

Hypersensitivity Reactions to Biological Drugs

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■ Abstract

Strictly speaking, biological drugs are defined as drugs obtained using biotechnology that act on the immune system. They encompass monoclonal antibodies, fusion proteins, and cytokines. Although they are restricted to specific diseases, they have been increasingly used in recent years, with the consequent reporting of adverse reactions, many of which occur during the postmarketing phase. Because of the characteristics of adverse reactions, a new classification has been proposed. Hypersensitivity reactions are beta-type reactions and include infusion reactions and injection site reactions. In some cases, an immune mechanism mediated by IgE, IgG, or T cells is involved. Clinical symptoms vary widely, from skin reactions to anaphylaxis. Diagnostic studies are based on skin tests and in vitro tests (specific IgE, basophil activation test). Most are not standardized and are conducted in small groups of patients, thus making it impossible to obtain sensitivity and specificity values. With some biological drugs, desensitization protocols have proven successful. In this review, we discuss hypersensitivity reactions to biological drugs and the diagnostic tests used to assess these reactions.

Key words: Biological drugs. Hypersensitivity. Skin tests. Diagnosis. Monoclonal antibodies.

■ Resumen

En sentido estricto se consideran fármacos biológicos aquellos fármacos obtenidos por biotecnología que actúan en el propio sistema inmune. Engloban básicamente anticuerpos monoclonales, proteínas de fusión y citocinas. Aunque su indicación está restringida a determinadas enfermedades, su uso ha ido en aumento en los últimos años y en consecuencia también la comunicación de reacciones adversas, muchas de ellas observadas post comercialización. Debido a sus características se ha propuesto una nueva clasificación para las reacciones adversas, en la que, las reacciones de hipersensibilidad corresponden a las reacciones de tipo β e incluyen reacciones de infusión y reacciones localizadas en el punto de inyección del fármaco. En algunas de estas reacciones se ha demostrado la participación de un mecanismo de hipersensibilidad inmune, bien sea mediado por IgE, IgG o por células T. Los síntomas clínicos que presentan los pacientes son muy variados, desde síntomas cutáneos a anafilaxia. Los estudios diagnósticos se basan en pruebas cutáneas, y en pruebas in vitro (IgE específica, TAB). La mayoría de pruebas no están estandarizadas y están realizadas en pequeños grupos de pacientes, lo que no permite obtener valores de sensibilidad y especificidad. Con algunos de estos fármacos se han aplicado protocolos de desensibilización con buenos resultados. En este artículo se revisan las reacciones de hipersensibilidad inducidas por los fármacos biológicos así como las pruebas utilizadas para el diagnóstico.

Palabras clave: Fármacos biológicos. Hipersensibilidad. Pruebas cutáneas. Diagnóstico. Anticuerpos monoclonales.

Introduction

Biological drugs are defined as drugs in which the active substance is produced or extracted from a biological source. According to the Spanish Agency for Medicines and Health Care Products (AEMPS), this definition includes around 2080 formulations corresponding to various products, including natural biological substances, hormones, nucleic acids, and monoclonal antibodies (mAbs). A specific group of biological drugs are obtained by biotechnological means (generally using recombinant DNA technology or hybrid technology) and are also known as biotechnology medicines [1].

Because production is individualized, there are no generic biological drugs. The same drugs obtained from different cell lines—biosimilar drugs—must meet a number of requirements specified by regulatory agencies prior to being marketed.

Several biological drugs act by modulating the immune system and acting on inflammation and cell proliferation. They encompass mAbs, fusion proteins, and cytokines (Table 1).

This review focuses on reports of hypersensitivity reactions to these drugs and the diagnostic studies used to assess the reactions. We performed an exhaustive search in PubMed, databases of scientific societies, and reports of the AEMPS, European Medicines Agency, and the United States Food and Drug Administration until May 2013.

The biological drugs reviewed included the following:

- (a) Monoclonal antibodies. mAbs are mouse IgG immunoglobulins. In order to reduce their immunogenicity, the murine fraction is decreased. All mAb names end with the suffix mab (monoclonal antibody), which is preceded by a syllable that is indicative of the degree of humanization, as follows:
 - *ximab*: chimeric mAb, which contains approximately 25% of the murine fraction in the Fab fragment of the immunoglobulin, the remainder being human IgG.
 - *zumab*: humanized mAb, which contains 2%-5% of the murine fraction in hypervariable regions of the Fab fragment.
 - *mumab*: human mAb.
- (b) Fusion proteins: Fusion proteins are the result of receptor or cell ligands binding to part of the Fc fragment of IgG1 (CH2, CH3). This binding increases solubility and half-life. The names of the fusion proteins end in *cept*.
- (c) Cytokines: Cytokines include interferons (IFNs), interleukins (IL), and colony stimulating factors (CSF).

1. Adverse Reactions

Adverse reactions caused by biological drugs differ from those produced by other types of drug. Unlike chemical drugs, biological drugs are highly immunogenic proteins that act on the immune system, are administered parenterally, and are not metabolized. Furthermore, the adverse effects of biological drugs can vary with the disease for which they have been prescribed or the concomitant treatment administered to the patient.

Therefore, adverse reactions cannot be classified according to the traditional classification of immune hypersensitivity reactions to drugs. Pichler [2] proposed a new classification for

these reactions, dividing them into 5 types, which are defined by Greek letters.

Alpha-type reactions result from an increase in levels of systemic cytokines, either by exogenous administration (they generally induce flu-like syndrome) or by endogenous cell activation, and cause a variety of symptoms known as cytokine release syndrome. The patient may experience fever, fatigue, myalgia, rash, and gastrointestinal symptoms. These reactions can result—albeit rarely—in a cytokine storm (release of proinflammatory cytokines and complement activation), which induces multiorgan dysfunction.

Beta-type reactions are hypersensitivity reactions. IgE, IgG, and complement or T cells can be involved.

Gamma-type reactions are due in part to the intrinsic activity of the drug, which leads either to impairment of the immune system by infection or malignancy, as a result of immunosuppression, or to an immune imbalance that manifests as autoimmune or inflammatory diseases. Thus anti-TNF- α drugs can lead to reactivation of tuberculosis or other infectious diseases.

Delta-type reactions are due to the action of the drug on molecules that are generally overexpressed in tumor cells, but which are also expressed in healthy cells. Specific mAbs act by inhibiting the epidermal growth factor receptor (EGFR), which is overexpressed in many carcinomas. Since this receptor is also expressed in the skin, acneiform rash is induced in approximately 89% of patients treated with cetuximab, panitumumab, or trastuzumab. This reaction is usually initiated in the first week of treatment and resolves after completion.

Epsilon-type reactions are those in which the immune system is not involved. In some cases, thrombosis and worsening of heart failure have been associated with administration of anti-TNF- α agents, and retinopathy and psychiatric disorders with interferon alfa.

1.1 Incidence of Adverse Reactions

Adverse reactions produced by biological drugs are varied, and their true incidence is unknown. According to the 2012 review of the Spanish Society of Rheumatology Biobadaser database, a total of 16 361 adverse reactions were recorded in 6754 patients treated with mAbs, predominantly anti-TNF- α agents. Of these reactions, 2788 were considered severe and 215 were fatal (1.3% of all reactions). The most frequent causes of death were infections (31%) and malignancy (19.5%), while immune disorders accounted for 0.5% [3].

In addition, as these drugs are species-specific, in many cases there are no preclinical data.

Regulatory measures in biological drugs are dynamic and are often based on effects recorded during the postmarketing period. A review conducted between January 1995 and June 2007 showed that 174 biological drugs (if biologics are considered in a more general sense) were approved. During the same period, 82 regulatory actions were taken regarding safety (measured on the basis of professional black-box warning or withdrawal). The probability of a regulatory action was 14% at 3 years after authorization and 29% at 10 years. The time it took to display a black-box warning of anaphylaxis was 0.8 years for gemtuzumab and 4 years for omalizumab [4].

