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REVIEW

Minimization protocols in pancreas transplantation

Diego Cantarovich and Fabio Vistoli

ITERT – Institut de Transplantation et de Recherche en Transplantation, Service de Néphrologie et d'Immunologie Clinique, Nantes University Hospital, Nantes, France

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Correspondence
Diego Cantarovich MD, PhD, ITERT – Institut de Transplantation et de Recherche en Transplantation, Service de Néphrologie et d'Immunologie Clinique, Nantes University Hospital, 30 Boulevard Jean Monnet, 44000 – Nantes – France. Tel.: +33 2 400 87440; fax: +33 2 400 87783; e-mail: diego.cantarovich@chu-nantes.fr

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Summary

Diagnosis of immunologic injury (acute and chronic) is much more difficult in pancreas transplants when compared with transplants of other organs. Currently, the immunosuppressive regimen for induction involves calcineurin inhibitors (CNI), antimetabolites and corticosteroids (Cs). This strong and nonspecific regimen does not take into consideration pancreas specificities (i.e. the need to avoid diabetogenic compounds). For obvious reasons, CNI might be calling for review, if permanently indicated in recipients of solitary pancreas with mild renal dysfunction. CNI as well as corticosteroids may induce hyperglycemia and contribute to differential diagnosis of a rejection process. However, in spite of the benefits accruing from withdrawal of above immunosuppressive agents, minimization or avoidance of these drugs could be dangerous and may end up with graft loss (i.e. antibody-mediated process). Long-term results of pancreas transplantation are now achieving comparable survival rates similar to the transplant of traditional organs such as kidney and liver. As a consequence, the physicians' objectives are to prolong the patient's quality of life and organ function as long as possible. Weaning strategies in regard to CNI and steroids are tested. Sirolimus, everolimus, CTLA-4 Ig, etc, are agents known to be either both nonnephrotoxic and nondiabetogenic or less so when compared with CNI. Their impact on pancreas transplantation is beginning to be evaluated. Large randomized trials in all pancreas categories, with long-term clinical and histologic results, are mandatory to establish new guidelines for immunosuppressive regimens for pancreas transplantation.

Introduction

In contrast to other solid-organ transplants, immunosuppressive regimens in pancreas transplant recipients should be adapted according to the time of transplantation and to the recipient's renal function stage (i.e. whether it is simultaneous pancreas and kidney transplantation, pancreas transplantation after successful kidney graft or pancreas transplantation in nonuremic patient). Pancreas allograft rejection is much higher in nonuremic recipients of a pancreas transplant alone (PTA), than in posturemic recipients of a pancreas after kidney transplant (PAK), and much lower in uremic recipients of simultaneous cadaver pancreas and living donor kidney (SPLK) and simultaneous cadaver pancreas and kidney (SPK) transplant [1–5]. As a consequence, type of induction and type of maintenance immunosuppression can vary between these categories and results need to be evaluated and interpreted accordingly.

Induction immunosuppression

Pancreas graft survival is statistically higher when antibodies (versus no antibodies) are used in all solitary and combined pancreas transplants. The use of antibody induction therapy remains higher for pancreas recipients than for recipients of any other solid organ with over 80% in the three main recipient categories: PTA 81%, SPK 80% and PAK 80% [2–5]. Polyclonal antibody induction with antithymocyte globulin (Thymoglobulin®; Genzyme S.A.S.,

Lyon, France) is the most frequent choice accounting for about half of all antibodies (poly and monoclonal) given. The monoclonal anti-CD-52-directed antibody alemtuzumab (Campath®; Genzyme Corporation, Cambridge, MA, USA) is coming into more frequent usage, accounting for 43% of PTA and 19% of SPK and PAK. It is the second most prevalent antibody used among all the three recipient categories. Anti-IL-2 receptor monoclonal antibodies are the third most commonly used group, with basiliximab (Simulect®; Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) use more common in SPK recipients and daclizumab (Zenapax®; Hoffman-La Roche Inc., Nutley, NJ, USA) in solitary pancreas. The use of muromonab-CD3 and horse antilymphocyte globulin has sharply decreased to less than 3%; muromonab-CD3 is still used to treat ongoing acute rejection [2–5].

