Efficacy and glucocorticoid sparing of dupilumab in IgG4-related disease: a case series and literature review

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Abstract

Objective

IgG4-related disease (IgG4-RD) is a multisystem fibro-inflammatory disorder for which glucocorticoids (GC) represent the initial therapeutic intervention. Second-line treatments are not currently codified. The use of dupilumab, an inhibitor of interleukin (IL)-4 and IL-13 signalling, has recently been described as a potential alternative treatment. The aim of this study was to describe the characteristics of patients IgG4-RD treated with dupilumab and to evaluate its impact on disease control.

Methods

We conducted a French multicentre retrospective study based on standardised questionnaires distributed to physicians via professional networks. The patients included had to meet 2019 ACR/EULAR criteria or the comprehensive diagnostic criteria for IgG4-RD, and to have been treated with dupilumab. Efficacy was assessed using the IgG4-Related Disease Responder Index.

Results

A total of seven patients were included in the study. The rationale for initiating dupilumab was based on the presence of severe asthma, nasosinusal polyps and/or atopic dermatitis. A complete response was observed in three patients, while four patients displayed a partial response. In all cases, GC sparing was achieved. A review of the literature revealed nine out of the ten cases reported where a partial or complete reduction of the disorder was documented, along with GC sparing.

Conclusion

These preliminary findings need to be confirmed, but may offer arguments in favour of a possible efficacy of dupilumab in the treatment of IgG4-RD.

Key words

dupilumab, IgG4-related disease, biological therapy

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Introduction

IgG4-related disease (IgG4-RD) is a rare fibro-inflammatory disorder that has the potential to affect almost any organ. Involvement of the pancreas was initially documented by Sarles *et al*. in 1961 (1). Subsequently, the same histological characteristics, including lymphoplasmacytic infiltration containing IgG4-positive plasma cells and storiform fibrosis, along with elevated serum IgG4 levels, were observed in various other organs, including the lungs, lymph nodes, salivary glands, lacrimal glands, liver, bile ducts and gallbladder, as well as the gastrointestinal system and retroperitoneum. In 2003, IgG4-RD was formally recognised as a distinct pathological entity (2). Phenotypes have been described in accordance with the organs involved or the fibrous or inflammatory nature of the damage (3-7). From a pathophysiological perspective, follicular helper T (Tfh) cells and T helper 2 (Th2) cells play a role in the development of IgG4-RD (8-9).

Glucocorticoids (GC) are the recommended first-line therapy for IgG4-RD, and failure to respond to GC is an exclusion criterion in the ACR/EULAR classification criteria (10). Nevertheless, a relapse following the discontinuation of GC therapy is common, affecting approximately 40% of patients (11). Furthermore, the potential for adverse effects, such as the development of diabetes in patients with pre-existing pancreatic involvement in IgG4-RD, has been well documented with GC therapy. Alternatives to GC include immunosuppressive agents (methotrexate, mycophenolate mofetil, azathioprine) and rituximab, which can be used in conjunction with GC (4-5). However, immunosuppressive agents and rituximab are highly immunosuppressive and associated with a range of side effects. Dupilumab, an inhibitor of interleukin (IL)-4 and IL-13 signalling, has been indicated for the treatment of Th2 inflammatory diseases, including severe allergic asthma, atopic dermatitis, chronic rhinosinusitis with nasal polyposis and eosinophilic oesophagitis. In IgG4-RD, 18% to 76% of patients present with allergic manifestations (13), and asthma and nasal polyposis are frequently observed. Dupilumab may therefore represent an original and well-tolerated approach for pulmonary and ENT localisations of IgG4-RD.

The objective of this study was to describe the characteristics of patients IgG4-RD treated with dupilumab and to evaluate its impact on disease control.

Methods

Patients

A nationwide, multicentre, retrospective study was conducted on IgG4-RD patients treated with dupilumab. The study required the administration of a standardised questionnaire to physicians via professional pulmonologists and internal medicine research networks, including the French Vasculitis Study Group, the French National Society of Internal Medicine, the National Network of Clinical Research in Severe Asthma, and the French National Reference Center for IgG4-RD. Patients were included in the study if they met the criteria for IgG4-RD according to the 2019 ACR/EULAR criteria (10) or the comprehensive diagnostic criteria (CDC) (14) and if data were available.