Table 1. Biological Drugs

Drug (Brand Name)	Molecule on Which it Acts	Indications
Monoclonal antibodies		
Abciximab (ReoPro)	Platelet glycoprotein IIB/IIIA	Ischemic heart disease, inhibition of platelet aggregation
Adalimumab (Humira)	TNF- α	Rheumatoid arthritis, psoriasis, inflammatory bowel disease
Basiliximab (Simulect)	IL-2R α	Allogeneic renal transplantation
Belimumab (Benlysta)	BLYS	Systemic lupus erythematosus
Bevacizumab (Avastin)	VEGF	Metastatic colorectal cancer, metastatic breast cancer
Brentuximab vedotin (Adcetris)	CD30	Hodgkin lymphoma
Canakinumab (Ilaris)	IL1 beta	Cryopyrin-associated periodic syndromes
Catumaxomab (Removab)	CD3/cellular accessibility/epithelial cell adhesion molecule	Carcinoma (malignant ascites)
Certolizumab pegol (Cimzia)	TNF- α	Rheumatoid arthritis
Cetuximab (Erbixub)	EGFR	Metastatic colorectal cancer
Denosumab (Prolia, Xgeva)	RANKL	Osteoporosis with increased risk of fractures
Eculizumab (Soliris)	C5 (complement terminal)	Paroxysmal nocturnal hemoglobinuria
Golimumab (Simponi)	TNF- α	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis
Ibritumomab tiuxetan (Zevalin)	CD20	Follicular non-Hodgkin lymphoma
Infliximab (Remicade)	TNF- α	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, Crohn disease
Natalizumab (Tysabri)	α 4-Integrin	Multiple sclerosis
Ofatumumab (Arzerra)	CD20	Chronic lymphocytic leukemia
Omalizumab (Xolair)	IgE	Allergic asthma
Palivizumab (Synagis)	Respiratory syncytial virus F protein	Prophylaxis of respiratory syncytial virus
Panitumumab (Vectivix)	EGFR	Metastatic colorectal carcinoma
Pertuzumab (Perjeta)	HER2	Metastatic breast cancer
Ranibizumab (Lucentis)	VEGF-A	Macular degeneration
Rituximab (Mabthera)	CD20	Diffuse non-Hodgkin lymphoma, follicular lymphoma, rheumatoid arthritis
Tocilizumab (RoActemra)	IL-6	Rheumatoid arthritis
Trastuzumab (Herceptin)	HER2	Metastatic breast cancer
Ustekinumab (Stelara)	IL-12/IL-23	Psoriasis
Receptor antagonists		
Anakinra (Kineret)	IL-1	Rheumatoid arthritis
Fusion proteins		
Etanercept (Enbrel)	TNF- α spondylitis, psoriasis	Psoriatic arthritis, rheumatoid arthritis, ankylosing
Abatacept (Orencia)	CD80/CD86	Rheumatoid arthritis
Aflibercept (Zaltrap, Eylea)	VEGF	Metastatic colorectal cancer, wet macular degeneration
Cytokines		
Interferons		
Interferon alfa-2a (Roferon)		Chronic hepatitis C
Interferon alfa-2b (Intron A)		Chronic hepatitis B, chronic hepatitis C, carcinoïd tumor, melanoma, multiple myeloma, leukemia
Interferon beta-1a (Rebif, Avonex)		Multiple sclerosis
Interferon beta-1b (Extavia, Betaferon)		Multiple sclerosis
Interferon gamma-1b (Imukin)		Severe infection in patients with chronic granulomatous disease
Pegylated interferon alfa-2a (Pegasys)		Chronic hepatitis B, chronic hepatitis C
Interleukin-2/Aldesleukin (Proleukin)		Metastatic renal carcinoma
Colony-stimulating factors		
Filgrastim (Neupogen, Nivestim, Zarzio)		Neutropenia induced by chemotherapy or radiotherapy
Lenograstim (Granocyte)		
Molgramostim		
Pegfilgrastim (Neulasta)		
Sargramostim		

Abbreviations: BlyS, B lymphocyte-stimulator protein; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; RANKL, receptor activator of nuclear factor kappa-B ligand; VEGF, vascular endothelial growth factor.

2. Hypersensitivity Reactions

This group includes infusion reactions and injection site reactions.

2.1 Infusion Reactions

Infusion reactions are defined as any adverse event occurring in relation to drug administration and may be immediate or delayed.

Immediate reactions: Immediate reactions appear during the first hours after administration and are very heterogeneous in etiology and presentation (nausea, vomiting, skin reactions, respiratory symptoms, hypotension). Some involve release of cytokines by immune system cells due to activation by the drug itself, other cases involve the participation of an IgE-mediated mechanism. There have been reports of anaphylaxis, urticaria, and angioedema.

It is important to know the mechanism of an infusion reaction, since this can help to decide on the action to be taken.

The incidence of reported reactions is variable and ranges from 0.09% of patients in the case of omalizumab to 40% for trastuzumab and 77% for rituximab [5,6].

Different mechanisms have been proposed as inducers of anaphylaxis [6], as follows:

- a) *IgE-mediated hypersensitivity:* Since a period of sensitization is generally required, reactions do not appear with the first infusion. However, there are reports of reactions after the first infusion of rituximab and cetuximab, as well as specific IgE or positive skin test results for these drugs.
- b) *Mechanism of non-IgE-mediated hypersensitivity with intervention of IgG, FcγRIII.* In this case, the effector cells are basophils, macrophages, and platelet-activating factor. In experimental models, anaphylaxis triggered by IgG antibodies is observed when significant amounts of antigen are used. This type of reaction would explain why, in some cases of anaphylaxis triggered by the administration of biological drugs, there were no measurable levels of tryptase, but there were measurable levels of serum histamine [7].
- c) *Activation of the complement system with production of anaphylatoxins and release of mediators from mast cells.* Activation is induced by specific IgG antibodies and depends on the affinity of the IgG subclass for the Fcγ receptor.

Risk factors for having a reaction depend on both the patient and the drug. In the former, important factors include the disease the treatment has been indicated for, the patient's immune status, and the concomitant treatments received. Drug-related risk factors include the degree of humanization, the glycosylation pattern, the type of cells from which it was obtained, the dosing interval, and excipients with allergenic potential.

Delayed reactions: Delayed hypersensitivity reactions can appear between 1-2 hours and 14 days after administration, often with serum sickness-like symptoms. There have also been reports of rash, vasculitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

2.2 Injection Site Reactions

Patients present itching, erythema, and edema at the injection site. The reaction may be immediate, although it usually appears within 24-48 hours and with variable incidence according to the drug administered (ustekinumab, 2.4%; anakinra, 71%).

Skin test results are positive in some cases.

2.3 Diagnostic Studies

In vitro and in vivo tests have been used for the diagnosis of hypersensitivity reactions, although published studies often include only 1 or very few patients.

2.3.1 In Vitro Tests

Various diagnostic techniques have been used, although not all of them are standardized.

Detection of IgG antibodies: Some patients present IgG antibodies to the drug during administration. The IgG antibodies may act by blocking the effect of the biological drug (mAb) or by participating in the development of reactions.

Detection of IgE antibodies: IgE is usually quantified using enzyme immunoassay or ImmunoCAP techniques.

Basophil activation test: The basophil activation test has been used in a few cases.

2.3.2 In Vivo Tests

Skin prick tests, intradermal tests, and patch tests can be used for diagnosis (Table 2).

Table 2. Biological Drugs. Concentrations Used for Prick Tests and Intradermal Tests

Drug	Prick Test	Intradermal Test	Reference
Abciximab	0.2-2 mg/mL	0.2-2 mg/mL	17
Basiliximab	4 mg/mL	0.4-400 µg/mL	18
Cetuximab	500 µg/mL	5-50-500 µg/mL	24
Natalizumab	20 mg/mL	2 mg/mL	36, personal experience
Omalizumab	12.5-125 mg/mL	1.25 µg/mL	43
Rituximab	10 mg/mL	0.10-1 mg/mL	32
Tocilizumab	20 mg/mL	0.2 mg/mL	P Gaig, personal communication
Trastuzumab	21 mg/mL	0.21-2.1 mg/mL	30
Adalimumab	50 mg/mL	5-50 mg/mL	13
Etanercept	25 mg/mL	5 mg/mL	13
Infliximab	10 mg/mL	0.1-1 mg/mL	30
Anakinra	As is		45
Filgrastim	300 µg/mL	As is	98, 112
Lenograstim		As is	98
Sargramostim	100-250 µg/mL		112

Table 3. Origin of Biological Drugs^a

Murine Cell Line	Chinese Hamster Ovary Cell	<i>Escherichia coli</i>	Rat/Mouse
Eculizumab	Rituximab	Ranibizumab	Catumaxomab
Natalizumab	Fusion protein	Certolizumab p	
Ustekinumab	IFN β 1a	Anakinra	
Canakinumab	Lenograstim	Cytokines	
Chimeric mAb	Humanized and human mAb	Pegfilgrastim	

^aMost chimeric mAbs are derived from murine cell lines, while many of the humanized and human mAbs are obtained from Chinese hamster ovary cells. The exceptions are detailed in the table.

