Trends in Hypersensitivity Drug Reactions: More drugs, More Response Patterns, More Heterogeneity

I Doña,[1] E Barrionuevo,[1] N Blanca-Lopez,[2] MJ Torres,[1] TD Fernandez,[3] C Mayorga,[3] G Canto,[2] M Blanca[1]

[1]Allergy Unit, Regional University Hospital of Malaga, Malaga, Spain
[2]Allergy Unit, Infanta Leonor Hospital, Madrid, Spain
[3]Research Laboratory of Allergy Diseases, Fimabis, Malaga, Spain

Abstract

Hypersensitivity drug reactions (HDRs) vary over time in frequency, drugs involved, and clinical entities. Specific reactions are mediated by IgE, other antibody isotypes (IgG or IgM), and T cells. Nonspecific HDRs include those caused by nonsteroidal anti-inflammatory drugs (NSAIDs). β-Lactams—the most important of which are amoxicillin and clavulanic acid—are involved in specific immunological mechanisms. Fluoroquinolones (mainly moxifloxacin, followed by ciprofloxacin and levofloxacin) can also induce HDRs mediated by IgE and T cells. In the case of radio contrast media, immediate reactions have decreased, while nonimmediate reactions, mediated by T cells, have increased. There has been a substantial rise in hypersensitivity reactions to antibiotics and latex in perioperative allergic reactions to anesthetics. NSAIDs are the most frequent drugs involved in HDRs. Five well-defined clinical entities, the most common of which is NSAID–induced urticaria/angioedema, have been proposed in a new consensus classification. Biological agents are proteins including antibodies that have been humanized in order to avoid adverse reactions. Reactions can be mediated by IgE or T cells or they may be due to an immunological imbalance. Chimeric antibodies are still in use and may have epitopes that are recognized by the immune system, resulting in allergic reactions.

Key words: Drug hypersensitivity. Trends. Mechanisms. β-lactams. NSAIDs. Quinolones. Contrast media. Biological agents.

Resumen

Las reacciones de hipersensibilidad a fármacos (RHF) varían en el tiempo en frecuencia, fármacos implicados y entidades clínicas. Las reacciones específicas están mediadas por anticuerpos IgE o de otro isotipo (IgG o IgM) y por células T. En las no específicas se incluyen las producidas por AINES. Los betalactámicos están implicados en los mecanismos inmunológicos específicos. La amoxicilina y el ácido clavulánico son los más frecuentemente implicados. Las FQ pueden inducir reacciones mediadas por anticuerpos IgE o linfocitos T. El primero es el moxifloxacino seguido por ciprofloxacino y moxifloxacino. Las reacciones inmediatas a medios de contraste radiológicos han descendido con un incremento de las reacciones no inmediatas, mediadas por linfocitos T. En lo que concierne a las reacciones en el periodo perianestésico, un incremento importante se ha producido en la hipersensibilidad a antibióticos y látex. Los AINES son los fármacos más frecuentemente implicados en reacciones de hipersensibilidad. Se han propuesto cinco entidades bien diferenciadas siendo la urticaria/angioedema inducida por AINES en ausencia de urticaria crónica espontánea la más frecuente. Los fármacos biológicos son proteínas incluidas anticuerpos que han sido humanizadas a fin de evitar efectos adversos. Las reacciones pueden estar mediadas por IgE o linfocitos T. Pueden aparecer reacciones debidas a un imbalance inmunológico. Debido a que anticuerpos quiméricos todavía están en uso, estos pueden tener epítopes que sean reconocidos por el sistema inmune e inducir las reacciones alérgicas que se describen.

Palabras clave: Hipersensibilidad a fármacos. Tendencias. Mecanismos. Betalactámicos. AINES. Quinolonas. Medios de contraste. Agentes biológicos.

Introduction

An adverse drug reaction (ADR) has been defined by the World Health Organization as any noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment [1]. ADRs are grouped into 2 broad categories (see Table 1): type A reactions, which are predictable, common, and related to the pharmacological actions of the drug, and type B reactions, which are unpredictable, uncommon, and usually not related to the pharmacological actions of the drug [2]. Approximately 80% of ADRs fall into the first category and include drug-induced toxicity, side effects, secondary effects, and drug interactions. Type B reactions comprise 6% to 10% of all ADRs and include drug intolerance (an undesired drug effect produced by the drug at therapeutic or subtherapeutic doses), idiosyncratic reactions (uncharacteristic reactions that are not explainable in terms of the known pharmacological actions of the drug), and hypersensitivity drug reactions (HDRs), mediated by immunological mechanisms [2-5].

It is hard to determine the true prevalence of HDRs due to difficulties in defining and identifying reactions as well as inadequate reporting mechanisms [6]. It has been estimated that HDRs account for 3% to 6% of all hospital admissions and occur in 10% to 15% of hospitalized patients [7,8]. However, epidemiological studies of HDRs report varying results, probably related to several biases, such as differences in study populations and diagnostic criteria [5,9-14]. Moreover, drug allergy is not a static process: it varies over the years and is related to changing drug consumption patterns, the introduction of new drugs and the withdrawal of others, and the establishment of new indications [15-22].

HDRs include reactions mediated by specific and nonspecific immunological mechanisms (Table 2). Reactions in the first category may be antibody-mediated, through IgE or other antibody isotypes (drug-specific IgG or IgM antibodies), or T-cell dependent [4,23]. Those mediated by specific IgE are type I reactions and are immediate, occurring less than 1 hour after drug administration; typical clinical manifestations are urticaria and anaphylaxis. Cytotoxic (type II) and immunocomplex-mediated reactions (type III) are mediated by drug-specific, complement-fixing IgG or IgM antibodies, and classic manifestations are hemolytic anemia and serum sickness syndrome. T cell–dependent reactions (type IV) are nonimmediate and usually occur 24 to 48 hours after drug intake; maculopapular exanthema (MPE) is the most frequent reaction [4-5].

Reactions mediated by nonspecific immunological mechanisms are more heterogeneous. A majority of patients have cross-intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs) [24]. Inhibition of the cyclooxygenase (COX) pathway and release of histamine and sulphidopeptide leukotrienes has been proposed as the underlying mechanism [25].

In this manuscript we analyze the major trends in the frequency and patterns of response to the drugs most frequently involved in HDRs. We have included a section devoted to biological agents because of the increasing role that these protein derivatives are playing in HDRs.

Hypersensitivity Drug Reactions Mediated by Specific Immunological Mechanisms

1 Immediate Reactions

1.1 β-Lactam Antibiotics

Hypersensitivity reactions induced by β-lactam antibiotics (BLs) continue to be considered the classical model of reactions mediated by specific immunological mechanisms, particularly those mediated by IgE antibodies. These antibiotics bind covalently to high-molecular-weight proteins that can later be processed and recognized by the immune system [26-28], although the details of how this occurs have not yet been fully determined [20]. BLs continue to be the most common cause of HDRs mediated by specific immunological mechanisms [29,30].

The skin is the organ most frequently involved in hypersensitivity reactions to BLs, with maculopapular, morbilliform, and urticarial rashes being the most common clinical entities. There may also, however, be systemic symptoms [10,20,30] and organ-specific responses [31].

