The evaluation of therapeutic outcomes of biologics in allergic fungal rhinosinusitis: a systematic review and meta-analysis *

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Dear Editor:

Allergic fungal rhinosinusitis (AFRS) is a localized inflammatory, hypersensitivity reaction affecting the nasal cavity and its sinuses secondary to fungal colonization. The burden of surgical revisions and recurrence rates in this disease led to a recent hypothesized advancement in the medical management being experimented, which is the use of biologics. Therefore, this systematic review analyzed nine articles to highlight the significance of biologics in the management of AFRS through a comprehensive strategy, as seen in Supplementary Methods Section [1-9].

These nine studies were a result of screening a total of 1105 studies, and they were assessed using the Joanna Briggs Institute critical appraisal tools (Figure 1 and Table S1). Further assessment of the quality of the studies can be found in Table S2. The included articles involved 77 patients who had been diagnosed with AFRS and were evaluated for clinical, laboratory, and radiological features before and after using biologics, as seen in Supplementary Results Section. Of these patients, 67 had received biologics as part of their management which were detailed in Table S3. Additionally, Table S4 briefly summarizes the post-treatment outcomes of the included patients after the use of biologics. Moreover, six studies have been included in the meta-analysis which comprised a total of 64 patients. Among the six included studies, three reported the use of Dupilumab, two reported the use of Omalizumab, and one reported the use of Mepolizumab.

One of the major methods to assess the clinical outcomes was by using SNOT-22, in which the overall mean score between all studies before administration of biologics was 66.1. Meanwhile, the total mean SNOT-22 score of all studies after biologics was 22.65. This makes the total mean percent improvement as 63%. Also, it was found that Dupilumab had the highest improvement rate among the different biological agents with a mean improvement of 77.5%. When analyzing the five studies that measured SNOT-22, it was found that biologics had significantly decrease SNOT-22 scores in patients with AFRS (2.39, 95% CI: 0.75–4.03; $p<0.004$; Figure 2A). However, there was a significant heterogeneity between these studies ($I^2 = 86\%$).

Regarding the laboratory findings, it was found that the serum eosinophil count and total IgE levels have dropped after using

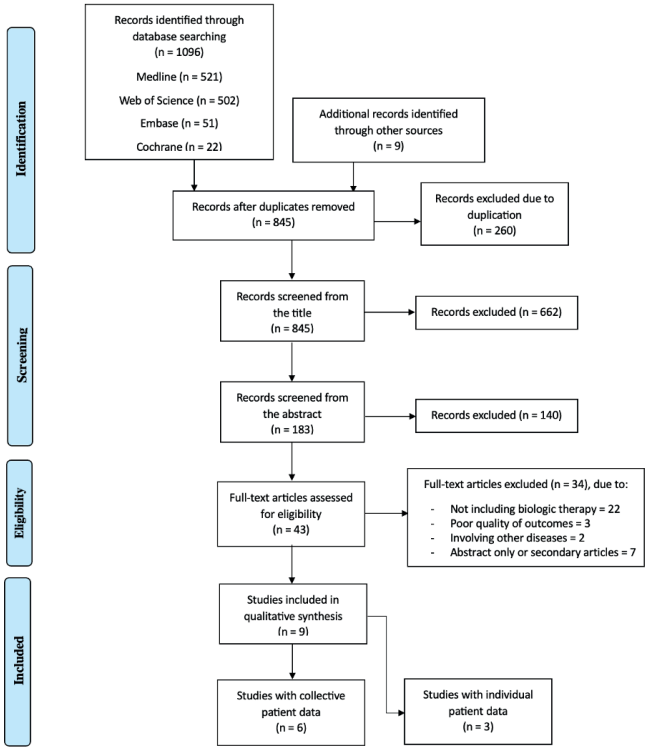

Figure 1. PRISMA flow-diagram of the search process.