Table 4. Excipients With Allergenic Potential in Biological Drugs

Mannitol	Albumin	Polysorbate 80	Latex	Papain	Trometamol
Adalimumab	Interferon beta-1a (Avonex)	Adalimumab	Adalimumab	Abciximab	Etanercept
Basiliximab	Interferon beta-1b (Betaferon)	Infliximab	Etanercept		
Palivizumab	Interferon alfa-2b (IntronA)	Omalizumab	Anakinra		
Etanercept		Alemtuzumab			
Interferon beta-1a (Rebif)		Natalizumab			
Interferon beta-1b (Betaferon)		Tocilizumab			
Interferon gamma-1b		Canakinumab			
Lenograstim		Belimumab			

In the study of hypersensitivity reactions, it is important to know the following:

- The degree of drug humanization.
- The cell line from which the drug was obtained. Cells from Chinese hamster ovary produce practically no 1,3-galactosyltransferase, with the result that the glycosylation pattern of the drug obtained in these cells differs from that of other drugs such as cetuximab (derived from the murine cell line SP2/O). Furthermore, drugs obtained from *Escherichia coli* cell lines should be avoided in patients allergic to L-asparaginase. The origin of the mAbs and other biologic drugs is detailed in Table 3.
- Excipients with likely allergenic potential. The list of excipients is shown in Table 4.

2.4 Desensitization

Successful desensitization protocols have been established for many biological drugs, although it is not always possible to demonstrate the pathogenic mechanism of the reaction [8].

3. Hypersensitivity Reactions to Monoclonal Antibodies (Other Than Anti-TNF- α Agents)

3.1 Abciximab

Abciximab is a chimeric mAb that binds to the glycoprotein IIb/IIIa receptor of human platelets and inhibits aggregation.

It also binds to the vitronectin receptor on platelets and endothelial cells. Abciximab is indicated in ischemic heart disease.

Guzzo et al [9] reported the case of a patient with anaphylactic shock, although they did not perform an allergy study. Hawkins et al [10] reported the case of a patient undergoing angioplasty who presented hypotension, erythema, and facial angioedema 7 minutes after receiving abciximab. Tryptase levels were elevated, and the result of an intradermal test was positive.

A patient with generalized rash, edema, and cervicofacial eosinophilia 9 days after receiving abciximab for a stent implant underwent skin tests (prick and intradermal) with the drug at 0.2-2 mg/mL. The results of the intradermal test were positive at 48 hours. Histopathology of the reaction produced by the skin test revealed a T-cell infiltrate with a predominance of CD8⁺ T cells [11].

3.2 Basiliximab

Basiliximab is an anti-IL2 receptor mAb (α chain) indicated for prevention of acute rejection in kidney transplant recipients. There have been reports of anaphylactic reaction in patients in whom the drug was administered for the first time and more frequently at readministration.

Diagnostic studies have been performed in patients who experienced reactions at readministration. In 1 case, the patient presented an immediate reaction (swelling of the tongue, bronchospasm, and rash) after administration of basiliximab in which a positive intradermal test result was obtained (1/10 000 to 1/10 dilution of a solution of basiliximab 4 mg/mL). The

intradermal test with a 1/10 dilution of daclizumab to 5 mg/mL was negative, and the patient tolerated the drug well [12]. This agent has since been withdrawn from the market.

Baudouin et al [13] reported a case of anaphylactic shock induced by re-exposure to basiliximab (9 months after the first injection) with positive specific IgE and leukotriene release by basophils and negative results for daclizumab.

Barros et al [14] reported a case of anaphylactic shock in a 4-year-old who was treated with basiliximab after kidney transplantation. Two years previously, at the time of the first transplant, the patient received 2 doses of basiliximab without side effects. No diagnostic studies were performed.

3.3 Cetuximab

Cetuximab is a chimeric anti-epidermal growth factor receptor mAb that is indicated for the treatment of metastatic colorectal cancer. It is produced in the SP2/O murine cell line, which expresses the gene for α -1,3 galactosyltransferase.

The percentage of treated patients with reactions varies depending on the geographical location. While the percentage of patients with severe reactions after infusion was 1.2% in Europe, in a study conducted in the United States, the percentage of patients with severe reactions was much higher in southern states (22% of patients in Tennessee and North Carolina had reactions after the first infusion) than in northern or western states (0.5%) [15].

Chung et al [16] studied a group of patients from different parts of the USA who had reactions with cetuximab and quantified anticetuximab IgE antibodies, demonstrating that these antibodies were specific for galactose- α -1,3-galactose. They found that 25 of 76 patients had anticetuximab antibodies and that 17 already had antibodies before the first dose. The study of the control group showed that 20% of the Tennessee samples had anticetuximab IgE antibodies, while for the Boston samples the percentage was 0.6%.

Anticetuximab IgE antibodies act against galactose- α -1-3 galactose (α -gal antigen) contained in the Fab region of the heavy chain of cetuximab [17]. Other mAbs contain α -gal epitopes, although these are found in the Fc portion of immunoglobulin and do not have the capacity to bind IgE.

α -gal is produced in nonprimate mammalian cells by β -galactosyl α -1,3 galactosyltransferase, an enzyme that is inactivated in humans. Anticetuximab antibodies are present before the start of therapy because patients already have antibodies against α -gal.

It has been suggested that the regional difference in terms of increased presence of anti- α -gal IgE antibodies in the population would be due to increased exposure of these individuals to tick bites, as a relationship has been found between the presence of IgE antibodies to α -gal and tick bites [18].

A French group used ELISA to study the presence of anticetuximab IgE antibodies (before drug administration) in patients with cancer and in a control group and found a similar percentage of patients with positive antibodies in both groups (26% vs. 28%). The authors observed that patients who previously had anticetuximab antibodies exhibited hypersensitivity reactions more frequently [19].

Patients with delayed anaphylaxis caused by intake of red meat have been shown to have specific IgE anti- α -gal, which

has also been seen in some cases of cat allergy, because IgA from cat saliva can express this antigen [17].

The participants in an expert panel held in 2011 presented cases of anaphylaxis caused by intake of red meat, with positive intradermal test results to cetuximab and positive specific IgE to α -gal. Drug concentrations used for diagnosis were 500 μ g/mL for prick test and 5, 50, and 500 μ g/mL for intradermal tests, which were negative in the control group. The experts advised that an allergy study should be performed prior to the administration of cetuximab [17].

3.3.1 Cross-reactivity

Patients with severe infusion reactions to panitumumab (anti-EGFR mAb) were successfully treated with cetuximab in an escalating dose protocol [20]. Similarly, patients with severe reactions to cetuximab have been treated effectively with panitumumab [21].

3.3.2 Desensitization

Desensitization protocols with cetuximab were successful [22].

3.4 Ibritumomab tiuxetan

Ibritumomab tiuxetan is an anti-CD20 mAb used for the treatment of follicular non-Hodgkin lymphoma. A case of anaphylaxis was reported during administration of the drug, and antimouse antibodies were detected [23].

3.5 Natalizumab

Natalizumab is a humanized IgG4k mAb against α -4 integrin that is used in the treatment of multiple sclerosis.

Muñoz-Cano et al [24] reported a case of anaphylaxis after the second infusion. The diagnostic study showed positive results for intradermal testing, specific IgE, and IgE immunoblotting against a 28-kD band corresponding to the Fab fragment. The concentrations used in the skin tests were 20 mg/mL (prick test, negative) and 0.002 mg/mL (intradermal test, positive). We examined patients with infusion reactions to natalizumab; the results of intradermal tests up to 2 mg/mL were negative.

Calabresi et al [25] detected natalizumab antibodies in approximately 6% of treated patients. Hypersensitivity reactions (urticaria, bronchospasm) have been shown to be more frequent in patients with anti-natalizumab antibodies than in those without them (21%-46% vs 0.6%-0.7%). In a series of 40 patients treated with natalizumab, 4 presented serum sickness-like symptoms. Antinatalizumab antibodies were detected in 1 patient [26].

3.5.1 Desensitization

Camacho-Halili et al [27] desensitized 3 patients who had infusion reactions and negative skin prick test results to natalizumab. The approach was successful in all 3 patients.

3.6 Omalizumab

Omalizumab is a humanized anti-IgE mAb indicated for the treatment of severe asthma. The incidence of anaphylaxis with this drug is lower than 0.2% of treated patients [28,29].

Scientific societies have published a number of recommendations on prevention or treatment of anaphylaxis, suggesting that during the first 3 doses, the patient must be kept under observation for 2 hours after administration and for 30 minutes after subsequent doses [28].

There are two published cases of patients with anaphylaxis in which an allergy study was performed. One showed a positive intradermal test result and negative prick and patch test result. In the other case, the patient was sensitized to polysorbate, an excipient in the marketed drug [30].

With the aim of identifying patients at risk for a reaction, the United States Food and Drug Administration performed a study to determine which *in vivo* and *in vitro* diagnostic tests could prove useful [31]. A group of experts designed a protocol to validate skin testing with omalizumab. In the first phase, the concentrations were not irritative, did not produce adverse effects, and did not induce an IgG response. Based on the results, the authors advised that for the diagnostic study, omalizumab should be diluted with normal saline, since sterile water proved to be irritative in some patients. The authors recommend performing the prick test at a maximum concentration of 1:10 to 1:1 and the intradermal test at 1:100 000 (1.25 µg/mL) [32].

3.7 Rituximab

Rituximab is a chimeric anti-CD20 mAb used for the treatment of rheumatoid arthritis, diffuse non-Hodgkin lymphoma, and follicular lymphoma.

