

Immediate adverse reactions to biologicals: from pathogenic mechanisms to prophylactic management

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Purpose of review

The rapid expansion of the use of biologics has resulted in an increase in adverse drug reactions, some of which can be life-threatening, due to the immunogenicity of these new drugs. This review summarizes the current knowledge of the pathogenic mechanisms of biologics-induced hypersensitivity reactions and highlights the most useful diagnostic and prophylactic tools now available in the clinical management of immunogenicity associated with biologics.

Recent findings

Over the last few years, many drug-related or patient-related factors contributing to the immunogenicity of biologics have been identified, thus allowing a better identification of patients at risk of reaction. Recent studies show that different mechanisms sustain hypersensitivity reactions toward biologics, and the application of novel methods for detecting antidrug antibodies has allowed the involvement of specific IgE isotypes. Additionally, experience with procedures of desensitization to biologics continues to grow.

Summary

Considering the increased use of the biological therapies in different clinical conditions, the definition of diagnostic and prophylactic strategies represents an unavoidable necessity in the management of potentially reactive patients in order to improve the safety profile of biologics.

Keywords

biological agents, drug allergy, hypersensitivity reactions

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Introduction

During the last decade, many biological agents have become available as new therapeutic principles, including cytokines, monoclonal antibodies (mAbs) and fusion proteins. Biologic response modifiers are intrinsically immunogenic and carry potential risks of adverse events [1]. Immediate infusion reactions occur during or within 1 h after infusion, and their clinical manifestations vary considerably, ranging from mild to severe and life-threatening. Considering the severity of the reactions, it is important for clinicians to recognize their symptoms, to know their pathophysiological mechanisms and to take risk assessment and prophylactic regimens.

In this review, recent evidence on the immunogenicity of biologics, pathogenic mechanisms of hypersensitivity reactions and useful diagnostic and prophylactic tools will be highlighted.

Immunogenicity profiles of biological agents

All the biologicals, including fully human proteins, have the potential to induce immunogenicity leading to the development of specific antidrug antibodies (ADAs). Chimeric mAbs such as infliximab, made from variable regions of a murine source and constant regions of a human immunoglobulin, may contain sequences (xenoantigens) recognized as nonself epitopes and stimulate immune response. The prevalence of anti-infliximab antibodies (ATI) varies from 12 to 44% in patients with rheumatoid arthritis (RA) [2,3], and between 6 and 61% in patients suffering from Crohn's disease [4,5]. In our experience with patients suffering from different immunomediated diseases, the incidence of ATI is about 14% ([6], unpublished data).

Attempts to reduce the immunogenicity of chimeric antibodies include total or partial removal of murine sequences to generate a fully human or humanized

mAb, respectively. However, reduced immunogenicity does not mean no immunogenicity. For example, humanized mAbs such as alemtuzumab is capable of triggering immune response in up to 23% of multiple sclerosis patients [7,8] and tocilizumab is associated with an overall incidence of ADA formation of 2.3% [9^{••}]. Interestingly, fully human antibodies can induce marked immune responses too. Adalimumab has been described as inducing ADAs in 2.8–3.7% of patients with Crohn's disease and up to 70% of RA patients [10,11^{••}]. Another fully human antibody that can induce an immune response is golimumab, an anti-TNF α mAb recently introduced in clinical practice. In fact, about 16% of RA patients showed golimumab-specific ADAs [12]. All these data can be explained with the ability of the human immune system to mount anti-idiotypic antibodies with specificity for the unique V region of other immunoglobulin molecules. Also, therapeutic recombinant biologic agents, such as abatacept and etanercept, can elicit an antibody response in 0–18 and 3% of patients, respectively [13,14].

The degree of humanization is not the only intrinsic determinant of immunogenicity. It is well known that the pattern of glycosylation, such as in the case of cetuximab, or other post-translational modifications of mAb (deamidation and oxidation), may represent other factors leading to the immunogenicity [15,16].

It is well known that extrinsic factors, such as aggregates, adjuvant-like contaminants, protocol of administration, and comedication, may also influence immunogenicity [17,18]. Among these factors the role of episodic administration of the drug in the induction of immunogenicity has to be underlined. Patients receiving infliximab episodically were ATI-positive more frequently than those receiving scheduled therapy (39 vs. 16%) [19]. Concomitant immunomodulator therapy is the main factor affecting development of ATIs, especially during episodic therapy in Crohn's disease patients [20].

