The safety and effectiveness of tocilizumab in elderly patients with rheumatoid arthritis and in patients with comorbidities associated with age

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Abstract

Objective
To examine the safety and effectiveness of long-term tocilizumab treatment in elderly patients with rheumatoid arthritis (RA) and patients with age-associated comorbidities.

Methods
ICHIBAN (NCT01194401) was a prospective, non-interventional study that observed adult patients with active moderate-to-severe RA in German rheumatology clinics and practices for up to two years. Patients were to be treated according to the tocilizumab label. Here, we present safety and effectiveness data analysed according to patient age.

Results
Of the 3,164 patients treated with at least one dose of tocilizumab, 924 patients were <50 years old, 1496 patients were 50–65 years old, and 744 patients were >65 years old at baseline. Patients >65 years had the highest baseline DAS28-ESR, CDAI, and HAQ-DI scores, along with the highest burden of comorbidities, such as diabetes, coronary heart disease, anaemia, and renal insufficiency. Under treatment with tocilizumab, patients >65 years had similar improvements in DAS28-ESR, CDAI and patient-reported outcomes (fatigue, pain, sleeplessness) with similar glucocorticoid savings compared to patient groups <65 years. Patients >65 years with late-onset RA achieved similar reductions in disease activity compared to early-onset patients. Despite numerically higher rates of adverse events (AEs), serious AEs and serious infections in patients >65 years, there were similar rates of AEs leading to withdrawal.

Conclusion
Elderly patients in ICHIBAN experienced improvements similar to younger patients in most effectiveness endpoints with only slightly higher rates of AEs, indicating an overall net-positive risk-benefit ratio of tocilizumab treatment regardless of patient age.

Key words
rheumatoid arthritis, tocilizumab, interleukin-6, elderly

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Introduction

Compared with the general population, patients with rheumatoid arthritis (RA) have a higher probability of experiencing comorbidities and multiple comorbidities (1), including depression, asthma, cardiovascular events and malignancies (2).

As the proportion of elderly individuals in the European population increases, and as patients with rheumatic diseases approach normal survival rates with 21st century therapies, questions on RA treatment in the elderly patient population inevitably arise. The age-associated increase in rates of hypertension, cardiovascular disease, diabetes, obesity, osteoporosis, and chronic obstructive pulmonary disease adds to the overall disease burden of elderly patients with RA, which is of itself not insubstantial. RA increases the risk of cardiovascular mortality compared with the general population (3) – a risk that rises with age. Furthermore, patients with multiple comorbidities have a lower probability of receiving effective RA treatment (4). Thus, physicians tend to treat elderly patients with RA less aggressively compared with younger patients, although effective RA treatment in elderly patients is essential for lowering the burden of disease (5). For instance, treating to target by switching from conventional synthetic (cs) to biologic disease-modifying anti-rheumatic drugs (bDMARDs) is implemented more often in younger than in older patients with RA (6). An analysis of the German Collaborative Arthritis Centres demonstrated that patients with disease onset prior to 65 years of age were three times more likely to be prescribed a bDMARD than those with an onset after 65 years (7). Furthermore, treatment with csDMARDs (as more often seen in elderly patients) is commonly associated with oral glucocorticoid (GC) use (8). This is also reflected in the analysis of the German Collaborative Arthritis Centres, where patients with disease onset after 65 years of age were treated with GCs significantly more often than those with disease onset prior to 65 years, regardless of disease duration (7). Patients with RA are already at risk of accelerated immunosenescence (9), and treatments such as GCs significantly increase the risks of osteoporosis and severe infections (10). Higher doses of GCs are also associated with increased cardiovascular disease and mortality (11, 12). Thus, safe and effective targeted treatment options for elderly patients with RA are indispensable.

Tocilizumab, a humanised monoclonal antibody that targets both membrane-bound and soluble interleukin-6 (IL-6) receptors, has been shown to be an efficacious treatment for RA in pivotal clinical trials (13-18). A small-scale retrospective study in French populations with RA has shown tocilizumab to be well-tolerated in patients >65 years old (19). However, larger studies in elderly populations are lacking. ICHIBAN (NCT01194401) was a large, prospective, non-interventional study that followed patients with RA treated with tocilizumab at 255 rheumatology centres in Germany for up to 2 years under real-life conditions (20). Overall, patients in ICHIBAN experienced good effectiveness with tocilizumab treatment regardless of prior RA therapy. Safety in ICHIBAN was similar to the pivotal clinical trials and other real-life tocilizumab studies. Here, we present an analysis of the ICHIBAN population examining the safety and effectiveness of long-term tocilizumab treatment in elderly patients and patients with comorbidities associated with age.

Materials and methods

ICHIBAN was a prospective, non-interventional study that observed adult patients with active moderate to severe RA in German rheumatology clinics and practices. Detailed methods on study design and inclusion criteria have been previously published (20). In short, adult patients were enrolled from January 2010 to January 2017. The decision to treat with tocilizumab (RoActemra®, Roche Pharma AG, Grenzach-Wyhlen, Germany) was made on a clinical basis prior to and independent of enrolment. Patients were to be treated according to the German Summary of Product Characteristics (SmPC). The treating physicians made all medical decisions. No interventions were made concerning therapeutic procedures. All patients

gave informed consent prior to enrolment. The ethics committee of the State Chamber of Physicians North Rhine (Germany) reviewed and approved this study, which was registered at the Paul-Ehrlich-Institute (ML22928).

