European Review for Medical and Pharmacological Sciences 2021; 25: 4687-4692

Iguratimod attenuates general disease activity and improves lung function in rheumatoid arthritis-associated interstitial lung disease patients

P. SHU[1], S.-Q. SHAO[1], X.-N. CAI[2], H. MA[2], L. LU[2], H.-Q. YIN[2], S.-L. YIN[2]

[1]The Graduate School, Xuzhou Medical University, Xuzhou, P.R. China
[2]Department of Rheumatology and Immunology, Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu, P.R. China

Peng Shu and Siqi Shao contributed equally to this work

Abstract. – OBJECTIVE: Iguratimod is a new kind of synthetic small molecule disease modified anti-rheumatic drug with good efficacy for rheumatoid arthritis (RA) treatment; meanwhile, it exhibits potency to alleviate alveolar inflammation and pulmonary fibrosis. However, its application in RA interstitial lung disease (ILD) patients is seldomly reported. Thus, the current study aimed to investigate the efficacy and safety of iguratimod plus glucocorticoid/cyclophosphamide vs. glucocorticoid/cyclophosphamide in treating RA-ILD patients.

PATIENTS AND METHODS: Totally 101 RA-ILD patients underwent glucocorticoid/cyclophosphamide (Control group: n=61) or iguratimod plus glucocorticoid/cyclophosphamide (Iguratimod group: n=40) treatment were analyzed. General inflammation, disease activity, serum disease marker levels, high resolution lung computed tomography (HRCT) score, lung function indexes were evaluated within 24-week (W) treatment.

RESULTS: No difference of baseline demographic or disease-related features was observed between Iguratimod group and Control group. Iguratimod group showed lower levels of CRP and ESR at W4, W12 and W24; as well as decreased DAS28 score, rheumatoid factor and anti-cyclic citrullinate peptide antibody levels at W12 and W24 compared to Control group. HRCT score showed no difference between Iguratimod group and Control group at any time points. As to lung function indexes, forced vital capacity percent predicted [FVC (% predicted)], carbon monoxide diffusion capacity percent predicted [DLCO (%predicted)] and 6-minute-walk distance (6MWD) were all higher in Iguratimod group compared with Control group at W4, W12 and W24. Besides, no difference in adverse events was discovered between these two groups.

CONCLUSIONS: Iguratimod attenuates general inflammation, disease activity, and improves lung function in RA-ILD patients.

Key Words:
Iguratimod, Rheumatoid arthritis, Interstitial lung disease, Efficacy, Safety.

Introduction

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases that affects around 0.5-1.0% population worldwide[1]. In recent decades, RA attracts more and more attention, which is not only due to its direct harm to the affected synovium and cartilage, but also result from its indirect extra-articular manifestations such as Sjögren's syndrome, interstitial lung disease (ILD), vascular damage, etc.[2,3]. Among these RA related extra-articular manifestations, ILD occurs in 7.7-67.0% RA patients; besides, ILD is obligated to the majority of cases of morbidity and/or mortality in RA[3,4]. In consequence, the effort to explore novel and effective treatment options for RA-ILD patients is never stopped.

Iguratimod, a new kind of synthetic small molecule disease modified anti-rheumatic drug (DMARD) which is recently marketed in China

Corresponding Authors: Songlou Yin, MD; e-mail: yinguan2416643@163.com
Hanqiu Yin, MD; e-mail: hanjiaoquan9465368@163.com

and Japan, presents with good treatment potency for RA benefiting from its inhibition of immunoglobulins, inflammatory cytokines, T lymphocytes; and its regulation of bone metabolism/formation via osteoclast differentiation, migration as well as bone resorption[5]. In clinical settings, iguratimod attenuates inflammation, disease activity and put off bone erosion to some extent in RA patients, which also shows good tolerance[6-8]. Besides, iguratimod exhibits potency to alleviate alveolar inflammation and pulmonary fibrosis via regulating matrix metalloproteinase-9 (MMP9) and fibroblast-to-myofibroblast transition[9,10]. Considering the above data, it is hypothesized that iguratimod may be an optional treatment for RA-ILD.

