



Hypersensitivity and Immune-related Adverse Events in Biologic Therapy

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Accepted: 13 July 2021

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Abstract

Biologic medications are an expanding field of therapeutics for various medical conditions including cancer and inflammatory diseases. Due to their targeted approach to therapy, biologics can be less toxic than traditional systemic medications. However, as use becomes more widespread, adverse effects from biologic administration have also become apparent. Immune-related adverse events are a common mechanism by which biologics can cause on-target immune-related toxicities and both immediate and delayed-type hypersensitivity reactions. Immediate hypersensitivity reactions can be mediated by cytokine release or antibody mediated reactions, while delayed-type hypersensitivity is most often caused by serum sickness-like reactions. Additionally, biologics used for treatment of cancer using checkpoint blockade and rheumatologic disease using cytokine blockade can result in autoimmunity. Finally, when inflammatory cytokines are targeted for treatment of autoimmune or autoinflammatory disease, the host immune defense can be compromised predisposing to secondary immunodeficiency. This review will discuss the mechanisms of these reactions and discuss examples of biologics implicated in each of these adverse events.

Keywords Biologics · Immune-related adverse events · Hypersensitivity · Checkpoint inhibitor

Introduction

Biologic drugs are an emerging category of pharmaceuticals broadly defined by their derivation from a biological source [1, 2]. They encompass a range of protein-based therapeutics, including monoclonal antibodies (mAb), fusion receptor proteins, hormones, and cytokines [1, 3]. In this review, we will focus mainly on mAbs, which are derived from a single clone binding to a single epitope. This method was first introduced by Kohler et al. in 1974 with the advent of hybridoma technology [2, 4]. Initial monoclonal antibody structure was comprised of a murine-derived variable region fused with a human IgG constant region [2]. Initially, mAbs were approximately 25% murine Fab fragments fused with a

human IgG heavy chain, referred to as chimeric mAbs and contain the highest percentage of murine-derived components [2, 3]. As murine sequence increases immunogenicity, production of therapeutic mAbs with reduced murine components occurred forming “humanized” mAb [2, 3]. Humanized mAbs contain 2–5% of murine sequence, limited to the hypervariable regions of the Fab fragment [1, 2]. Fully human mAbs are derived completely from human immunoglobulin IgG and do not contain murine components [1].

Biologics differ from conventional pharmaceutical drugs in many ways. They are structurally similar to autologous proteins, while conventional drugs are synthesized small-molecule chemicals [3, 5]. Most biologics are administered parenterally, while conventional drugs have numerous routes of administration [3]. Another distinction of biologics is they are metabolized like endogenous proteins [3]. Biologics are considered complete allergens capable of inducing IgE-mediated responses to murine epitopes or neoepitopes contained in these large molecular weight proteins [3]. Conventional drugs may require covalent binding to self-protein to elicit an immune response as they are not allergens [6]. Additionally, unique properties of biologics contribute to

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longer half-life and unique episodic dosing intervals contributing to increased risk of immunogenicity compared to conventional medications [5].

Adverse events related to biologics may limit use when few alternatives are available. As biologic medications represent a distinct group of therapeutics, adverse reactions do not fit into traditional Gel and Coombs reaction classification. Pichler et al. proposed new classification of adverse reactions to biologic medications encompassing five distinct adverse drug events [7, 8]. Alpha reactions occur from release of high levels of cytokines (cytokine release syndrome (CRS)). Beta reactions are hypersensitivity reactions (HSR) that are immediate (IgE/IgG) or delayed (IgG) antibody mediated reactions or T

cell mediated. Gamma reactions manifest as immune or cytokine imbalance syndromes such as immunodeficiency, autoimmune, or atopic disorders. Delta reactions occur due to cross reactivity based on biologic recognition of the target or similar antigen on normal or tumor cells. Epsilon reactions are non-immunological side effects [7]. This review will focus on adverse events that are immunologic, including immediate and delayed HSRs, and those due to biologic-induced alterations in the immune system leading to autoimmunity, inflammation, or immunosuppression.

The text for HSRs is summarized in Tables 1–4 with Table 1 listing immediate reactions and the associated biologics, Table 2 the delayed reactions and associated biologics, Table 3 listing single biologics and their

Table 1 Immediate hypersensitivity reactions and skin testing concentrations for biologics

Cutaneous reactions: Pruritus		
Infliximab	Reported in 5–8% of autoimmune patients [14]	
Rituximab	Reported in up to 20% of lymphoma patients [14]	
Cutaneous reactions: Urticaria and/or Angioedema		
Infliximab	Up to 3% of Crohn's disease patients and up to 6% of rheumatoid arthritis patients [13]	
Rituximab	Study reports vary from no reports to 3–14% of reactions [13]	
Etanercept	Reported in 38.5% of reactions [15]	
Adalimumab	Reported in up to 42.8% of reactions [15]	
Acute infusion reactions (including cytokine release syndrome (CRS))		
Infliximab	1.3–4.6% of initial infusions [17, 23–25]	
Rituximab	Acute infusion reactions in up to 70–78% of initial infusions; majority CRS [3, 20–22] Up to 50% of initial infusions for B-cell lymphoma [12, 22]Up to 25% of initial infusions for inflammatory disorders [12]	
Trastuzumab	16–40% of initial infusions for breast cancer [12, 26, 27]	
Cetuximab	Incidence of 15–20% of infusions [19]	
Immediate hypersensitivity reactions (HSR)		
Infliximab	Reported in up to 10% of patients; IgG mediated with incidence peaking at ~7th infusion [12, 33]	
Rituximab	Reported in 5–10% of infusions [3, 38]	
Trastuzumab	Rare reports at 0.6–5% of infusions [5, 12]	
Cetuximab	Up to 22% of initial infusions in Southeast USA. Due to preformed alpha-gal IgE [11, 12, 29, 59]	
Omalizumab	Rare reports at 0.1% of doses; 78% occur within the first 3 doses [1, 3, 12]Case reports of IgE-mediated anaphylaxis to polysorbate in Xolair formulation [1, 36]	
Natalizumab	Rare case reports [1, 3, 12]	
Non-irritating skin testing concentrations [12, 16]		
Medication	Skin prick testing concentration	Intradermal testing concentration
Infliximab [32, 154]	10 mg/mL (full strength)	1 mg/mL (1/10 dilution)
Rituximab [5, 154]	10 mg/mL (full strength)	1 mg/mL (1/10 dilution)‡
Etanercept [53]	50 mg/mL (full strength)	0.5 mg/mL (1/100 dilution)
Adalimumab [53]	40 mg/ mL (full strength)	0.4 mg/mL (1/100 dilution)
Trastuzumab [5]	21 mg/mL (full strength)	2.1 mg/mL (1/10 dilution)
Omalizumab [155]	125 mg/mL (full strength)†	0.00125 mg/mL (1/100,000 dilution)
Natalizumab [42]	20 mg/mL (full strength)	0.002 mg/mL (1/10,000 dilution)
Cetuximab [39, 154]	2 mg/mL (full strength)	0.2 mg/mL (1/10 dilution)*

* A concentration of 0.5 mg/mL was shown to be nonirritating in 8 controls [155], and another group reported a concentration of 5 mg/mL to be nonirritating [153]

† Omalizumab should be reconstituted with normal saline to avoid false positive results [154]

‡ 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 [153]

Table 2 Delayed hypersensitivity reactions with biologic use

Delayed cutaneous injection site reactions (ISR)	
Etanercept	20% of patients develop ISRs. Most ISRs occur in first 2 months [9, 12]
Adalimumab	20% of patients develop ISRs. Most ISRs occur in first 2 months [9, 12]
Certolizumab	2–6% of patients developed ISRs [12]
Golimumab	2–6% of patients developed ISRs [12]
Ustekinumab	ISRs develop in 2.4% of patients [1]
Anakinra	Up to 71% of patients develop ISRs [1]
Delayed generalized cutaneous reactions	
Infliximab	Generalized erythematous-squamous exanthema within 2–4 weeks following infusion [9]
Severe cutaneous adverse reactions (SCAR)	
Infliximab	1 case of Symmetrical Drug-Related Intertriginous and Flexural Exanthema (SDFRIFE) [60]
Rituximab	Small numbers of both SJS and SJS-TEN overlap. One case of TEN [13, 38, 59]
Cetuximab	1 case of TEN reported [9]
Checkpoint Inhibitors	SJS and TEN described with ipilimumab, nivolumab, and pembrolizumab [59]
Serum sickness like reactions (SSLR)	
Infliximab	2.5% of patients [9]. Described in IBD patients [8, 20]
Rituximab	85% of cases in patients with autoimmune disease 15% of cases in hematologic malignancy [56]
Trastuzumab	Described in treatment of breast cancer patients [9]
Omalizumab	Described in 0.4–0.6% patients overall Reported in up to 25% of patients with mast cell activation disorders [69]
Natalizumab	Described in MS patients [33]

associated reactions, while Table 4 lists management for the described hypersensitivity reactions.

