Hypersensitivity to Biological Agents—Updated Diagnosis, Management, and Treatment

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Activity Objectives

1. To comprehend indications and contraindications of specific desensitization to biological agents.
2. To recognize the clinical presentations of hypersensitivity reactions to biological agents.
3. To understand the management of hypersensitivity reactions to biological agents.
4. To become acquainted with monoclonal antibodies' targets and origins.

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Biological agents are used in the treatment of neoplastic, autoimmune, and inflammatory diseases and their clinical applications are becoming broader. Following their increased utilization, hypersensitivity reactions linked to these drugs have become more frequent, sometimes preventing the use of first-line therapies. The clinical presentation of hypersensitivity reactions to biological agents ranges from mild cutaneous manifestations to life-threatening reactions. In this scenario, rapid desensitization is a groundbreaking procedure that enables selected patients to receive the full treatment dose in a safe way, in spite of their immediate hypersensitivity reaction to the drug, and protects them against anaphylaxis. The aim of this review is to update and discuss some of the main biological agents used in clinical practice (rituximab, trastuzumab, cetuximab, ofatumumab, tocilizumab, brentuximab, omalizumab, and tumor necrosis factor alpha inhibitor agents) and their associated hypersensitivity reactions, including clinical presentations, diagnosis, and treatment in the acute setting. In addition, novel management options with rapid desensitization are presented. © 2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:175-85)

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Abbreviations used
AS- Ankylosing spondylitis
ASA- Acetylsalicylic acid
BAT- Basophil activation test
CD- Crohn's disease
CLL- Chronic lymphocytic lymphoma
EGFR- Epidermal growth factor receptor
HER-2- Human epidermal growth factor receptor 2
IBD- Inflammatory bowel disease
IDT- Intradermal test
IgE- Immunoglobulin E
ISR- Injection site reactions
IV- Intravascular
JIA- Juvenile idiopathic arthritis
MPA- Microscopic polyangiitis
NHL- Non-Hodgkin's lymphoma
PA- Psoriatic arthritis
PO- Per os
PsO- Plaque psoriasis
RA- Rheumatoid arthritis
SpO_2- Peripheral oxygen saturation
TCZ- Tocilizumab
TNF-α- Tumor necrosis factor alpha
UC- Ulcerative colitis
WG- Wegener's granulomatosis

Biological agents are applied in the treatment of neoplastic, autoimmune, and chronic inflammatory diseases, and their clinical applications are increasing and becoming broader. Hypersensitivity reactions linked to these drugs have become more frequent, sometimes preventing the use of first-line therapies on diseases that require precise management. Examples of immune-mediated and inflammatory diseases that respond to biological agents include rheumatoid arthritis (RA), Crohn's disease (CD), ulcerative colitis (UC), juvenile idiopathic arthritis (JIA), psoriasis and psoriatic arthritis (PA), Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), ankylosing spondylitis (AS), plaque psoriasis (PsO), and asthma. Neoplastic diseases include non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and colorectal, breast, gastric, and lung cancer.[1]

Hypersensitivity reactions to biological agents can occur on the first exposure (ie, cetuximab, trastuzumab) or after multiple exposures, similarly as what can be seen with platinum compounds.[2] The clinical presentation of hypersensitivity reactions secondary to biological agents may include cutaneous (erythema, flushing, pruritus, urticaria, angioedema, itching), cardiovascular (chest pain, tachycardia, presyncope, syncope, hypotension), respiratory (dyspnea, wheezing, oxygen desaturation, throat tightness), gastrointestinal (nausea, vomiting, diarrhea, abdominal pain), and neurological (mental confusion, visual disturbances, and numbness and/or weakness) signs and symptoms. Atypical manifestations such as fever, chills, rigors, back, and neck pain can also occur.

Immediate reactions can be considered mild, moderate, or severe and are classified according to Brown's grading system for immediate hypersensitivity reactions.[3] Mild (grade 1) reactions compromise skin and subcutaneous tissues only, whereas moderate (grade 2) and severe (grade 3) reactions may affect cardiovascular, respiratory, and neurological systems. In a study from 2009, Brennan et al[4] evaluated 105 desensitization procedures to monoclonal antibodies (infliximab, rituximab, and trastuzumab) in 23 patients. Initial reactions were considered mild in 26%, moderate in 48%, and severe in 26%. Reactions that involve cutaneous signs and/or symptoms were the most prevalent, followed by cardiovascular and respiratory reactions. Severe reactions to trastuzumab did not occur, possibly due to the fact that it is a humanized monoclonal and therefore presents less immunogenicity than rituximab and infliximab. Delayed hypersensitivity reactions to biologicals have been reported, with reports of rash, serum-sickness-like symptoms, vasculitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.[5-9]

When a patient presents a hypersensitivity reaction to a biological, rapid desensitization is a groundbreaking procedure that will enable the patient to receive the full treatment dose while protecting him from anaphylaxis. A standard desensitization protocol to monoclonal antibodies has been developed with 3 intravenous dilution bags, 12 steps, and an approximate total duration of 6 hours.[10] High-risk patients can be desensitized with additional dilutions and/or steps (16 or 20 steps).

