

Tacrolimus therapy in primary Sjögren's syndrome with refractory immune thrombocytopenia: a retrospective study

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Abstract

Objective

To evaluate the efficacy and safety of tacrolimus (TAC) for the treatment of primary Sjögren's syndrome (pSS) with refractory immune thrombocytopenia (RITP).

Methods

Twenty-three pSS patients with RITP treated with TAC from June 2018 to June 2021 at the First Affiliated Hospital of Soochow University were enrolled in this retrospective cohort study. Platelet response, clinical and immunological parameters, toxicity and safety were compared and analysed at baseline and different points after TAC treatment.

Results

At 4 weeks after treatment, 2 patients (8.7%) attained a complete response (CR, platelet count $\geq 100 \times 10^9/L$ and no bleeding), 15 patients (65.2%) achieved a partial response (PR, platelet count $\geq 30 \times 10^9/L$ but $< 100 \times 10^9/L$ and no bleeding or a platelet count at least twice that before treatment), and the other 6 patients (26.1%) did not respond to TAC treatment. At 8 weeks after treatment, a CR was seen in 4 patients (17.4%), and the percentage of patients with a PR increased to 78.3% (18 patients). The percentage of patients with a CR increased to 47.8% (11 patients), and 9 patients (39.1%) achieved a PR without relapse at 12 weeks after treatment. At 24 weeks after treatment, 14 patients (60.9%) achieved a CR, and 8 patients (34.8%) achieved a PR. Compared to before treatment, the level of IgG was decreased significantly at 24 weeks after treatment, whereas there was no significant difference in the levels of IgM or IgA between baseline and 24 weeks after treatment. Additionally, the absolute CD3⁺ T cell count, European SS Disease Activity Index (ESSDAI) score, and levels of IL-2 and INF- γ were significantly decreased at 24 weeks after treatment.

Conclusion

TAC is effective and well tolerated by pSS patients with RITP, and the mechanism underlying the effect of TAC in these patients may be related to reduced Th1 cytokine expression.

Key words

Sjögren's syndrome, tacrolimus, thrombocytopenia, refractory

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Introduction

Primary Sjögren's syndrome (pSS) is a multifactorial chronic systemic inflammatory disease characterised by keratoconjunctivitis sicca, xerostomia, and even thrombocytopenia (1, 2). The prevalence of thrombocytopenia has been reported to range from 3.7% to 7% in pSS patients (3, 4). At present, despite being treated with glucocorticoids (GCs), intravenous immunoglobulin (IVIG) and immunosuppressive agents, such as cyclophosphamide (CTX) and vincristine (VCR), some patients still remain refractory or develop intolerable toxicity, which is often called refractory immune thrombocytopenia (RITP). RITP can lead to visceral bleeding and can even be life-threatening. Therefore, it is urgent to explore effective and less toxic treatments.

Tacrolimus (TAC), also called FK506, is a powerful calcineurin inhibitor. TAC mainly plays an immunosuppressive role by inhibiting the activity of helper T (Th) cells and reducing the release of interleukin (IL)-2. In the past few years, TAC has been widely used in the treatment of a variety of rheumatic diseases and has shown a good therapeutic effect (5-8).

However, there are no data on the efficacy and safety of TAC in patients with RITP secondary to pSS. In this study, we aimed to evaluate the efficacy and safety of tacrolimus (TAC) therapy in patients with RITP secondary to pSS. The findings of this study could further provide data supporting the use of TAC therapy in pSS associated with refractory immune thrombocytopenia.

Patients and methods

Patient screening process

This retrospective study was approved by the First Affiliated Hospital of Soochow University (Suzhou, China) ethics committee (approval ID: 2021-023). A total of 106 patients diagnosed with pSS according to the European-American consensus group criteria (9) and hospitalised in the ward at the First Affiliated Hospital of Soochow University from June 2018 to June 2021 were enrolled in this cohort. The screening process is illustrated in Figure 1. RITP was defined as patients whose platelet

count was still $<20 \times 10^9/L$ or less than twice that before treatment after being treated with at least one course of GCs and more than 2 immunosuppressive agents. According to this definition, 45 pSS patients met the diagnostic criteria of pSS with ITP. The exclusion criteria were as follows: patients with thrombocytopenia due to other connective tissue diseases, antiphospholipid syndrome, infection, primary solid organ neoplasm, haematological diseases and metastatic neoplasm, drugs, radiation, the effects of chemotherapy on bone marrow, autoimmune lymphoproliferative syndrome and common variant immunodeficiency disease for younger patients. Finally, 23 patients with pSS with RITP were included in this study.