Immune-related Hypersensitivity Reactions

HSRs to biologic medications comprise a variety of immunologic and non-immunologic mechanisms leading to clinical reactions. The term allergic hypersensitivity refers to reactions attributed to underlying antibody- or cellular-mediated immune reactions [9]. The clinical manifestations of HSRs may vary depending on the underlying immune mechanism and range from cutaneous reactions (pruritus, rash, urticaria, flushing) to life-threatening reactions (e.g., anaphylaxis or severe cutaneous adverse reactions (SCARs)). Reactions are further classified by timing of presentation of symptoms; reactions may occur immediately (within 1–2 h of biologic administration) or be delayed (greater than 2 h and up to 14 days) [9]. Timing of the reaction within the therapeutic course may also reveal the underlying immune mechanism; reactions occurring with initial administration are attributed to cytokine release or existence of pre-formed antibodies versus reactions that occur after several administrations, indicating development of anti-drug antibodies (ADA). Isabwe et al. proposed a classification system for mAb-specific HSRs based on endotype, defined by biomarkers (specific laboratory values and test results)

and phenotype, defined by the clinical presentation, of the adverse reaction [10]. This system serves as a subclassification of Pichler's beta reactions (HSRs), and further characterizes the subcategories of mAb HSRs and includes type I/type I-like reactions, cytokine-release reactions, mixed reactions, and delayed type IV reactions [7, 10].

Immediate Hypersensitivity Reactions

Immediate or acute HSRs are defined by the presence of clinical symptoms within 1–2 h of biologic administration and includes type I-like reactions as defined by Isabwe et al. [1, 9–11]. Isabwe et al. define these type I reactions as symptoms of flushing, pruritus, urticaria, shortness of breath, hypotension, and anaphylaxis that occur within 1–2 h due to release of mast cell and basophil mediators, such as tryptase, histamine, leukotrienes, and prostaglandins [10]. In contrast, type IV reactions can manifest as nonsevere maculopapular rash to more severe cutaneous adverse reactions (SCARs) that arise 12 h to several weeks following biologic exposure [10]. Clinical manifestations may be limited to cutaneous symptoms or include more diffuse systemic involvement with symptoms reflective of anaphylactic reactions [9, 11]. Clinical symptoms may include pruritus, flushing, urticaria/angioedema, shortness of breath,

Table 3 Biologics and associated hypersensitivity reactions and immune-related adverse events

Infliximab	Hypersensitivity reactions	
	Cutaneous reactions	
	<i>Immediate</i>	Pruritus alone in 5–8% patients [15]
		Urticaria/angioedema in 3% of CD and 6% of RA patients [13]
	<i>Delayed</i>	Generalized erythematous-squamous exanthema. Onset 2–4 weeks following infusion [9]
	Systemic reactions	
	<i>Infusion Reactions/CRS</i>	Up to 1.3–4.6% of infusions in IBD patients [17, 23–25]
	<i>Immediate HSR</i>	Up to 10% of infliximab treated patients [12, 33]
	<i>SSLR</i>	Onset 5–7 days following infusion in 2.5% of patients [9, 12, 62]
	Immune-related adverse events (IRAE)	
	Inflammatory reactions	
	<i>Paradoxical Psoriasis</i>	Up to 1.4% of patients [91]
	<i>Lupus-like disease</i>	Incidence of 0.66% of patients [91]
	<i>Vasculitis</i>	0.7% of patients on biologics. A total of 94% of cases were RA/sJIA patients on infliximab or etanercept [91]
	<i>Anti-Drug Antibodies</i>	Highest rates of ADAs from infliximab and adalimumab in RA patients [104]
Rituximab	Opportunistic infection: Increased risk of <i>M. tuberculosis</i> infection [112, 136, 137]	
	Hypersensitivity reactions	
	Cutaneous reactions	
	<i>Immediate</i>	Pruritus alone in up to 20% lymphoma patients [13]
		Urticaria/angioedema varying from 3 to 14% [13]
	<i>Delayed</i>	Small numbers of SJS and SJS-TEN overlap
		1 case report of TEN [13, 38, 59]
	Systemic reactions	
	<i>Infusion reactions/CRS</i>	Up to 70–78% of initial infusions; majority CRS [3, 20–22]
		Up to 50% of initial infusions for B-cell lymphoma [12, 22] Up to 25% of initial infusions for inflammatory disorders [12]
	<i>Immediate HSR</i>	Reported in 5–10% of infusions [3, 38]
	<i>SSLR</i>	85% of cases in patients with autoimmune disease
		15% of cases in hematologic malignancy [56]
	Immune-related adverse events	
	Inflammatory reactions	
	<i>Paradoxical Psoriasis</i>	Very uncommon cause ($\leq 1\%$) of total cases [91]
	<i>Vasculitis</i>	Rare cases with rituximab [91]
Etanercept	Hypersensitivity reactions	
	Cutaneous reactions	
	<i>Immediate</i>	Reported in 38.5% of reactions [15]
	<i>Delayed</i>	ISRs in 20%. Most occur in first 2 months [9, 12]
	Immune-related adverse events	
	<i>Paradoxical Psoriasis</i>	Up to 0.19% of patients [91]
	<i>Lupus-like disease</i>	Incidence of 0.49% of patients [91]
	<i>Vasculitis</i>	0.7% of patients on biologics. A total of 94% of cases were RA/sJIA patients on infliximab or etanercept [91]
	Opportunistic infection: Increased risk of <i>M. tuberculosis</i> infection [112, 136, 137]	

Table 3 (continued)

Adalimumab	Hypersensitivity reactions	
	Cutaneous reactions	
	<i>Immediate</i>	Urticaria/angioedema reported in up to 42.8% of reactions [15]
	<i>Delayed</i>	ISRs in 20%. Most occur in first 2 months. [9, 12]
	Immune-related adverse events	
	<i>Paradoxical Psoriasis</i>	Up to 1.29% of patients [91]
	<i>Lupus-like disease</i>	Incidence of 0.11% of patients [91]
Trastuzumab	<i>Anti-drug antibodies</i>	Highest rates of ADAs from infliximab and adalimumab in RA patients [104]
	Opportunistic infection: increased risk of <i>M. tuberculosis</i> infection	[112, 136, 137]
	Hypersensitivity reactions	
	Systemic reactions	
	<i>CRS</i>	16–40% of initial infusions for breast cancer [12, 26, 27]
	<i>Immediate HSR</i>	Rare reports at 0.6–5% of infusions [5, 12]
	<i>SSLR</i>	Described in treatment of breast cancer patients [9]
Cetuximab	Hypersensitivity reactions	
	Cutaneous reactions	
	<i>Delayed</i>	1 case of TEN reported [9]
	Systemic reactions	
	<i>CRS</i>	Incidence of 15–20% of infusions [19]
	<i>Immediate HSR</i>	Up to 22% of initial infusions in Southeast USA
		Due to preformed alpha-gal IgE [11, 12, 29, 59]
Omalizumab	Hypersensitivity reactions	
	Systemic reactions	
	<i>Immediate HSR</i>	Rare (0.1% of doses); 78% occur within the first 3 doses [1, 3, 12] Case reports of anaphylaxis to polysorbate in formulation [1, 36]
	<i>SSLR</i>	Described in 0.4–0.6% patients overall
		Up to 25% of patients with mast cell activation disorders [69]
Natalizumab	Hypersensitivity reactions	
	Systemic reactions	
	<i>Immediate HSR</i>	Rare case reports [1, 42, 43]
	<i>SSLR</i>	Described in MS patients [33]
	Opportunistic infection: PML development due to JC virus reactivation	[143, 144, 146]

hypotension, and life-threatening anaphylaxis. Biomarkers include elevated serum tryptase and patients may have positive skin testing, although the utility of skin testing with mAbs remains limited [10]. For clinical management and evaluation of immediate HSRs, Picard and Galvao have previously published a useful algorithm (Fig. 1) [12].

