

The Complex Clinical Picture of Side Effects to Biologicals

Oliver V. Hausmann, MD^{a,*}, Michael Seitz, MD^a,
Peter M. Villiger, MD^a, Werner J. Pichler, MD^{a,b}

KEYWORDS

- Biological • Monoclonal therapeutic antibodies
- Adverse side effects • Hypersensitivity subclassifications
- Acute infusion reactions • Cytokine dysbalance syndrome

Adverse drug reactions (ADR) are a common phenomenon. For a long time, most drugs were small chemicals called xenobiotics that occasionally caused side effects. These were explained by the pharmacologic action of the drug (type A) or were related to the susceptibility of the individual to the drug (type B, idiosyncratic drug reactions). Most of the type B reactions were immune mediated. In addition, some investigators extended this classification and used type C for (chemical) reactions related to the chemical structure and its metabolism, for example, paracetamol hepatotoxicity; type D, corresponding to delayed reactions that appear after many years of treatment, for example, bladder carcinoma after treatment with cyclophosphamide; and type E (end of treatment) reactions occurring after drug withdrawal, for example, seizures after stopping phenytoin. This subclassification of side effects is focused on small chemical compounds, but is considered less suitable for proteins used as drugs.¹

Biological response modifiers, commonly abbreviated as “biologicals,” represent a new category of drugs designed to be as similar to human proteins as possible.¹ The nomenclature of biologicals seems to be arbitrary at first glance, but it is strictly regulated.² Taking infliximab as an example, the first 1 or 2 syllables can be chosen freely; in this case “inf-.” The following syllable derives from the target structure or target disease, here “-li-” for immune system. The next syllable denotes the species of origin, “-xi-” for chimeric murine-human origin. The last syllable stands for the therapeutic principle, in this case “-mab” for monoclonal antibody. Alternative final syllables are “-cept” for soluble receptors and “-inib” for receptor antagonists. Biological response modifiers interact specifically with the immune system (**Table 1**) and target distinct cell surface structures, for example, cytokine receptors, tumor-specific

^a Department of Rheumatology, Clinical Immunology and Allergology, Inselspital, University of Bern, Bern 3010, Switzerland

^b ADR-AC GmbH, Holligenstr. 91, CH-3008 Bern, Switzerland

* Corresponding author.

E-mail address: oliver.hausmann@insel.ch

Table 1 Biologicals grouped according to their therapeutic principle	
Biological Group	Examples
Cytokines	INF- α , GM-CSF
Monoclonal antibodies against	
Cytokines	Infliximab (anti-TNF- α)
Cell surface molecules	Rituximab (anti-CD20)
IgE	Omalizumab (anti-IgE)
Tumor antigens	Cetuximab (anti-EGFR)
Fusion proteins	
Soluble cytokine receptors	Etanercept (TNF- α -RII-IgG1)
Soluble cellular ligands	Abatacept (CTLA4-IgG1)

Abbreviations: EGFR, epidermal growth factor; GM-CSF, granulocyte macrophage colony stimulating factor; INF, interferon; TNF, tumor necrosis factor.

Data from Pichler WJ. Adverse side effects to biological agents. *Allergy* 2006;61(8):912–20.

antigens, or soluble mediators (cytokines, interferons). Biologicals have turned out to be potent and effective therapeutic tools for various inflammatory, autoimmune, and oncologic diseases. Their direct and focused effect renders them superior to classic immunosuppressive or cytotoxic drugs, whose use is often limited by unwanted and frequently severe generalized side effects. In 2006, the molecular targeted therapies in oncology accounted for 44% of the total sales of the top 20 cancer therapy brands, overtaking the cytotoxic therapies for the first time.³ The side effects seen with classic xenobiotics seem to differ considerably from the ones associated with biologicals concerning their pathogenesis and consequences for future therapy (Table 2). It is beyond the scope of this article to cover the adverse side effects of all biologicals in detail. Instead typical clinical manifestations are presented, and general rules for treating these and guiding later allergological workup as well as a possible classification scheme are proposed.

Table 2 Differences between classic xenobiotics and biologicals in view of their ADR		
	Xenobiotic	Biological
Structure	Low molecular weight chemical compound	High molecular weight protein
Metabolism	Important (reactive metabolites)	Not metabolized (processing, digestion)
Route of administration	Oral, topical, parenteral	Parenteral
Inherent immunologic activity	No (with exception of immunosuppressive drugs)	Yes
Drug interactions	Common	Rare
Immune response	Mostly cellular (T cells)	Mostly humoral (antibodies)
	(pro-) hapten Delayed type reaction	antigenic itself Immediate type
Examples	Penicillin (amoxicillin)	Monoclonal antibodies (anti-TNF- α) Cytokines (INF- α)

Data from Pichler WJ. Adverse side effects to biological agents. *Allergy* 2006;61(8):912–20.

