ICHIBAN

CLINICAL STUDY REPORT NO: ML22928

STUDY INFORMATION

TITLE:	**ICHIBAN - A prospective, non-interventional multi-center observational study to evaluate the long-term effectiveness and safety of tocilizumab in patients with active rheumatoid arthritis in daily practice**
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STUDIED MEDICINAL PRODUCT:	RoActemra® (tocilizumab)
COUNTRY OF STUDY POPULATION:	Germany
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(Medical Therapeutic Area Lead, Scientific Responsible)	**Date**
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1. SYNOPSIS/ABSTRACT

Title

ICHIBAN - A prospective, non-interventional multi-center observational study to evaluate the long-term effectiveness and safety of tocilizumab in patients with active rheumatoid arthritis in daily practice

Keywords

Rheumatoid arthritis, tocilizumab, clinical response, non-interventional

Research Question and Objectives

Study objectives

Primary objective:

- Effectiveness of therapy with tocilizumab (TCZ) in daily practice according to label; focus on clinical response for a follow-up of 2 years.

Secondary objectives:

- In case of an inadequate response to TCZ (TZC-IR) or discontinuation of TCZ due to other reasons (e.g. safety, clinical remission), the new RA treatment (so called “switch”) or de-escalation treatment was also to be documented until the end of observational time (2 years) irrespective of selected therapy and date; focus on clinical effectiveness.
- Safety of therapy with TCZ in daily practice.

Study design

This was a prospective, non-interventional, multi-center, observational study. Patients with active rheumatoid arthritis (RA) were treated with TCZ. The diagnosis of RA and decision for therapy with TCZ had to be reached prior to inclusion into ICHIBAN. Patients who already started their TCZ therapy prior to inclusion into this non-interventional study (NIS) could be enrolled, too. Such a therapy must have started at a maximum 1 year before inclusion into this NIS.

The maximum duration of the documentation of an individual patient was to be 104 weeks (2 years).The observational period per patient consisted of up to 10 documentations, planned in week 0, 4, 12, 24, 36, 52, 64, 76, 88 and 104.

The study was non-interventional in accordance with §4 (23) of the German Drug Law (AMG) and the planned sample size was n=3400 patients.

Target Population

Adult patients (≥18 years) with moderate to severe RA who required drug treatment as part of their therapy and for whom the physician decided on treatment with TCZ, based on individual medical circumstances, were included in this study by specialists in rheumatology and/or physicians working in rheumatology centers. Treatment with TCZ was to be in accordance with the label, especially regarding indication, contraindications, precautions and concomitant medication. The maximum duration of TCZ therapy prior to study entry was 1 year.

Study size

In this study, 3404 patients were enrolled across 255 sites in Germany. 126 patients were excluded from the analysis due to protocol deviations. Further 114 patients were excluded from the analysis as they had given their informed consent after the baseline (BL) visit.

Thus, 3164 patients constituted the main analysis set (= safety analysis set, SAF). From these, 2902 patients were analyzed in the effectiveness analysis set without previous therapy (EFF-NPT), 262 in the effectiveness analysis set with previous therapy (EFF-PT), 417 in the switch

analysis set (SW), and 180 in the changer from TCZ intravenous (iv) to subcutaneous (sc) set (CHG). Definitions of the analysis sets can be found in section 7.8.2.

Studied medicinal product

Marketed product RoActemra® (tocilizumab) as prescribed by the treating physician

Variables

- Primary variable:
  - Clinical remission defined by Disease Activity Score DAS28 of less than 2.6.
- Secondary variables:
  - Low disease activity (DAS28 ≤ 3.2, CDAI ≤ 10);
  - Time to reach clinical remission the first time
  - EULAR good/moderate response;
  - Type and number of adverse events (AEs) and serious adverse events (SAEs);
  - Systemic parameters such as CRP and other serological parameters;
  - Physical function (HAQ/FFbH) and working productivity;
  - Clinical effectiveness and safety of possible other RA therapies in case of an inadequate response to TCZ (TCZ-IR).

Data Sources

All study-relevant data collected during this study were entered into the electronic case report form (eCRF) by the participating physician and patients completed a paper questionnaire that was handed out by the physicians. The occurrence of AEs was assessed by the physicians based on patient reports, medical records, and physical examinations, if applicable.

