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Dupilumab as an emerging treatment for refractory allergic fungal rhinosinusitis: a case series and literature review*

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Abstract

Background: Allergic Fungal Rhinosinusitis (AFRS) is a chronic, inflammatory, non-invasive fungal disease of the nose, sinuses, and paranasal sinuses. Dupilumab is an emerging biological therapy with promising outcomes in the treatment of patients with refractory AFRS. In this case series, we aimed to assess the effectiveness and safety of dupilumab in the treatment of refractory AFRS.

Case description: Our case series included seven patients, all of whom met the inclusion criteria. Of these, four were male (57.1%) and three were female (42.9%). The ages of the patients ranged from 20 to 44 years, with a mean of 30.4. For post-treatment Sinonasal Outcome Test-22 (SNOT-22) scores, six patients (85.7%) reported improvement by one category (two from severe to moderate and four from moderate to mild). Only one patient (14.2%) reported an improvement by two categories (severe to mild). Post-treatment IgE levels ranged from 39 to 590 IU/mL, with a mean of 301.8 IU/mL. There was a significant decrease in the mean IgE level by 93% after dupilumab administration. The average number of surgeries in the included patients ranged from 2 to 4, with a mean of 2.7 surgeries. Post-treatment, none of the patients required revision surgery or steroids after three months of dupilumab therapy.

Conclusions: Dupilumab is an emerging biological therapy with promising benefits in the treatment of refractory AFRS. It can be used if functional endoscopic sinus surgery and steroid treatment do not improve symptoms.

Key words: allergic fungal rhinosinusitis, dupilumab, biologics, hypersensitivity, *Aspergillus flavus*

Introduction

Allergic Fungal Rhinosinusitis (AFRS) is a chronic, inflammatory, non-invasive fungal disease of the nose and sinuses [1–3]. It is a subtype of chronic rhinosinusitis (CRS), which is characterized by the presence of thick fungal mucin that is similar to that found in the lungs of patients with allergic bronchopulmonary asperfillosis [2,4]. AFRS is more common in areas with high humidity, which provides a good environment for mold growth. In addition, it is more common in younger populations aged 30 years or less, with a male predominance [5]. *Aspergillus flavus* is the most common causative agent of AFRS (3). Lower socioeconomic status is associated with advanced manifestations of the disease [5]. Patients with AFRS can present with many symptoms including nasal obstruction, rhinorrhea, loss or decrease in sense of smell, and postnasal drainage, which are the most common symptoms [4]. There are severe symptoms of AFRS that can impact the patient quality of life such proptosis, telecanthus, blindness, and bone erosions [2–4].

The Bent and Kuhn diagnostic criteria are the standard methods for diagnosing AFRS, which rely on the characteristics of several modalities, including histological samples, radiological imaging, and immunological markers [2]. The Bent and Kuhn major criteria include the following: 1) Type I hypersensitivity, 2) presence of nasal polyposis, 3) characteristic computed tomography (CT) findings, 4) eosinophilic mucus, and 5) presence of fungus in the sinuses or positive fungal stain. Additionally, minor criteria include asthma, unilateral disease, bone erosion, fungal cultures, Charcot-Leyden crystals, and serum eosinophilia [2,5]. For the treatment of AFRS, aggressive sinus surgery to remove all fungal contents and eosinophilic mucus is considered the first-line treatment, followed by postoperative topical and systemic steroids to prevent recurrence and maintain patient improvement [1,5].

Table 1. Demographic characteristics of the patients.

Patient	Age (years)	Sex	BMI	Diagnosis	Fungal culture	Comorbidities
1	20	Female	36.39	AFRS	*Aspergillus flavus*	None
2	42	Female	36.31	AFRS	*Aspergillus flavus*	Allergic dermatitis
3	24	Male	28.54	AFRS	*Aspergillus flavus*	Bronchial asthma
4	24	Male	37.24	AFRS	*Aspergillus flavus* + *Bipolaris* species	Bronchial asthma
5	44	Female	34.08	AFRS	*Aspergillus flavus*	None
6	31	Male	24.83	AFRS	*Aspergillus flavus*	Bronchial asthma
7	28	Male	27.49	AFRS	*Aspergillus flavus*	Bronchial asthma

BMI: Body mass index, AFRS: Allergic Fungal Rhinosinusitis.