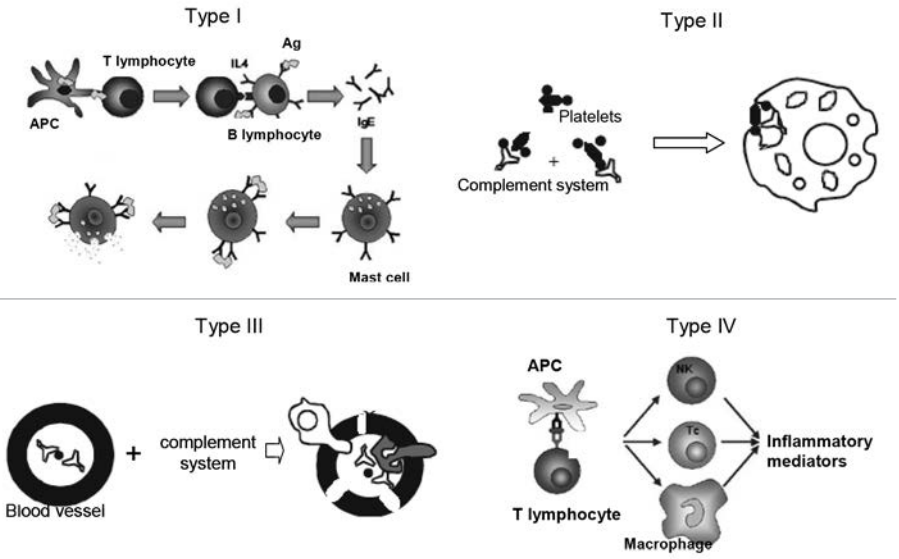
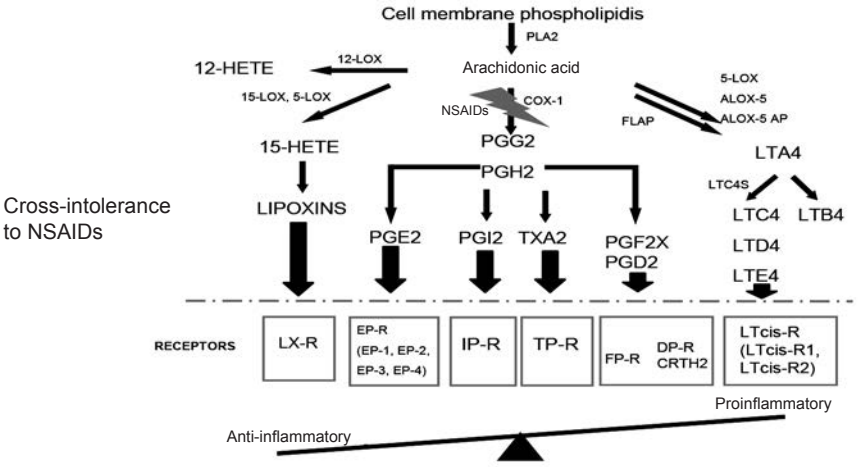
The prevalence and incidence of allergic reactions to BLs in the general population are not well known. Early

Table 1. Classification of Adverse Drug Reactions

Adverse drug reactions	Type A	Related to pharmacological actions	Drug induced-toxicity		
			Side effects		
			Secondary effects		
			Drug interactions		
	Type B	Not related to pharmacological actions	Drug intolerance		
			Idyosincratic reactions		
			Hypersensitivity reactions	Allergic mechanism	IgE-mediated
					T cell–mediated
				Nonallergic mechanism	Cross-intolerance to NSAIDs

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2. Mechanisms Involved in Hypersensitivity Drugs Reactions

Hypersensitivity reactions	Immunological mechanism	
	Nonspecific immunological mechanism	

Abbreviations: Ag, antigen; APC, antigen-presenting cell; COX, cyclooxygenase; LT, leukotriene; NSAIDs, nonsteroid anti-inflammatory drugs.

studies reported a prevalence of allergic reactions to penicillin ranging from 0.7% to 10% of the population, with anaphylaxis occurring in 0.015% to 0.004% of cases [32]. Moreover, a considerable proportion of patients with suspected hypersensitivity to BLs have shown good tolerance in allergy studies [29,33]. This may explain the wide range of prevalence rates found in published studies, with overreporting occurring when patients are classified by clinical history only as well as underreporting of mild and severe reactions [34].

In principle, all currently available BLs can induce an HDR, as they are able to spontaneously generate immunogenic conjugates [26-28,30]. Benzylpenicillin was the first BL implicated in an HDR, followed over the years by different penicillins and cephalosporins; amoxicillin has been the most frequently involved BL since the late 1980s [23], but clavulanic acid is gaining ground, and in our experience is more relevant than major and minor determinants of benzylpenicillin [23,29,35,36]. In the largest study of HDR published so far, we analyzed variations in response to a number of drugs over a 6-year period. We observed a decrease in reactions produced by benzylpenicillin and an increase in those induced by amoxicillin and amoxicillin plus clavulanic acid [29], confirming the tendency observed since the 1980s [23]. Patterns of consumption are in part responsible for the variation in drug response and clinical entities induced [36,37].

Changes in the patterns of reactions and drugs involved in HDRs to BLs have influenced the sensitivity of diagnostic tests. The role played by major and minor determinants of benzylpenicillin has decreased, while that of amoxicillin and more recently amoxicillin plus clavulanic acid has progressively increased [17,35,38,39]. A decrease in test sensitivity has also been observed [38] and new in vitro methods, such as the basophil activation test (BAT), are gaining importance in the diagnosis of immediate allergic reactions to BLs [40].

1.2 Quinolones

Fluoroquinolones (FQs) can induce hypersensitivity reactions mediated by IgE and T cells. IgE-mediated reactions are more common and are severe in over 70% of cases [41]; the most frequent clinical manifestations are anaphylaxis and anaphylactic shock [41-43]. T cell–dependent reactions have been reported less often and include MPE [44,45], fixed drug eruptions [46,47], acute generalized exanthematic pustulosis [45], Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) [48-50]. A considerable proportion of T-cell reactions are phototoxic [51]. The prevalence of HDRs induced by FQs has increased in the last decade [29,52,53], and FQs are now the most common non-BL antibiotic involved in HDRs [29]. Moxifloxacin, followed by ciprofloxacin and levofloxacin, is the most common FQ [41]. Moreover, moxifloxacin induces more severe reactions than other FQs [52].

We have observed an increase in the number of patients evaluated as having a clinical history compatible with hypersensitivity to FQs as well as confirmed hypersensitivity to these drugs [29]. This can be explained by both the increased prescription of FQs over the years and the introduction of moxifloxacin for therapeutic use [52]. In Spain, FQs are the second most frequently prescribed group of antibiotics, surpassed only by BLs [54]. Interestingly, patients with BL hypersensitivity are more prone to hypersensitivity to FQs mediated by specific IgE antibodies [41]. Although the reasons for this remain unknown, the fact that patients who are allergic to BLs are more likely to be prescribed FQs than those who are not is one possible explanation, although there may also be an as yet unidentified genetic predisposition.

The diagnosis of immediate hypersensitivity reactions is often difficult. Skin testing is not useful because of the high number of false positives [55,56], but in vitro tests such as immunoassays and the recently developed BAT have proven to be useful [57-59]. Although the sensitivity of BAT is not optimal, it is of value given the high number of severe reactions in patients who cannot be challenged because of the risks.