Data collection and outcomes
Data were collected at study visits at baseline (week 0) and weeks 4, 12, 24, 36, 52, 64, 76, 88 and 104 via an electronic case report form. Detailed methods have been previously published (20). Comorbidities shown in this manuscript were reported by the investigator at baseline, except anaemia. The presence of anaemia was based on patients with available baseline laboratory haemoglobin (Hb) measurements (men Hb <13 g/dl, women Hb <12 g/dl). The primary effectiveness outcome was the proportion of patients who achieved remission defined as a Disease Activity Score based on 28 joints and erythrocyte sedimentation rate (DAS28-ESR) of <2.6 at least once during the observation period. Secondary effectiveness outcomes included time to DAS28-ESR remission, Clinical Disease Activity Index (CDAI) score, physical functioning as measured by Health Assessment Questionnaire Disability Index (HAQ-DI), and patient-reported outcomes (PROs). Clinically relevant improvement in HAQ-DI score was defined as a decrease of ≥0.3. Safety outcomes included the number and type of adverse events (AEs) and serious AEs (SAEs).

Patient-reported outcomes
Disease activity, health status, fatigue, strength of pain and sleep disturbance were assessed by the patients, using visual analogue scales (VAS). A score of 0 mm indicated the best outcome, and 100 mm indicated the worst outcome.

Safety
Only treatment-emergent AEs were used for safety analysis. AEs were recorded using the Medical Dictionary for Regulatory Activities (MedDRA v. 13.0) coding. A list of AEs of special interest (AESI) can be found in the supplementary information.

Table I. Baseline characteristics by subgroups according to age groups (SAF).

Characteristic	<50 years (n=924)	50–65 years (n=1496)	>65 years (n=744)
Age, mean±SD, years	39.7 ± 8.1	56.9 ± 4.4	72.2 ± 4.3
Sex, % (n)			
Female	77.2 (713)	72.2 (1080)	77.2 (574)
BMI, mean±SD, kg/m^2	26.0 ± 5.8	27.5 ± 5.4	26.6 ± 4.4
Median duration of disease, years	7.0	6.0	10.0
Smoking behaviour, % (n)			
Smoker	25.2 (233)	22.3 (334)	6.3 (47)
Non-smoker	51.7 (478)	46.9 (701)	67.7 (504)
Ex-smoker	10.7 (99)	18.9 (282)	15.3 (114)
Prior treatment, % (n)			
Biologic naïve	24.0 (222)	31.2 (467)	34.9 (260)
Anti-TNF	72.3 (668)	65.4 (979)	60.9 (453)
Concomitant medication, % (n)			
csDMARDs	53.0 (490)	54.1 (810)	41.0 (305)
No csDMARDs	46.9 (433)	45.5 (681)	58.7 (437)
GCs	76.1 (703)	82.2 (1229)	83.1 (618)
GC dose, mean±SD, mg/d	7.1 ± 7.8	7.8 ± 19.8	7.0 ± 7.1
No GCs	23.8 (220)	17.5 (262)	16.8 (125)
Disease activity			
DAS28-ESR, mean±SD	4.69 ± 1.55	5.10 ± 1.51	5.21 ± 1.52
CDAI, mean±SD	24.59 ± 13.41	27.17 ± 13.74	27.39 ± 13.43
Physical functioning			
HAQ-DI, mean ± SD	1.07 ± 0.71	1.28 ± 0.71	1.48 ± 0.76
Comorbidities, % (n)			
At least one	51.8 (478)	76.5 (1142)	88.4 (657)
Hypertension	14.3 (132)	39.6 (591)	59.9 (445)
Depression	5.4 (50)	9.0 (134)	7.0 (52)
Anaemia, % (n)			
Hb <12 g/dl (females)	17.1 (158)	10.9 (163)	21.5 (160)
Hb <13 g/dl (males)	3.0 (28)	4.9 (74)	7.3 (54)
Renal insufficiency	0.5 (5)	1.7 (25)	8.1 (60)
Osteoporosis	6.4 (59)	15.8 (235)	33.4 (248)
Diabetes	3.6 (33)	9.6 (143)	18.6 (138)
Coronary heart disease	0.4 (4)	3.7 (55)	10.9 (81)

All baseline comorbidities shown in this manuscript were reported by the investigator except anaemia. Anaemia was based on the baseline clinical laboratory haemoglobin value (Hb).
BMI: body mass index; CDAI: Clinical Disease Activity Index; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; DAS28-ESR: Disease Activity Score-28 erythrocyte sedimentation rate; GC: glucocorticoids; HAQ-DI: Health Assessment Questionnaire Disease Index; Hb: haemoglobin; SAF: safety analysis set; TNF: tumour necrosis factor.