ADAPTED CLASSIFICATION FOR ADR TO BIOLOGICALS

With certain modifications but analogous to the aforementioned “type A to E scheme” for xenobiotics, ADR to biologicals can be classified as types α to ϵ , using the Greek alphabet to distinguish them from xenobiotic-induced side effects (Fig. 1). This classification is not based on similarity of clinical symptoms but is an attempt to classify ADR to biologicals according to their pathomechanism. This might help in guiding future therapy concerning reexposure, premedication, and/or switch to an alternative biological.

TYPE α (OVERSTIMULATION)

Most cytokines are produced locally and have a predominant local activity. Thus, for most cytokines, only the local concentration is relatively high.^{4,5} If the cytokine is applied therapeutically the situation is reversed: comparatively high systemic concentrations are applied to achieve a sufficiently high concentration locally. Such high systemic concentrations of cytokines can sometimes cause severe side effects limiting their use, for example, flu-like symptoms during interferon (INF)- α therapy. Alternatively, if a monoclonal antibody is directed against a potentially stimulatory receptor like CD3 on T cells (OKT3, muromunab) or CD28 on T cells (TGN1412), a substantial release of different cytokines can occur, which reaches high systemic levels and can cause various occasionally severe symptoms.⁶ In the phase 1 clinical trial of TGN1412, the previously mentioned anti-CD28 antibody, this principle led to a near-fatal “cytokine storm” in the first 6 healthy volunteers tested,⁷ and the product was withdrawn from further trials.

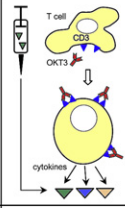
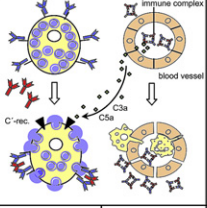
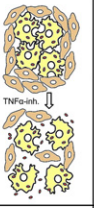
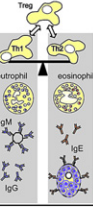
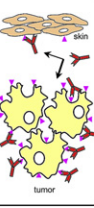
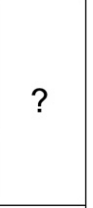
	Type α Overstimulation	Type β Hypersensitivity / Immunogenicity		Type γ Immunodeviation		Type δ Cross-reactivity	Type ϵ non-immunologic
mechanism	High cytokine levels (applied, released)	Immediate (IgE, IgG + C)	Delayed (T cells, IgG + C)	Immunodeficiency	Immune imbalance	target structure similarity	Additional effects
dose dependent	yes	yes	yes	yes	?	yes	?
related to function	yes	no	no	yes	?	yes	possibly
Clinical picture	acute infusion reactions flu-like symptoms (INF α) multiple organ dysfunction	acute infusion reactions, urticaria anaphylaxis	Loss of effect (IgG) Exanthema (rare)	opportunistic infections	autoimmunity atopic/allergic disorders	depending on target organ	?
Effects on	dependent on cytokine (interferon, interleukin)	mast cells basophils	FcR ϵ cells IgG + complement	granuloma maintenance cell migration	auto-Ab (auto-inflammation)	macrophages neutrophils	?
							
Example	OKT3 (“cytokine release syndrome”), TGN1412 (“cytokine storm”), INF α	celastimab (CCD-med. anaphylaxis)	infliximab (HACA) Serum sickness	TNF α -inhibitors (tuberculosis)	atopic eczema, SLE neutrophilic AGEP-like dermatitis	celastimab (acneiform lesions)	INF α (retinopathy, depression)

Fig. 1. Adapted classification for ADR to biologicals in a simplified illustration, with typical examples of each reaction type (for details see text). AGEP, acute generalized exanthematous pustulosis; HACA, human antichimeric antibodies; INF, interferon; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor. (Data from Pichler WJ. Adverse side effects to biological agents. Allergy 2006;61(8):912–20.)

Type α is very similar to the type A side effects of classic xenobiotics, because both are dose dependent, are somehow predictable, and are directly related to the function of the drug.

TYPE β (HYPERSENSITIVITY/IMMUNOGENICITY)

A substantial part of biologicals are monoclonal antibodies (mAbs) produced in cell lines of animal origin, therefore biologicals contain nonhuman parts either in their protein backbone or in their glycosylation pattern (posttranslational protein modification in the Golgi apparatus). Those nonhuman parts are immunogenic by definition, and like all foreign proteins can lead to a predominantly, but not exclusively humoral immune response.⁴ The therapeutic application of mAbs of murine origin in human disease was limited by the induction of human antimurine antibodies (HAMA). The generation of chimeric antibodies lessened the murine content to about 25% (Fab antibody portion) with a still considerable rate of human antichimeric antibodies (HACA). Further elimination of rodent sequences enabled the production of humanized mAbs (10% murine), followed by generation of fully human antibodies. Nevertheless, it must be pointed out that even “fully human” mAbs, with a given specificity, possess a unique (foreign) amino acid sequence at their antigen-binding site, which is also called idiotype. Therefore, even fully human mAbs can elicit the production of anti-idiotypic antibodies, also called human-antihuman antibodies (HAAH).

