
**IMMUNOGLOBULIN E IN PEDIATRIC ASTHMA:
ADVANCES IN UNDERSTANDING AND MANAGEMENT**

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Received: 24/03/2024

Reviewed: 16/05/2024

Accepted: 22/05/2024

ABSTRACT

Asthma, a pervasive chronic inflammatory ailment of the respiratory system, remains a global health conundrum. The Global Burden of Disease Study (GBD) of 2019 underscores its widespread impact, revealing that asthma afflicts 262 million individuals worldwide, translating into an age-standardized prevalence of 3,416 per 100,000 population. The incidence among children is particularly alarming, with nearly 14% of the global pediatric population diagnosed with the condition. This statistic positions asthma as the foremost chronic respiratory disease among children, a trend that is on the rise, especially across Asia and Europe, as evidenced by the International Study of Asthma and Allergies in Childhood (ISAAC). Characterized by variable airflow limitation, bronchial hyperresponsiveness, excessive mucus production, and airway inflammation leading to airway constriction, asthma's multifaceted nature complicates its management. In the realm of immunology, Immunoglobulin E (IgE) has been identified as a pivotal player. Recognized officially as the fifth class of serum immunoglobulins during the 1968 WHO International Reference Center for Immunoglobulins conference in Lausanne, IgE's crucial role in the pathophysiology of asthma has been rigorously studied. Serum IgE levels, both total and specific, have been proven instrumental in the diagnosis, treatment, and prevention of pediatric asthma. The landmark approval of Omalizumab by the US Food and Drug Administration in 2003 heralded a

new era in the biologic management of asthma, targeting children aged six and above. This was followed by the development of Ligelizumab and Quilizumab, innovative anti-IgE medications currently under investigation for their potential to alleviate symptoms and decelerate the disease's progression. The integration of Allergy Immunotherapy (AIT) alongside monoclonal antibody therapies like Omalizumab, Ligelizumab, and Quilizumab signifies a monumental shift toward personalized medicine in asthma care. These advances promise not only to ameliorate the quality of life for pediatric asthma patients but also to redefine the landscape of asthma management. Nonetheless, the quest for enhanced treatment modalities for young asthmatics necessitates further in-depth research. The burgeoning field of anti-IgE therapy, in concert with AIT, is poised to set new benchmarks in pediatric asthma management, steering us towards a future where asthma's grip on children's health is significantly loosened.

Keywords: IgE, allergy, pediatric asthma, Omalizumab, Allergen Immunotherapy (AIT).

I. INTRODUCTION

Asthma stands as a formidable adversary among non-communicable diseases, significantly diminishing the quality of life for countless individuals worldwide. It ranks as the sixteenth leading cause of years lived with disability globally. With over 300 million people currently grappling with asthma, projections indicate that by 2025, an additional 100 million may be afflicted [1]. The Global Burden of Disease Study (GBD) in 2019 highlighted that asthma affected 262 million individuals globally, resulting in an age-standardized prevalence of 3416 per 100,000 people. Notably, while children experience higher rates of asthma incidence and prevalence, adults suffer from increased morbidity and mortality associated with the condition [2].

A staggering 14% of children worldwide have been diagnosed with asthma, positioning it as the most common chronic respiratory disease among this demographic [3]. An upward trend in the incidence of asthma among children has been observed across Asia and Europe, as documented by the International Study of Asthma and Allergies in Childhood. In a study encompassing 11 countries, the incidence rates in Asia were found to range from 10 to 30 percent [4].

