Tocilizumab Treatment of Rheumatoid Arthritis among Filipino Patients

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ABSTRACT

Introduction. Studies have shown that tocilizumab (TCZ) is effective in the treatment of rheumatoid arthritis. This study examined the efficacy and safety of TCZ in Filipino patients with moderate to severe rheumatoid arthritis (RA).

Methods. This was an open-label, one-arm clinical trial approved by the Philippine Council Health Research Development-National Ethics Committee (PCHRD-NEC), among moderate-severe active RA Filipino patients in 4 RA clinics. The study consisted of a 28-day screening-baseline period; a 24-week treatment period, with once every-4-weeks TCZ 8mg/kg intravenous infusion (IV) and an efficacy-safety evaluation. Patients already receiving methotrexate (MTX) at study entry went on with MTX plus TCZ per medical discretion. Descriptive statistics computed for physician's and patient's global assessment of disease activity, patient's global assessment of pain, ACR20, ACR50 and ACR70. Analysis of variance (ANOVA) determined significant changes over time for DAS-28 ESR, FACIT and HAQ-DI fatigue scores. Twenty-nine of thirty patients were included in efficacy and safety analysis.

Results. After 24 weeks of TCZ: 86%, 66%, and 48% of 29 Filipino RA patients achieved ACR20, ACR50, ACR70, respectively, with 34% achieving remission according to DAS28-ESR. Median times to first achieving ACR20, ACR50 and ACR70 were 4, 12, and 24 weeks, respectively. There were also significant rapid reductions in physician's and patient's global assessment of disease activity, patient's global assessment of pain, HAQ-DI and FACIT scores noted over time. Tolerability profile was similar to published literature on TCZ.

Conclusions. TCZ has been shown to be effective in the treatment of Filipino patients with moderate to severe rheumatoid arthritis. TCZ can be given in an out-patient RA clinic setting.

Key Words: tocilizumab, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is the most common of the incurable and potentially disabling chronic systemic inflammatory autoimmune diseases. Affecting about 0.5-1% of the population worldwide, the disease onset occurs in the 4th and 5th decade of adult life, at a time most are economically active. It is 2.5-fold more prevalent in women than in men and is characterized by symmetric synovitis and erosive arthritis, often rapidly progressive with joint damage apparent soon after the onset of symptoms, effecting a progressive decline in functional status and work disability. Patients suffer chronic severe disability and are also likely to die prematurely.[1-3]

Timely diagnosis and early aggressive treatment with the goal of rapidly controlling symptoms, limiting joint damage, improving functional status and preventing disability is essential. Treatment modalities include methotrexate, other DMARDs and tumor necrosis factor α (TNF-α) antagonists. However, approximately 30-40% of RA patients fail to respond adequately to non-biologic DMARDs (disease modifying anti-rheumatic diseases) or to TNF-α antagonists and 50-60% of patients fail to achieve a major clinical ACR or good EULAR response. Even among responders, the majority do not achieve remission. Additionally, many patients experience toxicity or lose their response within 2-3 years, hence prompting development of biological therapies with alternative mechanisms of action.[1-3]

Interleukin-6 (IL-6) is a pleiotropic, pro-inflammatory, multi-functional cytokine produced by a variety of cell types. An elevated level of IL-6 has been implicated in RA pathology. IL-6 is involved in T-cell activation, differentiation of B cells into immunoglobulin-secreting plasma cells, maturation of megakaryocytes leading to platelet production and also induces the synthesis of the iron regulatory peptide hepcidin during inflammation. IL-6 is also known to promote osteoclast differentiation in the presence of soluble IL-6R (sIL-6R), indicating a role in bone resorption and the osteopenia associated with chronic inflammation.[1-3]

TCZ previously referred to as myeloma receptor antibody (MRA), is a recombinant humanized anti-human monoclonal antibody of the immunoglobulin-G1 (IgG1) sub-class. TCZ binds specifically to the sIL-6R and the membrane-expressed interleukin 6 receptor (mIL-6R), inhibiting both sIL-6R- and mIL-6R-mediated signaling. In vivo, TCZ has been shown to prevent onset of bone and cartilage destruction in a collagen-induced arthritis model in cynomolgus monkeys.[1-3]

