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# Cellular pattern and orbital fat involvement are possible risk factors for the failure of corticosteroids in patients with pure idiopathic orbital inflammation syndrome: lessons from the French prospective *SIOI* cohort study (part II)

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## ABSTRACT

**Purpose** To better characterise the effects of corticosteroids on the course of pure idiopathic orbital inflammation syndrome (pIOIS).

**Methods** This was a national, multicentre, prospective, non-interventional cohort study (*SIOI*). Among the 35 patients with histologically proven orbital inflammation who had previously been studied for their IgG4 immunostaining status, we selected those with a negative IgG4 status (ie, pIOIS) who received corticosteroids as single first-line treatment. Clinical, morphological and pathological findings at diagnosis and during follow-up from treatment initiation to study completion were analysed. Patients were assessed for their response to prednisone after the 24-month prospective phase in terms of remission (≤10 mg/d) or failure (>10 mg/d). Daily standard doses of prednisone (DSDP) were calculated at different time-points and compared between response groups.

**Results** Of the 17 patients with pIOIS included in the final analysis, two-thirds received corticosteroids only. DSDP (mg/kg-day) were significantly higher at the time of failure in eight patients (47%) than in nine (53%) remitting at M24 (0.16 vs 0.045; p: 0.03). Notably, patients with pIOIS with a cellular pattern or orbital fat involvement tended to receive higher daily corticosteroid doses in the event of failure than remission (0.16 vs 0.045 and 0.12 vs 0.042, respectively). During treatment, maximal DSDP was 0.52 in failed patients.

**Conclusion** The highest corticosteroid doses were insufficient to prevent failure in patients with pIOIS, particularly in those with a cellular pattern or orbital fat involvement. Large-scale interventional studies are now necessary to clarify prognostic factors and optimise corticosteroid management in patients with pIOIS.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Corticosteroids are used by consensus as first-line therapy for idiopathic orbital inflammation syndrome (IOIS).

### WHAT THIS STUDY ADDS

⇒ Little information exists regarding the impact of daily corticosteroid intake on the course of IOIS. Our multicentre, prospective, non-interventional cohort study suggests that a first-line corticosteroid therapy of 0.5 mg/kg-day prednisone or equivalent could be insufficient to prevent failure in some patients with pure IOIS (ie, with a negative IgG4 status), especially with a cellular pattern or orbital fat involvement.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings should aid physicians to better manage corticosteroid therapy for patients with pure IOIS.

## INTRODUCTION

Idiopathic orbital inflammation syndrome (IOIS) is defined as an inflammatory orbital process without any identified cause. It is therefore a diagnosis of exclusion, once sarcoidosis, granulomatosis with polyangiitis, thyroid disorders, lymphoma or any local or systemic cause has been ruled out.[1 2] Since 2009, there has been a growing body of evidence that IgG4-related disease (IgG4-RD) to be considered as an alternative diagnosis for IOIS, thus justifying the systematic IgG4

immunostaining of orbital tissue in order to conclude as to pure IOIS.

The clinical spectrum can be broad, and symptoms at presentation include orbital pain, oedema, diplopia and sight loss, depending on the structure infiltrated (lacrimal gland, extraocular muscles, orbital fat, globe or sclera, apex and optic or infraorbital nerve). Histological evidence of non-specific orbital inflammation (NSOI) is recommended before any course of treatment is initiated unless there is a risk that biopsy might cause loss of vision.[1]

The gold standard treatment for IOIS is corticosteroids.[2 3] Most authors report prescribing initial daily corticosteroid therapy of between 0.5 mg/kg and 1 mg/kg and then gradually tapering the dose. Treatment options include disease-modifying antirheumatic drugs (DMARDs), biologics, radiation therapy or surgical debulking in the event of a relapse or recalcitrance.[4–9]

However, before IgG4-RD was described, recurrences were reported in up to 52% of patients with IOIS.[3] Several risk factors for recurrence have been proposed, such as clinical factors, histological subtype and the modalities of the corticosteroid regimen, but these remain controversial.[2]

