

EDITORIAL

Clinical & Experimental Allergy

Advances in our understanding of drug hypersensitivity

This editorial discusses the findings of the paper in this issue by J. Yun et al. [10] pp. 1246–1255

K. Brockow^{1,2}

¹Department of Dermatology and Allergology Biederstein, Technische Universität Munich, Munich, Germany and

²Center for Allergy and Environment, Technische Universität und Helmholtz Center Munich, Munich, Germany

Drug hypersensitivity (DH) is a complicated area in allergology with a large variety of clinical reactions, different kinetics, a multitude of structurally different elicitors, and because of our inability to demonstrate an immunological mechanism in most of the cases [1]. We are in the process of realizing that the 'simple' Coombs and Gell classification of immunological reactions are not very helpful to explain the mechanism in the majority of DH reactions [2].

In the 1960–1970s, Levine and other have demonstrated that the hapten hypothesis can be applied for penicillin and other β -lactam allergens [3]. In this concept, low molecular drugs are first covalently bound to carriers in the blood, for example albumin, then processed by dendritic cells and finally presented with major histocompatibility complex (MHC) molecules to T cell receptors where they elicit a specific immune reaction. Unfortunately, this principle could subsequently be demonstrated only for few other non- β -lactam DH reactions. After 1980, some other cases of DH could be explained by bioactivation of a chemically inert drug, through metabolism to more reactive intermediates or haptens [e.g. sulfamethoxazole (SMX) to NO-SMX] [4]. Thus, in DH, not only the parent drug, but also a metabolite can be the immunogenic substance.

To rescue the Coombs and Gell classification for DH, an adaptation with four different subtypes of cellular type IV reactions has been proposed, which is needed to understand why the clinical picture may vary from contact dermatitis to typical maculopapular exanthemas, blisters or pustules [5]. It postulates that T

cells are able to exert different pathologies through their cytokines and effector molecules. Whereas contact dermatitis to drugs is characterized by interferon- γ - and TNF- α -producing T cells, leading to inflammation, the pathology in maculopapular exanthemas is rather dominated by release of IL-5 and IL4/13, resulting in eosinophilia. In bullous exanthemas, cytotoxicity is expressed by T cells positive for cytolytic perforin and granzyme B, and in pustular exanthemas, recruitment of neutrophils follows the production of IL-8.

But in the last decade, there has been a growing body of evidence that DH in many, probably most, reactions is not due to a classical immune reaction as pictured by Coombs and Gell and that we have to leave the concept for a better understanding of underlying mechanisms in DH. For many drugs and *in vitro*-specific T cell lines (TCL), the PI-concept, the 'pharmacological interactions of drugs with immune receptors', appears to be more appropriate, which is the principle that drugs interact with T cell receptors or MHC molecules on antigen-presenting cells, directly and reversibly after non-covalently binding in protein pockets and still provide a signal to stimulate a response [6]. Both are possible, that the drug binds first to MHC molecules and the T cell receptor recognizes the modified HLA molecule and that it might directly associate with T cell receptors.

In this line of thought, recently, genetic association studies have identified strong linkages between DH to some drugs and specific HLA alleles, the strongest being between abacavir hypersensitivity and HLA-B*57:01 status. Recently, one key element of this association has been identified to be an alteration of the MHC-presented self-peptide repertoire following the PI-concept. Abacavir can bind with the F-pocket of the peptide-binding groove of HLA-B*57:01, thereby altering its specificity [7]. In this way, abacavir may guide the selection of new endogenous peptides and may induce a marked alteration in 'immunological self' [8]. A similar mechanism may theoretically also be present in

Correspondence:

Knut Brockow, Department of Dermatology and Allergology Biederstein, Technische Universität Munich, Biedersteiner Strasse 29, D-80802 Munich, Germany.

E-mail: knut.brockow@lrz.tum.de

Cite this as: K. Brockow, *Clinical & Experimental Allergy*, 2013 (43) 1200–1201.

allopurinol hypersensitivity, which is strongly linked to HLA-B*58:01 status [9].

