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Tofacitinib plus iguratimod for improving rheumatoid arthritis-related usual interstitial pneumonia: a three-case report and literature review

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August 30, 2022

Abstract

RA-UIP has a poor prognosis, and how to reverse or stabilize the lesions remains challenging. Based on researches finding that tofacitinib and IGU might be effective in pulmonary fibrosis, we present 3 cases that treated with the combined strategy with significant improvement of DAS28-CRP score and reversals in HRCT.

Tofacitinib plus iguratimod for improving rheumatoid arthritis-related usual interstitial pneumonia: a three-case report and literature review

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consent statement

Written informed consents were obtained from the three patients to publish this report in accordance with the journal's patient consent policy.

Abstract

RA-UIP has a poor prognosis, and how to reverse or stabilize the lesions remains challenging. Based on researches finding that tofacitinib and IGU might be effective in pulmonary fibrosis, we present 3 cases of RA-UIP that treated with the combined strategy with significant improvement of DAS28-CRP score and reversals in chest HRCT assessment.

Keywords: Rheumatoid arthritis-related usual interstitial pneumonia; Combination therapy; Dual treat-to-target, Case report.

Background

Interstitial lung disease (ILD) is a relatively common and serious complication of rheumatoid arthritis (RA)[1]. Its prevalence varies widely from 3 to 67%, increasing from 2 to 10 fold the risk of death in

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RA patients[2]. Moreover, RA-ILD is considered the second most common cause of death in these patients, just behind cardiovascular disease[3].

RA-ILD is a heterogeneous disease, involving different ILD subtypes with different HRCT patterns. Usual interstitial pneumonia (UIP) is the most frequent imaging pattern, accounting for 40 60% of patients with RA-ILD, followed by nonspecific interstitial pneumonia for about 40%. Unclassifiable patterns can be observed in up to 6% of patients[3]. UIP and Idiopathic pulmonary fibrosis (IPF), the most frequent pattern, have a poor prognosis and low median survival rate[4]. A meta-analysis of 10 cohort studies, including 1256 patients with RA-ILD, estimated a 1.6-fold higher risk of death for those with a UIP pattern than other patterns[5].

RA-UIP shares radiological and histopathological similarities with IPF, indicating the necessity of saving RA-UIP. However, how to reverse or stabilize the lesions remains challenging.Therapeutic options in these patients are complicated by the possible pulmonary toxicity of many diseases modifying antirheumatic drugs (DMARDs) and by their unclear efficacy on pulmonary involvement[6].

Tofacitinib is a small-molecule Janus kinase (JAK)1/JAK3, and to a lesser extent, JAK2/tyrosine kinase(TYK)2 inhibitor approved for the treatment of RA. JAK/signal transducer and activator of transcription (STAT) pathway has been implicated in pulmonary fibrosis[7,8]. In vitro and in vivo studies investigated tofacitinib in ILDs. These results collectively indicated that tofacitinib is a potential therapeutic option for RA-UIP[9-12].

Iguratimod (IGU), a small molecule with new anti-inflammatory and immunomodulatory properties, was developed as a novel anti-rheumatic drug and is widely used for RA. Researches had also found that IGU could be an effective therapeutic strategy for pulmonary fibrosis[13-15].

Successful treatment of RA-UIP with tofacitinib combined with IGU has not been reported yet. Here, we report three cases of RA-UIP, and they were successfully treated with the combination therapy of tofacitinib combined with IGU .

Case presentation

The clinical characteristics, treatments, and outcomes of RA-UIP patients were described in **Table 1** .

Case 1

A 74-year-old woman developed RA in 2010 and had the complication of type 2 diabetes mellitus, but it was stable. She was treated with methotrexate (MTX) 10 mg weekly and 5 mg of prednisolone daily after using sulfasalazine 2000 mg daily and nonsteroidal anti-inflammatory drugs (NSAIDS). In September 2020, she was referred to our department for progressive arthralgia and morning stiffness. Tenderness of the proximal interphalangeal (PIP) joints of the bilateral 2, 3, 5 digits, wrists, knees, right ankle, and fine crackles in left lower lung field were revealed.