In 2012, a prospective, multicentre cohort of patients in France with IOIS, namely the *SIOI* cohort, was set up to better decipher the clinical course and outcome of the condition and its possible subentities. The initial results of this study cohort showed that almost two-thirds of patients with biopsy-proven IOIS did not satisfy the criteria for IgG4-ROD and could therefore be considered as having pure IOIS.[10]

The second part of this study cohort aimed to evaluate the response to corticosteroids of patients with pure IOIS and determine the corticosteroid intake in potentially risky groups in terms of corticosteroid relapse or recalcitrance.

## MATERIALS AND METHODS

The *SIOI* cohort (ClinicalTrials.gov number, NCT01443000) is a national, multicentre, observational cohort study. Written informed consent was obtained from all the patients before enrolment.

### Study participants

The patients were included consecutively between March 2012 and July 2015 at 12 University Hospitals throughout France (Avicenne, Quinze-Vingts, Caen, Rennes, Fondation A. de Rothschild, Reims, Nancy, Nantes, Nice, Limoges, Pitie-Salpetriere and Cochin) with expertise in the field of orbital inflammatory diseases. The study included ≥18-year-old patients with orbital inflammation (duration≥3 months) and no identifiable local or systemic cause (including lymphoma) despite an extensive workup. Patients fulfilling the classification criteria for an autoimmune disease (eg, Graves' disease, autoimmune thyroiditis, sarcoidosis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, systemic lupus erythematosus and Sjogren's syndrome) were excluded, as were those with an underlying infectious disease (eg, HIV, *Mycobacterium tuberculosis* or parasitic infections).

Patients were referred to as de novo when IOIS had been diagnosed during the 3 months prior to their inclusion. Beyond that period, they were considered as being *previously diagnosed*.

### Clinical, biological, imaging and pathological data

Clinical, biological and imaging data were retrieved from medical records using a standardised anonymous form, as detailed in the first study.[10]

Data from MRI or CT of the orbit were blindly reviewed in order to specify the anatomic structure(s) involved in the inflammatory process: lacrimal gland, extraocular muscles, orbital fat, globe or sclera, apex and optic and/or infraorbital nerve.

All biopsy specimens obtained at diagnosis were analysed blindly by two unrelated pathologists (AM and NC). As detailed previously,[10] histopathological features, especially fibrosis, were graded from 0 to 3 according to the system used by Andrew *et al*.[11]

In the absence of both features of granuloma and vasculitis, patients with a sclerosis score ≤1 or > 1 were classified as having cellular (cIOIS) or sclerosing (sIOIS) patterns of IOIS, respectively. In line with the 2017 consensus,[1] only patients with cellular or sclerosing patterns of IOIS were considered to have NSOI and were thus included in the current study.

The protocol for IgG4 staining was described in detail in the 2019 study.[10] Tissue specimens containing fewer than 10 IgG4-positive plasma cells per high-power field and with a IgG4+/IgG+ ratio of plasma cells of less than 40% were scored as negative. For the purposes of the current study, patients with a negative score were reclassified as having pure idiopathic orbital inflammation syndrome (pIOIS) and selected, so 66 patients were therefore excluded (figure 1).

### Treatment modalities

In the *SIOI* cohort, data including the type of treatment (treatment with or without corticosteroids and/or non-steroidal anti-inflammatory drugs, DMARDs, biologics, surgery or radiotherapy) and therapeutic protocol were gathered.

### Outcomes with corticosteroids

Only patients receiving corticosteroids were eligible for the current study. Patients were excluded from the analysis when they received immunosuppressant therapy at a critical time which rendered an analysis of the impact of corticosteroids on remission or failure status uninterpretable.