2 Nonimmediate Reactions

2.1 Antibiotics

Nonimmediate reactions (NIRs) consist of a spectrum of entities that usually occur within 24 to 48 hours of drug exposure, although the time can be as short as 1 to 2 hours following an exposure period of 48 hours or more [60]. Although the most common entities are benign conditions such as MPE, followed to a lesser extent by urticaria [61], severe reactions can also occur, such as drug rash with eosinophilia and systemic symptoms (DRESS) and TEN [62]. The different clinical manifestations are explained by differences in the underlying pathophysiological mechanisms, with different T-cell populations involved in all these entities [63]. Diagnosis is often complex because of the difficulty in obtaining a reliable clinical history, the importance of identifying concomitant factors such as viral diseases, and the low sensitivity of skin and in vitro tests [64,65]. Drug provocation testing is the best and often the only procedure to confirm a causal relationship between a drug and an NIR. However, it is not generally recommended and is in fact advised against in some cases, such as generalized bullous fixed drug eruptions, acute generalized exanthematous pustulosis, SJS, TEN, DRESS/drug-induced hypersensitivity syndrome, systemic vasculitis, specific organ manifestations (blood-cytopenia, hepatitis, nephritis, pneumonitis), and drug-induced autoimmune diseases [62,63].

The true prevalence of NIRs and less severe NIRs in particular is unknown for different reasons including confusion with viral and autoimmune diseases. Moreover, linking symptoms to a particular drug can also be difficult because of the long interval between drug intake and the onset of clinical symptoms, particularly in patients who take many drugs at the same time [62].

The reported incidence for SJS/TEN is between 1.4 and 6 per million person-years [62]. Various studies of severe NIR cases have been published since the 1990s in Europe, the United States, South Asia, and the Asia Pacific [62,66,67]. Antibiotics were the most commonly implicated class of drugs in most studies: between 10.5% and 41% of patients reacted to antibiotics and sulfonamides were the most common cause of NIRs in this group of drugs [62,66]. Several studies have reported the relevance of aminopenicillins in the development of NIRs [64,67,68]. In fact, aminopenicillins are the second most important NIR-inducing antibiotic worldwide [64]. However, analysis of data from the 6-year study carried out by our group revealed a decrease in HDRs due to sulfonamides but few changes in the prevalence of BL-induced reactions [29]. BLs are thus the most common NIR-inducing antibiotics in Spain. The decrease in the consumption of sulfonamides may partly explain these findings.

3 Radio Contrast Media

NIRs to radio contrast media (RCM) have increased in the last decade, in parallel with an increase in the use of these compounds [69,70]. In the past, the high osmolarity of ionic RCM was related to a high incidence of immediate reactions [71,72] due to the nonspecific release of vasoactive mediators [73-75]. Following the introduction of nonionic low-osmolarity RCM in the 1970s the incidence of immediate reactions to RCM decreased [71,72]. Conversely, NIRs have increased [29,70], to a point where they are now more common than immediate reactions [29]. A better recognition of the molecular structure of nonionic RCM by T cells may explain this.

NIRs induced by RCM are an important health problem because nearly 50% of patients with a suspected NIR to RCM are confirmed as allergic [70]. This proportion is higher than that reported for other drugs such as BLs [29,68]. The skin is the most commonly affected organ [69]. Reactions vary from mild to severe; MPE is the most frequently reported condition, followed by nonimmediate urticaria, which may be accompanied by angioedema [69,72,75].

Skin tests have a diagnostic sensitivity ranging from 43.6% to 47% [69,70]. Because of this low sensitivity, it is necessary to perform provocation tests in more than half of cases [69]. The 2 RCM most frequently involved in many places are iodixanol and iomeprol [70], and test sensitivity depends on the contrast agent: iomeprol is more likely to induce a positive skin test, whereas for iodixanol, drug provocation is usually needed to confirm diagnosis [69].

4 Neuromuscular Blocking Agents

Increasing attention has been paid to perioperative allergic reactions in recent decades. Depending on the underlying mechanism, these can be classified in 2 groups: reactions resulting from direct nonspecific mast cell and basophil activation [76] and IgE-dependent allergic reactions. Reactions resulting from direct histamine release are usually less severe than IgE-mediated reactions [76-80].

The true incidence of perioperative reactions is unknown [81]. Figures vary, probably reflecting differences in clinical practice and reporting systems across countries. The estimated incidence of all immune- and nonimmune-mediated immediate hypersensitivity reactions is 1 in 5000 to 13 000 anesthetic procedures [81-84], with anaphylaxis occurring in an estimated 1 in 10 000 to 1 in 20 000 cases [85-88].

However, the general view is that immediate-type hypersensitivity reactions are largely underreported. This observation has been confirmed in the largest cohort of patients available in the literature, with a higher incidence (100.6 [range, 76.2-125.3] per million procedures) of allergic reactions than previously reported [81]. Different populations show different patterns of sensitization [77,85-87,89,90]. Neuromuscular blocking agents (NMBAs) are the most common cause of perioperative reactions in France [78,79] with an incidence of 1 in 6500. However, IgE-mediated reactions involving NMBAs seem to be less frequent in Denmark, Sweden, and the United States [76,85]. In earlier studies, up to 70% of anaphylaxis episodes were reported to be caused by NMBAs [77,88]. However, changes in etiological patterns of anaphylaxis during anesthesia have occurred in the last 20 years, alongside changes in usage of anesthetic agents, with greater co-administration of other drugs such as antibiotics and analgesics and an increase in latex allergy. Studies from France and the United Kingdom over the last decade suggest a substantial rise in anaphylaxis due to antibiotics or latex during anesthesia. According to some studies, NMBAs may account for 50% of all cases of anaphylaxis during anesthesia, with 20% due to latex and 15% due to antibiotics [77,86,87].

Within the NMBAs, suxamethonium was previously shown to be the most common cause of anaphylaxis (43% of all NMBA reactions in France in 1990-1991) [77,85-88], but changing patterns of drug use have led to an increase in cases due to other agents, particularly atracurium, rocuronium, and cisatracurium. Pancuronium and cisatracurium are associated with the lowest incidence of allergic reactions during anesthesia [77,86-88]. It has been suggested that the lower incidence of cisatracurium allergy may have been due to underestimation, because positive skin tests have been mistakenly assumed to be due to nonspecific histamine release [81]. In fact, 20% to 50% of adverse reactions to NMBAs are considered to result from direct nonspecific mast cell and basophil activation [85-87].

A high incidence of allergy to rocuronium in Norway and France has been reported (26% of NMBAs) [78,82-86,89]. This may be the result of biased reporting of adverse effects of new drugs [90] or differences in the influence of environmental factors or genotypic differences [91]. More information is needed from large epidemiological studies.

5 Hypersensitivity Reactions by Other Mechanisms: Cross-Intolerance

Although many drugs can induce the release of histamine or other mediators through nonspecific immunological mechanisms, in recent years growing attention has been given to NSAIDs. The increasing global use [92] has resulted in this group of drugs being responsible for many adverse drug effects, including hypersensitivity reactions [93,94]. In fact, NSAIDs are now the most common class of drugs involved in HDRs [29,33,95,96].