Clinical and laboratory assessments

Patient characteristics were collected using a standardised form. The physicians participating in the study provided the following information: demographics, medical history, systemic disease characteristics and treatments, date of first symptoms, date of IgG4-RD diagnosis, clinical presentation at diagnosis, and biological, imaging, and histological data. Biological data included levels of IgG4 and eosinophils. Furthermore, the use of GC and immunosuppressive treatments, including their dosage and the chronology of different treatment lines, were recorded. The date of initiating dupilumab treatment, the scheme and dosage of dupilumab, the organs affected at the outset of dupilumab therapy, and the rationale for using dupilumab were all documented. Finally, the IgG4-RD responder index (15) at baseline and at the final follow-up visit, the duration of follow-up, and the outcomes (partial or complete) at final follow-up were also documented. A complete response to dupilumab was defined as an IgG4-

Table I. Characteristics of the seven patients affected with IgG4-RD and treated with dupilumab.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Sex (Female, Male)	F	M	M	M	M	M	F
Year of first symptoms	2005	2007	2013	2019	2021	2021	2023
Age at first symptoms	26	57	57	48	56	54	61
Age at diagnosis	33	65	62	48	56	54	61
Organs involved	Eyelid, lacrimal glands, orbits, sinus	Eyelid, lacrimal glands, orbits, sinus	Salivary glands, lymph nodes, duodenum, sinus	Lymph nodes, lung	Salivary glands, kidney, lung	Eyelid, lymph nodes	Salivary glands, aorta, pericardium
ACR/EULAR criteria (points for inclusion) or CDC	ACR/EULAR (30)	ACR/EULAR (33)	ACR/EULAR (47)	ACR/EULAR (26)	ACR/EULAR (31)	CDC	ACR/EULAR (21)
IgG4 rate at diagnosis (g/l)	9.2	2.9	5.27	8.97	5.3	11.1	3.15
Eosinophils at diagnosis (G/l)	0.64	0.6	0.3	1.14	0.2	0.36	2.3
History of treatment before Dupilumab	GC, Methotrexate, Rituximab, Azathioprine	GC, Methotrexate	GC, Mycophenolate mofetil, Rituximab, Belimumab	GC, Rituximab, Methotrexate	GC	None	GC
GC dosage at the introduction of Dupilumab (equivalent prednisone, mg/d)	5	0	15	7.5	60	0	5
IgG4-RD responder index at the introduction of Dupilumab	2	9	14	6	12	4	0
Organs involved at the introduction of Dupilumab	Lacrimal glands, sinus	Lung, orbits, lacrymal glands, prostate, skin	Lung, sinus	Orbits, sinus, lung	Lacrimal glands, parotid glands, sinus, lung	Sinus, lymph nodes	None (diffuse pain, asthenia, rise of IgG4 level)
Date of introduction of Dupilumab	February 2022	April 2022	November 2022	January 2022	June 2022	June 2022	March 2024
Follow-up with Dupilumab (months)	21	20	12	7	22	22	4
IgG4-RD responder index at last news	1	0	5	0	3	3	0
GC dose at last news (equivalent prednisone, mg)	0	0	0	5	10	0	5
Organs not responding to Dupilumab	Lacrimal glands		sinus		Lacrimal glands, parotid glands, sinus, lung	Lymph nodes	
Response (organ involvement)	partial	complete	partial	complete	partial	partial	complete

RD responder index of 0 at the final follow-up, while a partial response was defined as a decrease in the IgG4-RD responder index at the final follow-up. Tolerance data pertaining to dupilumab treatment were also collated.

Literature review

A literature search was also conducted using the PubMed search engine with the following combination of Medical Subject Headings (MeSH) terms: 'lgG4-RD' AND 'dupilumab'. Only articles published in English and French were included in this review. The relevance of the articles was discussed and their inclusion in the review was verified.

Statistical analysis

Continuous variables were expressed as medians (interquartile range [IQR]), while categorical variables were expressed as numbers (percentages).

Ethics

This study was conducted in accordance with the principles of Good Clinical Practice and the tenets of the Declaration of Helsinki. The study was approved by the Ethics Committee for Avicenne Hospital (CLEA IRB no. 2024-424). In accordance with French legislation, written informed consent was not required for this retrospective study.

Results

A total of seven patients (two women and five men) were included in the study according to our inclusion criteria. No patient was excluded from the study.

