

Effectiveness of tofacitinib monotherapy for patients with IgG4-RD or idiopathic retroperitoneal fibrosis

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Abstract

Objective

To explore the effectiveness of tofacitinib for immunoglobulin G4-related disease (IgG4-RD) and idiopathic retroperitoneal fibrosis (IRF), and investigate the expression of JAKs in the lesion of these diseases.

Methods

Clinical data of patients with IgG4-RD or IRF who were administered with tofacitinib monotherapy were collected. IgG4-RD responder index (IgG4-RD RI) was assessed. The expression of JAK1, JAK2, JAK3, and TYK2 were analysed with immunohistochemistry staining in three salivary glands specimens of IgG4-RD and one retroperitoneal tissue of IRF.

Results

Two patients with IRF and two patients with IgG4-RD used tofacitinib monotherapy. Two patients with IRF achieved complete remission with diminished retroperitoneal mass and decreased CRP, as IgG4-RD RI decreased from 6 to 1 in both of them. One with IgG4-RD achieved complete remission with alleviated enlargement of pancreas and IgG4 level decreased from 13.7 g/L to 2.4 g/L, as IgG4-RD RI decreased from 12 to 1. One with IgG4-RD achieved partial response with IgG4 level decreased from 77.1 g/L to 25.8 g/L as IgG4-RD RI from 18 to 6. JAK1, JAK2, JAK3, and TYK2 expression were detected in biopsy tissues. The staining intensity of the JAK family on the lesion from one IRF patient was similar to those from IgG4-RD patients.

Conclusion

Tofacitinib is a potentially effective treatment for IgG4-RD and IRF and it is reasonable to conduct clinical trial to validate its efficacy. The JAKs were expressed in the inflammatory lesions of IgG4-RD and IRF and they may share a common pathogenesis pathway that is independent of IgG4 production.

Key words

tofacitinib, immunoglobulin G4-related disease, idiopathic retroperitoneal fibrosis, JAK family, immunohistochemistry

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Introduction

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibro-inflammatory disease. Nearly any organs, including kidney, retroperitoneum, bilateral lacrimal, parotid, sublingual, and submandibular glands, and lymph nodes can be affected. In addition, IgG4-RD patients demonstrated a strong clinical heterogeneity, which poses a challenge for treatment (1). Idiopathic retroperitoneal fibrosis (IRF) is also a fibroinflammatory disease. IRF alone could be the clinical manifestation of IgG4-RD. Noteworthy, some patients with IRF had the involvement of other systems simultaneously, which could lead to a final diagnosis of IgG4-RD (2). Based on histological findings, at least over half of IRF is IgG4-RD (3).

Glucocorticoids (GCs) are the first-line treatment for IgG4-RD (1) and IRF (2). Almost all patients with IgG4-RD had a response to the treatment of GCs. However, approximately 40% of patients could not obtain complete remission (CR) or recur within one year (4). Although GCs combined with cyclophosphamide or mycophenolate mofetil can reduce disease relapse, the cumulative relapse rate during one year was still 12–20.59% (5, 6). In a meta-analysis, the pooled estimate of relapse rate with the therapy of rituximab (RTX) was up to 21% in IgG4-RD patients (7). As it is well recognised, GCs treatment had a lot of adverse reactions, such as hypertension, diabetes, and retention of water and sodium. Controlling the disease activity of IgG4-RD and IRF without GCs was an unmet clinical demand.

Many cytokines including IL-4, IL-5, IL-6, and IL-13 participated in pathogenesis of IgG4-RD (8). JAK mediated the signal transduction of these cytokines (9). Hence, Khan *et al.* indicated that JAK was a promising therapeutic target in IgG4-RD (8). In two patients, tocilizumab, an IL-6 receptor antibody, was reported to control active IgG4-RD refractory to RTX (10). Here, we reported four patients with IgG4-RD or IRF who improved remarkably after tofacitinib monotherapy. The expression of JAK1, JAK2, JAK3, and TYK2 in biopsy specimens of IgG4-RD or IRF

patients was further investigated by immunohistochemical (IHC) staining.

Materials and methods

It is a retrospective observational study. Our study complied with the Declaration of Helsinki. The Ethics Committee of Beijing Tiantan Hospital approved the study. The clinical data of patients diagnosed as IgG4-RD or IRF and treated with tofacitinib were reviewed. The diagnosis of IgG4-RD was established based on the 2019 American College of Rheumatology (ACR) /European League Against Rheumatism (EULAR) classification criteria for IgG4-RD (11). IRF was diagnosed according to clinical, radiological, and/or histological evaluation (2). Patients were treated with oral tofacitinib (5 mg twice daily). The choice of this medicine is due to either the relapse of disease despite GCs treatment or the concerns on the side effects of GCs. Informed consent before the treatment initiation was obtained. The change of IgG4-RD responder index (IgG4-RD RI) (12) was used to evaluate the efficacy of tofacitinib in IgG4-RD or IRF patients. In detail, CR was defined as IgG4-RD RI scores <3 and decreasing ≥2. Partial response (PR) was defined as IgG4-RD RI scores decreasing ≥2 but remaining ≥3 (13).