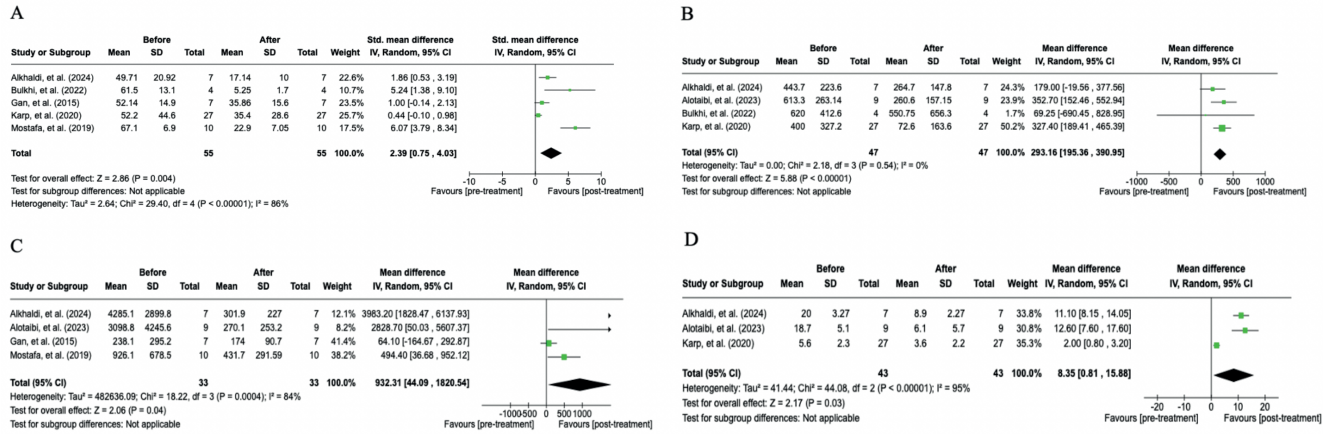

Figure 2. Forest plot of the change in (A) SNOT-22 score, (B) Lund -Mackay score, (C) serum eosinophil count, and (D) total IgE level after biologics.

biologics in four studies. Overall, the mean eosinophil count was 495.4, which fell to 261.7 after biologics. In the pooled analysis, it was found that serum eosinophil count had a significant reduction after the initiation of biologics (293.16, 95% CI: 195.36–390.95; p<0.00001; Figure 2B) with no significant heterogenicity (I^2 = 0%). Furthermore, the total mean IgE level has dropped from 4494.9 to 492.6 after the use of biologics. Similarly, biologics had significantly decrease total IgE level in the pooled analysis (932.31, 95% CI: 44.09–1820.54; p=0.03; Figure 2C), although there was a significant heterogeneity between these studies (I^2 = 84%). Regarding the radiological findings which was assessed by three studies using the Lund-Mackay score, it was found that the mean score before biologics was 14.8, and 6.2 after treatment with a significant diminution in the pooled analysis (8.35, 95% CI: 0.81–15.88; p<0.00001; Figure 2D), although there was a significant heterogeneity between these studies (I^2 = 95%).

In conclusion, this systematic review explored the literature extensively for the therapeutic outcomes of biologics in the management of AFRS. This study recognized several findings that may help in the setting of AFRS management. The initiation of treatment with biologics in patients who are deemed candidates, showed marked improvement in the clinical, laboratory, and radiological findings. We recommend further studies to be conducted in a reliable methodology design, long term, and large-scale clinical trials.

Abbreviations

AFRS: allergic fungal rhinosinusitis.

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Authorship contribution

MSA, TMM, AAM and MB conceptualized the review and wrote the final draft. HJJ performed the statistical analysis and edited the final draft. HJJ, RMA, OAB and AAF screened abstracts, extracted data and edited the final draft. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest

None.

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SUPPLEMENTARY MATERIAL

Methods

Protocol and registration

The study was formulated under the Cochrane Review methods and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered on Prospero (CRD42024518862)[1].

Information sources

A comprehensive exploration of the literature was done using Web of Science (Clarivate), Cochrane Central Register of Controlled Trials (OvidSP), MEDLINE (ProQuest, Ann Arbor, MI, USA), and Embase (OvidSP) databases. The databases were searched from inception until February 2024, with no linguistic preference or limitations. In addition, the references and cited papers were analyzed for possible inclusion. Moreover, we examined the references of all eligible articles and conducted a search on Google Scholar to locate any further suitable studies.

Search strategy

There were 2 sets of relevant keywords used to guarantee that all applicable inclusion criteria items were identified. The first group of keywords was associated with AFRS, while the other group was related to biological therapy.

Eligibility criteria

This review included studies based on a specific criterion. This criterion included patients who were diagnosed with AFRS, experiencing ongoing symptoms despite receiving standard treatments of any age, gender, race, or nationality. In addition, these studies' methodologies should be valid, conducted on human subjects with any type of biological therapy, and published in any language. On the other hand, studies that investigated non-biological interventions (medical or surgical), had poor quality methodology (unclear criteria or inappropriate measures), included patients with confounding comorbidities (e.g., active upper or lower respiratory tract infections, nasal cavity tumors, ciliary dyskinesia, or cystic fibrosis) were excluded. Furthermore, secondary studies, studies conducted on animals or in vitro experiments, or studies with duplicate data published elsewhere, were also excluded.