TAC treatment

All patients were monitored at baseline and after 4 weeks, 8 weeks, 12 weeks and 24 weeks of TAC treatment. TAC was taken twice daily at a dosage of 2-3 mg/d (body weight ≥ 60 kg, 3 mg/d; body weight < 60 kg, 2 mg/d). The dose of oral GCs was gradually reduced to the minimum maintenance dose, and all previous immunosuppressants were discontinued.

Response criteria

The response criteria were defined as follows (8, 10). A complete response (CR) was defined as a platelet count $\geq 100 \times 10^9/L$ and no bleeding. A partial response (PR) was defined as a platelet count $\geq 30 \times 10^9/L$ but $< 100 \times 10^9/L$ and no bleeding or a platelet count at least twice that before treatment. Both a CR and a PR excluded any bleeding events. No response (NR) was defined as a platelet count $< 30 \times 10^9/L$ or less than twice that before treatment. Unacceptable toxicity (UT) was defined with the occurrence of severe infection, bone marrow suppression, or moderate or severe hepatotoxicity.

Clinical and immunological assessments

The clinical effect of TAC treatment for patients was evaluated through the analysis of platelet counts at baseline and after 4 weeks, 8 weeks, 12 weeks and 24 weeks of TAC treatment. Dis-

ease activity for pSS patients was assessed by the authors using the European SS Disease Activity Index (ESS-DAI) score (8).

Nephelometry immunoassay

A 3 ml sample of venous blood was taken from all patients in the morning under fasting conditions. Samples were centrifuged for 10 min at 3000 r/min. The upper serum was taken and stored at -80°C. IgG, IgA, and IgM were determined by nephelometry immunoassay.

Multimicroglobular flow immuno-fluorescence spectrometry

The serum cytokines IL-2, IL-4, IL-10, and INF-γ were detected by FACS Calibur.

Flow cytometry

Anticoagulated whole blood was incubated with the following fluorescent antibodies for 30 min at 4°C: CD3-FITC, CD16-PE, CD45-PerCP-Cy5.5, CD4-PC7, CD19-APC, and CD8-APC-Cy7. Then, red blood cells were lysed with ammonium chloride potassium buffer, washed, and fixed for flow cytometry.

Statistical analysis

All data analysis was performed using GraphPad Prism 8 software. The data are expressed as the mean ± standard deviation (SD) or the median and interquartile range. Categorical data are presented as frequencies and percentages. In this study, due to the small sample size and uneven distribution, the Wilcoxon signed-rank test of non-parametric methods was used to compare parameters before and after TAC treatment. *p*<0.05 was considered statistically significant.

Results

Patient demographics and clinical characteristics

Table I shows the patients' main characteristics. Twenty-three pSS patients with RITP (18 females and 5 males, aged 16–74 years, mean 43.5±18.0 years) were enrolled and underwent TAC treatment. The mean disease duration was 16.9±10.4 months (range 2–48 months), and the follow-up time was 24 weeks. The medication history of the