Mostly all patients treated with antithymocyte globulin or anti-CD-25 antibodies are placed on tacrolimus [TAC – Prograf®; Astellas, Tokyo, Japan: mycophenolate mofetil – (MMF) Cellcept®; Hoffman-La Roche, Nutley, NJ, USA] based maintenance therapy. In contrast, a higher percentage of patients on alemtuzumab are treated with either TAC monotherapy or sirolimus (SRL – Rapamune®; Taplow, UK/MMF maintenance therapy) [2–5].

Seven main trials [6–12] evaluating induction therapies were identified: four [7–9,11] evaluated the benefits of daclizumab, basiliximab or antithymocyte globulin in addition to standard triple maintenance therapy (tacrolimus, MMF and steroids) versus same triple maintenance therapy without induction, one compared antithymocyte globulin versus no-induction therapy in patients who received cyclosporine (CyA), azathioprine (AZA) and corticosteroids (Cs) [6], one compared daclizumab versus antithymocyte globulin in solitary pancreas transplantation [12] and one [10] compared daclizumab in two different doses. None of these studies included any placebo arm. All these seven studies confirmed the beneficial impact of induction therapies in respect of reduction of biopsy-proven renal rejection rates from 76% to 36% ($P = 0.01$) [7]. However, no statistical difference in pancreas rejection rate was achieved (range: 3.6–10.3%, $P = 0.160$). One-year graft survival, in the no-induction group ranged from 86% to 90% whereas in the induction group the range was 84% to 96%. However, 3-year graft survival was statistically superior (92% vs. 82%) in the induction group ($P = 0.04$), suggesting beneficial long-term effects of this therapy [8].

Maintenance immunosuppression before hospital discharge

Excepted patients who received a solitary pancreas transplant, 90% or more of all other categories were under calcineurin inhibitors (CNI). Although recipients of isolated pancreas transplant are at higher risk of rejection than all other categories, some transplant centers prefer to avoid chronic CNI use to prevent native renal function impairment. Consequently and paradoxically this population received less maintenance immunosuppression than other pancreas categories. Four basic trends in maintenance immunosuppression during the initial hospitalization have been defined over time [2–5]:

1 Among CNI, TAC remains the dominant agent with over 80% use in all pancreas recipient categories. The use of CyA and its different formulations has been marginalized, from 1% in PTA to 9% in PAK [2–5].

2 The use of Cs for maintenance immunosuppression has slowly but steadily decreased. In 24% SPK and almost 50% PTA Cs were not given [2–5].

3 The antimetabolite of choice clearly is MMF: 80–85% of all SPK and PAK recipients and 63–71% of all PTA recipients are placed on MMF. Fewer than 2% of recipients in all three categories are placed on AZA [2–5].

4 The use of SRL remains fairly stable, ranging from 11% in PTA to 22% in PAK [2–5].

The combination of TAC and MMF is the most common grouping, accounting for 60–70% of all treatment regimens for SPK and PAK recipients. Only the PTA category has fewer than 60% of recipients placed on TAC/MMF [2–5]. The second most frequently used combination is TAC/SRL, accounting for 4–15% of protocols. CyA-based combination therapy (with MMF, AZA or SRL) has been used in fewer than 10% of recipients [2–5].

The CNI-free protocols during early transplant hospitalization remain uncommon. The use of SRL/MMF increased only in the PAK and SPK categories accounting for 2–7% of all combination regimens; its rate in the PTA category is less than 1% [2–5]. Interestingly, in the PTA and PAK, the use of other protocols such as the CNI- and Cs-free alemtuzumab-MMF-based protocol [13,14] has increased: these 'other' protocols accounted for 22% of therapy in the PTA, 10% in the PAK and 9% in the SPK category, respectively [2–5].

