MEGA JOURNAL OF CASE REPORTS

OPEN ACCESS

Case Presentation

Compiled Date: July 24, 2024

Differential Effects of TNFα and IL 6 Inhibitors on Glucose Tolerance and Lipid Metabolism - Clinical Retrospective Analysis in Patients with Rheumatoid Arthritis

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Abstract

Objectives: We have examined comparative effects of TNFα and IL-6 inhibitors on glucose tolerance and lipid metabolism in patients with rheumatoid arthritis (RA).

Methods: We have selected 30 cases of RA patients who were able to follow up for 12 months (M). Patients with RA were divided to 3 groups by the treatments as follows: TNF inhibitors (TNFi) with methotrexate (MTX) (TNFi+MTX), IL-6 with and without MTX (IL-6±MTX) and MTX alone. Body weight (BW), HbA1c, LDL-C, HDL-C, LDL-C/HDLC(L/H) and disease activity score (DAS) were measured before and after 6 and 12 M.

Results: There were no differences of DAS between each group before and after 6 and 12 M. DAS in each group was a significantly decreased compared with before ($P < 0.05$-0.001). HbA1c levels in TNFi+MTX were not significantly different, but those in MTX alone and IL-6±MTX were significantly improved, respectively ($P<0.01$-0.05). There were no significant differences of BW between each group. HDL-C and LDL-C in IL-6±MTX were significantly increased, respectively ($P< 0.01$). L/H in TNFi+MTX was significantly ($P<0.05$) decreased.

Conclusions: Effect of glucose tolerance in IL-6 inhibitors was better than TNFi in glucose intolerance. However, TNFi was better than IL-6 inhibitors in lipid metabolism.

Keywords: TNF inhibitors; IL-6 inhibitor; Glucose tolerance; Lipid metabolism; Rheumatoid arthritis

Introduction

Association between inflammation-mediated cytokines such as TNFα and IL-6 and glucose tolerance has been reported in animal models and

cultured insulin-sensitive cells [1-4]. In briefly, IL-6 stimulated glucose tolerance and increased skeletal muscle PPARα and UCP2 expression in rat [1], moreover, IL-6 enhanced glucose-stimulated insulin secretion via activation of PLC-IP3 pathway [2] and IL-6 improved energy and glucose homeostasis in mice [3], indicating that in both rat and mice experimental results showed IL-6-stimulated improvement of insulin action and secretion. Recently, Chen et al. [5] reported that blocking of IL-6 signaling improves glucose tolerance via suppression of glucagon secretion. On the other hand, TNF-α causes impaired glucose tolerance and increased insulin resistance in the insulin resistance atherosclerosis Study [4], and Guputa-Ganguli et al reported improvement of glucose tolerance by treatment with anti-THF-α antibody in patients with rheumatoid arthritis. However, it is not clear that TNFα and IL-6 actually influence on glucose tolerance positively or negatively in medical treatment. Recently, biologic agents such as TNFα and IL-6 inhibitors have been appeared in the treatment of rheumatoid arthritis. Patients with rheumatoid arthritis have been shared in the benefits of biologic agents. We have examined comparative effects of TNF-α and IL-6 inhibitors on glucose tolerance and lipid metabolism in patients with rheumatoid arthritis.

Methods

From 2013 to 2017, 589 patients with RA have been screened by HbA1c level (more than 5.6%), treatment with Methotrexate (MTX) and treatment with biologic agents with or without MTX. We have excluded patients with RA who are treated with glucocorticoids and/or insulin. Finally, we have selected 30 cases of RA patients who were able to follow up for 12 months. Patients with RA were divided into 3 groups by the treatments as follows: TNF-α inhibitors (Golimumab 100 mg /month in 4 cases, Etanercept 50 mg/week in 5 cases, infliximab 10 mg/kg/month with MTX (TNFi+MTX) in 1 case, IL-6 inhibitor (TCZ:tocilizumab 162 mg /2 weeks) with and without MTX (TCZ±MTX) and MTX alone. Body weight, HbA1c, LDL-C, HDL-C, LDL-C/HDLC(L/H) and disease activity score (DAS28ESR) were measured before and after 6 and 12 months as shown in Table 1. Each group has 2-3 diabetic patients treated with metformin and/or dipeptidyl peptidase 4 inhibitor (DPP-4 inhibitor). Statistical analyses were used by paired and unpaired t test using JMP 12.2.0.