Immunohistochemistry staining of tissue

Submandibular gland specimens were obtained from two patients with IgG4-RD (patient 2 and patient 4). A biopsy specimen of retroperitoneum was obtained from one patient (patient 3). There was another hospitalised IgG4-RD patient who performed a biopsy of the parotid gland. Finally, four biopsy specimens were obtained for analysis. The expressions of JAK1, JAK2, JAK3, and TYK2 in these four specimens were analysed by IHC. We purchased JAK1 monoclonal antibody (catalogue no.: 66466-1-Ig), JAK3 recombinant antibody (catalogue no.: 80331-1-RR), and TYK2 monoclonal antibody (catalogue no.: 67411-1-Ig) from Proteintech (Wuhan, China). We purchased JAK2 Rabbit pAb (catalogue no.: A11497) from ABclonal (Wuhan, China).

Competing interests: none declared.

Table I. Clinical characteristics of four patients with IgG4-RD or IRF treated with tofacitinib monotherapy.

Patient	Age	Sex	Disease duration [#] (months)	Diagnosis	CRP [*]	Serum IgG4	Lesion sites	Follow-up time (months)
1	43	Male	21	RPF ^{&}	17.4	0.564	soft tissues from lumbar vertebra 4 to sacral vertebra three and bilateral submandibular glands	23
2	74	Female	4	IgG4-RD [§]	0.418	13.7	bilateral lacrimal and submandibular glands, pancreas	12
3	67	Male	94	RPF ^{&}	32.5	0.777	soft tissues around the abdominal aorta initially; mass under the right renal hilus the last relapse	8
4	51	Male	120	IgG4-RD [§]	0.607	77.1	Lymph nodes, bilateral parotid glands, bilateral submandibular glands, eye sockets, and soft tissues around the thoracolumbar spine	8

[#]Disease duration was defined as the time interval from the disease onset to the usage of tofacitinib; [&]RPF: retroperitoneal fibrosis; ^{*}CRP: C-reactive protein;

[§]IgG4-RD: immunoglobulin G4-related disease.

The normal range of serum IgG4 was 0.03-2.01 g/L. The normal range of serum CRP was 0-2.87 mg/L.

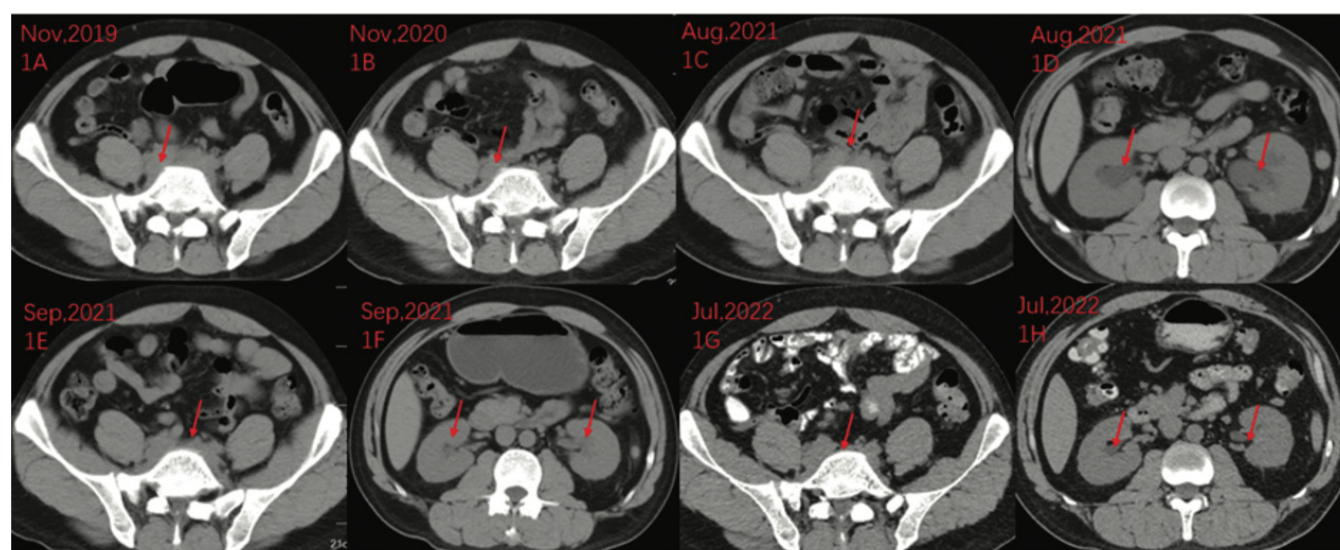


Fig. 1. Abdominal and pelvic CT images of patient 1 with idiopathic retroperitoneal fibrosis. The disease relapsed after the patient discontinued prednisone and immunosuppressants in August 2021. Then, the patient was taken with tofacitinib monotherapy.

