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How to manage hypersensitivity reactions to biological agents?

Biological agents induce cutaneous adverse drug reactions (CADR) different from those observed with xenobiotics. Type alpha is the cytokine release syndrome, type beta are hypersensitivity reactions and type gamma is a cytokine imbalance syndrome. Infusion-reactions, anaphylactoid reactions occur with various biological agents administered intravenously. In non-severe cases the infusion rate has to be reduced, in severe reactions, the treatment must be stopped and resuscitation carried out with corticosteroids and epinephrine. Reactions may be due to an alpha syndrome but a true allergy could be involved as demonstrated in some patients with IgE antibodies to the galactose-alpha-1,3-galactose portion of the cetuximab or anti infliximab-IgE. Some desensitisation protocols have been published. Non allergic itching and eczema-like lesions are frequent with epidermal growth factor receptor inhibitors. Rash or desquamation was observed in 40% of cases with anti-angiogenic agents, 90% of patients treated with imatinib have rashes, oedema or pruritus and a non-allergic periorbital oedema. Severe CADR, such as Stevens-Johnson syndrome, can be provoked. Delayed readings of intradermal tests could be of value in managing patients with a maculopapular rash due to interferon. Anaphylaxis attributed to omalizumab seems to be rare (0.2%) and skin rashes occur in 7% of cases. Anaphylactoid reactions occur in 1% of patients treated with natalizumab. In the case of anti-natalizumab antibody-mediated reactions, treatment should be stopped. These allergic-like side effects of new biological agents must be known and reported to Pharmacovigilance agency networks.

Key words: biological agents, cutaneous adverse drug reactions, infusion reaction

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During the last decade, new therapeutic principles have entered the market with the emergence of biological agents. These new molecules induce side effects different from those observed with xenobiotics. Some are manifestations of hypersensitivity, others induce clinical pictures that might be mistaken for hypersensitivity. It is important to learn how to identify these side effects and to suggest approaches to manage any such adverse effects. Biological agents are proteins, cytokines such as interferons or interleukins, antibodies and fusion proteins or soluble receptors. Their international common denomination is built as follows:

- the first syllable (the prefix) is free and has no specific meaning;
- the second or third syllable (the target infix) corresponds to the target of the biological agent (li or lim: immune system; tu or ti: tumour; kin: cytokine);
- the third or fourth syllable (the source infix) indicates the origin of the antibody: “zu” for humanised, “mo” or “mu” for murine and “xi” for chimeric;

– the last syllable (the suffix) refers to the mode of action of the biological agent : “mab” for monoclonal antibody or antibody fragment, “cept” for soluble receptor and “inhib” for receptor blocker.

Pichler [1] has proposed a classification of the side-effects to biological agents. He distinguished 5 different subclasses, from alpha to epsilon. *Type alpha* side-effects are cytokine release syndromes, such as the flu-like syndrome induced by interferons or acne-like lesions due to anti-epidermal growth factor receptors (EGFR). *Type beta* side-effects are hypersensitivity reactions, subdivided into immediate IgE-mediated hypersensitivity reactions and delayed IgG- and T cell-mediated reactions. Contrary to what has been observed with xenobiotics, type beta reactions are infrequent. *Type gamma* side-effects are immune or cytokine imbalance syndromes. This is the major group of side effects, itself divided into 3 different subclasses: either by impaired functions (immunodeficiency), by causing an immune imbalance leading to autoinflammatory disorders or autoimmunity, or finally by the development

of allergic reactions like atopy. *Type delta* side-effects concern cross-reactivity and *type epsilon* syndromes are non-immunological adverse effects, such as interferon-induced neurological syndromes or anti-tumour necrosis factor (TNF)-induced heart failure.

Anaphylactoid reactions to mouse chimeric anti-cytokine monoclonal antibodies, or human receptors: infusion-reactions

Infusion-reactions occur with various biological agents administered intravenously but they seem to be more frequent when using chimeric monoclonal antibodies. When comparing studies on monoclonal antibodies, very similar descriptions of clinical manifestations are found with anaphylactoid reactions. The management of such reactions is also quite similar and some proposals for induction of tolerance have been recently published.