Concerning the primary outcome, patients were assessed for their response to corticosteroids at the end of the 24-month prospective phase (July 2017), taking account of events before inclusion affecting patients

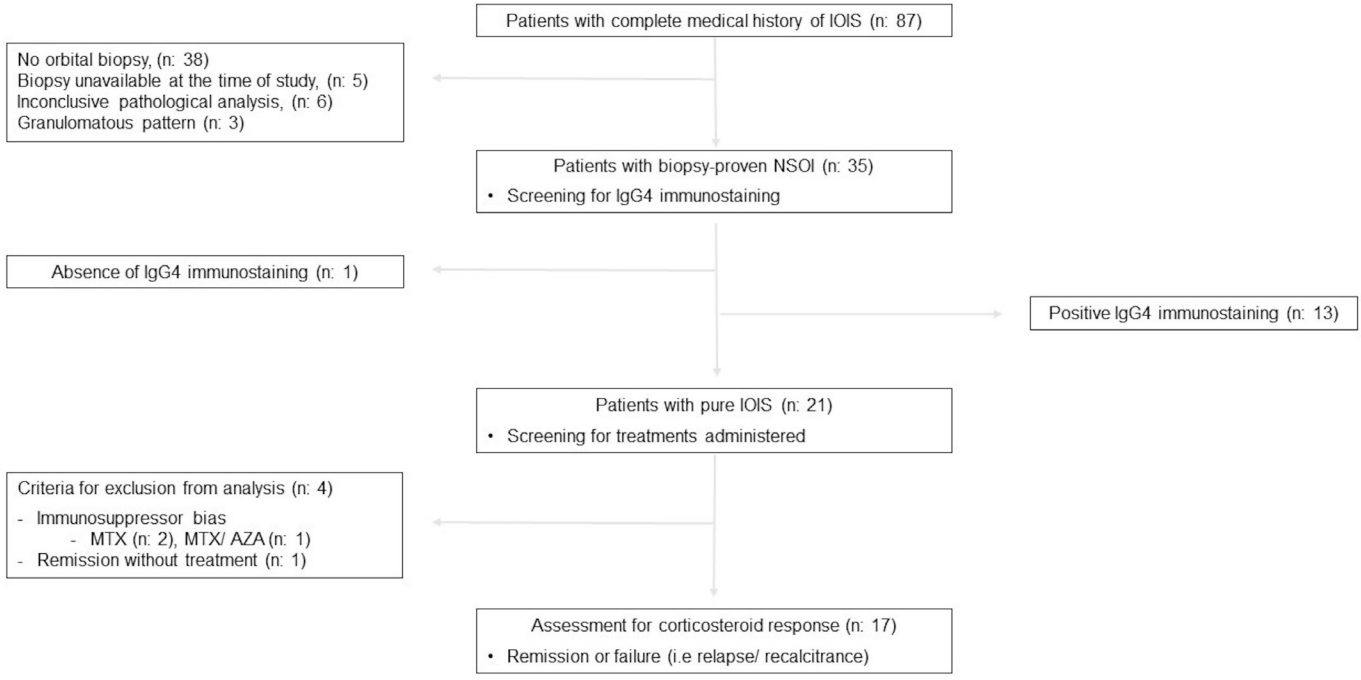


**Figure 1** Flow chart of the study cohort. IOIS, idiopathic orbital inflammation syndrome; NSOI, non-specific orbital inflammation; MTX, methotrexate; AZA, azathioprine.

with *previously diagnosed* pIOIS (figure 2). Given similarities with the management of non-infectious uveitis, the patients were classified in three groups according to their response to corticosteroids,[12] as detailed in:

- Remission when corticosteroids were withdrawn or maintained at a daily dose of prednisone or equivalent of 10 mg or less.
- Relapse when corticosteroids were reintroduced or the dose was increased to more than 10 mg/day.
- Recalcitrance if it was impossible to lower the daily corticosteroid dose to less than 20 mg prednisone or equivalent.

In view of the expected small number of patients with recalcitrant IOIS, these were pooled with relapsing patients in a single group of patients who failed.

