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AB0257

IMPACT OF CONVENTIONAL ANTIRHEUMATIC TREATMENT ON CARDIOVASCULAR RISK IN PATIENTS WITH RHEUMATOID ARTHRITIS

D. Gerasimova¹, E. Gerasimova², T. Popkova², A. Melkumyan¹. ¹I.M. Sechenov First Moscow State Medical University (Sechenov University), Department of Organization and Economy of Pharmacy, Moscow, Russian Federation; ²V.A. Nasonova Research Institute of Rheumatology, Systemic Rheumatic Diseases Laboratory, Moscow, Russian Federation

Background: Cardiovascular diseases (CVD) are the most common and socially significant comorbidities and the main cause of premature mortality in rheumatoid arthritis (RA). Appropriate RA therapy should not only suppress RA activity, but also reduce CVD risk.

Objectives: To evaluate CVD risk and analyze its association with the use of conventional therapy in RA patients (pts).

Methods: The study included 100 pts with RA (92 women and 8 men) aged 30 to 60 without established CVD. The median age was 49.5 [44.5;53] years, duration of RA was 144 [60;240] months, DAS28 was 4.4 [3.3;5.3] points. Eighty six RA pts (86%) treated with disease-modifying antirheumatic drugs (DMARDs) (methotrexate, n=55; leflunomide, n=12; hydroxychloroquine, n=8; sulfasalazine, n=11), including 33 pts (33%) in combination with glucocorticoids (GCs). Fourteen pts (14%) received monotherapy with GCs. Pts were divided into three treatment groups: DMARDs group, n=53; GCs group, n=14; DMARDs+GCs group, n=33. CVD risk was calculated with ASSIGN, QRISK3, and ERS-RA scales.

Results: No differences were found between the groups when calculating CVD risk using ASSIGN (table 1). Estimated CVD risk by QRISK3 was lower in DMARDs group (4.9 [3.0; 7.7]) than in DMARDs+GCs group (7.1 [4.1; 13.6], p<0.05). High CVD risk on the ERS-RA scale was determined less frequently (13%) and median CVD risk was lower in DMARDs group (4.2 [2.2; 5.4]) than in GCs group (5.7%; 8.9 [4.8; 11.7], p<0.01) and DMARDs+GCs group (39%; 6.6 [3; 9.3], p<0.05, respectively). In DMARDs group, significant differences in CVD risk by ERS-RA were found in pts treated with hydroxychloroquine (2 [1.4; 5.8]) and leflunomide (6.2 [2.8; 12.3], p<0.05).

Conclusion: RA pts treated with DMARDs have a reduced risk for CVD than pts treated with GCs or a combination of DMARDs and GCs. GCs significantly increase CVD risk. To clarify the impact of hydroxychloroquine and leflunomide on CVD risk, a study on a larger number of pts is required.

Table 1. The impact of conventional antirheumatic therapy on CVD risk.

Treatment	ASSIGN		QRISK3		ERS-RA	
	High CVD risk, %	median [25-75 percentiles]	High CVD risk, %	median [25-75 percentiles]	High CVD risk, %	median [25-75 percentiles]
DMARDs, n=53	6	11 [6.5;14]	2	4.9 [3;7.7] *	13*	4.2 [2.2;5.4] *
GCs, n=14	7	9.5 [7;13]	7	6.6 [4.4;15.8]	57*	8.9 [4.8;11.7] *
DMARDs+GCs, n=33	15	10 [5;13.5]	9	7.1 [4.1;13.6] *	39*	6.6 [3;9.3] *

Note: * - p<0.01 between pts receiving DMARDs and GCs; * - p<0.05 between pts receiving DMARDs and DMARDs+GCs.

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AB0258

DMARD-TREATMENT OF UNDIFFERENTIATED ARTHRITIS INTENSIFIED DURING THE LAST DECADE, BUT DID NOT RESULT IN IMPROVED LONG TERM OUTCOMES

M. Verstappen¹, X. Matthijssen¹, A. Van der Helm - van Mil^{1,2}. ¹Leiden University Medical Center, Rheumatology, Leiden, Netherlands; ²Erasmus University Medical Center, Rheumatology, Rotterdam, Netherlands

Background: EULAR guidelines stress timely initiation of DMARD-treatment in early arthritis patients also when classification criteria are not yet fulfilled. Consequently, undifferentiated arthritis (UA) patients may be increasingly treated with disease modifying antirheumatic drugs (DMARDs), despite inadequate placebo-controlled evidence for its effectivity. Implementation of this guideline also hampers future placebo-controlled trials in UA. However, historical data, with inclusion period as instrumental variable, can provide insight whether long term

outcome is improved with increased DMARD-use, and thus serve to investigate if DMARD-treatment is effective in UA.

