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Cyclosporine as a Steroid-Sparing Agent in Thyroid Eye Disease: A Single-Centre Retrospective Review

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Abstract

Background: Thyroid Eye Disease (TED) is an autoimmune orbital disorder that can cause significant morbidity. Intravenous methylprednisolone (IVMP) is the first-line treatment for active, moderate-to-severe TED, but reactivation following steroid discontinuation remains a challenge. Cyclosporine A (CsA) has been used as a steroid-sparing agent in this setting, yet real-world data on its effectiveness and tolerability remain limited. The aim of this study was to evaluate the steroid-sparing efficacy of CsA in a retrospective cohort of patients with TED. **Methods:** A retrospective review was performed of all patients treated with CsA for active TED at a single tertiary referral centre. The primary outcome was change in Clinical Activity Score (CAS) from baseline to 3 months, 6 months, and at the time of CsA discontinuation. Secondary outcomes included change in Gorman diplopia score, steroid discontinuation rates, reasons for stopping CsA, and adverse events. Statistical analysis was performed using the Wilcoxon signed-rank test. **Results:** Twenty-two patients were included (mean age 52.2 years; 72.7% female; 36.4% smokers). All had received prior IVMP (range 1.5 - 7.5 g). The median CAS fell significantly from 3 (IQR 3 - 4) at baseline to 2 (IQR 1 - 3) at 3 months ($p = 0.013$), 1 (IQR 1 - 2) at 6 months ($p = 0.0003$), and 1 (IQR 0 - 2) at CsA discontinuation ($p = 0.0002$). Inactive disease (CAS < 3) was achieved in 95.5% of patients at the time of stopping CsA. Of 7 patients on concomitant oral corticosteroids at CsA initiation, 5 (71.4%) successfully discontinued steroids. Disease inactivity was the reason for stopping CsA in 14/22 patients (63.6%). Adverse events occurred in 6/22 patients (27.3%), most commonly hypertension (5/22, 22.7%), which necessitated CsA discontinuation in 4 patients. **Conclusions:**

In this retrospective cohort, CsA was associated with significant reductions in disease activity over time and enabled corticosteroid discontinuation in the majority of patients receiving concomitant steroids. Hypertension was the most frequent adverse event and led to treatment cessation in a meaningful proportion of patients. These findings are consistent with a role for CsA in TED management, particularly in facilitating steroid reduction; prospective controlled studies are needed to confirm its efficacy.

Keywords

Thyroid Eye Disease, Graves' Ophthalmopathy, Cyclosporine, Steroid-Sparing, Clinical Activity Score, Immunosuppression, Orbital Inflammation

1. Introduction

Thyroid Eye Disease (TED) is an autoimmune inflammatory orbitopathy that develops in a subset of patients with Graves' disease and, less frequently, other thyroid disorders [1] [2]. It is characterised by the expansion of orbital soft tissues, extraocular muscle enlargement, and proptosis, leading to diplopia, visual impairment, and significant impact on quality of life [3]. The clinical course is biphasic, with an active inflammatory phase followed by a quiescent fibrotic phase; the duration and severity of the active phase determine the degree of long-term structural damage [4].

High-dose intravenous methylprednisolone (IVMP) is the established first-line treatment for active moderate-to-severe TED, producing response rates of approximately 70% - 80% [5] [6]. However, disease reactivation following steroid withdrawal is a recognized problem, and prolonged or repeated steroid courses carry substantial systemic toxicity. Steroid-sparing immunosuppressive agents are therefore employed in patients who relapse, are steroid-dependent, or in whom steroids cannot be used safely [7].

Cyclosporine A (CsA), a calcineurin inhibitor that selectively suppresses T-lymphocyte activation, was among the first immunosuppressive agents investigated in TED. A randomised controlled trial by Prummel and colleagues compared prednisolone monotherapy with cyclosporine monotherapy in moderate-to-severe Graves' ophthalmopathy; patients failing either monotherapy were subsequently treated with the combination, with both monotherapies demonstrating clinically meaningful reductions in orbital inflammation [8]. Nevertheless, real-world data on CsA as a steroid-sparing strategy, specifically its ability to facilitate steroid reduction while maintaining disease control, remain limited.

