Journal of Dermatological Treatment

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ijdt20

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To cite this article: Lisa P. van der Rijst, Annet van Royen-Kerkhof, Suzanne G. M. A. Pasmans, Renske Schappin, Marjolein S. de Bruin-Weller & Marlies de Graaf (2023) Biologicals for pediatric patients with atopic dermatitis: practical challenges and knowledge gaps, Journal of Dermatological Treatment, 34:1, 2254567, DOI: 10.1080/09546634.2023.2254567

To link to this article: https://doi.org/10.1080/09546634.2023.2254567

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Published online: 04 Sep 2023.

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JOURNAL OF DERMATOLOGICAL TREATMENT
2023, VOL. 34, NO. 1, 2254567
https://doi.org/10.1080/09546634.2023.2254567

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DISCUSSION

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Biologicals for pediatric patients with atopic dermatitis: practical challenges and knowledge gaps

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ABSTRACT

Biologicals are becoming increasingly important in the therapeutic landscape of pediatric patients with moderate-to-severe atopic dermatitis (AD). Currently, dupilumab and tralokinumab are registered for the treatment of moderate-to-severe AD, and novel biologicals are expected to follow. Dupilumab was the first biological registered for AD in pediatric patients and was recently approved for patients aged six months to five years. Current and emerging biologicals may address the unmet need for effective and safe treatment options for pediatric AD patients, however, little is known about the practical implementation of biologicals in infants and preschoolers (aged <6 years), including the timing of treatment initiation, discontinuation, and long-term administration of the subcutaneous injections. Currently, only a small number of biologicals are approved for the treatment of infants and preschoolers for other inflammatory diseases. Consequently, data on the practical implementation of biological treatment remain scarce. In addition, long-term effects, impact on co-morbidities, and impact on live-accentuated vaccination are still unknown. With the introduction of biologicals for AD from the age of six months, potential challenges within the implementation of biologicals may arise. Therefore, we aim to discuss current practical challenges and knowledge gaps of the treatment with biologicals in infants and preschoolers with AD.

ARTICLE HISTORY
Received 11 June 2023
Accepted 28 August 2023

KEYWORDS
Atopic dermatitis; biological therapy; pediatric dermatology; immunomodulating therapy; children

1. Introduction

Biologicals are becoming increasingly important in the therapeutic landscape of pediatric patients with moderate-to-severe atopic dermatitis (AD). Currently, dupilumab and tralokinumab are registered for the treatment of moderate-to-severe AD for pediatric patients, and novel biologicals are expected to follow (1–4). Dupilumab, a monoclonal antibody inhibiting interleukin (IL)-4 and IL-13 signaling, was the first biological registered for patients aged 6–17 years with AD, and was recently approved for patients aged 6 months to 5 years (1,5). Tralokinumab, a monoclonal antibody that specifically targets IL-13 signaling, is recently registered for the treatment of AD in adolescents (2). Registration of tralokinumab for younger patients is expected, as trials are currently running (6).

Current and emerging biologicals may be able to address the unmet need for effective and safe treatment options for AD in pediatric patients, leading to sustained disease control and improved quality of life for both patients and their families (7,8). However, little is known about the practical implementation of biologicals in infants and preschoolers (<6 years of age), including the timing of treatment initiation, discontinuation, and long-term administration of the subcutaneous injections. Currently, only a small number of biologicals are approved for the treatment of patients under six years of age for other inflammatory diseases (e.g., for juvenile idiopathic arthritis, uveitis, and auto-inflammatory diseases) (9–14). Consequently, data on the practical implementation of biological therapy remain scarce. In addition, in pediatric AD patients treated with biologicals, long-term effects, impact on co-morbidities, and impact on live-accentuated vaccination are not well known.

With the introduction of biologicals for AD from the age of six months, potential challenges within the implementation of biologicals may arise. Therefore, we aim to discuss current practical challenges and knowledge gaps of the treatment with biologicals in infants and preschoolers with AD.

2. Starting and discontinuing biologic treatment

Although biologic treatment in infants and preschoolers is expected to involve a relatively small group of patients, criteria for starting and discontinuing treatment needs to be further determined. Dupilumab is considered a long-term treatment. Young children will only have AD for a short period of time due to their age. In addition, about half of patients with childhood-onset AD

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achieve complete remission by the age of six to seven years (15–17). Considering these aspects, the indication for starting biological therapy may be challenging. Moreover, it can be questioned to what extent topical therapy has been given a chance at success at a young age. Topical therapy (including topical corticosteroids and emollients), the first-line therapy for AD, often leads to remission of signs and symptoms. However, adequate topical treatment requires considerable time and effort, as comprehensive education to improve adherence and ensure safe use of topical corticosteroids is essential (15, 18).

Once biological therapy is started, it can also be challenging to establish when to discontinue treatment due to the variable course of disease and the possibility of spontaneous remission or exacerbation after discontinuing the treatment (15,16). Data on intermittent treatment, discontinuing biological treatment after achieving long-term disease control and reinitiating in case of relapse of the disease, are lacking. Tapering treatment, by prolonging the interval in patients with controlled disease, may be a step toward discontinuation. In adult AD patients treated with dupilumab, interval prolongation has shown to be safe and effective (19). Yet little is known regarding the development of anti-drug antibodies in the pediatric population. Although, no meaningful impact on efficacy or safety has been observed in adult AD patients who developed anti-drug antibodies during dupilumab treatment (20).

