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Tacrolimus for Treating Orbital and Cranial Form of Idiopathic Inflammatory Pseudotumors

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Background and Purpose Orbital and cranial form of idiopathic inflammatory pseudotumors (IIPs) are rare disorders with heterogeneous clinical presentations. Corticosteroids have been the first-line treatment for IIPs, but they are not always effective.

Methods We reviewed the medical records of three patients with orbital or cranial form of IIP who were treated with tacrolimus as an adjuvant treatment.

Results The three patients showed favorable outcomes with the addition of tacrolimus, which is a calcineurin inhibitor that inhibits T-cell activation and T-cell-dependent B-cell activation.

Conclusions Tacrolimus may be a safe and effective immunosuppressant for refractory or relapsing form of orbital or cranial IIPs.

Key Words tacrolimus, inflammatory pseudotumor, Tolosa-Hunt syndrome, orbital pseudotumor.

INTRODUCTION

Idiopathic inflammatory pseudotumor (IIP) is a nonneoplastic inflammatory lesion with histological features of polymorphous inflammatory cell infiltration, fibrosis, necrosis, and a granulomatous reaction.[1] Such lesions commonly involve the orbit and so are often called orbital IIP, but the lesion may also spread through the superior orbital fissure to the intracranial structures. IIP can also develop solely within the cranium, and Tolosa-Hunt syndrome (THS)—which is an idiopathic granulomatous inflammation mostly involving the cavernous sinus and the superior orbital fissure—can be considered as cranial IIP because THS shares histological, radiological, and clinical features with orbital IIPs.[1] Both orbital and cranial IIPs are known to respond favorably to short-term systemic corticosteroids.[1,2] In refractory or relapsing forms of these disorders, treatment with long-term corticosteroids and second-line immunosuppressants may be attempted like they are in other autoimmune disorders.[1-4]

Tacrolimus forms a complex with the immunophilin-FK-binding protein that inhibits calcineurin, which is essential for activating NF-AT, the T-cell-specific transcription factor.[5] Therefore, tacrolimus exerts selective inhibitory effects on T-cell activation and T-cell-dependent B-cell activation, which becomes an immunological basis for immunosuppressive treatment. Tacrolimus is currently commonly administered to patients with organ transplantation, rheumatoid arthritis, and myasthenia gravis.[5] However, the effectiveness of tacrolimus has not been documented in orbital and cranial IIPs.

Here we report three patients with orbital or cranial IIP who showed favorable outcomes

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with the administration of tacrolimus as an adjuvant treatment.

METHODS

This study is a case series of three patients who were diagnosed with orbital or cranial IIP and treated with tacrolimus. The clinical course of each patient is depicted in Figs. 1A, 2A, and 3A. The details of each patient are reported in the Results and summarized in Table 1. The Institutional Review Board of Seoul National University Bundang Hospital approved the protocol applied in this study and did not require consent to be obtained from each patient (IRB number: B-2004-604-108).

RESULTS

Patient 1

A 43-year-old female presented with diplopia and left orbitofrontal pain that had first appeared 4 days earlier. She was previously diagnosed with fatty liver disease and was regularly monitored for elevated liver enzymes. A neurological examination showed a restriction and slowness of the left eyeball when attempting abduction, as well as hypesthesia of the left frontal region. The initial gadolinium-enhanced MRIs showed a heterogeneous contrast-enhanced mass involving the left cavernous sinus (Fig. 1B and C). The findings of routine serological tests and screening for autoimmune disorders were normal, including the white blood cell count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, antinuclear antibody, anti-double-stranded deoxyribonucleic acid antibody, antineutrophil cytoplasmic antibody, serum protein electrophoresis, and IgG4. The cerebrospinal fluid (CSF) was also normal.