Infusion reactions are common (29%–40% of patients), and most occur during the first infusion. These reactions have been associated with the release of cytokines, although in some cases positive skin test results and antirituximab IgE antibodies have been demonstrated. There is no clear explanation why these reactions occur after the first infusion, although it has been suggested that it might be because of the previous presence of IgE antibodies to the drug or antibodies to murine proteins.

Postinfusion urticaria, serum sickness–like symptoms [33], and hypersensitivity pneumonitis [34] have been reported.

In 1 of the patients with serum sickness–like symptoms, the results of skin tests (prick test, 10 mg/mL; and intradermal test, 1/100 and 1/10 of the prick) were negative, although the patient had a reaction to subsequent infusion [33].

The results of skin tests at the abovementioned concentrations were positive in 6 of 9 patients who had experienced hypersensitivity reactions [35].

Vultaggio et al [36] reported the case of a patient with infusion reactions and demonstrated the presence of antirituximab IgE antibody and a proliferative response associated with T_H2-type cytokines when cells from the patient were stimulated with the drug.

Hypersensitivity to rituximab was recently studied using the basophil activation test. Differences in basophil activation were observed between patients who presented reactions during treatment and those who did not or the control group [37].

3.7.1 Desensitization

Castells et al [38] successfully desensitized 3 patients who had reactions to rituximab. In a more recent desensitization study, Brennan et al [35] provided results for 14 patients, 11 of whom had reactions to the first administration. The

desensitization protocol of Brennan et al has been used successfully by other groups [39].

3.8 Tocilizumab

Tocilizumab is a humanized anti-IL6 receptor mAb used for the treatment of rheumatoid arthritis and active juvenile idiopathic arthritis. A hypersensitivity reaction with tocilizumab (positive skin prick test, 20 mg/mL; and a positive intradermal test, 1/100 of the prick) has been reported (P Gaig personal communication).

3.9 Trastuzumab

Trastuzumab is a humanized mAb (IgG1) that targets human EGFR2. Infusion reactions are uncommon, and in some cases the diagnostic workup was performed using skin tests (prick test to 21 mg/mL and intradermal test to dilutions of 1/100 and 1/10). One patient with positive skin test results had a severe reaction during the eighth desensitization [35].

4. Hypersensitivity Reactions to Anakinra

Anakinra is an IL-1 receptor antagonist protein that is indicated in the treatment of rheumatoid arthritis. There have been reports of injection site reactions and anaphylaxis after reintroduction of the drug [40]. One case of anaphylaxis occurred 20 minutes after administration 2 months after starting treatment [41]. The result of the prick test was positive, and the authors suggest that the reaction might be due to sensitization of the patient to *E coli*–derived proteins, since anakinra is obtained in an expression system of these bacteria.

5. Hypersensitivity Reactions to Anti-TNF Drugs (Infliximab, Adalimumab, Etanercept, Certolimumab, and Golimumab)

TNF- α antagonists have been used for many years in the treatment of rheumatic and inflammatory bowel diseases. They are also the most widely studied.

5.1 Infliximab

Infliximab is a chimeric mAb formed by binding of the specific variable region of murine anti-TNF- α to Fc of human IgG. It binds with high affinity to the soluble and transmembrane fraction of TNF- α , thus neutralizing its activity. Infliximab also causes complement-mediated lysis of cells synthesizing TNF- α .

Adverse reactions to infliximab appear in 3%–22% of patients with psoriasis treated with this drug [42]. Most reactions occur within the first 2 hours of infusion.

Anaphylactic reactions have been reported, and in most cases they usually appear after the fifth infusion, or on re-exposure after suspension of treatment [35]. One patient experienced anaphylactic shock after the second infusion.

Three days later the patient developed serum sickness–like symptoms. An allergy workup was not performed [43].

Other severe events include Kounis syndrome [44] and serum sickness–like reaction [45].

The frequency of reactions (which are mostly mild to moderate) is much higher in patients in whom human antichimeric antibodies are detected. There is a close correlation between antibody titers and incidence of reactions: an antibody titer ≥ 8 $\mu\text{g/mL}$ predicts an increased risk of reaction [45]. The presence of these antibodies is also related to loss of treatment efficacy [46].

5.1.1 Skin Tests

Brennan et al [35] performed skin tests in patients with reactions to infliximab (prick at 10 mg/mL and intradermal tests at 1/100 and 1/10 of the concentration of the prick test). Positive results were obtained in 4 of 6 patients.

Vultaggio et al [47] studied 11 patients. Anti-infliximab IgE antibodies were detected in 3, who had severe reactions and positive skin test results (intradermal at 1/10). Of the 11 patients, 8 had non–isotype-specific anti-infliximab antibodies. In addition, statistically significant levels of these antibodies were detected in reactive patients in comparison with nonreactive patients and controls.

5.1.2 Patch Tests

Patch tests were performed in 4 patients with skin reactions (3 with erythema multiforme and 1 with lichenoid eruption) after administration of infliximab and also in 1 patient who reacted to etanercept. One patient presented a flare-up of the reaction, and another patient experienced malaise and nausea (symptoms similar to those he had had with intravenous administration). The concentrations used and the results of the patch tests are not described in the report [48].

5.1.3 Cross-Reactivity

Reactions to infliximab and subsequent tolerance of adalimumab have been reported. One patient had an anaphylactic reaction to infliximab and later showed good tolerance to adalimumab [49]. In the case of an individual who presented general discomfort with urticaria during the fifth infusion of infliximab, administration had to be suspended. The results of skin tests (prick and intradermal) and the basophil activation test with infliximab and adalimumab were negative; however, infusion of infliximab at a lower rate induced a response after 2 minutes. The patient tolerated adalimumab [50].

5.1.4 Desensitization

Brennan et al [35] followed the standard desensitization protocol and performed 21 desensitizations in 6 patients who had experienced reactions to infliximab. One developed hypotension during the second desensitization; however, once this was controlled, the protocol could be continued.

5.1.5 Reactions to Infliximab in Children

In a retrospective study of 23 children with inflammatory bowel disease treated with infliximab, 7 had symptoms

suggestive of allergic reaction (2 experienced anaphylaxis). No allergy study was conducted. Reactions were more frequent in children aged under 10 years [51].

5.2 Adalimumab

Adalimumab is a recombinant human IgG1 mAb that binds with high affinity to soluble and transmembrane TNF- α , thus preventing its binding to surface receptors p55 and p75 of target cells.

The most common reactions reported were mild injection site reactions, which occurred in up to 20% of patients. Fewer than 1% of patients experienced allergic rash, and in some cases urticaria and angioedema were observed [52-55].

In 2 patients who experienced increasingly severe local reactions after the fourth and fifth injections of adalimumab, the drug was discontinued. In 1 case, the lesions appeared at distant sites. Skin tests (prick and intradermal) were performed at 32 mg/mL, with positive results in both patients. The result of the histamine release test was positive [56].

In the case of a patient with anaphylactic shock following the 11th injection of adalimumab (the patient had had acute urticaria at the tenth injection), the authors performed a prick test (50 mg/mL) that was not assessed owing to dermographism. The result of the intradermal test (1/100 and 1/10) was negative. Desensitization was performed in 4 steps (total 2 hours) after premedication with cetirizine and montelukast [57].

Benucci et al [58] reported on 4 patients with local reaction (2 with etanercept and 2 with adalimumab) that appeared after the second, third, and sixth dose in 3 patients and after 5 years of treatment in the fourth patient. Nonirritant drug concentrations were studied using skin tests in 10 controls. The concentrations for adalimumab were 50 mg/mL in the prick test, up to 5 mg/mL in the intradermal test, and 50 mg/mL in the patch test [58].

5.3 Golimumab

Golimumab is a human mAb that was approved by the United States Food and Drug Administration in 2009 to treat rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. There are no published diagnostic studies of hypersensitivity reactions.

5.4 Certolizumab Pegol

Certolizumab pegol is a TNF- α antagonist approved by the United States Food and Drug Administration for the treatment of adult patients with Crohn disease who do not respond to conventional therapy. Experience with this drug is limited, but there have been reports of local reaction, urticaria, dermatitis, and erythema nodosum.

5.5 Etanercept

Etanercept is a dimeric human recombinant protein constituted by the binding of 2 soluble TNF receptors (p75 and human IgG1 Fc). It binds irreversibly and competitively to circulating and membrane-bound TNF- α and TNF- β , thus preventing its interaction with membrane receptors of effector cells of the immune system.

Injection site reactions have been reported in 37% of patients with psoriasis treated with this drug [59]. Etanercept has been shown to induce antinuclear antibodies in the long term in 18.3% of patients [60], and there have been reports of different types of skin reactions: lichenoid rash, urticaria [61], and leukocytoclastic vasculitis.

