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Adverse Reactions to Biologic Medications Used in Allergy and Immunology Diseases

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Abstract

Purpose of Review The use of biologic therapies has risen exponentially over recent years, allowing for unprecedented disease control within numerous areas of Allergy/Immunology. With this expanded use, awareness and understanding of adverse reactions to biologic agents have also increased.

Recent Findings Multiple biologic adverse reaction phenotypes have been described, but significant overlap in clinical features across phenotypes exists. Given considerable phenotypic overlap, a targeted testing approach may not always be clear, and more recent classifications focus on management decision making using tools of diagnostic challenges and rapid drug desensitizations, guiding clinicians in developing a management plan when the exact underlying mechanism is not clearly known. With increased clinical experience with omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab, rituximab, and TNF-inhibitors, there is a growing appreciation to the spectrum and particularities of adverse reactions to these agents which are outlined in this review.

Summary Our understanding of the clinical presentation and management of adverse reactions to biologic medications encountered in Allergy/Immunology has grown. Opportunities remain to further define optimal diagnostic and management strategies for these reactions.

Keywords Adverse reaction · Biologic · Hypersensitivity · Desensitization · Rituximab · Omalizumab

Introduction

Since the first monoclonal antibody was approved by the FDA in 1986, the availability and use of biologic therapies have increased exponentially. In the field of allergy and immunology, these agents are now commonly used to help achieve unprecedented disease control and reduce exposure to systemic corticosteroids. As biologic use has expanded, so has awareness and understanding of adverse reactions related to these medications. This review will cover the types and classification of adverse biologic reactions, diagnostic strategies, and management. We will focus on monoclonal antibodies and fusion receptor proteins commonly used in allergy and immunology as well as reactions to monoclonals commonly referred to allergy/immunology specialists.

Classification Systems of Adverse Reactions to Biologics

Biologics are typically large complex molecules such as proteins or polypeptides that are derived from mammalian cells or microorganisms. There are several distinguishing features of biologics that differ in comparison to most drugs [1]. Most drugs are small molecules, with molecular weights less than 1 kilodaltons that are chemically synthesized and are well-characterized. In contrast, biologics are typically much larger and can include more complex tertiary polypeptide structures. After administration to patients, biologics are processed like other proteins, as opposed to drugs which are subject to various metabolic processes. In addition, fusion receptor proteins and monoclonal antibodies have immune-mediated effects inherent to their function and intended activity, as opposed to most drugs which do not function

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through an expected immune-mediated response [1, 2]. These differences have implications for the classification of adverse reactions to these agents. Traditionally, adverse drug reactions have been categorized based on dose, timing, and pharmacologic action of the drug, as in the type A through E classification system [3]. However, with the differences between most drugs and biologic agents, alternate classification systems have been proposed to emphasize underlying pathomechanisms of immune target-related reactions. Pichler proposed one such classification which includes 5 different types of reaction: α, β, γ, δ, and ε reactions [2, 4]. Type α reactions are overstimulation reactions caused by excess degree of the biologic agent's predicted pharmacologic activity, where manifestations can range from relatively mild flu-like symptoms with IFN-α to severe cytokine release syndrome as seen with the catastrophic phase 1 trial to TGN1412, an anti-CD28 antibody [5]. Type β reactions are hypersensitivity reactions. Type γ reactions are related to "immunodeviation" or secondary immunodeficiency arising from the biologic agent's action in disrupting normal immune homeostasis leading to infectious or immunodysregulatory consequences, as with the observed increase in tuberculosis infections with anti-TNF agents or autoimmune disorders associated with IFN-γ. Type δ reactions are due to cross-reactivity, where unintended "off-target" effects can arise when the targeted antigen is expressed on numerous tissues or a non-identical but structurally similar antigen binds with less affinity to the biologic agent. A classic type δ reaction is with cetuximab which targets epidermal growth factor receptor and can lead to acneiform reactions. Type ε reactions are non-immunologic reactions, neither arising from the intended biologic agent immune targeted effects nor the host immune response to the biologic agent, for example as in depression associated with IFN-α therapy. In addition, for type β hypersensitivity reactions, the Gell-Coombs classification remains useful in further describing underlying mechanisms of these reactions [6].

Briefly sketching the contours of clinical phenotypes of adverse reactions to biologic agents is a useful exercise to both frame further discussion on specific biologic agents used in allergy and immunology practice as well as to highlight overlapping clinical features across different adverse reaction mechanisms. Overall, adverse reactions to biologic agents are common, for example affecting up to 77% for patients starting rituximab [6, 7]. Common reactions include acute infusion reactions which are marked by fevers, rigors, nausea, vomiting, diarrhea, dyspnea, back pain, abdominal pain, dyspnea, flushing, pruritus, or changes in blood pressure or heart rate that occur during drug administration. While there is significant overlap in symptoms between acute infusion reactions and IgE-mediated reactions, infusion reactions are more common, occur predictably, often with initial doses, and improve with premedication and reducing the infusion rate [4, 5]. The mechanism of these reactions is not entirely clear. Acute infusion reactions to infliximab have been associated with pre-existing anti-infliximab antibodies, and infliximab-anti-infliximab antibody complex formation has been demonstrated which may activate complement [8]. Complement activation has also been demonstrated with rituximab, but notably obinutuzumab, another anti-CD20 monoclonal antibody with less complement activation compared to rituximab, had a higher frequency of infusion reactions suggesting complement activation may not necessarily be the most predominant driver of these reactions [9]. Most of these reactions appear to be non-immunologic in nature as reactions improve with further administration and with reducing the infusion rate. IgE-mediated reactions to biologics are well-documented and while specific incidence rates vary between specific biologics, these overall occur less frequently compared to presumed non-IgE acute infusion reactions [6, 7]. In comparison to acute infusion reactions, IgE-mediated reactions may include more urticaria, wheezing, or anaphylactic symptoms, although these are certainly not specific. These often occur with subsequent doses after initial tolerance but can present with first exposure as with cetuximab and omalizumab. Furthermore, non-IgE anti-drug antibodies may be a contributing mechanism to both immediate and delayed reactions [10, 11].

