JPPT | Review

Systematic Review of Adverse Events of IL-1 and IL-6 Inhibitor Use in Pediatrics

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OBJECTIVE Two, relatively new and potent, classes of biologicals are interleukin-6 (IL-6) and interleukin-1 (IL-1) inhibitors. As the use of these biologicals in children is more recent, the nature and incidence of adverse effects in the pediatric population are less well known. We systematically reviewed the available literature to elucidate the risks of IL-1 and IL-6 inhibitor use in the pediatric population.

METHODS A systematic literature search was conducted including English-language clinical studies of children who received IL-1 or IL-6 inhibitors for therapeutic purposes. Abstracts and full-text screening of manuscripts were carried out by 2 independent reviewers, based on predefined eligibility criteria. Any conflicts between the 2 reviewers were resolved by a third reviewer. Data extracted included characteristics such as intervention (drug, dose, method of administration, frequency), adverse events, and frequency of adverse events.

RESULTS A total of 2707 studies were screened and 38 studies were selected for inclusion. Of these 38 studies, 9 involved canakinumab, 12 involved anakinra, 2 involved rilonacept, 15 involved tocilizumab, and 1 involved an unspecified recombinant IL-6 antagonist. The most common adverse events included infection, local injection site reactions, headache, fever, arthralgia, and rash. There were 557 serious adverse events reported in 2208 patients (rate = 25%).

CONCLUSIONS Risks of biological use should be considered alongside the immunosuppressive benefits when prescribing IL-1 and IL-6 inhibitors in the pediatric population. Few data were available on long-term follow-up of these patients.

ABBREVIATIONS CAPS, cryopyrin-associated periodic syndromes; IL-1, interleukin-1; IL-6, interleukin-6; JIA, juvenile idiopathic arthritis; MAS, mast cell activation syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ROBINS-E, Risk of Bias in Non-Randomized Studies–of Exposures

KEYWORDS biological therapy; child; drug-related side effects and adverse reactions; interleukin-1; interleukin 1 receptor antagonist protein; interleukin-6; pediatrics

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Introduction

Recently, there has been a surge in the development of biologicals, which is a diverse group of medications often produced by using living organisms such as mammalian cells, microbial agents, plants, and yeast. A subclass of these biologicals is designed to specifically target the immune response, particularly for treating immune-mediated conditions. Several biological agents have emerged that work to regulate and block the activity of cytokines.

After exposure to inflammatory stimuli such as bacterial products, the concentration of proinflammatory cytokines, such as interleukin-1 (IL-1α and IL-1β) and interleukin-6 (IL-6), increase and feed a proinflammatory signaling cascade. Animal studies demonstrated that IL-6 promotes chronic autoimmune-driven inflammation. This cytokine seems to promote differentiation of proinflammatory T-helper lymphocytes and inhibits regulatory T-lymphocyte differentiation, although it likely interacts with other interleukins in humans.[1] Autoimmune conditions, such as cryopyrin-associated periodic syndrome (CAPS) and juvenile idiopathic arthritis, have also shown elevated concentrations of IL-1β. Interleukin-1 is known to promote the differentiation and migration of cytotoxic T lymphocytes and is involved in matrix enzyme activity leading to tissue damage.[2] Biologicals that target cytokines such as IL-1 and IL-6 have proved effective in treating pediatric patients with severe rheumatologic autoinflammatory conditions.[3] However, owing to the immunosuppressive effect of the drugs targeting IL-1 and IL-6, studies have suggested associated risks such as increased risks of new infections or reactivation of latent infections (e.g., tuberculosis), and infection related to live vaccines.[4–6]

In the past, studies of IL-6 and IL-1 inhibitor use specifically in children were limited, as information was often extrapolated from adult data. As the use of these biologicals in children is more recent, the adverse effects in the pediatric population are less well outlined, and some adverse events (e.g., developmental effects) may not be possible to glean from adult studies.

The aim of this study was to systematically review the adverse events that occur during treatment with IL-6 inhibitors (e.g., sarilumab and tocilizumab) and IL-1 inhibitors (e.g., anakinra) when used in the pediatric population.

Materials and Methods

Search Strategy and Selection Criteria. A literature search was conducted in Cochrane, Web of Science, and LILACS databases on June 5, 2022, and in Embase and MEDLINE on June 6, 2022, on articles published until these specified dates. There was no restriction applied on sex or ethnicity, in order to ensure a comprehensive understanding of a broad spectrum of populations. English-language clinical studies of children who received IL-1 or IL-6 inhibitors such as sarilumab, tocilizumab, or anakinra for therapeutic purposes were included. The search strategy was developed by using a combination of the following search terms: infant/child health/child/pediatric/juvenile/neonate, interleukin 1 receptor blocking agent/recombinant interleukin 1 receptor blocking agent/IL-1 inhibitor/anti-IL1, canakinumab/ilaris/anakinra/kineret/arcalyst, rilonacept/IL-6 inhibitor/interleukin-6 inhibitor/anti-IL6, or tocilizumab/Actemra/sarilumab/Kevzara. The main outcome measures were studies reporting quantitative and/or qualitative data of any adverse events after the administration of the specified drugs in the clinical trial. Adverse events are defined as unintended clinical outcomes occurring in patients receiving the specified intervention. Eligible study designs include prospective cohort, cross-sectional, case series, and case-control studies. Articles studying animal models, coronavirus treatment, or cancer treatment were excluded. The search was limited to publications in English.

Studies were included if they met the following criteria:

1. The study participants were younger than 18 years.
2. The administration of IL-1 or IL-6 inhibitors for therapeutic purposes.
3. Study designs: prospective cohort, cross-sectional, case series, and case-control studies.
4. The study reported quantitative and/or qualitative data of adverse events in the clinical trial.
5. The article was in the English language.