Two groups of reactions have been identified. The first is cross-intolerance (CI) [8,24], where the proposed mechanism is the inhibition of the COX enzyme and the release of histamine and sulphidopeptide leukotrienes [25]. This can be caused by more than one chemically unrelated NSAID. The second group is formed by is selective reactions (SRs); these involve a response to a single drug and patients have good tolerance to other chemically unrelated NSAIDs [97-100]. The first group of reactions is the most common and in our experience accounts for more than 75% of cases [24]. These 2 major groups can be subdivided into 5 subtypes, as presented in Table 3. This is the recent proposed classification for NSAIDs according to the interest group of the European Network of Drug Allergy [101]. Further subclassification providing more phenotypes has been proposed [102].

CI to NSAIDs may affect the skin and/or the respiratory airways [9,25,103]. Early studies of NSAID hypersensitivity reactions focused on respiratory airway involvement, including asthma and/or rhinitis and nasal polyposis [25,103,104]. However, skin is the most common organ affected in both CI and SR groups [24]. Two cutaneous conditions have been described: acute urticaria/angioedema in the absence of a history indicative of chronic spontaneous urticaria, called NSAID–induced urticaria/angioedema (NIUA), and reaggravation of pre-existing chronic spontaneous urticaria, called NSAID-exacerbated cutaneous disease (NECD) [101]. Although most studies focusing on CI with skin involvement have been carried out in NECD patients, NIUA is more common [24]. There are controversies concerning the natural course of NIUA, with some authors indicating that it can progress to NECD [105,106]. One recent study of a large group of patients with NIUA followed for 12 years showed that 6% developed chronic spontaneous urticaria, a similar rate to the control group [107].

In recent years, the increased consumption of propionic acid derivatives has resulted in increasing reports of adverse effects to these compounds, including gastrointestinal symptoms, renal failure, acute myocardial infarction, heart failure [108,109], and hypersensitivity reactions [24,29,94,110].

An analysis of the drugs involved in NSAID-induced HDRs over the last 30 years showed that in the period 1980 to 1990, pyrazolones and acetylsalicylic acid (ASA) were the drugs most frequently involved in hypersensitivity reactions to NSAIDs; in the period 1991 to 2000, ASA was the most frequent whilst pyrazolones decreased; and in the period 2001 to 2010, propionic acid derivatives were the most frequent, with ASA in second place and pyrazolones in last place. These changes may partly reflect the changing consumption patterns of each NSAID over time [24,29].

Table 3. Classification of Reactions Induced by NSAIDs

Type of Reaction	Clinical Manifestations	Timing of Reaction	Underlying Disease	Cross-reactivity	Putative Mechanism	
NSAID-exacerbated respiratory disease (NERD)	Bronchial obstruction, dyspnea and/or nasal congestion/rhinorrhea	Acute (usually immediate to several hours after exposure)	Asthma/ rhinosinusitis	Cross-reactive	Non-allergic	COX-1 inhibition
NSAID-exacerbated cutaneous disease (NECD)	Wheals and/or angioedema		Chronic urticaria			COX-1 inhibition
NSAID-induced urticaria/angioedema (NIUA)	Wheals and/or angioedema		No underlying chronic disease			Unknown, probably COX-1 inhibition
Single NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA)	Wheals and/or angioedema/anaphylaxis		No underlying chronic disease	Non cross-reactive	Allergic	IgE-mediated
Single NSAID-induced delayed reactions (SNIDR)	Various symptoms and organs involved (eg, fixed drug eruption, SJS/TEN, nephritis)	Delayed onset (usually >24 h after exposure)	No underlying chronic disease			T cell-mediated

Abbreviations: COX, cyclooxygenase; NSAID, nonsteroidal anti-inflammatory drug; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
Source: Kowalski ML et al. Allergy. 2013;68(10):1219-32.

When we compared drugs involved in both CIs and SRs, pyrazolones remained the most frequent drug involved in SRs [24]. The reasons for this are unclear but may be related to a lower capacity of propionic acid derivatives to induce an IgE-mediated response; pyrazolones, by contrast, may have a chemical structure that is better recognized by the immune system, and therefore more likely to induce a response.

6 Hypersensitivity Reactions to Biological Agents

In this section we will consider monoclonal antibodies (mAbs) and protein derivatives, which collectively are known as biological agents. Biologicals have a great impact in medicine, providing an unlimited source of therapeutic agents and representing more than 30% of all licensed products [111]. The first agents to be introduced were cytokine immunomodulatory biologics, followed by antibody-based immunomodulatory molecules [112]. So far, more than 180 new biologics have been registered [111,112] and more are currently being investigated in clinical trials [113]. Some of these new agents are antibody drug conjugates that can potentially induce allergic drug reactions [114]. The first therapeutic mAbs were mouse antibodies; these were immunogenic and produced a large number of adverse effects [112]. This problem has been tackled by replacing the murine sequences with their human counterparts [111], significantly reducing the adverse reactions [115,116]. Three major groups of mAbs are in use: chimeric antibodies (-ximab), humanized antibodies (-zumab), and human antibodies (-mumab). Chimeric antibodies are still the most widely used mAbs and therefore adverse reactions are expected to occur [117]. mAbs are used in transplantation, oncology, and autoimmune, cardiovascular, and infectious diseases. More recent applications include virus and toxin-neutralizing antibody fragments that can replace treatment with serum-derived polyclonal antibodies. In the future fully humanized mAbs will be available for a wide variety of indications [111].

Adverse effects can be caused by the suppression of the immune response, leading to decreased resistance to infectious agents or tumor cells. In other instances mAbs can enhance the immune response by stimulating immune cells, inducing autoimmunity [111,112]. Because they are immunogenic [117], they can also induce adverse effects through immunological mechanisms. The hypersensitivity reactions fall within the 4 categories reported by Gell and Coombs [4]. IgE-dependent reactions to basiliximab [118], infliximab [119], and cetuximab [120] have been reported, although other mAbs may also induce these reactions. There are other instances where immediate reactions have been reported but no clear evidence exists for an IgE-mediated mechanism [121-123]. Type II cytotoxic reactions have been mainly reported for blood components, such as platelets [124] and red blood cells [125]. In these cases cytotoxic antibodies are produced. Type III mediated reactions have also been reported [126-128], although evidence of the circulating immunocomplexes responsible for these reactions is still lacking. Type IV T-cell reactions such as SJS [129] and drug-induced reactions [130,131] have also been reported. Direct proof of the presence of a T-cell infiltrate in the skin, together with the presence of activated CD4+ and CD8+ cells and positive lymphocyte stimulation to infliximab, has been reported by our group [130]. Other adverse reactions may mimic those induced by the classical mechanisms of Gell and Coombs, but they are associated with immune deregulation rather than a specific immunological mechanism.

In summary, biologics represent a new group of agents with intriguing perspectives for allergologists in terms of hypersensitivity reactions.

Acknowledgments

We thank James Perkins for revising the English of the manuscript.