Another common adverse reaction for biologics is injection site reactions, the prevalence which varies between specific biologics. These are marked by erythema, edema, and infiltrated plaques at the injection site, occurring typically 24–48 h, but sometimes immediately, after injection. These can include the mechanisms of a and b reactions, as reviewed by Thomaidou and Ramot [12]. Local reactions at the site of previous injections, or recall reactions, have also been reported, most commonly to etanercept [13, 14]. These recall reactions can manifest as edematous papular plaques which arise at the site of previous drug administration, with lesional skin biopsies demonstrating superficial perivascular T cell lymphocytic infiltrates. These tend to improve with topical steroids, and do not necessarily recur with further administration [15, 16]. Recall urticaria, or urticaria occurring at site of previous injections, in the setting of intradermal testing for adalimumab reaction has also been reported [17].

Cytokine release reactions (type α) appear to be less common, accounting for 13% of reactions in one large cohort [7]. These are marked by headache, back pain, dizziness, fever, chills, oxygen desaturations, and hypotension; and typically do not improve with premedication or slowing the infusion rate [10]. These are mediated by targeted cell lysis through FcγR-mediated and complement-mediated activation of effector cells with subsequent elevation in serum levels of TNF-α, IFN-α, and IL-6 [10, 18].

Delayed reactions have also been reported with biologics, including more common reactions such as mild delayed maculopapular eruptions and serum sickness-like reactions (SSLRs). Of the biologic agents discussed in this review, SSLRs have been most frequently reported with rituximab and infliximab, but have also been reported to dupilumab and omalizumab [19–24]. Severe cutaneous adverse reactions such as Stevens-Johnson Syndrome/toxic epidermal necrolysis have been reported but are significantly more rare [25, 26].

As previously noted, there is a significant overlap of clinical features across adverse reaction phenotypes. Taking this into account, Isabwe et al. have proposed a classification system based on phenotypes, endotypes, and biomarkers. They identify 5 main categories of adverse reactions to biologics: cytokine release reactions, infusion-related reactions, type 1 reactions marked by mast cell or basophil degranulation through either IgE or non-IgE-mediated mechanisms, mixed reactions combining features of IgE-mediated and cytokine release reactions, and delayed reactions such as Gell-Coombs type III and type IV reactions [7]. While there is still a degree of imprecision with regards to clearly defining the boundary markers between one subtype compared to another, this classification system has a specific focus on management decision making, guiding clinicians in developing a management plan when the exact underlying mechanism is not clearly known [18].

In summary, while no classification system completely describes every aspect of adverse reactions, it is important for clinicians to be aware of the inherent immune-mediated targeted effects of biologic agents and the impact this has on adverse reactions to these agents in contradistinction to typical non-immune mediated effects of traditional drugs, see Table 1.

Diagnostic Strategies

Diagnostic strategies must be guided first by thorough clinical history. As reviewed earlier, particular clinical features can suggest a phenotype for which targeted testing may be of use. However, given the considerable overlap in symptoms across different phenotypes, a targeted testing approach may not always be clear, and diagnostic protocols have not yet been standardized. This review will consider the following skin testing, in vitro studies, and drug challenges.

Table 1 Adverse reactions to biologics: phenotypes

Phenotype	Mechanisms	Clinical Features	Examples
Acute Infusion reactions	Type α Likely non-immunologic although mechanism not fully elucidated	Fevers, rigors, nausea, vomiting, dyspnea, back pain, abdominal pain, flushing that occur during drug administration Occur predictably, most often with initial doses Improve with reducing infusion rate and premedication	Rituximab-related infusion reactions
IgE-mediated reactions	Type β; Gell-Coombs Type I hypersensitivity	Significant overlap with acute infusion reactions, may have more prominent wheezing, urticaria, or constellation of symptoms marking anaphylaxis. Do not improve with premedication	Cetuximab-related anaphylaxis
Injection site reactions (ISR)	Type α and β	Local cutaneous reactions at injection site	Omalizumab-related injection site reactions
Cytokine release reactions	Type α. FcγR-mediated and complement-mediated activation of effector cells leading to increased TNF-α, IFN-α, and IL-6	Fever, rigor, headaches, back pain, dyspnea, hypotension. May overlap symptomatically with acute infusion reactions, but does not improve with premedication or slowing infusion rate	Muromunab-related cytokine release syndrome
Delayed reactions	Gell-Coombs Type III, IV hypersensitivity	Common: maculopapular exanthems, serum sickness-like reactions (SSLR) Rare: Stevens Johnson Syndrome, toxic epidermal necrolysis	Infliximab-related serum sickness-like reactions

Type α: overstimulation reactions caused by excessive predicted pharmacologic action; Type β: immunologic hypersensitivity reactions
Tumor necrosis factor, TNF; Interferon alpha, IFN-α