Statistics
All safety analyses were performed in the safety analysis set (SAF), which comprised all eligible patients enrolled in the study who received at least one dose of tocilizumab, including patients with tocilizumab exposure prior to this study. Effectiveness outcomes were analysed in the effectiveness analysis set (EFF-NPT), which comprised all patients who received at least one dose of tocilizumab and had no prior tocilizumab therapy (NPT). For this analysis, patients were divided into groups according to baseline age (<50 years, 50–65 years and >65 years), and the presence of the following comorbidities as reported by the investigator at baseline (yes/no): diabetes, renal insufficiency, and coronary artery disease. Patients were categorised into anaemia subgroups according to the baseline Hb value (men Hb <13 g/dl, women Hb <12 g/dl). For further post hoc analysis, patients >65 years at baseline were divided into two subgroups: (1) patients diagnosed with RA prior to 65 years of age (early-onset) and (2) patients diagnosed with RA after 65 years of age (late-onset). All outcomes were analysed using descriptive statistics. Baseline characteristics are only pre-

sented descriptively. Exploratory tests for significance were performed on the primary endpoint using χ^2 test. Safety endpoints were also compared using χ^2 test. Multigroup comparisons on effectiveness endpoints were performed using ANOVA. Comparisons of 2 groups were performed using Student's t-tests. $p<0.5$ was considered significant. The last observation carried forward method was used for last visit (LV). Missing values were not substituted. Statistical analyses were performed using SAS® version 9.4, (Cary, NC, USA).

Results

Overall, 3,164 patients were treated with at least one dose of tocilizumab and were included in the SAF. Of these, 29.2% of patients were <50 years, 47.3% 50–65 years, and 23.5% >65 years old at baseline, with 39 patients of this group being ≥80 years old. With a median of 10.0 years, patients >65 years old had the longest RA disease duration. Furthermore, patients >65 years old had the numerically highest mean baseline DAS28-ESR, CDAI, and HAQ-DI scores (Table I). Comorbidities such as hypertension, anaemia, renal insufficiency, osteoporosis, diabetes, and coronary heart disease were most common in the oldest age group (Table I).

Patients >65 years were the least likely to smoke, to have been prescribed biologic medication in the past, and to be prescribed concomitant csDMARDs with tocilizumab (Table I). The median duration of tocilizumab exposure was similar for patients aged <50 and 50–65 years (1.48 and 1.43 years, respectively), but slightly shorter for the >65 year

Fig. 1. Effectiveness endpoints assessed according to patient age (EFF-NPT).
A: Proportion of patients in DAS28-ESR categories at baseline and last visit according to age group.
**B**: Mean change in DAS28-ESR from baseline at all study visits.
C: Proportion of patients in CDAI categories at baseline and last visit.
D: Mean change in CDAI from baseline at all study visits.
Error bars are standard deviation.
CDAI: Clinical Disease Activity Index; DAS28-ESR: Disease Activity Score-28 erythrocyte sedimentation rate; EFF-NPT: effectiveness analysis set – no prior tocilizumab therapy.
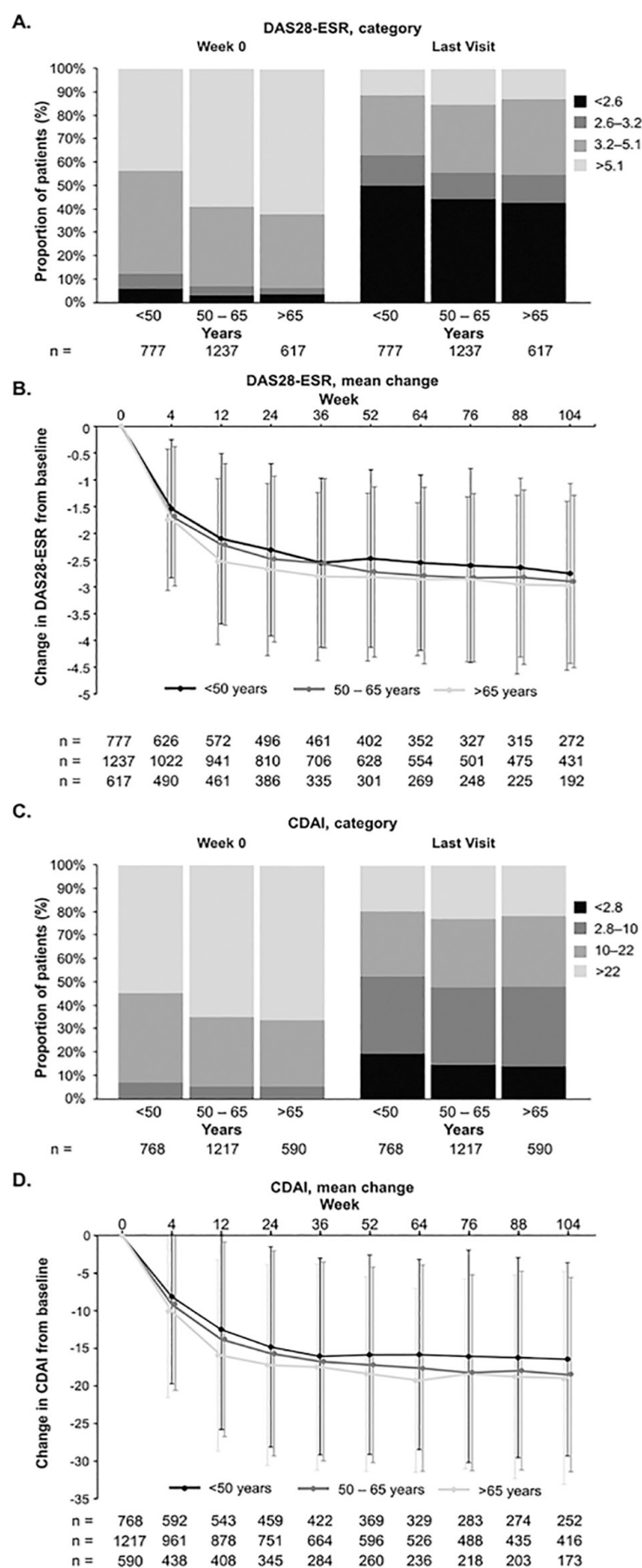
age group (1.26 years). A numerically higher proportion of patients in the >65 year age group discontinued treatment (61.4%) than did patients in the 50–65 year (58.0%) or <50 year (57.6%) age group. Overall, 5.4% of patients >65 years who discontinued did so because of lack of tolerability and 14.3% because of lack of effectiveness compared with 7.6% and 23.7%, respectively, in <50 years. Patients >65 years discontinued more often due to 'other reasons' (7.4%) and were more often lost to follow-up (55.9%) than were patients <50 years (5.5% and 51.1%, respectively). Overall, of the 744 patients who were >65 years at baseline, 59.9% were diagnosed with RA prior to their 65th birthday (early-onset group), 31.0% were diagnosed after their 65th birthday (late-onset group) and 9.1% had missing data. Patients in the early-onset group were 71.0 years (*vs.* 74.4 years), had 16.6 years of disease duration (4.1 years), and numerically lower proportions of age-related comorbidities such as hypertension (58.7 *vs.* 64.5%), renal insufficiency (5.8 *vs.* 11.7%), and diabetes (17.3 *vs.* 21.2%) than patients in the late-onset group. More patients in the early-onset group had prior therapy with tumour necrosis factor (TNF) inhibitors (66.7 *vs.* 47.2%), and fewer patients had prior therapy with csDMARDs only (29.2 *vs.* 48.5%) than in the late-onset group.