Cutaneous Reactions

Symptoms with cutaneous limited reactions may occur locally or have widespread involvement of the skin. Local injection site reactions result from immediate development of erythema, swelling, burning/stinging, pruritus, urticaria, and pain [8, 13]. These symptoms are more commonly

associated with subcutaneous injections and triggered by direct mast cell degranulation [8, 9, 13]. Pruritus, as a non-immunologic side effect, is associated with multiple biologic medications, including infliximab and rituximab [14].

Clinical manifestations of disseminated skin reactions may include diffuse pruritus, urticaria, and angioedema, and have been reported with several biologic agents. Urticaria has been reported with biologics including etanercept, infliximab, and rituximab [13, 15]. With infliximab therapy, up to 3% and 6% of Crohn's disease and rheumatoid arthritis (RA) patients, respectively, reported urticaria [13]. Subsequent cases of urticaria alone or with angioedema have been reported with infliximab, etanercept, and adalimumab [15]. Urticaria is also common with rituximab, ranging from 3 to

Table 4 Management of reactions

Cutaneous reactions	<i>Immediate</i>	
	Urticaria/pruritus	Slowing infusion rate (as low as 10 mL/h) or pretreatment with antihistamines [13] Recurrent symptoms with premedication or slower infusion rate may require desensitization [12, 16]
	<i>Delayed</i>	
	Injection site reactions	Apply ice, topical corticosteroids. Oral H1/H2 antihistamines and/or analgesics may also help [9, 12]
Systemic Reactions	Generalized	No consensus on management. Avoidance recommended [9]
	SCAR	Strict avoidance of biologic recommended [10]
	<i>Immediate*</i>	
	Infusion reactions	Stop infusion, then restart at a slower rate. Control or prevent symptoms with H1 antihistamines and corticosteroids during or prior to infusions [3, 9, 16, 18]
	CRS (severe infusion reaction)	Stop infusion, treat with rescue medications epinephrine, IV fluids, H1 antihistamine, oxygen, high dose IV steroids [9, 16] Premedication for prevention: [12, 15, 17]Acetaminophen 650 mg Corticosteroids: Options include the following: 1. Prednisone 50 mg, 3 doses in 12 h prior to infusion 2. Hydrocortisone 100 mg IV 20 min prior to infusion 3. Methylprednisolone 20–40 mg IV 20 min prior to infusion [16]
	HSR/Anaphylaxis	Stop infusion, treat with rescue medications epinephrine, IV fluids, H1 antihistamine, oxygen. Corticosteroids for delayed symptoms may be used [11] For further treatment: Referral to allergist: • Biologic skin testing for treatment guidance (Table 1) • Desensitization if consistent with IgE-mediated reaction. Protocols specific for each biologic. Many use a 3-bag/12-step protocol [5, 10, 16, 33] • Desensitization possible for IgG mediated immediate HSRs with infliximab [17, 53]
	<i>Delayed</i>	
	SSLR	Treatment of symptoms with corticosteroids Severe reactions may require plasma exchange Premedication: No established role [9] Desensitization: Not safe in most SSLRs [12, 61]

14% of patients receiving rituximab, though other studies have not reported urticaria [13].

Most reactions are mild and can be managed by the primary prescribing provider (the oncologist or rheumatologist) without need for allergy referral [16]. Management of urticaria may include slowing infusion rate to restart as low as 10 mL/h, depending on the biologic, and antihistamine premedication with H1 or H2 antihistamines administered orally 30 min to 1 h prior to subsequent doses [12, 13, 17]. Recurrent symptoms despite premedication and slowing infusion rate may require desensitization [12, 16].

Acute Infusion Reactions and CRS

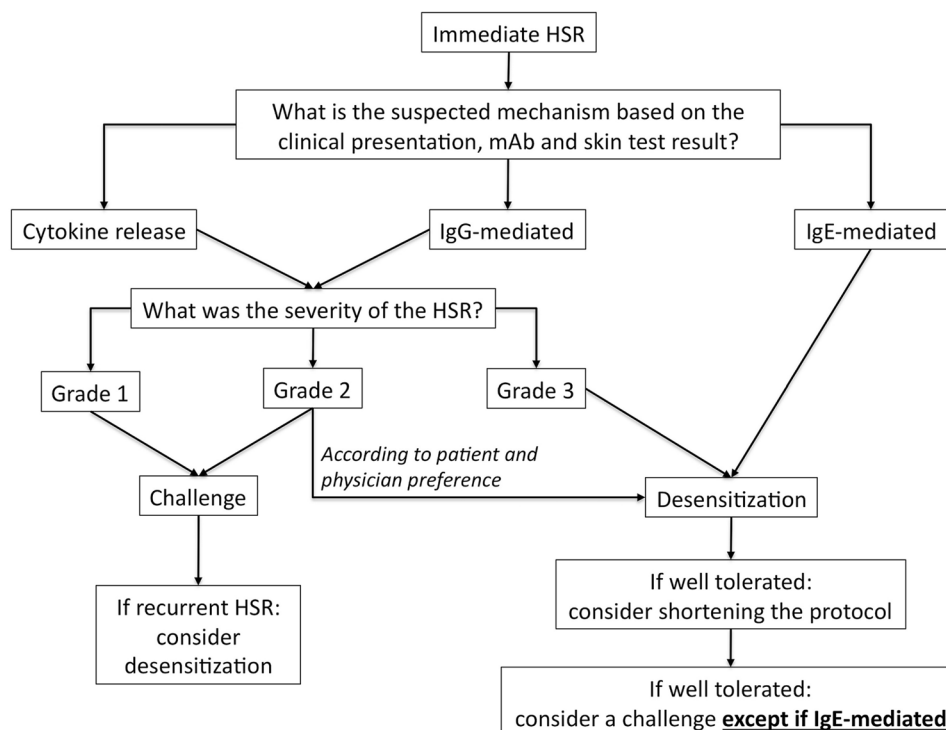
Acute infusion reactions are the most commonly reported reactions to mAbs, occurring in up to 50% of biologic administrations [3, 10]. Reactions are generally mild and may occur with initial administration. They are non-immunogenic, caused by non-specific release of proinflammatory cytokines IL-6, IFN- γ , and TNF- α [3, 8], often from binding of the mAb to the targeted molecule causing cell lysis and

cytokine release [3, 9, 10]. These reactions are considered predictable and related to rate of medication administration [3]. Clinical presentation includes fevers, rigors, back and abdominal pain, nausea, vomiting, diarrhea, dyspnea, flushing, pruritus, and changes to heart rate or blood pressure [3]. Rituximab and infliximab are implicated in these reactions [3, 8, 9, 18].

Management includes premedication with antihistamines (diphenhydramine 25–50 mg PO) and acetaminophen (650 mg PO) given 30 min prior to biologic administration, and slowing infusion rates; more severe reactions may warrant systemic corticosteroid premedication with either oral prednisone (3 doses of 50 mg given over 12 h prior to infusion) or intravenous hydrocortisone (100 mg) or methylprednisolone (20–40 mg) given 20 min before infusion [16, 17].

