Interleukin receptor antagonist induction in kidney transplantation: Is it worth the price?

Kidney disease improving global outcomes (KDIGO) clinical guidelines for kidney transplantation 2009, recommend IL_2RA induction in all recipients (Grade 1 b) however in high risk recipients they recommend rabbit ATG.[1] These recommendations are based on moderate quality evidence which implies that most transplant recipients should receive the recommended treatment. The basis of the KDIGO guidelines is the initial pivotal trials and a meta analysis which revealed an overall reduction in the risk of acute rejection (AR) at 1 year of 33%.[2,3] This analysis however was mostly based on studies where Cyclosporine was the main Calcineurin inhibitor and included only one study with Tacrolimus (Tac).[4] An updated meta analysis by the same authors included only three studies with Tac and MMF and showed similar results as the previous analysis.[5] There was significant reduction in AR but no impact on graft and patient survival. We also showed 44% reduction in AR rates with IL_2RA in Cyclosporine, Aza/MMF based immunosuppression in kidney transplantation.[6]

The incidence of AR with Tac and MMF as maintenance immunosuppressive agents has reduced to 10-12% in the current era.[7,8] The impact of IL_2RA induction in reducing AR may not be the same in Tac based immunosuppression. Infact this has been documented by Scientific Registry of Transplant Recipients (SRTR) data from USA which included 28686 first renal transplant adult recipients on Tac and MMF as immunosuppressive agents. The impact of IL_2RA in this study to reduce AR was still significant however the absolute benefit was smaller than when IL_2RA was used with Cyclosporine based immunosuppression.[9] The study demonstrates a decrease in risk reduction of AR of 11% (risk ratio 0.89 $P < 0.001$). Using these figures 70 patients need to be treated to prevent one episode of AR. In recipients with living donor transplants the benefit of IL_2RA was better and number needed to prevent one episode of AR was 53. This is in comparison to 7 to 9 patients to be treated to prevent one AR in the earlier Cyclosporine treated patients.[4,5]

The question which begs an answer from every transplant clinician: Is the benefit with IL_2RA induction worth its price for a transplant recipient? This question is of greater importance in countries where patients directly pay for their immunosuppression and have to be able to afford the cost of treatment. The study by Gundlapalli *et al*.,[10] published in this issue of IJN has shown no utility of IL_2RA induction in patients with intermediate risk on Tac and MMF based immunosuppression. The study has major limitations. It is not a randomized trial and has small number of patients. The conclusions therefore need to be confirmed by a larger, preferably a randomized trial.

How and what should clinicians counsel their patients about IL_2RA induction till such trials are available, which also seem to be unlikely to be performed. Is IL_2RA induction a cost-effective treatment? Two studies have looked at cost effectiveness of IL_2RA induction and concluded that IL_2RA induction is cost effective.[11,12] However this will vary depending on the cost of treatment of AR as well as the cost of induction therapy in various centers. Cost-effectiveness has to be studied at global level and such studies are needed for broad global clinical recommendations.

IL_2RA induction has been shown to provide benefit even if maintenance of Cyclosporine AUC levels are not achieved. In absence of IL_2RA, AR rates are high (39%) if Cycl AUC is not within recommended levels (4 hours AUC – > 4400 μgm/L); however with IL_2RA induction AR rates are lower (8-9%) even when 4 hours AUC of Cyclosporin is less than the recommended levels.[13] IL_2RA induction may also provide an immunosuppressive umbrella in situations like acute tubular necrosis where one would want to reduce Calcineurin exposure for quicker recovery of renal function without enhancing acute rejection rates. If one were to analyze the current evidence, IL_2RA induction does significantly reduces AR without impacting graft and patient survival even in the Tacrolimus based immunosuppression. For the clinician it will be important to counsel patients about the current evidence of benefit and the cost that patient has to pay for it. The transplant physician should help them to make a considered choice of being able to comfortably afford the cost of IL_2RA induction and also keeping an allowance for any untoward unexpected expenses. We do require more studies in different geographical areas to clarify the cost effectiveness of global use of IL_2RA induction.

V. Kher

Chairman, Division of Nephrology and Renal Transplant Medicine,
Medanta Kidney and Urology Institute,
Medanta – The Medicity, Gurgaon, Haryana, India

Address for correspondence:
Dr. V. Kher
Division of Nephrology and Renal Transplant Medicine,
Medanta Kidney and Urology Institute,
Medanta – The Medicity, Gurgaon, Haryana, India.
E-mail : vijay.kher@medanta.org

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