

Hypersensitivity reactions to biological agents with special emphasis on tumor necrosis factor- α antagonists

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Purpose of review

Several biological agents have been introduced into the drug market and more are emerging. Adverse reactions to these agents have recently been classified into five different subtypes. Some of these reactions are frequent but without consequences for the patients. Others are less frequent but potentially life-threatening, and they include allergic reactions.

Recent findings

Hypersensitivity reactions are well described adverse drug reactions, corresponding to the β -type of the newly proposed classification of adverse reactions induced by biological agents. We focus our search on tumor necrosis factor- α antagonists, as they represent a dramatic improvement in the therapy of both rheumatic and inflammatory bowel diseases and because adverse reactions have been closely scrutinized. We also add cases from our own experience. We found very few properly documented allergic reactions.

Summary

Hypersensitivity reactions to tumor necrosis factor- α antagonists are not rare. Whether these manifestations have to be considered type β or type γ reactions is still a matter of debate. There is a need for allergological tests *in vivo* and *in vitro*.

Keywords

biological agents, drug allergy, drug hypersensitivity, skin tests

Introduction

The immune system is regulated by a variety of lymphokines, monokines, and colony-stimulating factors. Most have now been cloned and it is clear that these cytokines have a broad range of overlapping immunological, inflammatory, and physiological properties. Some of these cytokines may favorably influence the biological therapy of inflammatory diseases and cancer and they have been collectively referred to by clinicians as 'biological response modifiers' or 'biological agents'.

This review summarizes current data about hypersensitivity reactions induced by biological agents. Adverse reactions to biological agents have been categorized by Pichler and Campi [1**] into five types (Table 1). We will deal with the β -type reactions. In these reactions an immune mechanism is demonstrated. We did a Medline search combining the terms 'allergy or hypersensitivity' with all the recombinant biological agents approved by the US Food and Drugs Administration (FDA) – abciximab, aldesleukin, alteplase, anakinra, basiliximab, cetuximab, denileukin diftitox, drotrecogin α , efalizumab, epoetin, darbepoetin, filgrastim, pegfilgrastim, sargramostim, molgramostim, ibritumomab tiuxetan, interferon α -2a, interferon α -2b, peginterferon α -2a, peginterferon α -2b, interferon α -N3, interferon alfacon-1, interferon β -1a, interferon β -1b, laronidase, muromonab-CD3, natalizumab, omalizumab, oprelvekin, rasburicase, rituximab, and trastuzumab. We focused on tumor necrosis factor (TNF)- α antagonists, as they represent a dramatic improvement in the therapy of rheumatic and inflammatory bowel diseases and because there is concern about some adverse reactions (Tables 2 and 3) [2–35].

Infliximab

First approved for Crohn's disease and extensively employed in the therapy of rheumatoid arthritis (RA) and psoriatic arthritis, it is a 149 kDa chimeric immunoglobulin (Ig)G1 anti-TNF- α antibody containing the antigen-binding region of the mouse antibody and the constant region of the human antibody. The murine portion, comprising 25% of the antibody, is antigenic.

Acute infusion reactions

These reactions occur within 24 h after administration, usually between 10 min and 4 h, with symptoms like hypotension/hypertension, chest pain, dyspnea, laryngospasm, fever, urticaria, angioedema. The frequency of

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Abbreviations

ATI antibody to infliximab
Ig immunoglobulin
ISR injection site reaction
TNF- α tumor necrosis factor- α

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Table 1 Classification of adverse effects of biological agents [1]**

Type α	High cytokine and cytokine release syndrome (anti-CD3)	Immediate (IgE) Delayed (IgG + C'; T cells) Impaired function (immunodeficiency) Immune or cytokine imbalance syndromes: autoimmunity autoinflammatory diseases
Type β	Hypersensitivity	
Type γ	Immune imbalance syndromes	
Type δ	Cross-reactivity	
Type ε	Nonimmunological side effects	

Ig, immunoglobulin.

acute infusion reactions is fairly high (Table 2). Young children seem to be more prone than older children and adults to severe acute infusion reactions. The pathophysiology of acute infusion reactions remains unknown. Clinical evidence argues against an immunoglobulin E (IgE)-mediated mechanism because

- (1) acute infusion reactions often occur at the first dose;
- (2) after an acute infusion reaction, most patients continue the infusion with reduction in the rate of infusion or can be retreated with premedication [15].