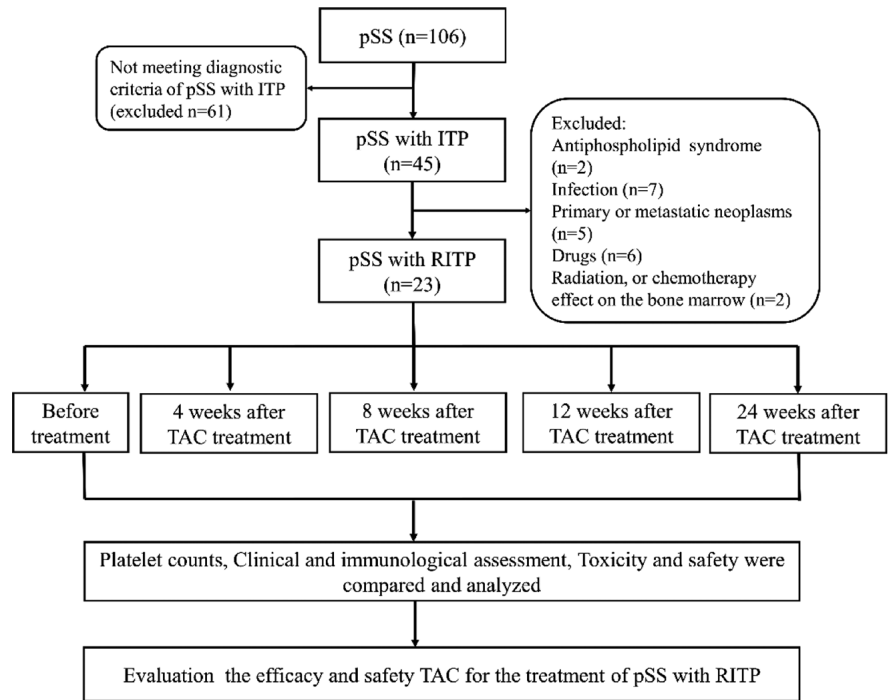


Fig. 1. Flowchart of patients' selection process and study design. pSS: primary Sjögren's syndrome; ITP: immune thrombocytopenia; RITP: refractory immune thrombocytopenia; TAC: tacrolimus.

pSS patients with RITP who underwent TAC treatment is listed in Table I.

TAC treatment response rate

All 23 patients had serious thrombocytopenia at baseline. Most patients showed a significant increase in platelet count (achieved a CR or PR) 4 weeks after the first TAC treatment, 2 patients (8.7%) attained a CR, 15 patients (65.2%) achieved a PR, and the other 6 patients (26.1%) did not respond to TAC treatment. After 8 weeks of TAC treatment, a CR was seen in 4 patients (17.4%), and the percentage of patients achieving a PR increased to 78.3% (18 patients). The percentage of patients achieving a CR increased to 47.8% (11 patients), and 9 patients (39.1%) achieved a PR without relapse at 12 weeks. At 24 weeks, 14 patients (60.9%) achieved a CR, and 8 patients (34.8%) achieved a PR (Table II, Fig. 2A-B). The ESSDAI scores before and after treatment are also shown in Figure 2C.

Clinical and immunological assessments of TAC treatment

As shown in Figure 2, the laboratory parameters and ESSDAI scores were also evaluated before and after TAC treat-

ment. Compared to before treatment, the level of IgG was decreased significantly at 24 weeks (Fig. 3A), whereas there was no significant difference in the levels of IgM or IgA at baseline and at 24 weeks (Fig. 3B-C). The absolute count of CD3⁺T cells was significantly decreased at 24 weeks (Fig. 3D). Additionally, the ESSDAI and Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ClinESSDAI) scores were markedly decreased at 24 weeks (Fig. 3E-F).

Comparison of Th1- and Th2-cell-related cytokines before and after TAC treatment

To elucidate the underlying mechanism of TAC treatment in pSS-RITP patients, we measured the levels of Th1- and Th2-cell-related cytokines at baseline and 24 weeks. The data showed that compared with before treatment, the levels of IL-2 and INF-γ decreased significantly at 24 weeks (Fig. 4A-B), but there was no significant difference in the levels of IL-4 or IL-10 (Fig. 4C-D).

Toxicity and safety

In this study, no severe or significant side effects were recorded. Only one

Table I. Patients' demographics and clinical characteristics.

