



Drug hypersensitivity reactions: more basic and clinical research is needed

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There has been increasing interest in the study of atopic diseases in recent years [1], extending to hypersensitivity drug reactions [2,3]. This has been demonstrated by the initiatives proposed in the periodic Drug Hypersensitivity Meetings (DHM) of which five editions have occurred so far, as well as the many activities organized by the European Academy of Allergy and Clinical Immunology (EAACI) and other societies [4]. This issue of the journal contains six reviews that deal with various topics in drug hypersensitivity, ranging from practical approaches for the clinician, aspirin desensitization for cardiovascular diseases, advances in the treatment of severe adverse drug reactions, diagnostic tests for allergy to beta-lactams, to more basic aspects such as the involvement of metabolites in drug allergy, and the pharmacogenetics of NSAID hypersensitivity. There is also a review on cutaneous adverse drug reactions in the elderly, an important subject that has not received much attention in the past.

Drug metabolites are known to play a key role in the induction of allergic reactions. Native drugs are often unable to bind proteins directly and will undergo metabolic biotransformation before becoming immunogenic [5,6]. Classical drugs that require metabolic transformation include sulfamethoxazole and carbamazepine. For sulfamethoxazole, a sulphonamide with antimicrobial activity is metabolized to a hydroxylamine by oxidation of the terminal amine, generating nitrososulfamethoxazole that binds to cysteine residues in proteins [7,8]. In the case of carbamazepine, although it can generate over 30 metabolites, the most important pathway in terms of drug hypersensitivity is the formation of carbamazepine 10,11-epoxide followed by hydroxylation to carbamazepine 10,11-trans-dihydroxy [9]. Regarding selective immunological reactions to NSAIDs, there is great interest in studying the metabolites involved in these reactions [10]. In this issue, Agúndez *et al.* [6] review the literature on such processes, focussing mainly on beta-lactams and NSAIDs, the two most common groups of drugs involved in hypersensitivity reactions [2,3,11]. They speculate on the potential

metabolites that may be involved in hypersensitivity reactions to amoxicillin, acetylsalicylic acid (ASA), metamizol and paracetamol, key drugs that can induce both IgE and T cell mediated allergic responses [6,10].

The review by Gómez *et al.* [12] provides an update on the most recent findings concerning the influence of genetics on NSAID hypersensitivity reactions. The authors emphasize that NSAIDs are the most frequent agents involved in hypersensitivity drug reactions, as reported by many groups [2,3,11]. Acute urticaria induced by NSAIDs in the absence of chronic spontaneous urticaria is the most common entity and constitutes a stable phenotype that does not seem to evolve to chronic urticaria [13–15]. Major efforts have been made in recent years to phenotype cases with hypersensitivity reactions to NSAIDs [13]. Although there is ongoing debate in this area [16,17], we appear to be reaching a consensus [13,18,19]. Mast cells are key players in these reactions and recent genetic studies have added more weight to this assertion [20]. Clearly, we will need to look beyond the prostaglandin pathway to explain the mechanisms involved [21]. Given that these reactions are relatively commonplace compared with other hypersensitivity drug reactions, and that their incidence may be increasing, more cases should become available for study in the near future [2,20]. It also appears that there is geographical variation in terms of the entities induced by NSAIDs hypersensitivity, with angioedema prevailing in those countries with a high prevalence of house dust mite sensitization [22,23]. NSAIDs hypersensitivity is also clinically relevant in children [23].

Several groups have emphasized the need to monitor the acute response in order to obtain

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information on the mechanisms involved in hypersensitivity drug reactions, for both immediate (IgE-mediated) reactions and nonimmediate (T cell dependent) responses [24,25]. In the case of immediate reactions, most studies have quantified inflammatory mediators in peripheral blood and urine [24,26], whilst for nonimmediate reactions, the skin and peripheral blood have been monitored concurrently [26]. On the basis of the idea that T cells express markers for skin-homing, this process can be closely followed prospectively at sequential time intervals in order to track the patterns of cells involved [27]. This is based on the interaction of cutaneous lymphocyte antigen (CLA), present in peripheral lymphocytes, with the corresponding ligand E-selectin in skin blood vessels. This process is accompanied by a characteristic set of interactions between chemokine receptors on lymphocytes and their corresponding ligands in the skin [25].

