Anti-interleukin-2 receptor monoclonal antibodies in renal transplantation

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Introduction

Although life-long administration of a multi-drug regimen of aspecific small-molecular immunosuppressants is most frequently used to prevent rejection of the transplanted organ, the administration of anti-T cell antibodies in the immediate post-transplant period (induction therapy) as prophylaxis against rejection or as anti-rejection therapy is still advocated to improve long-term allograft outcome. However, older polyclonal (ALS–ATG) and monoclonal (OKT3) anti-T cell antibodies are associated with different side-effects: (i) the development of anti-xenogeneic antibodies is associated with decreased immunosuppressive effects, serum sickness and anaphylactic reactions with repeated administration, (ii) cross-reactions with non-T cell tissue (e.g. thrombopenia, leukopenia), (iii) morbidity due to target cell activating antigen-specific reactions (cytokine release syndrome), and (iv) aspecific over-immunosuppression (e.g. CMV-infection, post-transplant lymphoproliferative disorder (PTLD)) due to interference with cells not involved in the rejection process or induction of microbial proliferation by substances released from anti-T cell antibody activated cells. Recently monoclonal antibodies (mAb) directed against the interleukin-2 receptor (IL-2R) have been tested for clinical use.

The IL-2/IL-2 receptor pathway

Because IL-2-driven T-cell proliferation is a major feature of the acute rejection process, several mAb directed to the IL-2R have been developed to suppress the immune response against an allograft. When an appropriately processed and presented antigen interacts with the T cell receptor for that specific antigen, the resting T cell is activated leading to de novo synthesis and secretion of IL-2 and to expression of high-affinity IL-2Rs [1]. The IL-2R on resting T cells is composed of two polypeptide chains—IL-2Rβ (CD122) and IL-2Rγ (CD132), forming an IL-2Rβγ complex capable of binding IL-2 with intermediate affinity. After T cell activation with antigen, the ω-chain (CD25, T-activation (Tac) antigen) is rapidly expressed and associates with the β and γ chains to form an IL-2αβγ complex, which in turn binds IL-2 with high affinity (Kd = 10^{-11} M). The interaction of IL-2 with this receptor results in a rapid proliferation of the antigen-activated T cells (clonal expansion) leading to effector T cells with helper, suppressor or cytotoxic abilities. Depending on the epitope, some anti-IL-2Rα mAbs block the association of the ω-chain with βγ complex and the binding of IL-2 with its high-affinity receptor. Hence, the duration and magnitude of this antigen-specific immune response is suppressed by blocking only antigen-activated T cells, while cells (resting T cells, B cells, monocytes-macrophages) not involved in the immediate rejection process are not or minimally affected; moreover, no cytokine-release is induced, possibly because the ω-chain is unable to cause signal transduction or internalization. In contrast, anti-IL-2Rβ mAbs are less selective and effective but they inhibit IL-2 binding as well as lymphocyte activation and proliferation [2].

Development of IL-2Rα monoclonal antibodies

Several murine and rat mAbs to the IL-2Rα (anti-Tac [murine IgG2a] [3], 33B3.1 [rat IgG2a] [4], LO-Tact-1 [rat IgG2b] [5], BT563 [murine IgG1] [6]) have been developed and tested with a variable degree of success in humans. However, some disadvantages hindered their widespread clinical use: they have short half-lives in the circulation (<48 h) compared to human IgG (21 days), probably due to quick removal induced by naturally occurring anti-rat or anti-mouse (anti-Galα1–3Gal) antibodies; they do not effectively recruit immune effector functions; and, sensitization (human anti-mouse [HAMA] or human anti-rat [HARA] antibodies), occurring in the majority of treated patients, may decrease their effect with repeated administration. In order to circumvent these drawbacks and to reduce the number of xenogeneic epitopes, hybridoma technology and recombinant genetic engineering with transfer of plasmids containing IgG gene sequences into mouse myeloma cells has been applied to produce chimeric and humanized antibodies. Chimeric antibodies consist of the entire variable region of the murine mAb fused with the human heavy and light chain constant regions; humanized antibodies only contain the hypervariable regions (complementarity-determining or antigen-specific)
Clinical studies with IL-2Rα monoclonal antibodies

