

## Ethical disclosures

**Protection of human subjects and animals in research.** The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

**Patients' data protection.** The authors declare that no patient data appear in this article.

**Right to privacy and informed consent.** The authors have obtained the informed consent of the patient mentioned in the article. The author for correspondence is in possession of this document.

## References

1. Liu A, Fanning L, Chong H, Fernandez J, Sloane D, Serra MS, et al. Desensitization regimens for drug allergy: state of the art in the 21st century. *Clin Exp Allergy*. 2011;41:1679–89.
2. Peroni DG, Pescolliderung L, Piacentini GL, Cassar W, Boner AL. Effective desensitization to imiglucerase in a patient with type I gaucher disease. *J Pediatr*. 2009;155:940–1.
3. Lachman RH. Enzyme replacement therapy for lysosomal storage diseases. *Curr Opin Pediatr*. 2011;23:588–93.
4. Nicolino M, Byrne B, Wraith JE, Leslie N, Mandel H, Freyer DR, et al. Clinical outcomes after long-term treatment with alglucosidase alfa in infants and children with advanced Pompe disease. *Genet Med*. 2009;11:210–9.
5. Oba-Shinjo SM, da Silva R, Andrade FG, Palmer RE, Pomponio RJ, Ciociola KMS, et al. Pompe disease in a Brazilian series: clinical and molecular analyses with identification of nine new mutations. *J Neurol*. 2009;256:1881–90.
6. Lipinski SE, Lipinski MJ, Burnette A, Platts-Mills TA, Wilson WG. Desensitization of an adult patient with Pompe disease and a history of anaphylaxis to alglucosidase alfa. *Mol Genet Metab*. 2009;98:319–21.
7. El-Gharbawy AH, Mackey J, DeArmedy S, Westby G, Grinnell SG, Malovrh P, et al. An individually, modified approach to desensitize infants and young children with Pompe disease, and significant reactions to alglucosidase alfa infusions. *Mol Genet Metab*. 2011;104:118–22.
8. Çelik G, Pichler WJ, Adkinson Jr NF. Drug allergy. In: Adkinson Jr NF, editor. *Middleton's allergy principles & practice*. 7th ed. Philadelphia: Mosby; 2009. p. 1205–26.
9. Cernades JR, Brocrou K, Romano A, Aberer W, Torres MJ, Bircher A, et al. General considerations on rapid desensitization for drug hypersensitivity: a consensus statement. *Allergy*. 2010;65:1357–66.
10. Kishnani PS, Goldenberg PC, DeArmedy SH, Heller J, Benjamin D, Young S, et al. Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants. *Mol Genet Metab*. 2010;99:26–33.
11. Messinger YH, Mendelsohn NJ, Rhead W, Dimmock D, Herskovitz E, Champion M, et al. Successful immune tolerance induction to enzyme replacement therapy in CRIM-negative infantile Pompe disease. *Genet Med*. 2012;14:135–42.
12. Rohrbach M, Klein A, Köhli-Wiesner A, Veraguth D, Scheer I, Balmer C, et al. CRIM-negative infantile Pompe disease: 42-month treatment outcome. *J Inher Metab Dis*. 2010;33:751–7.

I.H.E. Karagol<sup>a,\*</sup>, A. Bakirtas<sup>a</sup>, O. Yilmaz<sup>a</sup>, E. Topal<sup>a</sup>, A. Kucukcongar<sup>b</sup>, F.S. Ezgu<sup>b</sup>, M.S. Demirsoy<sup>a</sup>, I. Turktaş<sup>a</sup>

<sup>a</sup>Department of Pediatric Asthma and Allergy, Gazi University Faculty of Medicine, Ankara, Turkey

<sup>b</sup>Department of Pediatric Metabolism, Gazi University Faculty of Medicine, Ankara, Turkey

\*Corresponding author.

E-mail address: theilbilge@yahoo.com.au (I.H.E. Karagol).