TCZ represents a new therapeutic option with a novel mechanism of action for moderate to severe active RA. Regardless of duration of RA, RF status, treatment history, or concomitant RA medications, TCZ is effective for the treatment of moderate to severe RA. TCZ 8mg/kg has demonstrated consistent and robust effects on all primary and secondary efficacy endpoints in patients with an inadequate response to existing therapeutic agents (i.e., non-biologic and TNF-antagonist therapies) and in patients with earlier stage MTX/DMARD-naive RA. The clinical benefit of TCZ 8mg/kg in combination with non-biologic DMARDs was also demonstrated in patients with an inadequate response to previous non-biologic DMARD and TNF-antagonist therapies.[1-3]

This study, based on clinical experience of rheumatologists in the Philippines, demonstrates the effectiveness and safety of TCZ in the treatment of active RA.

Methods

This was a phase IIIb, open-label, one-arm clinical study at 4 Philippine RA clinics, among any sex, age >18 years old patients. The clinics are situated in major tertiary medical centers (1 in Pampanga and 3 in Metro Manila).

Included were patients with rheumatoid arthritis:

- diagnosed for at least 8 weeks prior to baseline, but no more than 4 years, according to the revised 1987 American College of Rheumatology (ACR) criteria for the classification of rheumatoid arthritis;
- naïve to, considered to be candidates for, or on treatment with methotrexate;
- with swollen joint count (SJC) ≥8 (66 joint count), and tender joint count (TJC) ≥8 (68 joint count);
- with CRP ≥ 1.0 mg/dL (10 mg/L);
- on glucocorticoids ≤ 10 mg/day prednisolone or equivalent permitted if stable for at least 4 weeks prior to baseline;
- with NSAIDs permitted if stable for at least 2 weeks prior to baseline;
- willing to receive oral folate, if on MTX; and
- for treatment for RA on an outpatient basis.

Excluded were patients with:

- rheumatic autoimmune disease other than RA, or significant systemic involvement secondary to RA;
- ACR class IV;
- inflammatory joint disease other than RA or other systemic autoimmune disorder;
- child-bearing potential without reliable means of contraception;
- pregnant/ breast feeding;
- major surgery within 8 weeks prior to screening or planned major surgery within 6 months following randomization;
- lack of peripheral venous access;
- serious uncontrolled concomitant cardiovascular, nervous system, pulmonary, renal, hepatic, endocrine or GI disease;
- primary or secondary immunodeficiency;
- active or recurrent bacterial, viral, fungal, mycobacterial, hepatitis B and C, and herpes zoster, or major infection requiring hospitalization or IV antibiotics within 4 weeks of screening or oral antibiotics within 2 weeks prior to screening;
- active malignant disease or diagnosed within the previous 5 years;
- any neurological, vascular or systemic disorder which could affect any of the efficacy assessments, in particular, joint pain and swelling (e.g. Parkinson's disease, cerebral palsy, diabetic neuropathy);
- active or history of alcohol or drug abuse;
- active TB requiring treatment within the previous 3 years;
- history of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies;
- previous treatment with any approved or investigational biologic agent for RA; previous treatment with an anti-alpha 4 integrin antibody or co-stimulation modulator;
- concurrent treatment with any biologic agent or DMARD other than MTX; treatment with any cell depleting therapies;
- treatment with any investigational agent within 28 days of baseline or 5 half-lives of the investigational drug;
- receipt of live or attenuated vaccine within 28 days prior to baseline;
- intra-articular or parenteral glucocorticoids within 4 weeks prior to baseline;
- intolerance or contraindications to i.v. glucocorticoids;
- positive serum human chorionic gonadotropin (hCG) measured prior to the first TCZ infusion; and
- serum creatinine > 142 μmol/L (1.6 mg/dL) in female patients and > 168 μmol/L (1.9 mg/dL) in male patients and no active renal disease,

hemoglobin < 8.5 g/dL, platelet count < 100 x 109/L (100,000/mm3), WBC count < 1.0 x 109/L (1000/mm3), absolute neutrophil count < 0.5 x 109/L (500/mm3), absolute lymphocyte count < 0.5 x 109/L (500/mm3), ALT or AST > 1.5 x ULN, total bilirubin > ULN, HIV positive, positive HBsAg or HCV antibody, and triglycerides > 10 mmol/L (> 900 mg/dL) at screening.

All patients signed a consent form, approved by the Philippine Committee on Health Research and Development-National Ethics Committee and study site Ethics Committee before any screening procedure was initiated.

