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BRIEF REPORT

Recombinant Soluble TNF-α Receptor Fusion Protein Therapy Reduces Insulin Resistance in Non-Diabetic Active Rheumatoid Arthritis Patients

Chrong-Reen Wang, and Ming-Fei Liu

Objective. Current evidence highlights a link between insulin resistance (IR) and disease activity in rheumatoid arthritis (RA), suggesting that insulin sensitivity can be improved by treating patients with TNF-α blockers. Although reduced IR has been shown in RA patients who receive monoclonal antibody treatment, the efficacy remains to be elucidated when using recombinant soluble receptor fusion proteins. In particular, etanercept (ETA) is capable of blocking lymphotoxin-α, a cytokine-related to IR-associated disease status.

Methods. A prospective study was carried out in nondiabetic active RA patients receiving a 25-mg subcutaneous ETA injection twice weekly.

Results. Thirty patients aged 31 to 73 years (50.9 ± 10.6), naïve to biological and targeted synthetic disease-modifying antirheumatic drugs with DAS28 scores of 5.17 to 7.49 (6.11 ± 0.66), were classified into high-IR and low-IR groups based on their baseline homeostatic model assessment (HOMA)-IR levels. No differences were found between the two groups in terms of age, sex, weight, body mass index, seropositivity, and medication profiles before the injection. After a 24-week therapeutic period, there were reduced HOMA-IR levels in all patients in the high-IR group (3.390 ± 0.636 to 2.234 ± 0.870, $P < 0.001$). A greater decrease in DAS28 values was found in patients with reduced IR than those without a reduction (2.54 ± 0.67 versus 1.46 ± 0.46, $P = 0.006$) in the low-IR group.

Conclusion. We observed an improvement in insulin sensitivity in nondiabetic active RA patients following 24-week recombinant soluble TNF-α receptor fusion protein therapy.

INTRODUCTION

Tumor necrosis factor (TNF)-α is involved in the pathogenic mechanisms of insulin resistance (IR) by reducing tyrosine phosphorylation of insulin receptor and insulin receptor substrate-1 (IRS-1), which decreases the insulin signaling transduction and induces serine phosphorylation of IRS-1 to act as a receptor inhibitor (1). Further studies examining the in vivo effects of anti–TNF-α therapy on IR reduction failed to demonstrate beneficial results in the investigated populations with type 2 diabetes and obesity, two less inflammatory IR-associated conditions (2). This proinflammatory cytokine plays a central role in the rheumatoid arthritis (RA) pathogenesis and progression, and its antagonizing biologics display significant efficacy in reducing the disease activity (3). Two strategies have been adopted to inactivate TNF-α: to use monoclonal antibodies (mAbs) and recombinant soluble receptor fusion proteins, both of which bind to this cytokine to prevent inflammatory processes (4). IR in RA is driven primarily by the disease activity with elevated circulating levels of TNF-α in patients with increased IR (5,6). For mAb therapy, despite the observation of reduced IR in patients receiving infliximab (IFX) treatment, there are contradictory findings for those treated with adalimumab (ADA) (7). The mixed therapeutic effects with a recombinant soluble receptor fusion protein and different mAbs in improving insulin sensitivity have been demonstrated in RA (8–11). Nevertheless, it remains to be elucidated whether soluble receptor fusion protein therapy alone can reduce IR in such patients.

In this prospective study, the efficacy of etanercept (ETA) therapy in IR reduction was examined in 30 nondiabetic patients with active RA who were sorted into high-IR and low-IR groups according to their baseline homeostatic model assessment (HOMA)-IR levels. In addition, the literature on the therapeutic

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influence of various TNF blockers on insulin sensitivity in nondiabetic patients with RA was reviewed.