The generation of ADAs was reported to significantly differ among treated disorders. In fact, with reference to rituximab, whereas patients with B cell malignancies and RA developed rituximab-specific antibodies in 1 and 4%, respectively [21], ADAs have been reported in about 25% of patients with primary Sjogren's syndrome and anti-neutrophil cytoplasmic auto-antibody-associated vasculitis and in up to 40% of patients with systemic lupus erythematosus (SLE) [22–24]. Concerning infliximab, we observed a higher incidence of ATI in patients suffering from RA (62.5%) than in patients with seronegative spondyloarthropathies (SpA) or vasculitis (37.5%) [6]. The reason for the variable occurrence of ADAs in different disorders is unclear but may be related to the pathogenic mechanisms of the disease itself. Further-

Key points

- Biologics-related infusion reaction are often clinically consistent with type I hypersensitivity.
- Antidrug antibodies are mostly represented by IgG isotype but a proportion of them may belong to IgE isotype.
- Many immediate adverse reactions occur at re-exposure to the biologic after an interruption of the therapy.

more, detection limits of the various assays for ADA detection may further explain the discrepancies.

Molecular mechanisms of acute hypersensitivity reactions

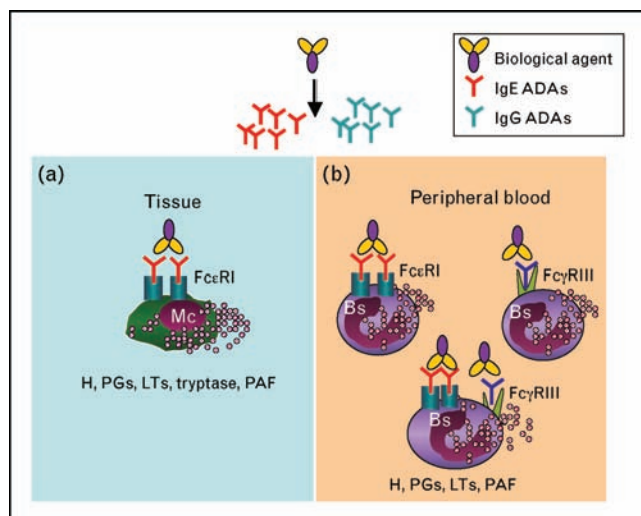
The consequences of immunogenicity to a biological agent range from transient appearance of ADAs without any clinical significance to severe life-threatening conditions such as anaphylaxis [25[•],26–29]. Patients who develop ADAs are more likely to show acute hypersensitivity reactions. Different antibody isotypes may be involved in the induction of immediate reactions to biologics. In particular, both IgE-mediated and non-IgE-mediated mechanisms may be involved. Moreover, several clinical features of acute reactions suggest an antibody-independent mechanism due to a massive cytokine release [30[•]].

IgE-mediated and non-IgE-mediated reactions

Although ADAs are mostly represented by the IgG isotype [2], a proportion of reactions have been associated with the presence of IgE isotype antibodies (Fig. 1a). Using CAP system we confirmed the hypothesis that infliximab-specific IgE Abs are involved in a part (27.2% of reactive patients) of immediate reactions [31]. The IgE-positive patients also developed a positive intradermal skin test, thus confirming the biological activity (skin mast cells activation) of IgE ADAs. Data provided recently correlate hypersensitivity reactions with IgE ADAs for several other mAbs, such as tocilizumab, cetuximab, natalizumab and muromonab [9^{••},16,32[•],33]. Also for rituximab and trastuzumab, the positive results of skin testing support an IgE-mediated mechanism of hypersensitivity reactions, at least in some patients [25[•]].