In the study of Bennucci et al [58], the nonirritant concentrations of etanercept obtained were 25 mg/mL in the prick test and 5 mg/mL in the intradermal test.

6. Hypersensitivity Reactions to Cytokines

Reactions occur with marketed drugs, namely, interferons, interleukin-2, and CSF.

6.1 Interferons

Interferons are a group of related proteins. They were originally classified according to the source from which they were obtained, although they currently have the following names:

- Interferon alfa, formerly leukocyte interferon.
- Interferon beta, formerly fibroblast interferon.
- Interferon gamma, formerly immune interferon.

6.1.1 Interferon Alfa

Interferon alfa is used for the treatment of chronic hepatitis, including hepatitis B, C, and D.

There are 4 types of interferon alfa: 2a and 2b, both of which are produced using recombinant techniques; con-1, or consensus interferon, which is a nonnatural recombinant interferon developed by scanning different alfa subtypes and assigning the most frequently observed amino acid sequences to obtain a consensus molecule; and, n1, which is a mixture of 9 subtypes of interferon produced by a human B lymphoblastoid cell line [62].

Finally, conjugates with polyethylene glycol increase serum half-life and thus reduce sensitivity to proteolysis and antigenicity (pegylated interferon alfa-2 and pegylated interferon alfa-2b) [63].

Interferon alfa is often associated with side effects, including eczematous injection site reactions (39%) and cutaneous pruritus (30%). In one case, the patient presented labial angioedema after the first dose [64], and in another, the patient had generalized urticaria after the third dose [65]. There has also been a report of a patient with symptoms of anaphylaxis after the third dose, although the involvement of IgE was not proven, since the study was negative by ELISA [66].

Pardini et al [67] reported the case of a patient in whom interferon was used for the treatment of systemic mastocytosis. The patient experienced symptoms suggestive of anaphylactic reaction after the first dose. Since the symptoms reappeared with subsequent doses, the drug was discontinued. No allergy study was performed.

Interferon alfa-2 frequently induces eczematous lesions. Clinical symptoms occur between 2 weeks and 3 months after initiation of treatment, and skin test results are negative in all cases [64]. One report of a fatal episode with the first dose suggests anaphylaxis [68]. In another case of urticaria

and angioedema with the second dose, the skin test results were negative. Desensitization was performed, and the skin symptoms reappeared on the second day, although the patient subsequently tolerated the maintenance dose [69].

Eczematous symptoms have been reported in up to 13% of cases at approximately 3 months after the start of treatment [70] and are more frequent when the drug is combined with ribavirin (33% of cases) [71].

Episodes of urticaria have been described with the first dose [72,73]. In one case, desensitization performed over 2 days was successful [73].

6.1.2 Interferon Beta

Interferon beta often induces skin symptoms, mainly in the form of erythematous reactions (75% of cases) [74]. Cases of progressive anaphylaxis [75] and severe urticaria have been reported with interferon beta-1a [76] and with interferon beta-1b [77]. Skin tests were performed in only 2 published studies. In the case of interferon beta-1a, negative results were obtained with the *as is* prick extract and a positive result in the intradermal test with a dilution of 1/1000 [76]. In a study with interferon beta, a positive result was also obtained with interferon beta-1b in the intradermal test (1/10 dilution); results with interferon beta-1a were negative [77]. In both studies, test results were negative in all 10 controls.

Skin reactions in the form of painful erythematous plaques are more common with interferon beta-1b than with interferon beta-1a [78], although a case of urticarial reaction was reported for interferon beta-1a, with positive prick and intradermal results, after 1 hour; desensitization was performed successfully in 4 days.

6.1.3 Conjugates With Polyethylene Glycol

Reactions to forms conjugated with polyethylene glycol are described in 50%-60% of cases and consist mainly of local injection site reactions, although there have been reports of lichen planus, vitiligo, hypopigmented atrophic plaques, facial erythema or eosinophilic pustular folliculitis [63,79]. These manifestations tend to appear from the first month of treatment. Severe eczematous reactions are reported in up to 30% of treatments, and some may even require treatment to be suspended [80]. These include local injection site reactions and distant reactions, which may boost the effect by associated drugs such as amantadine. However, the relationship between eczematous symptoms and the pegylated form suggests sensitization to polyethylene glycol [80]. These data are consistent with similar findings from other published reports [81,82]. None of these studies makes reference to an allergy workup.

Tang and Ward [83] reported a generalized vesicular skin reaction with pegylated interferon alfa-2b. Sato et al [84] reported a case of repeated symptoms compatible with fixed-drug exanthema, also suggesting that the reaction was due to polyethylene glycol, since the patient tolerated subsequent treatment with nonconjugated interferon alfa.

6.1.4 Desensitization with interferon

Three published studies demonstrated the possibility of desensitization in cases of allergic reaction and lack of

therapeutic options. All of them resulted in subsequent tolerance to the drug [73,78,79].

6.2 Interleukin-2 (Aldesleukin)

Aldesleukin (Proleukin) is a recombinant human interleukin-2 indicated for the treatment of advanced tumors, particularly metastatic renal cell carcinoma [85,86]. It triggers cytokine-mediated proinflammatory processes that result in a toxicity profile different from that of nonbiological chemotherapeutic drugs [87].

Very few published articles have examined hypersensitivity reactions to interleukin-2. A 2003 publication contains a case of angioedema in a patient receiving treatment for metastatic melanoma in whom specific IgE was determined [88]. In another case, erythematous subcutaneous nodules appeared within a few days of starting treatment and persisted after discontinuation until the patient died 2 years later [89]. In a series of 10 patients with lung metastases treated with inhaled interleukin 2, the authors observed clinical, functional, and inflammatory changes—similar to those described with bronchial asthma [86]—which reverted when medication was discontinued. These are related to the specific effects of the drug.

Junghans et al [90] reported a case of biventricular cardiac thrombosis associated with prominent endomyocardial eosinophilic infiltration in a patient treated for stage IV Hodgkin disease who developed cardiac symptoms 27 days after starting intravenous treatment. The patient died 2 days later. Finally, the presence of angioedema was associated with the induction of C-reactive protein, activation of the complement cascade, and elevated plasma levels of C3a and C5a, leading to a decrease in vascular integrity and subsequent edema [87].

6.3 Colony-Stimulating Factors

CSFs, also known as myeloid growth factors, are used to minimize the intensity and duration of neutropenia associated with intensive cytotoxic chemotherapy or radiotherapy.

The most commonly used are the granulocyte colony-stimulating factors (G-CSF) filgrastim, lenograstim, molgramostim (not marketed in Spain), and pegfilgrastim. Filgrastim is the deglycosylated form obtained from *E coli*, while lenograstim is the glycosylated form produced by mammalian cells [91]. Pegfilgrastim is the polyethylene glycol-conjugated formulation. Finally, the granulocyte-macrophage colony-stimulating factor (GM-CSF) sargramostim is also used.

Few hypersensitivity reactions to these factors have been reported. The results of a study on patients treated with filgrastim or lenograstim suggest that reactions are infrequent [92]. A follow-up study of 183 bone marrow donors (507 donations) revealed no severe reactions among donors or recipients. Cutaneous pruritus appeared in 2% to 3% of cases, regardless of whether patients received 1, 2, 3, or 4 injections of filgrastim or lenograstim [93].

6.3.1 Filgrastim

There are few reports on hypersensitivity reactions to filgrastim. In 1 case, a patient experienced symptoms of anaphylaxis immediately upon receiving the first dose [94];

a similar reaction has also been reported after the third dose [95,96].

Published studies confirm low cross-reactivity between these drugs. In one study, 2 patients experienced reactions at the third and ninth dose of the second course of treatment; in the first case, the reaction was associated with filgrastim, and negative skin test results were observed with lenograstim, which was prescribed as an alternative; in the second case, which was triggered by lenograstim, positive skin test results were obtained with both substances [91]. Viillard et al [97] reported a case of lichenoid eruption at the injection site with filgrastim, although the patient tolerated sargramostim. Chichmanian et al [98] reported a lack of reactivity between molgrastim and filgrastim in a patient with pruritic maculopapular rash that appeared on the third day of treatment with molgrastim and caused eosinophilia. The patient subsequently tolerated filgrastim.

6.3.2 Lenograstim

The literature contains few references to hypersensitivity reactions with this drug [99]. In a review of 20 established treatments, side effects were found in half of the cases, and some of them were compatible with anaphylaxis, which necessitates discontinuation of treatment. Lenograstim was reintroduced in 4 cases (40%) with premedication and corticosteroids, and tolerance was good in 2 [100]. Tulpule et al [101] reported a case of anaphylaxis in a bone marrow donor with the first injection of lenograstim, but no diagnostic study was performed. White et al [102] reported skin symptoms due to neutrophil accumulation (Sweet syndrome) on the third or fourth day of treatment with lenograstim or filgrastim, with lesions distant from the injection site. The lesions were probably related to the stimulating effects typical of this factor.

