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AB0434 TOFACITINIB IN RHEUMATOID ARTHRITIS: REAL LIFE EXPERIENCE

P. Sansinanea[1], A.C. Costi[1], A. Vulcano[2], A.P. Salas[2], J. Marcos[3], M.A. Belini[4], M.A. García[2]. *[1]Rheumatology Unit, Sanatorio Ipensa, HIGA San Martín la Plata; [2]Rheumatology Unit, HIGA San Martín la Plata; [3]Rheumatology Unit, Sanatorio IPENSA, Pfizer Inc., la Plata; [4]Medical Affairs, Pfizer Inc, CABA, Argentina*

Background: Tofacitinib is a new small molecule, Janus kinase 1 and 3 inhibitor, interfering with the JAK-STAT signaling pathway. The JAK-STAT transmits the extracellular information in the cell nucleus, influencing DNA transcription. Its efficacy and safety in Rheumatoid Arthritis (RA) has been demonstrated in different phase II, III and long-term clinical studies. It has been approved in Argentina for the treatment of patients with moderate to severe rheumatoid arthritis RA with failure to conventional DMARDs.
Objectives: To communicate real world safety data from patients with RA under treatment with Tofacitinib.
Methods: A retrospective, descriptive study from patients with RA (ACR/EULAR2010) under treatment with Tofacitinib from September 2014 to December 2016 was conducted. Medical records from patients being treated with Tofacitinib were reviewed and demographic data were recorded. Comorbidities, concomitant treatments, and reported adverse effects were documented.
Results: 62 patients were treated with Tofacitinib. 53 were female and 9 were male, with a mean age of 57.91±14.72 years and average disease duration of 140.09±130.83 months. 18 patients (29%) had at least one comorbidity, the most frequent being hypertension (77%).
Of the 62 patients studied, 54 (87%) had established RA (duration of illness greater than 24 months) and 8 patients (13%) with early RA (less than 24 months). In 54 patients Tofacitinib was indicated in combination with another DMARD (87%), and only 6 patients received treatment as monotherapy.
The most commonly used DMARD in combination therapy was methotrexate (MTX) in 92.5%
Treatments were indicated by failure to MTX or other conventional DMARDs, 12/62 treatments were indicated by failure to treatment with 1 biological DMARD and 13/62 treatments were indicated by failure to two or more biological DMARDs. The maximum exposure time was 21 months.
During the time of exposure to Tofacitinib the following adverse events were observed: Herpes Zoster infection 2 cases (monometameric, no visceral involvement in unvaccinated patients), upper airway infection 1 case, transient increase in liver enzymes 1 case, peripheral facial paralysis 1 case, tachycardia 1 case. There were no cases of serious infections, opportunistic infections, cytopenias, dyslipidemia, or increased CPK.
Three patients discontinued Tofacitinib: one due to tachycardia, another case peripheral facial paralysis and another case due inefficacy.
Conclusions: Most patients received combined treatment with DMARDs being the most commonly used Methotrexate. There were no cases of serious infections, opportunistic infections, cytopenias or dyslipidemia. The use of Tofacitinib in RA patients in our cohort showed a comparable safety profile with long-term extension studies in the treatment of patients with RA diagnosed with failure of conventional or biological DMARDs.
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AB0435 COMBINATION THERAPY IN EARLY STAGE OF RHEUMATOID ARTHRITIS

S.X. Matchanov. *Internal disease, Tashkent Medical Academy, Tashkent, Uzbekistan*