Patient characteristics

The median age at diagnosis was 56 years (IQR 51–61.5). The median disease follow-up period was 40 months (IQR 31.5–160), while the median follow-up period with dupilumab was 20 months (IQR 9.5-21.5). Six patients exhibited asthma, with five also presenting with Chronic RhinoSinusitis with nasal polyps (CRSwNP). One patient displayed CRSwNP and atopic dermatitis. Cases 1 and 2 were also classified as adult-onset asthma and periocular xanthogranuloma syndrome (AAPOXs). Only one case had no ENT involvement (case 4). The median eosinophil count was 0.64 G/l (IQR 0.48–1.03). Organs affected at the time of diagnosis were the sinuses (n=3), salivary glands (n=3), eyelids (n=3), orbits (n=2), lymph nodes (n=3), lungs (n=2), duodenum (n=1), kidneys (n=1), aorta (n=1) and pericardium (n=1). Six patients underwent a biopsy (Table I).

Treatments for IgG4-RD

Six patients were receiving GC therapy at the time of diagnosis, and in four cases, this was combined with at least one

other treatment for IgG4-RD. Rituximab or methotrexate were employed in three patients, while mycophenolate mofetil, azathioprine or belimumab were utilised in one patient.

The dosage regimen for dupilumab was consistently 300 mg every two weeks. The indication for dupilumab was asthma in three patients, CRSwNP in two patients, CRSwNP and atopic dermatitis in one patient, and asthma and CRSwNP in one patient.

Complete responses were observed in three patients and partial responses in four patients. No worsening of symptoms was observed in patients receiving dupilumab.

The median dose of prednisone prior to the initiation of dupilumab was 5 mg/day (IQR 2.5–11.25), with a subsequent reduction to 0 mg (IQR 0–5) following dupilumab. In five cases, GC therapy was reduced. One patient's GC dosage was not reduced, but the follow-up period with dupilumab was relatively brief (only four months) and the GC dose was low (5 mg prednisone/day). One patient (case 3) was concurrently receiving another medication (mycophenolate mofetil) in addition to dupilumab following the discontinuation of GC therapy. One patient had not received GC prior to dupilumab. The lacrimal glands, sinuses, lungs, parotid glands and lymph nodes were the organs that did not respond to treatment. Dupilumab therapy was consistently well tolerated, with no patients discontinuing its use and only one reporting eosinophilia during treatment.

Literature review

A total of 11 articles were reviewed and 10 cases were described (six cases by different teams and four by one team) (11, 15-20), and included five men and five women. Their median age was 56.5 years (IQR 51.5–65.5). Asthma was present in 80% of patients, with the most commonly involved organs being the salivary glands (n=7), lacrimal glands (n=6) and paranasal sinuses (n=5). Four patients had received no GC treatment prior to the initiation of dupilumab. Two patients received 300 mg dupilumab every four weeks, while the others were administered 300 mg every two weeks, with or without an initial dose of 600 mg. A review of the literature revealed that 90% of patients experienced a reduction in organ damage, whether partial or complete. Furthermore, GC sparing was documented as being achieved in nine cases.

Table II. Characteristics of current cases compared to those in the literature.

	Present series (n=7)	Literature (n=10)	All (n=17)
Clinical characteristics			
Male gender	5	5	10
Age, years at diagnosis	56 [51-61]	56.5 [51.5-65.5]	56 [51-61]
Comorbidities			
Asthma	6	8	14
Eosinophilic sinusitis	0	3	3
Nasosinusal polyposis	6	6	12
Atopic dermatitis	1	2	3
Organs involved at diagnosis			
Skin	0	1	1
Salivary glands	3	7	10
Lacrimal glands	2	6	8
Sinuses	1	5	6
Retroperitoneal	0	1	1
Lung	1	2	3
Kidney	1	0	1
Aorta	1	0	1
Lymph node	3	3	6
ACR/EULAR criteria	6	5	11
Previous therapy			
GC	6	6	12
Rituximab	3	2	5
Azathioprine	1	1	3
Mycophenolate mofetil	1	0	1
Methotrexate	3	0	3
no. of treatment lines before Dupilumab ≤1	3	6	9
no. of treatment lines before Dupilumab >1	4	4	8
Dose of Dupilumab			
At least 300 mg every 2 weeks	7	8	15
Less than 300 mg every 2 weeks	0	2	2
Organs involved not responding to dupilumab (n/n at treatment initiation)			
Sinus	2/4	1/5	3/9
Salivary glands	1/1	2/7	3/8
Lymph nodes	1/1	1/3	2/4
Lacrimal glands	2/3	0/6	2/9
Outcome			
Effective on organs involved (partial or complete)	7	9	16
Effective on GC sparing	7	9	16

Discussion

The present study reports seven new cases of IgG4-RD treated with dupilumab, in addition to the other cases published in the literature.

