ECRONICON OPEN ACCESS

EC MICROBIOLOGY
Research Article

Omalizumab for Treatment of Pediatric Atopic Dermatitis: A Systematic Review of Randomized Controlled Trials

Mostafa Abdelmordy Ibrahim[1]*, Abdulaziz Abdullah AlJaafary[2], Kholod Balkher Alamri[3], Shorouq Amer Alamer[3], Ahlam Muslih Al Ghamdi[3], Fahad Awadh ALNamassi[4], Shahad Daifalla Alsulaimani[5], Husam Majid Shahada[6], Amal Baalqasim Sulaimani[7], Hamza Sahl Zolali[7] and Afnan Owaytiq Al Johani[8]

[1]Department of Pediatrics, International Medical Center, Jeddah, Saudi Arabia

[2]College of Medicine, King Saud Bin Abdulaziz University for Health and Sciences, Riyadh, Saudi Arabia

[3]College of Medicine, King Khalid University, Abha, Saudi Arabia

[4]Department of Dermatology, King Salman Specialist Hospital, Hail, Saudi Arabia

[5]College of Medicine, Batterjee Medical College, Jeddah, Saudi Arabia

[6]Department of Pharmacology, Ohud Hospital, Medina, Saudi Arabia

[7]College of Medicine, Taibah University, Medina, Saudi Arabia

[8]Department of Dermatology, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia

***Corresponding Author:** Mostafa Abdelmordy Ibrahim, Department of Pediatrics, International Medical Center, Jeddah, Saudi Arabia.

Received: August 24, 2020; **Published:** October 15, 2020

Abstract

The design of Omalizumab (Xolair; Novartis) is based on binding to IgE, limiting the activation of mast cells and the subsequent release of inflammatory mediators. In the current study, we aim to conduct a systematic review of Omalizumab for the treatment of pediatric atopic dermatitis (AD). For that, a systematic electronic database search was conducted for relevant studies published from inception till 4th July 2020 in nine databases. Finally, we included four studies for this systematic review and meta-analysis. Our results showed that free IgE dropped from 963 IU/ml to 923 IU/ml in the placebo group while it dropped dramatically from 847 to 9.8 in the Omalizumab group. Moreover, Omalizumab decreased serum IgE levels from 16007 IU/ml to 6641 IU/ml. Furthermore, a significant decrease in the SCORAD index was observed from the two included RCTs ($p < 0.05$), after the administration of Omalizumab compared to the placebo group. For safety assessment, two studies did not report Omalizumab adverse events and one reported no serious adverse events. In conclusion, Omalizumab showed promising efficacy and reasonable safety index in the treatment of AD in the pediatric population.

Keywords: *Atopic Dermatitis; Omalizumab; Children; Pediatric*

Introduction

Atopic dermatitis (AD) is a common, persistent inflammatory disease of the skin with a prevalence of 7.7% in children up to 7 years old and 7.3% in adolescents aged 13 to 14 years [1,2]. AD is one of the most grueling skin conditions that any individual can experience [3]. Its course is usually long term and most outbreaks do not halt until a person is in their mid-twenties [3]. For this reason, children are most affected by AD and are forced to learn at a very early age how to overcome the negative aspects of this skin condition, both physical and psychological [4,5].

AD can also be referred to as eczema and can be experienced in many types of settings [6]. Physical symptoms of this skin condition include persistent itching, erythema, rashes all over the infected areas, and pain [7]. Children who have AD not only have to deal with these physical symptoms but consequently, they are forced with many negative psychological aspects as well [8]. Not being able to play sports, exercise, live in hot environments and being picked on for having abnormal skin are only some psychological problems that children are forced to deal with [8].

The pathophysiologic process of AD is complex and influenced by the interaction between different factors including environmental, immunological, and genetic ones [9]. The severity of the disease is proportional to IgE levels and AD lesions showed to bear considerable numbers of IgE-bearing cells [10]. The allergen-specific, receptor-bound IgE has the ability to effectively present allergens to T-cells, with subsequent activation and inflammatory reaction [10]. The itch-scratch cycle would aggravate AD through IgE-mediated histamine release from mast cells [11]. The design of Omalizumab (Xolair; Novartis) is based on binding to IgE, limiting the activation of mast cells and the subsequent release of inflammatory mediators [12].

Aim of the Study

In the current study, we aim to conduct a systematic review of Omalizumab for the treatment of pediatric AD.