The aim of this review is to discuss some of the main biological agents in clinical practice (rituximab, trastuzumab, cetuximab, ofatumumab, tocilizumab, brentuximab, omalizumab, and tumor necrosis factor alpha [TNF-α] inhibitor agents) (Table I), their associated hypersensitivity reactions, including clinical presentation, diagnosis, and treatment in the acute setting, and provide up-to-date management options, including novel desensitization protocols.

SPECIFIC AGENTS—CLINICAL PRESENTATION PARTICULARITIES

Rituximab

Rituximab is a chimeric mouse-human monoclonal antibody against CD20 used in the treatment of NHL, CLL, RA, WG, and MPA.[11,12] Infusion reactions may present with urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, and/or non—immunoglobulin E (IgE)-mediated reactions.[12] Reactions consistent with immediate hypersensitivity, potentially IgE-mediated, are estimated to account for 5% to 10%.[4,13] Severe reactions tend to occur during the first infusion with time to onset of 30-120 minutes.[12] There is a report of a possible Stevens-Johnson syndrome associated with rituximab,[5] but other authors argued that the diagnosis was more consistent with paraneoplastic pemphigus due to clinical description and time course of the reaction.[14] A fatal case of Stevens-Johnson and/or toxic epidermal necrolysis overlap syndrome associated with the concomitant administration of rituximab, allopurinol, and bendamustine has also been reported.[15]

Trastuzumab

Trastuzumab is a humanized mouse IgG1 monoclonal antibody against the extracellular domain of the human epidermal growth factor receptor 2 (HER-2) receptor, indicated for the treatment of HER2-overexpressing breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.[16] Typical first-time infusion reactions include chills and/or fever and occur in approximately 40% of patients.[17] Serious infusion reactions are reported to be relatively rare (0.5%).[18] One case of a serious adverse event to trastuzumab was observed in a 56-year-old woman with breast cancer.[19] During the first infusion and following premedication with paracetamol and antihistamines, she developed generalized tremor,

TABLE I. Biological agents: targets, incidence of overall injection and/or infusion site reactions and hypersensitivity reactions

Drug	Target	Overall injection and/or infusion reactions	HSR
Rituximab (Rituxan) IV	CD20	77% (first infusion)[12]	5% to 10%[13]
Ofatumumab (Arzerra) IV	CD20	44% (first infusion)[38] 67% (combination therapy)[104]	2%[104]
Trastuzumab (Herceptin) IV	Extracellular domain of the HER-2 receptor	40% (mild; first infusion)[17]	0.6% to 5%[18]
Cetuximab (Erbitux) IV	Extracellular domain of EGFR	15% to 21%[105]	1.1% to 5%[23-26] 14% to 27% (Southern USA)[28-30]
Tocilizumab (Actemra) IV	IL-6 receptor	7% to 8%[106]	0.1% to 0.7%[106]
Infliximab (Remicade) IV	TNF-α	18%[53]	1%*[53]
Etanercept (Enbrel) SC	TNF-α	15% to 37%[54]	<2%[54]
Adalimumab (Humira) SC	TNF-α	20%[55]	1%[55]
Golimumab (Simponi) SC	TNF-α	4% to 20%[64,107]	n/r
Certolizumab (Cimzia) SC	TNF-α	0.8% to 4.5%[65,108]	n/r
Brentuximab (Adcetris) IV	CD30	12%[45]	†[46-48]
Omalizumab (Xolair) SC	IgE	45%[50]	0.09% to 0.2%[50,52]

HSR, hypersensitivity reactions; *HER-2*, human epidermal growth factor receptor 2; *EGFR*, human epidermal growth factor receptor; *TNF-α*, tumor necrosis factor alpha; *n/r*, not reported; *IgE*, immunoglobulin E.
*Delayed HSR reactions.
†Case reports of anaphylaxis.

TABLE II. Subcutaneous desensitization to adalimumab in a 26-y-old woman treated for rheumatoid arthritis and presenting an immediate injection site reaction to the drug[60]

Step	Concentration (mg/mL)	Time (min)	Cumulative time (min)	Volume administered per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	4	30	30	0.25	1	1
2	4	30	60	0.5	2	3
3	40	30	90	0.1	4	7
4	40	30	120	0.2	8	15
5	40	30	150	0.4	16	31
6	40	30	180	0.6	24	55

Time per step: 30 min; number of steps: 6; total dose: 55 mg.

perspiration, mild dyspnea, hypertension, and tachycardia, with peripheral oxygen saturation (SpO_2) 90% on room air. The infusion was stopped; she received treatment, but went on to present with peripheral vasoconstriction, facial and neck erythema, and severe dyspnea. She was moved to the emergency department, treated, and observed for 24 hours. Reactions to trastuzumab typically occur during the first infusion, but there are reports on reactions that occur further along.[20] A patient with a severe anaphylactic reaction (respiratory distress, hypotension, abdominal pain, and facial erythema), followed by tremor and fever on her fourth infusion, was reintroduced to the drug 5 days later. The medication was administered in a decreased rate, and the patient developed facial erythema, intense lower back pain, and intense sweating.[20]