The recommended course of treatment is initially based on GC therapy, followed by the introduction of immunosuppressive agents. However, given the risk of relapse or adverse effects associated with GC or immunosuppressant drugs, there is a need for new therapeutic approaches involving a lower risk of such effects. In France, dupilumab is covered by health insurance for the treatment of severe Th2 asthma, nasal polyposis, atopic dermatitis and prurigo nodularis. These circumstances present a potential opportunity to treat IgG4-RD patients, who also have a reimbursable indication for dupilumab; treatment with dupilumab was initiated in our patients for one of the aforementioned indications. Furthermore, the clinical presentations of our cases displayed notable similarities. All cases presented with asthma and/or ENT involvement.

In this preliminary series of cases, we demonstrated that a partial or complete response was achieved in all patients.

In uncontrolled patients, GC therapy was either reduced or discontinued after dupilumab in five cases; in another case, GC therapy was maintained at a dose of 5 mg/day, and in the remaining case GC therapy was not initiated. Patients did not require the addition of any further treatment, other than what they had already been receiving at the initiation of dupilumab.

A comparison of our series with the existing literature revealed a high prevalence of asthma (82%) and head and neck involvement. With regards to treatment, our patients had undergone a larger number of therapeutic interventions prior to dupilumab than those previously reported in the literature. Only one patient in our study cohort did not receive GC, whereas it had been administered in 40% of patients in the literature. Efficacy in terms of organ involvement (partial or complete) and GC sparing was comparable between our series and the literature, with 94% of all patients attaining this outcome.

This large efficacy of dupilumab in a population with a high prevalence of asthma and ENT involvement suggests that dupilumab could be effective in the particular 'head and neck limited' phenotype of IgG4-RD.

Dupilumab is an antibody that specifically targets the alpha chain of the IL-4 receptor. This results in the blocking of IL-4 and IL-13 signalling. The pathophysiology of IgG4-RD is not yet fully understood, so it is challenging to elucidate the role of dupilumab in this condition. IL-4 is a pivotal cytokine in IgG4 class switching, which is orchestrated by T follicular helper cells (Tfh). Following dupilumab treatment, a reduction has been shown in both IgG4 levels and the number of Tfh cells in IgG4-RD patients (12, 16). However, the pathogenicity of IgG4 in IgG4-RD remains unknown. IL-13 is a fibrotic cytokine (22-23), and there is a continuum of pro-inflammatory and fibrotic manifestations in IgG4-RD, but it remains unclear whether IL-13 plays a specific role in IgG4-RD.

The ACR/EULAR criteria were verified in six patients and the CDC in one patient. Further, two patients exhibited AAPOXs with Touton cells and granulomatous inflammation, as evidenced by an ocular adnexal biopsy in case 1 and periorbital biopsy in case 2. The presence of granulomatous inflammation served to exclude a diagnosis of IgG4-RD (3). However, additional biopsies were performed in both patients (salivary gland in case 1, prostate in case 2) and the findings met the histological criteria for IgG4-RD. In 2017, Gallo and colleagues presented a case of AAPOX devoid of any hallmarks of IgG4-RD, and ultimately concluded that AAPOXs and IgG-RD are distinct entities (24). Nevertheless, our own observations, as well as those of other researchers, have documented instances of AAPOXs occurring in conjunction with IgG4-RD (25-27). The underlying pathophysiology of both conditions remains unclear, thus making it difficult to ascertain the relationship between them.

Our study had several limitations. The study was retrospective and observational, and lacked a control group, so the data on treatment efficacy should be interpreted with caution. There may also have been a reporting bias among patients who received dupilumab but did not improve their disease. Although dupilumab is safer than GC in the long term for patients with asthma or atopic dermatitis, its side effects were not systematically documented. Furthermore, some data were absent from the analysis, and the impact of dupilumab on IgG4 and Thf cell assays was not examined. As the known indications for dupilumab overlap with the "head and neck limited" phenotype of IgG4-RD, it is not possible to conclude whether dupilumab could be tested in patients with other IgG4-RD phenotypes. Nevertheless, four patients displayed a reduction or complete resolution of lung involvement, while one patient demonstrated the complete disappearance of skin and prostate involvement.

Conclusion

The present case series, which included our own and previously published cases of IgG4-RD treated with dupilumab, suggests that dupilumab is an efficacious and GC-sparing treatment for IgG4-RD. Nevertheless, a greater pathophysiological understanding of its activity, and a prospective study with a control group, are necessary to properly assess the role of dupilumab in IgG4-RD.

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