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ANALYSIS OF USE OF INTRAVENOUS AND SUBCUTANEOUS MONOCLONAL ANTIBODIES IN THE TREATMENT OF ASTHMA

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Abstract:

Introduction: *Asthma is an inflammatory chronic disease of multifactorial aetiology, including allergic asthma, which is characterized by eosinophilic airway inflammation, often sustained by allergic sensitization. IgE plays a central role in the pathogenesis of allergic diseases. After sensitization, atopic patients respond to allergen exposure through a number of IgE-dependent mechanisms.* ***Objectives of the study:*** *The main objective of the study is to analyze the use of intravenous and subcutaneous monoclonal antibodies in the treatment of asthma.* ***Methodology of the study:*** *This study was conducted in Nishtar hospital Multan during March 2018 to July 2018. Male or female allergic asthmatics aged 12 to 75 years who were symptomatic despite treatment with ICSs were eligible if they met the following criteria: duration of asthma, ≥1 year; positive immediate responses on skin prick testing to at least 1 common allergen.* ***Results:*** *Additionally, health-related quality of life was measured using SGRQ. At Week 24, there was a statistically significant improvement in the mean SGRQ score for mepolizumab compared with placebo: -5.8 (95% CI: -10.6,-1.0; P=0.019).* ***Conclusion:*** *It is concluded that omalizumab is effective and safe in patients with severe allergic asthma who experience poor disease control or exacerbations despite recommended therapy.*

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INTRODUCTION:

IgE plays a central role in the pathogenesis of allergic diseases. After sensitization, atopic patients respond to allergen exposure through a number of IgE-dependent mechanisms. By forming complexes with free IgE, mAbs against IgE block the interaction between IgE and mast cells and basophils. Thus the use of anti-IgE mAbs is considered to be a promising approach for the treatment of allergic conditions such as asthma [1].

Asthma is an inflammatory chronic disease of multifactorial aetiology, including allergic asthma, which is characterized by eosinophilic airway inflammation, often sustained by allergic sensitization. Asthma is typically associated with bronchial hyper-responsiveness to direct and indirect triggers. Severe asthma is defined as asthma that requires high-dose inhaled corticosteroids (ICS) plus a second controller (usually a long-acting β_2 agonist [LABA]) and/or systemic corticosteroids for adequate control, or which is uncontrolled despite this high-intensity treatment. An estimated 5–10% of all patients with asthma are believed to have severe refractory asthma [2].

For patients with severe uncontrolled asthma, four monoclonal antibodies (mAbs) against immunoglobulin E (IgE) or interleukin (IL)-5 are available for clinical use by either subcutaneous (SC) or intravenous (IV) administration as an add-on to ICS plus LABA therapy. The anti-IgE antibody omalizumab has been available for SC use in the USA since 2003, and has also been approved in Europe since 2009. The anti-IL-5 antibodies mepolizumab and benralizumab for SC administration and reslizumab for IV administration were approved in 2015, 2017 and 2016, respectively, in both the USA and Europe [3].

According to the Global Initiative for Asthma (GINA) 2017 guidelines, add-on therapy with omalizumab should be considered in patients aged ≥6 years with severe allergic asthma, while mepolizumab and reslizumab may be beneficial in patients with severe eosinophilic asthma aged ≥12 years. However, it is important to note that reslizumab has only been approved for adults (≥18 years) [4].

mAbs are made of two identical heavy and light chains held together by disulphide bonds at the hinge region to form a Y-shaped structure. They were first created as mouse mAbs using hybridoma technology, but to minimise the immunogenic mouse components, murine mAbs were replaced by chimeric, humanised and then fully human mAbs. The pharmacokinetics (PK) of mAbs is characterised by low distribution to the extravascular compartment, because of their large molecular size and long elimination half-life ($t_{1/2}$), which depends on slow intracellular catabolism, with no urinary excretion [5].

The most common route of administration of mAbs is IV, followed by SC administration, although intramuscular injection is also possible. Oral administration is precluded because of their large molecular size and gastrointestinal degradation. The rate and extent of absorption varies between mAbs and between individuals for the same mAb. For mAbs administered via the SC route, absorption into the systemic circulation first requires convective transport of the mAb through the interstitial space into the lymphatic system [6].

Objectives of the study

The main objective of the study is to analyze the use of intravenous and subcutaneous monoclonal antibodies in the treatment of asthma.

METHODOLOGY OF THE STUDY:

This study was conducted in Nishtar hospital Multan during March 2018 to July 2018. Male or female allergic asthmatics aged 12 to 75 years who were symptomatic despite treatment with ICSs were eligible if they met the following criteria: duration of asthma, ≥1 year; positive immediate responses on skin prick testing to at least 1 common allergen. This was a double-blinded, placebo-controlled, multicenter, parallel-group trial. On entry into the study, each patient was switched from his or her currently prescribed ICS to an equivalent dose of BDP. At the end of the second week of the 4- to 6-week run-in period, the dose of BDP was adjusted upward or downward to maintain previous asthma control. The patients were monitored to ensure both the presence of asthma symptoms at levels acceptable to the patients and investigators and patient safety.

Serum IgE levels

Serum samples were taken at baseline and before dosing at weeks 16 and 24 to determine IgE concentrations. In omalizumabtreated subjects, serum IgE comprised free IgE and IgE bound to omalizumab.

Statistical analysis

The data of respiratory function were compared between the smoker and non-smoker groups using the independent t-test for normally distributed data or the Mann-Whitney U test for other distributions.