The patient was diagnosed with THS and initially treated with 1 g of methylprednisolone for 5 consecutive days and then additionally with oral prednisolone starting from a dose of 50 mg that was gradually tapered off over 8 weeks. Her diplopia and headache disappeared at 1 month after treatment. However, after oral prednisolone was discontinued, she developed mild tightness in the left orbit with visual blurring. Follow-up MRIs obtained 3 months after the onset showed that the lesion in the left cavernous sinus had reduced, but the left lateral rectus, inferior rectus, and medial rectus muscles were newly enlarged and enhanced (Fig. 1D and E). The patient was started on oral prednisolone again at 30 mg per day, which was then tapered off over 8 weeks. She rejected

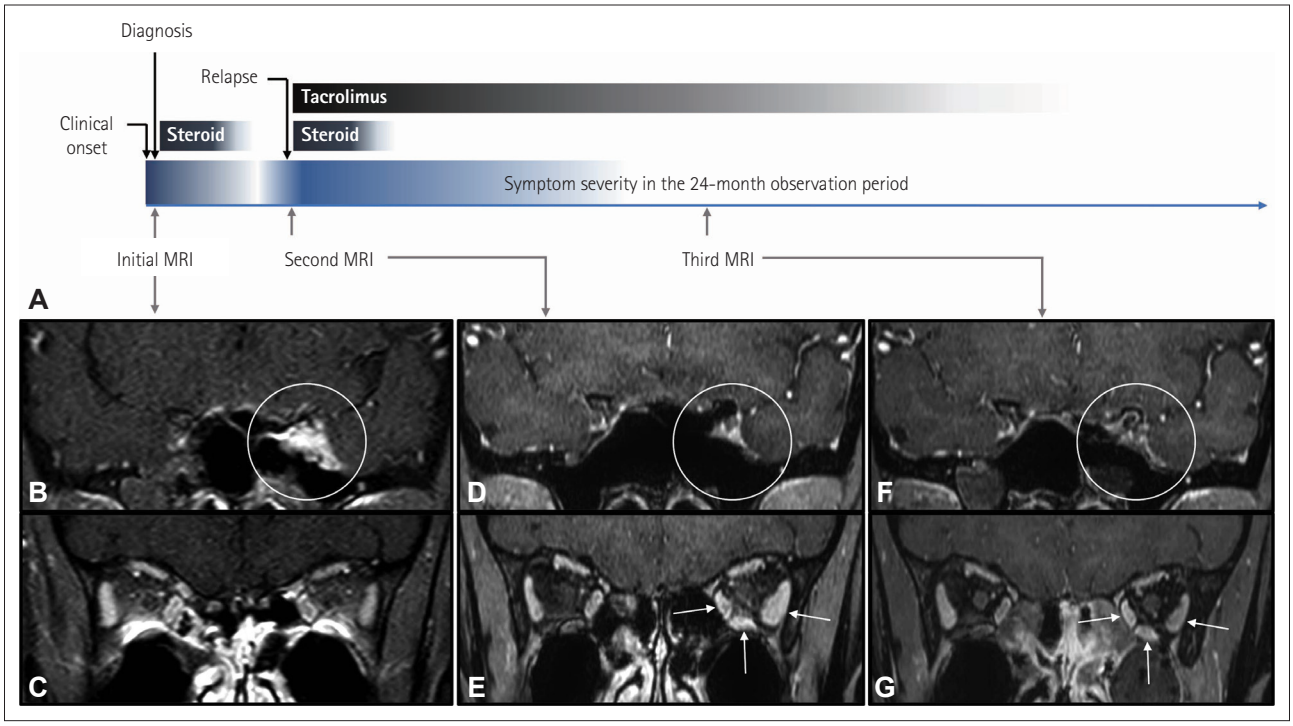

Fig. 1. Findings of a 43-year-old female patient with a cranial idiopathic inflammatory pseudotumor (Tolosa-Hunt syndrome). A: The summarized clinical course of the patient. The blue gradation box displays the symptom severity during follow-up, while the gray and blue-gray gradation boxes indicate the duration and dosage of steroid and tacrolimus, respectively. B and C: Initial MRIs show a heterogeneous contrast-enhanced mass in the left cavernous sinus (circle) without the involvement of extraocular muscles. D and E: The second MRIs obtained after 3 months reveal a decreased size and enhancement of the cavernous sinus lesions (circle), but the left extraocular muscles are newly enlarged. F and G: In the third MRIs obtained 1 year after the onset, the cavernous lesion has disappeared (circle), and the left extraocular muscles are normalized.

