

Management of adverse reactions to biologic agents

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ABSTRACT

Hypersensitivity reactions (HSR) to targeted biologic agents present as immediate reactions during infusion or as delayed reactions (after one or more exposures). The new classification includes phenotypes, endotypes, and biomarkers. Phenotypes include immediate type I (immunoglobulin E [IgE] or non-IgE mediated), cytokine release, mixed (type I/cytokine), and immune complexes type III (IgG mediated) reactions as well as delayed type IV reactions. Endotypes include IgE or non-IgE mediated mast cells/basophils activation with elevated serum tryptase and T cells values as well as macrophages, which lead to cytokine production, e.g., interleukin 6. A skin test is a valuable tool in evaluating HSRs to biologics; however, its predictive value depends on the type of reaction and the monoclonal antibody. Desensitization is a new approach to safely reintroduce biologics when they are first-line therapies, and it is available for immediate and delayed reactions. Research is needed to further understand the mechanisms of reactions to monoclonal antibodies and their management.

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Monoclonal antibodies (mAb) form one of the pillars of modern biotechnology. They are important tools used in diagnostics, and, more importantly, selected mAbs have been approved for therapeutic use and have benefited millions of patients with cancers, rheumatologic autoimmune, and inflammatory diseases. In 1975, the first mAb was generated by Kohler and Milstein¹ through hybridoma technology by fusion of mouse myeloma cells and mouse spleen cells from an immunized donor with a specific antigen. This first murine mAb (100% murine) (suffix “omab”), muromonab-CD3 (orthoclone OKT3), was approved in 1985 for clinical use in human as an antirejection agent for renal transplantation.² The dissimilarity between murine and human immune systems resulted in allergic reactions, including anaphylactic shock.³ This consequence led to the replacement of mouse sequence-derived amino acids for human sequences: partially in chimeric (75% human) (suffix “ximab”), humanized (95% human) (suffix “zumab”) mAb, and fully in hu-

man mAbs (100% human) (suffix “umab”)^{4–7} with decreased immunogenicity; however, the attachment of the carbohydrate side chain on the constant region may still contribute to mAb immunogenicity⁸ (Fig. 1).

The development of a new functionality of mAbs by engineering two different antigen-binding sites or conjugating drugs to antibodies has allowed the production of bispecific antibodies with their inherent ability to bring two different targets into proximity (catumaxomab). Three mechanisms through which mAbs act in cancer treatment were defined. First, mAbs act directly by binding to a cancer-specific antigen and, thus, induce immunologic responses that cause cancer cell apoptosis and growth inhibition by complement-dependent cytotoxicity or antibody-dependent cytotoxicity;^{9–11} second, a modified mAb can deliver toxin, radioisotope, cytokine, liposome, or other active conjugates, e.g., antibody-drug conjugate (brentuximab); third, bispecific mAbs bind with their fragment antigen-binding regions both to target antigen and to a conjugate or effector cell, which enhances their action (Fig. 1).¹²

Targeted biologic therapies are rapidly expanding, with, currently, 47 U.S. Food and Drug Administration approved mAbs and with the projection that there will be 70 mAbs by 2020 and a revenue of ~125 billion dollars.¹³ The mAbs most used in our clinical experience are summarized in Table 1. The clinical use of biologics has been complicated by the development of immunogenic responses, including antidrug antibody formation and hypersensitivity reactions (HSR). These consequences may negatively impact the efficacy and safety of biologic therapies. This review provided an overview of the current understanding of clinical manifestations of HSRs to biologic agents; diagnostic tools for HSRs, including skin testing (ST) and biologic

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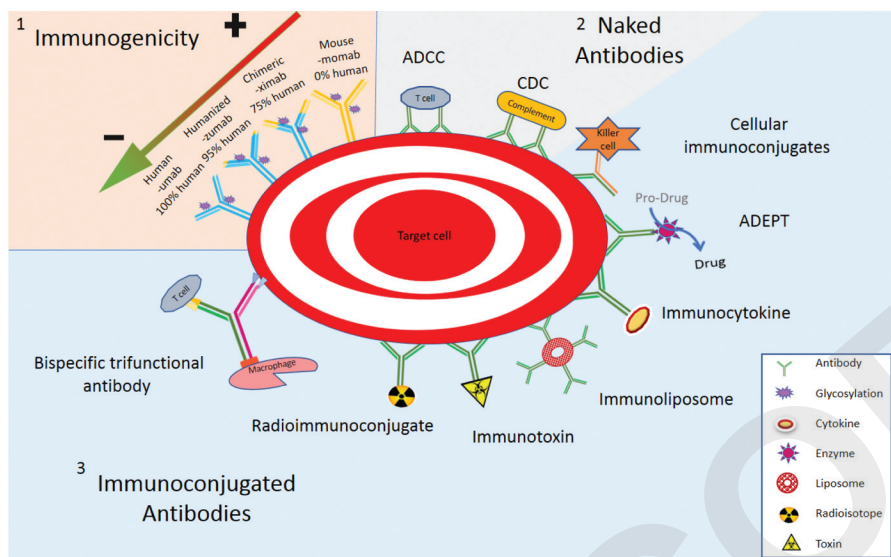


Figure 1. Monoclonal antibody (mAb) structure and targeted mechanisms. (1) Antibody immunogenicity. The immunogenicity of the mAb decreases with increasing human sequence-derived amino acids percentage, but it is not totally eliminated, probably due to the glycosylation; the yellow structure represents murine portion, and blue represents human portion of the antibody. (2) Naked antibodies. An isolated mAb acts on the target cell by antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. (3) Immunoconjugated antibodies structure. The mAb function is enhanced by attaching different effector cells (cellular immunoconjugated), cytokines (immunocytokine), Antibody Directed Enzyme Prodrug Therapy (ADEPT), liposomes (immunoliposome), and cytotoxic agents (radioisotope, toxin); bispecific trifunctional antibodies can simultaneously bind to two different types of antigen.

markers; and the management of HSRs through desensitization.

