Tailoring immunosuppressive therapy

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Introduction

In the last decade, a paradigm shift has occurred in the field of renal transplantation. The use of new and powerful immunosuppressive drugs has led to excellent short-term patient and graft survival and very low acute rejection (AR) rates. Two burning questions have become paramount. The first is how can we improve long-term patient and graft survival despite the fact that more elderly patients are transplanted and that the growing demand for donor organs is more often counterbalanced by the use of marginal donors? The second question is how should we tailor the optimal immunosuppressive therapy to the individual patient profile? It is clear, for example, that a patient suffering from osteoporosis and diabetes mellitus will not benefit from the same immunosuppressive drug protocol as a patient who has severe arterial hypertension and hyperlipidaemia (Table 1). The older principle of ‘one fits all’ has become more and more obsolete. The first step in solving these questions is to examine which tools can be employed to objectively assess the individual efficacy/toxicity profile of specific drug regimens and to test the validity and reproducibility of these tools in clinical practice. The second step is to evaluate the presumed net beneficial effect of the progress made in immunosuppressive drug therapy in order to improve the efficacy/toxicity profile.

In the last few years, very interesting and even controversial studies have been conducted in order to answer these questions. Steroid trials were the first attempt in that direction; reduced-dose calcineurin inhibitor (CNI) late introduction of CNI studies were soon to follow. At present, we are entering an era where CNI-free protocols are being put to the test and combinations that were initially considered impossible, such as mycophenolate mofetil (MMF)–rapamycin or tacrolimus–rapamycin, are under evaluation. Lastly, induction strategies using new monoclonal antibodies enable the use of minimal effective doses of concomitant immunosuppressive drugs. The challenge is to try and learn how patients might benefit in the long term from these new protocols rather than to focus on overall positive short-term results. As professionals involved in the daily care of patients living with a donor organ, we are experiencing exciting and provoking innovations. A brief and necessarily incomplete overview of recent studies trying to tackle these questions is presented here, focusing mainly on the results of randomized controlled trials.

Corticosteroids

Since transplanting without steroids is still a rare accomplishment reached by only a few [1], a low initial steroid dose followed by early complete elimination
has proven to be a realistic and achievable goal [2,3]. In a recent trial of the Steroid Dosing Study Group [2], patients were treated with cyclosporine A (CsA) and MMF in combination with a full steroid dose (30 mg/day) \((n = 248)\) or with a low steroid dose (15 mg/day) \((n = 252)\) that was stopped after three months. The overall incidence of AR at 1 year was significantly higher in the low/study group \((25 vs 15\%)\). The greatest difference in AR occurred in the first 15 days after transplantation \((day 0–28: AR 16.2 vs 9.7\%)\) and after stopping steroids at 3 months \((day 84–182: AR: 4 vs 0.4 \%)\). The difference was more pronounced between study subgroups for recipients who did not receive induction therapy, had a re-transplant or received a graft from a living related donor. One can speculate about the implications that two interventions were made at the same time in the low/study group (reducing and stopping). Limiting the intervention to just stopping the usual dose of steroids at 3 months might (in retrospect) have resulted in an estimated 1 year rejection rate around 18.5\%; however, this would have been achieved at the cost of a higher cumulative steroid dose. The latter is important because the lower 1 year cumulative steroid dose in the low/study group \((1678 vs 4413 mg)\) precisely resulted in an important reduction of steroid-related side effects. Both systolic and diastolic blood pressure as well as total serum cholesterol and triglycerides were significantly lower in the low/study group at the end of the study. Lumbar spine bone density was greater in the patients receiving a low dose of steroids. Patient and graft survival was excellent in both groups and the higher incidence of AR in the low/study group did not result in a worse 1 year graft function. Ninety-three percent of the patients who were able to stop steroids \((n = 174)\) remained free of steroids at 1 year.

In another large study [3], tacrolimus was used in combination with MMF and steroids. In this randomized controlled trial comprising 838 patients, steroids were stopped after 3 months in one-third of the eligible patients \((n = 220)\), MMF was stopped in another third of the patients \((n = 218)\) while the remaining patients \((n = 224)\) continued on triple therapy. Randomization into the three study groups was performed at the time of transplantation so as to avoid a selection bias. Pre-randomization total biopsy-proven AR incidence was 15.1\%. From randomization up to 6 months, the incidence of AR was 5.5\% in the steroid-stop group vs 3.7\% in the group that stopped MMF and 1.3\% in the triple drug group. The change in serum total cholesterol from baseline, which was the primary study endpoint, was significantly higher in patients who stopped steroids \((-19.7 + 6.6 mg/dl)\) in the triple group and \(+3 mg/dl)\) in the MMF-stop group, \(P < 0.001\); as was the change in LDL cholesterol \((-8.1 + 6.9 mg/dl, P < 0.001)\) and HDL cholesterol \((-7.36 + 0.386 1.931 mg/dl, P < 0.001)\). As a result, the LDL/HDL ratio was not different between the three arms \((2.67 vs 2.59 and 2.39)\). The changes in triglycerides were not significant amongst the three study arms. Discontinuing either of the two drugs in this study did not result in an inferior patient survival, graft survival or function after 6 months.