Statistical and Epidemiological Methods

The analysis of this non-interventional study was exploratory and primarily used descriptive statistical methods.

The following descriptive statistics were calculated for continuously distributed data and – where appropriate – for ordered categorical data (ordinal data): N (number of non-missing observations), Nmiss (number of missing observations), mean, standard deviation (SD), minimum (min), 1st quartile (Q1), median, 3rd quartile (Q3), maximum (max). For ordered categorical data and nominal data, absolute and relative frequencies (in %) will be calculated. Missing values are not used for calculating the percentages.

If not specified otherwise, descriptive statistics were presented by visit, where appropriate.

Demographic data, baseline characteristics and safety data were displayed for the SAF, SW, CHG, EFF-NPT, and EFF-PT. Effectiveness data were calculated for SW, CHG, EFF-NPT, and EFF-PT. In addition, the demographic data, baseline characteristics, and effectiveness evaluation was performed separately by subgroups. The percentage basis for each subgroup was the number of patients in the total group within this subgroup.

For an assumed remission rate of 50% a sample size of 3400 patients was planned to result in a two-sided 95%-confidence interval with a width of 3.4% (precision: ± 1.7%). Based on the proportion of patients treated with TCZ as monotherapy and in combination with methotrexate (MTX), observed in a previous interim analysis, it was assumed that the remission rates could be estimated with a precision of ± 2.5% (5% width for the two-sided 95%-confidence interval) for both subgroups, respectively.

Results

- Effectiveness Results

The analysis of effectiveness was performed for the EFF-NPT, i.e. the 2902 patients of the SAF without any previous TCZ therapy, as well as for the EFF-PT, SW and CHG.

Primary analysis of effectiveness

The primary effectiveness variable for this study was the clinical remission, defined by a DAS28 (ESR) of less than 2.6 at least once during the treatment period.

According to this definition, 1615 patients (61.4%) of the EFF-NPT (n=2902) reached a clinical remission. From these, 84 patients (5.2%) had a DAS28 (ESR) of less than 2.6 already at BL. In the patients, who were already treated with TCZ prior to study entry (EFF-PT set, n=262), the remission rate was 74.9% (164 of 219 patients). From these, 106 patients (64.6%) had a DAS28 (ESR) of less than 2.6 already at BL. In the patients, who switched to another RA therapy during the study (SW set, n=417), the remission rate was 33.3% (139 of 417 patients). In this analysis set there were no patients with a DAS28 (ESR) of less than 2.6 at BL. In the patients, who changed from TCZ i.v. to TCZ s.c. during the study (CHG set), the remission rate was 84.9% (141 of 166 patients). From these, 12 patients (8.5%) had a DAS28 (ESR) of less than 2.6 already at BL. Please note, that patients with missing data at BL (N=271, 43, 0, and 14 in the EFF-NPT, EFF-PT, SW, and CHG, respectively) were not considered for calculation of the percentages. In a subgroup analysis, performed for the EFF-NPT using the χ^2 test for independence, a trend favoring the following subgroups with respect to remission was seen for younger patients, patients with a lower disease activity (DAS28 (ESR)) at baseline (BL), patients with a lower CDAI category at BL, patients without asthma, COPD, anaemia, or renal insufficiency at BL, patients with concomitant therapy with csDMARDs (with or without GC), MTX, or other csDMARDs at BL, and patients with a combination of concomitant csDMARDs therapy at BL and previous therapy with csDMARDs only.

Secondary analysis of effectiveness

Results of the secondary analysis of effectiveness are described for the EFF-NPT.

Overall, for all secondary effectiveness parameters a moderate to distinct improvement was observed during the study. Most of the improvement was already reached within 12 weeks of TCZ therapy.

