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Efficacy and Safety of Adalimumab for Paediatric Crohn's Disease: A Systematic Review

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Abstract

Background and Aim: Adalimumab is well-established therapy for adults with Crohn's disease [CD]. The aim of the study was to systematically assess the published evidence on the efficacy and safety of adalimumab for Crohn's disease in children.

Methods: MEDLINE, EMBASE, the Cochrane Library, and abstracts from the main gastroenterological meetings in the past 5 years were systematically searched up to July 2015 for randomised controlled trials and observational studies on the efficacy and safety of adalimumab for Crohn's treatment in children and adolescents.

Results: A total of 14 studies [1 randomised controlled trial, 13 case series], altogether including 664 patients [age: 1.9 to 21 years] were available for analysis. The studies differed with respect to patients' characteristics, including percentage of infliximab-naïve patients, disease duration, site of the disease, adalimumab doses, treatment duration, and follow-up period. The pooled remission rates were: 30% [*n* = 93/309] at 4 weeks, 54% [*n* = 79/145] at 3 months, 45% [*n* = 18/40] at 4 months, 42% [*n* = 146/345] at 6 months, 57% [*n* = 20/35] at 8 months, and 44% [*n* = 169/383] at 12 months. Of the total patients, 6% [*n* = 13/207] were classified as primary non-responders and 12% [*n* = 69/599] had severe adverse events reported including 2 deaths and 1 medulloblastoma. Withdrawal rate due to adverse events reported in one study was 35% [*n* = 64/182].

Conclusion: According to low-quality evidence based mainly on case series, approximately half of children with Crohn's disease on adalimumab therapy achieve remission during the first year of the therapy with reasonable safety profile. There is still a need for high-quality evidence on effectiveness and safety of adalimumab for paediatric Crohn's disease.

Key Words: Case series; children; inflammatory bowel disease

1. Introduction

Anti-tumour necrosis factor alpha-based therapies are currently well established treatments in adults with moderate to severe Crohn's disease [CD] with an inadequate response, or with contraindications to, or with intolerance to conventional therapy including corticosteroids and immunomodulators.[1] Of the anti-tumour necrosis factor [TNF] alpha biologicals, the chimeric monoclonal antibody infliximab [IFX] is the major therapeutic agent. However, in some patients repeated administration of IFX was found to be immunogenic; which leads to loss of efficacy and delayed-type hypersensitivity. In the attempt to reduce the immunogenicity induced by chimeric antibodies, the mouse-derived sequence was removed to develop fully human monoclonal antibodies—adalimumab [ADA]. ADA is similar to IFX in the mode of action, but it has the potential advantage of less frequent immunogenic reactions. This makes ADA a viable treatment option in patients who have lost response or are intolerant to IFX, or in some primary non-responders to IFX.[1]

Recently published European consensus guidelines recommended both IFX and ADA for medical management of children with chronically active luminal disease, with active steroid-refractory disease, and as primary induction and maintenance therapy in children with active perianal fistulising disease, in combination with appropriate surgical intervention despite previous optimised immunomodulator therapy.[2] Nevertheless, despite increase in ADA use in children, there is still uncertainty on ADA efficacy and safety in the paediatric population.[3]

The aim of this study was to systematically evaluate the published evidence on the efficacy and safety of ADA for CD treatment in children.

2. Methods

2.1. Criteria for considering studies for this review

Randomised controlled trials [RCT] and observational studies [cohort studies, case series] carried out in children and adolescents with paediatric onset [< 18 years] CD, remaining under paediatric supervision, and assessed up to 21 years old were included. We excluded case studies and case series of less than five patients. The intervention had to be the administration of ADA either alone or with concomitant medications.

The primary outcome measures were the percentage of patients with short-term remission at 4 and 12 weeks after first dose of ADA, and the proportion of patients who maintained the remission at any of the study time points. The secondary outcome measures were: response rate at the any of the study time points, proportion of patients classified as primary non-responders, and percentage of children with loss of response. The other secondary outcome measures were safety measures defined as the proportion of patients with: any adverse event, serious adverse event [as classified by authors of the primary study], and withdrawals due to adverse event.