Cetuximab

Cetuximab is an IgG1 chimeric monoclonal antibody that binds specifically to the extracellular domain of the human epidermal growth factor receptor (EGFR). It is approved for the treatment of K-ras wild-type, EGFR-expressing metastatic colorectal cancer and head and neck cancer.[21,22] Severe reactions (grades 3 and 4) associated with its use vary between 1.1% and 5%[23-26] and tend to occur during the first administration.[27] A higher percentage of patients with severe reactions to cetuximab was found in some studies, mainly in the southeastern part of the USA.[28-30] Data from 125 patients treated at University of North Carolina (UNC) showed an incidence of grade 3 or 4 reactions of 14%. The percentage reached 22% when patients from two Vanderbilt centers in Tennessee were evaluated with patients from UNC.[29] Grade 2-4 hypersensitivity reactions were reported in 27% of 51 patients treated with cetuximab in a Florida Veterans Affairs facility.[30] With the same regional distribution, cases of adult-onset delayed anaphylaxis to red meat began to be reported.[31] This association was later explained by the role of α-1,3-galactose IgE antibodies possibly generated by tick exposure (*Amblyomma americanum*—lone star tick), whose geographical distribution matched that of cases of anaphylaxis to meat and cetuximab hypersensitivity. The carbohydrate galactose-α-1,3-galactose is expressed on nonprimate mammalian proteins[32] and present on the cetuximab heavy chain.[33] In a 2008 study, Chung et al[34] found that among 25 patients who had presented with a hypersensitivity reaction to cetuximab, 17 had a positive test for galactose-α-1,3-galactose IgE in pretreatment serum. In addition, this study also evaluated levels of anticetuximab IgE in healthy volunteers from different regions and found a prevalence of 20.8% (15 of 72) in samples from Tennessee when compared

TABLE III. Subcutaneous desensitization to etanercept in a 28-y-old man treated for ankylosing spondylitis and presenting an immediate injection site reaction and diffuse urticaria to the drug

Step	Concentration (mg/mL)	Time (min)	Cumulative time (min)	Volume administered per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
Day 1						
1	0.25	30	30	1	0.25	0.25
2	2.5	30	60	0.2	0.5	0.75
3	2.5	30	90	0.4	1	1.75
4	2.5	30	120	0.8	2	3.75
5	25	30	150	0.16	4	7.75
6	25	30	180	0.18	4.5	12.25
Day 2						
1	0.25	30	30	1	0.25	0.25
2	2.5	30	60	0.2	0.5	0.75
3	2.5	30	90	0.4	1	1.75
4	2.5	30	120	0.8	2	3.75
5	25	30	150	0.16	4	7.75
6	25	30	180	0.18	4.5	12.25
Day 3						
1	2.5	30	30	0.2	0.5	0.5
2	2.5	30	60	0.4	1	1.5
3	2.5	30	90	0.8	2	3.5
4	25	30	120	0.16	4	7.5
5	25	30	150	0.32	8	15.5
6	25	30	180	0.35	8.75	24.25
Day 4						
1	25	-		1	25	25

Number of days: 3; steps per day: 6; total dose: 25 mg.
Adapted from reference 59.

with only 6.1% (3 of 49) and 0.6% (2 of 341) in samples from California and Massachusetts, respectively.

Recently, 3 cases of severe hypersensitivity reactions secondary to cetuximab infusion were reported.[35] One of the patients was receiving treatment for metastatic colon cancer, and in spite of premedication, on the first infusion of cetuximab (after 1 minute), he developed a generalized rash, loss of consciousness, hypotension, followed by cardiorespiratory arrest. After initial support measures, the patient was transferred to the intensive care unit but ended up dying. Tryptase levels were high (277 μg/L; normal value <12.5 μg/L) at the first hour of the reaction. Retrospectively, anticetuximab IgE levels were highly positive (3300 arbitrary units [AU]: laboratory normal value <29 AU). An 81-year-old patient treated for locally advanced head and neck cancer had elevated anticetuximab IgE levels (480 AU) measured before cetuximab infusion. Cetuximab was given with premedication and at a slow infusion rate, but the patient reacted and presented with dyspnea, loss of consciousness, and respiratory arrest. This patient's tryptase level was also increased (64 μg/L). In the third case report, a 50-year-old patient treated for recurrence of mouth cancer had pretreatment anticetuximab IgE levels strongly positive (490 AU). The first infusion of cetuximab induced severe anaphylaxis, with tachycardia, oxygen desaturation, and bronchospasm. These cases support the notion that screening candidates to cetuximab with anticetuximab IgE may help predict high-risk patients who would present hypersensitivity and offer increased vigilance during the infusion.