Initial laboratory findings showed that he presented with mild anemia. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibody was positive (139.9 IU/mL and >200 U/mL, respectively), while anti-nuclear antibodies (ANA), extractable nuclear antigens (ENA), and antineutrophil cytoplasmic antibodies (ANCA) were negative. C-reactive protein (CRP,30.3 mg/L) and erythrocyte sedimentation rate (ESR,50 mm/h) were both increased. Markers of tumor, Hepatitis B virus (HBV), and Tuberculosis (TB) were negative. The pulmonary function test (PFT) showed normal ventilatory function with mild diffusion capacity impairment. The patient's laboratory findings during the hospitalization were shown in **Table 2** . The X-ray revealed bone erosion in both wrists. Chest HRCT images showed the peripheral regions of the upper and lower lobes are typically involved, basal and subpleural lung dominant reticular opacity, interlobular septal thickness associated with honeycombing and traction bronchiectasis (**Fig. 1 A, B, C, D,** more details seen in**Additional file 1**). GGO and fibrosis were scored to assess HRCT findings [16]. GGO and fibrosis were scored 4 and 7, respectively. Since HRCT showed a typical UIP pattern, the diagnosis was RA-UIP.

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With a 28-joint count CRP (DAS28-CRP) score of 5.49 showing high disease activity, she was prescribed initially with 15 mg of prednisolone daily, 5mg of tofacitinib 2 times daily, and 25mg of IGU 2 times daily. In May 2021, she visited our outpatient department with relief of arthralgia and morning stiffness. Close examination revealed decreased DAS28-CRP, GGO andfibrosis scores, PFT (**Table 2**), and improved lesions in the lower lobe of her right lung on chest HRCT (**Fig. 1 A1, B1, C1, D1** , more details seen in **Additional file 1**). The therapy was highly effective, and the prednisolone dose was reduced by 2.5 mg monthly. During the follow-up, no relapse has been observed to date, and the patent is in good condition without side effects of tofacitinib plus IGU.

Case 2

A 73-year-old woman developed RA at the age of 69 years and had a history of transient ischemic attack at 67 years of age but no recurrence. She was prescribed NSAIDS and Chinese herbs by local physicians. She was hospitalized in our department in March 2021 for poor disease control. She complained of intermittent arthralgia, morning stiffness over 2 h daily, and fever, T_{max} 38.5. Initial significant findings were tenderness and swelling of the metacarpophalangeal (MCP) joints of the left 2 5 digit, bilateral wrists, elbows, shoulders, and fine crackles in bilateral lower lung fields.

Initial laboratory findings showed that RF, CCP antibody, and ANA were positive (55.5 IU/mL, >200 U/mL, and 1:3200, respectively), while ENA and ANCA were negative. CRP and ESR increased to 30.3 mg/L and 50 mm/h, respectively. Markers of the tumor, HBV, and TB were negative. PFT showed normal ventilatory function and diffusion capacity. The X-ray revealed few erosions in both hands and wrists. **Table 2** showed the patient's laboratory findings during the hospitalization. Initial chest HRCT images showed a typical UIP pattern with marked honeycombing and traction bronchiectasis in anterior and subpleural upper lobes and left middle lobe, basal and subpleural right lower lobe, along with few gross glassy changes, sparing the central part of the lower lobes (**Fig. 1 E, F, G, H,** more details seen **in Additional file 2**). GGO and fibrosis were scored 5 and 10, respectively. Since the morphological pattern showed UIP with RA, the diagnosis was RA-UIP.

Regarding RA activity, DAS28-CRP scored 4.77 showing moderate disease activity. The fever was confirmed to be induced by the RA activity, excluding other conditions such as hypersensitivity pneumonia and pulmonary infections, and the treatment was initiated with 15 mg of prednisolone daily tapered by 2.5 mg every month, 5 mg of tofacitinib 2 times daily, and 25 mg of IGU 2 times daily.

She was referred again to assess the therapy 4 months later. The arthralgia improved gradually and the fever lessened. The prednisolone dose was 5 mg daily. Tofacitinib 10 mg daily plus IGU 50mg daily were maintained all the time. The chest HRCT demonstrated that lung lesions improved (**Fig. 1 E1, F1, G1, H1** , more details seen in**Additional file 2**). Laboratory findings, PFT, and HRCT scores improved (**Table 2**).