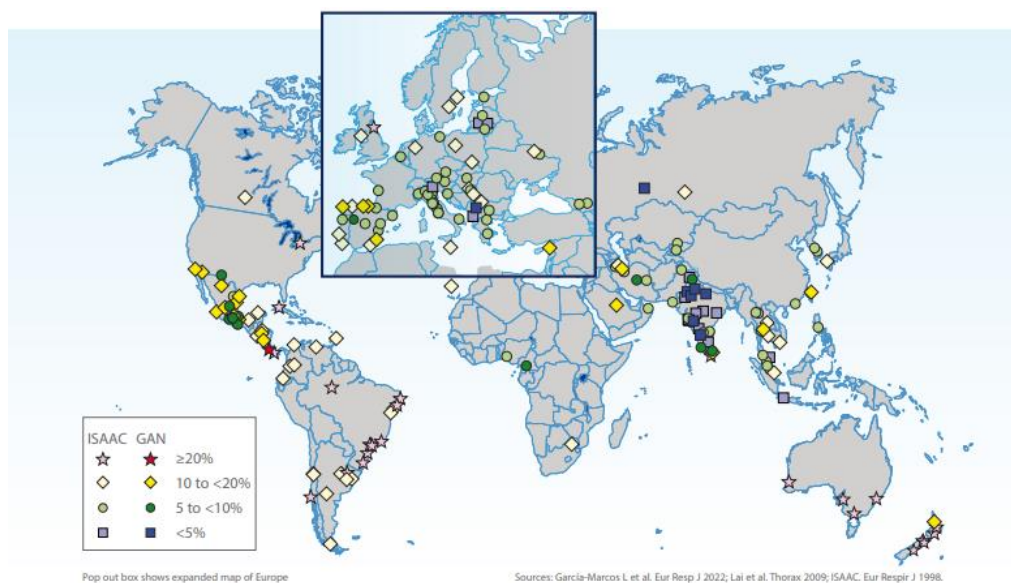


Figure 1. Current asthma symptom prevalence in 6-7 year old children [2]

Allergies emerge from an intricate immune response involving TH2 cells, mast cells, eosinophils, and Immunoglobulin E (IgE) against non-microbial environmental antigens or allergens. There exists a discernible genetic predisposition to atopic diseases, including asthma, urticaria, hay fever, and eczema, along with an identifiable IgE-mediated response post-allergen exposure. Key allergens include house dust mites, fungal spores, pollens, and animal dander [5]. Although total IgE serves as a broad measure for allergic conditions, it lacks specificity. Conversely, specific IgE presents a highly specific marker for diagnosing allergic conditions [4]. However, elevated total IgE levels may also be indicative of other conditions, including parasitic infestations, and hence are not solely attributable to allergic disorders. The limitations of testing methods and allergen selection mean that a negative specific IgE result cannot definitively exclude allergen sensitivity [5].

Asthma is a complex condition, varying widely in its etiology, triggers, clinical presentation, and crucial treatment responsiveness [6]. Epidemiological evidence strongly supports the link between IgE antibodies (both specific and total) and asthma, underscoring the allergic underpinnings of the disease. As Sporik et al. articulated, asthma is predominantly allergic and invariably associated with IgE-mediated reactions. Numerous studies corroborate the significant association between allergen sensitivity and asthma, as evidenced through skin tests or the detection of specific IgE in the blood [7]. The presence of allergen-specific IgE antibodies is a common trait among children with chronic and persistent asthma, establishing it as a critical factor for the onset of lifelong asthma [8]. The NIH Asthma Outcomes Task Force advises that aeroallergen sensitivity be evaluated as a vital biomarker for asthma classification, in addition to eosinophilia and antigen-specific IgE [9],[10].

This review aims to elucidate the intricate role of IgE in pediatric asthma, thereby contributing to a deeper understanding of its pathophysiology and aiding in the development of more effective diagnostic and therapeutic strategies.

II. CONTENT

2.1. Structure and function of IgE

The history of the discovery of IgE

Immunoglobulin E (IgE) stands as the most recently identified member of the immunoglobulin family, historically associated with the expulsion of worms and the onset of allergies [11]. The phenomenon of anaphylaxis, deriving from the Greek words “ana” (against) and “phylaxis” (protection), was first observed by Portier and Richet in 1902 in dogs following exposure to sea anemone toxin. This type of hypersensitive reaction was later observed in humans after injections of horse serum for passive immunity against diseases like tetanus and diphtheria [12]. Von Pirquet in 1906 succinctly described this phenomenon as “supersensitivity without immunity” [13]. The landmark Prausnitz-Küstner test, developed in 1921 by Prausnitz and Küstner, facilitated the passive sensitization of healthy individuals’ skin, transmitting positive skin test results [14].