Therefore, the current study aimed to investigate the efficacy and safety of iguratimod plus glucocorticoid/cyclophosphamide versus glucocorticoid/cyclophosphamide in treating RA-ILD patients.

Patients and Methods

Study Population

After the approval from the Institutional Review Board, 101 RA-ILD patients in Rheumatology Department of our hospital from August 2013 to March 2019 were enrolled in this study. The inclusion criteria were: (1) diagnosed as RA in terms of the 2010 Rheumatoid Arthritis Classification Criteria[11]; (2) complicated with ILD with definition in accordance with the International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias[12]; (3) age ≥18 years old; (4) underwent treatment of glucocorticoid in combination with cyclophosphamide, or iguratimod combined with glucocorticoid and cyclophosphamide. The exclusion criteria were: (1) complicated with other pulmonary diseases, such as occupational pneumoconiosis, lung interstitial lesions caused by inhalation of organic matter, pre-existing lung tumor, pulmonary infection, chronic obstructive pulmonary disease (COPD), tuberculosis, bronchiectasis, etc.; (2) had other autoimmune diseases (e.g., systemic lupus erythematosus); (3) had known connective tissue diseases (such as scleroderma, dermatomyositis, or sicca syndrome); (4) had history of kidney and liver dysfunction; (5) pregnant and lactating women. Written informed consents were collected from all patients.

Grouping and Treatment

Depending on the treatment regimen, patients were categorized as Control group (n=61) or Iguratimod group (n=40). In the Control group, patients received the treatment of glucocorticoid (0.5-1.0 mg/kg/day of prednisone) combined with intravenous drip of cyclophosphamide (20 mg/kg once a month for 6 consecutive months). In the Iguratimod group, patients received the treatment of iguratimod (25 mg each time, twice a day) combined with glucocorticoid and cyclophosphamide (the same usage and dosage as the Control group).

Data Collection and Assessment

The demographic characteristics including age and gender of patients were recorded, then the assessed data were collected as follows: (1) serum indexes: (a) erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) before treatment (W0), at week 4 after initiation of treatment (W4), at week 12 after initiation of treatment (W12), and at week 24 after initiation of treatment (W24); (b) rheumatoid factor (RF) and anti-cyclic citrullinate peptide antibody (CCP-Ab) at W0, W12 and W24; (2) disease activity: disease activity score using 28 joint counts based on ESR (DAS28 score (ESR)) at W0, W4, W12, and W24; (3) high resolution lung computed tomography (HRCT) assessment[13]: HRCT score (the higher score, the more severe disease) at W0, W12, and W24[13]; (4) pulmonary function: forced vital capacity percent predicted (FVC (% predicted)), carbon monoxide diffusion capacity percent predicted [DLCO (%predicted)][14,15], and 6-minute-walk distance (6MWD)[16] at W0, W4, W12, and W24; (5) adverse events occurred during the treatment.

Statistical Analysis

SPSS 24.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism 7.02 (GraphPad Software Inc., San Diego, California, USA) were applied for the data analyses and diagram plotting. The quantitative data were described in the form of median with interquartile range (IQR), or mean with standard deviation (SD). The categorized counting data were described with numbers and proportions. The Chi-square test (or Yates' corrected Chi-square), the Student's *t*-test, or the Mann-Whitney U test were carried out for the difference analyses between two groups. A two-side p-value <0.05 was defined as statistical significance.

Results

Patients' Characteristics

Patients had a mean age of 59.9±9.4 years with 77.5% females/22.5% males in Iguratimod group; while patients had a mean age of 58.1±9.8 years with 82.0% females/18.0% males in Control group. It was of note that no difference in any characteristics was observed between Iguratimod group and Control group regarding age, gender, CRP, ESR, DAS28 score, RF, CCP-Ab, HRCT score, FVC (%predicted), DLCO (% predicted) and 6MWD (Table I).