6.3.3 Molgramostim

One patient experienced a reaction to this drug. No cross-reactivity was reported with filgrastim or lenograstim [103].

6.3.4 Sargramostim

Engler and Weiss [104] reported what seemed to be an anaphylactic reaction. The results of prick tests with sargramostin (100 and 250 µg/mL) were positive; the results with a filgrastim prick test (300 µg/mL) were negative.

6.3.5 Pegfilgrastim

Hypersensitivity reactions to pegfilgrastim are uncommon. In a series of 35 patients treated with pegfilgrastim while receiving chemotherapy, a reaction compatible with anaphylaxis occurred in 1 case during the fourth cycle. The reaction required suspension of treatment [105]. Given the worsening of cancer, new cycles were performed with the same antineoplastic drugs using another conventional G-CSF (not named in the article), with good tolerance, suggesting lack of reactivity with other compounds or a potential relationship with polyethylene glycol, as described for interferons. Scott et al [106] reported a severe skin reaction that worsened with successive doses and was compatible with an allergic reaction,

although no diagnostic workup was performed. A prolonged anaphylactic reaction related to reduced renal clearance with persistence of elevated drug plasma levels has also been reported [107].

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

- Walsh G. Biopharmaceuticals and biotechnology medicines: an issue of nomenclature. *Eur J Pharm Sci.* 2002;15:135-138
- Pichler WJ. Adverse side effects to biological agents. *Allergy.* 2006;61:912-20.
- Biobadaser. Registro Español de acontecimientos adversos de terapia biológica en enfermedades reumáticas. Informe Enero 2013. www.biobadaser.ser.es
- Giezen TJ, Mantel-Teeuwisse AK, Straus SMJM, Schellekens H, Leufkens HGM, Egberts ACG. Safety-regulatory actions for biologicals approved in the United States and The European Union. *JAMA.* 2008;300:1887-96.
- Maggi E, Vultaggio A, Matucci A. Acute infusions reactions induced by monoclonal antibody therapy. *Expert Rev Clin Immunol.* 2011;7:55-63.
- Vultaggio A, Maggi E, Matucci A. Immediate adverse reactions to biologicals: from pathogenic mechanism to prophylactic management. *Curr Opin Allergy Clin Immunol.* 2011;11:262-8.
- Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, Plevy S. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol.* 2003;98:1315-24.
- Hong DI, Bankova L, Cahill KN, Kyin T, Castells MC. Allergy to monoclonal antibodies: cutting-edge desensitization methods for cutting-edge therapies. *Expert Rev Clin Immunol.* 2012;8:43-52.
- Guzzo JA, Nichols TC. Possible anaphylactic reaction to abciximab. *Catheter Cardiovasc Interv.* 1999;48:71-3.
- Hawkins C, Gatenby P, McGill D. Severe hypotension complicating primary angioplasty: allergy to abciximab. *Allergy.* 2003;58:688-9.
- Moneret-Vautrin DA, Morisset M, Vignaud JM, Kanny G. T cell mediated allergy to abciximab. *Allergy.* 2002;57:269-70.
- Leonard PA, Woodside KJ, Gugliuzza KK, Sur S, Daller JA. Safe administration of a humanized murine antibody, after anaphylaxis to a chimeric murine antibody. *Transplantation.* 2002;74:1697-700.
- Baudouin V, Crusiaux A, Haddad E, Schandene L, Goldman M, Loirat C, Abramowicz D. Anaphylactic shock caused by immunoglobulin E sensitization after retreatment with the anti-interleukin 2 receptor monoclonal antibody basiliximab. *Transplantation.* 2003;76:459-63.
- Barros VR, Rocha V, Garcia VD, Garcia CD. Anaphylactic shock after retreatment with basiliximab. *Transplant Proc.* 2003;35:579.
- O'Neil BH, Allen R, Spigel DR, Stinchcombe TE, Moore DT, Berlin JD, Goldberg RM. High incidence of Cetuximab-related infusion reactions in Tennessee and North Carolina and the association with atopic history. *J Clin Oncol.* 2007;25:3644-8.
- Chung CH, Mirakhur B, Chan E, Le QT, Berlin J, Morse M, Murphy BA, Satinover SM, Josen J, Mauro D, Slebob RJ, Zhou Q, Gold D, Hatley T, Hicklin DJ, Platts-Mills TAE. Cetuximab-induced anaphylaxis and IgE specific for galactosa- α -1,3-galactose. *N Engl J Med.* 2008;358:1109-17.
- Daguet A, Watier H. 2nd Charles Richet et Jules Héricourt Workshop. Therapeutic antibodies and anaphylaxis; May 31-June 1, 2011; Tours, France. www.landesbioscience.com
- Commins SP, James HR, Kelly ES, Pochan SL, Workman LJ, Perzanowski MS, Kocan KM, Fahy JV, Nganga LW, Ronmark E, Cooper PJ, Platts-Mills TAE. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose- α -1,3galactose. *J Allergy Clin Immunol.* 2011;127:1286-93.
- Mariotte D, DuPont B, Gervais R, Galasis MP, Laroche D, Tranchant A, Comby E, Bouhier-Leporrier K, Reimund JM, Le Mauff B. Anti-cetuximab IgE ELISA for identification of patients at a high risk of cetuximab-induced anaphylaxis. *Mabs.* 2011;3:396-401.
- Saif MW, Syrigos KI, Hotchkiss S, Shanley J, Grasso J, Ferencz TM, Syrigos K, Shah MM. Successful desensitization with cetuximab after an infusion reaction to panitumumab in patient with metastatic colorectal cancer. *Cancer Chemother Pharmacol.* 2009;65:107-12
- Nielsen DL, Pfeiffer P, Jensen BV. Six cases of treatment with panitumumab in patients with severe hypersensitivity reactions to cetuximab. *Ann Oncol.* 2009;20:798.
- Jerath MR, Kwan M, Kannarkat M, Mirakhur B, Carey L, Valgus J, Platts-Mills TAE, Tarrant TK. A desensitization protocol for the mAb cetuximab. *J Allergy Clin Immunol.* 2009;123:160-1.
- Jankowitz R, Joyce J, Jacobs SA. Anaphylaxis after administration of Ibritumomab Tixetan for follicular non-Hodgkin lymphoma. *Clin Nucl Med.* 2008;33:94-6.
- Muñoz-Cano R, Carnes J, Sanchez-Lopez J, Saiz A, Bartra J, Lopez-Matas MA, Picado C, Valero A. Biological agents: New drugs, old problems. *J Allergy Clin Immunol.* 2010;126:394-5.
- Calabresi PA, Giovannoni G, Confavreux C, Galetta SL, Havrdova E, Hutchinson M, Kappos L, Miller DH, O'Connor PW, Phillips JT, Polman CH, Radue EW, Rudick RA, StuartWH, Lublin FD, Wajgt A, Weinstock-Guttman B, Wynn DR, Lynn F, Panzara MA; AFFIRM and SENTINEL Investigators. The incidence and significance of anti-natalizumab antibodies: results from AFFIRM and SENTINEL. *Neurology.* 2007;69:1391-403.
- Hellwing K, Schimrigk S, Fisher M, Haghikia A, Müller T, Chan A, Gold R. Allergic and nonallergic delayed infusion reactions during natalizumab therapy. *Arch Neurol.* 2008;65:656-8.
- Camacho-Hallil M, George R, Gottesman M, Davis-Lorton M. An approach to natalizumab hypersensitivity: a case series of induction of tolerance. *Mult Scler.* 2011;17:250-3.
- Cox L, Platts-Mills TA, Finegold I, Lawrence B, Schwartz LB, Simons FE, Wallace DV. American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Omalizumab-Associated Anaphylaxis Joint Task Force report on omalizumab associated anaphylaxis. *J Allergy Clin Immunol.* 2007;120:1373-7.

