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Induction Therapy in Solid Organ Transplantation

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One of the key points to ensure the success of solid organ transplantation in the short and long term is an appropriate design of immunosuppression. In the pre-anti-calcineurin era, only steroids and azathioprine were available as maintenance immunosuppressive therapy. Acute rejection was the standard and long-term survival was poor. At that time, many groups began to use antilymphocyte or antithymocytes globulins from horse or rabbit in the first days posttransplantation in order to induce a limphocyte depletion. This depletion of lymphocytes produced potent immunosuppression, which prevented rejection in the first weeks posttransplantation and kept some patients free of rejection also in the longer term[1,2]. The price paid was an increase of opportunistic infections and cancer in the longer term.

The introduction of cyclosporin A, the first calcineurin inhibitor used in the clinic, revolutionized transplant therapy to allow reduction of the incidence of acute rejection and thereby achieve better rates of long-term graft survival. Despite the availability of this new, powerful immunosuppressive drug, many groups kept to antibody induction[3,4] with polyclonal or monoclonal (OKT3) depleting lymphocytes antibodies, with two purposes: first, to increase immunosuppression at the time of the abrupt antigenic exposure, and second, to delay the onset of use of cyclosporine A that was nephrotoxic, to avoid the delay in renal graft function or acute renal failure in other solid organ transplants. Again the price paid was an increase in the incidence of opportunistic infections and cancers. In the era of cyclosporin A, not all groups used antibody induction therapy with depleting lymphocyte antibodies. This practice was more widespread in the USA, but also in heart transplantation in Europe. With the introduction of tacrolimus, or mycophenolate mofetil or sodium, and the proliferation signal inhibitors (rapamycin or everolimus), things have changed in the design of immunosuppressive protocols since these drugs and their combinations are more potent. Nonetheless, many groups continue to use antibody induction therapy depleting cells for the reasons outlined above.

In the late 1990s, anti-interleukin-2 receptor monoclonal antibodies became available that did not deplete the lymphocytes, and exerted their immunosuppression blocking, such as anti-calcineurin, the action of interleukin-2, but without being nephrotoxic. These antibodies were shown to be effective in preventing acute rejection in renal transplantation when they were associated with cyclosporine therapy, which in turn could be associated with azathioprine or mycophenolate[5-12]. The novelty was that they had an excellent safety profile without increasing the incidence of opportunistic infections or cancer.

Although the studies conducted to show efficacy were associated with full doses of cyclosporin A, anti-interleukin-2 receptor antibodies were used to minimize other immunosuppressive drugs in the immediate

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posttransplant period. Since its approval, dozens of papers showing the efficacy in minimizing immunosuppression and in patients with a higher immunological risk (hyperimmunized patients, recipients of a second transplant, African Americans, etc.) have been published[13]. However, the immunosuppression achieved with an interleukin-2 receptor antibody is less potent than that produced by lymphocyte-depleting antibodies, although, interleukin-2 receptor antibodies present a better safety profile[13,14].

Today, there is some confusion in setting the indications of different antibodies used in induction immunosuppression in the immediate posttransplant period of the different solid organs.

This document aims to give some recommendations on how to use antibody induction in solid organ transplantation.

Before proceeding to the recommendations, the classification of biological products for induction immunosuppression available at this time should be clarified. The basic distinction is whether or not they are depleting lymphocytes. The terms "monoclonal" and "polyclonal" refer to their way of getting through hybridomas in the case of monoclonal or through immunization with lymphocytes or thymocytes to horses or rabbits and removing the formed antibodies against different antigens of thymocytes or lymphocytes in the case of polyclonal:

- Lymphocyte-depleting biological therapies:
  - Polyclonal: antithymocyte globulin (ATG) thymoglobulin from rabbit, ATG-Fresenius antilymphocyte globulin.
  - Monoclonal: Anti-CD3 (OKT3 or muromonab-CD3), and Campath (alemtuzumab or anti-CD52), anti-CD20 (rituximab).
- Non-lymphocyte-depleting biological therapies:
  - Biological CD25 receptor blockers (interleukin-2 receptor).
    - Monoclonal: basiliximab, daclizumab.
  - Biological therapy co-stimulation blocker.

The purpose of immunosuppressive therapy with biological agents administered immediately before and immediately after transplantation is to deplete lymphocytes and/or modulate the immune response of lymphocytes at the time that graft antigens are presented for the first time to the recipient's immune system. Thus pursuing, firstly, increased immunosuppressive efficacy by reducing the incidence of acute rejection (and even promoting tolerance-inducing mechanisms), and secondly, allowing the reduction of other immunosuppressive agents like calcineurin inhibitors, which can produce nephrotoxicity, or steroids that cause important infectious and cardiovascular comorbidity.

If these benefits are proven, why is antibody induction therapy not universally used in all transplants? The answer seems clear if we focus on agents that deplete lymphocytes: side effects related to opportunistic infections and cancer could appear, therefore these agents are used with caution and only indicated for some suitable patient groups[14-18]. In the case of interleukin-2 receptor blockers the reasons are more complex, but are based on findings by many transplants groups that obtained good results also without a general use of induction therapy with these antibodies. Although dozens of papers described a lower incidence of rejection with its use[13], not all groups consider the systematic use of induction therapy in the protocols of immunosuppression.

Much experience in the use of antibody induction has been accumulated in kidney and heart transplantation; however, the benefits of these therapies in other solid organ transplants have only emerged in recent years[19-27]. For this reason, we need a document of recommendations on the use of antibody induction in all types of transplants to try to optimize results with minimal morbidity.

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