Regarding the DAS28 (ESR) categories, up to 64% of the patients available at the respective visit reached a clinical remission at any time point during the study. At the last visit (LV) under TCZ this applied to 45.6% (1201 out of 2631) of patients. In contrast, the percentage of patients with high disease activity (i.e. DAS28 (ESR) > 5.1) decreased from 55.0% (1446 out of 2631 patients) at BL to only 4.8% (43 out of 895 patients) at week 104 (and 13.4% (352 out of 2631 patients) at LV). The mean DAS28 (ESR) level showed a reduction from 5.19 at BL to 2.31 at week 104 (3.05 at LV). The time-to-event analysis of the mean duration until reaching remission for the first time after BL using Kaplan-Meier estimates yielded a median value of 148 days with a 95%-CI from 113 to 163 days. Excluding the 104 patients in the EFF-NPT, who had a DAS28 (ESR) < 2.6 already at BL, the median value was slightly higher, i.e. 161 days (95%-CI from 127 to 168 days).

The analysis of the patient reported outcomes (PROs) via visual analogue scales (VAS) yielded a distinct improvement from mean values of 61.7 mm at BL to 41.8 mm at LV (disease activity), 59.2 mm at BL to 42.0 mm at LV (health status), 57.2 mm at BL to 44.1 mm at LV (exhaustion/tiredness), 61.8 mm at BL to 42.0 mm at LV (strength of pain), and 49.6 mm at BL to 39.4 mm at LV (sleep disturbances).

The functional capacity of the patients according to the Hannover Functional Ability Questionnaire (FFbH) increased from a mean score of 61.7% at BL to values above 70% from week 24 up to week 104 and to 66.8% at the LV under TCZ. At LV, the percentage of patients with a clinically relevant improvement, defined as an increase of ≥ 10%, (27.4%) was nearly threefold the percentage of patients with a relevant worsening, defined as a decrease of ≥ 10% (10.1%).

The mean Health Assessment Questionnaire (HAQ) score of the patients decreased from 1.302 at BL to values below 1 from week 24 up to week 104 and to 1.086 at the LV under TCZ. At LV, the percentage of patients with a clinically relevant improvement, defined as a decrease of ≥ 0.3, was 34.1% compared to 10.2% with a relevant worsening, defined as an increase of ≥ 0.3. The percentage of patients with a functional HAQ remission, defined as HAQ ≤ 0.5, increased from 17.1% at BL to 30.5% at LV.

The Clinical Disease Activity Index (CDAI) of the patients showed a distinct improvement of about 50% from 27.67 at BL to 14.18 at LV. Up to week 104 about 30% of the patients reached a CDAI remission (≤2.8). At LV this applied to 16.2% (417 out of 2575 patients). In contrast, the percentage of patients with high disease activity (>22) decreased from 61.8% at BL (1591 out of 2575 patients) to 21.4% (552 out of 2575 patients) at LV.

A good EULAR response at LV was observed for 50.5% of the patients. Further 24.4% of patients reached a moderate response at LV and 10.4% a Boolean-based EULAR remission.

Regarding the subgroup analysis, for most parameters a slightly stronger improvement was observed for patients with csDMARDs only as previous therapy compared to patients with prior anti-TNF therapy, and for patients with csDMARDs only as concomitant therapy as compared to the patients without concomitant csDMARDs. For patients with mono- or combi-therapy and with csDMARDs only as previous therapy also a stronger improvement was observed compared to patients with mono- or combi therapy and no prior csDMARDs. Beside this, a clear trend to better improvement could be observed for younger patients as well as for patients with a lower disease activity at BL.

- Safety Results

The safety analysis was performed for the SAF, i.e. all 3164 patients who were treated at least once with TCZ, as well as for the EFF-NPT, EFF-PT, SW and CHG. In the following, only the results for the SAF are described.

The mean duration of TCZ treatment was 1.25 ± 0.86 years. The majority of the SAF patients terminated the study prematurely, i.e. the observation period was less than 104 weeks (58.7%, n=1857); 1307 patients (41.3%) were observed for 104 weeks. In the patients with premature discontinuation of TCZ therapy/study, for nearly half of the patients (47.3%) no reason for premature discontinuation was given by the investigators. From the documented reasons for discontinuation as given in the eCRF, the most frequent were lack of effectiveness (21.3%), lack of tolerability (6.3%), lost to follow-up (5.4%), and patient's request / withdrawal of consent (5.0%). For 108 patients (5.9%) 'other reasons' was named as the main reason for discontinuation.

