

Transferability and curability of allergic disease by allogeneic hematopoietic stem cell transplantation

To the Editor,

Transfer of allergic diseases after allogeneic hematopoietic stem cell transplantation (HSCT) is described by several reports of patients who developed allergic diseases after HSCT.¹ It is generally thought that this is due to the adoptive transfer of allergen-specific B and T cells.² An alternative explanation for the acquisition of allergy is the transfer of lymphoid and myeloid cell precursors which have a tendency to differentiate into allergy prone cells such as T and B lymphocytes for their allergen-specific functions, dendritic cells and macrophages for their antigen-presenting cell property or mast cells and basophils for their IgE cross-linking-dependent effector cell function.³ Subsequently, cases of allergy transfer has also been described after solid organ transplantation.⁴ On the other hand, there are few reports of cure or remission of allergic diseases after HSCT from a nonallergic donor,¹ which is thought to be due to the transfer of allergy prone lymphoid and myeloid cells for healthy cells. However, the likelihood of curability is still unknown as there are few available data.

In this prospective case control study, donors and recipients of HSCT were evaluated for allergy and allergic diseases before HSCT and recipients were re-tested following the procedure. The main objective was to observe the allergic status in the case of atopic recipients and their nonatopic donors.

Nineteen subjects with a diagnosis of hematologic malignancy who were being prepared for HSCT in the Hematology Department of Ankara University were included in the study. Ethical permission was obtained from the ethical board of Ankara University. Their identical siblings (n:19) were also included as donors for atopy and allergy evaluation. The recipients and their donors replied the European Community Respiratory Health Survey (ECRHS), Turkish translation.⁵ Skin prick tests (SPT) were performed before HSCT with common inhalant allergens (house dust mites, storage mites, grass-tree-weed pollens, molds, cat, dog and latex; ALK) and a mean wheal diameter of 3 mm or greater was considered as positive. In all patients, pre-HSCT SPTs were performed, before the initial immunosuppressive treatment. Re-testing and survey were performed in the post-HSCT period (mean: 27.71, min-max: 12-44 months) in available recipients after the termination of pharmacologic immunosuppression. Minimum time between immunosuppressive treatment termination and post-HSCT SPTs was 11 months.

Demographic features of the study group are shown in Table 1. In the post-HSCT period; six recipients died and six were

lost to follow-up. Re-testing and the survey could be performed in the post-HSCT period in six recipients. Among them; four patients were nonallergic before HSCT and continued to be SPT negative following transplantation from nonallergic donors (patient number 3-5, 7). However, atopic status of the three recipients changed following HSCT. Patient number 6 was nonatopic and had no symptoms of allergy at baseline. However, SPTs became positive for house dust mites and tree pollens following transplantation from an atopic donor. She did not develop allergic symptoms during the follow-up. Two recipients were allergic before HSCT, but tests became negative following transplantation from nonallergic donors (patient number 1-2). Patient

TABLE 1 Patient characteristics

	Recipient	Donor
Number (n)	19	19 (HLA identical, sibling)
Gender m/f (n)	10/9	8/11
Age	38.37 ± 12.7	39.42 ± 11.5
Pre transplantation n (%)		
Sensitization	3 (15.7)	1 (5.2)
Grass pollens	1 (5.2)	1 (5.2)
Tree pollens	—	—
HDM	2 (10.5)	1 (5.2)
Storage mites	—	1 (5.2)
Allergy symptoms	2 (10.5)	1 (5.2)
Rhinitis	1 (5.2)	1 (5.2)
Rhinokonjonctivitis	1 (5.2)	—
Asthma	—	—
Post-transplantation n (%)		
Exitus	6 (31.5)	
Lost to follow-up	6 (31.5)	
Sensitization	1 (5.2)	
Grass pollens	—	
Tree pollens	1 (5.2)	
HDM	1 (5.2)	
Storage mites	1 (5.2)	
Allergy symptoms	—	

Abbreviation: HDM, house dust mite.

number 1 had been suffering from seasonal rhinoconjunctivitis for 3 years and SPTs showed sensitivity to grass and artemisia pollens in the pre-HSCT period. SPTs became negative with pollens 25 months after HSCT and she was free of rhinoconjunctivitis symptoms during the two pollen seasons following HSCT. Patient number 2 had sensitivity to *Dermatophagoides pteronyssinus* and tests turned negative after HSCT. He had no symptoms of allergy in pre and post-HSCT periods (Table 2; Table S1). HSCT protocols are given in Table S2.

