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Anti-Interleukin-2 Receptor Antibodies in Transplantation

What is the Basis for Choice?

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Abstract

Two monoclonal antibody preparations against the α-chain of the interleukin-2 receptor (IL-2Rα) are available for use, basiliximab and daclizumab, a chimeric and a humanised antibody, respectively. The first clinical studies have demonstrated the efficacy of these agents as induction therapy to reduce the rate of acute rejection after organ transplantation. Basiliximab and daclizumab have a similar effect on prevention of acute rejection. Likewise, incidence of infections and malignancies are not different between the two treatment options. Anti-IL-2Rα therapy was very well tolerated in clinical trials.

Phase III studies with basiliximab have been undertaken with a two-dose regimen, consisting of two doses of 20mg, in an attempt to saturate the IL-2Rα on peripheral blood T lymphocytes for an average of 4–6 weeks. In contrast, the daclizumab dose is corrected for bodyweight and the goal is to achieve IL-2Rα blockade for 12 weeks. Phase III efficacy trials with daclizumab have, therefore, been developed with five doses of 1 mg/kg every 2 weeks in the first 2 months after transplantation. Whether or not it is a benefit to have blockade of the IL-2Rα for 10–12 weeks (daclizumab) compared with 4–6 weeks (basiliximab) remains unknown. Assuming 4–6 weeks would be sufficient for prevention of acute rejection, many centres have changed the protocol of daclizumab administration to two doses, the first dose given at the time of transplantation, the second 10 or 14 days after, with good success. Therefore, it seems feasible to limit the dose of daclizumab, which increases the ease of administration and probably also the cost effectiveness of this agent.

There are no controlled studies comparing basiliximab and daclizumab, nor have different dose regimens been directly compared in renal transplantation. The data available suggest the differences are small, if present at all, and it is unlikely that such a trial will ever be done. With both compounds, a significant reduction in the number of acute rejection episodes following solid organ transplantation can be obtained without an increase in adverse effects or infectious complications.

Over the last few decades the results of renal transplantation have improved,[1] at least partially as the result of the use of new and powerful immunosuppressive agents. Monoclonal antibodies against the α-chain of the interleukin-2 receptor (IL-2Rα) are a new class of immunosuppressive agents with a highly specific mode of action.[2,3] Upon alloantigen encounter the α-chain of the IL-2R is induced on the surface of T lymphocytes, and combines with the β- and γ-chains to form the high affinity IL-2R complex. Monoclonal antibodies that bind to the α-chain will block the high affinity IL-2R on activated T lymphocytes, and inhibit the IL-2 induced phosphorylation of the Jak1, Jak3 and STAT5a/b components of the IL-2R-dependent activation pathway.[4] Blockade of the effects of IL-2 on lymphocytic activation and proliferation is supposed to be the main mechanism of action. Another potentially important mechanism of action could include lysis of antibody-coated cells via antibody-dependent cell-mediated cytotoxicity and/or their elimination by long-term IL-2 deprivation.[5]

Two antibody preparations are available for use: a chimeric antibody, basiliximab, and a humanised antibody, daclizumab. The first clinical studies have demonstrated the efficacy of these agents as induction therapy to reduce the rate of acute rejection after organ transplantation.[6] In general, studies have analysed the benefits of anti-IL-2Rα therapy either added to standard immunosuppressive regimens (additional immunosuppression) or as replacement of one or more components of the standard immunosuppressive therapy (for minimisation of adverse effects). In this paper we review the results obtained with both anti-IL-2Rα antibody preparations as induction therapy, and discuss similarities and differences and the reasons to choose one or the other. We do not review data on murine anti-IL-2Rα antibodies nor those of radio-labelled or immunotoxin-conjugates. Studies using anti-IL-2Rα antibodies to avoid calcineurin inhibitor or corticosteroid treatment, or for treatment of established rejection episodes, are also ignored.