PATIENTS AND METHODS

Study patients. Patients were recruited from the outpatient rheumatology clinic. They met the 2010 RA classification criteria (12) and were scheduled to receive the subcutaneous injection of ETA with a 25-mg twice weekly regimen. They had refractory therapeutic responses for at least 6 months to treatment with methotrexate 15 mg/wk plus at least one conventional synthetic disease-modifying antirheumatic drug (DMARD)—including hydroxychloroquine, leflunomide, and sulfasalazine—at an adequate daily dosage, as well as low-dose prednisolone (no more than 10 mg/d). There were detailed reviews of demographic, clinical, laboratory, and medication profiles. The Institutional Review Board approved this study, and informed consent was obtained from each participant. Patients were excluded from this study if they had received biological/targeted synthetic DMARDs or medications with established influence on glucose metabolism or if they were known to have diabetes, endocrine abnormalities, or other medical disorders involving any major organs, such as the heart, lung, liver, or kidney.

Study protocol. The DAS28 score and body mass index (BMI) were assessed in each participant prior to the evaluation of IR. Before the ETA injection, venous blood samples were obtained after patients fasted overnight in order to determine glucose, insulin, and C-reactive protein levels as well as the erythrocyte sedimentation rate. For the calculation of IR, HOMA-IR, insulin (μU/mL) × glucose (mg/dL)/405, and Quantitative Insulin Sensitivity Check Index (QUICKI), 1 / (log insulin (μU/mL) + log glucose (mg/dL)) were used in this study (13). The baseline HOMA-IR levels were used to classify patients into high-IR (>2.0) and low-IR (≤2.0) groups (11,14). HOMA-IR and QUICKI measurements were carried out in all participants before and after a 24-week therapeutic period. Serial calculations were performed in selected cases.

Statistical analysis. Results were expressed as the mean ± standard deviation. Serial HOMA-IR levels before and after starting the ETA injection were compared with the two-way analysis of variance with a post-hoc test. DAS28, HOMA-IR, and

Table 1. Baseline data of 30 nondiabetic patients with active RA before ETA therapy

Group (n)	All (n = 30)	High-IR (n = 12)	Low-IR (n = 18)	*P* value[a]
Sex (female %)	80.0	75.0	83.3	0.660
Age (y)	50.9 ± 10.6 (31-73)	54.5 ± 10.7 (34-73)	48.5 ± 10.2 (31-70)	0.079
Body weight (kg)	56.8 ± 6.2 (45-70)	57.8 ± 8.4 (45-70)	56.1 ± 4.4 (49-63)	0.539
Body height (cm)	159.5 ± 7.5 (148-175)	157.8 ± 6.6 (148-168)	160.6 ± 8.0 (150-175)	0.445
BMI (kg/m^2)	22.28 ± 1.96 (19.3-25.7)	23.08 ± 2.08 (20.0-25.7)	21.56 ± 1.59 (19.3-24.8)	0.069
Seropositivity (%)	83.3	83.3	83.3	1.0
DAS28	6.11 ± 0.66 (5.17-7.49)	6.61 ± 0.42 (5.73-7.31)	5.78 ± 0.59 (5.17-7.49)	<0.001
ESR (mm/hr)	38.7 ± 17.1 (3-75)	44.2 ± 14.7 (19-65)	35.1 ± 18.0 (3-75)	0.112
CRP (mg/L)	14.27 ± 5.60 (1.5-28.8)	15.58 ± 4.58 (9.0-23.5)	13.30 ± 6.01 (1.5-28.8)	0.162
Glucose (mg/dL)	88.3 ± 8.7 (70-108)	94.7 ± 8.6 (85-108)	84.1 ± 5.8 (70-94)	0.002
Insulin (μIU/mL)	8.77 ± 5.31 (2.1-18.1)	14.63 ± 2.72 (9.0-18.1)	4.87 ± 1.72 (2.1-8.2)	<0.001
HOMA-IR	1.963 ± 1.279 (0.451-4.437)	3.390 ± 0.636 (2.044-4.437)	1.012 ± 0.362 (0.451-1.638)	<0.001
QUICKI	0.361 ± 0.040 (0.307-0.442)	0.320 ± 0.010 (0.307-0.343)	0.389 ± 0.026 (0.354-0.442)	<0.001
MTX (%), Dosage (mg/wk)	100 15	100 15	100 15	1.0 1.0
GC (%), Dosage (mg/d)	80.0 6.0 ± 4.0	75.0 5.6 ± 4.3	83.3 6.3 ± 3.9	0.660 0.702
Hydroxychloroquine (%)	93.3	100	88.9	0.503
Sulfasalazine (%)	76.7	75.0	77.8	1.0
Leflunomide (%)	30.0	33.3	27.8	0.686