<http://dx.doi.org/10.1016/j.aller.2013.02.012>

## Drug allergy in haematopoietic stem cell transplantation

To the Editor,

Cutaneous eruptions emerging shortly after haematopoietic stem cell transplantation (HSCT) pose a particular diagnostic challenge for oncologists and consulting dermatologists. Many distinct dermatologic entities occur early in the post-HSCT period, including acute graft-versus-host disease (GVHD), viral exanthema, eruption of lymphocyte recovery, erythema multiforme, toxic erythema of chemotherapy and morbilliform drug eruptions.<sup>1–3</sup> These diseases are often clinically indistinguishable, and their similar histopathological features may preclude a definitive diagnosis, leading to unfavourable patient outcomes.

Exposure to medications that were previously allergenic to either the stem cell donor or recipient may have implications for the post-transplant course of the HSCT patient.<sup>3</sup> The interplay between donor and recipient drug allergy, and its influence on HSCT outcomes has yet to be studied in a systematic manner. It has been suggested that allogeneic HSCT patients can be safely exposed to medications

to which they were previously allergic,<sup>4</sup> but there are no reports in the literature addressing the consequences of post-HSCT patient exposure to drugs that caused an allergic response in donors. Furthermore, the potential relationship between drug allergy and other cutaneous complications in HSCT patients, such as GVHD, has not been examined.

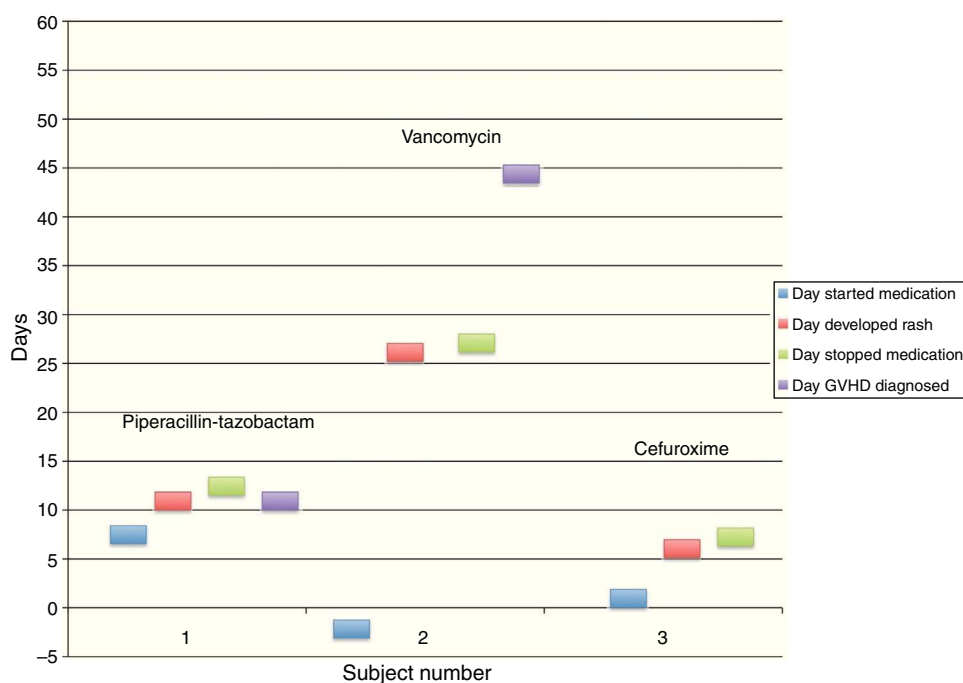
Our goal was to determine how many post-HSCT patients received medications that they or their donors were allergic to, and characterise any ensuing reactions (cutaneous or otherwise) that occurred. We additionally hypothesized the incidence of acute GVHD to be greater in HSCT recipients that received these medications post-transplant, assuming drug allergy as a contributor to immune activation.

A retrospective chart review was conducted to identify all first-time adult allogeneic HSCT recipients in the Northwestern Memorial Hospital system in 2009. Information collected included demographic and disease-specific information, as well as documented allergies of both stem cell donors and recipients. Medication exposures during the first 60 days post-transplant were recorded and cross-referenced with drug allergies. Incidence and diagnosis of all skin eruptions during this time were also recorded, including acute GVHD.

