

# Intraorbital corticosteroid injection for the treatment of IgG4-related ophthalmic disease

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## ABSTRACT

**Aim** To review the efficacy of intraorbital corticosteroid injection for the treatment of IgG4-related ophthalmic disease (IgG4-ROD).

**Methods** This study was a retrospective twin-centre histopathology review and observational case series. A chart review was undertaken for 10 cases of biopsy-confirmed IgG4-ROD treated with intraorbital corticosteroid injection. The main outcome measures were the magnitude, onset and duration of the clinical response.

**Results** All cases received intraorbital injection(s) of 20 or 40 mg doses of triamcinolone acetonide suspension (Kenacort-A 40, Bristol-Myers Squibb, Australia). Intraorbital corticosteroid injection was associated with a swift positive response in all cases. 50% of cases achieved complete and sustained clinical remission during mean follow-up of 41 months. This was achieved with a single injection in three cases and with repeat injections in two cases. Peak clinical improvement was reached in  $\leq 7$  days following 61% of injections. 60% of cases suffered relapse and 56% of relapses occurred during weeks 3 or 4 following injection. Sclerosing histology was associated with a clinical response that was gradual in onset ( $p=0.01$ ) and that tended to be incomplete ( $p=0.4$ ). There were no complications of injection other than brief discomfort.

**Conclusions** Intraorbital injection of corticosteroid may be a useful treatment option for IgG4-ROD. It may have a role as a first-line therapy in selected cases of IgG4-ROD centred in the anterior orbit. However, most cases require repeat injections due to incomplete response and relapse.

## INTRODUCTION

IgG4-related ophthalmic disease (IgG4-ROD), the preferred nomenclature for IgG4-related disease affecting the orbit and ocular adnexa, is usually managed with systemic corticosteroids as first-line therapy. Although most cases initially respond well to treatment, approximately 70% suffer disease relapses, usually during corticosteroid taper or shortly after corticosteroid cessation.<sup>1</sup> Patients with relapsing disease tend to require prolonged courses of systemic corticosteroids and are consequently at high risk of steroid-related side effects. In our experience, approximately 30% of IgG4-ROD cases ultimately require additional pharmacotherapies due to steroid intolerance or steroid resistance. Of all the steroid-sparing agents used in IgG4-ROD, rituximab is fast becoming established as the treatment of choice.<sup>2</sup> However, its use is limited by high cost and the risk of rare but catastrophic adverse events, including severe infusion reactions and progressive multifocal leukoencephalopathy.<sup>3</sup>

Both disease and treatment factors make intraorbital corticosteroid injections an attractive treatment modality for IgG4-ROD. Disease factors include steroid-responsiveness, anterior orbit predilection and the low frequency of synchronous extra-ophthalmic disease mandating systemic immunosuppression. Treatment factors include high perilesional corticosteroid concentration, negligible systemic complications, prolonged duration of action (depot formulations), repeatability, surgeon familiarity with the technique, assured compliance, and medication affordability and accessibility. In the appropriately selected patient, intraorbital corticosteroid injection could serve as a primary therapy or as a treatment adjunct to assist with tapering systemic agents. However, there are no reports in the literature describing the role of intraorbital corticosteroid injections in the management of IgG4-ROD.

The aim of this study was to retrospectively review cases of biopsy-confirmed IgG4-ROD treated with intraorbital corticosteroid injection, paying particular attention to the magnitude, onset and duration of the clinical effect. Our purpose was to share our collective experience with this treatment modality for IgG4-ROD.

## METHODS

This study was a retrospective, twin-centre, non-comparative histopathology review and observational case series. Cases of biopsy-confirmed IgG4-ROD treated with intraorbital corticosteroid injection were included. Cases were classified as IgG4-ROD if they presented with an orbital inflammatory syndrome and orbital biopsy revealed  $>10$  IgG4+ plasma cells per high power field, a ratio of IgG4+/IgG+ cells  $>40\%$  and histomorphology consistent with the diagnosis of IgG4-related disease.<sup>4</sup> Elevated serum IgG4 concentration was considered supportive of the diagnosis but was not required for inclusion. There were no exclusion criteria.