Methods

Search strategy and study selection

The study process was conducted following the accepted methodology recommendations of the PRISMA checklist for systematic review [13]. A systematic electronic database search was conducted for relevant studies published from inception till 4th July 2020 in nine databases including Google Scholar, Scopus, Web of Science (ISI), PubMed, metaRegister of Controlled Trials (mRCT), System for Information on Grey Literature in Europe (SIGLE), Clinical trials.gov, Virtual Health Library (VHL), and New York Academy of Medicine(NYMA); using keywords, medical subject (MeSH) terms. In databases not supporting MeSH terms, combinations of all possible terms were used. Moreover, We conducted a manual search of references from the included articles by searching the primary studies that had cited our included papers and scanning references of the relevant papers in PubMed and Google Scholar to avoid missing any relevant publications [14].

We included all original relevant studies which are discussing Omalizumab for the treatment of pediatric AD. Papers were excluded if there was one of the following exclusion criteria: pilot studies, duplicate records, data could not be reliably extracted or incomplete reports, abstract only articles, thesis, books, conference papers. Title and abstract screening were done independently by four reviewers. Then, three independent reviewers performed a full-text screening to ensure the inclusion of relevant papers in our systematic review. Any disagreement was resolved by discussion and referring to the senior author when necessary.

Data extraction

Two authors developed the data extraction sheet using the Microsoft Excel software. Data extraction was performed by three independent reviewers using the excel sheet. The fourth independent reviewer performed data checking to ensure the extracted data accuracy. All the disagreements and discrepancies were resolved by discussion and consultation with the senior author when necessary.

Risk of bias

Three independent reviewers evaluated the risk of bias in included studies. The National Institutes of Health (NIH) quality assessment tool was used to assess the quality of each included study [15]. The quality assessment of each study was obtained through a scoring sys-

tem [16]. Any discrepancy between the reviewers was solved by discussion.

Results

Study characteristics

We found 2300 records after searching for nine databases. We excluded 438 records as duplicates using endnote software. Title and abstract screening of 1862 records resulted in the inclusion of 81 full texts for further full-text screening. Finally, we included four studies for this systematic review and meta-analysis. No papers were found after manual search trials (Figure 1 and table 1) [17-20].

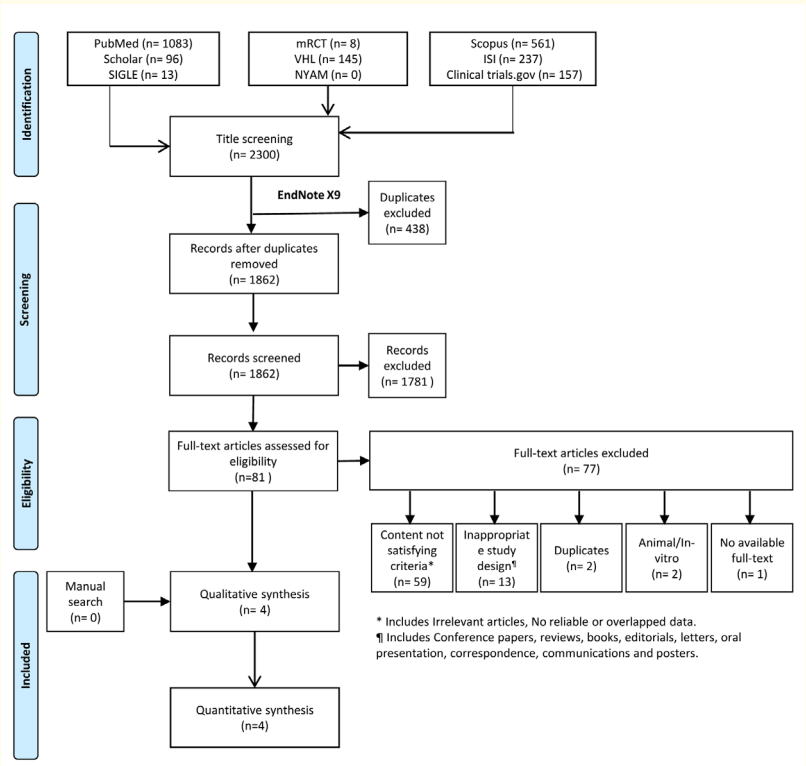

Figure 1: *PRISMA flowchart summarizing the search process in this study.*

Reference ID	Study design	Treatment arm	Sample size	Male (event)	Age (Mean (SD))	Follow up
Chan/2019/UK	RCT	Omalizumab	30	13	10.2 (0.1)	48 weeks
		Placebo	32	19	10.4 (4.3)	
Iyengar/2013/USA	RCT	Omalizumab	4	NR	7.4	24 weeks
		Placebo	4	NR	15.8	
Barrios/2013/ Canada	Case series	Omalizumab	7	4	10.6 (5.1)	29 months#
Lane/2006/USA	Case series	Omalizumab	3	2	11 (1)	24 weeks

Table 1: *Characteristics of the included studies.*

RCT: Randomized Controlled Trial; NR: Not Reported; #: Mean Follow Up Duration.