There are similar reactions with rituximab, which is an anti-CD20, made of human IgG1 constant regions with murine variable regions of light and heavy chains, with infliximab, which is an anti-TNF alpha agent and cetuximab, an EGFR inhibitor. The great majority of these adverse reactions are supposed to be type alpha syndromes and, less frequently, type beta syndromes. Whatever the incriminated biological agent, the same classification according to the grade of severity of these reactions can be used (*table 1*). These anaphylactoid reactions to chimeric monoclonal antibodies can occur as early as the first series of infusion. Their grade or the severity of the reaction must be determined in order to adapt the management of such events. For grades I and II, the infusion rate has to be reduced, and the patient closely monitored, hydrated, covered with blankets, administered with both antihistamines and if necessary corticosteroids. For grades III and over, the infusion must be discontinued then, depending on the clinical state, epinephrine, cortico-steroids, antihistamines and oxygen should be administered.

From the literature, Lenz [2] suggested a management strategy of infusion-reactions to most commonly used chemotherapy agents, rituximab, cetuximab but also human biological agents with reactions occurring in less than 1% of patients, such as trastuzumab, bevacizumab, alemtuzumab or panitumumab.

The pathomechanisms of these agents remain unclear, supposed to be due in some cases to an unspecific cytokine release from immune cells, but in some cases IgE antibodies against biological agents have been found. Cetuximab can trigger IgE-mediated reactions, therefore, when possible, IgE antibodies to the galactose-alpha-1,3-galactose portion of the cetuximab molecule should be determined. This derivative of galactose is present on the cetuximab fab

heavy chain. Recently, of 71 patients receiving infliximab, anti infliximab-IgE to this biological agent were demonstrated in 3 patients but also in 2 infliximab-non responder patients with a good tolerance of the infusion. In the 3 reactive patients, both IgE and intradermal tests carried out with infliximab diluted at 1/10 had positive results on immediate reading [3].

In anaphylactoid infusion-reactions, desensitisation protocols have been proposed in intensive care unit patients. In a few other cases which will be detailed later, a switch to another biological agent of the same class has been proposed, with a good tolerance. In order to analyze such infusion-reactions it would be absolutely necessary that each firm that commercializes biological agents inducing infusion-reactions, develops *in vitro* diagnosis tools to determine whether anti-biological agent-IgE or -IgG are involved or not in such severe side effects.

Eczema-like or pseudo-allergic reactions to anti-tumour necrosis factor (TNF) alpha agents

Anti-TNF agents have a similar therapeutic effect but different chemical structures. Infliximab is a murine chimeric monoclonal antibody against human TNF alpha. Adalimumab is a fully humanized IgG1 recombinant monoclonal antibody, with a specific binding site for TNF alpha. Etanercept is a fusion protein, analog to part of the human IgG1 type 2 receptor. Etanercept binds TNF alpha molecules and prevents them from binding to their receptors. Considering the very different structures of anti-TNF alpha agents, it cannot be considered that chemical cross-reactions exist explaining the side effects relapsing with anti-TNF alpha agents. Psoriasis-like reactions are common with treatment with anti-TNF agents, some have an aspect rather similar to eczema. These rashes are a type gamma syndrome. They occur with or without palmoplantar pustulosis, in 1/1,000 year patients [4].

All these series also report eczema-like rashes [4-9], in 3/51 cases of cutaneous side-effects due to anti-TNF agents [5], in 18/59 patients treated with anti-TNF agents but also in the same study in 36/128 patients suffering from rheumatoid arthritis without any anti-TNF treatment [6]. The authors [6] concluded that eczema-like lesions are not more frequent with anti-TNF treatment but it should be noted that the frequency of atopy in their patients suffering from rheumatoid arthritis was very high (40% of cases) whereas former studies underlined a reduced incidence of atopy in rheumatoid polyarthritis patients [10]. However, in the study by Esmailzadeh *et al.* [4], the follow-up of 51 Crohn's disease patients and 21 rheumatoid polyarthritis patients treated with anti-TNF agents showed that 19/92 patients (20% of cases) developed an eczema. Among

Table 1. Grading of hypersensitivity reactions to biological agents.