The aim of this study was to evaluate the effectiveness and tolerability of CsA as a steroid-sparing agent in a retrospective cohort of patients with active TED managed at a single tertiary ophthalmology center.

2. Materials and Methods

2.1. Study Design and Patients

A retrospective review was conducted of all patients treated with CsA for active TED at a single tertiary referral ophthalmology centre. Data were extracted from electronic and paper clinical records. Patients were included if they had a diagnosis of TED and had received CsA as part of their treatment regimen. Ethical considerations are described in Section 2.6.

2.2. Cyclosporine Protocol

CsA was initiated according to a standard departmental protocol. All patients commenced at 50 mg once daily for two weeks. If tolerated, the dose was increased to a maintenance dose of 100 mg once daily, which was the target dose in the majority of patients. A small number of patients required dose escalation to 150 mg once daily based on clinical response and tolerability. Baseline investigations prior to commencement included full blood count, renal profile, liver function tests, fasting lipid profile, and blood pressure measurement. Monitoring comprised blood pressure and renal function checks at two-week intervals for the first three months, followed by monthly reviews thereafter. The dose was reduced or CsA discontinued if clinically significant abnormalities were detected.

2.3. Data Collection

The following data were extracted: patient demographics (age, sex, smoking status), TED duration prior to CsA initiation, prior immunosuppressive therapy, CsA dose and duration, concomitant corticosteroid use, CAS at baseline and at 3 and 6 months and at the time of CsA discontinuation, Gorman diplopia score at each timepoint, reasons for stopping CsA, and adverse events including changes in blood pressure and renal function. Hertel exophthalmometry and extraocular motility data were available only for a subset of patients and were therefore excluded from formal analysis.

2.4. Outcome Measures

The primary outcome was the change in CAS from baseline to 3 months, 6 months, and at the time of CsA discontinuation. The CAS is a validated seven-item scale (0 - 7) assessing clinical signs of orbital inflammation; a score of ≥3 indicates clinically active disease, while a score of <3 indicates inactive disease [4]. Secondary outcomes included the change in Gorman diplopia score (0 = no diplopia; 1 = intermittent; 2 = inconstant; 3 = constant) [9], rate of successful corticosteroid discontinuation among patients receiving concomitant steroids at CsA initiation, reasons for CsA discontinuation, and adverse events.

2.5. Statistical Analysis

Data are presented as median (interquartile range, IQR) for non-normally distributed continuous variables, and mean (range) where appropriate. Categorical data

are presented as number and percentage. Changes in CAS and Gorman score over time were analyzed using the Wilcoxon signed-rank test with normal approximation for ties, comparing each follow-up timepoint against baseline. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS Statistics.

Paired analyses were conducted on all patients with data available at each timepoint; no imputation was performed for missing values. Missing data arose exclusively from patients who discontinued CsA before a scheduled assessment timepoint. CAS data at 6 months were available for 19/22 patients (3 patients discontinued CsA before the 6-month assessment and were captured at the time of discontinuation only). Gorman diplopia data were analysed at the timepoints at which assessments were recorded; where some patients were assessed at discontinuation rather than at the nominal 6-month visit, data are presented at the closest available timepoint. No correction for multiple comparisons was applied, given the exploratory and hypothesis-generating nature of this study.

2.6. Ethical Considerations

This study was a retrospective audit of de-identified clinical data. In accordance with Health Research Authority (HRA) criteria, the project did not constitute research requiring Research Ethics Committee (REC) review and was therefore exempt from formal ethical approval. The study was registered with the Caldicott Guardian at Leeds Teaching Hospitals NHS Trust in accordance with NHS information governance policy. Individual patient consent was not obtained. The use of de-identified, routinely collected clinical data without individual patient consent was authorised by the institutional Caldicott Guardian at Leeds Teaching Hospitals NHS Trust under NHS information governance policy, consistent with national requirements for retrospective audit activity. This institutional authorisation is distinct from, and supplementary to, the determination that formal REC review was not required. All procedures performed in this study were conducted in accordance with the ethical standards of the responsible institutional and national research committee(s) and with the principles of the Declaration of Helsinki as revised in 2013.

