

Hypersensitivity Reactions to Last Generation Chimeric, Umanized and Human Recombinant Monoclonal Antibodies for Therapeutic Use

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Abstract: A new class of drugs, produced with the hybridoma technique, has been introduced and employed to treat many immunological diseases. This class consists of recombinant monoclonal antibodies, which can be chimeric, humanized or human. Predictably, there has been a rise in adverse hypersensitivity reactions to these therapeutic agents, whose pathogenic mechanisms are not yet well understood. Specific IgE has been demonstrated in a very few cases, and only in some of these recombinant antibodies. Skin tests are not done as a clinical routine screening. In the present article the mechanisms underlying hypersensitivity reactions to these drugs are analyzed, also in the light of the personal experience and that reported in the literature, with the aim of identifying potential risk factors and means of prevention of these reactions. For some drugs, infusion reactions may be prevented thanks to the use of premedication. Moreover, symptoms of acute hypersensitivity during infusion can be successfully managed in the majority of cases by slowing the speed of administration. All these findings seem to confirm that the pathogenesis is not related to a true immediate (IgE-mediated) hypersensitivity in most cases. When the substitution of the drug that has triggered a hypersensitivity reaction is required, this is only possible if such an alternative drug exists (i.e., replacement of a chimeric antibody with a humanized or human antibody sharing the same target). As an alternative, desensitization protocols have been employed to induce a state of temporary tolerance to the drug in some cases, yielding successful results for infliximab and trastuzumab.

INTRODUCTION

In 1975, Kohler and Millstein set up the hybridoma technique at the Laboratory of Molecular Biology of the Cambridge University. Thanks to the fusion of splenic cells from mice sensitized toward a specific antigen with immortal myeloma cells, this method enabled the production of a murine monoclonal antibody (mAb) for diagnostic use [1]. The hybridoma technique offered the possibility to produce a host of mAbs with high specificity and effectiveness, that remain unchanged over time, and are not conditioned, as in previous techniques, by the age of the laboratory mice in which sensitization to a specific antigen (mainly human hormones or tumoral antigens employed for diagnostic uses) had been experimentally induced. This condition constituted a great advance in the field of radio-immuno-diagnostic assays.

Subsequently, the method was employed for the production of mAbs of murine derivation for therapeutic use. The first mAb produced for therapeutic use was muronomab-CD3 or OKT3, a murine antibody belonging to the IgG2a class directed against the molecular sub-unit binding to the T-Cell Receptor (TCR or CD3), which was employed in the prevention and treatment of acute rejection after organ trans-

plantation [2]. Although different studies confirmed the effectiveness of OKT3 in preventing and treating cases of acute organ rejection, inducing a rapid depletion of CD3+ CD4+ and CD3+CD8+ T lymphocytes from the peripheral blood within 2-7 days after the infusion, wide clinical use of such a therapeutic agent was limited by the reports of many serious side effects, such as the so called "aspecific cytokine release syndrome". This syndrome often appeared following the first administration of the mAb, being characterized by symptoms ranging from fever, nausea, muscular rigidity or tremors, asthenia, headache, dyspnea and cutaneous rash up to severe hypotension and acute pulmonary edema and even pictures of multi-organ failure (MOF). In the pathogenesis of this syndrome, increased concentrations of tumor necrosis factor (TNF)-alpha, interferon-gamma and of other inflammatory cytokines, such as interleukin (IL)-6 and IL-8, have been shown [3]. The clinical syndrome appears above all when most of the target cells are located in the bloodstream or the monoclonal antibody is administered too quickly. It was thought that the aspecific cytokine release syndrome caused by the administration of OKT3 might be due both to the activation and the destruction of opsonized T lymphocytes induced by the OKT3 mAb.

The aspecific cytokine release syndrome induced by recombinant biological drugs can cause the onset of an extremely dramatic and dangerous clinical picture for the patient, as occurred in the six unlucky volunteers who had taken a new drug, the anti CD-28 mAb called TGN 1412. In

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these subjects the "cytokine storm" appeared, in accordance with the definition of the syndrome made by the inventor of the drug [4], leading to MOF.