Several parameters were calculated as secondary outcomes (figure 2):

- Delay until treatment (DT): number of days elapsing between the first clinical symptoms and the first prednisone administration.
- Duration between first dose and failure (DFDF) or remission (DFDR): number of days elapsing between the first dose of corticosteroids and the time of failure or M24 in remitting patients.

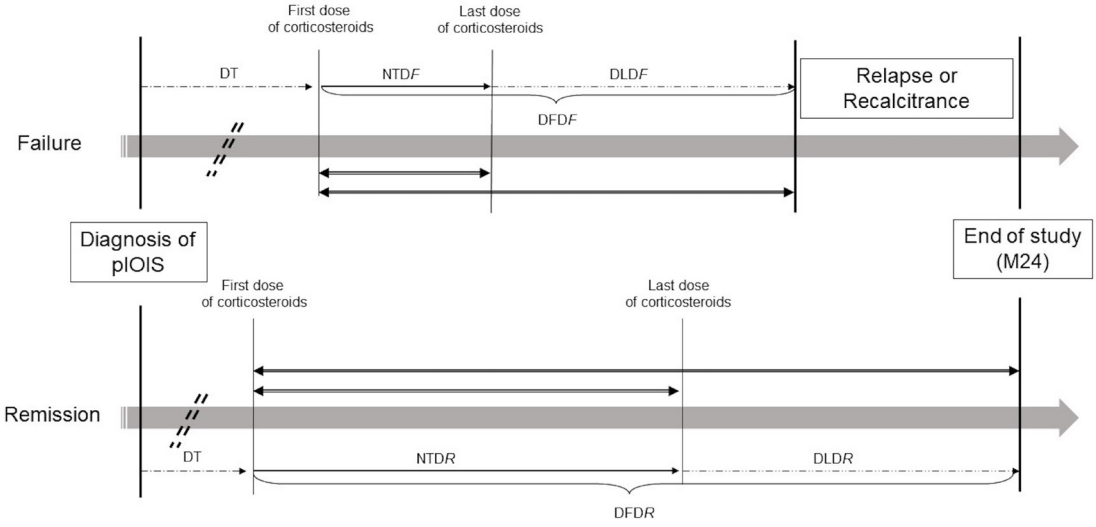


**Figure 2** Timeline of the study highlighting the time points for outcome measures. pIOIS, pure idiopathic orbital inflammation syndrome. ⟷ Daily standard prednisone dose until failure (DFD*F*) or remission (DFD*R*); ⟷ Daily standard prednisone dose during the treatment period in both groups (NTD*F* or NTD*R*).

- Duration between last dose and failure (DLDF) or remission (DLDR): number of days elapsing between treatment discontinuation and the time of failure or M24 in remitting patients.
- Number of treatment days until a failure (NTDF) or remission (NTDR): number of days of prednisone administration before failure or M24 in remitting patients.
- Body weight was recorded for each patient in order to calculate the individual standard prednisone dose (mg/kg).
- Daily standard dose of prednisone (DSDP) within DFDF or DFDR: standard-cumulative dose divided by DFDF or DFDR (mg/kg-day).
- DSDP within NTDF or NTDR: standard cumulative dose divided by NTDF or NTDR (mg/kg-day).

### Statistical analysis

Patient characteristics are reported as numbers and percentages for categorical variables and as medians (Q1–Q3, min–max) for continuous variables.

To determine prognostic factors, categorical variables were compared under univariate analysis using the $\chi^2$ test or Fisher's exact test, and continuous variables were compared using the Mann-Whitney-Wilcoxon test, as appropriate.

To assess the importance of corticosteroids to outcomes, we compared DSDP values over different time courses between the remitting and failed groups of patients with pIOIS.

All statistical analyses were performed using SAS software package V.9.4 (SAS Institute). P values lower than 0.05 were considered to denote significant differences.

