

Journal of Nephrologist



Effect of sirolimus as an immunosuppressive agent on kidney transplantation in patients with diabetes mellitus; a systematic review

Saeedeh Davar¹, Mohsen Mohammad Rahimi² , Maasoumeh Mahdi Akhgar^{3*} , Sajjad Saei⁴

¹Department of Biostatistics and Epidemiology, Urmia University of Medical Sciences, Urmia, Iran

²Nephrology and kidney Transplant Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

³Department of Biostatistics and Epidemiology, School of Health Hamadan University of Medical Sciences & Health Services, Hamadan, Iran

⁴Urmia University of Medical Sciences, Urmia, Iran

ARTICLE INFO

Article type:
Review

Article history:
Received: 10 August 2019
Accepted: 27 November 2019
Published online: 26 December 2019

Keywords:
Sirolimus
Diabetes mellitus
Kidney transplantation
End-stage renal disease

ABSTRACT

Introduction: Sirolimus is a macrolide and a type of immunosuppressant drug to prevent rejection of transplanted organs. This drug inhibits the activation of T and B lymphocytes and reduces the production of interleukin-2 (IL-2).

Objectives: This study aimed to review the effect of sirolimus in kidney transplantation in patients with diabetes mellitus as a systematic review.

Materials and Methods: International databases including PubMed, Web of Science and Scopus were considered for search of English articles by 29 June 2019. Twenty-one published articles were finally entered into the study. Keywords were sirolimus, rapamune, rapamycin, diabetes mellitus and kidney transplantation or a combination of them in the title/abstracts. Treatment using a combination of sirolimus and tacrolimus were excluded.

Results: There were more than 3244 subjects reviewed in this systematic review including 21 published articles (Total population of 21 articles: 3244 people).

Conclusion: According to the results, sirolimus-based immunosuppression for preventing kidney transplantation is effective and has a low-risk in diabetic patients resulting in suitable glucose control.

Implication for health policy/practice/research/medical education:

Sirolimus-based immunosuppression for preventing kidney transplantation is effective and has a low-risk in diabetic patients.

Please cite this paper as: Davar S, Mohammad Rahimi M, Mahdi Akhgar M, Saei S. Effect of sirolimus as an immunosuppressive agent on kidney transplantation in patients with diabetes mellitus; a systematic review. J Nephrologist. 2020;9(2):e13. DOI: 10.34172/jnp.2020.13.

Introduction

Nowadays, chronic diseases are prevalent such as chronic kidney disease and end-stage renal disease (ESRD), with an average increase of 6% per year (1). ESRD as a form of chronic kidney failure is an irreversible decrease in kidney function that results in death without dialysis or kidney transplantation (2, 3). Diabetes, hypertension, polycystic hereditary disease and glomerulonephritis are some important risk factors associated with ESRD (4). Renal replacement therapy (RRT) is a general term used in the treatment of patients with ESRD, including hemodialysis, peritoneal dialysis, and renal allograft transplantation (5). The quality of life of patients receiving kidney transplantation is better than others since the quality of life of hemodialysis patients was significantly lower than

other groups (6). Kidney transplantation was encountered with lots of challenges during the development, in which rejection of transplantation is the most important challenging issue. In this regard, some drugs are used to prevent the rejection of the kidney transplantation (7, 8). One of the well-tolerated drugs with acceptable results in this field is sirolimus. Sirolimus is a macrolide and a type of immunosuppressant drug to prevent rejection of transplanted organs. This drug inhibits the activation of T and B lymphocytes and reduces the production of interleukin-2 (IL-2) (9-11). There are some systematic reviews about the effect of sirolimus in the past decades e.g. Webster et al suggested that long-term hard-endpoint data from robust randomized trials are still required to make a decision (12). It is worthy to be noted that due to

*Corresponding author: Maasoumeh Mahdi Akhgar,
Email: maasoumehakhghar@gmail.com

the importance of sirolimus outcome on the transplanted patients, further studies are needed. Thus, this study aimed to review the effect of sirolimus on kidney transplantation in patients with diabetes mellitus as a systematic review.