In addition, many patients have developed antibodies against the xenogenic components of the murine antibody. Repeated administrations of the mAb have been shown to induce an immunological response toward the drug due to a confrontation with human anti-murine antibodies, the so-called HAMA. These heterophilic antibodies were responsible for immediate or delayed-type adverse reactions such as anaphylaxis or serum sickness during the following administrations, and loss of the therapeutic effectiveness of the mAb [5] with a rapid clearance from the serum of the immunocomplexes [6]. HAMA can be of the IgG, IgA, IgM and, rarely, the IgE class [5]. Human anti-animal antibodies can have both an anti-isotype and an anti-idiotypic specificity. The anti-idiotypic antibodies are directed against the hypervariable region of the mAb, while the anti-isotype antibodies are directed against the constant region of the immunoglobulin. Generally the production of anti-isotype antibodies is more frequent. In some cases, however, the production of anti-idiotypic antibodies is predominant. In a study of 9 patients treated with B-E8, a murine IgG1 against IL-6, all patients developed anti-idiotypic IgG against B-E8 within 7-15 days from administration [7]. Moreover, the production of anti-anti-idiotypic antibodies capable of recognizing the antigen-binding region of the anti-idiotypic antibody is possible. In such a way the antigen-binding region of the anti-anti-idiotypic antibody mimics the conformation of the antigen responsible for the original anti-idiotypic HAMA [5]. The production of a HAMA represents a potential indirect benefit for the induction of anti-anti-idiotypic antibodies reacting against the original antigen target of the mAb primitively administered, and in this way helps to maintain the therapeutic effect.

Finally, among the patients submitted to some murine mAbs such as anti-TAG-72 there was a higher incidence of infections and tumors, as well as autoimmune diseases, suggesting that such treatments may be responsible for an immune depression and dysregulation [8].

To remedy the induction of an excessive immune response toward the murine epitopes, engineering and genetic recombination techniques are used to produce chimeric human-murine antibodies. These so-called chimeric antibodies, identified by the suffix -ximab, show the C (constant) regions of the immunoglobulin of human derivation and the V (variable) portions of both the L and H chains, that account for 20-25% of the immunoglobulin, of murine origin [9].

Subsequently, an effect denominated "humanization" has been produced. A "humanized" antibody contains, as the only amino acid sequences of murine derivation, the six conclusive regions responsible for the complementarity (CDR), in the terminal "hypervariable" part of the VL and VH arms of the immunoglobulin, being grafted in the remainder portion with a human component, to reduce its xenogenetic immunogenicity [10]. In such "humanized" antibodies, identified by the suffix -zumab, the murine component coincides with the only hypervariable region of the immunoglobulin, accounting for a total of only 5-10% of the synthesized antibody.

Unfortunately, in this way, the antigenic specificity of the murine mAb loses its efficacy, since the recombinant humanized mAb produced showed a significantly lower affinity for the specific antigen as compared to the original murine or chimeric mAb [11].

To restore the original efficacy it was necessary to genetically replace the key points (loops) of the amino acid sequences of the variable regions with the original sequences of the murine mAb, because a part of the residual amino acid is usually involved in supporting the three-dimensional conformation of the regions responsible for the complementarity [12].

Cothia and Lesk have outlined the importance of some residual amino acid keys in establishing the conformation of the regions responsible for the complementarity [13], but Foot and Winter [14] were the first to identify and type them.

The "humanization" of a recombinant human-murine antibody is based on the production of some variants of the same antibody, in order to find the immunoglobulin with the most elevated specificity and affinity for the target antigen, and the implantation of the smaller murine component of the genome tract, responsible for the production of the murine amino acid sequences inserted with transgenic techniques in cultures of *Escherichia coli* strains [10]. The screening of "phagic displays", in which the genes of the hypervariable portion of the antibodies are obtained from B murine or human cells, allows the production of such humanized antibodies.