Table 1: Baseline characteristics.

	TNFi + MTX	MTX alone	TCZ ± MTX
Treatment episode	10	10	10
Women, %	90	50	100
Age, year	59.5 ± 14.37	56.2 ± 15.49	60.1 ±14.80

HbA1c, %	6.05 ± 0.39	6.42 ± 1.05	6.20 ± 0.15
Body weight, kg	55.56 ± 4.65	52.48 ± 10.62	52.61 ± 6.30
DAS28-ESR	4.95 ± 0.95	4.89 ± 1.31	5.26 ± 1.22
Positive anti-CCP	8 (80%)	5 (50%)	8 (80%)
Positive RF	8 (80%)	6 (60%)	8 (80%)
MTX dosage, mg/w	9.00 ± 2.16	8.40 ± 2.06	(7.71 ± 2.42)*
Diabetes mellitus	2 (20%)	2 (20%)	3 (30%)
Diabetic treatment	1 case; metformin 500 mg 1 case; DPP4 inhibitor	1case; DPP4 inhibitor 1 case; none	1 case; metformin 500mg+ DPP4 inhibitor 1 case; DPP4 inhibitor 1 case; none

Values are indicated as means ± SD. TNFi: tumor necrosis factor inhibitor; DMARDs: disease modifying antirheumatic drugs; ESR: erythrocyte sedimentation rate; anti-CCP: anti-cyclic citrullinated peptide antibodies; RF: rheumatoid factor; MTX: methotrexate; DPP4: dipeptidyl peptidase 4. * 7cases treated with MTX

Results

Change of DAS28ESR in each group

There were no differences of DAS28ESR between each group before and after 6 and 12 months. DAS28ESR in each group for 6M and 12M was a significantly decreased compared with before (P < 0.05- 0.001) as shown in **Figure 1**.

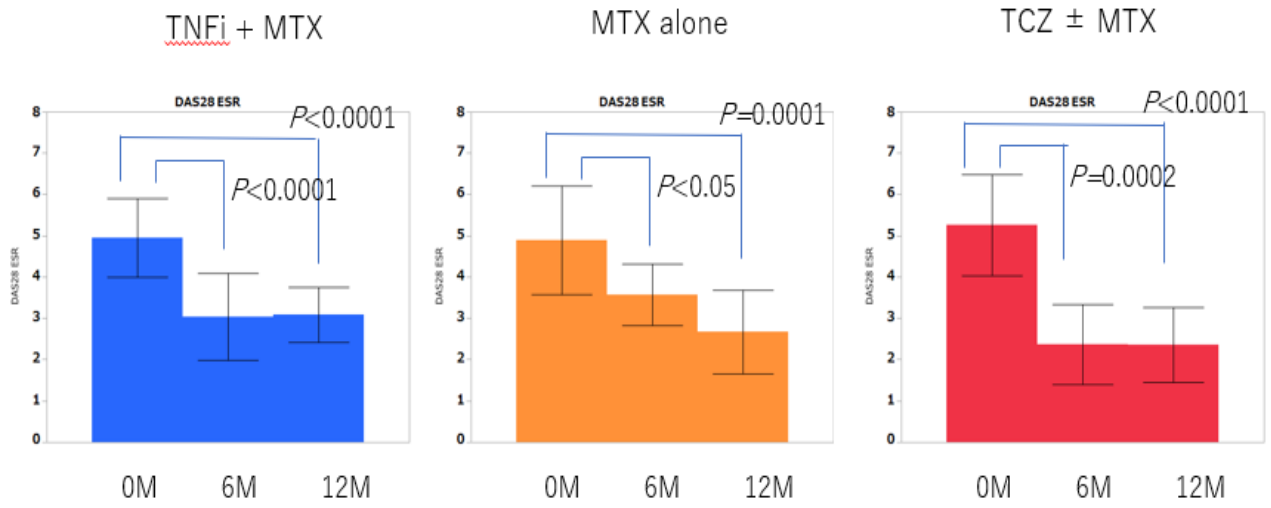

Figure 1: Alterations of disease activity before (0M)) and after treatment for 6 and 12 months (M). Values are indicated as means ± SD. Statistical significance indicated as P<0.0001-0.05. TNFi: tumor necrosis factor inhibitor MTX: methotrexate DAS28ESR: disease activity score 28 ESR.

