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ORIGINAL PAPER

Adalimumab in severe plaque psoriasis of childhood: A multi-center, retrospective real-life study up to 52 weeks observation

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Abstract

The objective of this study is to determine drug effectiveness and safety of the tumor necrosis factor-alpha blocker monoclonal antibody adalimumab in a real-life cohort of 54 children and/or adolescents with severe plaque psoriasis. Retrospective, multi-center analysis over a 52-week period is discussed in this study. Efficacy was determined by the percentage of patients achieving Psoriasis Area Severity Index (PASI 75) and PASI 90 at weeks 16, 24, and 52 and the response in biologic-naïve versus non-naïve patients. Safety was assessed by the number of patients experiencing at least one adverse event. At week 16, 29.6% of patients achieved a 90% PASI score reduction (PASI 90), while 55.5% of patients achieved a 75% PASI score reduction (PASI 75). Effectiveness was sustained through week 24, since PASI 90 response increased to 55.5% and PASI 75 response increased to 74.0% of patients. The PASI response rates did not differ between biologic-naïve and non-naïve patients. The drug was well tolerated and no serious infections were observed. Adalimumab was effective and safe in this cohort of children with severe plaque psoriasis in a 52-week observation. Effectiveness did not differ between biologic-naïve and non-naïve patients.

KEYWORDS

adolescence, childhood, psoriasis, therapy, treatment

[Correction added on 13 November 2019, after first online publication: the surname of the first author has been corrected from "Lernia" to "Di Lernia".]

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1 | INTRODUCTION

Over the last few years, several studies have demonstrated the efficacy of tumor necrosis factor (TNF)-alpha antagonists in the treatment of chronic plaque psoriasis of adults. However, limited data are available about the treatment with TNF-alfa blockers in childhood psoriasis. Among this class of drugs, adalimumab was the second TNF-alpha blocker to be approved by the European Medicines Agency (EMA) for the treatment of severe chronic plaque psoriasis in children from the age of 4 years (Di Lernia, 2017). The efficacy and tolerability of adalimumab have been investigated in a randomized, double-dummy, double-blind phase-3 trial which compared two different doses of adalimumab (0.8 or 0.4 mg/kg) with placebo and methotrexate in patients aged 4–17 years. Adalimumab was superior in terms of efficacy to methotrexate showing a similar safety profile (Papp et al., 2017). Recently, results of the 52-week extension of the above-mentioned trial showed efficacy and safety of adalimumab in children in the long-term (Thaci et al., 2019). The primary aim of this multicenter, retrospective study was to analyze the effectiveness and safety of adalimumab in an Italian cohort of pediatric patients with severe psoriasis, over a 52-week treatment period, in a daily clinical practice. The secondary objective was to assess potential clinical variables interfering with the therapy response.

2 | PATIENTS AND METHODS

2.1 | Patients and data collection

Data from a cohort of patients under 17 years of age who were given adalimumab between June 2016 and December 2017 for severe chronic plaque psoriasis with or without psoriatic arthritis. Psoriasis was considered severe if at least of one of the following criteria was present: psoriasis severity area index (PASI) ≥ 10 or psoriasis in difficult areas (face, hands, foot) with inadequate response to topical therapy (Belloni Fortina et al., 2017). The setting for the study was a number of academic and hospital centers belonging to the network of "Pediatric Dermatology Group" of the Italian Society of Dermatology and Venereology (SIDeMaST). Patients were identified through local databases or registries. Informed consent was obtained from patients and/or their parents prior to the patient's data entered into registries. For each patient the following information was collected: demographic (age, sex, height, weight, and body mass index), age at onset of psoriasis, involvement of difficult-to-treat areas as scalp, facial and genital area, hand and foot, nails, previous conventional and biologic systemic treatments, association with psoriatic arthritis and other comorbidities, age at onset of adalimumab treatment, psoriasis severity assessment using PASI at baseline. Eligible for this study were considered only patients ≤17 years who had all requested data available. Excluded were patients who were taking concomitant systemic antipsoriatic or immunosuppressant drugs including oral corticosteroids, psoralen ultraviolet A and narrow band ultraviolet B (NB-UVB) phototherapy or participating in clinical trials. Allowed concomitant medications included emollients, topical low-potency corticosteroids, and vitamin D3 ointments. All patients had baseline screening for full blood count, creatinine, liver function tests, urine analysis, B and C hepatitis markers, interferon-gamma releasing assays, and chest radiography. Safety was assessed by using the results of vital signs, physical examination, laboratory tests, physician and patient evaluation, and recording and reporting of adverse events.

3 | TREATMENT AND OUTCOME

All patients met the EMA requirements for the prescribing of adalimumab in pediatric psoriasis, namely severe chronic plaque psoriasis in individuals who have had an inadequate response to or were inappropriate candidates for topical therapy and phototherapies (EMA, 2019). Adalimumab was administered in a standard dosing regimen according to body weight (if 15 kg to <30 kg with an initial dose of 20 mg, followed by 20 mg given every other week starting one week after the initial dose; if ≥30 kg with an initial dose of 40 mg, followed by 40 mg given every other week starting one week after the initial dose). All patients received adalimumab originator, since biosimilars were not available yet during the study period.