Ofatumumab

Ofatumumab is a fully human monoclonal antibody that specifically binds to the human CD20 antigen inducing potent B-cell lysis. It has been approved for the treatment of CLL[36] and its efficacy on RA is being studied.[37] The trial that led to ofatumumab approval in 2009 evaluated 154 patients with CLL refractory to fludarabine and found an incidence of ≥5% of urticaria and rash.[38] Infusion reactions are less common after the first 2 infusions and can include bronchospasm, dyspnea, laryngeal edema, pulmonary edema, flushing, hypertension, hypotension, syncope, cardiac ischemia and/or infarction, back pain, abdominal pain, fever, rash, urticaria, and angioedema.[38]

Tocilizumab

Tocilizumab (TCZ) is an anti-IL-6 receptor humanized monoclonal antibody that binds to circulating soluble IL-6R and membrane-expressed IL-6R, blocking proinflammatory effects of IL-6. Its main clinical indications include moderate-to-severe RA in patients who have had inadequate responses to one or more disease-modifying antirheumatic drugs or TNF-α inhibitors, and systemic JIA.[39,40] Immediate[41] and delayed hypersensitivity reactions (skin lesions with $CD4^+$ T cells and eosinophils infiltrate in the upper dermis)[42] can occur secondary to the use of TCZ. The role of TCZ skin testing in the investigation of hypersensitivity reactions has been assessed in a study that evaluated 72 patients treated with TCZ in a 9-year period.[43] Among them, 5 patients presented with hypersensitivity reactions to TCZ: 4 had experienced anaphylaxis and 1 pruritus. All skin prick tests were

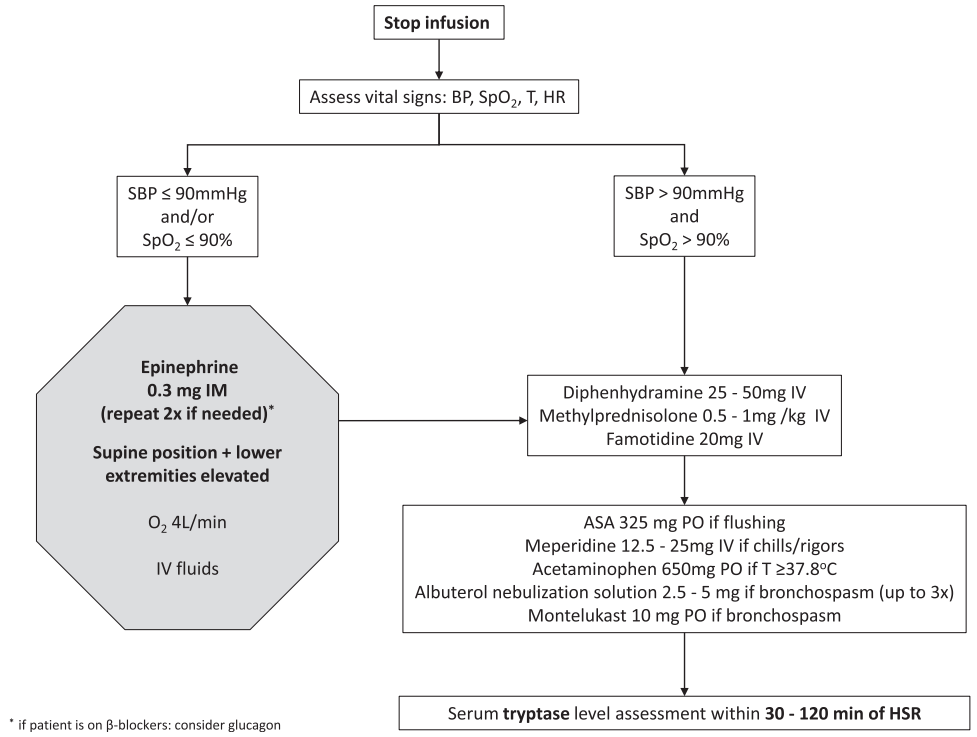

FIGURE 1. Algorithm for the management of hypersensitivity reactions secondary to biological agents. *BP*, blood pressure; *SBP*, systolic blood pressure; *SpO_2*, peripheral oxygen saturation; *IM*, intramuscular; *O_2*, oxygen; *IV*, intravascular; *PO*, per os; *HR*, heart rate; *HSR*, hypersensitivity reaction; *T*, axillary temperature; *C*, Celsius; *ASA*, acetylsalicylic acid.

negative (concentrations of 0.2, 2, and 20 mg/mL), and intradermal tests (IDT) (0.002, 0.02, 0.2, 2, and 20 mg/mL) turned out to be positive in 3 of the 4 anaphylaxis cases, 2 with the undiluted drug (20 mg/mL) and 1 with the 0.2 mg/mL dilution (a wheal area $\geq$3 mm was considered positive). Anti-TCZ antidrug antibodies are still being tested as an additional diagnosis tool, but have not been validated yet.[44]

Brentuximab

Brentuximab is an antibody-drug conjugate composed of an anti-CD30 monoclonal antibody linked by a protease-cleavable dipeptide to monomethyl auristatin E. It has been approved for the treatment of selected patients with Hodgkin lymphoma and for patients who have systemic anaplastic large cell lymphoma after failure of at least one prior multiagent chemotherapy regimen.[45] Infusion-related reactions tend to occur in approximately 12% patients and the most common signs and/or symptoms include chills, nausea, dyspnea, pruritus, pyrexia, and cough. There have been reports on anaphylaxis associated with brentuximab and desensitizations have been performed.[45-48] In one case report, the patient had presented with 3 severe anaphylactic reactions (hypotension in 3 infusions, syncope in the first infusion, tachypnea, nausea) before rapid desensitization. The patient was successfully desensitized at each subsequent infusion and during desensitization presented only with reactions less severe than the initial one (pruritus, periorbital edema).