Methods

Search strategy

International databases including PubMed, Web of Science and Scopus were considered for search of English articles by 29 June 2019. Twenty-one published articles were finally entered into the study. Keywords were sirolimus, rapamune, rapamycin, diabetes mellitus and kidney transplantation or a combination of them in the title/abstracts. Treatment using a combination of sirolimus and tacrolimus were excluded.

Search strategy for PubMed

(Sirolimus [MeSH] and Sirolimus* [TIAB] OR rapamycin [TIAB] OR Rapamune [TIAB]) AND (Diabetes mellitus [Mesh] OR Diabetes mellitus [TIAB]) AND (Kidney transplantation [MeSH] OR Kidney transplantation rejection [TIAB]). After collection of articles of interest, references were imported to Endnote software and removed duplicate titles. Then, after browsing titles, studies with irrelevant purposes were removed, and then the remaining studies assessed by two independent investigators. The selected studies were performed on humans and published in English.

Data extraction

Information dealing with the selected articles (the author's last name, year of publication, study design, sample size and the results of each article) was taken by two independent investigators. The differences observed in this process were corrected by a third investigator who was independent with the two previous investigators.

Results

There were more than 3244 subjects reviewed in this systematic review including 21 published articles consisted of two retrospective studies, two prospective studies and seventeen clinical trial studies (Total population of 21 articles: 3244 people). We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, a checklist of items that should be included in reports of interventional studies for selected articles (13,14). Figure 1 shows the selection process using PRISMA. The summary of the selected articles was shown in Table 1.

Discussion

Kidney transplantation is the best treatment for patients with renal failure after kidney transplantation. Improved

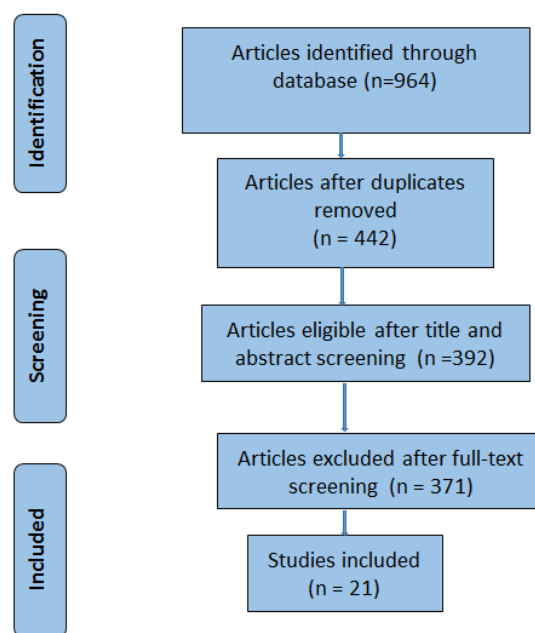


Figure 1. Flow chart of study selection based on PRISMA.

kidney function, survival and quality of life using anti-rejection drugs as suppressive agents had been observed in these patients. Immunosuppressive agents help to prevent graft rejection (36). Similar research done in other countries is largely similar to the results obtained in this review supporting the preventive effect of sirolimus following transplantation (37). A review study by Pascual et al has shown that using sirolimus can reduce the dose of calcineurin inhibitors and the combination results in better outcomes (38). Cooper et al showed sirolimus in combination with low-dose cyclosporine or tacrolimus is more effective in treating and preventing graft rejection, and improves graft transplant function (39). A systematic and meta-analysis performed by Araki et al has yielded similar results in comparison with our review (40). All studies approximately concluded the protective effect of sirolimus after kidney transplantation accompanied with the reduced dose of cyclosporine.

Conclusion

Based on the results, sirolimus-based immunosuppression for preventing kidney transplantation is effective and has a low-risk in diabetic patients resulting in suitable glucose control.

Conflicts of interest

The authors declare that there is no conflict of interest in this study.

Ethical considerations

Ethical subjects such as plagiarism and double publication have observed in this study.