Abbreviation: BMI, body mass index; CRP, C-reactive protein; DAS28, disease assessment score of 28 joints; ESR, erythrocyte sedimentation rate; ETA, etanercept; GC, glucocorticoid; HOMA, homeostatic model assessment; IR, insulin resistance; MTX, methotrexate; QUICKI, Quantitative Insulin Sensitivity Check Index; RA, rheumatoid arthritis.
[a] High IR versus low IR.

QUICKI levels before and after the study period were compared using the Wilcoxon signed-rank test, and different values and frequencies between high-IR and low-IR groups were compared using the Mann-Whitney and the χ^2/Fisher's exact tests, respectively. A Pearson correlation coefficient test with linear regression analysis was performed to correlate DAS28 and HOMA-IR levels. A *P* value less than 0.05 was considered significant in this study.

Literature review. The English literature on PubMed was reviewed for reported effects on IR reduction through use of TNF blockers in RA patients, excluding the studies that enrolled diabetic subjects. The clinical, laboratory, and medication data were examined in detail.

RESULTS

Baseline characteristics. Thirty cases, 24 females aged 31 to 73 years (50.9 ± 10.6), fulfilled the selection criteria in this study. Demographic, clinical, laboratory, and medication data before the ETA injection are shown in Table 1. No differences were found between the high-IR and low-IR groups in terms of age, sex, seropositivity, weight, and BMI. Regarding medication profiles, there were no differences in prescription frequencies of various conventional synthetic DMARDs and dosages of weekly methotrexate or daily prednisolone. Their weight, BMI, and medication profiles were stable without changes through the study period. A positive correlation with linearity was found between DAS28 values and HOMA-IR levels before the therapy ($r = 0.648$, $P < 0.001$), and higher DAS28 values were found in the high-IR group than in the low-IR group (6.61 ± 0.42 vs 5.78 ± 0.59, $P < 0.001$). These findings were consistent with the concept that IR in RA is driven principally by disease activity (5,6). In addition, one case had injection site reactions, a frequently observed adverse effect in patients receiving ETA therapy (15).

Therapeutic effects. In three patients with high baseline IR, serial measurements of HOMA-IR were performed before and after starting ETA therapy. Based on previous reports in RA patients treated with TNF blockers, HOMA-IR levels were calculated at weeks 0, 2, 4, 8, 16, and 24. Compared with the data at week 0, all patients had significantly lower levels only at week 24 but not at any other time points (Figure 1A, 3.531 ± 0.153 vs 2.048 ± 0.329, $P < 0.01$). Further measurements were carried out at weeks 0 and 24.

The levels of HOMA-IR before and after ETA therapy are listed in Table 2. Significant differences were observed in the high-IR group but not in the low-IR group (Figure 1B, 3.390 ± 0.636 to 2.234 ± 0.870, $P < 0.001$,and Figure 1C, 1.012 ± 0.362 to 0.796 ± 0.442, $P = 0.098$). A reduction in IR was observed in all patients in the high-IR group, whereas 11 patients in the low-IR group had reduced IR (high-IR vs low-IR, 100% vs 61%, $P = 0.024$). A greater decrease in DAS28 values was found in 11

