

### Effectiveness and safety of tocilizumab therapy for patients with rheumatoid arthritis and renal insufficiency: a real-life registry study in Japan (the ACTRA-RI study)

Renal involvement is frequently present in patients with rheumatoid arthritis (RA). Approximately 15–25% of patients with RA have renal insufficiency, defined as a glomerular filtration rate (GFR) <60 mL/min.<sup>1</sup> Although concomitant use of methotrexate (MTX) has been proven to be more effective than administration of biological agents alone,<sup>2</sup> MTX elimination is delayed in patients with renal insufficiency, which can increase the risk of adverse events.<sup>3 4</sup> Therefore we often use MTX at

**Table 1** Baseline characteristics and tocilizumab therapy for patients with RA who were registered in the ACTRA-RI study (n=405)

	With renal insufficiency* (n=102)	Without renal insufficiency (n=303)	p Value†
Baseline characteristics			
Age, years, mean (95% CI)	70.9 (69.4 to 72.5)	58.6 (57.1 to 60.0)	<0.0001
Male/female, number	12/90	66/237	0.027
RA duration, years, mean (95% CI)	13.7 (11.4 to 15.9)	9.9 (8.9 to 11.0)	0.001
CDAI, mean (95%CI)	22.8 (20.6 to 24.9)	22.0 (20.6 to 23.4)	0.59
High and moderate CDAI, number (%)	92 (90.2)	255 (84.2)	0.13
Previous biologics, number (%)			
Anti-TNF $\alpha$ agents	53 (52.0)	174 (57.4)	0.34
Abatacept	4 (3.9)	11 (3.6)	1.00
Serum creatine, $\mu$ mol/L, mean (95% CI)			
Total	99.9 (87.5 to 111.4)	57.5 (53.0 to 61.9)	<0.0001
Male	111.0 (84.9 to 136.1)	83.1 (79.6 to 87.5)	<0.0001
Female	98.1 (84.9 to 111.4)	50.4 (45.1 to 54.8)	<0.0001
Corrected eGFR, mL/min, mean (95% CI)	43.9 (41.5 to 46.3)	81.8 (80.0 to 83.7)	<0.0001
Severe renal insufficiency*, number (%)	14 (13.7)	–	–
End-stage renal disease*, number (%)	2 (2.0)	–	–
Haemodialysis, number (%)	1 (1.0)	0	–
Haemoglobin, g/dL, mean (95% CI)			
Total	11.5 (11.2 to 11.8)	12.2 (12.0 to 12.4)	<0.0001
Male	12.2 (10.8 to 13.5)	13.3 (13.0 to 13.7)	0.03
Female	11.4 (11.1 to 11.8)	11.9 (11.7 to 12.1)	0.004
Anaemia‡, number (%)	54 (52.9)	109 (36.0)	0.0025
Use of erythropoietin, number (%)	3 (2.9)	0	–
Amyloidosis, number (%)	1 (1.0)	0	–
Hypertension, number (%)	64 (62.7)	94 (31.0)	<0.0001
Diabetes, number (%)	20 (19.6)	31 (10.2)	0.014
Concomitant use of MTX, number (%)	33 (32.4)	188 (62.0)	<0.0001
Discontinuation within the first 24 weeks			
Total, number (%)	9 (8.8)	25 (8.3)	0.86
Adverse events, number (%)	8/9 (88.9)	16/25 (64)	0.23
Other reasons, number (%)	1/9 (11.1)	9/25 (36)	0.23
MTX user§, number (%)	5/33 (15.2)	15/188 (8.0)	0.19
MTX non-user§, number (%)	4/69 (5.8)	10/115 (8.7)	0.57
Severe renal insufficiency, number	3/14	–	–
End-stage renal disease, number	0/2	–	–
Adverse events within the first 24 weeks, number (%)			
Total	9 (8.8)	16 (5.3)	0.20
MTX user§, number (%)	4/33 (12.1)	9/188 (4.8)	0.11
MTX non-user§, number (%)	5/69 (7.2)	7/115 (6.1)	0.76
Severe renal insufficiency, number	3/14	–	–
End-stage renal disease, number	0/2	–	–
Severe adverse events¶, number (%)	5 (4.9)	6 (2.0)	0.12
MTX user§, number (%)	1/33 (3.0)	4/188 (2.1)	0.56
MTX non-user§, number (%)	4/69 (5.8)	2/115 (1.7)	0.20
Severe renal insufficiency, number	1/14	–	–
End-stage renal disease, number	0/2	–	–