Efficacy was assessed for all enrolled patients (intention-to-treat population) by recording the proportion of subjects who achieved 90 and 75% reduction in baseline PASI score (PASI 90 and PASI 75) after 16, 24, and 52 weeks of therapy. Reasons for withdrawal or switch were recorded. A comparison of the effectiveness of therapy in naive and biologic-exposed patients was made. The effectiveness of treatment was also compared between the patients with respect to age, sex, BMI-status, involvement of "difficult to treat" areas, and presence of psoriatic arthritis.

The safety population consisted of all patients who received at least a dose of study medication during the study period. Safety was assessed by recording of all adverse events, and assessment of blood examinations. Descriptive statistics (e.g., percentage, means) were used to summarize the data.

4 | RESULTS

4.1 | Patient characteristics

Baseline demographic and disease characteristics of the 54 patients who entered the study are reported in Table 1. All patients received

TABLE 1 Demographic and clinical data of the 54 patients treated with adalimumab

Male	29
Females	25
Age (range)	6–17
Age at diagnosis (mean ± *SD*)	6.3 ± 3.0
Age at commencement of treatment (mean ± *SD*)	11.6 ± 3.4
Body Mass Index (mean ± *SD*)	22.6 ± 5.3
Overweight/obesity	10
Psoriatic arthritis	6
Atopic diseases (asthma, allergic rhinoconjunctivitis)	4
Trisomy 21	2
Metabolic syndrome	1
Crohn's disease	1
Streptococcal recurrent pharyngo-tonsillitis	1
Previous etanercept exposure (%)	23 (42.5%)
Naïve to biologics (%)	31 (57.4%)
PASI baseline (mean ± *SD*) at the beginning of adalimumab	14.7 ± 7.0

adalimumab for moderate to severe plaque psoriasis recalcitrant to topical treatment and/or NB-UVB and/or systemic treatments. In particular, all patients had received topical treatment in the past, while eleven out of them (20.3%) had previously been treated with NB-UVB. Forty-nine patients (90.7%) had been treated with at least one systemic conventional therapy; eight patients received adalimumab as third-line treatment and five patients as fourth-line treatment (after cyclosporine, methotrexate, and acitretin). Five patients received adalimumab as a first-line systemic agent. Median baseline PASI score was 14.7 ± 7.0.

4.2 | Effectiveness

At week 16, 16 patients (29.6%) achieved a PASI 90 response, 30 (55.5%) a PASI 75 response. PASI response rates continued to improve through to week 24 and were generally sustained at week 52, although slightly lower, in particular about PASI 75 response (Figure 1). Absolute PASI values at the three different endpoints were as follows: 4.4 (interquartile range, IQR 1.0-7.0) at week 16, 2.5 (IQR 0.0-3-0) at week 24, and 4.6 (IQR 0.0-4.0) at week 52. At 52 weeks, 40 patients were still being treated. The global response and the relative response rates in naïve to biologic subjects versus patients with prior exposure to etanercept are shown in Table 2. There were no trends regarding the percentage of patients achieving PASI 90 and PASI 75 across sex-age categories, BMI-status, patients with involvement of "difficult to treat" areas, and presence of psoriatic arthritis.

4.3 | Reasons for discontinuation

A total of six patients (11.3%) discontinued treatment because of lack of efficacy at week 16. Additional six patients discontinued the study between 24 and 52 weeks because of secondary loss of response. After 52 weeks, one patient discontinued the study drug due to complete clearance of psoriasis and another one because of needle-phobia.

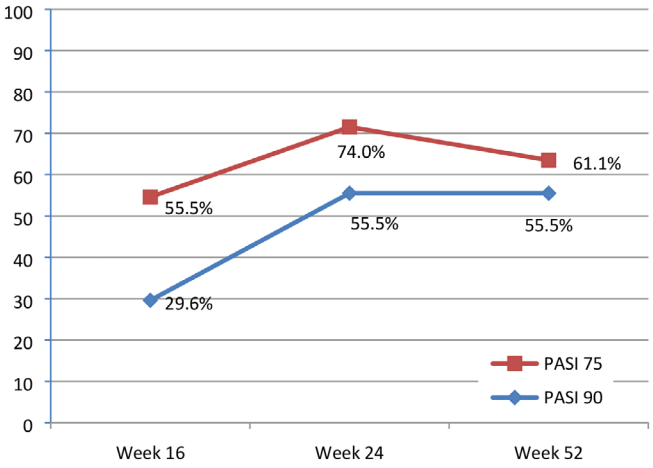

FIGURE 1 Proportion of patients achieving PASI 90 and PASI 75 at 16, 24, and 52 weeks. PASI response rates continued to improve through week 24: at week 24, PASI 75 and 90 response rates were higher than the corresponding rates at week 16

TABLE 2 PASI 75 and PASI 90 response rates in the whole patient population, naïve to biologic subjects, and patients with prior exposure to etanercept