Differences were considered statistically significant at $p<0.05$.

RESULTS:

Table 1 explains the demographical conditions of the patients. This table explains the co-efficient and standard error values. The level of confidence interval is 90 and 95 in this table for the significant value.

Table 01: Demographic characteristics and history of patients

Variables	**Co-efficient**	**SE**
Blood pressure	0.048	0.35
Healthy eating index (HEI)	−0.059	0.05
Smoker	0.060	0.80
Food security	0.106	0.12
Drinker	-0.343	0.08
Belong to city area	0.057	0.01
Belong to rural area	0.59	0.70
BMI	0.5460.24	

Additionally, health-related quality of life was measured using SGRQ. At Week 24, there was a statistically significant improvement in the mean SGRQ score for mepolizumab compared with placebo: -5.8 (95% CI: -10.6,-1.0; P=0.019). At Week 2, the proportion of subjects with a clinically meaningful decrease in SGRQ score (defined as a decrease of at least 4 units from baseline) was greater for mepolizumab (58%, 40/69) compared with placebo (41%, 27/66).

Table 2: Results of the primary and secondary endpoints in the Intent to treat population

	Number (%) of Subjects	
	Mepolizumab (100 mg SC) N= 69	**Placebo N= 66**
Primary Endpoint:		
Percent Reduction in OCS from Baseline at Weeks 20-24 (%)		
N		
90% - 100%	16 (23%)	7(11%)
75% - <90%	12 (17%)	5 (8%)
50% - <75%	9 (13%)	10 (15%)
>0% - <50%	7 (10%)	7(11%)
No decrease in OCS/lack of asthma control/	25 (36%)	37 (56%)
withdrawal from treatment		
Odds ratio (95% CI)	2.39 (1.25, 4.56)	-
p-value	0.00	-
Secondary Endpoints:		
Reduction in the daily OCS dose		
At least 50% reduction in daily OCS dose from baseline, n (%)	37 (54%)	22 (33%)
Odds ratio (95% CI)	2.26 (1.10, 4.65)	-
p-value	0.02	-
Reduction to ≤5 mg/day in daily OCS dose, n (%)	37 (54%)	21 (32%)
Odds ratio (95% CI)	2.45 (1.12, 5.37)	-

p-value	0.02	-
Reduction to 0 mg/day in daily OCS dose, n (%)	10 (14%)	5 (8%)
Odds ratio (95% CI)	1.67 (0.49, 5.75)	-
p-value	0.41	-
Median Percentage Reduction in Daily OCS Dose		
Median % reduction from baseline (95% CI)	50.0 (20.0, 75.0)	0.0 (-20.0, 33.3)
Median difference (95% CI)	-30.0 (-66.7, 0.0)	
p-value	0.007	

OCS: prednisone/prednisolone

DISCUSSION:

The availability of biological agents has changed the treatment strategies for severe asthma. Initially, the availability of omalizumab changed the treatment of asthma related to IgE-mediated allergic pathogenesis, and more recently, the availability of drugs targeting IL-5, which is a fundamental factor in the differentiation, activation and survival of eosinophils, changed the treatment strategy for the eosinophilic phenotype[7]. The therapeutic effect of mepolizumab, benralizumab and reslizumab is related to their capacity to bind with high affinity to IL-5 (dissociation constants in vitro of 100 and 81 pmol/L, respectively) and thus to block the interaction between IL-5 and its receptor on the surface of eosinophils [8]

Mepolizumab is an IgG1 kappa mAb. In patients with asthma and blood eosinophil counts > 300 cells/μL, dose- and time-dependent decreases in blood eosinophil counts were observed with IV mepolizumab 75 mg and SC mepolizumab 125 or 250 mg administration. However, authors concluded that the route of administration did not affect the drug exposure-response relationship. Furthermore, given that the reduction in blood eosinophils was evident as soon as three days from administration of the drug, whether SC or IV, there appears to be little significant difference in the PK-pharmacodynamics profile between the two routes of administration [9].

The biological effects of SC mepolizumab have translated into clinical therapeutic efficacy. SC mepolizumab was associated with a significant corticosteroid-sparing effect in patients with severe eosinophilic asthma who required daily oral corticosteroids for asthma control in the SIRIUS study[10]. The MENSA clinical trial results suggested an advantage of the SC over the IV formulation. In fact, the rate of exacerbations was reduced by 47% among patients receiving IV mepolizumab and by 53% among those receiving SC mepolizumab. In addition, emergency visits or hospitalizations were reduced by 32% and 61% in the group receiving IV and SC mepolizumab, respectively. The improvement in the Asthma Control Questionnaire-5 (ACQ-5) score was 0.42 points and 0.44 points greater in the two mepolizumab groups, respectively, than in the placebo group [11].

Benralizumab is a humanised, afucosylated, monoclonal antibody (IgG1, kappa) that directly binds to the alpha subunit of the human interleukin-5 receptor (IL-5Rα) [12]. The IL-5 receptor is expressed on the surface of eosinophils and basophils. In an in vitro setting, the absence of fucose in the Fc domain of benralizumab facilitates binding to FC gamma R (FcγRIII) receptors on immune effectors cells, such as natural killer (NK) cells, leading to apoptosis of eosinophils and basophils through antibody-dependent cell-mediated cytotoxicity (ADCC). Interestingly, patients receiving benralizumab achieved greater reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control [13].

CONCLUSION:

It is concluded that omalizumab is effective and safe in patients with severe allergic asthma who experience poor disease control or exacerbations despite recommended therapy.

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