REVIEW ARTICLE

Efficacy and safety of sirolimus (rapamycin) for thyroid eye disease: a systematic review

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Abstract

This systematic review aimed to summarize available evidence on the efficacy and safety of sirolimus (rapamycin) in the treatment of thyroid eye disease (TED). PubMed, Web of Science, and Medline were searched on 1 May 2025. Case reports, case series, and clinical trials that investigated the use of sirolimus with or without combined therapy in patients with moderate-to-severe TED were included. In total, two case reports, one case series, and three clinical trials involving 50 patients with moderate-to-severe TED with or without intractable diplopia who failed the first-line treatment of intravenous glucocorticoid and received either oral sirolimus or other immunosuppressants were included in the analysis. Sirolimus appears to be effective and safe in managing TED, as indicated by improvements in both clinical activity score and Gorman diplopia score, as well as satisfactory safety profile. However, further studies are warranted to fully elucidate its efficacy and safety.

Keywords: Graves ophthalmopathy; MTOR inhibitors; Sirolimus

Introduction

Graves' disease is an autoimmune disease that affects the thyroid gland and is the most common cause of hyperthyroidism. Thyroid eye disease (TED) is the most common type of extrathyroidal manifestation of Graves' disease. Its estimated prevalence is 150 to 300 per 100 000 individuals.[1,2] TED is potentially sight threatening and is associated with dry ocular sensation, excessive tearing, and double vision, impairing quality of life. Common clinical features include upper eyelid retraction, edema, erythema of the periorbital tissues, and proptosis.[3] TED is a dynamic disease that alters between an inflammatory stage and a fibrotic stage, also known as active and chronic phases, respectively. The severity of TED is classified as mild, moderate-to-severe, and sight threatening.[4]

Glucocorticoids are the mainstay of treatment for TED. Nonetheless, recurrence frequently occurs once glucocorticoids are withdrawn, resulting in suboptimal effects.[5] A watchful strategy and artificial tears are recommended for inactive mild TED, whereas a combination of intravenous methylprednisolone (IVMP) and oral mycophenolate mofetil is recommended as the first-line treatment for active moderate-to-severe TED. Second-line treatments include another course of IVMP, oral prednisolone with cyclosporine or azathioprine, orbital radiotherapy with oral or intravenous glucocorticoids, teprotumumab, rituximab, and tocilizumab.[4] Of these, only teprotumumab, an insulin-like growth factor 1 inhibitory monoclonal antibody, has been approved for the treatment of TED by the Food and Drug Administration.[6] However, its use is limited owing to high costs, limited availability, and the concern of hearing impairment.[6,7]

Sirolimus, also known as rapamycin, is an immunosuppressant mainly used as prophylaxis for organ rejection in patients with renal transplant and those with lymphangioleiomyomatosis due to its anti-proliferative, anti-fibrotic, and immunosuppressive properties.[8,9] It inhibits the mammalian target of rapamycin (mTOR) signaling pathway, which mediates the downstream pathway of insulin-like growth factor 1 receptors.[10,11] A case of steroid-refractory dysthyroid optic neuropathy, a common complication of TED, was successfully treated with sirolimus.[12] Inhibition of the mTOR pathway has been shown to regulate orbital fibroblast activity and extraocular tissue fibrosis[13] and suppress CD4+ cytotoxic T lymphocytes,[14] which play a pivotal role in immune-mediated inflammatory fibrosis.

This systematic review aimed to summarize available evidence on the efficacy and safety of sirolimus in the treatment of TED.

Methods

This review was registered in PROSPERO and was conducted in accordance with the PRISMA guidelines.[15] PubMed, Web of Science, and Medline were searched on 1 May 2025 using the terms: 'sirolimus', 'rapamycin', 'thyroid eye disease', 'thyroid disease', 'Graves disease', 'thyroid-associated ophthalmopathy', 'thyroid-associated orbitopathy', and 'TED'. Case reports, case series, and clinical trials that investigated the use of sirolimus with or without combined therapy in patients with moderate-to-severe TED were included. Reviews, letters, non-human studies, and in vitro studies were excluded, as were studies in which the full text was unavailable or related to other thyroid-related conditions.

Efficacy was evaluated in terms of improvements in clinical activity score (CAS) for inflammatory activity in TED and/or Gorman diplopia score (GDS) for diplopia severity. CAS and diplopia responders were defined as improvement in CAS and GDS by at least one point, respectively. Safety was evaluated in terms of frequency and severity of adverse events (AEs) and severe AEs. An AE was defined as any undesirable symptom or sign occurring after initiation of treatment, regardless of whether it was directly attributable to sirolimus.

