ICHIBAN, a non-interventional study evaluating tocilizumab long-term effectiveness and safety in patients with active rheumatoid arthritis

C. Specker[1], A. Alberding[2], M. Aringer[3], G.-R. Burmester[4], J.-P. Flacke[5], M.W. Hofmann[6], P. Kästner[7], H. Kellner[8], F. Moosig[9], M. Sieburg[10], H.-P. Tony[11], G. Fliedner[12]

[1]Clinic of Rheumatology and Clinical Immunology, Evangelical Hospital, Clinic Essen-Mitte, Essen; [2]Internal Rheumatology, St. Josef Hospital, Wuppertal; [3] Department of Medicine III, University Medical Center Carl Gustav Carus, TU Dresden; [4]Department of Rheumatology and Clinical Immunology Charité - Universitätsmedizin Berlin, Free University and Humboldt University Berlin; [5]Rheumatology, Roche Pharma AG, Grenzach-Wyhlen; [6]Rheumatology, Chugai Pharma Germany GmbH, Frankfurt am Main; [7]MVZ Ambulant Rheumatology Center Erfurt; [8]Rheumatology and Gastroenterology Specialty Practice, Munich, Germany; [9]Rheumatology Center Schleswig-Holstein Middle, Neumünster; [10]Allied Rheumatology Practice, Magdeburg; [11]Medical Clinic II, Department of Rheumatology and Clinical Immunology, University Clinic Würzburg; [12]Rheumatology Practice, Osnabrück, Germany.

Abstract

Objective

We aimed to measure long-term effectiveness and safety of tocilizumab in patients with rheumatoid arthritis in daily German practice.

Methods

ICHIBAN was a prospective, multi-centre, non-interventional study (ML22928) that enrolled adult patients with active moderate to severe rheumatoid arthritis. Patients were to be treated according to tocilizumab label and observed for up to two years. Effectiveness outcomes included DAS28-ESR remission, EULAR response, CDAI and HAQ.

Results

Overall, 3164 patients received at least one dose of tocilizumab. Patient mean age was 55.5±13.1 years (74.8% female). At baseline, 72.1% of patients had at least one comorbidity. Approximately 50.9% of patients received concomitant csDMARDs, mostly methotrexate, and 80.7% received concomitant glucocorticoids (GCs). In patients receiving GCs at baseline, the mean dose decreased from 9.32±16.36 mg/d to 4.60±4.48 mg/d at week 104. In the effectiveness population with no prior TCZ (n=2902), 61.4% of patients achieved the primary outcome, DAS28-ESR remission. Improvements were seen as early as week 4. At week 104, 77.9% of patients had DAS28-ESR low disease activity, 89.6% achieved good or moderate EULAR response, and 29.5% achieved a CDAI-based remission. Effectiveness outcomes were similar in all previous therapy subgroups. The incidence of serious infections was similar to the rates in former studies involving tocilizumab. Patients receiving GC at baseline experienced slightly higher rates of treatment-related serious adverse events, mainly infections. No new safety signals were observed.

Conclusion

Long-term effectiveness and safety in ICHIBAN were in line with previously reported tocilizumab efficacy and safety studies.

Key words

rheumatoid arthritis, interleukin-6, glucocorticoids, anti-rheumatic agents, anti-rheumatic disease-modifying second-line drugs, tocilizumab

Christof Specker, MD, PhD, Prof
Annette Alberding, MD
Martin Aringer, MD
Gerd-Rüdiger Burmester, MD, Prof.
Jan-Paul Flacke, MD
Michael W. Hofmann
Peter Kästner, MD, PhD
Herbert Kellner, MD, Prof.
Frank Moosig, MD, Prof.
Maren Sieburg
Hans-Peter Tony, MD
Gerhard Fliedner, MD

Please address correspondence to:
Christof Specker,
Klinik für Rheumatologie
& Klinische Immunologie,
Evangelisches Krankenhaus,
Kliniken Essen-Mitte,
Pattbergstrasse 1-3,
45239 Essen, Germany.
E-mail: specker@uni-duesseldorf.de

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For competing interests, see page 327.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to progressive joint destruction, pain, discomfort and decreased life expectancy, and affects about 1% of the German population (1). When patients respond inadequately to RA treatment with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and have unfavourable prognostic markers, national and international guidelines recommend adding biologic (b) DMARDS to treatment regimens (2, 3). The disease mechanisms of RA are complex and only partially known. Several cytokines may play a role in sustaining disease activity and inflammation. Cells in synovial tissue of patients with RA express the cytokine interleukin-6 (IL-6) (4). Although the IL-6 receptor is only expressed by specific cell types, trans-signalling enables IL-6 to target any cell of the body via soluble IL-6 receptors (5). Tocilizumab (TCZ) is a humanised, monoclonal antibody that targets both membrane-bound and soluble IL-6 receptors (6). Pivotal clinical trials have shown that TCZ is an efficacious treatment for RA with favourable safety and marked anti-inflammatory potency (7-12). In addition, TCZ treatment slows the progression of joint damage in patients with RA (13, 14). TCZ is approved in the EU for the treatment of adult patients with moderate to severe active RA who are intolerant to or inadequately respond to previous treatment with one or more DMARDs or TNF-inhibitors (TNFi) (15), and can be combined with methotrexate or given as monotherapy.

In Germany, TCZ has been studied in real-life populations for 24 weeks (16) and 52 weeks (17). The most recent analysis published on TCZ data from the RABBIT registry followed patients for up to three years (18). The objective of the present study, ICHIBAN, was to measure long-term effectiveness and safety of TCZ in patients with active RA in daily German practice. As TCZ treatment has recently been examined for its glucocorticoid (GC) saving effects (19), this aspect was addressed as well. The present large, prospective, multi-centre, non-interventional study followed patients treated with TCZ for up to two years, adding important long-term data to previous observational datasets.

