

Objectives: To evaluate outcomes of rapid dose escalation regimen of MTX compared with conventional treatment.

Methods: We implemented a randomized, controlled trial that enrolled patients with RA who fulfilled all of the following criteria: 20 to 70 years-old, disease duration ≤ 2 years, SDAI ≥ 11 , and without prior use of MTX, tacrolimus (TAC) or biologics. Patients were randomized into rapid escalation (RE) group or conventional treatment (CT) group at 1:1 ratio. In RE group, doses of MTX were escalated up to 0.25 mg/kg/wk within 8 wks after start of MTX and increased maximum tolerable dose or 16 mg/wk until wk 12. If a patient achieved SDAI remission at wk 12, MTX was continued at the same dose. If a patient did not achieve SDAI remission at wk 12 or showed intolerance to MTX, use of TAC or TNF inhibitor (TNFi) were allowed. In CT group, patients were treated with either MTX, TAC, salazosulfapyridine, or bucillamine by the discretion of physicians until wk 12. If a patient achieved SDAI remission at wk 12, same treatment was continued. If a patient did not achieve remission at wk 12, use of TNFi was allowed. Patients were treated by the discretion of physicians at wk 24 and onward. We set two primary endpoints; the percentage of patients achieving SDAI remission and Boolean remission at wk 24. We planned to enroll 120 patients per arm based on expected SDAI remission rates at wk 24, alpha and beta errors and dropout rates.

Results: Enrollment was terminated prematurely and all patients were followed for 48 wks. Of 115 enrolled patients, 57 were randomly assigned to RE group and 58 to CT group. Baseline demographics were similar between the two groups. The median baseline values (RE vs. CT) were 24.9 and 25.9 for SDAI, 0.88 and 0.69 for HAQ, and 0.64 and 0.61 for EQ-5D, respectively. At wk 24, the percentages of patients achieving remission in RE and CT groups were 42% and 28% by SDAI criteria ($p=0.1$, χ^2 test), and 35% and 17% ($p=0.03$, χ^2 test) by Boolean criteria, respectively. Median values of HAQ at wk 24 in RE and CT groups were 0 and 0.13 ($p=0.096$, M-W U test), and those of EQ-5D were 0.78 and 0.77 ($p=0.12$, M-W U test), respectively. At wk 48, these values were not statistically different between the two groups. There were no significant differences between the two groups with incidence of severe adverse events.

Conclusions: The rapid dose escalation regimen of MTX provided significantly superior Boolean remission rate and tended to provide superior SDAI remission than conventional treatment in patients with early RA in the short term.

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THU0171 INCREASED FUNCTIONAL ACTIVITY OF FOXP3+REGULATORY T CELLS IN THE PERIPHERAL BLOOD OF DMARDS-NAÏVE METHOTREXATE-TREATED PATIENTS WITH EARLY RA USING

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Objectives: To analyze the effect of methotrexate (MT) therapy on the percentage and absolute number of FoxP3+ regulatory T (Treg) cells in the peripheral blood of MT-naïve patients (pts) with early RA we used Treg immunostaining with antibodies to surface markers and Foxp3 with subsequent flow cytometric analysis

Methods: 45 MT-naïve pts with early RA (39 females, Me:IQR age 52.0 (32.5–57.5) years, RA duration 5 (4–6) months, DAS 28 5.01 (4.18–5.8), RF positive -71.1%, ACPA - positive-88.9%) were included into the study. All pts were administered subcutaneous MT as the first-line DMARD at 10 mg/week with rapid dose escalation up to 20–25 mg/week. Human blood mononuclear cells were isolated from whole venous blood by Ficoll-Hypaque centrifugation and subjected to multicolor flow cytometry analysis. Tregs were stained for different surface markers, and proportions of marker-positive subsets (FoxP3+CD25+; CD152+surface; CD152+intracellular; FoxP3+CD127+;

CD25+CD127-; FoxP3+ICOS+; FoxP3+CD154+; FoxP3+CD274+) were determined; 20 healthy donors made the control group