Skin Testing

Skin testing has been used to evaluate both immediate and delayed reactions to biologics. In a retrospective cohort of 104 patients with adverse reactions to biologics, skin prick and intradermal testing were performed in 58 patients regardless of presenting phenotype. Most patients in this study were receiving biologics for immunosuppressive or oncologic indications. Overall skin testing was positive in 41%. There were some differences in skin testing positivity rate, with 44% of patients who were classified as a type 1 hypersensitivity reaction (mast cell/basophil degranulation) exhibiting positive skin tests compared to 11% of patients with cytokine release reactions, which is consistent with the supposed endotype [7]. Sala-Cunill et al. reported a retrospective cohort of 28 patients with biologic reactions who underwent skin testing regardless of phenotype; only 12% demonstrated positive skin testing [27]. However, while the inciting biologic agents were similar across these two studies, comparisons are limited as the initial clinical symptoms were not classified in the same way making it difficult to ascertain if the Sala-Cunill cohort was enriched for a different index reaction profile. While more studies are needed to further characterize the performance of skin testing for different biologic agents, it is likely that the pre-test probability of skin testing is significantly impacted by the initial phenotype/endotype as demonstrated in other areas of allergy diagnostic testing.

Furthermore, standardized non-irritating concentrations need to be established for different biologic agents, a critical step to the correct interpretation of immediate skin testing. Multicenter studies validating non-irritating concentrations are lacking for most biologic agents. Numerous smaller reports of non-irritating concentrations for several biologics have been reported [18, 28, 29]. Non-irritating concentrations have not been established for dupilumab, mepolizumab, reslizumab, benralizumab, and tezepelumab. When performed, it is recommended that skin testing should occur at least 4–6 weeks after the reaction to reduce the theoretical concern of false-negative results [6, 18]. While the exact diagnostic properties of skin testing have not yet been elucidated, positive skin testing is broadly considered an indication for drug desensitization if there is no acceptable alternative agent available [7, 18]. Skin testing for delayed reactions has been reported less frequently; in one case report of fixed drug eruption to adalimumab, positive intralesional patch testing has been reported [30].

In addition to the lack of prospective studies showing the predictive value of either positive or negative skin tests to biologics, there are many logistic hurdles for use in clinical practice. Biologic agents are very expensive, and it can be extremely difficult to obtain material for skin testing. In non-academic settings, availability of biologic agents for skin testing becomes even more impractical. For these reasons, the most recent update to the Drug Allergy Practice Parameter suggests that skin testing for monoclonal antibodies is rarely clinically indicated [31].

In Vitro Tests

For cytokine release reactions, elevated serum levels of TNF-α, IFN-α, and IL-6 have been described with immediate rituximab reactions during infusion. Elevations of IL-6 have also been reported during desensitizations for cytokine release reactions; in a report of 8 patients with clinical features of cytokine-release, all 8 had elevated levels of IL-6 [7]. IL-6 has been suggested as a biomarker for cytokine-release reactions, although the specific diagnostic and prognostic properties of this measure require further study [10]. A study of 85 patients with acute allergic reactions (most attributed to food) in an emergency department setting found elevated IL-6 levels which were related to a greater erythema extent, lower mean arterial blood pressure, and a longer duration of symptoms [32]. IL-6 levels correlated with c-reactive protein levels with a trend toward correlating with serum tryptase. Patients with IL-6 levels ≥ 20 pg/mL had higher tryptase levels than other patients. This study would suggest that IL-6 levels may indeed be elevated in IgE-mediated reactions and thus may not be a discriminatory biomarker.

For reactions possibly related with Gell-Coombs type 1 hypersensitivity, an elevation of serum tryptase may be observed. However, in a retrospective review of 45 patients who had serum tryptase level drawn, including 9 who had sample drawn during desensitization reaction, only one patient had a significant elevation defined as 1.2 times baseline + 2 ng/mL [7]. Thus, while specific for mast cell activation, tryptase may lack sensitivity for other mast cell-mediated reactions.

Specific anti-drug antibody detection using ELISA has also been reported [11, 18]. The performance of anti-drug specific IgE assays likely depends on the biologic. The sensitivity and specificity of ImmunoCAP assays to cetuximab has been reported to be 68–92% and 90–92% respectively, whereas for infliximab, 26% and 90% respectively[33, 34]. Commercially available anti-drug specific IgE assays are not currently available. Non-isotype specific anti-drug antibody assays for some biologics such as infliximab are available, but the clinical utility of these for the diagnosis of adverse reactions is not well-established. However, meta-analyses have shown an increased risk of acute infusion reactions with antibodies to infliximab [35, 36]. With regard to other specific IgE-testing, anti-Galactose-α-1,3-galactose (alpha-gal) IgE testing may be helpful in predicting the risk of immediate reaction with first administration of cetuximab, demonstrating a pooled sensitivity of 73% (95% CI 62–81%)

and specificity of 88% (95% CI 79–94%) in a recent meta-analysis [18, 37, 38]. The alpha-gal epitope has also been demonstrated on abatacept and infliximab; reactions to abatacept and infliximab have been reported in patients with alpha-gal syndrome, although evidence is limited to whether these were directly due to alpha-gal. Alpha gal expression has not been demonstrated for most other monoclonal antibodies, but a theoretical risk may exist given many monoclonal antibodies are produced in mammalian cell lines [39].

Basophil activation testing has been reported for rituximab, but its clinical use is unclear with larger studies needed to validate initial findings [40].