Selection process

Then two reviewers (HJJ and RMA), independently, examined the studies following a three steps process (titles, abstracts, and full-text screening) of all potentially relevant studies. In case any variances between the two reviewers occurred, a discussion regarding whether to include or to exclude was done and the conflicts were resolved after consulting a third reviewer (OAB or AAF) for a final decision.

Data collection process

The authors had an agreement on several variables that were extracted from the included studies, such as the studies' population and setting, and the patient's clinical, endoscopic and radiological features pre-/post-biologics were involved in the data extraction. These features include SNOT-22 (a validated patient-reported questionnaire used to assess the impact of rhinosinusitis on quality of life), Lund-MacKay score (a radiological grading system used to assess the severity of sinus disease on CT scans, based on the degree of opacification in the paranasal sinuses and the osteomeatal complex), Serum eosinophil count, and total IgE level.

Study quality assessment

The Joanna Briggs Institute (JBI) critical appraisal tools for each study type (i.e., randomized single-blind clinical trial, retrospective cohort, case series, and case reports) were used by two independent authors (OAB and AAF) to assess the quality of included studies and assess the studies' design and statistical analysis. Each JBI appraisal tool contained questions with four possible answers: yes, no, unclear, or not applicable [2,3]. The questions' objective is to evaluate the bias category (e.g., information bias, selection bias or confounders) and classify each study as either low, intermediate, or high risk of bias.

Statistical analysis

RevMan (version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for all statistical analyses. Forest plots were generated and pooled using a random effects model. Higgins I^2 statistics was used to evaluate heterogeneity across included studies, with $I^2 > 50\%$ being considered significant. Inclusion of fewer than 10 studies eliminated the need for evaluation of publication bias. A p-value < 0.05 was considered significant in all cases.

Results

Study selection

A total of 1105 studies were involved at the beginning of our systematic review, which was reduced to 845 unique articles after removing duplications. The subsequent title and abstract screening further minimized the included studies to 183 studies by excluding 662 articles. The reason for exclusion was mainly due to their irrelevance to the use of biological therapy in AFRS. Out of these 183 studies, only nine articles were ultimately considered appropriate to be included in the systematic review after full-text screening, while the remaining were excluded for the reasons specified in Figure 1. This three-step screening process ensured that our systematic review included the most relevant studies related to the use of biologics in AFRS.

Studies and population characteristics

The publication year of the included studies was found to be between 2014 and 2024, with the majority of them being published from 2019 onward (n = 7). Furthermore, these studies were conducted in different countries across the world, including Saudi Arabia, Canada, Egypt, and the United States. Moreover, the most common study design involved was case series and case reports, followed by two retrospective cohort studies, and one randomized clinical trial. Regarding the demographic characteristics of the participants, the mean age of patients treated with biological therapy was 37.7 years, while in one of the studies that involved a control group, the mean age of this group was 24.3 years. Additionally, the average female and male percentages were 55% and 45%, respectively. Nevertheless, one of the articles did not specify the gender distribution.

Clinical features before and after biologics

This section provides details of the SNOT-22 before and after administration of biological therapy. In Mostafa et al.'s study, which used Omalizumab, the mean SNOT-20 score of the biologics group before therapy was 67.1 and after therapy was 22.9, showing an improvement of 66%. Karp et al. saw their patients' SNOT-22 improve by 32% with the use of Mepolizumab; from a mean of 52.2 to 35.4, before and after therapy respectively. Gan et al. found an improvement of 31% in the SNOT-22 scores with the use of Omalizumab; from a mean score of 52.14 before therapy to 35.86 after therapy. Also, Alkhaldi et al. saw an improvement of 66% in the SNOT-22 scores with the use of Dupilumab; from a mean score of 49.71 before therapy to 17.14 after therapy. Bulkhi et al. reported the mean SNOT-22 scores before and after the use of Dupilumab as 61.5 and 5.25, respectively, with an improvement of 91%. In Mujahed et al.'s study, the SNOT-22 score went from 93 to 21, showing a 77% improvement after the use of Dupilumab. Alotaibi et al.'s 2021 study showed an improvement of 76%, from 87 to 21 after the use of Dupilumab. All studies have used SNOT-22 and scored it out of 110, except for one study which used the SNOT-20 version. However, one of the studies reported the SNOT-22 findings in terms of severity. Before starting Dupilumab, four patients were classed as severe, two as moderate, and one as mild. After therapy, this changed to only two patients classed as moderate, and five as mild. Also, one study did not report the SNOT-22 results.

