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MINIREVIEWS

Immunomodulation with rabbit anti-thymocyte globulin in solid organ transplantation

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Abstract

Rabbit anti-thymocyte globulin's manifold mechanisms of action may be attributed to its polyclonal nature. Its T-cell depleting effect on lymphoid cells is well established: Occurring in the blood and secondary lymphoid tissues, depletion proceeds through complement-dependent lysis, opsonization and apoptotic pathways. Clinical studies have shown that rabbit anti-thymocyte globulin's immunomodulatory effect extends beyond the initial T-cell depletion and up to the period during which lymphocyte populations begin to recover. The drug is able to mediate immunomodulation and graft tolerance by functionally inactivating cell surface receptors involved in antigen recognition, leukocyte trafficking and leukocyte endothelium adhesion. The complex and prolonged immunomodulation induced by this drug contributes to its efficacy in solid organ transplantation, mainly by reducing the incidence of acute graft rejection.

Key words: Rabbit anti-thymocyte globulin; Solid organ transplantation; Induction therapy; Immunomodulation

Core tip: The effect of rabbit anti-thymocyte globulin on peripheral lymphocytes is believed to be cytolitic and hence to deplete, to opsonize and to apoptose T cells. Recent studies have shown that rabbit anti-thymocyte globulin also exerts an immunomodulatory effect on various components of immune response, such as adhesion molecules, dendritic cells and Foxp3$^+$ Tregs.

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INTRODUCTION

Rabbit anti-thymocyte globuline (RATG), which trades under the name "thymoglobulin" (producer: Genzyme Co, Cambridge, MA), is a rabbit-derived antibody that acts against human thymocytes. This rabbit preparation is probably the most exstensively studied polyclonal RATG and this paper will refer to it both as RATG and as thymoglobulin.

Thymoglobulin is produced by immunizing pathogen-free New-Zealand rabbits with fresh human thymocytes, obtained from cardiac surgery donors. The final product is a purified, pasteurized preparation of polyclonal Ig, produced in rabbits to act against human thymocytes. Because the distribution of cell types in the thymus includes differing cellular components (*e.g.*, T and B lymphocytes, antigen-presenting cells and stromal cells), the final product contains a multitude of cytotoxic antibodies directed against diverse antigens[1-4].

The spectrum of antigens recognised by thymoglobulin is reported in Table 1.

PHAMACOKINETIC

Knowledge of the pharmacokinetics of RATG is an important pre-requisite for understanding its action on the immune system. In a study of 30 cardiac transplant recipients, RATG half-life, as reflected by serum rabbit globulin clearance rates, was the most important variable in the assessment of RATG efficacy. The group with the shortest RATG half-life had significantly higher production of anti-RATG antibodies and poorer survival rates[5]. Ormond and Jarvis[6] studied the pharmacological properties of thymoglobulin in 16 patients who had received this treatment as prophylaxis against acute transplant rejection. Detectable concentration of RATG were still found in 80% of the cohort at one month from treatment and in 50% at three months. These findings demonstrate that thymoglobulin has a long life in human plasma.

Moreover, Rebellato *et al*[3] administered RATG to a cohort of rhesus monkey transplant recipients and found that the RATG antibodies, that persisted the longest in the cohort's plasma, were directed against CD3, CD4, CD8, CD11a, CD40, CD45, CD54 and class Ⅰ. The same antibodies, which were involved in a signal transduction and adhesion molecules, were present during the early period of lymphocyte recovery[3].

In renal trasplant patients, Regan *et al*[7] respectively used the Elisa method and flow cytometry to determine serum levels of total thymoglobulin or active thymoglobulin, the latter representing RATG binding to peripheral lymphocytes. The concentration profiles of total and active thymoglobuline differed notably. Active RATG disappeared rapidly and only 12% of patients had detectable levels by day 90. In contrast, total Thymoglobulin was detected, at the same time, in 81% of patients. Despite the differences in pharmacokinetics, no correlation was found between treatment efficacy and thymoglobulin concentrations, whether active or total fractions. These two thymoglobulin components, need further investigation to achieve clinical relevance[7].

