The rationale for treating allergic asthma with anti-IgE

E. Hamelmann

ABSTRACT: **An estimated two-thirds of asthma is allergic and >50% of severe asthma has an allergic component. An increased immunoglobulin (Ig)E production in response to environmental allergens (atopy) is the strongest detectable predisposing factor for the development of asthma, particularly when sensitisation occurs early in life.**

IgE binds to high-affinity receptors (FcεRI) on effector cells, such as mast cells and basophils. Allergen binds to IgE and initiates an inflammatory cascade resulting in release of pro-inflammatory mediators that contribute to the acute and chronic symptoms of allergic airway diseases. By reducing serum IgE levels and FcεRI receptor expression on key cells in the inflammatory cascade, omalizumab blocks the release of inflammatory mediators from mast cells and reduces the infiltration of inflammatory cells, notably eosinophils, into the airway. In patients with allergic asthma, omalizumab inhibits both the early and late asthmatic response and several other markers of inflammation, including the requirement for inhaled or oral corticosteroids.

The anti-inflammatory effects of omalizumab provide proof-of-concept of the key role played by immunoglobulin E in allergic respiratory disease. Omalizumab represents a novel approach to the treatment of asthma, inhibiting the inflammatory cascade before it starts.

KEYWORDS: Airway inflammation, allergic asthma, anti-immunoglobulin E, immune modulation, monoclonal antibody, omalizumab

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Approximately two-thirds of asthma is allergic and >50% of patients with severe asthma have allergic asthma [1–3]. Allergic (immunoglobulin (Ig)E-mediated) asthma is characterised by the presence of IgE antibodies against one or more common environmental allergens, such as house dust mite, animal danders and moulds [4]. Omalizumab represents a novel approach to the treatment of severe persistent allergic asthma. It is a humanised monoclonal anti-IgE antibody, the first therapeutic agent which has been demonstrated to bind free IgE and inhibit mast cell degranulation [5].

ATOPY

Atopy is the production of increased levels of IgE in response to common environmental allergens and is the strongest detectable predisposing factor for the development of asthma [4]. In the German Multicenter Allergy Study (MAS)-90, 499 newborns with risk factors for atopy and 815 newborns with no risk factors were followed up at specified intervals until they reached 13 yrs of age, using structured parental interviews (with special interest paid to asthmatic and atopic symptoms), blood sampling to determine specific IgE antibodies to food and inhalant allergens, and a bronchial histamine challenge performed at

7 yrs of age [6]. MAS-90 demonstrated that atopy and a positive family history for asthma/atopy was associated with the prevalence of asthma at age 7 yrs and that the prevalence of asthma was greatest in children with persistent sensitisation and a positive family history (fig. 1) [6].

The frequency of wheezing episodes from birth up to the age of 5 yrs was equivalent for children with atopic and nonatopic wheeze. Early onset of wheeze and repeated episodes of wheeze before the age of 3 yrs were not significantly different between groups. At school age (5–7 yrs), the severity of asthma symptoms was higher among the atopic group, as assessed by the frequency of wheezing episodes in the previous year [7]. After 5 yrs of age, the course of wheezing differed markedly between groups. In children with nonatopic wheeze, the prevalence of symptoms diminished substantially in subsequent years, whereas the prevalence of symptoms first increased and then remained stable over the following years among the children with atopic wheeze. At age 13 yrs, ~90% of children with nonatopic wheeze had a remission of symptoms, compared with ~56% children with atopic wheeze (p=0.0002; fig. 2). Early sensitisation to perennial allergens significantly affected lung
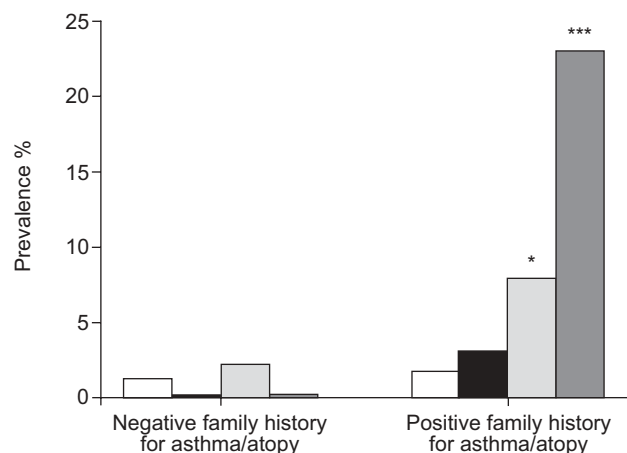
FIGURE 1. Prevalence of asthma at age 7 yrs, stratified for sensitisation pattern and family history. □: no sensitisation (n=183 and n=158 for the negative and positive groups, respectively); ■: transient sensitisation (n=47 and n=33, respectively); ■: late sensitisation (n=42 and n=74, respectively); ■: persistent sensitisation (n=29 and n=70, respectively). *: p<0.05; ***: p<0.001 in comparison to no sensitisation/negative family history (Chi-squared test). Data taken from [6].

