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REVIEW

Is clinical tolerance realistic in the next decade?

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Summary

Tolerance to allografts would mean a better quality of life and prognosis for transplant patients. Despite the first descriptions of tolerance to alloantigens over 50 years ago, deliberately induced tolerance in the clinic on a wide scale remains a goal that is not quite in reach. However, much progress has been made in understanding tolerance in rodent models and in the few reports of induced or spontaneously occurring tolerance in humans. Here, we review this progress made in the quest to achieve clinical tolerance.

Introduction

Tolerance – the 'holy grail' of transplantation

Allotransplantation is now a widely used treatment for end stage diseases such as renal, heart and liver failure, and is becoming more and more common for the replacement of other organs. Improvements in immunosuppressive drug treatments, surgical procedures and the clinical management of transplant patients mean that such patients can now expect lower risks of rejection and higher graft survival rates [1]. Nevertheless, immunosuppressors have to be given life-long, and long-term immunosuppression (IS) puts transplant recipients at risk of infectious complications [2] and malignancies [3,4], as well as in certain cases causing irreversible damage because of renal toxicity [5]. Moreover, IS poorly influences chronic rejection, the main cause of graft loss in renal transplantation [6,7]. In the calcineurin inhibitor (CNI) era, Major histocompatibility has a relatively weak effect, but still significantly influences long-term outcome [8]. For these reasons, a major goal in this field is to induce allograft tolerance.

Definitions of tolerance in transplantation

It was more than 50 years ago that Billingham, Brent and Medawar first described actively acquired immune tolerance to foreign cells in the neonate [9]. Since then, much effort has been made to extend this phenomenon to adult organisms and to translate it to the clinic. The strict definition of tolerance, as defined in animal models, is the specific long-term survival of a transplant displaying normal histological characteristics and function, in a nonimmunosuppressed recipient who retains the capacity to reject a third party graft but to accept a second donor-specific allograft. In the clinic, the term 'operational tolerance' is often cited, indicating the long-term survival of a graft showing stable function in a patient not taking maintenance IS and whose risk of infection is not increased [10]. Such an observation suggests that tolerance is already a reality in the clinic and that an unknown fraction of patients under life-long IS are actually tolerant. Another definition is referred to as 'Prope' or 'almost' tolerance, where stable long-term function of the transplant requires minimal IS, a concept introduced by Calne [11]. This latter type of tolerance is perhaps a more realistic one for the clinic that could nevertheless reduce drug-related complications. However, it is not known whether prope tolerance is in fact the minimal chronic IS required to maintain stable graft function. Therefore, we will only review here immunosuppressive drug-free tolerance.

Mechanisms of transplant tolerance in animal models

To date, the majority of data concerning the mechanisms of tolerance induction in transplantation come from rodent studies and can be categorized as being either central or peripheral. Strictly speaking, central tolerance to alloantigens refers to intrathymic deletion of alloreactive T cells [12]. However, 'peripheral' mechanisms have also been found to operate here [13]. In the periphery, tolerance can be mediated by several nonmutually exclusive pathways, including deletion, anergy, ignorance and regulation/suppression. Peripheral deletion refers to removal of alloreactive cells and can occur through both active and passive pathways (reviewed in [14]). Anergy is the term used to describe a persisting unresponsive state in cells primed by antigen presenting cells (APC) but lacking costimulatory signals [15] and forms the basis of co-stimulation blockade strategies [16]. Ignorance has been described to occur when the graft recipient lacks secondary lymphoid organs [17]. Regulation/suppression has been increasingly reported in rodent models of transplantation tolerance and various types of regulatory T cells responsible for suppressing alloimmune responses have now been defined (for a review see [18].

'Tolerance' in rodents – further proof needed?