MECHANISM OF ACTION

A well documented effect of RATG treatment is T-cell depletion. It induces lymphocyte depletion by a dose-dependent mechanism, which involves not only peripheral lymphocytes but also secondary lymphoid tissue of the spleen and lymphnodes, where most T cells resides and antigen presentation occurs. Notably, no lymphocyte depletion was observed in the thymus at any dosing level, a finding that indicates that RATG has limited access to this organ[8].

Nevertheless, other mechanisms should be considered, some of which could represent a therapeutic objective in the design of future protocols aimed at a more selective immunosuppression.

The mechanisms of T-cell depletion by RATG, include complement-dependent lysis, which occurs especially in the extravascular compartment, where complement concentrations are maximal. At low concentrations, RATG selectively targets activated but not resting T cells. This property could be used in protocols aimed at the selective elimination of *in vivo* activated T cells (*e.g.*, donor-specific alloreactive T cells in organ transplantation). Recovery of peripheral T cell counts occur gradually after cessation of RATG, with a partial increase at 3 mo[9].

Another mechanism is opsonization by immunoglobilin antibodies and complement, followed by phagocytosis of opsonized lymphocytes by liver, spleen and lung macrophages. This process may account for the massive and rapid lymphopenia observed after RATG infusion.

Finally, apoptosis, with subsequent phagocytosis by macrophages, occurs in lymphoid tissues of the spleen and in lymphnodes (where apoptotic cells can be demonstrated in T-cells zones); it is the main mechanism of depletion[10]. Apoptosis does not require prior exposure to interleukin-2, nor does it result in CD178/CD95 or tumor necrosis factor (TNF)/TNF receptor interactions. It is, therefore, clearly different from activation-induced cell death but associated with the release of active cathepsin B from lysosomes into the T-cell cytosol[11].

Beyond its effect on T cells, some studies have reported that thymoglobulin may affect B cells, which are involved in humoral rejection, because RATG contains antibodies specific to B and plasmacell antigens. These latter may induce apoptosis, prevent B cells proliferation and the onset of antibody-mediated rejection[12-14]. Moreover, Gurkan *et al*[15] reported that RATG did not significantly influence B cells numbers, but significantly

Table 1 Summary of known target antigens recognised by thymoglobulin

T cell depletion target antigens and immune response antigens		B cell target antigens		Adhesion and cell trafficking target antigens	
CD3/TCR	CD25	HLA DR	CD32	CD11a/CD18 (LFA-1)	CD102 (ICAM-2)
CD2	CD28	CD5	CD38	CD44	CD6
CD4	CD30	CD19	CD40	CD49/CD29 (VLA-4)	LPAM-1 (α4β7)
CD8	CD52	CD20	CD45	CD50 (ICAM-3)	CD195 (CCR5)
CD5	CD32	CD27	CD52	CD51/61	CD197 (CCR7)
CD6	CD40	CD30	CD80	CD54 (ICAM-1)	CD184 (CXCR4)
CD7	CD80	CD95	CD86	CD56	CD58 (LFA-3)
CD16	CD86	CD138			
HLA class I	HLA DR				
CD152 (CTLA-4)	β2-M				

TCR: T-cell receptor; HLA: Human leukocyte antigen.

decreased memory B cells.

NK cells too are influenced by RATG administration. Kho *et al*[16] showed that, after thymoglobulin infusion in kidney transplant recipients, the number of NK cells was significantly lower than in controls. One month later, NK cells reached parity with controls.

IMMUNOMODULATION BY THYMOGLOBILIN

Clinical studies have shown that thymoglobulin exerts an immunomodulatory effect beyond initial T-cell depletion and up to the period during which lymphocyte populations begin to recover. The drug possibly mediates immunomodulation and graft tolerance by functionally inactivating cell surface receptors involved in antigen recognition, leukocyte trafficking and leukocyte endothelium adhesion. RATG contains many antibody specificities and modulation, by the internalization of the antigen-antibody complex, is one of the pathway of its mechanism. Subsequent to modulation, surface antigens are internalized and their expression ceases until the action of RATG antibodies occurs.