There were two RCTs and two case series studies. The total sample size was 80 patients. The mean age ranges from 10.2 to 15.8 years. Two studies reported 24 weeks as a follow-up period, one reported 48 weeks and the last one reported 29 months as a mean follow up period for all patients. In the two RCTs, the comparison group was the placebo group. One RCT was graded as low risk of bias, the other one graded as high risk of bias while the two case series studies were of good quality (Table 2 and 3).

Reference ID	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Overall quality
Chan/2019/UK	1	1	1	1	1	1	0	0	1	1	1	1	1	1	Low risk
Iyengar/2013/USA	1	0	0	1	1	1	0	0	0	0	1	0	0	1	High risk
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?															
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?															
3. Was the treatment allocation concealed (so that assignments could not be predicted)?															
4. Were study participants and providers blinded to treatment group assignment?															
5. Were the people assessing the outcomes blinded to the participants' group assignments?															
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?															
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?															
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?															
9. Was there high adherence to the intervention protocols for each treatment group?															
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?															
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?															
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?															
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?															
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?															

Table 2: *Quality rating of the controlled intervention studies.*

Reference ID	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Overall quality
Barrios/2013/Canada	1	1	1	1	1	1	1	0	1	Good
Lane/2006/USA	1	1	1	1	1	1	1	0	1	Good
1. Was the study question or objective clearly stated?										
2. Was the study population clearly and fully described, including a case definition?										
3. Were the cases consecutive?										
4. Were the subjects comparable?										
5. Was the intervention clearly described?										
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?										
7. Was the length of follow-up adequate?										
8. Were the statistical methods well-described?										
9. Were the results well-described?										

Table 3: *Quality rating of the case series study.*

IgE level

The four studies reported the IgE level (Table 4). One reported total IgE [18], one reported free IgE level [17] and two reported serum IgE levels [19,20]. All studies reported baseline IgE levels while only two studies report the post-intervention IgE level. Iyengar., *et al*. indicated that free IgE dropped from 963 IU/ml to 923 IU/ml in the placebo group while it dropped dramatically from 847 to 9.8 in the Omalizumab group [17]. Moreover, Omalizumab decreased serum IgE levels from 16007 IU/ml to 6641 IU/ml, Barrios., *et al* [20].

Reference ID	Treatment arm	IgE level [IU/ml] (mean (SD))	
		Pre	post
Chan/2019/UK*	Omalizumab	8110.5 (4556.0-22 122.0)#	NR
	Placebo	8810.5 (4623.0-15 809.5)#	NR
Iyengar/2013/USA**	Omalizumab	847.5 (742.8)	9.8 (1.7)
	Placebo	963 (897.7)	923 (822.3)
Barrios/2013/Canada***	Omalizumab	16007 (10592)	6641.4 (7841.5)
Lane/2006/USA***	Omalizumab	3666 (6120)	NR

Table 4: *IgE level in the included studies.*

*NR: Not Reported; *: Total IgE; **: Free IgE; ***: Serum IgE; #: Median (IQR).*

SCORAD index

Three studies reported the change in the SCORAD index after the administration of Omalizumab or placebo (Table 5). A significant decrease in the SCORAD index was observed from the two included RCTs ($p < 0.05$), after the administration of Omalizumab compared to the placebo group [17,18]. Moreover, a sharp decrease was indicated in the case series study of Barrios and colleagues from 71.5 to 30 [20].

Reference ID	Treatment arm	SCORAD index (mean (SD))		P value
		Pre	Post	
Chan/2019/UK	Omalizumab	69.5 (10.7)	53.1 (15.4)	< 0.05
	Placebo	69.1 (9.2)	60.9 (13.5)	
Iyengar/2013/USA	Omalizumab	81 (29.2)	23 (22.5)	< 0.05
	Placebo	73.5 (22.5)	54.7 (22.3)	
Barrios/2013/Canada	Omalizumab	71.5 (9.7)	30.1 (9.8)	NR
Lane/2006/USA	NR			

Table 5: *SCORAD index for the included studies.*

NR = Not Reported.