Coca and Grove, in 1925, delved into the skin-sensitizing factor present in the sera of individuals suffering from ragweed hay fever, coining the term “atopic regains” for these skin-sensitizing antibodies. The breakthrough came in 1967 when Teruko Ishizaka, alongside her husband Kimishige Ishizaka, identified the reagin antibody IgE. Concurrently, Swedish scientists Hans Bennich and S.G.O. Johansson at Uppsala University isolated IgE from a multiple myeloma patient, labeling the discovery “IgND” after the patient’s initials. This discovery linked IgND to inhibition of the Prausnitz-Küstner (P-K) test, a connection

further strengthened by their findings of elevated serum IgND levels in individuals with asthma, differentiating between those with and without allergies. The 1968 WHO International Reference Center for Immunoglobulins conference in Lausanne officially recognized IgE as the fifth class of serum immunoglobulins [12].

IgE: A key biomarker in allergic asthma

Extensive research has consistently shown that individuals with asthma tend to have elevated levels of total serum IgE [15]. While the EGEA study did not find a direct correlation between total IgE levels and clinical severity scores, it did observe a positive relationship with a history of hospitalizations for asthma and the use of inhaled corticosteroids (ICS) in the preceding year. Another study pointed out that children with severe asthma exhibited significantly higher blood IgE levels compared to those with mild to moderate asthma. Given that asthma attacks are often triggered by environmental allergens, specific IgE antibodies against certain allergens signify sensitization and are associated with allergic asthma [16]. Thus, IgE levels are indicative of allergy presence in asthma cases [17].

Structure of immunoglobulin E

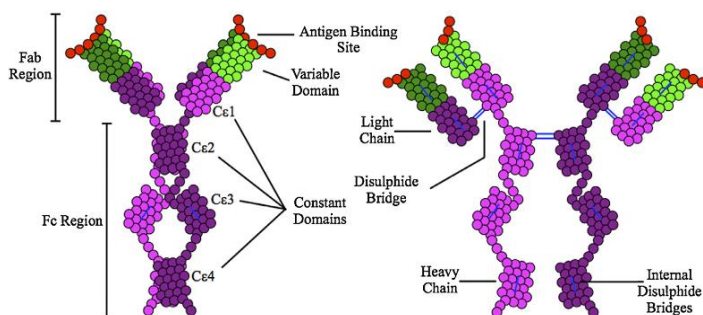


Figure 2. The structure of immunoglobulin E [12]

Similar to other immunoglobulins, IgE consists of two heavy chains and two light chains, with the heavy chain's constant (epsilon) region conferring isotype specificity [12]. Each chain is structured into immunoglobulin domains, approximately 110 amino acids in length. These chains are bonded covalently through disulfide links, with the variable regions pairing to form two antigen-binding sites.

The high-affinity IgE receptor (FcεRI), part of the immunoglobulin (Ig) superfamily, is prominently expressed on mast cells and basophils as an αβγ2 tetramer, hosting around 200,000 molecules per cell. It enhances allergen presentation to CD4+ T cells when expressed trimerically on monocytes, dendritic cells (DCs), and Langerhans cells. FcεRI's efficiency in allergen uptake is vastly superior to endocytosis or pinocytosis. Cross-linking of tetrameric FcεRI on basophils and mast cells triggers cell activation, leading to the release of mediators that amplify the allergic response [18].

CD23, the low-affinity IgE receptor or FcεRII, is crucial for IgE-mediated immune complex presentation and antigen transport, in addition to regulating IgE synthesis by B cells. This 45 kDa type II integral membrane protein belongs to the C-type lectin superfamily and comprises a lectin "head" domain connected to the membrane by an N-terminal stalk, which likely forms leucine-zipper type oligomers, generally as trimers [18].

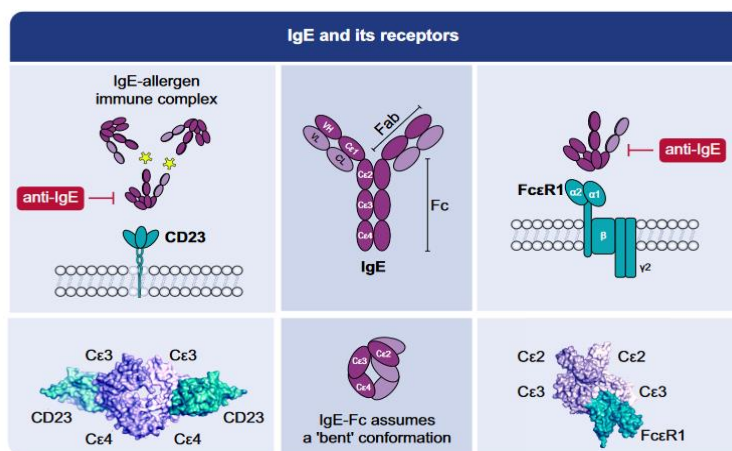


Figure 3. IgE and its receptor [19]