In a few cases, however, immunological studies, and in particular skin tests, have been performed on these patients. Case reports of acute type β infusion reactions are reported in Table 3. Most acute infusion reactions are mild or moderate and do not necessitate a suspension of the treatment [22,36]. Many authors consider acute infusion reactions similar to the 'red man syndrome' induced by vancomycin [29] or 'niacin-like reactions' described for vitamin PP [37]. Severe acute infusion reactions,

presenting with cardiovascular or respiratory symptoms, must be managed more carefully, because they are more prone to reappear in the case of readministration. In these cases a desensitization protocol has been proposed [25,32,38].

It has been demonstrated that the concomitant administration of an immunomodulatory drug, especially methotrexate, reduces the rate of the antibodies to infliximab (ATIs) and therefore, possibly, also the rate of infusion reactions (Table 2). Intravenous hydrocortisone premedication reduced ATIs in Crohn's disease [14], even if a premedication with β-methasone did not decrease the incidence and severity of infusion reactions in adults [19] and a premedication with antipyretic, antihistamine and corticosteroid was not able to prevent acute infusion reactions in children [18].

Delayed infusion reactions

When occurring from 24 h to 14 days after administration, usually after 5–7 days, with symptoms like arthralgias,

Table 2 Frequency of acute and delayed infusion reactions (IRs) and antibodies to infliximab (ATIs)

Disease	No. patients	Patients with acute IRs (%)	Patients with delayed IRs (%)	Patients with ATIs (%)	ATIs/IRs	ATIs/r.e.	ATIs/i.m.d.	Reference
RA	342 ad	18	0					[2]
CD	40 ad		25	13	Yes	Yes		[3]
CD	19 ch	15.7	0					[4]
CD, RA	771 ad + ch	17						[5]
CD	129 ad	24						[6]
RA	340 ad	3	0.3	8				[7,8]
CD	52 ad	5.7	15					[9]
CD	34 ch	3	0					[9]
CD	573 ad + ch	17	2.4	14	Yes	No	Yes	[10,11]
CD	57 ch	38 (patients)	1 (inf)					[12]
CD	125 ad	8 (inf)		61	Yes	Yes	Yes	[13]
CD	53 ad	27 (inf)		36	Yes	Yes	Yes	[14]
CD	165	13.2						[15]
IBD	34 ch	9.7	1.8	35	Yes	Yes	Yes	[16]
CD	500 ad + ch	23.5	2.8					[17]
IBD	243 ch	3.8	16.5					[18]
RA	355 ad		0					[19]
RA, PA	289 ad	13.5			Yes	Yes		[20,21]
RA, PA	203 ad	19	2.4					[22]
RA	51 ad	11.3		43	Yes	Yes		[23]
IBD	23 ch	5.8						[24]
		35						

ad, adults; ATIs/i.m.d., correlation between ATIs and concomitant immunomodulatory drugs (mainly methotrexate); ATIs/IRs, correlation between ATIs and IRs; ATIs/r.e., correlation between ATIs and reduced efficacy; CD, Crohn's disease; ch, children; IBD, inflammatory bowel disease; inf, infusion; PA, psoriatic arthritis; RA, rheumatoid arthritis.