CRS is considered the most severe type of acute infusion reaction [8]. These reactions are postulated to result from the biologic binding to Fc γ -receptors on monocytes and macrophages, cytotoxic T cells, and natural killer cells, inducing release of IL-6, IFN- γ , and TNF- α [8, 9, 12, 18]. CRS is associated with the initial administration of a biologic

Fig. 1 Suggested algorithm for the management of immediate hypersensitivity reactions to monoclonal antibodies. HSR hypersensitivity reaction, mAb monoclonal antibody. Adapted from Picard et al. [12]



and waning with subsequent doses in the therapeutic course [12]. Symptoms may be nonspecific, such as flushing, dyspnea, throat tightness, dizziness, hypotension, vomiting, diarrhea, and may be indistinguishable from anaphylaxis or symptoms may be more distinctive and include headache, increased blood pressure, chest and back pain, fever, chills, and rigors [3, 8, 9, 12, 18]. While clinical manifestations in CRS may be overlap with symptoms seen in immediate antibody mediated HSRs, elevation of tryptase and generation of drug specific IgE or IgG antibodies are not observed in CRS [12]. A number of biologics may cause CRS, including rituximab, trastuzumab, and cetuximab [8, 12, 19].

Management of cytokine release syndrome involves pre-medication with systemic corticosteroids and acetaminophen (650 mg PO), as well as slowing the infusion rate of the biologic medication [12]. The route, dose, and specific corticosteroid may vary depending on reaction severity, medication availability, and clinic protocol; this may range from a 50-mg oral dose of prednisone for three doses prior to infusion to 100 mg IV hydrocortisone or 20–40 mg IV methylprednisolone given 20 min prior to the infusion [12, 16, 17].

Rituximab

Up to 70–78% of initial rituximab infusions have been associated with acute infusion reactions [3, 20–22]. Most reactions are mild to moderate in severity and do not recur upon rituximab readministration [12]. Patients receiving rituximab for B-cell lymphoma have had reports of up to

50% infusion reaction rates, with inflammatory disorders such as rheumatoid arthritis patients experiencing a lower incidence with reaction rate around 25% per infusion [12, 21]. The majority of symptoms resolved with slowing of infusion rate or with antihistamines or acetaminophen [23].

Up to 50% of patients treated for B cell malignancy with rituximab experience CRS upon first exposure. These reactions are attributed to massive B-cell lysis with elevated levels of IL-6 and TNF- α correlating to reaction severity [12]. CRS reactions are less common in patients receiving rituximab for inflammatory disorders; in one study, 25% of RA patients were reported to have CRS upon initial drug exposure [12, 21]. This patient population consisted of majority females with a diagnosis of RA and a mean age of 51 years; patients in this study received 100 mg intravenous methylprednisolone prior to all rituximab infusions while on concurrent methotrexate (10–25 mg/week) and the majority also received acetaminophen and antihistamine premedication as well [21].

Infliximab

Lower rates of acute infusion reactions are reported with infliximab, mainly occurring in inflammatory bowel disease (IBD) patients, ranging from 1.3 to 4.6% [17, 23–25].

Trastuzumab

Trastuzumab, a biologic targeting the human epidermal growth factor receptor 2 (HER 2) in breast cancer, has also

been associated with CRS in 16–40% of patients [12, 26, 27]. Most patients who had CRS tolerated future infusions of trastuzumab with antihistamine and corticosteroid premedication [12].

Antibody-mediated Reactions

Immediate reactions may also be caused by anti-drug antibody (ADA)-mediated mechanisms. Reactions mediated by biologics may be triggered by drug-specific IgE or IgG. ADAs are induced after multiple tolerated exposures to the biologic agent [8, 9, 28]. However, immediate antibody-mediated reactions may also occur secondary to preformed anti-biologic IgE or IgG [9, 18, 29, 30]. Although the role of IgG antibodies as mediators of immediate HSRs is not as well established as IgE, they have been implicated in pathogenesis of HSRs for some biologics, such as infliximab [12]. The proposed mechanism is that IgG ADAs bind to Fc γ -receptors on basophils and neutrophils, stimulating release of platelet-activating factor [12, 31]. Additionally, large IgG ADA-drug complexes may activate complement, causing mast cell degranulation of anaphylatoxins [9, 12].

Clinical manifestations include GI symptoms, dyspnea, flushing, pruritus, back pain, and may overlap with symptoms due to acute infusion reactions or CRS [3, 12]. In order to distinguish these reactions from CRS, antibody-mediated reactions may be confirmed by elevated tryptase at the time of reaction for both IgG and IgE-mediated reactions, and through traditional allergy skin testing for IgE-mediated reactions [12]. However, as biologics are relatively new, studies are needed to determine appropriate reagent concentrations for allergy skin testing of specific biologics. Detection of drug specific IgE and IgG antibodies is also possible for the purposes of identifying adverse reactions, but are not commercially available [12]. Allergy skin testing with IgG-mediated HSRs is negative as they are mediated by IgG, not IgE [12].

Immediate IgE-mediated HSRs occur when repeated exposure to a biologic elicits drug-specific IgE [9, 12, 32]. Anti-biologic IgE binds to the Fc ϵ receptor I on mast cells and basophils and, upon re-exposure to the drug, IgE crosslinking leads to cellular degranulation and release of inflammatory mediators including histamine, cysteinyl leukotrienes, and tryptase [9, 18, 32]. Symptoms range from mild to anaphylaxis and may include flushing, urticaria, angioedema, airway obstruction, and hypotension [3, 9, 12, 18]. Several biologics are implicated in IgE HSRs including omalizumab, rituximab, infliximab, trastuzumab, and others [5, 12, 33].

Management includes referral to an allergist for skin testing and possible desensitization if the medication is necessary with no suitable therapeutic alternatives [16]. Multiple groups have successfully achieved desensitization to several

biologics and many of these protocols have been published [16]. Desensitization protocols vary depending on the biologic and route of administration, with several protocols based on a 3-bag /12-step protocol [5, 10, 16, 33].

It is notable that acute infusion or CRS reactions may be indistinguishable from IgE and IgG-mediated anaphylaxis [9, 12, 18], and also mixed reactions with symptoms from both cytokine release and ADA mechanisms may occur [12].

Omalizumab

Omalizumab is known to cause anaphylaxis, triggering a joint task force to further investigate reports of omalizumab anaphylaxis [3, 34]. Using NIAID/FAAN criteria, reported anaphylaxis was rare at 0.1% with the majority (78%) of reactions occurring within the first 3 doses of administration [1, 3, 12]. Notably, 44% of reactions occurred more than 1 h after administration, prompting a black box warning label to monitor patients for 2 h following the initial 3 doses [3, 34]. Follow-up in 2011 revealed an increased association of omalizumab HSR in those who reported a history of anaphylaxis from any cause [3, 35]. The suspected mechanism is development of drug-specific IgE, though this is incongruent for those reactions occurring with the first omalizumab dose [3]. Additionally, one study failed to demonstrate elevated serum tryptase or specific IgE or IgG antibodies in patients who experienced immediate omalizumab HSR [12].

Anaphylaxis due to preformed IgE anti-excipient antibodies in the omalizumab formulation have also been reported [36]. Two patients with anaphylaxis following omalizumab were triggered by polysorbate, confirmed through positive polysorbate intradermal testing and negative *in vitro* testing for omalizumab-specific IgE and IgG antibodies [1, 36]. Desensitization is available to patients who have experienced HSR to omalizumab, with recommendation to continue weekly or biweekly administration to maintain desensitized state [10, 37].