Nevertheless, in November 2021, she developed arthralgia continuously and coughed intermittently. Disease flares emerged when tofacitinib was discontinued for unavailablility in the local hospital 1 month after being discharged, though the prednisolone 5 mg daily plus IGU 50mg daily was maintained all the time. We observed increased CRP, ESR, worse PFT and HRCT scores (**Table 2**), and a progressive changes in the lower lobe of the lung on chest HRCT (**Fig. 1 E2, F2, G2, H2** , more details seen in **Additional file 2**). Considering that RA and UIP relapses might result from the unavailable tofacitinib, she was resumed with 5mg of tofacitinib 2 times daily.

In May 2022, tofacitinib was discontinued again due to the local outbreak of COVID-19 2 months later. Only the prednisolone 5 mg daily was maintained all the time. Besides the recurring arthralgia and cough intermittently, swelling in face and limbs and myalgia in upper limbs emerged and made her unable to lift her arms over the shoulders. The disease seemed to flare again (**Table 2**). CRP increased up to12.4 mg/L, and a progressive shadow in the lower lobe of the lungs appeared on chest HRCT compared with the previous scan (**Fig. 1 E3, F3, G3, H3** , more details seen in **Additional file 2**). Every time, a rapid arthritis control was obtained with the reintroduction of tofacitinib and IGU. She continued with 5 mg of prednisolone daily,

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5mg of tofacitinib 2 times daily, and 25mg of IGU 2 times daily and was prescribed enough for 3 months. So far, she is still being followed-up with and remains in remission (**Table 2**) of RA-UIP with the continued use of tofacitinib plus IGU.

Case 3

An 83-year-old man, a former smoker (36 pack-years), presented with progressive symmetric arthralgia and morning stiffness at the age of 80, and he underwent "appendectomy" due to "appendicitis" in the local hospital in 1984. The patient had been initially treated with the Chinese herbs for 3 months, but the symptoms had not improved significantly, and he was admitted to our department in July 2021. Tenderness and swelling in the PIP 2,3 and MCP 1,2,4 of both hands, wrists, elbows, and shoulders were presented. The auscultation detected fine crackles in both lower lung fields. The patient's main laboratory findings during the hospitalization were presented in **Table 2** .

RA was diagnosed because the RF and ACPA were positive (42 and 300 U/mL, respectively), and arthritis was aggressive and rapidly erosive in the hands and wrists. At chest HRCT, a pattern of UIP was characterized by reticular abnormalities and honeycombing aspects, particularly at the right lower lobe (**Fig. 1 I, J, K, L,** more details seen in**Additional file 3**). GGO and fibrosis were scored 4 and 12, respectively.

With DAS28-CRP of 5.26 and FVC% 75.8 showing high disease activity and mild restrictive ventilatory impairment, he was diagnosed as RA-UIP and treated initially with 15 mg of prednisolone daily, 5mg of tofacitinib 2 times daily and 25mg of IGU 2 times daily.

In December 2021, he was reassessed with relief of arthralgia and morning stiffness. Close examination showed a decreased DAS28-CRP, HRCT scores (**Table 2**), and improved lesions in the lower lobe of his lungs on chest HRCT (**Fig 1. I1, J1, K1, L1** , more details seen in **Additional file 3**).

In May 2022, he performed the second follow-up and reported a complete resolution of arthralgia. Furthermore, UIP features were kept improved in HRCT (**Fig. 1 I2, J2, K2, L2,** more details seen in**Additional file 3**), and DAS28-CRP, PFT, and HRCT scores remained stable over time (**Table 2**). No infections and other adverse events were claimed with continued use of tofacitinib plus IGU.

Discussion

Resembling IPF, honeycombing and traction bronchiectasis dominating the basal and subpleural lung are the typical morphological features of the RA-UIP. In most cases, RA-UIP could not be reversed, even partly with a poor prognosis. Consequently, new treatment strategies are needed. To the best of our knowledge, a retrospective review of the published literature was performed by searching the Medline and PubMed databases using the keywords "rheumatic arthritis," "usual interstitial pneumonia," "Tofacitinib," and "Iguratimod" (period 1 January 2000 and updated on 31 May 2022). Only articles available successfully treated in English were reviewed. No articles that matched the keywords were retrieved except for 2 partly relevant articles. Kodera et al.[17] described two cases with RA complicated by OP were successfully treated with tofacitinib therapy. Vacchi et al.[18] reported successful treatment of severe ILD related to RA with tofacitinib.