Drug Challenge Testing

Drug challenge testing (DC) for biologic adverse reactions has been used as diagnostic tool. In a prospective cohort of 95 patients with adverse reactions to biologics, most commonly to rituximab, infliximab, and cetuximab, seventy-nine patients had negative specific IgE or skin testing [41••]. Of these, sixty-four met criteria for low/medium risk which was defined as the onset of generalized urticaria or angioedema > 15 min after the start of infusion, pruritus, dyspnea with preserved oxygen saturations, throat tightness, irritative cough, nausea, abdominal pain, severe back pain, or fever. Low/medium risk patients were offered a diagnostic drug challenge with the full dose administered at standard infusion rates. Of the sixty patients who completed the challenge, forty-seven patients had no reactions during the challenge procedure and were able to proceed with regular infusions. Thirteen patients reacted during the challenge with the following severity grading: 38% Brown Grade 1, Brown Grade 2 54%, Grade 3 8%; the authors did not comment on treatments needed for these reactions [41••]. In a smaller study from the same group of 13 patients who underwent DC, four had a positive challenge with one reaction considered severe, characterized by urticaria, dyspnea with oxygen saturations less than 92%, throat tightness, abdominal pain, and vomiting which resolved within 30 min with intramuscular epinephrine [42]. Using similar low/medium risk criteria to determine eligibility for DC as Madrigal-Burgaleta et al., another Spanish center performed DC with biologics in 14 patients with no reactions observed [43]. As such, DC can be a useful tool for the accurate diagnosis of biologic hypersensitivity, but the risks of a potential severe reactions must be weighed before proceeding. Clinical pathways based on European experience suggesting clinical situations to consider DC have been proposed [44••]. Further study is needed to determine the specific patient populations for whom the safety and efficacy of DC as a diagnostic tool are balanced as well as the role of graded challenges compared to single dose challenges.

General Management Principles

The proposed classification system from Isabwe et al. which include infusion-related reactions, cytokine-release reactions, type 1 reactions, mixed reactions, and delayed reactions, can guide the management approach.

Acute infusion-related reactions are typically managed with premedication with corticosteroids, analgesics, antihistamines, and slower infusion rates [18, 29]. Cytokine-release reactions generally do not improve as significantly with premedication or decreasing infusion rates [45].

Rapid drug desensitization (RDD) protocols have been used to manage a wide spectrum of reactions and traditionally have been used for immediate reactions suggestive of an IgE-mediated reaction. While there are reports of successful RDD to other types of reactions including cytokine release reactions, mixed reactions, and delayed reactions, the true efficacy and mechanistic plausibility of this approach is unclear. Given that many patients with prior reactions to biologics can tolerate drug challenge, the true efficacy of these RDD protocols for non-IgE-mediated reactions requires further study. Contraindications for RDD include a history of severe cutaneous adverse reaction to the biologic in question which is rare. In a retrospective study from a single center of 526 desensitizations to intravenous and subcutaneous biologics in adults, the majority underwent a 3-bag RDD protocol, and the most common biologics included were rituximab, infliximab, tocilizumab, brentuximab, and trastuzumab. The severity of the index reaction was Brown Grade 2 in 48% and Brown Grade 3 in 29%. Seventy-seven percent completed the RDD procedure without reaction [7]. Of the 122 patients who had a reaction during RDD, 64% of reactions were Brown Grade 1, 34% Grade 2, and 2% Grade 3. Reactions during desensitization were generally less severe in terms of reaction grading compared to initial reaction. Despite reactions during desensitization, with premedication, intravenous fluids, and infusion rate adjustments, 99.4% were able to successfully complete desensitization with the majority using a 3 bag-12 step protocol [7].

Other protocols using single bag methods have been evaluated. In a recent study assessing the safety and efficacy of a 1-bag, 11 step protocol in 23 adult patients with reactions to similar profile of biologics as the cohort reported by Isabwe et al., 70% and 19% had index reactions of Brown Grade 2 and Grade 3, respectively. Fifty-seven percent tolerated with no reaction [27]. The majority of reactions that occurred during desensitization were mild, accounting for 60% of reactions. One patient required epinephrine and was managed as an outpatient with quick resolution of symptoms during rituximab desensitization. They also compared their 1-bag protocol to their experience with a 3-bag protocol and found

Table 2 Example 1-bag rapid drug desensitization protocol

Step	Rate (mL/h)	Time (min)	Dose administered per step (mg)	Cumulative dose (mg)
1	0.5	15	0.5	0.5
2	1	15	1	1.5
3	2	15	2	3.5
4	5	15	5	8.5
5	10	15	10	18.5
6	20	15	20	38.5
7	40	15	40	78.5
8	80	172.8	921.5	1000

Rituximab desensitization 1000 mg in 250 mL (final concentration 4 mg/mL). Total time: 4 h 38 min

comparable rates of reactions and successful completion of desensitization. The 1-bag protocol was on average 45 min shorter compared to 3-bag protocol for rituximab [27]. Further studies from more centers are required to determine which approach is optimal and whether risk stratification is needed prior to consideration of a 1-bag protocol. Examples of a 1-bag and 3-bag protocol for rituximab are included in Table 2 and Table 3 respectively. Taken together, RDD has been used to manage a wide range of biologic adverse reactions. Further study is needed to further define the optimal approach for managing specific phenotype/endotype across biologic agents. An algorithmic approach to managing different phenotypic reactions is outlined in Fig. 1.