Despite reports of tolerance in rodents, one must not overlook the fact that long-term survival in rodents does not necessarily equal tolerance. Indeed, long-term graft survival prolongation in rodents can be achieved by a multiplicity of protocols. However, little attention has been paid to graft histology in such long surviving animals and reports of 'tolerance' in rodents with long-term graft survival in the absence of reported histology should therefore be interpreted with caution. For example, the 'tolerance' in rats treated with donor-specific blood transfusion (DST) is now known to be a state of chronic rejection [19], thus revealing the phenomenon of regulation concomitant to chronic rejection, a subject that needs to be well scrutinized in rodents before it can be understood in humans. Thus, it is important not to confuse tolerance with inhibition of acute rejection. The possibility of a direct relationship between tolerance and CR still needs to be explored further as some evidence suggests that CR may be a 'by-product' of tolerance, for example, in the context of a tolerance-induced Th2 environment [20].

Another issue is the concept of time; several hundred days graft survival in a rodent is one thing, but several decades survival in a human may be quite another. Therefore, even in the best conditions, the generally accepted concept that tolerance operates in rodents is not always sustained by the available data and the situation prevailing in rodents may not in fact be very different from that in larger animals if longer surveys are considered.

Translation of tolerance to the clinic – how far have we come?

It is generally accepted that achieving tolerance is substantially harder in nonhuman primates (NHP) and humans than in rodents. Nevertheless, there are several examples, where tolerance has been achieved in the clinic. 'True' tolerance in recipients of organ allografts from the same donor of a previous bone marrow transplantation (BMT) has been documented in a few publications [21,22] and is sustained by numerous unpublished observations. 'Operational tolerance' operating for decades has also been reported [10]. Such rare reports of clinical tolerance, together with success in experimental models, have led to the implementation of inter-continental networks aimed at monitoring (or recognizing) tolerance in humans (Immune Tolerance Network, Indices of Tolerance, RISET EU), which has greatly boosted interest in this field. This review aims at critically reviewing tolerance-inducing approaches and at speculating on the actual chances of achieving tolerance to organ transplants in humans.

On the whole, strategies aimed at inducing clinical tolerance can be divided into two categories: non-BMT-based approaches and BMT-based approaches. The mechanisms involved in both approaches as well as their clinical application will be outlined and discussed below and in Table 1.

Non-BMT-based strategies

These include lymphocyte depletion, costimulatory blockade and donor antigen infusion. Lymphocyte depletion can be achieved by total lymphoid irradiation (TLI) or by the use of mono or polyclonal antibodies. The TLI approach met with some success (40% of recipients tolerant at more than 1 year post-transplantation) in dogs, but only when combined with antithymocyte globulin (ATG) [23]. In humans, the same group reported on three patients, from a series of 28 receiving TLI and ATG together with low-dose prednisone, who were successfully withdrawn from all IS [24] as well as a patient that had received TLI and was tolerant 12 years after IS withdrawal [25]. Nonetheless, the low percentage of success and the relative risks of TLI for routine use have limited its further exploitation in the transplantation context.

The more common approach to depletion is to use antibodies. Along these lines, several monoclonal antibodies have been tested for their tolerance-inducing capacities in both NHP and humans. In NHP, anti-CD3 combined

Table 1. Overview of tolerance-inducing strategies that have been tested in the clinical arena.