A chart review was undertaken for all cases. The following information was retrieved: demographic data (age, gender), clinical data (presenting features, symptom duration, laterality of IgG4-ROD), radiological data (orbital and extra-orbital structures involved by IgG4-ROD), pathology data (histomorphology, tissue IgG and IgG4 staining) and treatment data (dose, response relapse, adverse reactions). The surgeon evaluated the change in soft tissue swelling, erythema and globe displacement in making their assessment of clinical response. The clinical response to each corticosteroid injection was classified according to magnitude (complete vs partial vs no response) and onset (rapid vs gradual). For cases that responded to

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injection, inflammatory signs improved and then either remained stable until further treatment was given or recurred. A rapid onset of clinical response was defined as peak clinical improvement occurring within 7 days of injection. The follow-up protocol was not standardised, but all patients were reviewed once during days 7–14 and at week 4 following each injection. Institutional Human Research Ethics Committee approval was obtained for this study.

## RESULTS

Ten cases fulfilled the inclusion criteria. Demographic data and clinical features are summarised in [table 1](#). The mean age was 49.4 years (range 27–78 years) and mean follow-up duration was 41 months. Seven cases were women and three cases were bilateral but asymmetric. In bilateral cases, intraorbital corticosteroid injections were given to the most symptomatic side only. In total, 90% of cases presented with an insidious onset (eight cases) or subacute onset (one case) of mass effect. Inflammatory signs were mild to moderate, with erythema and soft tissue swelling not extending beyond the orbital rim. Seven cases presented with dacryoadenitis (three cases with spill over inflammation to contiguous structures), two cases presented with myositis and one case presented with an infiltrative lesion in the inferior orbit causing altered cutaneous sensation in the infraorbital nerve distribution.

Histopathology and treatment data are summarised in [table 2](#). Five cases were classified as sclerosing inflammation, defined as abundant interstitial connective tissue and a paucicellular inflammatory infiltrate. In four cases, the morphology resembled lymphoid hyperplasia, characterised by a diffuse, dense lymphoplasmacytic infiltrate organised into lymphoid follicles with germinal centres. Morphology was classified as mixed in one case, defined as sclerosing morphology interspersed with foci of dense lymphoplasmacytic infiltrate with occasional follicle formation.

All cases were treated with intraorbital injection of triamcinolone acetate suspension (40 mg/mL, Kenacort-A 40, Bristol-Myers Squibb, Australia). Injections were given slowly using a 2 mL syringe and a 25 mm long, 27-gauge needle oriented with the bevel facing towards the globe. The needle was directed just posterior to the orbital septum, near the orbital rim, into the region of the orbit most affected by disease (without ultrasound guidance). For cases of dacryoadenitis, the medication was delivered around (not into) the lacrimal gland by making two passes of the needle: one superomedial, and one inferotemporal to the gland. Needle tip entry into the gland was

felt as an increased resistance to injection. Before each injection the plunger was withdrawn to check for flash back of blood into the hub. A dose of either 20 mg (nine injections) or 40 mg (10 injections) was used. Dose selection was at the surgeon's discretion, but in general, a 40 mg dose was chosen when inflammatory signs or mass effect was of moderate intensity, or following an inadequate response to a 20 mg dose.

Injections were used as primary therapy in eight cases, following failure of systemic prednisolone (case 9), and as adjunctive treatment to help wean systemic prednisolone (case 10). All cases experienced clinical improvement following intraorbital corticosteroid injection. Five cases achieved complete and sustained clinical remission during follow-up (cases 1–5), which was achieved with a single injection in three cases and with repeat injections in two cases. Of the cases that failed to achieve complete and sustained clinical remission (n=5), one was observed (case 6), one settled following a 4-month course of oral prednisolone (case 7) and three settled with rituximab (cases 8–10). The 20 and 40 mg doses achieved similar rates of complete clinical response (44% vs 40%). However, since the 40 mg dose was given to recalcitrant cases and cases with more intense inflammatory signs, it is possible that this dose is more effective at treating IgG4-ROD.

The onset of clinical response was rapid following 61% of injections and gradual following 39%. Cases classified as having a gradual onset still experienced the majority of their clinical improvement within 7 days. Sclerosing histology was associated with a clinical response that was gradual in onset ( $p=0.01$ , two-tailed Fisher's exact test) and that tended to be incomplete ( $p=0.4$ , two-tailed Fisher's exact test). Six cases suffered relapses; 56% of relapses occurred during weeks 3 and 4 following injection. Other relapses occurred at 12 weeks (two cases), 16 weeks (one case) and 20 months (one case) following injection. All patients reported pain and pressure sensation at the time of injection; however, there were no significant complications of injection and no case experienced an intraocular pressure rise  $\geq 6$  mm Hg.