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Transient flushing or rash, mild fever	Rash, urticaria, dyspnea, high fever and/or non-symptomatic bronchospasm	Symptomatic bronchospasm with or without urticaria, angioedema, parenteral medication(s) indicated	Anaphylaxis	Death

the predictive risk factors for the occurrence of eczema, only a personal history of atopic symptoms was statistically significant with an odds ratio of 3.6 (CI 95%: 1-12.8 ; $p=0.04$). This induced atopic dermatitis is not a contraindication to continue the anti-TNF treatment if the cutaneous side-effects can be controlled by the use of topical corticosteroids.

Systemic infusion reactions to infliximab (a chimeric antibody) have been studied in several series [11-13], occurring in 4 to 5% of patients treated for Crohn's disease. They are either acute, soon after the infusion, or delayed, over 24 hours after the infusion; 50% of these side-effects occur after one of the 3 initial infusions, 25% as early as the second infusion. The presence of anti-infliximab antibodies is not specific as they are found in 61% of patients treated for Crohn's disease but they may favour the occurrence of these immediate or delayed infusion reactions [14]. The majority of these immediate reactions are not allergic but due to non-specific histamine liberation. They can associate flushing, headache, nausea, tachycardia, hypotension, hyperthermia, dyspnoea, sometimes bronchospasm, even severe anaphylactoid reactions. In mild to moderate reactions, it is possible to continue treatment. The infusion rate has to be slowed, antihistamines and corticosteroids administered and the patient very closely monitored. Severe cases are infrequent. There is no standardised approach. It should be noted that in one case, a 22-year-old female patient with Crohn's disease, infliximab was discontinued and adalimumab, used as a substitute, was well tolerated [15]. Puchner *et al.* [16] reported 2 cases of anaphylactoid reaction occurring with infliximab who underwent successful desensitisation in an intensive care unit using parenteral dose escalation of this anti-TNF agent.

Thus, from literature, it can be considered that when a serious anaphylactoid reaction to infliximab occurs, a switch to another anti-TNF alpha agent should be proposed, as neither cross-reactivity nor induction of tolerance seems to exist. In both cases, re-challenge must of course be carried out under strict medical surveillance in an intensive care unit.

Infliximab can also induce reactions that may be considered as delayed hypersensitivity. In the literature, there are 4 cases of generalised erythematous-squamous exanthema in patients treated for rheumatoid arthritis with infliximab, occurring 2-4 weeks after the treatment was introduced [17]. The authors reported erythema multiforme-like lesions. On the photos published with the article, they rather look like eczema-like or lichen-like reactions. In all 4 cases, there was a lymphocyte infiltration at the dermoepidermal junction. In 3 cases, infliximab discontinuation led to a disappearance of the lesions. In one case, the lesions disappeared when the anti-TNF agent was continued in conjunction with corticosteroid application. In 3 patients, patch tests with infliximab were carried out, all with negative results, but inducing a lesion flare up in one case.

In one case, etanercept was substituted for infliximab, which led to a relapse of the dermatosis. Thus in these lichen-like dermatoses, it might be interesting to carry out patch tests, generally negative, but which might re-induce a milder form of the dermatosis and enable continuation of infliximab with the application of topical corticosteroids, while closely monitoring the patient or which might suggest a switch to another anti-TNF alpha agent, keeping in mind that it will not necessarily be well tolerated.

Injection site reactions

Injection site reactions to anti-TNF alpha can occur within a month after starting treatment [7, 18]. Skin biopsy sample reveal a CD8+ T cell infiltration. Such reactions can disappear when the treatment is continued, which suggests that tolerance may be induced. These reactions are not dose-dependent, they can relapse at prior injection sites (recall phenomenon). They are more frequently reported with infliximab treatment and with this anti-TNF alpha agent, they occur in 40% of cases and in 29% with etanercept. With etanercept, the mechanism is still debated: it may be due to an irritation from high concentration of etanercept or to its excipients.

With adalimumab in the "Reveal" study [18], injection-site reactions occurred in 3.2% of the 814 adalimumab-treated patients but also in 1.8% of the 398 placebo-treated patients. These reactions were mild as they only led to one case of anti-TNF disruption. Benucci *et al.* [19] emphasized the value of intradermal tests with anti-TNF alpha agents to explore patients with serious injection site reactions to these biological agents. In 4 cases, 2 with etanercept and 2 with adalimumab, intradermal tests were positive after 15 minutes with etanercept and after 24-48 hours with adalimumab. The 4 patients had positive intradermal tests only with the suspected anti-TNF alpha agent (negative in 10 controls).