Modulation of adhesion and cell trafficking molecules by thymoglobulin

Due to the solid nature of the transplanted organ, transplantation necessarily involves ischemia and microcirculatory disturbance, and consequently causes reperfusion injury and functional impairment. Ischemia reperfusion injury (IRI) is an acute multifactorial process in which transplanted organs or cells are damaged firstly by ischemia and thereafter by reperfusion[17]. The interaction between endothelium and leukocytes at the moment of vascular reconnections causes leucocytes firstly to stick to, and subsequently to roll along with the surface of the endothelium, with consequent vascular and tissue damage. The subsequent activating signal induces rapid release of inflammatory mediators (adhesion molecules, chemokines) which change the state of endothelium from anti-adhesive to pro-adhesive. Finally, the transendothelial migration of effectors cells to reperfused tissues leads to organ damage[18].

Hammer and Thein[19] presented a video recording that demonstrated a significant decrease both in leukocyte rolling and adhesion activities and, hence in organ damage, after the administration of RATG. In contrast, controls treated with saline or anti-IL2r monoclonal antibody showed massive leukocyte rolling and sticking.

Chappell *et al*[20] studied the *in vivo* effects of RATG on leukocyte-endothelial interaction. In RATG treated-animals, the authors demonstrated rapid reperfusion repair and reduction in leukocyte clotting and capillary plugging. These protective mechanisms help to maintain post-transplant blood flow especially in the microcirculation.

Beiras-Fernandez *et al*[21] studied cynomologous monkeys to evaluate the effect of RATG on IRI. They demonstrated a significantly decrease in expression of adhesion molecules, namely ICAM-1, VCAM, PECAM, CD11b and CD62E, in RATG-treated group. They concluded that their results support the notion that thymoglobulin acts directly against some adhesion molecules expressed on the endothelium, and thus influences the expression and release of pro-inflammatory cytokines.

Finally, Goggins *et al*[22] demonstrated a significant decrease in the incidence of the delayed graft functions in a randomized trial that compared intra-operative with post-operative administration of thymoglobulin. After intra-operative administration, they observed a significant decreased in the incidence of hemodialysis, lower serum creatinine and shorter hospital admission periods. All these effects contribute to an improved graft outcome.

In conclusion, these data here presented support the use of RATG, in its capacity as a pre-transplant induction therapy, to download the effects of increasing numbers of adhesion molecules and their tissue location.

Modulation of dendritic cells

Dendritic cells (DCs) are the most potent antigen-presenting cells of the immune system, and they play a key role in the initiation and maintenance of immune responses to allografts. They consist in a heterogeneous population of bone marrow - derived cells that are specialized in capture, processing and presentation of antigens to immunocompetent cells[23]. DCs are

considered as potential targets for the suppression of alloreactivity and induction of allograft tolerance[24]. During differentiation from their progenitors, DCs can be identified in an immature stage, normally residing in peripheral tissues, where they are specialized for uptake of pathogens derived antigens. After contact with an inflammatory stimulus, mature DCs, (as characterized by changes in phenotype and function) are generated[25].

Because DCs are key players in immune regulation, interaction between DCs and RATG might significantly contribute to the immunomodulatory effect of DC cells. Monti *et al*[26] reported that, *in vitro*, RATG is able to interfere in the activation of T-cell by DCs in two different ways: By inhibiting the capacity of lymphocytes to proliferate after DCs stimulation and by inducing a complement-mediated lysis of DCs. Subsequently, Naujokat *et al*[27], reported, again on the basis of *in vitro* experiments, that DCs are important targets for the immunosuppressive action of RATG. The binding of RATG to various of the surface receptors expressed on DCs, results in the modulation and inhibition of multiple and essential functions of the DCs themselves, which in turn leads to an impaired stimulation of allogeneic and autologous T cells[27].