Changes of body weight in each group

Alteration of body weight affects on glucose tolerance. Therefore, we have measured body weight before and after treatment for 6 M and 12 M in each group. There were no significant differences of changes in body weight between each group. Body weight in MTX was only significantly increased after 12 M (before 52.4 kg, 6M 53.0kg, 12 M 54.2 kg, P< 0.05) as shown in **Figure 2**. These results do not depend on changes of body weight as shown in **Figure 1**.

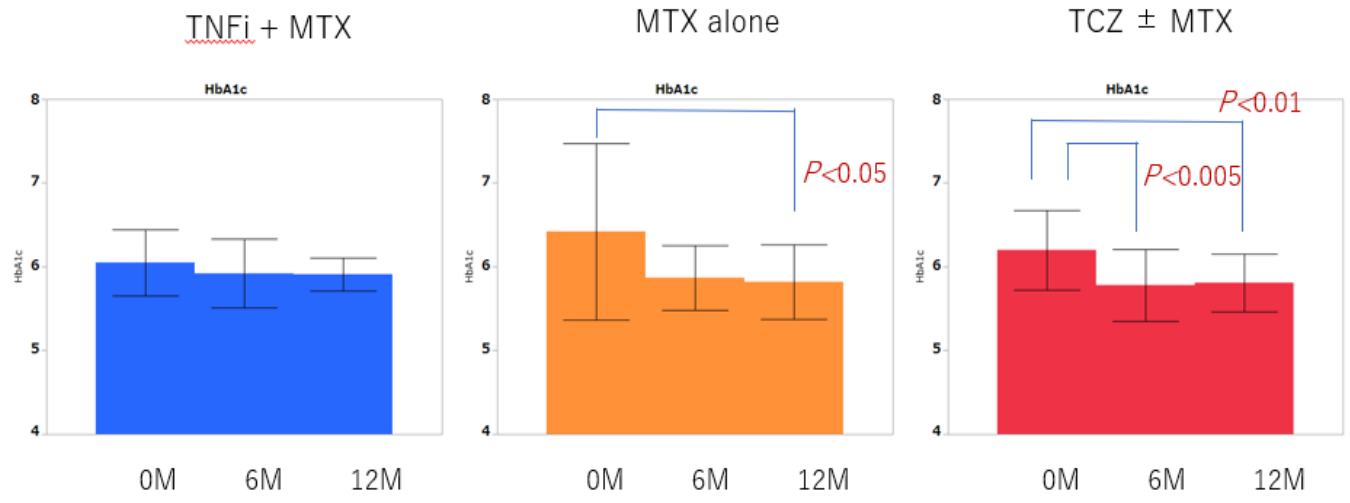

Figure 2: Alterations of HbA1c before (0M) and after treatment 6 and 12 months (M). Values are indicated as means ± SD. Statistical significance indicated as P<0.005-0.05. TNFi: tumor necrosis factor inhibitor MTX: methotrexate DAS28ESR:

Changes of HbA1c in each group

HbA1c level in TNFi+MTX were not significantly different (before 6.08%, 6 M 5.92%, 12 5.91), but those in MTX alone and TCZ±MTX were significantly improved (before 6.42% and 6.2%, 6M 5.87% and 5.78% (P< 0.05), 12M 5.82%, (P< 0.05) and 5.81%, (P< 0.01), respectively **(Figure 3)**.