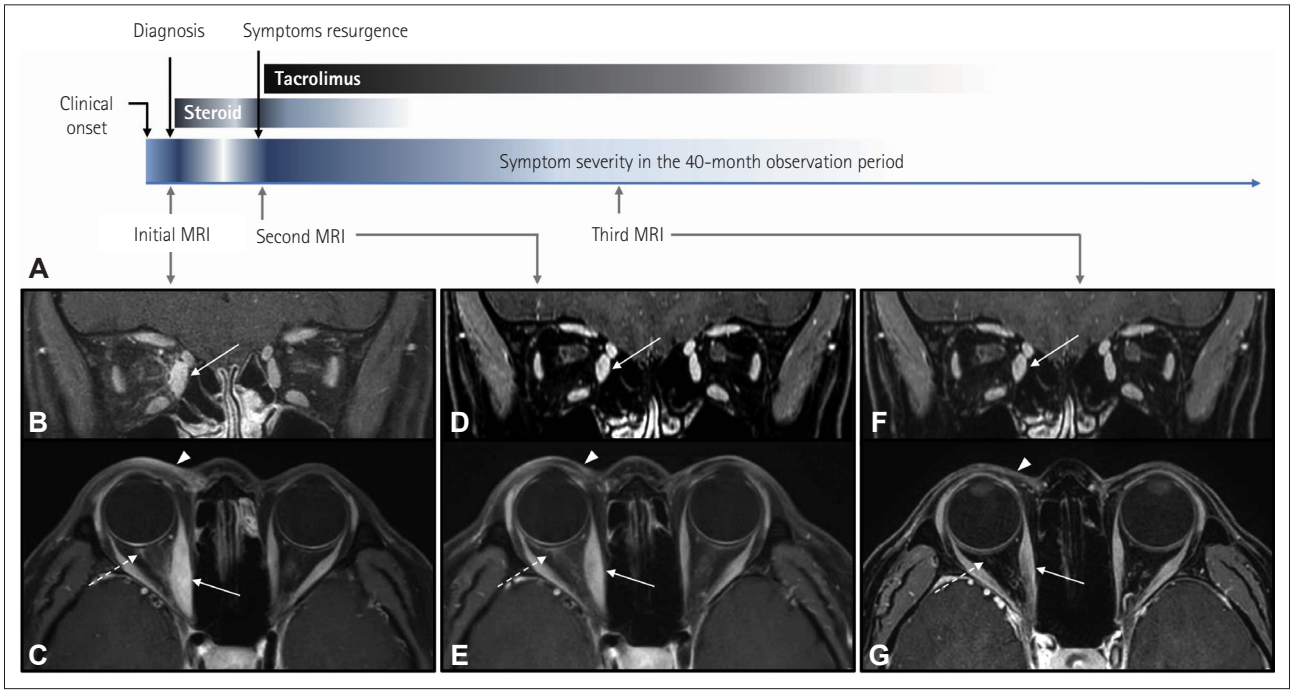

Fig. 2. Findings of a 40-year-old female patient with an orbital idiopathic inflammatory pseudotumor. A: Summary of the clinical course. The representations of the gradation boxes are the same as in Fig. 1. B and C: Initial MRIs show an enlarged right medial rectus muscle with contrast enhancement (solid arrows). There are additional enhancements in the right retrobulbar optic nerve sheath (dotted arrow) and preseptal area (arrowhead). D and E: In the second MRIs, the previous lesions are not notably changed. F and G: The third MRIs obtained after tacrolimus treatment show a remarkable improvement of the right medial rectus enlargement, with disappearance of the enhancement from the retrobulbar optic sheath and preseptal area.