CLASSIFICATION OF HSRs TO BIOLOGICS

The current clinical practice shows that the presentation of HSRs to biologics is not contained in the Gell and Coombs¹⁴ or Pichler¹⁵ classification of drug HSRs. A recent approach characterized drug HSRs by their phenotypes, endotypes, and biomarkers.¹⁶

Phenotypes and Severity

The timing and symptoms of the reaction determine the phenotype of HSR. Immediate reactions occur within 6 hours of drug exposure, and delayed reactions may occur after 6 hours but usually present days to weeks after drug administration.^{16,17} Clinical phenotypes of HSRs to mAbs are immediate reactions, including type 1 (IgE or non-IgE mediated), infusion-related reactions (IRR), cytokine storm, mixed reactions (association of type 1 and cytokine storm), immune-complexes reactions,¹⁸ and type IV delayed reactions. Within immediate reactions, IgE and non-IgE mediated type 1 HSRs present with cutaneous (erythema, pruritus, hives, angioedema), respiratory (nasal congestion, sneezing, chest pain and/or tightness, wheezing, dyspnea, oxygen desaturation), throat (itchiness, tightness, swelling), cardiovascular (syncope, bradycardia, hyper- or hypotension, ECG changes), gastrointestinal (nausea, vomiting, diarrhea, abdominal

pain), neurologic (vision changes; tingling, numbness, weakness; seizure; sense of impending doom; loss of consciousness), and anaphylaxis.¹⁹

IRRs to mAbs may manifest with nausea, chills, fever, and malaise.^{18,20,21} These reactions are likely due to proinflammatory cytokines release (such as interleukin [IL] 1 β , IL-6, and tumor necrosis factor [TNF] α), occur at the first infusion, with mild symptoms. The difference between IRRs and cytokine-like HSRs is that IRRs are self-limiting on repeated exposures and respond to premedication with nonsteroidal anti-inflammatory drugs (NSAID) and steroids.^{22–25} One study evaluated the incidence and management of IRRs to infliximab in 24,852 infusions and found that premedicating with antihistamine did not prevent reactions.²⁶ Cytokine-storm reactions are immediate reactions, which may present with similar symptoms to type I or more general symptoms, such as headache; fever; chills and/or rigors; and neck, chest, or back pain.^{19,27} Immune-complexes (immunoglobulin G [IgG] mediated) type III HSRs can present as acute or delayed, and can manifest either locally (Arthus reaction) or systemically with symptoms that resemble those presented in type I IgE-mediated reactions.¹⁷

Delayed type IV HSRs induced by mAbs are rare. The majority present cutaneously with a nonsevere maculopapular rash between 1 to 13 weeks after drug administration.²⁸ However, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichenoid dermati-

Table 1 **Biologic agents: Route, target, incidence of injection or infusion, and HSRs***

Agent/Company	Target	Type	Injection or Infusion Reactions, Ref. no.	HSR, Ref. no.
Rituximab (Rituxan) IV/ Biogen Inc., Cambridge, MA, USA	CD20	Chimeric IgG1	77% (first infusion) ⁹⁰	5–10% ⁹¹
Obinutuzumab (Gazyva) IV/ Genentech Inc., South San Francisco, CA, USA	CD20	Humanized IgG1	20–66% ^{92,93}	— ⁹⁴ #
Ofatumumab (Arzerra) IV/ GlaxoSmithKline, Research Triangle park, NC, USA	CD20	Human IgG1	44% (first infusion) ²⁰ ; 67% (combination therapy) ⁹⁵	2% ⁹⁵
Brentuximab (Vedotin) IV/ Genetics Inc., Seattle, WA, USA	CD30	Chimeric IgG1	12% ⁹⁶	— ^{97–99} #
Trastuzumab(Herceptin) IV/ Genentech Inc., South San Francisco, CA, USA	HER2	Humanized IgG4	40% (mild; first infusion) ¹⁰⁰	0.6–5% ¹⁰¹
Pertuzumab (Perjeta) IV/ Genentech Inc., South San Francisco, CA, USA	HER2	Humanized IgG1	≥1% ¹⁰²	11.3% ¹⁰²
Cetuximab (Erbix) IV/ Celgene Corp., Summit, NJ, USA	EGFR	Chimeric IgG1	15–21% ¹⁰³	1.1–5% ^{104–107} ; 14–27% (southern U.S.) ^{25,108,109}
Bevacizumab (Avastin) IV/ Genentech Inc., South San Francisco, CA, USA	VEGF	Humanized IgG1	<3% ¹¹⁰	Not reported
Omalizumab (Xolair) SC/ Genentech Inc., South San Francisco, CA, USA	IgE	Humanized IgG1	45% ¹¹¹	0.09–0.2% ^{111,112}
Mepolizumab (Nucala) SC/ GlaxoSmithKline Inc., GlaxoSmithKline, Research Triangle park, NC, USA	IL-5	Humanized IgG1	8% ¹¹³	1% ¹¹³
Tocilizumab (Actemra) IV/ Genentech Inc., South San Francisco, CA, USA	IL-6 receptor	Humanized IgG1	7–8% ¹¹⁴	0.1–0.7% ¹¹⁴
Abatacept (Orencia) IV/ BristolMyers Squibb, Princeton, NJ, USA	CD80/86	(Remicade) IV IgG1	2.5% ¹¹⁵	26.9% ¹¹⁵
Etanercept (Enbrel) SC/ Immunex Corp., Newbury Park, CA, USA	TNF- α	Human TNF receptor + Fc IgG1	15–37% ¹¹⁶	<2% ¹¹⁶
Infliximab (Remicade) IV/ Janssen Biotech Inc., Horsham, PA, USA	TNF- α	Chimeric IgG1	5–18% ¹¹⁷	1% ¹¹⁷ #
Adalimumab (Humira) SC/ Abbott Laboratories, Lake Bluff, IL, USA	TNF- α	Human IgG1	20% ¹¹⁸	1% ¹¹⁸
Golimumab (Simponi) SC/ Janssen Biotech Inc., Horsham, PA, USA	TNF- α	Human IgG1	4–20% ^{119,120}	Not reported
Certolizumab (Cimzia) SC/ UCB, Inc. Smyrna, GA, USA	TNF- α	Humanized IgG1	0.8–4.5% ^{121,122}	Not reported

Table 1 Continued

Agent/Company	Target	Type	Injection or Infusion Reactions, Ref. no.	HSR, Ref. no.
Nivolumab (Opdivo) IV/ BristolMyers Squibb, Princeton, NJ, USA	PD-1	Human IgG1, IgG2, IgG4	6.4% ¹²³	<1% ¹²⁴
Pembrolizumab (Keytruda) IV/ Merck and CO., Inc., Whitehouse Station, NJ, USA	PD-1	Humanized IgG4	3% ¹²⁵	0.4% ¹²⁵

HSR = Hypersensitivity reaction; CD = cluster of differentiation; IV = intravenous; IgG = immunoglobulin G; HER = human epidermal growth factor receptor; EGFR = human epidermal growth factor receptor; VEGF = vascular endothelial growth factor; SC = subcutaneous; IL = interleukin; CTLA = cytotoxic T-lymphocyte-associated protein; Fc = fragment crystallisable; TNF = tumor necrosis factor; PD = programmed cell death.