Table 3 Acute infusion reactions to infliximab

Disease	Symptoms	Onset of the reaction	Allergological studies	Desensitization	Drug tolerated afterwards	Reference
CD	Flush, chest tightness, dyspnea, nausea, hypotension (2 patients)	Second and third dose	ND	Successful		[25]
	Nausea, dizziness, dysphagia, urticaria, dyspnea	Second dose	Scratch negative	Unsuccessful	Etanercept	[26]
	Dyspnea	First dose	ND	ND	Infliximab	[4]
	Diffuse erythema, mild dyspnea	Second dose	ND	ND	Infliximab	[4]
	Diffuse erythema, facial swelling, dyspnea	Second dose	ND	ND		[4]
	Flushing, urticaria, chest pain, dyspnea, hypotension, nausea, vomiting	Second dose	ND	ND		[27]
	Flushing, urticaria, dyspnea, dysphagia, chest pain, hypotension	Second dose	ND	ND		[28]
	Flushing, urticaria, dyspnea, dysphagia, chest pain, hypotension	Third dose	ND	ND		[28]
	Flushing, tachycardia, dyspnea ('red man syndrome')	Second dose	ND	ND	Infliximab (starting slowly)	[29]
	Flushing, tachycardia, dyspnea ('red man syndrome')	First dose	ND	ND	Infliximab (starting slowly)	[29]
	Flushing, tachycardia, dyspnea ('red man syndrome')	Second dose	ND	ND	Infliximab (starting slowly)	[29]
	Flushing, tachycardia, dyspnea, vomiting	Third dose	ND	ND	Adalimumab	[30]
	Dyspnea, lightheadedness, hypotension, flushing, fever or rash (5 patients)	Third -eleventh dose	ND	ND	Adalimumab (4 out of 5)	[31]
	Dyspnea, angioedema	Sixth dose	I.d. negative	Successful		[32]
	Dysphagia, facial erythema, chest pain, tachycardia	Seventh dose	I.d. negative	Successful		[32]
Still PA	Dyspnea, tachycardia, angioedema	Second dose	I.d. negative	Successful		[32]
	Skin and mouth erythema, itching, dyspnea, chest pain 'Infusion reactions' (11 patients)	Fifth dose	I.d. negative	Successful		[32]
RA	Dyspnea, urticaria, hypotension	Third dose	Serum specific IgG (4/11) and IgE (3/11)	ND		[20]
	Dyspnea, laryngeal spasm, vomiting, hypoxemia	Second dose	I.d. positive (controls?)	ND		[33]
	Bullous skin lesions	Fourth dose	ND	ND		[34]
CD, Crohn's disease; I.d. intradermal test; Ig, immunoglobulin; ND, not done; PA, psoriatic arthritis; RA, rheumatoid arthritis; Still, adult onset Still disease.				ND		[35]

fevers, malaise, urticaria, myalgias, angioedema, lymphadenopathy, itching, the reactions are called delayed. These could well be considered as 'serum sickness-like' reactions and may represent mild type III (immune complex-mediated) Gell and Coombs reactions [9,36]. Serum sickness is largely a clinical diagnosis as there are no laboratory tests specific for this diagnosis in the acute setting. The incidence is lower than that of acute infusion reactions (Table 2). The prognosis is usually excellent with a lack of any serious long-term effects, even in severe cases, for instance when an acute respiratory distress syndrome is associated [39]. Potentially life-threatening serum sickness reactions should, however, be a contraindication to further infliximab treatment, even if uneventful retreatment cases have been described, in association with immunosuppressive therapy and premedication [9,40]. Severe delayed infusion reactions seem to occur more often in adults than in children with Crohn's disease [40]. In any case, in these patients high titres of ATIs are present and, as a consequence, a reduced efficacy of the treatment is likely.

Antibodies to infliximab

Formerly also called antichimeric antibodies, ATIs are produced by a substantial number of treated patients (Table 2). Most of the studies showed a positive statistical correlation between the presence of ATIs and both acute and delayed infusion reactions, together with a reduced efficacy of the treatment [23] and an enhanced clearance of infliximab from the circulation. Continuation of treatment with higher dosages of infliximab has been described to decrease levels of ATIs [23]. Not all patients with ATIs, however, suffer from infusion reactions; therefore there must be other cofactors responsible for these reactions. Shifting to another TNF- α antagonist seems to be safe [31,41,42]. Incidence of ATIs varies considerably among studies, not only because of the different methods of dosage but also in relation to the concomitant administration of immunomodulatory drugs, mainly methotrexate, and to the different time schedules of serum sampling. ATI prevalence seems to be lower in patients under 14 years of age and in adult patients [16].