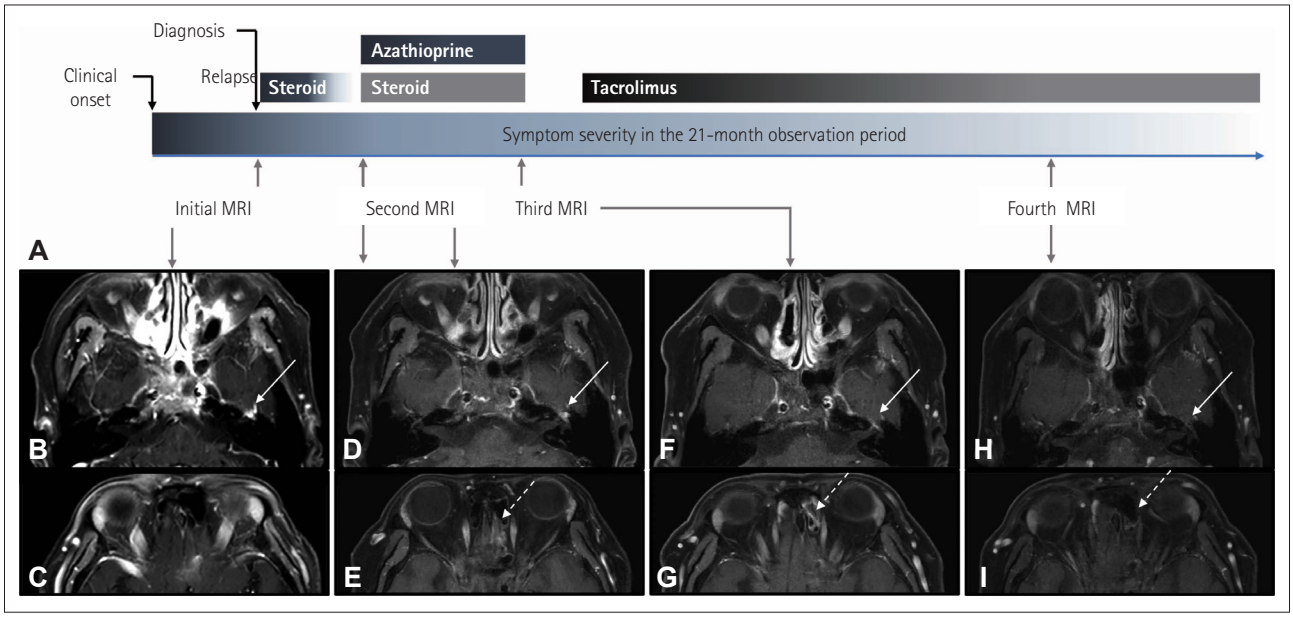

Fig. 3. Findings of a 56-year-old female patient with a cranial idiopathic inflammatory pseudotumor. A: Summary of the clinical course. The representations of the gradation boxes are the same as in Fig. 1. B and C: Initial MRIs show a contrast-enhanced lesion in the left facial and vestibular nerves at the distal auditory canal (arrow) but a normal left olfactory groove. D and E: The second MRIs obtained 4 months after the onset show no noticeable change in the lesions in the left auditory canal (solid arrow) but reveal a new contrast-enhanced lesion in the left olfactory groove (dotted arrow). F and G: In the third MRIs obtained 7 months after the onset, the previous lesions evident in the second MRIs have decreased slightly. H and I: The fourth MRIs obtained after 12 months of tacrolimus treatment reveal that the lesions have disappeared from both the internal auditory canals and olfactory groove.

Table 1. Summary of the clinical features of the three patients

	Patient 1	Patient 2	Patient 3
Age/sex	43 years/female	40 years/female	56 years/female
Symptoms	Horizontal diplopia Orbitofrontal pain (L)	Ptosis (R) Periorbital pain and tenderness (R) Diagonal diplopia	Spontaneous vertigo Facial palsy (L)
Past medical history	Nonalcoholic fatty liver disease	Chronic hepatitis C	-
Lesions	Cavernous sinus (L) Orbital apex (L) Extraocular muscles (L LR, IR, MR)	Extraocular muscle (R MR) Perioptic nerve sheath (R) Periorbital soft tissue (R)	Auditory canal (L VII, VIII) Olfactory groove (R) High-cervical lymph node (L)
Immunosuppressants before tacrolimus treatment	IV MP for 5 days (1 g per day)	Oral PD for 8 weeks (≤60 mg)	Oral PD for 4 weeks (≤55 mg)
	Oral PD for 8 weeks (≤50 mg)		Azathioprine (25 mg for 12 weeks)
Duration of tacrolimus treatment	18 months	29 months	13 months

IR: inferior rectus muscle, IV: intravenous, L: left, LR: lateral rectus muscle, MP: methylprednisolone, MR: medial rectus muscle, PD: prednisolone, R: right, VII: facial nerve, VIII: vestibulocochlear nerve.

taking azathioprine or mycophenolate mofetil due to potential liver toxicity, and instead was maintained on 3 mg of tacrolimus along with the prednisolone. The second follow-up MRIs performed 1 year after the onset revealed that the lesions had disappeared (Fig. 1F and G). Tacrolimus was gradually tapered for 6 months before being discontinued, and no relapse occurred during a subsequent 1-year follow-up.