Review of Adverse Drug Reactions to Specific Agents

Biologics Used in Allergic Disease

Omalizumab

Omalizumab, the first biologic approved specifically for an allergic disease, now holds approval for moderate to severe asthma, chronic spontaneous urticaria, and most recently nasal polyposis. Omalizumab is a humanized monoclonal antibody that binds IgE forming biologically inert complexes. This prevents IgE from binding and activating the FceR1 receptor on mast cells and basophils, leading to

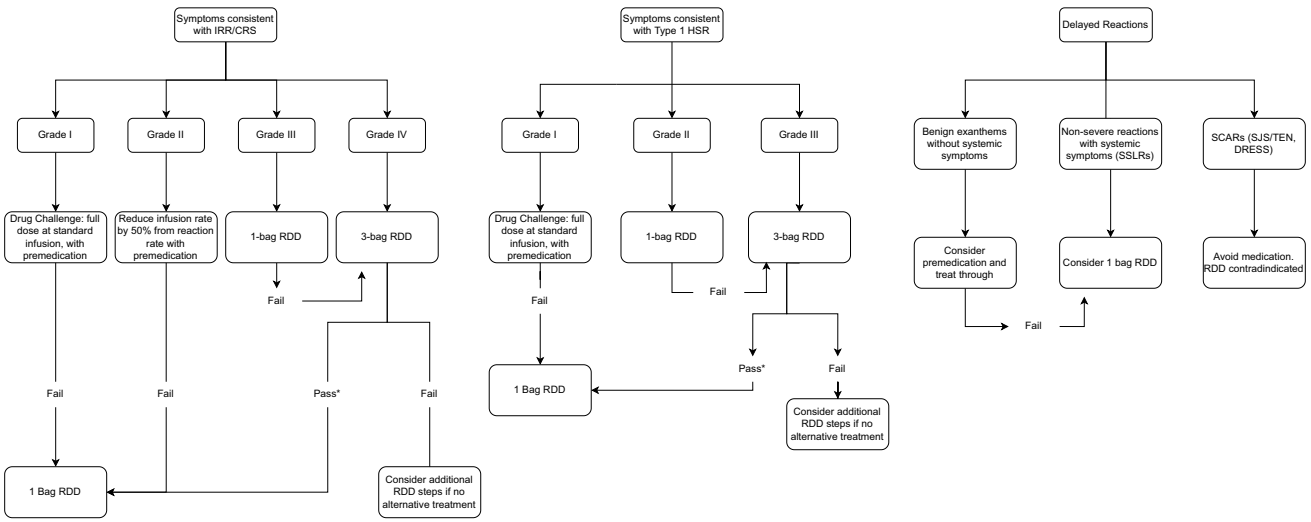

Fig. 1 A Proposed Algorithm to Approach Adverse Reactions to Biologics Treatment Algorithm For IRR and CRS reactions, reaction severity grade determined by the National Cancer Institute Common Terminology Criteria (NCI CTCAE) for infusion related reactions grading system. NCI CTCA grade I mild transient reactions not requiring infusion interruption; grade II reaction requiring infusion interruption but responds promptly to symptomatic treatment (antihistamines, NSAIDs, IV fluids); grade III: prolonged reaction not rapidly responsive to symptomatic medication or recurrence of symptoms following initial improvement, hospitalization required; grade IV life threating consequences. For Type 1 hypersensitivity reactions, reaction severity grade determined by the Brown grade system. Brown Grade I (mild) reaction: limited to skin and subcutaneous tissue only (generalized erythema, urticaria, periorbital edema, angioedema); grade II (moderate) reactions: involving 2 or more organ systems without change in vital signs (dyspnea, stridor, wheeze, nausea, vomiting, dizziness, diaphoresis, chest or throat tightness, abdominal pain); grade III (severe) reactions included 1 or more organs systems with vital signs changes such as hypotension, oxygen desaturation, throat closure, seizure, or loss of consciousness. Standard premedication with H1 blockers (cetirizine) and any other manufacturer-recommended premedication, consider symptom control with montelukast, NSAIDs. *For the 3-bag RDD, if tolerates this protocol twice, can consider consolidating to 1-bag RDD protocol. Abbreviations: IRR, infusion-related reaction; CRS, cytokine release syndrome; RDD, rapid drug desensitization; HSR, hypersensitivity reaction; SSLR, serum sickness-like reaction; SCAR, severe cutaneous adverse reaction; SJS, Stevens Johnson Syndrome; TEN, toxic epidermal necrolysis

Table 3 Example 3-bag rapid drug desensitization protocol

TABLE LV. Rituximab desensitization protocol (1000 mg)*

Solution 1	250 mL of	0.040 mg/mL
Solution 2	250 mL of	0.400 mg/mL
Solution 3	250 mL of	3.969 mg/mL

Step	Solution	Rate (ml/h)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.02	0.02
2	1	5.0	15	1.25	0.05	0.07
3	1	10.0	15	2.50	0.10	0.17
4	1	20.0	15	5.00	0.20	0.37
5	2	5.0	15	1.25	0.50	0.87
6	2	10.0	15	2.50	1.00	1.87
7	2	20.0	15	5.00	2.00	3.87
8	2	40.0	15	10.00	4.00	7.87
9	3	10.0	15	2.50	9.92	17.79
10	3	20.0	15	5.00	19.84	37.63
11	3	40.0	15	10.00	39.69	77.32
12	3	80.0	175	232.50	922.68	1000.00

*Total time 5 h 40 min.

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downregulation of FceR1 receptors and diminished reactivity to allergens.

Early studies reported anaphylaxis in 0.1–0.2% of patients with most events occurring within 2 h of the first 3 injections. This led to a black box warning and requirements for in-office administration and prescription of epinephrine autoinjectors for all patients. A retrospective review of anaphylaxis reports found that most cases occurred in women ages 18–44 years and life-threatening anaphylaxis was more common among patients with asthma than chronic urticaria. Fatal anaphylactic events were rare (0.28% of all reports) [46]. Limited access to in-office therapies during the COVID-19 pandemic led Shaker et al. to examine the cost-effectiveness of self-administration of omalizumab at home. They found the risk of automobile accidents en route to or from the office and cost of in-office injections outweighed the small reduction in anaphylaxis related mortality [47]. Subsequently, omalizumab's manufacturer suggested that prescribers may consider self-administration at home in patients without history of anaphylaxis who had tolerated 3 doses in clinic and were able to recognize and treat anaphylaxis.