Side effects

Two studies did not report Omalizumab adverse events [19,20] and one reported no serious adverse events [17]. While the RCT of Chan and colleagues [18] reported no significant difference in serious adverse events between Omalizumab or placebo group ($p > 0.05$) and it occurred in 20% and 19%, respectively. Moreover, the placebo group had higher rates of dermatological and respiratory side effects compared to the Omalizumab group 97% compared to 77% and 78% compared to 50%, in order.

Discussion

AD which affects children at an early age comprises a major challenge not only for children but for the community as well in the form of frequent hospital admission and the need for long term management [21]. In addition, the affected children are more prone to several forms of physical, emotional, and social disabilities due to the chronic nature of the disease. Moreover, their families suffer as well, such as worrying about the child's development compared to his peers, the child's health due to a long course of treatment, and their capacity to work derived from the continuous care of the deceased child [22].

AD is considered an allergic disease with frequent exacerbations and remissions with treatment. The treatment agents vary according to the degree of AD as the topical therapy is appropriate for mild and moderate cases while systemic therapy is recommended in severe cases of the disease [23]. Though choosing treatment agents should be wiseful as it may alter the child's development such as corticosteroids [24].

The activation of mast cells eosinophils with the liberation of inflammatory cytokines is the hallmark of AD pathophysiology [23]. Omalizumab is a recent IgE blocker that has been used to treat many allergic conditions such as asthma and chronic urticarial [25,26]. The drug acts mainly by blocking the binding of IgE to the surface of mast cells and eosinophils thus inhibit the vigorous immune activity of the liberated cytokines [27]. A meta-analysis conducted by Wang and colleagues suggested a potential benefit of AD patients when receiving Omalizumab; however, the meta-analysis combined the outcomes of adults and children [28].

The randomized controlled trial of Chan., *et al*. conducted on children aged 4 to 19 years, indicated a significant improvement of AD patients allocated to the Omalizumab group rather than the placebo group in the form of decreasing SCORAD index score which is a widely used score to assess the eczema severity [18]. Additionally, the Omalizumab group achieved a significant increase in the childhood dermatology life quality index questionnaire (CDLQI) [18]. In the same context, the trial of Iyengar., *et al*. demonstrated a significant decrease in the SCORAD index score in the patients randomized to the Omalizumab group compared to their peers of the placebo group [17]. Moreover, patients in the Omalizumab achieved a dramatic reduction in their free levels of IgE that dropped from 847.5 IU/ml as the mean levels of all participants to 9.8 IU/ml [17]. The same astonishing effect was observed in the case series of Barrios., *et al*. where serum IgE levels dropped form 16007 IU/ml as the mean serum IgE levels for all patients to only 6641 IU/ml [20]. The same effect was reported for the SCORAD index that decreased from 71.5 (mean) to 30.1 (mean) in all patients.

Despite showing varying degrees of efficacy in many outcomes, the side effects of Omalizumab was neglected in some studies [19,20]. On the contrary, the trial of Chan and colleagues indicated that several forms of adverse events can affect patients receiving the Omalizumab group where 20% of patients developed serious adverse events. However, the treatment was beneficial in regard to dermatologic and respiratory side effects [18].

Our study had several limitations. Firstly, the RCT of Iyengar., *et al*. recruited patients with range 4 - 22 years, though the exclusion of adult individuals in our study was not applicable as the individual data for each patient was not reached. Secondly, significant heterogeneity in the assessment of our outcomes was observed such as IgE levels. Thirdly, two studies did not report Omalizumab's side effects thus more care should be devoted regarding it is safety as well as efficacy.

Conclusion

In conclusion, our study highlights the possible benefit of children with AD when receiving Omalizumab. However, further studies with a long duration of follow up are needed to highlight the safety of Omalizumab in the long course of the management process.

Conflict of Interest

None.

Funding

None.