Patient 2

A 40-year-old female with chronic hepatitis C was referred for an evaluation of right periorbital pain, right eye ptosis, and diplopia that had first appeared 20 days earlier. She had restricted adduction of the right eyeball, but her eye velocity was normal within the available ocular motor range. There was painful tenderness of the right medial orbital region. The initial MRIs showed enlargement of the right medial rectus muscle with mild contrast enhancement, and additional lesions in the right retrobulbar optic nerve sheath and preseptal area (Fig. 2B and C). Routine serological tests, autoimmune screening tests, and CSF studies all produced normal findings. However, her hepatitis C virus RNA level was 1,724,673 IU/mL in the quantification test, indicating active hepatitis C.

The patient was diagnosed with orbital IIP and started on 60 mg of prednisone daily for 10 days, which greatly improved her symptoms. The dosage was gradually reduced over the next 8 weeks, but her symptoms relapsed when prednisone was reduced to below 20 mg per day. Follow-up MRIs obtained at the resurgence of symptoms showed no noticeable change compared with the previous MRIs (Fig. 2D and E). Because of its harmful effect on chronic hepatitis C, long-term corticosteroid treatment could not be administered. Azathioprine and mycophenolate mofetil also could not be administered because of potential direct hepatotoxicity. The patient was started on 3 mg of tacrolimus while discontinuing prednisolone over 8 weeks. After 6 months of tacrolimus administration, the right periorbital pain had completely disappeared, and the restriction of right eye abduction had resolved. The second follow-up MRIs were obtained at 16 months after the onset, by which time the lesions had nearly resolved (Fig. 2F and G). Tacrolimus was gradually reduced over a period of 7 months before being discontinued, and the patient had no further relapse during the 1-year follow-up.

Patient 3

A 56-year-old previously healthy female presented with spontaneous vertigo that had first appeared more than 2 weeks earlier. She had experienced left-sided facial palsy 2 months previously. A bedside examination showed spontaneous right-beating nystagmus that became stronger during rightward gaze or in darkness without visual fixation, and positive rightward head-impulse signs indicative of acute left vestibulopathy, in addition to preexisting complete left facial palsy. The initial MRIs revealed segmental enhancement in the left facial and vestibular nerves at the distal auditory canal (Fig. 3B and C). The findings of serological and CSF evaluations for infectious and autoimmune disorders were normal.

The patient was diagnosed with an inflammatory disorder of uncertain origin that involved the left internal auditory canal. She initially took oral prednisone at 1 mg/kg for 7 days. The dosage was then rapidly reduced over the following 4 weeks due to excessive weight gain, formation of a moon face, nervousness, and stomach irritation. The spontaneous nystagmus disappeared, but she still suffered from fluctuating dizziness. Follow-up MRIs obtained 4 months after the onset showed stable lesions in the left auditory canal and newly developed contrast-enhanced lesions in the left olfactory groove and right high-cervical lymph node (Fig. 3D and E). The findings of the second evaluations for autoimmune and

