Objectives: The objective of this work was to characterize the pharmacokinetics of ABT-494 with the extended-release formulation that is currently being utilized in Phase 3.
Methods: Comparison of ABT-494 pharmacokinetics from the immediate-release and extended-release formulations was conducted following multiple-dose administration in healthy subjects. Two cohorts of subjects were evaluated. In the first cohort, healthy subjects (N=12) received multiple 15 mg QD doses of the extended-release tablet formulation and multiple 6 mg BID doses of the immediate-release capsule formulation for 7 days. In the second cohort, healthy subjects (N=12) received multiple 30 mg QD doses of the extended-release tablet formulation and multiple 12 mg BID doses of the immediate-release capsule formulation for 7 days. Both evaluations were conducted following an open-label, randomized, 2-period, 2-sequence, crossover design under fasting conditions. ABT-494 plasma concentrations were measured and pharmacokinetic parameters were calculated using non-compartmental analyses.
Results: At steady-state, ABT-494 AUC0–24 ratio [and 90% confidence interval] was 0.94 [0.84 – 1.05], C_{max} ratio was 0.91 [0.74 – 1.12] and C_{min} ratio was 1.09 [0.85 – 1.40] for the 15 mg QD regimen of the extended-release formulation relative to the 6 mg BID regimen of the immediate-release formulation. Similarly, ABT-494 mean $AUC_{0–24}$ ratio was 0.97 [0.87 – 1.09], C_{max} ratio was 0.90 [0.73 – 1.11] and C_{min} ratio was 0.87 [0.75 – 1.02] for the 30 mg QD regimen of the extended-release formulation relative to the 12 mg BID regimen. All evaluated regimens were well-tolerated by healthy subjects.
Conclusions: ABT-494 regimens of 15 mg QD and 30 mg QD of the extended-release formulation, currently being utilized in Phase 3 RA studies, provide similar exposures to 6 mg BID and 12 mg BID, respectively of the immediate-release capsule formulation previously shown to provide optimal benefit-risk profiles in RA Phase 2 trials.
Disclosure of Interest: M.-E. Mohamed Shareholder of: AbbVie, Employee of: AbbVie, J. Zeng Shareholder of: AbbVie, Employee of: AbbVie, I.-H. Song Shareholder of: AbbVie, Employee of: AbbVie, A. Othman Shareholder of: AbbVie, Employee of: AbbVie
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THU0178 LONG TERM SAFETY PROFILE OF METHOTREXATE IN PATIENTS WITH RA IN ROUTINE CARE

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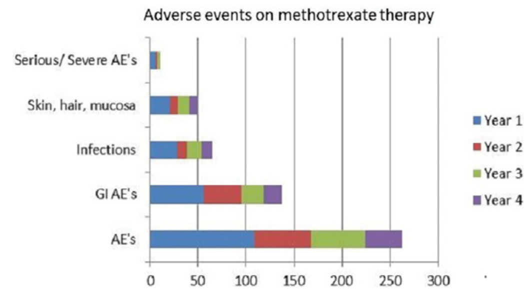
Background: Methotrexate is the anchor drug used most widely as monotherapy or combination therapy with other DMARDS & biologics in treatment of RA. It is widely perceived by clinicians to have potentially dangerous adverse effects (AE). The present study was designed to assess safety of long term methotrexate in patients with RA on standard care in clinical practice.
Objectives: To evaluate the safety of long term methorexate therapy in patients with RA
Methods: RA patients on methotrexate therapy at recommended doses (15–25 mg per week) as monotherapy or in combination with other conventional dmards or biologics for over 4 years were enrolled between Jan 2016 to Dec 2016. Since the objective was to assess safety, those patients initiated on methotrexate 4 years ago but had discontinued due to adverse effects were also included. Patients were analysed with a questionnaire and review of past records from the clinic. The questionnaire included questions about duration and compliance of methotrexate therapy, any untoward effects that patient felt were due to methotrexate and direct questions related to known methotrexate side effects. Investigations were reviewed from past records.Data were presented by 1- year intervals starting from the time patient received first dose of methotrexate. Adverse events (AE), rate of discontinuation and abnormal laboratory results were analysed per 100 patient (pt.) years in 1 year intervals.
Results:

Females, no. (%)	205 (89.9%)
Age, mean ± SD (years)	48.6 (±10.8)
Disease duration, mean ± SD (years)	8.4 (±5)
Seropositive (RF and/ or ACPA)	207 (91%)
Methotrexate monotherapy (%)	55 (24%)