The final step is the development of a specific human mAb, identified by the suffix -umab through the application of the hybridoma techniques to human B lymphocytes, through the immortalization of B cells following infection with the Epstein-Barr virus [15]. The technique has enabled the production of the so-called "fusion proteins", also genetically modified as a consequence of the fusion of a specific receptor or of its components with the Fc "domain" of a human IgG. This component, by binding with the specific mediator, removes it from the bond with its cellular receptor, preventing its biological activity or inactivating it. Such proteins are identified by the suffix -cept [9]. Fusion proteins will be not analyzed in the present article which refers only to mAbs.

Currently, more than twenty recombinant mAbs with high selectivity have been produced for therapeutic use (Table 1). They represent "magic bullets", being able to select the specific receptor or mediator, whose industrial production is based on the use of bacteria, yeast, transgenic mammalian cells and transgenic animals.

CLASSIFICATION, CLINICAL PICTURES AND PATHOGENETIC MECHANISMS

Besides the "aspecific cytokine release syndrome", chimeric mAbs can cause many other adverse reactions, despite their reduced immunogenicity. Recently, Pichler has suggested the subdivision of adverse reactions due to biological drugs in 5 subclasses, identified by the letters of the Greek alphabet, namely:

- Alpha-type reactions, identifiable as aspecific release of cytokines;

- Beta-type reactions: immediate and delayed hypersensitivity;
- Gamma-type reactions: over-reactions or depression of the immune functions like the immunodeficit, autoimmune or allergic phenomena;
- Delta-type reactions, correlated to cross-reactivity phenomena;
- Epsilon-type reactions, not correlated to the immune system [16].

Other authors have proposed the classification of adverse reactions to recombinant mAbs in 4 classes, although their experience was limited only to infliximab:

1. infections;
2. hypersensitivity;
3. opportunistic infections or neoplasms;
4. mAb-induced lysis of activated macrophages or T cells [17].

Different clinical manifestations of hyperreactivity have been reported in patients treated with mAbs: acute anaphylactoid symptoms, serum sickness-like disease, lupus-like syndrome, autoimmune hepatitis, aseptic meningitis, reactions involving hemopoietic components (i.e., thrombocytopenia, leukopenia, etc.), drug reaction with eosinophilia and systemic symptoms, cutaneous reactions with variegated clinical pictures (i.e., Stevens-Johnson syndrome, eczematous and lichenoid dermatitis, psoriasis or psoriasis-like lesions, etc.). In clinical practice, such pictures can sometimes overlap. Most of these clinical entities can be attributable to the above-mentioned beta- and gamma-type reactions, although other mechanisms, such as the aspecific release of cytokines, might be also involved. Few systematic studies have yet been reported in literature, conducted to gain an understanding of the immunological mechanisms capable of explaining the hypersensitivity reactions to these new therapeutic agents.

Some of these biological drugs interact with the immune and hemopoietic system, and for this reason it is difficult to understand where the action of the drug finishes, and the side effect or hypersensitivity reaction begins. For example, abciximab, a chimeric mAb of recent production, is a specific antagonist of the IIb-IIIa receptor (GP IIb-IIIa), a glycoprotein present in the platelets. Its administration prevents the activation and the adhesion of thrombocytes. Therefore, it is administered as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications [18]. Thrombocytopenia and hemorrhage are the principal side effects of abciximab. About 1% of patients receiving abciximab develops serious thrombocytopenia shortly after the first administration of the drug, while 5-10% of patients suffer hemorrhage during the second administration [19]. These patients who have manifested an abciximab-induced thrombocytopenia produce IgG or IgM that recognize abciximab-coated platelets [20].

The appearance of cutaneous lesions has been described in patients submitted to therapy with infliximab, featuring eczematous pictures, erythematosis or maculopapular [21] or lichenoid [22] and bullous eruptions [23]. Nevertheless,

sporadic reports have suggested the efficacy of infliximab in drug-induced toxic epidermal necrolysis [24]. Lichen planus or lichenoid reactions have been observed in patients receiving other TNF-alpha antagonists [25-27].