We performed immunohistochemical staining using a Roche fully automated staining machine (BenchMark ULTRA). The VENTANA automated staining system was adopted. The primary antibodies were the JAK1 monoclonal antibody, JAK2 Rabbit pAb, JAK3 recombinant antibody, and TYK2 monoclonal antibody. The concentration of the primary antibody was 1:500. Secondary antibody was chosen as the standard type. The experimental parameter of the machine was set.

The process was as follows:

1. Dewaxing, add dewaxing solution at 72°C for 16 minutes, and clean; 2. Antigen repair: Add antigen repair solution at 100°C for 64 minutes and wash; 3. Add the primary antibody and incubate

at 37°C for 16 minutes, then wash; 4. Add the secondary antibody and incubate at 37°C for 8 minutes, then wash. 5. Add DAB and incubate at 37°C for 8 minutes, then wash; 6. Add haematoxylin and incubate at 37°C for 8 minutes, then wash; 7. Add bluing solution and incubate at 37°C for 4 minutes, then wash; 8. Dehydrate with 80%, 95%, 95%, 100%, and 100% gradient alcohol in sequence. 9. Apply transparent solution for 1 minute and seal with neutral gum.

Two independent pathologists evaluated the intensity of IHC staining. The ratings were based on the methods previously reported (14, 15): -, no staining; +, weak staining; ++, moderate staining; +++, strong staining.

Results

Four patients with IgG4-RD or IRF were treated with tofacitinib monotherapy (Table I), three males and one female. The age ranged from 43 to 74 years old. Two patients were diagnosed as IRF (patient 1 and patient 3), and two were diagnosed as IgG4-RD (patient 2 and patient 4). Patient 1 initially complained of pain in the left abdomen and waist. Subsequently, retroperitoneal mass (Fig. 1A) and hydronephrosis were found by CT. 18F-FDG PET-CT detected hypermetabolism of soft tissues from lumbar vertebra 4 to sacral vertebra 3 and bilateral submandibular glands in this patient. Patient 1 received prednisone 60 mg/d treatment along with hydroxychloroquine and

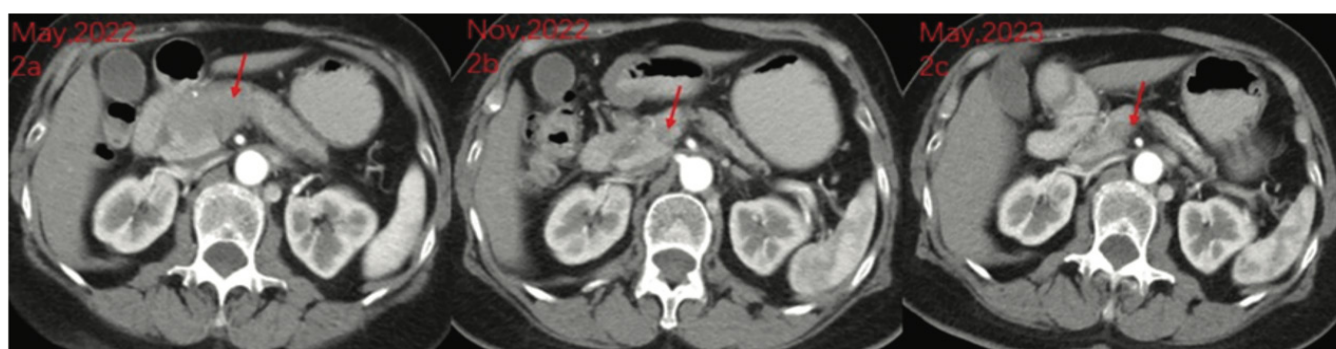


Fig. 2. The pancreatic involvement of patient 2 with IgG4-RD.