Patients and methods

Study design and patients

The non-interventional, prospective ICHIBAN study (NCT01194401) enrolled adult patients with active moderate to severe RA from January 2010 to January 2017 in both rheumatology clinics and practices in Germany. Patients were eligible for enrolment if the decision to treat with TCZ (intravenously) according to the German Summary of Product Characteristics (SmPC) was made prior to and independent of the decision to enrol the patient in the study. A maximum of one year of prior TCZ treatment was also permitted. All patients gave informed consent prior to study enrolment.

Effectiveness and safety data were collected in routine clinical practice. There was no intervention concerning therapeutic decisions or diagnostic procedures. All therapeutic and diagnostic decisions, including concomitant medications, were made by the treating physician. This study was reviewed and approved by the ethics committee at the State Chamber of Physicians in North Rhine (Germany) and registered at the Paul-Ehrlich-Institute (ML22928).

Data collection and outcomes

All data were collected via an electronic case report form (eCRF). Study visits were documented at baseline and at weeks 4, 12, 24, 36, 52, 64, 76, 88, and 104. Data collected at the initial visit included demographics and disease characteristics, medical history including comorbidities, treatment history, and concomitant treatment. At the initial visit and all follow-up visits, study centres collected data on disease activity and details on RA medication. Effectiveness was assessed using the Disease Activity Score based on 28 joints and erythrocyte sedimentation rate (DAS28-ESR, calculated according to (20)), European League Against Rheumatism (EULAR) response (21), Clinical Disease Activity Index (CDAI), Boolean-based ACR/EULAR remission (22), and measures of physical functioning (Health Assess-

Table I. Baseline characteristics (SAF).

Characteristic	SAF n=3164
Age, years	55.5 ± 13.1
Sex, n (%)	
Female	2367 (74.8)
BMI, kg/m^2	26.9 ± 5.3
Median duration of disease, years (Q1; Q3)	7 (3; 14)
Disease activity	
DAS28-ESR	5.01 ± 1.54
CDAI	26.45 ± 13.62
ESR (mm)	32.4 ± 25.3
CRP (mg/L)	28.74 ± 81.45
Physical Functioning	
HAQ (%)	1.27 ± 0.74
Anti-CCP status, n (%)	
Positive	773 (24.4)
Negative	165 (5.2)
Unknown	2226 (70.4)
RF status, n (%)	
Positive	937 (29.6)
Negative	263 (8.3)
Unknown	1964 (62.1)
Comorbidities, n (%)	
At least one	2277 (72.1)
Missing	6
Previous therapy, n (%)	
csDMARDs only	949 (30.0)
TNFi	2100 (66.4)
Non-TNFi bDMARDs	87 (2.7)
Missing/Other	28 (0.9)
Concomitant csDMARD, n (%)	
With	1604 (50.9)
Methotrexate, n (%)	1226 (38.7)
Leflunomide, n (%)	315 (10.0)
Without	1551 (49.1)
Missing	8
Concomitant GC, n (%)	
With	2545 (80.7)
>0–5 mg/d	1331 (42.2)
>5–10 mg/d	780 (24.7)
>10 mg/d	434 (13.8)
Without	607 (19.3)
Missing	12

BMI: body mass index; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28-ESR: Disease Activity Score based on 28 joints and erythrocyte sedimentation rate; GC: glucocorticoid; HAQ: Health Assessment Questionnaire; Q: Quartile; SAF: safety analysis set; TNFi: tumour necrosis factor inhibitor.

Table II. Baseline characteristics by previous therapy subgroup (SAF).

Characteristic	Previous csDMARD (n=949)	Previous TNFi (n=2100)	Previous non-TNFi bDMARD (n=87)
Age, years	57.7 ± 12.2	54.5 ± 13.4	55.6 ± 13.5
Sex, n (%)			
Female	689 (72.6)	1593 (75.9)	65 (74.7)
BMI, kg/m^2	27.1 ± 5.0	26.7 ± 5.3	27.5 ± 7.6
Median duration of disease, years (Q1; Q3)	4 (2; 10)	9 (4; 15)	8 (4; 14)
Disease activity			
DAS28-ESR	4.78 ± 1.73	5.13 ± 1.43	4.70 ± 1.33
CDAI	24.56 ± 14.14	27.40 ± 13.36	24.15 ± 11.99
Physical Functioning			
HAQ (%)	1.11 ± 0.71	1.34 ± 0.73	1.24 ± 0.76
Comorbidities, n (%)			
At least one	694 (73.1)	1509 (71.9)	63 (72.4)
Hypertension	383 (40.4)	743 (35.4)	34 (39.1)
Joint disorder or spinal disease	150 (15.8)	442 (21.0)	12 (13.8)
Osteoporosis	149 (15.7)	376 (17.9)	14 (16.1)
Diabetes	102 (10.7)	197 (9.4)	13 (14.9)
Coronary heart disease	38 (4.0)	97 (4.6)	4 (4.6)
GC dose mg/d	6.48 ± 8.22	7.8 ± 17.0	7.16 ± 8.73

bDMARD: non-TNFi biological DMARDs; BMI: body mass index; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying anti-rheumatic drugs; DAS28-ESR: Disease Activity Score based on 28 joints and erythrocyte sedimentation rate; GC: glucocorticoid; HAQ: Health Assessment Questionnaire; Q: Quartile; SAF: safety analysis set; TNFi: tumour necrosis factor inhibitor.

ment Questionnaire [HAQ]). Clinically relevant improvement or worsening in HAQ score was defined as a decrease or increase of ≥0.3 in HAQ score (23); functional HAQ remission was defined as HAQ <0.5.

The primary effectiveness outcome was the proportion of patients in DAS28-ESR remission (DAS28-ESR <2.6) at least once during the study. Secondary outcomes included time to DAS28-ESR remission, proportion of patients with good or moderate EULAR response as well as low disease activity, defined as DAS28-ESR ≤3.2 or CDAI ≤10.