From these few data, in order to manage injection site reactions to anti-TNF alpha agents, it is proposed: 1) to assess the severity of the reaction and discomfort for the patient, 2) to treat with topical corticosteroids then 3) to have a strict follow up of the resolution of the lesions. If symptoms persist, intradermal tests could be performed and, if positive, infliximab should be substituted for another anti-TNF alpha agent which has negative results on intradermal tests.

Allergic-like reactions to epidermal growth factor receptor (EGFR) inhibitors

There are two classes of EGFR inhibitors, monoclonal antibodies directed towards the extracellular EGFR domain (cetuximab, a chimeric antibody and panitumumab) and tyrosine kinase inhibitors which activate the receptor enzyme activity (ceftinib, erlotinib). These molecules are used in the treatment of solid tumours, overexpressing EGFR: colorectal cancer, breast cancer, pancreatic cancer, non-small-cell lung cancer or some epidermoid carcinomas on the head and neck. Type alpha syndromes are frequent, grouped under the acronym "PRIDE" and some of them can be mistaken for type beta hypersensitivity reactions. Most of the rashes are pharmacologically mediated and due to a blockade of EGFR and keratinocyte maturation abnormalities in the epidermis or skin appendages. Such reactions can be dose-dependent and are thought to reflect the EGFR inhibition and therefore the treatment efficacy. Papulopustular acne-like lesions cannot be mistaken for allergic reactions. The "PRIDE" syndrome includes Papulopustules or paronychia, Regulatory abnormalities of hair growth, Itching, Dryness and an aspect of Eczema-like

lesions that should not be mistaken for eczema caused by hypersensitivity. This reaction has to be known as dry skin associated with eczema-like lesions and itching might be mistaken for eczema due to hypersensitivity. Chronic eczema-like dermatoses are also observed. They are mainly located on the face and limbs and sometimes predominate in light-exposed areas. Their mechanism is unclear; it is probably a variant of the PRIDE syndrome, but it could also be a beta type syndrome caused by delayed hypersensitivity to EGFR inhibitors or a gamma type syndrome with the inducement of an atopic dermatitis. Whatever the mechanism involved, treatment is symptomatic and based on topical corticosteroids.

Anaphylactoid reactions to cetuximab

Anaphylactoid reactions to cetuximab are not rare, they occur in 3% of patients and lead to death in 0.1% of the cases. As previously stated, the grade of the hypersensitivity reaction must be determined and if possible, IgE antibodies to galactose- α -1,3-galactose should be searched for and titrated. Jerath *et al.* [20] reported induction of tolerance to cetuximab in 3 cases, using a five-step desensitisation protocol with graded increasing doses and infusion rates. In an intensive care unit, the patients received increasing concentrations and volumes every 15 minutes for the first steps. The wait periods were longer for the last four 30-minute (min) doses and for the last one-hour dose. This desensitisation protocol was carried out with premedication associating prednisone (20 mg), 12 hours and 1 hour before the infusion and an antihistamine taken 30 minutes before the infusion. Saif *et al.* [21] reported good tolerance to another EGFR inhibitor, panitumumab, in 3 patients who had developed a grade 3 immediate infusion reaction to cetuximab. Panitumumab is a fully human IgG2 anti-EGFR antibody. In these 3 cases, without premedication, it was administered at 6 mg/kg either 8 weeks, 3 months or 8 days after a grade 3 infusion-reaction to cetuximab and was well tolerated in all 3 cases. The authors reported good tolerance of this switch in 2 other published cases. Cerman *et al.* [22] suggested another approach by re-administering cetuximab, without premedication or a desensitisation protocol, in 2 patients who had experienced grade 4 anaphylactoid reactions a few hours before. In the first case, 30 minutes after the anaphylactoid reaction, cetuximab was re-started, causing abdominal pain. The infusion was stopped again for 30 minutes and then re-administered without associated treatment or any adverse reaction. Subsequent infusions were well tolerated. In the second case, in an intensive care unit, a patient who had experienced an infusion-reaction requiring epinephrine and hydrocortisone, was restarted with a cetuximab infusion 4 hours later but stopped again because of abdominal pain. Thirty minutes later, after corticosteroids, the rest of the infusion was given without any adverse reaction. Subsequent infusions were well tolerated. These authors suggested that the drug administered *via* catheter into the right atrium could result in uneven concentrations in the lung capillaries triggering an over-whelming inflammatory response. They conclude that the first dose of cetuximab should be administered in an intensive care unit. In case of immediate hypersensitivity or an anaphylactoid