Funding

The review was funded in part by the Instituto de Salud Carlos III-Thematic Networks of Cooperative Research Centers RIRAAF (RD07/0064) co-funded by the European Regional Development Fund.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. World Health Organization. International drug monitoring: the role of the hospital. Geneva: The Organization; 1966.
2. Rawlins M, Thompson W. Mechanisms of adverse drug reactions. In: Davies D, editor. Textbook of adverse drug reactions. New York: Oxford University Press; 1991. p.18-45.
3. Borda I, Slone D, Jick H. Assessment of adverse reactions within a drug surveillance program. JAMA. 1968;205:645-7.
4. Coombs R, Gell PG. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell P, Coombs RR, Lachman PJ, editors. Clinical aspects of immunology. Oxford: Blackwell Scientific Publications; 1975. p.761.
5. Demoly P, Hillarie-Buys D. Classification and epidemiology of hypersensitivity drug reactions. Immunol Allergy Clin N Am. 2004;24:345-6.
6. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P, Williams HC. Revised nomenclature for allergy for global use: report of the nomenclature review committee of the World Allergy Organization, October 2003. J Allergy Clin Immunol. 2004;113:832-6.
7. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. Curr Opin Allergy ClinImmunol. 2005;5:309-16.
8. Szczeklik A, Nizankowska-Mogilnicka E, Sanak M. Hypersensitivity to Aspirin and Nonsteroidal Anti-Infl amatory Drugs. In: Adkinson, Busse, Bochner, Holgate, Simons, Lemanske, editors. Middleton's Allergy Principles and Practice. Philadelphia: Mosby; 2009. p.1227-43.
9. Sánchez-Borges M. NSAID Hypersensitivity (Respiratory, Cutaneous, and Generalized Anaphylactic Symptoms). Med Clin N Am. 2010;94:853-64.
10. Gruchalla RS. Drug allergy. J Allergy ClinImmunol. 2003;111(2 Suppl)2:S548-59.
11. Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. Br J Clin Pharmacol. 2011;71:684-700.
12. Demoly P, Bousquet J. Epidemiology of drug allergy. Curr Opin Allergy Clin Immunol. 2001;1:305-10.
13. Demoly P, Bousquet J. Drug allergy diagnosis work up. Allergy. 2002;57 Suppl 72:S37-40.
14. Adkinson NF Jr, Essayan D, Gruchalla R, Haggerty H, Kawabata T, Sandler JD, Updyke L, Shear NH, Wierda D; Health and Environmental Sciences Institute Task Force. Task force report: future research needs for the prevention and management of immune-mediated drug hypersensitivity reactions. J Allergy Clin Immunol. 2002;109 Suppl(3):S461-78.
15. Mockenhaupt M. Epidemiology and causes of severe cutaneous adverse reactions to drugs. In: Pichler WJ, editor. Drug Hypersensitivity. Basel: Karger; 2007. p.18-31.
16. Romano A, Demoly P. Recent advances in the diagnosis of drug allergy. Curr Opin Allergy Clin Immunol. 2007;7:299-303.
17. Bousquet PJ, Demoly P, Romano A, Aberer W, Bircher A, Blanca M, Brockow K, Pichler W, Torres MJ, Terreehorst I, Arnoux B, Atanaskovic-Markovic M, Barbaud A, Bijl A, Bonadonna P, Burney PG, Caimmi S, Canonica GW, Cernadas J, Dahlen B, Daures JP, Fernandez J, Gomes E, Gueant JL, Kowalski ML, Kvedariene V, Mertes PM, Martins P, Nizankowska-Mogilnicka E, Papadopoulos N, Ponvert C, Pirmohamed M, Ring J, Salapatas M, Sanz ML, Szczeklik A, Van Ganse E, De Weck AL, Zuberbier T, Merk HF, Sachs B, Sidoroff A; Global Allergy, Asthma European Network (GALEN) and Drug Allergy and Hypersensitivity Database (DAHD) and the European Network for Drug Allergy (ENDA). Pharmacovigilance of drug allergy and hypersensitivity using the ENDA-DAHD database and the GALEN platform. The Galenda project. Allergy. 2009;64:194-203.
18. Torres MJ, Blanca M, Fernandez J, Romano A, Weck A, Aberer W, Brockow K, Pichler WJ, Demoly P; ENDA; EAACI Interest Group on Drug Hypersensitivity. Diagnosis of immediate allergic reactions to beta-lactam antibiotics. Allergy. 2003;58:961-72.
19. Gamboa PM. The epidemiology of drug allergyrelated consultations in Spanish Allergology Services: Alergológica-2005. J Investig Allergol Clin Immunol. 2009; 19 Suppl 2:45-50.
20. Blanca M, Romano A, Torres MJ, Férnandez J, Mayorga C,Rodriguez J, Demoly P, Bousquet PJ, Merk HF, Sanz ML, Ott H, Atanaskovi-Markovi M. Update on the evaluation of hypersensitivity reactions to betalactams. Allergy. 2009;64:183-93.
21. England RW, Ho TC, Napoli DC, Quinn JM. Inpatient consultation of allergy/immunology in a tertiary care setting. Ann Allergy Asthma Immunol. 2003;90:393-7.
22. Dietrich JJ, Quinn JM, England RW. Reasons for outpatient consultation in allergy/immunology. Allergy Asthma Proc. 2009;30:69-74.
23. Blanca M. Allergic reactions to penicillins. A changing world? Allergy. 1995;50:777-82.
24. Doña I, Blanca-López N, Cornejo-García JA, Torres MJ, Laguna JJ, Fernández J, Rosado A, Rondón C, Campo P, Agúndez JA, Blanca M, Canto G. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. Clin Exp Allergy. 2011;41:86-95.
25. Szczeklik A, Stevenson DD. Aspirin-induced asthma: advances in pathogenesis, diagnosis and management. J Allergy Clin Immunol. 2003;111:913-21.
26. Levine BB, Ovary Z. Studies of the mechanism of the formation of the penicillin antigen. III. The N-(D-alpha-benzylpenicilloyl) group as an antigenic determinant responsible for hypersensitivity to penicillin G. J Exp Med. 1961;114:875-904.