Safety

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA), v. 13.0. Treatment-emergent AEs were used for safety analysis. AEs of special interest (AESI) were infections (opportunistic and non-serious infections as defined by treatment with IV anti-infectives), myocardial infarction/acute coronary syndrome, gastrointestinal perforation and related events, malignant tumours, anaphylactic/hypersensitivity reactions, demyelinating diseases, stroke, bleeding and hepatic events.

Statistics

The safety analysis set (SAF) was composed of all eligible patients enrolled in the study who received at least one dose of TCZ, including patients with TCZ exposure prior to this study. All safety analyses were performed in the SAF. The effectiveness analysis set (EFF-NPT) was composed of all SAF patients without previous TCZ therapy. Patients with previous TCZ therapy, patients changing from intravenous to subcutaneous administration of TCZ, and patients switching to a new RA treatment were analysed separately.

Three subgroups were defined regarding previous therapy: csDMARDs only (all patients with previous csDMARDs only), TNFi (all patients with previous TNF inhibitor therapy), and non-TNFi bDMARD (all patients with previous bDMARDs therapy excluding TNFi and TCZ). For concomitant treatment at baseline subgroup analyses, patients were grouped into monotherapy with TCZ or combination therapy with csDMARDs at baseline (including both patients with or without GCs). In addition, four subgroups per baseline treatment with csDMARDs and/or GC were defined: monotherapy+GC (TCZ+GC), combination+GC (TCZ+csDMARD+GC), monotherapy-GC (TCZ only), and combination-GC (TCZ+csDMARD).

Descriptive statistics were used for all parameters. For time to reach DAS28-ESR remission, Kaplan-Meier estimates were calculated. Patients without DAS28-ESR remission were censored on the day following their last assess-

Table III. Baseline characteristics by concomitant therapy subgroup (SAF).

Characteristic	Monotherapy ± GC (n=1551)	Monotherapy - GC n=316)	Monotherapy + GC (n=1235)	Combination ± GC (n=1605)	Combination - GC (n=291)	Combination + GC (n=1314)
Age, years	56.6 ± 13.6	53.3 ± 14.3	57.4 ± 13.3	54.4 ± 12.5	54.4 ± 12.8	54.4 ± 12.5
Sex, n (%)						
Female	1218 (78.5)	263 (83.2)	955 (77.3)	1143 (71.2)	228 (78.4)	915 (69.6)
BMI, kg/m^2	26.6 ± 5.4	26.4 ± 5.4	26.6 ± 5.4	27.1 ± 5.3	27.2 ± 5.2	27.1 ± 5.3
Median duration of disease, years (Q1; Q3)	8 (3; 15)	7 (3; 13)	8 (4; 15)	7 (3; 13)	7 (3; 12)	7 (3; 13)
Disease activity						
DAS28-ESR	5.11 ± 1.47	4.73 ± 1.64	5.21 ± 1.41	4.91 ± 1.59	4.73 ± 1.59	4.95 ± 1.58
CDAI	26.91 ± 13.33	24.35 ± 13.16	27.53 ± 13.30	26.03 ± 13.89	24.62 ± 13.36	26.32 ± 13.98
Physical Functioning HAQ (%)	1.32 ± 0.75	1.16 ± 0.76	1.36 ± 0.74	1.22 ± 0.72	1.07 ± 0.69	1.25 ± 0.72
Comorbidities, n (%)						
At least one	1157 (74.6)	215 (68.0)	942 (76.3)	1118 (69.7)	197 (67.7)	921 (70.1)
Hypertension	598 (38.6)	105 (33.2)	493 (40.0)	568 (35.4)	108 (37.1)	460 (35.0)
Joint disorder or spinal disease	308 (19.9)	35 (11.1)	273 (22.1)	297 (18.5)	51 (17.5)	246 (18.7)
Osteoporosis	285 (18.4)	32 (10.1)	253 (20.5)	256 (16.0)	23 (7.9)	233 (17.7)
Diabetes	171 (11.0)	37 (11.7)	134 (10.9)	143 (8.9)	24 (8.2)	119 (9.1)
Coronary heart disease	82 (5.3)	13 (4.1)	69 (5.6)	58 (3.6)	8 (2.7)	50 (3.8)
GC dose mg/d	7.34 ± 8.06	–	9.22 ± 8.02	7.42 ± 18.95	–	9.06 ± 20.59

BMI: body mass index; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28-ESR: Disease Activity Score based on 28 joints and erythrocyte sedimentation rate; GC: glucocorticoid; HAQ: Health Assessment Questionnaire, Q: Quartile; SAF: safety analysis set.

ment/visit. Chi^2 tests used to analyse differences between subgroups for the primary endpoint should be considered exploratory. Missing values were not substituted and the last observation carried forward (LOCF) method was used for last visit (LV) data. Statistical analyses were performed using SAS® v. 9.4, (Cary, NC, USA).

Results

Patients and treatment

Between January 2010 and January 2017, 3404 patients were enrolled at 255 rheumatology centres in Germany; 3164 patients received at least one dose of TCZ (safety population, SAF). The mean age of patients was 55.5±13.1 years, and about three-quarters of patients were female. At baseline, 72.1% of patients had at least one comorbidity, the most common being hypertension (37.0%), degenerative joint disorder/spinal disease (19.2%), osteoporosis (17.2%) and diabetes (9.9%) (Table I).

More than two thirds of the patients had previously been treated with TNFi or other bDMARDs (Table I). Compared to these, the bDMARD-naïve subgroup, with previous csDMARD therapy only, was slightly older and had a shorter duration of disease (Table II). Patients previously treated with TNFi had slightly higher baseline disease activity (DAS28-ESR and CDAI) than those previously treated with csDMARDs or non-TNFi bDMARDs only (Table II). The primary reason for change to TCZ was lack of effectiveness of previous therapy (87.8%), as documented for 82% of the bDMARD-naïve patients and 91% of the patients with previous TNFi therapy. This was followed by lack of tolerability of the previous therapy (22.2%).