reaction, as soon as the patient is stabilised, infusion could be re-started on the same day, after systemic corticosteroid administration, obviously in an intensive care unit.

Antiangiogenic multikinase inhibitors, also called antiangiogenic agents (anti-VEGF agents/inhibitors)

Sorafenib tosylate and sunitinib are multikinase inhibitors that inhibit RAF gene products, BRAF and tyrosine kinase receptors involved in angiogenesis and tumour progression. They are mainly used for the treatment of hepatocellular carcinoma and advanced renal cell carcinoma and studies are being carried out regarding therapeutic effects in melanoma, pancreatic and colon cancer. They are administered orally at a dose of 400 mg twice daily and have many adverse effects. According to Escudier *et al.* [23] in 451 patients treated with sorafenib *versus* 452 subjects with placebo, a rash or desquamation was observed in 40% of cases, hand-foot skin reactions in 30%, alopecia in 27% and pruritus in 19% and these frequencies were statistically significant compared to the placebo group. Autier *et al.* [24], in the follow up of 85 patients with renal cell cancer, observed cutaneous adverse effects in 91% of cases (39/43 patients in the sorafenib group), whereas only 7% of 42 patients in the placebo group experienced such side-effects. Some manifestations can be mistaken for hypersensitivity reactions. Facial and scalp erythema is a frequent gamma effect with VEGF inhibitors. It occurs after 1 to 3 weeks of treatment and spontaneously disappears within 2 months. It was observed in 63% of the 39 patients examined by Autier *et al.* [24]. This face erythema can be mistaken for a seborrheic dermatitis. It requires neither treatment nor laboratory investigations. Facial edema can occur with sunitinib and imatinib, it remains mild. As reported by Autier *et al.* [24], antiangiogenic agents can induce eczema-like eruptions, reported in 7 cases (16%) with sorafenib. Painful hyperkeratosis of the nipples has been described and should not be mistaken for atopic dermatitis. Maculopapular exanthema was reported with sorafenib treatment [25], its mechanism is unknown and in the literature there is no case of drug patch tests being carried out.

Imatinib (Glivec®)

Imatinib is a tyrosine kinase inhibitor (BCR-ABL, PDGF and c-kit inhibitor). It is used to treat chronic myeloid leukemia, gastrointestinal stromal tumours but also non-cancerous diseases such as mastocytosis or hyper-eosinophilic syndromes. Cutaneous adverse reactions are frequent with imatinib treatment, some of them are severe. They can be dose-dependent [26]. Valeyrie *et al.* [27] observed cutaneous adverse effects in 89% of 54 patients treated with imatinib: 36 rashes (67%), 35 edemas (65%), 22 cases of pruritus (41%). Eighteen patients experienced only a single event, 14 had 2 events and 16 had all 3 events. The main – maybe constant – side-effect with imatinib is periorbital oedema, which should not be mistaken for angioedema or a lymphomatous eyelid infiltration. Such edema was found in 65% of cases (35 out of 54) [27], and