Results: After 24 weeks of MT therapy value DAS 28 was 3.1 (2.7–3.62); SDAI 7.4 (4.2–11.4); DAS 28 remission/low disease activity was achieved in 22 (56.4%) pts, based on SDAI – in 25 (64.1%) pts; while MT failure based on EULAR response was documented in 4 (10.3%) pts. Lower percentages of FoxP3+CD25+ cells ((5.53 (4.09–6.48 vs 6.92 (5.84–7.96))), percentages and absolute number of FoxP3+ICOS+ cells ((6.91 (2.14–11.47) vs 10.83 (9.27–13.7)); 0.0035 (0.0013–0.0067) vs 0.0068 (0.0039–0.009)), and percentages and absolute number of FoxP3+CD154+ cells ((0.47 (0.19–0.83) vs 1.51 (1.12–2.08)); 0.0002 (0.00009–0.0005) vs 0.00087 (0.00047–0.0014)), and FoxP3+CD274+ T-cells (0.63 (0.34–1.49) vs 1.94 (1.16–2.25)); 0.0003 (0.0002–0.00065) vs 0.001 (0.0006–0.0016), $p<0.05$ in all cases) were documented in early RA pts versus healthy donors.

An increase in the percentage of CD4+cells (from 45.0 (38.0–49.2) to 46.8 (39.9–53.2)); an increase in the relative and absolute number of CD152+surface 0.65 (0.22–1.67) vs 2.07 (1.11–3.81); 0.0002 (0.0001–0.0008) vs 0.0007 (0.0004–0.002); and moderate decrease in the relative and absolute number of FoxP3+ICOS+ cells 5.3 (2.1–11.3) vs 4.1 (1.6–6.6); 0.002 (0.001–0.006) vs 0.0015 (0.0006–0.003), $p<0.05$ in all cases, was registered after 24 weeks of MT therapy. After 24 weeks of MT therapy the level of CD152+surface in the RA pts group was higher compared with healthy donors 2.1 (1.11–3.81) and 0.51 (0.34–1.2); 0.0007 (0.0004–0.002) and 0.0003 (0.00014–0.0008), respectively, $p<0.05$

Treg levels and phenotype were analyzed in pts groups based on MT efficacy by 24th week of treatment. Higher percentages and absolute number of FoxP3+CD274+ cells (1.25 (0.43–2.3) 0.0004 (0.0002–0.001) were detected in patients achieving SDAI remission ($n=25$), compared to pts with moderate disease activity (SDAI >11 $n=14$) (0.44 (0.2–0.69) 0.00016 (0.0001–0.0004), $p<0.05$)

Conclusions: MT therapy in early RA pts results in increased Treg suppressor activity according to growing percentages and absolute number of CD152+surface and FoxP3+CD274+ cells, more pronounced among pts, achieving remission/low disease activity following treatment. Increased levels of these markers are indicative of improved Tregs functional activity after successful MT therapy

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THU0172 IMPROVEMENT OF DISEASE ACTIVITY IN A 5-YEAR COHORT OF RHEUMATOID ARTHRITIS PATIENTS TREATED UNDER TREAT TO TARGET RECOMMENDATIONS AND A MULTISPECIALTY CARE MODEL RECEIVING CONVENTIONAL DMARD THERAPY

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Background: Treat to Target (T2T) strategy becomes from the need to develop therapeutic targets and tools to achieve defined outcomes in rheumatoid arthritis (RA), this strategy has become recognized as a standard of good practice embodying the principle that rapid attainment of remission, or low disease activity, can halt joint damage and maintain good quality of life.

Objectives: The aim of this study was to describe global change in Disease Activity Score 28 (DAS28) using T2T strategy for a 5 year period in patients with conventional DMARD therapy in a large cohort of patients from a Colombian specialized in RA center with multidisciplinary care model (MCM).

Methods: A descriptive dynamic cohort study was performed. Records of patients using conventional DMARD treatment from specialized in RA center were reviewed; those patients were followed-up under T2T standards. Clinical follow-up was according to DAS28 as follows: every 3–5 weeks (DAS28 >5.1), every 7–9 weeks (DAS28 ≥ 3.1 and ≤ 5.1), and every 11–13 weeks (DAS28 <3.1). Therapy had to be adjusted with DAS28 >3.2 unless patient's conditions don't permit it. MCM model means that every patient is seen by the other specialties involved in care as a minimum three times a year. We divided patients in three groups: low disease activity (LDA), moderate disease activity (MDA) and severe disease activity (SDA) patients. Descriptive epidemiology was done, percentages and averages were calculated; the median of each variable was analyzed using t-Student assuming normality for DAS28 distribution and the level activity disease was analyzed using Pearson's statistics.