	PASI 90		
	16 weeks	**24 weeks**	**52 weeks**
Patient population as whole (*n* = 54)	16/54 (29.6%)	30/54 (55.5%)	30/54 (55.5%)
Naïve to biologics (*n* = 31)	8/31 (25.8%)	14/31 (45.1%)	15/31 (48.3%)
Patients with previous exposure to etanercept (*n* = 23)	8/23 (34.7%)	16/23 (69,5%)	15/23 (65.2%)
	PASI 75		
Patient population as whole (*n* = 54)	30/54 (55.5%)	40/54 (74.0%)	33/54 (61.1%)
Naïve to biologics (*n* = 31)	16/31 (51.6%)	22/31 (74.1%)	16/31 (51.6%)
Patients with previous exposure to etanercept (*n* = 23)	14/23 (60.8%)	18/23 (78.2%)	17/23 (73.9%)

4.4 | Safety

During the 52-week observational period, reported infections included recurrent pharyngo-tonsillitis (n = 2) and recurrent bacterial skin infections (n = 2). One patient demonstrated increased weight gain, two patients had injection site reactions. Such reactions were not serious and did not require interruption of therapy. Another patient had the treatment stopped when he underwent appendectomy because of acute appendicitis. No patient developed laboratory anomalies during treatment. No opportunistic infections or malignancies occurred.

5 | DISCUSSION

The present study provides information into the effectiveness and safety of adalimumab in children in a real world setting. Actually three biological agents (etanercept, adalimumab, and ustekinumab) are licensed for the treatment of severe pediatric psoriasis in Europe, while etanercept and ustekinumab received approval respectively in patients aged ≥4 and ≥12 years by the Food and Drug Administration.

Despite the availability of new drugs in children as well, there is still a scarce number of randomized controlled trials evaluating therapies of moderate-to-severe psoriasis in children and adolescents. Therefore standardized management guidelines are lacking (Eichenfield et al., 2018). Long-term analysis in childhood are available for open-label etanercept, ustekinumab versus placebo (Landells et al., 2015; Paller et al., 2016), and more recently for adalimumab as well (Thaci et al., 2019). Recommendations from a pediatric dermatology expert panel suggested adalimumab as first line treatment in moderate to severe psoriasis of childhood according to its level of evidence "A" and EMA approval (Belloni Fortina et al., 2017). Phan et al. found, in a real-life comparative study, that ustekinumab had the best drug survival outcome among the three biotherapies licensed in childhood psoriasis (Phan et al., 2019). Ustekinumab cannot be administered in children ≤12 years, anyway.

Results of our real life clinical experience showed that adalimumab 0.8 mg/kg every other week was effective in a population of 54 children and adolescents affected by moderate-to-severe plaque psoriasis. Effectiveness was also maintained through 52 weeks of treatment, since PASI 75 and PASI 90 response rates achieved at week 16 (55.5 and 29.6%, respectively) were maintained and improved through 52 weeks of treatment (61.1 and 55.5%, respectively). Such response rates do not differ significantly from those observed in the long-term extension of the randomized, double-blind, phase-3 trial evaluating efficacy and safety of adalimumab in children with severe plaque psoriasis (Thaci et al., 2019)]. Indeed this trial showed that 72.2 and 44.4% of the adalimumab 0.8 mg/kg treated patients maintained respectively a PASI 75 and PASI 90 clinical response at week 52. Switching to another anti-TNFα agent usually produce clinical responses inferior to previously untreated patients. However, adalimumab proved to be effective in a high proportion of adult patients after a first-line anti-TNFα failure in a real life study (Esposito et al., 2018). No difference in effectiveness in anti-TNF-alpha naïve compared with anti-TNF-alpha exposed patients was observed in our analysis. The low number of our patients means a certain obstacle to any interpretation of these data. For this same reason, there were too few patients in some categories, such as overweight, obese, patients with involvement of "difficult to treat" areas, to allow any interpretation of different therapeutic outcomes. The percentage of patients who stopped adalimumab within 16 weeks of treatment due to inefficacy was limited to 11.3%. This finding was not very different from the one observed in the long-term extension of the phase-3 trial with 16.7% of patients who discontinued the treatment. Adverse effects were mild and did not cause treatment withdrawal, although the study was underpowered to detect rare events. The incidence of adverse events, in particular of respiratory tract infection was lower with respect to the international long-term extension study (20% of patients with nasopharyngitis and headache) (Thaci et al., 2019). Underreporting for non-serious adverse events could not be excluded due to the retrospective nature of this study. No new safety risks were recognized.

Several limitations need to be considered. A major limitation of this study is the retrospective nature. The number of enrolled patients was limited. Patients were not randomized, treatment was not blinded and concomitant topical medications were allowed. Only some of the centers belonging to the Pediatric Dermatology Group of our dermatological society contributed to the study. Therefore, our sample is not representative of the Italian population. Although contributing centers were asked to report all patients treated with adalimumab, the data were gleaned by existing records. Consequently, the risk of a reporting selection bias cannot be totally excluded. Despite these possible limitations, we think that our findings may expand knowledge regarding the use of adalimumab as a long-term treatment option for pediatric patients with severe plaque psoriasis.

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