Prevention of Transplant Rejection
Current Treatment Guidelines and Future Developments

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Summary

In the past 2 decades, progressive improvements in the results of organ transplantation as a therapeutic strategy for patients with end-stage organ disease have been achieved due to greater insight into the immunobiology of graft rejection and better measures for surgical and medical management. It is now known that T cells play a central role in the specific immune response of acute allograft rejection. Strategies to prevent T cell activation or effector function are thus all potentially useful for immunosuppression.

Standard immunosuppressive therapy in renal transplantation consists of baseline therapy to prevent rejection and short courses of high-dose corticosteroids or monoclonal or polyclonal antibodies as treatment of ongoing rejection episodes. Triple-drug therapy with the combination of cyclosporin, corticosteroids and azathioprine is now the most frequently used immunosuppressive drug regimen in cadaveric kidney recipients.

The continuing search for more selective and specific agents has become, in
the past decade, one of the priorities for transplant medicine. Some of these compounds are now entering routine clinical practice: among them are tacrolimus (which has a mechanism of action similar to that of cyclosporin), mycophenolate mofetil and mizoribine (which selectively inhibit the enzyme inosine monophosphate dehydrogenase, the rate-limiting enzyme for *de novo* purine synthesis during cell division), and sirolimus (rapamycin) [which acts on and inhibits kinase homologues required for cell-cycle progression in response to growth factors, like interleukin-2 (IL-2)]. Other new pharmacological strategies and innovative approaches to organ transplantation are also under development. Application of this technology will offer enormous potential not only for the investigation of mechanisms and mediators of graft rejection but also for therapeutic intervention.

Organ transplantation as a treatment modality for patients with end-stage organ diseases of the kidney, heart, liver, pancreas and small bowel has achieved impressive results in the past 2 decades, thanks to a better understanding of basic immunobiology and more advanced measures for medical and surgical management. Although 1-year graft survival is now close to 85%, at least for cadaveric kidney transplantation, allograft rejection remains the major cause of loss of grafts in the first year. Moreover, although it can be overcome by antirejection therapy, once rejection occurs it may have a negative impact on long term graft survival.

Research in transplantation-related immunobiology has much improved our understanding of the alloimmune response and provides evidence of a complex interplay of T cell subsets and cytokines in the events of acute rejection. Direct manipulation of the host’s immune responses allows a practical means of achieving engraftment even when donor and recipient tissue matching is less than optimal. Although immunosuppressive therapies to overcome host reaction to allografts have been employed since the early days of clinical transplantation, immunosuppressive agents and treatment protocols are constantly evolving.

In the 40 years since corticosteroids were first found to be immunosuppressive in animals, only 4 drug classes (corticosteroids, azathioprine, cyclosporin and anti–T cell antibodies) have been widely employed in transplant patients. However, better understanding of the basic immune mechanisms has led to the development of several new xenobiotic immunosuppressants which have entered clinical trials in the past few years. Although their clinical utility remains to be determined, interest in these compounds will probably change the ways we control the immune system in organ transplantation. In view of the growing number of new, potentially clinically applicable immunosuppressive agents under development, the current field of anti-rejection drugs, and future developments in this field, will be reviewed.

### 1. T Cell Activation in the Immune Response to an Allograft

In experimental animals with congenital or induced T cell deficiency, organ or tissue grafts survive indefinitely, indicating that T cells play a central role in the specific immune response of allograft rejection. Strategies to prevent T cell activation or effector function are thus all potentially useful for immunosuppression. Binding of alloantigens presented in the context of the major histocompatibility complex (MHC) molecule to the T cell receptor (TCR) on the surface of T lymphocytes through direct and indirect recognition pathways[^1^][^2^] is the starting signal for T cell activation (fig. 1). Engagement of TCR with alloantigens recruits and activates a series of tyrosine kinases including p56^lck^, p59^fyn^ and ZAP-70, followed by phosphorylation and activation of phospholipase C, and ultimately a rise in intracellular calcium[^1^]. This leads to activation of calcineurin enzyme, a serine-threonine phosphatase, that transduces signals to the nucleus to transcribe genes encoding

[^1^]:...
[^2^]:...