Clinical transplantation tolerance: The promise and challenges

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Clinical transplantation tolerance: The promise and challenges. Organ transplantation is now well established as a preferred option for the treatment of end-stage organ failure. However, there is a severe shortage of donor organs and continued loss of a significant number of organ grafts due to chronic allograft dysfunction. Induction of tolerance of a transplant recipient toward their foreign organ graft, therefore, remains the “Holy Grail” of transplantation immunobiologists. Recently, clinical trials to explore pilot tolerance protocols in humans have been initiated. Defining the ideal strategy(ies) and the role of immunosuppressive drugs, developing tolerance assay(s), and enhancing cooperation between transplant professionals, industry, and the government are some of the challenges to achieving clinical transplantation tolerance. This article reviews the promise and the challenges of achieving clinical transplantation tolerance in human organ transplant recipients.

Over the last two decades there has been a progressive improvement of allograft survival, in particular kidney allografts [1]. Intriguingly, this improvement was seen only in recipients who never had an acute rejection episode, emphasizing the recipient’s alloimmune response as a major determinant of overall outcome of the transplant. Furthermore, the increasing demand of organs for transplantation [2] creates an urgent need for optimizing the outcome of transplantation by achieving long-term, drug-free, graft acceptance with normal organ function. The baffling array of potential complex treatment combinations currently available to the transplant immunobiologists [3] and the vast experimental data, on ways to achieve transplantation tolerance, that has amassed since the original description, half a century ago, of the phenomenon of tolerance in experimental animals implores us to evaluate where we stand on the road to achieving clinical transplant tolerance, and underscore the challenges that we face, so that we may choose the best course of action [4].

T cells are the vital elements of the immune response and interact with the alloantigen by the direct and indirect pathways, recognizing the foreign major histocompatibility complex (MHC) molecules directly on the donor antigen-presenting cells and processed donor antigens on self antigen-presenting cells, respectively [5]. The T cells reacting to their specific antigen can undergo a number of different responses, namely activation followed by proliferation and differentiation into effector and memory cells, and termination. Physiologic termination of the T-cell immune response is carried out by a number of mechanisms, specifically, deletion (central or peripheral); anergy, where T cells are unresponsive to restimulation with specific antigen; and regulation by regulatory cells and cytokines [6]. These physiologic mechanisms form the basis of inducing donor-specific tolerance in clinical transplantation [7–9]. Another possible mechanism of immunologic tolerance that is unique to the transplant setting is microchimerism, the persistence of a small number of donor-derived bone marrow cells in recipients [10–12].

It is imperative to define transplant tolerance at the outset so that we understand precisely our objective. Transplant tolerance does not mean complete unresponsiveness of the immune system toward the graft, rather a lack of a destructive immune response toward it, in the presence of generalized immune competence [13]. An operational definition of transplant tolerance in the clinical setting is the absence of acute and chronic rejection and indefinite graft survival with normal graft function in an immunocompetent host. The issue of ongoing immunosuppression remains to be resolved as to whether we should aim for a complete drug-free state or, more realistically, accept a minimal amount of ongoing immunosuppression/immunomodulation [14].

Generally, reports claiming tolerance induction cite graft survival in rodents of over 100 days with donor-specific hyporesponsiveness (indicated by acceptance of a second graft from the original donor strain and rejection of third-party grafts). It is impractical to confirm tolerance induction in this way, in humans, leaving a void in this crucial area. Consequently, devising an assay that allows us to prospectively follow the status of the immune response toward the graft and detect tolerance or early signs of rejection is an urgent necessity [15–18]. Yet, it seems unlikely that a single assay will provide an

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had received a previous bone marrow transplant from the patients receiving total body irradiation as induction therapy. This phenomenon has also been reported in patients of clinical transplant tolerance [19]. The basis of this immunosuppression-free tolerant state, however, remains intriguing and merits further study so that we may learn how this can be achieved reproducibly (if at all possible). This phenomenon has also been reported in patients receiving total body irradiation as induction therapy [20, 21] and in those kidney transplant recipients who had received a previous bone marrow transplant from the same donor, first reported by our group [22] and more recently by others in a patient with multiple myeloma complicated by end stage renal failure [23].

The utilization of bone marrow transplantation in order to induce tolerance through mixed chimerism of the immune system has been expansively studied in animal models and to a lesser extent in humans [24]. A major challenge that remains, for the induction of lasting tolerance to develop toward it too. Therefore, it seems prudent to exclude patients with certain chronic or latent infections (e.g., hepatitis B or C, cytomegalovirus, Epstein-Barr virus) from initial tolerance trials.