Interestingly, in the group that stopped steroids at 3 months, a transient but significant increase in the tacrolimus blood trough concentration was observed, possibly caused by a diminished steroid-induced metabolism of tacrolimus [4]. Transiently higher tacrolimus levels might have been responsible for rises in serum creatinine leading to more frequent biopsies in the group of patients who were followed particularly closely. This interpretation is somewhat speculative but considering the fact that most of the AR episodes after stopping steroids were graded as mild (70% Banff grade I), the pro and cons for performing routine renal biopsies to distinguish subclinical rejections under these study conditions, remain a subject of debate.

Whether the beneficial changes in lipids and blood pressure [2] induced by an early stop of steroids will translate into a decrease of overall cardiovascular morbidity and mortality remains to be seen. It seems that the small but significant increment in ARs, which is the price to pay for stopping steroids, does not influence graft survival and function, at least not up to 1 year of follow-up.

At present, results of a randomized controlled trial are expected, examining the possibility of using only intra-operative steroids together with tacrolimus and MMF or tacrolimus with basiliximab.

### Table 1. Toxicity profile of current immunosuppressive drugs

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>CsA</th>
<th>Tacrolimus</th>
<th>Rapamycin/RADB</th>
<th>MMF</th>
<th>Azathioprin</th>
<th>IL-2-Rb mAb</th>
<th>Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial hypertension</td>
<td>+ + +</td>
<td>+</td>
<td>-</td>
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<td>+ + +</td>
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<tr>
<td>Nephrotoxicity</td>
<td>+ + +</td>
<td>+ + (+)</td>
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<td>+ + +</td>
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<tr>
<td>Neurotoxicity</td>
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<td>+ + (+)</td>
<td>+</td>
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<td>+ + +</td>
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<td>PTDM(^a)</td>
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<td>+ +</td>
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<td>+ + +</td>
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<tr>
<td>Hyperlipidaemia</td>
<td>+ +</td>
<td>+ (+)</td>
<td>+ + +</td>
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<td>+ + +</td>
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<td>Gastrointestinal disorders(^d)</td>
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<td>+</td>
<td>+</td>
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<td>+ + +</td>
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<tr>
<td>Bone marrow</td>
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<td>+</td>
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<td>+ + +</td>
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<tr>
<td>Esthetical changes</td>
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</tbody>
</table>

\(^a\)IL-2-Rb mAb, IL-2 receptor blocking monoclonal antibodies (daclizumab, basiliximab).

\(^b\)PTDM, post-transplantation diabetes mellitus.

\(^c\)Rapamycin/RADB without calcineurin-inhibitor.

\(^d\)Gastrointestinal disorders (diarrhea, abdominal pain, nausea and vomiting) exclusive hepatotoxicity.
Calcineurin inhibitors

A trial that rekindled the interest in transplanting kidneys without using a CNI in order to avoid nephrotoxicity was published recently by Vincenti et al. [5]. Ninety-eight first kidney recipients were treated with MMF (3 g/day) in combination with steroids and induction with daclizumab (five doses). Fifty-two patients (53%) developed AR of whom 10 were steroid-resistant. A total of 62% of patients were started on a CNI during the trial. Patient and graft survival at 12 months was excellent (97 and 96%, respectively). Patients free of rejection and CNI treatment had a mean 1 year serum creatinine level of 1.28 mg/dl (113 μmol/l). Despite the fact that this was a single-arm multi-centre study with a high treatment failure rate, it has created the basis for new trials examining the feasibility of lowering the dose of CNI or stopping their administration early after transplantation. Another similarly structured single-centre study [6] using induction with anti-thymocyte globulin (ATG-Fresenius, 4 to 10 days) instead of daclizumab proved highly effective for elderly patients (64±5 years) who had received grafts from old donors (67±7 years). Only 25.5% of patients (n = 55) developed AR.

Flechner et al. [7] recently compared their CNI-free protocol of sirolimus in combination with MMF, basiliximab induction and steroids with a comparative CsA-based regimen. The incidence of AR was extremely low in both study groups (sirolimus 3.6% vs CsA 11.5%), especially when considering that one patient in four was of African American origin. Mean serum creatinine at 1 year was significantly lower for patients not receiving CsA (1.10 vs 1.88 mg/dl, P = 0.009).