Patient	Sex	Age (y)	Disease duration (m)	Pre-TAC Treatment	6-mo after TAC Treatment
1	F	71	26	P:25mg/d, CTX:0.8g/m(6m), HCQ:0.4g/d (19m), IVIG (20g*5d), CSA:150 mg/d (7m)	P:5mg/d, HCQ:0.2g/d, TAC:3mg/d
2	M	26	17	P:20mg/d, CTX:0.4g/2 w (6m), HCQ:0.4g/d(8m), CSA:200 mg/d (3m)	P:5mg/d, HCQ:0.2 g/d,TAC:3mg/d
3	F	53	23	MP:32mg/d, HCQ:0.4g/d(17m), CsA:150 mg/d (6m), MMF:1.0 g/d (7m)	MP:8mg/d, HCQ:0.2g/d, TAC:3mg/d
4	F	74	14	P:30mg/d, MMF:1.0g/d (6m), HCQ:0.4g/d(9m), IVIG (20g*5d)	P:10mg/d, HCQ:0.2 g/d, TAC:3mg/d
5	F	16	12	P:35mg/d, MMF:1.5g/d (10m), HCQ:0.4g/d(8m), VCR:2mg/w (1m)	P:15mg/d, HCQ:0.2 g/d, TAC:2mg/d
6	F	25	16	P:25mg/d, CsA:100mg/d (3m), HCQ:0.4g/d(7m), MMF:1.5g/d (6m)	P:10mg/d, HCQ:0.2g/d, TAC:2mg/d
7	F	23	19	MP:24mg/d, HCQ:0.4g/d(11m), CSA:150 mg/d (10m), IVIG (20g*5d), CTX:0.6 g/2 w (8m)	MP:8mg/d, HCQ:0.4gm/d, TAC:3mg/d
8	F	61	13	MP:16mg/d, CTX:0.4g/2 w (3m), HCQ:0.4g/d (13m), CSA:150 mg/d (7m)	MP:8mg/d, TAC:3mg/d
9	F	60	4	P:40mg/d, IVIG (20g*3d), CTX:0.4g/2w(2m), CSA:150 mg/d (2m), HCQ:0.4g/d(3m)	P:20mg/d, HCQ:0.4gm/d, TAC:2mg/d
10	F	50	9	MP:24mg/d, HCQ:0.4g/d(9m), CTX:0.8g/m (3m), MMF:1.0g/d (4m)	MP:8mg/d, TAC:3mg/d
11	M	66	12	P:50mg/d, LEF 20 mg/d (3m), HCQ:0.4g/d(9m), IVIG (20g*3d), CTX:0.4 g/2 w(3m)	P:15mg/d, HCQ:0.2g/d, TAC:3mg/d
12	M	19	6	P:15mg/d, CTX:0.6g/m (3m), HCQ:0.2g/d(6m), MTX10mg/w(4m)	P:5mg/d, HCQ:0.4g/d, TAC:2mg/d
13	F	28	10	P:20mg/d, TG:40mg/d(5m), HCQ:0.4gm/d(7m), MMF:1.0 g/d (4m)	P:5mg/d, HCQ:0.2g/d, TAC:2mg/d
14	F	20	24	MP:40mg/d, LEF 20 mg/d (10m), IVIG (20g*5d), CSA:150 mg/d (16m)	MP:12mg/d, TAC:2mg/d
15	F	64	48	P:25mg/d, IVIG (20g*3d), HCQ:0.4g/d(33m), MMF:1.5 g/d (17m), CSA:150 mg/d (13m)	P:10mg/d, HCQ:0.2g/d, TAC:2mg/d
16	F	42	36	P:20mg/d, TG:60mg/d (5m), HCQ:0.4 g/d (18m), CTX:0.4 g/2 w (12m), IVIG (20g*3d)	P:7.5mg/d, HCQ:0.4g/d, TAC:3mg/d
17	M	43	25	P:30mg/d, LEF 20 mg/d (6m), HCQ:0.4 g/d(8m), CSA:100 mg/d (9m)	P:5mg/d, HCQ:0.4g/d, TAC:2mg/d
18	F	26	13	MP:32mg/d, MMF1.5g/d (5m), HCQ:0.4gm/d (6m), VCR:2mg/w (2m),	MP:8mg/d, HCQ:0.4g/d, TAC:2mg/d
19	F	55	2	MP:24mg/d, CSA:100 mg/d (1m), HCQ:0.4 g/d (2m), CTX:0.6 g/m (1m)	MP:8mg/d, HCQ:0.4g/d, TAC:2mg/d
20	F	40	9	P:20mg/d, CTX:0.8 g/m (5m), HCQ:0.4 g/d (8m), MTX10mg/w (4m)	P:5mg/d, TAC:2mg/d
21	F	39	15	P:30mg/d, MTX10mg/w(8m), IVIG (20g*3d), CSA:150 mg/d (4m)	P:15mg/d, TAC:3mg/d
22	F	52	14	MP:20mg/d, CSA:100 mg/d (6m), HCQ:0.4g/d (10m), CTX:0.4 gm/2 w (7m),	MP:4mg/d, HCQ:0.4g/d, TAC:3mg/d
23	M	48	22	MP:32mg/d, MMF1.5g/d (4m), HCQ:0.4g/d (14m), IVIG (20g*5d) CSA:150 mg/d (7m)	MP:8mg/d, HCQ:0.2g/d, TAC:2mg/d