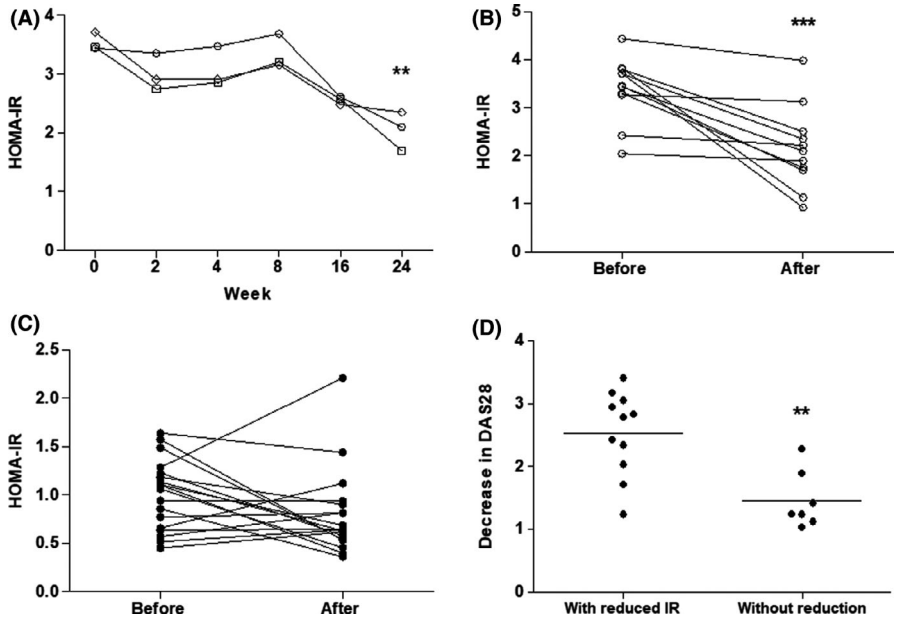

Figure 1. Homeostatic model assessment insulin resistance (HOMA-IR) levels in patients with rheumatoid arthritis (RA) before and after starting etanercept (ETA) therapy. **A**, Serial calculations of HOMA-IR levels in three patients with high baseline IR at weeks 0, 2, 4, 8, 16, and 24 after ETA therapy; there were significantly lower levels at week 24 compared with those at week 0 ($P < 0.01$). **B**, HOMA-IR levels in the high-IR group with 12 patients at weeks 0 and 24 after ETA therapy ($P < 0.001$). **C**, HOMA-IR levels in the low-IR group with 18 patients at weeks 0 and 24 after ETA therapy ($P = 0.098$). **D**, A decrease in DAS28 values in 18 patients in the low-IR group divided into 11 with reduced IR and 7 without a reduction after 24-week ETA therapy ($P = 0.006$). Empty circles represent patients with high baseline IR. Filled circles represent patients with low baseline IR. DAS28, disease activity score in 29 joints. $^{**}P < 0.01$, $^{***}P < 0.001$.

Table 2. Changes in DAS28 scores and IR before and after ETA therapy

Group (n)	Before	After	*P* value[a]
All (n = 30)			
DAS28	6.11 ± 0.66 (5.17-7.49)	3.52 ± 0.79 (1.61-4.47)	<0.001
Decrease in DAS28		2.59 ± 1.03 (1.03-4.82)	
HOMA-IR	1.963 ± 1.279 (0.451-4.437)	1.371 ± 0.957 (0.359-3.982)	<0.001
QUICKI	0.361 ± 0.040 (0.307-0.442)	0.383 ± 0.043 (0.312-0.462)	0.003
High IR (n = 12)			
DAS28	6.61 ± 0.42 (6.12-7.31)	3.30 ± 0.89 (1.61-4.38)	<0.001
Decrease in DAS28		3.31 ± 0.96 (1.88-4.82)	
HOMA-IR	3.390 ± 0.636 (2.044-4.437)	2.234 ± 0.870 (0.925-3.982)	<0.001
QUICKI	0.320 ± 0.010 (0.307-0.343)	0.343 ± 0.022 (0.312-0.389)	0.003
Low IR (n = 18)			
DAS28	5.78 ± 0.59 (5.17-7.49)	3.66 ± 0.71 (2.32-4.47)	<0.001
Decrease in DAS28		2.12 ± 0.79 (1.03-3.40)	
HOMA-IR	1.012 ± 0.362 (0.451-1.638)	0.796 ± 0.442 (0.359-2.209)	0.098
QUICKI	0.389 ± 0.026 (0.354-0.442)	0.409 ± 0.031 (0.343-0.462)	0.074

