Retrospective Study

Immediate-release tofacitinib reduces insulin resistance in non-diabetic active rheumatoid arthritis patients: A single-center retrospective study

Wang CR et al. Tofacitinib reduces insulin resistance in RA

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Abstract

BACKGROUND
An increased risk of insulin resistance (IR) has been identified in rheumatoid arthritis (RA), a chronic inflammatory disorder with elevated levels of pathogenic cytokines. Biologics targeting proinflammatory cytokines can control the disease and improve insulin sensitivity in RA. Although Janus kinase (JAK) signaling can regulate cytokine receptors and participate in RA pathogenesis, it remains to be elucidated whether there is a reduction of IR in such patients under JAK inhibitor (JAKi) therapy.

AIM
To study the effect of JAKi treatment on the reduction of IR in RA patients with active disease.

METHODS
A retrospective study was carried out from April 1, 2017 to March 31, 2021 in a population of non-diabetic patients with active RA who were undergoing tofacitinib (TOF) therapy with 5 mg twice-daily immediate-release formulation.

RESULTS
Fifty-six RA patients, aged 30 years to 75 years (mean ± standard deviation: 52.3 ± 11.1) with Disease Activity Score 28 values ranging from 4.54 to 7.37 (5.82 ± 0.74), were classified into high-IR (> 2.0) and low-IR (≤ 2.0) groups based on their baseline homeostatic model assessment (HOMA)-IR levels. They had no previous exposure to JAKi, and received TOF therapy for no less than 6 mo. In 30 patients who were naïve to biologics, after a 24-week therapeutic period, the high-IR group showed reduced HOMA-IR levels (3.331 ± 1.036 vs 2.292 ± 0.707, P < 0.001). In another 26 patients who were exposed to tumor necrosis factor-α or interleukin-6 blockers, the high-IR group, despite having achieved a decrease but with lower magnitude than in naïve patients, showed reduced HOMA-IR levels (2.924 ± 0.790 vs 2.545 ± 1.080, P = 0.018).
CONCLUSION
In this retrospective study, reduced IR was achieved in non-diabetic active RA patients following 24 wk of TOF therapy.

Key Words: Insulin resistance; Rheumatoid arthritis; Diabetes mellitus; Tofacitinib; Janus kinase inhibitor


Core Tip: An increased risk of insulin resistance (IR) has been identified in rheumatoid arthritis (RA), a chronic inflammatory disorder with elevated levels of pathogenic cytokines. In addition to controlling RA activity, biologics targeting proinflammatory cytokines have been shown to reduce IR, while it remains to be elucidated whether Janus kinase inhibitor (JAKi) therapy can cause IR reduction in such patients. This retrospective study carried out in non-diabetic active RA patients classified into high-IR and low-IR groups before tofacitinib (TOF) therapy demonstrated reduced IR by 24 wk of TOF treatment in the active RA patients with high baseline IR status.

INTRODUCTION
A critical mechanism causing diabetes development is the resistance of target cells to the action of insulin, with ineffective strength of signaling from the receptor to the final action substrates and requiring beyond-normal insulin concentrations to maintain euglycemic status\textsuperscript{[1,2]}. Insulin resistance (IR) manifests from a blockade of tissues to the insulin action upon the uptake, metabolism or storage of glucose, a common feature of human disorders such as diabetes, hyperlipidemia, metabolic syndrome, fatty liver, and obesity\textsuperscript{[1]}. Furthermore, an increased risk of IR has been identified in various
inflammatory disorders with increased levels of proinflammatory cytokines like interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α.\cite{1} Rheumatoid arthritis (RA), a chronic inflammatory disorder with elevated levels of proinflammatory cytokines, has been demonstrated to be associated with IR during its activity\cite{4}. TNF-α is involved in IR pathogenesis through the phosphorylation of inhibitory serine residue of insulin receptor substrate-1 (IRS-1) and reduction of tyrosine phosphorylation of IRS-1 and the β-subunit of the insulin receptor\cite{5,6}. Inactivation of TNF-α by use of recombinant soluble receptor fusion proteins or monoclonal antibodies for IR reduction has been successfully demonstrated in active RA\cite{7}. IL-6 can exert a negative influence on insulin signaling by decreasing tyrosine phosphorylation of IRS-1, inducing recruitment of IRS-1 to its receptor complex for serine phosphorylation, and reducing autophosphorylation of tyrosine residues in the insulin receptor\cite{8,9}. Under treatment with tocilizumab (TCZ; an IL-6 receptor antibody) to inhibit IL-6 signaling in RA, decreased IR was identified in an investigation of 221 active patients as well as in other studies with smaller sample sizes\cite{10-13}. IL-1β is able to impair insulin signaling through activation of the IKKβ/NF-κB pathway to target IRS-1 through serine phosphorylation\cite{14,15}. Anakinra (ANA), an IL-1 receptor antagonist, has been shown to reduce IR in active RA with comorbid type 2 diabetes\cite{16,17}. Altogether, these observations indicate that, biologic therapy targeting pathogenic cytokines can not only control disease activity but also improve insulin sensitivity in active RA patients.

