Current status of immunosuppressive minimization and tolerance strategies

Sophie Brouard, Klemens Budde

TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

GUEST EDITORIAL

Current status of immunosuppressive minimization and tolerance strategies

Transplantation is the treatment of choice for end-stage renal disease. Its success relies on effective immunosuppression to prevent allograft rejection. Previously, rejection rates were high, and graft loss due to rejection was frequent. As a consequence, we were taught over decades that a reduction in rejection rates is the main goal in transplantation to improve outcomes. Despite dramatic reduction in rejection rates, long-term graft survival has not improved over the last decades, partly due to acceptance of more marginal donors. Today, graft loss due to acute rejection is low (<5%) and short-term patient and graft survival are excellent leading to different expectations for future drug regimens. Such regimens should aim to improve suboptimal long-term outcomes, either by a reduction in the incidence of death with a functioning graft or by addressing the many causes of chronic allograft dysfunction (either immunologic or nonimmunologic).

Since the introduction of immunosuppression, patients have suffered from the many side effects of those drugs, which are given to protect the new allograft. Indeed, besides the cost, lifelong immunosuppression is associated with numerous side effects including infectious complications, malignancies, haematological and gastrointestinal toxicities as well as metabolic disorders that all contribute to morbidity and mortality among transplant recipients. Moreover, the nephrotoxicity of calcineurin inhibitors, which helped to revolutionize transplantation, is the most prominent example in this context. Together, these drug-associated problems are putting a high burden on our patients leading to additional healthcare costs, incompliance and dose reductions, which result in lower immunosuppressive efficacy and limited long-term success of current regimens. Overimmunosuppression (e.g. opportunistic infections and malignancies) caused by a too strong suppression of the immune system remains another important problem in our daily practice. We all know patients, who have died prematurely as a direct or indirect consequence of their immunosuppressive therapy. It is obvious that future immunosuppressive drug regimens should aim to have less toxic side effects and cause less frequently overimmunosuppression and by this means, it leads to an improved quality of life. As a consequence, it has been proposed for decades that the use of immunosuppressants should be reduced and/or limited, and numerous trials were undertaken to investigate safe minimization strategies. The current focus issue therefore tries to summarize the need for such strategies, who are aiming to reduce immunosuppressive side effect burden.

In the search for better outcomes with less side effects, the transplant community has gone a long and winding road over the last 60 years. This path included many detours, and many of those attempts were not successful. Since the early days of transplantation, the holy grail of transplantation always was the way towards tolerance. Any strategy which would cause acceptance of the graft would dramatically reduce immunosuppressive burden and enable long-term graft survival. Up to date, we did not find the holy grail. At best we found out, why our strategies did not work and learned a lot about the complexities of the immune system. This focus issue therefore summarizes the current status of tolerance and the recent discoveries in this field.

An alternative to complete avoidance of immunosuppression is minimization strategies. Today, standard immunosuppression comprises of a multidrug combination therapy with several components, each with a different mechanism of action. Ideally, such a drug regimen should provide synergistic efficacy. By this means, each individual drug can be substantially reduced without loosing efficacy to avoid dose-dependent drug toxicities. Together with the introduction of novel immunosuppressives, such strategies have gradually increased short-term outcomes over the last two decades. But a fundamental question remains: how much immunosuppression is needed in the individual? How low to go for effective prevention of acute rejection or HLA antibodies? Ideally, we would have an 'immunometer' to determine the actual strength of the immunosuppression. Many biomarkers are currently under investigation to fill this gap. Ideally, biomarkers would help to avoid rejections, side effects or overimmunosuppression and enable a prophylactic and rational adaption of the immunosuppressive load as discussed in a comprehensive review on this topic in this focus issue.

With the introduction of new immunosuppressants, novel combination therapies were possible, and over the last decade, numerous minimization trials with different drugs were undertaken. The focus issue tries to outline and summarize the most important strategies in different excellent reviews. But minimization may have risks and may lead to underimmunosuppression, most importantly the development of HLA antibodies, as discussed in another review in the focus issue. Ultimately, only well-designed prospective clinical trials, either in the context of minimization, with biomarkers or with tolerance protocols will advance the field and answer those questions we are asking since decades. Until then, practitioners should be reminded

that the goal of immunosuppression is to prevent rejection with acceptable side effects. Although difficult in the individual, we should always re-evaluate our therapy and aim to prescribe a dosage of drugs just high enough to suppress rejection without endangering the recipient's health or causing severe side effects.

We would like to thank all authors for their excellent and up-to-date reviews, which will enable the reader to get a thorough and well-balanced insight into the different topics. It is hoped that the focus issue starts discussion and new research projects to improve our patients live.

Sophie Brouard
INSERM, UMR 1064, Nantes, France
CIC biothérapie, Nantes, France
CHU de Nantes, ITUN, Nantes, France,
E-mail: sophie.brouard@univ-nantes.fr

Klemens Budde
Department of Nephrology, Charité Universitätsmedizin Berlin, Berlin, Germany,
E-mail: klemens.budde@charite.de

© 2015 Steunstichting ESOT **28** (2015) 889–890