ruperto, *et al*[20]. Three patients (4%) developed psoriatic skin lesions during IFX treatment; 1 of them had a family history of psoriasis. As described[41,42,43], the rash resolved without consequences in all patients with only local treatment after discontinuation of IFX. Therefore, we attributed the psoriatic skin lesions to the IFX treatment.

Our study is limited by the retrospective study design, the heterogeneity of our patients, and the lack of repeated measurements of anti-drug antibodies and drug levels throughout the IFX treatment. Further, many studies report findings from adult patients treated for rheumatoid arthritis, and those findings may be of limited value for our patients with different diseases and in a different age group. However, our findings may be helpful for clinicians dealing with children with difficult-to-treat arthritis and uveitis.

Our study describes in detail acute IR in children with inflammatory rheumatologic and ocular diseases. Acute IR to IFX occurred infrequently and were mostly mild and moderate. Treatment with antihistamine drugs, methylprednisolone, and increased/more frequent IFX administration allowed continuation of IFX treatment despite IR in > 50% of patients. Other SAE such as severe infections were infrequent.

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