1. Efficacy

In a recent meta-analysis, eight randomised controlled trials comparing anti-IL-2Rα antibodies with placebo or no additional treatment in patients with renal transplants receiving ciclosporin (cyclosporine)-based immunosuppression were reviewed.[6] It was found that anti-IL-2Rα antibodies significantly reduced the risk of acute rejection (odds ratio [OR] 0.51; 95% CI 0.42, 0.63). The different antibodies had a similar sized effect on acute rejection: basiliximab OR 0.56 (95% CI 0.44, 0.72) and daclizumab OR 0.46 (95% CI 0.32, 0.67). Similarly, incidence of infections and malignancies (within the first year post-transplantation) were not different between the two treatment options. Anti-IL-2Rα therapy was very well tolerated. There was no increase in the number of adverse events associated with the use of anti-IL-2Rα antibodies.[6] A meta-analysis from the Cochrane Library, including 117 reports from 38 trials, involving almost 5000 patients, also found a significantly reduced incidence of acute rejection in anti-IL-2Rα antibody treatment when compared with placebo.[7] When compared with other antibody therapy, no significant differences in treatment effects were demonstrated, but anti-IL-2Rα antibodies had significantly fewer adverse effects.[7] Like Adu et al.,[6] these authors did not find a difference between basiliximab and daclizumab.[7]

Anti-IL-2Rα therapy has also been demonstrated to decrease the acute rejection rate by ±60% when added to tacrolimus, mycophenolate mofetil (MMF) and prednisone.[8] No controlled studies have evaluated the benefits of anti-IL-2Rα therapy when added to sirolimus-based immunosuppressive regimens.

At present, there is no evidence that the 40% decrease in the acute rejection rate after induction therapy translates into an improvement of long-term renal allograft survival. In the 3-year follow-ups for the daclizumab trials no significant difference in graft survival was found between the different groups, despite a persistence of the significant reduction of acute rejection episodes.[9] This lack of a beneficial effect on graft survival challenges the view that it is worthwhile to increase the immuno-

suppressive load with anti-IL-2Rα therapy. Admittedly, longer follow-up or larger patient numbers might be required to detect a (small) survival advantage with anti-IL-2Rα therapy.

Anti-IL-2Rα antibodies have also been used in liver transplantation.[10] The conclusions of these studies are similar to those in renal transplantation: reduction of acute rejection episodes, with no increase in opportunistic infections or adverse effects.[11] Beniaminovitz et al.[12] used daclizumab in preventing rejection after heart transplantation. In a randomised trial of only 55 patients, they were able to show a benefit of daclizumab on the incidence and severity of acute rejection as well as the time to the first rejection episode. Daclizumab was used for the treatment of acute graft-versus-host disease (GVHD), with a response rate of 51%.[13] However, all 43 patients in this study also received high-dose corticosteroids and 17 patients (40%) were treated with antithymocyte globulin as well. The independent contribution of anti IL-2Rα antibodies to the treatment of GVHD requires further studies.[14]

2. Dosage Regimens

Phase III studies with basiliximab have been undertaken with a two-dose regimen, consisting of two doses of 20mg, in an attempt to saturate the IL-2Rα on peripheral blood T lymphocytes for an average of 4–6 weeks.[15] In one of the phase III studies a broad pharmacokinetic sampling programme was included to detect special populations in which the standard dose regimen might need to be altered or individualised.[16] Receptor saturating basiliximab concentrations were maintained for 36 ± 14 days (range 12–91 days).[17] In patients who experienced a rejection episode after basiliximab was eliminated from serum, basiliximab had not been cleared faster than in their rejection-free peers.[17] In adults, bodyweight could explain only 6% of the variability in clearance. It was concluded that giving doses of basiliximab on a mg/kg basis would not bring the systemic exposure to this agent into a narrower, more predictable range and would not yield benefit to the dose administration regimen.[17] For paediatric patients <35kg it was recommended to use two 10mg doses and (as for adults) two 20mg doses in those >35kg.[18]

In contrast, it was considered necessary to correct the daclizumab dosage for bodyweight. In the clinical development of daclizumab the critical post-transplant period was considered to last for 12 weeks, thus adopting a daclizumab dosage covering this period: 1 mg/kg pre-transplantation and then four further doses every 2 weeks.[19] Phase III efficacy trials with daclizumab have been developed with these five doses in 2-month protocols. Whether or not it is a benefit to have blockade of the IL-2Rα for 10–12 weeks (daclizumab) compared with 4–6 weeks (basiliximab) remains unknown. Assuming 4–6 weeks would be sufficient for prevention of acute rejection, many centres have changed the protocol of daclizumab administration into two doses: the first dose given at the time of transplantation, the second 10 or 14 days thereafter. With such two-dose regimens blood daclizumab concentrations were shown to decline to 1 μg/mL at 59 ± 13 days after kidney transplantation.[20] In our studies we have also administered daclizumab in a two-dose regimen with apparent success (rejection rate after renal transplantation ±15%).[21] In this study with two doses of daclizumab we found blockade of the IL-2Rα for ≥10 weeks.[22] Others have shown that even one dose of daclizumab (2 mg/kg) results in saturation of the IL-2Rα on circulating T lymphocytes,[20] and decreased the acute rejection rate by ±60%.[6] Therefore, it seems feasible to limit the dose of daclizumab, which increases the ease of administration and, probably, also the cost effectiveness of this agent.