Patients received 8 mg/kg TCZ in 100 mL NSS intravenous infusion 1x/4 weeks for 24 weeks, administered at room temperature by controlled infusion into an arm vein over a 60-minute infusion period. TCZ vials were stored between 2°-8°C, protected from light. The prepared infusion was used immediately.

All outcome assessments[4-6] were performed at the baseline visit, which occurred within 24-72 hours prior to the first dose of TCZ medication, and at day 1 and weekly from week 4-24: patient's global assessment of disease activity (100-mm visual analogue scale (VAS)), pain (VAS), HAQ-DI (Health Assessment Questionnaire-Disease Index), morning stiffness; FACIT-fatigue (Functional Assessment of Chronic Illness Therapy - at day 1, weeks 12 & 24); and rheumatologist's global assessment of disease activity (VAS), physical exam, vital signs, 66 joints for swelling and 68 joints for tenderness, ESR (erythrocyte sedimentation rate), CRP (C-reactive protein) and TCZ safety (CBC (complete blood count), blood chemistry, adverse events). ECG and chest x-ray were taken at baseline.

Data was encoded using Epi info 6. Data analysis was done using Stata ver 10. Mean and standard deviations were computed for numerical variables like DAS-28 (disease activity score-28) ESR score, FACIT and HAQ fatigue scores, tender and swollen joint counts, physician's and patient's global assessment of disease activity, patient's global assessment of pain, and ESR. Proportions were computed for categorical variables like ACR20, ACR50 and ACR70[7]. Analysis of variance (ANOVA) for repeated measures was used to determine if there were significant changes over time for DAS-28 ESR score, FACIT and HAQ fatigue scores.

Results

Study Population Profile

Thirty eligible RA patients out of 38 screened participated in the study; one patient withdrew her consent prior to start of treatment. Twenty-nine patients were included in the intent-to-treatment analysis. Nine (31%) patients had previous treatment with DMARDS (3 hydroxychloroquine, 3 leflunomide, 3 methotrexate, and 2 chloroquine); 20 patients were DMARD naïve.

There were 29 females and 1 male. Thirteen of 28 (46%) female patients were in the reproductive age group with negative pregnancy test at baseline.

The mean±sd age was 47±14.07 years (median= 48; range= 24-75). The mean±sd duration of RA was 24.9±18.20 months.

At baseline, 76% of the 29 patients were found positive for rheumatoid factor (RF) status whereas 24% were negative.

Five (17.2%) of the 29 patients had previous or current diseases under active treatment during the study (2 hypothyroidism, 1 hyperthyroidism, 1 cerebrovascular accident, 1 coronary artery disease, 1 hypertension, 1 keratoconjunctivitis; 2 patients had 2 ailments each). Three patients had atheromatous aorta (1) or pneumonitis (2) by chest x-ray, while 1 had lateral wall ischemia by ECG.

Response to TCZ Therapy

Twenty-eight (96.6%) of patients completed treatment; one did not complete treatment since she became pregnant. Median TCZ dose given was ~480 mg every 4 weeks (range 280-736 mg). Nine patients also had MTX (mean dose per week = 12.6 mg ± 6.3 SD; range 2.5-43.75 mg), mostly (82%) once a week.

Over time, ACR scores increased (Figure 1; Table 1). By week 4, there were 55% of patients with ACR20; by week 12, 52% with ACR50; and by week 24, 48% with ACR70. Median time to first achieve ACR20 was 4 weeks, ACR50 12 weeks and ACR70 24 weeks.

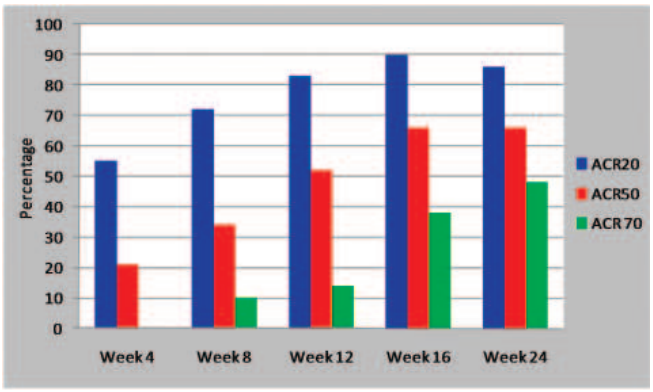

Figure 1. Proportion of Patients with ACR20, ACR50, and ACR70 by Follow-up Week (n=29)

At week 24, 6 (66.7%) of the 9 patients who were on TCZ + MTX, attained ACR20 compared to 19 (95%) of 20 patients who were on TCZ alone (p-value=0.076, Fischer's Exact test); likewise 3 (33.3%) versus 16 (80.0%) for ACR50 (p=0.032) and 3 (27.0%) versus 11 (55.0%) for ACR70 (p=0.427), respectively. There were 6 (67%) DMARD-naive

patients in the TCZ-MTX arm compared to 14 (70%) in the TCZ arm.