Evidence regarding the use of antifungal treatment for AFRS is controversial and insufficient to make recommendations for or against it [5]. However, biological therapy has shown significant and promising benefits for patients with CRS and AFRS [5]. Several biological treatments, including omalizumab, dupilumab, and mepolizumab, have been approved for CRS treatment. However, clinical trials that investigated the efficacy and safety of biological treatments only included patients with CRS and did not include patients with AFRS [6]. Dupilumab is an emerging biological therapy with promising outcomes in the treatment of patients with refractory AFRS [7–9]. There is only one ongoing clinical trial assessing dupilumab's efficacy to reduce the need for revision surgery or additional medical treatment (Clinical Trial ID: NCT04684524). A few case reports and case series concluded that dupilumab showed positive outcomes and significant improvement in several parameters for the treatment of refractory AFRS, with minimal to no side effects [7–10]. While there are no current retrospective studies assessing dupilumab effectiveness, one retrospective study that assessed omalizumab, another biological therapy, concluded that it could be used as an adjunct therapy to reduce steroid dependence in patients with AFRS [11]. There are few studies in the literature that have assessed the promising effects of dupilumab on patients with AFRS, and the indications for its use remain unclear.

In this case series, we aimed to assess the effectiveness and safety of dupilumab in the treatment of refractory AFRS after exhausting all surgical and medical treatment options in our tertiary care hospital.

Methods

In this case series, which reviewed patient charts from a tertiary care hospital in Saudi Arabia, we evaluated patients with refractory AFRS. The inclusion criteria were as follows: 1) patients above the age of 16 years diagnosed with AFRS based on the Bent and Kuhn criteria, 2) underwent extensive functional endoscopic sinus surgery and did not improve with maximal medical therapy. We excluded immunocompromised patients and those who did not receive dupilumab for at least three months. All patients received 600 mg of dupilumab as the first dose, followed by 300 mg once every two weeks for a total of three months. We collected data on patient demographics, including age, sex, body mass index (BMI), comorbidities, fungal cultures, and number of previous sinus surgeries. We also collected data on pre- and post-dupilumab treatment parameters, including the Sinonasal Outcome Test-22 (SNOT-22), serum IgE and eosinophil levels, subjective olfactory function, and Lund Mackay Score. We collected SNOT-22 scores before starting dupilumab therapy and three months after and it was considered as the primary outcome measure in this study. We used the SNOT-22 stratification system from a previous study to categorize the severity of patients' symptoms [12]. We categorized the severity of symptoms into mild (score of 8-20), moderate (score of 21-50), and severe (score of 51 or more). These categories were used as outcome measures to evaluate patients' responses to treatment. We also used the SNOT-22 questionnaire as an outcome measure to assess pre- and post-treatment subjective olfactory function. Olfactory function was categorized into anosmia, hyposmia, and normosmia. Due to the descriptive nature of this case series, no statistical analysis was performed. Data were collected from medical records from January 2023 to December 2023. This study did not require institutional review board approval because of the nature of the study design. Consent was obtained from all the included patients.

Results

Our study included seven patients, all of whom met the inclusion criteria. Of these, four were male (57.1%) and three were female (42.9%). The age of the patients ranged from 20 to 44 years, with a mean of 30.4. The BMI of the included patients ranged from 24.83 to 37.24 with a mean of 32.12. Four patients had bronchial asthma, one had allergic dermatitis, and two had no comorbidities. All the patients were diagnosed with AFRS

Table 2. Sinonasal Outcome Test-22 (SNOT-22) scores and olfactory function pre- and post-treatment with dupilumab for three months.