The studies of Groth et al. [8] and Kreis et al. [9] have both shown that using sirolimus in combination with azathioprin or MMF resulted in a higher (but not significant) incidence of AR compared with CsA (41 vs 38% and 27.5 vs 18.4%, respectively). Graft function was better in the CNI-free study groups although not significantly so after 1 year. Sirolimus-treated patients suffered more frequently from hyperlipidaemia, thrombocytopenia, leukopenia and pneumonia while patients on CsA more often had arterial hypertension [8], tremor, gingival hyperplasia and hyperuricaemia.

The fact that tacrolimus is more efficient in preventing AR than CsA [10,11] and Neoral [12] has neither resulted in better graft function [10,11] nor in reduced biopsy-proven CNI nephrotoxicity [13]. The Cardiff trial biopsy data [14], however, contradicts the latter finding. What is clear from the US trial [10] and the European trial [11] is that systemic blood pressure, total serum cholesterol, LDL cholesterol and triglycerides (US trial only) are significantly lower in tacrolimus-treated patients [15–17]. Esthetical side-effects such as hypertrichosis and gum hyperplasia were not seen with tacrolimus. The incidence of post-transplantation diabetes mellitus (PTDM) is a serious complication of tacrolimus therapy, more so because the deleterious effects on graft survival only become apparent after many years [18]. However, the incidence of PTDM seems to decline with growing clinical experience with the drug [10–12,19], as reflected by lower target trough levels. Especially for patients at risk for PTDM (advanced age, obesity, pre-diabetes, African Americans), careful monitoring of glucose metabolism is indicated [20] and tacrolimus should probably not be the first choice calcineurin inhibitor.

mTOR inhibitors

The finding that sirolimus and everolimus augment CsA-induced nephrotoxicity [21] has led to new studies examining the feasibility of withdrawing CsA from a sirolimus-based regimen early after transplantation. In the CsA-elimination trial [22], 525 patients were initially treated with a combination of sirolimus, CsA and steroids. After 3 months, eligible patients were randomized to either continue on the triple regimen (n = 215) or to stop CsA (n = 215). Consequently, the target pre-dose trough blood levels for sirolimus were raised from 5 to 20–30 ng/ml in the first year and 15–25 ng/ml thereafter. The total pre-randomization AR incidence was 13%. Stopping CsA resulted in 9.8% additional AR vs 4.2% in the control group. After 2 years of follow-up, graft function remained significantly better in the CsA-free group (glomerular filtration rate 64.8 vs 54.7 ml/min, P < 0.001). Furthermore, patients who stopped cyclosporine maintained a better systolic blood pressure control and treatment-emergent arterial hypertension was less frequent in the CsA-elimination arm after 2 years (9.3 vs 22.3%, P < 0.001). Total cholesterol and HDL cholesterol were both higher in the CsA-elimination arm; use of lipid-lowering drugs was similar in both groups (86 vs 87.4%).

The results of a similar US-based trial (n = 246) confirmed these findings [23].

The combination of sirolimus and tacrolimus has long been deemed impossible. Recently, two phase 2 trials have been conducted following the positive experience in pancreas, kidney and liver transplantation [24]. The preliminary 3 months’ results of one of these dose-finding studies [25] indicate that patients treated with a usual dose of tacrolimus and 0.5 mg rapamycin (and steroids) have a low biopsy-proven rejection rate (8%). Adding 1 or 2 mg of rapamycin did not improve efficacy but increased the incidence of hypercholesterolaemia. In the second of these phase II trials, the same combination (standard tacrolimus and low-dose rapamycin) resulted in 7.7% AR at 6 months [26]. This 7.7% AR is based on 92 patients enrolled instead of 30 or 40 before, and thus is much more accurate. Whether combining these two drugs will produce better long-term side-effect profiles remains to be determined.

Drugs that enable the use of lower concomitant drug concentrations

The IL-2 receptor blocking monoclonal antibodies daclizumab [27,28] and basiliximab [29] have proven
their efficacy in combination with CNI and are currently under investigation in pilot studies with new combinations (sirolimus, FTY720, MMF and CTL4Ig analogues). These pilot studies are primarily aimed at efficacy-endpoints but will possibly produce new incentives for low-toxicity immunosuppressive drug combinations.

**Conclusion**

Evidence-based tailoring of immunosuppressive drug combinations to the individual patient profile is an emerging aspect of third millennium transplantation medicine. Over the last 5 years an increasing number of well-designed studies have been conducted to answer, although only indirectly, clinically relevant questions as to the optimization of immunosuppressive therapy according to the patient profile. The fact that in recent trials the classical ‘secondary (safety) endpoints’ have been promoted to the status of ‘primary endpoints’ is an important step towards ‘tailoring’ immunosuppression to individual needs.

**References**


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