Etanercept

Etanercept is a 150 kDa soluble TNF- α receptor fusion protein composed of two dimers, each with an extracellular, ligand-binding portion of the higher-affinity type 2 TNF- α receptor (p75) linked to the Fc portion of human IgG1. It binds to both TNF- α and TNF- β . It is approved for use in the treatment of RA, ankylosing spondylitis, juvenile rheumatoid arthritis, psoriasis, and psoriatic arthritis.

Injection site reactions

Erythema, edema and itching at the site of subcutaneous administration may appear within 24–48 h, peaking at 48 h and lasting 3–5 days. Most injection site reactions (ISRs) resolve without treatment. Usually they occur in the first–second month of therapy and fade over time. The incidence varies in relation to the trials, from 20% to 49% (Table 4) [43–50]. They rarely cause discontinuation of treatment. These patients usually have a good response to treatment with etanercept. Forty percent of these patients also develop 'recall ISRs', that is similar reactions in the sites of previous injections [43]. This phenomenon does exclude an irritative etiology of ISRs, at least in these patients, and may only be explained by an immune reaction. An ISR at the fourth dose, followed by a 'macrophage activation syndrome', characterized by fever, diffuse urticarial eruption, relative cytopenia and elevation of liver enzymes, D-dimer, triglycerides, and ferritin has been described in an 8-year-old girl [51].

Which mechanism underlies ISRs is still a matter of debate. Histopathologic studies on skin biopsies provided contrasting results [43,52,53^{*}]. Zeltser *et al.* [43] compared recall ISRs to fixed drug eruptions, known to be T-cell-dependent allergic reactions in which patch tests at the site of the reaction are frequently positive. Interestingly, a patient with a previous ISR to adalimumab experienced another ISR to etanercept at the first dose: histopathologic findings were compatible with an eosinophilic cellulitis-like reaction, a Th2-mediated phenomenon; the author explained this 'cross reactivity'

Table 4 Frequency of injection site reactions (ISRs) and antibodies to etanercept (ATEs) and adalimumab (ATAs)

Disease	Patients with ISRs to etanercept (%)	Patients with ISRs to adalimumab (%)	Patients with ATEs (%)	Patients with ATAs (%)	Reference
RA, PA, PS, BD	20% (21/103)				[43]
RA	42% (25/49)				[44]
RA	45% (70/154)				[45]
RA	29.3% (64/222)		5.6% (12/222)		[46]
RA	37% (129/349)		6%		http://www.enbrel.com
RA	18% (67/367)				[47]
RA			0%		[48]
PA		6.6% (10/151)			[49]
RA		15.3% (33/209)		1% (2/209)	[50]
All	Mean 30% (376/1254)	Mean 12% (43/360)			

PA, psoriatic arthritis; PS, psoriasis; RA, rheumatoid arthritis.

by the rheumatoid factor autoantibody binding to the FcIgG component found in both etanercept and adalimumab [53^{*}]. Werth and Levinson [54] provide an extensive discussion about possible immune mechanisms underlying ISRs [54]. Allergological tests such as prick, intradermal or patch tests are not reported in the literature in these patients.

Our personal experience refers to two patients: both female, 58 and 62 years old, affected by RA, with ISRs occurring respectively after 5 min and 6 h. An intradermal test with the commercial preparation was positive at the immediate reading (20 min), and negative in 10 controls. This result is suggestive of an immediate-type allergic reaction, possibly IgE-mediated. Interestingly, both patients experienced ISRs at the first dose of adalimumab. With this drug the intradermal test was positive in one patient at the immediate reading and, in the second, only at the late reading (24 h) and lasted 3–5 days; the patch test was negative. An intradermal test with mannitol, an excipient of both drug preparations, was negative in the two patients and in the controls (unpublished data).