Patient	Pre-Treatment SNOT-22 Category and Score	Post-Treatment SNOT-22 Category and Score	Pre-treatment Subjective Olfactory Function	Post-treatment Subjective Olfactory Function
1	Severe (79)	Moderate (24)	Anosmia	Normosmia
2	Moderate (48)	Mild (8)	Anosmia	Hyposmia
3	Moderate (32)	Mild (11)	Anosmia	Hyposmia
4	Severe (74)	Moderate (36)	Hyposmia	Normosmia
5	Moderate (31)	Mild (9)	Anosmia	Hyposmia
6	Moderate (28)	Mild (14)	Hyposmia	Normosmia
7	Severe (56)	Mild (18)	Hyposmia	Normosmia

Table 3. Immunological markers, imaging scores, pre- and post-treatment with dupilumab for three months, and number of previous surgeries.

Patient	Pre-Treatment IgE Levels	Post-Treatment IgE Levels	Pre-Treatment Eosinophil Levels	Post-Treatment Eosinophil Levels	Pre-Treatment Lund Mackay Score	Post-Treatment Lund Mackay Score	Number of Surgeries
1	8936	432	709	480	24	12	4
2	3269	590	342	113	22	8	2
3	1052	39	207	159	20	8	2
4	6437	553	564	332	22	12	3
5	928	116	151	143	14	8	2
6	5433	96	695	428	20	6	3
7	3941	287	438	198	18	8	3

according to the Bent and Kuhn criteria. All patients had a positive fungal culture of *Aspergillus flavus*, except one that had *Aspergillus flavus* in addition to bipolaris species. Further details of patients' characteristics are shown in Table 1.

Sinonasal Outcome Test-22 (SNOT-22)

Pre-treatment, three patients (42.9%) reported having severe symptoms, four (57.1%) reported having moderate symptoms, and none of the seven patients had mild symptoms before starting dupilumab. For post-treatment SNOT-22 scores, six patients (85.7%) reported improvement by one category (two from severe to moderate, and four from moderate to mild). Only one patient (14.2%) reported an improvement by two categories (severe to mild). All pre-treatment and post-treatment SNOT-22 categories and scores are shown in Table 2 and Figure 1.
For pre-treatment, four patients (57.1%) had anosmia, and three patients (42.9%) had hyposmia. For post-treatment subjective olfactory, six patients (85.7%) reported improvement by one category (Three from anomsia to hyposmia, and three from hyposmia to normosmia). Only one patient (14.2%) reported improvement by two categories (anosmia to normosmia) (Table 2).

Serum IgE levels

We collected the IgE levels of all seven patients in this study before starting dupilumab and three months after treatment. The pre-treatment IgE levels ranged from 928 to 8936 IU/mL, with a mean of 4285.1 IU/mL. The post-treatment IgE levels ranged from 39 to 590 IU/mL, with a mean of 301.8 IU/mL. This shows a significant decrease in mean IgE levels by 93% after dupilumab administration (Table 3 and Figure 2).

Eosinophil serum levels

We collected eosinophil counts of all seven patients in this study before starting dupilumab and three months after treatment. The pre-treatment eosinophil counts ranged from 151 to 709 cells/μL, with a mean of 443.7 cells/μL, while the post-treatment eosinophil counts ranged from 113 to 480 cells/μL, with a mean of 264.7 cells/μL. This shows a decrease in mean eosinophil levels by 40.3% after dupilumab administration (Table 3 and Figure 3).

Lund-Mackay scores

We also collected pre- and post-treatment Lund-Mackay Scores of all patients before starting dupilumab and three months after treatment. The pre-treatment Lund-Mackay Scores ranged from 14 to 24, with a mean of 20, while the post-treatment Lund-Mackay scores ranged from 6 to 12, with a mean of 8.9 (Table 3 and Figure 4).

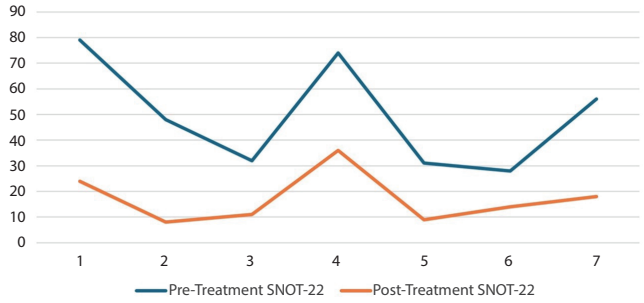

Figure 1. SNOT-22 scores before and after dupiluamb administration at three months follow-up.