At baseline, approximately half of the patients received concomitant csDMARDs, mostly methotrexate, and four fifths were on concomitant GCs (Table I). Patients with previous csDMARDs therapy only received a lower mean baseline dose of GC (6.48±8.22 mg/d) than those with previous TNFi (7.8±17.0 mg/d) or other bDMARD-therapy (7.16±8.73 mg/d). Patients receiving TCZ monotherapy with GC were older, had a longer duration of RA, higher disease activity, more comorbidities and worse physical functioning than other subgroups (Table III). The median duration of the observational period was 1.96 years, and 1307 patients remained in the study until week 104.

Among 1830 patients with premature study discontinuation, the most common documented reasons were lack of effectiveness (21.3%) and intolerance (6.3%). Twenty-eight patients (1.5%) discontinued TCZ treatment because of remission. Unfortunately, 964 patients (52.7%) were lost to follow-up.

Among all concomitant therapy subgroups, the most common documented reason for premature study discontinuation was lack of effectiveness. Approximately 13.0% of patients receiving csDMARDs at baseline discontinued due to lack of effectiveness (11.7% of patients receiving no csDMARDs at baseline). These rates were similar regardless of the patient receiving methotrexate (MTX) or not at baseline (12.8% with MTX; 12.0% without MTX)

Of the SAF, 2902 (91.7%) patients with no previous TCZ were included in the EFF-NPT population. All effectiveness analyses were performed on the EFF-NPT population only. The proportions of patients with concomitant csDMARDs and with concomitant GC decreased over time. At baseline, 50.6% of patients were receiving csDMARDs compared to 44.9% at week 104 (LV: 46.3%). At baseline, 81.5% of patients were receiving GC compared to 66.9% at week 104 (LV: 74.4%). Mean GC dose of patients with GC treatment at baseline decreased from 9.32±16.36 mg/d to 4.60±4.48 mg/d at week 104 (LV:

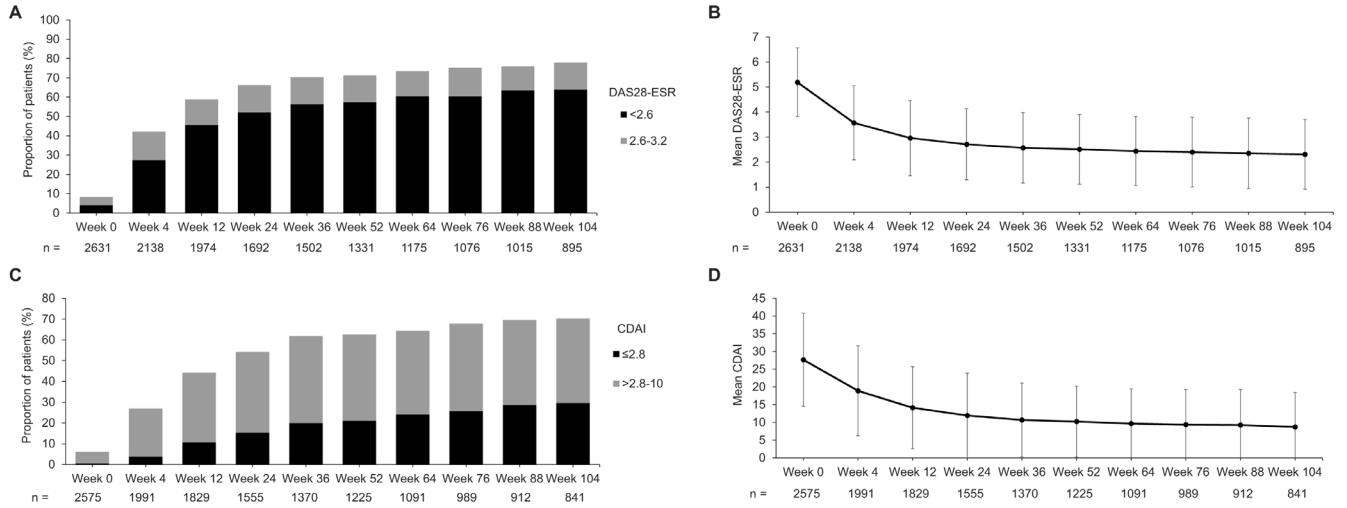

Fig. 1. DAS28-ESR and CDAI over time in the effectiveness population with no previous TCZ therapy (EFF-NPT)**.**
A: DAS28-ESR categories and (**B**) mean score over time. **C**: CDAI categories and (**D**) mean score over time. Error bars represent standard deviation.
CDAI: Clinical Disease Activity Index; DAS28-ESR: Disease Activity Score based on 28 joints and erythrocyte sedimentation rate; effectiveness analysis set – no previous TCZ treatment.

6.24±6.12 mg/d), with similar GC decreases in patients on TCZ+csDMARDs combination therapy (9.31±21.45 mg/d at baseline to 4.46±4.08 mg/d at week 104) and patients on TCZ monotherapy (9.34±8.16 mg/d at baseline to 4.78±4.92 mg/d at week 104).