Comparison of different biological agents in terms of clinical features

In terms of biological agents, Dupilumab was the most used biological agent across the included studies. Among these studies, the total mean SNOT-22 score was 72.8 before therapy, while the post-treatment value was 16.1. On the other hand, two studies have measured the SNOT-22 before and after the use of Omalizumab. The total mean score before and after therapy of these two studies was 59.62 and 29.38, respectively. Lastly, only one study has used Mepolizumab as a biological agent, which resulted in a total mean SNOT-22 score of 52.2 before therapy and 35.4 after therapy.

Laboratory and radiological features before and after biologics

Five studies measured the serum eosinophil count before and after biologic therapy. The overall pattern was a fall in eosinophil count after administering biologics. The eosinophil count dropped from 400 before therapy to 72.6 after therapy In Karp et al.'s study, from 443.7 to 264.7 in Alkhaldi et al. study, from 613 to 250.6 in Alotaibi et al.'s 2023 study, from 620 to 550.75 in Bulkhi et al.'s study, and from 400 to 160 in Alotabi et al.'s 2021 study. Additionally, six studies have measured the total IgE count, resulting in a range of 238.1 to 13,360 before treatment, and 174 to 1473 after treatment. Mostafa et al. measured a change in total IgE count from 926.1 to 431.7, before and after biologics therapy, respectively. Gan et al.'s patients saw a minor decrease in mean total IgE; from 238.1 to 174. Meanwhile, Alkhaldi et al. reported a huge drop in mean total IgE; from 4285.1 to 301.9. In Alotabi et al.'s 2023 patients a drop in mean total IgE count was detected, from 3098.8 to 270.1. A marked decrease was seen in Alotaibi et al.'s 2021 study; from 13,360 to 305. Lastly, Evans et al. found the mean total IgE to go from 5061 to 1473.

Regarding the radiological evaluation, three studies have used the Lund-Mackay score to assess the patient's radiological findings before and after the use of biological therapy. In the first study, the pre-treatment and post-treatment scores exhibited a noteworthy reduction, decreasing from 5.6 to 3.6. Similarly, the second study demonstrated a substantial decrease in Lund-Mackay scores, shifting from 20 before treatment to 8.9 post-treatment. The last study showed a reduction in Lund-Mackay scores from 18.7 before treatment to 6.1 post-treatment.

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Table S1. Joanna Briggs Institute (JBI) critical appraisal checklists which were used to assess the risk of bias among the included articles.

RCT	Question	Low risk of bias	Intermediate risk of bias	High risk of bias
Information bias	4,5,6,10,11	Answer Yes 4/5 times	Answer Yes 3 times	Answer Yes 0/1/2 times
Selection bias	1,2,3,7,8,9	Answer Yes 5/6 times	Answer Yes 3/4 times	Answer Yes 0/1/2 times
Confounding	-	-	-	-
Statistical quality	12,13	Answer Yes 2 times	Answer Yes 1 times	Answer Yes 0 times
Cohort	**Question**	**Low risk of bias**	**Intermediate risk of bias**	**High risk of bias**
Information bias	2,3,7,8,9,10	Answer Yes 5/6 times	Answer Yes 3/4 times	Answer Yes 0/1/2 times
Selection bias	1,6	Answer Yes 2 times	Answer Yes 1 times	Answer Yes 0 times
Confounding	4,5	Answer Yes 2 times	Answer Yes 1 times	Answer Yes 0 times
Statistical quality	11	Answer Yes 1 times		Answer Yes 0 times

Table S2. The results of the different JBI questionnaires (questionnaire for randomized controlled trial, cohort studies, case series and case reports). Available on: https://jbi.global/critical-appraisal-tools

RCT	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13
Mostafa, et al. (2019)	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cohort	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**		
Karp, et al. (2020)	NA	NA	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes		
Gan, et al. (2015)	NA	NA	Yes	Yes	No	Yes	Yes	Yes	NA	NA	Yes		
Case Series	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**			
Bulkhi, et al. (2022)	No	Yes	Yes	No	No	Yes	Yes	Yes	No	NA			
Alotaibi, et al. (2023)	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	NA			
Alkhaldi, et al. (2024)	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	NA			
Case Report	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**					
Mujahed, et al. (2022)	No	UC	Yes	Yes	Yes	No	No	Yes					
Alotaibi, et al. (2021)	No	No	Yes	Yes	Yes	Yes	No	Yes					
Evans et al. (2014)	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes					

Abbreviations: NA=not applicable, Q=question, RCT=randomized controlled trial, UC=unclear

Table S3. Baseline characteristics of included articles.