Results: We included 1443 patients, 84% were women and 16% were men. Mean age was 62 \pm 11 years; mean DAS28 at beginning was 4.0 \pm 1; regarding disease activity 57% were in moderate disease activity and 17% in severe disease activity. While at 5 year follow up mean DAS was 2.92 \pm 0.65, 48% achieved remission, 30% low disease activity, with decrease to 20% in moderate disease activity and 2% in severe disease activity.

| ACTIVITY LEVEL | TIME 0 n(%) | 2012-2013 n(%) | 2013-2014 n(%) | 2014-2016 n(%) |
|----------------|-------------|----------------|----------------|----------------|
| REM | - | 380(26%) | 530(37%) | 698(48%) |
| LDA | 380 (26%) | 495(34%) | 487(34%) | 437(30%) |
| MDA | 782 (54%) | 439(30%) | 401(28%) | 284(20%) |
| SDA | 281 (19%) | 129(9%) | 25(2%) | 24 (2%) |

Conclusions: There is a significant improvement of DAS28 in a cohort of RA

patients receiving only conventional DMARDs therapy, treated and followed under T2T strategy recommendations and a MCM model.

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THU0173 LONG TERM SAFETY AND EFFICACY OF FILGOTINIB IN A PHASE 2B OPEN LABEL EXTENSION STUDY IN PATIENTS WITH RHEUMATOID ARTHRITIS: RESULTS UP TO 144 WEEKS

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Background: Filgotinib (GLPG0634, GS-6034) is an oral JAK1 selective inhibitor with a favorable safety and efficacy profile in two 24-week Phase 2b studies as add-on to methotrexate (DARWIN 1) or as monotherapy (DARWIN 2) in patients with active rheumatoid arthritis (RA). Three daily doses were tested (50mg, 100mg or 200mg) in comparison to placebo.

Objectives: To assess long term safety and efficacy of filgotinib 200mg daily in patients from the DARWIN 3 Phase 2 open-label extension study.

Methods: Patients who completed DARWIN 1 or 2 and enrolled in DARWIN 3 received filgotinib 200mg once daily or 100mg twice daily, depending on prior treatment assignment. The DARWIN 3 data cut off was when the last patient reached extension Week 60. For safety, all data from the first intake of filgotinib in DARWIN 1/2/3 were analysed (up to 144 weeks).

Results: 877 patients participated in DARWIN 1 or 2, 790 completed and 739 entered DARWIN 3 from 22 countries (82% females, mean age 53y). 559 patients (75.6%) completed Week 60, 9.3% discontinued due to positive Quantiferon, 7.8% due to other adverse events, 6.8% for other reasons and 0.3% due to insufficient response. Overall exposure to filgotinib was 1314 patient-years (PYE). Treatment-emergent adverse events (157.7/100PYE), serious adverse events (5.3/100PYE) and serious infections (1.9/100PYE) occurred at similar rates compared to the core studies, however infections decreased on a percentage basis from 15% (109/739, W0–12) to 5% (25/549, W85–96). 16 cases of Herpes zoster were reported (1.2/100PYE), 6 cases of malignancy (excl. NMSC) (0.5/100PYE) and 1 case of MACE (0.1/100PYE). There was no active case of tuberculosis. Three fatalities were reported (0.2/100PYE). Mean change from baseline (CFB) at Week 96 and CTCAE toxicity grading in lab parameters of special interest are shown in table 1.

Table 1. Mean CFB at Week 96 and CTCAE toxicity grading of selected lab parameters

| | Mean CFB | CTCAE Grade 3–4 (%) |
|--------------|--------------|---------------------|
| Hb | +6.5 g/L | 0.4 |
| Neutrophils | -1.73 giga/L | 1 |
| Lymphocytes | -0.19 giga/L | 2 |
| Creatinine | +8.2 µmol/L | 0 |
| ALT | +6.1 U/L | 0.4 |
| LDL | +13% | – |
| HDL | +23% | – |
| Tot chol/HDL | -4% | – |
| NK cells | -0.02 giga/L | – |

Based on an observed case analysis 84% (505/601), 65% (389/601), 44% (267/601) and 51% (299/587) of patients reached ACR20, ACR50, ACR70 and DAS28(CRP) remission at Week 60 respectively.