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, including JAKs 1 to 3, STATs 1 to 6, and tyrosine kinase 2, regulates many cytokine and hormone receptors with pathogenic roles in a variety of inflammatory disorders\cite{18}. Notably, different cytokine receptors can recruit their own combinations of JAKs and STATs to activate distinct processes in individual targeted cells, while antagonizing a JAK can suppress more than one cytokine pathway, expanding the efficacy in using such an antagonist in cytokine-targeted therapy\cite{19}. Notably, tofacitinib (TOF) is the first small-molecule pan-JAK inhibitor (JAKi) targeting JAKs 1 to 3\cite{20}. It has been approved by the United States’ Federal Food and Drug Administration (FDA) in
2012 and by European Medicines Agency (EMA) in 2017 for the treatment of RA patients with moderate to high activity and an inadequate response to methotrexate\textsuperscript{21}. This JAKi can act on the JAK/STAT pathway to block the intracellular signaling of multiple cytokines and hormones involved in the pathogenesis of RA and IR\textsuperscript{20,22}. In RA patients, significantly reduced circulating levels of pro-inflammatory cytokines IL-6 and TNF-\(\alpha\), two crucial mediators of IR, were observed since week 4 after initiation of TOF therapy\textsuperscript{23,24}. Furthermore, in a recent large-scale survey of 10,019 RA patients with type 1 or 2 diabetic co-morbidity, the diabetic treatment intensification, \textit{i.e.} addition of a new anti-diabetic medication, was found to be lower for those using TOF than for those using other TNF-\(\alpha\) inhibitors or non-TNF-\(\alpha\)-targeted biologics\textsuperscript{25}. Based on the above findings, there is a therapeutic potential to reduce the IR in active RA patients by TOF therapy.

In this retrospective investigation, the effect of TOF treatment (specifically, 5 mg twice-daily immediate-release formulation) on IR reduction was investigated in 56 non-diabetic patients with active RA, naïve or exposed to biologic therapy and classified into high- and low-IR groups according to the baseline levels of the homeostatic model assessment (HOMA)-IR score.

**MATERIALS AND METHODS**

*Study design and patients*

This study was carried out to analyze the effect of TOF on IR in active RA patients who met the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria\textsuperscript{26}. Each patient received regular monthly follow-up at an outpatient rheumatology clinic of National Cheng Kung University Hospital (NCKUH) from April 1, 2017 to March 31, 2021. This study was approved by the Institutional Review Board and conducted according to the guidelines of Declaration of Helsinki. Before receiving the 5 mg twice-daily immediate-release TOF formulation, all patients had manifested inadequate therapeutic responses to methotrexate for at least 6 mo, having received a weekly dosage of up to 15 mg and at
least one conventional synthetic disease-modifying anti-rheumatic drug (DMARD) at an adequate daily dosage. In addition, low-dose prednisolone was selectively prescribed (daily dosage of no more than 10 mg). Furthermore, patients were excluded from this study if they had previous exposure to targeted synthetic DMARDs treatment or were known to have diabetes, endocrine abnormalities, or critical medical disorders involving heart, lung, liver, and kidney.

