Safety of Adalimumab in Pediatric Patients with Polyarticular Juvenile Idiopathic Arthritis, Enthesitis-Related Arthritis, Psoriasis, and Crohn's Disease

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Objective To evaluate the safety of adalimumab in pediatric patients who participated in clinical trials of juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and pediatric enthesitis-related arthritis), psoriasis, and Crohn's disease.

Study design This analysis included data from 7 global, randomized, and open-label AbbVie-sponsored clinical trials of adalimumab and their open-label extensions conducted between September 2002 and December 31, 2015 (cutoff date for ongoing studies). Patients who received ≥1 dose of adalimumab subcutaneously were included. Adverse events that occurred after the first dose of adalimumab and up to 70 days (5 half-lives) after the last dose were reported and events per 100 patient-years were calculated.

Results The analysis included 577 pediatric patients, representing 1440.7 patient-years of adalimumab exposure. Across indications, the most commonly reported adverse events (events/100 patient-years) were upper respiratory tract infections (24.3), nasopharyngitis (17.3), and headache (19.9). Serious infections (4.0 events/100 patient-years) were the most frequent serious adverse events across indications; the most commonly reported was pneumonia (0.6 events/100 patient-years). Serious infection rates were 2.7, 0.8, and 6.6 events/100 patient-years in patients with juvenile idiopathic arthritis, psoriasis, and Crohn's disease, respectively. No events of malignancies were reported. One death (accidental fall) occurred in a patient with psoriasis.

Conclusions The safety profile of adalimumab in pediatric patients with polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis, psoriasis, and Crohn's disease was generally similar across indications; no new safety signals were identified in the treatment of pediatric patients with adalimumab. *(J Pediatr 2018;■■:■■-■■).*

Trial registration Clinicaltrials.gov: NCT00048542, NCT00775437, NCT00690573, NCT01166282, NCT01251614, NCT00409682, and NCT00686374.

Adalimumab is an anti–tumor necrosis factor (TNF) monoclonal antibody that has demonstrated safety and efficacy in multiple pediatric conditions, including polyarticular juvenile idiopathic arthritis (pJIA),[1-3] enthesitis-related arthritis (ERA),[4] pediatric psoriasis,[5] and pediatric Crohn's disease (CD).[6,7] Currently, the approved pediatric indications for adalimumab in the US and European Union include moderately to severely active pJIA in patients ≥2 years of age and moderate to severely active pediatric CD in patients ≥6 years of age with previous inadequate response to conventional therapy.[8] Additional approved indications for adalimumab in the European Union include the treatment of active ERA in patients ≥6 years of age with an inadequate response to or intolerance of conventional therapy and the treatment of severe chronic plaque

AE	Adverse event
CD	Crohn's disease
CHF	Congestive heart failure
ERA	Enthesitis-related arthritis
JIA	Juvenile idiopathic arthritis
NCT	National Clinical Trial
pJIA	Polyarticular juvenile idiopathic arthritis
PY	Patient-year
SAE	Serious adverse event
TB	Tuberculosis
TNF	Tumor necrosis factor

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psoriasis in children and adolescents ≥4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies.[9]

The safety of adalimumab, especially long term, is an important consideration in the pediatric population, as each indication represents a distinct chronic condition. An analysis of adverse event (AE) data across multiple indications from 23 458 patients (mostly adults), some of whom had clinical trial exposure to adalimumab for almost 12 years, found that although rates of specific AEs varied by disease, the overall safety profile was consistent with that of anti-TNF agents as a class[10]; no new safety signals were identified. Although interim data from ongoing pediatric registries for pJIA, CD, and psoriasis are emerging,[11-15] pediatric safety data for adalimumab remain limited relative to adult safety data. Therefore, examining safety data within and across multiple therapeutic areas specifically in pediatric populations from controlled clinical trials may provide additional, valuable safety information. Safety events of special interest in the pediatric population include infections (particularly serious infections and opportunistic infections), malignancies, and hypersensitivity.