Table 1. The detail of reviewed articles in this systematic study

First author	N	Age (y)	Design	Conclusion
Almeida et al (15)	30	41±10.5	Cross-sectional	Conversion to SRL was safe. There was no deterioration in renal function nor episodes of acute rejection. There was a significant increase in cholesterol values after conversion.
Anil Kumar et al (16)	150	49±13.7	Prospective	It needs further studies to be evaluated.
Arellano et al (17)	50	Not reported	Prospective	Sirolimus monotherapy is safe in a selected group of immunological low-risk patients without increasing the risk of rejection.
Ciancio et al (18)	150	14-78	RCT	This three-year (interim) analysis has indicated a trend towards better graft function, fewer endocrine disorders, and fewer acute rejection episodes comparing adjunctive MMF and Tacro vs. Siro.
Ferreira et al (19)	70	34.4 ± 11.6	RCT	In black recipients of primarily living renal allograft donors reduced CsA exposure and SRL concentration-controlled regimens produced low incidences of acute rejection, post-transplant diabetes mellitus and CMV disease, with no significant impairment in graft function.
Gatault et al (20)	150	18-65	RCT	Sirolimus improved renal graft function at 8 years without increased risk of donor-specific antibodies appearance.
Gyurus et al (21)	514	42.2±1.1	RCT	Our 10-year experience revealed SRL to be an etiologic agent for NODAT, displaying interactive, possibly pharmacokinetic, and pharmacodynamic effects with concomitant CsA in combination treatment.
Havrdova et al (22)	30	42.5±6.0 vs. 42.3±6.1	RCT	Recipients on sirolimus treatment had significantly lower insulinemia during the test and consequently more favorable indices of insulin action
Jaber et al (23)	84	45 ± 14 vs. 46± 16	RCT	Early steroid-withdrawal in renal transplant recipients with a sirolimus and mycophenolate mofetil-based and calcineurin inhibitor-minimization protocol can effectively reduce many of the steroid-related side effects, decrease risk factors for cardiovascular disease, and is associated with improved recipient survival without compromising graft function.
Johnston et al (24)	124	47±14.6	Cross-sectional	Sirolimus is independently associated with non-onset diabetes. Given the negative impact of NOD on post-transplantation outcomes, these findings should be confirmed in prospective studies or in meta-analyses of existing trials that involved sirolimus.
Kahan et al (25)	149	18-65	RCT	SRL in combination with CsA and steroids not only lowers the incidence of biopsy-proven acute renal allograft rejection episodes, but also may permit CsA sparing, at least among Caucasian patients, without an increased risk of rejection
Legendre et al (26)	161	Not reported	RCT	Patients receiving sirolimus experience an initial increase in lipid levels, but these effects are manageable with the use of lipid-lowering agents. Hypertension was less frequent and renal function was improved with CsA-free, sirolimus-based therapy. Based on this early experience, overall cardiovascular risk does not appear to be increased with sirolimus-based compared with CsA-based therapy
Mital et al (27)	37	2-63	RCT	This study demonstrates the exciting prospect of safe and effective sirolimus-based immunosuppression in renal transplantation without the need for any maintenance steroids.