29. Corren J, Casle TB, Lanier B, Buhl R, Holgate S, Jimenez P. Safety and tolerability of omalizumab. *Clin Exper Allergy*. 2009;39:788-97.
30. Price KS, Hamilton RG. Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy. *Allergy Asthma Proc*. 2007;28:313-9.
31. Cox L, Lieberman P, Wallace D, Simons FE, Finegold I, Platts-Mills T, Schwartz L. American Academy of Allergy, Asthma and Immunology/Omalizumab-Associated Anaphylaxis Joint Task Force follow-up report. *J Allergy Clin Immunol*. 2011;128:210-2.
32. Lieberman P, Rahmaoui A, Wong DA. The safety and interpretability of skin tests with omalizumab. *Ann Allergy Asthma Immunol*. 2010;105:494-5.
33. Finger E, Scheinberg M. Development of serum sickness-like symptoms after rituximab infusion in two patients with severe hypergammaglobulinemia. *J Clin Rheumatol*. 2007;13:94-5.
34. Tonelli AR, Lottenberg R, Allan R, Sriram PS. Rituximab-induced hypersensitivity pneumonitis. *Respiration*. 2009;78:225-9.
35. Brennan PJ, Rodriguez Bouza T, Hsu I, Sloane DE, Castells MC. Hypersensitivity reactions to monoclonal antibodies: 105 desensitizations in 23 patients, from evaluation to treatment *J Allergy Clin Immunol*. 2009;124:1259-66.
36. Vultaggio A, Matucci A, Nencini F, Pratesi S, Petroni G, Cammelli D, Alterini R, Rigacci L, Rogmanani S, Maggi E. Drug-specific Th2 cells and IgE antibodies in a patients with anaphylaxis to Rituximab. *Int Arch Allergy Immunol*. 2012;159:321-6.
37. Piva E, Chieco-Bianchi, Krajcar V, Aversa S, Plebani M. Adverse reactions in patients with B-cell lymphomas during combined treatment with rituximab: In vitro evaluation of rituximab hypersensitivity by basophil activation test. *Am J Hematol*. 2012;87:E130-1.
38. Castells M, Tennant NM, Sloane DE, Hsu FI, Barret NA, Hong DI. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol*. 2008;128:574-80.
39. Abadoglu O, Epozturk K, Atayik E, Kaptanoglu E. Successful and rapid desensitization for hypersensitivity reactions to monoclonal antibodies in a patient with rheumatoid arthritis: a remarkable option. *J Investig Allergol Clin Immunol*. 2011;21:319-21.
40. Vila AT, Puig L, Fernández-Figueras MT, Laiz AM, Vidal D, Alomar A. Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. *British J Dermatol*. 2005;153:417-23.
41. Desai D, Goldbach-Mansky R, Milner JD, Rabin RL, Hull K, Pucino F, Colburn N. Anaphylactic reaction to anakinra in a rheumatoid arthritis patient intolerant to multiple nonbiologic and biologic disease-modifying antirheumatic drugs. *Ann Pharmacoth*. 2009;43:967-72.
42. Puig-Sanz L, Saez E, Lozano MJ, Bordas X, Carrascosa JM, Gallardo F, Luelmo J, Sanchez-Regana M, Alsina M, Garcia-Patos V. Reactions to infliximab infusions in dermatologic patients: consensus statement and treatment protocol. Working Group of the Grupo Español de Psoriasis de la Academia Española de Dermatología y Venereología. *Actas Dermosifiliogr*. 2009;100:103-12.
43. Soykan I, Ertan C, Ozden A. Severe anaphylactic reaction to infliximab: report of a case. *Am J Gastroenterol*. 2000;95:2395-6.
44. Gori T, Munzel T. A case of coronary hypersensitivity (Kounis) syndrome associated with mid-ventricular ballooning pattern, intracoronary thrombosis and troponin elevation. *Int J Cardiol*. 2011;149:377-8.
45. Lecluse LL, Piskin G, Mekkes JR, Bos JD, de Rie MA. Review and expert opinion on prevention and treatment of infliximab-related infusion reactions. *Br J Dermatol*. 2008;159:527-36.
46. Baert F, Noman M, Vermeire S, Van Assche G, D'Haens G, Carbonez A, Rutgeerts P. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med*. 2003;348:601-8.
47. Vultaggio A, Matucci A, Nencini F, Pratesi S, Parronchi P, Rossi O, Romagnani S, Maggi E. Anti-infliximab IgE and non-IgE antibodies and induction of infusion-related severe anaphylactic reactions. *Allergy*. 2010;65:657-61.
48. Vergara G, Silvestre JF, Betloch I, Vela P, Albares MP, Pascual JC. Cutaneous drug eruption to infliximab: report of 4 cases with an interface dermatitis pattern. *Arch Dermatol*. 2002;138:1258-9.
49. Stallmach A, Giese T, Schmidt C, Meuer SC, Zeuzem SS. Severe anaphylactic reaction to infliximab: successful treatment with adalimumab - report of a case. *Eur J Gastroenterol Hepatol*. 2004;16:627-30.
50. Manso L, Polo B, Fernandez-Nieto M, Sastre LB, del Pozo V, Sastre J. Basophil activation test in a case of systemic hypersensitivity reaction to infliximab with good tolerance to another anti-TNF-alpha agent (adalimumab). *J Investig Allergol Clin Immunol*. 2010;20:537-8.
51. Kolho KL, Ruuska T, Savilahti E. Severe adverse reactions to Infliximab therapy are common in young children with inflammatory bowel disease. *Acta Paediatr*. 2007;96:128-30.
52. Borrás-Blasco J, Navarro-Ruiz A, Borrás C, Castera E. Adverse cutaneous reactions induced by TNF-alpha antagonist therapy. *Cutane Med J*. 2009;102:1133-40.
53. George SJ, Anderson HL, Hsu S. Adalimumab-induced urticaria. *Dermatol Online J*. 2006;12:4.
54. Mallo S, Santos-Juanes J. Adalimumab-induced urticaria. *Actas Dermosifiliogr*. 2007;98:511-2.
55. Nikas SN, Voulgari PV, Drosos AA. Urticaria and angioedema-like skin reactions in a patient treated with adalimumab. *Clin Rheumatol*. 2007;26:787-8.
56. Paltiel M, Gober LM, Deng A, Mikdashi S, Aleexeve I Sami SS. Immediate type I hypersensitivity response implicated in worsening injection site reactions to adalimumab. *Arch Dermatol*. 2008;144:1190-4.
57. Quercia O, Emiliani F, Foschi FG, Stefanini GF. Adalimumab desensitization after anaphylactic reaction. *Ann Allergy Asthma Immunol*. 2011;106:547-8.
58. Benucci, M Manfredi, P Demoly, P Campi. Injection site reactions to TNF-alpha blocking agents with positive skin tests. *Allergy*. 2008;63:138-9.
59. Puig L, Bordas X, Carrascosa JM, Dauden E, Ferrandiz C, Hernanz JM, Lopez-Estebarez JL, Moreno JC, Sanchez-Carazo JL, Vanaclocha F, Vazquez-Veiga H. Consensus document on the evaluation and treatment of moderate-to-severe psoriasis. Spanish psoriasis group of the Spanish Academy of Dermatology and Venereology. *Actas Dermosifiliogr*. 2009;100:277-86.