F: female; M: male; GCs: glucocorticoids; IVIG: intravenous immunoglobulin; HCQ: hydroxychloroquine; CSA: cyclosporine; CTX: cyclophosphamide; VCR: vincristine; MMF: mycophenolate mofetil; MTX: methotrexate.

Table II. Platelet response to TAC treatment.

Patients	Before ($\times 10^9/L$)	4 weeks ($\times 10^9/L$)	8 weeks ($\times 10^9/L$)	12 weeks ($\times 10^9/L$)	24 weeks ($\times 10^9/L$)	Response
1	10	35	47	123	156	CR
2	18	78	84	107	216	CR
3	17	112	147	135	120	CR
4	5	49	37	55	81	PR
5	19	23	47	21	70	CR
6	5	17	35	21	28	NR
7	7	37	96	129	217	CR
8	11	28	44	79	105	CR
9	4	17	46	74	69	PR
10	10	94	78	69	83	PR
11	13	55	47	89	115	CR
12	2	19	58	73	87	PR
13	6	45	67	136	120	CR
14	1	13	17	27	65	PR
15	10	59	179	126	183	CR
16	9	34	57	93	117	CR
17	15	46	44	72	58	PR
18	9	39	33	45	68	PR
19	13	101	145	164	155	CR
20	19	95	103	136	215	CR
21	10	67	89	123	193	CR
22	13	79	68	115	203	CR
23	17	37	75	201	224	CR

CR: complete response; PR: partial response; NR: no response.

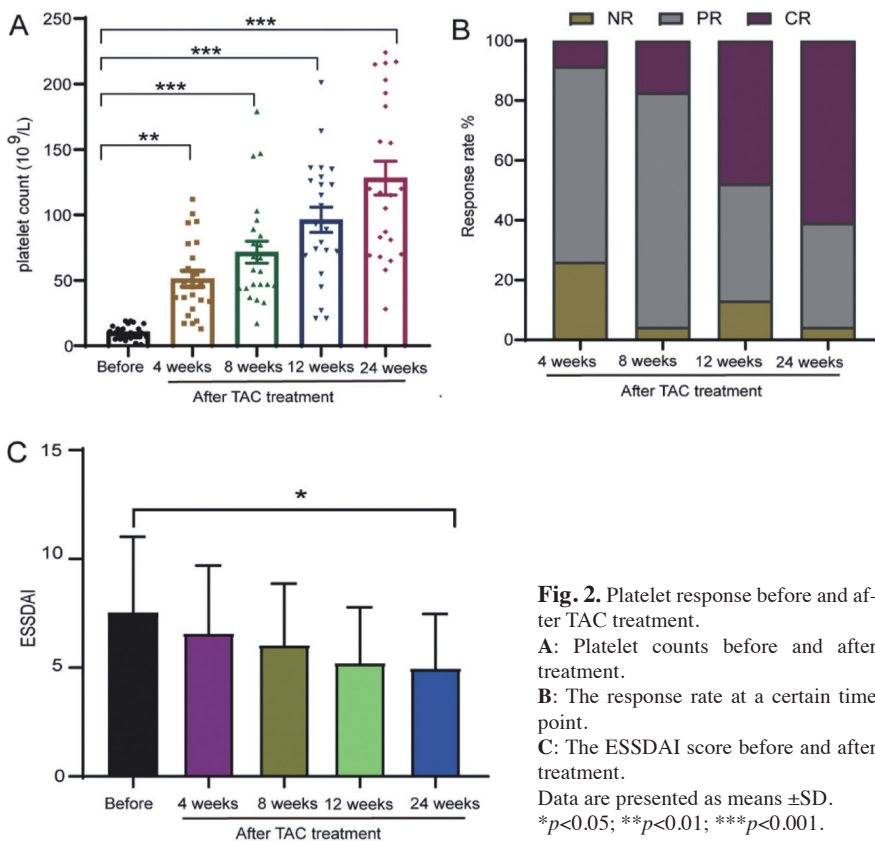


Fig. 2. Platelet response before and after TAC treatment. **A:** Platelet counts before and after treatment. **B:** The response rate at a certain time point. **C:** The ESSDAI score before and after treatment. Data are presented as means \pm SD. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

patient suffered mild hypertension and abnormal liver function. Neither allergic reactions nor infections were observed during or after TAC treatment.