Antibodies to etanercept

Antibodies to etanercept are found with a much lesser frequency than for infliximab (Table 4) and do not seem to correlate with ISRs or reduced activity [46].

Adalimumab

Adalimumab is a 148 kDa recombinant human high-affinity IgG1 monoclonal antibody against TNF- α preventing cytokine binding to its receptor and lysing cells that express TNF- α on their surface. It is approved for the treatment of RA, ankylosing spondylitis, psoriatic arthritis and Crohn's disease.

Injection site reactions

ISRs to adalimumab are rarer in relation to etanercept (Table 4). Systemic reactions, like urticaria, are rarely described [55].

Our personal experience refers to two patients: one 65-year-old male affected by psoriatic arthritis and one 61-year-old female affected by RA, with ISRs to adalimumab. An intradermal test was positive in both patients at late reading (24 h) and lasted 3–5 days; the test was negative in 10 controls. A patch test was negative (unpublished data).

Conclusion on tumor necrosis factor- α antagonist hypersensitivities

Hypersensitivity reactions to TNF- α antagonists are not uncommon. Whether these manifestations should be considered as type β or type γ reactions is still a matter of debate.

The first hypothesis – type β reactions [1^{**}] – is that these molecules are recognized as foreign antigens and symptoms are due to the appearance of antibodies or cells directed to these antigens. It is sustained by the following data:

- (1) frequency and severity of adverse reactions are directly proportional to the quantity of murine constituent of the molecule and then to immunogenicity, and are higher for infliximab than for adalimumab;
- (2) serum sickness disease and leukocytoclastic vasculitis are typical immune-mediated adverse drug reactions;
- (3) recall ISRs are highly suggestive of an immune underlying mechanism;
- (4) allergological studies – skin tests and specific IgE – have been rarely and badly performed so far, so they could not exclude this hypothesis at present;
- (5) withholding of the drug is usually followed by prompt recovery;
- (6) high frequency of ATIs indirectly witnesses the immunogenicity of infliximab;
- (7) the presence of ATIs correlates with infusing reactions.

The second hypothesis – type γ reactions [1^{**}] – is that these patients are prone to these diseases, as leukocytoclastic vasculitis in RA, and TNF- α antagonists induce a cytokine imbalance that favors their appearance: it would be a 'class effect'. In particular, there would be a switch from the predominant T helper type 1 (Th1) profile of lymphocyte response in RA to a Th2 response. RA is a Th1 disease, involving mainly TNF- α , interleukin (IL)-2, interferon (IFN)- γ , and IL-12. Evidence is growing that vasculitis is a Th2 lymphocyte-mediated disease. Moreover, patients with preexisting autoantibodies may be reflecting the predominance of a Th2 response; TNF- α antagonists may promote an increased expression of this phenotype with consequent vasculitis [56]. An alternative view is that anti-TNF- α /TNF- α immune complexes may deposit in small capillaries, activating complement, and triggering a type III hypersensitivity reaction.

The type γ reaction hypothesis is sustained by the following data:

- (1) very often the reaction occurs at the first dose;
- (2) scarce efforts to demonstrate antibodies or cells directed to the TNF- α antagonists failed, with the exception of IgG against infliximab; however, all patients with infusion reactions have these antibodies but the majority of the patients showing these antibodies do not present with infusion reactions;
- (3) the same reaction is provoked at fairly high frequency by different molecules which share the same mechanism of action;

Table 5 Hypersensitivity reactions to biological agents: recombinant monoclonal antibodies