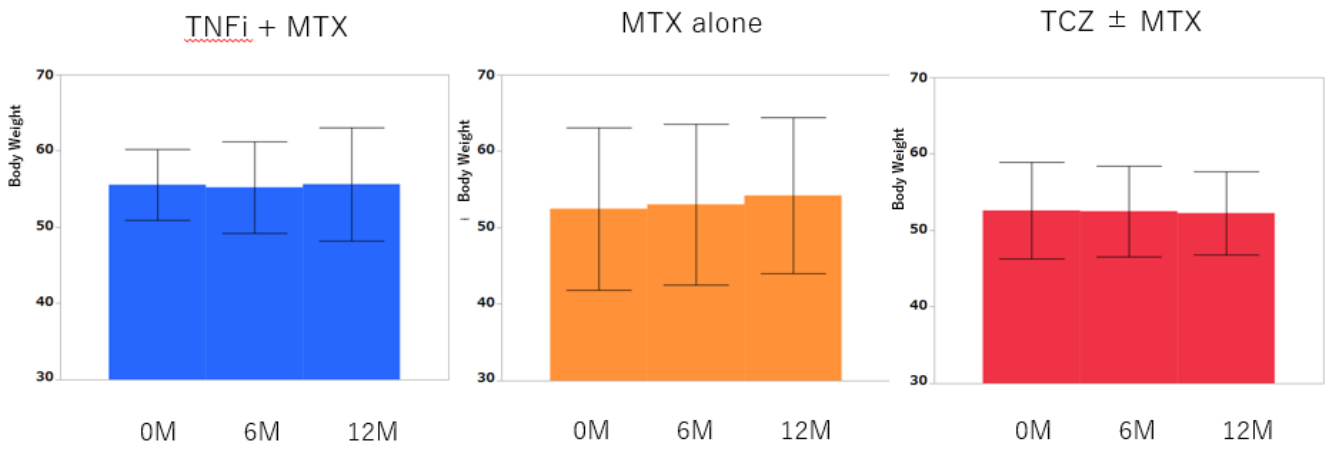

Figure 3: Alterations of body weight and before (0M) and after treatment for 6 and 12 months (M). Values are indicated as means ± SD. Statistical significance indicated as P<0.05.

Changes of Lipid profile in each group

HDL-C and LDL-C in TCZ±MTX were significantly (P< 0.01) increased (before 58.2 mg/dl and 123.2 mg/dl, 6M 71.7 mg/dl and 148.5 mg/dl, 12M 63.4 mg/dl and 144.2 mg/dl), respectively **(Figure 4 and 5)**. L/H in TNF+MTX was significantly (P<0.05) increased (before 2.13, &M 1.81, 12M 1.88) **(Figure 6)**.

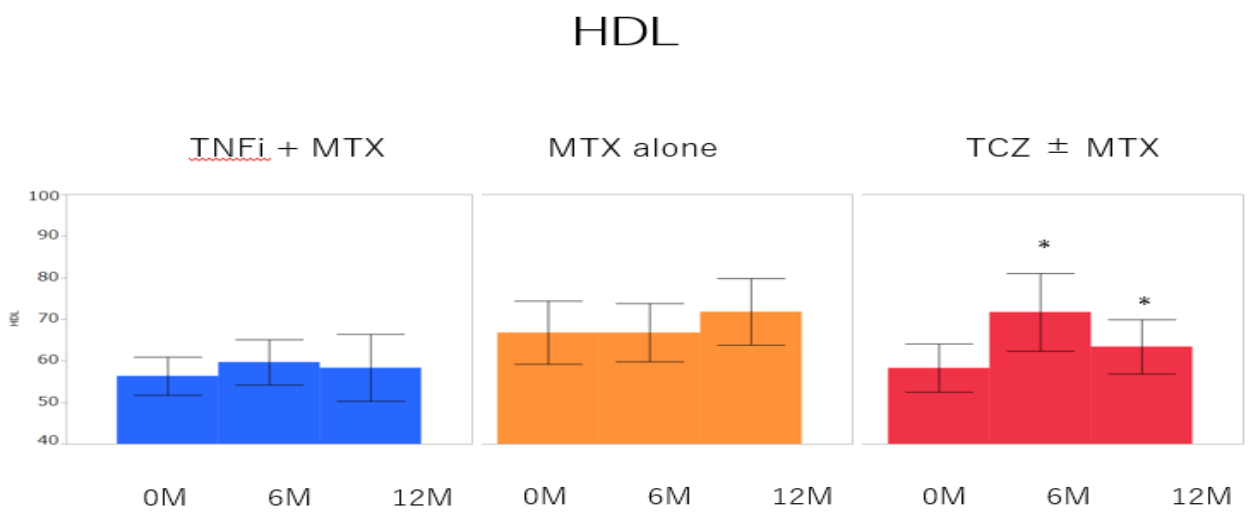

Figure 4: Alterations of HDL levels before and after treatment for 6 and 12 months (M). Values are indicated as means ± SD. There are significant differences before (0M) and after treatment with TCZ±MTX for 6 and 12 months (M) (* P<0.01), but not treatment with TNFi+MTX and MTX alone.

