A PROSPECTIVE STUDY OF TAPERING CONVENTIONAL DISEASE MODIFYING ANTI-RHEUMATOID DRUGS (c-DMARDs) IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA) IN STABLE REMISSION

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Background: Remission in RA is being achieved more often nowadays with effective early aggressive therapy with DMARDs. Studies ((1 2 3 4)) have shown it is possible to taper and stop biologic DMARDs in patients with RA in stable remission. However there are no such studies or recommended protocols for c-DMARDs treated patients.

Objectives: To study the incidence and timing of flares in RA patients in sustained remission of at least 6 months duration on slow withdrawal of c-DMARDs and to identify predictors of flares.

Methods: Consenting adult (age >18 years) RA patients satisfying the ACR 2010 criteria attending our outpatient department with a disease duration of minimum 1 year and a stable remission (CDAI <2.8) were included. Patients receiving steroids or biologics were excluded.

Protocol for tapering: On monotherapy: 50% dose reduction 3 weekly and stop eventually
On combination therapy: sequential dose reduction as monotherapy followed by stoppage of cDMARDs(in order from first to last: hydroxychloroquine, sulphasalazine, leflunomide, methotrexate)
Fibre was defined as CDAI >2.8. Number of RA flares and timing of flares were noted. Predictors of flare were analysed using univariate and multivariate regression

Results: 66 patients satisfied inclusion criteria of which 5 did not consent, 5 committed protocol violation and 2 lost to follow up. Total 54 patients were included in the final analysis. 42 patients (77.78%) flared during the study period. Of these 42 patients, 29(69.05%) flared whilst on the tapering protocol whereas, 13 (30.95%) flared after complete withdrawal of c-DMARDs. 20 patients (47.62%) flared during the study period. Of these 42 patients, 29(69.05%) committed protocol violation and 2 lost to follow up.

Conclusion: UPA both as monotherapy, and in combination with background MTX, was effective in inhibiting the progression of structural joint damage through Week 48 in MTX-naive, and MTX-IR patients, respectively.

REFERENCES:

Acknowledgement: AbbVie, Inc was the study sponsor, contributed to study design, data collection, analysis, interpretation, writing, reviewing, and approval of the final version of the abstract. Medical writing support: Siddharth Mukherjee, PhD, from Abbvie, Inc.

Disclosure of Interests: Charles Peterly Shareholder of: Spire Sciences, Inc, Consultant for: AbbVie, Acerta, Amgen, AstraZeneca, Bristol-Myers Squibb, Centervion, Dalichi Sankyu, Five Prime Therapeutics, Genentech, Hoffmann-La Roche, Janssen, Lilly USA, Medimmune, Merck, Novartis, Plexikon, Pfizer, Sanofi, Salix-Santarus, Samsung, Employee of: Spire Sciences, Inc, Speakers bureau: Amgen, Mark C. Genovese Grant/ research support from: Sanofi/Genzyme, Genentech/Roche, RPharm, Consultant for: Sanofi/Genzyme, Genentech/Roche, RPharm, In-Ho Song Shareholder of: AbbVie Inc, Employee of: AbbVie Inc, Alan Friedman Shareholder of: AbbVie, Employee of: AbbVie, Stephen Hall Grant/ research support from: AbbVie Inc, BMS, Lilly, Janssen, Pfizer, UCB, and Novartis, Consultant for: AbbVie Inc, BMS, Lilly, Janssen, Pfizer, UCB, and Novartis, Eduardo Mysler Grant/research support from: AbbVie, Bristol-Myers Squibb, Eli Lilly, Pfizer, Novartis, Janssen, research support from: AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Medimmune, Pfizer Inc and Roche, Consultant for: AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Medimmune, Pfizer Inc and Roche, Speakers bureau: AbbVie, Bristol-Myers Squibb, Eli Lilly, Pfizer, Novartis, Janssen, Speakers bureau: AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Medimmune, Pfizer Inc and Roche, Patrick Durez Speakers bureau: Bristol-Myers Squibb, Eli Lilly, Sanofi, Celltrion, Xenofon Baraliakos Grant/research support from: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Centocor, Chugai, Janssen, MSD, Novartis, Pfizer Inc, Roche and UCB, Grant/ research support from: AbbVie, Pfizer, Merck Sharp & Dohme, UCB Pharma, Novartis, Consultant for: AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Chugai, Janssen Biologics, Novartis, Pfizer, UCB Pharma, Galapagos, Speakers bureau: AbbVie, Chugai, Janssen, Novartis, Pfizer, UCB Pharma, Jose Jeffrey Enejosa Shareholder of: AbbVie Inc, Employee of: AbbVie Inc, Tim Shaw Shareholder of: AbbVie Inc, Employee of: AbbVie Inc, Yihan Li Shareholder of: AbbVie, Employee of: AbbVie, Su Chen Shareholder of: AbbVie Inc, Employee of: AbbVie Inc, Vibeke Strand Consultant for: AbbVie, Amgen, Bayer, BMS, Boehringer Ingelheim, Celgene, Chugai, Genentech/Roche, GSK, Horizon, Inmedix, Janssen, Kezar, Lilly, Merck, Novartis, Pfizer, Regeneron, Samsung, Sandoz, Sanofi, Servier, UCB.


THU0189

Table 1.

Abstract THU0189 – Table 1.

Table: Radiographic Progression at Week 48 in MTX-naive (LE and AO) and COMPARE. Following the switch of all PBO pts to UPA in COMPARE by Week 26, no further change in mean mTSS was observed through Week 48 (AO, Table). The inhibition of radiographic progression vs comparators was not only observed for the overall mTSS scores but also for all the components of JSN and ES in both RCTs (LE and AO).