During evolution, antibodies in general developed to enhance the immunogenicity and hence the elimination of foreign proteins by linking them to Fc γ receptors on macrophages and neutrophils as well as through direct activation of the complement cascade, a process called opsonization.⁴ Antibody binding to Fc γ receptors and complement activation are mediated by carbohydrate determinants in the Fc region and are most effective in the IgG1 subclass. Hence, the constant region of human IgG1 is preferentially used for mAbs designed for high cytotoxicity, for example, tumor lysis in oncology. For rheumatic diseases, this additional complement activation does not seem to be crucial for the intended effect, but can lead to substantial side effects. In the development of acute infusion reactions, complement activation most probably plays a key role.^{8,9} Complement cleavage products such as C3a and C5a are potent mast cell stimulators⁴ and can therefore trigger IgE-independent histamine release, which can mimic full-blown allergic shock depending on the number of mast cells involved. On the other hand, serum sickness-like reactions based on complement-binding immune complexes in the course of treatment with various biologicals have been reported.^{10–13}

The precise pathogenesis of acute infusion reactions remains unknown, and the term itself is merely descriptive. In principle, an IgE-mediated mechanism is possible, because the relevant Fab portion of mAb contains foreign amino acid sequences and is perfectly bivalent. Those reactions are potentially more dangerous. In most cases, clinical evidence argues against an IgE-mediated mechanism, because many patients can be kept on the same biological therapy with a slower infusion rate and/or premedication with antihistamines and corticosteroids.¹⁴ Only in a few cases have skin tests and/or serologic studies been done, and firm conclusions cannot be drawn from the current data (see section on acute infusion reactions).

In contrast to this, cetuximab (anti-epidermal growth factor receptor (EGFR) in cancer therapy) has been well studied in this regard. Preformed IgE antibodies against an environmental component (galactose- α -1,3-galactose) cross-react with a similar nonhuman part of cetuximab's glycosylation pattern and could be held responsible for the sometimes severe anaphylactic reactions, even when first encountered with

cetuximab. Sensitization has probably taken place through cow's milk or meat (skin contact?) and is a phenomenon restricted to certain rural parts of the United States.^{15,16}

In certain circumstances, infusion or injection excipients such as carboxymethylcellulose^{17,18} or polysorbate 80^{17,19–21} could be identified as the culprit elicitors of anaphylactic IgE-mediated or nonimmunologic anaphylactoid reactions; this might be of special importance for the excipient-rich subcutaneous drug formulations. Sensitization may have taken place through the use of the same excipients in various vaccines and cosmetics.

Concerning T-cell-mediated delayed type hypersensitivities, various cutaneous ADR ranging from generalized pruritus without exanthema to single cases of toxic epidermal necrolysis,²² have been reported. Unfortunately, the underlying pathomechanism has not been studied in detail. In fact, infliximab has even been successfully used in the treatment of toxic epidermal necrolysis.²³ Single case reports, for example, a maculopapular exanthem due to abciximab with a positive intracutaneous test after 48 hours,²⁴ have been published, which might indicate biological-specific delayed type hypersensitivities (type IV, Coombs and Gell classification). In tumor necrosis factor (TNF)- α blocker treatment, no correlation between the atopic status and the incidence of immediate or delayed type hypersensitivity reactions was found.²⁵

TYPE γ (IMMUNODEVIATION)

The immune system has evolved to control infections and to prevent them from becoming harmful for the infected individual. Therefore, it is constantly active without causing clinical symptoms in apparently healthy individuals. The immune system controls invading organisms, for example, intracellular herpes viruses and various intracellular bacteria, and stimulates the innate immunity, especially in border regions such as mucosal surfaces or the skin. Important players in this silent but highly effective control mechanism are cytokines produced predominantly by T cells.