*Adapted from Ref. 22.

#Case reports of anaphylaxis.

Table 2 Grading system for drug HSRs*

Grade	Severity	Organ or System Involvement	Symptoms Examples
I	Mild	Skin or one organ and/or system	Erythema, pruritus, urticaria, angioedema
II	Moderate	Two or more organs without vital signs changes	Flushing and dyspnea Chest tightness and abdominal pain Back pain and fever
III	Severe	Vital signs changes	Oxygen desaturation ($SpO_2 \leq 88\%$) Hypotension (SBP < 90 mm Hg in adults) Throat closure Confusion Collapse Seizure Loss of consciousness

HSR = Hypersensitivity reaction; SpO_2 = peripheral capillary oxygen saturation; SBP = systolic blood pressure.

*Adapted from Ref. 34.

tis, vesiculobullous dermatitis, and paraneoplastic pemphigus in response to biologics have been reported that implicate agents, such as catumaxomab, tositumomab, bevacizumab, denosumab, ipilimumab, and panitumumab.²⁷ The underlying mechanisms have not been clearly elucidated.^{29–31} The incidence of serious mucocutaneous reactions was evaluated in patients with lymphoma treated with rituximab in which some reactions were thought to be due to the disease instead of rituximab HSRs.^{29,32} Anaphylaxis may occur during any immediate HSR to mAb, regardless of the endotype,³³ and a useful grading system for generalized drug HSRs has been published (Table 2).³⁴

Endotypes and Biomarkers

The endotype refers to the mechanism that underlies the HSR. Three endotypes were defined, including IgE or non-IgE with mast cell activation endotype (implicated in HSRs to biologics) and two other

endotypes not seen with mAbs, such as asthma-exacerbated respiratory disease and human leukocyte antigen endotypes.¹⁶ With regard to mAb HSRs, the mast cell and/or basophil activation endotype (IgE and non-IgE mediated) results in release of tryptase, chymase, histamine, leukotrienes, prostaglandins, and other mediators that are implicated in immediate symptoms. Furthermore, T cells and macrophages are also implicated in HSRs to biologics by releasing cytokines, such as IL-1 β , IL-6, and TNF- α among others.^{16,35}

Serum tryptase, an important clinical marker of mast cell activation, is elevated during drug HSRs, and it is helpful in the diagnosis of anaphylaxis.^{36–38} Two case reports of grade III HSRs to rituximab of patients who presented with elevated serum tryptase levels, to 50.7 and 26 ng/mL from a baseline of 6.8 and 2.7 ng/mL, respectively, with a positive ST result that confirmed type I HSR to rituximab; both patients had successful

Table 3 ST concentrations for mAbs*

Agent	SPT, mg/mL (full strength)	IDT, mg/mL#
Adalimumab§	40	0.4 (1/100 dilution)
Bevacizumab§	25	2.5 (1/10 dilution)¶
Cetuximab§	2	0.2 (1/10 dilution)
Etanercept§	50	0.5 (1/100 dilution)
Infliximab§	10	1 (1/10 dilution)
Omalizumab§	125**	0.00125 (1/100.000 dilution)
Pertuzumab	1.6 (~1/20)##	0.16 (~1/200 dilution)
Rituximab§	10	1 (1/10 dilution)§§
Tocilizumab§	20	20 (full strength)
Trastuzumab	21	2.1 (1/10 dilution)

ST = Skin testing; SPT = Skin-prick test; mAb = monoclonal antibody; IDT = intradermal test.

*Adapted from Ref. 27.

#All dilutions should be made with normal saline solution.

§Concentrations shown to be nonirritating by testing on healthy control subjects.

¶A concentration of 25 mg/mL was also shown to be nonirritating (from Ref. 49).

||A concentration of 0.5 mg/mL was shown to be nonirritating in eight controls (from Ref. 126), and another group reported a concentration of 5 mg/mL to be nonirritating (from Ref. 49).

**Omalizumab should be reconstituted with normal saline solution to avoid false-positive results (from Ref. 51).

##Full-strength concentration is 30 mg/mL; pertuzumab was only tested on one subject, who was reactive, with negative results at 1.6 mg/mL (SPT) and up to 0.16 mg/mL (IDT); higher concentrations could be nonirritating.

§§Although 1 mg/mL (IDT) is more commonly used, a maximal concentration of 10 mg/mL (full strength) for rituximab IDT is recommended by the European Network on Drug Allergies and does not seem irritating (from Ref. 49).

desensitizations.³⁹ The same correlation between a positive ST result and an elevated tryptase level during HSR has been demonstrated for antibiotics and chemotherapy agents.^{40–45} The ST has also been shown to be useful for risk stratification in clinical practice; however, its predictive value varies with the drug tested.⁴⁶ Also, mAb nonirritating ST concentrations were suggested for adalimumab,⁴⁷ bevacizumab,^{48,49} cetuximab,^{48,49} etanercept,⁴⁷ infliximab,^{49,50} omalizumab,⁵¹ pertuzumab,⁵² rituximab,^{18,49} tocilizumab,⁵³ and trastuzumab¹⁸ (Table 3). Although the ST is used as a diagnostic tool for HSRs to biologics, its sensitivity, specificity, and predictive values are still unknown, and the cost is a limitation to the widespread usage of ST to biologics.

In vitro diagnostic tools, such as specific IgE (sIgE) and sIgG assessment, and basophil activation test (BAT), have been used in evaluating drug HSRs with high specificity; however, their main limitation is the lack of sensitivity.^{54,55} A positive sIgE result to rituximab was reported in a patient who also had a positive ST result, which confirmed type I IgE-mediated hypersensitivity.⁵⁶ The sIgE value for disaccharide α -D-galactose-(1–3)- β -D-galactose has also been reported in a patient with an anaphylactic reaction to cetuximab.⁵⁷ The role of sIgE to infliximab has been questioned in one study, which showed that sIgE was detected in <1% of patients with HSRs to infliximab.⁵⁵