This analysis was conducted to evaluate the totality of safety findings from pediatric studies of adalimumab, including long-term analyses (>52 weeks), by assessing AEs in pediatric patients who participated in clinical trials of juvenile idiopathic arthritis (JIA; pJIA and ERA), psoriasis, and CD. Data from these studies reflect the longest clinical study exposure to adalimumab published to date for each indication.[1-7]

Methods

Clinical Trials

Safety findings from 7 AbbVie-sponsored, global clinical trials of adalimumab (subcutaneous injection; 40 mg/0.8-mL or 20 mg/0.4-mL formulation) in pediatric patients were included in this analysis: 4 studies of rheumatic disease, including pJIA (National Clinical Trial [NCT] no. 00048542, NCT00775437, NCT00690573) and ERA (NCT01166282); 1 study of pediatric psoriasis (NCT01251614); and 1 study of pediatric CD (NCT00409682), including its ongoing open-label extension (NCT00686374). Methods and results from these studies are published (briefly summarized in **Table I**)[1-7] All study protocols were approved by an institutional review board or independent ethics committee, and written informed consent was obtained from patients, parents, or legal guardians.

Safety Assessments

This analysis included all AEs that occurred after the first dose of adalimumab and up to 70 days (5 half-lives) after the last dose (ie, all treatment-emergent AEs); data are presented through December 31, 2015. An analysis of infections by concomitant corticosteroid use also was conducted. AEs were coded using the *Medical Dictionary for Regulatory Activities*, version 18.1. AEs of special interest included infections and serious infections, opportunistic infections (due to bacterial, mycobacterial, invasive fungal, viral, parasitic, or other opportunistic pathogens),[16] malignancies, and hypersensitivity reactions. Serious adverse events (SAEs) were defined as events that were fatal or immediately life-threatening; required inpatient or prolonged hospitalization; resulted in persistent or significant disability/incapacity, congenital anomaly, or spontaneous or elective abortion; or required medical or surgical intervention to prevent a serious outcome.

Growth/height analyses were performed in 2 patient populations. In the pJIA study,[3] patients were pooled and divided into 2 groups based on their baseline height percentile (<33 or >33) on the Centers for Disease Control and Prevention growth chart.[17] Height and body mass index and improvement of pJIA signs and symptoms were evaluated. In the CD study,[6] height velocity z scores based on bone age were calculated using reference standard height velocity tables according to the following equation: (observed height velocity – median height velocity for age and sex)/SD of the median. Patients with height velocity z score ≤–1.0 were considered to have growth delay at baseline.[18] Change from baseline in height velocity z score was evaluated in patients with and without growth delay at baseline.

Statistical Analyses

Patients who received ≥1 dose of adalimumab were included in this pediatric safety analysis. AEs are presented as the number and proportion of patients experiencing each event and as the number of events and rate of events per 100 patient-years (PY). A Kaplan–Meier analysis was used to evaluate the time to first serious infectious event for each indication. Height and growth analyses were reported as observed data. For the CD growth analyses, the Wilcoxon rank sum test was used to compare change from baseline (2-sided, 5% level of significance).

Results

Baseline Characteristics and Adalimumab Exposure

This analysis included 577 pediatric patients (**Figure 1**; available at www.jpeds.com), representing 1440.7 PY of exposure (**Table II**). A total of 274 patients with JIA (806.9 PY), including 228 patients representing 662.3 PY in 3 pJIA studies and 46 patients representing 144.5 PY in the pediatric ERA study, 111 patients with pediatric psoriasis (121.5 PY), and 192 patients with pediatric CD (512.3 PY), were included in the analysis. Baseline characteristics for these pediatric populations are summarized in **Table II**.

AEs

Most patients in each therapeutic area reported at least 1 AE (**Table III**). The most common types of AEs (including both serious and nonserious events) were infections and injection-site reactions, including injection-site pain. Overall, infections occurred in 82% of patients with JIA (150.7 events/100 PY), 74% of patients with psoriasis (168.7 events/100 PY), and 76% of patients with CD (132.0 events/100 PY). Across all pediatric indications, the most commonly reported individual AEs were upper respiratory tract infections (27%; 24.3 events/100 PY), nasopharyngitis (24%; 17.3 events/100 PY), and

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