This may be the first report of RA cases complicated with UIP that was effectively treated with tofacitinib combined with IGU. This combined strategy realizes that RA and RA-UIP can be relieved simultaneously, that is, "dual treat-to-target." In the three cases, the DAS28-CRP score was controlled under 2.6 (complete remission) , HRCT scores and PFT were kept stable. The lesions in chest HRCT of the three cases are improved, even significantly reversed as few as in 3 months, not only kept in stable or unexpanded. Generally, for RA-UIP, an irreversible pattern, if the original lesions are kept stable or unexpanded, the "treat-to-target" would be permissibly achieved.

Furthermore, the results in our cases seem to provide two clues. One is that dissimilar to IPF, early or mild RA-UIP can be significantly reversed in morphology if treated by the combined strategy for as short as 3 months. Another is that similar to classical anti-fibrotic agents to some extent, tofacitinib combined

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with IGU may have some potential anti-fibrotic effects besides anti-inflammatory activities, and these effects appeared to be synergistic more than administrated alone. These reversible changes may result from the combined therapy's potential anti-fibrotic effectiveness, but not anti-inflammation effectiveness. Fibrotic diseases, including RA-UIP, tend to be less responsive to glucocorticoids and most DMARDs, and the course of disease resembles that of IPF. In some cases, RA-UIP has been reported to progress quickly and have a fatal course despite strong treatments such as cyclophosphamide and steroidal pulse therapies.

As a bridging therapy, 15 20 mg of prednisolone was given to control RA's inflammation activity in the three cases rapidly. Here, prednisolone may not affect RA-UIP.

Tofacitinib is, a JAK1/JAK3 inhibitor, approved for RA. JAK/STAT pathway has been implicated in pulmonary fibrosis[7,8]. Tofacitinib suppresses the differentiation of human T cells and dendritic cells in vitro[19]. In studies, tofacitinib significantly increases the myeloid-derived suppressor cells (MDSCs) and suppresses Th17 cells, group 1 innate lymphoid cells in the inflamed lungs. Tofacitinib also facilitates MDSC expansion in vitro. The pretreatment with tofacitinib could abrogate fibrotic responses induced by IL-6 in normal skin fibroblasts in vitro. Likewise, tofacitinib acted as a fibrosis preventive agent in a BLM-induced fibrosis mouse model[20]. In SKG mice, tofacitinib suppressed the progression of RA-ILD by facilitating the expansion of myeloid-derived suppressor cells in the lungs[10], and in the SS-associated ILD HOCl mouse model, it ameliorated the pro-fibrotic and proinflammatory markers[11]. Kurasawa K, et al. reported that tofacitinib might control refractory ILD in dermatomyositis[21]. Recently a retrospective study showed that JAK inhibitors are effective in slowing down fibrosis in RA-ILD[12]. These results collectively indicated that tofacitinib is a potential therapeutic option for RA-UIP.

IGU was developed as a novel anti-rheumatic drug and is widely used for RA. Pharmacological studies have showed that IGU can inhibit the production of various inflammatory cytokines and reduce the production of immunoglobulin, and accelerate bone formation by inhibiting the activation of osteoclasts and promoting osteoblasts differentiation[22]. Research has also found that IGU could be an effective therapeutic strategy for pulmonary fibrosis[12]. And it was reported that IGU was effective in attenuating biylayer lipid members-induced alveolar inflammation and pulmonary fibrosis, and it can reduce cytokine levels of IL-1, IL-6 and matrix metalloprotein (MMP)-9[13]. By inhibiting B-cell activation and immunoglobulin production, IGU can effectively reduce alveolar inflammation and pulmonary fibrosis caused by BLM and may play an anti-pulmonary fibrosis role[14].

When tofacitinib is combined with IGU, anti-fibrosis effects were showed in HRCT findings in the three cases and might slow down fibrosis in RA-UIP. Nintedanib and pirfenidone were approved in chronic fibrosing progressive ILD, including RA-ILD. Certainly, anti-fibrotic drugs offer a very important therapeutic option in progressive RA-UIP as adjunctive therapy to DMARDs. However, it could lead to additional side effects (liver toxicity and diarrhea) besides the high prices reducing adherence to treatment. Therefore, it would be advisable using a drug that can be effective against both articular and extra-articular manifestations and tofacitinib plus IGU might be the best choice.

