

ANTI-IG_E AS A PRACTICAL TOOL IN ASTHMA MANAGEMENT: OBSERVATIONS AND WARNINGS FROM CLINICAL EXPERIENCE

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ABSTRACT

Moderate to severe allergic asthmatics represent a challenging group of patients that have unmet needs with regard to asthma management. Current guidelines have resulted in significant improvements in asthma outcomes yet do not affect the underlying disease process. Omalizumab is the first biological agent introduced to specifically manage allergic disease by specifically targeting IgE. It is a recombinant DNA-derived humanised monoclonal IgG1 antibody with unique antihuman IgE-binding specificities. But the mechanism of action as down-regulation of FcεR1 receptors in the presence of low free IgE is incomplete. Some severe allergic asthmatic patients respond almost immediately, others take months, some never respond. Other unexplained phenomena include the presence of positive skin tests for much longer than 3 months – some for years, raising the possibility of anaphylaxis with concomitant allergy immunotherapy. Some patients may have exquisitely sensitive B cell production. Current guidelines for anti-IgE use in asthmatics may require re-examination as data from broad clinical experience are gathered.

INTRODUCTION

The development of asthma is a multifactorial process involving genetics and environmental exposure. Allergic asthma occurs in patients with sensitivities to allergens such as house-dust mite, animal dander and cockroaches. Of the patients with asthma, most have evidence of IgE-mediated sensitivity to airborne allergens.¹ This is especially true in children, where over 85% of asthmatic children show positive skin tests to one or more airborne allergens.^{2,3} With improved knowledge of the mechanisms of allergy, novel inflammation and asthma treatments have been developed.

IgE AND ALLERGY

Development of allergic asthma is driven by the production of IgE antibodies that are specific to a given allergen. In the case of asthma, important allergens include house-dust mite, animal dander, cockroaches and alternaria. Once allergen-specific IgE has been produced, it binds via the Fc segment to the high affinity receptor, FcεRI on mast cells and basophils. Cross-linking of bound IgE with allergen leads to mast cell degranulation with immediate release of inflammatory mediators resulting in symptoms developing within 10-15 minutes. These mediators cause smooth-muscle contraction, increased mucus production and oedema in tissues. This process drives the bronchoconstriction

and inflammation that characterises asthma.

Mechanism of action of anti-IgE

The effect of anti-IgE is produced as a function of complexing free IgE to reduce mast cell placement. As total free IgE drops below 10 ng/ml, downregulation of IgE receptors on circulating basophils, skin mast cells, IgE+ bronchial mast cells, Langerhans cells, and circulating (precursor) dendritic cells occurs.^{4,5} This effect on dendritic cells may lead to a reduction in allergen presentation, and TH2 activation and proliferation.^{6,7} Eosinophils, T and B cells are also reduced in the sub-mucosa.

In addition to the high-affinity FcεRI, IgE binds to a low affinity receptor, FcεRII or CD23, which is found on lymphocytes, epithelial cells, macrophages and other cells. It is felt that upregulation of this receptor increases allergic responses in the bronchial mucosa.⁸

Effect of anti-IgE on asthma

The efficacy of anti-IgE in severe asthma has been established in both short- and long-term studies. Five hundred and twenty-five subjects with severe allergic asthma requiring daily inhaled corticosteroids (ICS) were randomised to receive placebo or omalizumab subcutaneously every 2 or 4 weeks, with stable ICS doses for the initial 16 weeks of treatment and tapered doses during a further 12-week treatment period. Treatment resulted in significantly fewer asthma exacerbations per subject and in lower percentages of subjects experiencing an exacerbation than those on placebo treatment during both the stable-steroid and the steroid-reduction phases. Inhaled steroid reduction was significantly greater with omalizumab treatment than with placebo and ICS discontinuation was more likely with anti-IgE treatment. Improvements in asthma symptoms and pulmonary function occurred along with a reduction in rescue beta-agonist use.⁹ In the longer-term study, 460 patients continued a 24-week, double-blind extension phase to a previous 28-week core study (16 weeks in addition to their existing ICS therapy followed by a 12-week phase in which controlled attempts were made to gradually reduce ICS therapy).¹⁰ Both placebo and active patients were maintained on the lowest sustainable dose of BDP. The use of other asthma medications was permitted during the extension phase. Omalizumab-treated patients experienced significantly fewer exacerbations vs placebo during the extension despite a sustained significant reduction in their use of ICS.

ANOMALIES IN ASTHMA – DO PATIENTS WITH LOW TOTAL IgE LEVELS RESPOND?

