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UPDATE IN INTENSIVE CARE: TRANSPLANTS

Advances in immunosuppression after lung transplantation☆

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Abstract Immunosuppression in transplantation has experienced changes in recent years as a result of the introduction of new drugs that act upon the different pathways of the host immune response with the purpose of securing more individualized immune suppression, with fewer side effects.

Although following in the steps of other solid organ transplant modalities, lung transplantation, because of its special characteristics, has not yielded similar middle- and long-term results.

Improved understanding of the underlying rejection mechanisms, the pharmacodynamic control of drugs, new administration routes designed to reduce the side effects, and new drug substances or immune modulating processes will all contribute to improve the expectations associated to lung transplantation in the near future.

PALABRAS CLAVE
Inmunosupresión;
Pulmón;
Trasplante;
Inducción

Avances en la inmunosupresión del trasplante pulmonar

Resumen La inmunosupresión en el trasplante se ha modificado en los últimos años con el descubrimiento de nuevos fármacos que intentan atacar las distintas vías de la respuesta inmunológica, con la idea de conseguir una inmunosupresión más personalizada y con menores efectos secundarios.

A pesar de seguir los pasos de los otros trasplantes de órganos sólidos, el trasplante pulmonar, por sus especiales características no ha conseguido similares resultados a medio y largo plazo.

El mejor entendimiento de los mecanismos de rechazo, el control farmacodinámico de los fármacos, las nuevas vías de administración que disminuyan los efectos secundarios y los nuevos fármacos o procesos inmunomoduladores contribuyen a mejorar las expectativas de este trasplante en un próximo futuro.

Introduction

Lung transplantation was the last solid organ transplant modality incorporated to the group of transplantation procedures known to afford good results. At present, it is an accepted treatment choice for a selected group of patients with end-stage lung disease.

While taking advantage of the experience gained with other types of organ transplants, lung transplantation, because of its special characteristics, has not yielded similar long-term results. In this context, survival rates of 80% in the first year and of 50% after 5 years of follow-up are regarded as adequate.

Regarding the immunological factors, the main problems posed by lung transplantation are:

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- Direct graft contact with the exterior through the upper airway. Such direct communication not only facilitates exposure to germs and the development of infections, but also constitutes a vehicle for other harmful factors produced by the body itself (e.g., gastroesophageal reflux or nasal or oral cavity colonizations) or contained in the air we breathe. Such aggression in some cases triggers the host immune response, which can lead to rapid or progressive graft rejection if not adequately controlled.
- The impossibility of cross-matching prior to transplantation.
- The high antigen content of the donor lung.

These factors imply that lung transplantation requires important immunosuppression, particularly in the immediate postoperative period. Despite such measures, however, the acute rejection rate in this period remains high.

The introduction of new and more potent immunosuppressors that act upon the different pathways mediating the immune response allow us to provide more individualized immunosuppression. In the early days, the immunosuppressive therapy used was fundamentally supported by the experience gained in the transplantation of other organs, followed later on by the findings of retrospective studies often corresponding to a single center, and which documented the first specific experiences in lung transplantation. The lack of scientific evidence led to the conduction of randomized multicenter studies, which produced ideas but were unable to establish conclusive evidence reinforcing the use of such drugs in lung transplantation. For this reason, in the course of the present study most of the recommendations are based on publications with a low grade of evidence, and some of the recommended drugs have not been approved for use in lung transplantation.[1]

Classical immunosuppression has always included the utilization of three drugs, associated or not to induction, using mono- or polyclonal antibodies.

The inclusion of three drugs helps minimize their side effects and allows us to attack different pathways of the immune response. With this aim in mind, we usually combine a calcineurin inhibitor (cyclosporine or tacrolimus), an antiproliferative drug (azathioprine or mycophenolate mofetil) and corticosteroids.[2]

The present study reviews and offers an update on some of the most important aspects of immunosuppression in lung transplantation.

The current state of induction

The main objective of induction treatment is to reduce acute rejection in the first moments of transplantation through inhibition of the proliferation or depletion of the T lymphocytes, which are regarded as the main effectors of the host cellular immune response.

Induction with OKT3 was used in the first cardiopulmonary transplants, and posteriorly the polyclonal antibodies played an important role in the beginning of lung transplantation–though the high infection rate involved encouraged the avoidance of induction except in selected cases. In 2001, a comparative study of OKT3, ATG and daclizumab showed an increased bacterial infection rate among the patients treated with OKT3, in comparison with the other two induction regimens; as a result, OKT3 was abandoned as an induction agent in lung transplantation. None of the induction agents delayed the development of chronic rejection or improved patient survival.[3]

Polyclonal antibodies and IL-2 antagonists usually have been found to be effective in reducing the number of acute rejections in the immediate postoperative period. On the other hand, these drugs allow us to postpone the start of immunosuppression in cases of postsurgical renal failure.[4]

Although the main randomized, prospective multicenter trial (LUNAS) only reported a lesser number of acute rejections among the patients treated with Basiliximab®, and showed no significant differences with respect to the development of bronchiolitis obliterans syndrome (BOS) or survival (personal communication), the absence of side effects recorded in this trial and in other clinical studies made with other chimeral monoclonal antibodies[4,5] is possibly the main reason why in recent years a larger number of transplant groups have again started to use induction in the initial management of lung transplantation, as it can be seen in the figures of the ISHLT registry (Fig. 1).[6]

The data of this international registry, which show improved survival among patients with induction (Fig. 2),[6] the possibility of reducing the number of acute rejections and of avoiding renal damage, with a reduction in the start or a lowering of the levels required for correct immunosuppression, are all sufficiently important factors that likewise support the use of induction therapy.[5]

A relatively new development is the use of alemtuzumab for induction in a limited number of hospitals. This is a humanized monoclonal antibody targeted not only to antigen CD52, present on the surface of the B and T cells, but also in macrophages, monocytes, NK cells and thymocytes. Alemtuzumab produces important leukocyte depletion, with recovery of the different cell populations in different post-transplantation periods,[7] resulting in less severe acute rejection episodes and a decrease in cytomegalovirus (CMV) rates compared with induction using thymoglobulin. However, a current publication has found no differences in survival or acute rejection in patients treated with and without alemtuzumab.[8] A recent retrospective study has analyzed the data collected on a prospective basis in a single center corresponding to 336 lung graft recipients classified according to the type of induction used: thymoglobulin, alemtuzumab, daclizumab, or no induction. An analysis was made of patient and graft survival, the acute cellular rejection rate, lymphocytic bronchiolitis and bronchiolitis obliterans, and lymphoproliferative disorders following transplantation. Alemtuzumab offered better results in comparison with the other options, except as regards the lymphoproliferative syndromes, where no differences were observed.[9]

New developments in maintenance immunosuppression

Anticalcineurinic drugs remain the basic option in immune suppression among lung transplant patients. Tacrolimus and Neoral® cyclosporine have been shown to be excellent immunosuppressors. Monitorization, which is exclusively