Overall effectiveness of TCZ

Overall, 61.4% of patients in the EFF-NPT achieved the primary effectiveness outcome, DAS28-ESR remission documented at least once during the treatment period, after a median time of 148 days on TCZ treatment. Excluding the 104 patients that were already in DAS28-ESR remission at baseline, the median duration to DAS28-ESR remission was 161 days (Suppl. Fig. S1). TCZ treatment resulted in a quick response, as reflected in the proportion of patients achieving low disease activity (DAS28-ESR ≤3.2) and the reduction of mean DAS28-ESR already by weeks 4 and 12 (Fig. 1A-B). Similar improvements were also seen in the proportion of patients achieving CDAI low disease activity (≤10) within 12 weeks (Fig. 1C) and in the decrease of mean CDAI (Fig. 1D). At week 104, 77.9% of patients were in DAS28-ESR low disease activity (Fig. 1A) (LV: 57.6%) and 89.6% had achieved good or moderate EULAR response (LV: 74.9%). CDAI-based and Boolean-based ACR/EULAR remission were achieved for 29.5% and 17.5% of the patients, respectively, at week 104 (LV: 16.2 and 10.4%, respectively).

Patients on TCZ treatment had rapidly improved physical functioning. At week 4, 27.7% of patients experienced a clinically relevant improvement in HAQ score. HAQ improvement plateaued between week 12 and 24 and was sustained with only marginal changes throughout the observational period. By week 104, the proportion of patients achieving a clinically relevant improvement of HAQ had increased to 47.9% (LV: 34.1%) and 38.7% were in HAQ remission (LV: 30.5%). Only 10.6% of patients experienced clinically relevant worsening (LV: 10.2%).

TCZ effectiveness according to previous therapy

The proportion of patients achieving DAS28-ESR remission was comparable among subgroups per previous therapy, albeit slightly higher among patients previously receiving csDMARDs only (65.1%) compared to previous TNFi (60.3%) or non-TNFi bDMARDs (56.5%; *p*-value for χ^2 test: 0.0591) (Suppl. Table S1). Excluding patients in DAS28-ESR remission at baseline, the median duration to reach DAS28-ESR for the first time was 105 days in previous csDMARDs-only, 168 days in TNFi, and 93 days in non-TNFi bDMARDs subgroups.

With TCZ therapy, proportions of patients achieving remission or low disease activity according to DAS28-ESR or CDAI over time were similar across previous treatment subgroups (Fig. 2 A-C). Patients in the previous csDMARDs-only subgroup had only slightly higher mean changes from baseline in CDAI than patients with previous TNFi at both early and late time points (LV: -15.34±13.73 for csDMARDs *vs*. -12.87±13.88 for TNFi, respectively). There were no relevant differences in the proportions of patients achieving good or moderate EULAR response by week 104 or LV between the previous csDMARDs-only subgroup and patients with previous TNFi or non-TNFi bDMARDs. Patients in the previous csDMARD-only subgroup had slightly greater gains in physical functioning at early and late time points. The proportion of patients that had a clinically relevant improvement of the HAQ score at week 104 was 50.2% of patients with previous csDMARDs *vs*. 47.6% of previous TNFi (LV: 38.3% *vs*. 32.8% respectively).

TCZ effectiveness according to concomitant therapy

According to an exploratory post-hoc analysis, the primary outcome was comparable between patients with and without concomitant GC therapy at baseline. However, patients receiv-