There are no controlled studies directly comparing the efficacy of different dose regimens in renal transplantation. Such a comparison has only been performed after simultaneous kidney-pancreas transplantation.[23] In this study, no difference in acute rejection rate was found between a two- and five-dose regimen.[23] In liver transplantation, the half-life of the antibody is much shorter than in renal transplant patients.[24] Pharmacokinetic studies showed a decreased half-life of basiliximab in liver transplantation compared with renal transplantation,

especially in patients with drainage of extreme amounts of ascitic fluid.[25] The increased clearance may also be due to differences in protein binding in patients with impaired liver function or could be due to peri- and postoperative blood loss. With a two-dose regimen of daclizumab 1.0 mg/kg on day 0 and 0.5 mg/kg on day 4 after liver transplantation, CD25 staining was suppressed for 28 days after transplantation.[24]

3. Monitoring Treatment

We have developed an alternative method for monitoring the presence of daclizumab in serum by measurement of the fractional excretion of soluble IL-2Rα.[26] This method proved more sensitive than the current gold standard, flow cytometric measurement of IL-2Rα on peripheral lymphocytes. The clinical value of monitoring the level and duration of IL-2Rα blockade has still to be determined. While therapeutic drug monitoring is not necessary in patients treated with a standard dose of anti-IL-2Rα monoclonal antibodies,[27] monitoring might be of value to determine the minimum dose of the (expensive) IL-2Rα-blocking monoclonal antibodies required for effective rejection prophylaxis. Furthermore, monitoring might become relevant if alternative treatment protocols using anti-IL-2Rα therapy are developed, that is, prolonged treatment in patients with severe toxicity to standard immunosuppressive drugs.

4. Economic Analyses

In The Netherlands, the direct costs of treatment with basiliximab (two doses of 20mg) amount to €2325 as compared to €5074 for treatment with daclizumab (five doses of 1 mg/kg) [2001 values].[21] Several studies suggest that as a result of the reduced need for admissions for acute rejection and treatment with anti-T-cell therapy, the use of basiliximab in a standard dose does not increase overall cost.[28,29] No such studies have been performed for the use of daclizumab.

5. Hypersensitivity

Basiliximab and daclizumab both contain murine sequences, and both carry the risk of inducing IgE-mediated hypersensitivity reactions. Basiliximab, the chimeric antibody, is composed of approximately 30% murine variable region sequences. The humanised daclizumab contains only 10% murine sequences and is less immunogenic.[30] However, for both preparations, developing anti-idiotypic IgE antibodies is very rare.[31]

6. Conclusion

A head-to-head comparison between basiliximab and daclizumab has not been performed. There are no randomised studies comparing the two antibodies within one patient population. The data available suggest the differences between the two agents are small, if present at all, and it is unlikely that such a trial will ever be performed. With both compounds, a significant reduction in the number of acute rejection episodes following solid organ transplantation can be obtained, without an increase in adverse effects or infectious complications. A benefit in graft survival has not been demonstrated for either of the two agents so far, despite the fact that 3-year follow-up data of phase III studies are now available. The main differences between the two antibodies are the dose administration regimens used in clinical trials. Basiliximab has typically been used in a two-dose regimen, with fixed amounts (20mg on days 0 and 4) in all patients. In contrast, the classical daclizumab regimen consists of five bodyweight-adjusted doses in the first 8 weeks. Clearly, the former regimen has advantages regarding the costs and the logistics of administration. In many renal transplant centres daclizumab is now also used as a two-dose regimen, and first results show that with a two-dose regimen, similar efficacy can be achieved as a with a five-dose regimen. This limited dose regimen probably increases the cost effectiveness of anti-IL-2R therapy with daclizumab after renal transplantation. Whether this is also true for liver, heart or bone marrow transplantation remains to be seen.

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