With regards to management of omalizumab-related anaphylaxis, omalizumab RDD procedures have been reported [48•, 49, 50]. For omalizumab RDD, the largest cohort reported 12 patients, 67% of whom had Brown grade 2 reactions, and 33% who had a Brown grade 3 reaction [48•]. Skin testing was not performed. These patients underwent 97 omalizumab desensitization procedures, beginning with a two-bag, 7 step protocol with subsequent consolidation if tolerated. Of these treatments, 96% were tolerated with either no reaction or mild cutaneous symptoms. Of the four patients who had a systemic reaction, 2 had Brown grade 3 reactions during desensitization, one of whom had airway concerns and documented vocal cord dysfunction, and the other who developed wheezing and hypotension and required multiple doses of intramuscular epinephrine [48•]. As discussed above, the role of skin testing in biologic reactions is not clearly defined and practically difficult in most practice settings. Omalizumab is the only biologic discussed in this section for which non-irritating skin prick concentrations have been defined [28]. These concentrations are exceptionally dilute (1:100,000), which raises the question of whether skin testing of other biologics using higher concentrations may be affected by false positivity from irritant effects.

Several other unusual ADRs have been reported in association with omalizumab, though the incidence of these is unknown. Methemoglobinemia occurred with repeated exposure to omalizumab after other potential causative agents had been stopped in a 50-year-old woman treated for CSU [51]. Transient hair loss (telogen effluvium) has been reported in the first 1–2 months after initiation of omalizumab for CSU [52, 53]. Four incidents of serum sickness like reactions occurred in the original preclinical trials and symptoms resolved despite continuation of therapy (3 omalizumab and 1 placebo). Case reports of serum-sickness like reactions involving arthralgias, fever, and malaise occurring within a week of administration have been reported [23, 54]. However, these are not common; a retrospective review involving 923 patient-years of omalizumab therapy from a single center found no cases of serum sickness [55].

Mepolizumab

Mepolizumab is a humanized IL-5 blocking monoclonal antibody, first approved in 2015 for severe eosinophilic asthma. It has subsequently gained approval for eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndromes, and chronic rhinosinusitis with nasal polyps. Multiple long-term open label studies have examined the safety of both in-clinic and at-home administration of mepolizumab [56, 57]. Adverse events were similar between mepolizumab and placebo. Nasopharyngitis, headache, upper respiratory tract infections, and injection site reactions were most common [56–58]. No anaphylactic reactions were reported. Mepolizumab was approved for self-administration in 2019.

Reslizumab

Reslizumab is a humanized anti-IL-5 monoclonal antibody that is administered intravenously using weight-based dosing. A phase 3 trial including 492 patients found fewer overall adverse events with reslizumab compared to placebo (55% vs. 74%) and fewer treatment related AEs (7% vs. 16%). The most common AEs were asthma, URI, and sinusitis. Serious AEs occurred in 4% in both groups. One subject had anaphylaxis felt to be related to reslizumab, which responded to epinephrine [59]. A follow up long-term open label study found a similar safety profile with only 2% discontinuing due to treatment related AEs over 12–24 months [60]. A pooled analysis of multiple trials found a 0.3% risk of anaphylaxis with reslizumab leading to a black box warning [61]. Although only reslizumab and omalizumab carry this warning (Table 4), a retrospective review of biologic related anaphylaxis reports from 2004 to 2020 found increased rates of anaphylaxis with mepolizumab, benralizumab, omalizumab, and reslizumab (reporting odds ratios ranged from 4.65 to 24.19). Only dupilumab did not have an increased signal for anaphylaxis [46]. Most patients with biologic associated anaphylaxis were female and ages 18–64. Hospitalization occurred in 25% to 43% of cases and deaths were rare (0% to 1.92% of all events) [46].

Benralizumab

Benralizumab is a humanized monoclonal antibody that binds to the α-subunit of the IL-5 receptor on eosinophils and basophils, leading to antibody dependent cell mediated cytotoxicity. It was approved for severe eosinophilic asthma in 2017. Adverse events, most commonly nasopharyngitis and worsening asthma, were not significantly different between placebo and treatment groups in phase 2b and phase 3 trials; drug related hypersensitivity reactions were also similar between groups, occurring in 3%, with no anaphylactic events [62–64]. A two-year extension study examining risks related to prolonged eosinophil depletion found no increase in parasitic infections [65, 66].

Dupilumab

Dupilumab is an anti-IL4Rα human monoclonal antibody approved for allergic asthma, nasal polyposis, and atopic dermatitis. It blocks signaling of both IL-4 and IL-13. Early studies and later meta-analyses found similar overall adverse event rates between dupilumab and placebo groups, while severe AEs were less common with dupilumab (2.6% vs. 6.3%) [67–69]. Increased severe AEs in the placebo group were primarily skin infections, such as eczema herpeticum, and felt to be related to uncontrolled atopic dermatitis. Three AEs have been found more commonly with dupilumab than placebo, including injection site reactions (15–18% vs. 5–10%), eosinophilia (4.1% vs. 0.6%), and conjunctivitis (5–28% vs. 2–11%) [67–69]. Eosinophilia peaks 16–20 weeks after initiating dupilumab with an average increase in the absolute eosinophil count of 10%. Of 52 patients on dupilumab who developed eosinophilia, only 4 had symptoms and 2 were reported as serious AEs (chronic