As the initial antigen exposure is required for sensitization, type I hypersensitivity reactions cannot occur during the first infusion of a mAb. However, pre-existing cetuximab-specific IgE antibodies and crossreacting with an oligosaccharide shared by some mammalian proteins and ticks have been detected [15]. Some authors have identified additives present in the drug formulation as the culprit factor of IgE-mediated reactions in biologicals

Figure 1 IgE-mediated and non-IgE-mediated mechanisms of hypersensitivity reactions to biological agents



(a) Crosslinking of FcεRI induced by specific IgE ADAs on mast cells; (b) mechanisms of basophil activation and mediator release through both IgE and IgG ADAs in peripheral blood. Bs, basophil; H, histamine; LTs, leukotrienes; Mc, mast cells; PAF, platelet-activating factor; PGs, prostaglandins.

treated patients. This event has been described for polysorbate in omalizumab-treated, erythropoietin-treated and darbepoetin-treated patients [34,35]. Sensitization may be derived from previous contact with the same excipients used in the formulation of vaccines and/or cosmetics. In our experiment with infliximab, a pre-existing sensitization was excluded [31].

Murine models revealed that anaphylaxis may occur in an IgE-independent manner, involving specific IgG, FcγRIII, macrophages, basophils, and the platelet activating factor (PAF) as the major mediator [36]. Whether the alternative IgG pathway is operative in humans remains at present an open question. Because allergen-specific IgG antibodies have been detected in patients who experienced anaphylaxis during infliximab infusion [2], this alternative pathway may in fact be involved (Fig. 1b).

The development of mAbs-specific IgG may lead to another effector mechanism involving Complement activation with subsequent production of anaphylatoxins and the release of mediators from mast cells. Worthy of note, effector functions for the different IgG subclasses are directly correlated with their affinity to FcγRs. Regarding infliximab, a proportion of ADAs are IgG4, a subclass with low Complement activating capacity and low avidity to FcγR [37]. Regarding infliximab, using a modified ELISA test, significantly higher levels of ATI IgM have been detected in reactive patients compared with unreactive patients and controls [31].

Infusion reactions induced by cytokine release

A proportion of infusion reactions is the result of massive cytokine release by different types of immune cells, including monocytes or macrophages, T cells, B cells and natural killer cells. This acute phase reaction, usually called cytokine release syndrome (CRS), may be clinically indistinguishable from type I hypersensitivity even though it is, in most cases, a first-dose effect.

Both in-vivo and in-vitro studies indicate that TNF-α, IFN-γ, IL-8 and IL-6 are the main actors of CRS [37]. The postulated mechanism is related to the interaction of the mAb with the FcγR of immune cells, leading to their activation and cytokine release. CRS can also result from the direct activation of target cells by the biologic. For example, OKT3 by direct binding of the CD3 molecule is able to activate T cells as well as rituximab activates B cells upon CD20 binding [38]. There is some evidence that Complement activation, at least in some cases, may result in the cytokine appearance in the serum, suggesting a role of Complement cascade as initiator of CRS [39]. These mechanisms are not mutually exclusive and may simultaneously participate in the induction of CRS *in vivo* (Fig. 2). It is important to underline that FcεRI engagement may also play a role in CRS. In fact, FcεRI-mediated mast cell or basophil activation leads to the release of inflammatory mediators such as TNF-α [40]. Thus, CRS may amplify the classical IgE-mediated anaphylaxis.

Differently from immune-mediated disorders, CRS is largely dependent on the disease burden during the treatment of malignancies. Accordingly, in non-Hodgkin lymphoma, the severity of rituximab-induced CRS is related to the number of circulating target cells and the density of antigen expression [37].

Prophylactic management of hypersensitivity

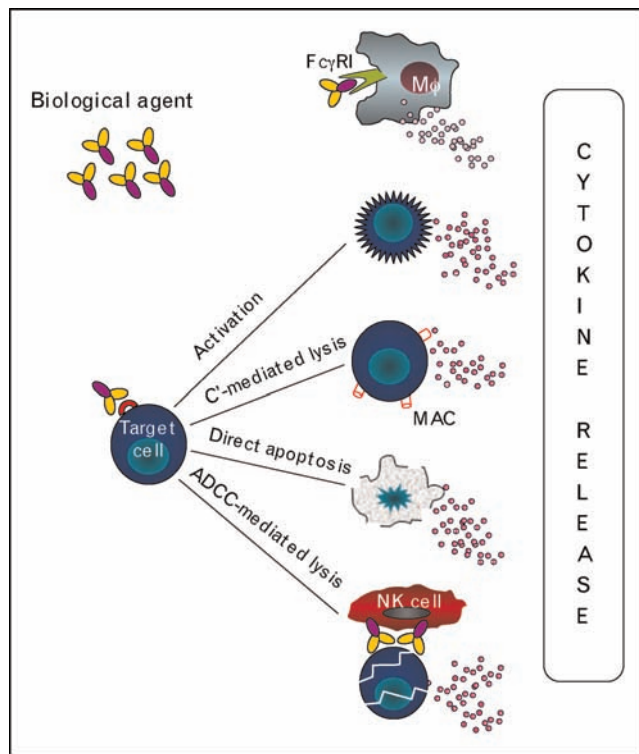
The prophylactic management of hypersensitivity to biologics may contemplate some clinical and laboratory procedures.