The potent effect of various biologicals in eliminating clinically obvious inflammations in colitis or arthritis also has an effect, beyond any doubt, on this "natural" control mechanism of predominantly intracellular pathogens and border regions. This means that biologicals, which successfully interfere with inflammation, also interfere with the well-balanced control of constantly occurring infections. Consequently, biologicals may cause immune deviations or a cytokine imbalance syndrome, and have an immunosuppressive effect, which may cause an exacerbation of an (opportunistic) infection: a typical example is the exacerbation of tuberculosis due to anti-TNF- α therapy whereby, through diminishing the TNF- α level, not only the intended attenuation of the ongoing colitis or arthritis is achieved but also the crucial TNF- α effect on granuloma maintenance to control this intracellular pathogen is lost, with sometimes fatal consequences.²⁶

This immune deviation may not only result in obvious immunodeficiency: cytokines also have a regulatory function, which is also documented for the antagonistic effect of Th2-type cytokines (interleukin [IL]-4, IL-5, IL-10, IL-13) on Th1-immune responses and vice versa.²⁷ Consequently, a suppression of Th1 responses (TNF- α , INF- γ) may enhance Th2 responses. A patient treated with a biological suppressing the Th1-biased immune response, being the case in most autoimmune diseases, may develop a Th2-related reaction: Months after starting treatment, a hitherto nonallergic patient may develop a new-onset respiratory allergy (house dust mite, pollen).²⁸ Alternatively, if the shift in cytokine balance resulting from treatment with a given biological possibly results in an inadequate handling of apoptotic cells, the patient may develop

autoantibodies to DNA, and rarely even an overt systemic lupus erythematoses.^{29–31} The immune deviation or cytokine dysbalance syndrome reflects complex clinical pictures that are far from being understood. The analysis of the effects of a certain biological on the “natural” immunity has rarely been investigated, and the effect on distinct parameters has not yet been analyzed. Moreover, the effect may also be related to the individual predisposition: if a person already has a slightly dysbalanced immune system (without causing symptoms), this person may be more susceptible to a further intervention by a biological, whereas others tolerate the same biological well.

At present, diagnosis of this immune deviation relies on clinical symptoms. Certain laboratory parameters may support the diagnosis of a new autoimmune or allergic disorder. Tests to detect hypersensitivities directed to the biological, such as skin tests with the biological agent itself as well as in vitro detection of antibodies (IgG, IgE) to the biological in question, are negative.

TYPE δ (CROSS-REACTIVITY)

Especially in oncology, the target cell surface structures (over-)expressed on tumor cells are usually to some extent also present on healthy tissues such as skin or intestinal mucosa. Therefore, monoclonal antibodies directed against these shared antigens may lead to considerable “off-target” tissue damage. The well-known phenomenon of acneiform lesions during cetuximab treatment is an illustrative example for this mechanism, because the targeted epidermal growth factor receptor is not only present on carcinoma cells but also plays an important role in epidermal homeostasis.³²

It cannot be ruled out that some monoclonal antibodies binding to their target structure with high affinity may also bind to others, which are structurally similar but not identical proteins, with lower affinity, thus causing unexpected side effects.

TYPE ϵ (NONIMMUNOLOGIC SIDE EFFECTS)

Many molecules that are defined as therapeutic target structures on a certain disease background may well be involved in other physiologic functions that are not known until the routine use of a certain biological. Daily clinical practice may actually reveal these to date unknown functions of a targeted molecule. An intense postmarketing surveillance is therefore not only important for patient safety but also for deepening the knowledge of the role of the targeted structure in human physiology.

ADR TO BIOLOGICALS: CLINICAL PICTURE IN DAILY PRACTICE

The presented subclassification of ADR to biologicals may be helpful for physicians using biologicals in their daily clinical practice, especially for allergologists who are trying to clarify the underlying pathomechanism for a firm diagnosis. Depending on the type of reaction, dose adjustments, change of preparation, or stoppage of therapy may be advised based on a balanced evaluation of the pros and cons of the treatment.

The clinician directly involved in the treatment of the affected patient is frequently confronted with acute infusion or injection site reactions and delayed reaction primarily affecting the skin. The clinician has to decide how to treat the acute ADR, primarily irrespective of the often unclear underlying pathomechanism. The clinical presentation and procedures of these acute reactions are dealt with in detail in the next sections.

Acute Infusion Reactions

Case

A 25-year-old woman was treated for her methotrexate-resistant rheumatoid arthritis with infliximab, a TNF- α blocking antibody. During the fifth infusion, she developed a pruritic rash with small isolated urticarial lesions and dyspnea. Infusion was discontinued, and the patient was treated with antihistamines and corticosteroid. After switching to an alternative TNF- α blocker, adalimumab, which was applied every second week subcutaneously, she developed a local urticaria at the injection site after the second application. Immediately after the third exposure, this urticaria spread over the whole body and adalimumab had to be stopped.

Allergological workup revealed intradermal skin test positivity for adalimumab and not for infliximab. Because no serologic test system for IgE to biologicals was available at that time, basophil activation tests were performed, which were negative for infliximab and again positive for adalimumab. Taking into account that the reaction to infliximab occurred only at the highest infusion rate (160 mL/h) and not just after the start of infusion and skin test as well as the basophil activation test (BAT) showed no positivity, the reaction was classified as non-IgE mediated acute infusion reaction (most probably IgG and/or complement mediated). The patient was safely reexposed with a pre-medication of antihistamines (no corticosteroids) at a maximum infusion rate of 100 mL/h. On the contrary, the reaction to adalimumab was classified as IgE-mediated urticaria specific for adalimumab or its excipients, and a reintroduction was not recommended.