## RESULTS

Of the 87 patients included in the *SIOI* cohort, 35 (40%) were suffering from biopsy-proven IOIS. Of these, 21 (60%) were reclassified as pure IOIS, although 4 of them were ultimately excluded: 1 did not receive any corticosteroids during follow-up, while immunosuppressive drugs administered at the initiation of corticosteroids could have biased the outcome in the 3 remaining patients. Seventeen patients (81%) with pIOIS were thus included in the final analysis. In all these cases, the administration of corticosteroids could be fully recorded during follow-up, thus making them suitable for outcome analysis (figure 1).

### Sample characteristics

The epidemiological, histopathological, ophthalmological and systemic characteristics of patients with pIOIS had been fully analysed in the previously published study cohort.[10]

### Treatment modalities and outcomes

As expected, all 17 included patients received corticosteroid therapy. Seven (41%) of them, referred as de novo, had been treatment free prior to inclusion. Corticosteroids were administered as a single therapy in two-thirds of the patients (table 1).

Nine patients (53%) with pIOIS achieved a remission at the end of the prospective phase. Remission was only confirmed in patients who had only received corticosteroids, except for one who was also administered hydroxychloroquine, considered as a non-DMARD. Of the eight patients who failed, only one was recalcitrant. Among the latter, only three (37.5%) had not received any additional treatments such as DMARDs, biologics, surgery or radiotherapy by the end of the prospective phase (table 1).

### Factors associated with a poor prognosis

DSDP values were significantly higher in patients at the time of failure (DLDF) than when achieving remission at M24 (DLDR) (0.16 vs 0.045 mg/kg-day, p: 0.03). In case of failure, patients received during treatment a maximal daily standard dose of 0.52 mg/kg-day prednisone or equivalent. DLDF values were significantly lower than DLDR (85 vs 545 days, p: 0.003) while patients did not differ in terms of other time courses (table 1).

A subgroup analysis of DSDP in patients previously thought to be at risk of a poor prognosis was then performed. Regarding the patients with cellular pattern or orbital fat involvement, their DSDP until failure (DFDF) tended to be higher than the values until remission at M24 (DFDR) (0.16 vs 0.045 mg/kg-day, p: 0.07 and 0.125 vs 0.042 mg/kg-day, p: 0.08, respectively) (table 2). The highest DSDP during the treatment period was 0.52 mg/kg-day in failed patients from both subgroups (data not shown).

## DISCUSSION

Since the first report by Mombaerts *et al* regarding the impact of corticosteroids on the course of IOIS, other authors have found that recurrence ranged widely from 37% to 52% of patients in the setting of retrospective studies, thus raising the issue of numerous biases related to their design.[2 3 13 14]

Here, in this non-interventional multicentre cohort study, we were able to show strikingly that almost half of patients with pure IOIS failed under higher prednisone doses than those who achieved remission.

Even though there has been consensus regarding corticosteroids as first-line therapy, there is a lack of guidelines on administration modalities (ie, initial dosing, tapering schedule) and how to assess their effects.[1] Contrary to previously published studies, we here measured outcomes on the basis of standardised criteria. As proposed in the setting of chronic uveitis trials, we chose to use prednisone thresholds to define relapse or resistance in patients who received prednisone as first-line treatment.[12 15] This was made possible thanks to complete records on the corticosteroids administered during follow-up in all patients, including those previously diagnosed with pIOIS.

An additional bias has arisen because of growing evidence regarding the histological characteristics of