Background: It is known that the early period of rheumatoid arthritis (RA) has a critical role in the development and progression of immune inflammation. Allocation of early RA is due to the need for timely appointment of basic anti-inflammatory drugs to prevent the development of destructive changes in the joints and improve its current forecast. We have proposed a combination of two basic drugs for the treatment of RA, methotrexate (MTX) and leflunomide (LF). While this combination, we proceeded from the basic principles of combination therapy: each of the drugs has an independent clinical effect in early RA, the drugs have different mechanisms of action and different spectrum of side effects.
Objectives: Investigating of clinical efficacy of combination therapy with MT and LF in patients with RA in its early stages
Methods: We observed 80 patients with early RA, 50 patients of them were women and 30 patients were male. The age of patients ranged from 24 up to 42 years old (31,7±7,6), the duration of illness was 6 months. Activity of RA was corresponded to the II degree (DAS 28 <4.7) in 48 patients, III degree (DAS28>5,1) was in 32 patients. 1st group consisted of 40 patients and the 2nd group involved 40 patients. Patients in 1st group received combination therapy with LF in doses 20 mg/day and MT in doses 7.5 mg/week. 2nd group received just MT as a single basic anti-inflammatory drug in doses 7.5 mg/week. In order to improve portability of MT was administered to all patients folic acid in doses 1.2 mg/day, 5 days in a week. The efficiency of the intervention was evaluated after 6 months by reducing of the final value of the indicator of inflammatory activity.
Results: The results of observation of patients for 6 months were showed that, combination therapy with MT and LF provides a quick and pronounced clinical effect in patients in the early stages of RA. Patients of 1st group according to criteria ACR 50- 70% improvement was achieved in 50% of patients, while figure of all indicators of patients in 2nd group was 33.4%. During the treatment was indicated improvement of laboratory parameters of disease activity of RA in both groups, features of activity of 1st group were decreased up to (DAS28 =2,9), signs of 2nd group were (DAS28 =3,6). However, there were 26% of cases of clinical remission of the disease in patients of 1st group than patients of 2nd group. Known side effects of combination therapy with MT and LF in most cases have not been severe, reversible and demanded the abolition of drugs in rare (11.2%) cases.
Conclusions: Combined basic therapy of patients in the early stages of RA with LF and MT has more efficiency than mono therapy.
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AB0436 COMPARISON OF TOFACITINIB EFFICACY IN PATIENTS WITH MODERATE VS SEVERE RHEUMATOID ARTHRITIS: POOLED ANALYSIS OF PHASE 3 STUDIES

S. Schwartzman[1], P. Sunkureddi[2], L. Takiya[3], M. Snyder[3], H. Fan[4], T. Lukic[5], J. Roberts[6], W.F.C. Rigby[7]. *[1]Hospital for Special Surgery, New York, NY; [2]Clear Lake Rheumatology, Nassau Bay, TX; [3]Pfizer Inc, Collegeville, PA; [4]Pfizer Inc, Groton, CT; [5]Pfizer Inc, New York, NY, United States; [6]Pfizer Inc, Tadworth, United Kingdom; [7]Geisel School of Medicine at Dartmouth, Lebanon, NH, United States*

Background: Tofacitinib is an oral JAK inhibitor for the treatment of RA.
Objectives: To evaluate tofacitinib 5 and 10 mg twice daily (BID) efficacy in patients (pts) with moderate vs severe RA.
Methods: Tofacitinib 5 and 10 mg BID efficacy data were obtained from 6 randomised double-blind Phase 3 studies of 6–24 months' duration. Tofacitinib was administered as monotherapy (NCT00814307 ORAL Solo; NCT01039688 ORAL Start) or with csDMARDs, mainly MTX (NCT00960440 ORAL Step; NCT00847613 ORAL Scan; NCT00856544 ORAL Sync; NCT00853385 ORAL Standard). Pts receiving MTX monotherapy (ORAL Start), or placebo (±csDMARDs) were combined as a single "placebo" group. Baseline (BL) disease severity was classified as moderate or severe using Disease Activity Score in 28 joints with erythrocyte sedimentation rate (DAS28: moderate 3.2 to ≤5.1; severe >5.1) and Clinical Disease Activity Index (CDAI: moderate 10 to ≤22; severe >22). Month 3 (M3) efficacy outcomes included: pts (%) achieving low disease activity (LDA; DAS28 ≤3.2, CDAI ≤10), remission (DAS28 <2.6, CDAI ≤2.8), HAQ-DI <0.5 (normal physical functioning), HAQ-DI improvement >0.22 and mean change from BL (Δ) in DAS28, CDAI and HAQ-DI. This post hoc analysis had no multiplicity adjustments.
Results: Overall, more pts had severe BL disease by DAS28 (91.0%) and CDAI (89.5%). The table shows BL disease characteristics and M3 efficacy outcomes for pts classified by BL DAS28 disease severity; CDAI classification demonstrated similar trends.