Conclusions: With 1314 patient-years of exposure, the safety profile of filgotinib appears consistent with that of previously reported double-blind studies and the clinical response appears durable.

References:

[1] Westhovens R et al. Ann Rheum Dis 2016;0:1–11.

[2] Kavanaugh A et al. Ann Rheum Dis 2016;0:1–11.

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THU0174 DRUG RETENTION OF TOFACITINIB VERSUS BIOLOGIC ANTIRHEUMATIC AGENTS IN RHEUMATOID ARTHRITIS: OBSERVATIONAL DATA FROM THE SWISS SCQM REGISTRY

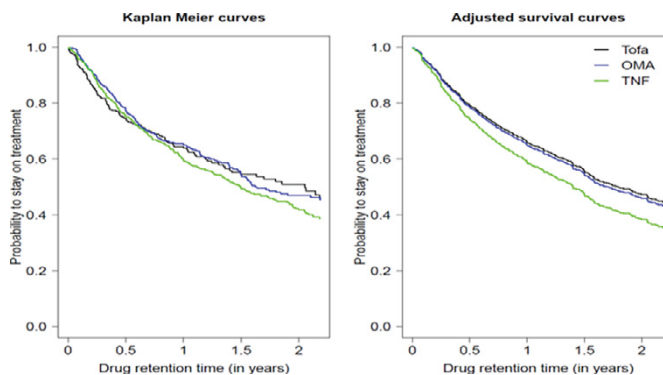
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Background: The oral Janus kinase inhibitor tofacitinib (Tofa) was licensed in Switzerland in 2013 for the treatment of moderate to severe rheumatoid arthritis (RA) patients having failed methotrexate. Besides Tofa, rheumatologists in Switzerland have the choice between 7 alternative bDMARDs licensed with similar indications, including 5 TNF inhibitors (TNFi) and 2 bDMARDs with other modes of action (OMA-bDMARDs).

Objectives: To compare the drug retention rate of three alternative treatment options licensed with a similar indications, namely Tofa, TNFi and OMA-bDMARDs, using data from the Swiss registry.

Methods: This is an observational cohort study within the Swiss Clinical Quality Management registry (SCQM). All therapies with Tofa, TNFi, and OMA-bDMARDs initiated in adult RA patients between August 1, 2013 and Dec 1, 2016 were considered. The exposure of interest was treatment with Tofa vs TNFi and vs OMA-bDMARDs (Abatacept or Tocilizumab). The primary outcome was drug retention defined as the time from initiation to discontinuation of treatment. We used Kaplan Meier curves to display drug retention and Cox proportional hazard models stratified by seropositivity to analyze the hazard for treatment discontinuation. We adjusted for potential confounders, including gender, age, disease duration, seropositivity, BMI, smoking status, DAS28-CRP and the total number of previous bDMARDs. We applied multiple imputation to account for missing baseline covariate data.

Results: A total of 1996 therapies were initiated during the study period (376 Tofa, 928 TNFi, 692 OMA-bDMARDs). Some differences in disease and treatment characteristics existed between the 3 groups, in particular TNFi tended to be used in patients with fewer previous bDMARDs experience, younger age and shorter disease duration. The crude overall drug retention was similar between the 3 three drug groups ($p=0.24$) (Figure 1A). The adjusted analysis demonstrated a slightly higher hazard of drug discontinuation with TNFi compared to Tofa [HR 1.27 (95% CI: 1.02 – 1.57, $p=0.03$)], while no difference was observed for OMA-bDMARDs and Tofa [HR 1.03 (95% CI: 0.83 – 1.28, $p=0.76$)] (Figure 1B). Complete case results were consistent with results using multiple imputation of baseline covariates. Other variables significantly associated with drug discontinuation were a higher number of previous bDMARDs ($p < 0.001$) and increasing BMI values ($p=0.03$), while combination therapy with sDMARDs tended to decrease discontinuation ($p=0.08$)



Conclusions: The results of this observational study suggest that Tofa is a valuable alternative to treatment options in RA, with Tofa drug retention at least comparable to other available bDMARDs.

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