Transpl Int (2000) 13 [Suppl 1]: S20–S23

Clinical immunosuppression 2000

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Key words Clinical immunosuppression

Introduction

A review of the topic immunosuppression at the end of this century cannot be restricted to a discussion of a list of immunosuppressive drugs. Indeed, rather than presenting the basic knowledge about the most usual and new immunosuppressive drugs, and those in the pipeline, the optimal strategies for diverse categories of patients, the diverse constraints and the best assessment of long-term risk/benefit ratio must retain all our attention. In addition, the immunosuppression of transplant recipients is intimately related to the general management of their treatment, a task which becomes more difficult as a result of the recent diversity of the available drugs and of the fact that a single centre, even a large one, can hardly have an exhaustive knowledge of all immunosuppressive drugs available, as was the case in the last decade.

Reducing early rejection incidence in transplantation

One of the main achievements of immunosuppression is to reduce the incidence of early acute rejection. The need for total control of immunosuppression within the first months is strongly suggested by the impact of an early acute graft rejection episode on long-term function. This is, together with the quality of the graft (ischemia time, age of the donor, etc), the most important parameter of long-term graft survival [1]. It is therefore important to consider the hypothesis that a complete control of the immunoresponse within the first 3 months is mandatory. However, it is a risky goal because of the possibility of over immunosuppression. Nevertheless, interestingly, there is no indication that patient survival has decreased during the last decade whereas contraindications related to the clinical status of the recipients have decreased and the effectiveness of the immunosuppressive drugs have dramatically increased, suggesting that, within certain limits, the efficiency of early immunosuppression could indeed be further increased. It is interesting to note that some induction regimens, for instance the association of antithymocyte globulin (ATG) or anti-CD3 with MMF and steroids and with sequential administration of calcineurin inhibitors (CNIs), or again the association of rapamycin and CNIs have been reported to control rejection in 90% of patients [2], suggesting that only 10% of recipients would not be appropriately immunosuppressed. However, despite the fact that list of identified risk factors for acute rejection is long (transfusion, matching, multiple graft, panel-reactive antibody, age, sex, race, TNFα, TGF, genotype, etc), there is no convincing method for determining whether a given patient will have a rejection or not. Therefore, until this prediction is achievable increasing the immunosuppression in all patients remains questionable since the risk for a minority is not a relevant risk for the majority.

These last years have brought further refinement and precision in the use of new immunosuppressive treatments in the first months following transplantation. It has been made clear that the interleukin-2 receptor antibodies (IL-2R) combine a significant effect on prevention of kidney rejection with an almost total absence of side effects, making these antibodies of first interest in the majority of patients who are low-risk recipients [3].

Restricting these comments to agents that have entered the clinical scene, the possibility that mAbs such as anti-LFA1 or anti-CD2 could be of some use is under investigations. Both of these molecules are involved in T cell activation in which they are instrumental in the building of synapse-type areas allowing optimal activation and also play a role in the adhesion process and interaction with endothelial cells and thus in the resulting trafficking of activated leukocytes into the graft, making it theoretically possible (particularly for anti-LFA1) to decrease reperfusion syndrome in ischemic organs. Some preliminary results show that anti-LFA1 could indeed decrease the incidence of delayed graft function as well as of early kidney rejection in patients at risk [4]. Anti-CD2 is able to significantly decrease the incidence of rejection and is useful in the treatment of ongoing rejection, but whether this treatment will bring further advantage to the treatments available is yet unclear.

The results of a recent randomized study have shown that sirolimus is a potent immunosuppressive drug of similar strength to cyclosporine A [5]. However, when used alone in triple therapy, as for cyclosorine A, the incidence of acute rejection is high (38% versus 41%), suggesting that these drugs would be better combined. In addition, despite lacking graft nephrotoxicity, sirolimus shows other disadvantages being associated with hyperlipemia and more rarely bone marrow depression.

Of first importance are two studies [6, 7] that have shown a significant effect of statins (pravastatin and simvastatin, respectively) in heart transplant recipients. Interestingly, these drugs have a significant effect on patient and graft survival, the most relevant and demonstrative end-point, and as early as 6 months, justifying their mention in this part of this short review. Despite the fact that these drugs are aimed at decreasing hyperlipemia, most of their effects are achieved within the first 6 months, suggesting that statins also play a role at the immunological level. Indeed preliminary data show that they may operate at different stages of the immune response. Clearly, owing to the magnitude of their impact on graft survival, more information is urgently required on the usefulness of these compounds in other types of transplantation.

Conversion and maintenance treatment

Even though the capacity of early immunosuppression to improve long-term graft function has been clearly documented, only limited information is available on the possibility that strong immunosuppression is necessarily linked to a better long-term result. Because of the need for studies to involve long surveys, the data on this point are scarce. Research in this field is complex and expensive and is not supported by pharmaceutical companies. However, this should be the first objective, as well as duty, of academic investigators. Analysis of graft survival in recipients who have received HLA-identical sibling kidneys versus those who were grafted with one haplotype-related kidney demonstrates clearly that the immune response is still ongoing years after transplantation. It is a situation which is also likely to operate even more strongly in cadaverous grafts. However, if we have to admit the continuous effect of the immune system on the graft, likely operating through the indirect pathway as in an autoimmune disease, it is worthy of note that the increasing efficiency of immunosuppressive regimens since the introduction of cyclosporine A in the early 1980s has not shifted significantly the long-term graft half-life slope. This observation urges a consideration of the working hypothesis mentioned above as a first objective of the forthcoming decade. Indeed it is possible that the risk of having some patients presenting a late rejection could be balanced by a decrease in long-term side effects of the drugs, including kidney toxicity of (CNIs) (a major problem in all type of organ recipients), hyperlipemia, high blood pressure, and high cancer incidence [8]. In addition, although this problem is mostly addressed in kidney recipients (owing to the non-life-threatening nature of terminal kidney diseases), this concept may also be relevant in the future for recipients of other grafts, considering, for example, the high percentage of kidney failure resulting from calcineurin toxicity after heart or lung/heart transplantations.