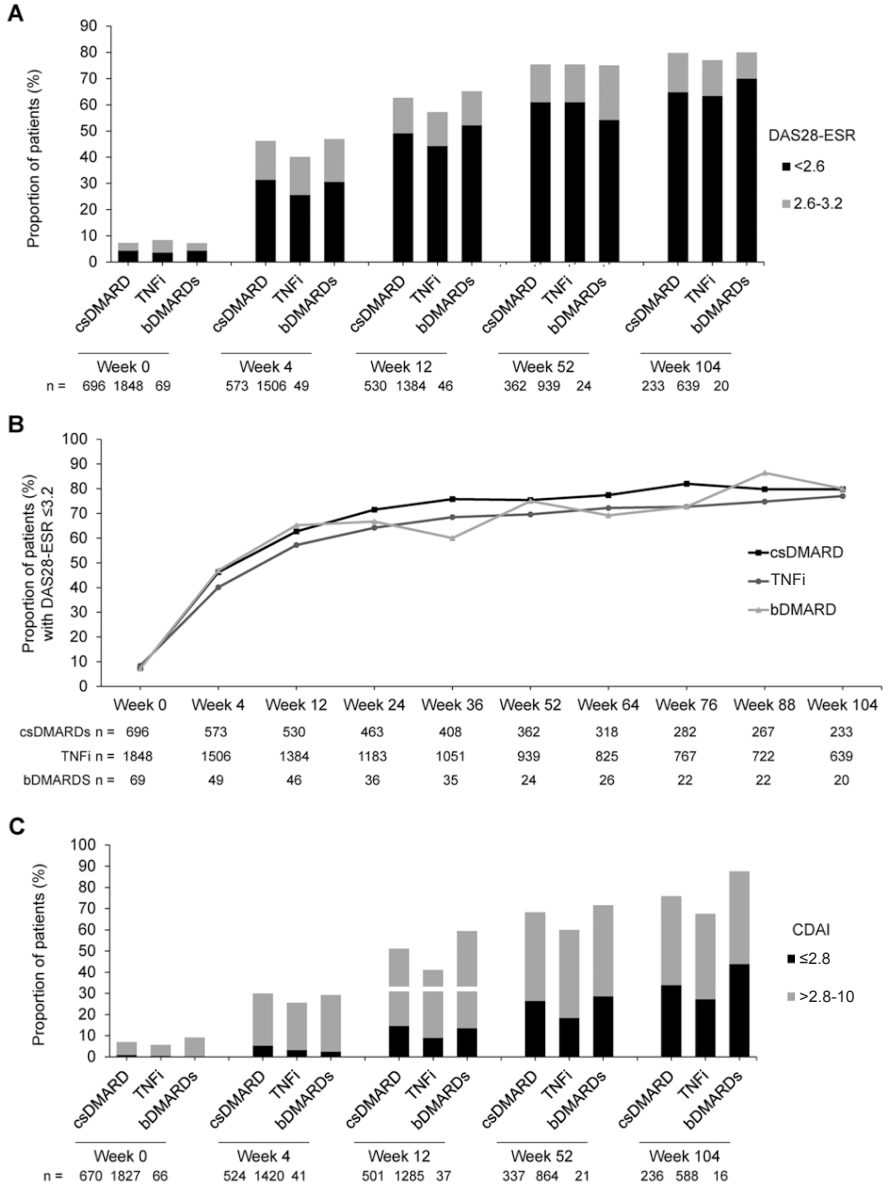

Fig. 2. DAS28-ESR categories, and EULAR response over time per previous therapy (EFF-NPT).
A: DAS28-ESR categories and (**B**) proportion of patients to achieve DAS28-ESR low disease activity (≤3.2) over time in subgroups per previous therapy. **C**: CDAI low disease activity over time in subgroups per previous therapy.
bDMARD: non-TNFi bDMARDs; csDMARD: only previous csDMARD therapy; DAS28-ESR: Disease Activity Score based on 28 joints and erythrocyte sedimentation rate; EFF-NPT: effectiveness analysis set – no previous TCZ treatment; TNFi: previous TNF inhibitor therapy.

ing concomitant csDMARDs at baseline had a significantly higher rate of reaching the primary outcome during the study than those without (64.4% with csDMARDS *vs*. 58.4% without) (Suppl. Table SI). Mean changes in DAS28-ESR from baseline, changes in CDAI category (Fig. 3 A-D), proportions of patients achieving good or moderate EULAR response and improvement in physical functioning were similar in patients receiving TCZ as monotherapy or in combination with concomitant csDMARDs, both with and without GCs. Excluding patients in DAS28-ESR remission at baseline, the median duration to DAS28-ESR remission was 149 days for patients receiving concomitant csDMARDs and 166 days for those without csDMARDs at baseline (Suppl. Fig. S1). Excluding patients in DAS28-ESR remission at baseline, the median duration to DAS28-ESR remission was 169 days for monotherapy+GC (TCZ+GC), 158 days for combination+GC, 116 days for monotherapy-GC, and 114 days for combination-GC groups.

Safety

Overall, 46.6% of 3164 patients in the SAF experienced 4278 AEs over 3948 patient years (PY) of TCZ exposure (Table IV). The most commonly documented AEs considered related to TCZ treatment – infections and infestations (9.5% of patients) – consisted largely of nasopharyngitis (2.1% of patients) and bronchitis (1.4% of patients). Other frequent AEs considered related to TCZ treatment were gastrointestinal disorders (3.7% of patients), skin and subcutaneous tissue disorders (3.3% of patients), and general disorders and administration site conditions (3.2% of patients).

In patients with previous TNFi and csDMARDs only, rates of treatment-related SAEs were comparable with 5.5 and 5.6 events/100 PY, respectively. However, more treatment-related SAEs were seen in patients with previous non-TNFi-bDMARDs (11.9 events/100 PY; n=87). Patients receiving GCs at baseline experienced higher rates of TCZ-related SAEs than those receiving none (6.4 events/100 PY *vs*. 3.0 events/100 PY, respectively) and serious infections (4.3 events/100 PY *vs*. 2.4 events/100 PY, respectively). Thirty-six patients (1.1%) died during this study; 19 of these deaths occurred while a patient was receiving TCZ (0.5 events/100 PY) (Suppl. Table. S2), and 11 of these patients had SAEs considered to be related to TCZ treatment. AESIs were reported in 422 patients (13.3%). The most common AESIs were infections requiring treatment with intravenous anti-infectives (2.5 events/100 PY). Nine patients (0.3%) experienced gastrointestinal perforations (0.3 events/100 PY) (Table IV), and three of these patients died (Suppl. Table S2).

Discussion

The present non-interventional study ICHIBAN evaluated the long-term effectiveness and safety of TCZ in patients with active RA in daily practice. Baseline characteristics, such as age, severity and disease duration were similar to recent observational studies with