Screening and Data Extraction. Following the search, the studies were collated and uploaded onto Covidence, a review management software, which was used to screen titles, abstracts, and full-text articles. Abstracts and full-text screening of manuscripts were carried out by 2 independent reviewers (AP, NC), based on predefined eligibility criteria, where 2707 studies were screened, following duplicate removal, and 2380 studies were excluded. Any conflicts between the 2 reviewers were resolved by a third reviewer (FG-B). During the full-text assessment stage, the reviewers assessed 327 studies for inclusion. Of these, 289 studies were excluded for the following reasons: abstract presentation; study design, study outcome, intervention, or patient populations not aligning with inclusion criteria; unavailable full text; English version unavailable; older reports of a study; and absence of separate pediatric and adult outcome data.

Following the finalization of included studies (n = 38), 2 reviewers (AP, NC) independently extracted data by using a data extraction form with characteristics such as intervention (drug, dose, method of administration, frequency), adverse effects, and frequency of adverse effects. This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines of 2020, ensuring transparency and comprehensiveness in the review process (see Figure).[7]

Risk of Bias. To assess risk of bias, the Cochrane Risk of Bias in Non-Randomized Studies–of Exposures (ROBINS-E) was used in the data extraction phase.[8] The ROBINS-E framework allowed us to systematically assess various domains of bias, including confounding, selection bias, exposure measurement, and outcome assessment. The factors influencing bias aid in determining whether the adverse events were more likely related to biological use rather than other factors such as concurrent disease or other drugs.

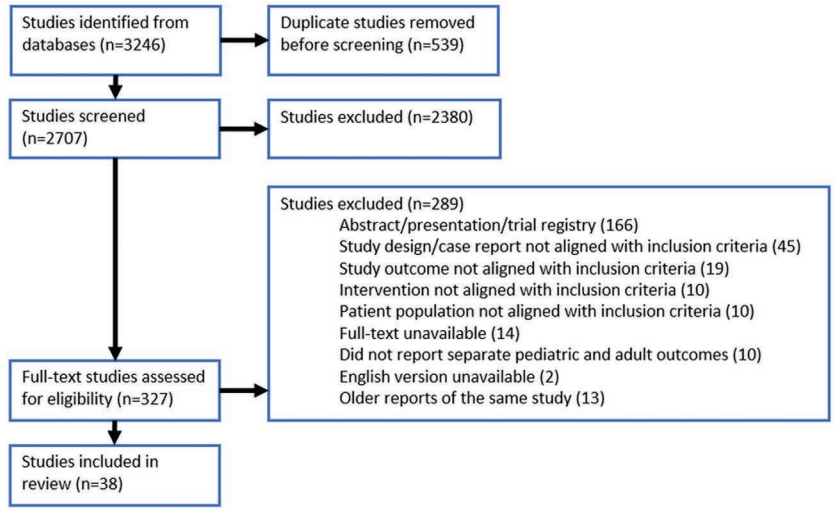
Data Charting and Analysis. In the data charting and analysis phase of our study, we systematically summarized the information extracted from eligible articles through a qualitative analysis approach. This analysis encompassed a comprehensive evaluation of various study and sample characteristics, including study design, year of publication, type of inhibitor used, specific drug or treatment, method of administration, patient demographics such as age and underlying medical conditions, and the number of pediatric patients involved in each study. Additionally, we recorded the number of patients who experienced adverse events and the total count of adverse events reported across the included studies.

Results

After 2707 studies underwent initial title and abstract screening, 327 studies were assessed for eligibility through full-text screening (Figure). Of these, 38 studies fulfilled all inclusion criteria and were included in this review (Table 1.)[9–46]

The ROBINS-E tool resulted in a scoring of “some concerns” or “high risk” for the risk of bias of the studies

Figure. PRISMA diagram outlining study screening process.



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Summary of Included Studies

Drug		Number of Studies
IL-1 inhibitor	Canakinumab	9
	Anakinra	12
	Rilonacept	2
IL-6 inhibitor	Tocilizumab	15
	Recombinant IL-6 receptor antagonist	1

IL-1, interleukin-1; IL-6, interleukin-6

included. The main concerns were related to lack of reporting on or control of confounding variables such as concomitant medications and comorbidities. In many cases, comorbidities and other medications being taken by patients were not specified in the studies, but immunosuppressants such as corticosteroids or anti–tumor necrosis factor drugs were often discontinued prior to the study period.

Interleukin-1 Inhibitors. ***Canakinumab.*** Nine studies assessed canakinumab as an intervention (Table 2). Treatment doses were either 150 mg or 2 to 4 mg/kg. This treatment was studied in patients with CAPS, colchicine-resistant familial Mediterranean fever, hyperimmunoglobulin D syndrome–mevalonate kinase deficiency, systemic juvenile idiopathic arthritis (JIA), idiopathic recurrent pericarditis, pyoderma gangrenosum, and sickle cell anemia. The number of patients in each study ranged from 16 to 177, with an overall total number of 560, and a median number of 47 patients per study. Study duration was a mean of 32.3 (range, 6–90) months, for studies that provided this information. Adverse events included infections (e.g., upper and lower respiratory tract infections) (n = 58 patients or 122 events in studies not reporting number of patients). Other reported events included local injection site reactions (n = 2, events = 1), fever (n = 76), headache (n = 63), arthralgia (n = 50), diarrhea (n = 42), and rash (n = 30). Elevated transaminase concentration (n = 6), thrombocytopenia (n = 12), neutropenia (n = 13), and leukopenia (n = 1) were also reported. More rarely reported events included abscess following appendicitis, anaphylaxis, mast cell activation syndrome (MAS), urticaria, and splenic cyst. Studies that identified serious adverse events reported 95 events (rate = 0.17, of 560 total studied patients).