**Table 1** Characteristics of subjects exposed to medications with prior hypersensitivity.

| Subject | Age | Sex | Race      | Disease | Type of HSCT | Donor allergies | Recipient allergies | Medication received     | Acute GVHD |
|---------|-----|-----|-----------|---------|--------------|-----------------|---------------------|-------------------------|------------|
| 1       | 53  | F   | Caucasian | MDS     | MUD          | None            | Penicillin          | Piperacillin-tazobactam | Yes        |
| 2       | 55  | F   | Caucasian | ALL     | MSD          | None            | Vancomycin          | Vancomycin              | Yes        |
| 3       | 60  | M   | Caucasian | AML     | Mini-MUD     | Cefaclor        | Sulfa               | Cefuroxime              | No         |

MUD, matched unrelated donor Mini; MUD, non-myeloablative matched unrelated donor; MSD, matched sibling donor; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

**Figure 1** Timeline of HSCT subjects.

We found 59 first-time adult allogeneic HSCT patients in 2009. Two patients were exposed to previously documented allergenic medications (subject 1: piperacillin-tazobactam; subject 2: vancomycin), and both patients developed acute GVHD with cutaneous involvement (Table 1). One additional patient (subject 3) received cefaclor post-HSCT without subsequent development of GVHD, despite the fact that the stem cell donor was allergic to cefuroxime, also a cephalosporin (Fig. 1).

Subject 1 developed a morbilliform eruption on the arms on post-HSCT day +14, four days after starting piperacillin-tazobactam. Diarrhoea was reported concurrently with the skin eruption, while serum total bilirubin remained within normal limits. While the patient was diagnosed clinically with acute GVHD of the skin and gut, the dermatology service was not consulted, and no skin biopsy was performed.

Subject 2 developed an erythematous and petechial eruption on the dorsal and plantar feet on post-HSCT day +30, 31 days after starting vancomycin. Skin biopsy was consistent with grade II GVHD, and no diarrhoea or abnormal liver function tests were present.

Subject 3 was exposed to cefuroxime on post-HSCT day +2; the donor had a documented allergy to cefaclor, another second-generation cephalosporin with similar chemical structure.

The patient subsequently developed an episode of "hives" on the left chest and jaw five days later, accompanied by mild diarrhoea and an increased serum total bilirubin of 1.7 mg/dL. Dermatology did not evaluate the patient and GVHD was never diagnosed. Cefuroxime was discontinued without any subsequent cutaneous events.

We observed the development of acute GVHD in 2/2 patients exposed to prior allergenic medications following myeloablative allogeneic HSCT. An urticarial reaction was also observed in a non-myeloablative allogeneic HSCT recipient after receipt of a structurally similar donor-allergenic medication; though we cannot entirely exclude the possibility that this urticarial reaction did not represent acute GVHD, as no dermatologic consultation or skin biopsy was provided. The context for prescribing these medications in all three cases (risk-benefit analysis versus clerical oversight) is unknown. Under ideal circumstances, medications administered post-HSCT would exclude agents to which the recipient or donor previously demonstrated a hypersensitivity reaction.

There are limitations to the conclusions drawn from these observations, most notably the small sample size and the high incidence of acute GVHD following allogeneic HSCT.

Additionally, this was a retrospective review and only one of the three subjects was evaluated by a consulting dermatologist. While oncologists and other health care providers may routinely evaluate skin eruptions in HSCT patients, clinical assessment by an experienced dermatologist remains the standard of care at most centres.

Transfer of atopy and contact allergy from donor to recipient following bone marrow transplantation has been described,<sup>5,6</sup> and the presumed mechanism is via adoptive transfer of donor memory T cells to a newly reconstituted recipient immune system. There is also evidence of allergen-specific IgE-mediated hypersensitivity passed from donors to recipients of stem cell transplantation via B cell transfer.<sup>7</sup> Thus, HSCT may predispose certain patients to the development of atopy or new environmental and medication allergies.

Whether drug allergies persist in patients undergoing non-myeloablative HSCT or in HSCT recipients with less than total donor chimerism is unknown, and there are no published data on drug allergy persistence following HSCT.

