



Advances in hypersensitivity drug reactions

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Adverse reactions to drugs are becoming more complex every day, with more drugs and more mechanisms involved [1]. In this issue of the Journal, six reviews dealing with different major topics on drug hypersensitivity reactions (DHRs) are presented, covering a wide spectrum of DHRs mediated by both immunological and nonimmunological mechanisms. These include immediate reactions such as IgE-mediated reactions or T-cell dependent responses. The reviews also provide possible alternatives for improving the diagnosis of DHR.

The progress in nanoscience and the applications to medicine are increasing, and these can be extended to both diagnosis and therapeutic applications. In the review by Mayorga *et al.* [2], the authors present an overview of the potential applicability to the diagnosis of allergic reactions to betalactams (BLS) by in-vitro testing. A major problem in the diagnosis of IgE-mediated reactions to BLS, which is also extended to other drugs, is the lack of appropriate in-vitro assays for the diagnosis [3].

The group of Perez-Inestrosa *et al.* have been working for more than 10 years on the development of structures, and they mimic the complex hapten carrier, which is formed *in vivo*, in order to develop a sensitive immunoassay that can be applied for the diagnosis of immediate reactions to BLS. For many years, it has been known that human albumin was not the ideal carrier for using in the diagnosis of IgE-mediated reactions and in many instances, different spacers or polylysine gave better results in terms of sensitivity [4,5]. The advantages of using penicilloyl-polylysine have been that a high density of epitope is formed, and it enables the capture of IgE antibodies. With these techniques, the appropriate use of the carrier needs to be controlled in order to not compromise specificity, as in many instances positive values are low [4,6]. All these steps are controlled with the tool of nanomedicine, in which the precise build-up of the nanostructure is known and the conditions for an optimal assay can be controlled [7]. At least from the theoretical point of view, these are major advantages.

The article by Torres *et al.* [8] deals with accelerated drug reactions. This term is still used and it is more related to the time of appearance of the

reactions than with the mechanism/mechanisms involved. Accelerated reactions constitute a major issue in drug allergy as they were originally described [3]. In the classical literature, accelerated drug reactions are considered by some groups as IgE-mediated reactions, although this has never been proved [9].

The temporal association between drug intake and appearance of symptoms in hypersensitivity reactions to BLS indicates that those reactions greater than one hour after drug intake are likely to be T-cell-dependent responses [10]. The first proposal for differentiating was made by our group dividing the reactions between immediate and non-immediate [10].

One major problem is that this classification cannot be applied to other drugs such as NSAIDs, in which both cross-intolerant and selective responders may develop urticarial reactions several hours after drug intake [11,12].

The same happens with other drugs such as ibuprofens, diclofenac and other NSAIDs. It is clear that with some drugs, it is possible that within time intervals of between one and six hours an IgE-mediated reaction can occur. This is the case of pirazolones [12,13]. In cases with less than one hour, T-cell response is a matter of debate but in a study carried out by Torres *et al.* [13], it was shown that in those cases with negative skin test and RAST those cases who became positive by challenge at higher doses required a larger time interval approaching one hour than those with more severe reactions. In another study published by Gomez *et al.* [14], it has been shown that in accelerated reactions to amoxicillin, a T-cell effector mechanism is implicated.

Heparins and related anticoagulants are widely used for the treatment or prevention of thrombosis and can either be used as short-term period treatment or prolonged over time. In the article by

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Gonzalez-Delgado and Fernandez [15], an updated review is presented concerning both high and low-molecular weight heparins and novel oral anticoagulants. In most instances heparins may induce local delayed responses [16], whereas in some instances severe immediate reactions [15] or thrombocytopenia may occur [17]. Authors do not only provide relevant information on the mechanisms involved, but also provide recommendations on the performance of skin testing for both immediate and delayed responses. Also, alternatives for the use of other anticoagulants are provided.

The article by Giavina-Bianchi *et al.* [18] is devoted to the most important medicaments involved in DHRs. This large group of entities can be classified into two major categories and within each of these, further divisions can be made [19,20].