function at school age; later sensitisation to these allergens had a less pronounced effect.

ROLE OF IgE IN ALLERGIC ASTHMA

Binding of IgE to high-affinity receptors (FcεRI) on effector cells, such as mast cells and basophils, and subsequent exposure to allergen initiates an inflammatory cascade resulting in release of pro-inflammatory mediators, which contribute to the acute and chronic symptoms of allergic airway diseases [8].

The IgE molecule is comprised of fragments known as the antigen-binding fragment (Fab) and the crystallisable fragment (Fc; fig. 3). The Fab region binds to specific components (or

FIGURE 2. Prevalence of current wheeze from birth to age 13 yrs in children with any wheezing episode at school age (5–7 yrs), stratified for atopy (●: nonatopic; ▲: atopic) at school age. The boxes demonstrate that atopy is a risk factor for persistent/chronic asthma at school age, whereas it does not discriminate early wheezers in infancy. Reproduced, with modifications, from [7] with permission from the publisher.

epitopes) of the allergen, whereas the Fc region binds to FcεRI present on mast cells and circulating basophils. FcεRI consist of four polypeptide chains, $\alpha\beta\gamma_2$. The α chain binds to five amino acids (330–335) of the Cε3 domain of the Fc segment of IgE in order to orientate the IgE molecule such that it lies with the allergen-binding site facing outwards (fig. 4) [8].

The binding of allergen to two or more adjacent α chains results in receptor clustering and, through interactions involving the α and β chains, sets into motion intracellular biochemical events that trigger mast cell activation [8]. This activation releases a variety of pre-formed and newly generated pro-inflammatory mediators and cytokines, including histamine, interleukins (ILs), leukotrienes and prostaglandins (type I hypersensitivity reaction). The release of IL-4, IL-13 (increasing IgE synthesis) and IL-5 (increasing eosinophil accumulation) contributes to the chronic inflammatory response (fig. 5). Eosinophilia is a well-recognised feature of inflammation in asthma and it reflects asthma severity and the risk of exacerbations [9, 10].

IgE upregulates FcεRI on mast cells and basophils [11]. This upregulation of FcεRI expression in the presence of higher concentrations of serum IgE results in mast cell stimulation and mediator release at lower concentrations of allergen, and/ or in the release of increased amounts of mediators and cytokines for a given level of stimulus [12]. IgE also binds FcεRI on dendritic cells and enhances allergen uptake and presentation to T-cells [13], leading to increased T-cell proliferation and eosinophil differentiation and activation.

It is well established that the risk of developing asthma increases with increasing levels of serum IgE (fig. 6) [14]. However, asthma severity is poorly associated with total IgE levels [15]. The association between specific IgE and asthma severity is currently under investigation. FcεRI are upregulated on eosinophils, mast cells, macrophages and dendritic cells in patients with rhinitis [16] and allergic asthma [17]. In addition, a significant correlation has been observed between serum IgE levels and FcεRI expression on precursor dendritic cells from subjects with allergic asthma [18]. A possible relationship between FcεRI expression and fatal asthma has also been reported [19]. This study examined *post mortem* human lung tissue and found that cases of fatal asthma were associated with higher levels of FcεRI-positive cells within the lamina propria, compared with subjects who died of other causes or with biopsy tissue from patients with mild asthma (fig. 7).