Some patients present with IgG antibodies to biologics, which may act by blocking the effect of the drug or by participating in the development of HSRs.⁵⁸ IgG can potentially cause transient sensitization and leads to symptoms comparable with those of IgE-mediated reactions.⁵⁹ An elevated anti-infliximab IgG was reported in a patient with an acute severe anaphylactic reaction to infliximab, whereas anti-infliximab IgE antibodies were not found.⁶⁰ Results of studies indicate that the formation of antidrug IgG antibodies is related to lower functional drug levels and a diminished clinical response in patients treated with adalimumab and infliximab.^{61–63} Although IgG4 antibodies cannot activate complement and have a low affinity for Fc receptors (receptor of crystallisable fragment), they may still be able to compete with a drug by binding to the anti-TNF- α drugs and thus lead to a clinical nonresponse.⁶⁴ Monitoring serum levels of anti-infliximab IgG by novel radioimmunoassay techniques seemed promising for evaluating and optimizing efficacy and safety of infliximab therapy in Crohn disease.⁶⁵

The BAT seemed promising in the diagnosis of immediate HSRs to various agents, such as platinum, antibiotics, neuromuscular blockers, and NSAIDs, and has been qualified as a safe and suitable complement of *in vivo* testing in immediate HSRs.^{66–71} A positive BAT result for pertuzumab was reported in a patient with breast cancer who presented with a grade III, type I

Table 4 Intravenous desensitization protocol to brentuximab: Solution preparation*

Bag	Volume per Bag, mL	Concentration, mg/mL	Total Dose per Bag, mg	Amount of Bag Infused, mL
1	100	0.0087	0.870	9.38
2	100	0.087	8.700	18.75
3	100	0.85287	85.287	100.00

*Target dose, 87 mg; standard volume per bag, 100 mL; final rate of infusion, 80 mL/hr; standard time of infusion, 100 min.

reaction during infusion of pertuzumab; the patient was treated with intramuscular epinephrine. A serum tryptase sample collected 2 hours after the onset of symptoms was elevated; the ST results to pertuzumab at 2 and 8 weeks after the reaction were negative, and the patient underwent a successful desensitization.⁵² A BAT result to rituximab was also positive in 18 patients who reacted to rituximab (urticaria, hypotension, angioedema, and bronchospasms); it was concluded that the BAT could be useful in evaluating patients with suspected HSR to rituximab, especially in the absence of other diagnostic tests.⁷² On the contrary, BAT was performed with infliximab and adalimumab (to assess tolerance to other anti-TNF- α) in a patient who reacted to infliximab with general malaise, cutaneous flushing, palpitations, and urticaria, with negative results for both agents, and the patient later tolerated an adalimumab injection.⁷³

DESENSITIZATION TO BIOLOGIC AGENTS

Drug desensitization is an induction of temporary clinical unresponsiveness by gradual reintroduction of small incremental doses of drug antigens at fixed time intervals that reach the target dose at the end of the protocol.^{74,75} It aims to protect against anaphylaxis and to allow a safe reintroduction of the first-line therapy.

Desensitization Mechanisms

The cellular and molecular mechanisms that underlie drug desensitization have been explored through *in vitro* and *in vivo* models, which show the inhibition of mast cell activation hallmarks in an antigen-specific fashion. Desensitization has an impact on antigen-IgE-high-affinity receptor for IgE complex internalization by blocking calcium flux and preventing mast cell mediators production (acute and late phase).^{76–78} Other mechanisms (the immunoreceptor tyrosine-based inhibitory motif inhibitory pathway, actin remodeling, conformational changes in calcium channels) have been proposed;^{76,77,79–83} however, there is still much to be learned about the mechanisms of inhibitory molecules and their receptors during desensitization.

Desensitization Protocols

Desensitization to IV or subcutaneous biologics have been successfully performed; the majority are mAbs

(rituximab, trastuzumab, infliximab, cetuximab, bevacizumab, tocilizumab, ofatumumab, brentuximab, alemtuzumab, adalimumab) and a few fusion proteins, including abatacept and etanercept.^{18,22,27,48} A desensitization protocol recommendation depends on the risk stratification, which takes into consideration the phenotype, severity of initial reaction, result of ST, tryptase level (baseline and/or during initial reaction), and patient's comorbidities. A standard desensitization protocol to IV mAbs consists of three bags and 12 steps, and is based on an *in vitro* model.⁷⁶ Antigen doses are doubled every 15 minutes, starting at 1/100 of the final dose.^{18,24} Three solutions are administered sequentially. The first bag contains a solution with a 1/100 dilution and the second bag contains a 1/10 dilution; the third concentration is calculated by subtracting the cumulative dose administered in steps 1 to 8 from the total target dose.^{18,22} The final step is the longest and provides the highest dose that the patient will receive (Tables 4 and 5). Successful desensitization to subcutaneous biologics have been performed with adalimumab^{21,84} and etanercept.⁸⁵ Desensitization provides a transient tolerance, and it has to be repeated for subsequent biologic administration. It is contraindicated in severe cutaneous or systemic reaction, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, and serum sickness.

Premedication with antihistamine (H₁, H₂), leukotrienes blockers, acetylsalicylic acid and/or NSAIDs and/or acetaminophen, and as-needed steroids and IV fluids, allows prevention of breakthrough reactions during desensitization.⁸⁶ The choice of a premedication drug is based on the type of symptoms during the initial reaction. Acetylsalicylic acid is given for flushing; montelukast for flushing and bronchospasm; and NSAIDs for fever, chills, and pain.^{87,88}

HSRs During Desensitization

Evaluation of the safety and efficacy of desensitization to biologic agents in 104 of 105 desensitizations to 23 patients with mAbs was successfully completed and has been published.¹⁸ HSRs were observed during 29% of desensitizations;¹⁸ a comparable percentage was

Table 5 Intravenous desensitization protocol to brentuximab: Protocol for administration

Step	Bag	Rate, mL/hr	Time, min	Cumulative time	Volume Infused per Step, mL	Dose Administrated per Step, mg	Cumulative Dose, mg	Fold Increase per Step
1	1	2.5	15	15	0.63	0.0054	0.0054	0
2	1	5	15	30	1.25	0.0109	0.0163	2
3	1	10	15	45	2.5	0.0218	0.0381	2
4	1	20	15	60	5	0.0435	0.0816	2
5	2	5	15	75	1.25	0.1088	0.1903	2.5
6	2	10	15	90	2.5	0.2175	0.4078	2
7	2	20	15	105	5	0.4350	0.8428	2
8	2	40	15	120	10	0.8700	1.7128	2
9	3	10	15	135	2.5	2.1322	3.8450	2.45
10	3	20	15	150	5	4.2644	8.1094	2
11	3	40	15	165	10	8.5287	16.6381	2
12	3	80	15	226.875	82.5	70.3619	87.000	

Total time to administer: 3.78 hr.