Drug	Disease	Symptoms	Onset of the reaction	Immunological studies	Reference
Abciximab (Fab antiplatelet glycoprotein IIb/IIIa receptor)	Myocardial infarction; post PTCA	Thrombocytopenia	3–6 days after discontinuation	IgG and IgM to abciximab-coated platelets	[65]
	Myocardial infarction; post PTCA	Shock, rash, facial angioedema	First dose, immediate	I.d. positive	[66]
	Coronary artery stenting	Shock, acute airway obstruction	First dose, immediate	ND	[67]
	Coronary artery stenting	Generalized exanthema, cervicofacial swelling, eosinophilia	First dose, delayed (9 days)	I.d. positive at 48 h. Biopsy: T cell-mediated allergy	[68]
	Coronary artery stenting	Shock, edema, itching, nausea	Second course, immediate	ND	[69]
Basiliximab (chimeric, murine/human, anti CD25 – IL-2 receptor α -chain)	Renal transplant	Shock	Second dose, immediate	ND	[70]
	Renal transplant	Dyspnea, angioedema, rash	Second dose, immediate	I.d. positive – daclizumab negative	[71]
Muromonab-CD3 (murine anti CD3)	Renal transplant	Shock, bronchospasm	Second dose, immediate	Serum IgE (ELISA) and CAST positive	[72]
	Renal transplant	Anaphylactic shock, bronchospasm	Second course, immediate	Serum IgE (ELISA)	[73]
	Renal transplant	Urticaria, lips and eyelids and glottis angioedema	Second course, immediate	ND	[74]
	Renal transplant	Shock, urticaria, dyspnea	First dose, immediate ^a	I.d. positive, serum IgE (ELISA)	[75]
	Renal transplant	Shock, dyspnea, facial edema, laryngeal stridor	First dose, immediate	Serum IgE and IgG absent; antimouse IgE negative	[76]
Natalizumab (humanized anti α 4-integrin)	Renal transplant	Angioedema (1 patient), hypotension (1 patient) and serum sickness (1 patient)	First course, immediate	Serum IgG at low titre	[77]
	Multiple sclerosis	Erythema, itching, dizziness, eyelids edema	Second dose, immediate	ND	[78]
	Multiple sclerosis	Diffuse erythema and urticaria, wheezing	Seventh dose, immediate	ND	[78]
	Multiple sclerosis	'Hypersensitivity' reactions in 4% patients (25/627), loss of efficacy	Second to seventh dose, immediate	Serum antibodies (ELISA + flow cytometry)	[79]
	Asthma	Urticaria (5/225 patients)	Fourth dose	ND	[80]
Omalizumab (human anti-IgE)	Asthma	Shock	First dose in 19/48	Serum specific IgE absent	[81]
	Asthma	Anaphylaxis in 48/39 500 patients (0.1%)	First course, delayed	Serum IgG against murine Fab' fragment	[82]
	Autoimmune polyneuropathy	Serum sickness	First course, delayed	ND	[83]
	Autoimmune thrombocytopenia	Serum sickness	First or second course, delayed	ND	[84]
	Mixed cryoglobulinemia	Serum sickness	First course, delayed	ND	[85]
Rituximab (chimeric, murine/human, anti CD20)	Non-Hodgkin lymphoma	Leukocytoclastic vasculitis	Third dose, delayed	Skin biopsy	[86]
	B-cell chronic lymphocytic leukemia	Leukocytoclastic vasculitis	First dose, delayed	Skin biopsy	[87]
	B-cell lymphoma	Fatal interstitial pneumonia; pigmented purpuric dermatitis	Fifth course, delayed	Skin and lung biopsy, autopsy	[88]
	Cutaneous B-cell lymphoma	Urticaria in the sites of lymphoma	First dose, immediate	ND	[89]
	B-cell lymphoma	Serum sickness	First or second dose, delayed	ND	[90]
Trastuzumab (humanized anti HER2)	Autoimmune thrombocytopenia	Serum sickness	First or second course, delayed	ND	[91]
	B-cell lymphoma	Stevens–Johnson syndrome	Second dose	ND	[92]
	B-cell chronic lymphocytic leukemia	Autoimmune hemolytic anemia	Fourth dose	ND	[93]
	Breast cancer	Rash, angioedema, nausea, vomiting	Fourth dose, immediate	I.d. positive	[94]
	Breast cancer	Itching, throat tightening	After 9 months, immediate	I.d. negative	[94]
	Breast cancer	Shock, hypoxia (collapsed lung), severe headache, back pain, general fatigue	First dose, immediate	ND	[95]

CAST, cellular antigen stimulation test; ELISA, enzyme-linked immunosorbent assay; HER2, human epidermal growth factor receptor 2; I.d. intradermal test; Ig, immunoglobulin; IL, interleukin; ND, not done; PTCA, percutaneous transluminal coronary angioplasty.