Adverse events

Overall, 4278 treatment emergent AEs (TEAEs) were reported for 1474 of the 3164 patients in the SAF (46.6%). TEAEs were defined as AEs with an onset at or after the day of first intake of TCZ (with a cut-off after last TCZ administration + 42 days). Non-TEAEs were defined as AEs before or after TCZ therapy.

On a MedDRA SOC basis, the most frequently reported TEAEs were 'Infections and infestations', mainly represented by the MedDRA PTs 'nasopharyngitis' (6.6% of patients) and 'bronchitis' (2.6%), followed by SOC 'Musculoskeletal and connective tissue disorders', mainly PTs 'rheumatoid arthritis' and 'osteoarthritis' (1.3%, each), SOC 'Gastrointestinal disorders', mainly PTs 'nausea' and 'diarrhea' (1.6%, each), and SOC 'Skin and subcutaneous tissue disorders', mainly PTs 'rash' (1.4%) and 'pruritus' (1.3%).

943 TEAEs in 472 patients (14.9%) were assessed by the investigators as serious. The serious TEAEs were mostly from the MedDRA SOC categories 'Infections and infestations', mainly represented by the MedDRA PTs 'pneumonia' (0.7% of patients), followed by SOC 'Musculoskeletal and connective tissue disorders', mainly PTs 'rheumatoid arthritis' (0.6%), 'osteoarthritis' and 'intervertebral disc protrusion' (0.5%, each), and SOC 'Injury, poisoning and procedural complications', mainly PT 'fall' (0.4%).

699 patients (22.1%) had TEAEs considered related to TCZ, while 146 patients (4.6%) had treatment emergent SAEs considered related to TCZ treatment. The most frequently reported TEAEs with causal relationship to TCZ were from the SOC 'Infections and infestations', mainly represented by the MedDRA PTs 'nasopharyngitis' (2.1% of patients) and 'bronchitis' (1.4%), followed by SOC 'Gastrointestinal disorders', mainly PTs 'nausea' (0.8%) and 'diarrhea' (0.7%), SOC 'Skin and subcutaneous tissue disorders', mainly PTs 'rash' and 'pruritus' (0.7%, each), and SOC 'General disorders and administration site conditions', mainly PT 'fatigue' (0.6%).

943 AEs of special interest (AESIs) were documented for 422 patients (13.3%). This included infections (82 patients, 2.6%), medically significant hepatic events (51 patients, 1.6%), anaphylaxis (42 patients, 1.3%), myocardial infarction /acute coronary syndrome (23 patients, 0.7%), serious or spontaneous bleeding events (13 patients, 0.4%), stroke (13 patients, 0.4%), gastrointestinal perforation and related events (9 patients, 0.3%), malignant neoplasms (8 patients, 0.3%), and demyelinating diseases (2 patients, 0.1%).

TEAEs with a MedDRA SOC 'infections and infestations' were reported for 676 patients (21.4%). Treatment emergent SAEs with the MedDRA SOC 'infections and infestations' were documented for 113 patients (3.6%).

A total of 267 patients (8.4%) in the SAF suffered from TEAEs that led to the withdrawal of the patient.

In 19 patients (0.6%) the outcome of the TEAE(s) was fatal. In addition, for 17 patients (0.5%) in the SAF non-TEAEs with fatal outcome were reported. For 11 of these 36 patients the investigator assessed a causal relationship of the event(s) to the TCZ treatment. On a MedDRA PT basis, this applied to the following events: Sepsis (3x), multi-organ failure (2x), diverticular perforation, peritonitis, infection, large intestine perforation, acute respiratory failure, diffuse alveolar damage, pulmonary congestion, ovarian cancer, empyema, myocardial infarction, renal failure, pneumonia, right ventricular failure, gallbladder perforation, cholecystitis, and death.

Regarding the subgroup analyses of the TEAEs as well as of the non-TEAEs, the AE profiles were similar with no remarkable differences between the subgroups with different disease activity, previous and concomitant medication at BL.

Laboratory data

The two liver parameters SGOT and SGPT showed a slight increase during the study. The mean SGOT level was 25.6 U/L at BL. The increase ranged between 3.5 and 4.9 U/L up to a mean value of 28.5 U/L at week 104 (28.7 U/L at the LV). From a mean SGPT level of 26.4 U/L at BL there was an increase ranging between 4.1 and 5.8 U/L to a mean value of 30.4 U/L at week 104 (31.1 U/L at the LV).