The risk of bias for non-randomized clinical trials was evaluated by two reviewers independently using ROBINS-I.[16] Disagreements were resolved through discussion with the third reviewer. Publication bias was not assessed owing to the limited number of studies included.

Results

Of 831 articles identified (415 from PubMed, 385 from Web of Science, and 31 from Medline), 307 were duplicates and were removed and 524 were screened. Of the latter, 509 were excluded and 15 were retrieved to determine eligibility. Of the latter, nine were excluded owing to wrong study design (n=5), wrong outcome measures (n=1), and in vitro studies (n=3), and the remaining six studies (two case reports, one case series, and three clinical trials) were included in the analysis (**Table**).

Table. Findings of the six included studies.

Study	Design	No. of patients	Mean patient age, y	Disease activity (clinical activity score)	Disease severity	Intervention	Clinical activity score decrease ≥1 point*		Gorman diplopia score decrease*	
							24 weeks	48 weeks	24 weeks	48 weeks
Chang et al,[12] 2007	Case report	1 man	49	-	Sight threatening	Oral sirolimus 1-2 mg/day (alternately) for 24 months + orbital decompression surgery and oral prednisolone	-	-	-	-
Roos et al,[20] 2019	Case report	1 man	43	Inactive	Moderate to severe	Oral sirolimus 6 mg/day, followed by 4 mg/day + oral prednisolone	-	-	-	-
Lanzolla et al,[17] 2022	Clinical trial	1 men, 14 women	55.6	Active (4.6)	Moderate to severe	Oral sirolimus 2 mg on day 1, followed by 0.5 mg/day for 12 weeks vs intravenous methylprednisolone 4.5 g/week for 12 weeks	13/15 (86.6)	-	7/11 (63.6)	-
Comi et al,[18] 2024	Clinical trial	4 men, 16 women	62.6	Active (3.5)	Moderate to severe	Oral sirolimus 2 mg on day 1, followed by 0.5 mg/day for 12 weeks vs intravenous methylprednisolone 4.5 g/week for 12 weeks	17/20 (85.0)	15/20 (75.0)	7/18 (38.9)	9/18 (50.0)
Zhang et al,[14] 2023	Clinical trial	3 men, 2 women	47.2	Inactive (1.8)	Intractable diplopia	Oral sirolimus 2 mg/day for 12 months	-	5/5 (100.0)	2.3	3/5 (60.0); 1.8
Lai et al,[19] 2023	Case series	6 men, 4 women	53.9	-	Intractable diplopia	Oral sirolimus 2 mg/day vs oral mycophenolate mofetil 750 mg/day (in two doses) + intravenous methylprednisolone 4.5 mg 12 weekly and radiotherapy 20 Gy for 2 weeks	1.3	1.7	1.2	6/10 (60.0); 1.2

* *Data are presented as No. (%) of patients and/or mean score.*

In total, there were 50 patients (28% men and 72% women) with moderate-to-severe TED with or without intractable diplopia who failed the first-line treatment of intravenous glucocorticoids and received either oral sirolimus (2 mg/day or 2 mg on day 1, followed by 0.5 mg/day for 12 weeks) or other immunosuppressants. Two of the clinical trials compared oral sirolimus with IVMP; the one case series compared oral sirolimus with oral mycophenolate mofetil, in combination with IVMP and orbital radiotherapy.

The risk of bias was assessed for the three clinical trials and one case series (**Figure**). Regarding efficacy, the overall risk of bias was moderate for the four studies. Regarding safety, the overall risk of bias was moderate for two of the clinical trials and high for the case series (in the domain of outcome measurement).

Overall, sirolimus reduced the CAS by at least one point in >80% of patients at 24 weeks and in >70% of patients at 48 weeks.[14,17-19] In one clinical trial, the proportion of CAS responders (improvement in CAS by at least one point) was greater at 24 weeks in the sirolimus group than in the IVMP group (86.6% vs 33.3%, odds ratio [OR]=13, 95% confidence interval [CI]=2-81.4, p=0.0062).[17] In another clinical trial, the proportion of CAS responders remained significantly greater (but less so) at 48 weeks (75.0% vs 60.0%, OR=2, 95% CI=0.5-7.7, p=0.031).[18]