Tocilizumab effectiveness
Overall, 2,902 patients had no prior tocilizumab treatment and were included in the EFF-NPT; 854 were <50 years, 1372 were 50–65 years, and 676 were >65 years old at baseline. A greater proportion of patients <50 years old (65.4%, 95% confidence interval [CI]: 61.9–68.7%) achieved the primary outcome of DAS28-ESR remission at least once during their treatment period, than did patients aged 50–65 years (59.8%, 95% CI: 57.0–62.6%), or patients >65 years (59.5%, 95% CI: 55.5–63.4%) (χ^2 p=0.024). Patients <50 years also had the shortest median duration to achieve the primary endpoint (85.5 days *vs.* 90.0 days for 50–65 year-old patients and 91.0 days for >65 year-old patients). Of patients achieving DAS28-ESR remis-
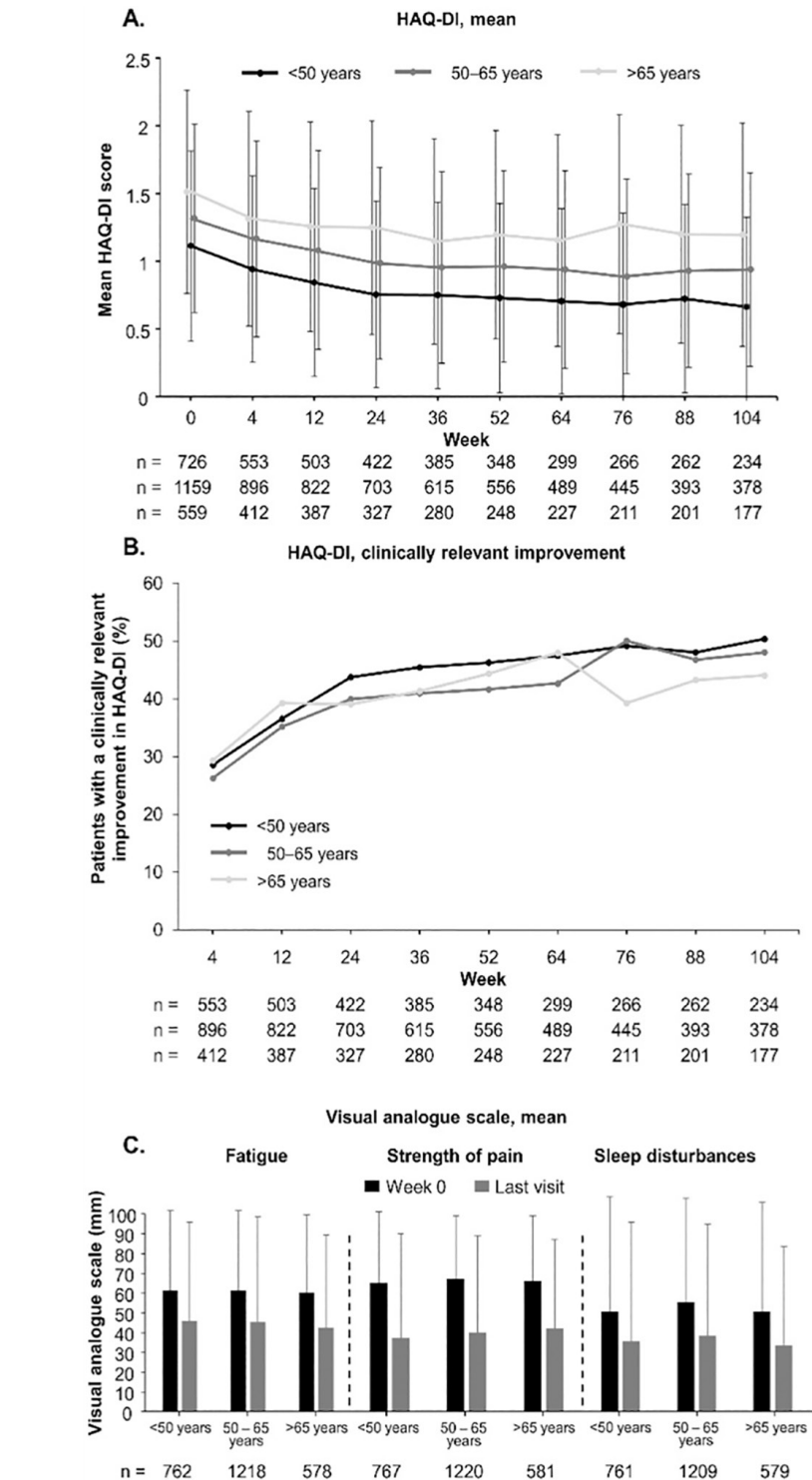
Fig. 2. Physical functioning and patient-reported outcomes (PROs) according to patient age (EFF-NPT).
A: Mean HAQ-DI score at all study visits. **B**: Proportion of patients with a clinically relevant improvement in HAQ-DI at all study visits. **C**: PROs at baseline and last visit.
Error bars are standard deviation.
EFF-NPT: effectiveness analysis set – no prior tocilizumab therapy; HAQ-DI: Health Assessment Questionnaire Disease Index.