Omalizumab

Omalizumab is a recombinant humanized monoclonal antibody, which targets the high-affinity receptor binding site on human IgE and is currently approved as add-on therapy for patients with moderate-to-severe persistent allergic asthma and for the treatment of chronic idiopathic urticaria in adults and adolescents who remain symptomatic despite H1 antihistamine treatment.[49,50]

Anaphylaxis has been reported as a serious hypersensitivity reaction associated with the use of omalizumab, with postmarketing reports showing an incidence of 0.2% of anaphylaxis in 57,300 patients in a period of 3.5 years.[50] These reports led to a 2007 FDA alert on anaphylaxis related to the drug and an updated package insert. Signs and symptoms present in those cases included bronchospasm, hypotension, syncope, urticaria, angioedema of the throat or tongue, dyspnea, cough, chest tightness, and/or cutaneous angioedema. The majority of anaphylaxis cases (68%) occurred in the first 3 administrations of the drug, but one case was reported after a 3-month gap in the treatment of a patient who had been receiving omalizumab continuously for 19 months.[50]

In 2007, the Omalizumab Joint Task Force reviewed omalizumab clinical trials and postmarketing surveillance data and found an overall anaphylaxis frequency of 0.09%. The majority of reactions occurred within 2 hours after one of the first 3 doses of the medication (61%) and justifies the recommendation of an observation period of 2 hours for the first 3 injections and 30 minutes for subsequent injections. Delayed onset anaphylaxis cases have also been reported among patients with asthma receiving omalizumab, with 5% of cases exceeding 1 day of the administration.[51] It is advisable that patients who receive omalizumab are instructed to recognize signs and symptoms of anaphylaxis and to use the epinephrine autoinjector.[52]

TABLE IV. Intravenous desensitization to ofatumumab in a 68-y-old man treated for chronic lymphocytic leukemia who presented a grade 2 reaction to the drug (throat tightness, cough and angioedema)

Bag	Volume per bag (mL)	Concentration (mg/mL)	Total dose per bag (mg)	Amount of bag infused (mL)
1	250	0.04	10	9.38
2	250	0.4	100	18.75
3	500	1.98425	992.125	500

Step	Bag	Rate (mL/h)	Time (min)	Cumulative time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)	Fold increase per step
1	1	2.5	15	15	0.63	0.025	0.025	0
2	1	5	15	30	1.25	0.05	0.075	2
3	1	10	15	45	2.5	0.1	0.175	2
4	1	20	15	60	5	0.2	0.375	2
5	2	5	15	75	1.25	0.5	0.875	2.5
6	2	10	15	90	2.5	1	1.875	2
7	2	20	15	105	5	2	3.875	2
8	2	40	15	120	10	4	7.875	2
9	3	10	15	135	2.5	4.9606	12.8356	1.24
10	3	20	15	150	5	9.9213	22.7569	2
11	3	40	15	165	10	19.8425	42.5994	2
12	3	80	361.875	526.88	482.5	957.4006	1000	2

Bag 3/step 12: if the patient tolerates the final step at 80 mL/h for 15 min, the rate may be increased in 15 min intervals to 120 mL/h, to 160 mL/h, to 200 mL/h, and then to 240 mL/h until infusion is completed.
Total infusion time: 8.78 h.
Standard volume per bag: 250 mL.
Final rate of infusion: 80 mL/h.
Number of bags: 3; time per step: 15 min; total number of steps: 12; total dose: 1000 mg.

Symptoms suggestive of type III hypersensitivity reaction (serum-sickness-like), such as fever, arthritis/arthralgia, rash, fever, and lymphadenopathy, have been reported, occurring after 1 to 5 days after the administration of omalizumab.