3. Results

3.1. Patient Demographics and Baseline Characteristics

Twenty-two patients were included. Baseline characteristics are summarised in Table 1. The mean age was 52.2 years (range 34 - 65) and 16/22 (72.7%) were female. Eight patients (36.4%) were current or ex-smokers. Dysthyroid Optic Neuropathy (DON) was present at the time of TED diagnosis in 8/22 patients (36.4%), reflecting a clinically severe cohort. All 22 patients had received at least one course of IVMP prior to CsA initiation, with cumulative IVMP doses ranging from 1.5 g to 7.5 g. Seven patients (31.8%) were receiving concomitant oral corticosteroids at the time CsA was started.

Table 1. Baseline patient demographics and disease characteristics (n = 22).

Variable	Value
Mean age, years (range)	52.2 (34 - 65)
Female sex, n (%)	16 (72.7%)
Current or ex-smokers, n (%)	8 (36.4%)
DON at TED diagnosis, n (%)	8 (36.4%)
Median TED duration before CsA start, months (range)	24 (1 - 240)
Prior intravenous methylprednisolone, n (%)	22 (100%)
Median cumulative prior IVMP dose, g (range)	4.5 (1.5 - 7.5)
Concomitant oral corticosteroids at CsA initiation, n (%)	7 (31.8%)
Median CAS at baseline (IQR)	3 (3 - 4)
Patients with active disease (CAS ≥3) at baseline, n (%)	18 (81.8%)

CAS, Clinical Activity Score; CsA, cyclosporine A; DON, dysthyroid optic neuropathy; IQR, interquartile range; IVMP, intravenous methylprednisolone; TED, thyroid eye disease.

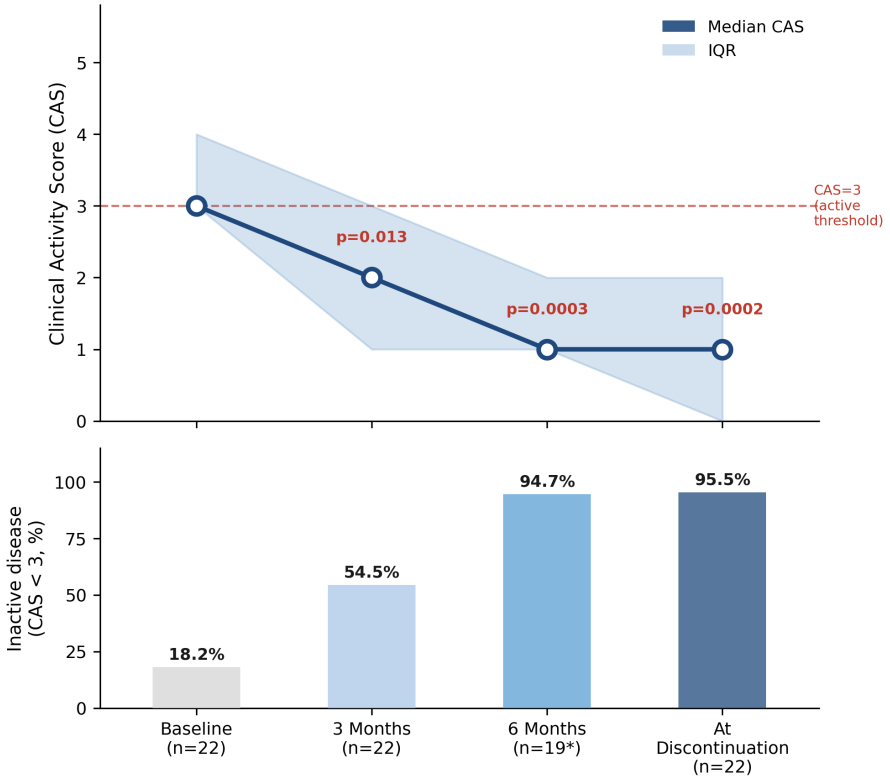
3.2. Cyclosporine Dosing and Treatment Duration

