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Clinical Tolerance 2008

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Abstract

In 2008, three publications highlighted the transition of tolerance from experimental to experiential. These included the first study to both anticipate and reproducibly deliver HLA-disparate allograft survival without continuous immunosuppressive drug administration. The other two highlighted unique episodes of clinical tolerance. The results from these studies are summarized and discussed.

Keywords

Tolerance; Immunosuppression; Organ Transplantation

It has been observed that rare allograft recipients can be withdrawn from immunosuppression without apparent clinical consequence, a condition reflecting Medawar's pioneering description of acquired immunological tolerance [1,2]. These exceptional spontaneous cases have demonstrated that tolerance is possible in humans, and fostered substantial debate regarding the mechanisms to be exploited in the clinic. However, the ability to intentionally induce tolerance to an MHC disparate allograft through a prospectively defined protocol has eluded clinicians and served as a focal point for achievement in the field.

The year 2008 saw substantial change in the landscape of tolerance research with the publication by Kawai, et al, from the Massachusetts General Hospital (MGH) of the first consecutive series of HLA-disparate allografts intentionally transplanted without maintenance immunosuppression [3]. The study reported 4 of 5 recipients of haplo-identical live donor kidneys weaned from all immunosuppressive medications for greater than 2-years with stable normal function and relatively preserved histology. The treatment varied substantially from patient to patient, but at its core was a protocol that involved a conditioning regimen of cyclophosphamide, T cell depletion the CD2-specific monoclonal antibody MEDI 507, and thymic irradiation, followed by donor bone marrow infusion and kidney transplantation. Maintenance therapy with cyclosporine ensued and was gradually weaned off over several months. Myriad caveats aside, primarily those related to the long-term outlook for these patients and the inherent ethical dilemma of radically departing from a standard of care with very acceptable short term results, this report represented the execution of an exceptionally difficult trial, particularly in the modern regulatory environment. It was commendable not only for its results, but also for the means by which the study was developed: based on decades of preparative work in animals, and formulated, to the extent possible, on empirically tested methods rather than opinion.

Several observations from this landmark study deserve comment. First, although the therapy was predicated on a mixed chimerism approach, durable mixed chimerism was not achieved in any individual. This is in stark contrast to preparatory mouse studies in which lasting

chimerism was a prerequisite for success, and similar to non-human primate studies that preceded the clinical study [4]. Nevertheless, some multi-lineage chimerism was transiently seen in all patients. This distinguishes the protocol from bone marrow infusion protocols in which macro-chimerism is not evident at any point post transplantation [5]. Thus, the induction regimen was sufficiently vigorous to prevent marrow elimination, a condition apparently necessary for success. This speaks to the importance of vigorous immunosuppression at the time of graft implantation, and the transplant community should continue to work to identify those conditions that are required during engraftment to facilitate tolerance. It may also signal that more aggressive attempts to achieve persistent chimerism may unnecessarily risk graft versus host disease (GVHD).

The work highlighted both the critical nature of, and poor understanding relative to, humoral immunity. Four patients experienced humoral immune complications. The lone graft loss occurred in a patient with high preoperative levels of class I, non-donor specific alloantibody who developed donor specific antibody (DSA) and an irreversible antibody mediated rejection. This suggests that patients who have shown propensity to form alloantibody may be best avoided in tolerance protocols. Importantly, two additional patients developed post-transplant DSA, which persisted in one, and was associated with mild glomerulopathy on surveillance biopsy. This chronic finding clearly cannot be considered unique to this protocol, but nevertheless remains concerning [6]. Another patient had an early C4d positive rejection that was presumably antibody mediated, but DSA was not detected. Although several protocol changes were initiated to thwart humoral immunity, including the use of rituximab, the data cannot be viewed as indicative of efficacy of these maneuvers. As the humoral rejection rate in haploidentical live donor transplants is very low, it is reasonable to consider the humoral rejections directly related to the therapy's shortcomings. It is thus clear that discovery in the area of humoral immunity remains a priority for the transplant community. It also speaks to a need for a better understanding of the role of B cells in driving cellular rejection.

Patients receiving this therapy appeared to be grossly immunocompetent, a defining characteristic of tolerance. The index patient was able to eliminate debilitating viral warts post transplant. This is encouraging, but additional attention to the interface between protective and allospecific immunity is certainly warranted. Donor specific hyporesponsiveness and regulation was evaluated and detected to some extent in all patients. There was intriguing but inconclusive data regarding regulatory T cell function suggesting regulation should remain a fruitful area of investigation. Nevertheless, there is no surrogate marker for tolerance and the prognosis for these patients remains a matter of speculation.

