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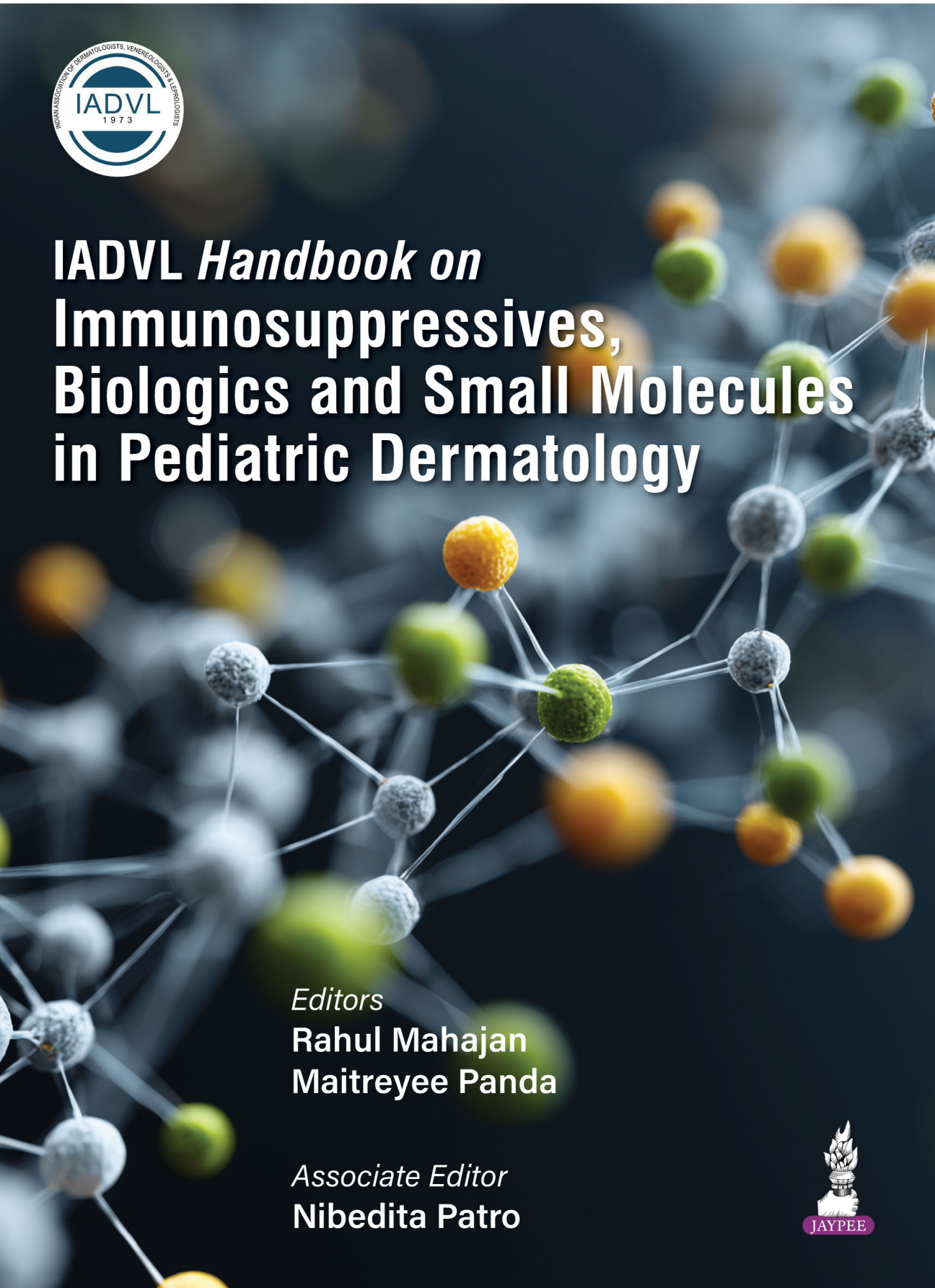

IADVL *Handbook on* Immunosuppressives, Biologics and Small Molecules in Pediatric Dermatology

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CHAPTER 14

Anti-immunoglobulin E Monoclonal Antibody (Omalizumab and Others)