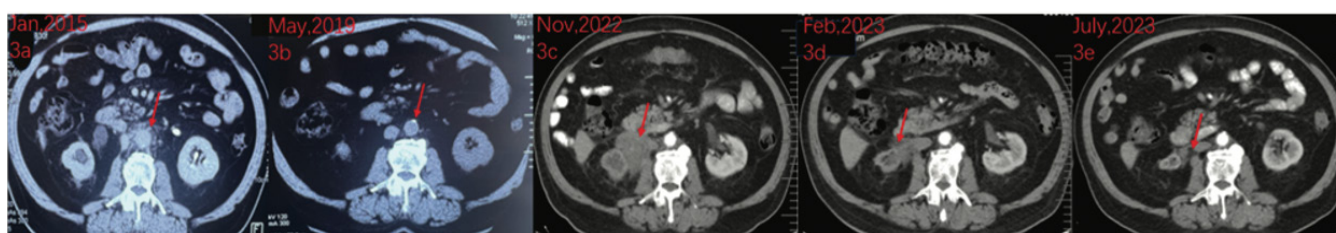


Fig. 3. Patient 3, with idiopathic retroperitoneal fibrosis, experienced relapse and remission of the disease. He was first treated with GCs and immunosuppressant. After achieving remission, the patient stopped drug administration. However, idiopathic retroperitoneal fibrosis relapsed in November 2022. Tofacitinib was prescribed subsequently.

leflunomide, and the retroperitoneal lesion reduced significantly (Fig. 1B). No hydronephrosis was found by ultrasound. After discontinuation of GCs and immunosuppressants in March 2021, the IRF relapsed with recurrence of soft tissue around iliac artery and hydronephrosis detected by CT in August 2021 (Fig. 1C-D). Patient 2 complained swelling of bilateral lacrimal and submandibular glands, which was confirmed by B ultrasound. CT showed diffuse pancreas enlargement (Fig. 2a) in this patient. Patient 3 presented with pain in the right waist and bilateral groin. CT revealed soft tissues around the abdominal aorta and hydronephrosis (Fig. 3a) at disease onset. High dose GCs and leflunomide was applied and the lesion of IRF alleviated totally (Fig. 3b). This patient experienced relapse in 2019, and high dose GCs and mycophenolate mofetil were applied and the lesion disappeared totally again but shrink of left kidney left. However, his disease relapsed again after stopping GCs and immunosuppressants administration. CT showed the mass under the right renal hilus but not the previous site around abdomen aorta (Fig. 3c). Patient 4 presented with enlargement of bilateral eyelid for ten years, enlargement of axillary lymph nodes for two

years, and abdominal pain for one year. The 18F-FDG PET/CT showed hypermetabolism in the upper and lower lymph nodes of the diaphragm, bilateral parotid glands, bilateral submandibular glands, eye socket, and soft tissues around the thoracolumbar spine (Fig. 4 above).

Regarding laboratory testing, serum IgG4 level in patients with IRF (patient 1 and patient 3) was normal. Serum IgG4 level was 13.7g/L (normal range: 0.03–2.01g/L) and 77.1g/L in patients 2 and 4, respectively. Elevated serum CRP was observed in two patients (patient 1 and patient 3). Serum IgG level was elevated in all four patients. Serum C3 was decreased in two patients (patient 2 and patient 4).

We performed biopsy of tissues in patient 2, patient 3, and patient 4. In patient 2, the histopathology examination demonstrated diffuse and focal infiltration of numerous lymphocytes and plasma cells. Abundant fibroblasts and tissue fibrosis were detected. Scattered ducts and atrophy of acini were seen. IgG4+ cells/HPF are more than 10. The ratio of IgG4 and IgG was less than 40% due to extensive presence of IgG+ cells. In patient 3, the pathological results revealed infiltration of numerous lymphocytes and plasma cells. Fibro-

blasts, adipose tissue and fibrous connective tissue were also demonstrated. IgG+ cells were abundant, IgG4+ cells was <10/HPF, and IgG4+/IgG+ was minimal. In patient 4, acinar duct, adipose tissue and fibrous tissue were revealed in pathological findings. It also showed diffuse infiltration of plasma cells and lymphocytes. There were lymphoid follicles formation with >50 lymphocytes/HPF in lesions. The number of IgG-positive plasma cells was approximately 100/HPF. The number of IgG4-positive plasma cells was approximately 70/HPF, and the IgG4+: IgG+ ratio was approximately 70%.

Patient 2 and patient 4 were newly diagnosed. Patient 1 and patient 3 suffered from disease remission and recurrence. At the time of relapse, GCs and immunosuppressants were discontinued for more than one year and five months in patient 3 and patient 1, respectively. Tofacitinib monotherapy was prescribed for all of them.