## DISCUSSION

To the best of our knowledge, this is the first study dedicated to intraorbital corticosteroid injections for the management of biopsy-confirmed IgG4-ROD. All cases experienced some clinical improvement following injection; however, the majority of cases required multiple injections and half of our cases failed to achieve complete and sustained clinical remission during

**Table 1** Clinical data for cases of IgG4-ROD treated with intraorbital corticosteroids

| Case/age/gender/side | Presentation   | Orbital structures involved on imaging     | Extra-ophthalmic structures involved on imaging   |
|----------------------|----------------|--------------------------------------------|---------------------------------------------------|
| 1/27/F/right         | Dacryoadenitis | LG                                         | Nil                                               |
| 2/47/M/left          | Dacryoadenitis | LG                                         | Nil                                               |
| 3/36/F/bilateral     | Dacryoadenitis | LG, contiguous orbital fat, lateral rectus | Nil                                               |
| 4/71/F/bilateral     | Dacryoadenitis | LG, contiguous orbital fat                 | Submandibular glands, parotid glands, hard palate |
| 5/36/M/left          | Dacryoadenitis | LG                                         | Nil                                               |
| 6/78/F/left          | Myositis       | Levator palpebrae superioris               | Nil                                               |
| 7/56/F/left          | Infiltrative   | Inferior orbit, infraorbital nerve         | Nil                                               |
| 8/46/F/left          | Myositis       | Medial rectus, contiguous orbital fat      | Nil                                               |
| 9/48/F/left          | Dacryoadenitis | LG                                         | Nil                                               |
| 10/49/M/bilateral    | Dacryoadenitis | LG, lateral rectus                         | Submandibular glands, cervical lymph nodes        |

IgG4-ROD, IgG4-related ophthalmic disease; LG, lacrimal gland.

**Table 2** Histopathology and treatment data for cases of IgG4-ROD treated with intraorbital corticosteroids

| Case | IgG4+/<br>HPF | IgG4:IgG<br>(%) | Morphology              | Intraorbital<br>triamcinolone<br>acetone regimen              | Clinical response                         |                                        |                                                                                                            | Follow-up<br>(months) |
|------|---------------|-----------------|-------------------------|---------------------------------------------------------------|-------------------------------------------|----------------------------------------|------------------------------------------------------------------------------------------------------------|-----------------------|
|      |               |                 |                         |                                                               | Magnitude                                 | Onset                                  | Sequelae                                                                                                   |                       |
| 1    | 34            | 40              | Sclerosing              | 20 mg                                                         | Complete                                  | Rapid                                  | Nil                                                                                                        | 12                    |
| 2    | 89            | 91              | Mixed                   | 40 mg                                                         | Complete                                  | Rapid                                  | Nil                                                                                                        | 9                     |
| 3    | 186           | 93              | Lymphoid<br>hyperplasia | 20 mg                                                         | Complete                                  | Rapid                                  | Nil                                                                                                        | 39                    |
| 4    | 270           | 79              | Lymphoid<br>hyperplasia | 20 mg<br>20 mg (week 8)                                       | Partial<br>Complete                       | Rapid<br>Rapid                         | Nil                                                                                                        | 24                    |
| 5    | 16            | 40              | Sclerosing              | 20 mg<br>20 mg (week 4)<br>20 mg (week 8)<br>40 mg (month 22) | Partial<br>Partial<br>Partial<br>Complete | Rapid<br>Gradual<br>Gradual<br>Gradual | Relapse week 4 (injection given)<br>Relapse week 8 (injection given)<br>Relapse month 22 (injection given) | 42                    |
| 6    | 40            | 67              | Sclerosing              | 40 mg                                                         | Partial                                   | Gradual                                | Mild relapse week 16 (observed)                                                                            | 7                     |
| 7    | 34            | 41              | Sclerosing              | 40 mg<br>40 mg (week 4)<br>40 mg (week 8)                     | Complete<br>Partial<br>Complete           | Rapid<br>Gradual<br>Rapid              | Relapse week 3 (injection given)<br>Relapse week 8 (oral prednisolone given)                               | 24                    |
| 8    | 266           | 94              | Lymphoid<br>hyperplasia | 40 mg<br>20 mg (week 6)                                       | Partial<br>Complete                       | Rapid<br>Rapid                         | Relapse week 18 (rituximab given)                                                                          | 64                    |
| 9    | 73            | 48              | Sclerosing              | 20 mg<br>40 mg (week 6)<br>40 mg (week 12)                    | Partial<br>Partial<br>Nil                 | Gradual<br>Gradual<br>N/A              | Relapse week 24 (rituximab given)                                                                          | 66                    |
| 10   | 280           | 93              | Lymphoid<br>hyperplasia | 40 mg                                                         | Partial                                   | Rapid                                  | Relapse week 4 (rituximab given)                                                                           | 124                   |

