Biologic Treatments for Severe Asthma: 4 Years of Experience at a Single Medical Center

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ABSTRACT: **Background:** Severe asthma affects up to 20,000 citizens of Israel. Novel biological therapies, which individually have been proven to reduce asthma morbidity in clinical trials, have become available in recent years. Comparative data among different drugs are scarce.

Objectives: To describe and compare the clinical outcomes of biological therapies in severe asthma patients treated at Shamir Medical Center.

Methods: We conducted a cohort study based on a review of cases treated with monoclonal antibodies for severe asthma at our center. Data were extracted for demographics, eosinophil count, lung function (FEV1), exacerbation rate, and median dose of oral prednisone. Between-drug comparison was conducted by repeated measures ANOVA.

Results: The cohort included 62 patients receiving biological therapy. All biologic drugs were found to reduce exacerbation rate [$F(1, 2) = 40.4$, $P < 0.0001$] and prednisone use [$F(1, 4) = 16$, $P < 0.001$] significantly. ANOVA revealed no difference of efficacy endpoints between the different drugs. Eosinophil count was significantly reduced post-biologic treatment in the anti-interleukin-5 agents ($P < 0.001$) but not under treatment with omalizumab and dupilumab.

Conclusions: All of the biological therapies were effective for improving clinical outcomes. None of the agents was clearly superior to any other. These data emphasize the need for severe asthma patients to be seen by pulmonary medicine specialists and offered, where appropriate, biological therapies.

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KEY WORDS: anti-immunoglobulin E (IgE) monoclonal, anti-interleukin-5 (anti-IL-5) monoclonal, anti-interleukin-4 (anti-IL-4) monoclonal, eosinophilia, severe asthma

Severe asthma is defined as uncontrolled asthma despite adherence to maximal optimized therapy and treatment of contributory factors, or asthma hat worsens when high dose treatment is decreased [1]. It affects 5% of all asthma patients worldwide, with a rough estimate of approximately 20,000 citizens of Israel possibly meeting the criteria for severe asthma. Recent years have brought about a major development in treatment options for severe asthma. If in the past the main treatment for severe asthma was based on systemic glucocorticoids, the treatment now has majorly changed to a phenotypic characterization of the disease with appropriate biologic targeting. Patients are generally grouped into three phenotypic groups: atopic asthma, eosinophilic asthma, and non-eosinophilic non-atopic asthma [2]. The agents available on the market include three drug classes: anti-immunoglobulin E (anti-IgE; omalizumab), anti-interleukin-5 (anti-IL5)/IL5 receptor (mepolizumab, reslizumab, benralizumab), and anti-IL4/IL13 (dupilumab). The anti-IgE monoclonal is indicated primarily for severe atopic asthma in patients with positive skin tests and high levels of IgE in serum. The other agents are indicated for severe eosinophilic asthma. There is no approved biological agent for non-atopic non-eosinophilic asthma.

All five drugs were found to reduce exacerbation rate in severe asthma in phase III trials [3-7]. Some agents were shown to improve forced expiratory volume (FEV1). Further studies showed that all of the available drugs showed reduction of chronic corticosteroid dose required to achieve disease control [8-12]. To date, no direct comparison was conducted, and this kind of a randomized controlled trial is not likely to take place.

Several studies have performed indirect retrospective comparisons between biologic agents, between drug classes [13], or between specific drugs [14-17]. The results, combined, are conflicting and confusing; hence, the results are hard to interpret to make a clear conclusion.

In this study, we summarized and reviewed our experience with prescribing biologic treatment for severe asthma at Shamir Medical Center and performed a retrospective comparison of treatment outcomes between drugs.

PATIENTS AND METHODS

We queried the hospital database for ICD9 code for ambulatory injection or infusion of immunoglobulin (99.14) in the pulmonary institute between 1 January 2017 and 31 July 2020. We performed a complementary search in the pulmonary institute schedules for all patients who received biologic treatment to identify patients that were not properly coded. For all patients,

we extracted demographic data (age, sex, ethnicity), disease duration, blood eosinophils pre- and post-treatment, IgE pre-treatment, type of biologic agent, and clinical parameters concerning treatment efficacy. These parameters included the number of exacerbations pre- and post-treatment, corticosteroid therapy pre- and post-treatment, spirometry FEV1 pre-and post-treatment, major side effects of treatment, treatment duration, and changes to other biologic treatments in cases of treatment failure.