Table 1. Continued

First author	N	Age (y)	Design	Conclusion
Podder et al (28)	470	Not reported	RCT	A concentration-controlled sirolimus-cyclosporine-prednisone regimen (with steroid withdrawal by 3 months) reduced the incidence of acute rejection episodes and increased 6-year graft survivals.
Romagnoli et al (29)	86	47.7 ±9	RCT	Careful monitoring of blood levels is mandatory in the SRL + CsA combination to avoid pleiotropic toxicity.
Steigerwalt et al (30)	40	54.7±9.0 vs. 51.8±10.5	RCT	The lower 24-hour SBP seen in the SRL group by AMBP may lead to improved cardiovascular and renal outcomes over time. Long-term patient follow-up will be needed to clarify the effect of the lower 24-hour SBP.
Sundberg et al (31)	21	23-70	Retrospective	Daclizumab bridge therapy provides safe and effective immunosuppressive coverage while converting renal transplant recipients from CI- to SRL-based maintenance immunosuppressive therapy.
Veroux et al (32)	344	48 ± 12	RCT	Conversion from CNI to SIR in patients could improve significantly the metabolic parameters of patients with NODAT, without increasing the risk of acute graft rejection.
Teutonico et al (33)	26	42.8±10.4 vs. 46.9±10.6	RCT	In conclusion, the discontinuation of calcineurin inhibitors and their replacement by sirolimus fail to ameliorate the glycometabolic profile of kidney transplant recipients. Rather, it is associated with a worsening of insulin resistance and an inappropriately low insulin response
Veroux et al (34)	396	52.3 ±8 9.4 vs. 49.28±11.4	RCT	Sirolimus-based immunosuppression is safe and efficacious in type 2 diabetic patients who underwent a kidney transplantation, allowing a better glucose metabolism control.
Lebranco et al (35)	162	47.4±11.9 vs.47.7 ±10.5	RCT	Renal benefits associated with conversion of CsA to SRL, at 3 months post-transplantation, in combination with MMF were maintained for 4 years post-transplantation.

CsA; cyclosporine A, Tacro; tacrolimus, Siro; sirolimus; RCT, randomized controlled trial.

Funding/Support

None.