HPF, high-power field; IgG4-ROD, IgG4-related ophthalmic disease.

follow-up. A total of 56% of relapses occurred within 1 month and 78% occurred within 3 months.

Corticosteroids suppress inflammation by switching off multiple inflammatory genes and upregulating the synthesis of anti-inflammatory proteins.<sup>5</sup> Corticosteroids also cause a transient lymphopaenia affecting T cells more than B cells, which is mediated by both redistribution of peripheral lymphocytes to the bone marrow and by lymphocyte apoptosis.<sup>5</sup> The cell infiltrate in IgG4-ROD predominately comprised plasma cells and T lymphocytes, with T lymphocytes thought to mediate the inflammation and sustain the plasma cell and B-cell populations.<sup>6</sup> The impact of corticosteroids in IgG4-ROD could be explained by direct anti-inflammatory effects on leucocytes and by peripheral T-cell depletion. Corticosteroids may also improve fibrosis in IgG4-ROD by inhibiting fibroblast division and collagen production, and by remodelling scar tissue.<sup>7</sup>

Systemic corticosteroids are considered first-line treatment for IgG4-ROD, yet approximately 70% of cases suffer relapses during or after treatment.<sup>1</sup> Relapses are typically managed with a 6-week to 10-week course of oral prednisolone, and since patients may suffer numerous relapses, many courses may be needed over the disease history. This exposes the patient to a high risk of corticosteroid side effects, including weight gain, hyperglycaemia, hypertension, osteoporosis, peptic ulcers, mood changes, hirsutism and skin changes. In addition, adverse effects and complicated dosing regimens can result in poor medication compliance.

Intraorbital corticosteroid injection has a well-established risk profile and is generally better tolerated than systemic dosing. It is an established treatment option for uveitis, idiopathic orbital inflammation, orbital capillary haemangiomas, orbital lymphoid hyperplasia and orbital xanthogranuloma.<sup>8,9</sup> Most ophthalmologists are comfortable performing the procedure in their consultation rooms and the intervention is quick and repeatable. The most serious complication is retinal artery occlusion caused by inadvertent catheterisation of an orbital artery, retrograde

arterial flow induced by high injection pressure and embolisation of corticosteroid particulates in the central retinal artery.<sup>8</sup> Fortunately this rare complication is generally limited to injections into capillary haemangiomas. It can be avoided by checking for flash back of blood before injecting and using a 27-gauge needle or larger (to reduce injection velocity). Ocular hypertension is a well-described complication that can be avoided by identifying steroid-responders prior to injection and by placing depot preparations near the orbital rim where they are not in direct contact with the globe. Other possible adverse effects include skin necrosis, fat atrophy, scleral melt (now considered exceedingly rare) and cataract.<sup>10</sup>

Although this series is the first of its kind in IgG4-ROD, we acknowledge certain limitations. First, the sample size is small, which impacts the generalisability of our results. Second, cases 1–8 received their first corticosteroid injection during the second postoperative week following orbital biopsy. It is therefore possible that some of the early improvement was attributable to the debulking effect of biopsy and not the corticosteroid injection.

In conclusion, intraorbital corticosteroid injection is a safe, fast acting and relatively effective management option for IgG4-ROD. It may have a role as a first-line therapy in IgG4-ROD of the anterior orbit not associated with extra-ophthalmic lesions that mandate systemic immunosuppression. The majority of patients will require multiple injections due to incomplete clinical response and/or relapse, which is most likely to occur 4–12 weeks after injection. Key benefits over systemic prednisolone include a better safety profile, high perilesional corticosteroid concentration and assured compliance. We recommend reviewing cases at 2 weeks to check intraocular pressure and at 4 weeks to check for recrudescence of inflammation.

**Contributors** All authors contributed to study design, data collection and manuscript preparation.

**Competing interests** None declared.

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