**Data collection and measurements**

A detailed review was performed to collect data on the patients’ demographic, clinical, laboratory and medication profiles. In addition to body mass index (BMI), clinical data included the 28-joint Disease Activity Score (DAS28) for RA activity\[^{27}\], classifying as high (> 5.1), moderate (3.2-5.1) or low activity (2.6-3.2) and remission (< 2.6)\[^{28}\]. Laboratory parameters included rheumatoid factor (RF)/anti-citrullinated peptide antibody (ACPA), C-reactive protein (CRP)/erythrocyte sedimentation rate (ESR), and fasting blood levels of glucose and insulin. Seropositive RA was defined by the presence of either ACPA or RF. In addition to TOF, medication profiles were reviewed for use of prednisolone, conventional synthetic DMARDs with cyclosporin, hydroxychloroquine, leflunomide and sulfasalazine, and biologic synthetic DMARDs with abatacept (ABA), adalimumab (ADA), etanercept (ETA), golimumab (GOL), rituximab (RTX), and tocilizumab (TCZ). For the calculation of IR, HOMA-IR, insulin (\(\mu U/mL\)) × glucose (mg/dL)/405, and Quantitative Insulin Sensitivity Check Index (QUICKI), 1/\(\log\) insulin (\(\mu U/mL\)) + glucose (mg/dL) were used in this study. The baseline HOMA-IR levels before TOF therapy were used to classify patients into high-IR (> 2.0) and low-IR (≤ 2.0) groups\[^{7,29}\]. HOMA-IR and QUICKI measurements were obtained from all participants before and after a 24-wk therapeutic period. Furthermore, in the high-IR group, serial calculation data were available in selected patients before and after the TOF treatment.

**Statistical analyses**

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Results were expressed as the mean ± standard deviation. Serial HOMA-IR levels before and after starting TOF therapy were compared with the two-way analysis of variance with a post-hoc test. DAS28, HOMA-IR and QUICKI levels before and after a 24-wk therapeutic period were compared by using the Wilcoxon signed rank test. Different values and frequencies between high-IR and low-IR groups were compared using the Mann-Whitney and the chi-square/Fisher’s exact tests, respectively. Spearman correlation coefficient test was used to correlate DAS28 values and HOMA-IR levels. A P value less than 0.05 was considered as significant in this study.

RESULTS

Baseline characteristics of active RA patients before TOF therapy

Fifty-six patients with 84% females and 88% seropositivity, aged 30 years to 75 years (52.3 ± 11.1 years), received TOF therapy for no less than 6 mo. They had BMI ranging from 19.2 kg/m² to 26.3 kg/m² (22.6 ± 2.0 kg/m²), following the obesity definition of at least 27 kg/m² by the Ministry of Health and Welfare, Taiwan. Their DAS28 values varied from 4.54 to 7.37 (5.82 ± 0.74), all with moderate to high activity. None had exposure to JAKi or succumbed to diabetes, endocrine or critical medical disorders involving major organs, fulfilling the selection criteria in this study.

Before the TOF treatment, 30 patients were naïve to biologic synthetic DMARDs therapy, and their DAS28 values varied from 5.16 to 7.37 (6.291 ± 0.530), all with high disease activity. Table 1 shows the demographic, clinical, laboratory and medication data for 30 naïve patients, classified into high- (n = 18) and low-IR (n = 12) groups according to their baseline HOMA-IR levels. There were no differences between high- and low-IR groups regarding age, sex, BMI, seropositivity and medication profile with prescription frequencies of various conventional synthetic DMARDs and low-dose prednisolone, as well as weekly methotrexate or daily/total prednisolone dosages. Before TOF therapy, there was a positive correlation between DAS28 values and HOMA-IR levels (r = 0.379, P = 0.039; Figure 1A), whereas a negative correlation was
found between DAS28 values and QUICKI levels \(r = -0.423, P = 0.020\). Furthermore, higher DAS28 values were found in the high-IR group compared to the low-IR group \(6.499 \pm 0.472 vs 5.980 \pm 0.470, P = 0.008\), indicating that IR is driven by disease activity in RA patients\(^{[7,34]}\). Notably, there were no changes in the patients’ medication profiles during the 24-wk therapeutic period, with the exception of additional use of TOF.