Anakinra. Twelve studies included anakinra as an intervention. Treatment doses ranged from 0.5 to 4 mg/kg, with 1 study allowing up to 11 mg/kg and a maximum dose of 100 mg/day. Conditions treated included CAPS, chronic infantile neurological cutaneous and auricular syndrome, Muckle-Wells syndrome, recurrent pericarditis, systemic JIA, juvenile rheumatoid arthritis, Kawasaki disease, and neonatal-onset multisystem inflammatory disease. The overall total number of patients was 299 and the median number of patients was 22 per study. Study duration was a mean of 22.5 (range 1.5–60) months. Commonly reported adverse events include local injection site reactions (n = 42 patients, and 16 events in studies that did not report number of patients), headache (n = 52), arthralgia (n = 18), fever (n = 43, events = 40), infection (including upper respiratory tract infections) (n = 107, events = 235), rash (n = 28, events = 59), ocular hyperemia (n = 12), fatigue (n = 10), diarrhea (n = 19, events = 1), nausea/vomiting (n = 9, events = 26), oropharyngeal pain (n = 9), musculoskeletal pain (events = 118), and elevated liver enzymes (n = 2, events = 13). More rarely reported events included

Table 2. Reported Adverse Events With IL-1 and IL-6 Inhibitor Use in Children

Drug	Dose and Method of Administration	Patient Age	Patient Condition	Number of Pediatric Patients (Unless Age Otherwise Specified)	Number of Patients With AEs	Number of AEs (for Studies That Did Not Present Data on the Number of Patients With AEs)	Author
IL-1 inhibitor: canakinumab	150 mg for patients with body weight >40 kg, 2 mg/kg for ≥15 kg and ≤40 kg, 4 mg/kg for ≥7.5 kg and <15 kg every 8 wk subcutaneous. Median treatment duration 16 (range, 8–33) mo	Median 9 yr	Cryopyrin-associated periodic syndromes	20	Infections: 7 (bacterial tracheitis, presumed upper respiratory tract infection, lower respiratory infection, uncomplicated varicella zoster, presumed viral gastroenteritis)		Elmi[15]
	150 mg or 2 mg/kg (≤40 kg) every 8 wk for up to 2 yr, subcutaneous For residual symptoms, increased dose and/or dosing frequency	Mean 10.2 yr (range, 3–17)	Cryopyrin-associated periodic syndrome	47	Infections: 35 Intra-abdominal abscess following appendicitis: 1 Severe tonsillitis: 2	6 serious AEs (SAEs, 3 likely related to drug, 3 unrelated)	Kuemmerle-Deschner[23]
	Initial dose of 2 mg/kg if needed, gradually increased (2 mg/kg per each increment) every 1 or 2 mo until disease controlled, subcutaneous. Duration of 21.8 ± 15.8 mo (6–54)	Mean 2.8 ± 2.2 yr	Colchicine-resistant familial Mediterranean fever (19) Hyperimmunoglobulin D syndrome–mevalonate kinase deficiency (3) Cryopyrin-associated periodic syndrome (3) Systemic JIA† (2) Idiopathic recurrent pericarditis (1) Pyoderma gangrenosum (1)	29	Impetigo: 1 Upper respiratory tract infection: 5		Çakan[12]
	2–4 mg/kg (<40 kg) and 150 mg (≥40 kg), subcutaneous. Mean duration of canakinumab use 31.4 ± 10.57 (range, 6–52) mo	Mean age at diagnosis was 5.59 ± 3.9 (range, 4–19) yr	Colchicine-resistant familial Mediterranean fever	65	Local injection site reaction: 2 Cervical lymphadenitis: 1		Yücel[46]
	2.5–4 mg/kg every 1–2 mo, subcutaneous, with median follow-up at 7.5 yr (range, 1–17)	3–16 yr	Familial Mediterranean fever	14	No adverse events		Ekinci[20]

(Table cont. on page 156)

Table 2. Reported Adverse Events With IL-1 and IL-6 Inhibitor Use in Children *(cont.)*

Drug	Dose and Method of Administration	Patient Age	Patient Condition	Number of Pediatric Patients (Unless Age Otherwise Specified)	Number of Patients With AEs	Number of AEs (for Studies That Did Not Present Data on the Number of Patients With AEs)	Author
	Dose not stated, subcutaneous, duration 16 mo, (range, 4–58)	Median 7.4 yr (range, 1.8–17.3)	sJIA	26		Infections: 6 Headache: 5 Neutropenia: 3 Elevated transaminase: 6 Proteinuria: 2 Local site reaction: 1 Thrombocytopenia: 1 Stomach pain: 1 Breast pain: 1	Lainka[25]
	Phase 1: 4 mg/kg subcutaneous every 4 wk. Mean observation 450 days Phase 2: (patients in clinical remission) randomly assigned to 2 mg/kg then 1 mg/kg then discontinued OR every 8 wk then 12 wk then discontinued, subcutaneous. Mean observation 596 days	Median 9 yr (range, 6–14)	sJIA	Cohort 1 (inactive disease): 68 Cohort 2 (active disease): 98		Cohort 1: Pyrexia: 13 Nasopharyngitis: 32 Headache: 21 Arthralgia: 14 Diarrhea: 3 Cough: 10 Rash: 5 URTI: 22 Viral infection: 4 Cohort 2: Pyrexia: 63 Nasopharyngitis: 38 Headache: 37 Arthralgia: 36 Diarrhea: 39 Cough: 29 Rash: 25 URTI: 18 Viral infection: 8 SAEs: 55	Quartier[33]
	Trial 1: 29 days, single subcutaneous dose (4 mg/kg) Trial 2: open-label phase–treatment every 4 wk for 12 to 32 wk	Median 8 yr	sJIA	Trial 1: 43 Trial 2: Open label (177), Canakinumab in withdrawal phase (50)	Trial 1: Mast activation syndrome: 5 Varicella: 1 Trial 2–open label: Thrombocytopenia: 11 Neutropenia: 10 Non-opportunistic infections: 7 Trial 2, patients who continued treatment in withdrawal phase: Arm pain and lymphadenopathy: 1 Otitis media and leg fracture: 1 Leukopenia, thrombocytopenia, aminotransferase elevation: 1 Respiratory tract infection: 1 Splenic cyst: 1	SAEs: 15	Ruperto[36]