After the tofacitinib monotherapy treatment, three patients (patient 1, patient 2 and patient 3) achieved CR (Fig. 5). One (patient 4) achieved PR (Fig. 5). In patient 1, retroperitoneal soft tissues decreased, and hydronephrosis was improved (Fig. 1E-H). In July 2023, the CRP and IgG decreased normal. B

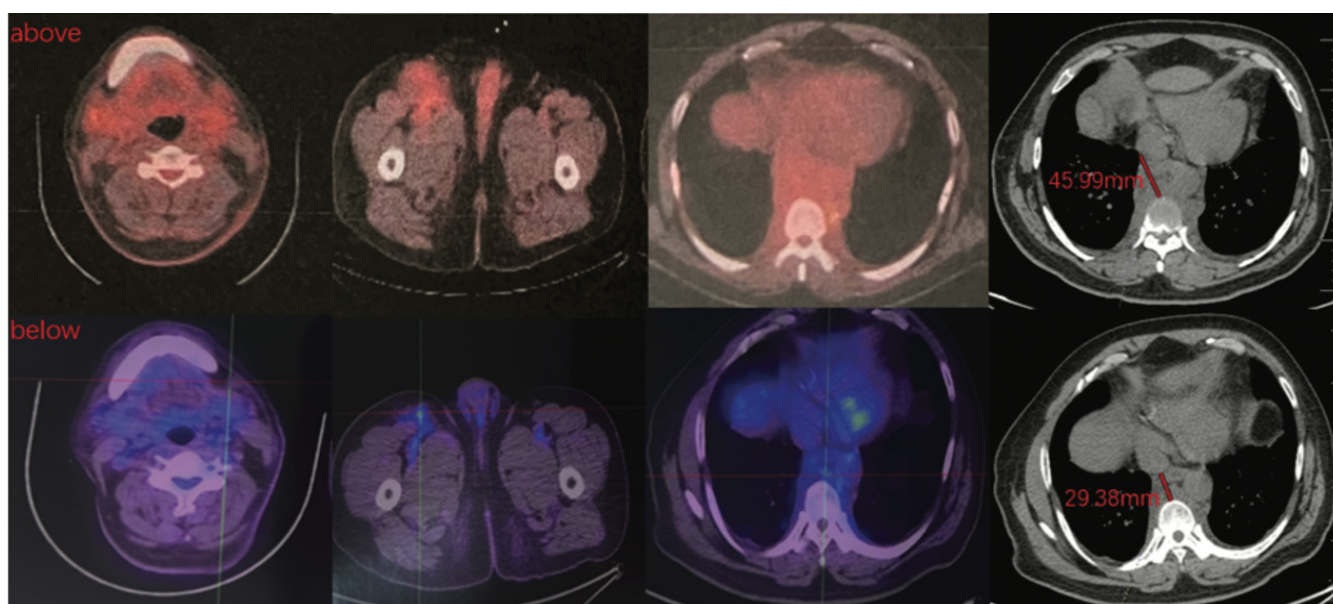


Fig. 4. The FDG take was decreased, and lesions in parotid glands, swollen lymph nodes in right groin, and mass around the thoracolumbar spine (above) shrank after (below) the tofacitinib monotherapy in patient 4.

ultrasound did not show hydronephrosis. After 23 months of treatment, IgG 4-RD RI decreased from 6 to 1 (Fig. 5). In patient 2, tofacitinib was prescribed for three months and stopped due to herpes zoster infection. The disease was still stable after 9 months of discontinuation of tofacitinib. IgG reduced to normal. Serum IgG4 dropped to 2.4 g/L, which was still slightly high. Serum C3 level was increased but was still not normal. Lacrimal and submandibular glands returned to normal size. Pancreatic lesions gradually reduced to normal (Fig. 2b-c). IgG4-RD RI reduced from 12 to 1 (Fig. 5).

In patient 3, the elevated CRP and IgG decreased to normal. The CT showed the lesion under right renal hilus gradually shrank (Fig. 3d-e). After eight months of treatment, the IgG4-RD RI dropped from 6 to 1 (Fig. 5).

In patient 4, serum IgG and IgG4 descended but not to normal. Serum C3 increased but still did not recover. Orbit lesions were unchanged. Swollen lymph nodes, submandibular and parotid glands, and mass around the thoracolumbar spine were improved (Fig. 4 below). After a treatment period of eight months, IgG4-RD RI declined from 18 to 6 (Fig. 5). We detected no adverse effects of tofacitinib apart from patient 2, who suffered from herpes zoster infection.