\*An eGFR was first calculated using the following equation:  $eGFR (mL/min/1.73 m^2) = 194 \times (\text{serum creatine (mg/dL)})^{-1.094} \times (\text{age})^{-0.287} \times 0.739$  (if female) and was then corrected for each patient's BSA (corrected  $eGFR = GFR \times BSA/1.73$ ). Renal insufficiency is defined as an eGFR corrected for each patient's BSA  $<60$  mL/min. Severe renal insufficiency is defined as a corrected eGFR  $<30$  mL/min and  $\geq 15$  mL/min. End-stage renal disease was defined as a corrected eGFR  $<15$  mL/min.

†Statistical analyses were performed using the independent-measures t test, the  $\chi^2$  test, or Fisher's exact test for comparisons of measures between the groups with and without renal insufficiency. For all tests, p values  $<0.05$  were considered to indicate statistical significance.

‡Anaemia was defined as haemoglobin  $<11.5$  g/dL (female) or  $<13.5$  g/dL (male).

§There were no significant differences in rates of discontinuation, adverse events or severe adverse events between MTX users and non-users (the  $\chi^2$  test or Fisher's exact test). p Values for comparisons between MTX users and non-users: (1) discontinuation rates,  $p=0.14$  in the renal insufficiency group and  $p=0.83$  in the group without renal insufficiency; (2) adverse events,  $p=0.47$  in the renal insufficiency group and  $p=0.62$  in the group without renal insufficiency; (3) severe adverse events,  $p=1.00$  in the renal insufficiency group and  $p=1.00$  in the group without renal insufficiency.

¶Severe adverse events in the renal insufficiency group were heart failure after pneumonia, acute coronary disease, pyogenic arthritis, diverticulitis and aggravation of asthma; and those in the group without renal insufficiency were intestinal perforation, lung abscess, pleurisy, pulmonary mucormycosis, pneumonia and acute gastric haemorrhage.

ACTRA-RI, Actemra for RA patients with renal insufficiency; anti-TNF $\alpha$ , antitumor necrosis factor- $\alpha$ ; BSA, body surface area; CDAI, clinical disease activity index; eGFR, estimated glomerular filtration rate; MTX, methotrexate; RA, rheumatoid arthritis; TCZ, tocilizumab.

**Table 2** Effects of tocilizumab on CDAI and haemoglobin levels in patients with RA who completed the 24-week treatment course (n=371)

	Patients with renal insufficiency (n=92)		Patients without renal insufficiency (n=279)		p Values between patient groups*
	TCZ (n=64)	TCZ+MTX (n=28)	TCZ (n=106)	TCZ+MTX (n=173)	
CDAI, mean (95%CI)					
Week 0	22.9 (19.9 to 25.9)	23.5 (20.1 to 26.9)	23.2 (20.7 to 25.7)	21.5 (19.6 to 23.3)	0.60
Week 24†	9.8 (7.9 to 11.6)	9.9 (7.3 to 12.4)	8.4 (6.9 to 9.8)	9.3 (8.1 to 10.6)	0.62
Low CDAI or remission, number (%)					
Week 0	7 (10.9)	1 (3.6)	16 (15.1)	27 (15.6)	0.32
Week 24	37 (57.8)	16 (57.1)	73 (68.9)	109 (63)	0.44
CDAI reduction ≥6.5, number (%)					
Week 24	48 (75)	22 (78.6)	78 (73.6)	120 (69.4)	0.66
Δ CDAI, mean (95%CI)	13.1 (10.4 to 15.8)	13.6 (9.5 to 17.7)	14.9 (12.7 to 17.1)	12.1 (10.5 to 13.8)	0.25
Haemoglobin, g/dL, mean (95% CI)					
Week 0	11.5 (11.1 to 11.9)	11.5 (10.9 to 12.0)	12.3 (12 to 12.6)	12.1 (11.9 to 12.4)	0.008‡, 0.04§
Week 24†	12.5 (12.1 to 12.9)	12.0 (11.5 to 12.4)	13.2 (12.9 to 13.5)	12.9 (12.7 to 13.2)	0.01‡, 0.001¶, 0.007**
Anaemia, number (%)					
Week 0	36 (56.3)	12 (42.9)	36 (34)	65 (37.6)	0.004‡, 0.01§
Week 24	24 (37.5)	9 (32.1)	21 (19.8)	25 (14.5)	0.01‡, 0.0001§, 0.02**
Δ haemoglobin, mean (95% CI)	0.96 (0.67 to 1.26)	0.48 (0.16 to 0.81)	0.89 (0.61 to 1.16)	0.81 (0.65 to 0.98)	0.33

Renal insufficiency, anaemia and abbreviations are defined in table 1. Δ CDAI, change from baseline in CDAI; Δ haemoglobin, change from baseline in haemoglobin.