Two multicenter- [15,16] and two single center [17,18] studies compared the effects of the two available CNI, CyA and TAC. The results of 54 patients receiving either CyA or TAC with MMF were compared to a historical control group ($n = 18$) who received a CyA-AZA-based immunosuppression. There was no significant difference between TAC and CyA regarding kidney rejection rates (11% in each group), but patients receiving MMF (independently of the CNI) had a significant decrease in biopsy-proven kidney rejection rates from 77% to 11% ($P = 0.01$) [17]. A multicenter trial [15] including 150 patients showed a lower 6-month graft survival rate in the CyA group (70%) compared to TAC group (87%) ($P = 0.04$). The results of a larger multicenter trial with

induction, MMF, short-term Cs and CyA in 102 versus TAC in 103 patients demonstrated a lower rejection rate in favor of TAC (27.2% vs. 38.2%, $P = 0.09$). One-year pancreas graft survival was significantly higher in TAC group: 91.3% vs. 74.5%, $P < 0.0005$ [16]. These results were not confirmed by a randomized single center pilot study comparing CyA and TAC in the setting of systematic basiliximab-MMF-Cs immunosuppression and portal-enteric drainage in SPK transplant [18]. These two last characteristics in addition to a much lower incidence of graft thrombosis could be responsible of different final results.

Two randomized controlled trials [17,19] and one retrospective study [20] analyzed the outcome in patients with AZA in comparison to MMF. Two trials [17,20] suggested a benefit of MMF regarding rejection rates: 11% vs. 77% ($P < 0.01$) and 7% vs. 24% ($P = 0.003$), respectively; one trial [19] showed a trend (27% vs. 39%; $P = 0.3$). Patient survival rates were comparable between groups ranging from 93% to 100%. Graft survival was significantly lower for AZA in the retrospective report [20]; 83% vs. 95% ($P < 0.05$), whereas the two prospective trials [17,19] showed similar high rates of graft survival irrespective of the immunosuppression ranging between 85% and 100%. Differences between studies evaluating immunosuppression with AZA or MMF may be explained by number of included patients, different induction strategies and different primary endpoints. Altogether results indicate a superiority effect of MMF in main efficacy transplant parameters.

All immunosuppression regimens analyzed above included Cs. However, to prevent common side-effects of Cs therapy, there has been an increasing interest in favoring Cs-free multimodal immunosuppressive therapy for pancreas transplantation.

From published studies, it can be concluded that both CNI (CyA and TAC) confer similar protection against rejection with a possible benefit on graft survival for TAC. MMF is superior to AZA regarding rejection rates, and induction therapy decreases rejection rates and increases long-term graft survival. Rapid Cs elimination (1 week) appears to be a safe strategy. However, a recently published evidence-based analysis demonstrates that induction, TAC, MMF (or derivate) and Cs still remain the cornerstone drug combination [21].

Maintenance immunosuppression 1 and 2 years following pancreas transplantation

At the end of the first year following transplantation, 83% of all recipients receive a CNI. TAC is the predominant CNI employed. Excepted for PTA (53%), the pancreas transplant category less performed worldwide and more frequently 'experimented' with new immunosuppressive drugs, 75% or more of maintenance immunosuppression regimens include also an antimetabolite (MMF in the vast majority) [2–5]. The use of SRL generally increases during the first year. This may be because of the supposedly reduced diabetogenicity of m-TOR inhibitors, theoretically reduced fibrotic stimulation, and principally in order to avoid the delayed healing of the wounds, which is certainly to be reckoned in this major abdominal surgery. By the end of the first year, it is administered in 23% of the SPK, 23% of the PAK and 21% of the PTA [2–5]. Despite the growing application of Cs avoidance and withdrawal, 'triple immunosuppression' with a CNI, Cs and either an antimetabolite or SRL predominates at discharge and at 2 years following transplantation for those patients transplanted more recently. The trends in maintenance immunosuppression within the first year following pancreas transplantation have been similar to trends during the initial pancreas transplant hospitalization [2–5]:

1 Beginning in the mid-1990s, TAC is the most common CNI, even at the first year following transplantation: 74% (PTA), 76% (PAK) and 82% (SPK) of recipients are on TAC at 1 year follow-up. Percentage of CyA-based maintenance immunosuppression decreased to about 10% for SPK, 8% for PAK and 8% for PTA recipients [2–5].

2 About 20% of SPK and PAK recipients and about 40% of PTA recipients are receiving Cs-free regimens. These numbers are slightly lower than that during the initial transplant hospitalization, indicating that some recipients are administered Cs later on [2–5].

3 Among antimetabolites, MMF is most commonly used for maintenance. About 80% of PAK and SPK recipients are receiving MMF at 1 year after transplantation; only for PTA recipients, the percentage is lower (59% in 2003). Since 2001, ≤3% of the recipients in all the three categories is given AZA [2–5].

4 The use of SRL increases within the first year following transplantation (versus the initial transplant hospitalization): 25–32% of all recipients are receiving SRL, about 10% more than during the initial transplant hospitalization. This trend toward greater usage of SRL after transplantation may be again explained by concern over a higher incidence of SRL-associated wound complications immediately following transplantation [2–5].

The most common combination therapy for the first year in all the three recipient categories is now TAC/MMF: it is given to 55–60% of SPK and PAK recipients. Only in the PTA category, a decrease in the use of this combination is noted (as previously commented). This immunosuppressive combination, however, seems to be responsible for a high incidence of BK virus infection and nephropathy [22].

The administration of 'other' protocols (18% PTA) has become important only in PTA category in most recent years. This finding may also reflect the increased use of alemtuzumab-MMF-based protocols that are free of both CNI and Cs (to prevent native kidney renal function impairment). Over a period, the use of TAC-SRL (versus TAC-MMF) had increased. In the second year following transplantation, about 17–20% of recipients in all pancreas transplant categories received TAC-SRL (versus 55% on TAC-MMF). This change may reflect TAC-MMF-associated gastrointestinal problems, and/or TAC-induced renal and/or pancreas toxicity. In the second year following transplantation, ≤2% of all protocols is SRL-MMF (CNI-free) [2–5].

Outcome by maintenance regimen

According to the last published IPTR reports, the 1-year pancreas graft survival rates for 2000–2004, for recipients of primary deceased donor pancreas transplants who were given anti-T-cell induction therapy and TAC-MMF for maintenance therapy, were as follows: 88% for SPK, 83% for PAK and 80% for PTA recipients. If TAC-SRL was used for maintenance therapy, the rates were quite similar: 87% for SPK recipients and 83% for both PAK and PTA recipients. Multivariate model analysis showed a highly significant reduction in early and late pancreas graft failure rates with TAC-MMF. The use of SRL also decreased, independently, the hazard ratios for pancreas graft failure as TAC-MMF [3,5].

Besides the nephrotoxic effect, CNI have other deleterious effects, including diabetogenicity, which is an important factor in pancreas transplantation [23]. These two factors may provide reasons to minimize or to avoid CNI; however, one has to consider the disadvantages as regarding chronic rejection rate mediated by de novo anti-donor antibodies.