Table 1. Patients with ACR20, ACR 50, and ACR 70 by Week of Follow-up

Week	ACR20 (n=29)		ACR50 (n=29)		ACR70 (n=29)	
	No.	%	No.	%	No.	%
Week 4	16	55	6	21	0	0
Week 8	21	72	10	34	3	10
Week 12	24	83	15	52	4	14
Week 16	26	90	19	66	11	38
Week 24	25	86	19	66	14	48

The DAS-28 ESR scores significantly declined over time (Table 2). At week 24, 34% were in remission, while 45% had low disease activity and 21% high disease activity (Table 3). There were 8 (40%) of patients on TCZ alone who achieved DAS <2.6 or who went in remission compared to 2 (22%) of patients on TCZ+MTX.

Table 2. DAS28-ESR Scores by Week of Follow-up (n=29)

Week	Mean	SD	p-value[a]
Baseline	6.94	0.53	-
Week 4	4.26	0.32	0.001
Week 8	3.50	0.32	0.001
Week 12	3.11	0.30	0.001
Week 16	2.94	1.04	0.001
Week 20	2.97	1.16	0.001
Week 24	2.73	0.93	0.001
p-value[b]			0.001

[a]*Comparison of follow-up measurement with baseline*
[b]*Overall ANOVA p-value*

Table 3. Distribution of Disease Activity Categories (by DAS28-ESR Scores) by Follow-up Week (n=29)

Week [a]	Remission		Low Disease Activity		High Disease Activity	
	No.	%	No.	%	No.	%
Baseline	0	0	0	0	29	100
Week 4	2	7	2	7	25	86
Week 8	6	21	5	17	18	62
Week 12	7	24	9	31	13	45
Week 16	10	34	4	14	15	52
Week 20	11	38	7	24	17	59
Week 24	10	34	13	45	6	21

[a]*DAS28-ESR score of <2.6= Remission; >2.6 and <3.2=Low Disease Activity; and >3.2=High Disease Activity*

The average number of tender and swollen joints markedly decreased from baseline leveling from week 8 to week 24. The average scores during the follow-up weeks were all significantly lower (p-values < 0.05) compared to baseline (Table 4). The proportion of patients without morning stiffness increased from baseline (10%) to week 24 (65%).

Table 4. Tender and Swollen Joint Counts (34 joint pairs) by Follow-up Week (n=29)

Week	Tender Joint Counts			Swollen Joint Counts		
	Mean	SD	p-value[a]	Mean	SD	p-value[a]
Baseline	22.72	10.90	-	16.17	5.92	-
Week 4	7.59	6.49	<0.001	3.83	4.60	<0.001
Week 8	4.55	4.82	<0.001	2.52	3.57	<0.001
Week 12	3.34	4.62	<0.001	1.86	2.43	<0.001
Week 16	3.59	3.69	<0.001	2.00	2.43	<0.001
Week 20	3.86	4.29	<0.001	2.00	3.09	<0.001
Week 24	3.03	3.47	<0.001	2.17	4.38	<0.001
p-value[b]		<0.001			<0.001	

[a]*Comparison of follow-up measurement with baseline*
[b]*Overall ANOVA p-value*

The number of patients with abnormal CRP decreased by 34% at week 4, leveling off at weeks 8- 24 by ~50%; ESR significantly decreased compared to baseline (Table 5)

Table 5. Distribution by ESR and CRP by Follow-up Week (n=29)

Week	CRP				ESR (mmHr)		
	Normal		Abnormal		Mean	SD	p-value[a]
	No.	%	No.	%			
Baseline	0	0	29	100	59.03	25.03	-
Week 4	10	34	19	66	20.48	18.54	<0.001
Week 8	14	48	15	52	15.14	13.95	<0.001
Week 12	11	38	18	62	13.97	10.71	<0.001
Week 16	16	55	13	45	14.55	16.54	<0.001
Week 20	17	59	12	41	13.69	12.94	<0.001
Week 24	14	48	15	52	14.41	16.29	<0.001
p-value[b]							<0.001

[a]*Comparison of follow-up with baseline*
[b]*Overall ANOVA p-value*

There was an average of 3 rheumatoid nodules at baseline which was reduced to 1 nodule at week 4 and 0 after this week.