60. Tying S, Gordon KB, Poulin Y, Langley RG, Gottlieb AB, Dunn M, Jahreis A. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol.* 2007;143:719-26.
61. Borrás-Blasco J, Gracia-Perez A, Rosique-Robles JD, Nunez-Cornejo C, Castera MD, Abad FJ. Urticaria due to etanercept in a patient with psoriatic arthritis. *South Med J.* 2009;102:304-5.
62. Lindsay KL. Therapy of hepatitis C: overview. *Hepatology.* 1997;26:71S-7S.
63. Hashimoto Y, Kanto H, Itoh M. Adverse skin reactions due to pegylated interferon alpha 2b plus ribavirin combination therapy in a patient with chronic hepatitis C virus. *J Dermatol.* 2007;34:577-82.
64. Dereure O, Raison-Peyron N, Larrey D, Blanc F, Guilhou JJ. Diffuse inflammatory lesions in patients treated with interferon alfa and ribavirin for hepatitis C: a series of 20 patients. *Br J Dermatol.* 2002;147:1142-6.
65. Guillot B, Blazquez L, Bessis D, Dereure O, Ghilhou JJ. A prospective study of cutaneous adverse events induced by low-dose alpha-interferon treatment for malignant melanoma. *Dermatology.* 2004;208:49-54.
66. Beckman DB, Mathisen TL, Harris KE, Boser MB, Grammer LC. Hypersensitivity to IFN-alpha. *Allergy.* 2001;56:806-7.
67. Pardini S, Bosincu L, Bonfigli S, Dore F, Longinotti M. Anaphylactic-like syndrome in systemic mastocytosis treated with alpha-2-interferon. *Acta Haematol.* 1991;85:220.
68. Kendirli T, Kismet E, Demirkaya E, Aydin HI, Kesik V, Köseoglu V. Death possibly associated with interferon use in a patient with chronic hepatitis. *Acta Paediatr.* 2005;94:984-5.
69. Kilic M, Dogan Y, Taskin E, Sen Y, Kalpaklioglu AF. Desensitization protocol administered successfully with interferon-alpha 2a in a child with chronic hepatitis B infection. *J Invest Allergol Clin Immunol.* 2010;20:447-8.
70. Manjón-Haces JA, Vázquez-López F, Gómez-Díez S, Hidalgo-García A, Pérez-Álvarez R, Soler-Sánchez T, Pérez-Oliva N. Adverse cutaneous reactions to interferon alfa-2b plus ribavirin therapy in patients with chronic hepatitis C virus. *Acta Derm Venereol.* 2001;81:223.
71. Sookoian S, Neglia V, Castaño G, Frider B, Kien MC, Chohuela E. High prevalence of cutaneous reactions to interferon alfa plus ribavirin combination therapy in patients with chronic hepatitis C virus. *Arch Dermatol.* 1999;135:1000-1.
72. Helbig D, Simon JC, Treudler R. Urticaria, angioedema and dyspnoea in adjuvant therapy of melanoma with interferon alpha-2b. *Acta Derm Venereol.* 2010;90:308-9.
73. Taghavi SA, Eshraghian A. Successful interferon desensitization in a patient with chronic hepatitis C infection. *World J Gastroenterol.* 2009;15:4196-8.
74. Walther EU, Hohfeld R. Multiple sclerosis: side effects of interferon beta therapy and their management. *Neurology.* 1999;53:1622-7.
75. Corona T, Leon C, Ostrosky-Zeichner L. Severe anaphylaxis with recombinant interferon beta. *Neurology.* 1999;52:425.
76. Mazzeo L, Ricciardi L, Fazio MC, Fogliani O, Fedele R, Ferlazzo E, Isola S. Severe urticaria due to recombinant interferon beta-1a. *Br J Dermatol.* 2003;148:172.
77. Brown DL, Login IS, Borish L, Powers PL. An urticarial IgE-mediated reaction to interferon beta-1b. *Neurology.* 2001;56:1416-7.
78. Fusun Kalpaklioglu A, Baccioglu Kavut A, Erdemoglu AK. Desensitization in interferon-beta1a allergy: a case report. *Int Arch Allergy Immunol.* 2009;149:178-80.
79. Lübbe J, Kerl K, Negro F, Saurat JH. Clinical and immunological features of hepatitis C treatment-associated dermatitis in 36 prospective cases. *Br J Dermatol.* 2005;153:1088-90.
80. Cottoni F, Bolognini S, Deplano A, Garrucciu G, Manzoni NE, Careddu GF, Montesu MA, Tocco A, Lissia A, Solinas A. Skin reaction in antiviral therapy for chronic hepatitis C: a role for polyethylene glycol interferon? *Acta Derm Venereol.* 2004;84:120-3.
81. Veldt BJ, Schalm SW, Janssen HL. Severe allergic eczema due to pegylated alpha-interferon may abate after switching to daily conventional alpha-interferon. *J Clin Gastroenterol.* 2007;41:432.
82. Barut S, Yuksek J, Sezer E, Gunal O, Koseoglu D. Morbiliform drug eruption due to pegylated α -interferon can show complete regression after switching to non-pegylated interferon. *J Dermatol.* 2011;38:479-81.
83. Tang DM, Ward L. Rash form hepatitis C treatment. *Cleve Clin J Med.* 2011;78:472-4.
84. Sato M, Sueki H, Iijima M. Repeated episodes of fixed eruption 3 months after discontinuing pegylated interferon-alpha-2b plus ribavirin combination therapy in a patient with chronic hepatitis C virus infection. *Clin Exp Dermatol.* 2009;34:e814-7.
85. Motzer RJ, Mazumdar M, Bacik J, Russo P, Berg WJ, Metz EM. Effect of cytokine therapy on survival for patients with advanced renal cell carcinoma. *J Clin Oncol.* 2000;18:1928-35.
86. Loppow D, Huland E, Heinzer H, Grönke L, Magnussen H, Holz O, Jorres RA. Interleukin-2 inhalation therapy temporarily induces asthma-like airway inflammation. *Eur J Med Res.* 2007;12:556-62.
87. Banerji A, Weller PF, Sheikh J. Cytokine-associated angioedema syndromes including episodic angioedema with eosinophilia (Gleich's Syndrome). *Immunol Allergy Clin North Am.* 2006;26:769-81.
88. Abraham D, McGrath KG. Hypersensitivity to aldesleukin (interleukin-2 and proleukin) presenting as facial angioedema and erythema. *Allergy Asthma Proc.* 2003;24:291-4.
89. Assmann K, Nasham D, Grabbe S, Luger TA, Meetze D. Persistent inflammatory reaction at the injection site of IL-2 with lymphoma-like inflammatory infiltrates. *Hautarzt.* 2002;53:554-7.
90. Junghans RP, Manning W, Safar M, Quist W. Biventricular cardiac thrombosis during interleukin-2 infusion. *N Engl J Med.* 2001;344:859-60.
91. Sasaki O, Yokoyama A, Uemura S, Inoue N, Hiwada K. Drug eruption caused by recombinant human G-CSF. *Intern Med.* 1994;33:641-3.
92. Martin M, Pienkowski T, Mackey J, Tomiak E, Al-Tweigeri T, Chap L, Juhos E, Guevin R, Howell A, Fornander T, Hainsworth J, Coleman R, Vinholes J, Modiano M, Pinter T, Tang SC, Colwell B, Prady C, Provencher L, Walde D, Rodríguez-Lescure A, Hugh J, Loret C, Rupin M, Blitz S, Jacobs P, Murawasky M, Riva A, Vogel C. Adjuvant docetaxel for node-positive breast cancer. *New England J Med.* 2005;352:2302-13.
93. Bux J, Cassens U, Dielschneider T, Duchscherer M, Edel E, Eichler H, Haas C, Moog R, Peschke H, Peters C, Ryzenkov I,

- Schlenke P, Ulrich H, Wiesneth M. Tolerance of granulocyte donors towards granulocyte colony-stimulating factor stimulation and patients towards granulocyte transfusions: results of a multicenter study. *Vox Sang*. 2003;85:322-5.
94. Batel-Copel L, Mommeja-Marin H, Oudard S, Chauvenet L, Pujade-Lauraine E, Coupier J, Bernadou A. Anaphylactic reaction after a first filgrastim (granulocyte-colony stimulating factor) injection. *Eur J Cancer*. 1995;31A:2428.
95. Jayesimi I, Giralt SS, Wood J. Subcutaneous granulocyte colony stimulating factor and acute anaphylaxis. *N Eng J Med*. 1991;325:587.
96. Martín Muñoz R, Gómez-Bellver MJ, Navarro Pulido AM, Orta Cuevas JC. Probable hypersensitivity reaction to filgrastim. *Am J Health Syst Pharm*. 1996;53:1607.
97. Viillard AM, Lavenue A, Balme B, Pincemaille B, Raudrant D, Thomas L. Lichenoid cutaneous drug reaction at injection sites of granulocyte colony-stimulating factor (Filgrastim). *Dermatology*. 1999;198:301-3.
98. Chichmanian RM, Heudier P, Taillan B, Fuzibet JG. No cross hypersensitivity between molgrastim and filgrastim: apropos of a case. *Thérapie*. 1995;50:478-9.
99. Tsavaris N, Polyzos A, Kosmas C, Giannikos L, Gogas J. A feasibility study of 1-h paclitaxel infusion in patients with solid tumors. *Cancer Chemother Pharmacol*. 1997;40:353-7.
100. Khoury H, Adkins D, Brown R, Vij R, Westervelt P, Trinkaus K, Goodnough L, DiPersio JF. Adverse side-effects associated with G-CSF in patients with chronic myeloid leukaemia undergoing allogeneic peripheral blood stem cell transplantation. *Bone Marrow Transplant*. 2000;25:1197-201.
101. Tulpule S, Shaw BE, Makoni P, Little AM, Madrigal JA, Goldman JM. Severe allergic reaction with anaphylaxis to G-CSF (lenograstim) in a healthy donor. *Bone Marrow*. 2009;44:129-30.
102. White JM, Mufti GJ, Salisbury JR, du Vivier AW. Cutaneous manifestations of granulocyte colony-stimulating factor. *Clin Exp Dermatol*. 2006;31:206-7.
103. Cernelc P, Andoljsek D, Mlakar U, Pretnar J, Modic M, Zupan IP, Zver S. Effects of molgramostim, filgrastim and lenograstim in the treatment of myelokathesis. *Pflugers Arch*. 2000;440:R81-2.
104. Engler RJ, Weiss RB. Immediate hypersensitivity to human recombinant granulocyte-macrophage colony-stimulating factor associated with a positive prick skin test reaction. *Ann Allergy Asthma Immunol*. 1996;76: 531-4.
105. Montella L, Addeo R, Guarrasi R, Cennamo G, Faiola V, Caspasso E, Caraglia M, Del Prete S. Once-per-cycle pegfilgrastim in breast cancer patients treated with docetaxel/epidoxorubicin/cyclophosphamide. *Eur J Cancer Care (Engl)*. 2010;19:200-4.
106. Scott WR, Silberstein L, Flatley R, Ardeshtna KM, Korostoff N, Dawe S. Cutaneous reaction to pegfilgrastim presenting as severe generalized skin eruption. *Br J Dermatol*. 2009;161:717-9.
107. Hanna GG, Edgar D, Clarke JE. A case of prolonged type 1 hypersensitivity reaction to pegfilgrastim. *Clin Oncol*. 2008;20:315-6.

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