Maintenance regimen change and discontinuation

A relatively low percentage of recipients in all categories continue on their original immunosuppressive discharge protocol throughout the first 3 years following transplantation. The highest rate of regimen change occurred within the first year, but modifications continued throughout the second and third year. From recipients placed on a regimen of TAC-MMF, only about 40–60% remained on it 3 years later. Likewise, from recipients on TAC-SRL, only 33% (PTA) remained on it 3 years later. Of note, the relatively small fraction of recipients on SRL-MMF (CNI-free) at the time of their initial transplant hospitalization is similar to that seen 3 years later [2–5]. As previously mentioned and according to evolution in transplantation techniques, changes in immunosuppressive protocols are regularly done with the objective of prolonging the graft survival. Numerous reasons are responsible for drug dose modifications, interruptions and switches. In the absence of guidelines for the long term follow-up of these transplants, each center provides its better knowledge to each single patient.

Corticosteroid withdrawal and avoidance

The use of Cs following pancreas transplantation does not seem to be indicated as Cs may induce hyperinsulinemia, hyperinsulinism and insulin resistance, all conditions favoring the development of hyperglycemia. This abnormal metabolic status could interfere with normal graft function and mimic graft rejection. So far, rates of both the Cs withdrawal and avoidance have been applied later than the same in other organ transplant. In 2004 (vs. 2000), 49% (vs. 17%) of PTA recipients and 24% (vs. 3%) of SPK recipients were on Cs-avoidance regimens. The Cs-withdrawal rates at 1 and 2 years following transplantation have remained stable (at about 10%) for SPK recipients; this rate represents a clear increase from 1998 (<3%) [2–5]. In general, Cs avoidance has been more adaptable than Cs withdrawal for the pancreas recipients. Cs-avoidance protocols were more commonly used in patients treated prophylactically by antithymocyte globulin or alemtuzumab, and much least commonly if anti-CD-25 antibodies (or no antibodies at all) are given [2–5].

Minimization of immunosuppression (one-drug regimen)

In general and surprisingly, minimization of immunosuppression to one maintenance drug is less frequent in SPK recipients and more common in PAK and PTA recipients. PAK patients are under immunosuppression at the time of pancreas transplantation. The new graft does not increase the incidence of rejection and so far it may be safer to minimize to one drug in this setting. PTA recipients are much more exposed to rejection and autoimmune recurrence than other categories. However, the selected immunosuppressive regimen may include drugs that avoid renal function impairment and potential need for renal replacement therapy in the long-term. This may partially explain this confounding finding.

The percentage of SPK recipients receiving only one drug at the time of their hospital discharge and within the first 3 years following transplantation ranges from 0.4% to 6.4%; the most commonly used drug for monotherapy is TAC (≥50%), followed by MMF and SRL [3–5]. Up to 11% of PAK recipients are on only one drug

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at discharge, but the percentage decreases within the first 2 years post-transplant (down to 4%), and increases again in the third post-transplant year (up to 12%). For PAK recipients, MMF is the most commonly used drug for monotherapy [3–5]. For PTA recipients, an increase in monotherapy during the initial transplant hospitalization is noted in more recent years (up to 33%) [3–5]. Over time, monotherapy is not sustained because of high degree of rejection, and by the third year, no more than 6% remains on monotherapy. MMF is the most commonly used drug for monotherapy during the initial hospitalization and in the third year following transplantation, but TAC is the most commonly used drug in the first and second year.

One-drug minimization therapy (TAC, MMF, SRL etc) although possible in some patients, seems not applicable to the majority of them. In clinical practice, rejection side-effects and graft function represent the main reasons to move from monotherapy to low-level dual or triple therapy. This cross-over attitude is very common in the mid- and long-term follow-up, impeding a true analysis of a single immunosuppressive regimen.

Calcineurin inhibitors avoidance/withdrawal in corticosteroid-based regimen

There are sporadic reports of CNI being withdrawn or avoided in pancreas transplantation. Knight *et al.* [24] reported 125 pancreas recipients in whom CyA was converted to MMF at 6 months post-transplant using SRL-based regimen. There were no rejections or losses at 9-month follow-up. Interestingly, eight of 12 patients who were considered at immunological risks were off Cs at the time of conversion. Gautam *et al.* [25] reported conversion of TAC to SRL in seven PAK recipients who had more than 25% increase in serum creatinine from baseline. This was in the setting of an MMF-Cs-based regimen. Renal function as measured by serum creatinine stabilized or improved in all cases. However, there were four cases (36%) of early rejection of the pancreas graft.

