AVESTA Study
An Iranian Verification of Everolimus Success in Transplantation Aspects:
A Randomized Clinical Trial

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Introduction and Objectives

Many years have passed from the first successful kidney transplantation and the cornerstone of current immunosuppression regimens is still achieved by using calcineurin inhibitors however it is shown that long-term use of these drugs may be associated with reversible changes accompanying by irreversible damage to all kidney compartments leading to both acute and chronic nephrotoxicity. Nowadays the goal is to optimize available immunosuppressive regimens and reduce the calcineurin inhibitor dose as much as possible while protecting the transplanted kidney from rejection processes . The AVESTA study designed to compare renal function , Cytomegalovirus infection and BK nephropathy rate and biopsy-proven acute rejection in two regimens: an everolimus plus reduced calcineurin inhibitor-based regimen versus a standard dose calcineurin-inhibitor protocol with mycophenolic acid in 60 de novo Iranian kidney transplant recipients.

Methods

AVESTA was a 12-month, open-label, randomized, parallel-group study in 60 Iranian kidney transplant recipients (aged between 18 to 65) received renal allografts from deceased or living donors.

* Eligible patients randomized (1:1) prior to transplantation to one of the following two treatment arms:
* 1- Sandimmun 3.5mg/kg(with C0 100-200 ng/ml in first month,75-100 ng/ml in second and third month,50-100 ng/ml in fourth month and 25-50 ng/ml in sixth-twelfth month) + Everolimus (starting dose 0.75mg/bid; C0 3– 8 ng/mL) in combination with corticosteroids
* 2- Sandimmun 6mg/kg divided dose with C0 150-300 ng/ml in three month + Cellcept 1gr/bid or Tacrolimus 0.1mg/kg divided with tacro level 7-10 ng/ml in three month +Cellcept 500mg/bid in combination with corticosteroids
* All patients receive induction therapy with 4.5mg/kg Thymoglobulin.The primary endpoint was to demonstrate non-inferiority of renal function by estimated -GFR in everolimus arm compared with the standard group 6 and 12 months after kidney transplantation. The secondary objectives were to evaluate and compare the incidence of biopsy-proven acute rejection and severity of viral infections including CMV and BK nephropathy between two arms .

Results

Mean time post-transplant follow-up was 13±2 months with each arms. Renal function based on eGFR(CKD-EPI & MDRD formula) showed no statistical differences (p = 0.130) between two arms at 6 month (68.6 (95% CI 58.1, 65.1) mL/ min/1.73 m2 with everolimus and 64.6 (95% CI 55.2, 62.3) mL/min/1.73 m2 with calcineurin –inhibitor based group) and at 12 month post transplantation(52 mL/ min/1.73 m2 with everolimus and 54 mL/min/1.73 m2 with calcineurin –inhibitor based group) (p = 0.145) No statistical differences also were found in regard to incidence of biopsy proven acute rejection or severity of fibrosis in biopsies in cause and protocol biopsies at the end of first year post transplantation (67% protocol biopsies achieved at the end of 12th month post transplant) . Rate of CMV and biopsy-proven BK nephropathy were significantly lower at 12th month post transplantation in everolimus-based treatment group (p = 0.0001 and p= 0.0005 respectively).

Conclusion

AVESTA study suggested non-inferiority and overall safety of de novo everolimus-based regimen in Iranian kidney transplant recipients with preserved renal function and significantly lower viral infections without increasing the risk of acute rejection in the first post operation year which could impact long-term outcomes and offer renal benefits versus the standard calcineurin-inhibitor based immunosuppression regimens .The study population will be followed for 3 years after transplantation to determine whether these encouraging results are maintained long-term.

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