Table 1. Main Recombinant Monoclonal Antibodies (mAbs) for Therapeutic Use

mAb	Target
ABCIXIMAB	Platelet receptor IIb/IIIa
ADALIMUMAB	TNF-alpha
ALEMTUZUMAB	CD52
BASILIXIMAB	IL-2 receptor (CD25)
DACLIZUMAB	IL-2 receptor (CD25)
BEVACIZUMAB	VEGF
CETUXIMAB	EGFR
EFALIZUMAB	LFA-1 (CD11a subunit)
GEMTUZUMAB	CD33
IBRITUNOMAB	CD20
INFLIXIMAB	TNF-alpha
LUMILIXIMAB	CD23
MEPOMALIZUMAB	IL-5
MUROMAB	CD3
VISILIZUMAB	CD3
NATALIZUMAB	VLA-4
OMALIZUMAB	IgE Fc
PAVILIZUMAB	RSV
PANITUMUMAB	EGFR
PERTUZUMAB	HER-2
RITUXIMAB	CD20
TRASTUZUMAB	HER-2

A case of Stevens-Johnson syndrome has been reported with the use of rituximab [28], while a maculopapular exanthema has been described after the administration of abciximab, with positive intradermal test after 48 hours [29].

In the case of infliximab, some cutaneous reactions, such as vasculitis, can be correlated to an immune response toward the murine component of the mAb, despite the appearance of the same lesions following the administration of etanercept, a recombinant human fusion protein consisting of the TNF 75 kDa receptor and the Fc portion of human IgG [30,31]. The latter phenomenon suggests that the development of cutaneous lesions after the administration of such drugs can be caused, at least in some cases, by the involvement of immune mechanisms, with a strong inhibition of the mediator-target, TNF-alpha, rather than by an allergic reaction to the drug.

Moreover, the appearance or aggravation of atopic dermatitis in patients treated with infliximab can be considered secondary to the induction of the "shift" from a TH1 immune response to a TH2 response [32]. Another reaction resulting

from cytokine imbalance may be represented by new-onset psoriasis or exacerbation of psoriasis observed during treatment with all TNF-blocking agents, even though these drugs are used for the treatment of psoriasis. Flare of preexisting psoriasis often involves areas previously unaffected and developed as new clinical variants (e.g., intertriginous psoriasis, eruptive guttate psoriasis, or palmoplantar pustulosis) never presented by patients in their lifetime. The pathogenesis of these reactions is not well known, although several hypotheses have been proposed, including the involvement of autoimmune phenomena, the dual role of TNF- α in immune homeostasis and apoptosis, the triggering effect of infectious factors, and the production of IFN- α due to the up-regulation of plasmacytoid dendritic cells [33, 34].

Generalized inflammatory flare of psoriasis can occur during and after treatment with efalizumab, an anti-CD11a mAb effective in plaque psoriasis, which may also cause new psoriatic lesions appearing as papular eruptions [35, 36].

Immune mechanisms have also been implicated in hematological manifestations rarely reported in efalizumab-treated patients [37, 38].

During treatment with anti-TNF- α drugs the appearance of generalized infections is possible, due to an increased immunodepression. Sometimes, dermatological pictures mimicking autoimmune or allergic reactions require numerous investigations before it is possible to clarify their infectious etiology and so to administer suitable treatment [39].

The most common side effects of anti-TNF drugs administered subcutaneously are injection site reactions, which are generally mild to moderate and transient, and did not require drug discontinuation. In placebo-controlled trials, they were reported in 17-20% of patients treated with adalimumab (vs 11-14% of patients receiving placebo), and 37% of patients receiving etanercept for rheumatologic indications (vs 9% placebo). These reactions usually consist of erythema, edema and itching and appear at the site of injection within 24-48 hours lasting a few days [33, 40]. Irritative and immune mechanisms have been advocated in the pathogenesis of such reactions. Of note, there are also anecdotal reports of 'recall' injection site reactions, resembling the clinical features of fixed drug eruption, a well-known T-cell-dependent reaction, as well as of reactions with an eosinophilic cellulitis pattern, which is known to be Th2-mediated [40].