We performed repeated-measures analysis of variance of each dependent variable (FEV1, eosinophil count, exacerbation rate and prednisolone dose) as a function of time (before/after therapy) and either each drug individually or grouped by drug-class. *P*-value of < 0.05 was considered significant.

The study was approved by the hospital's local ethics committee.

RESULTS

We found 62 patients who were treated with any type of biologic treatment for severe asthma. The mean age of the cohort was 54 years; 34% of the cohort were males. Of 62 patients included in the cohort, only one was of Arab origin.

Of 62 patients, 19 patients were on anti-IgE treatment, 40 patients on anti-IL5 treatment, and 3 on anti-IL4/IL13 treatment. Baseline patient characteristics by treatment groups are summarized in Table 1.

TREATMENT OUTCOMES

Exacerbation rate decreased in all treatment groups over time under biologic treatments from 2.9 per year to 0.8 per year ($P < 0.0001$). There was no difference between drugs in the decline of exacerbation rates under treatment [$F(1, 2) = 0.15$, $P = 0.86$] [Table 2]. The results remained similar when ANOVA was performed for drug classes.

Mean prednisone dose was reduced in all treatment groups during biologic treatment from 13.2 mg to 2.9 mg ($P < 0.0001$). The mean reduction was 10 mg. There was no difference between drugs in the dose reduction of prednisone before and after biologic treatment [$F(1, 4) = 0.29$, $P = 0.88$] [Table 2]. The results remained similar when ANOVA was performed for drug classes.

In an additional post-hoc analysis, we evaluated the effect of drug class on the number of patients weaned from oral steroids. For that analysis, baseline prednisone dose was defined as > 0 and final prednisone dose = 0. Of 23 patients on baseline prednisone, 12 (52%) were completely weaned at the end of the study. No effect of different drug class could be determined on the proportion of patients weaned (Fisher's exact test $P = 0.50$).

FEV1 increased in all treatment groups under biologic treatment, an increase of 318 ml (mean). This change, however, was not statistically significant [$F(1, 4) = 1.6$, $P = 0.2$]. There was no difference between drugs in the change of FEV1 under treatment [$F(1, 4) = 0.03$, $P = 0.99$] [Table 2]. The results remained similar when ANOVA was performed for drug classes.

Blood eosinophil count decreased under biologic treatment ($P < 0.0001$). There was a significant between-group difference in the eosinophil reduction [$F(1, 4) = 2.88$, $P = 0.04$] with anti-IL5 drugs mepolizumab, reslizumab, and benralizumab showing greater reductions than omalizumab (anti-IgE) and dupilumab (anti-IL4). There was no significant difference between the individual anti-IL5 medications in change in eosinophil count. When ANOVA was performed for drug classes, the results remained significant [$F(1, 2) = 3.85$, $P = 0.02$] [Table 2].

TREATMENT CHANGES

Seven patients switched to a different biologic agent, one of them switched twice.

Four patients who failed on omalizumab treatment switched to an anti-IL5 agent: three to mepolizumab with good results, and one to reslizumab. The patient who switched to reslizumab continued to exacerbate and switched again to dupilumab.

Two patients on anti-IL5 drugs had adverse events and switched to a different anti-IL5 agent with no further adverse events.

One patient switched from reslizumab to benralizumab due to convenience considerations, with good treatment outcomes for both drugs.

Table 1. Demographic and baseline characteristics of cohort patients

	All (n=62)	Omalizumab (n=19)	Mepolizumab (n=26)	Reslizumab (n=2)	Benralizumab (n=12)	Dupilumab (n=3)
Age, years (mean)	54	51	54	53	58	56
Sex (male %)	34%	21%	46%	50%	33%	0%
Baseline blood eosinophils (mean)	791	502	1094	700	682	666
Baseline IgE (mean)	600	524	647	39	444	1726
Baseline FeNO (mean)	47	37	69	NA	34	20