in all the 12 patients who underwent systematic ophthalmic examination in the series of Esmaeli *et al.* [28]. Edema can be generalised and associated with weight gain or can only be located on the eyelids. It can be severe enough to prevent the patient from wearing glasses. It is a swelling of the soft tissues of anterior orbits. It could be due to an alpha type syndrome of imatinib, by inhibition of the platelet-derived-growth factor which regulates the interstitial fluid homeostasis. Several approaches have been proposed but when edema is moderate, no treatment is required. If edema is severe, topical corticosteroids associated with oral diuretics can be necessary. Maalouf *et al.* [29] reported a case for which palpebral surgery was necessary. Under imatinib treatment, some eruptions can be severe, similar to those observed with xenobiotics in 3 cases of acute generalised exanthematous pustulosis, in which no patch-tests were carried out [30-32], 2 cases of drug reaction with eosinophilia and systemic symptoms (DRESS) [33, 34] where no patch-tests carried out and with recurrence in one case following re-challenge with imatinib. One case of erythroderma with hypereosinophilia and two cases of Lyell's or Stevens-Johnson syndromes have also been reported [35, 36]. Less severe cases of cutaneous adverse reactions, such as maculopapular exanthema, were also reported by Ujiie *et al.* [37], and were treated with topical corticosteroids without any discontinuation of imatinib. Nelson *et al.* [38] reported another 10 cases for which they had tried to induce tolerance by administering incremental dosages of oral imatinib every 15 minutes (beginning with 10 ng) to reach the therapeutic dosage. This oral desensitisation protocol was effective in 4 cases of urticaria which resolved. In another 4 cases, this desensitisation allowed treatment continuation as the rash was much milder and could be controlled with temporary corticosteroid and antihistamine administration. However, in 2 cases, despite desensitisation, a delayed exanthema could not be controlled and treatment had to be discontinued.

From these data in the literature, it has to be underlined that imatinib might induce serious cutaneous adverse reactions, similar to those observed with xenobiotics. In the case of maculopapular exanthema or urticaria, it might be interesting to analyze the mechanisms responsible by carrying out drug skin tests, although no positive case has been reported in the literature. From the literature, in the case of urticaria, a desensitisation protocol can be suggested, beginning with 10 ng of imatinib and increasing dosages every 15 minutes until the therapeutic dosage is reached. In the case of delayed exanthema, signs of severity – such as DRESS or Stevens Johnson syndrome – should obviously be looked for and, if present, treatment should be immediately discontinued. A non-severe exanthema might be controlled with topical corticosteroids associated with antihistamines, but if the dermatitis persists, the imatinib treatment should be discontinued.

Lichenoid eruptions under imatinib treatment are not rare. Their mechanism remains unknown and no patch tests have been carried out. In 2 of the 3 cases reported by Dalmau *et al.* [39], acitretin (25 mg daily) led to progressive improvement which allowed the continuation of imatinib. Thus, for such eruptions, the following approach could be recommended: at first topical corticosteroid application associated with antihistamines and, if not sufficient, starting acitretin 25 mg daily and finally, if the dermatitis remains incapacitating, imatinib has to be discontinued.

Rituximab

This is a chimeric murine and human monoclonal antibody (human IgG1 and variable murine regions of light and heavy chains) directed against CD20 antigens. It is used in lymphoma chemotherapy but also in the treatment of autoimmune diseases.

The most commonly described side-effect is an infusion-reaction, mainly observed during the treatment of lymphoma. It can be related to the sudden lyses of a large number of B-lymphocytes (cytokine release) associated with a complement activation due to massive elimination of B-cells. This reaction is reported to occur in 7% of cases, particularly when the lymphomatous tumour mass is important.

Within two hours after the beginning of the first infusion, this reaction associates severe dyspnea, bronchospasm, hypoxia, fever, chills, tremor, urticaria and angio-edema. At worst, acute respiratory syndrome occurs with interstitial pulmonary infiltrates or pulmonary edema which may be fatal in 0.04 to 0.07% of cases.

The infusion rate has been suspected but a recent study has shown that for the second and subsequent courses of rituximab, changing the administration duration from a 90 min rate infusion to a 60 min rate infusion did not increase the risk of infusion-reactions [40].

Such infusion reactions are not prevented by use of antihistamines. Their association with a previous history of allergic reaction to murine protein sensitization [41] has not been studied. It has been recommended that patients with a history of asthma should have hand-held bronchodilators available. In the case of maculopapular exanthema or urticaria, the use of antihistamines is recommended. Should an anaphylactic reaction occur, epinephrine and oxygen should be administered, then, in order to distinguish it from a non-allergic infusion-reaction, a blood sample should be collected to determine the tryptase level.