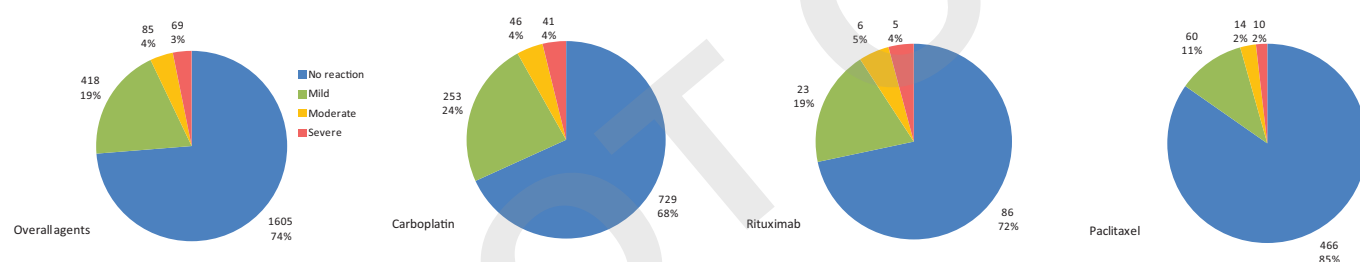


Figure 2. Severity of hypersensitivity reactions (HSR) during desensitization (adapted from Ref. 48). The frequency and severity of hypersensitivity reaction, occurring during 2177 desensitizations for overall agents and for rituximab compared with carboplatin and paclitaxel specifically.

noted during chemotherapy desensitization (33%).²⁴ Most reactions were mild (90%) and usually occurred at the last step, and no fatality was reported.¹⁸ In a recent study,⁴⁸ HSRs to chemotherapy and mAbs were evaluated in 370 patients during 2177 desensitizations. The majority of desensitizations had no (74%) or mild (19%) reactions whereas moderate-to-severe reactions occurred in 154 desensitizations (7%); reactions to rituximab were 28% (Fig. 2).⁴⁸ Studies looked at the results of the ST and the outcomes of desensitization to mAbs, and found a correlation between negative ST results and a lower rate of reactions during desensitization.^{18,48}

The management of HSRs during desensitization includes stopping the infusion and treating according to the phenotype and severity of the reaction. For an anaphylactic reaction, epinephrine should be given first. Other therapies, such as antihistamines, bronchodilators, montelukast, aspirin and/or NSAIDs, steroids, and IV fluids, should be considered based on symptoms,⁸⁹ and a tryptase level with or without cytokines levels should be assessed when the patient's clinical status permits.^{16,44} Once the symptoms resolve, the infusion can be resumed from where it was

stopped. Strategies used to prevent HSRs during subsequent desensitizations include administering intrastep medications (similar to premedication drugs), starting or increasing IV fluids to dilute the antigens and the mediators, adding or lengthening steps before the step at which a reaction occurred, reducing the final infusion rate, and using a four-bag/16-step desensitization protocol in patients with a very low reaction threshold.²⁷ If desensitization remains unsuccessful, then a dose reduction to 25, 50, and 75% of the target dose may be considered.

CONCLUSION

HSRs to biologics present with various phenotypes, including immediate type I; IRRs; cytokine release; mixed; immune complex type III; and delayed type IV reactions with endotypes, including IgE or non-IgE mediated mast cell and/or basophil activation; and T cells and/or macrophages involvement with the release of mediators, such as tryptase and IL-6. ST is a valuable diagnostic tool for diagnosis of HSRs to biologics; however, its predictive value remains unknown. Desensitization for immediate and delayed HSRs allows a safe reintroduction of first-line biologic agent.

