Re: Association of Programmed Cell Death 1 and Programmed Cell Death 1 Ligand Gene Polymorphisms With Delayed Graft Function and Acute Rejection in Kidney Allograft Recipients

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Dear Editor,

We read with interest the article published in the *Iranian Journal of Kidney Diseases*, entitled "Association of Programmed Cell Death 1 and Programmed Cell Death 1 Ligand Gene Polymorphisms With Delayed Graft Function and Acute Rejection in Kidney Allograft Recipients.[1]" Zolfaghari and colleagues have focused on the association of) single nucleotide polymorphism (SNPs) of the programmed cell death 1 gene (*PDCD1*) and programmed cell death 1 ligands (*PDCD1LG1* and *PDCD1LG2*) with delayed graft function and acute rejection in kidney transplant patients. One of the main mediators of acute kidney allograft rejection as well as graft dysfunction is T lymphocytes, which act as key initiators, mediators, and effectors of the alloimmune response through their stimulatory and inhibitory receptor signaling ("co-signaling").[2-4] Programmed cell death 1 (PD1) and its ligands, trigger the main inhibitory signaling pathways that regulate T cell response and retain peripheral tolerance. Upregulation of *PDCD1* on T cells and *PDCD1LG1* on hematopoietic and nonhematopoietic cells might serve as negative regulatory mechanism to manage the alloimmune response and restrict allospecific T-cell activation and proliferation against the allograft.[5] Numerous SNPs are documented in the genes coding PD1 and its ligands. Since costimulatory molecule function of an individual may be affected by gene polymorphisms, lots of studies have investigated the relationship of *PDCD1* and *PDCD1LG1* genetic variations with the outcome of transplantation. Among the 4 SNPs investigated by Zolfaghari and colleagues,[1] including PD-1.3 (+7146 G>A), PD-1.9 (+7825 C>T), PD-L1(8923 A>C), and PD-L1 (+6777 C>G), a higher frequency of C>T genotype and T allele was found in the recipients suffering from delayed graft function compared to stable graft function group. Also, high frequencies of PD-1.9 (+7625 C>T) genotype and T allele were demonstrated in the patients with delayed graft function and biopsy-proved acute rejection.

The *PDCD1* contains 5 exons: exons 1 to 5 encode leader peptide, extracellular Ig-like domain, transmembrane domain, and 2 intracellular domains, respectively. Until now, more than 30 SNPs have been recognized in the *PDCD1* gene. The PD-1.9 (rs2227982, +7625 C>T) is a C>T single-nucleotide variation located in the exon 5 region of the *PDCD1* gene. The C>T transition in the PD-1.9 SNP replaces valine by alanine.[6] The influence of PD-1.9 SNP on graft outcome has been studied frequently. Iravani-Saadi and colleagues found the significant associations between CC genotype and C allele of PD.1.9 and severe grade of graft-versus-host disease in Iranian patients.[7] Studying the association between costimulatory molecule gene polymorphisms with hepatitis B virus infection in hematopoietic stem cell transplant patients, researchers revealed that C allele of the PD.1.9 was more frequent in hepatitis B virus-infected allogeneic hematopoietic patients experiencing graft-versus-host disease. Also, the frequency of CT genotype and T allele of the PD.1.9 were significantly higher in hepatitis B virus-infected allogeneic hematopoietic stem cell transplant patients suffering from low-grade graft-versus-host disease.[8]