All patients commenced CsA at 50 mg once daily in accordance with the departmental protocol, with the intention to uptitrate to the maintenance dose of 100 mg once daily after two weeks if tolerated. The documented maintenance doses were: 100 mg once daily in 12/22 patients (54.5%), 50 mg once daily in 6/22 (27.3%), 150 mg once daily in 3/22 (13.6%), and 50 mg three times daily in 1/22 (4.5%). Patients maintained on 50 mg once daily either did not tolerate or did not require dose escalation. The median treatment duration was 12 months (range 0 - 46 months).

3.3. Clinical Activity Score

Serial CAS values are illustrated in Figure 1. At baseline, the median CAS was 3 (IQR 3 - 4). Notably, four patients had a CAS of <3 at the time CsA was initiated; in these cases, CsA was commenced to facilitate corticosteroid tapering, as repeated attempts to reduce or discontinue steroids had resulted in disease reactivation. Overall, only 4/22 patients (18.2%) had inactive disease at baseline.

There was a statistically significant reduction in CAS at all subsequent timepoints compared to baseline. At 3 months, the median CAS decreased to 2 (IQR 1 - 3; $p = 0.013$ vs. baseline), with 12/22 patients (54.5%) achieving inactive disease. At 6 months, the median CAS was 1 (IQR 1 - 2; $p = 0.0003$ vs. baseline), with 18/19 patients (94.7%) in the inactive phase; CAS data at 6 months were available for 19/22 patients, as three had stopped CsA before this timepoint. At the time of CsA discontinuation, 21/22 patients (95.5%) had achieved inactive disease (CAS < 3), with a median CAS of 1 (IQR 0 - 2; $p = 0.0002$ vs. baseline). At 3 months, 14/22 patients (63.6%) demonstrated a reduction in CAS from baseline; by 6 months, this had increased to 17/19 (89.5%).



*6-month data available for 19 of 22 patients (3 had stopped CsA before this timepoint).

Figure 1. Change in median Clinical Activity Score (CAS) during cyclosporine A (CsA) treatment (n = 22). The solid line represents the median CAS at each timepoint; the shaded band represents the interquartile range (IQR). Bars indicate the proportion of patients with inactive disease (CAS < 3) at each timepoint (right y-axis). The dashed red line denotes the CAS = 3 threshold separating active from inactive disease. p-values are from the Wilcoxon signed-rank test versus baseline. *6-month CAS data were available for 19 of 22 patients, as three patients had stopped CsA before this timepoint. CAS, Clinical Activity Score; CsA, cyclosporine A; IQR, interquartile range.

3.4. Gorman Diplopia Score

Gorman scores are presented in **Table 2**. At baseline, 9/22 patients (40.9%) had no diplopia (Gorman 0) and 6/22 (27.3%) had constant diplopia (Gorman 3). By 6 months, the proportion with no diplopia had increased to 12/22 (54.5%) and the proportion with constant diplopia had decreased to 2/22 (9.1%). There was a statistically significant improvement in Gorman score at 6 months compared to baseline (Wilcoxon p = 0.028). The change at 3 months did not reach statistical significance (p = 0.068).

It should be noted that four patients underwent orbital decompression surgery during the period of CsA treatment. Orbital decompression is known to independently affect diplopia outcomes and extraocular motility [10] [11]. Gorman score changes in this cohort should therefore be interpreted with caution, as the observed improvement in diplopia cannot be attributed solely to the pharmacological effects of CsA.

3.5. Steroid-Sparing Effect

Of the 7 patients who commenced CsA while receiving oral corticosteroids, 5 (71.4%) successfully discontinued steroids during the course of CsA treatment, defined as complete cessation of corticosteroid therapy. Individual baseline and final corticosteroid doses and time to discontinuation were not systematically recorded in the retrospective dataset and could not be reported. The remaining 2 patients continued on reduced steroid doses for ongoing disease management.