In this issue, Shiohara *et al.* [28] review severe drug reactions, including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DRESS). The main focus of the review is to compare data obtained from peripheral blood very early during the acute stages of these severe drug reactions. The authors study a model in which challenge is well tolerated and there is strong T cell involvement and provide a detailed review of the recent literature in this area. Although monitoring of the acute phase is not regularly carried out in clinical practice during severe drug reactions, it could potentially be an interesting approach, not only to aid diagnosis but also to choose the best therapeutic option to arrest (if possible) progression of such drug reactions.

Although considerable progress has been made in the understanding of T cell mediated reactions, differentiating this into four major categories being a major step forward [29], it is now clear that even more subtypes can be identified. This may be particularly relevant in the elderly. The review by Heng and Lim [30] studies this issue in more detail, providing a broad overview of drug eruptions in elderly patients, a particularly important topic given the rapidly ageing population worldwide who accrue increasing numbers of medical comorbidities requiring pharmacotherapy [30]. Some of these cutaneous adverse reactions that mimic drug allergy may be due to the inherent pharmacological properties of the drug with resultant effects on the skin, rather than immunological mechanisms alone. For instance, chronic eczematous drug eruptions on underlying xerotic skin and chemotherapy induced cutaneous eruptions [31,32]. Photoageing

may also affect skin test responses [33] and affect the reliability of diagnostic tests. Elderly patients who develop severe cutaneous adverse reactions such as SJS/TEN tend to have poorer outcomes in view of baseline age-related organ impairments and underlying comorbidities. Dry eyes, a sequelae of ocular involvement in SJS/TEN, may be accentuated as tear production diminishes physiologically with ageing [33], further impacting quality of life in the elderly.

From a clinical point of view, hypersensitivity drug reactions to beta-lactams are highly relevant because they are the most frequent triggers of hypersensitivity drug reactions that are mediated by specific immunological mechanisms [3]. Since the mid-80s, when side chain specific reactions to amoxicillin were frequently reported by different groups in several countries, the ‘changing world’ view has been accepted, which asserts that as new beta-lactams enter the market and are prescribed, the possibility of finding selective reactions to these new drugs occurs [34,35]. For many years, amoxicillin was the most frequently reported culprit [34], but more recently, clavulanic has become increasingly relevant [36,37]. It is crucial that the evidence base for this be constantly reviewed and diagnostic procedures updated accordingly [38,39]. It could be argued that the views of Macy *et al.* are very similar to other American authors working in this area, but in strong disagreement with the European view [40,41]. The position of an expert group from the European Academy of Allergy and Clinical Immunology is that in addition to major and minor determinants of benzyl penicillin, amoxicillin and where necessary other culprit drugs should be used in the diagnosis of immediate hypersensitivity to beta-lactams [39,40]. This contrasts with the position stated by Macy [42] that the use of major and minor determinants of penicillin for diagnosis is sufficient, and in the case of drug administration to patients with negative skin tests to these determinants, the possibility of developing an anaphylactic reaction should be low. For European allergists familiar with hypersensitivity reactions to beta-lactams, this statement is refutable [40,41].

When evaluating hypersensitivity reactions to beta-lactams according to clinical history, it is often unclear whether the initial reaction was immediate or nonimmediate [43–45]. For example, the so-called accelerated reactions to penicillins can occur as soon as 1 h after drug intake and as such cannot be clearly distinguished from immediate reactions in many cases. Patients with accelerated reactions can develop generalized erythema, facial angioedema and systemic pruritus; however, recent evidence indicates that these are associated with a T cell effector response [46]. For this purpose, when patients

are evaluated following an acute reaction, they should not be observed for only 1 hour, but ideally the patient should continue to be observed for a period of 24–48 h, with the first 8 h being the most critical. Reactions due to amoxicillin (AX) can occur as soon as several hours after drug intake [45,46].