Calcineurin inhibitors avoidance in corticosteroid-free regimen

There are only two centers with significant experience in dual CNI- and Cs- avoidance in pancreas transplantation: Northwestern University and the University of Minnesota. Northwestern University [26] reported a retrospective study of 54 SPK recipients on MMF-SRL compared to 50 historical controls on TAC-SRL. A single dose of alemtuzumab 30 mg was used for induction. Mean follow-up was 14.5 months. The rejection rate in the CNI-free group at 1 year was about 25%, compared to 10% for the control group. However, the serum creatinine in the CNI-free patients was lower than in the CNI-maintained patients. Another more recent retrospective study [27], comparing alemtuzumab (single dose of 30 mg) and antithymocyte globulin, in patients who were also receiving SPK transplants showed excellent 3-year graft and patient survival rates with no acute rejection rate difference. Incidence of viral infections and cost of induction was significantly lower in the alemtuzumab group.

The University of Minnesota experience with dual CNI- and Cs-avoidance was initially reported in 2005 [14]. They reported the first 75 patients treated with alemtuzumab for induction and maintained with MMF as the only oral agent. This is an interesting report in that alemtuzumab was given in four 30 mg doses over the first 42 days together with one dose of antithymocyte globulin on day 4 to remove any CD52 cells. Alemtuzumab was then given whenever the total lymphocyte count was greater than 200/mm^3, along with treatment for acute rejection, for a maximum of 12 doses. This group was compared with historical controls (2000–2003) on TAC-MMF (n = 266). The two study groups were subdivided into SPK, PAK, and PTA. With a minimum follow-up of 6 months, there was no significant difference in patient and graft survival rates between the two groups or between the subgroups. No grafts were lost from rejection during the first 6 months. The incidence of acute rejection was not significantly different in the PAK and PTA subgroups but was significantly higher in the alemtuzumab-treated SPK group compared with the antithymocyte globulin-treated SPK group. In view of the fact that alemtuzumab was used for maintenance immunosuppression in this trial, it is important to note that the investigators found no increase in infection compared with the control group and there were no instances of post-transplantation lymphoproliferative disease (PTLD).

Between May 2003 and July 2005, there were 156 pancreas transplant recipients treated with this protocol. A new analysis was performed again on the first 140 patients (51 PAK, 50 PTA, and 39 SPK) and reported [28,29]. Incidence of immunologic graft loss was higher for PTA recipients in the CNI-free group. Incidence of rejection episodes was also higher for SPK and PAK recipients in CNI-free group. In addition, incidence of infections (both intra-abdominal: 17% vs. 7%, and systemic: 33% vs. 14%) was increased in the CNI-free group. The CMV and PTLD rates were not different in the study groups; however six cases of red cell aplasia in the CNI-free group and none in the controls were recorded. At 1 year post-transplant, about 50% of recipients remained on MMF monotherapy. On the positive side, there was improved creatinine clearance (estimated with the modified diet in renal disease method) at 6 months in the PAK group.

Because of the increased rejection and infection rates with alemtuzumab maintenance, the protocol was discontinued and solitary transplant recipients resumed the previous original protocol of antithymocyte globulin induction (7.5 mg/kg) and TAC-MMF maintenance since August 2005. Some of SPK recipients were being enrolled in a CNI-withdrawal trial as part of a larger prospective randomized trial in kidney transplants comparing TAC-MMF versus CyA-MMF with CNI conversion to SRL at 6 months.