This observational study suggests that there may be an important immunologic component of drug allergy that may influence the development of acute GVHD. A prospective multi-centred trial with dermatologist evaluation of skin eruptions in HSCT patients would help to further elucidate both the role of medication allergy as a risk factor for GVHD and the presence or absence of drug allergy following transplant.

## Ethical disclosures

**Protection of human subjects.** The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

**Confidentiality of data.** The authors declare that no patient data appears in this article.

**Right to privacy and informed consent.** The authors declare that no patient data appears in this article.

## Conflict of interest

The authors have no conflict of interest to declare.

## Acknowledgements

This research was supported in part by NIH grants 3R01CA125077-01A1 (D.P.W.) and 3R01CA125077-01A1S1 (D.P.W.). Dr. Cotliar is supported by a career development award from the Dermatology Foundation.

## References

1. Horn TD, Redd JV, Karp JE, Beschoner WE, Burke PJ, Hood AF. Cutaneous eruptions of lymphocyte recovery. *Arch Dermatol.* 1989;125:1512–7.
2. Bolognia JL, Cooper DL, Glusac EJ. Toxic erythema of chemotherapy: a useful clinical term. *J Am Acad Dermatol.* 2008;59:524–9.
3. Conlon JD, Dauenhauer M, Tonkovic-Capin V, Talano J, Margolis D, Drolet BA, et al. Voriconazole-induced blistering in the setting of graft versus host disease: a report of 2 patients. *J Am Acad Dermatol.* 2008;58:484–7 [Case Reports].
4. Au WY. Relevance of drug allergy history after allogeneic hemopoietic stem cell transplantation. *Bone Marrow Transplant.* 2007;40:179–80 [Research Support, Non-U.S. Gov't].
5. Bellou A, Kanny G, Fremont S, Moneret-Vautrin DA. Transfer of atopy following bone marrow transplantation. *Ann Allergy Asthma Immunol.* 1997;78:513–6 [Case Reports].
6. Olaguibel J, Almodovar A, Giner A, Serrano G, Martinez J, Basomba A. Passive transfer of contact sensitivity to colophony as a complication of an allogeneic bone-marrow transplant. *Contact Dermatitis.* 1989;20:182–4 [Case Reports].
7. Agosti JM, Sprenger JD, Lum LG, Witherspoon RP, Fisher LD, Storb R, et al. Transfer of allergen-specific IgE-mediated hypersensitivity with allogeneic bone marrow transplantation. *N Engl J Med.* 1988;319:1623–8 [Research Support, U.S. Gov't, P.H.S.].

J. Gordon<sup>a</sup>, E. Damstetter<sup>a</sup>, B. Nardone<sup>a</sup>, J. Mehta<sup>b,c</sup>, D.P. West<sup>a,c</sup>, J. Cotliar<sup>a,c,\*</sup>

<sup>a</sup> Department of Dermatology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

<sup>b</sup> Department of Medicine, Division of Hematology/Oncology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

<sup>c</sup> Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

\*Corresponding author.

E-mail address: [j-cotliar@northwestern.edu](mailto:j-cotliar@northwestern.edu) (J. Cotliar).

<http://dx.doi.org/10.1016/j.aller.2013.01.006>

## Adverse reaction after administration of progesterone

To the Editor,

Progesterone is a hormone that inhibits contractions of uterus, facilitates the implantation of the embryo and maintains the pregnancy. In the pregnant uterus, progesterone plays a role in controlling the development of endometrial receptivity and in the processes of an angiogenesis and trophoblast invasion.<sup>1,2</sup>

An inadequate secretion of progestogens in the early phases of pregnancy seems to be related to many cases of miscarriage. Therefore, a progesterone supplementation therapy has been used to prevent spontaneous pregnancy loss and also to prevent the preterm birth.<sup>3</sup> There is some evidence, too, to indicate that women with idiopathic recurrent miscarriage may benefit from the immunomodulatory properties of progesterone in early pregnancy.<sup>4</sup> In some cases vaginal progesterone therapy has been demonstrated effective to reduce the risk of miscarriage and without important side effects.<sup>5</sup> However, until now there has been