Today, there is general consensus that AX must be used as a reagent for skin testing, especially in those countries where this drug is frequently prescribed and involved in hypersensitivity drug reactions [39,40]. Given that it is often the most frequent drug involved in drug allergy, our view is that the term minor determinant, as used by Macy [42], should be avoided. In Spain, France, Portugal and other countries, AX should not be considered a minor determinant. In fact, classical benzyl-penicillin determinants (i.e. penicilloyl-polylysine, and benzylpenicillin and benzylpenicillin, benzylpenicilloate and benzylpenilloate as a minor determinant mixture) now behave like minor determinants because of the low frequency of skin test responses [36,37,41]. The use of other penicillin determinants, for example ampicillin, has been shown not to be relevant, as selective immediate reactions to these drugs are uncommon [47].

Concerning cephalosporin determinants, these should be used when major and minor penicillins have been discounted due to negative skin test results [40].

In-vitro testing remains an unviable diagnostic technique in most situations due to the inadequate sensitivity of commercially available reagents [48]. As a result, a number of laboratories have developed their own techniques in order to measure specific IgE antibodies. This has not only allowed diagnosis but also improved our understanding of these reactions [49,50]. The development of cell assays based on lymphocyte stimulation and other immune processes may provide a solution for the future; however, such techniques are currently reserved for specialized laboratories [51,52].

Another approach to the in-vitro diagnosis of immediate reactions is the basophil activation test. A lot of effort has been made in recent years to improve the performance of this test [53]. It has been applied to the diagnosis of several drugs, including pirazolones [54], quinolones [55], omeprazole and others [53]. The best performance to date has been achieved for beta-lactams [56]. In spite of these applications, there are still many outstanding issues to be resolved if we are to create an accurate, generalizable and easily implemented test. As such, these cannot be recommended as part of routine clinical practice for now. Before an international consensus is made with respect to the provision of guidelines for evaluating patients with

hypersensitivity reactions to beta-lactams, two conditions are required: a fluid exchange of information amongst all experts in this area from different parts of the world and the acceptance that the pattern of beta-lactam allergy may vary between different countries not only in terms of prevalence of IgE and T cell dependent responses but also in the specificity of immunological recognition. The idea that major and minor determinants of penicillin are sufficient for diagnosis needs to be re-examined.

The final article in this issue of *Current Opinion in Allergy and Clinical Immunology* is devoted to aspirin desensitization in cardiovascular disease [57]. Although mechanistically similar to the use of high-dose aspirin desensitization in chronic rhinosinusitis and nasal polyposis, the target dose of ASA needed for cardiovascular disease is lower (75–100 mg/day). The role of ASA is well established in the treatment of these diseases [58]; however, its usage is clearly limited for patients with a history of hypersensitivity to NSAIDs. The term ‘aspirin allergy’ should be replaced with ‘aspirin hypersensitivity’, as both immunological and nonimmunological mechanisms may take part and in fact nonimmunologically mediated reactions are the most common [13].

Whether ASA can induce anaphylaxis or not is a matter of debate, but if we consider anaphylaxis as a clinical entity in which both specific immunological and nonimmunological mechanisms can occur, following the recent recommendations for evaluating anaphylaxis [59], a number of skin reactions to ASA and other NSAIDs can be considered anaphylactic reactions [13]. In fact, one recent study [60] has shown that NSAIDs are major causes of drug-induced anaphylaxis in patients who attend hospital emergencies. Although the authors point out that desensitization often fails for patients with chronic urticaria, very little is known about desensitization in cases of acute urticaria/angioedema induced by NSAIDs in patients without underlying chronic spontaneous urticaria. It should be pointed out again that the terminology to describe this disease has changed, and instead of aspirin exacerbated respiratory disease (AERD), we should now use NSAIDs exacerbated respiratory disease (NERD) [13], as in many parts of the world, other drugs are more commonly involved than ASA [2,3].