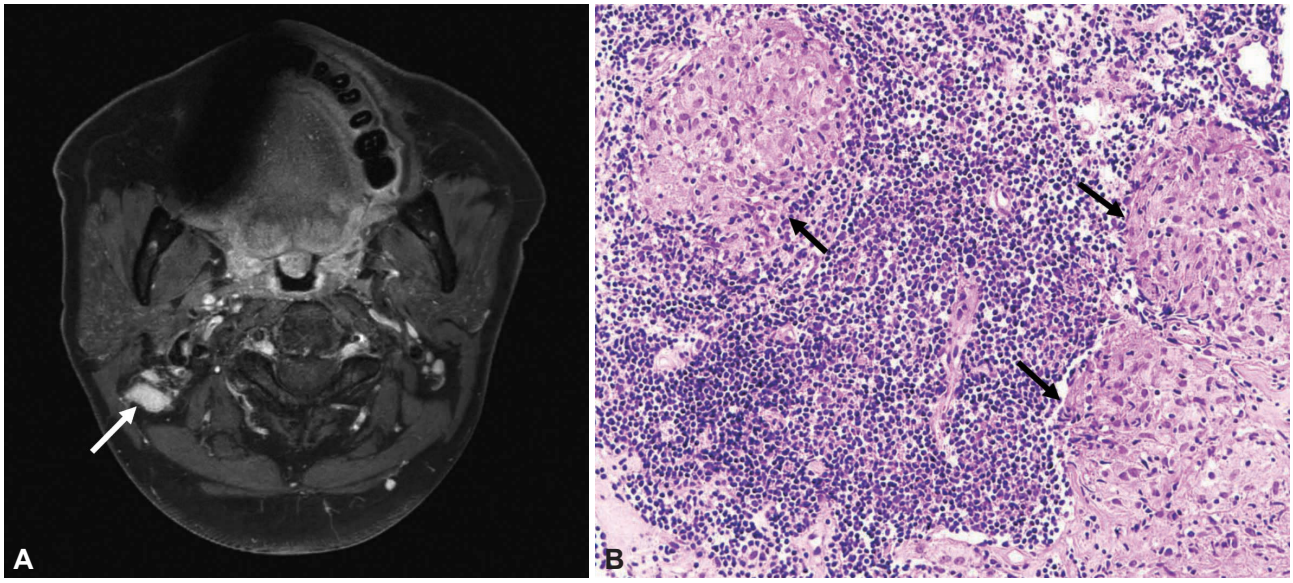

Fig. 4. Histopathology of the neck lymph node in the patient with a cranial idiopathic inflammatory pseudotumor. A: Second MRIs of patient 3 reveal right high-cervical lymph node enlargement (white arrow). B: The lymph node biopsy shows nonnecrotizing multiple granulomatous changes (black arrows) with chronic inflammatory cell infiltration (hematoxylin-eosin stain, original magnification ×200).

infectious disorders were also normal, and a histopathological evaluation performed at the right neck lymph node revealed chronic granulomatous inflammation without evidence of tuberculosis, nontuberculous mycobacterial infection, or malignancy such as lymphoma (Fig. 4).

The patient was finally diagnosed with cranial IIP and started on azathioprine with short-term prednisolone. Her symptoms remained stable while taking azathioprine, and a second follow-up MRI obtained at 7 months after the onset showed mild improvement of lesions involving the left olfactory groove and internal auditory canal (Fig. 3F and G). However, serum aspartate and alanine aminotransferases had increased sixfold, while other liver enzymes were also elevated. Hence, despite some clinical improvements, the patient discontinued azathioprine and then was started on tacrolimus after normalization of the liver enzymes. The third follow-up MRIs obtained 17 months after the onset showed further improvement of the previous lesions (Fig. 3H and I). Her facial palsy and vertigo had also improved—though not completely—through treatment with tacrolimus alone.

DISCUSSION

The three patients in this study showed incomplete responses to conventional corticosteroid treatment. In addition, common immunosuppressants could not be administered due to the presence of comorbidities or side effects. However, tacrolimus was able to produce clinical and radiological remission without significant adverse effects.

Intravenous and/or oral corticosteroids are the first-line treatments for orbital or cranial IIP, and marked improvement within 48 hours has been reported in approximately three-quarters of patients.[6] However, relapse occurs in more than half of patients with orbital or cranial IIP.[2] Recurrence has been found in approximately 78% of patients treated with corticosteroids alone, with this proportion decreasing to 16% through combination treatment with immunosuppressants.[7] Therefore, immunosuppressants could be empirically used with corticosteroids to improve symptoms, at least in patients who are resistant to corticosteroids or exhibit recurrence;[8] these immunosuppressants include folic acid antagonists, methotrexate, purine analogs, azathioprine, alkylating agents, cyclophosphamide, purine synthesis inhibitors, and mycophenolate mofetil. However, tacrolimus was developed more recently than these other agents, and the present report is the first suggesting that tacrolimus exhibits therapeutic efficacy in patients with orbital or cranial IIP.