The cumulative exposure to methotrexate was 926 patient years. Of 228 patients, 218 continued methotrexate through 4 years. Overall 10 patients discontinued methotrexate over 4 years, 5 due to GI intolerance and 1 due skin allergy in the first year. In subsequent years 2 patients were withdrawn due to chronic cough, 1 due to raised transaminases and 1 patient after severe infection and pancytopenia. Incidence of AEs, severe AEs, infections, laboratory abnormalities and discontinuations due to AE's declined during 4 years exposure. The most common AEs included nausea and dyspepsia (24.6/ 100 pt. years in first year with declining incidence through 4 years). The second most common AE reported was infections (7/100 pt. years). Most common infections were mild UTI & respiratory tract infections.14 patients initially asymptomatic or having mild nausea reported significantly increased nausea in year 4 and beyond, all responding to reduction of methotrexate dose. The incidence of severe AE that needed hospitalisation &/ or discontinuation of methotrexate was 2.6/100 pt. years in year 1 with declining events over time. The cumulative risk of serious AE over 4 years was 1.2/ 100 pt. years.



Conclusions: Methotexate therapy was well tolerated over 4 years treatment period with a good safety profile. Most of the AE's were mild to moderate severity not needing discontinuation of methotrexate. Study has limitations since it is retrospective observational study with small patient number from two outpatient rheumatology clinics. Some AE's may have been underestimated as patient compliance not ascertained and patients with AE's may have lost to follow up. Some effects may have been overestimated as precise causality is not proven. During the 4 years methotrexate treatment, no new safety concerns emerged.
Disclosure of Interest: None declared
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THU0179 INCIDENCE OF DEEP VEIN THROMBOSIS AFTER TOTAL HIP REPLACEMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: The purpose of this study was to compare incidences of VTE in patients with rheumatoid arthritis (RA) and osteoarthritis (OA) after total hip arthroplasty, different strategies for prevention of VTE and evaluate their efficiency.
Objectives: To evaluate the efficiency of prevention of VTE in patients with rheumatoid arthritis and osteoarthritis after total hip replacement under comparable conditions.
Methods: A one-year prospective cohort study was performed on 173 primary THA patients operated in V.A. Nasonova Research Institute of Rheumatology for the period 2016. Of these, 91 patients with RA (52.6%) and 82 patients with OA (47.4%). For a comparative analysis of the efficiency of anticoagulant therapy, each patient group was divided into 2 subgroups by type of drug therapy. The first - nadroparin calcium (the drug therapy was started for 12 hours after the operation at a dose of 0.1 ml per 10 kg of body weight one time per day), the second - nadroparin calcium with transfer to dabigatran etexilate (the first stage of 4 hours after the operation was started therapy by nadroparin calcium, and then after the removal of the epidural catheter moved to the dabigatran etexilate).Doppler ultrasonography (DUS) was routinely performed preoperatively and on postoperative day 7, 14, then 1 time a month for diagnosing a deep venous thrombosis (DVT). Time of observation was 6 months.
Results: DVT were reported in 8 (4.8%) patients, 2 of them (1.2%) with RA and 6 (3.4%) with OA. Distal DVT developed on 8 and 17 days after total hip replacement in RA patient's group. They received nadroparin calcium only. 5 patients with VTE after surgery from OA group used nadroparin calcium and 1 patient was on combined drug therapy. Of the 8 cases of VTE - 6 (75%) were asymptomatic and 2 (25%) with development of clinical and laboratory picture. All cases of thrombosis in a group of RA was asymptomatic. In a perioperative period of clinically significant bleeding was not seen.
Conclusions: Cases of VTE in patients with RA, despite the large number of risk factors, under comparable conditions is significantly lower than patients with OA. The number of asymptomatic DVT dominates symptomatic both comparison groups. In patients with RA and OA who were from the first group have reported 6 cases of VTE and only 1 case of VTE have reported in patients who were from second group. Prevention of VTE by combination of LMWH and NOACs was more effective and safety in RA and OA patients.
Disclosure of Interest: None declared
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THU0180 SYSTEMS BASED INVESTIGATION OF THE ANTI-IMMUNOGENIC POTENTIAL OF DMARDS FOR RHEUMATOID ARTHRITIS USING HUMAN PRIMARY CELL-BASED BIOMAP® PHENOTYPIC PROFILING

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Background: Biologics represent a rapidly growing class of approved and investigational drugs routinely used to treat multiple diseases, including inflammatory and rheumatic diseases[1]. Unfortunately, the success of such therapeutics is undermined by their immunogenicity and the development of anti-drug antibodies (ADA) associated with treatment failure and hypersensitivity reactions[2]. Methotrexate (MTX) has been shown to reduce the generation of an ADA response[3]. The ability of other conventional synthetic Disease Modifying Anti-Rheumatic Drugs (csDMARDs) to mitigate unwanted immunogenicity, and prolong efficacy in patients who cannot tolerate methotrexate, is less clear.