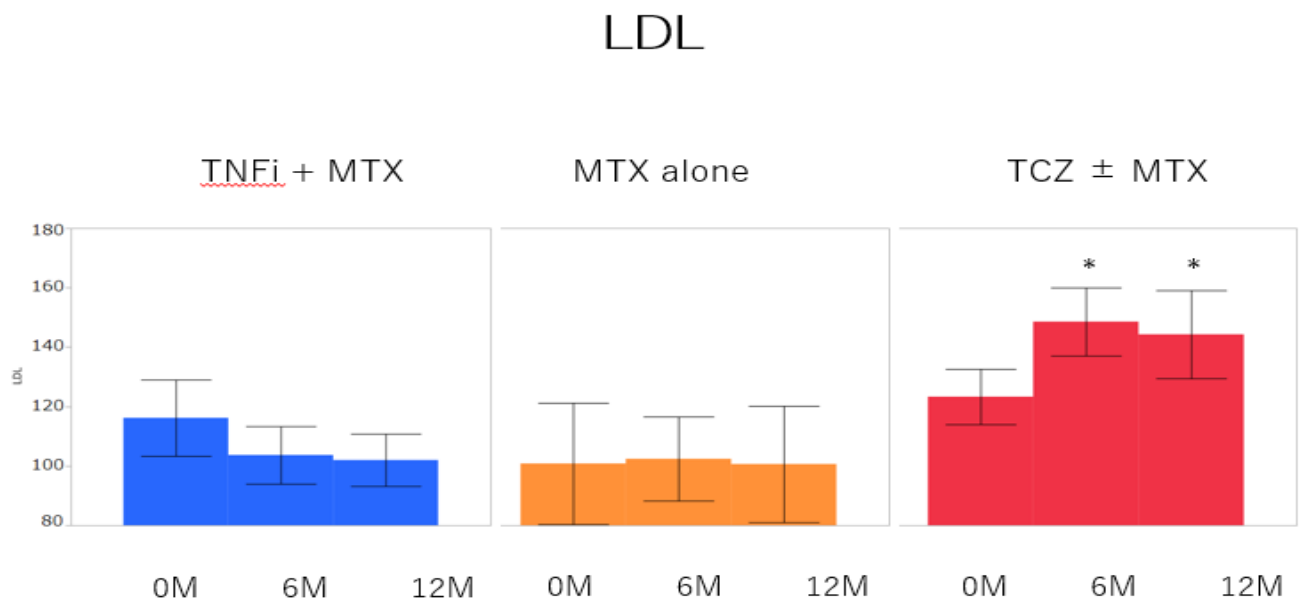

Figure 5: Alterations of LDL levels before and after treatment for 6 and 12 months(M). Values are indicated as means ± SD. There are significant differences before (0M) and after treatment with TCZ±MTX for 6 and 12 months (M) (* P<0.01, but not treatment with TNFi+MTX and MTX alone.