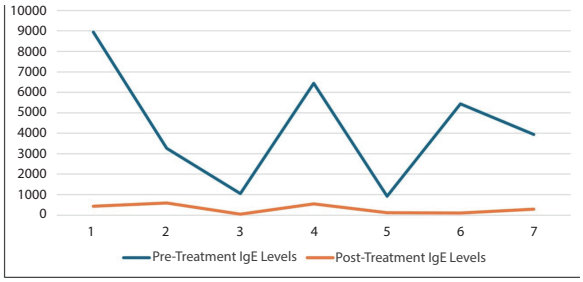

Figure 2. IgE levels before and after dupilumab administration at three months follow-up.

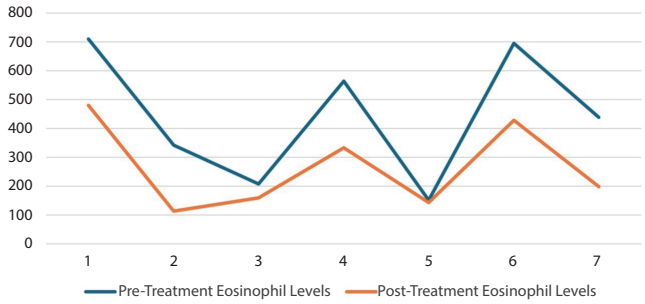

Figure 3. Eosinophil levels before and after dupilumab administration at three months follow-up.

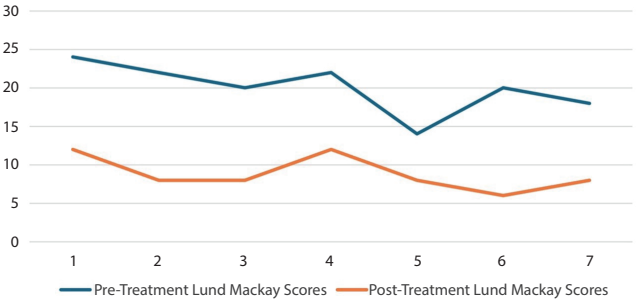

Figure 4. Lund Mackay scores before and after dupilumab administration at three months follow-up.

Number of surgeries

Another parameter used to assess the effectiveness of dupilumab therapy was the number of surgeries prior to dupilumab administration treatment, the average number of surgeries of the included patients ranged from 2 to 4, with a mean of 2.7 surgeries. Post-treatment, none of the patients required revision surgery or steroids during three months of dupilumab therapy (Table 3).

Discussion

In this case series, we aimed to assess the effectiveness and safety of dupilumab for the treatment of refractory AFRS in our tertiary care hospital. None of the patients required revision surgery or systemic steroid therapy during the three months of dupilumab therapy. None of the patients experienced side effects. The change between the pre- and post-treatment SNOT-22 scores are the most important outcomes because they provide an objective and subjective way of assessing patients' responses to treatment. Other outcomes such as serum IgE, eosinophil levels, and Lunk Mackay scores provide laboratory and radiological findings that reflect treatment response.

Only one ongoing clinical trial has assessed the effectiveness and safety of dupilumab for the treatment of refractory AFRS. (Clinical Trial ID: NCT04684524) There are only a few studies in the literature that evaluated the use of dupilumab in patients with AFRS [7–10].

Demographic characteristics

The ages of the patients in this study ranged from 20 to 44 years, with a mean of 30.4. This is similar to the study by Alotaibi et al., which had a mean age of 34.4 and ranged from 16 to 60 years [9]. In contrast, the mean age of patients with AFRS in the study by Bulkhi et al. was 23 years [8]. Alotaibi et al. and Mujahed et al. studies had a mean age of 40 and 33 years, respectively [7,10]. Of the seven patients included in the present study, four were male and three were female. The male predominance is similar to that in a previous study by Alotaibi et al., which included nine patients, six of whom were male and three were female (9). Similar to previous studies, the Bent and Kuhn criteria were used to diagnose AFRS in this study [7–9]. In this study, all patients had a positive fungal culture of *Aspergillus flavus*, except one that had *Aspergillus flavus* in addition to the bipolaris species. In contrast, most previous studies had no positive cultures of *Aspergillus flavus*, except for one case reported by Bulkhi et al. [8].