Tacrolimus is known to have excellent safety and efficacy. Tacrolimus has less hepatotoxicity than cyclosporine, which belongs to the same group of calcineurin inhibitors as tacrolimus. Dosage adjustment is essential for every patient receiving cyclosporin treatment due to the propensity of multiple drug interactions metabolized by cytochrome P450 3A, but the bioavailability of tacrolimus is superior.[9,10] In addition, tacrolimus is 10- to 100-fold more potently immunosuppressive than cyclosporine at the same weight,[9] which results in a higher survival rate and a lower mortality in patients with kidney transplantation.[11] Moreover, the rate of reactivation of hepatitis B and C viruses appears to be lower for tacrolimus than for systemic corticosteroids.[12-16] A meta-analysis assess-

ing the risk of adverse events in patients with systemic lupus erythematosus found that the rate of serious adverse events was lower for tacrolimus than for other immunosuppressants such as glucocorticoids, cyclosporine, azathioprine, cyclophosphamide, mycophenolate mofetil, methotrexate, and rituximab.[17] Tacrolimus was also suitable for controlling ocular inflammatory diseases including Behçet's disease and Vogt-Koyanagi-Harada syndrome without inducing increases in infection and malignancy.[18]

The therapeutic mechanism of tacrolimus in orbital or cranial IIP remains to be determined, but at least two mechanisms can be speculated. First, the immunosuppressive mechanism of tacrolimus might be similar to that of cyclosporine, which can also be efficacious in orbital IIP. Second, IIP occurs in the CNS and was histologically revealed to be associated with a high density of IgG4-positive plasma cells, which suggests that a considerable proportion of IIP cases belong to the subgroup of IgG4-related syndromes.[19] Specimens obtained from patients with orbital IIP show high levels of interleukin (IL)-2, IL-8, IL-10, IL-12, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α.[1] Tacrolimus is known to inhibit IL-2, IL-3, IL-4, TNF-α, CD40L, granulocyte-macrophage colony-stimulating factor, and IFN-γ. It also prevents T-cell activation and inhibits follicular helper T cells, which play a key role in IgG4 production.[20] Therefore, unlike steroid and azathioprine that interrupt the cell cycle of lymphoid cells and inhibit the production of both B and T cells, tacrolimus might exert its therapeutic effects on IIP mainly by affecting T-cell immune mechanisms.

There are some aspects to consider when interpreting the findings of this study. First, the effect of tacrolimus observed in all three patients could be distinguished from the delayed effects of steroids or azathioprine. There would have been a belated partial effect of prednisolone, but the duration of anti-inflammatory effects of prednisolone is known to be relatively short, at typically 12−36 hours.[21] While tapering steroids, all patients showed the aggravation or recurrence of symptoms. The effects of azathioprine are usually expected to occur at 2−3 months after initiating the therapy.[22] In patient 3, azathioprine might have been discontinued before the effects fully developed. Thus, the previous immunosuppressive treatments with azathioprine do not necessarily disprove the effect of tacrolimus in our patients.

The second aspect to consider is whether relapsing or refractory IIP can be clearly differentiated from other disorders including IgG4-related diseases, sarcoidosis, lymphoma, or chronic infection such as tuberculosis. The lack of a histological confirmation would not completely exclude these disorders. However, performing a biopsy of a brain lesion is often difficult. Thus, extensive serological and imaging evaluations along with careful monitoring of treatment responses are necessary, and this protocol can lead to a reliable diagnosis of IIP, as shown by the present study.

In summary, tacrolimus can be an alternative option when treating patients with orbital or cranial IIP who exhibit an insufficient response to steroids, need long-term treatments, or have comorbidities restricting the use of other immunosuppressants. Further investigations are necessary to confirm the efficacy of tacrolimus.

Author Contributions

Conceptualization: Jeong-Yoon Choi. Data curation: Jeong-Yoon Choi, Hyun Jae Kim, Eunjin Kwon. Formal analysis: Seonkyung Lee, Yu Jin Koo, Eunjin Kwon, Hyo-Jung Kim, Jeong-Yoon Choi, Ji-Soo Kim. Supervision: Jeong-Yoon Choi. Writing—original draft: Hyun Jae Kim, Jeong-Yoon Choi. Writing—review & editing: Jeong-Yoon Choi, Ji-Soo Kim.

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Conflicts of Interest

Dr. JS Kim serves as an associate editor of Frontiers in Neuro-otology and on the editorial boards of the Journal of Clinical Neurology, Frontiers in Neuro-ophthalmology, Journal of Neuro-ophthalmology, Journal of Vestibular Research, Journal of Neurology, and Medicine. The other authors have nothing to disclose.