Iguratimod Decreased Inflammation and Disease Activity

Iguratimod group showed lower levels of CRP and ESR at W4, W12 and W24 (Figure 1A-B), as well as decreased DAS28 score at W12 and W24 (Figure 1C) compared to Control group. Furthermore, Iguratimod group exhibited lower RF and CCP-Ab levels at W12 and W24 compared to Control group (Figure 1D-E).

Iguratimod Improved Lung Function

HRCT score showed no difference between Iguratimod group and Control group at any time points (Figure 2). Notably, FVC (%predicted), DLCO (% predicted) and 6MWD were all higher in Iguratimod group compared with Control group at W4, W12 and W24 (Figure 3A-C).

Adverse Events

The most common adverse events were WBC decrease (10.0%), followed by ALT increase (5.0%) and upset stomach (2.5%) in Iguratimod group. Further analyses observed no difference of WBC decrease, ALT increase, upset stomach or PLT decrease between Iguratimod group and Control group (Table II).

Discussions

Since introduction to the market, iguratimod has been proposed to treat several autoimmune diseases such as RA, Sjögren's syndrome and ankylosing spondylitis, etc.[6,17,18]. In RA patients, a previous randomized controlled trial reveals that iguratimod plus methotrexate attenuate lesioned joints, inflammation, disease activity and quality of life compared to methotrexate alone[19]; besides, another study[20] discloses that for refractory RA patients who respond inadequately to methotrexate, cyclosporin A, hydroxychloroquine and prednisone, the addition of iguratimod would cripple disease inflammation and activity; furthermore, a recent meta-analysis[6] reports that addition of iguratimod improves treatment response but does not increase adverse events in RA patients. However, the application of iguratimod in RA-ILD patients is never reported. So, we performed this study and aimed to explore

Table I. Characteristics of RA-ILD patients.

Items	Control group (n = 61)	Iguratimod group (n = 40)	*p*-value
Age (years)			0.364
Mean ± SD	58.1 ± 9.8	59.9 ± 9.4	
Median (IQR)	58.0 (52.0-66.5)	59.0 (54.0-67.5)	
Range	21.0-74.0	40.0-78.0	
Gender, No. (%)			0.582
Female	50 (82.0)	31 (77.5)	
Male	11 (18.0)	9 (22.5)	
CRP (mg/L), median (IQR)	29.6 (15.6-74.5)	28.8 (12.2-77.0)	0.455
ESR (mm/h), median (IQR)	54.0 (40.5-82.5)	56.0 (28.5-80.8)	0.266
DAS28 score (ESR), mean ± SD	4.0 ± 1.3	4.2 ± 1.4	0.456
RF (IU/mL), median (IQR)	280.6 (104.4-626.5)	233.0 (61.9-894.0)	0.607
CCP-Ab (U/mL), median (IQR)	205.9 (124.8-250.1)	199.8 (153.8-229.7)	0.939
HRCT score, mean ± SD	8.4 ± 2.7	8.6 ± 2.3	0.778
FVC (% predicted), mean ± SD	72.1 ± 9.5	73.2 ± 9.1	0.553
DLCO (% predicted), mean ± SD	62.8 ± 6.3	61.7 ± 6.6	0.417
6MWD (m), mean ± SD	426.8 ± 90.0	425 ± 65.5	0.916

RA-ILD, rheumatoid arthritis (RA) associated interstitial lung disease (ILD); SD, standard deviation; IQR, interquartile range; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; DAS28, disease activity score using 28 joint counts; RF, rheumatoid factor; CCP-Ab, cyclic citrullinated peptide antibody; HRCT, high-resolution computed tomography; FVC, forced vital capacity; DLCO, carbon monoxide diffusion capacity; 6MWD, 6-minute-walk distance.

