

Immediate allergy from valacyclovir

D. G. Ebo, C. H. Britts, L. S. De Clerck, W. J. Stevens*

Key words: acyclovir; allergy; basophil; blot; valacyclovir.

A 50-year-old woman was referred because of general malaise, diffuse pruritus, angio-oedema of hands and feet and lowered consciousness and faintness within 5 min of intake of a tablet of 500 mg valacyclovir (Zelitrex®; GSK, Genval, Belgium) for genital herpes simplex. History revealed no prior allergies.

Flow cytometric analysis (FACScan; BD, Immunocytometry Systems, San Jose, CA, USA) of activated basophils was performed using quadruple labelling with Alexa 448-coupled anti-IgE (Sigma-Aldrich, Chemic GmBH, Steinheim, Germany), anti-phospho-p38 MAPK (T180/Y182) conjugated with Alexa Fluor 647 (BD Biosciences), anti-CD203c (kindly provided by HJ Bühring, Department of Internal medicine, University of Tübingen, Germany) and phycoerythrin-conjugated anti-CD63 antibodies [Pharmingen; BD Biosciences, Erembodegem, Belgium; for details: (1)]. The test included a negative control (stimulation buffer), a positive control (anti-IgE; Pharmingen) and stimulation with acyclovir (Zovirax®; GSK, dilution 1 up to 10^3 µg/ml). The test was also performed in a healthy control individual tolerant for acyclovir. Upon challenge with acyclovir, basophils of the patient showed a manifest dose-dependent phosphorylation of p38 MAPK from 0% to 78% and up-regulated CD63 and

CD203c expression from 0% to 43% and 8% to 47%, respectively (Fig. 1). Phosphorylation of p38 MAPK and expression of CD63 and CD203c on basophils from the control individual remained unchanged.

A lymphocyte transformation test (LTT) with acyclovir assessed by the incorporation of [methyl- ^{3} H] thymidine (2) was borderline with a stimulation index (SI), i.e. counts per minute (cpm) of the acyclovir-challenged lymphocytes divided by the cpm cultured with serum-free medium of 2.1 for two consecutive stimulation concentrations of 10 and 100 µg/ml (normal < 2). In the control individual, LTT with acyclovir was negative (SI > 1.6).

Skin prick tests for acyclovir were positive in the patient with a wheal and flare reaction of 5/27 mm for a 10^{-3} dilution but negative in an acyclovir-tolerant control individual (up to neat solution). There is no serological assay for acyclovir-specific IgE that is readily available.

Valacyclovir is the L-valine ester of acyclovir. After oral administration, valacyclovir is rapidly absorbed and extensively metabolized by gut hydroxylases into acyclovir and the essential amino acid L-valine (3). The mode of

action and spectrum of anti-viral activity of valacyclovir are thus identical to acyclovir (4). In contrast to valacyclovir, acyclovir is available in a parenteral (intravenous) formulation that can be readily applied for *in vitro* and *in vivo* allergy-testing.

Acyclovir and valacyclovir are considered effective and safe drugs (4, 5) and severe related immunologic adverse events remain anecdotal. However, systemic reactions, such as urticaria, angio-oedema and wide-spread erythematous dermatoses have been described (6–8). Note that several patients with systemic reactions had already presented an allergic contact dermatitis to topical application of acyclovir and that on several occasions cross-reactivity with famciclovir that also contains a 2-aminopurine nucleus has been reported (7, 9, 10). Foscarnet and cidofovir do not contain that core, and might, therefore be considered as potential alternative antiviral drugs.

We present a patient in whom the temporal relationship between intake and symptoms and results of additional tests are highly indicative of a valacyclovir-related adverse event. Finally, our results endorse the basophil activation test (BAT) to be a potential additional tool to diagnose drug allergy [for review: (11)]

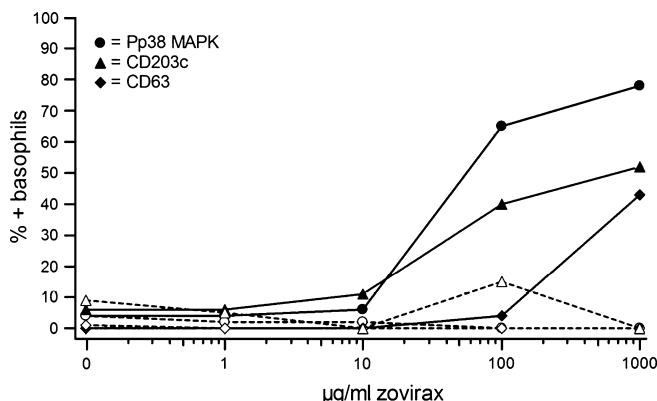


Figure 1. Percentages of CD63, CD203c and phosphorylated p38 MAPK positive basophils in the patient (closed symbols) and an acyclovir-tolerant control individual (open symbols).

and phosphorylated p38 MAPK to constitute a novel read-out (1).

The authors would like to thank Ms Christel Mertens for her skilful technical assistance and Hans-Jörg Bühring (Department of Internal Medicine, Division of Haematology, Immunology and Oncology, University of Tübingen, Germany) for kindly providing the CD203c antibodies.