There was a decreasing trend in both the physician's and the patient's assessment of disease activity, and in patient's global assessment of pain from baseline to week 24 (Figure 2; Table 6).

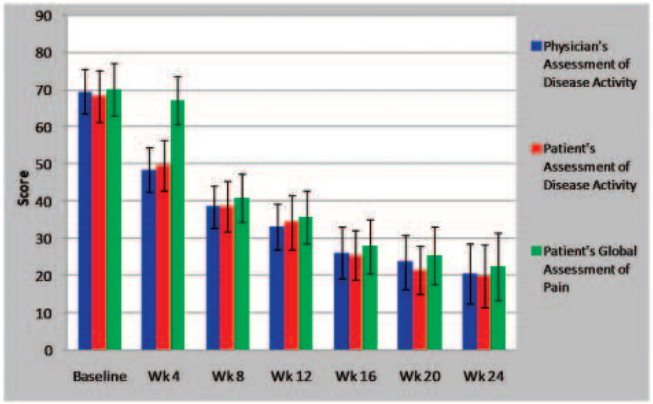

Figure 2. VAS Assessment of Disease Activity and Pain by Follow-up Week with 95% confidence intervals.

Table 6. VAS Scores of Disease Activity and Pain by Follow-up Week (n=29)

Week	Physician's Assessment of Disease Activity			Patient's Assessment of Disease Activity			Patient's Global Assessment of Pain		
	Mean	SD	p-value[a]	Mean	SD	p-value[a]	Mean	SD	p-value[a]
Baseline	69.48	15.49	-	68.28	18.29	-	70.03	18.72	-
Week 4	48.45	15.53	<0.001	49.66	17.57	<0.001	67.24	16.93	0.412
Week 8	38.62	14.87	<0.001	38.62	17.67	<0.001	40.86	16.96	<0.001
Week 12	33.10	16.00	<0.001	34.31	18.98	<0.001	35.69	18.79	<0.001
Week 16	26.21	18.06	<0.001	25.52	17.70	<0.001	27.86	19.20	<0.001
Week 20	23.72	19.05	<0.001	21.48	16.88	<0.001	25.45	20.62	<0.001
Week 24	20.55	21.32	<0.001	19.86	21.99	<0.001	22.62	23.71	<0.001
p-value[b]		<0.001			<0.001			<0.001	

[a]*Comparison of follow-up measurement with baseline*
[b]*Overall ANOVA p-value*

The FACIT fatigue index (mean±SD) declined (p<0.001; ANOVA) from baseline (1.93±0.61) to week 12 (1.23±0.59) to week 24 (1.03±0.46). See Figure 3.

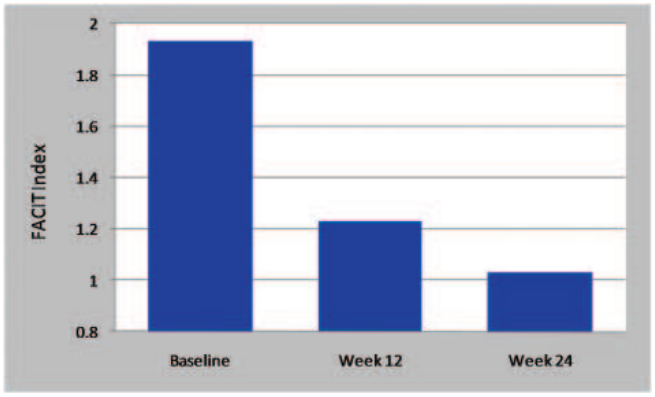

Figure 3. Trend of FACIT Fatigue Index by Week of Follow-up (n=29)

The HAQ index significantly decreased over time (Table 7). More than half (62%) of the patients had significant HAQ index improvements (>0.22 decrease from baseline compared to week 24).

TCZ Safety Profile

Body temperature, systolic blood pressure (BP), diastolic BP, and pulse rate were clinically stable across time (p>0.05, ANOVA).