sion, 9.3% of patients <50 years old, 7.8% of patients 50–65 years old, and 4.1% of patients >65 years old later discontinued due to lack of effectiveness (secondary treatment failure). Furthermore, despite fewer patients achieving

Fig. 3. Proportion of patients treated with GCs and GC dose at baseline (week 0) and last visit (effectiveness set; EFF-NPT).
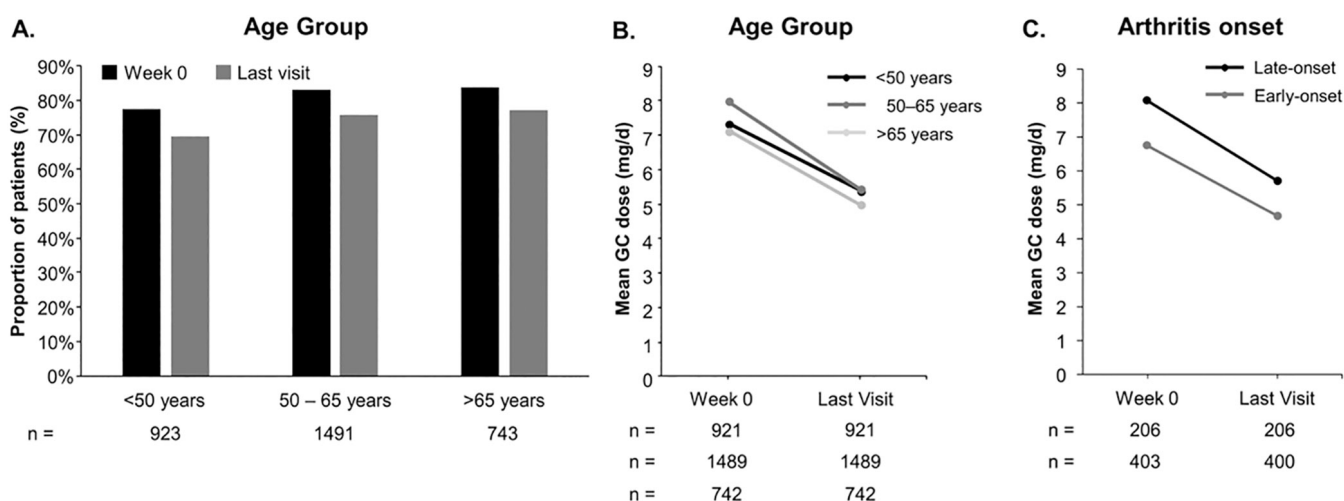**A**: Proportion of patients on GCs and mean dose of GCs by **B**) age group and **C**) arthritis onset.
Patients >65 years diagnosed with RA prior to 65 years of age were considered early-onset and patients diagnosed with RA after 65 years of age were considered late-onset.
EFF-NPT: effectiveness analysis set – no prior tocilizumab therapy; GCs: glucocorticoids; RA, rheumatoid arthritis.

remission, the >65 year age group had a numerically greater mean reduction in DAS28-ESR (LV=2.24, 95% CI 2.10–2.37) than the 50–65 year age group (LV=2.16, 95% CI 2.06–2.26), or the <50 year age group (LV=2.04, 95% CI 1.92–2.16) (p=0.11) (Fig. 1A-B).