Objectives: With 25-years of observational data of newly referred UA-patients, we studied whether enhanced treatment strategies resulted in better long term outcomes for UA.

Methods: Between 1993 and 2019, 1132 consecutive UA-patients, not fulfilling the 1987/2010 criteria for RA or any other distinct diagnosis, were included in the Leiden Early Arthritis Cohort; patients were divided in 5 inclusion periods (1993-1998, 1999-2005, 2006-2010, 2011-2014, 2015-2019). Frequency of DMARD-initiation after diagnosis was compared. We studied the following outcomes: the course of disease activity scores (DAS28-CRP) and Health assessment questionnaires (HAQ), progression to RA after 1-year (according to the 1987 and/or 2010 criteria) and the frequency of prolonged DMARD-free status within 10-years of follow-up (this was defined as either spontaneous remission or sustained remission after discontinuation of DMARD-treatment).

Results: The current population of UA-patients, thus not fulfilling 1987 or 2010 criteria, had rather mild disease: the median SJC was 1, the median TJC 2, 95% was autoantibody-negative and the median HAQ was 0.6. These characteristics were similar in the different inclusion periods. Initiation of DMARD-treatment in UA increased over time: 18%, 35%, 38%, 43% up to 55% in respectively 1993-1998, 1999-2005, 2006-2010, 2011-2014 and 2015-2019, in which methotrexate became more common in the last decade. Frequency of progression to RA after 1-year did not decrease and was 14%, 21%, 26%, 19% and 28% in the respective inclusion periods. Long-term DAS28CRP-scores improved from 2011 onwards (range -0.18, -0.24; p<0.05). However HAQ-score over time did not improve compared to the 1993-1998 period (range -0.00, -0.08; p>0.05). Also the percentages of patients in DMARD-free status after 10-years of follow-up did not significantly improve over time: 57%, 58%, 59% (for 1993-1998, 1999-2005, 2006-2010 respectively, p=0.59).

Conclusion: Intensified DMARD-treatment of patients with UA did not result in improved outcomes. These data may indicate overtreatment of UA-patients. Yet, methods to stratify which UA-patients should be treated remains warranted.

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AB0259

EVALUATION OF THE EFFECT OF FILGOTINIB ON THE PHARMACOKINETICS OF ROSUVASTATIN, ATORVASTATIN, AND PRAVASTATIN

K. Anderson¹, C. Nelson¹, Q. Gong¹, M. Alani¹, T. Tarnowski¹, A. A. Othman¹.

¹Gilead Sciences, Inc., Foster City, United States of America

Background: Filgotinib is an orally administered small molecule that preferentially inhibits Janus kinase 1 and is approved for use in Europe and Japan in adult patients with rheumatoid arthritis (RA) who have had an inadequate response to conventional therapies. Patients with RA are at a higher risk of cardiovascular morbidity and mortality relative to the general population¹. Thus, it is important to understand potential drug-drug interactions of filgotinib with lipid-lowering agents such as statins. Based on in vitro studies, filgotinib is not expected to significantly increase exposure of statins via inhibition of the organic anion transporting peptide (OATP) at clinically relevant exposures. Hence, in Phase 2 and Phase 3 clinical studies, statins were allowed for use with filgotinib. A post-hoc analysis showed no increase in statin-induced AEs such as muscle or liver toxicities when statins were coadministered with filgotinib ("Concomitant Use of Statins in Filgotinib-Treated Patients with Rheumatoid Arthritis: A Post Hoc Analysis", submitted to EULAR 2021).

Objectives: The objectives of this study (NCT04608344) were to evaluate the effect of filgotinib on the pharmacokinetics of atorvastatin, pravastatin, and rosuvastatin, which are sensitive substrates for the OATP-1B1/1B3, and the short-term safety of administering filgotinib with or without statins.