Recognition of patients at risk

The identification of patients at risk is a key point in clinical practice. Taking a thorough history, particularly including atopic status and any previous allergic reactions, is one of the most useful risk-assessment tools in drug allergy. However, a similar prevalence of atopy and previous adverse drug reactions in reactive and unreactive patients was seen [6].

A higher incidence of infliximab reactions in RA patients than in patients suffering from seronegative SpA and vasculitis confirmed that the underlying disease itself can be an important factor in the context of developing

Figure 2 Cellular and molecular mechanisms of monoclonal antibody-induced cytokine release syndrome



Different immunologic pathways, involving both macrophages and target cells, that may lead to cytokine release during monoclonal antibody infusion are displayed. A combination of them may occur during CRS. ADCC, antibody-dependent cellular cytotoxicity; C', Complement; Mφ, macrophage; NK, natural killer.

an unwanted immune response toward the therapeutic agent [6]. Concordantly, a higher detection rate of anti-rituximab antibodies in SLE than in lymphoma patients suggests that chimeric antibodies may be more immunogenic in autoimmune disease because of the highly activated B-lymphocytes status [41,42]. The higher expression of costimulatory molecules on dendritic cells in patients with immune-mediated diseases may accelerate the development of ADAs [43].

Intermittent therapy or re-exposure after a long treatment-free interval may be associated with an enhanced immune response (or loss of tolerance) to the biological agent, and thus retreated patients must be considered at risk of reactions [5,20,44–46]. Even if some conflicting results have recently been reported [47,48], in our case series, we confirmed a higher incidence of infliximab-related reactions at the beginning of the second course of therapy [6]. It is likely that regular drug infusion may induce a high-dose tolerance through efficient peripheral mechanisms which need the continuous antigen intake. Thus, the avoidance of long intervals between infusions represents a useful strategy to increase the safety of biologicals.

Allergological work-up in clinical practice with biologicals

In this field of drug allergy, up to now exact diagnostic tools to identify potentially reactive patients have not been defined. Monitoring for ADAs is not necessary during routine clinical treatment, whereas the evaluation of immunogenicity in a symptom-driven manner when a change in safety or efficacy profile is suspected is highly recommended.

A panel of methods is usually reported for ADA detection and characterization, but all the different techniques show benefits and limitations [49], thus a diagnostic strategy including various methods is essential. The most commonly used assay is a solid-phase double antigen bridging test, characterized by acceptable sensitivity but, because it is able to detect only nonisotype-specific ADAs, it only represents a screening test to identify positive or negative patients. In a second step, ADA-positive samples should be analyzed to confirm the result, to estimate the levels and then to define the neutralizing activity and the isotype. This latter point is really interesting taking into account that different isotypes may drive different biological phenomena. Using ImmunoCAP platform and other immunoassays mAbs-specific IgE antibodies have been found in a proportion of patients with mAbs-related anaphylaxis [15,31,32*,33]. The identification of mAbs-specific IgE may be difficult because of the small quantities of this isotype, and IgG antibodies, which may share the same specificities, may interfere in the assay.

The diagnostic work-up of reactions toward biologicals may be complicated by some interfering factors in the ADA assay, such as the presence of rheumatoid factors and/or heterophilic antibodies in the serum of reactive patients, leading to false-positive results [50]. The availability of a pretreatment sample may be useful as negative control. Detectable serum levels of biologicals may reduce the sensitivity of the tests, so it is highly recommended that the ADA assay could be performed at a certain distance in time from the infusion to avoid false-negative results [49]. Worthy of note, when high drug levels are present in the serum, new assay protocols, including an acid dissociation step, appear to be useful in the detection of ADAs [11**,51].