To prevent infusion reactions, these authors recommend the use of antihistamines, possibly associated with corticosteroids, even histamine 2 blockers, in the 12 hours preceding the beginning of the infusion that will last from 60 to 90 minutes. The patient has to stay under hospital surveillance for the first 2 hours. In the case of a moderate infusion-reaction, the infusion rate should be reduced and corticosteroids prescribed. In the case of a severe infusion-reaction, infusion should be stopped. The first subsequent infusion should begin at a rate of 50 mg/h and the tolerance evaluated every 30 minutes, then the rate should be increased to a maximum of 400 mg/h. In severe reactions, the infusion should be interrupted until the reaction has subsided, then the infusion should be re-started at half rate and be adapted every 30 minutes. For subsequent treatments, infusions should begin at a rate of 100 mg/mL for 15 minutes and, if they are well tolerated, the rate can be increased to complete the infusion over the next 30 to 45 minutes.

In the case of infusion reactions, Castells *et al.* [42] proposed a 12-step, 5.85 hour desensitisation protocol for intravenous rituximab. These authors applied the protocol to 7 patients, in an intensive care unit, with a good tolerance in 4 cases and mild, controllable reactions in 3 other cases.

Hastings *et al.* [43] reported the efficacy of plasmapheresis therapy in a life threatening infusion-reaction to rituximab. A kidney transplant recipient treated with rituximab for acute rejection developed, 35 minutes after the beginning of the first infusion, a grade 4 infusion-reaction despite treatment with antihistamines. Despite a symptomatic treatment, her clinical condition worsened with major respiratory deterioration. After 30 hours of evolution, the patient received 3 plasmapheresis therapies and her symptoms improved markedly. She received another plasmapheresis therapy on day 4 and was dismissed on day 5.

Dillman *et al.* [41] reported a serum-sickness-type illness two weeks after rituximab treatment. It was due to anti-mouse antibodies and associated fever, headache, myalgias, arthralgias and maculopapular exanthema. For serum sickness, these authors recommended the use of non steroidal anti-inflammatory drugs and antihistamines (without providing any pathophysiological explanation), with corticosteroids in case of non-response.

Interferon and delayed hypersensitivity

There are a few cases of tests being carried out when generalised cutaneous exanthemas occurred with interferon (IFN) treatment. Serarslan *et al.* [44] reported a positive prick test with IFN beta-1a in a 41-year-old female patient with a multiple sclerosis. She had a maculopapular exanthema which occurred just after the second injection of interferon beta-1a. On skin biopsy samples there was lymphocytic exocytosis and a perivascular lymphocytic infiltrate. The exanthema vanished with antihistamines and topical corticosteroids but relapsed after the 3rd injection.

Poreaux *et al.* [45] reported the value of IFN skin tests in both localised injection-site reactions and also in maculopapular rashes and assessed the interest of topical corticosteroids to control such reactions. Fifteen patients (8 males, 7 women, mean age 54 years) had developed cutaneous reactions to IFN: 12 were treated with IFN alpha and 3 with IFN beta. Clinical features were maculopapular rash in 5 cases, eczema on the injection site eczema (1 case), generalised eczema-like lesions in 7 cases and urticaria in 2 cases. Delayed positive reactions of intradermal tests done with the suspected IFN occurred in 6 out of the 9 patients tested (delay from 24 hours to 6 days). Patch tests and prick tests were all negative. Among 7 patients tested for several interferons, evidence of cross-reactivity was found in 4 cases within the same class of IFN and between different classes. Interferon treatment had to be stopped in 8/15 patients, despite topical corticosteroid treatment. In 4 of them, owing to the results of allergological tests, a therapeutic alternative (using an IFN for which the intradermal test was negative) was proposed. Among the 7 patients who continued treatment, topical corticosteroids and antihistamines led to improvement of the cutaneous reactions in 3 cases. Contrary to previously published reports [46], the efficacy of topical corticosteroids was inconstant in our patients. Allergological tests have often been considered useless since they are always positive in generalised reactions to IFN, but our results demonstrated otherwise. Besides, they emphasized the value of intradermal tests

with different interferons of the same class in order to guide future therapeutic choice. They also underlined the importance of delayed reading of intradermal tests over 24 hours (mean delay for positive test: 65 hours) as well as the existence of possible intra- and inter-class cross-reactions. Finally, topical corticosteroids associated with antihistamines did not always lead to sufficient improvement for the IFN treatment to continue. It might be interesting to propose UVBTL01 or topical tacrolimus as they were effective in 3 patients.