REFERENCES

- Kohler G, and Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. 1975. *Biotechnology* 24:524–526, 1992.
- Smith SL. Ten years of orthoclone OKT3 (muromonab-CD3): A review. *J Transpl Coord* 6:101–109; quiz 120–121, 1996.
- Stern M, Herrmann R. Overview of monoclonal antibodies in cancer therapy: Present and promise. *Crit Rev Oncol Hematol* 54:11–29, 2005.
- Chadd HE, and Chamow SM. Therapeutic antibody expression technology. *Curr Opin Biotechnol* 12:188–194, 2001.
- Lonberg N, and Huszar D. Human antibodies from transgenic mice. *Int Rev Immunol* 13:65–93, 1995.
- Riechmann L, Clark M, Waldmann H, and Winter G. Reshaping human antibodies for therapy. *Nature* 332:323–327, 1988.
- Hwang WY, and Foote J. Immunogenicity of engineered antibodies. *Methods* 36:3–10, 2005.
- Arnold JN, Wormald MR, Sim RB, et al. The impact of glycosylation on the biological function and structure of human immunoglobulins. *Annu Rev Immunol* 25:21–50, 2007.
- Andreev J, Thambi N, Perez Bay AE, et al. Bispecific antibodies and antibody-drug conjugates (ADCs) bridging HER2 and prolactin receptor improve efficacy of HER2 ADCs. *Mol Cancer Ther* 16:681–693, 2017.
- Zhang X, Yang Y, Fan D, and Xiong D. The development of bispecific antibodies and their applications in tumor immune escape. *Exp Hematol Oncol* 6:12, 2017.
- Parslow AC, Parakh S, Lee FT, et al. Antibody-drug conjugates for cancer therapy. *Biomedicines* 4:p11PE14, 2016.
- Carter P. Improving the efficacy of antibody-based cancer therapies. *Nat Rev Cancer* 1:118–129, 2001.
- Ecker DM, Jones SD, and Levine HL. The therapeutic monoclonal antibody market. *MAbs* 7:9–14, 2015.
- Rajan TV. The Gell-Coombs classification of hypersensitivity reactions: A re-interpretation. *Trends Immunol* 24:376–379, 2003.
- Pichler WJ. Adverse side-effects to biological agents. *Allergy* 61:912–920, 2006.
- Muraro A, Lemanske RF Jr, Castells M, et al. Precision medicine in allergic disease—food allergy, drug allergy, and anaphylaxis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology. *Allergy* 72:1006–1021, 2017.
- Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. *Allergy* 69:420–437, 2014.
- Brennan PJ, Rodriguez Bouza T, Hsu FI, et al. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol* 124:1259–1266, 2009.
- Levin AS, Otani IM, Lax T, et al. Reactions to rituximab in an outpatient infusion center: A 5-year review. *J Allergy Clin Immunol Pract* 5:107–113.e1, 2017.
- Lemery SJ, Zhang J, Rothmann MD, et al. U.S. Food and Drug Administration approval: Ofatumumab for the treatment of patients with chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab. *Clin Cancer Res* 16:4331–4338, 2010.
- Quercia O, Emiliani F, Foschi FG, and Stefanini GF. Adalimumab desensitization after anaphylactic reaction. *Ann Allergy Asthma Immunol* 106:547–548, 2011.
- Galvao VR, and Castells MC. Hypersensitivity to biological agents—Updated diagnosis, management, and treatment. *J Allergy Clin Immunol Pract* 3:175–185; quiz 186, 2015.
- Doessegger L, and Banholzer ML. Clinical development methodology for infusion-related reactions with monoclonal antibodies. *Clin Transl Immunol* 4:e39, 2015.
- Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 122:574–580, 2008.
- O’Neil BH, Allen R, Spigel DR, et al. High incidence of cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. *J Clin Oncol* 25:3644–3648, 2007.
- Choquette D, Faraawi R, Chow A, et al. Incidence and management of infusion reactions to infliximab in a prospective real-world community registry. *J Rheumatol* 42:1105–1111, 2015.
- Picard M, and Galvao VR. Current knowledge and management of hypersensitivity reactions to monoclonal antibodies. *J Allergy Clin Immunol Pract* 5:600–609, 2017.
- Baldo BA. Adverse events to monoclonal antibodies used for cancer therapy: Focus on hypersensitivity responses. *Oncoimmunology* 2:e26333, 2013.
- Kimby E. Tolerability and safety of rituximab (MabThera). *Cancer Treat Rev* 31:456–473, 2005.
- Lowndes S, Darby A, Mead G, and Lister A. Stevens-Johnson syndrome after treatment with rituximab. *Ann Oncol* 13:1948–1950, 2002.
- Scheinfeld N. A review of rituximab in cutaneous medicine. *Dermatol Online J* 12:3, 2006.
- Hellerstedt B, and Ahmed A. Delayed-type hypersensitivity reaction or serum sickness after rituximab treatment. *Ann Oncol* 14:1792, 2003.
- Maggi E, Vultaggio A, and Matucci A. Acute infusion reactions induced by monoclonal antibody therapy. *Expert Rev Clin Immunol* 7:55–63, 2011.
- Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 114:371–376, 2004.
- Sala-Cunill A, and Cardona V. Biomarkers of anaphylaxis, beyond tryptase. *Curr Opin Allergy Clin Immunol* 15:329–336, 2015.
- Schwartz LB, Bradford TR, Rouse C, et al. Development of a new, more sensitive immunoassay for human tryptase: Use in systemic anaphylaxis. *J Clin Immunol* 14:190–204, 1994.
- Ordoqui E, Zubeldia JM, Aranzabal A, et al. Serum tryptase levels in adverse drug reactions. *Allergy* 52:1102–1105, 1997.
- Craig SS, and Schwartz LB. Tryptase and chymase, markers of distinct types of human mast cells. *Immunol Res* 8:130–148, 1989.
- Giannetti MP, et al. Elevated serum tryptase levels during rituximab hypersensitivity reaction. *J Allergy Clin Immunol* 135[suppl]:AB116, 2015(Abs).
- Sullivan TJ, Wedner HJ, Shatz GS, et al. Skin testing to detect penicillin allergy. *J Allergy Clin Immunol* 68:171–180, 1981.
- Sogn DD, Evans R III, Shepherd GM, et al. Results of the National Institute of Allergy and Infectious Diseases Collaborative Clinical Trial to test the predictive value of skin testing with major and minor penicillin derivatives in hospitalized adults. *Arch Intern Med* 152:1025–1032, 1992.
- Picard M, Pur L, Caiado J, et al. Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions. *J Allergy Clin Immunol* 137:1154–1164.e1–12, 2016.
- Lax T, Long A, and Banerji A. Skin testing in the evaluation and management of carboplatin-related hypersensitivity reactions. *J Allergy Clin Immunol Pract* 3:856–862, 2015.
- Castells MC. Anaphylaxis to chemotherapy and monoclonal antibodies. *Immunol Allergy Clin North Am* 35:335–348, 2015.