Methods: This was an open-label, randomized, two-way, crossover study in healthy adult volunteers (n = 27). Study participants received a single dose of atorvastatin (ATV 40mg) and a single dose of a cocktail of pravastatin (PRA 40mg)/rosuvastatin (ROS 10mg), on two different occasions with washout in between, alone or in combination with filgotinib (200mg QD for 11 days). Serial pharmacokinetic sampling was performed and pharmacokinetic parameters for each statin were calculated. Safety was assessed throughout the study. An analysis of variance using a mixed-effects model was applied to the natural logarithmic transformation of pharmacokinetic parameters (C_{max} and AUC_{inf}) for ATV, 2-OH-ATV (active metabolite of ATV), PRA, and ROS. Geometric-least squares means (GLSM) ratios and 90% confidence intervals (90% CI) of pharmacokinetic parameters were estimated for each analyte and were compared against pre-specified lack of pharmacokinetic alteration boundaries of 70 to 143%.

Results: Of the 27 enrolled participants, 25 participants completed all study treatments. Most AEs and laboratory abnormalities were Grade 1 or 2 in severity; 1 participant discontinued due to a Grade 3 increase in creatine kinase and 1 participant discontinued due to difficulty in blood draws. Following coadministration of filgotinib with ATV, relative to ATV alone, ATV AUC_{inf} was unaffected

(GLSM ratio (90% CI): 0.91 (0.84, 0.99)), but ATV C_{max} was slightly reduced (GLSM ratio (90% CI): 0.82 (0.69, 0.98)). 2-OH-ATV exposure (C_{max} and AUC_{inf}) were unaffected (GLSM ratio (90% CI): 0.98 (0.81, 1.18) for C_{max} and 1.12 (1.02, 1.22) for AUC_{inf}), and were within the pre-specified lack-of-effect bounds. Following coadministration with filgotinib, PRA AUC_{inf} was unaffected (GLSM ratio (90% CI): 1.22 (1.06, 1.42)), but PRA C_{max} was slightly higher (1.25 (1.01, 1.54)). ROS exposure (C_{max} and AUC_{inf}) were moderately higher upon coadministration with filgotinib (GLSM ratio (90% CI): 1.68 (1.43, 1.97) for C_{max} and 1.42 (1.30, 1.56) for AUC_{inf}), and these changes in rosuvastatin exposure are not considered to be clinically relevant.

Conclusion: All study treatments were generally well tolerated. Co-administration with filgotinib did not have a clinically meaningful impact on the exposure of ATV, PRA, and ROS. These data support concomitant use of filgotinib with OATP substrates such as statins.

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AB0260

LONG-TERM EFFICACY AND SAFETY OF UPADACITINIB IN PATIENTS FROM CHINA, BRAZIL, AND SOUTH KOREA WITH RHEUMATOID ARTHRITIS AND AN INADEQUATE RESPONSE TO CONVENTIONAL SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS: RESULTS AT 64 WEEKS

X. Zeng^{1,2}, D. Zhao³, S. Radominski⁴, M. Keiserman⁵, C. K. Lee⁶, N. Martin⁷, S. Meerwein⁸, Y. Sui⁹, W. Park¹⁰. ¹Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences, Beijing, China; ²National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Dermatology and Immunology, Beijing, China; ³Shanghai Changhai Hospital, Rheumatology and Immunology, Shanghai, China; ⁴Universidade Federal do Paraná, Rheumatology, Curitiba, Brazil; ⁵Pontifical Catholic University, Rheumatology, Porto Alegre, Brazil; ⁶Asan Medical Center, Rheumatology, Seoul, Korea, Rep. of (South Korea); ⁷AbbVie Inc, Immunology, Quebec, Canada; ⁸AbbVie Deutschland GmbH & Co. KG, Immunology, Ludwigshafen, Germany; ⁹AbbVie Inc, Immunology, North Chicago, Illinois, United States of America; ¹⁰School of Medicine, Inha University, Rheumatology, Incheon, Korea, Rep. of (South Korea)

Background: Upadacitinib (UPA), an oral Janus kinase inhibitor, in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), showed significant improvements in clinical and functional measures compared with placebo (PBO) up to 12 weeks (wks), in patients (pts) from China, Brazil, and South Korea with rheumatoid arthritis (RA) and prior inadequate response to csDMARDs (csDMARD-IR).¹

Objectives: To assess the efficacy and safety of UPA up to 64 wks (long-term extension; LTE) in csDMARD-IR pts with RA from China, Brazil, and South Korea.