2.2. The impact of total and specific IgE in pediatric asthma

Asthma, a leading non-communicable disease, profoundly affects the quality of life across the globe [1]. This chronic respiratory condition exhibits a spectrum of symptoms due to varying degrees of airflow limitation, bronchial hyperresponsiveness, mucus hypersecretion, and airway inflammation. Such factors lead to airway constriction, manifesting as wheezing, dyspnea, and chest tightness in patients [20]. Asthma's complexity stems from an interplay of host factors, environmental influences, and genetic predispositions, encompassing obesity, nutritional deficiencies, infections, allergic sensitization, air pollution, pollens, molds, other aeroallergens, weather conditions, and asthma-predisposing genes [9].

Pathophysiology of asthma and the role of IgE

The hallmark of asthma is airway obstruction, primarily due to a reduction in airway diameter [21]. This condition is further characterized by the thickening of the airway walls, which is due to airway smooth muscle hyperplasia, increased extracellular matrix deposition, thickening of the basement membrane lamina reticularis, and enhanced submucosal gland production [10]. Chronic inflammation leads to the narrowing of the airways, fueled by the infiltration and activation of immune cells, including eosinophils, lymphocytes, neutrophils, mast cells, and innate lymphoid cells (ILCs) [21].

IgE antibodies play a pivotal role in the biological cascade following allergen exposure, promoting the development of additional IgE antibodies and compromising innate antiviral immune responses [8]. Allergic (or atopic) asthma triggers a chronic Th2-type inflammatory response upon exposure to specific inhaled allergens, activating dendritic cells (DCs) and the airway epithelium to produce targeted IgE antibodies [22]. Th2 cells facilitate IgE synthesis through IL-4 and IL-13 cytokines. Immunologically, IgE contributes to asthma by binding to cells displaying the high-affinity IgE receptor (FcεRI), leading to the release of pro-inflammatory mediators and the onset of asthma symptoms [23]. The discovery of FcεRI receptors on airway smooth muscle cells indicates a role for the IgE pathway in airway remodeling, suggesting that targeting IgE could be an effective strategy to prevent or mitigate allergic responses [7], [24].

Asthma phenotypes and endotypes

Phenotypes in asthma, shaped by the interaction between genetics and environmental factors, are observable traits influenced by clinical, biochemical, functional, and pharmacological factors. While these phenotypes can evolve, they provide valuable insights for patient differentiation and may predict treatment efficacy. The most commonly identified asthma phenotypes include late-onset asthma, allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, infection-related asthma, asthma with fixed airflow obstruction, and obesity-associated asthma. Phenotyping has evolved to associate distinct patterns with specific triggers, patient characteristics, or clinical manifestations [6].

Further refinement comes with endotyping, categorizing asthma based on underlying pathophysiological mechanisms. Two principal endotypes are recognized: T2-high (Th2 cell-mediated) and T2-low asthma. Recent research on children and adolescents with severe asthma has delineated two major inflammatory endotypes: non-type 2, subdivided into neutrophilic, mixed, and pauci-granulocytic patterns, and type 2, marked by eosinophilic (allergic and non-allergic) inflammation. The most common endotype in pediatric asthma is allergic eosinophilic severe asthma, which is associated with validated non-invasive prognostic biomarkers [26].

2.3. Application of Total and Specific IgE in Pediatric Asthma

Serum IgE levels as biomarkers for allergic asthma phenotypes

Serum IgE is a cornerstone in understanding allergic asthma, reflecting the atopic status of individuals. Both in children and adults, serum IgE levels have been demonstrated to correlate positively with asthma severity. Although total serum IgE doesn't track treatment response, it plays a crucial role in predicting the efficacy of anti-IgE therapies. The presence of IgE+ mast cells within the bronchial mucosa offers a promising biomarker for identifying allergic asthma [9].