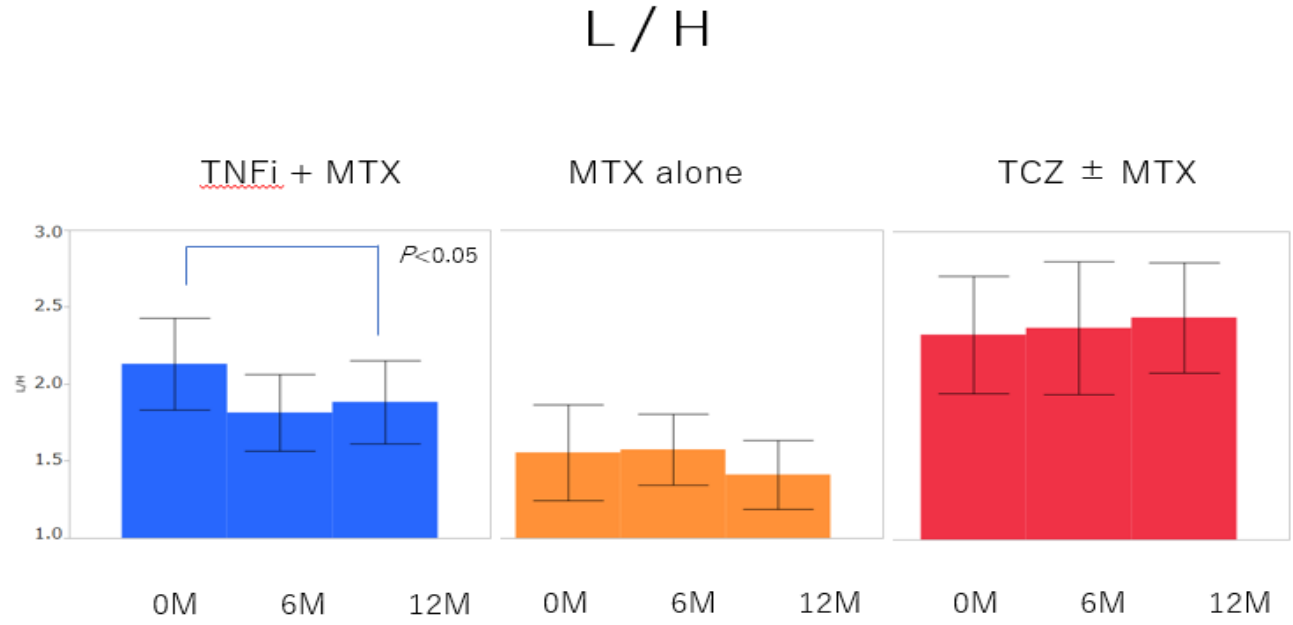

Figure 6: Alterations of L/H and before (0M) and after treatment for 6 and 12 months(M). Values are indicated as means ± SD. There is significant difference before and after treatment with TNFi+MTX for 12 months (M) (P<0.05), but not treatment with MTX alone and TCZ±MTX. L/H: LDL cholesterol/HDL cholesterol

Discussion

Rheumatoid Arthritis (RA) is associated with accelerated atherosclerosis and increased risk of Cardiovascular (CV) event 818, 19). These CV risk in RA are mediated by chronic inflammation and increased prevalence of CV risk factors such as glucose intolerance, lipid metabolism and obesity. Pathophysiological mechanism in RA has been suggested mainly increased TNF-α and IL-6. Our results in patients with RA treated by TNFi with MTX, TCZ with MTX, MTX alone indicated that TCZ with MTX apparently improve glucose tolerance shown by decreased HbA1c level. MTX alone also improved HbA1c level. However, TNFi with MTX does not significantly improved HbA1c level, although various kinds of TNFi were treated. Previously each IL-6 and TNF-α positively or negatively affect glucose tolerance in animal models [1,5-7] and cultured cells [2]. Guputa-Ganguli et al. strongly insist treatment with anti-TNF-α antibody improves HbA1c in patients with type 2 diabetes, and Olson et al. reported that circulating levels of TNF-α are associated with impaired glucose tolerance and insulin resistance. Our data indicated in **Figure 2** TNF-α with MTX slightly decreased HbA1c levels, but not significant which was depend on improvement of disease activities such as DAS28ESR, CRP and ESR. Sergej et al showed MTX-induced increases in glucose uptake in skeletal muscle [10]. As shown in **Figure 2** MTX alone decreased HbA1c level in patients with RA which is correspond with Perkmyer's report. On the other hand, blocking IL-6 signaling improves glucose tolerance via suppression of glucagon secretion in monkey [5]. In patients with RA we have reported IL-6 inhibitor tocilizumab with MTX significantly decreased HbA1c level for 6 and 12 months.

However, we have to show slight increases in HDL and LDL cholesterol after treatment with TCZ with MTX, TCZ. Recently, Ferraz-Amaro et al. reported that tocilizumab-related increased triglyceride and HDL cholesterol is independent of key molecules such as apolipoprotein C-III, angiopoietin-like protein 4 and lipoprotein lipase regulating lipid metabolism [11]. Therefore, the attention concerning about effect of TCZ on lipid metabolism should be require. Based on our data we have indicated IL-6i with MTX strongly improve glucose tolerance which will protect cardiovascular events in patients with RA.

Conclusion

Effect of glucose tolerance in IL-6 inhibitors was better than TNF inhibitors in RA patients with glucose intolerance. However, TNF inhibitor in lipid metabolism was better than IL-6 inhibitors.

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Citation of this Article

Mori I, Fujioka K, Tangiku M, Tani H, Oida H, Maeda A and Ishizuka T. Differential Effects of TNFα and IL6 Inhibitors on Glucose Tolerance and Lipid Metabolism - Clinical Retrospective Analysis in Patients with Rheumatoid Arthritis. Mega J Case Rep. 2024;7(7):2001-2008.

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