27. Dewdney JM. Immunology of the antibiotics. In: Sela M, editor, The antigens,vol. 4. New York: Academic Press; 1977. p.114-22.
28. Naisbitt D, Williams D, Pirmohamed M, Kitteringham N, Park K. Reactive metabolites and their role in drug reactions. Curr Opin AllergyImmunol. 2001;1:317-25.
29. Doña I, Blanca-López N, Torres MJ, García-Campos J, García-Núñez I, Gómez F, Salas M, Rondón C, Canto MG, Blanca M. Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients. J Investig Allergol Clin Immunol. 2012;22:363-71.
30. Antúnez C, Martín E, Cornejo-García JA, Blanca-Lopez N, R-Pena R, Mayorga C, Torres MJ, Blanca M. Immediate hypersensitivity reactions to penicillins and other betalactams. Curr Pharm Des 2006;12:3327-33.
31. Castell JV, Castell M. Allergic hepatitis induced by drugs. Curr Opin Allergy Clin Immunol. 2006;6:258-65.
32. Weiss ME, Adkinson NF. Immediate hypersensitivity reactions to penicillin and related antibotics. Clin Allergy. 1988;18:515-40.
33. Messaad D, Sahla H, Benahmed S, Godard P, Bousquet J, Demoly P. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. Ann Intern Med. 2004;140:1001-6.
34. Rebelo-Gomez, Demoly P. Epidemiology of hypersensitivity drug reactions. Curr Opin Allergy Clin Immunol. 2005;5:309-16.
35. Torres MJ, Ariza A, Mayorga C, Doña I, Blanca-Lopez N, Rondon C, Blanca M. Clavulanic acid can be the component in amoxicillin-clavulanic acid responsible for immediate hypersensitivity reactions. J Allergy Clin Immunol. 2010;125:502-5.
36. Torres MJ, Blanca M. The complex clinical picture of beta-lactam hypersensitivity: penicillins, cephalosporins, monobactams, carbapenems, and clavams. Med Clin North Am. 2010;94 :805-20.
37. Ponvert C, Perrin Y, Bados-Albiero A, Le Bourgeois M, Karila C, Delacourt C, Scheinmann P, De Blic J. Allergy to betalactam in children. Pediatr Allergy Immunol. 2011;22:411-8.
38. Torres MJ, Blanca M. The contribution of major and minor determinants from benzylpenicillin to the diagnosis of immediate allergy to beta-lactams. J Allergy Clin Immunol. 2006;117:220-1.
39. Torres MJ, Mayorga C, Blanca M. Nonimmediate Allergic Reactions Induced by Drugs: Pathogenesis and Diagnostic Tests. J Investig Allergol Clin Immunol. 2009;19:80-90.
40. Torres MJ, Padial A, Mayorga C, Fernández T, Sanchez-Sabate E, Cornejo-García JA, Antúnez C, Blanca M. The diagnostic interpretation of basophil activation test in immediate allergic reactions to betalactams. Clin Exp Allergy. 2004;34:1768-75.
41. Blanca-López N, Ariza A, Doña I, Mayorga C, Montañez MI, Garcia-Campos J, Gomez F, Rondón C, Blanca M, Torres MJ. Hypersensitivity reactions to fluoroquinolones: analysis of the factors involved. Clin Exp Allergy. 2013;43:560-7.
42. Sachs B, Riegel S, Seebeck J, Beler R, Schichler D, Barger A, Merk HF, Erdmann S. Fluoroquinolone-associated anaphylaxis in spontaneous adverse drug reaction reports in Germany: differences in reporting rates between individual fluoroquinolones and occurrence after first-ever use. Drug Saf. 2006;29:1087-100.
43. Aranda A, Mayorga C, Ariza A, Doña I, Rosado A, Blanca-Lopez N, Andreu I, Torres MJ. In vitro evaluation of IgE-mediated hypersensitivity reactions to quinolones. Allergy. 2011;66:247-54.
44. Seitz CS, Bröcker EB, Trautmann A. Diagnostic testing in suspected fluoroquinolone hypersensitivity. Clin Exp Allergy. 2009;39:1738-45.
45. Schmid DA, Depta JP, Pichler WJ. T cell-mediated hypersensitivity to quinolones: mechanisms and cross-reactivity. Clin Exp Allergy. 2006;36:59-69.
46. Fernandez-Rivas M. Fixed drug eruption (FDE) caused by norfloxacin. Allergy. 1997;52:477-8.
47. Alonso MD, Martín JA, Quirce S, Dávila I. Fixed eruption caused by ciprofloxacin with cross-sensitivity to norfloxacin. Allergy. 1993;48:296-7.
48. Davila G, Ruiz-Hornillos J, Rojas P, De Castro F, Zubeldia JM. Toxic epidermal necrolysis induced by levofloxacin. Ann Allergy Asthma Immunol. 2009;102:441-2.
49. Yoon SY, Bae YJ, Cho YS, Moon HB, Kim TB. Toxic epidermal necrolysis induced by ofloxacin. Acta Derm Venereol. 2010;90:550-1
50. Islam AF, Rahman MS. Levofloxacin-induced fatal toxic epidermal necrolysis. Ann Pharmacother. 2005;39:1136-7.
51. Cuquerella MC, Miranda MA, Bosca F. Role of excited state intramolecular charge transfer in the photophysical properties of norfloxacin and its derivatives. J Phys Chem A. 2006;110:2607-12.
52. Blanca-López N, Andreu I, Torres Jaén MJ. Hypersensitivity reactions to quinolones. Curr Opin Allergy Clin Immunol. 2011;11:285-91.
53. Lobera T, Audícana MT, Alarcón E, Longo N, Navarro B, Muñoz D. Allergy to quinolones: low cross-reactivity to levofl oxacin. J Investig Allergol Clin Immunol. 2010;20:607-11.
54. Lazaro E, de abajo F. Uso de antibióticos en España. Spanish Agency for drugs, Pharmaco-epidemiology Division (AEMPS) Publication 2010;1-9.
55. Empedrad R, Darter AL, Earl HS, Gruchalla RS. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. J Allergy Clin Immunol. 2003;112:629-30.
56. Scherer K, Bircher AJ. Hypersensitivity reactions to fluoroquinolones. Curr Allergy Asthma Rep. 2005;5:15-21.
57. Manfredi M, Severino M, Testi S, Macchia D, Ermini G, Pichler WJ, Campi P. Detection of specific IgE to quinolones. J Allergy Clin Immunol. 2004;113:155-60.
58. Ben Said B, Berard F, Bienvenu J, Nicolas JF, Rozieres A. Usefulness of basophil activation tests for the diagnosis of IgE-mediated allergy to quinolones. Allergy. 2010;65:535-6.
59. Rouzaire P, Nosbaum A, Denis L, Bienvenu F, Bérard F, Cozon G, Bienvenu J. Negativity of the basophil activation test in quinolone hypersensitivity: a breakthrough for provocation test decision-making. Int Arch Allergy Immunol. 2012;157:299-302.
60. Gomez E, Blanca M, Torres MJ, Mayorga C. Immunologic evaluation of drug allergy. Allergy Asthma Immunol Res. 2012;4:251-63.
61. Mayorga C, Torres MJ, Fernandez J, Canto G, Blanca M. Cutaneous symptoms in drug allergy: what have we learnt? Curr Opin Allergy Clin Immunol. 2009;9:431-6.

62. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, Auquier A, Bastuji-Garin S, Correia O, Locati F, Mockenhaupt M, Paoletti C, Shapiro S, Neil Shear N, Schöpf E, Kaufman DW. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N Engl J Med. 1995; 333: 1600-7.
63. Fernandez TD, Canto G, Blanca M. Molecular mechanisms of maculopapular exanthema. Curr Opin Infect Dis. 2009;22:272-8.
64. Romano A, Blanca M, Torres MJ, Bircher A, Aberer W, Brockow K, Pichler WJ, Demoly P; ENDA; EAACI. Diagnosis of nonimmediate reactions to betalactams antibiotics. Allergy. 2004;59:1153-60.
65. Gerber BO, Pichler WJ. Cellular mechanisms of T cell mediated drug hypersensitivity. Curr Opin Immunol. 2004;16:732-7.
66. Rzany B,Mockenhaupt M, Baur S, Schröder W, Stocker U, Mueller J, Holländer N, Bruppacher R, Schöpf E. Epidemiology of erythema exsudativum multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolisis in Germany (1990–1992): structure and results of a population-based registry. J Clin Epidemiol. 1996; 49: 769-73.
67. Kamaliah MD, Zaimal D, Mokhtar N, Nazmi N. Erythema multiforme, Steven Johnson Syndrome and toxic epidermal necrolysis in North East Malaysia. Int J Dermatol. 1998; 37:520-3.
68. Blanca-Lopez N, Zapatero L, Alonso E, Torres MJ, Fuentes V, Martinez-Molero MI, Blanca M. Skin testing and drug provocation in the diagnosis of nonimmediate reactions to aminopenicillins in children. Allergy. 2009;64:229-33.
69. Brockow K, Christiansen C, Kanny G, Clement O, Barbaud A, Bircher A, Dewachter P, Guéant JL, Rodriguez Guéant RM, Mouton-Faivre C, Ring J, Romano A, Sainte-Laudy J, Demoly P, Pichler WJ; ENDA; EAACI interest group on drug hypersensitivity. Management of hypersensitivity reactions to iodinated contrast media. Allergy. 2005;60:150-8.
70. Gomez E, Ariza A, Blanca-Lopez N, Torres MJ. Non-immediate hypersensitivity reactions to contrast media. Curr Opin Allergy Clin Immunol. 2013;13:345-53.
71. Wolf GL, Arenson RL, Cross AP. A prospective trial of ionic vs non-ionic contrast agents in routine clinical practice: Comparison of adverse effects. Am J Roentgenol. 1989;152:939-44.
72. Palmer FJ. The RACR survey of intravenous contrast media reactions. Final report. Australas Radiol. 1988;32:426-8.
73. Ring J, Arroyave CM, Frizler MJ, Tan EM. In vitro histamine and serotonin release by radiographic contrast media (RCM). Complement-dependent and -independent release reaction and changes in ultrastructure of human blood cells. Clin Exp Immunol. 1978;32:105-18.
74. Stellato C, de Crescenzo G, Patella V, Mastronardi P, Mazzarella B, Marone G. Human basophil/mast cell releasability. XI. Heterogeneity of the effects of contrast media on mediator release. J Allergy Clin Immunol. 1996;97:838-50.
75. Laroche D, Aimone-Gastin I, Dubois F, Huet H, Gerard P, Vergnaud M-C, Mouton-Faivre C, Guéant JL, Laxenaire MC, Bricard H. Mechanisms of severe, immediate reactions to iodinated contrast material. Radiology. 1998;209:183-90.
76. Bhananker SM, O'Donnell JT, Salemi JR, Bishop MJ. The risk of anaphylactic reactions to rocuronium in the United States is comparable to that of vecuronium: an analysis of food and drug administration reporting of adverse events. Anesth Analg. 2005;101:819-22.
77. Laxenaire MC. Drugs and other agents involved in anaphylactic shock occurring during anaesthesia. A French multicenter epidemiological inquiry. Ann Fr Anesth Reanim. 1993;12:91-6.
78. Mertes PM, Laxenaire MC. Anaphylactic and anaphylactoid reactions occurring during anaesthesia in France. Seventh epidemiologic survey (January 2001–December 2002). Ann Fr Anesth Reanim. 2004; 23:1133-43.
79. Moneret-Vautrin DA, Widmer S, Gueant JL, Kamel L, Laxenaire MC, Mouton C, Gerard H. Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases. Br J Anaesth. 1990; 64:743-5.
80. Sanchez-Guerrero IM, Tortosa JA, Hernandez-Palazon J, Escudero AI. Anaphylactoid reaction induced by pancuronium during general anaesthesia. Eur J Anaesthesiol. 1998; 15:613-4.
81. Lagneau F, Corda B, Marty J. Possible underestimation of the relative incidence of anaphylactic reactions to benzylisoquinoline neuromuscular blocking agents. Eur J Anaesthesiol. 2003; 20:577-8.
82. Laxenaire MC, Moneret-Vautrin DA. Anaphylactic reactions to rocuronium. Br J Anaesth. 2000; 85:325-6.
83. Rose M, Fisher M. Rocuronium: high risk for anaphylaxis? Br J Anaesth. 2001; 86:678-82.
84. Heier T, Guttormsen AB. Anaphylactic reactions during induction of anaesthesia using rocuronium for muscle relaxation: a report including 3 cases. Acta Anaesthesiol Scand. 2000;44:775-81.
85. Harboe T,Guttormsen AB, Irgens A, Dybendal T, Florvaag E. Anaphylaxis during anesthesia in Norway: a 6-year single-center follow-up study. Anesthesiology. 2005;102:897-903.
86. Mertes PM, Laxenaire MC, Alla F. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999–2000. Anesthesiology. 2003;99:536-45.
87. Light KP, Lovell AT, Butt H, Fauvel NJ, Holdcroft A. Adverse effects of neuromuscular blocking agents based on yellow card reporting in the U.K.: are there differences between males and females? Pharmacoepidemiol Drug Saf. 2006;15:151-60.
88. Fisher M, Baldo BA. Anaphylaxis during anaesthesia: current aspects of diagnosis and prevention. Eur J Anaesthesiol. 1994;11:263-84.
89. Laxenaire MC, Gastin I, Moneret-Vautrin DA, Widmer S, Guéant JL. Cross-reactivity of rocuronium with other neuromuscular blocking agents. Eur J Anaesthesiol Suppl 1995;11:55-64.
90. Mertes PM, Guttormsen AB, Harboe T, Johansson SG, Florvaag E, Husum B, Garvey LH, Kroigaard M, Gramstad L, Kvande KT, Trechot P, Malinovsky JM. Can spontaneous adverse event reporting systems really be used to compare rates of adverse events between drugs? Anesth Analg. 2007;104:471-2.
91. Gueant JL, Gueant-Rodriguez RM, Cornejo-Garcia JA, Viola M, Blanca M, Romano A. Gene variants of IL13, IL4, and IL4RA are predictors of beta-lactam allergy. J Allergy Clin Immunol. 2009;123:509-10.
92. Fosbol EL, Gislason GH, Jacobsen S, Abildstrom SZ, Hansen ML, Schramm TK, Folke F, Sørensen R, Rasmussen JN, Køber L,