Tolerance-inducing strategies	Preclinical experience	Clinical experience	Future directions
1. Non-bone marrow transplantation (BMT) based			
A. Lymphocyte depletion			
(i) Total lymphoid irradiation	Some success in dogs when used in combination with antithymocyte globulin [23].	Some success but in a small proportion of patients [24].	Not suitable for routine use
(ii) Antibodies	Anti-CD3-immunotoxin very successful in primates when combined with deoxyspergualin [28] but no human equivalent as yet.	Monoclonal anti-CD52 Ab CAMPATH-1H has shown potential in inducing prope tolerance [11], but true tolerance elusive [31,32].	
B. Costimulation blockade	Tolerance-inducing in rodents but immunosuppressive only in nonhuman primates (NHP) [35,37,42].	Evidence to suggest that CTLA4-Ig can obviate the need for calcineurin inhibitor [38]. No tolerance-inducing study as yet.	Possible need for simultaneous blockade of multiple costimulation pathways. Specific antagonism of CD28 [39] may be beneficial, but remains to be tested clinically.
C. Donor antigen infusion	Much experience with donor-specific blood transfusion in rodents but, at least in certain models, the indefinite survival previously thought to be the result of tolerance is now known to be associated with chronic rejection [19].	Not tolerance-inducing and beneficial effects unclear [45,46].	Sensitization fears and agency recommendations make this approach less popular.
2. BMT based			
Consecutive bone marrow (BM) and organ transplantation		Performed as a consequence of patient disease. Successful in a handful of isolated cases [21,53–55].	Not applicable on a wide scale because of risks of GVHD.
Simultaneous BM and organ transplantation	Successful in NHP depending on the type of organ transplant [50–52].	Deliberately performed and successful in several cases [58,59].	Again not applicable on a wide scale but promising in that this is the first time tolerance has been deliberately and successfully achieved in humans.

to an immunotoxin led to long-term kidney allograft survival in half of the recipients [26], but the grafts of long-surviving animals were later found to show signs of humoral rejection [27]. Tolerance was, however, achieved when deoxyspergualin (DSG) was added to the protocol, with 87% of recipients showing long-term renal graft function in the absence of chronic rejection [28]. Even up to over 3 years later, the grafts of these animals displayed no signs of chronic rejection [29], making this model the archetype of successful long-term tolerance in NHP. One important point in Thomas' model is that the CD3-immunotoxin seems to more profoundly deplete T cells from all biological compartments, which may make its actions different to those of other 'depleting' antibodies. The DSG effect in this model is still unclear. Interestingly, a robust state of tolerance to histo-incompatible hearts was obtained using a DSG derivative in rodents with the differentiation of highly efficient TReg cells [30]. In the clinic, a similar approach was less successfully undertaken using the anti-CD52 T cell-specific monoclonal antibody campath-1H. This reagent not only depletes approximately 99% of blood T cells, but also B cells monocytes and natural killer (NK) cells. The first clinical study of this agent was in a small cohort of 13 renal transplant recipients receiving only low-dose cyclosporin as maintenance IS where, at 6 and 11 months after surgery, only two patients had experienced rejection episodes, the others displaying so-called 'prope' tolerance [11]. Kirk *et al.* also tested campath-1H with the aim of inducing tolerance to renal allografts in humans, either alone [31] or in combination with a 2-week perioperative course of DSG [32] to simulate the NHP studies mentioned above. Neither regimen proved tolerogenic as all patients experienced early rejection episodes and ultimately required maintenance sirolimus monotherapy. Of interest is that a recent follow-up study of patients receiving campath-1H induction therapy with maintenance sirolimus revealed a subset of patients who had become completely unresponsive to donor alloantigen *in vitro* [33]. The consequences of this remain to be seen. Thus, the use of lytic anti-T-lymphocyte Abs can induce tolerance in NHP, but has not been tested in humans. Depleting monoclonal antibodies (and possibly ATG) on the other hand may allow for stable graft function in the clinic, but only in the presence of minimal IS. Other T-cell depleting strategies using pharmacological agents such as harnessing the immunosuppressive properties of the enzyme indoleamine 2,3-dioxygenase or its metabolites [34] may also prove useful, but have yet to be tested in NHP or humans.