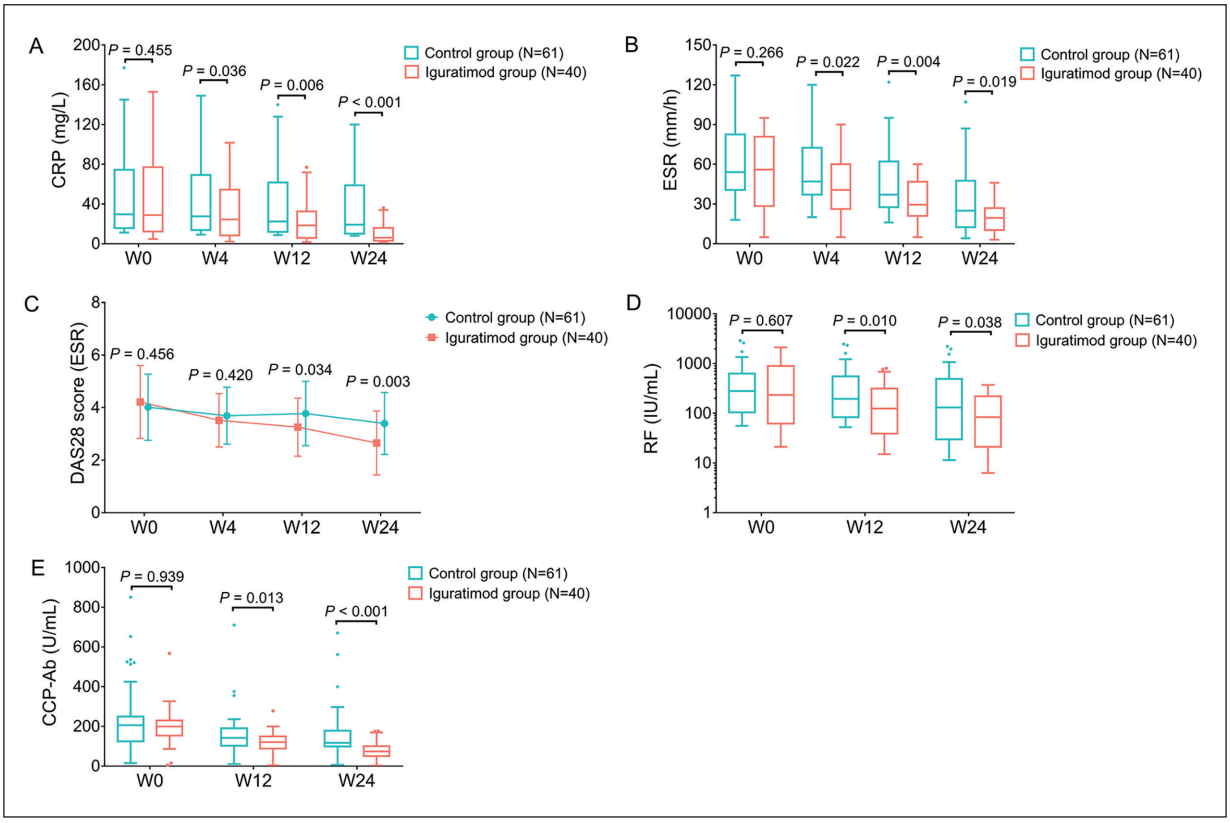

Figure 1. Comparison of inflammation and disease activity. Comparison of CRP (**A**), ESR (**B**), DAS28 (**C**), RF (**D**) and CCP-Ab (**E**) at each time point between Iguratimod group and Control group.

this issue, which found that iguratimod plus glucocorticoid/cyclophosphamide significantly decreased inflammation, disease activity and serum markers compared to glucocorticoid/cyclophosphamide in RA-ILD patients. The possible explanations were as follows: (1) iguratimod attenuated systemic inflammatory cytokines and regulated T cell subsets to decrease inflammation and serum marker levels[21]; (2) iguratimod relieved synovium hyperplasia and inflammation, as well as cartilage damages/absorption to decrease overall disease activity[5].