TARGETING IgE

Omalizumab (Xolair®) is a recombinant, humanised monoclonal antibody and it is the first treatment to target IgE. Omalizumab reduces free IgE by ~95% by binding to the Cε3 region on free IgE, thereby blocking the binding of IgE to its specific high-affinity receptor. IgE enhances the expression of FcεRI on effector cells [11] and, in conditions of reduced levels of plasma IgE, the reverse is also true. In a series of *in vitro* studies [5, 20], the effect of anti-IgE treatment on the expression of FcεRI on basophils in subjects with perennial allergic rhinitis and with positive skin test to dust mite was examined. Basophil receptor density measurements were taken prior to treatment and 3 months after treatment initiation. With omalizumab treatment, total FcεRI density was decreased
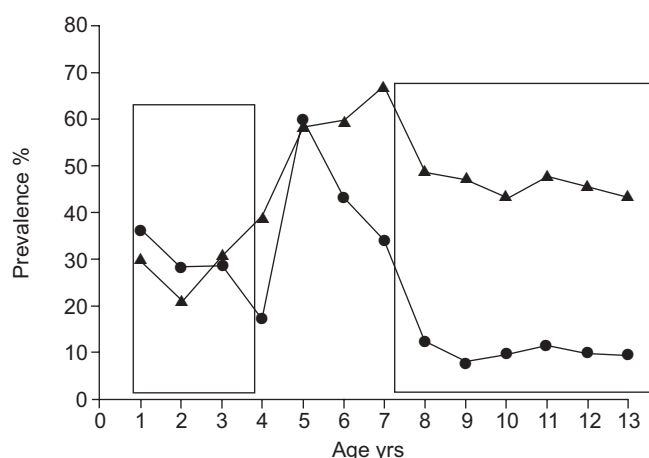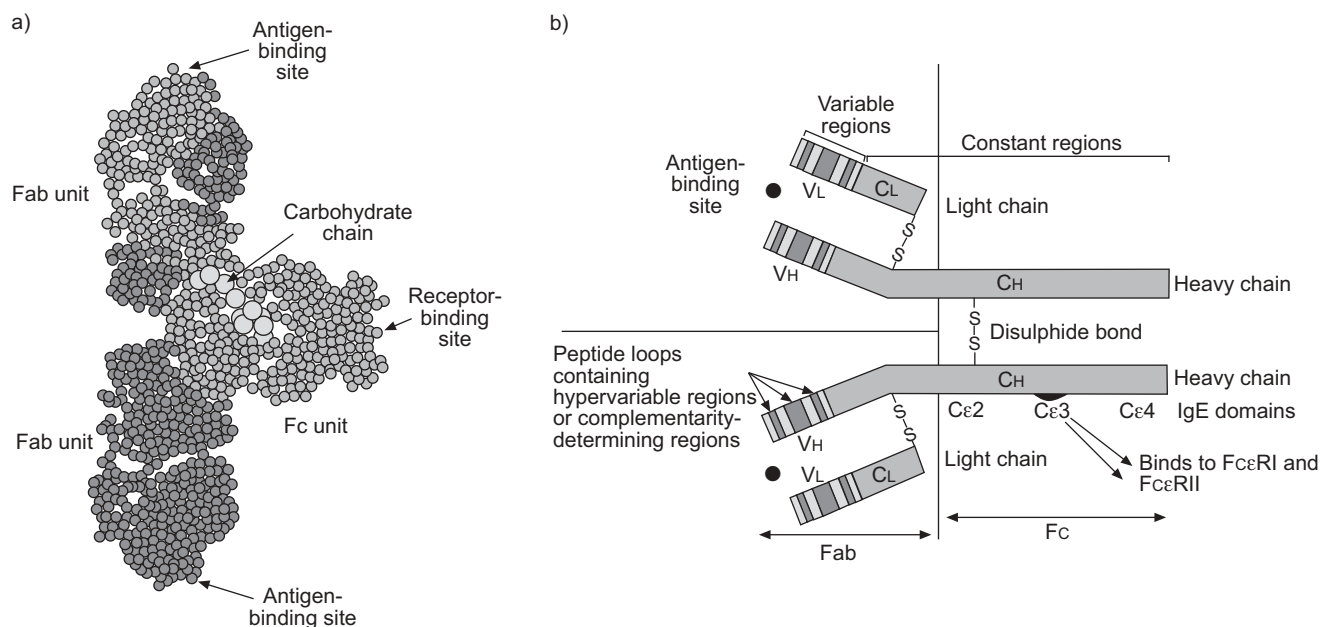
FIGURE 3. a) Molecular structure and b) schematic diagram of immunoglobulin (Ig)E. The variable domain (V) binds antigen. The constant region (C) domains determine secondary biological function (e.g. cell-surface binding). FcεRI and FcεRII are high-affinity IgE receptors. Fab: antigen-binding fragment; Fc: crystallisable fragment; VH: heavy-chain variable domain; VL: light-chain variable domain; CH: heavy-chain constant domain; CL: light-chain variable domain.