The allergological work-up should be completed by the measurement of serum tryptase, the classical mediator accounting for mast cell activation, even if normal values do not exclude IgE-mediated anaphylaxis. In these cases, the attention has been placed on basophils that express the high-affinity FcεRI and, after stimulation, release mediators such as histamine, but not tryptase. Basophils usually circulate in the bloodstream and are easily triggered by intravenously administered agents such as

mAbs. In recent years, the use of the basophil activation test (BAT) method has emerged to determine the response of basophils to drugs or allergens [52]. A role of the BAT as a method to assess the IgE-mediated hypersensitivity induced by biologics may be envisaged.

Even if skin testing is usually done in diagnosis of drug allergy, in-vivo tests are not currently standardized and approved for biologics. Only in a few cases skin testing has been performed [25[•],32[•],53]. In our experience with infliximab, we found great correlation between serological IgE positivity and intradermal test results ([31], unpublished data). Patients with a history suggestive of type I hypersensitivity reactions according to timing, symptoms and severity should undergo skin testing with serial dilution of the culprit drug (biologic). For skin testing too, the time between the reaction and the evaluation is a crucial point, due to temporary unresponsiveness of the skin mast cells following massive activation during the reaction. At the moment, the unknown diagnostic accuracy of the skin testing for biologicals may represent a limitation.

How to reduce the risk of reaction?

In clinical practice, the increase of safety profile of biological therapy can be achieved by several procedures.

Premedication

Solid evidence that prophylactic medication with acetaminophen and/or antihistamines can prevent infusion reactions in immune-mediated disease is lacking, whereas a high dose of intravenous corticosteroid was associated with a reduced, if not absent, risk of reaction [54–58]. In our experience we did not find a protective role for pretreatment in ATI-positive patients [6]. On the contrary, premedication with acetaminophen plus histamine blockers is recommended as prophylaxis for CRS induced by mAbs employed in cancer therapy [30[•]]. The incidence and severity of CRS may also be reduced by premedication with high-dose steroids given before the administration of the first dose of the biological agent. In oncology some authors reported, even if in small-case series, a protective role of anti-TNF α agents toward CRS induced by rituximab and muromonab [59,60].

Rate of infusion

Each biological agent is supported by specific guidelines of use and administration, in order to significantly reduce the risk of reaction. In our experience, mild infliximab-related infusion reactions were responsive to the reduced infusion rate in ATI-negative but not in ATI-positive patients [6,31].

The severity of some CRS symptoms can be reduced by careful patient management. For example, in contrast to

type I hypersensitivity reactions, CRS may be managed by short-term cessation of the mAbs infusion (fractionized dosing) and restarting the infusion at a slower rate. These reactions can also be minimized by cautious incremental increases in the rate of infusion and ensuring appropriate hydration and diuresis.

Desensitization

The decision to rechallenge or discontinue treatment after a reaction occurs depends on the severity of the reaction and other clinical factors. Desensitization has been described for several mAbs (rituximab, trastuzumab, infliximab, muromonab) to allow the continuation of treatment in reactive patients with no suitable therapeutic alternatives [31,33,37,53]. Desensitization is mainly performed in IgE-mediated reactions (skin testing and/or serum IgE ADAs positivity) and also when clinical features are highly suggestive of a type I hypersensitivity reaction. It is typically achieved by the gradual re-introduction of small doses of drug antigens at fixed time intervals until the delivery of the therapeutic dose. It is well known that the protection provided by desensitization is dependent on the ongoing antigen exposure. Taking into account the long interval between drug administrations, especially for some mAbs such as infliximab, repeated desensitization procedures are required before each mAbs infusion. Overall, these findings reiterated the role for high-dose tolerance mechanism toward biological drugs and the relationship between infusion reactions and the interruption of the therapy [43].