Physicians in the process of evaluating potential candidates for anti-IgE are frustrated by the current provisions requiring a minimum IgE level of <30 kU/l before application of this new treatment. Characteristics of 11 female patients with moderate to very severe asthma and IgE levels less than 34 kU/l and their unexpectedly encouraging progress with anti-IgE injections are presented in Table I.¹¹ 'Wow' response refers to a dramat-

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Table I. Response and characteristics of patients entering omalizumab treatment below 34 kU/l

	CA	VC	TC	DC	JC	GG	NJ	SP	TT	GW	LW
Age	45	54	45	53	56	65	32	49	52	64	53
Sex	F	F	F	F	F	F	F	F	F	F	F
Eczema	N	Y	N	N	N	N	N	N	N	N	N
Oral Steroid	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
High ICS	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Length asthma (years)	>20	>20	>28	>8	>20	>9	>20	>20	>10	>20	>20
ER/Hosp	Mult	2/2	1/0	0/0	0/0	0/2	0/0	0/0	0/0	0/0	2/1
Prick entry	+++	++	+++	+	+++	+	+++	+++	++	+	+
Prick 6 months	-	+	-	+	+	-	+	+	+	-	-
Entry FVC/FeV1	80/78	85/91	90/84	88/93	71/60	45/75	97/93	77/75	91/88	94/94	81/65
6 mo. FVC/FeV1	93/97	93/98	89/85	n/a	103/89	45/69	n/a	81/96	103/89	95/94	85/75
Baseline IgE	25	19	26	22	3	<2	33	33	32	7	12
6 mo. IgE	281	30	67	50	8	10	117	165	133	23	31
Rise %	11.2	1.6	2.6	3.3	2.7	5	3.5	5	4.2	3.3	2.6
Wt (kg)	107	100	87	86	125	60	54	60	147	66	58
Dose Anti-IgE	300/4	150/4	150/4	150/4	150/4	150/4	150/4	150/4	150/4	150/4	150/4
Response QOL	WOW	Mod	Good	Mod	WOW	Poor	Good	Mod	WOW	Good	Good
Length anti-IgE (mo.)	16	8	18	6	14	12	15	16	18	10	8

ic improvement, primarily in activity, as judged by patients. These patients, except for discernable prick-puncture skin tests, would historically be classified as intrinsic asthmatics. IgE levels are predictive for the incidence of asthma, but not the severity. The current literature suggests that the sickest asthmatics with the highest level of IgE tend to be the best responders.¹² However, clinical trials excluded individuals with total IgE levels below 30 kU/l, and may have excluded a host of legitimate responders. It is possible a clone of IgE may produce significant disease while not elevating the total level.

WARNINGS ABOUT CONCOMITANT TREATMENT WITH ALLERGY IMMUNOTHERAPY AND ANTI-IgE

Much recent speculation involves the use of anti-IgE as a protective mechanism since this drug is understood

to bind free IgE and downregulate the high affinity receptors.^{13,14} Table II outlines the characteristics of 3 asthmatic patients from a cohort of 58 who experienced an anaphylactic reaction to their pollen specific antigen immunotherapy in spite of pretreatment with omalizumab for over 6-12 months.¹⁵

Omalizumab-treated patients consistently retain positive skin tests to pollens and moulds, although in many cases the reactivity is less after 3-6 months.¹⁶ While studies suggest omalizumab reduces the incidence of anaphylaxis and has been proven to inhibit nasal responses on challenge, the possibility of life-threatening allergic reactions still exists in patients receiving specific immunotherapy (SIT). Concomitant use of SIT and omalizumab should not suggest a change in the practice parameters for doses and frequency of SIT and should not lull practitioners into a sense of false security.

CONCLUSION

Omalizumab in practice is a highly effective and indeed life-altering drug in many asthmatic patients, but not all. Profiling for this intensive therapy has not been well established, but clinical evidence is beginning to mount that some asthmatics below the total IgE level discussed in the package insert may respond well.

Table II. Characteristics of three patients experiencing anaphylaxis following pre-treatment with anti-IgE

Patient ID	VC	JV	WE
+ SIT @ 6 months	Reduced	Same	Reduced (on AH)
SIT content	HD, MC	Grass, MC	MC, RW, HD
IgE baseline	19	125	215
IgE 6 months	30	493	910
Duration SIT prior to event	6 months	12 months	Day (RUSH)
Months of omalizumab before event	6 months	12 months	6 months
Symptoms of event	Wheeze, itch, angio	Angio, sneeze, congestion	Wheeze, sneeze, congestion
Intervention	Epi x3 AH	Epi x2 AH	Epi x2 AH
Resolution	30 mins	120 mins	20 mins
Serum markers	Not done	Not done	Not done

AH - antihistamine; HD - house-dust mite; MC - mountain cedar (tree); RW - ragweed; RUSH - Rush immunotherapy, a mechanism of accelerating the patient from baseline to maintenance in a short period; Epi - epinephrine

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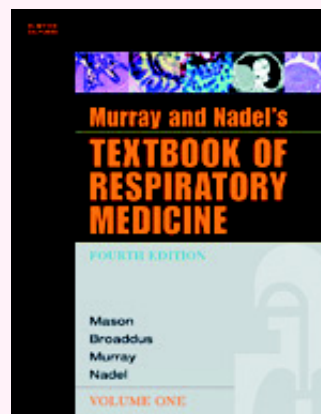
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