Table 2. Gorman diplopia score distribution at each timepoint.

Gorman Score	Baseline n (%)	3 Months n (%)	6 Months n (%)
0 - No diplopia	9 (40.9%)	10 (45.5%)	12 (54.5%)
1 - Intermittent	2 (9.1%)	3 (13.6%)	2 (9.1%)
2 - Inconstant	5 (22.7%)	6 (27.3%)	6 (27.3%)
3 - Constant	6 (27.3%)	3 (13.6%)	2 (9.1%)
Median (IQR)	**1.5 (0 - 3)**	**1.0 (0 - 2)**	**0 (0 - 2)**
p-value vs. baseline	—	0.068	0.028

Wilcoxon signed-rank test vs. baseline. CAS data at 6 months were available for 19/22 patients; three patients discontinued CsA before this timepoint. Gorman diplopia data were analysed at the nearest available assessment; denominators are 22 at each timepoint. Four patients underwent orbital decompression during CsA treatment; Gorman score changes should be interpreted with caution given the confounding effect of surgery on diplopia outcomes. IQR, interquartile range.

3.6. Reasons for CsA Discontinuation

Achievement of disease inactivity was the most frequent reason for stopping CsA, accounting for 14/22 patients (63.6%). Hypertension was the reason in 4 patients (18.2%), patient-initiated discontinuation in 2 (9.1%), renal impairment in 1 (4.5%), and gastrointestinal intolerance concurrent with disease flare in 1 (4.5%). Reasons for discontinuation are summarised in Table 3.

Table 3. Reasons for cyclosporine A discontinuation.

Reason for Discontinuation	n (%)
Achievement of disease inactivity (CAS < 3)	14 (63.6%)
Hypertension	4 (18.2%)
Patient-initiated discontinuation	2 (9.1%)
Renal impairment (reduced eGFR)	1 (4.5%)
Gastrointestinal intolerance/concurrent disease flare requiring IVMP	1 (4.5%)
Total	**22 (100%)**

CAS, Clinical Activity Score; eGFR, estimated glomerular filtration rate; IVMP, intravenous methylprednisolone. One patient had hypertension during CsA treatment but discontinued due to disease inactivity; she is counted under Achievement of disease inactivity above.

3.7. Adverse Events

Adverse events attributable to CsA were documented in 7/22 patients (31.8%), comprising hypertension (5/22, 22.7%), renal impairment (1/22, 4.5%), and gastrointestinal intolerance (1/22, 4.5%). Hypertension was the most common adverse event and led to CsA discontinuation in 4 of these 5 patients (80%). The fifth patient who developed hypertension during CsA treatment did not require discontinuation on this basis; CsA was subsequently stopped following achievement of disease inactivity. One patient (4.5%) developed renal impairment with a reduction in eGFR to 44 mL/min/1.73 m^2, necessitating cessation of CsA. No haematological or hepatic adverse events were documented.

4. Discussion

This retrospective review demonstrates that CsA was associated with significant reductions in disease activity at 3 months, 6 months, and at the time of treatment discontinuation in this cohort of patients with active TED. Nearly all patients (95.5%) achieved inactive disease by the time CsA was stopped, and the majority of patients on concomitant corticosteroids at initiation (71.4%) were successfully weaned off steroids. These findings are consistent with the immunological rationale for CsA use in TED: by suppressing T-cell-mediated orbital inflammation, CsA may facilitate steroid dose reduction while maintaining disease control [7] [8].

The randomised trial by Prummel *et al.* [8] compared prednisolone monotherapy with cyclosporine monotherapy; combination therapy was offered to initial non-responders. This trial established the immunological rationale for both agents in TED management. Our cohort reflects a real-world application of this principle in clinical practice: CsA was used primarily following or alongside IVMP, in patients whose disease remained active or who were steroid-dependent. The observed reduction in CAS is clinically meaningful; a score of <3 achieved by 94.7% at 6 months in this series represents the threshold below which surgical rehabilitation may safely proceed [4] [5].