Abbreviation: DAS28, disease activity score of 28 joints; ETA, etanercept; HOMA, homeostatic model assessment; IR, insulin resistance; QUICKI, Quantitative Insulin Sensitivity Check Index.
[a] Before versus after.

patients with reduced IR than in the 7 patients without a reduction in the low-IR group (Figure 1D, 2.54 ± 0.67 vs 1.46 ± 0.46, $P = 0.006$), which suggests that IR reduction is involved in the therapeutic responses to ETA injection in RA.

Low-dose prednisolone was prescribed to 24 patients, with similar use frequencies and daily dosages between the two groups. Significant differences in HOMA-IR levels after therapy were shown in the high-IR group (n = 9, 3.460 ± 0.640 to 2.412 ± 0.908, $P = 0.004$) but not in the low-IR group (n = 15, 1.022 ± 0.347 to 0.815 ± 0.478, $P = 0.135$).

Literature review. Table 3 lists 12 studies that examines the effects on IR reduction by antagonizing TNF-α in nondiabetic patients with RA (7–11,16–22). One was treated with ADA alone, four with at least two TNF blockers, and seven with IFX alone. One only used the hyperinsulinemic euglycemic glucose clamp to measure IR. Eleven calculated the HOMA-IR levels and ten had significant IR reduction.

DISCUSSION

IR is a crucial pathophysiological feature of type 2 diabetes and obesity, both of which are conditions characterized by low-grade chronic inflammation with increased TNF-α levels (2). Because hyperglycemia, a critical contributor to IR, can interfere with the effects of TNF-α blockers on insulin sensitivity, nearly all published reports examined the studied population in non-diabetic patients. It is well recognized that persistent inflammation is a crucial cause of obesity-induced IR, with expanded adipose tissues containing TNF-α–producing adipocytes and macrophages, further reducing insulin sensitivity of the muscle through the stimulation of JNK and NF-κB signaling pathways (23). TNF-α antagonists can decrease lipolysis within the muscle, leading to lower production of intramuscular fatty acid metabolites and reduced serine phosphorylation of IRS-1, followed by a reduction in IR (1,23). An improvement in insulin sensitivity has been identified in patients with RA who are within a normal weight range but not an obese range receiving the anti–TNF-α therapy (11). None of the patients in this study were obese, with BMI ranging from 19.3 to 25.7, where obesity is defined as no less than 27 kg/m^2 by the Ministry of Health and Welfare in Taiwan.

The administration of glucocorticoid can impair the metabolic actions of insulin in the liver and adipose tissues, and recent investigations have indicated that when prescribed chronically, such a medication may interfere with glucose tolerance, even at lower dosages (24). In this study, a significant decrease in HOMA-IR levels after ETA therapy was demonstrated in patients receiving low-dose prednisolone prescription, which indicates that TNF-α is a dominant contributor to IR in active RA. Notably, previous reports suggest that the use of conventional synthetic DMARDs in RA can have a significant influence on insulin sensitivity (25). Despite the conflicting results related to the effects of methotrexate use on glucose tolerance, most studies support a favorable outcome in IR reduction following hydroxychloroquine therapy. In our patients, no differences were found in the prescription frequencies of conventional synthetic DMARDs between the two groups with different baseline IR, and the medication profiles were stable through the therapeutic period. Because of the lack of obesity-induced IR in the investigated population, the beneficial effects of ETA therapy on insulin sensitivity could be demonstrated in patients with RA, particularly in those with high baseline IR.