Diagnosing respiratory allergic diseases necessitates a comprehensive approach, focusing on the upper and lower respiratory tracts, clinical manifestations, patient history, and the seasonality and chronicity of symptoms. Comparable diagnostic accuracy can be achieved through skin testing and serological assessments (total and specific IgE) for patients experiencing respiratory symptoms after aeroallergen exposure. Skin testing, an in vivo method, detects allergies by inducing an immediate hypersensitive reaction through the interaction of specific allergens with IgE antibodies on mast cells. The Radioallergosorbent Test (RAST) is an in vitro technique for quantifying specific IgE levels in blood. Despite its utility, the total IgE test has limitations, including the fact that not all allergic individuals exhibit elevated IgE levels, and elevated levels can also occur in non-allergic conditions like parasitic infections [5].

Omalizumab: a paradigm shift in asthma management

Omalizumab, a humanized anti-IgE monoclonal antibody, has revolutionized asthma management in the U.S. and E.U., marking the first biologic approved for this purpose [27]. It targets free circulating IgE, binding to the Ce3 domain of the IgE heavy chain and reducing the high-affinity FcεRI receptor on mast cells and basophils. This dual action decreases free IgE levels and eosinophilic inflammation, disrupting the allergic cascade and preventing mast cell degranulation [28]. Omalizumab has shed new light on allergen-IgE-receptor interactions and their implications for allergic inflammation [29]. It has been proven to reduce asthma exacerbations during viral seasons and restore the IFN-α response to rhinovirus [8].

Recommended as a first-line treatment for children as young as six with severe allergic asthma, omalizumab is indicated for those with specific IgE sensitivity to at least one aeroallergen and elevated serum IgE levels (between 30 and 1500 IU/mL) [30]. Administered subcutaneously every 2-4 weeks, dosages are determined by a weight and pretreatment serum IgE level-based nomogram, with final dosages given at intervals of every four weeks, ranging from 75–600 mg. The maximum dosages differ between Europe and the USA, set at 600 mg and 375 mg every two weeks, respectively, with a plasma half-life of approximately 26 days. Available in 150 mg ampoules and 75 and 150 mg pre-filled syringes, omalizumab facilitates easy home administration [31]. Notably, the incidence of anti-drug antibodies is below 3%, with omalizumab exhibiting the lowest incidence in comparison to other asthma biologics, reinforcing its safety profile [32]. Real-world trials have also demonstrated omalizumab’s effectiveness in reducing exacerbations and hospitalizations [27].

The PARK trial, involving a 2-year treatment phase followed by a 2-year observational phase, explores whether omalizumab can delay or even prevent the onset of asthma in children, a prospect that could redefine early asthma management [32]. This highlights the critical need for further research to refine treatment criteria for young children, potentially establishing omalizumab as a disease-modifying agent in the early years of life. The advent of monoclonal antibody therapies like omalizumab represents a significant leap toward personalized medicine in asthma treatment, fundamentally altering the approach to managing severe childhood asthma [26].

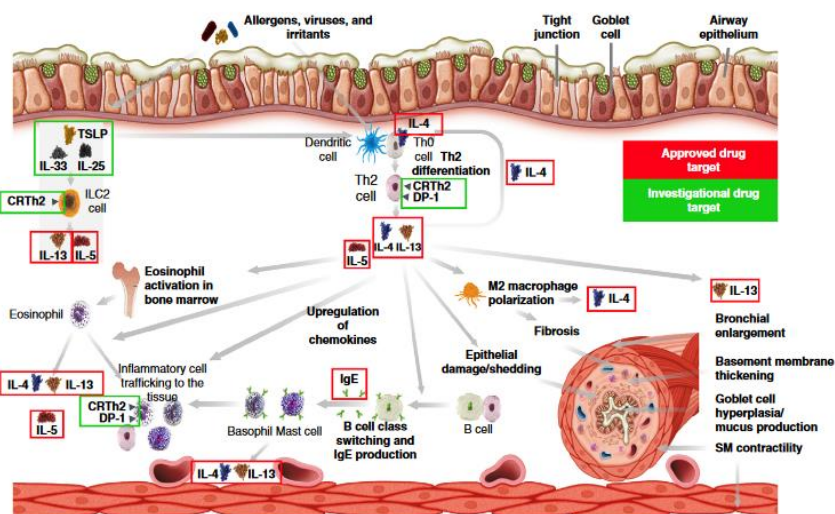


Figure 4. Schematic illustration of asthma immunopathobiology with targeted treatment sites for approved and investigational monoclonal antibodies highlighted [27]