Discussion

RITP secondary to pSS is a challenging issue and is often associated with poor outcomes (11). However, until now,

there has been no definition and consensus of pSS-RITP. In this study, we enrolled patients after treatment with at least one course of GCs and more than 2 immunosuppressive agents whose platelet count was still $< 20 \times 10^9/L$ or less than twice that before treatment for RITP. Furthermore, whether TAC can improve the platelet count in patients with pSS-RITP has yet to be determined. In the present study, we retrospectively analysed the TAC treatment data for 23 patients, and the results showed that the platelet counts of all but 1 patient significantly improved, and the overall response rate was 95.7% at 24 weeks. In addition to evaluating platelet counts, we analysed the levels of immunoglobulins, the absolute T lymphocyte count, the disease activity index and the levels of cytokines. The results revealed that compared with pre-treatment, the level of IgG, the absolute CD3⁺T cell count, ESSDAI scores and Th1-cell-related cytokines were significantly decreased after 24 weeks of TAC treatment. These results suggest that TAC can improve not only the platelet count but also laboratory indicators in these patients. TAC, a powerful calcineurin inhibitor, was initially used to treat patients undergoing organ transplantation, and the underlying mechanism of TAC for this indication has been well studied (12). In recent years, TAC has also been shown to be promising in treating autoimmune diseases. Miyasaka *et al.* (13) reported that compared with placebo, the addition of TAC at 3 mg/day to GCs treatment for 28 weeks significantly alleviated lupus nephritis. Praga *et al.* (14) found that the effective rate of TAC in the treatment of idiopathic membranous nephropathy was 82% at 12 months compared with 24% in the control group. A 52-week placebo-controlled trial showed that compared with 45.2% in the placebo group, the ACR20 response of TAC was 70.5% in patients with early RA who did not respond adequately to other cDMARDs (15).

The pathogenesis of thrombocytopenia in pSS remains unclear. Although abnormal activation of B cells has been considered an important pathogenesis in pSS-ITP (16-18), the persistence

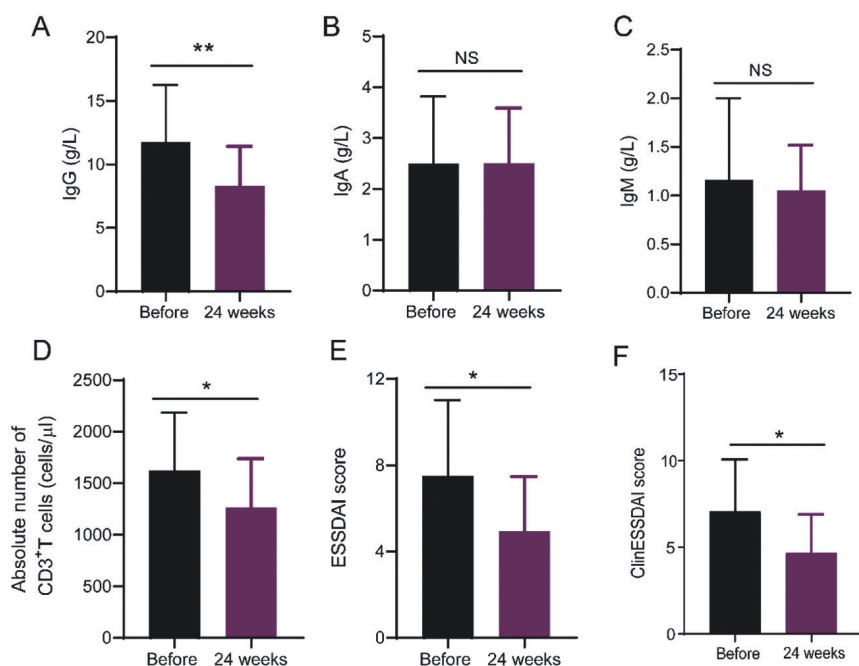


Fig. 3. Laboratory parameters and ESSDAI before and 24 weeks after TAC treatment. **A-C:** The levels of immunoglobulin IgG, IgA, IgM following TAC treatment. **D:** Changes in the absolute count of CD3⁺T cells following TAC treatment. **E:** The ESSDAI score before and 24 weeks after TAC treatment. **F:** The ClinESSDAI score before and 24 weeks after TAC treatment. Data are presented as means \pm SD. * p <0.05; ** p <0.01; *** p <0.001.