As illustrated by this case, 2 different reaction types within 2 biologicals with the same target (TNF- α inhibitors) can occur in the same patient.

A thorough documentation of the acute reaction type with special attention on a clear-cut differentiation between subjective and objective symptoms is crucial for further workup (**Table 3**). Grading of the reaction severity analogous to hymenoptera venom allergy (I–IV according to Mueller³³) facilitates the communication with other specialties.

In clinical trials,^{34–38} acute infusion reactions were defined as any adverse event occurring during or within 1 to 2 hours after an infusion. This definition comprises everything ranging from a simple headache to dyspnea, cardiovascular symptoms, and loss of consciousness. Hence, there is considerable controversy regarding the optimal emergency treatment of acute infusion reactions. Based on a large clinical experience showing mainly mild reactions, some investigators suggest that stopping the infusion may be sufficient.³⁹ However, some reactions do not appear clinically harmless: from an allergological and pharmacological point of view as well as in the authors' experience, anaphylactic reactions with rapidly evolving symptoms including

Table 3
Subjective versus objective symptoms in the evaluation of ADR to biologicals

	Subjective	Objective
Skin/Mucosa	Itch	Flush, exanthema, urticaria, angioedema
Eye/Nose	Itch, disturbed vision	Rhinoconjunctivitis
Gastrointestinal Tract	Nausea, crampy pain	Vomiting, diarrhea
Lung	Tightness, dyspnea	Obstruction (peak expiratory flow, lung function)
Heart/Brain	Chest pain, dizziness, vertigo	Hypotension, unconsciousness, incontinence, cardiac arrest

of this premedication, some clinicians argue for a regular use for all patients regardless of their disease background or comedication. In the setting of autoimmune diseases, most clinicians disapprove a regular premedication because of the resulting difficulties in assigning the therapeutic benefit to the biological or the corticosteroids applied.^{39,46} At least 2 open studies on ADR to infliximab suggest that there is no advantage of a routine premedication for patients with no history of a prior infusion reaction,⁴⁷ whereas another randomized controlled trial showed a reduction in antibody production against infliximab (HACA) and consecutively also in acute infusion reactions using high-dose intravenous hydrocortisone premedication.⁴⁸

After stabilization of the patient and complete resolution of the symptoms without suspicion of an IgE-mediated mechanism according to symptom severity and timing, a restart of infusion at a slower infusion rate (maximal 60–100 mL/h in the case of infliximab⁴⁹) is usually possible. For further allergological workup, determination of the tryptase level during the acute phase of the reaction (within 90–120 minutes) can help to elucidate the underlying mechanism. This mast cell specific enzyme is released during degranulation and an increase to more than 150% of baseline level, even within normal limits, proves mast cell involvement and is suggestive of an IgE-mediated mechanism.⁵⁰ Further investigations (skin test, sIgE, sIgG, BAT), including determination of baseline tryptase levels, should be postponed for 4 to 6 weeks because of the refractory state of unresponsiveness of the effector cells involved (Fig. 3). For proven (or highly suggestive) IgE-mediated reactions, several desensitization protocols have been successfully applied.^{51–55}

Acute infusion reactions were more common when biological therapy was reinstated following an extended period without treatment (>16 weeks in the case of infliximab^{56,57}). Patients who developed antibodies against infliximab (HACA) had a 2- to 3-fold higher chance of having an acute infusion reaction than patients who did not develop antibodies against infliximab.^{58,59} According to recent studies, the use of concomitant immunosuppressive agents such as methotrexate reduced the frequency of antibodies to infliximab and infusion reactions.^{59–61}

Injection Site Reactions

Pruritic erythema, swelling, and infiltrated plaques are typical clinical manifestations at the injection site of subcutaneously applied biologicals. These manifestations usually appear within the first 2 days of each treatment cycle, usually within minutes of

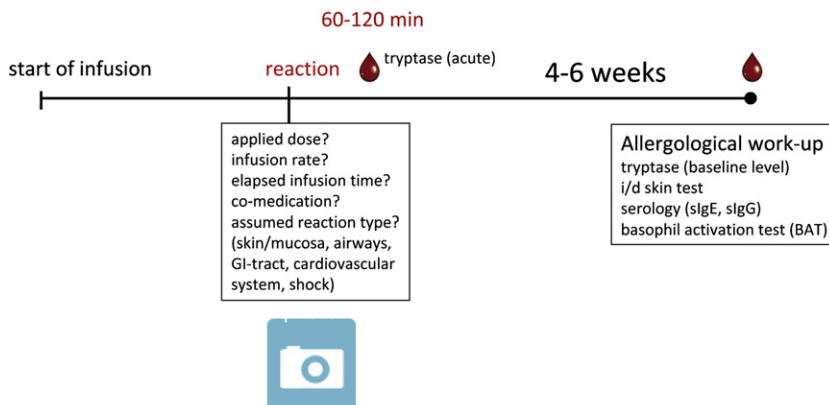


Fig. 3. Schematic course of allergological workup of acute infusion reactions. GI, gastrointestinal.