(Table cont. on page 157)

Table 2. Reported Adverse Events With IL-1 and IL-6 Inhibitor Use in Children *(cont.)*

Drug	Dose and Method of Administration	Patient Age	Patient Condition	Number of Pediatric Patients (Unless Age Otherwise Specified)	Number of Patients With AEs	Number of AEs (for Studies That Did Not Present Data on the Number of Patients With AEs)	Author
	300 mg (4 mg/kg for weight ≤40 kg), 6 monthly treatments every 4 wk, subcutaneous. Total duration of treatment 48 wk	Mean 15.8 (SD, ±2.69) yr	Sickle cell anemia	16	Study drug–related events: 4 events in 3 patients Infection: 8 events total (1 URTI) Serious adverse events: 19 events in 11 patients (10 hospitalizations for acute pain crisis)	SAEs: 19 in 11 patients	Rees[35]
IL-1 inhibitor: anakinra	Initial dose 0.5 to <1.5 mg/kg/day but higher starting doses (1.5–2.5 mg/kg/day) were allowed later, subcutaneous. Median duration of 4.9 patient years	8–46 yr (84% pediatric)	Severe cryopyrin-associated periodic syndromes	43	Headache: 21 Arthralgia: 18 Pyrexia: 17 Upper respiratory tract infection: 17 Nasopharyngitis: 15 Rash: 14 Ocular hyperemia: 12 Sinusitis: 12 Ear infection: 11 Otitis media: 11 Fatigue: 10 Diarrhea: 10 Oropharyngeal pain: 9 Urinary tract infection: 6 Note: Refer to the study for less frequently reported AEs Post–lumbar puncture syndrome: 5, serious AEs in 4 patients Cardiac catheterization: serious AE in 1 patient Cellulitis, wound infection, chest pain: serious AEs in 1 patient Uveitis: serious AE in 1 patient Gastroenteritis: serious AEs in 2 patients MAS, postoperative wound infection: serious AEs in 1 patient Meningitis enteroviral: serious AE in 1 patient Arthritis bacterial, lymphadenitis bacterial: serious AEs in 1 patient Traumatic lumbar puncture: serious AE in 1 patient Convulsion: serious AE in 1 patient Pneumonia: serious AE in 3 patients Sinusitis: serious AE in 1 patient	SAEs: 24 in 14 patients	Kullenberg[24]

(Table cont. on page 158)

Table 2. Reported Adverse Events With IL-1 and IL-6 Inhibitor Use in Children *(cont.)*

Drug	Dose and Method of Administration	Patient Age	Patient Condition	Number of Pediatric Patients (Unless Age Otherwise Specified)	Number of Patients With AEs	Number of AEs (for Studies That Did Not Present Data on the Number of Patients With AEs)	Author
	1 mg/kg/day (maximum 100 mg), subcutaneous, dose escalation according to physician judgment. Median follow-up at 37.5 mo	3–13 yr	Chronic infantile neurological cutaneous and auricular syndrome or Muckle-Wells syndrome	14	Local erythematosus skin reaction at injection site: 1 Excessive weight gain: 2 Severe oral aphthosis: 1		Lepore[26]
	Mean initial dose 1.3 mg/kg/day (range, 1–2),* median time of 12 mo (range, 5–17)	Median 14 yr (range, 6–56)	Corticosteroid-dependent and colchicine-resistant recurrent pericarditis	12 children, 3 adults	Skin reactions: 5		Finetti[16]
	2–4 mg/kg.* Median duration 3 (range, 3–18) mo	2.75–9.25 yr	Systemic JIA	4	Local injection site inflammation and pruritus: 3		Hedrich[17]
	Dose not stated,* 34 mo, (range, 6–116)	Median 5.5 yr (range, 0.5–17.5)	Systemic JIA	78		Infections: 15 Headache: 8 Neutropenia: 9 Elevated transaminase: 11 Urticaria: 2 Hematuria: 4 Skin reaction: 2 Proteinuria: 4 Local injection site reaction: 5 Nausea: 1 Leucopenia: 1 Nocturnal sweating: 1 Acne: 3	Lainka[25]
	Median starting dose of anakinra was 1.5 mg/kg/day. IV route for 1 patient.* Median duration of observation 14.5 (range, 7.5–25) mo	Median 9.7 yr	sJIA	10	Serious infection (parainfluenza, feeding tube site infection, pneumonia): 3 Bronchitis: 1 Recurrent viral respiratory illness: 1 Eosinophilic hepatitis: 1 (drug discontinuation) Elevation of liver enzymes: 2 Mild asymptomatic neutropenia: 1 Injection site reactions: 19 (1 noted drug discontinuation)	SAEs: 4	Nigrovic[32]

(Table cont. on page 159)

Table 2. Reported Adverse Events With IL-1 and IL-6 Inhibitor Use in Children *(cont.)*