Pratibha Gupta, Deepika Pandhi

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INTRODUCTION

Immunoglobulin E (IgE) is implicated in the pathogenesis of various dermatological disorders. It consists of two light and two heavy chains. The constant region, C-epsilon-3 of the heavy chain in IgE binds with both low- and high-affinity IgE receptors present on mast cells, basophils, and other cells, triggering an allergic cascade.[1] Multiple antibodies targeting IgE have been developed since the discovery of IgE including TES-C21, TESC-2, talizumab, omalizumab, quilizumab, MEDI4212, XmAb7195, 39D11 and 026sdab.[2] **Table 1** summarizes the status of various anti-IgE biologicals. Omalizumab is the sole approved antibody against IgE and will be discussed in detail in the present chapter. It is currently Food and Drug Administration (FDA)-approved for the treatment of chronic spontaneous urticaria and moderate-to-severe uncontrolled allergic asthma in children. However, it has been used as an off-label drug in other IgE-mediated dermatological diseases in the pediatric population and is effective and well tolerated.[3]

PHARMACOKINETICS

Omalizumab exhibits first-order absorption kinetics at low doses and linear kinetics with doses greater than 0.5 mg/kg. After a

TABLE 1: Biologics targeting immunoglobulin E (IgE).

Anti-IgE antibody name	*Composition*	*Clinical status*
TES-C21	First murine anti-human IgE monoclonal antibody	Not used
TESC-2/CGP51901	Chimeric murine/human monoclonal antibody	Not used
TNX-901 or Talizumab	Humanized anti-IgE monoclonal antibody	Not used
Omalizumab	Humanized anti-IgE monoclonal antibody	Food and Drug Administration (FDA)-approved for chronic spontaneous urticaria and allergic asthma
Ligelizumab	A variant of talizumab with higher affinity	Clinical trial phase III
Quilizumab	Afucosylated monoclonal antibody	Clinical trial phase II
MEDI4212	Afucosylated monoclonal anti-IgE antibody	Clinical trial phase I
XmAb7195	Humanized affinity enhanced version of omalizumab	Clinical trial phase I

single-dose subcutaneous administration of 75–600 mg of omalizumab, the peak serum concentration of omalizumab reaches in 6–8 days and the terminal half-life is around 17–23 days. The average bioavailability of subcutaneous omalizumab administration is 62%. Intrinsic factors such as age, body weight, body mass index, and race do not affect the pharmacokinetics.[4,5]

The apparent volume of distribution following subcutaneous administration of omalizumab was found to be 78 ± 32 mL/kg. The elimination of omalizumab consists of two parts. The free form of omalizumab is eliminated primarily by the liver using the reticuloendothelial system and a small amount is excreted through bile. However, the omalizumab-IgE complex is cleared through a much faster mechanism, that is endocytosis.[6]

MECHANISM OF ACTION

It is a humanized IgG1 κ monoclonal antibody against IgE, derived from recombinant DNA technology. Omalizumab specifically targets free IgE at the C-epsilon-3 domain present on its heavy chain; the domain at which IgE attaches to high-affinity FcεRI receptors on eosinophils, basophils, and mast cells. It leads to a decrease in free IgE levels preventing its interaction with the receptors and release of histamine and other allergy mediators. The maximum reduction in free IgE levels occurs 3 days after the subcutaneous injection. Repeated weekly doses lead to prolonged suppression of circulating free form of IgE.

Omalizumab induces downregulation of FcεRI receptors on mast cells and basophils as decreased circulating free IgE leads to nonbound states, instability, degradation, and endocytosis of these receptors. It is seen in basophils and mast cells after 1 and 10 weeks of starting treatment, respectively. Hence a greater amount of allergen is required for degranulation of mast cells. It also targets B cells expressing IgE and further inhibits the IgE production or inducing their apoptosis. It prevents the free IgE binding to CD23 receptors on B cells and other antigen-presenting cells. It also reduces expression of FcεRI on dendritic cells, resulting in decreased presentation of allergens to T cells, thereby attenuating the Th2-mediated immune pathway.[2,7]

INDICATIONS

- *FDA-approved*: Omalizumab is approved by FDA for chronic idiopathic urticaria (CIU) in patients aged 12 years and older who are not responding to H1 antihistamines.
- *Off-label*: Omalizumab is also being used in children with inducible urticaria, including solar urticaria and cold urticaria, atopic dermatitis, mastocytosis, bullous pemphigoid, hyper-IgE syndrome, and urticarial vasculitis.