injection. Most of the time, these are benign and self-limiting on continuation of therapy^{62,63}; only in rare cases has an exanthematous dissemination been reported.⁶⁴ Studies on injection site reactions are scarce, and case descriptions or small case series dominate the field.^{65–67} These studies conclude that further studies with more patients are needed including biopsies of lesions, skin testing and, if available, determination of sIgE and sIgG against the biological in question, to elucidate the precise immune mechanism behind these reactions.

Of note, similar large local reactions following hymenoptera stings are frequently observed in patients with sIgE and sIgG against the respective venoms.⁶⁸

SUMMARY

The clinical picture of ADR to biologicals can be misleading with regard to pathogenesis of the reaction, because different pathomechanisms may lead to similar symptoms. This is especially important for acute infusion reactions, whereby no clear clinical distinction between allergic, IgE-mediated, and the more frequent nonallergic, most probably complement-mediated reactions is possible. Emergency treatment of those reactions is identical, but they differ substantially according to their further management, because only an IgE-mediated mechanism necessitates a strict avoidance or a repetitive desensitization procedure. The authors have therefore proposed a classification of the ADR to biologicals based on their pathomechanism, and suggest a strong effort for classifying preferably every ADR encountered in collaboration with the local allergologists, if necessary and possible. For the patients, the advantage is a precise advice for safe future application concerning threshold infusion rates (eg, 60–100 mL/h for infliximab), a meaningful premedication (antihistamines without repetitive corticosteroids), a possible desensitization procedure, or a switch to an alternative biological. For the scientific community, the understanding of these complex phenomena would grow, and allow for safe future treatments and drug development.

KEY MESSAGES

- Biologicals differ from classic drugs in their mode of action and ADR
- ADR to biologicals are a common phenomenon but not well understood
- Acute infusion reactions and injection site reactions are the most common clinical presentation
- Not all acute infusion reactions are allergic (on the contrary, it seems to be the exception rather than the rule)
- Most acute infusion reactions are mild, and the culprit biological can be restarted at a slower infusion rate
- For proven or highly suggestive IgE-mediated allergic reactions, desensitization protocols allow for a safe reexposure with the culprit biological
- The role of a premedication with corticosteroids or antihistamines is still a matter of debate.

REFERENCES

1. Pichler WJ. Adverse side effects to biological agents. *Allergy* 2006;61(8):912–20.
2. Saxon A. Who-mab's on first and what-cept's on second. I don't know—third base. *Clin Immunol* 2008;127(3):267.