2.2. Search strategy

The following electronic databases were searched up to July 2015: MEDLINE via PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for interventional and observational trials. Searches for primary studies were restricted with the use of the terms that met the concept of the study: Crohn's disease, adalimumab and paediatric population [Supplementary Table I, available as Supplementary data at *ECCO-JCC* online].

To find additional studies, manual searches of reference lists from identified papers and from all available guidelines, systematic reviews, and meta-analyses pertaining to the therapeutic use of anti-TNF agents in CD published from 2010 were performed. Moreover, the abstracts from the main gastroenterological meetings [annual meetings of the: European Society of Pediatric Gastroenterology, Hepatology and Nutrition; North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; American Gastroenterology Association; European Crohns and Colitis Organisation; and United European Gastroenterology Week] in the past 5 years were reviewed for any additional potentially relevant studies.

2.3. Study selection

The search and selection of the trials were conducted by two reviewers [AH, PD] independently. All of the potentially relevant articles were retained and their full texts or abstracts [if the study was presented only as an abstract] were critically reviewed according to the predefined inclusion and exclusion criteria.

2.4. Data extraction

Data extraction was performed by each reviewer using a standard data extraction form, before being then checked by a second reviewer. For the included studies, information was extracted on study design, patient characteristics (age, baseline severity of disease, disease behaviour [luminal, fistulising or penetrating], percentage of IFX-naïve patients), ADA dosage, duration of follow-up, clinical efficacy, and adverse effects. Discrepancies between the extracted data were resolved via consensus.

2.5. Methodological assessment

Methodological quality of case series was assessed using an 18-item validated quality appraisal tool for case series.[4] Quality appraisal judgments for each item are determinations of various features of the study including study objectives, population, interventions and co-interventions, outcome measures, statistical analysis, results and conclusions, and competing interests.

2.6. Statistical analysis

Descriptive statistics are provided. Continuous nonparametric data are presented as median followed by range or interquartile range, parametric data as mean and standard deviation unless otherwise specified. The categorical data for outcome measures are presented as percentage of total cases with 95% confidence interval [95% CI].

3. Results

A total of 35 studies on ADA treatment in children were retrieved and evaluated in more detail. Of these, 21 were excluded for various reasons [Figure 1], leaving 14 articles including a total of 664 patients aged between 1.9 and 21 years. [5,6,7,8,9,10,11,12,13,14,15,16,17,18] Only one RCT [n = 188] comparing two different doses of ADA was identified.[5] The remaining 13 studies were either retrospective or prospective case series. Characteristics of the included studies are listed in Table 1. The studies differed with respect to baseline disease severity, number of included patients [7–188], concomitant treatment, duration of treatment and, in some cases, remission and response criteria. There was no unified ADA dosage scheme found across all the studies. Moreover, in most of the case series there were differences between individual patients regarding ADA dosage [Table 2].

3.1. Outcome measures

Short-term remission rate at the 4th week of therapy ranged from 24% to 61% [four studies][4,7,12,16] and at the 12th week of treatment ranged from 30% to 88% [three studies].[10,14,16] For maintenance therapy the remission rates were as follows: 45% at 4 months [one study][8] ranged from 28% to 55% at 6 months [five studies], [4,11,12,14,15] 57% at 8 months [one study][8] ranged from 23% to 97% at 12 months [eight studies],[4,6,8,9,10,11,12,14] 97% at 24 months [one study],[8] and 67% at 36 months [one study].[8]

The short-term response rates at 4 weeks ranged from 50% to 87% [four studies][4,7,12,16] and at 12 weeks ranged from 65% to 91% [three studies].[10,14,17] The long-term response rates were as follows: 55% at 4 months [one study][8] ranged from 64% to 87% at 6 months [three studies],[4,7,15],74% at 8 months [one study][8] ranged from 53% to 92% at 12 months [six studies],[4,8,9,10,12,15] 47% at 24 months [one study],[8] and 83% at 36 months [one study].[8]

The pooled results for remission rates, response rates, primary non-response rates, and loss of response rates are presented in Table 3.