by ~97% (p=0.0022; fig. 8) [5]. Reflecting the reduction in receptor density, the responsiveness of the basophils to challenge with dust mite antigen (*Dermatophagoides farinae*) was decreased by ~90% (p=0.0022) [5]. During the period following discontinuation of omalizumab treatment, basophil FcεRI were upregulated, concurrent with a gradual rise of serum-free IgE levels to 16% of pre-treatment levels over an 8-week period [20]. However, a more rapid rise in antigen-triggered histamine release responses by the cells implies a reduction of the threshold for basophil activation. Thus, the effects of omalizumab treatment on mast cells and basophils are achieved through a combination of reduced free IgE levels and IgE receptor downregulation, leading to the inhibition of

IgE-mediated pro-inflammatory mediator release. These dual effects of omalizumab are important, since without the FcεRI downregulation almost complete removal of free IgE would be necessary to elicit functional consequences on mast cells and basophils [5, 20].

Omalizumab significantly reduces submucosal IgE-positive and FcεRI-positive cells in patients with allergic asthma. The effect of omalizumab on the number of cells expressing IgE or FcεRI was assessed in a placebo-controlled study of 45 patients with corticosteroid-naïve, mild-to-moderate asthma [21].
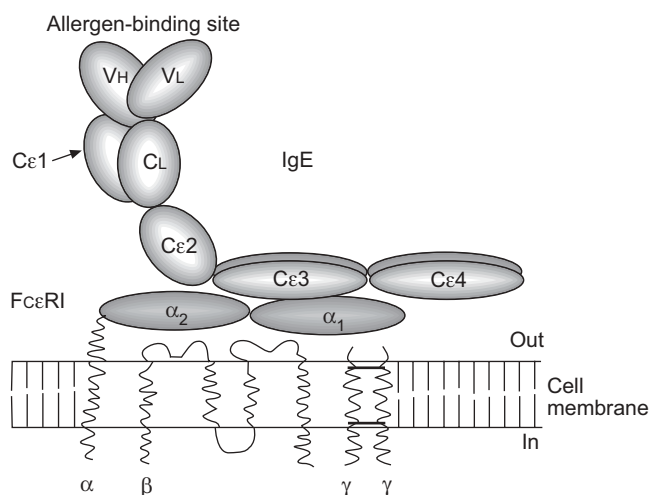

FIGURE 4. Binding of immunoglobulin (Ig)E to the high-affinity receptor (FcεRI). Reproduced from [8] with permission from the publisher.
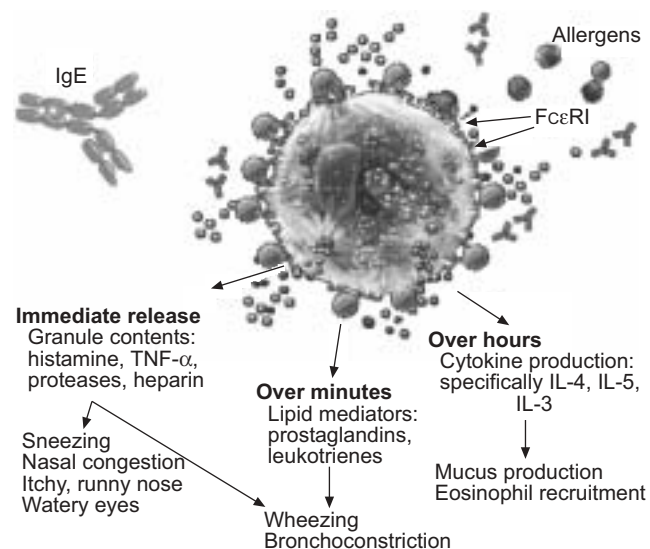