Costimulation blockade is a prime example of a tolerance-inducing strategy that has been successful in rodents, but much less so in NHP. Two key costimulation pathways include the B7-CD28 pathway (blocked by CTLA4Ig or anti-B7 antibodies) and the CD40-CD154 pathway (blocked by anti-CD154 or anti-CD40 antibodies). In NHP, blockade of the B7-CD28 pathway using CTLA4Ig [35] or anti-B7 antibodies [36,37] does not induce tolerance despite prolonging graft survival. No study specifically focusing on the application of this tolerance-inducing strategy to the clinic has been published to date. However, a recent clinical trial of CTLA4Ig in renal allotransplantation showed that, when used at a sufficient dose, this agent is not inferior to cyclosporin A at preventing acute rejection and may preserve glomerular filtration rate and reduce the rate of chronic allograft nephropathy when administered indefinitely i.v. in the absence of CNI, but in association with mycophenolate mofetil and steroids [38].

A new B7-CD28 costimulation blocker that may have great potential for the induction of tolerance is an antagonistic anti-CD28 derivative, a single chain Fv-alpha-1 antitrypsin fusion protein (ScFv28AT) that recognizes and binds with high affinity to human CD28 without causing receptor cross-linking or inhibiting potentially useful CTLA4-B7 interactions [39]. This molecule blocks CD28, thus, in theory, enabling the development of regulatory mechanisms through CTLA4-B7 interactions. This agent can induce true tolerance (without signs of chronic rejection) to rat renal allografts [40] and is now in preclinical development. It will be interesting to see how this molecule will fair in the clinical arena.

Blockade of the other major pathway, that of CD40-CD154, has been more successful in NHP with survivals of >476 days for islet allografts [41] and >500 days for renal allografts [42]. Again, tolerance was not achieved as, at least in the case of renal allografts, the animals developed signs of chronic allograft nephropathy and alloantibodies. Translation of this particular costimulation blockade strategy to the clinic using anti-CD154 unfortunately met with serious toxicity problems manifest as the occurrence of thromboembolic events and ultimately leading to suspension of the clinical trial in question. So on the whole, current costimulation blockers seem to be immunosuppressors rather than tolerance inducers in large animals and humans. New agents blocking other co-stimulation pathways or combinations of costimulation blockers are now emerging in rodent models, but their efficiency in NHP or the clinic remains to be evaluated.

Another non-BMT-based tolerance-inducing strategy is donor antigen infusion in the form of DST. In rodents, DST can lead to permanent engraftment [43,44]. However, a study in a rat model of cardiac allotransplantation with DST revealed that despite being 'operationally tolerant', the indefinitely surviving grafts actually displayed

overt signs of chronic rejection [19] (see above). DST on its own has not been shown to induce tolerance when tested in NHP either, and it remains unclear whether it does indeed have any beneficial effect. [45,46]. However, patients with operational tolerance may be low responders to non-deleukocyted blood [10]. Nevertheless, fears of sensitization and specific agency recommendations have now made this approach less popular.

Finally, regulation, which has been used to induce tolerance in rodents, has also been applied to NHP, where the preliminary results were impressive. Renal allograft recipients receiving adoptively transferred anergic T cells generated *ex vivo* displayed prolonged graft survival, with 3/6 animals surviving long term [47]. These data now need confirmation on a larger series. So far, however, no reports of utilization of regulatory cells in clinical transplantation tolerance have appeared in the literature. Moreover, no increase in CD4+CD25+ cells has been reported in the blood of operationally tolerant kidney recipients, although a lack of these cells has been reported in patients presenting chronic rejection [48]. This area of research therefore requires more research in the future in the clinical context.

On the basis of the results described above, non-BMT-based tolerance-inducing strategies appear to have shown only limited success in the clinic. On a more positive note, co-stimulation blockers or combinations of blockers combined with BMT-based strategies (see below) may be met with clinical success in the future.