Ligelizumab: a promising alternative to omalizumab

Ligelizumab, a humanized IgG1 monoclonal anti-IgE antibody, exhibits a high affinity (KD = 0.13 nM) for human IgE, blocking its interaction with the high-affinity IgE receptor (FcεRI) effectively. In trials involving patients with moderate allergic asthma, ligelizumab surpassed omalizumab in reducing reactions to cutaneous and inhalation allergen provocations. This double-blind, multi-center, randomized trial aimed to assess ligelizumab’s efficacy in severe asthma patients unresponsive to high-dose inhaled corticosteroids and long-acting β2-agonists. Preclinical studies have shown ligelizumab to

possess about 50 times higher affinity for human IgE than omalizumab, with clinical trials confirming its superior efficacy in reducing free IgE levels and skin prick reactions in atopic individuals. Notably, ligelizumab has demonstrated enhanced suppression of IgE binding to FcεRI and basophil activation over omalizumab, although it is less effective at inhibiting IgE:CD23 interactions. It also shows greater efficacy in reducing IgE production by B cells and preventing systemic anaphylaxis in vivo mouse models [33], [34].

Quilizumab: targeting IgE production

Quilizumab, a humanized monoclonal antibody, specifically targets the M1 prime segment of human membrane IgE. By focusing on this specific region, quilizumab effectively reduces the emergence of new IgE-producing plasma cells, leading to a notable decrease in circulating IgE levels. In clinical trials, quilizumab has been observed to lower both total and allergen-specific serum IgE, curbing new IgE production and attenuating early and late asthmatic responses post-allergen challenge. Although it showed a reduction in sputum eosinophil counts and blood IgE levels, its effects on lung function, patient-reported symptoms, or asthma exacerbations were not significant, with a modestly lower rate of asthma exacerbations observed in the quilizumab group[28], [35].

Allergen immunotherapy (AIT): a long-term approach

Allergen immunotherapy (AIT) represents a cornerstone in the management of allergic asthma, offering long-term cost-effectiveness and significant improvements in clinical outcomes and quality of life. Its mechanism includes modulating memory type allergen-specific T- and B-cell responses towards a regulatory phenotype, reducing type 2 responses, suppressing allergen-specific IgE while increasing IgG1 and IgG4 levels, decreasing mast cell and eosinophil presence in allergic tissues, and raising the activation threshold. AIT, administered either sublingually (SLIT) or subcutaneously (SCIT), builds immunological tolerance, protecting against symptomatic IgE-mediated allergic reactions to specific allergens [36], [37].

Systematic reviews and meta-analyses affirm AIT's therapeutic efficacy in treating allergic asthma, recommending its consideration as adjunctive therapy alongside inhaled corticosteroids for those with concurrent asthma and allergies. Both SLIT and SCIT have been validated by double-blind, placebo-controlled trials and meta-analyses as effective for patients suffering from allergic asthma triggered by dust mites and pollen, often associated with allergic rhinitis. AIT's general anti-inflammatory effect is evidenced by reduced exacerbations and lower required doses of inhaled glucocorticosteroids (ICS), along with a modest decrease in non-specific airway hyperresponsiveness and a more pronounced effect on allergen-specific airway hyperresponsiveness [36], [38].

III. CONCLUSION

IgE plays a crucial role in the pathophysiology, management, and prevention of acute asthma episodes in children. Its utilization in various therapeutic approaches is enhancing the quality of life for individuals with asthma, with omalizumab being a prime example of this trend. Currently, omalizumab's application is limited to children aged six years and older, with considerable restrictions on its use in younger populations. In the realm of severe asthma, a number of biologic therapies have received approval, and several others are in the pipeline. A key advancement in the fight against asthma, particularly in young patients exhibiting early symptoms, is the strategic combination of biological therapies with allergen immunotherapy. This integrated approach marks a significant milestone in both the

prevention and treatment of pediatric asthma, offering hope for more effective management and potentially long-term relief for affected children.

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