Objectives: We previously reported that MTX markedly inhibited the production and release of soluble immunoglobulin (sIgG) by human primary B cells co-cultured with PBMC (BT system) in the *in vitro* BioMAP® phenotypic screening panel[4,5]. MTX also had anti-proliferative effects on human primary tissue and immune cell types[6]. We evaluated other csDMARDs to determine if they were broadly active or, were more similar to MTX in selectively blocking sIgG production and therefore would be more likely to reduce ADA associated with biologics.

Methods: A series of csDMARDS (sulfasalazine, hydroxychloroquine, cyclosporine, leflunomide and azathioprine) were profiled at 4 concentrations across the BioMAP Diversity PLUS™ panel to generate phenotypic activity profiles. In addition to assessing sIgG production, effects on a broad scope of disease-relevant readouts related to primary cell activation and proliferation, inflammation, wound healing, tissue/matrix remodeling, and fibrosis were also evaluated.

Results: Similar to MTX, cyclosporine, leflunomide and azathioprine strongly inhibited sIgG production at all tested concentrations. In contrast, treatment with sulfasalazine or hydroxychloroquine did not decrease sIgG indicating these compounds may not mitigate the immunogenicicty of biologics. In contrast to MTX, several csDMARDS were broadly active in many BioMAP systems. Bioinformatics analysis was used to identify distinct mechanistic signatures for these agents in the BioMAP Panel.

Conclusions: These results support application of the BioMAP *in vitro* assay systems, widely utilized for preclinical drug discovery, to determine the suitability of csDMARDS as anti-immunogenic co-treatments to extend the clinical efficacy of biologics. Clinical studies are needed to confirm these results, however, in inflammatory bowel diseases and to a less extent in rheumatoid arthritis, azathioprine has been shown to reduce immunogenicity of biologics[7].

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THU0181 CLINICAL CHARACTERISTICS OF RHEUMATOID ARTHRITIS PATIENTS ONGOING METHOTREXATE THERAPY NOT ACHIEVING DAS28 "LOW DISEASES ACTIVITY": A MATCHED CASE-CONTROL ANALYSIS FROM THE MARI STUDY

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Background: Methotrexate (MTX) is the DMARD of first choice in the treatment of rheumatoid arthritis (RA).

Objectives: To investigate the clinical characteristics and describe therapeutic approaches in RA patients ongoing MTX not achieving a DAS28 "low disease activity" score.

Methods: This is a case-control analysis including 186 patients (mean age±SD, 61±12 years, 16% males) who did not achieve a DAS28 "low disease activity" score (defined by a value $\leq$3.2) and 558 age- and gender-frequency-matched (1:3), randomly selected controls (mean age age±SD, 61±13 years) who achieved a DAS28 "low disease activity" from the original cohort investigated in the MARI study. The MARI study enrolled RA patients on treatment for at least 12-month with MTX. Demographic, clinical, laboratory and pharmacological characteristics of patients recorded at baseline visit were considered for the current analysis. We first compared the characteristics of patients who reached the endpoint with those of subjects who did not by univariate analyses, thereafter, we performed a multivariate model to identify predictors of not achieving the endpoint. We further investigated the therapeutic approaches in patients not achieving the endpoint.

Results: Compared to patients with a DAS28 $\leq$3.2, subjects not achieving the endpoint presented with a significant higher (mean±SD) weight and BMI (DAS28 $\leq$3.2: 25±4 versus DAS28 $>$3.2: 26±5, P=.022), and longer duration of symptoms (months±SD) before the RA diagnosis (11±15 versus 15±20, P=.009). A higher proportion of subjects within the group not achieving the endpoint presented with polyarticular disease (DAS28 $\leq$3.2: 57% versus DAS28 $>$3.2: 96%, P$<$.001), erosive arthritis (49% versus 73%, P$<$.001), extra-articular symptoms (3% versus 10%, P$<$.001), positive RF test (63% versus 73%, P=.013), and increased CRP (13% versus 53%, P$<$.001). The proportion of patients treated with oral MTX was 25% in the subgroup with DAS28 $\leq$3.2 and 15% in the subgroup with DAS28 $>$3.2 (P=.004). In the logistic regression analysis, the variables predictive of a DAS28 $>$3.2 were polyarticular disease (OR 4.0, 95% CI 2.4–6.7, P$<$.001), erosive arthritis (OR 2.2, 95% CI 1.4–3.4, P$<$.001), and increased CRP (OR 7.4, 95% CI 4.9–11.4, P$<$.001). In patients who did not reach the endpoint, the main therapeutic strategies were: a change in the route of administration of MTX (DAS28 $>$3.2: 13% versus DAS28 $\leq$3.2: 4%, P$<$.001) in favor of subcutaneous MTX, an increase of the dose of MTX (13% versus 2%, P$<$.001), and the prescription of a new biologic (12% versus 1%, P$<$.001).