**Table 1** Prognostic factors in patients with pIOIS

| | Remission n : 9 | Failure n : 8 | Total n : 17 | P value |
|---|---|---|---|---|
| Epidemiological characteristics | | | | |
| Mean age years (SD, 95% CI) | | | | |
| At onset | 50.2 (11.6; 45 to 56) | 50.75 (14.7; 41.5 to 62) | 50.45 (12.7; 44 to 57) | 0.73 |
| At diagnosis | 51.4 (9.9; 45 to 56) | 51.5 (15.1; 42.5 to 63) | 51.45 (12.2; 45 to 58) | 0.8 |
| Sex ratio (M/F) | 5/4 | 2/6 | 7/10 | 0.33* |
| Origin, # (/n%) | | | | 1* |
| European | 6 (66) | 5 (62.5) | 11 (64.5) | |
| Others | 3 (33) | 3 (37.5) | 6 (35.5) | |
| Histological forms, # (/n%) | | | | 0.33* |
| Cellular type (fibrosis score 0–1) | 7 (78) | 4 (50) | 11(65) | |
| Sclerosing type (fibrosis score 2–3) | 2 (22 | 4 (50) | 6 (35) | |
| Orbital site involvement, # (/n%) | | | | |
| Lacrimal gland | 6 (67) | 3 (37.5) | 9 (53) | 0.34* |
| Extraocular muscles | 1 (11) | 3 (37.5) | 4 (23.5) | 0.29* |
| Globe/sclera | 2 (22) | 2 (25) | 4 (23.5) | 1 |
| Orbital fat | 6 (67) | 6 (75) | 12 (70.5) | 1 |
| Apex | 2 (22) | 2 (25) | 4 (23.5) | 1 |
| Optic nerve | 2 (22) | 1 (12.5) | 3 (17.5) | 1 |
| Infraorbital nerve† | 1 (11) | 0 (0) | 1 (6) | 1 |
| Bilateral presentation | 3 (33) | 4 (23.5) | 7 (41) | 0.57* |
| Ophthalmological manifestations, # (/n%) | | | | |
| Orbital pain | 5 (55.5) | 4 (50) | 9 (53) | 1* |
| Palpebral swelling | 5 (55.5) | 6 (75) | 11 (64.5) | 0.61* |
| Lacrimal gland hypertrophy | 2 (22) | 2 (25) | 4 (23.5) | 1* |
| Proptosis | 6 (67) | 6 (75) | 12 (70.5) | 1* |
| Diplopia | 3 (33) | 5 (62.5) | 8 (47) | 0.34* |
| Systemic manifestations, # (/n%) | | | | 0.57* |
| None | 6 (66.6) | 7 (87.5) | 13 (76.5) | |
| Yes | 3 (33) | 1 (12.5) | 4 (23.5) | |
| Sinusitis or, | 1 | 1 | 2 | |
| Serum IgG4 at inclusion ≥1.35 g/L or, | 1 | 0 | 1 | |
| ANCA at diagnosis (MPO positivity) | 1 | 0 | 1 | |
| Medical background, # (/n%) | | | | 0.33* |
| De novo | 5 (55.5) | 2 (25) | 7 (41) | |
| Previously diagnosed | 4 (44.5) | 6 (75) | 10 (59) | |
| Therapeutic protocol, # (/n%) | | | | 0.29* |
| Prednisone or methylprednisolone alone | 8 (89) | 3 (37.5) | 11 (64.5) | |
| Prednisone+other treatment(s) | 1 (11) | 5 (62.5) | 6 (35) | |
| + Hydroxychloroquine | 1 | 0 | 1 | |
| + Methotrexate | 0 | 2 | 2 | |
| + Methotrexate/radiotherapy | 0 | 1 | 1 | |
| + Methotrexate/debulking | 0 | 1 | 1 | |
| + Excisional biopsy | 0 | 1 | 1 | |
| Follow-up and corticosteroid intakes | | | | |
| Median (Q1–Q3, min–max) | | | | |