Drug	Dose and Method of Administration	Patient Age	Patient Condition	Number of Pediatric Patients (Unless Age Otherwise Specified)	Number of Patients With AEs	Number of AEs (for Studies That Did Not Present Data on the Number of Patients With AEs)	Author
	2 mg/kg/day, maximum 100 mg, subcutaneous. Duration 1 mo	Mean 8.5 (SD, ±4.54) yr	sJIA	24	Adverse events including post-injection erythema, infections, vomiting, abdominal pain: 22		Quartier[34]
	12 wk of 1 mg/kg/day, up to a maximum daily administration of 100 mg/day, subcutaneous	2–17 yr	Polyarticular-course juvenile rheumatoid arthritis	50	(Open-label, double-blind and extended phases combined) Application site reaction: 69 Fever: 26 Body pain: 9 Headache: 31 Nausea: 12 Diarrhea: 9 Abdominal pain: 25 Vomiting: 9 Musculoskeletal pain: 22 Limb pain: 10 Cough: 8 URTI: 29 Rash: 13	SAEs: 6 (unrelated to study drug)	Ilowite[18]
	2 mg/kg (patients <10 kg and <8 m received 4 mg/kg) (although doses were changed in fever conditions), 45 days, subcutaneous	Median 31 mo (range, 3–83)	Patients with Kawasaki disease unresponsive to intravenous immunoglobulin	16	Increased coronary dilatation with pericarditis: 1 MAS and polyarthritis: 1 Chalazion: 1 Anemia: 1 Hepatitis: 1 Hepatic cytolysis: 1 Hypereosinophilia: 1 Edema and itching at injection site: 1 Rash with pruritus: 1	SAEs: 5 in 3 patients	Kone-Paut[21]
	2–11 mg/kg/day (maximum dose of anakinra was 100 mg/day), 6 wk initial IV dose in 15 min, then q12h for 24 hr, then subcutaneous	1.1 yr (range, 0.3–10)	Acute Kawasaki disease with coronary artery aneurysms	22		Increased coronary artery aneurysm: 3 Rash/skin reaction: 13 Vomiting: 5 Bruising at injection site: 1 Nosebleed: 1 Anemia: 1 Diarrhea: 1 Elevated aminotransferase: 2 Fever: 6 Neutropenia: 1 URTI: 1 Allergic reaction to peanuts: 1 Arthritis: 1 Nasal congestion: 1 Otitis media: 1	Yang[43]

(Table cont. on page 160)

Table 2. Reported Adverse Events With IL-1 and IL-6 Inhibitor Use in Children *(cont.)*

Drug	Dose and Method of Administration	Patient Age	Patient Condition	Number of Pediatric Patients (Unless Age Otherwise Specified)	Number of Patients With AEs	Number of AEs (for Studies That Did Not Present Data on the Number of Patients With AEs)	Author
	Initial dose 1 mg/kg/day, stepwise inclusion dose every 2 wk, subcutaneous for 36 or 60 mo	Mean 11.53 (SD, ±9.12)	Neonatal-onset multisystem inflammatory disease	26	Suspected viral pneumonia: 3 patients	Wound infections: 2 events MAS: 1 event Posttraumatic hypopyon: 1 Vertigo: 1 Gastroenteritis: 23 Chest pain: 8 Injection reactions: 11 Abdominal discomfort: 24 Nausea/vomiting: 21 Dizziness: 10 Nasal congestion: 33 Ear infection: 33 Sinusitis: 24 Upper respiratory infection: 120 Urinary tract infection: 16 Musculoskeletal pain: 118 Headache: 88 Fever: 34 Conjunctivitis: 33 Rash: 59 SAEs: 6 No drug discontinuations	Sibley[38]
IL-1 inhibitor: rilonacept	Loading dose (4.4 mg/kg, maximum dose 320 mg), then weekly maintenance doses (2.2 mg/kg, to a maximum dose 160 mg), subcutaneous 4–24 wk, with long-term extension phase for up to 21 mo	Mean 9.5 yr	Systemic juvenile idiopathic arthritis	36	Elevations in liver transaminases: 4 Serious AEs (most commonly sJIA flares): 9	Upper abdominal pain: 4 Arthralgia: 3 Cough: 4 Headache: 5 Nausea: 4 Pharyngitis streptococcal: 6 Pyrexia: 6 Rash: 4 URTI: 7 Vomiting: 6 Serious AEs: Gastroenteritis: 1 Histiocytosis hematophagic: 1 Juvenile arthritis: 2 Abnormal liver function test: 1 Mental status change: 1 Pericarditis: 1 Varicella: 1	Ilowite[19]

(Table cont. on page 161)

Table 2. Reported Adverse Events With IL-1 and IL-6 Inhibitor Use in Children *(cont.)*

Drug	Dose and Method of Administration	Patient Age	Patient Condition	Number of Pediatric Patients (Unless Age Otherwise Specified)	Number of Patients With AEs	Number of AEs (for Studies That Did Not Present Data on the Number of Patients With AEs)	Author
	2.2 mg/kg or 4.4 mg/kg, subcutaneous, 5 days in 4-wk period. Mean duration of 19 mo	Median 12.6 ± 4.3 yr (range, 5–20)	sJIA	Initial double-blind phase: 24 Open label: 23	Initial phase: Withdrawal due to depression with no history of depression: 1 Injection-site reactions: 1 Open-label phase: Fatigue, pyrexia, injection-site reactions: 17 Infections: 16 3 study withdrawals due to AEs	SAEs: 8 in 4 patients (unrelated to study drug)	Lovell[27]
IL-6 inhibitor: tocilizumab	Patients weighing ≥30 kg received TCZ 8 mg/kg, patients weighing <30 kg randomly assigned to receive TCZ at either 8 or 10 mg/kg, intravenous.† Maximum length of treatment 84 wk	Up to 104 wk	pJIA	188	Pneumonia: 4 patients Bronchitis: 2 Cellulitis: 2 Uveitis: 2 Varicella in unvaccinated patient: 2 Nonserious AEs, infection most common: 169 Note: Patients enrolled in phase 1 of study, 9 study withdrawals due to AEs	SAEs: 26 in 24 events	Brunner[11]
	sJIA: 162 mg subcutaneous once weekly (or every 10 days for <30 kg) pJIA: 162 mg subcutaneous every 2 wk (or every 3 wk for <30 kg) Duration 52 wk	1–17 yr	sJIA and pJIA	sJIA: 44 pJIA: 46	sJIA: serious infection: 5 Vertigo: 1 Pulmonary hemorrhage: 1 Death considered related to drug: 2 (1 patient with oral candidiasis and pneumonia who died of pulmonary hemorrhage, 1 patient with suspected sepsis) pJIA: Croup: 1 Varicella: 1 Worsening of anorexia: 1 Worsening of arthralgia: 1	SAEs: 9 in 6 patients with sJIA, 4 in 3 patients with pJIA	Ruperto[37]
	12 mg/kg if the weight was <30 kg or 8 mg/kg if the weight was ≥30 kg, intravenous.† Maximum treatment duration 2.15 yr, study duration up to 5 yr	2–17 yr	sJIA	75	Infection: 41 Death from suspected tension pneumothorax: 1 Grade 3 neutropenia: 17 Grade 4 neutropenia: 2 Elevated alanine aminotransferase concentration: 21 Elevated cholesterol: 23 Macrophage activation syndrome: 3	SAEs: 39 (18 infections)	De Benedetti[13]

