Uroscan

The SMART trial; does it make us wiser in choosing between sirolimus in preference to cyclosporine – A postrenal transplant?

Ankit Mishra*

Department of Urology, AIIMS, Bhubaneshwar, Odisha, India
*E-mail: urol_swarnendu@aiimsbhubaneswar.edu.in

SUMMARY

The follow-up analysis of the SMART trial[1] assessed the role of sirolimus (mTOR inhibitor) as an alternative option to cyclosporin A (calcineurin inhibitor) in the renal transplant patients' maintenance regimen in a randomized controlled multicenter trial. Induction was given with anti-thymocyte globulin and methylprednisolone. Cyclosporin A, along with mycophenolate mofetil, was started in all within 24 hours of transplant. Those randomized to sirolimus arm were switched two to three weeks after transplant. The original trial indicated that early conversion to sirolimus might improve renal function; however, is limited by significantly higher adverse effects. The role of donor-specific antibody (DSA) was not studied.

140 patients initially randomized in the SMART trial were corresponded with via mail or telephone. The final analysis included 71 patients with functional graft who provided a blood sample for assessing the presence of DSA and renal function. Information obtained retrospectively from records, primary physicians, and patients themselves was used to analyze the graft and patient survival. The primary objective was to assess the development of de novo DSA in blood samples collected on an average of 8.7 years after transplantation. No difference was noted in the development of de novo DSA. Secondary objectives were to assess the patient and graft survival, renal function, therapy discontinuation, malignancy incidence, and adverse events. Transplant function assessed by the estimated glomerular filtration rate (calculated by the Nankivell formula) remained significantly improved in the sirolimus arm (sirolimus, 64.37±26.44 ml/min/1.73 m2 vs. cyclosporin A, 53.19±19.83 ml/min/1.73 m2; p= 0.04). Although no survival benefit was noted at ten years, a trend towards reduced graft failure rate and lesser tumor incidence was noted in the sirolimus arm.

COMMENTS

A triple maintenance regimen with steroids, tacrolimus, and mycophenolate mofetil is the standard treatment in renal transplant patients.[2] Both sirolimus and cyclosporin-A suppress IL-2 expression, which keeps the immune response in check but act through different molecular targets. Early switch to a sirolimus regimen was associated with improved renal function. Data is unclear regarding the donor-specific antibodies (DSA) occurrence and its effect on renal function and graft survival. DSA positivity has been associated with more T cell-mediated rejection, inflammation, and fibrosis in liver transplantation patients.[3]

The use of mTOR inhibitor-based immunosuppression following renal transplant remains underutilized, currently below 5%. Ten-year graft loss of deceased donor renal transplant is 51.6%.[4] Following renal transplantation, DSA develops de novo in 13–27% of patients, mainly within the first year and many years after that.[5] mTOR inhibitors form a complex with intracellular protein FKBP-12, inhibiting mTOR activity and interrupting the downstream cell signaling.

Although studies have proved mTOR inhibitors' role in combination with calcineurin inhibitors to reduce dosage and toxicity of the regimen, evidence regarding their role as an alternative to calcineurin inhibitors is scarce. No clear evidence is present in the literature on the difference of expression of DSA between sirolimus and cyclosporin A in transplant recipients. The results of this trial suggest that there may be no difference, suggesting that the use of sirolimus would not lead to an increased incidence of graft failure. Long-term data regarding immunosuppression in renal transplant is inadequate. Record-based data has the drawback of being inaccurate. This study boasts a robust ten-year follow-up analysis on DSA, transplant function, graft, and patient survival. Though six centers participated in the study, all samples were processed at a single lab to maintain uniformity.

DSA was measured only once in the follow-up, and the timing was not standardized. Therapy discontinuation was significantly greater in the sirolimus arm, which may have affected the net result. There was attrition in the studied population due to a long follow up with 49% of the original population being excluded in the final analysis. Histopathology/imaging data was not used to corroborate the data on transplant function. The trial did not study tacrolimus, which has since supplanted cyclosporin A as the calcineurin inhibitor used in immunosuppression.

The authors reported no difference in the occurrence of DSA under sirolimus as compared to cyclosporin A. Graft function was significantly better under sirolimus in the long-term follow-up (eGFR). Thus, shifting to sirolimus can be an option after initial treatment if tolerable. Sirolimus is available in India as a 1mg oral tablet at the cost of about two hundred rupees, and depending on the dose, it may cost up to a thousand rupees a day, which is almost same as the cost of cyclosporin A. Whether this improved graft function with sirolimus transcribes to a better transplant survival remains to be seen.

REFERENCES

1. Andrassy J, Guba M, Habicht A, Fischereder M, Pratschke J, Pascher A, *et al*. Early conversion to a CNI-free immunosuppression with SRL after renal transplantation—Long-term follow-up of a multicenter trial. PLoS ONE 2020;15:e0234396.
2. Ekberg H, Tedesco-Silva H, Demirbas A, Vítko S, Nashan B, Gürkan A, *et al*. ELITE-symphony study. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med 2007;357:2562-75.
3. Höfer A, Jonigk D, Hartleben B, Verboom M, Hallensleben M, Hübscher SG, *et al*. DSA are associated with more graft injury, more fibrosis, and upregulation of rejection-associated transcripts in subclinical rejection. Transplantation 2020;104:551-61.
4. Hart A, Smith JM, Skeans MA, Gustafson SK, Wilk AR, Robinson A, *et al*. OPTN/SRTR 2016 annual data report: Kidney. Am J Transplant. 2018; 18 Suppl 1:18-113.
5. Everly MJ, Rebellato LM, Haisch CE, Ozawa M, Parker K, Briley KP, *et al*. Incidence and impact of de novo donor-specific alloantibody in primary renal allografts. Transplantation 2013;95:410-7.

Received: 31.10.2020, **Revised:** 23.03.2021,

Accepted: 31.05.2021, **Published:** 01.07.2021

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/iju.IJU_591_20

How to cite this article: Misra A. The SMART trial; Does it make us wiser in choosing between sirolimus in preference to cyclosporine – A postrenal transplant? Indian J Urol 2021;37:297-8.