Bibliography

1. Kowalska-Olędzka E., *et al.* "Epidemiology of AD in Europe". *Journal of Drug Assessment* 8.1 (2019): 126-128.
2. Ricci G., *et al.* "AD in adolescence". *Dermatology Reports* 4.1 (2011): e1.
3. Abuabara K., *et al.* "The Long-Term Course of AD". *Clinics in Dermatology* 35.3 (2017): 291-297.
4. Xie Q-W., *et al.* "Risk of Mental Disorders in Children and Adolescents With AD. "A Systematic Review and Meta-Analysis". *Frontiers in Psychology* 10.1773 (2019).
5. Lifschitz C. "The Impact of AD on Quality of Life". *Annals of Nutrition and Metabolism* 66.1 (2015): 34-40.
6. Brown SJ. "Atopic eczema". *Clinical Medicine* 16.1 (2016): 66-69.
7. Siegfried EC and Hebert AA. "Diagnosis of AD: Mimics, Overlaps, and Complications". *Journal of Clinical Medicine* 4.5 (2015): 884-917.
8. Silverberg JI. "Associations between AD and other disorders". *F1000 Research* 7 (2018): 303.
9. McPherson T. "Current Understanding in Pathogenesis of AD". *Indian Journal of Dermatology* 61.6 (2016): 649-655.
10. Tanei R., *et al.* "Abundant immunoglobulin E-positive cells in skin lesions support an allergic etiology of AD in the elderly". *Journal of the European Academy of Dermatology and Venereology* 27.8 (2013): 952-960.
11. Rinaldi G. "The Itch-Scratch Cycle: A Review of the Mechanisms". *Dermatology Practical and Conceptual* 9.2 (2019): 90-97.
12. Hu J., *et al.* "Anti-IgE therapy for IgE-mediated allergic diseases: from neutralizing IgE antibodies to eliminating IgE(+) B cells". *Clinical and Translational Allergy* 8 (2018): 27.
13. Liberati A., *et al.* "The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration". *PLoS Medicine* 6.7 (2009): e1000100.
14. Vassar M., *et al.* "Manual search approaches used by systematic reviewers in dermatology". *Journal of the Medical Library Association: JMLA* 104.4 (2016): 302.
15. Health NIo. "Quality assessment tool for observational cohort and cross-sectional studies". *National Heart, Lung, and Blood Institute* (2014).
16. El-Qushayri AE., *et al.* "Fourniers gangrene mortality: A 17-year systematic review and meta-analysis". *International Journal of Infectious Diseases* 92 (2020): 218-225.
17. Iyengar SR., *et al.* "Immunologic effects of Omalizumab in children with severe refractory AD: a randomized, placebo-controlled clinical trial". *International Archives of Allergy and Immunology* 162.1 (2013): 89-93.
18. Chan S., *et al.* "Treatment effect of Omalizumab on severe pediatric AD: the ADAPT randomized clinical trial". *JAMA Pediatrics* 174.1 (2020): 29-37.
19. Lane JE., *et al.* "Treatment of recalcitrant AD with Omalizumab". *Journal of the American Academy of Dermatology* 54.1 (2006): 68-72.

20. Barrios JL., *et al.* "Anti-IgE therapy and severe AD: a pediatric perspective". *Journal of the American Academy of Dermatology* 69.5 (2013): 832-834.

21. Kemp AS. "Cost of illness of AD in children : a societal perspective". *Pharmacoeconomics* 21.2 (2003):105-113.

22. Chamlin SL., *et al.* "Effects of AD on young American children and their families". *Pediatrics* 114.3 (2004): 607-611.

23. Akdis CA., *et al.* "Diagnosis and treatment of AD in children and adults: European Academy of Allergology and Clinical Immunology/ American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report". *Journal of Allergy and Clinical Immunology* 118.1 (2006): 152-169.

24. Drucker A., *et al.* "Use of systemic corticosteroids for AD: International Eczema Council consensus statement". *British Journal of Dermatology* 178.3 (2018): 768-775.

25. Maurer M., *et al.* "Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria". *New England Journal of Medicine* 368.10 (2013): 924-935.

26. Normansell R., *et al.* "Omalizumab for asthma in adults and children". *Cochrane Database of Systematic Reviews* 1 (2014): CD003559.

27. Prussin C., *et al.* "Omalizumab treatment downregulates dendritic cell FcεRI expression". *Journal of Allergy and Clinical Immunology* 112.6 (2003): 1147-1154.

28. Wang H-H., *et al.* "Efficacy of Omalizumab in patients with AD: a systematic review and meta-analysis". *Journal of Allergy and Clinical Immunology* 138.6 (2016): 1719.

Volume 16 Issue 11 November 2020
©All rights reserved by Mostafa Abdelmordy Ibrahim., *et al.*