45. Markman M, Zanotti K, Peterson G, et al. Expanded experience with an intradermal skin test to predict the presence or absence of carboplatin hypersensitivity. *J Clin Oncol* 21: 4611–4614, 2003.
46. Brockow K, and Romano A. Skin tests in the diagnosis of drug hypersensitivity reactions. *Curr Pharm Des* 14:2778–2791, 2008.
47. Bavbek S, Ataman S, Akinci A, and Castells M. Rapid subcutaneous desensitization for the management of local and systemic hypersensitivity reactions to etanercept and adalimumab in 12 patients. *J Allergy Clin Immunol Pract* 3:629–632, 2015.
48. Sloane D, Govindarajulu U, Harrow-Mortelliti J, et al. Safety, costs, and efficacy of rapid drug desensitizations to chemotherapy and monoclonal antibodies. *J Allergy Clin Immunol Pract* 4:497–504, 2016.
49. Alvarez-Cuesta E, Madrigal-Burgaleta R, Angel-Pereira D, et al. Delving into cornerstones of hypersensitivity to antineoplastic and biological agents: Value of diagnostic tools prior to desensitization. *Allergy* 70:784–794, 2015.
50. Matucci A, Pratesi S, Petroni G, et al. Allergological in vitro and in vivo evaluation of patients with hypersensitivity reactions to infliximab. *Clin Exp Allergy* 43:659–664, 2013.
51. Lieberman P, Rahmaoui A, and Wong DA. The safety and interpretability of skin tests with omalizumab. *Ann Allergy Asthma Immunol* 105:493–495, 2010.
52. Gonzalez-de-Olano D, Morgado JM, Juarez-Guerrero R, et al. Positive basophil activation test following anaphylaxis to pertuzumab and successful treatment with rapid desensitization. *J Allergy Clin Immunol Pract* 4:338–340, 2016.
53. Rocchi V, Puxeddu I, Cataldo G, et al. Hypersensitivity reactions to tocilizumab: Role of skin tests in diagnosis. *Rheumatology (Oxford)* 53:1527–1529, 2014.
54. Rive CM, Bourke J, and Phillips EJ. Testing for drug hypersensitivity syndromes. *Clin Biochem Rev* 34:15–38, 2013.
55. Decuyper II, Mangodt EA, Van Gasse AL, et al. In vitro diagnosis of immediate drug hypersensitivity anno 2017: Potentials and limitations. *Drugs R D* 17:265–278, 2017.
56. Vultaggio A, Matucci A, Nencini F, et al. Drug-specific Th2 cells and IgE antibodies in a patient with anaphylaxis to rituximab. *Int Arch Allergy Immunol* 159:321–326, 2012.
57. Arnold DF, and Misbah SA. Cetuximab-induced anaphylaxis and IgE specific for galactose- α -1,3-galactose. *N Engl J Med* 358:2735; author reply 2735–2736, 2008.
58. Corominas M, Gastaminza G, and Lobera T. Hypersensitivity reactions to biological drugs. *J Investig Allergol Clin Immunol* 24:212–225; quiz 1p following 225, 2014.
59. Parish WE. Short-term anaphylactic IgG antibodies in human sera. *Lancet* II:591–592, 1970.
60. Steenholdt C, Svenson M, Bendtzen K, et al. Acute and delayed hypersensitivity reactions to infliximab and adalimumab in a patient with Crohn's disease. *J Crohns Colitis* 6:108–111, 2012.
61. van Kuijk AW, de Groot M, Stapel SO, et al. Relationship between the clinical response to adalimumab treatment and serum levels of adalimumab and anti-adalimumab antibodies in patients with psoriatic arthritis. *Ann Rheum Dis* 69:624–625, 2010.
62. Bartelds GM, Wijbrandts CA, Nurmohamed MT, et al. Clinical response to adalimumab: Relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann Rheum Dis* 66:921–926, 2007.
63. Takahashi K, Fujimoto T, Shioya M, et al. A case of Crohn's disease that developed anti-infliximab and anti-adalimumab antibodies. *Clin J Gastroenterol* 8:88–91, 2015.
64. Benucci M, Li Gobbi F, Meacci F, et al. Antidrug antibodies against TNF-blocking agents: Correlations between disease activity, hypersensitivity reactions, and different classes of immunoglobulins. *Biologics* 9:7–12, 2015.
65. Steenholdt C. Use of infliximab and anti-infliximab antibody measurements to evaluate and optimize efficacy and safety of infliximab maintenance therapy in Crohn's disease. *Dan Med J* 60:B4616, 2013.
66. Caiado J, Venemalm L, Pereira-Santos MC, et al. Carboplatin-, oxaliplatin-, and cisplatin-specific IgE: Cross-reactivity and value in the diagnosis of carboplatin and oxaliplatin allergy. *J Allergy Clin Immunol Pract* 1:494–500, 2013.
67. Giavina-Bianchi P, Galvao VR, Picard M, et al. Basophil activation test is a relevant biomarker of the outcome of rapid desensitization in platinum compounds—Allergy. *J Allergy Clin Immunol Pract* 5:728–736, 2017.
68. Mangodt EA, Van Gasse AL, Decuyper I, et al. In vitro diagnosis of immediate drug hypersensitivity: Should we go with the flow. *Int Arch Allergy Immunol* 168:3–12, 2015.
69. Thong BY, Mirakian R, Castells M, et al. A world allergy organization international survey on diagnostic procedures and therapies in drug allergy/hypersensitivity. *World Allergy Organ J* 4:257–270, 2011.
70. Romano A, Torres MJ, Castells M, et al. Diagnosis and management of drug hypersensitivity reactions. *J Allergy Clin Immunol* 127(suppl.):S67–S73, 2011.
71. Steiner M, Harrer A, and Himly M. Basophil reactivity as biomarker in immediate drug hypersensitivity reactions—potential and limitations. *Front Pharmacol* 7:171, 2016.
72. Piva E, Chieco-Bianchi F, Krajcar V, et al. Adverse reactions in patients with B-cell lymphomas during combined treatment with rituximab: In vitro evaluation of rituximab hypersensitivity by basophil activation test. *Am J Hematol* 87:E130–E131, 2012.
73. Manso L, Polo B, Fernandez-Nieto M, et al. Basophil activation test in a case of systemic hypersensitivity reaction to infliximab with good tolerance to another anti-TNF-alpha agent (adalimumab). *J Investig Allergol Clin Immunol* 20:537–538, 2010.
74. Castells M. Desensitization for drug allergy. *Curr Opin Allergy Clin Immunol* 6:476–481, 2006.
75. Castells M. Rapid desensitization for hypersensitivity reactions to medications. *Immunol Allergy Clin North Am* 29:585–606, 2009.
76. Sancho-Serra Mdel C, Simarro M, and Castells M. Rapid IgE desensitization is antigen specific and impairs early and late mast cell responses targeting Fc ϵ RI internalization. *Eur J Immunol* 41:1004–1013, 2011.
77. Oka T, Rios EJ, Tsai M, et al. Rapid desensitization induces internalization of antigen-specific IgE on mouse mast cells. *J Allergy Clin Immunol* 132:916–922.e1–16, 2013.
78. Andrews NL, Pfeiffer JR, Martinez AM, et al. Small, mobile Fc ϵ 1RI receptor aggregates are signaling competent. *Immunity* 31:469–479, 2009.
79. Katz HR. Inhibitory receptors and allergy. *Curr Opin Immunol* 14:698–704, 2002.
80. Katz HR. Inhibition of anaphylactic inflammation by the gp49B1 receptor on mast cells. *Mol Immunol* 38:1301–1305, 2002.
81. Mahajan A, Barua D, Cutler P, et al. Optimal aggregation of Fc ϵ RI with a structurally defined trivalent ligand overrides negative regulation driven by phosphatases. *ACS Chem Biol* 9:1508–1519, 2014.
82. Lu-Kuo JM, Joyal DM, Austen KF, and Katz HR. gp49B1 inhibits IgE-initiated mast cell activation through both immunoreceptor tyrosine-based inhibitory motifs, recruitment of src homology 2 domain-containing phosphatase-1, and suppression of early and late calcium mobilization. *J Biol Chem* 274: 5791–5796, 1999.
83. Ang WX, Church AM, Kulis M, et al. Mast cell desensitization inhibits calcium flux and aberrantly remodels actin. *J Clin Invest* 126:4103–4118, 2016.
84. Bavbek S, Ataman S, Bankova L, and Castells M. Injection site reaction to adalimumab: Positive skin test and successful rapid desensitization. *Allergol Immunopathol (Madr)* 41:204–206, 2013.