PREPARATION/FORMULATION

Omalizumab is available in two dosage forms. It is supplied in a 6 mL vial as a sterile lyophilized powder, requiring reconstitution with sterile water. A single vial contains 202.5 mg of omalizumab and other nonactive ingredients including sucrose, L-histidine hydrochloride monohydrate, L-histidine, and polysorbate. A total of 1.2 mL of omalizumab is yielded upon reconstitution with 1.4 mL of sterile water. It is also available as a single-use 0.5 mL and 1 mL prefilled syringes delivering 75 mg and 150 mg omalizumab, respectively. It should be stored at 2–8°C.[4]

DOSING SCHEDULE

Dosage and dosing frequency of omalizumab for CIU are not dependent on total or free serum IgE levels or total body weight unlike in cases of asthma. It is administered as

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4-weekly subcutaneous injections in doses of 150 or 300 mg for patients >12 years of age. The dosage can be increased to 450 or 600 mg in case of inadequate response to treatment. The dose of omalizumab for children <12 years of age is not defined. However, a systematic review on treatment of chronic urticaria in patients under 12 years old with omalizumab showed that younger children generally require lower doses of the medication. The study showed that children under 12 years old may require a monthly dosage ranging from 150 to 300 mg while a lower dose of 75 or 150 mg is deemed adequate for those under 6 years of age.[8] Dosing in other dermatological diseases is variable. The standard asthma regimen has also been used in dermatological disorders as 150–375 mg every 2 or 4 weeks.[9]

Administration

Omalizumab is administered by subcutaneous route. The solution is slightly viscous, hence it takes 5–10 seconds to administer. Only up to 150 mg of amount should be administered per injection site. More than 150 mg dose should be divided among two or more injection sites. The reconstituted solution should be used within 8 hours if stored between 2° and 8°C or within 4 hours of reconstitution if kept at room temperature.[4]

USE IN SPECIFIC DERMATOSES

Chronic Idiopathic Urticaria

The primary treatment approach for CIU usually begins with antihistamines. Omalizumab should be added, if there is no satisfactory improvement after 2–4 weeks of treatment with fourfold the normal dose of H1 antihistamines used. However, it is FDA-approved for use in patients aged 12 years and older.

Two randomized controlled trials (RCTs) of 24 weeks' duration (n = 319) and 12 weeks' duration (n = 323), respectively, assessed the efficacy of omalizumab in patients of CIU (>12 years of age) refractory to antihistamines. Patients were given placebo or 4-weekly subcutaneous omalizumab in dosages of 75, 150, or 300 mg alongside anti-H1 antihistamines. In both studies, weekly assessment of itch severity score and hive frequency count showed greater decrease in patients who received 150 or 300 mg at 12 weeks; only 6% and 3% of patients were between 12 and 17 years of age.[10,11]

There have been few trials that also demonstrated the efficacy of omalizumab in children younger than 12 years. A study on 38 pediatric patients with chronic urticaria having urticaria severity scores of >16 despite the maximum dose of antihistamines showed good or complete response in 76.3% of patients who received omalizumab.[12] Another study on 19 pediatric patients aged 6–16.9 years with refractory chronic spontaneous urticaria showed significant improvement in 16 patients.[13]

Inducible Urticaria

- *Cold urticaria*: Data regarding the use of omalizumab in chronic urticaria in cases of children is limited. 13 children of age ranging from 4 to 16 years were recruited retrospectively who were given omalizumab due to reduced efficacy, nonresponse, or adverse effects with high doses of antihistamines and montelukast. These patients were given 75, 150, 300, and 450 mg omalizumab 4-weekly. Twelve patients showed clinical improvement.[14] Omalizumab has been successfully used in pediatric patients with cold urticaria in some case reports.[15-17] Omalizumab can be considered in cold urticaria, especially in refractory cases.
- *Solar urticaria*: Similar to cold urticaria, omalizumab can be considered in cases with no response to high doses of

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antihistamines and leukotriene receptor antagonists. Limited case reports are available corroborating the use of omalizumab in solar urticaria patients.[18,19]