^a The patient had preexisting IgE to rodents.

Table 6 Hypersensitivity reactions to biological agents: recombinant cytokines and hormones

Drug	Disease	Symptoms	Onset of the reaction	Immunological studies	Reference
Aldesleukin (human IL-2)	Metastatic melanoma	Face and neck edema, diffuse erythema	First dose, immediate	I.d. positive but also in controls; serum specific IgE (ELISA)	[100]
Epoetin α and β (human erythropoietin)	HCV infection treated with peginterferon and ribavirin	PRCA	After 4 months	Neutralizing IgG anti erythropoietin, cross reacting with darbepoetin	[101]
	Chronic renal failure	ISRs with epoetin; urticaria with darbepoetin; PRCA	After 10 months	IgG anti erythropoietin, cross-reacting with darbepoetin	[102]
	Chronic renal failure	Fatal DRESS	First course, delayed	ND	[103]
Darbepoetin (closely related to human erythropoietin)	Chronic renal failure	Widespread eczema	After 1 month	Patch and I.d. negative, challenge positive	[104]
	Chronic lymphocytic leukemia	Generalized angioedema, erythema	Third dose, immediate	ND	[105]
	Neutropenia	Urticaria, angioedema of lips and hands	Third dose, delayed	I.d. positive; serum specific IgE (ELISA) absent	[106]
Sargramostim (human GM-CSF)	Bone marrow transplantation	Urticaria-angioedema		Prick positive; negative with filgrastim	[107]
Molgramostim (human GM-CSF)	Neutropenia due to chemotherapy	Maculopapular eruptions with itching and eosinophilia	First dose, delayed	ND	[108]
Interferon α -2b	Chronic hepatitis C	Urticaria, dyspnea	Second dose, delayed	Serum specific IgG (ELISA)	[109]
Interferon α -2a and α -2b	Chronic myelogenous leukemia	ISRs	Second course, delayed	Type III hypersensitivity (biopsy)	[110]
Peginterferon α -2a	Chronic hepatitis C	Generalized maculopapular exanthema	After 2 months, delayed	I.d. positive at 72 h; negative with interferon α -2a	[111]
Peginterferon α -2a and α -2b	HBV infection	Diffuse urticaria, with each one dose, respectively	After 2 months and second dose, respectively	ND	[112]
Interferon β -1a	Multiple sclerosis	Reduced effect	After 12–18 months	Neutralizing antibodies in 20% of treated patients	[113]
Interferon β -1b	Multiple sclerosis	Reduced effect	After 12–18 months	Neutralizing antibodies in 60% of treated patients	[113]
	Multiple sclerosis	Shock, dyspnea, facial erythema, flushing	After 6 months, immediate	ND	[114]
	Multiple sclerosis	Urticaria	After 9 months, immediate	I.d. positive – negative with interferon β -1a	[115]
	Multiple sclerosis				

DRESS, drug reaction with eosinophilia and systemic symptoms; ELISA, enzyme-linked immunosorbent assay; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HBV, hepatitis B virus; HCV, hepatitis C virus; I.d., intradermal test; Il, interleukin; ISR, injection site reaction; ND, not done; PRCA, pure red cell aplasia.

- (4) in the same patient different molecules induced the same reaction, sometimes at the first dose [56–58];
- (5) TNF- α antagonists can induce allergic diseases like asthma [59], atopic dermatitis or allergic drug reactions [60], perhaps by means of a switch towards Th2 cytokines, autoimmune diseases like antinuclear antibodies, psoriasis, and in particular the palmoplantar pustular variant [61–63] and leukocytoclastic vasculitis, which is a paradox because TNF- α antagonists are also used as therapy for these diseases [64].