Recently, two anti-IL-2Rα mAbs have completed phase III trials [7–10]: (i) basiliximab (Simulect®; t1/2: 6.5 days), a chimeric antibody and (ii) daclizumab (Zenapax®; t1/2: 20 days), a humanized anti-Tac antibody. At a dose of 20 mg given prior to transplantation and at day 4, basiliximab maintains CD25 receptor saturation for 30 days. In two placebo-controlled phase III trials, basiliximab in combination with steroids and cyclosporin, significantly decreased the incidence of acute rejection at 6 months (−26 to −31%) and 12 months (−23 to −29%). Overall graft and patient survival rates at 12 months however, were similar with basiliximab and placebo. Daclizumab at a dose of 1 mg/kg given prior to transplantation and every 2 weeks thereafter for a total of five doses, provided effective CD25 saturation for a period of 90 days. A significant reduction in incidence of acute rejection episodes at 6 months was demonstrated in two placebo-controlled phase III studies, either in combination with steroids and cyclosporin (28 vs 47%) or with steroids, cyclosporin and azathioprine (22 vs 35%). Moreover, in combination with triple therapy, 6-month graft survival was significantly better in the daclizumab group. In the double therapy trial, 6-month patient survival was significantly better in the daclizumab group. Whether daclizumab is superior to basiliximab in terms of incidence of acute rejection, graft and patient survival needs to be determined; one might speculate that the slightly better results obtained with daclizumab in these trials is related to the more prolonged CD25 receptor saturation due to a longer half-life and the longer dosing schedule in the daclizumab studies. Basiliximab has the advantage that only two doses in the early postoperative days were given.

Both preparations are safe and well tolerated (no cytokine release syndrome) with comparable incidence and pattern of infections and so far no increase in malignancies compared with the placebo groups. Anaphylactic or allergic reactions and clinically significant antibody production has not been described until now. No significant changes in total T-cells, activated T-cells or T-cell subsets are noticed, apart from a significant decrease in circulating CD25+ lymphocytes and lymph node lymphocytes [9,11]; this suggests that besides competitive binding and saturating the CD25 receptor, down-regulation of IL-2R expression, shedding of antibody-bound IL-2R or destruction of activated T-cells by ADCC may play a role in the mechanism of action. Both agents are easy to administer via peripheral IV infusion during 15 min in an easy dosing schedule. Because of their pharmacokinetic properties, no adjustments in adults have to be made for weight, age, gender, race or presence of proteinuria [12–14].

IL-2Rα monoclonal antibodies: future prospects

Despite the promising results obtained with IL-2Rα monoclonal antibodies, some questions have not been answered at present.

(i) Although the IL-2/IL-2R pathway is a critical step in the activation of alloreactive T-cells, about 1/3 of the acute rejection episodes occur during effective CD25 blockade. This observation reflects the redundancy of the rejection cascade. This interpretation is in accordance with the observation that IL-2 knockout mice are capable of rejecting a transplanted organ. The ever-present IL-15 may be a candidate substituting for IL-2 [15].

(ii) Controlled randomized studies with IL-2Rα mAbs were performed using conventional immunosuppressive therapy (corticosteroids + cyclosporine +/− azathioprine). It is not known whether IL-2Rα mAbs are able to significantly reduce the incidence of acute rejection using double or triple immunosuppressive regimens incorporating newer small molecular agents, which reduce acute rejection episodes (mycophenolate mofetil, FK-506, rapamycin).