Two accompanying articles highlighted the relationship between chimerism and tolerance. Scandling, et al, described one of three patients rendered tolerant to an HLA-identical graft following an induction regimen including prednisone and rabbit anti-thymocyte globulin (RATG), and total lymphoid irradiation (TLI) followed by the infusion of donor bone marrow that was enriched for CD34+ hematopoietic progenitor cells and substantially depleted of donor T cells to reduce the risk of GVHD [7]. A maintenance regimen of cyclosporine and mycophenolate mofetil (MMF) was gradually weaned over the ensuing months. Unlike the current MGH work, mixed chimerism was achieved and persisted in this patient. Two subsequent patients failed this approach, one to recurrent primary disease (an oft overlooked potential benefit of immunosuppression), and one who experienced mild rejection associated with loss of chimerism who remained on monotherapy cyclosporine (a result achievable with depletion induction alone) [8].

Alexander et al, described a dramatic case in which a recipient of a fully HLA- and sex-mismatched liver allograft treated with tacrolimus, prednisone and azathioprine in the setting of profound lymphopenia and multiple viral infectious complications spontaneously developed

multi-lineage chimerism and tolerance [9]. The study confirms the known phenotype of tolerance associated with complete chimerism as is seen following bone marrow transplantation [10].

Clinicians and patients contemplating therapies such as these should realize that a single therapeutic regimen has yet to be described. Rather, their commonality is a conceptual intention-to-treat involving antigen administration during aggressive immunosuppression. Indeed, each patient received a unique combination of between 5 and 12 immunomodulatory therapies in response to unique problems (Table). This is both a tribute to the clinical acumen and flexibility of the clinical investigative teams, and an indication of how much needs to be learned before a true tolerance regimen exists. Patients from these reports were given a huge array of therapies (Table) variably including cyclophosphamide, cyclosporine and/or tacrolimus, MMF, thymic irradiation, unfractionated bone marrow, MEDI 507, and/or RATG, plasmapheresis, IVIg, and/or rituximab. The role of rituximab is unknowable at this early stage, and transient humoral rejection developed in a patient despite pre-emptive rituximab. Corticosteroids were also given to combat capillary leak or as prophylaxis for RATG, and although not advertised as part of the regimens, must be viewed as having contributed to the results. Thus, this approach must be considered difficult at best. In trying to determine a common theme amongst all of these patients, profound and prolonged lymphopenia was present in all patients during the initial alloantigen exposure. As such, a better understanding of lymphocyte behavior during lymphopenia and repopulation remains an important research focus.

Where do these studies leave us? Certainly they highlight the potential for tolerance strategies and underscore the need for targeted research into the areas highlighted above. The field is not in a position to pass judgment on tolerance regimens largely because no single regimen has been yet described. However, these questions will not be answered unless work continues in this area. Although the success rate in well-matched recipients of live donor kidneys should be essentially 100% [11], failures in these experimental settings should not be over-blown. They should, however, clearly be noted and incorporated into the consenting process. Deliberate, dispassionate clinical investigation in centers willing to put forth the exceptional effort required to safely perform these difficult trials remains appropriate. It should continue to be governed by review agencies that maintain a comprehensive view of their responsibilities to patients through risk minimization, assessing both the risk of failure to induce tolerance, and the risk of failure to offer tolerance.

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Table 1

Therapy	1 [*]	2 [*]	3 [*]	4 [*]	5 [*]	1 ^{**}	2 ^{**}	3 ^{**}	1 ^{***}
azathioprine									x
bone marrow	x	x	x	x	x	x	x	x	
cyclosporine	x	x	x	x	x	x	x	x	
cyclophosphamide	x	x	x	x	x				
IVIg		x	x						x
Medi-507 (anti-CD2)	x	x	x	x	x				
mycophenolate		x	x		x	x	x	x	
steroids		x	x	x	x	x	x	x	x
tarolimus		x	x	x	x				x
thymic irradiation	x	x	x	x	x	x	x	x	
plasmapheresis		x	x		x		x		
RATG			x		x	x	x	x	
rituximab (anti-CD20)			x	x	x		x		
total lymphoid irradiation						x	x	x	
Clinical Outcome									
donor specific alloantibody			x	x	x				
C4d		x	x	x	x				
lymphopenia at transplant	x	x	x	x	x	x	x	x	x
chimerism	brief	brief	brief	brief	brief	persistent	none	brief	persistent
tolerance	yes	yes	no	yes	yes	yes	no	no	yes

* reference 3

** reference 7

*** reference 9