Hypersensitivity reactions to recombinant mAbs have been subdivided into immediate and delayed type reactions.

Delayed Hypersensitivity Reactions

Delayed reactions are of type III, according to Gell and Coombs: these reactions are mediated by the formation of immunocomplexes among the chimeric or humanized mAb and anti-mAb antibodies, produced during previous administrations. Delayed reactions appear after 24 hours from the administration of the drug up to 14 days after, but they are most frequent on the 5th-7th day. The symptoms are characterized by "serum sickness"-type pictures. This phenomenon is most frequent with rituximab, an anti-CD-20 antibody [41-45], although other authors have outlined a role for infliximab [46,47]. For the latter mAb, the incidence of serum

sickness reactions is around 2-3%, as found in studies conducted in a large number of patients [48,49]. Nevertheless, some cases resembling serum sickness have also been described with omalizumab, a humanized mAb used for respiratory allergies [50], and recently also with natalizumab, another humanized mAb used in multiple sclerosis patients [51].

Moreover, it has been observed that patients taking chimeric mAb like infliximab and developing anti-chimeric human antibodies (HACA) are more prone to develop infusional and postinfusional reactions as compared with patients not developing such antibodies [52]. An adverse "serum sickness"-like reaction due to infliximab suggests some differential diagnosis problems with drug-induced lupus, both because the clinical pictures are quite similar and characterized by fever, urticarial vasculitis, edema, arthralgias, lymphadenopathy, or more serious pictures like serositis and peripheral neuropathies, and because patients receiving infliximab can develop elevated serum titers of antinuclear antibodies (ANA) and anti-ds-DNA antibodies [53].

The occurrence of these autoantibodies is quite frequent and is considered without clinical relevance, unless symptoms of lupus-like syndrome develop. Reasons for the development of ANA and anti-ds-DNA might comprise release of antigens during apoptotic processes, bacterial infections leading to polyclonal B cell stimulation, or switch towards a Th2 response [33].

In our clinical experience with infliximab, the most frequent features of delayed hypersensitivity reactions consist in arthralgias and/or myalgias, which are likely to be mild immune complex-mediated reactions and can be misdiagnosed as worsening of joint involvement in patients with psoriatic arthritis.

Patients developing a serum sickness-type reaction following the administration of a chimeric mAb usually have a good prognosis, with resolution after suspension of the therapy or after treatment with systemic steroids [48,54]. Nevertheless, in some cases "serum sickness" due to the administration of biological drugs has been described to evolve toward a life-threatening respiratory distress syndrome (ARDS), due to the probable involvement of the pulmonary blood vessels, following the deposition of immunocomplexes [55]. Complications of serum sickness have caused exitus [50].

Acute Hypersensitivity Reactions

Acute reactions can appear within 24 hours from the administration of the mAb, but most frequently from 10 minutes to 4 hours after the beginning of the administration.

They are characterized by general malaise, cutaneous flushing, moderate dyspnea, headache, nausea, palpitations, fever, but they are not usually severe enough to require treatment discontinuation. However, in a very few cases symptoms suggestive of anaphylaxis appear, with bronchospasm, urticaria, angioedema, and hypotension up to cardiac circulation shock. Severe symptoms have been described in association with the use of basiliximab [56,57] and abciximab [58-60], sometimes combined with thrombocytopenia [61], with infliximab [62-65], omalizumab [66-69]

and cetuximab [70]. Cases of asthma [71] and urticaria [72] have been recently observed with adalimumab.

The pathogenesis is unclear, although specific IgE toward the recombinant chimeric antibody have been found in isolated cases [56, 70]. However, evidence argue against the involvement of true IgE-mediated mechanisms in the majority of cases with infliximab-related acute reactions [40, 48].