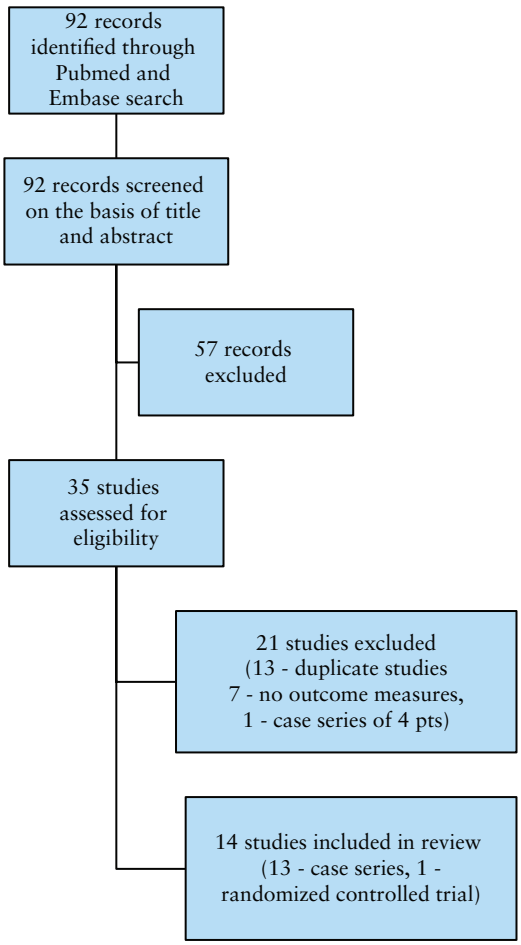

Figure 1. Flowchart of existing studies.

Altogether, 11/14 studies including 599 patients reported adverse effects [49%; 95% CI: 45–53%] and serious adverse events [12%; 95% CI: 9–14%] [Table 4]. Only one study [n = 188] recorded withdrawal rate due to adverse effects which occurred in 35% of patients [95% CI: 29–42%]

Methodological quality of case series assessed with an 18-item validated quality appraisal tool for case series is available as Supplementary data at *ECCO-JCC* online.

4. Discussion

The results of this systematic review showed that majority of paediatric data on the efficacy and safety of ADA for CD treatment are of a descriptive nature; 13 of 14 identified studies are case series. Only one RCT compared two doses of ADA and was not placebo controlled because of ethical considerations.[5] The overall pooled remission rate following the different time points between 3 and 12 months of therapy occurs in approximately 50% of patients. The remission rates of RCT are lower than in case series and do not exceed 1/3 of trial participants.

Case series are a useful source of evidence on safety, because compared with randomised controlled trials, they usually have longer follow-up and their inclusion criteria may be less strict than those in RCTs.[19] The safety profile of ADA appears to be favourable. In paediatric patients, the risk of serious adverse event seems to be reasonably low: it appears in one out of eight children. Both fatalities reported by Russel *et al*. were a result of central line sepsis in children treated with ADA, immunosuppressants, and parenteral nutrition. The combination of immunosuppressive medications is a widely recognised risk factor for opportunistic infections in CD patients.[20] There is also some evidence that treatment with anti-tumour necrosis factor alpha agents may increase the risk for malignancies including lymphoma; however, in our systematic review we identified only one case of medulloblastoma and no case of lymphoma. [21] Nevertheless, further studies with more patients and with longer follow-up are required to better assess the safety profile of ADA therapy in children.