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Table 2. Reported Adverse Events With IL-1 and IL-6 Inhibitor Use in Children *(cont.)*

Drug	Dose and Method of Administration	Patient Age	Patient Condition	Number of Pediatric Patients (Unless Age Otherwise Specified)	Number of Patients With AEs	Number of AEs (for Studies That Did Not Present Data on the Number of Patients With AEs)	Author
	Dose not stated.* Median treatment duration 23 mo, followed for up to 12 mo	Median 14.9 (range, 1–48) mo	sJIA	46	Leukopenia, infections, elevated transaminases: 11 Hodgkin lymphoma: 1 Gut perforation: 1 5 drug discontinuations	SAEs: 2	Bielak[9]
	12 mg/kg every 2 wk, intravenous,† minimum 12 wk. Duration up to 12 mo	Mean 1.3 yr (range, 0.83–16)	sJIA	11	Infection: 32 patients with AEs, 2 patients with serious AEs Hypersensitivity reactions: 5 patients with AEs, 4 patients with serious AEs Neutropenia: 6 Thrombocytopenia: 1 Note: 43 patients had at least 1 AE, 7 serious AEs. One study withdrawal	SAEs: 5 in 3 patients (2 related to drug)	Mallalieu[29]
	8–12 mg/kg slow intravenous infusion every 2 wk, until 1 yr follow-up	Median 6.5 yr (range, 2-15)	sJIA	65	MAS: 1 moderate elevation of liver enzymes: 2 Severe injection site reactions: 2		Nada[31]
	12 mg/kg if the child's weight was <30 kg and 8 mg/kg if the weight was ≥30 kg, infusion* every 4 wk for 456–1000 days	6–12.8 yr	sJIA	33	SAEs/Infusion reactions and a diagnosis of early MAS: 3 Death: 1	SAEs: 3 Death: 1	Kostik[22]
	12 mg/kg for body weight <30 kg, 8 mg/kg for ≥30 kg) with a slow intravenous infusion† every 2 wk. After 12 wk, it was given every 4 wk and every 6 wk after an initial 24 wk. Treatment duration up to 11.7 mo	Median 6.3 yr (range, 2.5 –12)	sJIA	77	Leukopenia: 7 Fever, chills, facial blushing: 2 Elevated transaminase: 5 Infusion reactions: 3 MAS: 2 Pneumonia: 2 Septicemia: 1 Streptococcal infection: 1 2 treatment discontinuations		Yan[42]

(Table cont. on page 163)

Table 2. Reported Adverse Events With IL-1 and IL-6 Inhibitor Use in Children *(cont.)*

Drug	Dose and Method of Administration	Patient Age	Patient Condition	Number of Pediatric Patients (Unless Age Otherwise Specified)	Number of Patients With AEs	Number of AEs (for Studies That Did Not Present Data on the Number of Patients With AEs)	Author
	8 mg/kg every 2 wk.* Mean duration of treatment was 3.4 yr (range, 0.04–6.22)	8.0 yr (range, 2–19)	sJIA	67	AE: 67 patients (most were mild including infections, lab test abnormalities, MSK and connective tissue disorders, GI disorders)	Infections: 776 (29 SAEs) Skeletal: (8 SAEs) Lab test abnormalities: 143 (12 SAEs) Immune system: (2 SAEs) Hepatobiliary: (2 SAEs) Surgical/medical procedures/eye disorders: (5 SAEs) Blood/lymphatic system: (1 SAE) Metabolism: (1 SAE) Gastrointestinal disorders: 76 (9 SAEs) Skin/subcutaneous disorders: 100 (3 SAEs) Respiratory/thoracic/mediastinal: 71 (1 SAE) Injury/poisoning/procedural: 49 (2 SAEs) Nervous system: 13 General/injection site: (2 SAEs)	Yokota[44]
	8 mg/kg once every 2 wk, intravenous.† Observation time of 52 wk	Mean 11.2 yr (range, 0–53)	sJIA	417	Most common AEs: infections and infectations; respiratory, thoracic, and mediastinal disorders; decreased platelet count, decreased white cell count, MSK and connective tissue disorders, blood and lymphatic disorders, GI disorders Most common serious AEs: infections and infectations	Infections (gastroenteritis, influenza, bronchitis, pharyngitis, nasopharyngitis): 284 (74 serious AEs) Respiratory, thoracic, mediastinal disorders: 142 (9 serious AEs) Musculoskeletal and connective tissue disorders, including JIA: 69 (17 serious AEs) Blood and lymphatic system disorders: 57 (40 serious AEs) Gastrointestinal disorders: 56 (15 serious AEs) Skin/subcutaneous tissue disorders: 43 (3 serious AEs)	Yokota[45]

(Table cont. on page 164)

Table 2. Reported Adverse Events With IL-1 and IL-6 Inhibitor Use in Children *(cont.)*