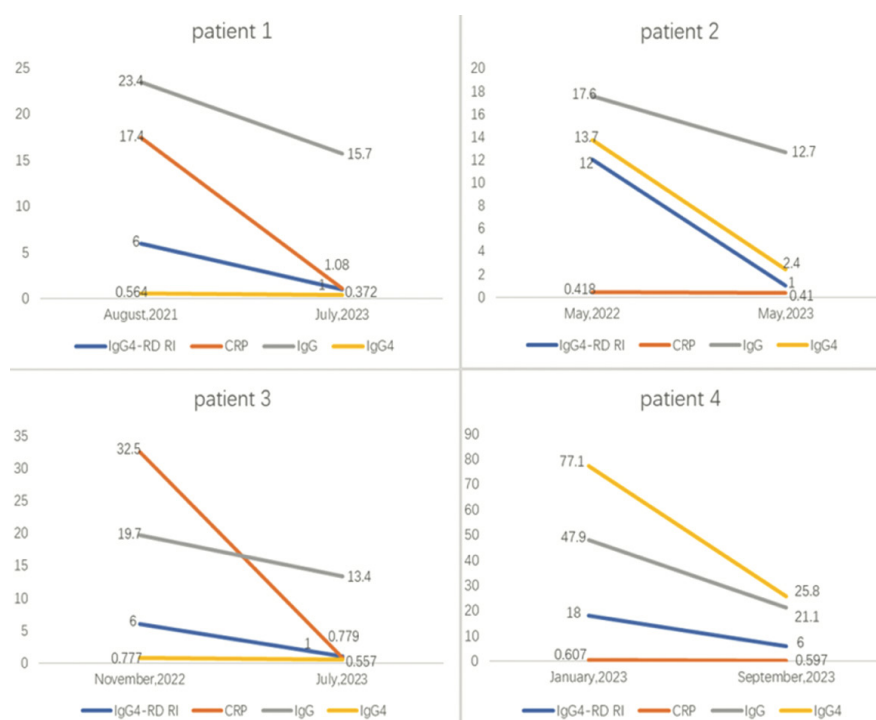


Fig. 5. The change of IgG4RD-RI, CRP, IgG, and IgG4 before and after the tofacitinib treatment.

The JAK1, JAK2, JAK3, and TYK2 positive cells were found in tissues of patients with IgG4-RD or IRF

Our study collected submandibular gland specimens from two patients with IgG4-RD (patient 2 and patient 4), retroperitoneum specimen from one patient with IRF (patient 3), and parotid gland specimen from another patient with IgG4-RD (patient 5). The

expression of JAK1, JAK2, JAK3, and TYK2 was analysed in biopsied specimens by IHC staining. All patients yielded an evaluable IHC staining of the cell slides (Table II). Overall, JAK1 IHC staining was rated “++” or “+++.” The intensity of JAK2 staining was assigned “+++”. JAK3 IHC staining was graded “+”. TYK2 IHC staining was assigned “+” or “++.”

Table II. The assessment of immunohistochemical staining in four specimens.

Patient	Diagnosis	Biopsied sites	JAK1	JAK2	JAK3	TYK2
2	IgG4-RD	submandibular gland	++	+++	+	+
3	IRF	retroperitoneum	++	+++	+	+
4	IgG4-RD	submandibular gland	+++	+++	+	+
5	IgG4-RD	parotid gland	+++	+++	+	++

IRF: idiopathic retroperitoneal fibrosis. IgG4-RD: immunoglobulin G4-related disease.

In detail, in salivary glands of patients with IgG4-RD (patient 2, patient 4 and patient 5), JAK1 and JAK2 were highly expressed in nearly all infiltrating lymphocytes, and also fibroblasts. Strong JAK2 staining was also observed in acinar epithelial cells and ductal epithelial cells. Weak expression of JAK3 was detected in part of infiltrating lymphocytes, epithelial cells and fibroblasts. TYK2 expressed moderately in majority of infiltrating lymphocytes, epithelial cells, and fibroblasts. The representative imaging of IHC staining of JAK family in patient 2 was shown in upper lane of Figure 6, which showed infiltrating lymphocytes predominantly consisted of IgG expressing cells with increasing number of IgG4 positive cells.

The lane in Figure 6 shows representative imaging of biopsied retroperitoneal tissue of patient 3, JAK1 and JAK2 were strongly expressed in nearly all of infiltrating lymphocytes and fibroblasts. Comparing JAK1 and JAK2, JAK3 was expressed in less extent in fibrocytes, lymphocytes, and adipose cells. TYK2 was expressed moderately in lymphocytes and adipose cells. The similarity of IHC staining of JAK1, JAK2, JAK3 and TYK2 in salivary

glands from IgG4-RD and retroperitoneal tissue from IRF was demonstrated in Figure 6, along with differentially presented IgG4 positive cells.

