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#### DISEASE ACTIVITY IN ESCALATION OR DE-ESCALATION OF DOSAGE OF TOFACITINIB IN RHEUMATOID ARTHRITIS PATIENTS – THE FIRST RESULTS OF RUSSIAN NATIONAL REGISTER OF PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH TOFACITINIB

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**Background:** In previous studies tofacitinib (TF) had demonstrated efficacy of two dosages (10 and 20 mg/day) in patients with rheumatoid arthritis (RA). However, the expected results of switching of TF dosages are unknown.

**Objectives:** The aim of the study was to evaluate the results of switching of TF's dosages in RA patients.

**Methods:** Were analyzed the data from Russian national register of patients with RA treated with TF (tofacitinib). 415 patients were involved in the register (aug 2018). In statistical analysis were included data from 41 patients with RA (EULAR 2010), who switched dosage of TF at visit 3 and had complete clinical and laboratory data from 5 consecutive visits with an interval of 3 months between the visits. Demographical (age, sex) data, disease activity data DAS28 (Disease activity score), C-reactive protein level were collected, table 1. Changes in disease activity were calculated to patients with switching of the tofa's dosage (the visit before and after the switching).

**Results:** 1.28 (68%) of patients were treated with NSAIDs, 24 (50%) with 5-10 mg of prednisolone, 34 (82.9) – with methotrexate (10-25 mg/week), biologics – 5 (4.2%).

**Table 1.** Baseline characteristics of the patients with RA included in the study (n=41)

Parameter	Characteristics
Male, n (%)	10 (24.3)
Caucasians, n (%)	41 (100)
Asians, n (%)	0 (0)
Age of disease onset, years (mean ±SD)	40.1±10.5
Symptoms duration, month (mean ±SD)	98.7± 87.1
Positive rheumatoid factor, n (%)	32 (78)
Positive antibodies to cyclic citrullinated peptide (anti-CCP), n (%)	37 (90.2)
BMI, kg/m <sup>2</sup> (mean ±SD)	25.12±5.98
Smokers (current and in the anamnesis), n (%)	33 (80)

From 41 persons with RA 32 patients, who never achieved low disease activity (DAS28<3.2) or remission (DAS28<2.6) elevated the dosage of tofa from 10 to 20 mg/day and 9 patients with DAS28 < 3.2 decreased the dosage from 20 to 10 mg/day.

After escalation of TF dosage DAS28 decreased from 5.42±1.22 to 4.22 ±1.22 (p<0.00), n=32. In 10 patients escalation lead to DAS28-remission (DAS28 <2.6) and in 12 patients - to low disease activity (DAS28<3.2).

10 patients had no clinical or laboratory response on escalation of TF dosage. Interestingly, that responders before escalation of dosage had mean DAS28 3.54 (min 3.2 – max 4.9) and non-responders – 5.54 (min 5.3-max 6.9), p<0.000.

De-escalation of the dosage from 20 to 10 mg/day was not associated with significant changes of DAS28 (1.99 ± 1.25 increased to 2.1 ±0.96 respectively, p=0.82).

**Conclusion:** Escalation of dosage of TF in RA lead to improvement of the disease activity in non-complete responders, who achieved DAS 28 3.2-5.1, but not in patients with absence of any response (DAS28 before escalation 5.3-6.9). De-escalation of TF dosage in patients with DAS28 < 2.6 dose not lead to significant changes of RA's activity.

#### REFERENCES:

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#### GS-9876, A NOVEL, HIGHLY SELECTIVE, SYK INHIBITOR IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS: SAFETY, TOLERABILITY AND EFFICACY RESULTS OF A PHASE 2 STUDY

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**Background:** Spleen tyrosine kinase (SYK) mediates immunoreceptor signaling and is essential in activation of cells including B lymphocytes, monocytes, macrophages, dendritic cells, and osteoclasts. SYK may play an important role in the initiation and progression of autoimmune diseases, including rheumatoid arthritis (RA) and lupus. GS-9876 is a novel, potent, highly selective oral inhibitor of SYK in phase 2 trials for autoimmune diseases.

**Objectives:** To evaluate the efficacy, safety, and pharmacokinetics of GS-9876, and its impact on biomarkers relevant to RA as well as the SYK and JAK pathways.

**Methods:** Patients with active RA with prior inadequate response to methotrexate (MTX) or a biologic antirheumatic drug were randomized 1:1:1 to receive GS-9876 30 mg, GS-9876 10 mg, selective JAK1 inhibitor filgotinib (FIL) 200 mg, or matching placebo (PBO) once daily for 12 weeks on a stable background of oral MTX. The primary endpoint for GS-9876 was the change in DAS28(CRP) at week 12. Pharmacokinetics and various biomarkers were evaluated at several time points, including VectraDA and stimulation of whole blood in TruCulture (MyriadRBM) tubes.

**Results:** A total of 83 patients received the study drug and 79 completed the study. Fourteen patients (16.9%) were male and 69 (83.1%) were female. The majority were white (77, 92.8%). The mean (SD) age at baseline (BL) was 55 (11.5) years (range 18 to 73). The primary and secondary endpoints are reported in Table 1. For DAS28(CRP), the mean (SD) at BL was 5.75 (0.961) with a median of 5.69; a statistically significant reduction at week 12 was observed only in patients receiving FIL as compared to PBO (Table 1). Adverse events (AEs) were reported across all groups (37.5% in the combined GS-9876 arms, 38.1% in FIL, 40.9% in PBO). No deaths or serious AEs were reported. Plasma exposures of all study drugs were comparable to those observed in healthy subjects and historical data. *Ex vivo* stimulated whole blood identified differential responses between GS-9876 and PBO.