Other biological agents

Among the several monoclonal antibodies in use, mur-omonaab deserves special attention (Table 5) [65–95]. It is a murine monoclonal antibody directed against the ϵ chain of the CD3–T-cell receptor complex that acts as an immunosuppressant by blocking human T-cell proliferation, and it is used in kidney transplant recipients. Out of 181 treated patients examined for the production of specific IgE during the 8 weeks after the first administration, six positive samples were found, showing an exclusive antiidiotypic specificity in three out of four cases and an antiisotypic in the fourth. In addition, they all had high titres of specific IgG, with blocking activity. In 86 patients high levels of specific IgG were present: the remaining had low levels and none of these showed specific IgE. Anaphylactic reactions, however, are rare, and with the odd exception they occur at the second course [96]. An early secretion of IL-4 has been demonstrated after administration of mitogenic anti-CD3 monoclonal antibodies, enhancing the specific IgE response in these patients [97–99].

In relation to the rare cases of anaphylaxis due to omalizumab (Table 5), the occurrence at the first dose in 40% of patients does exclude the responsibility of specific IgE to omalizumab, opening the door to speculation about possible mechanisms [82].

Pure red cell aplasia induced by epoetin (human erythropoietin) seems to be due to a cross-reactivity among recombinant erythropoietins and the endogenous erythropoietin (Table 6) [100–115]; cross-reactivity among epoetins is also suggested by the case of Weber *et al.* [102], who showed skin reactions at the sites of former subcutaneous injections following the intravenous administration of different epoetins.

Regarding alteplase (recombinant tissue-type plasminogen activator), angioedema, urticaria and shock are not uncommon, but the mechanism seems to be related to the activation of the complement pathway or the kinins cascade in most cases (Table 7) [116–123]. It seems to be a 'class effect', as demonstrated by the patient described by Pechlaner *et al.* [122], who had the same

Table 7 Hypersensitivity reactions to other biological agents

Drug	Disease	Symptoms	Onset of the reaction	Immunological studies	Reference
Anakinra (IL-1 receptor antagonist)	Rheumatoid arthritis	ISRs + dyspnea, abdominal pain, facial and abdominal erythema, itching	After 1 month, delayed (3h)	Skin biopsy	[116]
Alteplase (tissue plasminogen activator)	Acute stroke	Shock	First dose, immediate	Serum-specific IgE (ELISA)	[117]
	Acute myocardial infarction	Urticaria and facial, tongue, and neck edema	First dose, immediate	I.d. negative	[118]
	Acute myocardial infarction	Shock, urticaria, facial and glottis edema, dyspnea	First dose, immediate	Serum specific IgE and IgG absent	[119]
	Stroke	Shock, urticaria, tongue edema, dyspnea	First dose, immediate	ND	[120]
	Acute myocardial infarction	Shock, dyspnea, abdominal pain	First dose, immediate	ND	[121]
	Deep vein thrombosis	Urticaria, angioedema, epigastric cramps	First course, delayed	Prick and I.d. negative, serum-specific IgE absent	[122]
Denileukin diftitox (diphtheria toxin and IL-2)	Lymphoma	Fatal TEN	First dose, delayed	ND	[123]

ELISA, enzyme-linked immunosorbent assay; I.d., intradermal test; Ig, immunoglobulin; IL, interleukin; ISR, injection site reaction; ND, not done; TEN, toxic epidermal necrolysis.

anaphylactic-like reaction with two nonrelated molecules – alteplase and urokinase – and negative results on searching for specific IgE.

Conclusion

The therapeutic use of the new biological response modifiers, and in particular their adverse effects, offers an exciting occasion for immunological studies, which could also lead to a better understanding of how these molecules actually work *in vivo*.

There is a need for allergological tests *in vivo* and *in vitro*, performed on more cases. Therefore, collaboration is required between the disciplines of allergy and clinical immunology and laboratory immunology, on the one hand, and rheumatology and gastroenterology on the other.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 454).

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