Hematopoietic stem cell transplantation is a potentially curative treatment and currently expanding its scope from immune deficiencies and malignancies to severe autoimmune and atopic disease. Complete restoration of a functional immune system after HSCT can take months to years.¹ Several reports have shown that allergy can be transferred with HSCT.^{2,3,6} The most likely mechanism of allergy transfer is the passage of hematopoietic cell precursors or mature and memory allergen-specific B and/or T cells. A prospective study reported that allergen-specific IgE transferred from donor to recipient following HSCT frequently persisted.³ It has been argued that the post-transplant diagnosis of allergy in a pre-transplant nonallergic recipient of HSCT from a related allergic donor does not necessarily imply the transfer of allergy. It may be due to the development of new allergies in a genetically predisposed individual.² Similarly, the donor was the brother of the patient, who became atopic following HSCT in our study. As she developed complete chimerism (Tcell 98%, Non-Tcell 99%) post-HSCT, it can be argued that allergen-reactive cells in the patient were fully derived from the donor rather than genetic disposition. A strong additional argument can be based on the allergy profile being different from the donor in this case. In the prospective study in which allergic donors were siblings, approximately 50% rate of acquisition of new allergic sensitization was observed in the recipients at 14-16 years after HSCT.³ It is tempting to explain the mechanisms of this finding by the transfer of allergy prone adaptive immune cells, such as T and B cells from atopic donor to recipient. It is hypothetically possible that T cells that are already biased toward a Th2 phenotype due to genetic and/or environmental factors in the donor were transferred to the recipient causing new sensitizations. In accordance with these findings, our results show that the recipient does not have to become allergic to the same allergen as the donor. Taken together, the data suggest that allergy was transferred from the atopic sibling to the previously nonatopic patient resulting with different sensitivities in this study.

Remission of allergic diseases after HSCT was described in several case reports. The first report was on a patient with sensitivity to multiple aeroallergens and history of anaphylaxis due to latex allergy before transplantation. After HSCT, levels of latex and aeroallergen specific IgE gradually decreased and became undetectable at 14 months and remained negative until the end of follow-up.⁷ Another patient was reported to become eczema free after HSCT until the end of follow-up at 4 years.⁸ Peanut specific IgE levels became undetectable and SPTs for peanut were found negative after HSCT in a peanut allergic patient with eczema and asthma and remained negative during 2 years follow-up.⁹ The mechanism of

TABLE 2 Allergic and clinical evaluation of recipients before and after HSCT

Patients	Donor allergic disease and symptoms	Recipient basal skin prick test positivity	Recipient basal skin prick (grass, artemisia)	Recipient post-HSCT atopy	Recipient post-HSCT symptoms	Recipient post-HSCT allergy symptoms	Time between immunosuppressive treatment discontinuation and post-HSCT SPTs (mo)
1	NA, no symptoms	Atopic (grass, artemisia)	NA	NA	Seasonal rhinoconjunctivitis symptoms ^a	No symptoms in and out of the season after HSCT	11
2	NA, no symptoms	Atopic (der p)	NA	NA	No symptoms	No symptoms	32
3	NA, no symptoms	NA	NA	NA	No symptoms	No symptoms	
4	NA, no symptoms	NA	NA	NA	No symptoms	No symptoms	
5	NA, no symptoms	NA	NA	NA	No symptoms	No symptoms	
6	SPT positive (derp, der f, storage mites, grass) rhinitis symptoms ^b	NA	NA	Atopic (der p, storage mites, alnus, betula, corylus pollen)	No symptoms	No symptoms	16
7	NA, no symptoms	NA	NA	NA	No symptoms	No symptoms	

Abbreviations: Der p, *Dermatophagoides pteronyssinus*; NA, non atopic.

^aSymptoms of rhinitis and conjunctivitis for 3 y, diagnosed as seasonal rhinoconjunctivitis at baseline evaluation, no history of allergen immunotherapy.