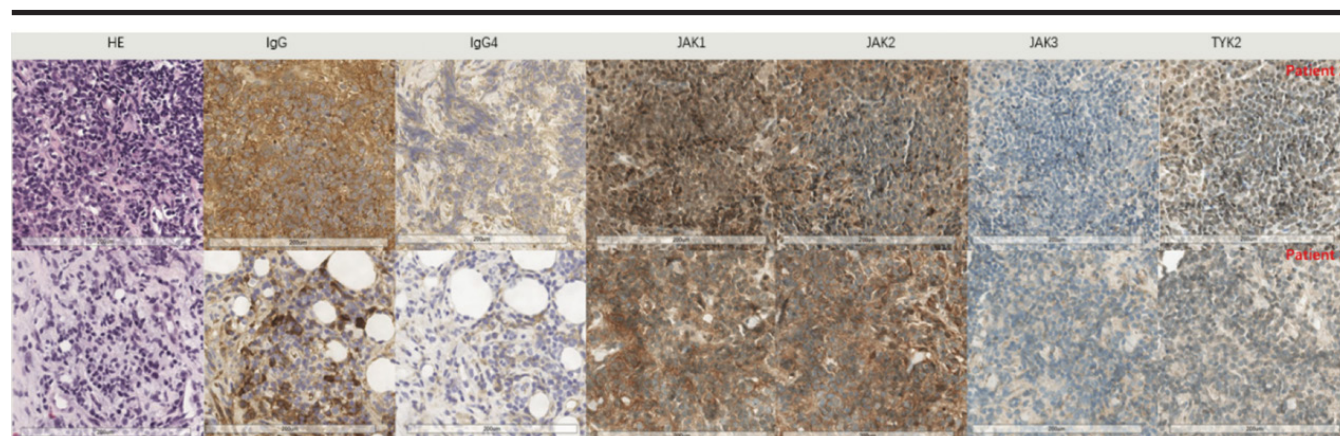
Discussion

We reported two patients with IgG4-RD and two patients with IRF have been successfully treated by tofacitinib. Due to occurrence of hydronephrosis, patient 1 and patient 3 conducted radiological investigation and found soft tissue surrounding iliac artery or abdomen aorta which is characteristic for IRF. After the relapse of disease in patient 3, new lesion presented under right renal hilus which is not a common manifestation of IRF. According to the clinical practice recommended by expert (2), biopsy was conducted and pathological analysis revealed heavy lymphocyte infiltration with scattered IgG4+ cells and without evidence of other diseases. Both of them did not show elevated serum IgG4 level (Table I). Among patients with IRF, they are clinically as IgG4-related or IgG4-unrelated subgroups (16). They all had shown good response to GCs treatment previously supporting the diagnosis of IRF and suggesting an underlying auto-immunological aetiology. Both patients

presented elevated CRP (Table I), thus the diagnosis of IRF with features of active inflammation was definite (2). According to the 2019 ACR/EULAR classification criteria for IgG4-RD, the total points of patient 2 and 4 was 44 and 53 respectively. In patients 2 histopathological manifestation of dense lymphocytic infiltrate (+4), the IgG4+/IgG+ ratio is 0–40% and the number of IgG4+ cells/hpf is ≥ 10 (+7), bilateral lacrimal and submandibular glands involved (+14), and serum IgG4 concentration $> 5 \times$ upper limit of normal (+11), and diffuse pancreas enlargement (loss of lobulations) (+8).

In patient 4, the total points were as follows: histopathology revealed dense lymphocytic infiltrate (+4), the IgG4+/IgG+ ratio is 41–70% and the number of IgG4+ cells/HPF is > 10 (+14), serum IgG4 concentration $> 5 \times$ upper limit of normal (+11), two or more sets of glands involved (+14), and paravertebral band-like soft tissue in the thorax (+10); Patient 4 showed soft tissue in front of thoracic vertebra which is included in the classification criteria of IgG4-RD (11). Patient 2 and 4 fulfilled the diagnostic criteria and showed typical clinical, serological, radiological and pathological features.

If asymptomatic or only salivary/lacrimal glands involved IgG4-RD patients need to be treated is still controversial. However, treatment should be initiated when important organs are involved or the progression of disease is ongoing, and the goal of treatment should include alleviating enlargement of involved organs or tissues and termi-

**Fig. 6.** Immunohistochemical staining images of JAK family on biopsy cell block slides (patient 2 and patient 3, x200).

nating abnormal immune reaction. GCs were effective for initiating treatment in IgG4-RD, but the relapse or incomplete remission frequency was about 40% within one year (4). After the first relapse, 30% of patients experienced a second relapse despite combination therapy of GCs and immunosuppressants (17). For IRF patients who suffered from hydronephrosis, prompt application of double-J stent implantation or other procedures to alleviate the ureteral obstruction is important for saving renal function. However, pharmaceutical treatment to control the fibroinflammation is required, and the goal of treatment should be alleviating the retroperitoneal mass to relieve the compression of the ureter and remove the ureteral or renal pelvis implantations. GCs are also applied in patients with IRF without evidence of IgG4-RD (3). The relapse is also common in patients with IRF (2). Patient 2 showed involvement of pancreas, which may cause biliary obstruction with the disease progresses. Patient 4 were with lesions around the thoracolumbar spine, and serum IgG4 level was very high. Patient 1 and patient 3 suffered disease relapses, and were with elevated serum CRP. These four patients all had the indications for treatment.