FeNO = fractional exhaled nitric oxide, IgE = immunoglobulin E

Table 2. Clinical outcomes of biologic agents by drug

	All (n=62)	Omalizumab (n=19)	Mepolizumab (n=26)	Reslizumab (n=2)	Benralizumab (n=12)	Dupilumab (n=3)	*P* value for drug effect
Exacerbations pre-treatment* (mean)	2.88	2.7	2.6	2	3.9	2.3	0.86
Exacerbations post-treatment* (mean)	0.8	0.9	0.9	0.5	0.4	0.3	
Prednisone pre-treatment (mean)	13.2	14.7	13.8	10	9.2	20	0.88
Prednisone post-treatment (mean)	2.9	3.2	3.8	0	1.2	0	
Complete prednisone withdrawal n (%)**	12/23 (52%)	4/6	7/16	1/1	0.50		
FEV1 abs pre-treatment (mean)	1.66	1.63	1.6	2	1.56	2.1	0.99
FEV1 abs post-treatment (mean)	1.9	1.9	1.8	2.3	1.8	2.3	
EOS baseline (mean)	791	502	1094	700	682	666	0.04
EOS post-treatment (mean)	206	393	150	N/A	0	0	

*Events per year
**Data regarding complete steroid withdrawal includes only patients on prednisone dose > 0 pre-biologic treatment; hence, the number of total patients is lower
EOS = eosinophil count, FEV1 = lung function

ADVERSE EVENTS

Few adverse events were reported during follow-up (mean treatment duration 12.5 months). One patient developed angioedema following the first injection of benralizumab. Treatment was stopped and switched to a different agent. Two patients developed herpes zoster infection under dupilumab treatment. The infection developed after 4 and 8 months of treatment. One patient complained of knee arthralgia under omalizumab treatment, without overt arthritis and no need to stop treatment. Another patient reported abdominal pain under benralizumab treatment, with no need to stop treatment.

DISCUSSION

We performed a cohort study of 62 patients receiving biologic therapies for severe asthma at our center. Most patients received either anti-IgE or anti-IL5 medications. Dupilumab (anti-IL4/13) was not included in the Israeli government health basket during the study period; hence, the low rate of its use in this study. Another important factor affecting drug choice is the choice to use omalizumab as first line therapy in patients with combined allergic and eosinophilic phenotype and changing to an anti-IL-5 only in cases of failure. This choice was recently changed. All of the medications studied were equally effective in reducing asthma exacerbations and reducing dependence on oral prednisone. Eosinophil counts were suppressed in all patients receiving anti-IL5 medications. No clear effect was seen on FEV1, although there was a trend for increase/improvement.

These findings are comparable with the outcomes of randomized clinical trials. All of these outcomes are well documented in previous studies, with exacerbation rate reduction of 50%–70% in different studies [3,5,6,7,9], and systemic corticosteroid reduction of up to 50% in steroid dependent patients [8-12]. FEV1 was found to significantly increase in some drug specific phase III trials but was not found to increase significantly in this study, probably due to small numbers and lack of power.

Eosinophil count was decreased over time under treatment, and found to be significantly different among drugs, a finding that is explained by the different pharmacologic mechanism of the drugs. Omalizumab, an anti-IgE agent, is not expected to reduce eosinophils as much as other agents of the anti-IL5 class, and even in this class there may be differences in eosinophil reduction between agents that target either anti-IL5 or anti-IL5 receptor. The clinical significance of the magnitude of eosinophil reduction is not clear.

To the best of our knowledge, no direct head-to-head comparison between biologic drugs exists. There are few retrospective studies comparing pooled data regarding specific drugs. Bateman and colleagues [13] performed an indirect treatment comparison of dupilumab versus the other drugs (anti-IL5 and anti-IgE pooled together). In their meta-analysis, dupilumab was associated with lower severe asthma exacerbation rates and greater improvements in lung function than anti-IL-5s and omalizumab together. Busse et al. [14] compared the three medications of the anti-IL5 class

to each other, with an analysis stratified by baseline blood eosinophil count. The findings suggested that mepolizumab was associated with significantly greater improvements in clinically significant exacerbations and asthma control, compared with reslizumab or benralizumab, in patients with similar blood eosinophil counts. Bourdin and co-authors [15] studied the oral corticosteroid dosage reduction, comparing two anti-IL5 drugs (mepolizumab and benralizumab) and anti-IL4/IL13 (dupilumab), demonstrating comparable effect of all three drugs. Cockle and colleagues [16] performed a meta-analysis comparing treatment efficacy of mepolizumab and omalizumab, with no clear significant advantage of one over the other in terms of exacerbation rates or tolerability. Based on these results, no clear and consistent advantage of one drug or one drug-class over the other can be inferred. All comparisons are retrospective, thus limited, and evidence of single drugs comparisons is still scarce. Our study, even though has small number of patients, adds some more data of drug-to-drug comparisons to the pool of knowledge.