Drug	Dose and Method of Administration	Patient Age	Patient Condition	Number of Pediatric Patients (Unless Age Otherwise Specified)	Number of Patients With AEs	Number of AEs (for Studies That Did Not Present Data on the Number of Patients With AEs)	Author
						Hepatobiliary disorders: 41 (9 serious AEs) "General" or injection site conditions: 32 (9 serious AEs) Injury, poisoning, procedural complications: 32 (11 serious AEs) Eye disorders: 18 Vascular disorders: 17 (4 serious AEs) Metabolism/nutrition disorders: 14 Nervous system disorders: 12 (7 serious AEs) Renal and urinary disorders: 7 (4 serious AEs) Immune system disorders: 5 (1 serious AE) Cardiac disorders: 3 (1 serious AE) Surgical/medical procedures: 1	
	Duration of current biologic exposure (mo, average for all types of biologics included in study): 11.4 (0.5–71.2), subcutaneous and intravenous†	Mean age 14.6 ± 5.7 yr	JIA	35		Serious opportunistic infections: 31 in 27 patients	Brunelli[10]
	Not available*	Mean 13.3 ± 4.0 yr	JIA	12	Nausea/vomiting: 1		Vinod[341]
	10 mg/kg (<30 kg) and 8 mg/kg (>30 kg) (every 4 wk–polyarticular, every 2 wk–systemic JIA).* Median duration 15 (range 12–20) mo	0–18 yr	JIA (polyarticular and systemic)	20	Thrombocytopenia: 2 Macrophage activation syndrome: 1 Transaminase elevation: 1 Anaphylaxis: 2 (leading to drug discontinuation)		Demir[14]

(Table cont. on page 165)

Table 2. Reported Adverse Events With IL-1 and IL-6 Inhibitor Use in Children *(cont.)*

Drug	Dose and Method of Administration	Patient Age	Patient Condition	Number of Pediatric Patients (Unless Age Otherwise Specified)	Number of Patients With AEs	Number of AEs (for Studies That Did Not Present Data on the Number of Patients With AEs)	Author
	8 mg/kg every 4 wk, intravenous.† Mean duration 25.25 mo (SD, ±17.8)	Median 29 mo (range, 12–105)	Childhood chronic noninfectious uveitis, idiopathic uveitis, Behçet syndrome	18	Mild neutropenia, mildly increased transaminase: 1 Upper airway infection with a concomitant rash: 1 Discontinued tocilizumab at 9 mo owing to persistent joint activity but persistent ocular remission: 1		Maccora[28]
	8 mg/kg.* Mean duration of 5.4 yr	Mean 3.5 yr	JIA-associated uveitis	7	GI upset: 1 (drug discontinued)		Marelli[30]
Recombinant IL-1 receptor antagonist	2 mg/kg/day subcutaneous, with a maximum dosage of 100 mg/day) after failure of NSAID (indomethacin). Mean follow-up 32 (range, 12–54) mo	Mean 7.9 (1.1–15.3) yr	New-onset systemic JIA	20	Local skin reactions: 13 Mild cutaneous/upper airway infection/reactivation of HSV1: several patients		Vastert[40]
Multiple biologicals	Anakinra (subcutaneous), anakinumab (subcutaneous), tocilizumab (intravenous†)	14.6 yr (9.9–16.9 yr)		128	Anakinra–local drug hypersensitivity reaction at injection site: 3 Canakinumab–diffuse urticaria: 1 patient with familial Mediterranean fever Tocilizumab – Anaphylaxis: 3		Soyer[39]

AE, adverse event; HSV1, herpes simplex virus 1; GI, gastrointestinal; IL-1, interleukin-1; IL-6, interleukin-6; IV, intravenous; JIA, juvenile idiopathic arthritis; MAS, macrophage activation syndrome; MSK, musculoskeletal; NSAID, non-steroidal anti-inflammatory drugs; pJIA, polyarticular juvenile idiopathic arthritis; SAE, serious adverse event; sJIA, systemic juvenile idiopathic arthritis; URTI, upper respiratory tract infection

*Route of administration not specified.
†Duration of intravenous infusion not specified.

weight gain, oral aphthosis, urticaria, post–lumbar puncture syndrome, chest pain, convulsion, neutropenia, serious infection (such as parainfluenza and pneumonia), hepatitis, abdominal pain, MAS, and other serious adverse events.[24] Studies that identified serious adverse events reported 45 events (rate = 0.15, of a total of 299 studied patients).

Rilonacept. Two studies included rilonacept as a treatment. They used a dose of 2.2 mg/kg or 4.4 mg/kg and both involved systemic JIA, with a total number of 60 patients, or 36 and 24 patients per study, respectively. Study duration was 19 and 27 months. Reported adverse events included liver enzyme elevation (n = 4 patients), abdominal pain (events = 4), headache (events = 5), nausea/vomiting (events = 10), cough (events = 4), rash (events = 4), infection (n = 16, events = 16), and a grouped set of reactions including fatigue, pyrexia, and injection site reactions (n = 18). Serious adverse events included infection such as gastroenteritis (n = 1) and varicella (n = 1), arthritis (events = 2), liver function abnormality (n = 1), mental status change (n = 1), and hemophagocytic histiocytosis (n = 1). Serious adverse events included 16 events (rate = 0.27, of 60 total studied patients).

Interleukin-6 Inhibitors: *Tocilizumab.* Fifteen studies assessed tocilizumab as an intervention. The total number of treated patients from all studies was at least 1161, with a median number of 46 patients per study. This total is estimated because some studies did not report stratified sample sizes based on treatment given. The dose

ranged from 8 to 12 mg/kg. Study duration was a mean of 25.9 (range, 11.4–64.8) months. Conditions treated included polyarticular JIA, systemic JIA, childhood chronic noninfectious uveitis, idiopathic uveitis, Behcet syndrome, and JIA-associated uveitis. Commonly reported adverse events included infection (n ≥ 102, events = 318), respiratory/thoracic conditions (events = 142), local injection site reactions (n = 5, events = 32), neutropenia (n = 26 patients), leukopenia (n = 7), elevated liver enzymes (n = 30), elevated cholesterol (n = 23), and a reported group of symptoms such as leukopenia, infections, and elevated liver enzymes (n = 11).[9] More rarely reported events included serious infections, vertigo, pulmonary hemorrhage, MAS, lymphoma, gut perforation, death (4 reported), fever/chills, nausea/vomiting, and anaphylaxis. Brunner et al[11] reported 169 "nonserious" adverse events, with infections being the most common. Studies that identified serious adverse events reported 401 events (rate = 0.35, of 1161 total studied patients).