In fact, anaphylactoid symptoms have been sometimes observed at the first infusion, and most patients have safely continued infliximab treatment after premedication or only after slowing the rate of infusion. By contrast, another plausible hypothesis is that such immediate reactions could be mediated by HACA of the IgG class, since high antibodies titers directed against the mAb idiotypes have been shown [56]. This is explainable on the basis that immunoglobulins of the IgG class are able to determine a complement activation through the classic pathway [73]. The occurrence of IgG-mediated anaphylactic reactions has been stressed for drugs like dextrans [74,75], recombinant hirudins [76,77], and protamine [78,79].

It is well known that true IgE-mediated reactions depend on previous exposure to the drug. This event represents the sensitization dose and can also appear at the following administrations [59,65], otherwise these reactions can be considered as anaphylactic or pseudoallergic, due to the aspecific release of histamine from the mast cells. This can also happen in the case of recombinant antibodies [58,61,66], but the use of cetuximab has introduced a change. Cetuximab is a chimeric mAb of the IgG1 class directed against the Epidermal Growth Factor receptor (EGFR) and, like trastuzumab and rituximab, it is active in numerous tumors [80]. In a multicentric European study recruiting 329 patients with colon tumor with metastatic diffusion taking cetuximab, alone or in association with irinotecan, only 4 patients (1.2%) had a serious hypersensitivity reaction to cetuximab. For this reason, cetuximab seems to be a drug with a good safety profile [81]. Nevertheless in the USA, the incidence of severe hypersensitivity reactions to the drug was higher in comparison to the study conducted in Europe, ranging from 8% to 22%, above all in subjects with a history of atopic diseases [82]. Chung *et al.* showed the presence of pre-existing and measurable IgE toward cetuximab in the patients' serum even before the administration of the chimeric antibody [70].

The risk of allergic sensitization after exposure to a murine allergen is well known in subjects who have contact with animals for professional reasons, such as employees working with caged animals and in research laboratories [83]. People who keep domestic animals like rabbits or mice can develop heterophilic antibodies that are able to interfere with hormone titers during radio-immunoassays [84] and probably these subjects are also pre-sensitized to therapies with chimeric antibodies. Blood transfusions are also associated with an increased incidence of heterophilic antibodies. A study conducted in 2,829 patients showed that heterophilic antibodies occurred more frequently in individuals with a history of blood transfusion [85].

Recent studies conducted in the USA confirm that murine allergens are an important cause of allergic sensitization,

provoking respiratory symptoms in the presence of mouse allergens [86,87]. This phenomenon is common in American houses in urban and suburban environments, despite a notable variability [88], and for this reason, mouse proteins must be considered as hidden allergens. The allergenic mouse proteins identified are Mus m 1, previously known as MUP (Major Urinary Protein), a 19 kDa molecular weight albumin precursor whose presence has been found in mouse urine, hair follicles and dandruff [89]. A second allergen, so-called Mus m 2, a 16 kDa glycoprotein, has been found in the dander and in the hair follicles, but not in the urine, while a third one, Mus m 3, is an albumin with an allergenic capacity in 30% of patients sensitized to mouse [90]. However, it is not clear what epitopes are responsible for the allergenicity and specific IgE production in patients sensitized to chimeric mAbs.

In fact, the IgE are not always raised against the murine component, but they can also be directed against the chimeric antibody idotype [56]. Above all if the drug has been previously administered [56], it can be directed against the carbohydrate components of the protein, and in the case of cetuximab, toward the oligosaccharide galactose- α -1,3-galactose [70,91], a xenoantigen of animal origin that could be introduced with a meat diet [91]. Cetuximab is produced in various mammalian cell lines and is glycosylated in the Golgi apparatus of such cells. Nevertheless, it has been reported that if the production of cetuximab occurs in ovarian cells of the Chinese hamster, that do not produce α 1,3-galactose residues in the glycosylation sites of the chimeric protein [70,91], the IgE mediated reaction is not evoked [91].