\*p Values for comparisons of measures between the patient groups were determined using ANOVA (analysis of variance) with a Tukey's HSD (honesty significant difference) post hoc test or the  $\chi^2$  test. For all tests, p values <0.05 were considered to indicate statistical significance.

†Mean CDAI and haemoglobin levels were significantly improved at week 24 in all four groups, when compared with those at baseline (p<0.0001 with the matched-pair t test).

‡Based on comparisons between TCZ in the renal insufficiency group and that in the group without renal insufficiency.

§Based on comparisons between TCZ in the renal insufficiency group and TCZ+MTX in the group without renal insufficiency.

¶Based on comparisons between TCZ+MTX in the renal insufficiency group and TCZ in the group without renal insufficiency.

\*\*Based on comparisons between TCZ+MTX in the renal insufficiency group and that in the group without renal insufficiency.

reduced dosage for these patients in daily practice, which may result in inadequate responses.

The ACTRA-RI (Actemra for RA patients with renal insufficiency) study was designed to evaluate the efficacy and safety of tocilizumab (TCZ) therapy in the real-life registry of patients with RA and renal insufficiency. For this study, we registered all patients with RA who had begun TCZ therapy in participating hospitals as of January 2014 (total 405 patients with RA: 102 with renal insufficiency and 303 without). An estimated GFR (eGFR) was first calculated using an equation that had been officially approved by the Japanese Society of Nephrology.<sup>5</sup> The calculated value was corrected for each patient's body surface area to arrive at an absolute eGFR value for patients with RA.<sup>6</sup>

As shown in table 1, approximately 60% of the registered patients switched from another biological therapy because of inadequate responses or adverse events. Patients with renal insufficiency were significantly older and had RA for a longer duration. Mean serum levels of haemoglobin were significantly lower in the renal insufficiency group. Hypertension and diabetes, which are traditional risk factors for chronic renal disease, were more frequently complicated in this patient group. Sixty-eight per cent of patients with renal insufficiency received TCZ therapy without MTX because of concerns of MTX-related adverse effects. Nine patients (8.8%) with renal insufficiency and 25 (8.3%) without this complication discontinued TCZ therapy within the first 24 weeks. In both patient groups, the most frequent reason for withdrawal was adverse events. Regardless of MTX use, there were no significant differences in rates of dropout, adverse events, or severe adverse events between the groups with and without renal insufficiency. In addition, these rates were not significantly different between MTX users and non-users, even in patients with renal insufficiency.

A total of 371 patients (91.6%) completed the 24-week TCZ therapy. We divided these patients into four groups according to the status of MTX use and renal insufficiency. As shown in table 2, significant improvements in mean clinical disease activity index values were observed at week 24 in all groups. Although the differences observed between these groups at baseline remained at week 24, mean haemoglobin levels were significantly increased over time during TCZ therapy, even in patients with renal insufficiency. There were no significant differences in efficacy among the four groups. Efficacy parameters in the renal insufficiency group were comparable with those in the group without this complication whether patients received MTX concomitantly or not.

In this multicentre study, the 24-week TCZ therapy had good efficacy parameters as well as stable safety and tolerability profiles in patients with RA and renal insufficiency, regardless of MTX use. A recent randomised, double-blind clinical trial (ACT-RAY) indicated that there is no clinically relevant superiority of TCZ plus MTX therapy over TCZ monotherapy in patients with MTX-resistant RA even if some end points after 1 year favoured the combination treatment.<sup>7 8</sup> Accompanying the increased number of elderly patients with RA and significant comorbidities such as hypertension and diabetes, renal insufficiency has been seen more commonly in this patient population.<sup>9 10</sup> TCZ is considered one of the promising options for treatment of patients with RA and renal insufficiency in a real-life medical practice. To evaluate long-term efficacy and safety issues, a further follow-up survey is required for the patients registered in the ACTRA-RI study.

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