In two of the clinical trials, >60% of patients were diplopia responders (improvement in GDS by at least one point) at 48 weeks.[14,19] This was associated with an improvement in extraocular muscle thickness. CD4+ cytotoxic T lymphocytes are associated with various inflammatory and fibrotic diseases, and are partly responsible for diplopia and edema in TED.[14] Sirolimus achieved greater improvement in intractable diplopia between weeks 24 and 48 than mycophenolate mofetil (p=0.049).[19] The proportion of diplopia responders tended to be greater in the sirolimus group than in the IVMP group at 24 weeks (63.6% vs 23.0%, OR=5.8, 95% CI=0.1-3.7, p=0.052),[17] but the difference became insignificant at 48 weeks.[18]

No severe AE attributable to sirolimus was observed. No patient required dose adjustments or discontinuation. A total of 17 (37.8%) of 45 patients had mild AEs, which were mainly related to metabolic effects and infection, such as hyperglycemia, hypercholesterolemia, hyperkalemia, elevated low-density lipoprotein, cystitis, and impaired fasting glucose.[17-19] Other AEs included tachycardia, arthralgia, and asthenia. In line with other immunosuppressive regimens, patients should undergo tests for full blood count, urea and electrolytes, lipid profile, and trough-level monitoring, as well as pretreatment assessment for impaired glucose tolerance and hypertension.[20]

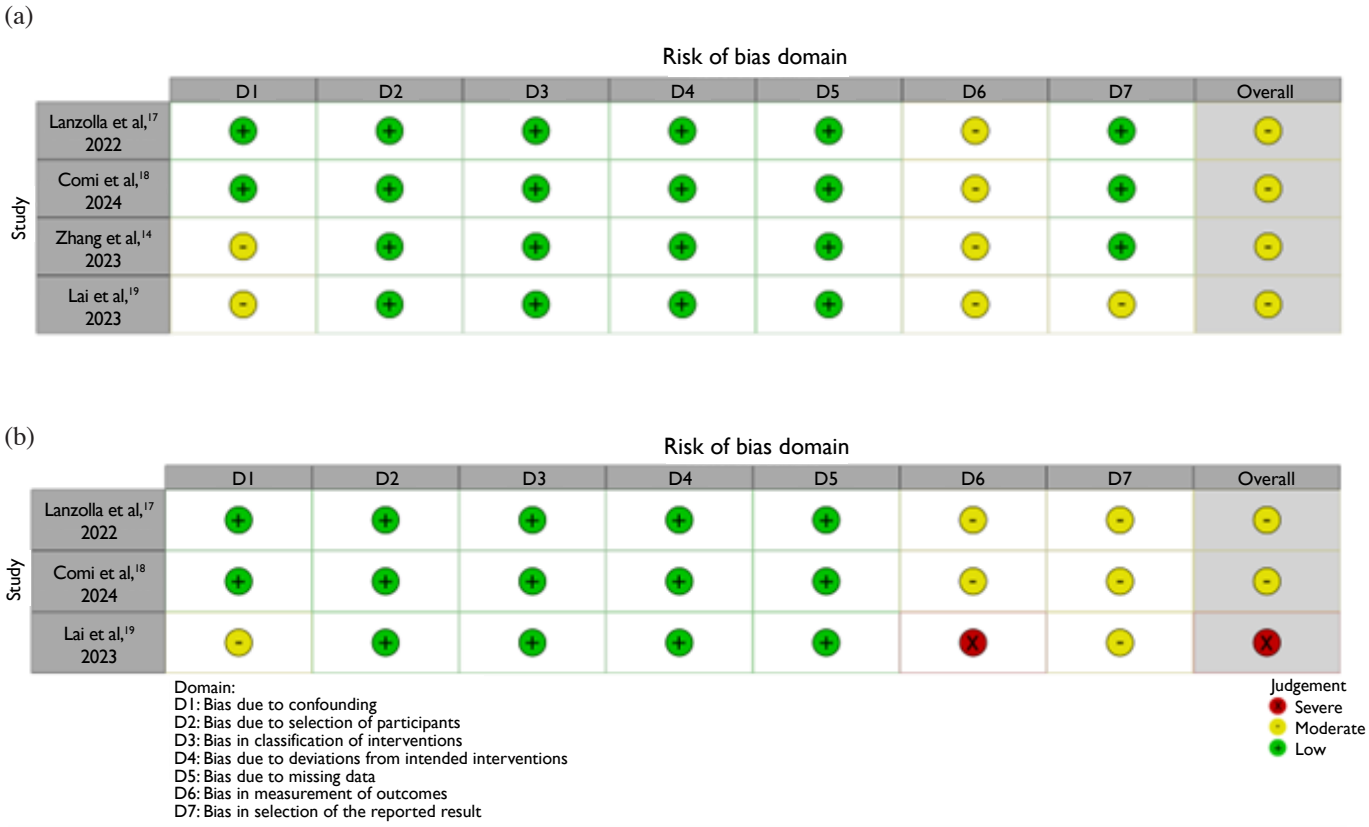

Figure. Risk of bias for (a) efficacy and (b) safety of sirolimus among the three clinical trials and one case series.