Injection site reactions (ISR) related to omalizumab occur in approximately 45% of patients and can manifest with redness, warmth, burning, stinging, itching, urticaria, pain, indurations, and inflammation. Typically, these reactions occur within 1 hour of the injection and tend to subside in the following 8 days.[50]

TNF-α inhibitor agents

Infliximab is a chimeric monoclonal antibody against TNF-α used for the treatment of CD, UC, RA, AS, PA, and PsO.[53] Etanercept is a TNF receptor-IgG fusion protein approved for the treatment of RA, polyarticular JIA in patients aged 2 years or older, PA, AS, and PsO.[54] Adalimumab was the first fully human monoclonal antibody approved by the FDA, and it is an anti-TNF-α used in RA, JIA, PA, AS, CD, UC, and PsO.[55,56] Golimumab is a human IgG1κ monoclonal antibody against TNF-α, used in specific cases of RA, active PA, AS, and UC.[57] Certolizumab pegol is applied in patients with CD who have had an inadequate response to conventional therapy, patients with severely active RA, PA, or AS,[58] and unlike other anti-TNF-α monoclonals, it is composed of the antibody binding fragment of a humanized monoclonal antibody conjugated to polyethylene glycol (pegylated). Whereas infliximab is administered intravenously, etanercept, adalimumab, golimumab, and certolizumab are administered subcutaneously. ISR for etanercept and adalimumab are mostly mild, rarely causing drug discontinuation, and include erythema, itching, and swelling.[54,55] They are believed to be T-lymphocyte-mediated delayed hypersensitivity reactions,[7] but possible IgE-mediated immune reactions may also develop.[59] ISR can occur in up to 37% patients treated with etanercept and in 20% with adalimumab.[54,55] In spite of being a fully humanized monoclonal antibody, adalimumab can elicit immediate and delayed hypersensitivity reactions.[60,61] An immediate local reaction to adalimumab with pruritus, redness, and swelling at the site of the 11th injection, reproducible at other 2 injections, has been reported.[60] IDT was positive at 1:1000 dilution and the patient was successfully desensitized with a 6-step subcutaneous desensitization protocol (Table II). Benucci et al have reported a prolonged ISR to adalimumab with positive IDT at late reading,[61] suggestive of a cell-mediated reaction. Anaphylaxis to adalimumab has been described with rash, urticaria, bronchospasm, facial angioedema, generalized itching, and severe hypotension occurring after 20 minutes of the 10th injection.[62] Bavbek et al have described an immediate ISR to etanercept associated with whole body urticaria and pruritus with a positive IDT at 1:100 dilution in a 28-year-old patient with AS.[59] The patient was desensitized subcutaneously with a 3-day protocol (Table III). ISR to golimumab (none severe) occurred in 4.4% to 11% of patients in a study that evaluated methotrexate-naive patients with active RA.[63] No anaphylactic reactions to golimumab were reported during this study and rash was a clinical manifestation in 3.1% to 5.1% patients.[63] Another study found 20% of patients presented with ISR to golimumab (55 treated patients) and 10.9% with rash.[64] Certolizumab was evaluated as an adjunctive therapy to methotrexate in 781 patients with RA.[65] In this group of patients, there was a low incidence of ISR, which ranged from 0.8% to 2.3%. There were no anaphylactic reactions reported.

Infliximab infusion reactions are acute, which occur during the first 24 hours. Headache, dizziness, nausea, injection site irritation, flushing, chest pain, pruritus, fever, hypotension and/

or hypertension, or dyspnea have been described.[66] Soykan et al[67] reported an anaphylactic reaction to infliximab during the second infusion in a 33-year-old man with CD with a clinical presentation of flushing, urticaria, tachycardia, chest pain, hypotension, dyspnea, nausea, and vomiting.

The presence of IgE and IgM antibodies to infliximab has been correlated with the development of acute infusions,[68-71] and even with severe infusion reactions.[69] It was found in one study that 38% of patients who had positive anti-infliximab antibodies reacted in one or more infusions, as compared with 24% who had negative titers.[68] Data from a 2014 meta-analysis showed a 2-fold risk increase of acute infusion reactions and 6-fold risk increase of serious acute infusion reactions in patients with inflammatory bowel disease (IBD) treated with infliximab who presented with anti-infliximab antibodies.[69] It has been reported that concomitant treatment with immunosuppressive agents such as azathioprine, mercaptopurine, methotrexate, or low-dose glucocorticoids can help prevent the formation of antibodies to infliximab, therefore decreasing the risk of infusion reactions.[70,72] High titers of anti-infliximab antibodies have been associated with poor response in dose increase, as opposed to anti-TNF class switching.[73]

Delayed reactions to infliximab occur 24 hours to 14 days after infusion and mimic type III hypersensitivity reactions (serum-sickness-like), with symptoms such as myalgia, rash, fever, polyarthralgias, pruritus, edema, and fatigue.[74,75] They tend to occur with repetitive treatment with infliximab, but cases at the first dose have been reported.[76] To make the diagnosis, other causes (infections, IBD flare, or lupus-like reaction) need to be ruled out.[74]

MANAGEMENT OF HYPERSENSITIVITY REACTIONS TO BIOLOGICALS IN THE ACUTE SETTING

The first step when managing a hypersensitivity reaction related to biological agents is the interruption of the infusion. Vital signs should be quickly assessed and the following treatment depends on clinical presentation. Figure 1 summarizes treatment steps in the acute setting.