Limitations

This study has some limitations. It is a case series report with a small number of patients. Furthermore, the three cases didn't experience the washout period before the tofacitinib plus IGU was given. In addition, lung fibrosis in the cases is mild to moderate with less than 15 fibrosis scores, so our results cannot be generalized to patients with severe forms of RA-UIP, which can lead to respiratory failure or death.

Conclusions

In conclusion, we believe that tofacitinib combined with IGU can simultaneously relieve RA and RA-UIP, and thus realize "dual treat-to-target". In addition, as most DMARDs are usually ineffective for RA-UIP, the combined strategy could be used in most cases, especially where DMARDs are not sufficiently effective or poorly tolerated. Prospective studies with a larger cohort must be accumulated in the future to clarify whether this finding applies to other cases and how to explain these anti-fibrosis effects exerted by the

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combined therapy.

ACKNOWLEDGEMENTS

No

CONFLICTS OF INTERESTS

The authors have no financial or nonfinancial conflict of interest that is relevant to the manuscript.

AUTHOR CONTRIBUTIONS

All authors were involved in cases management. Weilin Xie: conception, design, preparation of the manuscript, review of criteria and final approval of the manuscript. Shuhua Wang: conception, design, and preparation of the manuscript. Yao Li: conception, design, and preparation of the manuscript. Yanchun Tang: conception, design, and preparation of the manuscript. All the authors did the final approval of the version.

ETHICAL APPROVAL

This material is the authors' original work, which has not been published elsewhere. It is not being considered for publication elsewhere. All authors made meaningful contributions to the paper.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Figure Legends

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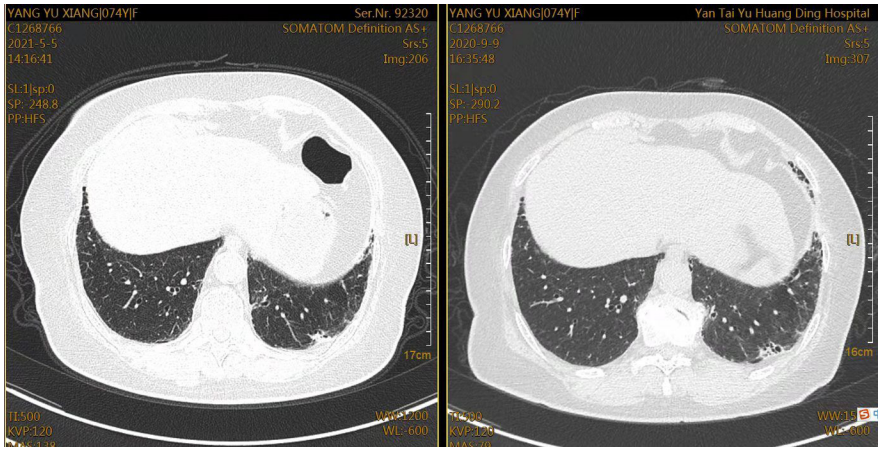
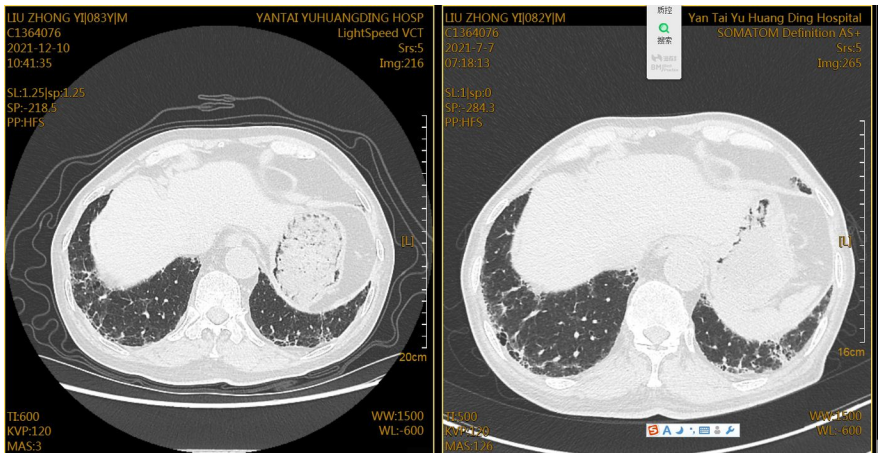


Fig. 1 HRCT features of cases before/after tofacitinib plus IGU treatment



Arrowheads show decreased reticular opacity, consolidations, the extension of interlobular septal thickness, traction bronchiectasis, and honeycombing (more details seen in **Additional files 1,2,3**). Aarrows show the increased or newly emerged lesions.