^bPerennial symptoms of rhinore and sneezing for 10 y, increase in symptoms during the pollen season, diagnosed as allergic rhinitis before, using antihistamines irregularly, no history of allergen immunotherapy.

disappearance of allergy is suggested to be due to the exchange of allergy prone lymphoid and myeloid cells for healthy donor cells in patients, who outgrow allergic disease after HSCT. The development of complete chimerism in our patients (98% and 99% chimerism, respectively for patients number 1 and 2) supports this mechanism, showing that cells in the patients were fully derived from the donors.

The relationship between allergen-specific responses and immunosuppressive treatment has been a matter of interest regarding the potent immunosuppressive properties of the post-transplantation protocol on specific immune response development. Mostly, it is questioned whether post-transplantation therapy with immunosuppressive drugs account for the cure of allergy in these cases (1). Re-evaluation of their atopic status was made 11 and 36 months after discontinuation of their immunosuppressive medication in our cases. Allergy did not recur after the discontinuation of immunosuppressive drugs. We think that this is a sufficient period for the immunosuppression to disappear.

As a limitation of this study, almost two-thirds of the patients died after HSCT or lost to follow-up. Despite the reduction in sample size, we think the findings of three patients contribute to enhance our knowledge on the potential role of HSCT in transfer or cure of allergy.

In conclusion, our findings contribute to the knowledge on the likelihood of transferability and curability of allergic diseases in patients undergoing allogeneic HSCT. However, many factors including specific and nonspecific external exposures should also be taken into account in the evaluation of allergy development which is based on highly complex mechanisms. To determine the probabilities, large studies including allergic patients and nonallergic donors as well as nonallergic patients and allergic donors with appropriate controls are needed. The clarification of the likelihood of cure will be important for HSCT as a potential therapy for severe allergic disease in the future.

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CONFLICT OF INTEREST

All authors have nothing to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Table S1: History of allergy in the subjects

SUBJECTS	
RECIPIENT NUMBER 1	She had been suffering from seasonal rhinoconjunctivitis symptoms for 3 years and skin prick tests showed sensitivity to grass and artemisia pollens in the pre HSCT period. She was diagnosed as seasonal allergic rhinoconjunctivitis in our clinic during the baseline evaluation. Her skin prick tests became negative to pollens 25 months after HSCT and she was free of rhinoconjunctivitis symptoms during the two pollen seasons following HSCT.
RECIPIENT NUMBER 2	He had sensitivity to <i>Dermatophagoides pteronyssinus</i> (Der p) but he had no symptoms of allergy in pre and post HSCT periods. Tests with Der p turned negative 36 months after HSCT.
RECIPIENT NUMBER 6	She was nonatopic and had no symptoms of allergy at baseline. However, skin prick tests became positive for house dust mites, storage mites and tree pollens following transplantation from an atopic donor. She did not develop clinical allergic symptoms during the 3 year follow up.
DONOR OF NUMBER 6	He was atopic with sensitivity to Der p, Der f, storage mites and grass pollens. He was describing perennial symptoms of rhinorrhea and sneezing for 10 years with an increase in symptoms during the pollen season. He was diagnosed as allergic rhinitis and was using antihistamines irregularly. He did not receive AIT.

Table S2: Hematologic diagnosis, HSCT and pharmacologic treatment in 7 recipient-donor pairs (supplementary)

Patient number	Diagnosis	Stem cell source	Initial treatment*	Immunosuppressive treatment
1	AA	PB+BM	Cy-ATG	CsA/MTX
2	AML	PB	Bu-Cy	CsA/MTX
3	AML	PB	Bu-Cy	CsA/MTX
4	ALL	PB	Cy-TBI	CsA/MTX
5	ALL	PB	Cy-TBI	CsA/MTX
6	AML	PB	Bu-Cy	CsA/MTX
7	AML	PB	Cy/TBI/ATG	CsA/MTX

*began after baseline SPTs

AA Aplastic anemia; AML acute myelogenous leukemia; ALL acute lymphoblastic leukemia

PB Peripheral blood; BM Bone marrow

Cy Cyclophosphamide; Bu Busulfan; TBI total body irradiation; ATG anti-T lymphocyte globulin

CsA cyclosporin; MTX Methotrexate