BMT-based strategies

Bone marrow transplantation-based approaches to tolerance induction usually involve the consecutive or simultaneous administration of donor-derived haematopoietic cells. This approach is unique in that such cells can reach the recipient thymus and mediate negative selection of newly generated donor-reactive T cells, thereby creating a robust form of tolerance through central deletion. In rodents, mixed haematopoietic chimerism following simultaneous BMT and solid organ transplantation leads to stable tolerance with a low risk of inducing graft versus host disease (GVHD) (reviewed in [49]). This approach has also been successfully applied to NHP [50,51]. However, there does seem to be some organ-specific effects as tolerance to heart transplants in this way seems to be more difficult to achieve [52].

In the clinic, although reports of tolerance to transplanted organs achieved in this manner have been based on small patient numbers or case reports, this has been enough to encourage clinicians and researchers alike that tolerance is not an unrealistic goal. It was 15 years ago that tolerance was reported to renal allografts in two patients that had received prior BMT from the same donor [21]. Numerous other cases have been reported, where patients who received a BMT to treat hematological malignancy subsequently received an organ transplant from the same donor and did not require long-term IS [53–55]. Renal tolerance occurring from this procedure has even been confirmed after a follow-up of 6 years [22]. Nevertheless, this approach of consecutive BM and organ transplantation is limited by the risk it carries of complications such as GVHD.

Simultaneous BM and organ transplantation has also been reported in the clinic, but seems to only improve graft outcome [56]. Very few deliberate attempts to induce tolerance through mixed chimerism in the clinic have been reported. One of these concerned four patients who received a haplo-identical or HLA-identical living donor kidney together with mobilized donor-derived CD34 progenitors, two of whom were off all IS at 12 months [57]. The follow-up of these patients has not yet been reported. Two other reports concerning a total of three patients treated for multiple myeloma and end-stage renal disease [58,59] gave encouraging results in that mixed haematopoietic chimerism and importantly, stable renal function, was observed in all three patients and all were off IS at the time of publication with a follow-up of more than 170 days and nearly 2 and 4 years. Interestingly, mixed chimerism in the latter patients was transient as it disappeared after approximately 3 months [59]. Despite its limitations (its toxicity, which reduces its applicability to the general transplant recipient community), this approach to tolerance induction may yet hold the key to clinical tolerance induction in the future.

Can transplantation tolerance occur 'naturally'?

Under some circumstances tolerance can occur spontaneously following the cessation of a standard IS regimen. This observation represents the most convincing argument that tolerance is achievable in the clinic. Although spontaneously occurring tolerance appears to be a rare phenomenon, its actual occurrence is unknown because of the recommendation for the vast majority of patients to never interrupt their IS medication. Understanding this type of tolerance may give us clues as to how tolerance can be achieved more easily in the clinic. Most cases of spontaneous tolerance reported in animals refer to the liver, as the characteristics of this organ make it particularly susceptible to being tolerated [60]. Tolerance to liver grafts has been observed in rodents [61,62] as well as in pigs [63]. In humans, the liver is also the organ that is more frequently tolerated. Certain clinical teams even progressively diminish immunosuppressive treatments deliberately in liver transplant patients meeting specific clinical criteria. Such immunosuppressive weaning

protocols (that are not without potential hazards in the absence of biological markers of tolerance) have revealed that approximately a quarter of such patients tolerate their liver transplant [64,65].

Spontaneous tolerance to other organ transplants, however, is rare. For the kidney, several anecdotal cases of spontaneous tolerance following interruption of IS have been reported in the literature (Table 2). The reasons for IS withdrawal are predominantly noncompliance but also drug toxicity or malignancy. A survey of 6000 renal transplant recipients in the US performed over 20 years ago by Zoller *et al.* [66] showed that among 48 patients who stopped immunosuppressive therapy, only six conserved stable renal function for more than 3 years; most cases of stable function following IS withdrawal were transient and resulted in degradation of renal function. This was corroborated by another report by Uehling *et al.* of five noncompliant recipients of living-related donor kidney transplants of whom only one maintained stable function without IS (two underwent severe rejection and two resumed treatment) [67]. Interestingly, a recent follow-up report of the latter patient revealed her to be tolerant 32 years on, showing that tolerance can be life long [68].