There was no clinically significant change in overall RBC (red blood cell), WBC (white blood cell), platelet counts, and Hb (hemoglobin) level from baseline to week 24 (Table 8).

Triglyceride/ cholesterol and AST/ALT/ alkaline phosphatase levels over 24 weeks from baseline are shown in Tables 9-11. AST and ALT elevations were the most common adverse events (47 adverse events (AEs) in 20 patients or 2.20±1.3SD AEs per patient; all mild except for 1 moderately severe; 55% occurring at week 4).

Table 7. HAQ Index by Follow-up Week (n=29)

Week	Mean	SD	p-value[a]
Baseline	0.75	0.53	-
Week 4	0.47	0.33	<0.001
Week 8	0.32	0.32	<0.001
Week 12	0.28	0.30	<0.001
Week 16	0.22	0.26	<0.001
Week 24	0.23	0.31	<0.001
p-value	<0.001		

[a]*Comparison of follow-up measurements with baseline*
[b]*Overall ANOVA p-value*

Table 8. Distribution of Patients by RBC, WBC, Platelet & Hb Status by Follow-up Week (n=29)

Week	RBC (10^{12}/L)		WBC (10^{12}/L)		Platelets (10^{12}/L)		Hb (mg/dL)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	4.35	0.50	8.72	2.98	344.28	84.64	120.55	13.44
Week 4	4.51	0.59	7.80	2.39	259.52	55.08	126.17	14.37
Week 8	4.52	0.65	7.20	2.66	259.76	49.73	128.79	14.52
Week 12	4.53	0.61	7.13	3.06	270.79	66.84	129.97	13.76
Week 16	4.52	0.70	7.32	2.48	290.72	139.50	129.52	13.65
Week 20	4.49	0.71	6.35	2.48	265.76	65.45	129.34	15.20
Week 24	4.47	0.66	6.41	2.28	269.10	71.75	128.97	14.65
p-value	0.144		0.001		0.002		0.001	

[a]*Overall ANOVA p-value*

Twenty-four (83%) of the patients experienced AE (Table 11) during the study. Each patient experienced a mean 2.83±2.21 SD AE episodes (median=3; range 0-8). About one-third (24) of the AEs were given treatment.

There was 1 serious adverse event (pregnancy; removed from study, followed-up, and delivered without untoward events), which was immediately reported to the ethical committee, Philippine Food & Drugs Administration, and sponsor. Sixteen percent (13) of the AEs were infections (7 suspected bacterial; 6 suspected viral), not reported as serious nor opportunistic. The AEs with causal relationship to the drug were elevated ALT (7), elevated AST (7), UTI (3), elevated AST & ALT (2), hypercholesterolemia (1), and paresthesia at palm of infusion (1). The unresolved AEs at end of study period were elevated ALT (14), elevated AST (9), elevated AST & ALT (2), and 1 each of carpal tunnel

syndrome, colonic diverticulitis, fatty liver, internal hemorrhoids, trigger finger, uterine myoma, and contact dermatitis.

Table 9. Triglyceride and Cholesterol Status by Follow-up Week (n=29)

Week	Triglyceride (mmol/L)		Cholesterol (mmol/L)	
	Mean	SD	Mean	SD
Baseline	11.52	23.86	33.49	65.14
Week 4	15.24	30.09	39.05	75.69
Week 8	15.39	30.18	38.38	73.67
Week 12	15.29	29.52	36.64	69.78
Week 16	16.07	32.62	37.48	72.58
Week 20	14.16	28.04	37.22	72.14
Week 24	15.40	31.11	39.16	76.37
p-value[a]		0.107		0.027

[a]*Overall ANOVA p-value*

Table 10. AST/ALT & Alkaline phosphatase Status by Follow-up Week (n=29)

Week	AST (u/L)		ALT (u/L)		Alkaline Phosphatase (u/L)	
	Mean	SD	Mean	SD	Mean	SD
Baseline	17.90	6.52	17.24	10.81	78.79	20.18
Week 4	30.14	32.39	33.09	40.93	72.02	26.48
Week 8	25.33	9.25	28.81	20.30	71.54	28.29
Week 12	27.85	12.28	35.55	31.08	70.90	27.90
Week 16	30.10	11.50	40.10	28.31	69.50	26.64
Week 20	28.65	14.18	36.32	28.44	71.58	29.30
Week 24	28.87	14.84	37.45	33.55	69.36	29.05
p-value[a]	0.066			0.014		0.0511

