The impact of regulatory T cells in acute rejection

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For a long time, a large number of researchers investigated the process of acute rejection. However, for a long time, the most important question seemed to be how the process got started and how one could interfere with the beginning. A lot of progress has been made with broad implications for the whole field of medicine, not only transplantation. Acute rejection was crucial to the understanding of the role of dendritic cells, the concept of professional and unprofessional antigen presenting cells and tissue typing in general.

About 40 years ago, a new concept came into play, which involved the role of effector and suppressor cells. In mice, it was possible to suppress acute rejection with a parallel infusion of so-called suppressor cells [1]. Unfortunately, this concept did not seem to hold true in humans. As a result even the name suppressor cell was not used anymore and those that used it were considered old-fashioned and somewhat out of the loop. About 10 years ago, however, the so-called Tregs (regulatory T cells) were found to be important in tumour growth and rejection [2]. This time, the news came from oncology and was tested in transplantation. With improved tools in fluorescence-activated cell sorting (FACS) analysis, it was possible to better characterize the cells and define their functions more precisely. Surprisingly, what had been found in mouse and rats was still valid when tested with the new antibodies against the T-cell markers, and more importantly, the concept worked in humans.

While there have been a lot of efforts to prevent acute rejection in humans, less work has been done on the treatment of rejections and very few linked acute rejection to the presence or absence of Tregs.

In their article, Krystufkova et al. [3] investigated the effects of induction therapy on the number of regulatory T cells prospectively in an open trial. They described a high number of CD4+FoxP3+ following treatment with rATG (rat antithymocyte globulin) and a high ratio CD4+FoxP3+/Teffs (effector T cells) following basiliximab induction. They did not observe similar results in controls. The presence or absence of CD4+FoxP3+ or their ratio to Teffs correlated with the number of steroid-resistant rejections.

However, the study has a number of limitations. The number of patients included (71) was low and patients were not randomly assigned to groups but assigned based on clinical conditions such as preformed antibodies or no apparent risk. Nonetheless, the FACS analyses were made on days 0, 7, 14, 21, 28, 60 and 90 and there were no differences on day 0. Thus, the effects on CD4+FoxP3+ were most likely due to the respective treatment.

Furthermore, the correlation between the number of CD4+FoxP3+ or the CD4+FoxP3+/Teffs ratio to certain types or the incidence of rejection is limited by the low number of patients per se, within the groups and the even lower number of rejections.

In summary, while this is the first time a correlation between induction therapy and the number of Tregs has been investigated, the study is all but conclusive. It is, however, stimulating to speculate on the real contribution of these cells to rejection. There are still more open questions than answers. In this study, the cells were detected from peripheral blood. Does this correlate to the number
of infiltrating cells? We know from other experimental studies that Tregs are able to proliferate [4]. Do these cells proliferate in the grafts as well? Are the cells alloantigen-specific or do they reflect a state of suppression, which is related to the higher incidence of infections in the rATG arm?

And finally the crucial question is Can we stop rejection by the injection of Tregs specific to the alloantigen in vivo in humans as well?

If it was possible to prove such a concept in man, it might be possible to preserve graft function and prevent acute rejection by a regular infusion of alloantigen-specific Tregs, a concept similar to a kidney transplantation following bone marrow transplantation.

What do these data indicate with regard to the use of induction therapy? There are a number of trials, which investigated the use of induction therapy. A recent Cochrane analysis suggested a longer graft survival and less rejection episodes with the use of basiliximab [5]. It may be that these effects are due to a modified ration between CD4⁺FoxP3⁺ and Teffs. Furthermore, rATG was associated with less rejection episodes and a longer graft half-life as well. It was speculated for a long time as to how this was possible. The higher number of CD4⁺FoxP3⁺ may be the explanation.

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References


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