In addition, 2 patients had an episode of single-dermatome herpes zoster (HZ) infection, both of which responded to valacyclovir therapy, with an incidence rate of 3.03 per 100 person-years. There is a general increased risk of HZ infection in RA patients\(^{[31]}\), but especially in those receiving specific immunosuppressive therapy, including prednisolone (no less than 10 mg/d), methotrexate and anti-TNF-\(\alpha\) biologics\(^{[32]}\). Interestingly, by analyzing health plan data from the United States, TOF-treated RA patients show an incidence rate of 3.87 per 100 person-years in HZ infection\(^{[33]}\).

**Effects of TOF therapy on IR in 30 active RA patients naïve to biologics**

For 3 patients in the high-IR group, there were serial HOMA-IR calculations available for baseline at week 0 and after starting TOF therapy at weeks 4, 8, 12 and 24 (Figure 1B). In comparison with baseline levels, these patients who were naïve to biologics showed significantly lower levels only at week 24 but not at weeks 4, 8 or 12 (Figure 1B, week 0 vs weeks 24, 5.243 \(\pm 0.571\) vs 3.433 \(\pm 0.664\), \(P < 0.01\)). Further comparison with baseline HOMA-IR levels was carried out at week 24.

The levels of HOMA-IR and QUICKI before and after TOF therapy in the high-IR and the low-IR groups are shown in Table 2 and Figure 2. There were significantly reduced DAS28 values in both the high-IR and low-IR groups after the 24-wk TOF treatment (high-IR: 6.499 \(\pm 0.472\) vs 3.006 \(\pm 0.445\), \(P < 0.001\); low-IR: 5.980 \(\pm 0.470\) vs 3.244 \(\pm 0.614\), \(P < 0.001\)). Significantly decreased HOMA-IR levels were found in the high-IR group (3.331 \(\pm 1.036\) vs 2.292 \(\pm 0.707\), \(P < 0.001\); Figure 2B) but not in the low-IR group (1.602 \(\pm 0.294\) vs 1.430 \(\pm 0.293\), \(P = 0.139\); Figure 2C), while significantly increased QUICKI levels were observed in the high-IR group (0.3207 \(\pm 0.0135\) vs 0.3397 \(\pm 0.0154\), \(P\)
< 0.001; Figure 2E) but not in the low-IR group (0.3573 ± 0.0117 vs 0.3634 ± 0.0122, \( P = 0.156 \); Figure 2F). Furthermore, reduced HOMA-IR levels were observed in 17 patients in the high-IR group, while 7 patients in the low-IR group had a reduction in IR (high-IR vs low-IR: 94.4% vs 58.3%, \( P = 0.026 \)). Despite observing no reduced IR after the TOF treatment in the low-IR group, a greater decrease in the values of DAS28 was found in 7 patients with decreased HOMA-IR levels, compared to 5 patients who showed no decrease (2.977 ± 0.237 vs 2.529 ± 0.362, \( P = 0.018 \)), implicating reduced IR involvement in the responses to TOF therapy in active RA patients.

Effects of TOF therapy on IR in 26 active RA patients exposed to biologics

Before TOF therapy, 26 patients had been exposed to biologic synthetic DMARDs for at least 6 mo; the DMARDs included ADA, ETA, GOL and TCZ. This group of patients was consisted of 85% females, 89% with seropositivity, ages 40 years to 75 years (54.7 ± 10.6) and BMI 19.2 to 26.2 (22.96 ± 2.02). Their DAS28 values varied from 4.54 to 6.74 (5.265 ± 0.547), lower than that in those naïve to biologics (5.16 to 7.37, 6.291 ± 0.530, \( P < 0.001 \)). The patients were divided into high- (\( n = 19 \)) and low-IR (\( n = 7 \)) groups according to the baseline levels of HOMA-IR. All patients received methotrexate, while 5 patients in the high-IR group and 1 patient in the low-IR group received low-dose prednisolone therapy. No differences were found in the prescription frequencies of conventional synthetic DMARDs and low-dose prednisolone between two groups of patients.