Rituximab

Rituximab associated immediate HSRs are reported at a high rate of 5–10% of infusions [3, 38]. Anti-rituximab IgE likely mediate these reactions [3]. Positive intradermal testing has been reported in 67% of patients with rituximab HSRs with follow-up studies reporting similar rates, but studies failed to use non-allergic controls [5, 9, 39]. This group also successfully desensitized patients experiencing HSR with rituximab, further supporting an IgE mechanism [39]. More recently, positive skin testing was reported in 60% of patients with immediate HSRs to rituximab, and nearly all patients underwent successful desensitization [20]. Multiple desensitization protocols, including rapid

desensitization, have been published [20, 40]. In addition to these published protocols for adults, pediatric patients have also successfully undergone desensitization to rituximab using a similar 12-step protocol [41]. For younger pediatric patients unable to tolerate this protocol due to significant reactions, weight-based adjustments in rituximab rates were utilized for successful desensitization [41].

Natalizumab

Natalizumab targets $\alpha 4$ -integrin in the treatment of multiple sclerosis (MS); rare cases of anaphylaxis have been reported [1]. There are two case reports describing anaphylaxis with natalizumab with confirmatory work up: one patient with positive intradermal testing and anti-natalizumab IgE and the other patient with positive IgE [42, 43]. Another group found that up to 6% of patients developed natalizumab ADAs; ADA positive patients had higher rates of HSRs (21–46%) compared to ADA negative patients (0.6–0.7%) [44]. Several published case reports describe successful desensitization utilizing varying protocols [45–48].

Infliximab

Immediate HSRs with infliximab occur frequently (10% of infliximab treated patients) and account for 60% of TNF-inhibitor (TNFi) associated immediate HSRs [12, 33]. Immediate HSRs with infliximab may occur with initial infusions, but incidence peaks after multiple (7) infusions and are linked to anti-infliximab IgG ADAs. While most immediate infliximab HSRs are IgG-mediated, some are associated with anti-infliximab IgE [12, 15, 49]. This has been confirmed by a number of studies demonstrating that with infliximab HSRs, 13–27% had detectable infliximab ADAs, and in one study 30% had positive infliximab intradermal skin testing [5, 12, 32, 39]. Additionally, the presence of infliximab ADAs was associated with increased odds of developing immediate HSR to infliximab along with an associated loss of drug efficacy due to the antibody-mediated neutralizing effect compared to ADA negative patients [12, 50]. Conversely, 10% of infliximab ADA positive patients continued to tolerate infliximab therapy [5, 12, 32, 39]. Finally, infliximab ADA positive patients were more likely to become anti-adalimumab IgE positive [12, 49]. While infliximab ADAs are not predictive of cross-reactivity between TNFis, there are case reports of immediate HSR with adalimumab in patients who have had previous infliximab related HSR [12, 49]. Concomitant use of immunosuppressants (e.g., methotrexate or azathioprine) may reduce ADA development [12, 51, 52]. Successful desensitization protocols

have been published with weekly infliximab administration to maintain desensitization [17, 53].

Trastuzumab

While most immediate HSRs to trastuzumab are due to CRS, other patients have HSRs after previous tolerance, suggestive of antibody-mediated reactions [12]. Additionally, patients with positive skin testing have successfully undergone trastuzumab desensitization with subsequent tolerance, further supporting an IgE mechanism [5].

Cetuximab

Cases of immediate HSRs have occurred with initial infusions and are attributed to preformed IgE antibodies to antigens in the formulation or preformed IgE that are cross-reactive with the structure of the mAb itself. The prototypic example is an immediate HSR upon initial cetuximab infusion [11, 12]. While worldwide studies reported <3% immediate HSRs to cetuximab, studies focused in the southeastern USA revealed increased incidence rates up to 22% [11, 12, 29, 54]. Preformed IgE antibodies were directed against the oligosaccharide galactose- α -1,3-galactose (alpha-gal) present on the murine F(ab')₂ component of cetuximab [12, 29]. Patients with alpha-gal IgE prior to cetuximab treatment were more likely to have severe immediate HSRs upon initial cetuximab exposure [11, 12]. Alpha-gal IgE formation is thought to be secondary to Lone star tick exposure, which resides geographically in the southeastern USA [12, 55]. More recently, alpha-gal IgE cross-reactivity has been described in a case of anaphylaxis with initial infliximab dose [56]. Although discontinuation of cetuximab is indicated with immediate HSRs, there have been case reports of successful desensitization to cetuximab, utilizing both rapid desensitization protocols and a modified 1-bag, 5-step protocol [16, 57].

Delayed Hypersensitivity Reactions

Delayed HSRs occur greater than 1–2 h after drug administration, with most presenting within 2 weeks following biologic administration [9]. Delayed HSRs encompass a wide range of clinical presentations and include local cutaneous lesions, generalized cutaneous symptoms, severe cutaneous adverse reactions (SCARs) (e.g., Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), and serum sickness-like reactions (SSLR)) [9].

Delayed Local Cutaneous Reactions

Delayed cutaneous symptoms following biologics may be limited to a distinct location [9]. Similar to immediate

cutaneous reactions, patients may present with delayed cutaneous symptoms at injection sites (injection site reaction: ISR). Delayed ISRs are more common with subcutaneous dosing and are characterized by erythema, swelling, itching, or infiltrated plaques that present 1–2 days following injection [9]. They are most commonly associated with TNFis, especially etanercept and adalimumab, and usually occur within the first 2 months of therapy [9]. Approximately 20% of patients treated with adalimumab and etanercept develop ISRs, while 2–6% receiving certolizumab or golimumab develop ISRs [12]. ISR rates vary widely depending on the biologic, and range from 2.4% of ustekinumab injections to 71% of anakinra injections [1]. Recall ISRs may also develop at previous injection sites with subsequent medication administrations; these have been reported with TNFi therapy [58].

As these reactions are self-limited and improve with subsequent administrations, management is limited to symptomatic treatment with ice, topical corticosteroids, and oral H1 or H2 antihistamines [9, 12, 16].

Delayed Generalized Cutaneous Symptoms

Some cases of delayed systemic HSRs are limited to cutaneous symptoms. These reactions encompass a broad range of symptoms, including maculopapular, eczematous, lichenoid, and granulomatous exanthems with the majority consisting of mild maculopapular lesions [9, 10]. The underlying pathophysiology is not well defined, but suspected to be cell-mediated immune responses [9]. Generalized erythematous-squamous exanthema have been reported in multiple patients treated with TNFis, specifically infliximab, with onset delayed 2–4 weeks following biologic administration [9].

There is no consensus on management of delayed generalized cutaneous symptoms and avoidance of the biologic is often recommended [9].

Severe Cutaneous Adverse Reactions

Other delayed hypersensitivity reactions to biologics are rare, but recognition is important given the severity and life-threatening nature of these reactions [9]. These include severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Although uncommon, there have been a small number of cases of SJS, SJS-TEN overlap, and one case of TEN following rituximab administration [13, 38, 59]. SJS and TEN reactions have also occurred with checkpoint inhibitor therapy (e.g., ipilimumab, nivolumab, and pembrolizumab) [59]. TEN also occurred with cetuximab administration [9]. One case of symmetrical drug-related intertriginous and flexural exanthema (SDFRIFE), also

referred to as baboon syndrome, has been reported with infliximab used in the treatment of psoriasis [60]. Strict avoidance of the instigating medication is recommended [10].

Serum Sickness-like Reactions

The most common non-immediate hypersensitivity reactions to biologics are serum sickness-like reactions (SSLR). Pathophysiology is secondary to deposition of biologic-ADA immune complexes in small blood vessels that activate the complement cascade, subsequently inducing inflammatory infiltration [9, 12]. Although SSLRs may occur with the first infusion, they commonly occur after tolerance of at least one administration [12]. Patients present with fever, malaise, arthralgia or arthritis, jaw pain or tightness, erythematous skin eruption, purpura, and conjunctival hyperemia occurring several days after biologic infusion [9, 12]. Some patients with severe or progressive symptoms require treatment with corticosteroids with some severe cases requiring plasma exchange [9]. Management of SSLRs is not clear as desensitization is not safe with SSLRs and avoidance is most often recommended [12, 61], although some patients tolerate subsequent doses with steroid premedication [5, 12]. Multiple biologics have been associated with SSLRs, including infliximab, rituximab, omalizumab, natalizumab, adalimumab, and trastuzumab [9, 12].