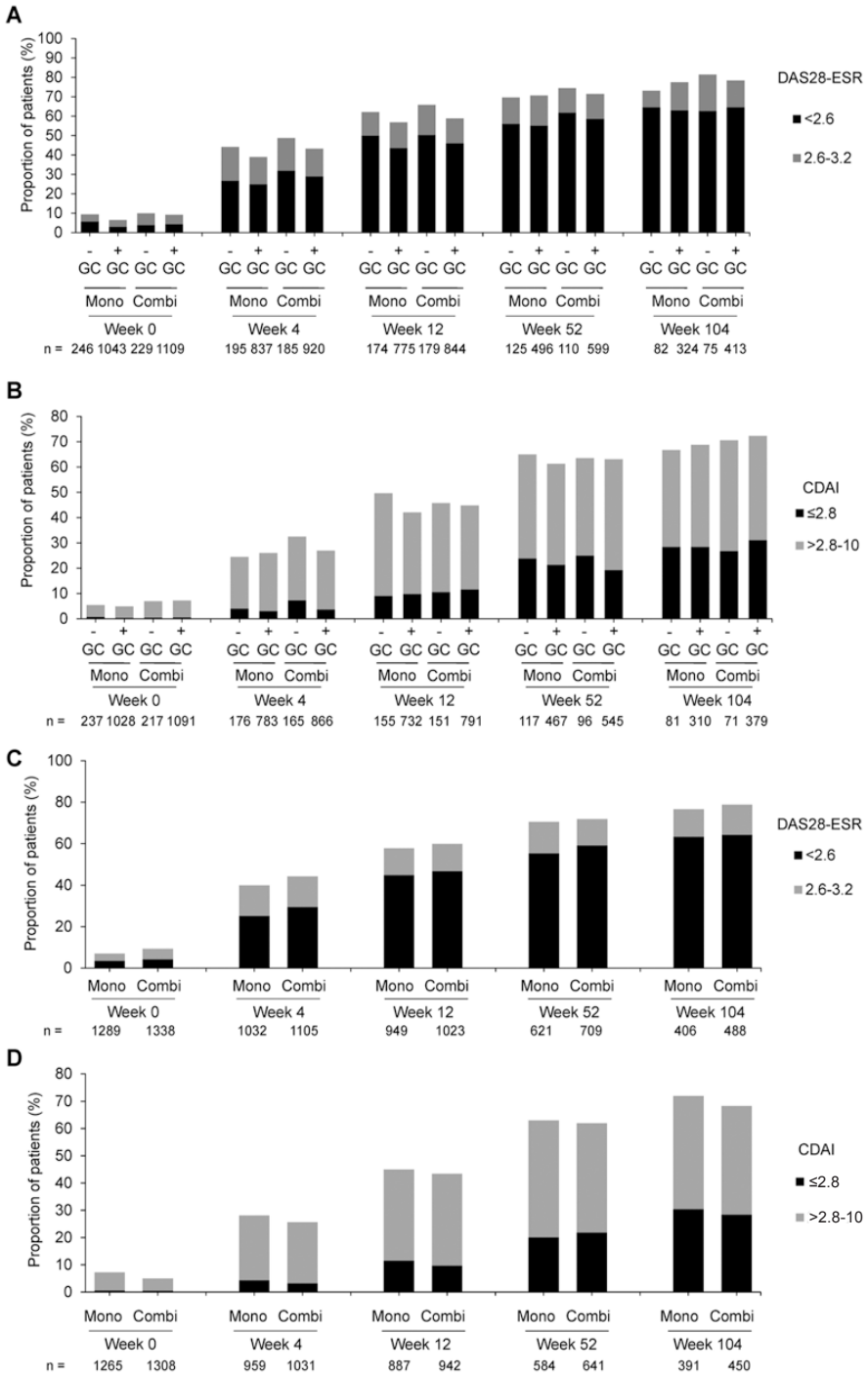

Fig. 3. DAS28-ESR, EULAR response, CDAI and mean GC dose over time per concomitant therapy at baseline.
A: DAS28-ESR categories and (**B**) CDAI categories over time in subgroups per concomitant therapy and GC use. **C**: DAS28-ESR categories and (**D**) CDAI categories over time in subgroups per concomitant csDMARD therapy regardless of GC use.
CDAI: Clinical Disease Activity Index; Combi: TCZ + csDMARD combination therapy at baseline; DAS28-ESR: Disease Activity Score based on 28 joints and erythrocyte sedimentation rate; EFF-NPT: effectiveness population with no prior TCZ treatment; EULAR: European League Against Rheumatism; GC: glucocorticoid; Mono: tocilizumab monotherapy at baseline.

TCZ in Europe (17, 18, 24-27). However, ICHIBAN had a relatively high proportion of patients with hypertension or diabetes, which is consistent with the German data from the international, cross-sectional study, COMORA (28).
Results over up to 104 weeks showed that TCZ was effective in routine care as reflected by the proportions of patients achieving DAS28-ESR remission, CDAI remission and clinically relevant improvement in physical functioning. Moreover, 61.2% patients achieved DAS28-ESR remission at least once during TCZ treatment. Considering the relatively long disease duration of this population, these remission rates underscore the effectiveness of TCZ. TCZ treatment also improved all other effectiveness outcomes (CDAI, DAS28-ESR, Boolean EULAR remission), with results comparable with other TCZ real-world datasets (17, 26, 29).

Previous therapy subgroups
Patients with previous TNFi therapy on average were younger, had longer duration of disease and worse physical function at baseline compared to the subgroup of biological-naïve previous csDMARD only patients. This observation corresponds with results from studies based on the German RABBIT registry (18) and British BSRBR-RA study (25). Furthermore, the ICHIBAN population also had a higher proportion of biologic-naïve patients compared to Scandinavian datasets (24, 26).
In ICHIBAN, 64.7% of patients with previous csDMARDs therapy only achieved the primary outcome compared to 60.1% of the previous TNFi subgroup, only a 4.6% difference, although the previous TNFi group had a 5-year longer median duration of disease at baseline. This is consistent with other real-world studies that showed no statistically significant differences in TCZ effectiveness outcomes between patients previously treated with other bDMARDs (including TNFi therapy) or csDMARDs only (17, 25). The present data supports results from the German RABBIT registry that found TCZ to be similarly effective in biologics-naïve patients and those with three or more previous bDMARD failures (18) and data from global the ACT UP project, which showed similar effectiveness of TCZ among biologics-exposed and naïve patients (30).

Concomitant therapy and GC saving
In the present study, a six-percent-higher proportion of patients treated with

Table IV. Summary of treatment emergent adverse events (SAF).

Event, SAF (n=3164)	Total events	Patients, n (%)	Rate per 100 patient years
AE	4278	1474 (46.6)	108.4
AE considered related to treatment	1435	699 (22.1)	36.3
SAE	943	472 (14.9)	23.9
Fatal	37	19 (0.6)	0.9
SAE considered related to treatment	224	146 (4.6)	5.7
AE leading to withdrawal	364	267 (8.4)	9.2
Infections	1160	676 (21.4)	29.4
SAE	153	113 (3.6)	3.9
AESI	718	422 (13.3)	18.2
Infection[#], n (%)	98	82 (2.6)	2.5
Medically significant hepatic event, n (%)	62	51 (1.6)	1.6
Anaphylaxis, n (%)	56	42 (1.3)	1.4
Myocardial infarction/Acute coronary syndrome, n (%)	28	23 (0.7)	0.7
Serious or spontaneous bleeding, n (%)	17	13 (0.4)	0.4
Stroke	15	13 (0.4)	0.4
Gastrointestinal perforation and related events	10	9 (0.3)	0.3
Malignant neoplasms	8	8 (0.3)	0.2
Demyelinating diseases	2	2 (0.1)	0.1