Atopic Dermatitis

Omalizumab is found to be effective in the treatment of severe and refractory cases of atopic dermatitis in children in a few case series and case reports as shown in **Table 2**.[20-22]

However, there have been studies that have shown minimal or no improvement with omalizumab. A systematic review of 34 studies including a total of 214 patients reported that 21% of patients had no improvement on omalizumab.[23] Another systematic review of 13 studies showed that fewer than half of all included patients exhibited significant clinical improvement. The patients carrying a filaggrin mutation did not respond to omalizumab suggesting that individuals with compromised skin barrier are unlikely to benefit from anti-IgE treatment. The conflicting results may be attributed to the complex pathogenesis of atopic dermatitis including immune dysregulation other than the role of IgE. Also, most of the nonresponders had high IgE levels of >700 IU/mL suggesting the use of higher dosage for better IgE neutralization in such patients.[24]

Bullous Pemphigoid

Immunoglobulin E autoantibodies are implicated in the pathogenesis of early stages and atypical presentations of bullous pemphigoid such as severe erythematous and urticarial forms supporting the role of anti-IgE antibodies in their treatment. A systematic review was done by D'Aguanno et al.[25] to evaluate the effectiveness of omalizumab in patients with refractory bullous pemphigoid. The review included 22 articles, involving a cumulative total of 56 patients; 87.5% of patients responded to omalizumab, 7.1% discontinued the treatment and 5.4% of patients did not respond to omalizumab. Most patients managed to either stop or reduce systemic steroid intake to <10 mg daily. However, the percentage of pediatric patients included in the study was not mentioned.

A 5-month-old male infant with severe bullous pemphigoid not responding to oral prednisolone, methylprednisolone pulse,

TABLE 2: Studies showing effectiveness of omalizumab in patients of atopic dermatitis.

Study	*Age-group*	*Disease severity*	*Omalizumab dosage*	*Treatment outcome*
Alzyoud et al.[20]	6-year-old male	Severe atopic dermatitis, nonresponsive to cyclosporine or prednisolone	300 mg omalizumab subcutaneous injection twice weekly	Decrease in SCORAD index from 70 to 57 at 12 weeks and to 55 at 18 weeks
Lacombe Barrios et al.[21]	7 patients (6–19 years age)	Severe atopic dermatitis nonresponsive to cyclosporine, IVIG, azathioprine, and MMF	225–375 mg omalizumab subcutaneous injection twice weekly	Decrease in SCORAD index from 69 to 27 at 36 months of treatment
ADAPT, placebo-controlled randomized controlled trial[22]	62 patients (aged 4–19 years)	Severe atopic dermatitis nonresponsive to systemic immunosuppressants or steroids	Dose on the basis of IgE levels and body weight of patient	Significant difference in mean improvement in SCORAD index and quality of life after 24 weeks of treatment

(IVIG: intravenous immunoglobulin; MMF: mycophenolate mofetil; SCORAD: SCORing Atopic Dermatitis)

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and dapsone with elevated total serum IgE levels and peripheral eosinophilia was given omalizumab. The child responded dramatically with a decrease in blisters and urticarial lesions and no clinical relapse in the 7-month follow-up period.[26]

Mastocytosis

Omalizumab has demonstrated efficacy in managing indolent and refractory cases of systemic mastocytosis not responding to conventional treatment in various case reports.[27] It acts as a steroid-sparing agent and has a quick onset of action and greater effectiveness in controlling severe mast cell-related symptoms. It has also been successfully used in cutaneous mastocytosis and idiopathic mast cell activation syndrome.[28-30]

Hyper-immunoglobulin E Syndrome

Omalizumab has been found to decrease eczematous lesions, pruritus, and respiratory and ocular symptoms seen in hyper-IgE syndrome. However, the dose and duration of omalizumab given in various case reports were variable from 300 mg every 2 weeks or 4 weeks to 450 mg every 2 weeks given for 1 month to 4 years.[31-33] Omalizumab can be considered in cases with elevated serum IgE levels, inadequate control of cutaneous and respiratory symptoms, and long-term corticosteroid usage. There are limited case reports documenting effective use of omalizumab in children with hyper-IgE syndrome. A 7-year-old female child of hyper-IgE syndrome with minimal response in eczematous lesions to oral steroids and cyclosporine was successfully treated with omalizumab 150 mg subcutaneously every 2 weeks till 4 doses followed by monthly injection.[34] Similarly, an 11-year-old male who was given omalizumab in 300 mg dose subcutaneously showed marked improvement in eczematous lesions in 2 months.[35]