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Table 1 Clinical characteristics, treatment and outcomes of RA-UIP patients No.	**Table 1** Clinical characteristics, treatment and outcomes of RA-UIP patients Gender/age, years	**Table 1** Clinical characteristics, treatment and outcomes of RA-UIP patients Course, years	**Table 1** Clinical characteristics, treatment and outcomes of RA-UIP patients Smoke	**Table 1** Clinical characteristics, treatment and outcomes of RA-UIP patients Comorbidity	**Table 1** Clinical characteristics, treatment and outcomes of RA-UIP patients Systemic involvement	**Table 1** Clinical characteristics, treatment and outcomes of RA-UIP patients Follow up, months	**Table 1** Clinical characteristics, treatment and outcomes of RA-UIP patients Previous treatment	**Table 1** Clinical characteristics, treatment and outcomes of RA-UIP patients Base line	**Table 1** Clinical characteristics, treatment and outcomes of RA-UIP patients Follow up 1	**Table 1** Clinical characteristics, treatment and outcomes of RA-UIP patients Follow up 1	**Table 1** Clinical characteristics, treatment and outcomes of RA-UIP patients Follow up 2	**Table 1** Clinical characteristics, treatment and outcomes of RA-UIP patients Follow up 2	**Tab** Clinical characteristics, treatment and outcomes of RA-UIP patie Follo up 3
								Regime	Regime /months	Systemic involvemen/clinical evaluation	Regime /months	Systemic involvemen/clinical evaluation	Regi /mo
Case 1	F/75	12	No	Diabetes	Arthritis+UIP	8	Pred5+MTX	PEX/TA Pred15+Tof+IGU	SP+ Pred5+IGU/8	NSAIDs+Arthritis+Relieved	UIP/		
Case 2	F/73	4	No	transient ischemic attack	Arthritis+UIP	14	NSAIDS, Herb	Pred15+Tof+IGU	Pred5+IGU/4	Tofacitinib+Arthritis+Relieved	Pred5+IGU/1, Pred5+IGU/3	Arthritis+Aggravated	Pred IGU Pred
Case 3	M/83	2	Yes	Appendectomy	Arthritis+UIP	10	Herb	Pred15+Tof+IGU	Pred5+IGU/5	Tofacitinib+Arthritis+Relieved	Pred5+IGU/5	Tofacitinib+Arthritis+Relieved	UIP

F: female; M: male; Tofa: tofacitinib; S: steroids; Pred: prednisolone

Relieved/unrelieved/aggravated status was defined as a decrease/no change/increase in the DAS-28 or HRCT score.

Table 2 Disease activity before/after tofacitinib plus IGU treatment No.	**Table 2** Disease activity before/after tofacitinib plu Case 1
Index	Base line
RBC($\times 10^{12}$L)	3.89
HGB(g/l)	99
WBC($\times 10^{9}$/L)	6.8
PLT($\times 10^{9}$/L)	260
ANA	(-)
RF($<$20IU/ml)	139.9
CCP($<$5RU/ml)	$>$200
AKA	(-)

APF	(-)
CRP(<10mg/L)	30.3
ESR(<15mm/h)	56
IgG(<16g/l)	13.7
NO. of Swollen Joints	9
NO. of Tenderness Joints	10
DAS28-CRP	5.49
PGA	7
TLC-SB	88.2
FVC%	85.2
FEV1%	76.4
DLCO SB%	70.1
Total GGO score	6
Total fibrosis score	7

RBC: Red blood cells; HBG: Haemoglobin; WBC: White blood cells; PLT: Platelets; ANA: anti-nuclear antibody; CCP: anti-cyclic citrullinated peptide; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; AKA: antikeratin antibody; APF: anti-perinuclear factor; IgG: Immunoglobulin G; PGA: physician global access; TLC: total lung capacity; FVC: forced vital capacity; FEV1: the first second forced expiratory volume; DLCO SB: carbon monoxide diffusion capacity single-breath method;GGO: ground glass opacity;

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