The PD1.3 (rs11568821, +7146 G>A) is located on exon 4. The A allele of this SNP may alter the regulation of gene expression, and thus, it bears a functional significance; it has been shown that patients systemic lupus erythematosus homozygous for PD-1.3 (AA), but not heterozygous for PD-1.3 (AG) have reduced basal and induced *PDCD1*

expression on activated CD4+ T cells. Also, allele A promotes decreased transcriptional activity in transfected Jurkat cells.[6] In studies on the PD-1.3 association with transplantation, Iravani-Saadi and colleagues showed that PD-1.3 was irrelevant to the outcome of bone marrow transplant patients.[7] Although they also studied the association between some costimulatory molecule gene polymorphisms including *PDCD1* with a variety of posthematopoietic stem cell transplantation and viral-related clinical outcomes, no correlation was seen between PD1.3 and the outcomes of active cytomegalovirus infection.[9] The association between cytomegalovirus infection risk after kidney transplantation and PD1.3 SNP was the only allograft study that has previously done on this genetic variation. The researchers found that recipients with the PD-1.3 A allele had a much higher risk of cytomegalovirus infection as compared the ones that lack it.[10] Although some studies investigated the association of other *PDCD1* SNPs with kidney graft outcome,[11] the importance of Zolfaghari and colleagues' work is that, except of another recent study,[12] no other investigations have been performed on the association of PD-1.9 and PD-1.3 gene polymorphisms and kidney transplantation outcome. Niknam and associates showed that PD-1.9 and PD-1.3 SNPs were not different between acute rejected and nonrejected kidney transplants.[12]

The PD-1.3 SNP has been shown to be associated with lupus, rheumatoid factor-negative rheumatoid arthritis, and insulin-dependent diabetes mellitus. That is why it is referred to it as "autoimmune gene," which emphasizes its role in the regulation and function of the immune system.[13] Also, the influence of PD-1.9 on the occurrence of ankylosing spondylitis as well as systemic lupus erythematosus has been determined.[14] Karimi and colleagues showed that PD-1.3 (rs11568821, +7146 G>A) and PD-1.9 (rs2227982, +7625 C>T) had no association with acute rejection or stable graft function in liver transplant patients.[15] Such results are consistent with Zolfaghari and colleagues' observations.[1] In the mentioned article,[15] PD-L1 (8923 A>C), and the PD-L1 (+6777 C/G) association with graft function and acute rejection after kidney transplantation was also examined. However, in Zolfaghari and colleagues' study, SNP frequencies were not significantly different between patients and healthy groups. The PD-L1 (8923 A>C) polymorphism was considered to be related to some autoimmune diseases. The C allele frequency of this SNP was shown to be higher in patients with Graves disease than in controls.[16] Apart from these studies, there are not any investigations explicitly reported the role of PD-L1 (8923 A>C) in autoimmune diseases or graft outcome.

Genotype distribution of another PD-L1 SNP (+6777 C>G) was studied by Wang and colleagues. They found that patients with PD-L1 6777 G had a higher prevalence of rheumatoid nodule compared to those without PD-L1 6777 G.[17] According to the limited transplant studies on these SNPs, Zolfaghari and colleagues' investigation is informing. In their article, none of the genetic variation frequencies are stated to be different between healthy and patients groups. However, comparing the healthy ones, they showed PD-1.9 (+7625 CT) genotype and T allele are significantly more frequent in all patients. Also, a higher frequency of PD-1.9 (+7625 CT) genotype as well as T allele was reported in the patients with delayed graft function compared to those without delayed graft function. Since the interactions between PD1 and its ligand 1 are required for both the induction and maintenance of CD4+ T cell tolerance,[5] it seems that among these thought-out SNPs, PD-1.9 (+7625 CT) genotype and T allele (studied by Zolfaghari and colleagues) is the major one that can alter the PD1/PD1 ligand 1 pathway in regulation of T cells alloimmunity. Such an SNP may reduce the affinity of PD1 to PD ligand 1 and thus increase the possibility of graft rejection through changing intracellular signaling pathway which triggers the processes such as decreased T-cell proliferation, cytokine production and reduced cell survival. However, there is a strong contradicting finding by Niknam and coworkers who showed no association between PD-1.9 and kidney allograft rejection. Resolving such controversy, Zolfaghari and colleagues group should consider a larger sample size to confirm their results.