References

- Zhang Q-L, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. *BMC Public Health*. 2008;8:117. doi: 10.1186/1471-2458-8-117.
- Harrison TR, Kasper DL. *Harrison's Principles of Internal Medicine*. 16th ed. New York: McGraw-Hill; 2005.
- Shaheen FA, Al-Khader AA. Epidemiology and causes of end stage renal disease (ESRD). *Saudi J Kidney Dis Transpl*. 2005;16:277-81.
- Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med*. 2009;169:342-50. doi: 10.1001/archinternmed.2008.605.
- Pannu N, Klarenbach S, Wiebe N, Manns B, Tonelli M, Alberta Kidney Disease Network. Renal replacement therapy in patients with acute renal failure: a systematic review. *JAMA*. 2008;299:793-805. doi: 10.1001/jama.299.7.793
- Chkhotua A, Pantsulaia T, Managadze L. The quality of life analysis in renal transplant recipients and dialysis patients. *Georgian Med News*. 2011;11:10-7.
- Halloran PF. Immunosuppressive drugs for kidney transplantation. *N Engl J Med*. 2004;351:2715-29. doi: 10.1056/NEJMra033540
- Nankivell BJ, Alexander SI. Rejection of the kidney allograft. *N Engl J Med*. 2010;363:1451-62. doi: 10.1056/NEJMra0902927.
- Sehgal SN. Sirolimus: its discovery, biological properties, and mechanism of action. *Transplant Proc*. 2003; 35:7S-14S. doi: 10.1016/s0041-1345(03)00211-2.
- Johnston O, Rose CL, Webster AC, Gill JS. Sirolimus is associated with new-onset diabetes in kidney transplant recipients. *J Am Soc Nephrol*. 2008;19(7):1411-8. doi: 10.1681/ASN.2007111202.
- Asrani SK, Leise MD, West CP, Murad MH, Pedersen RA, Erwin PJ, Tian J, Wiesner RH, Kim WR. Use of sirolimus in liver transplant recipients with renal insufficiency: A systematic review and meta-analysis. *Hepatology*. 2010; 52:1360-70. doi: 10.1002/hep.23835.
- Webster AC, Lee VW, Chapman JR, Craig JC. Target of rapamycin inhibitors (sirolimus and everolimus) for primary immunosuppression of kidney transplant recipients: a systematic review and meta-analysis of randomized trials. *Transplantation*. 2006;81:1234-48. doi: 10.1097/01.tp.0000219703.39149.85.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700.
- Centre for Reviews and Dissemination: Systematic reviews: CRD's 16 guidance for undertaking reviews in health care. York: University of York; 2009.
- Almeida M, Martins LS, Dias L, Figueiredo MJ, Henriques AC, Sarmiento AM, et al. Conversion to sirolimus in a population of kidney and kidney-pancreas transplant recipients. *Transplant Proc*. 2005;37:2777-80. doi: 10.1016/j.transproceed.2005.06.088
- Anil Kumar MS, Heifets M, Fyfe B, Saeed MI, Moritz MJ, Parikh MH, et al. Comparison of steroid avoidance in tacrolimus/mycophenolate mofetil and tacrolimus/sirolimus combination in kidney transplantation monitored by surveillance biopsy. *Transplantation*. 2005;80:807-14. doi: 10.1097/01.tp.0000173378.28790.0b
- Arellano EM, Campistol JM, Oppenheimer F, Rovira J, Diekmann F. Sirolimus monotherapy as maintenance immunosuppression: single-center experience in 50 kidney transplant patients. *Transplant Proc*. 2007;39:2131-4. doi: 10.1016/j.transproceed.2007.06.056
- Ciancio G, Burke GW, Gaynor JJ, Ruiz P, Roth D, Kupin W, et al. A randomized long-term trial of tacrolimus/sirolimus versus tacrolimus/mycophenolate versus cyclosporine/sirolimus in renal transplantation: three-year analysis. *Transplantation*. 2006;81:845-52. doi: 10.1097/01.tp.0000203894.53714.27
- Ferreira AN, Machado PG, Felipe CR, Motegi SA, Hosaka BH, Tanaka MK, et al. Concentration-controlled use of sirolimus associated with reduced exposure of cyclosporine in black recipients of primarily living renal allograft donors: 12-month results. *Clin Transplant*. 2005;19:607-15. doi: 10.1111/j.1399-0012.2005.00331.x.
- Gatault P, Bertrand D, Buchler M, Colosio C, Hurault de Ligny B, Weestel PF, et al. Eight-year results of the Spiesser study, a randomized trial comparing de novo sirolimus and cyclosporine in renal transplantation. *Transplant Int*. 2016;29:41-50. doi:10.1111/tri.12656
- Gyurus E, Kaposztas Z, Kahan BD. Sirolimus therapy predisposes to new-onset diabetes mellitus after renal transplantation: a long-term analysis of various treatment regimens. *Transplant Proc*. 2011;43:1583-92. doi: 10.1016/j.transproceed.2011.05.001.
- Havrdova T, Saudek F, Boucek P, Adamec M, Koznarova R, Jedinakova T, et al. Metabolic effect of sirolimus versus mycophenolate mofetil on pancreatic graft function in the early posttransplant period. *Transplant Proc*. 2005;37:3544-5. doi: 10.1016/j.transproceed.2005.09.056
- Jaber JJ, Feustel PJ, Elbahloul O, Conti AD, Gallichio MH, Conti DJ. Early steroid withdrawal therapy in renal transplant recipients: a steroid-free sirolimus and CellCept-based calcineurin inhibitor-minimization protocol. *Clin Transplant*. 2007;21:101-9. doi: 10.1111/j.1399-0012.2006.00613.x
- Johnston O, Rose CL, Webster AC, Gill JS. Sirolimus is associated with new-onset diabetes in kidney transplant recipients. *J Am Soc Nephrol*. 2008;19:1411-8. doi: 10.1681/ASN.2007111202.
- Kahan BD, Julian BA, Pescovitz MD, Vanrenterghem Y, Neylan J. Sirolimus reduces the incidence of acute rejection episodes despite lower cyclosporine doses in caucasian recipients of mismatched primary renal allografts: a phase II trial. *Rapamune Study Group. Transplantation*. 1999; 68:1526-32. doi: 10.1097/00007890-199911270-00016