Some attempts have been made to characterize the mechanisms arising in these circumstances. For example, Burlingham studied the case of a patient who had received a kidney transplant from his mother and presented stable graft function despite stopping IS [69]. Analysis of the blood of this patient revealed a microchimerism linked to unresponsiveness within the cytotoxic lymphocyte compartment. The same group recently demonstrated that tolerance can occur without loss of immunological memory to donor antigen as they found the co-existence of both regulatory and effector memory CD8+ T cells specific for the same minor H antigen in the blood of a recipient of a minor antigen-mismatched kidney graft who had been tolerant (off all IS and with stable graft function) for 32 years [68]. Another case concerned a patient who had stopped IS because of a post-transplant lymphoproliferative disorder [70]. Again, analysis of the blood of this patient revealed donor-specific unresponsiveness in a mixed leukocyte reaction concomitant to a reduction in Th1-type cytokines. One can note that many of the anecdotal cases of spontaneous tolerance involve living-related donors, which raises the question of the influence of histocompatibility matching on tolerance induction. This question has not been able to be adequately addressed in humans, but some evidence from large animal models suggests that class II matching may be important [71]. We have recently reported on 10 cases of spontaneous operational tolerance to renal transplants [10]. Exploration of the medical history of these patients revealed several factors potentially favouring the development of tolerance, including immunosuppressive weaning over long periods, young donor age and poor response to blood transfusions. All of these patients received cadaveric transplants with a mean HLA incompatibility of 3 ± 1.5 [10] indicating that a close HLA match did not play a role in this particular cohort. Indeed, two of the 10 patients even displayed antidonor class II antibodies, showing that operational tolerance can occur in the presence of a concurrent antibody response [10]. These patients seem to respond normally to other antigens as they do not have an increased rate of infection [10]. These patients

Table 2. Characteristics of spontaneously induced tolerance in renal allotransplantation.

Characteristics	Comments
Occurrence	Following immunosuppression (IS) withdrawal because of noncompliance, drug toxicity or malignancy. Some evidence to support withdrawal over a period of several years [10].
Stability	Can be meta-stable [10], but can be stable for several decades [68]
Donor specificity	Evidence for donor-specific unresponsiveness in a mixed leukocyte reaction [70,78].
Immune regulation	Evidence for donor antigen-linked delayed-type hypersensitivity (DTH) nonresponsiveness mediated by TGFβ and IL10 [78]. Evidence for unresponsiveness in the cytotoxic compartment and for the co-existence of regulatory and effector memory CD8 T cells according to the '*trans-vivo*' DTH assay [68]. No increase in numbers of CD4+CD25+FoxP3+ T cells compared with healthy individuals but rather a decrease of these cells in patients with chronic rejection [48].
Peripheral blood phenotype	Similar to healthy individuals but contrasted with patients experiencing chronic rejection [48,72].
T-cell repertoire	Paradoxically altered T-cell receptor (TCR) Vbeta usage and high TCR transcript accumulation in selected T cells compared with healthy individuals and patients with stable graft function [73].
Microchimerism	Evidence for donor microchimerism in some cases [68,69].
Graft histology	Only two descriptions available during the actual tolerance period: 1. a moderate and focal infiltrate with an arteriolar intimal hyperplasia, suggesting the beginnings of chronic allograft nephropathy lesions [69] and 2. a focal infiltrate of CD4 and CD8 T cells separated from nearby tubules and glomeruli and therefore appearing noninvasive [78].

have peripheral blood CD4+CD25+ and CD8+CD28− numbers similar to healthy individuals [48,72] and display particular T-cell receptor (TCR) repertoires [73]. Further studies to characterize the immune function of these patients are ongoing and although much has to be learned, the very existence of such patients is encouraging for the goal of achieving clinical transplant tolerance on a less serendipitous and infrequent basis.