Urticarial Vasculitis

Omalizumab may be an alternative option for the treatment of urticarial vasculitis in children nonresponsive to first-line therapies. Managing urticarial vasculitis in children poses challenges due to potential side effects associated with long-term systemic corticosteroids and immunosuppressive agents. A case series involving four children, aged 4–6 years old, with glucocorticoids refractory urticarial vasculitis were successfully treated with omalizumab.[36]

PRETREATMENT EVALUATION

A comprehensive diagnosis and assessment of the condition is essential before starting the patient on omalizumab. Proper evaluation of concomitant drug intake and coexisting medical conditions is required. Baseline serum IgE levels could be performed to predict the clinical response; however, no such correlation has been seen in the studies.

MONITORING GUIDELINES

The patients should be closely observed for signs of anaphylaxis for an appropriate duration following omalizumab administration. Resuscitation equipment should be ready while giving omalizumab. The patient should receive comprehensive information regarding the signs and symptoms of anaphylaxis.

Serum IgE levels are not used for monitoring the effect of omalizumab or the decision for administration of the drug, as serum IgE levels continue to remain elevated during the treatment or even after discontinuation of omalizumab.

ADVERSE EFFECTS

A meta-analysis of RCT in the treatment of CIU was done and the common adverse effects shown were pain at the injection site,

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headache, upper respiratory tract infection, sinusitis, and pharyngitis.[37]

Information regarding the safety of omalizumab in children is limited. The majority of studies have focused on children with allergic asthma. A meta-analysis was conducted on three RCTs (n = 1381) examining the efficacy of omalizumab in patients <18 years of age with allergic asthma showed a similar frequency of adverse events in the omalizumab group (76.3%) and placebo (74.2%). There was no increased risk of anaphylaxis, hypersensitivity reaction, or malignancies in the omalizumab group. The most frequent side effects were nasopharyngitis, sinusitis, and upper respiratory tract infection.[38]

Research on the safety of omalizumab for treating chronic urticaria in children is restricted to a small number of case reports. A recent study done on children showed that the most common side effect was headache (41.7%) followed by fatigue (16.8%), flu-like symptoms (8.3%), injection site reaction (8.3%), joint pains (8.3%), and alopecia (8.3%).[12] There are rare reports of other side effects seen in post-marketing observations. A list of adverse effects that have been reported with omalizumab is listed below:

Malignancies: *A higher occurrence of malignancy was observed in omalizumab group (0.5%) compared to control group* (0.2%) in phase 1 and 2 clinical trials; however, the malignancies were variable including breast, prostate, parotid, melanoma and non-melanoma skin cancer and there was relatively shorter duration of exposure to omalizumab.[39] Malignancy risk was seen for elderly patients, those with longer exposure to omalizumab, and recurrence of malignancy in patients with a history of malignancy or premalignant condition. No cases of malignancy are reported in children of age 6–12 years.

Anaphylaxis: Omalizumab has a black-boxed warning regarding the risk of anaphylaxis. It can manifest as early as following the initial dose of omalizumab but has been reported even after 1 year of regularly administered treatment. The frequency of anaphylaxis and anaphylactoid reaction was found to be 0.2% with most reactions occurring within the first 2 hours of omalizumab administration in post-marketing clinical trials.[40]

Parasitic infection: In a clinical trial conducted in Brazil, an increased incidence of helminthic infection including roundworm, whipworm, threadworm, and hookworm was seen in the omalizumab group (53%) compared to the placebo (42%). However, the severity of infection and response to antihelminthic treatment were similar in both groups.[41]

Infections: Infections include nasopharyngitis, sinusitis, and upper respiratory tract infection.

Hematopoietic system: Idiopathic severe thrombocytopenia

Musculoskeletal system: Arthralgia, myalgia, and skin rash resembling serum-sickness-like reaction can be seen after omalizumab administration.