### Table 1. Potential tolerance assays [4]

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Abbreviations are: MLR, mixed lymphocyte reaction; CML, cell-mediated lymphocytotoxicity; ELISA, enzyme linked immunosorbent assay; ELISPOT, enzyme-linked immunospot assay; CFSE, carboxyfluorescein diacetate succinimidyl ester; DTH, delayed-type hypersensitivity; DC, dendritic cell; TCR, T cell receptor.

in non-human primates and clarifying the risks associated with such approaches are the first hurdles to be overcome before moving on to clinical trials of these strategies.

Other strategies, utilizing T-cell depleting agents or costimulatory blockade with or without donor-specific transfusion, appear to achieve tolerance in a variety of animal models [7] but not in a true sense of the word in primate models [29]. In the past several years there has been great enthusiasm about the potential of translating strategies targeting the CD28/CTLA-4:B7-1/2 and the CD40:CD154 T-cell costimulatory pathways to the clinic [5, 30]. Our understanding of these important costimulatory pathways and their interaction with each other and other novel pathways such as ICOS:ICOSL, CD134:CD134L, CD27:CD70, and PD-1:PD-L1/2 are still unfolding. These novel pathways appear to play greater roles under some circumstances [31–36]. Targeting of these pathways may however only work when the alloreactive T-cell repertoire is rendered to a manageable size with adjunctive depleting or deletional therapies [8]. The new immunosuppressive drug rapamycin may play such a role by inducing T-cell apoptosis [37]. There remains a challenge, however, of defining how much deletion is enough and how safe it is in humans. Further, the precise impact of the conventional immunosuppressive drugs on tolerizing strategies needs to be reevaluated, since the initial suggestion that certain drugs impair the generation of tolerance in some models [37, 38] have not proven founded in others [39, 40].

Another major challenge is the resolution of the relationship of tolerance with chronic allograft dysfunction. There are conflicting data from experimental models on the impact of alloantigen-dependent and alloantigen-independent mechanisms on chronic allograft dysfunction [41–43]. However, some data indicate that donor-specific hyporesponsiveness is associated with protection from chronic rejection in humans [44].

The impact of tolerizing regimens on the risk of infectious complications and likewise the detrimental effect of previous, ongoing or later infections on the induction or maintenance of tolerance and also on the course of infection itself is uncertain. Indeed, certain tolerizing strategies are ineffective if performed during ongoing infectious episodes [45] and a recent study sheds more light on the possible mechanism responsible for this phenomenon, suggesting that individuals harboring virally induced memory T cells that are crossreactive with donor alloantigen (a phenomenon termed heterologous immunity) are resistant to tolerance induction [12, 46]. On the other hand, attempting to use a tolerizing regimen in the presence of a latent infectious agent may allow tolerance to develop toward it too. Therefore, it seems prudent to exclude patients with certain chronic or latent infections (e.g., hepatitis B or C, cytomegalovirus, Epstein-Barr virus) from initial tolerance trials.
The choice of which patient population will be the first to be enrolled into such trials is a very difficult one, especially when the clinicians are faced with the ethical issue of risking possible rejection from a failed tolerance protocol in an era when 1-year graft survival rates exceed 90% and few grafts are lost to rejection. There is added convolution, due to conflict of interest of pharmaceutical companies manufacturing immunosuppressive agents currently used, because such tolerizing strategies may not benefit them. An altruistic cooperation between the biotechnology industry and the transplant biologist is needed to successfully achieve the necessary development of the appropriate tolerizing agents. Finally, the proper conduct and execution of the clinical trials cannot be overemphasized and will need to be focused on the biotechnology industry and the transplant network. The Immune Tolerance Network (ITN) NIH (USA) (http://www.immunetolerance.org) was expressly instituted for this sole purpose. It provides a platform for sharing of ideas as well as core facilities and provides a focus for the development of the most suitable strategies. The ITN is sponsoring several research projects in focus for the development of the most suitable strategies and then translating them to larger animals to establish assay studies and special projects such as “The ITN Tolerant Kidney Transplant Patient Registry,” to establish a world-wide registry of kidney transplant recipients who are off all immunosuppression.

CONCLUSION

We have learned that the goal of clinical transplant tolerance is achievable especially in animal models but also in a few humans. Identifying the most successful of these strategies and then translating them to larger animals to test their suitability for the patients is the next step. This demands persistence and meticulous investigation to confirm the robustness and longevity as well as safety of the tolerance inducing regimens. If we are successful in doing this, then we may still arrive at our chosen destination, although it may seem very distant.

REFERENCES


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