Author	Country	Sample size (total; biologic group)	Mean age	Female %	Number of previous FESS	Last FESS prior to biologic	Number of patients with systemic corticosteroid used within 1 year
Randomized, single blind clinical trial							
Mostafa, et al. (2019)	Egypt	20; 10	Case: 24.6 ± 8.57 Control: 24.3 ± 7.24	Case: 60 Control: 50	1 surgery (15 patients), 2 or more surgeries (15 patients)	NR	NR
Retrospective cohort study							
Karp, et al. (2020)	Canada	27; 27	57 ± 11	NR	1 surgery (19 patients), 2 or more surgeries (8 patients)	Within 1 year (6 patients), more than 1 year (21 patients)	6 (22.2%)
Gan, et al. (2015)	Canada	7; 7	48.1 ± 11.8	57	2	NR	3 (42.8%)
Case series							
Alkhaldi, et al. (2024)	Saudi Arabia	7; 7	30.4 ± 9.3	42.9	2.7	NR	NR
Alotaibi, et al. (2023)	Saudi Arabia	9; 9	34.1 ± 11	33.3	3.1	NR	NR
Bulkhi, et al. (2022)	Saudi Arabia	4; 4	31 ± 1.6	50	5.25	NR	1 (25%)
Case report							
Mujahed, et al. (2022)	Saudi Arabia	1; 1	33	100	16	2 years	NR
Alotaibi, et al. (2021)	Saudi Arabia	1; 1	40	100	4	1 year	NR
Evans et al. (2014)	USA	1; 1	41	0	7	NR	NR

NR: not reported; USA: The United States of America.

Table S4. Post-treatment surveillance and key findings of included studies.

Author	Intervention					Key findings
	Biologic agent	Dose	Route	Regimen	Follow-up	
Randomized, single blind clinical trial						
Mostafa, et al. (2019)	Omalizumab	150 mg	Subcutaneous	once monthly	6 months	• 66% improvement in SNOT-22 • 63% improvement in total nasal symptoms score • 70% improvement in Philpott-Javer staging score • 53% reduction in total IgE level
Retrospective cohort study						
Karp, et al. (2020)	Mepolizumab	100 mg	Subcutaneous	once monthly	224 days	• 32% improvement in SNOT-22 • 36% improvement in Lund-MacKay score • 82% reduction in serum eosinophil count
Gan, et al. (2015)	Omalizumab	285.7 ± 57.5 mg (200–375 mg)	Subcutaneous	once or twice monthly	9.7 months	• 31% improvement in SNOT-22 • 61% improvement in Philpott-Javer staging score • 27% reduction in total IgE level • 9.4% improvement in FEV1
Case series						
Alkhaldi, et al. (2024)	Dupilumab	600 initially then 300 mg	Subcutaneous	Biweekly	6 months	• 66% improvement in SNOT-22 • 56% improvement in Lund-MacKay score • 40% reduction in serum eosinophil count • 93% reduction in total IgE level
Alotaibi, et al. (2023)	Dupilumab	601 initially then 300 mg	Subcutaneous	Biweekly	3 months	• 80% improvement in nasal polyp score • 67% improvement in Lund-MacKay score • 58% reduction in serum eosinophil count • 91% reduction in total IgE level
Bulkhi, et al. (2022)	Dupilumab	600 initially then 300 mg	Subcutaneous	Biweekly	5.25 months	• 91% improvement in SNOT-22 • 11% reduction in serum eosinophil count • 10% improvement in FEV1 • 8% improvement in FEV1/FVC • 25% improvement in asthma control test
Case report						
Mujahed, et al. (2022)	Dupilumab	600 initially then 300 mg	Subcutaneous	Biweekly	6 months	• 77% improvement in SNOT-22
Alotaibi, et al. (2021)	Dupilumab	NR	NR	NR	NR	• 76% improvement in SNOT-22 • 100% improvement in nasal polyp score • 43% improvement in smell diskettes test score • 60% reduction in serum eosinophil count • 98% reduction in total IgE level
Evans et al. (2014)	Omalizumab	375 mg	Subcutaneous	biweekly	20 months	• 71% reduction in total IgE level • 51% improvement in FEV1

NR: not reported.