Concerning angioedema, this is a frequent entity induced by drugs particularly NSAIDs. In an important number of cases, classified within the non steroidal antiinflammatory induced urticaria-angioedema (NIUA) group, an important proportion of patients develop angioedema. Within the NSAIDs hypersensitivity reactions, the major number of cases belongs to the cross-intolerance (CI) and thus NIUA is the most frequently recognized entity [21]. On the question of whether NIUA can evolve into non steroidal antiinflammatory exacerbated cutaneous disease (NECD), a study published recently by Doña *et al.* [22] has shown that patients with NIUA did not develop NECD in a follow-up period of 10 years.

There is an agreement in that those cases wherein patients respond to a single NSAID or drug, group patients are selective responders, and those patients who respond to other strong COX-1 inhibitors belong to the CI group [20,23]. However, in both selective and nonselective responders, patients may develop reactions with a time interval longer than 1 h indicating that we are not dealing with IgE-mediated reactions [11].

The concept of single and multiple reactions is also considered in the article and actually, this has become clearer [24]. Single reactors are those responding only to one drug and usually considered the SNIUA group, and multiple reactors are those responding to several NSAIDs [20,24]. However, if in these cases patients tolerate acetylsalicylic acid, they are considered multiple selective reactors, a concept that has been now reported by different authors and that may constitute a new phenotype within the European Network for Drug Allergy classification [24,25].

In cases of mixed reactions, also known in the American literature as blended reactions, it has been reported that both skin and respiratory

manifestations may appear but usually, the dermatological manifestations involved urticaria and angioedema. The association of angiodema with the absence of urticaria and respiratory manifestations has never been reported [21].

Drug hypersensitivity syndrome (DRESS) is an adverse reaction that has deserved considerable attention in the last few years. In this interesting article, the relationship between DRESS and virus and the possible relapse of this entity area are analyzed [26].

Although T-cell reactions to drugs are the less frequent of adverse drug reactions, these are among the most severe. Since late 1980 a considerable degree of research has been performed demonstrating that in T lymphocyte response to drug, the skin is one of the target organs most frequently involved [27]. The reason for this tropism is not known, and the possibility of some erratic metabolism of drug by skin cells can be one explanation [28], but skin involvement occurs even with drugs that do not require biotransformation for inducing a T-cell response like BLS [29].

Within the T-cell response to drugs, four major categories are now recognized and although not all of them fit within this classification, the door is open for including more categories and possibly in the future, this division will be further increased [27,28].

There are a number of drugs that are commonly involved such as anticonvulsants, allopurinol and abacavir, and both the native drug and metabolites can be involved.

The way for the diagnosis of these diseases is that in addition to the classical manifestations, systemic symptoms and liver involvement are required.

Very often, delayed drug responses mimic viral diseases and a differential diagnosis needs to be made [30], but there are instances in which both viral and drugs are required for inducing the symptoms. This entity must be recognized very early in order to establish the treatment.

Although a larger series are needed to prove the value of corticoids, there is some consensus on the agreement of corticoids in the treatment of DRESS. The sequence of events is that after the reaction to a drug, a reactivation of a viral infection may occur that is responsible for the subsequent symptoms that appear in this entity [26].

Concerning the mechanisms possible, a mutation of the genes involved in the enzymes that detoxify the drug leading to drug accumulation may induce the pathological response leading to DRESS. These individuals are more prone to have certain HLA haplotypes, and the virus must also react in order to trigger the complete clinical syndrome. In

some cases but not all, a DRESS is accompanied by a viral exacerbation.

Of particular interest is the fact that these patients may subsequently relapse with response to other drugs that very often are not chemically related. Many patients have sensitized T cells that recognize other drugs that they have taken in the past and in the context of the T cells expansion that they suffer during the DRESS, subsequent responses to other drugs may occur.

Once the entity is resolved, and particularly in those cases in which patients have taken several drugs, it is necessary to identify the culprit in order to avoid future exposures to these drugs and search for safer alternatives.

In line with the T-cell responses, the article by Wang *et al.* [31] deals with the immunopathogenesis and risk factors for allopurinol hypersensitivity.

As occurs with other drugs in addition to the well known genetic markers that can act as predictive for establishing the risk, there are other factors that must be recognized for allopurinol-induced severe T-cell responses. Allopurinol is the classical drug in the event that any exanthematic reaction occurs, and special attention should be paid in order to deal with the possible complications that may appear, particularly such as those cases having the marker HLA-B*58:01 allele. As occurs with other drugs, there is a very high difference among certain populations, with those of Asian ancestry more frequently affected.

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