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REFERENCES

1. Yeşiltaş YS, Gündüz AK. Idiopathic orbital inflammation: review of literature and new advances. *Middle East Afr J Ophthalmol* 2018;25:71-80.
2. Carreón E, Muñiz S, Di Capua D, Porta-Etessam J. Tolosa-Hunt syndrome with spontaneous remission and recurrence. *Neurologia* 2018;33:68-70.
3. Mombaerts I, Koornneef L. Current status in the treatment of orbital myositis. *Ophthalmology* 1997;104:402-408.
4. Yan J, Wu P. Idiopathic orbital myositis. *J Craniofac Surg* 2014;25:884-887.
5. Dheer D, Jyoti, Gupta PN, Shankar R. Tacrolimus: an updated review on delivering strategies for multifarious diseases. *Eur J Pharm Sci* 2018;114:217-227.
6. Chaudhry IA, Shamsi FA, Arat YO, Riley FC. Orbital pseudotumor: distinct diagnostic features and management. *Middle East Afr J Ophthalmol* 2008;15:17-27.
7. Arthur A, Sivadasan A, Mannam P, Prabakhar AT, Aaron S, Mathew V, et al. Tolosa-Hunt syndrome: long-term outcome and role of steroid-sparing agents. *Ann Indian Acad Neurol* 2020;23:201-205.
8. Schoser BG. Ocular myositis: diagnostic assessment, differential diagnoses, and therapy of a rare muscle disease - five new cases and re-

view. *Clin Ophthalmol* 2007;1:37-42.
9. Lake DF, Briggs AD. Immunopharmacology. In: Katzung BG, editor. *Basic & Clinical Pharmacology*. 14th ed. New York, NY: McGraw-Hill, 2017.
10. Sánchez-Román J, Varela-Aguilar JM, Bravo-Ferrer J, Sequeiros Madueño E, Fernández de Bobadilla M. Idiopathic orbital myositis: treatment with cyclosporin. *Ann Rheum Dis* 1993;52:84-85.
11. Boots JM. Is tacrolimus superior to ciclosporin microemulsion in preventing long-term acute renal transplant rejection? *Nat Clin Pract Nephrol* 2005;1:16-17.
12. Vento S, Cainelli F, Mirandola F, Cosco L, Di Perri G, Solbiati M, et al. Fulminant hepatitis on withdrawal of chemotherapy in carriers of hepatitis C virus. *Lancet* 1996;347:92-93.
13. Perrillo RP. Hepatitis B reactivation from immunosuppressive drug therapy: a global menace. *Clin Liver Dis (Hoboken)* 2015;5:39-42.
14. Bessone F, Dirchwolf M. Management of hepatitis B reactivation in immunosuppressed patients: an update on current recommendations. *World J Hepatol* 2016;8:385-394.
15. Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, management strategies, and future directions. *Gastroenterology* 2017;152:1297-1309.
16. Tran-Minh ML, Sousa P, Maillet M, Allez M, Gornet JM. Hepatic complications induced by immunosuppressants and biologics in inflammatory bowel disease. *World J Hepatol* 2017;9:613-626.
17. Tian J, Luo Y, Wu H, Long H, Zhao M, Lu Q. Risk of adverse events from different drugs for SLE: a systematic review and network meta-analysis. *Lupus Sci Med* 2018;5:e000253.
18. Hornbeak DM, Thorne JE. Immunosuppressive therapy for eye diseases: effectiveness, safety, side effects and their prevention. *Taiwan J Ophthalmol* 2015;5:156-163.
19. Lui PC, Fan YS, Wong SS, Chan AN, Wong G, Chau TK, et al. Inflammatory pseudotumors of the central nervous system. *Hum Pathol* 2009;40:1611-1617.
20. Takanashi S, Kaneko Y, Takeuchi T. Effectiveness of tacrolimus on IgG4-related disease. *Mod Rheumatol* 2019;29:892-894.
21. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol* 2013;9:30.
22. Anstey AV, Wakelin S, Reynolds NJ; British Association of Dermatologists Therapy, Guidelines and Audit Subcommittee. Guidelines for prescribing azathioprine in dermatology. *Br J Dermatol* 2004;151:1123-1132.