Most of the comparisons using alemtuzumab for induction immunosuppression in pancreas transplantation involve the use of historical controls in which antithymocyte globulin [14,27,28] was used for induction. The results are mixed, although, in general, they tend to suggest that the incidence of acute rejection might be lower in the short-term but higher in the mid- long-term in the presence of alemtuzumab induction. Therefore, at this moment in time, there is no sound evidence that induction with alemtuzumab is superior in terms of prevention of rejection than antithymocyte globulin or monoclonal anti-IL-2 receptor antibody. Because of the long-lasting lymphopenia, especially of B and T lymphocytes, produced by alemtuzumab, it had been hoped that its use might facilitate the development of Cs-free and CNI-sparing or CNI-free regimens to avoid the long-term complications of these agents, particularly nephrotoxicity in the case of the latter.

Most of the studies have used alemtuzumab induction with a Cs- and CNI–free protocol [14,26–28]. As of yet, none of the retrospective studies of CNI-free or CNI-reduced immunosuppression and alemtuzumab induction in renal transplantation have been able to show any significant improvements in renal function compared with conventional therapies. This may be a reflection of the limited follow-up in these studies. At the longest follow-up reported in a kidney transplant setting (5 years) [30], there was no significant difference in renal function in the alemtuzumab group that received reduced CyA as maintenance immunosuppression, despite the fact that the patients in this group received significantly less CyA than the control group for the first 2 years after transplantation. Alemtuzumab induction allowed achieving spaced weaning of TAC to every other day or less in 74% of patients, but at 1-year follow-up, there was no significant difference in renal function [31]. In a Cs- and CNI-free protocol, no significant difference in renal function was seen in a series of SPK transplants, but it was recorded in a small PAK series [28]. In general, CNI avoidance appears to have a negative effect on rejection rates in most trials, even though there seems to be a beneficial effect on kidney function. The exception to this trend is the Belatacept study on kidney transplantation where at 12 months, there is not only less rejection but also less chronic allograft nephropathy and less hypertension and hypercholesterolemia in the calcineurin avoidance group receiving Belatacept CNI-free maintenance [32]. This certainly suggests that nondepleting antibody maintenance may be a new promising strategy to be explored for avoiding CNI in pancreas transplantation. The risks and benefits of CNI- and/or Cs-avoidance should be evaluated in prospective randomized studies; in the meantime this balance can be only evaluated individually according to each center's experience.

Conclusion

Not being yet able to achieve transplant tolerance (i.e. zero drug), transplant physicians try to diminish the number of immunosuppressive drugs currently used (minimization) in order to prevent or avoid side-effects and adverse events, potentially more serious than the benefit obtained by continuing the drug. This critical balance is somewhat brittle and differs with respect to the vital transplant organs such as the heart or the liver. Surveillance biopsy of the pancreas can represent an important tool in deciding drug minimization; however such procedure is much more risky as compared with other solid organs mostly when repeated systematically. In addition, there is no available data describing this strategy as a major end-point. Although histologic informations may be relevant including new histopathologic schema [33], the true specificity is still a matter of debate and the balance between benefit and risk must be discussed case to case. Furthermore combination of anti-HLA antibodies screening [34] plus protocol pancreas biopsy monitoring could represent the new-gold-standard surveillance for future randomized studies. The pancreas graft is a composite organ including the duodenum, lymph nodes, exocrine and endocrine tissues. Antigenicity as well as immunogenicity is more pronounced than other organs. In addition, recipient auto-immunity is always present and represents an additional risk-factor for graft failure.

So far, and in order to prevent allo- and auto-immune reactions, 'heavy immunosuppression' is required (even started months before transplantation) including T-cell depletion antibodies in association with well-known maintenance combination such as CNI, MMF and Cs. Whether minimization can be applied to all pancreas transplant categories is not yet established. SPK are lowest immunologic risk group and PTA the highest one. Majority of experiments are successfully conducted in SPK patients, however long-term results and histologic confirmation of no major chronic lesions are lacking. For PTA, avoidance of nephrotoxic drugs seems mandatory. At present, this approach does not seem realistic.

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