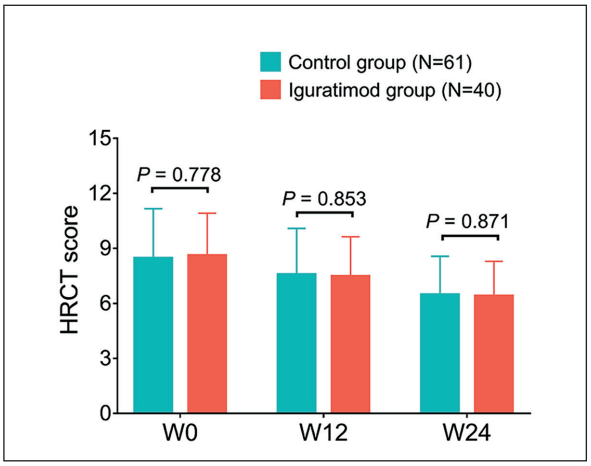

Figure 2. Comparison of HRCT score at each time point between Iguratimod group and Control group.

Apart from the effect of iguratimod on general disease activity of RA-ILD patients, its effect on HRCT score and lung function indexes were also evaluated in our study. We observed that iguratimod plus glucocorticoid/cyclophosphamide did not decrease HRCT score, but markedly increased lung function indexes such as FVC (% predicted), DLCO (% predicted) and 6MWD compared to glucocorticoid/cyclophosphamide in RA-ILD patients. The possible explanations were as follows: (1) iguratimod alleviated alveolar inflammation and pulmonary fibrosis via regulating MMP9 and fibroblast-to-myofibroblast transition, therefore increased the lung function of patients directly[9,10]; (2) iguratimod showed better efficacy regarding overall inflammation and disease activity of RA, then indirectly increased the lung