In the subgroup analysis, the changes in mean SGOT values from BL to week 104 or LV were relatively small with no remarkable differences between the groups. A similar picture could be observed regarding the changes in the mean SGPT values. Only in the subgroup analysis of the disease activity at BL by means of the DAS28 (ESR) level a slightly stronger increase in the mean SGPT value from BL to the last value under TCZ was observed in patients with moderate or high disease activity (+4.3 U/L and +6.3 U/L, respectively) compared to the patients with remission or low disease activity (-1.7 U/L and +0.7 U/L, respectively).

For the two blood parameters leucocytes and neutrophils a slight decrease during the study was observed. The mean leucocyte level was $8.7*10^9$/L at BL and decreased to a mean value of $6.8 *10^9$/L at week 104 ($7.3 *10^9$/L at the LV). The mean decrease from BL ranged between -1.3 and $-2.0*10^9$/L. The mean neutrophils level was $11.9*10^9$/L at BL and decreased to a mean value of $8.6*10^9$/L at week 104 ($-3.0*10^9$/L) and $10.4*10^9$/L at the LV ($-1.5*10^9$/L). For the platelets level, the decrease during the study was more distinct. The mean value was 292399/µL at BL and decreased to 222902/µL at week 104 (-68800/µL) and to 237509/µL at the LV (-54890/µL).

Regarding the subgroup analysis of the leucocyte level, the mean decrease from BL to the LV under TCZ was proportional to the disease activity at BL, i.e. $+0.3*10^9$/L, $-1.1*10^9$/L, $-1.4*10^9$/L and $-1.6*10^9$/L in the patients with remission, low, moderate, and high disease activity, respectively, according to the DAS28 (ESR) at BL. The decrease in the mean neutrophils level from BL to the LV under TCZ was stronger with a higher age of the patients, i.e. $-0.7*10^9$/L, $-1.2*10^9$/L and $-3.2*10^9$/L in the patients aged < 50, 50-65, and > 65 years, respectively. Otherwise, there were no remarkable differences between the groups.

For the levels of the lipid metabolism parameters a slight increase during the study was observed. The mean total cholesterol level was 220.8 mg/dL at BL and increased to a mean value of 233.2 mg/dL at week 104 and 228.2 mg/dL at the LV, corresponding to a mean increase of 8.8 and 7.4 mg/dL, respectively. Also, for LDL only a small increase in the mean value from 130.4 mg/dL at BL to 136.5 mg/dL at week 104 (+ 5.7 mg/dL) and 134.7 mg/dL at

the LV under TCZ (+ 4.3 mg/dL) was observed. Compared to the BL level of 65.7 mg/dL, the mean HDL value was nearly unchanged at week 104 (64.8 mg/dL, i.e. + 0.1 mg/dL) and at the LV under TCZ (65.8 mg/dL, i.e. + 0.1 mg/dL). The largest changes were observed for the triglycerides, that increased from a mean value of 136.4 mg/dL at BL to 168.7 mg/dL at week 104 and 154.3 mg/dL at the LV under TCZ, corresponding to a mean increase of 27.7 and 18.0 mg/dL, respectively.

In the subgroup analysis, the mean changes in total cholesterol, LDL and HDL values from BL to the LV under TCZ were relatively small with no remarkable differences between the groups. Although there was a clear increase in the mean triglyceride values from BL to the LV under TCZ, no remarkable differences between the subgroups could be observed.

Conclusions

In conclusion, results over up to 104 weeks of observation show that TCZ was effective in routine care as reflected by the proportions of patients achieving a clinical remission, good EULAR response and relevant improvement in physical functioning. The data based on treatment regimens individually selected by the treating physician in this non-interventional study were comparable or even better as reported in randomized clinical trials (SAMURAI, LITHE, ADACTA, AMBITION, FUNCTION, OPTION, RADIATE, ROSE, TOWARD). No new safety signals were detected. The safety results of former interventional and non-interventional studies have been verified. RoActemra® (TCZ) as monotherapy or combined with DMARDS showed good tolerability in the therapy of moderate to severe RA.