Continued

**Table 1** Continued

| | Remission n : 9 | Failure n : 8 | Total n : 17 | P value |
|---|---|---|---|---|
| Delay until treatment, days | 184 (103–450, 3–2347) | 187 (35–798, 0–1918) | 184 (41–450, 0–2347) | 0.73 |
| Duration between last dose and primary outcome (DLDR or DLDF), days | 545 (449–647, 343–1392) | 85 (54–362, 1–464) | 448 (98–545, 1–1392) | 0.003 |
| Duration between first dose and primary outcome (DFDR or DFDF)†, days | 799 (743–954, 729–1455) | 499 (293–891, 115–1164) | 773 (598–942, 115–1455) | 0.11 |
| Number of treatment days to achieving primary outcome (NTDR or NTDF)†, days | 214 (104–351, 55–544) | 403 (227–542, 78–793) | 295 (126–478, 55–793) | 0.13 |
| DSDP within DFDR or DFDF†, mg/kg-day | 0.045 (0.03–0.09, 0.02–0.17) | 0.16 (0.1–0.25, 0.02–0.52) | 0.09 (0.035–0.17, 0.02–0.52) | 0.03 |
| DSDP within NTDR or NTDF†, mg/kg-day | 0.345 (0.145–0.39, 0.08–0.51) | 0.235 (0.145–0.35, 0.04–0.52) | 0.27 (0.145–0.38, 0.04–0.52) | 0.66 |

Duration between First Dose and Remission (DFDR) or Failure (DFDF): number of days elapsing between the first dose of corticosteroids and M24 in remitting patients or the time of failure.
Number of Treatment Days until Remission (NTDR) or a Failure (NTDF): number of days of prednisone administration before M24 in remitting patients or failure.
*P values are based on the $\chi^2$ test or Fisher's exact test, as appropriate. P values below 0.05 were considered to denote *significant differences*.
†See figure 2.
DSDP, daily standard dose of prednisone; pIOIS, pure idiopathic orbital inflammation syndrome.

IgG4-RD in patients with IOIS. Indeed, retrospective reviews of the biopsy specimens of non-granulomatous IOIS, accompanied by IgG4 immunostaining, revealed that 27%–52% of cases could be classified as IgG4-ROD.[10 11 16–18] Given the absence of IgG4 immunostaining in earlier studies assessing the effects of corticosteroids in patients with IOIS, one of our aims was to assess it in light of the findings of IgG4 immunostaining that was performed retrospectively in the setting of the first part of the *SIOI* cohort study.[10]

That prospective multicentre cohort study analysed a large population of patients classified as having pure IOIS on the basis of negative IgG4 immunostaining. Remarkably, 47% of these patients failed under a maximal DSDP of 0.52 mg/kg-day. Compared with them, daily corticosteroid intakes during treatment were similar in patients whose remission status was strongly supported by longer follow-up from last dose to primary outcome (DLDR of 585 vs DFDF of 85 days, p: 0.003). However, the treatment durations were not significant (p: 0.13),

**Table 2** Daily standard dose of prednisone until failure or remission among patients with pure IOIS

| DSDP within DFDR or DFDF mg/kg-d; median (Q1–Q3, min–max)* | Remission n : 9 | Failure n : 8 | Total n : 17 | P value† |
|---|---|---|---|---|
| Histological characteristics | | | | |
| Cellular form (fibrosis 0–1) | 0.045 (0.022–0.11, 0.02–0.17) (n : 7) | 0.16 (0.11–0.35, 0.09–0.52) (n : 4) | 0.09 (0.035–0.16, 0.02–0.52) (n : 11) | 0.07 |
| Sclerosing form (fibrosis 2–3) | 0.04 (0.032–0.05, 0.03–0.05) (n : 2) | 0.16 (0.06–0.25, 0.02–0.29) (n : 4) | 0.081 (0.032–0.2, 0.02–0.29) (n : 6) | 0.48 |
| Anatomical involvement | | | | |
| Lacrimal gland involvement | 0.047 (0.032–0.11, 0.02–0.17) (n : 6) | 0.088 (0.019–0.52, 0.02–0.52) (n : 3) | 0.049 (0.032–0.11, 0.02–0.52) (n : 9) | 0.69 |
| Ocular muscle involvement | 0.049 (n : 1) | 0.11 (0.019–0.18, 0.02–0.18) (n : 3) | 0.081 (0.034–0.15, 0.02–0.27) (n : 4) | 1 |
| Orbital fat involvement | 0.042 (0.032–0.09, 0.02–0.11) (n : 6) | 0.12 (0.088–0.29, 0.02–0.52) (n : 6) | 0.09 (0.0.34–0.12, 0.02–0.52) (n : 12) | 0.08 |