Conclusion

Advances in the knowledge of pathogenic mechanisms of biologic-related hypersensitivity reactions have been made. The use of new immunoassay in the detection of ADAs, as well as of in-vivo allergic work-up, may represent useful strategies in the diagnosis and prophylaxis of immediate adverse reactions to biologics. Considering the increased use of biological therapies in the treatment of immunomediated diseases and malignancies, it is advisable that these procedures be applied in clinical practice.

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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

- 1 Beck A, Wurch T, Bailly C, Corvaia N. Strategies and challenges for the next generation of therapeutic antibodies. *Nat Rev Immunol* 2010; 10:345–352.

- 2 Svenson M, Geborek P, Saxne T, Bendtzen K. Monitoring patients treated with anti-TNF- α biopharmaceuticals: assessing serum infliximab and anti-infliximab antibodies. *Rheumatology* 2007; 46:1828–1834.
- 3 Wolbink GJ, Vis M, Lems W, *et al.* Development of anti-infliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. *Arthritis Rheum* 2006; 54:711–715.
- 4 Targan SR, Hanauer SB, van Deventer SJ, *et al.* A short term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease Crohn's disease cA2 study group. *N Engl J Med* 1997; 337:1029–1035.
- 5 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; 348:601–608.
- 6 Vultaggio A, Matucci A, Parronchi P, *et al.* Safety and tolerability of infliximab therapy: suggestions and criticisms based on wide clinical experience. *Int J Immunopathol Pharmacol* 2008; 21:367–374.
- 7 Weinblatt ME, Maddison PJ, Bulpitt KJ, *et al.* CAMPATH-1H, a humanized monoclonal antibody in refractory rheumatoid arthritis: an intravenous dose-escalation study. *Arthritis Rheum* 1995; 38:1589–1594.
- 8 Coles AJ, Compston DA, Selman KW, *et al.* Alemtuzumab vs interferon beta-1a in early multiple sclerosis. *N Engl J Med* 2008; 359:1786–1801.
- 9 Stubenrauch K, Wessels U, Birnboeck H, *et al.* Subset analysis of patients experiencing clinical events of a potentially immunogenic nature in the pivotal clinical trials of tocilizumab for rheumatoid arthritis: evaluation of an antidrug antibody ELISA using clinical adverse event-driven immunogenicity testing. *Clin Ther* 2010; 32:1597–1609.
- Detection and characterization of antidrug antibodies in a large population with clinical adverse reactions to tocilizumab.
- 10 West RL, Zelinkova Z, Wolbink GJ, *et al.* Immunogenicity negatively influences the outcome of adalimumab treatments in Crohn's disease. *Aliment Pharmacol Ther* 2008; 28:1122–1126.
- 11 Van Schouwenburg PA, Bartelds GM, Hart MH, *et al.* A novel method for the detection of antibodies to adalimumab in the presence of drug reveals 'hidden' immunogenicity in rheumatoid arthritis patients. *J Immunol Methods* 2010; 362:82–88.
- A recent paper that reports a new approach to improve the sensitivity of antidrug antibodies assay.
- 12 Kay J, Matteson EL, Dasgupta B, *et al.* Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2008; 58:964–975.
- 13 DeVries MK, van der Horst-Bruinsma IE, Nurmohamed MT, *et al.* Immunogenicity does not influence treatment with etanercept in patients with ankylosing spondylitis (AS). *Ann Rheum Dis* 2009; 68:531–535.
- 14 Orencia (abatacept) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2009.
- 15 Chung CH, Mirakhor B, Chan E, *et al.* Cetuximab-induced anaphylaxis and IgE specific for galactose- α 1,3-galactose. *N Engl J Med* 2008; 358:1109–1117.
- 16 Timm V, Gruber P, Wasiliu M, *et al.* Identification and characterization of oxidation and deamidation sites in monoclonal rat/mouse hybrid antibodies. *J Chromatogr B Anal Technol Biomed Life Sci* 2010; 878:777–784.
- 17 Sauerborn M, Brinks V, Jiskoot W, Schellekens H. Immunological mechanism underlying the immune response to recombinant human protein therapeutics. *Trends Pharmacol Sci* 2009; 31:53–59.
- 18 Rosenberg AS. Effects of protein aggregates: an immunologic perspective. *AAPS J* 2006; 8:E501–E507.
- 19 Cassinotti A, Travis S. Incidence and clinical significance of immunogenicity to infliximab in Crohn's disease: a critical systematic review. *Inflamm Bowel Dis* 2009; 15:1264–1275.
- 20 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; 2:542–553.
- 21 Schmidt E, Hennig K, Menged C, *et al.* Immunogenicity of rituximab in patients with severe pemphigus. *Clin Immunol* 2009; 132:334–341.
- 22 Pijpe J, van Imhoff GW, Spijkeret FK, *et al.* Rituximab treatment in patients with primary Sjogren's syndrome: an open-label phase II study. *Arthritis Rheum* 2005; 52:2740–2750.