With this background, the study by Yun et al. [10] adds several insights to the pathomechanism of DH to allopurinol. Allopurinol is among the top 10 elicitors for DH reactions and particularly prominent in inducing severe cutaneous adverse reactions (SCARs, such as toxic epidermal necrolysis, Stevens–Johnson syndrome). This retrospective/prospective clinico-experimental study examined *in vitro* responses of T cells from patients with allopurinol hypersensitivity reactions as determined by positive history and compatible clinical picture as well as from HLA-B*58:01-positive and negative controls. Increasing concentrations of allopurinol and its metabolite oxypurinol were given in the lymphocyte transformation test (LTT) and to TCL isolated from the peripheral blood mononuclear cells (PBMCs). It showed that (i) 46% of patients had positive LTTs to oxypurinol, but only one patient (4%) had a positive LTT to allopurinol, (ii) that from PBMCs of HLA-B*58:01-positive naïve non-allopurinol-exposed donors more TCL with higher avidity could be generated than from HLA-B*58:01-negative donors and (iii) that the drug concentration influenced the induction of TCL and the avidity of these cells.

Firstly, most patients with allopurinol hypersensitivity had an immunological response not to the parent drug allopurinol, but to its metabolite oxypurinol [10]. The immunogenicity *per se* appeared not different between allopurinol and oxypurinol. No allopurinol metabolism could be demonstrated in PBMCs and cell lines. There was no cross-reactivity between allopurinol- and oxypurinol-specific TCL. Thus, it was concluded that the predominance of oxypurinol-specific lymphocyte responses in patients with allopurinol hypersensitivity should be

rather explained by the rapid conversion of allopurinol to oxypurinol *in vivo*.

Secondly, a positive HLA-B*58:01 status is a risk factor for allopurinol-induced SCARs [9] and in the present study also for the generation of cytotoxic T cells [10]. This study is the first one that shows that in allopurinol hypersensitivity, the HLA status is important for a drug-specific T cell response *in vitro* and may explain its relevance *in vivo*. Further studies have to clarify on how the HLA type influences the induction of drug-specific T cells.

Thirdly, in allopurinol DH, high drug concentrations were important to induce TCL and influence functional avidity of cytotoxic T cells [10]. This finding may explain the clinical observation that patients with SCARs were treated with higher concentrations of allopurinol in comparison with tolerant patients and that the former mostly had renal insufficiency, which might have further increased allopurinol concentrations [11, 12]. This example shows that dose independency in DH is no prerequisite, but has to be further studied.

In conclusion, the study presented in this issue of *Clinical & Experimental Allergy* shows that DH may be drug-specific and sometimes metabolite-specific, may be influenced by HLA alleles and appears not to be dose-independent [10]. In general, it demonstrates that if we want to understand DH, we have to be open-minded and should rather search for mechanistic explanations of clinical observations than clinging to old beliefs.

Conflict of Interest: The authors declare no conflict of interest.

References

- Demoly P, Adkinson N, Brockow K *et al.* International Consensus (ICON) on Drug Allergy. *Allergy* 2013. [In press].
- Gell P, Coombs R. The classification of allergic reactions underlying disease. In: Gell P, Coombs R, eds. *Clinical aspects of immunology*. Oxford: Blackwell Science, 1963:217–37.
- Levine B, Ovary Z. Studies on the mechanism of the formation of the penicillin antigen. *J Exp Med* 1961; 114:875–904.
- Castrejon JL, Berry N, El-Ghaiesh S *et al.* Stimulation of human T cells with sulfonamides and sulfonamide metabolites. *J Allergy Clin Immunol* 2010; 125:411–8.
- Pichler WJ. Drug hypersensitivity reactions: classification and relationship to T-cell activation. In: Pichler WJ, ed. *Drug hypersensitivity*. Basel: Karger, 2007:168–89.
- Pichler WJ. Pharmacological interaction of drugs with antigen-specific immune receptors: the p-i concept. *Curr Opin Allergy Clin Immunol* 2002; 2:301–5.
- Ostrov DA, Grant BJ, Pompeu YA *et al.* Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire. *Proc Natl Acad Sci USA* 2012; 109:9959–64.
- Illing PT, Vivian JP, Dudek NL *et al.* Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. *Nature* 2012; 486:554–8.
- Phillips EJ, Chung WH, Mockenhaupt M, Roujeau JC, Mallal SA. Drug hypersensitivity: pharmacogenetics and clinical syndromes. *J Allergy Clin Immunol* 2011; 127:S60–6.
- Yun J, Mattsson J, Schnyder K *et al.* Allopurinol hypersensitivity is primarily mediated by dose-dependent oxypurinol-specific T cell response. *Clin Exp Allergy* 2013; 43:1246–55.
- Stamp LK, Taylor WJ, Jones PB *et al.* Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. *Arthritis Rheum* 2012; 64:2529–36.
- Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. *Am J Med* 1984; 76:47–56.