Table 4 Common adverse drug reactions, anaphylaxis, and black box warnings for biologic agents

Biologic agent	Rate of anaphylaxis in phase II/III Trials	Common ADRs (> 10%)	FDA black box warnings
Omalizumab	0.1–0.2%	Headache	Anaphylaxis
Mepolizumab	0%	Nasopharyngitis, headache, arthralgia (EGPA only), URI	None
Reslizumab	0.3%	Worsening asthma, nasopharyngitis	Anaphylaxis
Benralizumab	0%	Worsening asthma, nasopharyngitis, URI	None
Dupilumab	0%	Nasopharyngitis, URI, conjunctivitis/ocular surface disease (atopic dermatitis only)	None
Tezepelumab	0%	Nasopharyngitis, URI	None

URI upper respiratory infection, *FDA* food and drug administration, *ADRs* adverse drug reactions, *EGPA* eosinophilic granulomatosis with polyangiitis

Table 5 Dupilumab associated ocular surface disease

Clinical features	Proposed mechanisms	Management options
Dry eye Conjunctivitis Keratitis Blepharitis	Mucin/Epithelial barrier dysfunction Increased Th1 inflammation Goblet cell hypoplasia secondary to IL-13 blockade	Artificial tears Topical corticosteroids Topical tacrolimus Topical cyclosporine Discontinuation of dupilumab

eosinophilic pneumonia and hypereosinophilia) [67]. A subsequent retrospective review of 653 patients treated with dupilumab for atopic dermatitis found 9% had hypereosinophilia defined as 1500/mm^3 or higher (mean 2600/mm^3). This developed around 2.5 months after dupilumab initiation and although no clinical signs of organ involvement were detected, 25% of patients with hypereosinophilia discontinued therapy. Among those who continued, absolute eosinophil counts trended downwards with time [70].

In studies of atopic dermatitis but not other indications, dupilumab was associated with an increase in conjunctivitis compared to placebo. The original RCTs reported an incidence of 5% to 28% compared to 20% to 25% in subsequent open label studies [71•, 72, 73]. Symptoms develop in the first weeks to months after drug initiation (average 6 weeks). New terminology, dupilumab associated ocular surface disease (DAOSD), has been suggested to better capture the spectrum from mild, self-limited conjunctivitis and dry eye to more severe forms of keratitis, blepharitis, and cicatricial conjunctivitis, see Table 5. Proposed mechanisms for DAOSD include increased Th1 inflammation and goblet cell hypoplasia due to IL-13 blockade resulting in decreased mucin and epithelial barrier dysfunction. More severe atopic dermatitis at baseline and preexisting conjunctivitis appear to augment the risk of DAOSD [71•, 73]. Topical therapies, including artificial tears, corticosteroids, tacrolimus, and cyclosporine eyedrops, result in resolution or disease control in most cases. However, 3.6% to 15% of patients with DAOSD (less than 1% of all patients on dupilumab for atopic dermatitis) experience severe symptoms requiring discontinuation of dupilumab [71•, 73–75].

Tezepelumab

Tezepelumab, the newest biologic in this field, was approved in 2021 for severe asthma of any endotype. It is a human monoclonal antibody directed against thymic stromal lymphoprotein (TSLP). TSLP is a cytokine released by respiratory epithelium in response to allergic and non-allergic stimuli. One case of Guillain–Barre syndrome was seen with Tezepelumab in the phase 2 trial [76]. None occurred in the phase 3 trial and both overall and serious AEs were similar between placebo and treatment groups. The most common AEs were nasopharyngitis, URI, headache, and asthma, the last of which was more frequent in the placebo group [77].

Biologics Used in Immunologic Conditions

Rituximab

Rituximab is a chimeric anti-CD20 monoclonal antibody used to achieve B cell depletion in a variety of inflammatory, autoimmune, and malignant conditions. It is associated with Pichler types α (cytokine release), β (hypersensitivity), and γ (immunomodulatory) adverse events.

Type α events include infusion reactions and, more rarely, cytokine release syndrome. While the pathophysiology is not fully understood, these are felt to be non-immunologic AEs and are associated with elevated levels of IL-6 and TNF-α. Infusion reactions are most common during the initial rituximab infusion, affecting up to 77% of patients [78]. Symptoms may include flushing, fever, chills, heart rate or blood pressure changes, nausea, dyspnea, and syncope. Infusion reactions tend to subside with subsequent infusions. They also respond to infusion rate reduction and various premedication regimens, including antihistamines, systemic steroids, antipyretics, and leukotriene receptor antagonists. Cytokine release syndrome results from target cell lysis and typically occurs in the context of lymphoma rather than autoimmune disease or immunodeficiency.

Allergy to rituximab (type β reactions) occur more rarely in roughly 3–10% of patients [45]. Both immediate IgE-mediate and delayed type hypersensitivity reactions may occur. The latter include serum sickness-like reactions, Steven Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS). A systematic review of rituximab induced serum sickness identified fever (78.8%), arthralgia (72.7%), and rash (69.7%) as the most common presenting symptoms, with 48.5% exhibiting the entire triad [20]. On average, symptoms developed 6–7 days after rituximab infusion. Most cases were treated with corticosteroids and mean time to resolution of symptoms was 2 days. Four patients were retreated with rituximab and all were premedicated with 100 mg prednisolone or methylprednisolone. Two of the 4 tolerated subsequent rituximab infusions, 1 had recurrent serum sickness, and 1 had angioedema. Although there is limited data on retreatment, this is emerging as an acceptable course in patients with SSLR who require further therapy [20, 31]. Patients should be informed of the potential risk of recurrence, which may be attenuated using premedication with steroids and/or a steroid taper following future infusions.