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REFERENCES

- Papadopoulos NG, Agache I, Bavbek S, *et al.* Research needs in allergy: an EAACI position paper, in collaboration with EFA. *Clin Trans Allergy* 2012; 2:1–23.
- Doña I, Barrionuevo E, Blanca-Lopez N, *et al.* Trends in hypersensitivity drug reactions: more drugs, more response patterns, more heterogeneity. *J Investig Allergol Clin Immunol* 2014; 24:143–153.
- Doña I, Blanca-Lopez N, Torres MJ, *et al.* Drug hypersensitivity reactions: response patterns, drug involved, and temporal variations in a large series of patients. *J Investig Allergol Clin Immunol* 2012; 22:363–371.
- Romano A, Torres MJ, Castells M, *et al.* Diagnosis and management of drug hypersensitivity reactions. *J Allergy Clin Immunol* 2011; 127:S67–S73.
- Faulkner L, Meng X, Park BK, *et al.* The importance of hapten-protein complex formation in the development of drug allergy. *Curr Opin Allergy Clin Immunol* 2014; 14:293–300.
- Agúndez JAG, Mayorga C, García-Martin E. Drug metabolism and hypersensitivity reactions to drugs. *Curr Opin Allergy Clin Immunol* 2015; 15:277–284.
- Cribb AE, Spielberg SP. Sulfamethoxazole is metabolized to the hydroxylamine in humans. *Clin Pharmacol Ther* 1992; 51:522–526.
- Naisbitt DJ, Farrell J, Gordon SF, *et al.* Covalent binding of the nitroso metabolite of sulfamethoxazole leads to toxicity and major histocompatibility complex-restricted antigen presentation. *Mol Pharmacol* 2002; 62:628–637.
- Lu W, Uetrecht JP. Peroxidase-mediated bioactivation of hydroxylated metabolites of carbamazepine and phenytoin. *Drug Metab Dispos* 2008; 36:1624–1636.
- Canto MG, Andreu I, Fernandez J, *et al.* Selective immediate hypersensitivity reactions to NSAIDs. *Curr Opin Allergy Clin Immunol* 2009; 9:293–297.
- Messaad D, Sahla H, Benahmed S, *et al.* Drug provocation tests in patients with a history of suggestive immediate drug hypersensitivity. *Ann Intern Med* 2004; 140:1001–1006.
- Gómez F, Perkins JR, García-Martin E, *et al.* Genetic basis of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs. *Curr Opin Allergy Clin Immunol* 2015; 15:285–293.
- Kowalski ML, Asero R, Bavbek S, *et al.* Classification and practical approach to the diagnosis and treatment of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy* 2013; 68:1219–1232.
- Blanca-Lopez N, Torres MJ, Doña I, *et al.* Value of the clinical history in the diagnosis of urticaria/angioedema induced by NSAIDs with cross-intolerance. *Clin Exp Allergy* 2013; 43:85–91.
- Doña I, Blanca-López N, Torres MJ, *et al.* NSAID-induced urticaria/angioedema does not evolve into chronic urticaria: a 12-year follow-up study. *Allergy* 2014; 69:438–444.
- Asero R. Multiple nonsteroidal anti-inflammatory drug-induced cutaneous disease: what differentiates patients with and without underlying chronic spontaneous urticaria? *Int Arch Allergy Immunol* 2014; 163:114–118.
- Viola M, Rumi G, Valluzzi RL, *et al.* Assessing potential determinants of positive provocation tests in subjects with NSAID hypersensitivity. *Clin Exp Allergy* 2011; 41:96–103.
- Cornejo-García JA, Blanca-Lopez N, Doña I, *et al.* Hypersensitivity reactions to nonsteroidal antiinflammatory drugs. *Curr Drug Metab* 2009; 10:971–980.
- Ayuso P, Cornejo-García JA, Blanca-López N, *et al.* Advanced phenotyping in hypersensitivity reactions to NSAIDs. *Clin Exp Allergy* 2013; 43:1097–1109.