Methods: Pts were randomized to 12 wks of blinded treatment with UPA 15 mg once daily (QD) or PBO, in combination with csDMARDs. From Wk 12 onward, pts could continue to receive open-label UPA 15 mg QD. Efficacy endpoints were analyzed by original randomized treatment group sequences over 64 wks and included American College of Rheumatology (ACR) responses, and key remission and low disease activity measures. Non-responder imputation was used to handle missing data for binary endpoints. Treatment-emergent adverse events (TEAEs) per 100 patient-years (PY) were summarized for pts receiving ≥ 1 dose of UPA from baseline through to Wk 64.

Results: Of 338 randomized pts who received ≥ 1 dose of study drug, 310 (91.7%) entered the LTE and 275 (81.4%) completed 64 wks of treatment. Among those initially randomized to UPA, the proportion of pts achieving 20%/50%/70% improvement in ACR criteria, and key remission and low disease activity measures increased over 64 wks of treatment (Figure 1). Improvements from baseline in the Health Assessment Questionnaire-Disability Index and pts' assessment of pain were observed over 64 wks of UPA treatment (data not shown). By Wk 64, efficacy results for pts who switched from PBO to UPA at Wk 12 followed a similar trajectory to those originally randomized to UPA.

The observed rate of serious infections was 8.1 events/100 PY. Herpes zoster events were mostly non-serious, involving only 1 or 2 dermatomes. Most cases of hepatic disorders were Grade 1 or 2 hepatic transaminase elevations. There was 1 case of venous thromboembolic event (VTE; concurrent pulmonary embolism and deep vein thrombosis [DVT] in a patient with a history of DVT) and 3 cases of malignancy. Adjudicated major adverse

cardiovascular events (Table 1) occurred in 2 pts (1 with non-fatal myocardial infarction and 1 with non-fatal stroke) who had underlying risk factors for cardiovascular disease. There were no deaths, active tuberculosis, or renal dysfunction.

Conclusion: UPA 15 mg was effective in treating the signs and symptoms of RA and in improving physical function over 64 wks with no new safety signals¹ in csDMARD-IR pts with RA from China, Brazil, and South Korea.

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Table 1. TEAEs at Wk 64

Event (E/100 PY)	UPA 15 mg (n=322; PY=334.5)
Any AE	421.5 (399.8–444.1)
Serious AE	19.1 (14.7–24.4)
AE leading to discontinuation of study drug	9.0 (6.1–12.8)
Deaths ^a	0
AEs of special interest	
Serious infection	8.1 (5.3–11.7)
Opportunistic infection	0.9 (0.2–2.6)
Herpes zoster	9.0 (6.1–12.8)
Hepatic disorder	42.2 (35.5–49.7)
Gastrointestinal perforation (adjudicated)	0.3 (0.0–1.7)
Any malignancy (excluding NMSC)	0.6 (0.1–2.2)
NMSC	0.3 (0.0–1.7)
MACE (adjudicated) ^b	0.6 (0.1–2.2)
VTE (adjudicated) ^c	0.3 (0.0–1.7)
Anemia	11.1 (7.8–15.2)
Neutropenia	11.7 (8.3–15.9)
Lymphopenia	7.8 (5.1–11.4)
CPK elevation	11.1 (7.8–15.2)

^aIncluding non-treatment-emergent deaths. ^bDefined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. ^cIncluding DVT and pulmonary embolism. AE, adverse event; CPK, creatine phosphokinase; E, events; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer

Figure Efficacy over 64 wks (non-responder imputation)

ACR20/50/70, 20%/50%/70% improvement in American College of Rheumatology criteria; DAS28(CRP), Disease Activity Score in 28 joints using C-reactive protein; PBO, placebo; QD, once daily; SDAI, Simple Disease Activity Index; UPA, upadacitinib; wks, weeks

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