Comorbidities

In the present study, four patients had bronchial asthma, one had allergic dermatitis, and two had no comorbidities. Similarly, Bulkhi et al. reported two patients with AFRS who had bronchial asthma [8]. The cases reported by Alotaibi et al. and Mujahed et al. also reported co-morbid asthma [7,10]. Two cases reported by Bulkhi had food allergies and atopic dermatitis, while the case reported by Mujahed et al. had a broad history of allergies, inclu-

ding many allergens such as fruits, shrimps, eggs, and painkillers [8,10].

Dupilumab effectiveness and follow-up duration

SNOT-22 scores were the main outcome measures in this case series to assess the effectiveness of dupilumab in patients with refractory AFRS. Pre-treatment, three patients reported having severe symptoms and four reported having moderate symptoms before starting dupilumab. Similarly, Bulkhi et al. reported that of the four patients included in their case series, three reported having severe symptoms and one had moderate symptoms [8]. Furthermore, Alotaibi et al. reported that of the nine patients included in their case series, five reported severe symptoms, three reported moderate symptoms, and only one reported mild symptoms [9].

In the present study, the SNOT-22 questionnaire was administered to patients after three months of dupilumab therapy to assess symptom improvement, five of whom reported having mild symptoms after dupilumab treatment and two reported having moderate symptoms. Similarly, Alotaibi et al. had the same follow-up duration and outcome measures, and of the nine patients included in their study, five reported mild symptoms following dupilumab treatment, two reported moderate symptoms, and two did not repeat the SNOT-22 questionnaire [9]. In contrast, Bulkhi et al. had a follow-up duration of five months after dupilumab therapy, and of the four patients included in their study, all of them reported mild symptoms after dupilumab administration [8]. Mujahed et al had a follow-up of six months after dupilumab administration and SNOT-22 score declined from 93 (severe symptoms) to 21 (moderate symptoms) [10]. Alotaibi et al did not report the follow-up duration of their patient but their SNOT-22 score declined from 87 (severe symptoms) to 21 (moderate symptoms) [7].

Subjective olfactory function

In this study, of the seven included patients, four reported having anomsia and three reported having hyposmia before dupilumab administration. This is similar to the Alotaibi study that included nine patients, of which five reported anosmia, two reported hyposmia, and two had normosmia before dupilumab treatment. Post-treatment, the current study included four patients who reported having normosmia, and three patients who reported having hyposmia. The study by Alotaibi et al. included six patients who reported having normosmia, one patient who reported having hyposmia, and two patients who did not repeat the SNOT-22 questionnaire after dupilumab administration [9].

Immunological markers

In the present study, IgE levels prior to dupilumab therapy ranged from 928 to 8936 IU/mL, with a mean of 4285.1 IU/mL. In the Alotaibi study, IgE levels before dupilumab administration ranged from 346 to 13,360 IU/mL, with a mean of 3098.8 IU/mL. Furthermore, the IgE levels in this study three months after biological therapy ranged from 39 to 590 IU/mL, with a mean of 301.8 IU/mL which is similar to the Alotaibi study, which reported IgE levels that ranged from 12 to 700 IU/mL, with a mean of 270.1 IU/mL. This study and the previous study showed very similar significant decreases in mean IgE levels by 93% and 91.3% respectively after three months of dupilumab therapy [9].

In the present study, the eosinophil counts prior to dupilumab therapy ranged from 151 to 709 cells/μL, with a mean of 443.7 cells/μL, whereas in the Alotaibi study, the eosinophil counts before dupilumab administration ranged from 200 to 900 cells/μL, with a mean of 613.3 cells/μL. Moreover, the eosinophil counts in this study at three months post-treatment ranged from 113 to 480 cells/μL, with a mean of 264.7 cells/μL. Similarly, a study by Alotaibi et al. reported that post-treatment eosinophil counts ranged from 160 to 600 cells/μL, with a mean of 260.6 cells/μL. This study and the previous study showed similar decreases in mean eosinophil counts by 40.3% and 57.5% respectively after three months of dupilumab therapy [9].

