**Supplemantary Methods**

**“TAMARA” Study Burmester et al**

**Study design and Patients**

TAMARA (***T****ocilizumab* ***A****nd D****M****ARDs:* ***A****chievements in* ***R****heumatoid* ***A****rthritis),* a multi-centre, open-label, non-controlled, single-arm study, was performed at 70 centres in Germany (13 university hospitals, 24 hospitals, 33 medical practice) from September 2008 until July 2009. Men and women > 18 years with moderate to severe active RA of ≥ 6 months duration who had an inadequate clinical response (DAS28 > 3.2) to a stable dose of conventional or biological DMARDs were included. Different DMARD therapies were permitted including e.g. MTX, chloroquine, gold, sulfasalazine, and leflunomide in monotherapy or combination. The combination of MTX and leflunomide was not allowed. DMARD dose reductions or a change of route of administration could be performed at anytime for safety. After reduction of dose, re-increase to the baseline dose was allowed. Temporarily interruption of DMARD was recommended for patients who experienced an increase in ALAT (SGPT) or ASAT (SGOT) ≥ 3 ULN. Maximum of 10 mg/day prednisone or equivalent and NSAIDs were permitted if the dose was stable for at least 4 weeks prior to baseline. Patients may be treated with NSAIDs up to the maximum recommended dose, (including COX-2 inhibitors) throughout the study. An alteration in the NSAID dose was strongly discouraged over the first 27 weeks of the study and should be avoided. Dose adjustments could be made for safety reasons, and if absolutely required to treat disease flares. Aspirin can be taken to reduce cardiovascular risk, not to exceed 350 mg/day. Oral corticosteroid (≤10 mg/day prednisone equivalent) doses were allowed if stable for at least 4 weeks prior to baseline. Alterations in the dose of background oral corticosteroid dose were strongly discouraged during the whole study period and should be avoided. To treat non-RA conditions, such as asthma, increased doses of oral corticosteroids, up to 40 mg of prednisone (or equivalent) daily for 2 weeks or less, were permitted. TNF antagonists had to be discontinued for ≥2 weeks (etanercept) and for ≥8 weeks (infliximab or adalimumab).

Main exclusion criteria were other autoimmune diseases, functional class IV rheumatoid arthritis, previous or current inflammatory joint disease other than RA, current or history of recurrent bacterial, viral, fungal, mycobacterial or other infections, current liver disease, evidence of serious uncontrolled concomitant disease or major surgery within eight weeks prior to screening or planned major surgery within six months following screening. Patients were excluded if they had had previous treatment with tocilizumab, rituximab, abatacept, with alkylating agents or with total lymphoid irradiation.

The study was conducted in accordance with the principles of the Declaration of Helsinki, international Good Clinical Practice standards, and local laws and regulations concerning clinical studies. The study was approved by institutional review boards/ethic committees with written informed consent obtained from each patient before study participation.

Patients were treated with the study medication tocilizumab, and a stable background DMARD therapy (at a stable dose for at least 8 weeks prior to baseline). All patients received, according to the german treatment guidelines, tocilizumab intravenously over a 1-hour period at a dose of 8 mg/kg at 4-week intervals at week 0 (day 1), 4, 8, 12, 16 and 20.

Patients were assessed for safety and effectiveness parameters at weeks 1, 2, 4, and then every 4 weeks until week 24. AEs of special interest, which are known to occur at increased frequencies under tocilizumab therapy, were LDL >160 mg/dL, infections (requiring antiinfective treatment), AST or ALT ≥3 ULN, and low neutrophil counts (<1000/mm³).

**Study endpoints**

The primary objective was to determine the proportion of patients reaching a DAS ≤ 3.2 after 24 weeks in patients with active RA who had responded inadequately to previous therapy with DMARDs or TNF antagonists.

The secondary objectives were improvements in the outcome measures EULAR response, ACR responses) and the safety of tocilizumab with regard to AEs, laboratory assessments and physical examination. In addition, effects on health related quality of life outcomes in this population were assessed with the SF-36, the HAQ-DI , the short FACIT-Fatigue and the PTHFs (patient take home form).

Secondary endpoints were assessed by longitudinal analysis of DAS28, ACR20, ACR50 and ACR70 responses, mean DAS28 reduction at week 4, proportion of patients showing a clinically significant reduction in DAS28 (≥1.2) or DAS28 remission (<2.6) at week 4, change in DAS28 from baseline to week 24, proportion of patients with DAS28 of <2.6,, EULAR response, ACR20, ACR50 and ACR70 responses and mean changes from baseline in the individual parameters of ACR core set at week 24, change in CDAI, hemoglobin, CRP and ESR from baseline at week 24, HAQ-DI and SF-36 scores, FACIT fatigue scale and Treatment Satisfaction Questionnaire for Medication (TSQM) scores at week 24, change from baseline in daily pain, morning stiffness and fatigue/tiredness at weeks 1, 2 and 4, proportion of patients who withdrew due to lack of sufficient therapeutic response, evaluation of the prognostic value of different parameters (e.g. CRP) at baseline and week 4 on response at week 24.

**Statistical methods**

A sample size of 258 patients was calculated to provide a power of 80% for the primary effectiveness analysis using two-sided Chi-square test for single proportion with a significance level of 0.05, allowing a maximum drop out rate of 20%.

For numerical data sample statistics were calculated, for categorical data frequency tables were used. For the primary effectiveness analysis the observed proportion of patients reaching LDAS (DAS28 ≤ 3.2) at week 24 was compared to the expected proportion using the exact binomial test on single proportions (intention-to-treat (ITT) population).

A logistic regression model including baseline DAS28, CRP at baseline and CRP at week 4 as independent parameters and patient's sex as independent factor with LDAS at week 24 as dependent parameter was fitted to the data.

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