3. Practical challenges

Administration of biologicals *via* subcutaneous injections can be challenging for both child and caregiver. Biologicals for AD are administered every two to four weeks, depending on age and weight (1,2). Administration can take place at home or in the hospital (inpatient administration). Home administration is time-saving and cost-sparing for both patient and healthcare providers, and may lead to improved quality of life by allowing more independence and less frequent hospital visits (21). Home administration is however not always feasible for children and their families, as it can be a significant stressor: traumatization was observed in parents administering enoxaparin to their children, and anxiety, frustrations, and doubt were reported in parents injecting insulin to their children at home (22,23). In addition, needle phobia, which is common in children but also in parents, has been reported to lead to resistance or even noncompliance of treatment (21). Caregivers may benefit from structured educational programs to address these issues, by enhancing their knowledge and confidence for administration, and needle phobia and the development of a stress and anxiety reducing administration routine can be addressed by a psychologist (22,24,25). Nevertheless, in our experience, most children (age <12 years) need inpatient administration of subcutaneous injections, with the help of (specialized) nurses and/or educational support.

As biologicals will continue to be approved for younger children and the number of pediatric patients starting biologicals will slowly increase, above mentioned economic and psychological challenges in the management of administration require attention. An increase of inpatient administration of biologicals, although costly and time-consuming, can be anticipated. Moreover, psychological challenges, such as distress, fear, resistance and ultimately traumatization in children, insecurity and emotional stress in parents, and negative impact on the child-parent relationship, will require psychological support. In order to provide this specialized care, treatment at experienced centers for pediatric AD patients is desirable.

4. Knowledge gaps

Despite the availability of biologicals for young AD patients, little is known about the impact of inhibiting signaling of IL-4/IL-13 on long-term effects, comorbidities, and live-accentuated vaccines. Long-term studies and daily practice data in adult AD patients have shown favorable safety results and provided insight in important side-effects, such as the most frequently reported side effect dupilumab associated ocular surface disease (DAOSD) (26). However, long-term data about these side effects in children is scarce (27). Achten et al. showed that ocular surface disease (OSD) is a common finding in adult patients with moderate-to-severe AD, although many patients did not report OSD symptoms (26). Symptoms of DAOSD may be even more difficult to recognize in infants and preschoolers, leading to delayed diagnosis and referral to an ophthalmologist. Furthermore, dupilumab treatment is associated with a decrease in number and function of conjunctival goblet cells in adult AD patients treated with dupilumab (28). Goblet cells are also present in the respiratory and gastrointestinal epithelia, however, a possible effect of dupilumab on these organs is yet unknown. Scarce literature describes varying results of patients developing inflammatory bowel disease during dupilumab treatment for AD, but the pathophysiology and possible relation is not well understood (29,30). Moreover, associations between dupilumab treatment in AD patients and the development of other Th17-related immune diseases, such as enthesitis, enthesopathy and psoriasis, have been described (31,32). Future long-term studies are needed to investigate the potential development of other inflammatory diseases and their immunological pathways during long term treatment with biologicals in young children.

Biologicals for AD block type 2-inflammatory pathways, however, the impact on associated comorbidities in pediatric AD patients, such as asthma, allergic rhinoconjunctivitis, and food allergy, has not yet been investigated. As dupilumab is also indicated for other inflammatory diseases, such as moderate-to-severe asthma, chronic rhinosinusitis with nasal polyposis, and eosinophilic oesophagitis, additional advantage could be achieved in AD patients with these comorbidities. Potentially, biologicals could prevent the development of comorbid atopic diseases, by achieving well-controlled disease at an early age (e.g., by restoring the skin barrier and reducing the risk of sensitization through the skin) and possibly by modifying the immune system. Recent studies in adult AD patients showed positive effects of dupilumab on comorbid food allergy and asthma (33,34). Nevertheless, it can be challenging to evaluate the effectiveness of biologicals on atopic comorbidities in young pediatric AD patients. Better understanding of the effect of biologicals on disease prevention and/or disease modification and the effect on associated comorbidities is necessary.

Lastly, data regarding the efficacy, immunogenicity, and safety of vaccination with live-attenuated vaccines (e.g., the measles, mumps and rubella vaccine) in children treated with biologicals for inflammatory diseases, are scarce. Although limited, current data in the field of rheumatic diseases, inflammatory bowel disease and moderate-to-severe asthma are encouraging to promote vaccinations in children treated with biological treatment for chronic inflammatory diseases (35,36). Long-term follow up is needed to evaluate persistence of

antibodies after vaccination of young children treated with biologicals.

5. Conclusion

Current and emerging biologicals may address the unmet need for effective and safe treatment options pediatric AD patients, leading to sustained disease control and improved quality of life for the patients and their families. Psychological challenges related to long term subcutaneous administration within infants and preschoolers, such as distress, fear, traumatization, and impact on the parent-child relationship, will require psychological support. In order to provide this specialized care and to address the current knowledge gaps and practical challenges, treatment in experienced centers and data collection in (inter)national registries is recommended.

Disclosure statement

- Lisa P. van der Rijst is a speaker for AbbVie.
- Suzanne G.M.A. Pasmans has been a consultant, advisory board member, and/or speaker for Leo Pharma, Pfizer, Regeneron, and Sanofi-Genzyme.
- Renske Schappin has no conflicts of interest.
- Annet van Royen-Kerkhof has received travel grants, speaking fees (less than €1000,-) for Novartis, Roche, Shire, AbbVie, SOBI, and Baxalta.
- Marjolein S. de Bruin-Weller has been a consultant, advisory board member, and/or speaker for AbbVie, Almirall, Amgen, Aslan, Eli Lilly, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron, and Sanofi-Genzyme
- Marlies de Graaf is a consultant, advisor and/or speaker for AbbVie, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals and Sanofi.

Funding

This work was not supported by funding.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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