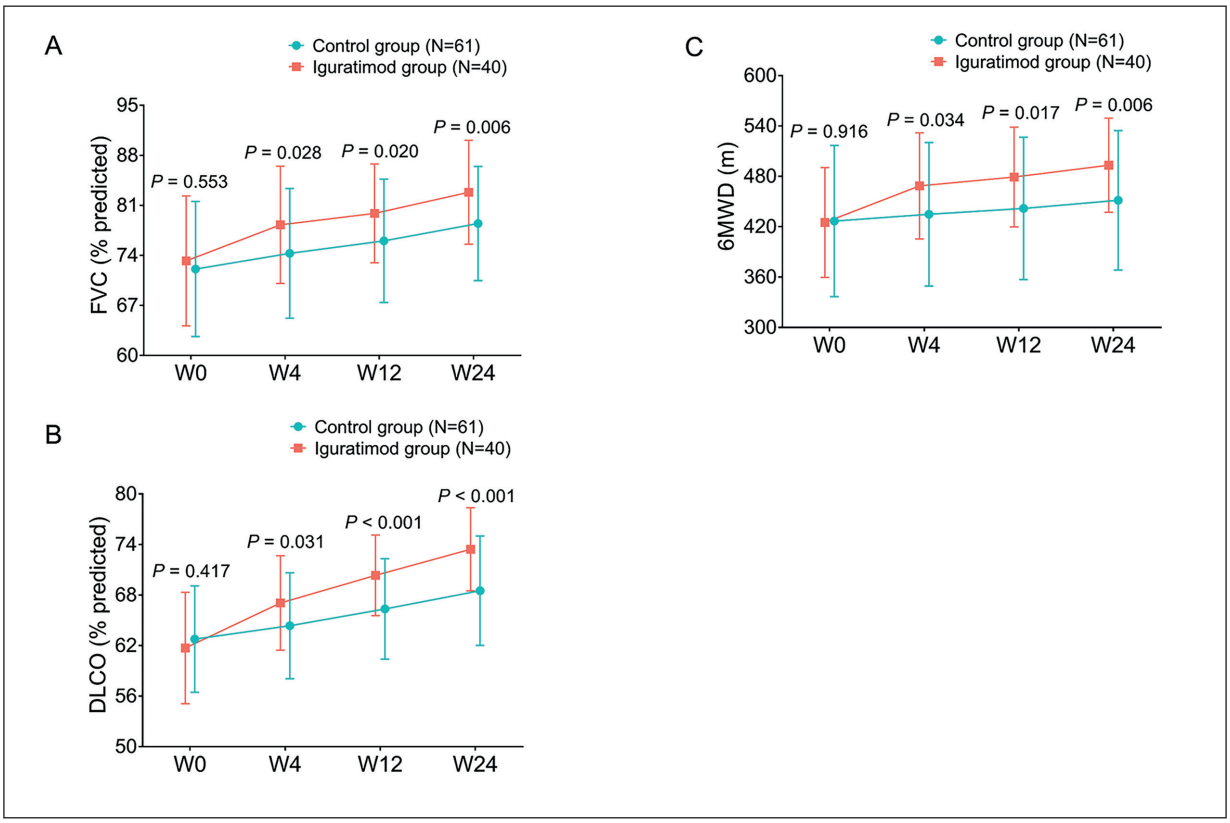

Figure 3. Comparison of lung function indexes. Comparison of FVC (% predicted) (**A**), DLCO (% predicted) (**B**) and 6MWD (**C**) at each time point between Iguratimod group and Control group.

function of patients. Besides, iguratimod plus glucocorticoid/cyclophosphamide showed similar adverse events compared to glucocorticoid/cyclophosphamide, indicating the iguratimod was well tolerated in RA-ILD patients.

There were some limitations in this study: (1) The study was a cohort-study design instead of randomized, controlled study, so some potential compounding factors might exist to affect the results; (2) the follow-up duration was a little short with 24 weeks, thus, long-term efficacy and safety profile of iguratimod in treating RA-ILD patients needed further exploration; (3) this was a single-center study, evaluation and patient chosen bias existed, therefore, subsequent multiple-center study was needed.

Conclusions

In summary, iguratimod attenuates general inflammation, disease activity, and improves lung function in RA-ILD patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Table II. Adverse events.

Parameters	Control group (n = 61)	Iguratimod group (n = 40)	*p*-value
WBC decrease, No. (%)	0 (0.0)	4 (10.0)	0.046
ALT increase, No. (%)	5 (8.2)	2 (5.0)	0.827
Upset stomach, No. (%)	3 (4.9)	1 (2.5)	0.930
PLT decrease, No. (%)	2 (3.3)	0 (0.0)	0.670

WBC, white blood cell; PLT, platelet; ALT, alanine transaminase.