If systolic blood pressure is less than or equal to 90 mmHg and/or SpO_2 is less than or equal to 90%, epinephrine should be promptly administered in the dose of 0.3 mg intramuscular. Additional doses may be required and should not be delayed,[77] because postponing its use is associated with mortality.[78] Proper positioning of the patient is important because it helps preserve fluid in the circulation and prevents the empty vena cava and/or empty ventricle syndrome. Whenever possible, the patient must be placed on his or her back (if there is no respiratory distress or vomiting) with elevated lower extremities.[77] Volume expansion with isotonic crystalloid solutions has to be instituted when hypotension or shock occurs and severe cases may require vasopressor agents. Lack of response to epinephrine should always point out to the possibility of intravascular (IV) volume depletion and fluids can be given in large amounts. Isotonic crystalloid solutions are the preferred resuscitation fluids in this setting to compensate for peripheral vasodilation and plasma leakage to extravascular space. Oxygen should be supplemented if SpO_2 <90%.

Adjuvant measures include the administration of diphenhydramine 25-50 mg IV; methylprednisolone 0.5-1 mg/kg; famotidine 20 mg IV; acetylsalicylic acid (ASA) 325 mg per os (PO) in case of flushing; meperidine 12.5-25 mg IV in case of chills and/or rigors; acetaminophen 650 mg PO if $T \geq 37.8°C$; albuterol nebulization solution 2.5-5 mg q20min (up to 3 times), and montelukast 10 mg PO in case of bronchospasm. A blood sample should be obtained in the first 30-120 minutes of the reaction to assess tryptase levels.[79-81]

There have been reports of increased anaphylaxis severity and impaired response to epinephrine among beta-blocker users[82-84] and severe anaphylactic reactions in patients with hymenoptera venom allergy related to use of angiotensin-converting enzyme inhibitors.[85] A study evaluating patients with peanut allergy who had cardiac disease (congestive heart failure or postmyocardial infarction) observed that beta-blocker use should not be avoided, because heart disease mortality was markedly reduced and outweighed beta-blocker usage risks.[84] Glucagon can be administered in patients who receive beta blockers and are resistant to epinephrine treatment, presenting with persistent hypotension and bradycardia.[86,87] It features positive inotropic and chronotropic effects that are independent of β-receptors.

DIAGNOSIS

Skin tests, such as prick test and IDT, can be performed in patients with a history suggestive of a mast cell-mediated or possibly IgE-mediated reaction and help assessing the presence of IgE-specific antibodies to the possible offending agent. Investigation of a suspected hypersensitivity reaction to a biological agent should wait 2-4 weeks to minimize the chances of false-negative skin test results, because there can be a depletion in specific IgE antibodies after anaphylaxis.[88] When skin testing is positive, it helps formalize the desensitization indication.

Data on skin testing with rituximab, infliximab, and trastuzumab on patients who were candidates to desensitization have been published.[4] Of the 18 patients who were skin tested, the prick test using the undiluted drug was positive in only one patient, allergic to trastuzumab. IDT was done using 0.03 mL of a 1:100 dilution of full strength solutions (rituximab 10 mg/mL, infliximab 10 mg/mL, and trastuzumab 21 mg/mL) and if results were negative, a 1:10 dilution. A reaction was considered positive if it produced a wheal with a diameter at least 3 mm larger than that generated by the negative control (diluent). IDT was positive in 4/6 patients with a suspected type I hypersensitivity reaction to infliximab; 2/2 to trastuzumab, and 6/9 patients to rituximab.[4] Regarding specifically infliximab hypersensitivity reactions, Matucci et al[89] evaluated 23 patients and found positive skin tests in 30.4% of them, with no positive results in the control groups. All positive tests were obtained at IDT, except one positive prick test in a patient with a severe reaction. In this study, all patients who presented with anti-infliximab IgE serum antibodies also had positive skin tests.

Tryptase is a mast cell protease released in immediate IgE and non-IgE mediated reactions and its measurement can help the evaluation of patients who present with suspected hypersensitivity reactions to biological agents. Immediate hypersensitivity reactions may present with normal tryptase levels, which can be attributed to anaphylaxis secondary to the release of basophil mediators.[80-91] The best time to obtain a blood sample to test for tryptase is 30 to 120 minutes after the onset of reaction.[79,91] If initial levels are elevated, another blood sample should be withdrawn for comparison at least 2 days after the resolution of

the reaction,[90] because conditions such as systemic mastocytosis and mast cell activation syndrome[90,92-95] can elevate baseline tryptase levels, and also predispose individuals to anaphylaxis.

If skin tests are negative, tryptase levels obtained during the reaction are within normal range and/or the clinical history is not suggestive of a true, IgE-mediated, allergic reaction, a graded challenge with the medication can be performed. The challenge consists of providing the patient with 1/10 of the total dose of the offending drug under medical surveillance and if no reactions occur in this first moment, he receives the rest of the dose. If the challenge is positive, the patient may be a candidate to desensitization; likewise, if the challenge is negative, the patient can resume regular infusions.[96,97]

Piva et al[98] evaluated the role of basophil activation test (BAT) in 5 patients treated for lymphoproliferative diseases suspected of having hypersensitivity reactions (urticaria, hypotension, angioedema and bronchospasm) secondary to rituximab infusion. BAT was performed testing 2 rituximab doses correspondent to *in vivo* concentrations and the authors showed that the percentage of CD63 expression in basophils was higher in patients presenting with the reactions compared to those without (18 healthy controls). Further studies in a larger group of patients are needed to confirm the findings and to stablish BAT as a potential diagnostic tool.