Infliximab

SSLRs with infliximab are less common than immediate HSRs, occurring in 2.5% of patients [9, 12]. Infliximab SSLRs usually occur about 5–7 days following infusion [12, 62].

Rituximab

Rituximab-related SSLRs have been reported, with most occurring with treatment of inflammatory disorders [5, 12, 63]. Specifically, a review of rituximab-induced SSLRs found that the majority (85%) of cases were in patient with underlying autoimmune disease (e.g., immune thrombocytopenic purpura, Sjogren syndrome, and RA), while those with hematologic malignancies, such as lymphoma, comprised only 15% of reactions [63]. Symptoms presented 6–10 days after second rituximab infusion, in the first cycle; the most common symptoms were fever, arthralgias, and rash [63].

Corticosteroids (most commonly IV methylprednisolone) were used for treatment and resulted in complete resolution of symptoms in most cases [63, 64]. Wong et al. reported successful desensitization of 2 patients with serum sickness and SSLR with subsequent tolerance of rituximab with corticosteroid premedication in both patients [20].

Omalizumab

While reactions consistent with SSLR are included in the reported adverse effects of omalizumab clinical trials, cases of omalizumab-induced SSLR are rare [65]. Dreyfus et al. reported the development of generalized pruritic petechia presenting 1–2 days after tolerating multiple previous omalizumab doses diagnosed as SSLR [66]. Pilette et al. also reported a SSLR 5 days following an initial omalizumab injection. A second omalizumab injection resulted in soft tissue necrosis in one of the affected joints despite corticosteroid treatment [67]. SSLRs have also been reported in pediatric patients; Eapen et al. has reported a reaction in a 12-year-old female treated for urticaria and angioedema [68]. More recently, Molderings et al. reviewed SSLRs in patients treated with omalizumab and found that 25% of mast cell activation disorder (MCAD) patients developed SSLR compared to 0.4–0.6% in all omalizumab-treated patients, suggesting a higher incidence of SSLRs in this condition [69]. They suggested that long-term glucocorticoid use in MCAD patients may predispose to increased risk of omalizumab induced SSLRs [69].

Natalizumab

SSLRs have been reported with natalizumab. One group reported 3 cases of SSLRs in a cohort of MS patients receiving natalizumab [43]. These patients developed symptoms of arthralgia, neck stiffness, and fever approximately 1 day after receiving the first natalizumab infusions; symptoms self-resolved, and they were able to tolerate subsequent natalizumab therapy with slower infusion rates and corticosteroid premedication. However, one patient discontinued natalizumab therapy due to presence of serum ADAs [43].

Autoimmunity

Biologic therapies for the treatment of autoimmune disease and cancers have led to remarkable improvements in outcomes for this broad collection of diseases [70, 71]. These biologics work by interfering with cytokine-to-cytokine receptor interactions and reversing negative regulation through checkpoint inhibition. Cytokine antagonism may alter immunity to pathogens while checkpoint inhibition predisposes to autoimmunity and inflammation.

Checkpoint Inhibitors

Immune checkpoint inhibitors for cancer treatment are a transformative approach to cancer immunotherapy [72]. MAbs blocking the negative regulator proteins cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed

death 1 (PD-1), and its ligand programmed death ligand 1 (PD-L1) have FDA approval for the treatment of numerous malignancies. CTLA-4 is up-regulated during T cell responses and inhibits T cell co-stimulation by binding to co-stimulatory molecules CD80 and CD86, decreasing T cell activation intracellular signaling [71]. PD-1, expressed on T cells, is a negative regulator of anti-tumor T cell function when engaged by PD-L1 expressed and up-regulated on tumor cells [71, 73]. Under homeostatic conditions, these checkpoint molecules regulate aggressive immune responses and prevent autoimmunity [72]. Checkpoint inhibition with mAbs blocking the CTLA-4 or PD-1 pathways, either alone or in combination, allows release of negative regulators of immune activation, allowing an anti-tumor immune response [71]. MAbs blocking CTLA-4 (ipilimumab), PD-1 (pembrolizumab, nivolumab), and PD-L1 (atezolizumab, avelumab, durvalumab) are FDA-approved for treating specific cancers individually or in combination therapy [74–76].

Although highly beneficial in treatment of cancer, inhibition of CTLA-4 and PD-1 pathways may lead to immune-related adverse events (irAE) [71]. These toxicities are predictable based on the mechanism of action of checkpoint inhibitors. The proposed mechanisms of checkpoint inhibitor irAE involve activation of T cells against cross-reactive antigens from tumor and healthy tissue [74], reduction of regulatory T cell function with loss of peripheral tolerance, increasing levels of pre-existing autoantibodies, and increasing levels of inflammatory cytokines including IL-17 and IL-6 [77]. Cross-reactivity for specific antigens is proposed with vitiligo, which is markedly increased in patients being treated for melanoma versus other cancers [74]. These are relatively common, with grade 1 toxicities (those clinically detectable but not requiring therapy) occurring in 90% of patients, whereas grade 3 or higher occur in 60% [72].

Checkpoint inhibitor-induced irAE may occur in nearly all vital organs and almost any time after treatment, though a majority occur in the first 2–16 weeks [74, 77]. Dermatologic manifestations typically occur first and range in severity from eczema and pruritus to vitiligo to drug reaction with eosinophilia and systemic symptoms (DRESS) and SJS. Endocrinopathies are also relatively common. Hypophysitis occurs with CTLA-4 blockade, while thyroid dysfunction is more common in PD-1 pathway inhibition [78, 79]. Type 1 diabetes mellitus is less common (<1%) [80]. Unlike other irAE-mediated systemic toxicities, endocrinopathies often require lifelong replacement of hormones, even after treatment with immunosuppressive therapy [72].

Gastrointestinal manifestations include colitis, occurring in up to 20% of individuals on combination ipilimumab/nivolumab pathway blockade, and hepatitis [72, 79, 81]. Cardiac toxicity is rare, (<1%) and myocarditis occurs most often, but cardiac involvement may include pericarditis, Takotsubo cardiomyopathy [72], and temporal arteritis

[82]. Pneumonitis is relatively rare (1–3%), and unlike the toxicities listed above, is more frequent in PD-1 pathway targeting therapies [72]. Rheumatologic disease characterized by arthritis, arthralgia, or polymyalgia rheumatica is common (up to 26%) [72], and neurologic diseases including peripheral neuropathy, myasthenia gravis, and encephalopathy are also described [83]. In studies of pharmacovigilance databases, the most common irAE associated with death in CTLA-4 blockade was colitis, PD-1 was pneumonitis, and combination therapy was colitis and myocarditis [84].

Immune-related adverse events in the setting of checkpoint inhibitors are graded based on severity [85]. Grade I symptoms are mild, not requiring intervention in many cases. Grade 2 are moderate symptoms that are noninvasive. Grade 3 adverse effects are severe, requiring hospitalization but not immediately life threatening. Grade 4 are life-threatening consequences requiring immediate intervention. In general, immune checkpoint inhibitors can be continued with grade 1 toxicity. Immune checkpoint inhibitors may be held for most grade 2 toxicities and then resumed when symptoms improve to grade 1 or resolve [86]. Treatment of grade 3 irAE involves systemic glucocorticoids [74], at prednisone or methylprednisolone doses of 1 mg/kg/day over a course of at least 4 weeks [74]. In steroid-refractory cases (non-responsive after 72 h of intravenous corticosteroids), adjunctive immunosuppressant medications (e.g., mycophenolate) and biologics (e.g., TNFi including infliximab, anti- $\alpha 4\beta 7$ integrin with vedolizumab, and anti-IL-6 with tocilizumab) have been used as second-line immunosuppressants [81]. In most grade 4 toxicities, checkpoint inhibitor therapy should be permanently discontinued, with the exception of some cases of endocrinopathy treated with hormone replacement [86].