Hypersensitivity and omalizumab (Xolair®)

Omalizumab is a recombinant humanised monoclonal anti-IgE antibody with proven efficacy in patients with moderate-to-severe and severe persistent IgE-mediated allergic asthma. Between January 1, 2007 to June 30, 2008, The US Food and Drug Administration Adverse Event Reporting System received 118 reports of anaphylactic reactions associated with omalizumab treatment, including 33 cases with multisystem allergic reactions, mostly respiratory and skin reactions [47]. Of these 118 cases, 32 were after the first dose and 14 after the second dose of omalizumab. Seventy-seven cases required hospital admission or prolongation, had life-threatening reactions, underwent treatment with epinephrine or corticosteroids, or had omalizumab treatment discontinued. The reactions occurred rapidly, since in 19 cases they occurred within 1 hour of omalizumab infusion.

Using data from completed clinical studies, the tolerability of omalizumab was assessed in over 7,500 patients. The frequency of injection-site reactions was similar in the omalizumab group (45%) and the placebo group (43%). The incidence of anaphylaxis was low in both the omalizumab group (0.14%) and in the placebo group (0.07%). On the estimated exposure of 57,300 patients (June 2003-December 2006), the frequency of anaphylaxis attributed to omalizumab was 0.2% [48]. In the all-controlled-studies population the frequency of skin rashes was 6.9% (5.3% in the control group), urticaria was infrequent, in 1.3% of cases (1.3% in the control group), the incidence of anaphylaxis was rare (omalizumab 0.14%, control group 0.07%) and no case of serum sickness was reported. The post-marketing safety database (based on an estimated exposure of 57,300 patients) reported 124 cases of anaphylaxis attributed to omalizumab (0.2%) and 24% of these 124 patients had a previous history of anaphylaxis. Reactions occurred with the first dose in 39% of cases, with the second in 19% and with the third in 10% of cases, and the remainder after subsequent doses, some occurring after more than one year of omalizumab treatment and not due to anti-omalizumab antibodies.

Thus, it is important to observe the patient carefully for 2 hours post-administration for the first 3 doses, to observe him for 30 minutes after each subsequent dose, to prescribe and educate him on the proper use of an epinephrine autoinjector and to advise him to carry the epinephrine auto-injector before omalizumab administration and for 24h post-administration.

Natalizumab

This is a recombinant humanised anti- α 4-integrin monoclonal antibody used in the treatment of multiple sclerosis. Systemic allergic reactions occur in about 4% of treated patients while anaphylactoid reactions are reported to occur in 1% of cases [49]. Hypersensitivity reactions usually occur within 1 hour after the infusion. Anti-natalizumab antibodies are found in 6% of natalizumab-treated patients. If anaphylactoid reactions occur and anti-natalizumab antibodies are found, the treatment should be discontinued. In the other cases, corticosteroid treatment in combination with a reduction of the infusion rate can be suggested. Serum sickness-type reactions can be observed with fever, headache, arthralgia and lymphadenopathy appearing several hours after the infusion and progressing for several days. In patients without antibodies against natalizumab, corticosteroid administration improves the natalizumab tolerability in further infusions [49]. In cases of anti-natalizumab antibody-mediated reactions, treatment should be stopped immediately. Krumbholz *et al.* [50], reported a case of fever that occurred 8 hours after the 2nd infusion associated 3 days later with a papular rash, progressive edema of the lower lip, arthralgias and a concomitant increase of anti-natalizumab antibodies in the following weeks. Symptoms resolved with corticosteroid treatment and infusions were discontinued.

Conclusion

The hypersensitivity, but mostly allergic-like, side effects of these new biological agents must be made known. It is obviously extremely important to report adverse effects to the Pharmacovigilance agency Networks. In February 2009, such vigilance led to the withdrawal of efalizumab (anti-CD11a) from the market, following lethal progressive multifocal leukoencephalopathy. ■

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