Disease activity measured by CDAI showed similar results to those measured by DAS28-ESR. The greatest reductions in mean CDAI from baseline were seen in the >65 years age group (LV=14.28, 95% CI 13.17–15.40), followed by the 50–65 year age group (LV=13.77, 95% CI 12.99–14.56), and then the <50 year age group (LV=12.45, 95% CI 11.49–13.41) (p=0.03) (Fig. 1C-D).

Patients <50 years had the best physical functioning at baseline (as measured by HAQ-DI score). These patients also showed the greatest reduction in HAQ-DI score over the duration of the study (LV=0.27, 95% CI 0.22–0.31) compared with the 50–65 year age group (LV=0.20, 95% CI 0.17–0.23) and the >65 year age group (LV=0.19, 95% CI 0.14–0.24) (p=0.01) (Fig. 2A). A greater proportion of the patients <50 years old also achieved a clinically relevant improvement (≥0.3 decrease) in HAQ-DI (LV=37.1%, 95% CI 33.5–40.7) as compared with patients 50–65 years old (week LV=32.8%, 95% CI 30.1–35.6) or >65 years old (LV=32.9%, 95% CI 29.0–37.0) (Fig. 2B).

Table II. Mean DAS28-ESR according to presence of comorbidities associated with age (EFF-NPT).

Baseline comorbidity	Week 0	Last visit	Change	p-value**
Diabetes*				
Yes (n=263)	5.5 ± 1.3	3.3 ± 1.6	-2.2 ± 1.8	0.82
No (n=2365)	5.2 ± 1.4	3.0 ± 1.7	-2.1 ± 1.7	
Renal insufficiency*				
Yes (n=77)	5.4 ± 1.3	3.4 ± 1.6	-2.0 ± 1.8	0.50
No (n=2551)	5.5 ± 1.3	3.3 ± 1.6	-2.2 ± 1.7	
Coronary artery disease*				
Yes (n=118)	5.4 ± 1.3	3.4 ± 1.7	-2.0 ± 1.8	0.50
No (n=2510)	5.2 ± 1.4	3.0 ± 1.7	-2.2 ± 1.7	
Anaemia*				
Men				
Hb <13 g/dl (n=141)	5.7 ± 1.4	3.3 ± 2.0	-2.4 ± 2.1	0.14
Hb ≥13 g/dl (n=447)	5.0 ± 1.3	2.9 ± 1.7	-2.1 ± 1.8	
Women				
Hb <12 g/dl (n=437)	5.7 ± 1.3	3.3 ± 1.7	-2.3 ± 1.7	0.07
Hb ≥12 g/dl (n=1327)	5.1 ± 1.3	3.0 ± 1.6	-2.1 ± 1.7	

*Only patients with data at baseline are presented. **p-values based on t-test. All baseline comorbidities shown in this manuscript were reported by the investigator except anaemia. Anaemia was based on the baseline clinical laboratory haemoglobin value (Hb).
DAS28-ESR: Disease Activity Score-28 erythrocyte sedimentation rate; EFF-NPT: effectiveness analysis set – no prior tocilizumab therapy; Hb: haemoglobin.

Patients of all age groups had similar reductions in the severity of PROs such as fatigue, strength of pain, and sleep disturbances (Fig. 2C).

By the end of the study, in the EFF-NPT population, similar changes in the proportions of patients who received GCs were observed across all ages (Fig. 3A). Reductions in mean GC dose (SD) were similar in all age groups (week 104: <50 years 3.1±7.16 mg/d; 50–65 years 4.35±30.54 mg/d; >65 years 3.35±7.95 mg/d) (Fig. 3B).

Patients in the oldest age group were at the greatest risk for having comorbidities at baseline. Thus, effectiveness was analysed in patient subgroups according to baseline comorbidities. Patients with diabetes, anaemia or coronary heart disease had numerically greater mean baseline DAS28-ESR (Table II). Reductions in DAS28-ESR over the

Table III. Treatment-emergent adverse events according to patient baseline age (SAF).