The results of our review mirror the real world situation in paediatric CD, where therapy is often based on expert opinion, extrapolated from studies performed in adults and from descriptive studies in youngsters, rather than the best evidence supported by well-performed and well-presented RCTs in children.[22] Clinical research involving children with inflammatory bowel disease seems to be more challenging in several aspects than research involving adults.[22] Moreover, ethical considerations of medical experts on performing placebo-controlled trials in children with inflammatory bowel disease limits the available evidence based on the placebo-controlled trials.[22]

4.1. Strengths and limitations.

Strengths of this review lie in the use of transparent and rigorous methodology. We applied appropriate methods to reduce bias at different stages of review, starting from a comprehensive literature search to complete reporting and analysis of the data. In our study we applied the outcome measures proposed by the recently published European Crohn's and Colitis Organisation statement.[21] The other strengths of our review include attempts to identify unpublished trials, and no use of language restrictions.

Nevertheless, this review has several limitations. These include the questionable methodological quality of most of the studies. Lack of placebo/standard therapy and even the absence of a control group do not imply that effectiveness is attributed to the intervention and limit the relevance of the studies included in this systematic review. The relapsing nature of CD additionally undermines the assessment of causal relationships between interventions and outcomes. However, the use of ADA in the paediatric population is usually reserved for patients with the most severe form of the disease not responding to standard therapy, without expectation of self-limitation of symptoms.

Furthermore, in primary studies there were considerable variations in ADA dosage and remission and response criteria; these additionally attenuate the applicability of this systematic review.

Moreover, the case series are prone to several biases, such as selection bias, observer bias, and reporting bias; thus inherent methodological weakness places them at the lowest level of evidence. However, by including patients with a broad range characteristics and co-interventions, case series samples are supposed to be more likely to have external validity, ie to be representative of the 'real-life' population of interest. In an RCT, rigorous inclusion criteria and selection of patients who are willing to participate, potentially decrease the extent to which the results can be applied to common clinical practice.[23] The published case series on ADA treatment seems to represent the actual and vast experience of paediatric centres in a range of different countries and health care systems.

The role of case series data in systematic reviews of health care interventions is applicable particularly to reviews of rapidly

Table 1. Characteristics of included studies.

Study characteristics			Adalimumab dose in miligrams		Outcome definitions	
First author [year]	Full text	Design	Induction	Maintenance every other week	Response criteria	Remission criteria
Hyams [2012][5]	Yes	RCT	> 40 kg: 160/80 < 40 kg: 80/40	High-dose group: > 40 kg:40, < 40 kg: 20 Low-dose group: > 40 kg: 20 < 40 kg: 10 At week 26, dosing adjusted for weight	Decrease in PCDAI > 15 points from baseline	PCDAI < 10
Fumery [2015][6]	Yes	Case Series	NR	NR	PGA decrease ≥ 2 points	PGA = 1
Pichler [2015][7]	Yes	Case Series	> 40 kg: 160 < 40 kg: 80	> 40 kg: 80 < 40 kg: 40	An improvement in PCDAI	NR
Cameron [2015][8]	Yes	Case Series	NR	NR	Improved symptoms but continuing disease activity assessed with PGA	Improvement to inactive disease assessed with PGA
Cozijnsen [2015][9]	Yes	Case Series	< 40 kg: 40/80 40 kg: 80/160 [*n* = 39]; < 40 kg: 20/40 > 40 kg:40/80 [*n* = 20]	< 40 kg: 20/40 > 40 kg: 40/80	PCDAI decrease ≥ 17.5 points, or PGA decrease from either moderate or severe to mild disease	PCDAI < 12.5 or PGA = 0
Nobile [2014][10]	Yes	Case Series	160/80 [*n* = 16]; 80/40 mg[*n* = 3]	40	PGA decrease either from moderate or severe to mild/inactive or from mild to inactive	PGA standard definition
Martin–de Carpi [2014][11]	No	Case Series	160/80 [*n* = 22]	40	NA	PCDAI < 10 points
Alvisi [2013][12]	No	Case Series	NR	NR	NR	NR
Russel [2011][13]	Yes	Case Series	160/80 [*n* = 3] 80/40 [*n* = 41] 24/m^2 [*n* = 16] Other doses [*n* = 10]	160/80 [*n* = 3] 80/40 [*n* = 41] 24/m^2 [*n* = 16] Other doses [*n* = 10]	PCDAI decrease > 12.5 points or PGA standard definition	PCDAI ≤ 10 or PGA standard definition
Rosenbach [2010][14]	Yes	Case Series	160/80/1.73 m^2	40/1.73 m^2	NR	HarveyBradshaw score < 4
Rosh [2009][15]	Yes	Case Series	160/80 [*n* = 22] 80/40 [*n* = 51] 40/40 [*n* = 17] Other doses/no data [*n* = 9]	80 [*n* = 6] 40 [*n* = 101] 30 [*n* = 2] 20 [*n* = 4]	PGA decrease either from moderate or severe to mild/inactive or from mild to inactive or if PCDAI > 30 points decrease to ≥ 15 points	PCDAI ≤ 10
Viola [2009][16]	Yes	Case Series	160/80 [*n* = 13] 120/80 [*n* = 2] 80/40 [*n* = 8]	80 [*n* = 15] 40 [*n* = 8]	PCDAI decrease ≥ 50% from baseline value	PCDAI ≤ 10
Noe [2008][17]	Yes	Case Series	80 [*n* = 3] 40 [*n* = 4]	40	Decrease in disease severity	PCDAI < 10
Wyneski [2008][18]	Yes	Case Series	80 [*n* = 13] 160 [*n* = 1]	80 [*n* = 1] 40 [*n* = 13]	Steroid-free interval longer than 3 months	NR