Switching drug treatment from one class to another, or between drugs of the same class, is another field with little evidence. Switching from an anti-IgE to an anti-IL5 is logical for patients who have prominent blood eosinophilia alongside with allergic asthma phenotype. A real-world study of 41 patients demonstrated improved asthma control results in patients failing omalizumab treatment who were switched to mepolizumab [18]. Our experience of three patients switched from omalizumab to mepolizumab is in line with these findings. Another study demonstrated better asthma control when switching patients failing on anti-IL5 (mepolizumab) to an anti-IL-5 receptor (benralizumab) [19]. No clear data exists about the safety of switching from one anti-IL5 drug due to severe adverse event to another drug of the same class. Our patient who developed angioedema to benralizumab had no adverse events to mepolizumab.

PATIENT SAFETY

In general, there were very few adverse effects. Of slight concern were two episodes of herpes virus reactivation seen among our very small (n=3) cohort of patients receiving dupilumab. This adverse effect was not reported at all in the LIBERTY phase 3 asthma clinical trial and was reported only in a single case in another phase 3 clinical trial [20]. Zoster infections were reported in 1% of patients in dupilumab treatment for atopic dermatitis clinical trials, with clinically important herpes viral infections (eczema herpeticum, herpes zoster) less common with dupilumab versus placebo [21]. It cannot be determined from our study whether this is simply a statistical anomaly or a worrying trend for the safety of the drug.

LIMITATIONS

The main limitation in our study was the relatively small cohort size, especially for medications that were either approved/reimbursed relatively recently (dupilumab) or where clinical use by the treating physicians was low (reslizumab was not prescribed often because it is administered intravenously rather than subcutaneously like other anti-IL5). However, based on inspection of the baseline data it does not appear that there was any specific bias of physicians for or against the different agents, except in previous examples. The only clear difference was the high IgE levels in patients allocated to omalizumab. This result can be explained by the guidelines of the Israeli health basket, which mandate that physicians try omalizumab as first-line in a patient who qualifies for either anti-IgE or anti-IL5. The data in this study partially support the medical validity of this approach since as a group, patients receiving omalizumab experienced similar improvements in asthma control as those who received anti-IL5 therapy. However, the specific subset of patients who might have received either was not specifically analyzed, and 4 of 19 patients did switch to anti-IL5 during follow up.

Another interesting limitation was that only one patient in the cohort was of Arab heritage. The exact prevalence of severe asthma in the Arab community is not known. In a national survey of children aged 13–14 years performed in 1997, the asthma prevalence in the Jewish population was significantly higher than in the Arab population (7.8% vs 4.9%, respectively) [22]. Another interesting finding is a significantly higher rate of non-atopic non-eosinophilic severe asthma (related to obesity) in Arab populations in northern Israel, compared with Jewish populations [23]. Both findings explain the low use of biologics for severe asthma in the Arab population. Another possible explanation may be referral bias or even self-referred bias. More research on the topic is required and efforts should be made to reach out to Arab citizens of Israel to ensure that they may benefit from severe asthma therapies.

Conclusions

All the novel biological drugs for asthma that are available in Israel are comparably effective in reducing exacerbations and dependence on oral steroids. These data emphasize the importance of referring all severe asthma patients in Israel and in other nations for expert evaluation by a pulmonologist.

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Capsule

Targeting the host instead of the virus

Despite the efficacy of vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there is a continuing need to develop new therapeutics to treat COVID-19. **Yaron** and colleagues identified multiple phosphorylation sites in a conserved region of the viral nucleocapsid (N) protein, which is critical for viral replication. Biochemical analyses identified the host kinases that sequentially phosphorylated distinct motifs in the N protein. A drug approved by the U.S. Food and Drug Administration, which inhibits the first kinase in the phosphorylation sequence, reduced N protein phosphorylation and blocked viral replication in vitro.

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Eitan Israeli

Capsule

Leukemia treatment risks viral resurgence

Cytomegalovirus (CMV) establishes a persistent, lifelong latent infection. However, various forms of immune dysregulation can result in the reactivation of CMV replication, posing a serious risk of morbidity and mortality. **Wass** et al. found that the CMV protein US28, in coordination with the host Ephrin receptor A2 (EphA2), controls Src-MAPK-c-Fos signaling, which in turn controls CMV latency. The authors showed that an EphA2 inhibitor, dasatinib, results in CMV reactivation. This drug is clinically used to treat leukemia and may inadvertently reactivate CMV. Indeed, clinical data showed that dasatinib treatment is associated with increased CMV-associated disease.

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