26. Legendre C, Campistol JM, Squifflet JP, Burke JT. Cardiovascular risk factors of sirolimus compared with cyclosporine: early experience from two randomized trials in renal transplantation. *Transplant Proc.* 2003; 35:151s-3s. doi: 10.1016/s0041-1345(03)00241-0
27. Mital D, Podlasek W, Jensik SC. Sirolimus-based steroid-free maintenance immunosuppression. *Transplant Proc.* 2002; 34:1709-10. doi: 10.1016/S0041-1345(02)02992-5
28. Podder H, Forgacs B, Csapo Z, Kahan B. [Improved outcome with sirolimus-cyclosporine regimen in high-risk renal transplant recipients]. *Orvo Hetil.* 2005;146:1641-6.
29. Romagnoli J, Citterio F, Nanni G, Favi E, Tondolo V, Spagnoletti G, et al. Incidence of posttransplant diabetes mellitus in kidney transplant recipients immunosuppressed with sirolimus in combination with cyclosporine. *Transplant Proc.* 2006;38:1034-6. doi: 10.1016/j.transproceed.2006.03.072
30. Steigerwalt SP, Brar N, Dhungel A, Butcher D, Steigerwalt S, El-Ghouroury M, et al. Improved 24-hour blood pressure control with sirolimus versus calcineurin inhibitor based immunosuppression in renal transplant recipients. *Transplant Proc.* 2009;41:4184-7. doi: 10.1016/j.transproceed.2009.07.109.
31. Sundberg AK, Rohr MS, Hartmann EL, Adams PL, Stratta RJ. Conversion to sirolimus-based maintenance immunosuppression using daclizumab bridge therapy in renal transplant recipients. *Clin Transplant.* 2004; 18 Suppl 12:61-6. doi: 10.1111/j.1399-0012.2004.00220.x
32. Veroux M, Tallarita T, Corona D, Sinagra N, Giaquinta A, Zerbo D, et al. Conversion to sirolimus therapy in kidney transplant recipients with new onset diabetes mellitus after transplantation. *Clinical & developmental immunology.* 2013; 2013:496974. *Clin Dev Immunol.* 2013; 2013:496974. doi: 10.1155/2013/496974.
33. Teutonico A, Schena PF, Di Paolo S. Glucose metabolism in renal transplant recipients: effect of calcineurin inhibitor withdrawal and conversion to sirolimus. *J Am Soc Nephrol.* 2005;16:3128-35. doi: 10.1681/ASN.2005050487
34. Veroux M, Corona D, Giuffrida G, Gagliano M, Vizcarra D, Tallarita T, et al. Sirolimus-based immunosuppression in kidney transplantation for type 2 diabetic nephropathy. *Urol Int.* 2010;84:301-4. doi: 10.1159/000288232.
35. Lebranchu Y, Thierry A, Thervet E, Büchler M, Etienne I, Westeel PF, et al. Efficacy and safety of early cyclosporine conversion to sirolimus with continued MMF—four-year results of the Postconcept study. *AM J Transplant.* 2011; 11:1665-75. doi: 10.4103/0971-4065.176146
36. Fleming GM. Renal replacement therapy review: past, present and future. *Organogenesis.* 2011;7:2-12. doi: 10.4161/org.7.1.13997
37. Saturnino LTM, Ceccato MGB, Cherchiglia ML, Andrade ELG, Giordano LFC, Acurcio FA. Target of rapamycin inhibitors (TORi) as maintenance immunosuppression for kidney transplant recipients. *Cochrane Database Syst Rev* 2015;3:CD009637. doi: 10.1002/14651858.CD004290.pub2
38. Pascual J, Zamora J, Galeano C, Royuela A, Quereda C. Steroid avoidance or withdrawal for kidney transplant recipients. *Cochrane Database Syst Rev.* 2009;(1):CD005632. doi: 10.1002/14651858.CD005632.pub2
39. Cooper JE, Christians U, Wiseman AC. Everolimus in kidney transplantation. *Transplant Res Risk Manag.* 2011;3: 97-112.
40. Araki M, Flechner SM, Ismail HR, Flechner LM, Zhou L, Derweesh IH, et al. Posttransplant diabetes mellitus in kidney transplant recipients receiving calcineurin or mTOR inhibitor drugs. *Transplantation* 2006;81:335-41. doi: 10.1097/01.tp.0000195770.31960.18

Copyright © 2020 The Author(s); Published by Society of Diabetic Nephropathy Prevention. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.