After tofacitinib treatment without concomitant GCs or other immunosuppressants, retroperitoneal soft tissues were reduced, and hydronephrosis was improved in patient 1. The CRP and IgG returned to normal. In patient 2, IgG reduced to normal. Swelling lacrimal glands, submandibular glands, and pancreas decreased to normal. In patient 3, elevated CRP and IgG reduced to normal. Mass under right renal hilus gradually diminished. In patient 4, serum IgG and IgG4 levels were reduced. Swollen lymph nodes, submandibular gland, parotid gland, and mass around the thoracolumbar spine were reduced. All patients had a good treatment response to tofacitinib monotherapy and suggesting the possible efficacy of tofacitinib monotherapy in IgG4-RD and IRF patients. Other drugs for the treatment of refractory IgG4-RD and IRF patients were reported. RTX is another effective treatment for selected IgG4-RD

patients; 40% of patients achieved CR at a 12-month time point (18). Immunosuppressants and RTX have shown the efficacy in IRF (2). Our data support to apply tofacitinib to induce remission without GCs quickly. Comparing RTX, oral tofacitinib is convenient for patient to use and with reasonable safety data accumulated by its application in rheumatoid arthritis. The further RCT studies investigating the efficacy and safety of tofacitinib in patients with IgG4-RD and IRF were warranted.

Tofacitinib is a JAK 1/2/3 inhibitor. JAK1 is vital for signalling many cytokines, including IL-6 (9). It was reported that the frequency of CD4+CD28- and CD8+CD28- cytotoxic T lymphocytes in IgG4-RD are increased after stimulating with IL-7. The JAK inhibitor tofacitinib could inhibit the effects of IL-7 (19). JAK inhibitor was a new possible therapeutic target in IgG4-RD (8). Tocilizumab was reported effective in patients with chronic periaortitis (20, 21) and IRF (22, 23). Therefore, JAK inhibitor may also be effective for IRF. The detection of JAK1, JAK2, JAK3, and TYK2 on biopsied specimens by IHC staining confirmed the presence of the targets of tofacitinib and may provide an explanation for its effectiveness.

29–58% of IPF patients belonged to IgG4-RD (24). The extra-retroperitoneal manifestations and laboratory features of IgG4-RD deserve attention in the follow-up of patients with IRF. Pérez-Sanz *et al.* (25) presented a 59-year-old woman with IRF, periarteritis, and orbital pseudotumor, and there is no evidence of IgG4-RD. Noteworthy. Hypermetabolism of bilateral submandibular glands was prominent in patient 1 with IRF by 18F-FDG PET. According to the 2019 ACR /EULAR classification criteria for IgG4-RD, the total score was 14. In detail, one set of glands involved (bilateral submandibular glands) (+6), and circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries (+8). The diagnosis of IgG4-RD was not fulfilled. In patient 3, although pathologic findings showed dense lymphocytic infiltrate, IgG4+cells was <10/HPF, and IgG4+/IgG+ ratio was <40%. The clas-

sification criteria for IgG4-RD were not met. Both of two patients showed normal IgG4 level, but pathology revealed active immune reaction with heavy infiltrating IgG-positive lymphocyte and presence of fibroblast similar to that of IgG-RD except the amount of IgG4+ cells at the inflammatory site. We demonstrated the expression of JAK1, JAK2, JAK3, and TYK2 in biopsied specimens of patients with IgG4-RD and IRF. The staining pattern of the JAK family on tissues of patients with IgG4-RD and IRF was similar. It hints that IgG4-RD and IRF may be the different pattern of the same disease spectrum. These two diseases may share a similar mechanism, that is involved abnormally upregulated JAK signalling pathway causing immune dysregulation, and is independent of IgG4 production.

This study preliminarily investigated the effectiveness of tofacitinib monotherapy for patients with IgG4-RD or IRF from clinical to pathology. Given the encouraging result, we hope our study could provide a clue for the possible treatment options for these two diseases. The limitations of this study include a small sample size and not investigating the specific cells expressing JAK1, JAK2, JAK3, and TYK2 by IHC staining. In addition, time of follow-up for patients is short, from 8 months to 23 months, does not allow to draw firm conclusions on long term efficacy. Our observation should be a base for further investigation. Observational studies with large sample size or clinical trials are needed to evaluate the possibility of administering tofacitinib as monotherapy without GCs in patients with IgG4-RD or IRF.

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