PGA, Physical Global Assessment; PCDAI, Paediatric Crohn's DIsease Activity Index; NR, not reported.

developing pharmacological interventions and in small populations of patients, where case series are usually the only available clinical evidence.[24] According to *Health Technology Assessment* reports, case series can be incorporated in systematic reviews if comparative evidence is available only in a selected population, and to supplement more rigorous evidence.[25]

4.2. Comparison with other studies

In the recently published large registry data set of paediatric Crohn's disease patients treated with anti-tumour necrosis factor alpha, the remission rates at the 26th and 52nd weeks of therapy were, respectively, 54% [95% CI: 48–61%] and 66% [95% CI: 60–73%], which were higher than the results of the current study. However, these results apply to patients naïve to biological therapy, contrary to the children included in this systematic review which consisted mainly [≈ 75%] of subjects previously treated with IFX. The studies performed in adults showed that remission rates among biological therapy-naïve patients are higher than in patients already treated with IFX.[26,27]

The pooled remission rates in our study are comparable to the results of a recently published systematic review of placebo-controlled

Table 2. Baseline characteristics of the patients included in systematic review.

Study ID		No of patients	Age years: median [range] *Mean ± SD*	Baseline severity PCDAI mean ± SD	Proportion of patients naïve to biological therapy	Concomitant medication	Disease behaviour[a]
Hyams[5]	Low dose	95	*13.5 ± 2.47*	40.8 ± 6.8	105/188	CS: 38/95 IS: 57/95 ASA: 33/95 Antibiotics: 11/95	NR
	High dose	93	*13.7 ± 2.52*	41.3 ± 7.2		CS: 33/93 IS: 60/93 ASA: 35/93 Antibiotics: 4/93	NR
Fumery[6]		27	15 IQR [QQ3 12–15]	NR	0/27	CS: 5/27 AZT: 2/27 MTX: 1/27	NR
Pichler[7]		18	14.4 [5.3–19.1]	52 ± 16	1/18	CS: 11/18 5ASA: 14/18 AZA/6MP: 4/18 MTX: 5/18 Ciclosporin: 2/18	NR
Cameron[8]		28	13.8 [6.8–17.2]	Mild: 7 moderate/severe: 21	1/28	CS: 15/28 MTX: 18/28 AZA/6MP: 4/28	B1: 21/28 B2: 5/28 B3: 2/28
Cozijnsen[9]		59	14 [13–16]	NR	0	AZT/6MP: 21/59 MTX: 11/59 CS: 7/59 EN:2/59	B1: 42/59 B2: 8/59 B3: 1/59 B2&B3: 2/59
Nobile[10]		19	18.6 [13.5–21]	NR	3/19	CS: 5/19 AZA/6MP: 19/19	B1: 8/19 B2: 4/19 B3: 7/19
Martin de Carpi[11]		40	*12.6 ± 2.5*	Median:25 [IQR: 15–30]	0/40	NR	NR
Alvisi[12]		42	14.6	25	0/42	NR	NR
Russell[13]		70	14.8 [6.1–17.8]	Median: 37.5 [7.5–65] [*n* = 48]	4/70	Steroids:26/70 AZA/6MP: 27/70 MTX: 19/70	NR
Rosenbach[14]		14	13.4 [1.9–19.1]	Median:12 [range:9–13] [Harvey-Bradshaw score]	4/14	CS: 14/14 MTX: 6/14 AZA/6MP: 12/14 Ciclosporin: 1/14	NR
Rosh[15]		115	*15.8 ± 3.*	25 15	6/115	CS: 44/115 AZT/6MP: 47/115 MTX: 26/115	NR