FIGURE 5. Immunoglobulin (Ig)E-dependent release of inflammatory mediators. IL: interleukin; FcεRI: high-affinity IgE receptor; TNF: tumour necrosis factor.
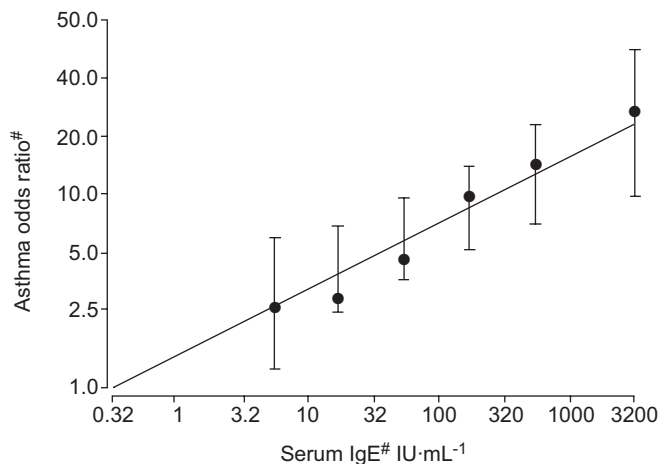
FIGURE 6. The likelihood of having asthma increases with increasing serum immunoglobulin (Ig)E (n=2,657). The error bars represent the 95% confidence intervals. [#]: logarithmic scale. Reproduced from [14] with permission from the publisher.

FIGURE 8. Omalizumab downregulates immunoglobulin E receptors in patients with perennial allergic rhinitis (○; p=0.0022). The horizontal lines represent the median values for omalizumab-treated patients. ●: controls. Reproduced from [5] with permission from the publisher.

Treatment with omalizumab for 16 weeks significantly reduced IgE-positive cells in the bronchial submucosa compared with baseline or placebo (both p<0.001). Similarly, treatment with omalizumab for 16 weeks significantly reduced FcεRI-positive cells in the bronchial submucosa compared with baseline or placebo (both p<0.001). As mentioned previously, a close correlation has also been observed between serum IgE levels and FcεRI expression on precursor dendritic cells (pDCs) from subjects with allergic asthma [18]. The effect of omalizumab on FcεRI receptor expression on pDC subtypes 1 and 2 (these subtypes promote the shift of the T-cell towards the T-helper cell type 1 and 2 phenotype, respectively) has been assessed in a randomised, double-blind, placebo-controlled study in patients with seasonal allergic rhinitis [22]. Omalizumab significantly reduced FcεRI expression (p ≤ 0.002) from day 7 onwards for both pDC1 and pDC2 cells, indicating that omalizumab causes a rapid decrease in FcεRIα surface expression by dendritic cells. By downregulating FcεRI
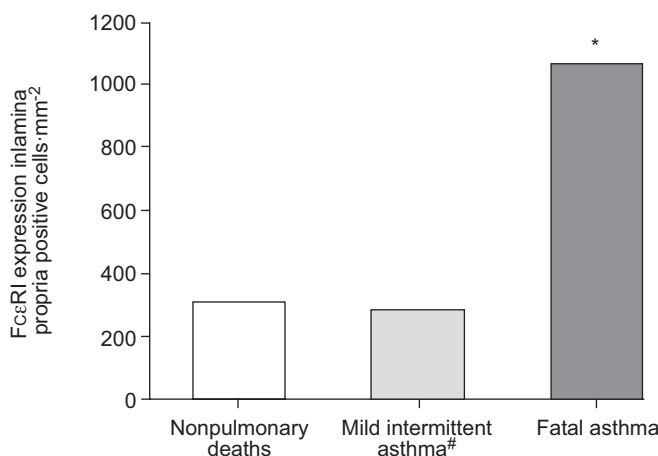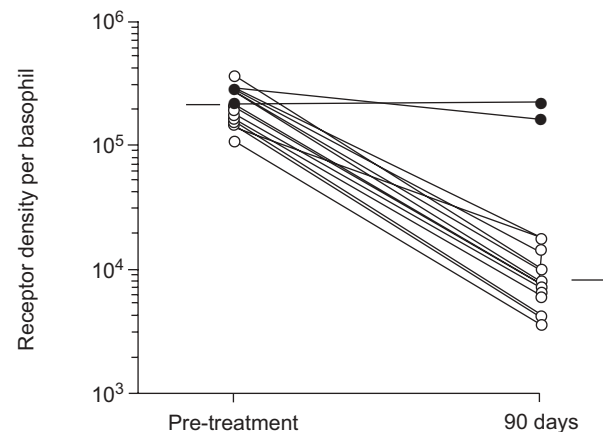
expression on dendritic cells, omalizumab may inhibit antigen processing and presentation to T-cells.