Finally, additives like polysorbate, employed to increase the solubility of the commercial antibody, may be responsible for allergic reactions, in particular in the case of omalizumab [68]. For this mAb an IgE-mediated mechanism has been hypothesized, but in view of the characteristics of omalizumab [11] and its elevated affinity for the Fc of IgE, there is also the possibility that it may evade an IgE-mediated mechanism [68].

"*In vivo*" allergic tests for biological agents have been carried out in some cases [57,58,64,67,68,92] although such tests are not sufficiently standardized and the high cost discourages their use for merely diagnostic purposes. In a patient with an immediate adverse reaction to infliximab, sensitization tests to the murine component, in particular, resulted positive, as elicited in skin prick tests and an intradermal-reaction to commercial extracts of murine allergens [64]. Instead, omalizumab can also be administered to patients with positive allergic tests for the commercial extracts of the mouse allergens [93]. The use of cutaneous tests is useful in cases of adverse reactions to omalizumab, due to the presence of specific IgE for the recombinant mAb free from Fc interference, as it is already hooked on cellular receptors at cutaneous level.

STRATEGIES TO AVOID OR MINIMIZE IMMEDIATE TYPE HYPERSENSITIVITY REACTIONS

Strategies to avoid or to minimize the appearance of immediate type adverse reactions have been elaborated. In most cases the experience has been gained using infliximab. It has been suggested that the speed of infusion of intravenous im-

munoglobulins should be adapted [94,95], so as to reduce the appearance of adverse reaction due to the presence of macroaggregates, while previous or concomitant administration of immuno-suppressive agents like azathioprine or methotrexate, acting on the B-lymphocyte clones that produce the HACA, can help to reduce the presence of circulating antibodies and hence the risk of activating the anaphylatoxins of the complement cascade. Maini *et al.* noted that in patients treated with infliximab in association with methotrexate the appearance of HACA was reduced, and the combination was associated with a lower incidence of adverse reactions [96]. The administration of azathioprine at regular doses also decreased the development of HACA and was therefore recommended in patients undergoing therapy with infliximab [97]. The formation of HACA has been associated with an increased risk of non-serious infusion reactions to infliximab, as well as with a reduction in clinical response to the drug [98].

HACA can augment the clearance of infliximab, thus resulting in a more rapid decline of serum concentrations of the drug. These antibodies have been found to be inversely related to the dosage of infliximab. Therefore, another way to reduce the risk of infusion reaction to infliximab is the use of regular maintenance infusions after the first loading phase. In fact, episodic treatment, especially with lower doses, have been shown to increase the risk of infusion reactions [33].

A premedication with diphenhydramine and paracetamol has been suggested in cases of infusional reactions [48], in association with oral corticosteroids, generally prednisone, 3 times per day in the 24 hours preceding the administration [99]. However, the clinical experience with other recombinant mAb and with other drugs shows that in cases of true IgE-mediated reactions premedication can only mitigate the symptoms but does not prevent the appearance of adverse reactions [56,70], as in cases of non IgE-mediated reactions.

Therefore, the employment of human or humanized mAb with the same target has been proposed, instead of the chimeric human-murine antibody; both to avoid the murine component and to avoid the development of specific anti-idiotypic IgE. In subjects who suffered anaphylactic reactions to basiliximab, daclizumab has been employed [56,57], and adalimumab was used to replace infliximab [100,101], with good results.