[a]*Overall ANOVA p-value*

Table 11. Distribution of Adverse Events (n=82)

Adverse Event[a]	No.	%
Gastrointestinal (47 elevated AST/ALT, hemorrhoid, diverticulitis, fatty liver, abdominal pain, dyspepsia)	52	63
Infection, suspected (URTI/ UTI)	13	16
Dermatological (rashes, folliculitis, pruritus)	7	8
Neurological (3 headache, paresthesia)	4	5
Musculoskeletal (knee effusion, trigger finger, carpal tunnel)	3	4
Reproductive (myoma, pregnancy)	2	2
Metabolic (hypercholesterolemia)	1	1

[a]*Multiple adverse events per patient*

Discussion

TCZ is the first biologic therapy with a tolerable safety profile for RA that inhibits the actions of IL-6, the most abundant cytokine in the rheumatoid synovium and a key driver of chronic inflammation and autoimmunity.

Eight mg/kg TCZ (Actemra®) in 100 mL NSS once every 4 weeks for 24 weeks, administered immediately at room temperature via a 60-minute arm-vein intravenous infusion was done with ease and tolerable safety profile in out-patient RA clinics in the Philippines.

Eighty-six percent, 66%, and 48% of 29 Filipino RA patients achieved ACR20, ACR50, ACR70, respectively, after TCZ 8 mg/kg 6 intravenous infusions after 24 weeks; further, 34% achieved remission according to DAS28-ESR. There were also significant rapid reductions of disease activity based on physician's and patient's assessment, patient's assessment of pain and in HAQ-DI and FACIT scores across time.

Similar to this study, TCZ demonstrates a rapid, potent, comprehensive effect on RA in patients on monotherapy (AMBITION[8] study – average 6.4 years RA, 67% methotrexate naive, average age 50.7 years, 83% females), which showed 70% ACR20, 44% ACR50, and 28% ACR70 at week 24, with 34% achieving remission according to DAS28-ESR. TCZ has also been shown to be effective (DAS28<2.6 of 28-34% at 24 weeks) in RA among patients with inadequate response to DMARDs (OPTION[9], TOWARD[10], and LITHE[11] studies), and in patients with inadequate response to anti-TNFs (RADIATE[12] study).

This study showed that TCZ given as single agent or with MTX was effective against DMARD-naive and post-DMARD RA. In this study, patients on combination (MTX/TCZ) seemed to fare poorer compared to TCZ alone according to their ACR, but disease picture of the two groups seemed comparable albeit of small patient numbers.

A total of 3,778 patients were in the safety data of TCZ clinical studies,[8-13] with generally good safety profile across different patient groups, with most AEs mild-moderate. In the AMBITION[8] study, the most common serious adverse event was infection/infestation as observed in 4 TCZ patients (1.4%) versus those observed in 2 patients on placebo (0.7%); any AE was 79.9% versus 77.5%, respectively. TCZ should not be initiated in patients with active infection; TCZ should be interrupted if serious infection occurs; caution is exercised in patients with history of recurring or chronic infections or underlying conditions (e.g., diabetes, diverticulitis).

This study showed elevations of hepatic transaminases and cholesterol, which were predominantly not clinically significant, mainly at less then 2-fold rise. Transient mild and moderate elevations of hepatic transaminases and lipids have been observed commonly with TCZ treatment, particularly when TCZ is administered in combination with DMARDs (for AST/ALT, mainly MTX).[13] Although these elevations have not been treatment-limiting in the vast majority of patients and have been observed without progression to hepatic injury or clinical symptoms, respectively, caution is recommended when considering treatment of patients with active hepatic disease or hepatic impairment (enzymes >1.5x ULN), or cardiovascular disease. TCZ should not be started when baseline ALT/AST is >5x ULN. Data indicates that treatment can be successfully resumed (when enzymes <3x ULN) without recurrence of elevations following decrease of hepatic transaminases. High lipid levels can be controlled with use of statins. AST/ALT and lipids should be monitored every 4-8 weeks for the first 6 months and then every 12 months thereafter.

TCZ has been shown to be effective in the treatment of Filipino patients with moderate to severe rheumatoid arthritis, and that TCZ can be given in an out-patient RA clinic setting.

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