85. Bavbek S, Aydin O, Ataman S, et al. Injection-site reaction to etanercept: Role of skin test in the diagnosis of such reaction and successful desensitization. *Allergy* 66:1256–1257, 2011.
86. Castells Guitart MC. Rapid drug desensitization for hypersensitivity reactions to chemotherapy and monoclonal antibodies in the 21st century. *J Investig Allergol Clin Immunol* 24:72–79; quiz 2 p following 79, 2014.
87. Breslow RG, Caiado J, and Castells MC. Acetylsalicylic acid and montelukast block mast cell mediator-related symptoms during rapid desensitization. *Ann Allergy Asthma Immunol* 102:155–160, 2009.
88. Vultaggio A, Maggi E, and Matucci A. Immediate adverse reactions to biologicals: From pathogenic mechanisms to prophylactic management. *Curr Opin Allergy Clin Immunol* 11: 262–268, 2011.
89. Hsu Blatman KS, and Castells MC. Desensitizations for chemotherapy and monoclonal antibodies: Indications and outcomes. *Curr Allergy Asthma Rep* 14:453, 2014.
90. Rituxan (rituximab) [package insert]. Cambridge, MA: Biogen Idec Inc., 2011.
91. Grillo-Lopez AJ, White CA, Varns C, et al. Overview of the clinical development of rituximab: First monoclonal antibody approved for the treatment of lymphoma. *Semin Oncol* 26(suppl. 14):66–73, 1999.
92. Dawson K, Moran M, Guindon K, and Wan H. Managing infusion-related reactions for patients with chronic lymphocytic leukemia receiving obinutuzumab. *Clin J Oncol Nurs* 20:E41–E48, 2016.
93. Gazyva (obinutuzumab) [package insert]. South San Francisco, CA: Genentech Inc., 2015.
94. Guan M, Zhou YP, Sun JL, and Chen SC. Adverse events of monoclonal antibodies used for cancer therapy. *Biomed Res Int* 2015:428169, 2015.
95. Arzerra (ofatumumab) [package insert]. Research Triangle Park, NC: GlaxoSmithKline, 2011.
96. Adcetris (brentuximab) [package insert]. Seattle, WA: Genet-ics, Inc., 2012.
97. DeVita MD, Evens AM, Rosen ST, et al. Multiple successful desensitizations to brentuximab vedotin: A case report and literature review. *J Natl Compr Canc Netw* 12:465–471, 2014.
98. Story SK, Petrov AA, and Geskin LJ. Successful desensitization to brentuximab vedotin after hypersensitivity reaction. *J Drugs Dermatol* 13:749–751, 2014.
99. O'Connell AE, Lee JP, Yee C, et al. Successful desensitization to brentuximab vedotin after anaphylaxis. *Clin Lymphoma Myeloma Leuk* 14:e73–e75, 2014.
100. Herceptin (trastuzumab) [package insert]. South San Francisco, CA: Genentech, Inc., 2011.
101. Cook-Bruns N. Retrospective analysis of the safety of Herceptin immunotherapy in metastatic breast cancer. *Oncology* 61(suppl. 2):58–66, 2001.
102. Perjeta (Pertuzumab) [package insert]. South San Francisco, CA: Genentech Inc., 2016.
103. Erbitux (cetuximab) [package insert]. Summit, NJ: Celgene Corp., 2012.
104. Yamaguchi K, Watanabe T, Satoh T, et al. Severe infusion reactions to cetuximab occur within 1 h in patients with metastatic colorectal cancer: Results of a nationwide, multicenter, prospective registry study of 2126 patients in Japan. *Jpn J Clin Oncol* 44:541–546, 2014.
105. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 351:337–345, 2004.
106. Siena S, Glynne-Jones R, Adenis A, et al. Reduced incidence of infusion-related reactions in metastatic colorectal cancer during treatment with cetuximab plus irinotecan with combined corticosteroid and antihistamine premedication. *Cancer* 116: 1827–1837, 2010.
107. Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: Phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol* 26:2311–2319, 2008.
108. Keating K, Walko C, Stephenson B, et al. Incidence of cetuximab-related infusion reactions in oncology patients treated at the University of North Carolina Cancer Hospital. *J Oncol Pharm Pract* 20:409–416, 2014.
109. George TJ Jr, Laplant KD, Walden EO, et al. Managing cetuximab hypersensitivity-infusion reactions: Incidence, risk factors, prevention, and retreatment. *J Support Oncol* 8:72–77, 2010.
110. Avastin (bevacizumab) [package insert]. South San Francisco, CA: Genentech Inc., 2017.
111. Xolair (omalizumab) [package insert]. South San Francisco, CA: Genentech, Inc., 2010.
112. Cox L, Lieberman P, Wallace D, et al. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Omalizumab—Associated Anaphylaxis Joint Task Force follow-up report. *J Allergy Clin Immunol* 128:210–212, 2011.
113. Nucala (mepolizumab) [package insert]. Ontario, Canada: GlaxoSmithKline Inc., 2016.
114. Actemra (tocilizumab) [package insert]. South San Francisco, CA: Genentech, Inc., 2016.
115. Orencia (abatacept) [package insert]. Ontario, Canada: Bristol-Myers Squibb, 2016.
116. Enbrel (etanercept) [package insert]. Newbury Park, CA: Immunex Corp., 2013.
117. Remicade (infliximab) [package insert]. Horsham, PA: Janssen Biotech, Inc., 2013.
118. Humira (adalimumab), [package insert]. Lake Bluff, IL: Abbott Laboratories, 2017.
119. Judson MA, Baughman RP, Costabel U, et al. Safety and efficacy of ustekinumab or golimumab in patients with chronic sarcoidosis. *Eur Respir J* 44:1296–1307, 2014.
120. Smolen JS, Kay J, Landewe RB, et al. Golimumab in patients with active rheumatoid arthritis who have previous experience with tumour necrosis factor inhibitors: Results of a long-term extension of the randomised, double-blind, placebo-controlled GO-AFTER study through week 160. *Ann Rheum Dis* 71:1671–1679, 2012.
121. Keystone E, Heijde Dv, Mason D Jr, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: Findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 58:3319–3329, 2008.
122. Fleischmann R, Vencovsky J, van Vollenhoven RF, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: The FAST4WARD study. *Ann Rheum Dis* 68:805–811, 2009.
123. Opdivo (nivolumab) [package insert]. Montreal, Quebec, Canada: Bristol-Myers Squibb, 2017.
124. Nayar N, Briscoe K, and Fernandez Penas P. Toxic epidermal necrolysis-like reaction with severe satellite cell necrosis associated with nivolumab in a patient with ipilimumab refractory metastatic melanoma. *J Immunother* 39:149–152, 2016.
125. Keytruda (pembrolizumab) [package insert]. Kirkland, Quebec, Canada: Merck Canada Inc., 2017.
126. Jacquenet S, Moneret-Vautrin DA, and Bihain BE. Mammalian meat-induced anaphylaxis: Clinical relevance of anti-galactose-alpha-1,3-galactose IgE confirmed by means of skin tests to cetuximab. *J Allergy Clin Immunol* 124:603–605, 2009. □

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