Many questions remain about irAE in checkpoint inhibitor therapy. In a pharmacovigilance study on recurrence of irAE with checkpoint inhibitors on re-challenge, there was a 28.8% rate of recurrence of the same irAE with re-introduction of the original checkpoint inhibitor [87]. Colitis, hepatitis, and pneumonitis were associated with higher recurrence rate than other irAE. Risk factors for irAE include personal or family history of autoimmune disease but no HLA risk allele has been identified [72, 74]. The association of irAE with treatment efficacy has been suggested with supportive data indicating irAE association with recurrence-free survival [88–90]. However, irAE development is not required for treatment efficacy. Furthermore, there are no reliable biomarkers available to predict the development of irAE or which organ systems will have involvement [72].

Paradoxical Inflammation

Biologics targeting pro-inflammatory cytokines may cause paradoxical inflammation driving autoimmune or

autoimmune-like disease resembling psoriasis, systemic lupus erythematosus (SLE), and vasculitis [70, 91].

Paradoxical psoriasis is described in 1.34% of patients on biologics with the majority (99%) on TNFi therapy with a very small proportion with rituximab treatment [91]. Infliximab (1.4%) and adalimumab (1.29%) are more frequently associated with this condition than etanercept (0.19%). The most common underlying diseases include IBD, RA/systemic juvenile idiopathic arthritis (sJIA), and spondyloarthropathies. Unlike spontaneously occurring psoriasis, dependent on T cell derived IL-17/-23 and TNF to drive disease pathogenesis, paradoxical psoriasis is induced by TNFi treatment [92, 93]. TNF blockade releases negatively regulated plasmacytoid dendritic cells (DCs) allowing proliferation and type-I interferon-dependent, T cell-independent psoriatic inflammation [93]. In mild cases, topical steroid therapy for management while continuing the TNFi can be employed. However, more severe psoriatic symptoms should prompt discontinuation of the biologic [81]. In 80% of cases, discontinuation of the TNFi and topical steroids leads to the resolution of symptoms. In approximately 50% of cases, re-introduction of TNFi, either with the same or a different agent, induces recurrence of paradoxical inflammation-driver psoriasis [94]. Methotrexate and ustekinumab have been used successfully for the treatment of TNFi induced paradoxical psoriasis and the underlying autoimmune disease.

Lupus-like disease occurs in 0.33% of individuals on biologics, with 97% on TNFi therapies [91]. The frequency of this condition is most common with use of infliximab compared to etanercept or adalimumab (0.66% incidence compared to 0.49% and 0.11%, respectively). Biologic-induced lupus has also been described during treatment with bevacizumab, efalizumab, rituximab, ustekinumab, and ipilimumab. Approximately 30% of cases meet diagnostic criteria for SLE including positive ANA, clinical symptoms, and immunologic parameters [95, 96], with the majority limited to cutaneous involvement. Lupus-like syndrome resolved in all cases with discontinuation of therapy implying a drug-induced lupus phenotype [97]. However, 99% of TNFi-induced lupus cases were anti-dsDNA antibody positive with a lower rate of anti-histone antibodies compared to typical drug-induced lupus suggesting an alternate mechanism.

Vasculitis resulting from biologic therapy is rare, occurring in 0.7% of individuals, all with RA or sJIA [91]. In 94% of cases, TNFi therapy was identified as the causative agent, most commonly etanercept or infliximab. Rare cases have identified rituximab, alemtuzumab, tocilizumab, ustekinumab, daclizumab, ipilimumab, pembrolizumab, and bevacizumab. Cutaneous involvement predominates in 65–90% of biologic-induced vasculitis cases, with systemic involvement in only 10% including ANCA-vasculitis, giant cell arteritis (GCA), Takayasu arteritis, Henoch-Schönlein purpura, and polyarteritis nodosa [91, 92, 98]. The most

common findings were purpura clinically and leukocytoclastic vasculitis on histology. A small case series showed resolution of vasculitis with discontinuation of anti-TNF therapy [99]. With lupus-like disease and vasculitis secondary to TNFi, cessation of TNFi therapy may be adequate to allow for symptom resolution [100]. In cases where TNFi therapy is essential for control of the underlying autoimmune disease, close monitoring of symptoms with continuation of TNFi has also been described. When end-organ damage occurs, TNFi should be discontinued and immunosuppressive treatment with glucocorticoids is used.

Immunogenicity and Development of Anti-biologic Antibodies

The production of ADAs during biologic treatment can impact effective therapy, leading to secondary treatment failure [101]. In RA patients, development of anti-adalimumab antibodies was associated with lower drug concentrations and lower likelihood of reduced disease activity or clinical remission [102]. This was illustrated in another study examining treatment of RA with etanercept, adalimumab, or infliximab which demonstrated patients without ADAs had better clinical outcomes [103]. The highest rates of ADA formation occurred with infliximab and adalimumab [104].

The mechanism of ADA generation is an anti-idiotypic response producing high affinity IgG antibodies [101]. While chimeric, humanized, and fully human mAbs are less immunogenic than murine counterparts, formation of ADAs have been described in all cases. The ADA response begins with IgM response that undergoes typical maturation including isotype switching to IgG and affinity maturation. While development of ADAs cannot be predicted, there is increased risk with certain HLA alleles (HLA-DRB1*03 and HLA-DRB*011 and lower risk with HLA-DQB1*05, HLA-DRB1*01, and HLA-DRB1*07). Use of methotrexate along with biologics is associated with decreased ADA formation [101].

Immune Deficiency

The use of biologics targeting cytokines, T cell co-stimulatory molecules, B cells, complement cascade, and cell adhesion molecules for autoimmune and autoinflammatory disease treatment is associated with an increased rate of infections [105–107]. Immune modulation by specific biologic therapy may mimic aspects of primary immunodeficiency (PID) resulting from genetic mutations in these immune pathways. However, the biologic phenotype does not always coincide with the PID [106]. Many excellent reviews detail the diverse infection-related adverse events of biologics based on their target [70, 106, 107]. We will discuss the most common

irAEs of biologics by types of infections associated with their use, specifically bacterial, opportunistic, viral, and fungal infections.

Bacterial Infections

As the majority of biologics used for autoimmune disease target innate pro-inflammatory cytokines TNF, IL-1, and IL-6, the initial response of neutrophils, macrophages, and other epithelial immune defenses to bacterial infection may be attenuated [107].

TNF Inhibitors

TNF is a pleiotropic cytokine, with important roles in germinal center formation, host infection defense, and induction of autoimmune disease including RA and IBD [108]. Antagonism of TNF to treat RA has longstanding success since infliximab approval in 1998. However, the impact of TNFi therapy on serious bacterial infection is variable. Risk of serious bacterial infection in some studies ranged from 2 to threefold above non-biologic DMARD, while other studies did not detect significant increase above controls [109, 110]. Others demonstrated an increased frequency of severe skin and soft tissue infections which has been contradicted in other studies where pneumonia is the predominant infection. Overall, risk of bacterial infection appears to be highest in the first six to twelve months of therapy [111–113].

IL-1 Antagonists

Interleukin-1 (IL-1) is important in innate immune responses to infection [114, 115]. IL-1 α and IL-1 β both bind and activate the IL-1R1. The IL-1 receptor antagonist (IL-1RA) regulates activity of both cytokines as an endogenous antagonist of IL-1R1. IL-1 α often acts as an alarmin when it is released from epithelial cells, leading to recruitment of neutrophils. IL-1 β is important for elimination of bacteria, endothelial activation, pro-inflammatory cytokine production, and leukocyte recruitment [116]. IL-1 is dysregulated in autoinflammatory syndromes such as the cryopyrinopathies and some autoimmune diseases including sJIA [114]. Treatment with the recombinant IL-1RA anakinra in RA and sJIA was associated with an increased risk of severe infections, most often bronchopulmonary infections, particularly at higher doses [105, 117, 118]. IL-1 β blockade with canakinumab was associated with a higher rate of fatal infections and sepsis in treatment of atherosclerotic disease [119].