Problem-solving before clinical tolerance

Despite being achievable in rodents, tolerance has proved more difficult to obtain in large animal models and in the clinic. The reasons for this are not fully understood but one hypothesis is that of heterologous immunity, whereby T-cell memory resulting from previous immunological exposure acts as a barrier to tolerance induction [74]. The size of the memory cell pool in inbred rodents used for experimental research is limited compared with large animals and humans. However, it is not yet clear whether this phenomenon is restricted to experimental conditions in which memory T cells are committed to donor major histocompatibility complex (MHC). A related question is whether concurrent infection, providing a 'danger signal', may brake a tolerance state in humans. No abrupt rupture of tolerance was observed in our short series of patients displaying operational tolerance over decades [10].

Another problem facing tolerance is its stability over time. A number of factors including heterogeneity of donor–recipient combinations, underlying disease, and disturbance of the immunological state by infections and allergies may make stable tolerance difficult to achieve in humans. This so-called 'metastable' tolerance, where graft function eventually declines after long periods of stable function (recently reviewed in [75]), has been observed both in monkeys [76] and in humans [10]. Such a phenomenon gives credence to the idea of 'prope' tolerance discussed earlier, where patients are maintained on very low-dose IS.

One key issue that has to be resolved if tolerance is to reach the clinic on a routine basis is the need for reliable and both logistically and financially acceptable assays to identify and diagnose the state of tolerance or conversely, its breakdown. Such diagnostic tests will be fundamental to any potential immunosuppressive drug-weaning protocol in less permissive organs such as the kidney and heart and may reveal a higher frequency of tolerance than previously thought. However, the multiplicity of mechanisms involved in the phenomenon of tolerance means that its diagnosis will probably not be based on a single assay but rather on multiple parameters derived from complementary assays. To date, no test can single-handedly predict tolerance in the clinic. Nevertheless, certain analyses can give an indication of regulatory mechanisms, such as measurement of changes in dendritic cell subset ratios [77] or contrasting FoxP3/CD4+CD25+ and CD8 lymphocyte populations compared with patients presenting chronic rejection [48,72] or the use of the so-called '*trans-vivo*' delayed-type hypersensitivity assay [78]. One exciting new technical approach that is starting to be adopted in the field of transplantation and that could prove invaluable for the diagnosis of tolerance in the future is genome-wide gene expression profiling using microarrays, where thousands of genes can be measured simultaneously from a relatively small quantity of starting material such as a blood sample or biopsy. This approach therefore holds great promise as a diagnostic tool to identify patients under IS who are tolerating their graft and may therefore benefit from IS weaning.

Finally, ethical issues in tolerance induction trials also have to be considered (see [79] for review). The fact that immunosuppressive morbidity is now clearly less than the morbidity of a failed organ [80] challenges the assumption that immunosuppressive weaning would be worth the risk of graft loss. The success of a tolerance-inducing trial must therefore be better or equivalent to standard IS care and the patients participating in such trials must be chosen carefully.

Tolerance in the next decade – fact or fancy?

Despite the time lapse of 50 years since the first description of transplantation tolerance, there has been only modest success in achieving tolerance in the clinic, at least on a large scale. The most promising approach so far appears to be the use of BMT, although its applicability is currently limited to very small cohorts of patients meeting very specific clinical criteria. Further exploration of this approach as well as the co-stimulation strategy is warranted. The difficulties in achieving clinical tolerance question whether tolerance-inducing strategies in the rodent are really relevant to humans. Is tolerance in humans a completely different phenomenon? Looking at the literature, it does seem that rodent models unexpectedly do share a common trait with the human situation; this is that true tolerance in the absence of chronic rejection may not be as easy to achieve as one might think. Thus, in the clinic, different approaches such as drug minimization and combined procedures may be necessary. Finally, understanding spontaneous tolerance in humans may hold the key for achieving large-scale clinical tolerance in the future.

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