- Cornejo-García JA, Liou BL, Blanca-López N, *et al.* Genome-wide association study in NSAID-induced acute urticaria/angioedema in Spanish and Han Chinese populations. *Pharmacogenomics* 2013; 14:1857–1869.
- Perkins JR, Sanak M, Canto G, *et al.* Unravelling adverse reactions to NSAIDs using systems biology. *Trends Pharmacol Sci* 2015; 36:172–180.
- Sánchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A. Aspirin exacerbated cutaneous disease. *Immunol Allergy Clin North Am* 2013; 33:251–262.
- Zambonino MA, Torres MJ, Muñoz C, *et al.* Drug provocation tests in the diagnosis of hypersensitivity reactions to nonsteroidal antiinflammatory drugs in children. *Paediatr Allergy Immunol* 2013; 24:151–159.
- Fernandez J, Blanca M, Moreno F, *et al.* Role of tryptase, eosinophil cationic protein and histamine in immediate allergic reactions to drugs. *Int Arch Allergy Immunol* 1995; 107:160–162.
- Mayorga C, Pena RR, Blanca-López N, *et al.* Monitoring the acute phase response in nonimmediate allergic drug reactions. *Curr Opin Allergy Clin Immunol* 2006; 6:249–257.
- Galvão VR, Giavina-Bianchi P, Castells M. Perioperative anaphylaxis. *Curr Allergy Asthma Rep* 2014; 14:452.
- Blanca M, Torres MJ, Leyva L, *et al.* Expression of the skin-homing receptor in peripheral blood lymphocytes from subjects with nonimmediate cutaneous allergic drug reactions. *Allergy* 2000; 55:998–1004.
- Shiohara T, Mizukawa Y, Aoyama Y. Monitoring the acute response in severe hypersensitivity reactions to drugs. *Curr Opin Allergy Clin Immunol* 2015; 15:294–299.
- Pichler WJ. Delayed drug hypersensitivity reactions. *Ann Intern Med* 2003; 139:683–693.
- Heng YK, Lim YL. Cutaneous adverse drug reactions in the elderly. *Curr Opin Allergy Clin Immunol* 2015; 15:300–307.
- Burch JB, Augustine AD, Frieden LA, *et al.* Advances in geroscience: impact on health span and chronic disease. *J Gerontol A BiolSci Med Sci* 2014; 69 (Suppl 1):S1–S3.
- King MJ, Phillips SE, Lockey RF. Effect of photoaging on skin test response to histamine independent of chronologic age. *Ann Allergy Asthma Immunol* 2014; 113:647–651.
- Farid M, Agrawal A, Fremgen D, *et al.* Age-related defects in ocular and nasal mucosal immune system and the immunopathology of dry eye disease. *Ocul Immunol Inflamm* 2014; 1–21.
- Blanca M. Allergic reactions to penicillins. A changing world? *Allergy* 1995; 50:777–782.
- Antunez C, Martin E, Cornejo-García JA, *et al.* Immediate hypersensitivity reactions to penicillins and other betalactams. *Curr Pharm Design* 2006; 12:3327–3333.
- Torres MJ, Blanca M. The complex clinical picture of beta-lactam hypersensitivity: penicillins, cephalosporins, monobactams and clavams. *Med Clin North Am* 2010; 94:805–820.
- Torres MJ, Ariza A, Mayorga C, *et al.* Clavulanic acid can be the component in amoxicillin-clavulanic acid responsible for immediate hypersensitivity reactions. *J Allergy Clin Immunol* 2010; 125:502–505.
- Blanca M, Mayorga C, Torres MJ, *et al.* Side-chain-specific reactions to betalactams: 14 years later. *Clin Exp Allergy* 2002; 32:192–197.
- Blanca M, Romano A, Torres MJ, *et al.* Continued need of appropriate betalactam-derived skin test reagents for the management of allergy to betalactams. *Clin Exp Allergy* 2007; 37:166–173.
- Torres MJ, Blanca M, Fernandez J, *et al.* Diagnosis of immediate allergic reactions to beta-lactam antibiotics. *Allergy* 2003; 58:961–972.