Although the inconsistent efficacy in IR reduction by antagonizing TNF-α in RA could be due to low patient numbers and considerable heterogeneity of enrolled participants, such as disease activity and BMI, the changes in insulin sensitivity might be determined by various entities of TNF-α blockers. Favorable results were obtained from all investigations receiving IFX infusion (16–22), whereas one study with ADA therapy failed to demonstrate a beneficent outcome in insulin sensitivity (7), raising a concern regarding the diverse therapeutic potency in IR reduction among different mAbs. In comparison with antibodies, soluble receptor fusion proteins have the distinct pharmacokinetic and pharmacodynamic actions in patients with RA (4,26). In particular, ETA is

Table 3. Studies on the effects of TNF blockers on IR reduction in nondiabetic RA

No.	Year	Character	Pt Number, TNF Blockers	Clinical Features	Duration	Effect on IR in RA	Ref.
1	2004	mAb	2, IFX	Nondiabetic	4 or 8 months	Improved HOMA-IR only in high IR	16
2	2005	mAb	28, IFX	Nondiabetic	6 months	Improved HOMA-IR only in high IR	17
3	2006	mAb	27, IFX	Nondiabetic	2 hours after infusion	Improved HOMA-IR	18
4	2007	mAb	5, IFX	Nondiabetic	6 weeks	Improved CLAMP	19
5	2007	mAb	9, ADA	Nondiabetic, high IR	8 weeks	No effect on HOMA- IR, CLAMP	7
6	2007	mAb	19, IFX	Nondiabetic	14 weeks	Improved HOMA-IR	20
7	2007	mAb	7, IFX	Nondiabetic	5-15 months	Improved HOMA-IR	21
8	2008	mAb	21, IFX	Nondiabetic	24 weeks	Improved HOMA-IR	22
9	2008	mAb, rSTNFRFP, mixed	20, ETA, 18, IFX, (38 total)	Nondiabetic	24 weeks	Improved HOMA-IR	8
10	2011	mAbs, rSTNFRFP, mixed	8, ADA, 6, IFX, 1, ETA, (15 total)	Nondiabetic	12 months	No effect on HOMA- IR	9
11	2012	mAbs, rSTNFRFP, mixed	49, IFX, 11, ADA, 1, ETA, (61 total)	Nondiabetic	12 weeks	Improved HOMA-IR in high IR	10
12	2012	mAbs, rSTNFRFP, mixed	20, IFX, 11, ETA, 1, ADA, (32 total)	Nondiabetic	6 months	Improved HOMA-IR in high IR, non-obese	11
13	2020	rSTNFRFP	30, ETA	Nondiabetic, non-obese	24 weeks	Improved HOMA-IR in high IR	PS

Abbreviation: ADA, adalimumab; CLAMP, hyperinsulinemic euglycemic glucose clamp; ETA, etanercept; HOMA, homeostatic model assessment; IFX, infliximab; IR, insulin resistance; mAb, monoclonal antibody; No., number; PS, present study; Pt, patient; RA, rheumatoid arthritis; rSTNFRFP, recombinant soluble TNF-α receptor fusion protein; TNF, tumor necrosis factor.

a TNF-α antagonist capable of blocking lymphotoxin (LT)-α (27). Genetic analyses have linked polymorphisms in genes encoding LT-α to individuals with IR-associated disease status, including type 2 diabetes and metabolic syndrome (28,29). In spite of an observation of improved insulin sensitivity in 16 patients receiving the ETA injection, there was no exclusion of diabetes and no IR classification in the studied population (30). Our report with 30 nondiabetic patients demonstrated a reduction in IR after ETA therapy, especially in the high-IR group.

In conclusion, we observed an improvement in insulin sensitivity following 24-week recombinant soluble TNF-α receptor fusion protein therapy in nondiabetic patients with active RA.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article and responsible for article revision. All authors approved the final version to be submitted for publication. All authors had full access to all data in the study and take responsibility for the integrity of the data and accuracy of data analysis.

Study concept and design. Wang.

Acquisition of data. Wang, Liu.

Analysis and interpretation of data. Wang, Liu.

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