Event, SAF n (%) [rate/100 PY]	<50 years (n=924)	50–65 years (n=1496)	>65 years (n=744)	p-value*
AEs	411 (44.5) [103.1]	706 (47.2) [106.3]	357 (48.0) [119.7]	0.29
AEs considered related	206 (22.3) [37.2]	328 (21.9) [36.0]	165 (22.2) [35.8]	0.98
SAEs	106 (11.5) [18.3]	216 (14.4) [20.8]	150 (20.2) [37.9]	<0.0001
Patients died, n	2	3	14	<0.0001
Deaths with AEs considered related, n	1	1	3	0.15
SAEs considered related	36 (3.9) [4.5]	66 (4.4) [5.0]	44 (5.9) [8.7]	0.13
AEs leading to withdrawal	65 (7.0) [7.4]	144 (9.6) [10.5]	58 (7.8) [8.8]	0.06
Infections	210 (22.7) [32.9]	323 (21.6) [29.2]	143 (19.2) [25.2]	0.21
Infections considered SAEs	30 (3.3) [3.3]	47 (3.1) [3.4]	36 (4.8) [5.7]	0.10
AESIs				
Anaphylaxis	15 (1.6) [1.8]	18 (1.2) [1.2]	9 (1.2) [1.5]	0.65
Demyelination-related events	1 (0.1) [0.1]	1 (0.1) [0.1]	0 (0.0) [0.0]	0.68
Gastrointestinal perforations	0 (0.0) [0.0]	4 (0.3) [0.2]	5 (0.7) [0.7]	0.04
Hepatic events	11 (1.2) [1.0]	34 (2.3) [2.3]	6 (0.8) [0.8]	0.02
Infections**	9 (1.0) [1.1]	47 (3.1) [3.0]	26 (3.5) [3.3]	0.001
Malignant neoplasms	1 (0.1) [0.1]	3 (0.2) [0.2]	4 (0.5) [0.5]	0.19
Myocardial infarction/acute coronary syndrome	3 (0.3) [0.3]	11 (0.7) [0.8]	9 (1.2) [1.1]	0.11
Spontaneous/serious bleeding	3 (0.3) [0.3]	4 (0.3) [0.2]	6 (0.8) [1.0]	0.15
Stroke	3 (0.3) [0.4]	7 (0.5) [0.4]	3 (0.4) [0.3]	0.87

*p-values based on χ^2 tests.
**Infections considered AESIs were opportunistic and non-serious infections as defined by treatment with intravenous anti-infectives.
AE: adverse event; AESI: AE of special interest; PY: patient year; SAE: serious AE; SAF: safety analysis set.

course of this study were similar for patients, regardless of the presence of an age-associated comorbidity (Table II).
Of the patients with RA who were >65 years old at baseline, 403 early-onset (<65 years) patients and 207 late-onset (>65 years) patients were included in the EFF-NPT (66 patients had missing data). Similar proportions of patients in the early-onset and late-onset groups achieved DAS28-ESR remission at least once during the study (59.4 *vs.* 60.4%, respectively). Furthermore, patients in both onset groups experienced similar reductions in mean DAS28-ESR, CDAI, HAQ-DI scores (Suppl. Table S1) and GC dose (Fig. 3C) throughout the study.

Safety
The proportion of patients with at least one AE numerically increased with age (<50 years=44.5%; 50–65 years=47.2%; >65 years=48.0%). However, patients >65 years and <50 years had similar proportions of AEs considered related to treatment (Table III). Greater proportions of patients in the 50–65 year (21.6%) and >65 year (20.2%) age groups experienced a SAE than in patients <50 years old (11.5%; p<0.0001). Patients >65 years had a greater proportion of SAEs considered

related to treatment (5.9% *vs.* 3.9% in the <50 years age group). Patients >65 years old experienced infections considered as SAEs numerically more often than younger patients, and more infections considered AESIs (3.5% *vs.* 50–65 years=3.1%, <50 years=1.0%; p=0.001). Still, similar proportions of AEs led to withdrawals regardless of age (Table III).
Finally, numerically greater proportions of patients in the >65 year age group experienced AESIs such as myocardial infarction/acute coronary syndrome and malignant neoplasms and significantly greater proportions of gastrointestinal perforation (p=0.04) (Table III). Of the 14 patients in the >65 year age group who died, 3 patients experienced AEs that were considered related to treatment (Table III; details in Suppl. Table S2).
Similar proportions of patients in the early and late RA onset groups experienced AEs (49.4% *vs.* 48.1%), SAEs (18.7% *vs.* 22.1%), AEs leading to withdrawal (7.0% *vs.* 9.5%) and serious infections (5.6% *vs.* 3.5%).

Discussion
In this analysis of the ICHIBAN study, we examined the long-term safety and effectiveness of tocilizumab in elderly

patients and patients with comorbidities typically seen in older age groups. Overall, patients >65 years had numerically higher baseline disease activity according to both DAS28-ESR and CDAI, worse baseline physical functioning and a greater number of age-associated comorbidities at baseline, such as hypertension, anaemia, renal insufficiency, osteoporosis, diabetes, and coronary heart disease. Consistent with previous findings that antirheumatic medication is less often switched in elderly patients (6), patients >65 years were more likely to not have received biologic or anti-TNF therapy in the past, despite the higher disease activity at baseline. This, coupled with the higher baseline disease activity, may have led to compensatory treatment – *i.e.* more patients >65 years that were treated with GCs (albeit at a slightly lower mean dose). Reduction in disease activity on treatment with tocilizumab was associated with a reduction of both the proportion of patients receiving GCs and the dose of GCs in all age groups.
In this study, because of the baseline disease activity and likelihood of baseline comorbidities, a smaller proportion of patients >65 years achieved DAS28-ESR remission than did patients <50 years. This is consistent with previous-