Viola[16]		23	16.1 [9–20]	36.5 ± 5.7	9/23	CS: 18/23 MTX: 2/23 AZA/6 MP: 11/23	B1: 10/2 B2: 9/23 B3:4/23
Noe[17]		7	16 [14–18]	5 [median]	0/7	NR	NR
Wyneski[18]		14	17.9 [10.3–21.8]	NR	0/14	NR	NR

SD, standard deviation; IQR, interquartile range; PCDAI, Paediatric Crohn's DIsease Activity Index; CS, corticosteroids, AZT/MP-azathioprine/6-mercaptopurine; MTX-methrotrexate; EN: enteral nutrition; NR = not reported.

[a]According to Montreal scale.

RCTs conducted in adults.[28] In luminal CD, remission rates for the induction phase ranged from 12% to 67%, and for maintenance therapy varied from 29% to 72%. Nevertheless, this comparison must be interpreted with caution because of the differences in primary study design.

Concerning the safety issues, the results of our study are similar to the results of a systematic review on the risk of serious adverse events, which included 5528 children [84% patients with CD on anti tumour necrosis alpha therapy, 10% treated with ADA, 90% treated with IFX].[29] Dulai *et al.* found that the risk of lymphoma was comparable to the risk in patients treated with other therapies, and even lower with respect to serious infections.[29]

4.3. Implications for future research

Every systematic review has a potential to influence the design of future primary studies. Based on the results of this systematic review showing that the majority of paediatric data are of low quality,

Table 3. The efficacy of adalimumab in paediatric Crohn's disease—pooled results of systematic review.

Outcome measure	Number of studies	Overall [percentage; 95% CI]	RCT [percentage; 95% CI]	Case reports [percentage; 95% CI]
Remission				
4 weeks	4	93/309 [30; 25–35]	52/188 [28; 21–34]	41/121 [34; 26–43]
3 mo	4	79/145 [49; 45–62]	NA	79/145 [49; 45–62]
4 mo	1	18/40 [45; 30–60]	NA	18/40 [45; 30–60]
6 mo	5	146/345 [42; 37;48]	ITT: 63/188 [34; 27–41] PP: 63/152 [41; 34–49]	83/157 [52; 44–60]
8 mo	1	20/35 [57; 41–72]	NA	20/35 [57;41–72]
12 mo	9	169/383 [44; 39–49]	ITT: 53/188 [28; 22–35] PP: 53/124 [43; 34–52]	116/195 [59; 52–66]
24 mo	1	33/34 [97; 85–99]	NA	33/34 [97; 85–99]
36 mo	1	4/6 [67; 30–90]	NA	4/6 [67; 30–90]
Response				
4 weeks	4	232/309 [75; 70–80]	155/188 [82; 76–87]	77/121 [64; 55–72]
3 mo	3	75/105 [71; 62–79]	NA	75/105 [71; 62–79]
4 mo	1	26/47 [55; 41–69]	NA	26/47 [55; 41–69]
6 mo	5	206/323 [64; 58–69]	ITT: 98/188 [52; 45–59] PP: 98/152 [64; 60–72]	108/135 [80; 72–86]
8 mo	1	26/35 [74; 58–86]	NA	26/35 [74; 58–86]
12 mo	6	165/315 [52; 47–58]	ITT: 66/188 [35; 29–42] PP: 66/124 [53; 44–62]	99/127 [78; 70–84]
24 mo	1	9/19 [47; 27–68]	NA	9/19 [47; 27–68]
36 mo	1	5/6 [83; 44–97]	NA	5/6 [83; 44–97]
Primary non-response	7	13/207 [6; 3–10]	NA	13/207 [6; 3–10]
Loss of response	8	38/323 [12; 9–16]	NA	38/323 [12; 9–16]