DESENSITIZATION AND BIOLOGICAL AGENTS

Desensitization should only be performed when a biological agent is needed as first-line therapy.[99] In the context of neoplastic and inflammatory diseases, desensitization would allow adequate and targeted treatment in spite of initial allergic or other immediate onset hypersensitivity reactions. It is important to point out that delayed onset reactions such as exfoliative dermatitis syndromes, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, fixed drug eruption, erythema multiforme, bullous dermatitis, and acute generalized exanthematous pustulosis constitute absolute contraindications for desensitization,[96] as well as severe, life-threatening immunocytotoxic reactions and vasculitis.[99]

Examples of biologicals to which desensitizations have been successfully performed include rituximab, trastuzumab, infliximab, cetuximab, bevacizumab, tocilizumab, ofatumumab, brentuximab, alemtuzumab, etanercept, and adalimumab. The standard desensitization protocol to monoclonal antibodies consists of 12 steps and is based on an *in vitro* model[100] in which antigen doses are doubled each 15 minutes, starting at 1/1000 to 1/10,000 the final dose.[2,4] Three solutions are administered sequentially: the first bag contains a solution with 1/100 dilution, the second a 1/10 dilution, and the third concentration is calculated by subtracting the cumulative dose administered in steps 1 to 8 from the total target dose.[4] The final step lasts longer and provides the highest dose the patient will receive. Tolerance acquired at the end of the protocol is transient; therefore, the procedure has to be repeated for every future biological infusion. Table IV shows an example of a desensitization protocol to ofatumumab.

There are also protocols for desensitization to subcutaneous biological agents, such as adalimumab and etanercept, with successful outcomes. For adalimumab, desensitization consisted of 6 steps and was done in a 26-year-old woman with RA who presented with immediate ISR[60] (Table II). Weekly adalimumab self-injections were planned for 3 months, and because she tolerated them, injections were then spaced to every other week. Desensitization to etanercept has also been published, as previously reported.[59] In both cases, patients began to tolerate the implicated drugs and presented only with mild local redness. Quercia et al reported a rush desensitization protocol to adalimumab (2-hour duration) applied in a patient who had an anaphylactic reaction on her 10th exposure and presented inconclusive skin test results.[62] This patient did not react at any step of the desensitization and has been receiving full adalimumab doses for the past 2 years.

Reactions during desensitization to biological agents are not uncommon, and can occur in approximately 29% of procedures,[4] in a similar rate to what is observed in desensitization to chemotherapeutics (33%).[2] The majority of reactions tend to be mild (90%), predominantly with cutaneous signs and symptoms and less severe than the original reaction.[4] It is important to point out that 70% of reactions during desensitization occur during the last step, so surveillance should be increased at that moment.[4] No deaths have been reported.

Premedication with antihistamines, leukotriene blockers, and corticosteroids can protect against mild-to-moderate hypersensitivity reactions during desensitization.[101] ASA and montelukast administration before desensitization to platinum compounds has been associated with a decrease in cutaneous and respiratory symptoms, because prostaglandins and leukotrienes play a role in their development.[102] ASA at 325 mg PO and montelukast at 10 mg PO can be given as premedication if flushing and bronchospasm occur during the initial reaction, respectively. Acetaminophen 500 mg PO can be administered if the patient presents fever in the initial reaction.[103]

If a reaction occurs during desensitization, the infusion must be stopped. Treatment is guided according to the clinical presentation and may include epinephrine in the event of anaphylaxis, antihistamines, corticosteroids, acetaminophen (fever), ASA (flushing), montelukast, and broncodilators (bronchospasm)[96] (Figure 1). As soon as the reaction subsides, infusion can resumed from the point it was stopped. Adding or lengthening steps before the step at which a reaction occurred can be done in subsequent desensitizations[101]; the same way additional medications can be given preceding the step at which the patient reacted.[96,101]

CONCLUSIONS

We reviewed some of the most commonly used biological agents in clinical practice. We described the presentation of hypersensitivity reactions, updated treatment recommendations for acute reactions and provided protocols for the management with rapid desensitization. Many agents elicit immediate hypersensitivity reactions, some of those in spite of a potentially low immunogenic profile, as seen with human and humanized monoclonal antibodies. Acute reactions have to be promptly managed and the cornerstone of this treatment is the use of epinephrine when indicated. Mortality is reduced when epinephrine use is not postponed and our recommendations help identifying patients who have clear indications of epinephrine. Allergists have a fundamental role in evaluating and managing hypersensitivity reactions to biologicals by reviewing the patient's history, assessing tryptase levels, performing skin tests to the offending drug, and recommending rapid desensitization when

appropriate. Rapid desensitization is an innovative and safe procedure that allows selected reactive patients to receive the full dose of essential first-line medications, while minimizing the risk of anaphylaxis and treatment failure.

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