It must be borne in mind that although the mechanisms involve the same receptor or mediator target, there may be pharmacodynamic or pharmacokinetic or affinity differences among the chimeric mAbs, resulting in a different pharmacological and clinical effectiveness among the recombinant mAbs and, consequently, also a different immune response. In the case of infliximab, for instance, the higher acute exposure than that of other anti-TNF drugs triggers a greater TNF- α bond produced by the organism to the inhibiting molecule, with marked modifications in the biological defense reactions to this cytokine [102]. It is possible that such pharmacological differences also apply to the new human or humanized mAbs like trastuzumab, pertuzumab, panitumumab, bevacizumab, aletuzumab, employed in the therapy of solid neoplasias instead of rituximab or cetuximab [80]. However, while it is possible to modify the therapy in cases

of chronic conditions like psoriasis, inflammatory bowel diseases, or rheumatic disorders, in the case of a solid tumor it will be necessary to replace a recombinant with a homologous mAb, to avoid cancer progression.

Such human antibodies can induce adverse reactions, possibly of a lesser clinical entity in comparison to the chimeric mAbs. In the case of anti-TNF mAbs, the long-term immunogenicity of adalimumab is not known, although the drug is thought to be less immunogenic than the chimeric infliximab. However, anti-adalimumab antibodies have been detected in patients receiving this drug, without any apparent correlation to adverse events, in terms of both frequency and pattern. High concentrations of antibodies has been associated with non-response to adalimumab therapy, as well as with lower serum adalimumab concentrations [103].

One useful strategy to manage acute infusion reactions is to induce pharmacological desensitization and temporary immune tolerance. Muronomab, an anti-CD3 antibody, was the first to undergo desensitization protocols [104], and then infliximab, for which several desensitization protocols have been proposed. Puchner *et al.* experimented the first protocol with infliximab in 2 patients who had serious and repeated episodes of anaphylaxis [105]. Bangash *et al.* report a desensitization protocol in 6 patients, in whom no adverse reactions appeared during the procedure [106]. The protocol began with 0.01 mg of intravenous infliximab, progressively increasing up to the recommended therapeutic dose [106]. Another desensitization protocol has been carried out in 8 patients with Crohn's disease, with premedication with paracetamol and diphenhydramine [107]. The use of premedication has also been recommended by other authors [108]. Not all authors are in agreement with the use of desensitization strategies. In fact, the appearance of an anaphylactic reaction can be underestimated during the procedure and it is possible that this protocol may induce tolerance to the drug rather than desensitization [109]. The time for the procedure varies from three [108,109] to six hours [105] and since the maximum dose is not standardized but varies according to the patient's weight or to the quantity of drug to be administered [102], an allergologist or a clinical pharmacologist familiar with the desensitization procedure should be present [109]. Desensitization protocols have also been performed with trastuzumab [110].

CONCLUSIONS

The new recombinant mAbs represent an innovative therapeutic strategy for use in many oncologic and chronic autoimmune diseases, but they pose risks of hypersensitivity reactions, whose underlying mechanisms are not yet completely clear. The ENDA (European Network for Drug Allergy) has proposed the institution of a task force to investigate cases of hypersensitivity reactions to biological drugs, including recombinant mAbs, and to standardize and validate allergological tests "*in vivo*", in order to prevent such adverse reactions.

ABBREVIATIONS

ANA	=	Anti Nuclear Antibodies
Anti-TNF	=	Anti Tumor Necrosis Factor

ARDS	=	Acute Respiratory Distress Syndrome
B-E8	=	Anti IL-6 Antibody
EGFR	=	Epidermal Growth Factor Receptor
ENDA	=	European Network for Drug Allergy
GP IIb-IIIa	=	Glyco Protein IIb-IIIa
HACA	=	Human Anti-Chimeric Antibodies
HAMA	=	Human Anti-Murine Antibodies
IgE	=	Immunoglobulin E
IgG	=	Immunoglobulin G
IgGM	=	Immunoglobulin GM
IFN-alpha	=	Interferon alpha
IL	=	Interleukin
kDa	=	Kilo Daltons
mAb	=	Monoclonal Antibody
MOF	=	Multi Organ Failure
MUP	=	Major Urinary Protein
OKT3	=	Muronomab-CD3
TGN 1412	=	Super agonistic anti-CD28 Antibody
Th	=	T helper
TNF α	=	Tumor Necrosis Factor α

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