Focus on presumed features associated with failure.
*Daily standard dose of prednisone (DSDP) within period between First Dose and Remission (DFDR) or Failure (DFDF): standard-cumulative dose divided by DFDF or DFDR (mg/kg-d).
†P values below 0.05 were considered to denote *significant differences*.
IOIS, idiopathic orbital inflammation syndrome.

but numerically shorter in remitting patients (NTDR of 214 days) compared with those who failed (NTDF of 403 days). Unlike a recent study that was designed to analyse IgG4-negative patients only, the number of days between onset and the initiation of corticosteroid therapy (DT) in our study was similar in remitting and failed patients, thus supporting the theory of pejorative prognostic factors other than a delay in starting corticosteroids.[19]

In line with the study mentioned above, we suggested that intraconal diffuse lesions could negatively impact the response to corticosteroids.[19] Despite receiving the highest doses of prednisone (0.52 mg/kg-day at maximum), patients with pIOIS failed when they had orbital fat involvement.

A similar observation was made when patients with IOIS tended to have predominantly lymphocytic and/or plasmacytic infiltration of the orbit rather than extensive fibrosis in orbital tissue, suggesting that IOIS with a cellular pattern could be an additional prognostic factor for a poor corticosteroid response. This was in line with the large study by Swamy where patients with classical orbital pseudotumour (ie, the cellular form) relapsed more than those with a sclerosing form (0.29 vs 0.15 person year of follow-up).[14]

A recent systematic review of the literature,[2] based on the analysis of data prior to individual IgG4-RD determinations, listed other risk factors for a recurrence of IOIS, involving a diffuse and myositis subtype,[20 21] multiple involved extraocular muscles,[22] enlarged infraorbital nerve,[23] contralateral recurrence and migratory relapse.[24] A younger age, bilateral presentation, optic disc oedema and a sclerosing variant could be risk factors for multiple recurrences.[25] However, and contrary to our cohort, the patients included were highly heterogeneous in the absence of knowing their IgG4 status, thus hampering the identification of clear prognostic factors for pure IOIS.

Our work had some limitations. As stated in part 1 of the cohort study,[10] the lack of guidelines regarding the performance of tissue biopsies might have led to the selection of patients to be treated. Next, although the medical history of patients did not significantly impact the primary outcomes of this underpowered study, failures were numerically more frequent in previously diagnosed patients compared with de novo patients, possibly leading to an overestimated prevalence of relapsing or recalcitrant pIOIS. Last, the corticosteroid regimens were not standardised, which made it impossible to determine the effects of dosage tapering on primary outcomes.

In conclusion, our findings suggest that outcomes under corticosteroid therapy are not exclusively dependent on either their doses or the duration of treatment, or even a delay in initiation, but on a cellular subtype infiltrate or orbital fat involvement in patients with pure IOIS. These findings are of special interest to determining optimal treatment for patients with pIOIS. Indeed, it could be reasonably hypothesised that patients with these pejorative prognostic factors might benefit from treatment other than a first-line corticosteroid therapy of 0.5 mg/kg-day prednisone or equivalent. This point therefore raises the question of induction treatment using higher corticosteroid doses and/or involving frontline immunosuppressive drugs. According to international guidelines for the management of both large-vessel or ANCA-associated vasculitides,[26 27] a DSDP of 0.5 mg/kg-day during the treatment period is considered as a moderate dose of systemic corticosteroids.

As successfully used after intravenous pulse methylprednisolone in such vasculitis,[26 27] a high-dose oral prednisone of 1 mg/kg-day and/or immunosuppressants might be assessed to induce remission in patients with pIOIS with pejorative risk factors.

Based on these preliminary findings, larger and standardised studies now need to be considered in order to optimise the doses and durations of systemic corticosteroids in patients with pIOIS.

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