The severity of this cohort warrants emphasis. All patients had received prior IVMP, 36.4% had DON at diagnosis, and a proportion had undergone prior orbital decompression. Four patients had a baseline CAS of <3 at CsA initiation, reflecting steroid-dependent disease rather than spontaneously quiescent TED; these patients had experienced disease reactivation with each attempt to taper corticosteroids. CsA in this subgroup was intended to provide an immunological scaffold permitting safe steroid withdrawal rather than to treat overtly active inflammation, a recognised indication for steroid-sparing agents [7].

The improvement in Gorman diplopia score at 6 months reached statistical significance ($p = 0.028$), with the proportion of patients free of diplopia rising from 40.9% at baseline to 54.5% at 6 months. However, four patients underwent orbital decompression during CsA treatment, and this surgery independently alters diplopia status and extraocular muscle mechanics [10] [11]. Consequently, it is not possible to attribute all improvement in Gorman scores to CsA, and these data

should be interpreted with caution.

Hypertension was the most frequent adverse event, occurring in 5/22 patients (22.7%) and leading to CsA discontinuation in four. This is consistent with the recognised pharmacological profile of calcineurin inhibitors, which induce vasoconstriction and sodium retention through afferent arteriolar constriction and activation of the renin-angiotensin-aldosterone system [12]. The structured monitoring protocol employed—two-weekly blood pressure and renal function checks for the first three months, followed by monthly surveillance—enabled early detection and prompted discontinuation before serious end-organ complications occurred. Pre-existing or borderline hypertension should be considered a relative contraindication to CsA, and vigilant monitoring is mandatory throughout treatment.

The therapeutic landscape of TED has evolved considerably in recent years, with the approval of teprotumumab (an IGF-1R inhibitor) in the United States and the ongoing evaluation of novel biological agents including tocilizumab, rituximab, and mycophenolate mofetil [13] [14]. These agents may offer superior efficacy with improved tolerability compared to conventional immunosuppressants. However, their cost, availability, and reimbursement status vary internationally, and CsA remains a practical, affordable option in many healthcare systems, particularly for patients for whom biological therapy is not available or appropriate.

Several limitations of this study warrant acknowledgement. The retrospective, single-centre design limits generalisability, and the sample size (n = 22) reduces statistical power, particularly for subgroup analyses. The cohort is heterogeneous with regard to disease duration, prior therapy, and concomitant treatments, making it difficult to isolate the specific contribution of CsA to disease outcomes. Hertel exophthalmometry and formal extraocular motility assessments were insufficiently complete for inclusion. There was no control group, precluding causal inference. The confounding effect of concurrent orbital decompression on diplopia outcomes has been discussed above. These limitations are inherent to retrospective case series and underscore the need for prospective controlled studies to definitively characterise the role of CsA in TED management.

In conclusion, in this retrospective cohort, CsA was associated with disease inactivity in the great majority of patients and facilitated corticosteroid discontinuation in steroid-dependent cases. Blood pressure and renal function require structured monitoring throughout treatment. These real-world findings are consistent with a continued role for CsA in TED management pathways, particularly in settings where access to novel biologic therapies is limited.

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Author Contributions

Kit May Chow: Data collection (lead); formal analysis (lead); writing—original

draft (lead); writing—review and editing (equal). Ramzi Ajjan: Clinical supervision (lead). Khyatisha Seejore: Clinical supervision (supporting). Bernard Chang: Conceptualization (lead); clinical supervision (lead); writing—review and editing (equal). Gabriella Guevara: Conceptualization (lead); methodology (lead); data collection (supporting); clinical supervision (lead); writing—review and editing (equal).

Conflicts of Interest

Kit May Chow, Ramzi Ajjan, Khyatisha Seejore, Bernard Chang, Gabriella Guevara: No competing financial interests.

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