The depletion of IgE in airway tissue is associated with a marked reduction in airway eosinophils [21]. Omalizumab significantly reduces eosinophil numbers in airway tissue and induced sputum in patients with mild or moderate allergic asthma (fig. 9) [21]. Omalizumab treatment reduced the proportion of inflammatory cells in the sputum that were identified as eosinophils (4.8% at baseline, 0.6% post-treatment; p<0.001; p=0.05 *versus* placebo). The reduction in sputum eosinophil counts with omalizumab treatment was mirrored by a significant decrease in the numbers of eosinophils in both the epithelial and submucosal compartments.

The effects of omalizumab at a cellular level are reflected in clinical observations and the symptoms experienced by patients with asthma. Omalizumab inhibits the early- and late-phase asthmatic responses to inhaled allergens, as demonstrated in

FIGURE 7. Expression of high-affinity receptors (FcεRI) is increased in fatal asthma [19]. □: n=9; light grey: n=16; dark grey: n=10. [#]: biopsy. *: p<0.05 *versus* other groups. Data taken from [19].
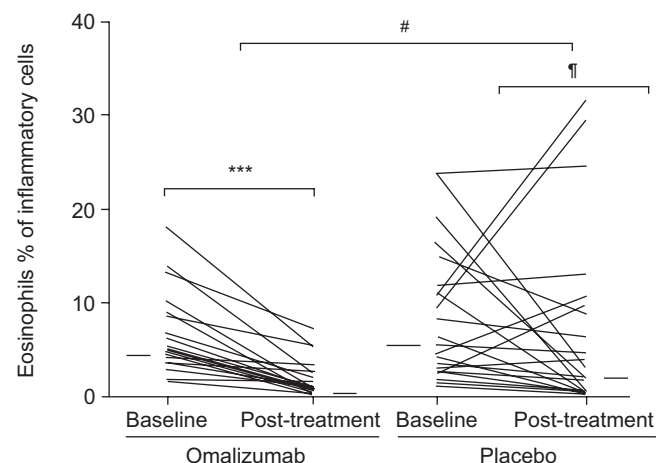

FIGURE 9. Omalizumab significantly reduces median (horizontal markers) sputum eosinophil counts. [#]: p=0.05; [¶]: p=0.16, n=22; ***: p<0.001, n=19. Reproduced from [21] with permission from the publisher.

bronchial challenge tests [23, 24]. Assessed as the mean maximal fall in forced expiratory volume in one second, omalizumab reduced the early asthmatic response by 85% (p=0.01) and the late asthmatic response by 65% (p=0.047) compared with placebo in 18 patients with mild allergic asthma [23]. Omalizumab has also been shown to decrease several markers of inflammation, including the requirement for inhaled or oral corticosteroids, in patients with moderate-to-severe persistent allergic asthma [25–27]. Omalizumab significantly (p<0.001) reduced the required dose of inhaled corticosteroid compared with placebo by 75 *versus* 50% [25] and 83 *versus* 50% [26].

As omalizumab binds to the Cε3 site on free IgE, the same site that binds FcεRI, omalizumab cannot interact with IgE molecules bound to FcεRI on basophils and mast cells, and does not activate effector cells by receptor cross-linking [28]. Omalizumab is, therefore, expected to be nonanaphylactogenic in clinical use.

CONCLUSIONS

The anti-inflammatory effects of omalizumab provide proof-of-concept of the key role played by immunoglobulin E in allergic respiratory disease. By reducing serum immunoglobulin E levels and receptor expression on key cells in the inflammatory cascade, omalizumab limits the release of inflammatory mediators from mast cells and reduces the infiltration of inflammatory cells, notably eosinophils, into the airway. Omalizumab represents a novel approach to the treatment of asthma, inhibiting the inflammatory cascade before it starts.

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