Finally, in contrast with other experiments, Leitner *et al*[28] found that RATG treatment of immature DCs leads to the induction of a surface marker profile that is consistent with DCs activation. These researchers used a new methodology, to identify DCs surface antigens recognized with RATG. Consisting in the screening of an eukaryotic expression library generated from DCs with RATG, this methodology enables the researchers to identify several novel RATG antigens, including CD81, CD82, CD98, CD99 and CD147. Probing of these antigens with engineered cells revealed that some, but not all, of these cells were strongly bound. These *in vitro* results, might not fully reflect the interaction of RATG and DCs that occurs in treated patients, but they expand perceptions of the immunomodulatory capacity that RATG enjoys to affect the immune system[28].

Modulation of Tregs Foxp3$^+$

Modulation of the immune response by Tregs Foxp3$^+$, the subpopulation with the greatest suppressive abilities[29], provides one possible mechanism to control the immune response.

An experimental study in mouse demonstrated that Tregs Foxp3$^+$ were resistant to RATG mediated depletion[30].

Lopez *et al*[31] showed that RATG was able to expand a population of CD4$^+$CD25$^+$ Foxp3$^+$ in culture, but that neither an anti-IL2r nor an anti-CD52 monoclonal antibody (alemtuzumab) was similarly able. Comparable results were obtained by Feng *et al*[32], who observed that RATG expanded Tregs, generates CD4$^+$CD25$^+$ Foxp3$^+$ T cells and a regulatory activity. Thus, the therapeutic effects of RATG may be related not only to lymphocyte depletion but also to enhanced Tregs number and their regulatory function.

Various *in vivo* studies, have evaluated the effect of thymoglobulin administration in transplant patients. Sewgobind *et al*[33] evaluated the effect of RATG on Tregs in kidney transplants patients. Pre-transplant levels of Tregs Foxp3$^+$ cells were equivalent to 6% of CD4$^+$ T-cells. After administration of RATG, no measurable Tregs Fop3$^+$ cells were detectable after one week, because of low number of CD4$^+$ T cells within the T-cell population. After 26 wk, the regulatory capacity of Tregs Foxp3$^+$ remained unaffected. They fully preserved their suppressive activity and were able to effectively govern allogeneic immune responses by effector T cells as before RATG treatment[33]. The ability of RATG to induce Tregs Foxp3$^+$ was subsequently confirmed in patients with end-stage renal disease by the same author[34]. After kidney transplantation, Tang *et al*[35] evaluated the effect of RATG post-transplant induction on Tregs Foxp3$^+$. They observed a prolonged and significant increase Tregs percentage, in association with the expression of CD25 and Foxp3, along with a prolonged reduction in effector CD4$^+$ T cells. From the clinical point of view, the authors hypothesized that these results may further confirm the efficacy of thymoglobulin induction in controlling transplant rejection[35].

Clinical testing by Krystufkova *et al*[36], monitored regulatory and effector T cells in peripheral blood in 71 kidney transplanted patients. Induction therapy with RATG was associated with an expansion of Tregs Foxp3$^+$ and a low incidence of rejection.

Finally, Gurkan *et al*[15] found that the percentage of CD4$^+$ Foxp3 T cells, in pediatric and adult renal transplant recipients, was significantly higher in patients that received RATG at all post-transplant time points.

To summarise, in both *in vitro* and transplanted patients studies, thymoglobulin induction induces a prolonged reduction in effector CD4$^+$ T cells and a persistent increase in Tregs Foxp3$^+$, thus modulating the post-transplant immune response and reducing the incidence of acute rejection beyond T cell depletion.

CONCLUSION

Thymoglobulin is widely used after solid organ transplantation as an induction therapy. Its polyclonal nature reflects its variable effects on the immune system: (1) T-cell depletion in peripheral blood and in secondary lymphoid tissues through complement- dependent lysis, opsonization and apoptosis; (2) modulation of adhesion and cell trafficking molecules by downloading the effects of increasing numbers of adhesion molecules and their tissue location; (3) modulation of dendritic cells, which play a key role in the initiation and maintenance of immune responses to allografts; and (4) modulation of Tregs Foxp3$^+$, by a prolonged reduction in effector CD4$^+$ T cells and a persitent increase of Tregs Foxp3$^+$. All these functions extend thymoglobulin's mechanisms of action beyond that T cell depletion and enable a reduction in the burden of immunotherapy in transplanted patients, and thus optimize the outcome of

graft transplants.

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