Table. Baseline disease characteristics (A) and Month 3 efficacy outcomes (B) by baseline disease severity assessment using DAS28
A) Mean (SD) baseline demographics and characteristics

Baseline disease severity	Moderate (3.2 to ≤5.1)			Severe (>5.1)		
Treatment group	Tofacitinib 5 mg BID N=120	Tofacitinib 10 mg BID N=127	Placebo N=76	Tofacitinib 5 mg BID N=1427	Tofacitinib 10 mg BID N=1438	Placebo N=766
Disease duration, years	7.1 (7.6)	7.7 (9.2)	8.7 (8.1)	7.4 (7.9)	7.7 (8.0)	7.7 (8.3)
CDAI	20.7 (6.2)	19.5 (5.4)	20.3 (6.9)	39.4 (11.7)	39.1 (11.8)	39.3 (12.1)
DAS28	4.6 (0.5)	4.7 (0.4)	4.7 (0.4)	6.7 (0.8)	6.6 (0.8)	6.6 (0.9)
HAQ-DI	1.0 (0.7)	0.8 (0.7)	0.9 (0.7)	1.5 (0.6)	1.5 (0.6)	1.5 (0.6)
B) Month 3 efficacy outcomes						
Remission (DAS28<2.6), % (CI)	20.0** (14.9, 31.5)	22.8** (18.3, 35.3)	5.3 (1.7, 14.6)	6.2*** (5.6, 8.5)	9.0*** (8.5, 11.9)	2.0 (1.2, 3.5)
LDA (DAS28≤3.2), % (CI)	36.7*** (31.7, 51.1)	32.3*** (28.0, 46.6)	9.2 (4.3, 20.4)	13.8*** (13.6, 17.6)	19.1*** (19.1, 23.6)	4.6 (3.5, 6.9)
HAQ-DI <0.5, % (CI)	45.0 (35.9, 54.4)	60.6*** (51.6, 69.2)	32.9 (22.5, 44.6)	24.5*** (22.6, 27.2)	30.0*** (28.0, 32.8)	12.8 (10.6, 15.5)
HAQ-DI improvement >0.22, % (CI)	50.8* (41.6, 60.1)	55.9** (46.8, 64.7)	31.6 (21.7, 43.8)	66.2*** (64.8, 69.8)	72.4*** (71.0, 75.7)	50.7 (47.6, 54.8)
ΔDAS28, LS mean (CI)	-1.1*** (-1.4, -0.9)	-1.3*** (-1.6, -1.1)	-0.1 (-0.3, 0.2)	-2.0*** (-2.1, -2.0)	-2.3*** (-2.3, -2.2)	-1.1 (-1.2, -1.0)
ΔHAQ-DI LS mean (CI)	-0.3*** (-0.4, -0.3)	-0.4*** (-0.5, -0.3)	-0.1 (-0.1, 0.1)	-0.5*** (-0.6, -0.5)	-0.6*** (-0.7, -0.6)	-0.3 (-0.3, -0.2)

*p<0.05, **p<0.001, ***p<0.0001 vs placebo
BID, twice daily; CDAI, clinical disease activity index; CI, 95% confidence interval; DAS28, Disease Activity Score in 28 joints with erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; LDA, low disease activity; LS, least squares; SD, standard deviation