*Department of Immunology – Allergology – Rheumatology
University of Antwerp
Campus Drie Eiken T401
Universiteitsplein 1
B 2610 Antwerpen
Belgium
Tel.: ++ 32 (0) 3 8202595
Fax: ++ 32 (0) 3 8202655
E-mail: immuno@ua.ac.be

Accepted for publication 8 February 2008
Allergy 2008; 63:941–942

© 2008 The Authors

Journal compilation © 2008 Blackwell
Munksgaard

DOI: 10.1111/j.1398-9995.2008.01700.x

References

1. Ebo DG, Dombrecht EJ, Bridts CH, Aerts NE, de Clerck LS, Stevens WJ. Combined analysis of intracellular signalling and immunophenotype of human peripheral blood basophils by flow cytometry: a proof of concept. *Clin Exp Allergy* 2007;**37**: 1668–1675.
2. Ebo DG, Stevens WJ, Bridts CH, de Clerck LS. Latex-specific IgE, skin testing, and lymphocyte transformation to latex in latex allergy. *J Allergy Clin Immunol* 1997;**100**:618–623.
3. Soul-Lawton J, Seaber E, On N, Wootton R, Rolan P, Posner J. Absolute bioavailability and metabolic disposition of valaciclovir, the L-valyl ester of acyclovir, following oral administration to humans. *Antimicrob Agents Chemother* 1995;**39**:2759–2764.
4. Acosta EP, Fletcher CV. Valaciclovir. *Ann Pharmacother* 1997;**31**:185–191.
5. Brantley JS, Hicks L, Sra K, Tying SK. Valaciclovir for the treatment of genital herpes. *Expert Rev Anti Infect Ther* 2006;**4**:367–376.
6. Henry RE, Wegmann JA, Hartle JE, Christopher GW. Successful oral acyclovir desensitization. *Ann Allergy* 1993;**70**:386–388.
7. Lammintausta K, Makela L, Kalimo K. Rapid systemic valaciclovir reaction subsequent to aciclovir contact allergy. *Contact Dermatitis* 2001;**45**:181.
8. Vernassiere C, Barbaud A, Trechot PH, Weber-Muller F, Schmutz JL. Systemic acyclovir reaction subsequent to acyclovir contact allergy: which systemic antiviral drug should then be used? *Contact Dermatitis* 2003;**49**:155–157.
9. Bayrou O, Gaouar H, Leynadier F. Famciclovir as a possible alternative treatment in some cases of allergy to acyclovir. *Contact Dermatitis* 2000;**42**:42.
10. Khunda A, Kawsar M, Parkin JM, Forster GE. Successful use of valciclovir in a case of recurrent urticaria associated with genital herpes. *Sex Transm Infect* 2002;**78**:468.
11. Ebo DG, Sainte-Laudy J, Bridts CH, Mertens CH, Hagendorens MM, Schuerwegh AJ et al. Flow-assisted allergy diagnosis: current applications and future perspectives. *Allergy* 2006;**61**:1028–1039.

The secretory tailpiece isoform of IgE is not associated with Allergy

A. Aslam*, R. J. Lewis, A. Wheatley, R. J. Pleass, I. Sayers

Key words: atopy; hayfever; IgE; IgE tailpiece.

Atopy, an exaggerated IgE-mediated immune response, is a common feature in many inflammatory diseases, including bronchial asthma and allergic rhinitis (hayfever). Type-I hypersensitivity reactions underlying all atopic conditions and indicators, such as positive skin prick tests to common environmental allergens, correlate well with increased IgE levels in serum or plasma (1, 2). Tailpiece (IgE-tp) is a novel secreted isoform of IgE, formed by alternative splicing of the ϵ gene locus, whose precise role in inflammation is unknown (3, 4). Our preliminary study herein has for the first time attempted to

address the role of IgE-tp in the inflammatory process. Using indirect sandwich ELISAs specific for either IgE-tp or total IgE, we have investigated their levels in plasma from atopic and non-atopic subjects.

Plasma was obtained from three cohorts ($n = 80, 33$ and 34 , respectively). These subjects were originally recruited as families with two siblings with doctor-diagnosed asthma (5). In the current analyses, cohort 1 represents the parents (mean age = 42.7 ± 10.1), cohort 2 asthma sibling A (mean age = 15.3 ± 9.2) and cohort 3 asthma sibling B (mean age = 13.7 ± 9.6). For quantifying IgE-tp and total IgE, ELISA plates were coated with a tp-specific mAb (367) and an anti- $\epsilon\epsilon 2$ mAb (4.15), respectively. Wells were then incubated with plasma preceded by incubation with a polyclonal anti-human IgE-Fc ϵ antibody (Serotec)-conjugated to HRP. IgE levels were compared to atopy data (as assessed by subjects suffering from hayfever (questionnaire) or with positive skin prick tests to common allergens (e.g. Derp1, Feld1). Total IgE levels were significantly increased in atopic subjects when compared with control subjects for all the three cohorts (Fig. 1A and C). This was not the case with IgE-tp, with similar levels observed in all subjects (Fig. 1B and D). Measurements of lung function [including forced expiratory volume in 1 s (FEV₁), FEV₁/forced vital capacity (FVC) ratio and bronchial hyper-responsiveness (BHR)] were also compared with the IgE levels for cohorts 2 and 3; however, no significant correlations were observed with either isoform (data not shown). Lung function data were not available for cohort 1.

Our preliminary studies have confirmed the previous observations that total IgE in plasma or serum samples from atopic subjects is elevated (1, 2). This was not, however, accompanied with an increase in IgE-tp, suggesting that the Th2-type inflammatory responses observed in allergy occur through other isoforms of IgE (3, 4). Though lung function data did not correlate with total IgE levels, there were trends for differences in bronchial hyper-responsiveness in cohorts 2 and 3. Higher numbers of subjects in each group may well elicit a better relationship between

Levels of IgE tailpiece isoform are unchanged in atopy and may not be a major determinant of allergic inflammation.