of T-cell activation and cytokine secretion also plays an essential role in the development of ITP (19-22). As calcineurin is a critical phosphatase in TCR signalling, TAC can restrain the activation and differentiation of helper T cells. Consistent with this, the absolute CD3⁺T cell count significantly decreased in the patients evaluated in the present study. Additionally, as TAC has been proven to inhibit the differentiation of T follicular helper cells and suppress B-cell function (23, 24), we found that the level of IgG was significantly decreased at 24 weeks of treatment. Previous studies have shown that TAC can downregulate the expression of IFN- γ and upregulate IL-4 in an ITP mouse model (25). In the patients in the current study, we found that the cytokines IFN- γ and IL-2 were reduced significantly, but there was no significant difference between IL-4 and IL-10 after TAC administration. Although nephrotoxicity is a major concern in the use of calcineurin inhibitors, in general, TAC at the dosage that we used in our cohort was well tolerated, and side effects were mild. Only one patient suffered mild hypertension and

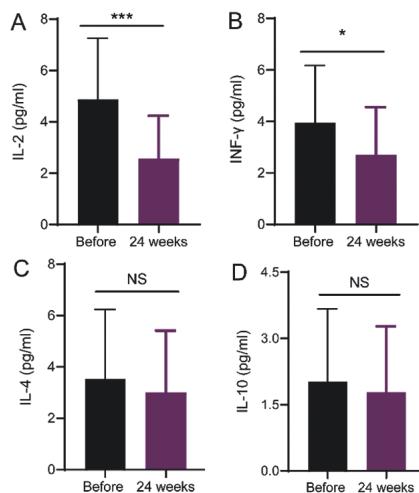


Fig. 4. Comparison of Th1 and Th2 related cytokines before and after TAC treatment. **A-D:** The levels of IL-2, IFN- γ , IL-4 and IL-10 before and after TAC treatment. Data are presented as means \pm SD. * p <0.05; ** p <0.01; *** p <0.001.

pecially opportunistic infections, were another potential problem for the patients in our study because all of them had received high-dose or long-term glucocorticoid therapy, and tacrolimus may have additional immunosuppression effects. However, in our study, no patient suffered a serious infection,

which may be related to the low dose of TAC administered, the gradual tapering of glucocorticoids and the high use rate of IVIG.

In addition, an interesting phenomenon that we are concerned about is that TAC has been shown to increase the oncogenic risk of patients receiving the drug after organ transplantation (26) but not in those receiving the drug for the treatment of autoimmune diseases, which could be due to the utilisation of high-dose TAC in organ transplant recipients. Therefore, clinicians should determine for the optimal dose for each patient to reduce oncogenic risk. To our knowledge, this is the first study on the efficacy and safety of TAC treatment for RITP in pSS patients.

Some limitations of our study should be acknowledged. First, the sample size was relatively small, and the sample was limited to patients from a single centre. Second, this study had a retrospective design, and a large-scale clinical controlled study is warranted. Third, the follow-up time of observation was not long enough, and the long-term efficacy and safety need to be studied further. Finally, the exact mechanism of the effect of TAC on pSS-ITP needs to be further clarified.

Conclusions

In conclusion, our findings indicate that a 24-week course of TAC treatment in pSS patients with RITP is safe and effective, and the mechanism underlying the effect of TAC in these patients may be related to reduced Th1 cytokine expression.

Ethical approval

All procedures involving human participants conformed to the ethical guidelines of the institutional and national research committee and the 1964 Declaration of Helsinki. The study was approved by the hospital ethics committee (approval ID:2021-023). All patients enrolled in this study were informed and signed the consent forms.

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