- 23 Smith KJ, Jones RB, Burns SM, Jayne DR. Long-term comparison of rituximab treatment for refractory systemic lupus erythematosus and vasculitis: remission, relapse and re-treatment. *Arthritis Rheum* 2006; 54:2970–2982.
- 24 Tanaka Y, Yamamoto K, Takeuchi T, *et al.* A multicenter phase I/II trial of rituximab for refractory systemic lupus erythematosus. *Mod Rheumatol* 2007; 17:191–197.
- 25 Brennan PJ, Bouza TR, Hsu FI, *et al.* Hypersensitivity reactions to mAbs:105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol* 2009; 124:1259–1266.
- A manuscript showing the usefulness of desensitization to biologicals in a wide cohort of patients.
- 26 Chavez-Lopez MA, Delgado-Villafana J, Gallaga A, *et al.* Severe anaphylactic reaction during the second infusion of infliximab in a patient with psoriatic arthritis. *Allergol Immunopathol* 2005; 33:291–292.
- 27 Soykan I, Ertan C, Ozden A. Severe anaphylactic reaction to infliximab: report of a case. *Am J Gastroenterol* 2000; 95:2395–2396.
- 28 Kolho KL, Ruuska T, Savilahti E. Severe adverse reaction to infliximab therapy are common in young children with inflammatory bowel disease. *Acta Paediatr* 2007; 96:128–130.
- 29 Puchner TC, Kugathasan S, Kelly KJ, Binion DG. Successful desensitization and therapeutic use of infliximab in adult and pediatric Crohn's disease patients with prior anaphylactic reaction. *Inflamm Bowel Dis* 2001; 7:34–37.
- 30 Vogel WH. Infusion reactions: diagnosis, assessment, and management. *Clin J Oncol Nursing* 2010; 14:E10–E21.
- An interesting and complete review on immediate adverse reaction to biological agents in oncology.
- 31 Vultaggio A, Matucci A, Nencini F, *et al.* Anti-infliximab IgE and non IgE antibodies and induction of infusion-related severe anaphylactic reactions. *Allergy* 2010; 65:657–661.
- 32 Munoz-Cano R, Carnes J, Sanchez-Lopez J, *et al.* Biological agents: new drugs, old problems. *J All Clin Immunol* 2010; 126:394–395.
- The description of IgE sensitization in a patient with natalizumab-induced anaphylaxis.
- 33 Georgitis JW, Browning MC, Steiner D, Lorentz WB. Anaphylaxis and desensitization to the murine monoclonal antibody used for renal graft rejection. *Ann Allergy* 1991; 66:343–347.
- 34 Price KS, Hamilton RG. Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy. *Allergy Asthma Proc* 2007; 28:313–319.
- 35 Steele RH, Limaye S, Cleland B, *et al.* Hypersensitivity reactions to the polysorbate contained in recombinant erythropoietin and darbepoetin. *Nephrology* 2005; 10:317–320.
- 36 Finkelman FD. Anaphylaxis: lessons from mouse model. *J Allergy Clin Immunol* 2007; 120:506–515.
- 37 Wing M. Monoclonal antibody first dose cytokine release syndrome: mechanisms and prediction. *J Immunotoxicol* 2008; 5:11–15.
- 38 Brennan FR, Morton Dill L, Spindeldreher S, *et al.* Safety and immunotoxicity assessment of immunomodulatory monoclonal antibodies. *MABs* 2010; 2–3:233–255.
- 39 Bugelski PJ, Achuthanandam R, Capocasale RJ, *et al.* Monoclonal antibody-induced cytokine-release syndrome. *Exp Rev Clin Immunol* 2009; 5:499–521.
- 40 Brown JM, Wilson TM, Metcalfe DD. The mast cell and allergic diseases: role in pathogenesis and implications for therapy. *Clin Exp Allergy* 2008; 38:4–18.
- 41 Lee S, Ballow M. Monoclonal antibodies and fusion proteins and their complications: targeting B cells in autoimmune disease. *J Allergy Clin Immunol* 2010; 125:814–820.
- 42 Sehn LH, Donaldson J, Filewich A, *et al.* Rapid infusion rituximab in combination with corticosteroid-containing chemotherapy or as maintenance therapy is well tolerated and can safely be delivered in the community setting. *Blood* 2007; 109:4171–4173.
- 43 Anderson PJ. Tumor necrosis factor inhibitors: clinical implications of their different immunogenicity profiles. *Semin Arthritis Rheum* 2005; 34 (Suppl 1): 19–22.
- 44 Pan SM, Dehler S, Ciurea A, *et al.* Comparison of drug retention rates and causes of drug discontinuation between antitumor necrosis factor agents in rheumatoid arthritis. *Arthritis Rheum* 2009; 61:560–568.
- 45 Rutgeerts P, Feagan BG, Lichtenstein GR, *et al.* Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004; 126:402–413.
- 46 Colombel JF, Sandborn WJ, Rutgeerts P, *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; 132:52–65.
- 47 Domènech E, Zabana Y, Mañosa M, *et al.* Infliximab reintroduction is not associated to a higher rate of immune-related adverse effects in patients with inflammatory bowel disease initially treated with a three-infusion induction regimen. *J Clin Gastroenterol* 2010; 44:34–37.