AE: adverse event; AESI: adverse event of special interest; SAE: serious adverse event; SAF: safety analysis set.
[#]Infections including all opportunistic and non-serious infections as defined by treatment with IV anti-infectives.

concomitant csDMARD at baseline achieved DAS28-ESR remission than those on TCZ monotherapy (64.4% *vs*. 58.4%). While monotherapy may have resulted in an insufficient response in some patients, we believe that the decision not to add a csDMARD was made in a responsible way by the individual treating physicians. Not all patients may tolerate csDMARDs, and there was indeed a further reduction of patients receiving csDMARDs throughout the study (50.7% baseline *vs*. 46.3% LV). Furthermore, similar to other real-world studies (17, 18, 25, 27), concomitant therapy subgroups had similar mean changes in DAS28-ESR from baseline, proportions of patients achieving good or moderate EULAR response, changes in CDAI category and improvements in physical functioning. Due to the natural limitations of a non-interventional study, such as the lack of randomization of subgroups, patients receiving monotherapy at baseline were on average slightly older, had a longer duration of disease, more comorbidities and higher disease activity. Thus, effectiveness results should be interpreted with caution.

ICHIBAN had a higher proportion of patients on concomitant GCs at baseline compared to Danish (26), British (25), and pan-European (27) registry studies. However, throughout ICHIBAN, the percentage of patients receiving GCs decreased from 80.6 to 66.9%, and mean GC dose was reduced from 9.32 to 4.60 mg/d, in line with previous studies (18, 19). In the SPARE-1 study, 40% of the patients treated with TCZ were able to achieve the GC-saving target dose of ≤5 mg/d (19). Furthermore, in an analysis of the German RABBIT cohort, numbers of patients receiving GCs decreased under TCZ and so did the numbers of patients receiving high doses of GCs (18). In the SEMIRA study, a randomised clinical trial (NCT02573012), GC discontinuation could be achieved in patients treated with TCZ without an increased risk of flares (31).

Safety

Overall, the rate of AEs in ICHIBAN was lower than that of integrated safety data from randomised controlled TCZ clinical trials (32) or cumulative analysis of controlled clinical trials and extension phases (33); however, the rate of SAEs in ICHIBAN was higher. The lower incidence of AEs may be caused by underreporting, while the higher incidence of SAEs may reflect the inclusion of higher risk patients and patients with multiple comorbidities usually excluded from clinical trials.

The incidence of anaphylaxis in ICHIBAN (1.4/100 PY) was higher than that of integrated safety data from TCZ clinical trials (0.1/100 PY) (32). None of these events were fatal. The incidence of serious infections observed during ICHIBAN (3.9 events/100 PY) was similar to that of integrated safety data from TCZ clinical trials (4.7 events/100 PY) (32) and other real-world studies such as REGATE (4.7 events/100 PY) (34) and ROUTINE (4.4 events/100 PY) (17). However, we observed an incidence of myocardial infarction and acute coronary syndrome in ICHIBAN, which, at 0.7 events/100 PY, was higher than reported in integrated safety data from TCZ clinical trials (0.25 events/100 PY) (32), as was stroke (0.4 events/100 PY in ICHIBAN *vs*. 0.19 events/100 PY in integrated trials). These findings may reflect the cardiovascular risk profile of the German real-world population: of 17 countries in the COMORA study, patients with RA in Germany had the third highest prevalence of myocardial infarction and stroke (28). Furthermore, incidence rates from 15,164 TCZ-naïve RA patients of the US-based MarketScan for myocardial infarction (0.8 events/100 PY) and stroke (0.51 events/100 PY) were similar to those seen in ICHIBAN (35). The rate of gastrointestinal perforations was not increased by the inclusion of real-life populations. Incidence of gastrointestinal perforations in ICHIBAN (0.3 events/100 PY) corresponded with integrated safety data from TCZ clinical trials (0.28/100 PY) (32) and German RABBIT registry studies (0.27/100 PY) (36).

The incidence of malignancies in ICHIBAN (0.2/100 PY) was lower than integrated safety data from TCZ clinical trials (1.1/100 PY) (32) or a Swedish register-based cohort study (0.96/100 PY).(37), possibly due to underreporting.

Limitations

Several limitations are inherent within non-interventional studies, such as the possibility of selection bias. Given the nature of non-interventional studies,

there was no control arm or randomisation, meaning that physician or patient perception of effectiveness could bias the results. Furthermore, due to the real-world nature of physician treatment decisions, there may have been a risk of underreporting of safety data and a possible exclusion of patients that had adverse events during TCZ exposure prior to this study. Moreover, a total of 104 patients (of 2902 in the EFF-NPT) had already achieved baseline DAS28-ESR remission, when given the first dose of TCZ. Another limitation of ICHIBAN was the missing data for RF- and anti-CCP-status at baseline. Importantly, documentation was incomplete for 964 patients, leading to a 58.7% proportion of patients prematurely ending the study. To address this, LOCF analyses were conducted for all endpoints, and Kaplan-Meier analyses were conducted for the primary endpoint. The proportion of patients prematurely ending the study was higher than in comparable real-world studies that had discontinuation rates of only about 35% (17, 24, 26). This may in part be related to the larger size and longer duration than other observational studies, and may also be related to alterations in the monitoring due to a change in the clinical research organization during the ongoing study.

In summary, this prospective, multicentre, non-interventional study showed rapid and long-term effectiveness and safety of TCZ in daily practice in Germany and adds data supporting the GC saving potential of TCZ. Tolerability was similar to other real-world data and no new safety signals were observed. Effectiveness was similar to other observational studies and thus supports the use of TCZ both after bDMARD failure and in biologic-naïve patients. Effectiveness of TCZ was not markedly influenced by concomitant csDMARDs (*e.g.* methotrexate), in line with previous literature on TCZ monotherapy in RA.

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