The levels of HOMA-IR and QUICKI before and after TOF therapy in the high-IR and low-IR groups are shown in Table 3 and Figure 3. There were significantly reduced DAS28 values in both the high-IR and low-IR groups after the 24-wk TOF treatment (high-IR; 5.316 ± 0.807 vs 3.070 ± 0.466, \( P < 0.001 \); low-IR: 5.124 ± 0.470 vs 3.000 ± 0.672, \( P = 0.016 \)). Significantly decreased HOMA-IR levels were found in the high-IR group (2.924 ± 0.790 vs 2.545 ± 1.080, \( P = 0.018 \); Figure 3B) but not in the low-IR group (1.527 ± 0.159 vs 1.453 ± 0.478, \( P = 0.781 \); Figure 3C), while significantly increased QUICKI levels were observed in the high-IR group (0.3273 ± 0.0117 vs 0.3372 ± 0.0214, \( P = 0.008 \); Figure 3E) but not the in low-IR group (0.3589 ± 0.0059 vs 0.3648 ± 0.0204, \( P = 0.813 \); Figure 2F).
DISCUSSION

In this retrospective study, active RA patients receiving a 24-wk TOF treatment had significantly reduced IR among those with high baseline HOMA-IR levels. Furthermore, the clinical use of biologic synthetic DMARDs, including IL-6 and TNF-α blockers, has been demonstrated to reduce IR in non-diabetic active RA patients\textsuperscript{[22]}. For patients with high IR before TOF therapy, baseline HOMA-IR levels were greater in those naïve to biologic agents than in those with an exposure history to anti-IL-6/TNF-α blocker (3.331 ± 1.036 vs 2.924 ± 0.790), while after therapy, there was a decrease in HOMA-IR levels with higher magnitude in naïve than exposed patients (31% vs 13% reduction, respectively). These results demonstrated, in this study, the effect of prescribed biologics on IR in active RA patients before TOF therapy. In addition to type 2 diabetes, IR is a crucial pathophysiological feature of obesity, with both conditions being characterized by persistent low-grade inflammation with increased levels of proinflammatory cytokines\textsuperscript{[34]}. A reduction in IR has been identified in RA patients with a normal weight but not in those with obese status under anti-TNF-α therapy\textsuperscript{[35]}. Despite no identified obesity in the present investigation (all patients had BMI < 27 kg/m\textsuperscript{2}), there were higher BMI levels for patients without IR reduction (n = 7) when compared to those with reduced IR (n = 30) in the high-IR group of patients naïve or exposed to biologic therapy (without vs with IR reduction: 24.53 ± 2.07 vs 22.49 ± 1.91 kg/m\textsuperscript{2}, P = 0.019), reflecting an influence of increased BMI on IR.

Recent investigations have indicated that when prescribed chronically, glucocorticoid (GC) can impair glucose tolerance and induce IR through stimulation of hepatic gluconeogenesis, alteration of insulin release from pancreatic β cells, and decrease in the sensitivity of the liver and muscle to insulin\textsuperscript{[36]}. Since GC therapy is associated with a risk of developing type 2 diabetes, the EULAR recommends to wean RA patients off prednisolone use as early as possible\textsuperscript{[37]}. Although methotrexate may enhance the actions of insulin on glucose transport and metabolism by increasing the extracellular concentration of adenosine, a retrospective study with 21,340 RA patients
under a 12-year follow-up demonstrated that the risk of type 2 diabetes was not lower with the use of methotrexate\textsuperscript{[38]}. Hydroxychloroquine has beneficial effects on the release and sensitivity of insulin, and a multicenter prospective study with 4,950 RA patients showed a lower risk of developing type 2 diabetes in those receiving hydroxychloroquine treatment\textsuperscript{[39]}. In this study, only 14 patients (25\%) received low-dose prednisolone prescription before TOF therapy, and most of them (86\%) had reduced HOMA-IR levels after therapy. Furthermore, there were no differences in the prescription frequencies and the dosages of various conventional synthetic DMARDs between the two patient groups with different baseline IRs, and their medication profiles were stable throughout the therapeutic period. In the present investigation, the effects of 24-wk TOF therapy on IR reduction could be identified in RA patients with high baseline DAS28 values and HOMA-IR levels. Notably, reduced IR in active RA only with high baseline IR has been demonstrated by studies with IR classification occurring before anti-IL-6 or anti-TNF-\(\alpha\) therapy\textsuperscript{[7,11,35,40-42]}.