Prior surgeries

In this study, the average number of surgeries before dupilumab therapy ranged from 2 to 4, with a mean of 2.7 surgeries. Similarly, the average number of previous surgeries reported by Alotaibi et al. ranged from 1 to 7, with a mean of 3.1 surgeries [9]. One case report described a female patient who underwent four surgeries before dupilumab therapy, and another reported a female patient who underwent 16 functional endoscopic sinus surgeries prior to starting dupilumab treatment [7,10].

AFRS treatment options include allergen avoidance, topical corticosteroids, surgery, oral corticosteroids, and immunotherapy, with surgical removal of mucin as the most effective and feasible treatment option to date [2, 6, 13]. However, recurrence of AFRS is considerably higher in patients treated with surgical therapy alone than in those treated with surgery and other concurrent medications such as oral corticosteroids. Furthermore, even patients treated with combined surgical and medical therapy can develop recurrent and refractory AFRS that is difficult to treat by established effective and safe treatment options; therefore, it is essential to investigate biological treatments that show promising outcomes in similar rhinological diseases such as chronic rhinosinusitis with and without nasal polyposis [14–18].

Our findings demonstrate the efficacy of dupilumab as a novel treatment option for AFRS. Only a few studies with small sample sizes have investigated the efficacy of this biological agent [7–9]. Our results are consistent with those of previous studies regarding the effectiveness of dupilumab, provide to the small literature on this topic, and encourage conducting larger studies on this topic to establish clear evidence regarding its use in clinical settings.

Dupilumab is a human monoclonal antibody that inhibits cytokines such as interleukin 4 alpha, which plays a significant role in inflammation in allergic conditions [19,20]. Chronic rhinosinusitis is a type 2 inflammation with cytokines that are targeted by dupilumab, as well as other inflammatory biomarkers such as total IgE and eosinophils, which are significantly decreased with dupilumab administration [21,22].

The promising outcomes of dupilumab for the treatment of refractory AFRS means that patients who fail standardized and established therapy regimens, such as surgical therapy or combined surgical and medical therapy, may undergo biological therapy to relieve their symptoms and improve their health. This study followed a previously published protocol, and our findings were consistent with the positive outcomes of dupilumab as a biological therapy for patients with AFRS [9].

Limitations

Although this study provides novel insights into the effectiveness of dupilumab in the treatment of patients with AFRS refractory to medical and surgical treatment options, a few limitations of this study need to be addressed. The small sample size, retrospective chart review nature of this study, and short follow up duration limit the comprehensive assessment of dupilumab therapy. Additionally, this study was conducted at one center, which indicates that the results may not be generalizable to other populations. However, this case series investigated a topic that has not been comprehensively covered in the literature and provides results that can lead to future research. Future recommendations include conducting multi-central, randomized, double-blinded, controlled clinical trials with diverse patient populations that objectively and subjectively assess symptom improvement in patients with refractory AFRS with longer follow-up duration lasting one to two years.

Conclusions

Dupilumab is an emerging biological therapy with promising benefits for the treatment of refractory AFRS. Patients with AFRS who were treated with dupilumab showed improvement after three months of treatment in several parameters, including the SNOT-22 questionnaire, IgE serum levels, eosinophil count, Lund Mackay scores, and number of surgeries following dupilumab administration.

List of abbreviations

AFRS: Allergic Fungal Rhinosinusitis, CRS: Chronic Rhinosinusitis, BMI: Body Mass Index. CT: Computed Tomography, SNOT-22: Sinonasal Outcome Test-22.

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Authorship contribution

Conception and design: MA, BA; Administrative support: MA; Provision of study materials or patients: AA, BAR; Collection and assembly of data: AA, BAR; Data analysis and interpretation: AA, BAR; Manuscript writing: AA, BAR, BA; All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that they have no competing interests.

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