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REFERENCES

1. Zolfaghari L, Solgi G, Nafar M, et al. Association of programmed cell death 1 and programmed cell death 1 ligand gene polymorphisms with delayed graft function and acute rejection in kidney allograft recipients. Iran J Kidney Dis. 2015;9:138-45.
2. Heeger PS. T-cell allorecognition and transplant rejection: a summary and update. Am J Transplant. 2003;3:525-33.
3. Issa F, Schiopu A, Wood KJ. Role of T cells in graft rejection and transplantation tolerance. Expert Rev Clin Immunol. 2010;6:155-69.
4. Valujskikh A. Memory T cells in allograft rejection. Adv Exp Med Biol. 2007;601:247-56.
5. Riellaa LV, Patersonb AM, Sharpeb AH, Chandrakera A. Role of the PD-1 Pathway in the Immune Response. Am J Transplant. 2012;12:2575-87.
6. Karabonand L, Frydecka I. The role of polymorphisms in co-signalling molecules' genes in susceptibility to B-cell chronic lymphocytic leukaemia. In: Oppezzo P, editor. Chronic lymphocytic leukemia. InTech; 2012. p. 179-200.
7. Iravani-Saadi M, Karimi MH, Yaghobi R, et al. Polymorphism of costimulatory molecules (CTLA4, ICOS, PD.1 and CD28) and allogeneic hematopoietic stem cell transplantation in Iranian patients. Immunol Invest. 2014;43:391-404.
8. Yaghobi R, Iravani Saadi M, Karimi MH, Geramizadeh B, Ramzi M, Zakerinia M. Relation between costimulatory molecule polymorphism and hepatitis B infections in hematopoietic stem cell transplant recipients. Exp Clin Transplant. 2014;12:357-66.
9. Saadi MI, Yaghobi R, Karimi MH, Geramizadeh B, Ramzi M, Zakerinia M. Association of the costimulatory molecule gene polymorphisms and active cytomegalovirus infection in hematopoietic stem cell transplant patients. Mol Biol Rep. 2013;40:5833-42.
10. Hoffmann TW, Halimi JM, Büchler M, et al. Association between a polymorphism in the human programmed death-1 (PD-1) gene and cytomegalovirus infection after kidney transplantation. J Med Genet. 2010;47:54-8.
11. Ebadi P, Karimi MH, Tahoori MT, et al. Polymorphisms of the programmed cell death 1 and ICOS genes and kidney transplant rejection in Iranian patients. Afr J Microbiol Res. 2012;6:6918-23.
12. Niknam A, Karimi MH, Geramizadeh B, Roozbeh J, Yaghobi R, Salehipour M. Polymorphism of the costimulatory genes (CTLA-4, CD28, DD-1, ICOS) and outcome of kidney transplantation in Iranian patients. Exp Clin Transplant. In press.
13. Kristjansdottir H, Saevarsdottir S, Grondal G, et al. Association of three systemic lupus erythematosus susceptibility factors, PD-1.3A, C4AQ0, and low levels of mannan-binding lectin, with autoimmune manifestations in Icelandic multicase systemic lupus erythematosus families. Arthritis Rheum. 2008; 58:3865-72.
14. Lee SH, Lee YA, Woo DH, et al. Association of the programmed cell death 1 (*PDCD1*) gene polymorphism with ankylosing spondylitis in the Korean population. Arthritis Res Ther. 2006;8:R163.
15. Karimi MH, Motazedian M, Abedi F, Yaghobi R, Geramizadeh B, Nikeghbalian S. Association of genetic variation in co-stimulatory molecule genes with outcome of liver transplant in Iranian patients. Gene. 2012;504:127-32.
16. Hayashi M, Kouki T, Takasu N, Sunagawa S, Komiya I. Association of an A/C single nucleotide polymorphism in programmed cell death-ligand 1 gene with Graves' disease in Japanese patients. Eur J Endocrinol. 2008;158:817-22.
17. Wang SC, Lin CH, Li RN, et al. Polymorphisms of genes for programmed cell death 1 ligands in patients with rheumatoid arthritis. J Clin Immunol. 2007;27:563-7.