It is therefore understandable that many studies have been devoted to conversion of immunosuppressive drugs 1 year after transplantation. However, it is not clear whether these studies were aimed at switching one drug for another or actually questioning the need to expose the recipient to strong immunosuppression in the long-term, which is not always similar. Most of these attempts have been aimed at decreasing or suppressing the effects of CNIs in patients under MMF or more recently rapamycin treatment. A large enough randomized study and a long enough survey have not yet been carried out to allow a firm conclusion. However, these studies must proceed with great caution particularly because, since the basis of the treatment of the grafted recipient is immunosuppression, immune regulatory mechanisms are likely not to take place in these recipients, making early and important decreases or withdrawal of the immunosuppressive drugs hazardous. Nevertheless, these studies have to be conducted and the results concerning steroid withdrawal in patients under calcineurin and MMF treatment are extremely encouraging.

Another consequence of long-term exposure to immunosuppressive drugs is increasing cancer incidence. Indeed, our group has recently shown in a prospective randomized trial that there is a direct and significant link between exposure to cyclosporine A (as defined by trough levels and AUC) and cancer incidence. Even

though these changes were more obvious for skin cancers, the incidence of all "virus-related" cancers was also increased [8]. This report is in agreement with the overall increase in cancer noticed in large series. Recent in vitro data and data from mice have also offered an alternative to a lack of "immunosurveillance" by showing a possible direct effect of cyclosporine A on the phenotype of transformed cell lines and its capacity to increase the rate of metastasis and growth of tumors in SCID mice with beige mutation (making them unable to mount an adequate immunoresponse) [9]. The fact that about 50% of kidney recipients are exposed to at least one type of cancer in 10 years, and extrapolating these results to a cohort exposed to a regimen involving increased immunosuppression, is another reason to test as a first objective for the next decade whether strong immunosuppression is actually required long-term.

Future trends

The Grail of transplantation immonologists is to achieve tolerance. Despite a decade of active research in this field, this has not been possible yet. However, recent results from several experimental approaches conducted on primates have brought the unexpected hope of achieving this goal. This breakthrough could come from several new approaches, the most encouraging being the use of antibodies interacting with so-called "second signal" or that must be provided, together with antigen recognition, to T cells to develop an optimal and aggressive response. First, the blockade of B7 molecules at the antigen-presenting cell (APC) surface through the CTLA4Ig fusion molecules, associated with cyclosporine A, has been shown to result in long-term survival (but not true tolerance) of kidney transplants in primates. This strategy is now entering the clinic. However, more recently, antibodies against CD40L, controlling both the maturation of APC but also likely providing a negative signal to T cells, have been shown to be more efficient, as single agents, in primates. Furthermore, in contrast to what has been observed with CTLA4Ig, cyclosporine A, FK 506 and steroids antagonize this effect, suggesting that a state of activation of the recipient immune system is required to achieve the stage of unresponsiveness already noted in several models of tolerance induction. Indeed, as recently shown by Kirk et al. [10] some primates do keep their functioning grafts after prolonged monotherapy even though the antibody against CD40L had been interrupted.

A similar phenomenon, although less thoroughly documented, has been shown with an antibody against CD45RB determinant in the monkey [11]. Using a more aggressive scheme, worthy of mention because there is some in vitro evidence of a possible induction of a tolerant state, Thomas et al. administered anti-CD3 antibody linked to a toxin which, together with desoxyspergualine (DSG), resulted in long-term graft acceptance in the monkey. In this last example, rather than the blocking of a unique accessory determinant, the anti-CD3 toxin plus DSG may reduce the immune system of the recipient to a quiescent milieu for several weeks and the DSG affects dendritic cells during the phase of immune recovery, favoring the establishment of a tolerant state.

Immunosuppression versus tolerance and global management of graft recipients

In this short review we have tried to advocate that administering stronger immunosuppressive agents may not further improve the long-term result in transplantation, particularly when the maintenance regimen is discussed. Furthermore, there is now compelling evidence that immunosuppression counteracts the effect of some "anti-second-signal" antibodies able to induce a tolerance-like state. This is indicated in humans by the remarkably good results of sequential therapy with ATG and anti-CD3 and now demonstrated in primates for anti-CD40L and anti-CD45 RB. This need for revisiting our ideas on manipulating immunnosuppressive drugs also appears when the general management of recipients with long-term functioning grafts is considered. Indeed, CNIs and steroids are nephrotoxic and can induce diabetes. Similarly, the use of steroids is linked with severe side effects and a poor quality of life in the long term. Cyclosporine A, rapamycin and steroids have been shown to increase hyperlipemia and blood pressure, two conditions recognized as promoting "chronic rejection" following transplantation of various organs. Furthermore, cancer incidence dramatically increases one decade after transplantation. All these conditions lend urgency to the establishment of whether the immunosuppression must be stronger in the first months but also strongly reduced in the long term and which combination of drugs must be used. Finally, and particularly in kidney recipients, an understanding of the ultimate risk/benefit ratio must avoid an assessment based on the graft survival only and take into account the general patient survival and quality of life.

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