References

1) Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet 2016; 388: 2023-2038.
2) Conforti A, Di Cola I, Pavlych V, Ruscitti P, Berardicurti O, Ursini F, Giacomelli R, Cipriani P. Beyond the joints, the extra-articular manifestations in rheumatoid arthritis. Autoimmun Rev 2020: 102735.
3) Dai Y, Wang W, Yu Y, Hu S. Rheumatoid arthritis-associated interstitial lung disease: an overview of epidemiology, pathogenesis and management. Clin Rheumatol 2020; 40: 1211-1220.
4) Cassone G, Manfredi A, Vacchi C, Luppi F, Coppi F, Salvarani C, Sebastiani M. Treatment of Rheumatoid Arthritis-Associated Interstitial Lung Disease: Lights and Shadows. J Clin Med 2020; 9.
5) Xie S, Li S, Tian J, Li F. Iguratimod as a new drug for rheumatoid arthritis: current landscape. Front Pharmacol 2020; 11: 73.
6) Chen LJ, Zhou YJ, Wen ZH, Tian F, Li JY. Efficacy and safety of iguratimod combined with methotrexate vs. methotrexate alone in rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials. Z Rheumatol 2020. doi: 10.1007/s00393-020-00944-7. Online ahead of print.
7) Nozaki Y, Inoue A, Kinoshita K, Funauchi M, Matsumura I. Efficacy of iguratimod vs. salazosulfapyridine as the first-line csDMARD for rheumatoid arthritis. Mod Rheumatol 2020; 30: 249-258.
8) Suto T, Yonemoto Y, Okamura K, Sakane H, Takeuchi K, Tamura Y, Kaneko T, Ayabe K, Chikuda H. The three-year efficacy of iguratimod in clinical daily practice in patients with rheumatoid arthritis. Mod Rheumatol 2019; 29: 775-781.
9) Lin H, Wu C, Zhu F, Zhang G, Xie Y, Cui Y, Dong G, Zhang X. Anti-fibrotic effect of iguratimod on pulmonary fibrosis by inhibiting the fibroblast-to-myofibroblast transition. Adv Med Sci 2020; 65: 338-347.
10) Zhao L, Mu B, Zhou R, Cheng Y, Huang C. Iguratimod ameliorates bleomycin-induced alveolar inflammation and pulmonary fibrosis in mice by suppressing expression of matrix metalloproteinase-9. Int J Rheum Dis 2019; 22: 686-694.
11) Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Menard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovsky J, Wolfe F, Hawker G. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62: 2569-2581.
12) American Thoracic S, European Respiratory S. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2002; 165: 277-304.
13) Helbich TH, Heinz-Peer G, Eichler I, Wunderbaldinger P, Gotz M, Wojnarowski C, Brasch RC, Herold CJ. Cystic fibrosis: CT assessment of lung involvement in children and adults. Radiology 1999; 213: 537-544.
14) Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET. Standardisation of spirometry. Eur Respir J 2005; 26: 319-338.
15) Stanojevic S, Graham BL, Cooper BG, Thompson BR, Carter KW, Francis RW, Hall GL, Global Lung Function Initiative Twg, Global Lung Function Initiative T. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. Eur Respir J 2017; 50.
16) Chambela MC, Mediano MFF, Ferreira RR, Japiassu AM, Waghabi MC, da Silva GMS, Saraiva RM. Correlation of 6-min walk test with left ventricular function and quality of life in heart failure due to Chagas disease. Trop Med Int Health 2017; 22: 1314-1321.
17) Shao Q, Wang S, Jiang H, Liu L. Efficacy and safety of iguratimod on patients with primary Sjogren's syndrome: a randomized, placebo-controlled clinical trial. Scand J Rheumatol 2020: 1-10.
18) Liu S, Cui Y, Zhang X. Molecular mechanisms and clinical studies of iguratimod for the treatment of ankylosing spondylitis. Clin Rheumatol 2021; 40: 25-32.
19) Duan XW, Zhang XL, Mao SY, Shang JJ, Shi XD. Efficacy and safety evaluation of a combination of iguratimod and methotrexate therapy for active rheumatoid arthritis patients: a randomized controlled trial. Clin Rheumatol 2015; 34: 1513-1519.
20) Zheng N, Guo C, Wu R. Iguratimod is effective in refractory rheumatoid arthritis patients with inadequate response to methotrexate-cyclosporin A-hydroxychloroquine-prednisone. Scand J Rheumatol 2018; 47: 422-424.
21) Xu Y, Zhu Q, Song J, Liu H, Miao Y, Yang F, Wang F, Cheng W, Xi Y, Niu X, He D, Chen G. Regulatory Effect of Iguratimod on the Balance of Th Subsets and Inhibition of Inflammatory Cytokines in Patients with Rheumatoid Arthritis. Mediators Inflamm 2015; 2015: 356040.