Discussion

We identified six studies demonstrating that sirolimus improves signs and symptoms of steroid-refractory TED. A 2007 case report illustrated the potential of sirolimus for treating dysthyroid compressive optic neuropathy, an extreme manifestation of TED.[12] Another case report showed the resolution of diplopia and binocular single vision after sirolimus treatment in a patient with inactive TED.[20] The three clinical trials and one case series showed that sirolimus improves moderate-to-severe TED in terms of CAS and GDS reduction, supporting sirolimus as a second-line treatment for TED.[21]

In two of the clinical trials, compared with IVMP, sirolimus had greater efficacy at 24 weeks in terms of CAS, reduction in exophthalmos, eyelid aperture, increase in eye muscle ductions, and Graves' orbitopathy-specific quality of life.[17,18] However, the difference was not significant at 48 weeks. Compared with mycophenolate mofetil, sirolimus tended to be more effective for diplopia resolution.[19] Nonetheless, differences in efficacy between various second-line treatments are yet to be determined.

The dosage of sirolimus for TED (either 2 mg/day or 2 mg on day 1, followed by 0.5 mg/day) is lower than that for preventing organ rejection in patients with renal transplant (6 mg on day 1, followed by 2 mg/day).[9] Common complications include anemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, thrombocytopenia, peripheral edema, hypertension, increased creatinine, diarrhea, vomiting, anorexia, proteinuria, leucopenia, lymphedema, and mucositis.[9,22] The median serum sirolimus concentration for the regimen involving 2 mg on day 1, followed by 0.5 mg/day ranged from 2.3 to 3.9 ng/mL; the trough serum sirolimus concentration for the regimen involving 2 mg/day ranged from 5.0 to 10.0 ng/mL. The target level should be about half of that used in preventing organ rejection and lymphangioleiomyomatosis.[23] Nonetheless, further studies are warranted regarding the optimal dosage and duration of sirolimus.

Sirolimus shows superior safety over IVMP, which is associated with risks of peptic ulcer, osteoporosis, hepatotoxicity, and cardiovascular complications. Sirolimus did not elicit severe AEs. Approximately 30% of patients receiving mycophenolate mofetil for TED developed AEs or, occasionally, severe AEs such as infection, impaired liver function, and arrhythmia.[24,25] For teprotumumab, 80% of patients experienced AEs, including muscle spasm, hearing loss, and hyperglycaemia.[26] For rituximab, most AEs were mild to moderate and self-limiting, including transient fever (30%), chills (23%), asthenia (23%), and pruritus (20%).[27] For tocilizumab, no severe AE was found; common AEs included increased liver enzyme and plasma lipid levels.[28] Compared with other second-line treatments, sirolimus demonstrates a better safety profile for TED treatment.

To ensure long-term safety, regular trough-level monitoring through blood tests is recommended. Additionally, glucose levels, lipid profile, liver function, urea and electrolyte levels, and blood pressure should be monitored. Patient education and effective communication should be emphasized to enhance awareness and encourage self-monitoring practices.

The role of thyroid-stimulating hormone receptor autoantibodies (TRAb) in monitoring the response to sirolimus in treating TED remains unclear. TRAb levels did not significantly differ between sirolimus and IVMP groups at 24 and 48 weeks, despite the improvement in TED.[17] Sirolimus, an mTOR inhibitor, targets the downstream signal pathway regardless of the serum concentrations of TRAb.[18] This should be considered when assessing efficacy. Serum sirolimus concentration at 12 weeks can be used to predict dose-dependent response to treatment, enabling earlier identification of non-responders.[29]

This review had several limitations. First, long-term outcomes of sirolimus treatment were not assessed. Second, the number of randomized controlled trials and the overall sample size of 50 were insufficient, limiting the generalizability of the findings. Third, patients who failed the first course of IVMP were included; reproducibility of results on naive patients may be restricted. Fourth, heterogeneity in study designs and comparator groups among the included studies hindered interpretation of findings. Further studies are warranted to investigate the optimal dosage and duration of sirolimus, biomarkers for monitoring treatment progress, and efficacy among various second-line treatments.

Conclusion

Sirolimus appears to be effective and safe in managing TED, as indicated by improvements in both CAS and GDS, as well as satisfactory safety profile.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an editor of the journal, KKLC was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

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Data availability

All data analyzed in this study are available from the corresponding author upon reasonable request.

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