3. Friedmann B. Commercial insight: top 20 cancer therapy brands—sales of targeted therapies overtake cytotoxics in 2006. A Datamonitor 2007. Product Code DMHC2299. 2007. Available at: <http://www.datamonitor.com>. Accessed March 9, 2010.
4. Abbas AK, Lichtman AH. Cellular and molecular immunology. 6th edition. Philadelphia: Saunders; 2009. Accessed March 9, 2010.
5. Desgeorges A, Gabay C, Silacci P, et al. Concentrations and origins of soluble interleukin 6 receptor-alpha in serum and synovial fluid. *J Rheumatol* 1997; 24(8):1510–6.
6. Vasquez EM, Fabrega AJ, Pollak R. OKT3-induced cytokine-release syndrome: occurrence beyond the second dose and association with rejection severity. *Transplant Proc* 1995;27(1):873–4.
7. Suntharalingam G, Perry MR, Ward S, et al. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. *N Engl J Med* 2006;355(10):1018–28.
8. van der Kolk LE, Grillo-Lopez AJ, Baars JW, et al. Complement activation plays a key role in the side effects of rituximab treatment. *Br J Haematol* 2001; 115(4):807–11.
9. Raasveld MH, Bemelman FJ, Schellekens PT, et al. Complement activation during OKT3 treatment: a possible explanation for respiratory side effects. *Kidney Int* 1993;43(5):1140–9.
10. Lees CW, Ali AI, Thompson AI, et al. The safety profile of anti-tumour necrosis factor therapy in inflammatory bowel disease in clinical practice: analysis of 620 patient-years follow-up. *Aliment Pharmacol Ther* 2009;29(3):286–97.
11. Medeot M, Zaja F, Vianelli N, et al. Rituximab therapy in adult patients with relapsed or refractory immune thrombocytopenic purpura: long-term follow-up results. *Eur J Haematol* 2008;81(3):165–9.
12. Pilette C, Coppens N, Houssiau FA, et al. Severe serum sickness-like syndrome after omalizumab therapy for asthma. *J Allergy Clin Immunol* 2007;120(4):972–3.
13. Gamarra RM, McGraw SD, Drelichman VS, et al. Serum sickness-like reactions in patients receiving intravenous infliximab. *J Emerg Med* 2006;30(1):41–4.
14. Cheifetz A, Smedley M, Martin S, et al. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol* 2003;98(6):1315–24.
15. Arnold DF, Misbah SA. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med* 2008;358(25):2735 [author reply: 2735–6].
16. Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med* 2008;358(11):1109–17.
17. Grims RH, Kranke B, Aberer W. Pitfalls in drug allergy skin testing: false-positive reactions due to (hidden) additives. *Contact Dermatitis* 2006;54(5):290–4.
18. Steiner UC, Gentinetta T, Hausmann O, et al. IgE-mediated anaphylaxis to intra-articular glucocorticoid preparations. *AJR Am J Roentgenol* 2009;193(2): W156–157.
19. Coors EA, Seybold H, Merk HF, et al. Polysorbate 80 in medical products and nonimmunologic anaphylactoid reactions. *Ann Allergy Asthma Immunol* 2005; 95(6):593–9.
20. Price KS, Hamilton RG. Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy. *Allergy Asthma Proc* 2007; 28(3):313–9.
21. Steele RH, Limaye S, Cleland B, et al. Hypersensitivity reactions to the polysorbate contained in recombinant erythropoietin and darbepoietin. *Nephrology (Carlton)* 2005;10(3):317–20.

22. Lin WL, Lin WC, Yang JY, et al. Fatal toxic epidermal necrolysis associated with cetuximab in a patient with colon cancer. *J Clin Oncol* 2008;26(16):2779–80.
23. Fischer M, Fiedler E, Marsch WC, et al. Antitumour necrosis factor-alpha antibodies (infliximab) in the treatment of a patient with toxic epidermal necrolysis. *Br J Dermatol* 2002;146(4):707–9.
24. Moneret-Vautrin DA, Morisset M, Vignaud JM, et al. T cell mediated allergy to abciximab. *Allergy* 2002;57(3):269–70.
25. Benucci M, Manfredi M, Saviola G, et al. Correlation between atopy and hypersensitivity reactions during therapy with three different TNF-alpha blocking agents in rheumatoid arthritis. *Clin Exp Rheumatol* 2009;27(2):333–6.
26. Clay H, Volkman HE, Ramakrishnan L. Tumor necrosis factor signaling mediates resistance to mycobacteria by inhibiting bacterial growth and macrophage death. *Immunity* 2008;29(2):283–94.
27. Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. *Nature* 1996;383(6603):787–93.
28. Bennett AN, Wong M, Zain A, et al. Adalimumab-induced asthma. *Rheumatology (Oxford)* 2005;44(9):1199–200.
29. Gonnet-Gracia C, Barnetche T, Richez C, et al. Anti-nuclear antibodies, anti-DNA and C4 complement evolution in rheumatoid arthritis and ankylosing spondylitis treated with TNF-alpha blockers. *Clin Exp Rheumatol* 2008;26(3):401–7.
30. Krause I, Valesini G, Scrivo R, et al. Autoimmune aspects of cytokine and anticytokine therapies. *Am J Med* 2003;115(5):390–7.
31. Costa MF, Said NR, Zimmermann B. Drug-induced lupus due to anti-tumor necrosis factor alpha agents. *Semin Arthritis Rheum* 2008;37(6):381–7.
32. Perez-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? *J Clin Oncol* 2005;23(22):5235–46.
33. Mueller HL. Diagnosis and treatment of insect sensitivity. *J Asthma Res* 1966;3(4):331–3.
34. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;350(9):876–85.
35. Fidler H, Schnitzler F, Ferrante M, et al. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut* 2009;58(4):501–8.
36. Schnitzler F, Fidler H, Ferrante M, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. *Gut* 2009;58(4):492–500.
37. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;353(23):2462–76.
38. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT study group. *Lancet* 1999;354(9194):1932–9.
39. Prupas M. Reactions to infliximab in patients with rheumatoid arthritis. *J Rheumatol* 2005;32(7):1411 [author reply: 1411].
40. Kemp SF, Lockey RF, Simons FE. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy* 2008;63(8):1061–70.
41. Sany J, Kaiser MJ, Jorgensen C, et al. Study of the tolerance of infliximab infusions with or without betamethasone premedication in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2005;64(11):1647–9.