- Bousquet PJ, Pipet A, Bousquet-Rouanet L, Demoly P. Oral challenges are needed in the diagnosis of beta-lactam hypersensitivity. *Clin Exp Allergy* 2008; 38:185–190.
- Macy E. Penicillin allergy: optimizing diagnostic protocols, public health implications, and future research needs. *Curr Opin Allergy Clin Immunol* 2015; 15:308–313.
- Terrados S, Blanca M, García J, *et al.* Nonimmediate reactions to betalactams: prevalence and role of the different penicillins. *Allergy* 1995; 50:563–567.
- Padial A, Antunez C, Blanc-Lopez N, *et al.* Nonimmediate reactions to β -lactams: diagnostic value of skin testing and drug provocation test. *Clin Exp Allergy* 2008; 38:822–828.
- 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.
- Gómez E, Blanca-Lopez N, Salas M, *et al.* Induction of accelerated reactions to amoxicillin by T-cell effector mechanisms. *Ann Allergy Asthma Immunol* 2013; 110:267–273.
- Romano A, Torres MJ, Fernandez J, *et al.* Allergic reactions to ampicillin. Studies on the specificity and selectivity in subjects with immediate reactions. *Clin Exp Allergy* 1997; 27:1425–1431.
- Fontaine C, Mayorga C, Bousquet PJ, *et al.* Relevance of the determination of serum-specific IgE antibodies in the diagnosis of immediate β -lactam allergy. *Allergy* 2007; 62:47–52.
- Blanca M, Mayorga C, Perez E, *et al.* Determination of IgE antibodies to the benzyl penicilloyl determinant. A comparison between poly-L-lysine and human serum albumin as carriers. *J Immunol Methods* 1992; 153:99–105.
- Moreno F, Blanca M, Mayorga C, *et al.* Studies of the specificities of IgE antibodies found in sera from subjects with allergic reactions to penicillins. *Int Arch Allergy Immunol* 1995; 108:74–81.
- Adam J, Pichler WJ, Yeryl D. Delayed drug hypersensitivity: models of T cells stimulation. *Br J Clin Pharmacol* 2011; 71:701–707.
- Rodríguez-Pena R, Lopez S, Mayorga C, *et al.* Potential involvement of dendritic cells in delayed-type hypersensitivity reactions to β -lactams. *J Allergy Clin Immunol* 2006; 118:949–956.
- Mayorga C, Sanz ML, Gamboa PM, *et al.* In vitro diagnosis of immediate allergic reactions to drugs: an update. *J Investig Allergol Clin Immunol* 2010; 20:103–109.
- Gómez E, Blanca-Lopez N, Torres MJ, *et al.* Immunoglobulin E-mediated immediate allergic reactions to dipyrone: value of basophil activation test in the identification of patients. *Clin Exp Allergy* 2009; 39:1217–1224.
- Blanca-López N, Ariza A, Doña I, *et al.* Hypersensitivity reactions to fluoroquinolones: analysis of the factors involved. *Clin Exp Allergy* 2013; 43:560–567.
- Fernandez TD, Torres MJ, Blanca-López N, *et al.* Negativization rates of IgE radioimmunoassay and basophil activation test in immediate reactions to penicillins. *Allergy* 2009; 64:242–248.
- Woessner KM. Aspirin desensitization for cardiovascular disease. *Curr Opin Allergy Clin Immunol* 2015; 15:314–322.
- Antithrombotic Trialists C. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002; 324:71–86.
- Simons FE, Arduzzo LR, Dimov V, *et al.* World Allergy Organization Anaphylaxis Guidelines: 2013 update of the evidence base. *Int Arch Allergy Immunol* 2013; 162:193–204.
- Aun MV, Blanca M, Garro LS, *et al.* Nonsteroidal anti-inflammatory drugs are major causes of drug-induced anaphylaxis. *J Allergy Clin Immunol* 2014; 2:414–420.