Madsen M, Torp-Pedersen C. The pattern of use of non steroidal anti-inflammatory drugs (NSAIDs) from 1997 to 2005: a nationwide study on 4.6 million people. Pharmacoepidemiol Drug Safety. 2008;17:822-33.
93. Roberts LJ, Morrow JD. Analgesic-antipyretic and antiinflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LL, Goodman Gilman A, editors. The pharmacological basis of therapeutics, 10th edn. New York: McGraw-Hill; 2001. p.687-731.
94. Manfredi G. Adverse drug reactions prevalence in south Italy. Allergy. 2008;63:S110-1.
95. Gomes E, Cardoso MF, Praça F, Gomes L, Mariño E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. Clin Exp Allergy. 2004;34:1597-601.
96. Chen CJ, Cheng CF, Lin HY, Hung SP, Chen WC, Lin MS. A comprehensive 4-year survey of adverse drug reactions using a network-based hospital system. J Clin Pharm Ther. 2012;37:647-51.
97. Himly M, Jahn-Schmid B, Pittertschatscher K, Bohle B, Grubmayr K, Ferreira F, Ebner H, Ebner C. IgE-mediated immediate type hypersensitivity to the pyrazolone drug propyphenazone. J Allergy Clin Immunol. 2003; 111: 882-8.
98. Schneider CH, Kasper MF, de Weck AL, Rolli H, Angst BD. Diagnosis of antibody-mediated drug allergy. Pyrazolinone and pyrazolidinedione cross-reactivity relationships. Allergy. 1987;42:597-603.
99. Blanca M, Perez E, Garcia JJ, Miranda A, Terrados S, Vega JM, Suau R. Angioedema and IgE antibodies to aspirin: a case report. Ann Allergy. 1989;62:295-298.
100. Canto MG, Andreu I, Fernandez J, Blanca M. Selective immediate hypersensitivity reactions to NSAIDs. Curr Opin Allergy Clin Immunol. 2009;9:293-7.
101. Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G, Brockow K, Campo P, Celik G, Cernadas J, Cortellini G, Gomes E, Nižankowska-Mogilnicka E, Romano A, Szczeklik A, Testi S, Torres MJ, Wöhrl S, Makowska J. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. Allergy. 2013;68(10):1219-32.
102. Ayuso P, Cornejo-Garcia JA, Blanca-Lopez N, Doña I, Torres MJ, Gueant-Rodriguez R, Canto G, Sanak M, Mayorga C, Gueant JL, Blanca M. Advanced phenotyping in hypersensitivity drug reactions to NSAIDs. Clin Exp Allergy. 2013; 43(10):1097-9.
103. Stevenson DD, Szczeklik A. Clinical and pathologic perspectives on aspirin sensitivity and asthma. J Allergy Clin Immunol. 2006;118:773-86.
104. Micheletto C, Visconti M, Tognella S, Facchini FM, Dal Negro RW. Aspirin induced asthma (AIA) with nasal polyps has the highest basal LTE4 excretion: a study vs AIA without polyps, mild topic asthma, and normal controls. Eur Ann Allergy Clin Immunol. 2006; 38:20-3.
105. Asero R. Intolerance to nonsteroidal antiinflammatory drugs might precede by years the onset of chronic urticaria. J Allergy Clin Immunol. 2003;111:1095-8.
106. Asero R. Multiple nonsteroidal anti-inflammatory drug-induced cutaneous disease: what differentiates patients with and without underlying chronic spontaneous urticaria? Int Arch Allergy Immunol. 2013;163(2):114-8.
107. Doña I, Blanca-López N, Torres MJ, Gómez F, Fernández J, Zambonino MA, Monteseirín FJ, Canto G, Blanca M, Cornejo-García JA. NSAID-induced urticaria/angioedema does not evolve into chronic urticaria: a 12-year follow-up study. Allergy. 2014;69:438-44.
108. Lafrance JP, Miller DR. Selective and non-selective non-steroidal anti-inflammatory drugs and the risk of acute kidney injury. Pharmacoepidemiol Drug Saf. 2009; 18:923-31.
109. Gislason GH, Rasmussen JN, Abildstrom SZ, Schramm TK, Hansen ML, Fosbøl EL, Sørensen R, Folke F, Buch P, Gadsbøll N, Rasmussen S, Poulsen HE, Køber L, Madsen M, Torp-Pedersen C. Increased mortality and cardiovascular morbidity associated with use of nonsteroidal anti-inflammatory drugs. Arch Intern Med. 2009;169(2):141-9.
110. Nettis E, Giordano D, Colanardi MC, Paradiso MT, Ferrannini A, Tursi A. Delayed- type hypersensitivity rash from ibuprofen. Allergy. 2003; 58:539-40.
111. Nassim A, Chernajovsky Y. Historical development of antibody therapies. In: Nassim A, Chernajovsky Y, editors. Therapeutic Antibodies. Berlin: Sprringer Verlag;2010.
112. Sathish JG, Sethu S, Bielsky MC, de Haan L, French NS. Challenges and approaches for the development of safer immunomodulatory biologics. Nat Rev Drug Discov. 2013;12:306-24.
113. Reichert JM. Antibodies to watch in 2013. Mid-year update. mAbs. 2013;5:513-17.
114. Carter PJ, Senter PD. Antibody-drug conjugates for cancer therapy. Cancer J. 2008;14:154-69.
115. Boulianne GL, Hozumi N, Shulman MJ. Production of functional chimaeric mouse/human antibody. Nature. 1984; 312:643-6.
116. Hwang WY, Foote J. Immunogenicity of engineering antibodies. Methods. 2005;36:3-10.
117. Pichler JW. Adverse side-effects to biological agents. Allergy. 2006;61:912-20.
118. Badouin V et al. Anaphylactic shock caused by IgE sensitisation after treatment with the chimeric anti-IL2R mAb basiliximab. Transplantation. 2003;15:76.
119. 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
120. Chung CH, Mirakhur B, Chan E, Le QT, Berlin J, Morse M, Murphy BA, Satinover SM, Hosen J, Mauro D, Slebos RJ, Zhou Q, Gold D, Hatley T, Hicklin DJ, Platts-Mills TA. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. N Engl J Med. 2008;358:1109-17.
121. Cox L, Platts-Mills TA, Finegold I, Schwartz LB, Simons FE, Wallace DV; American Academy of Allergy, Asthma & Immunology; American College of Allergy, Asthma and Immunology. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. J Allergy Clin Immunol. 2007;120:1373-7.
122. Cohen M, Rocher F, Vivinus S, Thomas P, Lebrun C. Giant urticaria and persistent neutralizing antibodies after the first natalizumab infusion. Neurology. 2010;74:1394-5.
123. Paltiel M, Gober LM, Deng A, Mikdashi J, Alexeeva I, Saini SS, Gaspari AA. Immediate type I hypersensitivity response

implicated in worsening injection site reactions to adalimumab. Arch Dermatol. 2008;144:1190-4.
124. Bishara AI, Hagmeyer KO. Acute profound thrombocytopenia following abciximab therapy. Ann Pharmacother. 2000;34:924-30.
125. Kwan JM, Reese AM, Trafeli JP. Delayed autoimmune hemolytic anemia in efalizumab-treated psoriasis. J Am Acad Dermatol. 2008;58:1053-5.
126. Ashraf-Benson S, Wall GC, Veach LA. Serum sickness-like reaction associated with efalizumab. Ann Pharmacother. 2009;43:383-6.
127. Gamarra RM, McGraw SD, Drelichman VS, Maas LC. Serum sickness–like reactions in patients receiving intravenous infliximab. J Emerg Med. 2006;30:41-4.
128. Pilette C, Coppens N, Houssiau FA, Rodenstein DO. Severe serum sickness-like syndrome after omalizumab therapy for asthma. J Allergy Clin Immunol. 2007;120:972-3.
129. Salama M, Lawrance IC. Stevens-Johnson syndrome complicating adalimumab therapy in Crohn disease. World J Gastroenterol. 2009;15:4449-52.
130. Torres MJ, Chaves P, Doña I, Blanca-López N, Canto G, Mayorga C, Blanca M. T-cell involvement in delayed-type hypersensitivity reactions to infliximab. J Allergy Clin Immunol. 2011;128:1365-7.
131. Moneret-Vautrin DA, Morisset M, Vignaud JM, Kanny G. T cell mediated allergy to abciximab. Allergy. 2002;57:269-70.

Miguel Blanca

Servicio de Alergología, Hospital Civil
29009 Malaga, Spain
E-mail: mblancago@gmail.com