(iii) The safety and efficacy of IL-2Rα mAbs raises questions whether it is possible to reduce other immunosuppressive agents, such as corticosteroids and calcineurin inhibitors. Two studies are being performed (one using daclizumab, one using basiliximab) to assess safety and efficacy of a steroid-free immunosuppressive regimen; no data are available at present. One study is underway to assess safety and efficacy of a daclizumab—MMF—steroid regimen free of calcineurin inhibitors [16]. As expected from initial studies showing a synergistic effect of calcineurin inhibitors and IL-2Rα mAbs, a higher incidence of acute rejections at 3 months (45%) was noted in the latter study. However, approximately 60% of patients did not require institution of calcineurin inhibitors, and therefore may benefit in the long run by not being exposed to calcineurin inhibitor nephrotoxicity.

(iv) Controlled randomized trials in immunologically high-risk patients (sensitized recipients, regrafts, paediatic patients, simultaneous kidney-pancreas recipients) or patients with delayed graft function are not available. Besides scarce anecdotal reports

binding regions) of the parent murine mAb fitted in the framework of a human IgG molecule. With these techniques, chimeric and humanized antibodies were produced without loss of antigen-specificity or significant loss of receptor-affinity but with longer half-lives and without the potential to produce neutralizing antibodies. Moreover, chimeric and humanized antibodies are not only capable of reversible blocking of the IL-2R, but—unlike murine antibodies—also of inducing antibody-dependent cellular cytotoxicity (ADCC) with human targeted cells; the magnitude of ADCC is isotype-dependent (IgG1 > IgG2b > IgG2a).
of safety and efficacy in these patients, only sub-
group analyses from the large phase III trials are 
available but they are mostly not powered to detect 
statistical differences within demographic sub-
groups. The US Simulect® Study [8] suggested a 
benefit of basiliximab on the evolution of renal 
function after transplantation (adverse influence 
of IL-2 on recovery of allograft from ischemia, 
comparable with cytokine release syndrome 
induced nephropathy[7]). It was also shown that 
reduction of acute rejection was not limited to 
cadaveric kidney graft recipients, but extended to 
recipients of living donor allografts as well [17]. 
In a recent small study in children, a significant 
decrease in B cells was noticed after administration 
of daclizumab 1 mg/kg; the relevance of it is not 

(v) A multicentre randomized open-label trial compar-
ing basiliximab with early cyclosporin versus poly-
clonal antibody induction therapy with delayed 
cyclosporine—both in conjunction with steroids 
and MMF—showed comparable effectiveness in 
preventing acute rejection and similar safety pro-
files [18]. Because of the convenient way of admin-
istration, anti-IL-2Rα mAb induction therapy may 
become very attractive as induction therapy, if 
proven equal effectiveness in controlled long-term 
studies. However, based on the scarce data at 
present, projections suggest that Thymoglobulin® 
induction with MMF substituted for azathioprine 
in high risk patients is the most effective and cost-
effective protocol at 10 years post-transplant; more 
data are necessary to draw definitive conclusions 
[19].

(vi) No data are available on efficacy of IL-2Rα mAbs 
as a strategy for treatment of acute rejections.

Conclusion

Monoclonal antibody therapy (no cross-reactivity with 
non-T cell tissue) against a carefully selected target 
antigen of a limited T cell population involved in the 
allograft immune response (IL-2Rα) allows selective 
immunosuppression without morbidity due to antigen-
specific target reactions (no cytokine-mediated first 
dose reaction) or over-immunosuppression (infection/ 
malignancy). Chimerization or humanization of the 
antibody resulted in a prolonged circulatory half-life 
and the absence of clinically significant antibody 
response producing a more prolonged exposure to the 
infused immunosuppressant and the possibility of 
re-administration. Initial reports about their efficacy 
asbestos and safety and the ease of administration makes the 
use of anti-IL-2 receptor monoclonal antibodies very 
attractive for induction after renal transplantation. 
They probably will allow sparing of more toxic and 
less specific small-molecular immunosuppressive agents 
causing substantial long-term morbidities. However, 
controlled studies comparing IL-2Rα mAbs with newer 
immunosuppressive agents, studies in high-risk renal 
allograft recipients, and long-term efficacy studies are 
warted to determine their definitive place in the 
field of immunosuppressive therapy.

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