42. Tramer MR, von Elm E, Loubeyre P, et al. Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. *BMJ* 2006;333(7570):675.
43. Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist* 2007;12(5):601–9.
44. Chung CH. Managing premedications and the risk for reactions to infusional monoclonal antibody therapy. *Oncologist* 2008;13(6):725–32.
45. Augustsson J, Eksborg S, Ernestam S, et al. Low-dose glucocorticoid therapy decreases risk for treatment-limiting infusion reaction to infliximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2007;66(11):1462–6.
46. Wasserman MJ, Weber DA, Guthrie JA, et al. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. *J Rheumatol* 2004;31(10):1912–7.
47. Ricart E, Panaccione R, Loftus EV, et al. Infliximab for Crohn's disease in clinical practice at the Mayo Clinic: the first 100 patients. *Am J Gastroenterol* 2001;96(3):722–9.
48. Farrell RJ, Alsahli M, Jeen YT, et al. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. *Gastroenterology* 2003;124(4):917–24.
49. Lequerre T, Vittecoq O, Klemmer N, et al. Management of infusion reactions to infliximab in patients with rheumatoid arthritis or spondyloarthritis: experience from an immunotherapy unit of rheumatology. *J Rheumatol* 2006;33(7):1307–14.
50. Borer-Reinhold M, Haeberli G, Bitzenhofer M, et al. A definite increase of serum tryptase within normal limits indicates a systemic allergic reaction [abstract 14]. Abstracts of the XXVIII EAACI Congress of the European Academy of Allergy and Clinical Immunology, Warszawa, Poland, 6–10 June 2009. *Allergy* 2009;64(Suppl 90):7.
51. Puchner TC, Kugathasan S, Kelly KJ, et al. Successful desensitization and therapeutic use of infliximab in adult and pediatric Crohn's disease patients with prior anaphylactic reaction. *Inflamm Bowel Dis* 2001;7(1):34–7.
52. Lelong J, Duburque C, Fournier C, et al. [Desensitisation to infliximab in patients with Crohn's disease]. *Rev Mal Respir* 2005;22(2 Pt 1):239–46 [in French].
53. Duburque C, Lelong J, Iacob R, et al. Successful induction of tolerance to infliximab in patients with Crohn's disease and prior severe infusion reactions. *Aliment Pharmacol Ther* 2006;24(5):851–8.
54. Jerath MR, Kwan M, Kannarkat M, et al. A desensitization protocol for the mAb cetuximab. *J Allergy Clin Immunol* 2009;123(1):260–2.
55. Brennan PJ, Rodriguez Bouza T, Hsu FI, et al. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol* 2009;124(6):1259–66.
56. Hanauer SB, Wagner CL, Bala M, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. *Clin Gastroenterol Hepatol* 2004;2(7):542–53.
57. Kavanaugh A, Cush J, Clair ES. Anti-TNF-alpha monoclonal antibody (mAb) treatment of rheumatoid arthritis (RA) patients with active disease on methotrexate (MTX): results of open label, repeated dose administration following a single dose double-blind, placebo controlled trial [abstract]. *Arthritis Rheum* 1996;39(Suppl 9):1296.

58. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;359(9317):1541–9.
59. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003;348(7):601–8.
60. Sandborn WJ. Preventing antibodies to infliximab in patients with Crohn's disease: optimize not immunize. *Gastroenterology* 2003;124(4):1140–5.
61. Vermeire S, Noman M, Van Assche G, et al. Effectiveness of concomitant immunosuppressive therapy in suppressing the formation of antibodies to infliximab in Crohn's disease. *Gut* 2007;56(9):1226–31.
62. Dore RK, Mathews S, Schechtman J, et al. The immunogenicity, safety, and efficacy of etanercept liquid administered once weekly in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2007;25(1):40–6.
63. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003;48(1):35–45.
64. Vila AT, Puig L, Fernandez-Figueras MT, et al. Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. *Br J Dermatol* 2005;153(2):417–23.
65. Zeltser R, Valle L, Tanck C, et al. Clinical, histological, and immunophenotypic characteristics of injection site reactions associated with etanercept: a recombinant tumor necrosis factor alpha receptor: Fc fusion protein. *Arch Dermatol* 2001;137(7):893–9.
66. Winfield H, Lain E, Horn T, et al. Eosinophilic cellulitis-like reaction to subcutaneous etanercept injection. *Arch Dermatol* 2006;142(2):218–20.
67. Benucci M, Manfredi M, Demoly P, et al. Injection site reactions to TNF-alpha blocking agents with positive skin tests. *Allergy* 2008;63(1):138–9.
68. Severino M, Bonadonna P, Passalacqua G. Large local reactions from stinging insects: from epidemiology to management. *Curr Opin Allergy Clin Immunol* 2009;9(4):334–7.