One study also reported on a recombinant IL-6 receptor antagonist in new-onset systemic JIA but did not specify the drug name. The study duration was 32 months. Reported adverse events included local skin reactions (n = 13 patients), upper respiratory tract infection, and reactivation of herpes virus 1 in several patients.[40]

Discussion

The objective of this systematic review was to summarize the adverse events occurring with IL-1 and IL-6 inhibitor treatment, when used in a pediatric population. The review identified a total of 38 studies, and the study designs included prospective cohort, cross-sectional, case series, and case-control studies.

The IL-1 and IL-6 inhibitors, including canakinumab, anakinra, tocilizumab, and rilonacept, were studied for a range of conditions such as CAPS, colchicine-resistant familial Mediterranean fever, hyperimmunoglobulin D syndrome–mevalonate kinase deficiency, systemic JIA, idiopathic recurrent pericarditis, pyoderma gangrenosum, and sickle cell anemia. Canakinumab and anakinra displayed some common adverse events including infections (rate = 0.19), headaches (rate = 0.13), local site injection reactions (n = 0.05), and fever (rate = 0.14). Rilonacept showed adverse events such as liver enzyme elevation (rate = 0.25), abdominal pain (rate = 0.25, using n = 4 events), and infections (rate = 0.27). Studies including the administration of tocilizumab reported adverse events including neutropenia (rate = 0.02), elevated transaminase concentration (rate = 0.03), and infections (rate = 0.09). There were also serious adverse events reported at a rate of 0.25, although multiple events may have occurred in individual patients. Given the variability of the format in which adverse events were reported across studies for both types of inhibitors, it is difficult to draw definitive conclusions about their safety profiles or whether some drugs are better tolerated. Regarding concomitant disease and drug interactions, information in the literature is limited, and these were not clearly reported in most of the reviewed studies. Synergistic effects with other immunosuppressants such as tumor necrosis factor-alpha inhibitors, leading to increased infection risk, have been suggested.[47] However, several included studies did discontinue use of other immunosuppressants prior to the study period.

However, the findings of this review provide additional evidence summarizing some of the most reported and serious adverse events observed in patients after the intake of these medications and corroborate our knowledge of their safety profiles in children specifically. The reported adverse events highlight the need for careful monitoring, individualized management, and an assessment of the risk and benefits for the administration of the medicine for each patient. The administration of interleukin inhibitors in children should be made after a thorough evaluation of patients' medical conditions, disease severity, and previously reported adverse events for the medication. There is currently a paucity of evidence regarding monitoring strategies in this population, but screening of immunization status, tuberculosis screening, baseline blood tests (e.g., complete blood counts and liver function tests), and regular follow-up monitoring of bloodwork is generally encouraged. The evaluation of adverse events noted in this review may suggest the need for further research on monitoring strategies, regular screening for infectious symptoms, or patient/parent education regarding when to seek medical care if specific symptoms are observed.[48,49]

While the medications reviewed are also used in adult patients, comparison of the nature and incidence of adverse events is difficult owing to the differences in diseases (and comorbidities) treated in children versus adults. However, many adverse events seem to be similar and have similar incidences (taking into account that, in general, pediatric trials were smaller and often focused on specific types of pediatric diseases that involve some degree of immunosuppression and/or inflammation). Notably, a relatively common incidence of infections and hematologic adverse events can be observed in both populations, as well as hypersensitivity reactions for biologicals. Perhaps the main differences among age groups can be observed for canakinumab, which can produce hyperuricemia and vertigo more commonly in adults than in children (possibly because adults have higher risk for predisposing comorbidities such as kidney impairment).[50] Rilonacept and tocilizumab did not seem to cause hyperlipidemia in children, as opposed to adults, but the experience in children is much more limited.[51,52] Finally, there is a suggestion that canakinumab-related infections are more frequent in children, with the caveat that many of the children receiving this medication had some form of

congenital autoinflammatory condition with an immune dysfunction component.[21]

There are several limitations to be considered in this systematic review. Included studies had different designs, data collection methods, sample sizes, and reporting of adverse events. Some studies also did not categorize their reported adverse events as serious or nonserious events. Some studies reported only the number of patients with adverse events, and some reported only the number of adverse events. These factors may introduce heterogeneity into the results and potential bias while making comparisons. Studies with smaller sample sizes also could affect the generalizability of the data reported and limit the statistical power required to detect rare adverse events in children. Where available, the duration of study observation was averaged and few studies reported on safety profiles for long-term data exceeding 3 years. There has also been considerable variability with the reporting format of adverse events across different studies, which prevented the ability to conduct a meta-analysis and could affect the reliability of the data owing to differences in terminology and grading scales. Lastly, for studies that did not separate pediatric and adult data, the decision was made to include studies with a mean age of less than 18 years because the data were relevant to this review. Despite the inclusion of adult adverse events from these studies, capturing this pediatric data reduces the likelihood that pediatric adverse events are missed in this review. Specific trends related to sex or age within pediatrics were not elucidated within studies included in this review.

Despite these limitations, this review holds importance owing to the evidence gap it addresses and its clinical implications. It will help clinicians and health care providers assess the risks and safety profiles of administering interleukin inhibitors to a pediatric population. It will assist pediatricians to make evidence-based treatment decisions and have informed discussions with patients about possible therapeutic routes. It also serves as a reference for health care professionals to help with the monitoring, and early detection of adverse events after the administration of the medication. However, further research is warranted to provide more conclusive data in the pediatric population, such as with randomized controlled trials. Furthermore, long-term studies are also required to expand our understanding of the long-term safety outcomes of interleukin inhibitors in children.

Article Information

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