Conclusions: Our results identified a number of variables potentially associated the risk of not achieving a DAS28 "low disease activity" score in RA patients ongoing MTX treatment. Longitudinal studies are warranted.

Disclosure of Interest: None declared

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THU0182 MONOTHERAPY WITH THE JAK1-SELECTIVE INHIBITOR FILGOTINIB DISPLAYS AN ANTI-INFLAMMATORY BIOMARKER PROFILE IN RHEUMATOID ARTHRITIS PATIENTS

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Background: Janus kinases (JAKs) are key proteins in the signal transduction of many cytokines and growth factors. The selective JAK1 inhibitor filgotinib (GLPG0634, GS-6034) has been evaluated in a 24-week phase 2B study (DARWIN 2) as monotherapy in active rheumatoid arthritis (RA) patients with inadequate response to methotrexate and has shown a good safety and efficacy profile[1].

Objectives: To gain insight into filgotinib mode of action as monotherapy in RA patients by analysing the impact of filgotinib on a broad panel of immune modulators in the serum.

Methods: RA patients received either placebo (PBO), or filgotinib monotherapy at 50mg, 100mg or 200mg once daily (QD). Serum samples were collected at baseline, week 4 and week 12 and analysed using the 18-plex bead-based immunoassay (HSTCMAG-28SK Merck-Millipore) on BioPLEX-200 instrument to measure cytokine concentration. Median % change from baseline for biomarkers are reported for week 4 and 12. Wilcoxon rank-sum test assessed the significance of difference between filgotinib treated groups and PBO.

Results: Following treatment with filgotinib at 100 mg QD and 200mg QD, there were significant reductions in cytokines important in expansion and activity of multiple T cell subsets and innate immunity compared to PBO (see Table). These changes include decreases in proinflammatory cytokines (IL-6, IL-1β, and TNFα), T_H1-related (IL-2, IFN-γ and IL-12), T_H2-related (IL-4, IL-5, and IL-13) and T_H17-related cytokines (IL-1β, IL-6, IL-17A, IL-21 and IL-23). All doses of

Table 1. Median percent change of biomarkers from baseline

	Week 4			Week 12		
	PBO (N=61)	Filgotinib 100mg QD QD (N=62)	Filgotinib 200mg QD (N=65)	PBO (N=61)	Filgotinib 100mg QD (N=63)	Filgotinib 200mg QD QD (N=65)
GM-CSF	0	-11***	-9***	6	-11***	-21***
IFN-γ	13	-15***	-13***	6	-21***	-23***
IL-1β	6	-10**	-13***	8	-24***	-16***
IL-2	4	-9**	-13***	10	-22***	-21***
IL-4	10	-8***	-8***	21	-17***	-22***
IL-5	2	-10**	-3*	3	-20***	-14***
IL-6	17	-20**	-35***	-13	-34*	-52***
IL-7	2	-10***	-1^{NS}	0	-22***	-21**
IL-8	1	-1^{NS}	-1^{NS}	-7	-4^{NS}	-8^{NS}
IL-10	6	-12***	-17***	13	-18***	-26***
IL-12	8	-7***	-14***	6	-20***	-23***
IL-13	1	-10**	-13**	13	-8***	-20***
IL-17A	7	-9***	-12***	1	-21***	-16**
IL-21	11	-14***	-10***	4	-26***	-23***
IL-23	3	-12***	-12***	-4	-24***	-31***
MIP-1α	5	-5***	-8***	3	-7***	-6**
MIP-1β	3	-6**	-6*	3	-5^{NS}	3^{NS}
TNF-α	5	-7***	-12***	5	-11**	-14**

P values comparing % changes between filgotinib and PBO groups: NS p$>$0.05; *p$<$0.05; **p$<$0.01; ***p$<$0.001.