- 48 Baraliakos X, Listing J, Rudwaleit M, *et al.* Safety and efficacy of readministration of infliximab after longterm continuous therapy and withdrawal in patients with ankylosing spondylitis. *J Rheumatol* 2007; 34:510–515.
- 49 Aarden L, Ruuls SR, Wolbink G. Immunogenicity of antitumor necrosis factor antibodies-toward improved methods of anti-antibody measurement. *Curr Opin Immunol* 2008; 20:431–435.
- 50 Tatarewicz S, Miller JM, Swanson SJ, Moxness MS. Rheumatoid factor interference in immunogenicity assays for human monoclonal antibody therapeutics. *J Immunol Methods* 2010; 357:10–16.
- 51 Patton A, Mullenix MC, Swanson SJ, *et al.* An acid dissociation bridging ELISA for detection of antibodies directed against therapeutic proteins in the presence of antigen. *J Immunol Methods* 2005; 304:189–195.
- 52 Hausmann OV, Gentinetta T, Fux M, *et al.* Robust Expression of CCR3 as a single basophil selection marker in flow cytometry. *Allergy* 2011; 66:85–91.
- 53 Lelong J, Duburque C, Fournier C, *et al.* Desensitization to infliximab in patients with Crohn's disease. *Rev Mal Respir* 2005; 22:239–246.
- 54 Lecluse LLA, Piskin G, Mekkes JR, *et al.* Review and expert opinion on prevention and treatment of infliximab-related infusion reactions. *Br J Dermatol* 2008; 159:527–536.
- 55 Colombel JF, Loftus EV Jr, Treiman WJ, *et al.* The safety profile of infliximab inpatients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology* 2004; 126:19–31.
- 56 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; 1647–1649.
- 57 Moss AC, Fernandez-Becker N, Jo Kim K, *et al.* The impact of infliximab infusion reactions on long-term outcomes in patients with Crohn's disease. *Aliment Pharmacol Ther* 2008; 28:221–227.
- 58 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; 124:917–924.
- 59 Lin S, Lucas MS, Heerema NA, *et al.* A Phase II study of the TNF- α inhibitor etanercept and thrice weekly rituximab in relapsed CLL/SLL: clinical activity in the absence of del(17p13) genomic abnormalities. *Blood* 2006; 108:804A.
- 60 Eason JD, Pascual M, Wee S, *et al.* Evaluation of recombinant human soluble dimeric tumor necrosis factor receptor for prevention of OKT3-associated acute clinical syndrome. *Transplantation* 1996; 61:224–228.