Respiratory system: Rarely Churg–Strauss syndrome can be seen in asthma patients treated with omalizumab.

Injection site reaction: Higher injection site reactions including redness, pain, swelling, bruising, and urticaria are seen in the omalizumab group (2.7%) compared to control (0.8%).

Cutaneous: Alopecia.

CONTRAINDICATIONS

Omalizumab should not be used in individuals with hypersensitivity to omalizumab itself or any of its nonactive ingredients.

DRUG INTERACTIONS

Clearance of omalizumab does not involve cytochrome P450 enzymes or protein

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binding thus, the drug–drug interactions are not expected with the commonly prescribed medications in the treatment of CIU. However, there is no available data on the concurrent use of omalizumab and immunosuppressive therapies.

SPECIAL SITUATIONS

- *Pregnancy*: A study was conducted in the United States (EXPECT) on 250 pregnant women who were treated with omalizumab which was compared with a matched group of 1,153 pregnant women who had no exposure to omalizumab. There was no significant difference in the prevalence of major congenital anomalies between the omalizumab (8.1%) and control group (8.9%). However, increased cases of low birth weight were noted in the omalizumab group than in the control group.[42] Studies in cynomolgus monkeys did not show any teratogenicity or fetal growth retardation. A risk–benefit analysis should be done before starting the omalizumab in a pregnant patient.
- *Breastfeeding*: Evidence from studies indicates that the concentration of omalizumab in breast milk is minimal. Furthermore, it is likely that it is broken down in the infant's digestive system, resulting in minimal absorption. Omalizumab is considered safe to use in breastfeeding.
- *Patients with hepatic and renal impairment*: Patients with renal or hepatic dysfunction do not need any dose adjustment for omalizumab.

OTHER ANTI-IMMUNOGLOBULIN E MONOCLONAL ANTIBODIES

- *Monoclonal anti-IgE antibody/ligelizumab*: Ligelizumab targets a unique IgE epitope that partially overlaps with omalizumab's epitope. It exhibits significantly greater affinity (~50 times higher) for IgE as compared to omalizumab and demonstrates superior inhibition of IgE interaction with FcεRI. However, it is less efficient in blocking the IgE and CD23 interaction.

  Several clinical trials are underway to evaluate the efficacy of ligelizumab alone or in comparison to omalizumab in cases of CIU given at a dose of 240 mg every 4 weeks. A randomized controlled phase II clinical trial showed higher efficacy and long-lasting effect of ocrelizumab over omalizumab in the treatment of CIU.[43] Ligelizumab could be a potential alternative in the treatment of refractory cases of CIU, even in those cases who are nonresponsive to omalizumab. Ligelizumab has also been found to control refractory severe solar urticaria.[44]
- *Quilizumab*: It is an afucosylated, humanized monoclonal anti-IgE. Removal of the fucose group increases the affinity of binding of the drug to FcγRIIIa and increases the elimination of mIgE-positive B cells. However, quilizumab has been found to only partially decrease the serum IgE levels in chronic spontaneous urticaria patients and clinical outcomes were not satisfactory.[45]

FUTURE PERSPECTIVES

Continued monitoring and long-term studies are necessary to assess any potential rare or long-term side effects. Additionally, exploring the use of omalizumab in other dermatological conditions and identifying predictive biomarkers for the treatment response are areas of ongoing research. Various next-generation anti-IgE variants are in development which shows higher specificity as compared to previous anti-IgE antibodies. These include anti-IgE-designed ankyrin repeat proteins, IgG-Fc fusion proteins (GE2 and DE53-Fc), and anti-IgE nanobodies (39D11 and 026 sdAb). There are various biosimilars in development including CMAB007, STI-004, FB317, GBR 310, CTP-39, and BP001.

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CONCLUSION

Omalizumab has emerged as a valuable therapeutic option for patients with various dermatological disorders including CIU, solar urticaria, cold urticaria, bullous pemphigoid, atopic dermatitis, mastocytosis, hyper-IgE syndrome, and urticarial vasculitis and found to have promising efficacy. The safety profile of omalizumab has been favorable. Hence the targeted mechanism of action, proven efficacy, and lesser side effects make it a valuable addition to the treatment armamentarium in allergic disorders.

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