Immediate hypersensitivity reactions to rituximab have some similarity to and may coexist with infusion reactions. As these are often difficult to distinguish some authors suggest managing reactions according to severity rather than mechanism. A retrospective review of 67 patients with reactions to initial rituximab infusions found that 88% were NCI grade 1 or 2 [78]. This grading system does not account for etiology (e.g., IgE vs. non-IgE mediated). Reactions were treated with antihistamines, steroids, beta-agonists, and/or IV fluids. No patients required epinephrine. Fifty-one patients were rechallenged the same day using a 50% infusion rate reduction and 37 tolerated this without ADRs. Reactions to rechallenge increased with severity of initial reaction: none of the grade 1 patients reacted, 5 of 35 grade 2 patients, and all of grade 3 patients reacted. Reactions to same-day rechallenge were predominantly grade 1–2. This suggests that most patients with mild initial reactions can safely tolerate rituximab with premedication, rate reduction, and symptomatic treatment, whereas skin testing and desensitization procedures should be reserved for those with severe (grade 3 or 4) reactions.

Lastly, rituximab can cause a secondary immunodeficiency, predispose to infections, or lead to reactivation of latent virus (type γ events). Some patients experience prolonged B cell depletion and secondary hypogammaglobulinemia (defined as low IgG levels) persisting beyond the expected duration of rituximab efficacy. The incidence is not clearly defined and hypogammaglobulinemia may or may not be associated with impaired specific antibody responses and a clinical syndrome of recurrent infections. A recent AAAAI work group statement on secondary hypogammaglobulinemia recommends checking immunoglobulin levels at baseline and 4–6 months after each infusion [79••]. Depending on infection history and plans for immunosuppression, B cell enumeration and vaccine responses can help further define the presence of immunodeficiency. Pre-treatment hypogammaglobulinemia is a predictor of more severe post-rituximab hypogammaglobulinemia and infection risk [80, 81]. Lower respiratory tract infections are most common, similar to primary hypogammaglobulinemia disorders. Immunoglobulin replacement therapy may be indicated in patients with significant infectious complications, particularly if they require ongoing rituximab therapy [79••]. Late onset neutropenia (ANC < 1000/mm^3) has also been observed in 6.6% of patients receiving rituximab for autoimmune conditions. Most cases are reversible with filgastim and fewer than half are associated with fever or infection [82]. Finally, Hepatitis B reactivation is a well-known risk of rituximab therapy and screening prior to initiation is recommended.

Anti-TNF

Anti-tumor necrosis factor (TNF) biologics include both monoclonal antibodies infliximab, adalimumab, golimumab, and certolizumab, as well as etanercept, a soluble TNF receptor that competitively binds TNF. These medications are used to treat autoinflammatory conditions such as common variable immunodeficiency and immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome-associated enteropathies.

Type α events include infusion reactions and injection site reactions with intravenous and subcutaneous anti-TNF therapies, respectively. Infusion reactions occur immediately, and are generally rate-dependent and responsive to premedication. Injection site reactions are thought to be mediated by local binding of soluble antigen that aggregates near the injection site; these are typically self-limited [10].

Similar to rituximab, immediate, serum sickness-like, and delayed hypersensitivity (type β) reactions have been reported with anti-TNF biologics [18]. Immediate reactions can be IgE mediated via FceR1 activation as well as IgG mediated through FceγRIIA and generation of complement anaphylatoxins [10]. Non-irritating concentrations for skin prick and intradermal testing are reported for etanercept, infliximab, and adalimumab [18]. In addition to immediate reactions, neutralizing anti-drug antibodies may develop over time leading to loss of therapeutic efficacy. Anti-drug antibodies are detected in 10–50% of patients receiving infliximab and 25–30% receiving adalimumab. If patients lose response to a particular agent, switching to a different anti-TNF monoclonal antibody is often successful [83].

Type γ reactions include both predisposition to new infections as well as reactivation of latent tuberculosis, hepatitis B, and hepatitis C. Reactivation of tuberculosis often manifests as extrapulmonary disseminated disease. Screening for these infections and administration of age-appropriate vaccinations prior to initiating anti-TNF therapies are recommended. Opportunistic infections, particularly fungal, are increased with anti-TNF therapies. The risk of infections is greatest during the first 12 months of therapy and is higher with anti-TNF monoclonal antibodies compared to etanercept [83]. Anti-TNF therapies are also associated with an increased development of auto-antibodies, such as ANA and anti-double-stranded DNA. However, these infrequently lead to symptoms of autoimmunity, which usually present as a lupus-like syndrome or vasculitis [83].

Conclusion

Biologic therapies have revolutionized the treatment of allergic and immunologic diseases. Rather than conforming to the classic Gell and Coombs reactions associated with small molecule medications, biologics can cause a spectrum of hypersensitivity, immunomodulatory, and non-immune-mediated events. Phenotypes often overlap making it challenging to identify the pathophysiology solely based on history, and the optimal diagnostic strategy for numerous biologics remains unclear. Nevertheless, allergy/immunologists have a number of management tools available to be able to help address adverse reactions to biologic agents and optimize safe drug delivery when no reasonable alternatives exist. As the use of biologic agents has become widespread, allergy/immunology clinicians are well-positioned to provide expertise in the management of adverse reactions to these agents.

Clinical Trial Registration

Not applicable.

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•• Of major importance

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