ly published findings from French and Japanese retrospective cohort studies that found elderly patients treated with tocilizumab were less likely to achieve DAS28 remission and EULAR (European League Against Rheumatism) response than younger patients (19, 21). However, in this study, despite more comorbidities and numerically higher disease activity at baseline, patients >65 years treated with tocilizumab had numerically greater reductions of DAS28-ESR over the course of treatment than patients <50 years. Furthermore, as ESR can be influenced by age, CDAI was also used as an effectiveness endpoint for disease activity (22). CDAI results mirrored DAS28-ESR, with patients >65 having the highest CDAI reductions throughout this study. Moreover, fewer patients >65 years who discontinued tocilizumab did so due to lack of effectiveness than patients <50 years, and there was a numerically lower risk of secondary treatment failure, suggesting that the treating physicians were often satisfied with the treatment response in these elderly patients. This is in line with other real-world studies showing long durations of tocilizumab therapy without treatment failure (23), and the recommendation of rheumatologists in Germany who suggest more frequent use of bD-MARDs in elderly RA patients to reduce RA disease activity and associated comorbidities (24). At baseline, fewer patients >65 years were treated with concomitant csDMARDs and more patients >65 years were treated with concomitant GCs than in the <50 year age group. However, analysis of the entire ICHIBAN population shows that comparable effectiveness was achieved in groups with and without concomitant csDMARDs and/or GCs (20).

Patients with diabetes, renal insufficiency, coronary artery disease or anaemia experienced similar reductions in DAS28-ESR when compared to those without. Furthermore, elderly patients treated with tocilizumab had a similar response regardless of early or late disease onset. Moreover, the likelihood of a patient requiring surgery can increase with age, and studies show that patients treated with tocilizumab have a low rate of postoperative complications after surgeries (8.6%) (25). Taken together, these data suggest that elderly patients with RA, patients with comorbidities, and patients that require surgery can benefit from a more assertive treatment such implementing treat-to-target approach.

Patients >65 years also experienced similar improvements in PROs over the course of this study as compared with their younger counterparts. PROs such as fatigue, pain and sleeplessness improved in elderly individuals despite a disproportional load of baseline comorbidities. Physical functioning in patients >65 years improved over the course of this study. Elderly patients, however, did not show the same overall gains as younger patients did. Patients >65 years had the worst HAQ-DI at baseline. Furthermore, the oldest patients in ICHIBAN were also less likely to be treated aggressively with bDMARDs and more likely to be on GCs. High disease activity coupled with less aggressive prior treatment and age may have led to permanent joint damage in these patients, limiting their overall capacity to improve in physical function. Results consistent to these were found in Swiss RA patients >65 years treated with TNF inhibitors who also showed limited improvement in physical functioning mainly due to the absence of improvement of patients >75 years (26).

As expected, the proportion of patients with AEs increased with age, and patients >65 years experienced the most AEs and nearly twice the rate of SAEs as patients <50 years. However, the rate of AEs related to treatment were similar, regardless of age, and the increase in the rate of SAEs related to treatment was in line with the general increase of SAEs. As compared to patients <50 years old, patients >65 years had a similar rate of infections, a 1.8-fold higher rate of serious infections, and a nearly 3-fold higher rate of infections considered AESIs (opportunistic and non-serious infections as defined by treatment with intravenous anti-infectives). However, results from an integrated safety analysis of the tocilizumab randomised controlled trials showed that the control group had a 5.7-fold higher rate of serious infections in patients ≥65 years of age compared with patients <50 years (27). Hence, the increase in serious infections seen in this analysis was well within the range of infection risk associated with age regardless of treatment in controlled trials. Age-associated AESIs, such as myocardial infarctions/acute coronary syndromes and malignancies, were increased in patients >65 years old, but not greater than in the normal population (28). Overall, the rates of AEs leading to withdrawal were comparable between the three different age groups. Taken together, tocilizumab appears to constitute an effective treatment with good safety and an overall net benefit regardless of age.

The limitations of this analysis were mostly inherent limitations of non-interventional real-world studies and are consistent with the limitations reported in the primary analysis of ICHIBAN, such as the small proportion of patients enrolled in it who had already achieved DAS28-ESR remission (20). Other limitations included the absence of a control arm or of patient randomisation in this study, that neither investigators nor patients were blinded, and that there may have been a risk of underreporting of safety data. Due to the influence of confounding factors, inferential statistics were only considered appropriate for a limited number of endpoints. It was our goal to display confidence intervals to describe the degree of uncertainty around the parameter estimates and describe results as observed. Furthermore, 58.7% of patients in ICHIBAN left the study prematurely, with a large proportion lost to follow up. This was higher than rates in comparable studies (29, 30) and may have been related to the study duration and changes in monitoring due to a switch in the clinical research organisation while the study was ongoing (details in (20)).

In summary, patients >65 years old had the highest baseline DAS28-ESR, CDAI, and HAQ-DI scores, along with the highest burden of comorbidities such as diabetes, coronary heart disease, anaemia, and renal insufficiency. During tocilizumab treatment, patients >65 years had similar improvements in effectiveness endpoints and GC reduction

as their younger counterparts. Patients with selected age-associated comorbidities experienced similar reductions in RA disease activity compared with those without. Although patients >65 years experienced more AEs, treatment-related SAEs and serious infections than their younger counterparts, the rates of infections in general, of treatment-related AEs, and of AEs leading to withdrawal were comparable. Overall, we conclude that benefits of tocilizumab outweighed the risks in the majority of elderly patients with RA.

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