CI, confidence interval; mo, months; NA, non available; RCT, randomised controlled trial; PP, per protocol analysis; ITT, intention-to-treat analysis].

and in the light of the fact that the European Crohn's and Colitis Organisation panel of experts unanimously agreed that placebo-controlled trials, without an active treatment in each treatment arm, are not appropriate for most paediatric trials, it seems there is a need for the establishment of an international collaboration registry using already existing national registries with possible inclusion of other countries. Such partnership could be the basis for performing observational trials like open-label long-term cohort studies, case-control trials, or interventional trials of innovative designs which minimise the use of placebo-like withdrawal trials, early escape trials, or adaptive trials.[30] These kinds of studies could give more firm evidence providing an achievable alternative to randomised, parallel-group placebo-controlled trials.

5. Conclusion

According to low-quality evidence provided by several case series and one RCT comparing two different ADA doses, approximately half of children with CD achieve remission during the first year of the therapy with reasonable safety profile. There is still a need for more robust evidence assessing the efficacy and safety of ADA therapy for CD in the paediatric population.

Table 4. Adverse events during adalimumab therapy.

Any adverse event, n	Serious adverse event, n	Withdrawals due to adverse events, n
Overall, 293/599:	*Overall, 69/599*	64/182
Infections, 162	Deaths from central catheter sepsis, 2	
Injection sites reactions, 89	Medulloblastoma, 1	
Arthralgia/myalgia, 7	Meningitis, 1	
Xerosis, 6	Haematological, 24	
Abdominal pain, 5	Allergic reactions, 10	
Headache, 5	Hepatic-related, 10	
Nausea, 5	*C. Difficile* infection, 2	
Allergy, 4	Perianal abscess, 2	
Depigmentation acne, 3	Anal abscess, 1	
Fever, 3	Stomal abscess with fistula, 1	
Rash, 3	Abdominal abscess, 3	
Psoriasis, 2	Colonic obstruction and abscess, 1	
Tiredness, 2	Seton placement, 1	
Tympanic perforation, 1	Staphylococcal folliculitis, 1	
Dizziness, 1	Scarlet fever, 1	
Hair loss, 1	Disseminated histoplasmosis	
Dyspnoea, 1	1	
Transient visual loss, 1	Gastroenteritis, 1	
Stomal bleeding, 1	H1N1 influenza, 1	
Itching, 1	Viral infection, 1	
Numbness, 1	Yersinia infection, 1	

Conflict of Interest

PD, speaker honoraria: Nutricia. AH, speaker honoraria: Nutricia, research grant: Nutricia. JK, speaker honoraria: MSD, Egis, Nutricia, and Abbvie, Mundipharma research grant: Nestle, Nutricia.

Author Contributions

PD, AH, JK contributed to the concept and design of the study. PD, AH, contributed to acquisition of data. PD, AH, JK contributed to analysis and interpretation of data. PD, AH, JK contributed to drafting the article and its critical revision. PD, AH, JK approved final version of the article.

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