IL-6 Receptor Antagonists

IL-6 has many roles in immunity including acute phase reactions, B cell activation, T effector cell differentiation,

oncogenesis, tissue regeneration, and metabolism [120, 121]. IL-6 is the main driver of hepatic acute phase responses, including C-reactive protein during bacterial infection [122]. Targeting IL-6 and IL-6R with mAbs has been effective therapy in autoimmune and autoinflammatory diseases including RA, sJIA, and GCA [121]. Anti-IL-6 pathway therapies are FDA-approved for RA, sJIA, GCA [123], multi-centric HIV-negative/HHV8-negative Castleman's disease [124], and CRS secondary to chimeric antigen receptor (CAR)-T cell therapy [121]. Inhibition of IL-6 can lead to severe bacterial infections, which could reflect impaired acute phase response or impaired T_H17 differentiation and function [125, 126]. Adverse infectious events are serious infections in the respiratory tract and skin/soft tissue infections [127–129]. The most common pathogens are *Staphylococcus* and *Streptococcus* followed by enteric bacteria [130].

C5 Inhibitor

The use of biologics inhibiting complement component C5 for treatment of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, and myasthenia gravis predisposes to bacterial infections [106]. Eculizumab prevents the cleavage of C5 and the formation of the terminal complement cascade important for host defense against *Neisseria* [131]. The incidence of *Neisseria meningitidis* in individuals receiving anti-C5 therapy is 1000–2000-fold higher than untreated controls [132]. Before initiation of therapy, meningococcal vaccination (MenACWY and MenB) is required along with risk evaluation and plan to identify and treat early meningococcal disease. Even with vaccination, non-groupable meningococcal infection [132] and disseminated gonococcal infections are an ongoing risk [133].

Opportunistic Infections

A key example of opportunistic infection that occurs with biologic therapy is *Mycobacterium tuberculosis* (Mtb) [134]. Control of Mtb, by creating and maintaining granulomas to prevent disseminated disease, involves interplay between innate and adaptive responses, including DCs, macrophages, and T cells, and multiple cytokines including TNF, IL-6, IL-12, IL-23, and IFN γ . Inhibition of these cytokines has been associated with risk for Mtb re-activation. The American College of Rheumatology recommends Mtb screening in all patients initiating biologic therapy for RA [135].

TNFi treatment has been associated with increased risk of Mtb infection in patients with RA, ankylosing spondylitis, psoriasis, and Crohn's disease [136, 137] without significant difference between therapeutics [112]. Opportunistic infections with anti-IL-6 therapy have also been described including tuberculosis, nontuberculous mycobacteria, invasive forms of candidiasis, and fungal infections including

Pneumocystis jiroveci and cryptococcal pneumonias being described, with little real-world data [120, 126].

IL-12/-23 inhibition with anti-IL-12p40 mAb, ustekinumab, blocks the shared receptor β chain and is used in psoriasis and IBD [138–140]. IL-12 secreted by DCs induce T cells to differentiate into T_H1 cells that release IFN γ [141]. IL-23 is produced by DCs in response to microbes promotes the maintenance of T_H17 differentiation. Although mutations in these cytokines result in Mendelian susceptibility to mycobacterial disease [106], there were no cases of Mtb, atypical mycobacterial diseases or disseminated salmonellosis in psoriasis patients on ustekinumab over a 5 year period [142].

Viral Infections

An increase in nasopharyngeal and other minor viral infections is noted with immunosuppressive biologics. However, certain therapies are implicated in more severe infections including progressive multifocal leukoencephalopathy (PML) caused by the JC virus. PML is a demyelinating disease of the central nervous system caused by lytic JC virus infection. [143] Biologics targeting cell adhesion molecules have been linked to development of PML, presumably through decreased CNS immune surveillance [143, 144]. Natalizumab targets the α 4 chain of both α 4 β 1 and α 4 β 7 integrins, expressed on lymphocytes and monocytic cells [144, 145]. By blocking α 4 β 1 from binding vascular cell adhesion protein 1 (VCAM-1), natalizumab impairs lymphocyte binding to endothelium and trafficking into sites of neural inflammation and is the mechanism of action in treatment of MS. While rates of PML were relatively low in clinical trials (1:1000), in practice, increased risk of PML occurs with duration of treatment over 24 months, JC virus seropositivity (at least 30% of the population), and prior treatment with immunosuppressive therapy and is as high as 1 in 44 patients [146]. In contrast, with vedolizumab, used in the treatment of IBD by selectively targeting gut-specific α 4 β 7 integrin, the risk appears to be similar to that of the general population [145].

Fungal Infections

T_H17 cells secrete IL-17 and are maintained by IL-23. They are important for host defense against fungal infections, particularly at epithelial surfaces [147]. Ustekinumab therapy for psoriasis has not demonstrated a marked increase in systemic fungal infections and minimal change in mucocutaneous candidiasis [142, 148]. Primary immunodeficiency resulting from mutations in IL-17A and IL-17F and STAT3 and STAT1 that prevent normal T_H17 development lead to chronic mucocutaneous candidiasis (CMC) and invasive fungal infections, respectively [149]. IL-17A blockade in

psoriasis and ankylosing spondylitis results in increased risk of CMC only [150]. IL-17 has an important role in skin barrier protection, and treatment with IL-17 targeting medications secukinumab and ixekizumab and IL-17R targeting medication brodalumab can predispose to this class of infections [147, 150].

Vaccination

Individuals with autoimmune and autoinflammatory conditions are at higher risk of infection than the general population especially with use of targeted biologic therapy [151]. The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) recommend vaccination before the initiation of biologic DMARD therapy, if possible, specifically for live vaccinations [135, 152]. The ACR recommends administration of pneumococcal vaccination (PCV13 and PPSV23), influenza, hepatitis B, human papilloma virus, and herpes zoster. If an individual is already on a biologic therapy, ACR recommends avoidance of live vaccines, including the live herpes zoster vaccination and live virus yellow fever vaccine. With the availability of the recombinant protein herpes zoster vaccine (Shingrix), the safety of administration of herpes zoster vaccination during biologic therapy will likely improve, but new recommendations have not yet been released [152]. In individuals treated with rituximab, multiple studies have demonstrated a reduced humoral immune response to influenza vaccination and polysaccharide pneumococcal vaccine (PPSV23) [151]. Recommendations from ACR and EULAR support vaccination for influenza and pneumococcus before initiation of rituximab therapy when possible [135, 152]. However, in the case of the T cell dependent protein vaccine tetanus toxoid, individuals receiving rituximab developed protective immune responses [153].

Conclusions

Adverse effects of biologics are broad and variable, ranging from transient infusion symptoms to increased susceptibility to infections. As biologic medications, specifically mAbs, expand into fields outside of cancer and inflammatory diseases, it will be important to recognize risk for immediate and delayed onset HSRs and the potential for immune modulation leading to autoimmunity or immunodeficiency. Acute-onset side effects from antigen-driven hypersensitivity reactions can be unpredictable and, in some cases, interfere with ongoing therapy. As the number of biologic medications increases and the range of diseases treated using these medications expands, a better understanding of the underlying mechanisms of HSRs, irAEs, and on and off target effects of these medications will help practitioners

predict what reactions might occur, identify at risk patients, and improve management plans. This is a significant stumbling block with reactions to biologics and will be an ongoing need going forward. Areas for improvement for treating immediate and delayed HSRs and irAEs (autoimmune side effects in checkpoint inhibitors and paradoxical inflammation with anti-cytokine therapies) would be the identification of improved biomarkers, risk factors, and the development of treatments which could be improved perhaps with the introduction of precision medicine. In the case of secondary immunodeficiency, understanding how biologics suppress immune responses and how pathogens exploit pharmacologic inhibition of these immune pathways provides a framework for monitoring for infectious complications.

Author Contribution JLW, SAS, and MK performed literature search and wrote the article. JLW and SAS contributed equally to the article as co-first authors.

Funding SAS is supported by the National Institute of Allergy and Infectious Diseases, National Institutes of Health, through Grant T32AI007062.

Declarations

Conflict of Interest The authors declare no competing interests.

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