Accumulated evidence has indicated that the JAK-STAT pathway is required for normal homeostasis of metabolic processes, and when it is dysregulated it contributes to the development of obesity and diabetes type 2 associated with chronic low-grade inflammatory response\textsuperscript{[43]}. Numerous investigations have found the involvement of JAK-STAT signaling in peripheral metabolic organs with adipose, liver, muscle and pancreas, and in diabetes types 1 and 2\textsuperscript{[44]}. A crucial role of JAK signaling, involving JAK2 in particular, has been recognized in regulating metabolic processes with glucose tolerance, insulin sensitivity and adiposity through studies using conditional genetic ablation mouse models. Mice with hepatocyte-specific deletion of JAK2 had reduced adiposity, increased pancreatic \(\beta\)-cell mass and complete protection against high-fat diet (HFD)-induced IR and glucose intolerance\textsuperscript{[45]}. Mice with adipocyte-specific loss of JAK2 showed increased insulin sensitivity and resistance to HFD-induced metabolic inflammation\textsuperscript{[46]}. Furthermore, besides an involvement in the activation of cytokine signaling pathways, the JAK-STAT pathway has been shown to regulate the function and survival of the \(\beta\) cells\textsuperscript{[43,44]}. In the non-obese diabetic mouse model, disruption of
STAT1 could inhibit interferon-γ-induced β cell apoptosis[47], while treating mice with a JAK1/JAK2 inhibitor reversed diabetes through blockade of the MHC class I upregulation on β cells[48]. Notably, experiments with diabetic animal models have demonstrated that systemic administration of TOF, a pan-JAKi, could normalize impaired glucose tolerance and insulin response in Lnk deficient mice, and reduce IR and improve β-cell function in fructose/streptozotocin-induced rats[49,50]. In this clinical study, oral TOF therapy showed a beneficent effect on IR reduction in active RA patients. In sum, these findings implicate JAK-STAT signaling as a pharmacological target in diabetes and the potential for JAKi use in treating diabetic patients.

CONCLUSION
In this retrospective study, we observed a reduction of IR following 24-wk TOF therapy with 5 mg twice-daily immediate-release formulation in non-diabetic RA patients with active disease. Further prospective studies can be performed in both non-diabetic patients and those with comorbid diabetes to clearly elucidate the effect of TOF on IR in active RA.

ARTICLE HIGHLIGHTS

Research background
An increased risk of insulin resistance (IR) has been identified in rheumatoid arthritis (RA), a chronic inflammatory disorder with elevated levels of pathogenic cytokines. Biologics targeting proinflammatory cytokines can control the disease and improve insulin sensitivity in RA.

Research motivation
Although Janus kinase (JAK) signaling can regulate cytokine receptors and participate in RA pathogenesis, it remains to be elucidated whether there is a reduction of IR in such patients under JAK inhibitor (JAKi) therapy.
Research objectives
This study examined the effect of JAKi treatment on the reduction of IR in RA with active disease.

Research methods
A retrospective study was carried out in non-diabetic active RA patients under tofacitinib (TOF) therapy with 5 mg twice-daily immediate-release formulation from 2017 to 2021.

Research results
Fifty-six RA patients aged 30 years to 75 years (52.3 ± 11.1) with DAS 28 values 4.54 to 7.37 (5.82 ± 0.74), were classified into high- and low-IR groups based on the baseline homeostatic model assessment (HOMA)-IR levels. For the 30 patients naïve to biologics, after a 24-wk therapeutic period, reduced levels of HOMA-IR were observed in the high-IR group (3.331 ± 1.036 vs 2.292 ± 0.707, \( P < 0.001 \)). In another 26 patients exposed to tumor necrosis factor-a or interleukin-6 blockers, despite showing a decrease with lower magnitude than that observed in the naïve patients, reduced HOMA-IR levels were also identified in the high-IR group (2.924 ± 0.790 vs 2.545 ± 1.080, \( P = 0.018 \)).

Research conclusions
In this retrospective study, our results demonstrated reduced IR following 24-wk TOF therapy in non-diabetic active RA patients.

Research perspectives
Further prospective studies can be performed in both non-diabetic patients and those with comorbid diabetes to clearly elucidate the effect of TOF on IR in active RA.

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