Conclusion: UPA both as monotherapy, and in combination with background MTX, was effective in inhibiting the progression of structural joint damage through Week 48 in MTX-naive, and MTX-IR patients, respectively.

REFERENCES:
THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF BMS-986166, A NOVEL, SELECTIVE, PARTIAL AGONIST OF THE SPHINGOSINE-1-PHOSPHATE (S1P) SUBTYPE 1 RECEPTOR IN HEALTHY PARTICIPANTS

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Background: S1P mediates a number of immune processes including the egression of lymphocytes from lymphoid organs via stimulation of the S1P subtype 1 receptor (S1P1R). S1P1R inhibition has the potential to suppress abnormal immune responses and modulate autoimmune inflammatory diseases. BMS-986166, a novel, selective partial agonist of S1P1R, which is phosphorylated in vivo to its pharmacologically active form, BMT-121795, may have utility for the treatment of autoimmune and/or inflammatory diseases.

Objectives: To investigate safety, pharmacokinetics (PK), and pharmacodynamics (PD) of BMS-986166 in single- and multiple-ascending dose (SAD/MAD) placebo (PBO)-controlled studies in healthy participants.

Methods: SAD study (NCT02790125): BMS-986166 was administered as a single dose of 0.75, 2.0, or 5.0 mg (n=10/group; 4:1 ratio of BMS-986166/PBO); a series of upwardly titrated single daily doses of 0.25, 0.5, 0.75, 1.0, then 1.5 mg over 14 days (n=16; 3:1 ratio); or as a single 2.0-mg dose in participants who were fed, fasted, or administered famotidine prior to dosing (n=8/group). MAD study (NCT03039871): BMS-986166 was administered as once-daily doses of 0.25 (n=12; 2:1 ratio), and 0.75 or 1.5 mg (n=10/dose; 4:1 ratio), for 28 days. Safety, PK, and PD (absolute lymphocyte count [ALC]) were assessed. Cardiac safety was assessed by continuous cardiac monitoring and at intervals by 12-lead electrocardiogram.

Results: 70 (80 BMS-986166, 10 PBO; mean [standard deviation (SD)] age: 32.8 [8.5] years) and 32 (24 BMS-986166, 8 PBO; mean [SD] age: 35.8 [8.6] years) participants were randomised to dosing in the SAD and MAD studies, respectively. Participants were predominantly male. Mean (SD) body mass index was 26.8 (2.9) and 27.2 (2.5) kg/m², respectively. Multiple oral doses of BMS-986166 up to 1.5 mg daily for 28 days were generally well tolerated, and all treatment-related adverse events were mild (Grade 1). In the MAD (Figure 1) and SAD studies, a clinically insignificant, dose-related decrease in mean hourly heart rate (HR) was observed following administration of BMS-986166 compared with PBO, based on a time-matched analysis of nominal hourly HR data from continuous cardiac monitoring over 72 hours post dose. Compared with participants receiving PBO, a mean decrease from baseline in hourly HR was apparent for participants in the 2 higher dose panels (2.0 mg, 5.0 mg) in the SAD study. In the SAD study, the largest decreases in PBO-corrected, time-matched, nadir hourly HR were –0.29, –6.38, and –8.37 bpm for the 0.75, 2.0, and 5.0 mg dose panels, respectively. Similarly, in the MAD study, these numbers were –0.83, –3.46, and –5.54 bpm at the 0.25, 0.75, and 1.5 mg dose levels, respectively. Increases in systemic plasma exposure (maximum concentration and area under the curve from time 0–24 hours) of BMS-986166 and its active metabolite BMT-121795 were approximately proportional to dose increases over the range of 0.75–5 mg with single doses, and of 0.25–1.5 mg on Days 1, 14, and 28 with multiple doses. Decreases in percent change from baseline in ALC in ALC with multiple doses of BMS-986166 vs PBO were dose-related over the 28-day treatment period. Between Day 0 and 35, median (range) nadir in lymphocyte reductions were 53.7% (31.7–55.9%), 75.9% (63.3–85.8%), and 81.9% (37.9–92.2%) at 0.25, 0.75, and 1.5 mg BMS-986166 dose levels, respectively. Recovery of ALC levels began 14, 14–21, and 7 days after the last dose of 0.25, 0.75, and 1.5 mg, respectively, on Day 28.

Disclosure of Interests: None declared

THU0190 – Figure 1

Abstract THU0190 – UPADACITINIB AS MONOTHERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS: RESULTS AT 48 WEEKS FROM THE SELECT-MONOTHERAPY STUDY

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Background: In the SELECT-MONOTHERAPY trial, upadacitinib (UPA), an oral JAK1-selective inhibitor, showed efficacy when used as monotherapy over 14 weeks (wks) in rheumatoid arthritis (RA) patients (pts) with an inadequate response to methotrexate (MTX).

Objectives: Safety and efficacy of UPA monotherapy were assessed through 48 wks in an ongoing long-term extension period of SELECT-MONOTHERAPY.

Methods: At baseline (BL), pts on stable MTX were randomized to either continue MTX (cMTX, given as a blinded study drug) or switch to once-daily (OD) UPA at 15 (UPA15) or 30 mg (UPA30) monotherapy for 14 wks. From Wk14, the start of a long-term blinded extension, pts randomized to cMTX were switched to UPA15 or 30 mg per pre-specified assignment at BL, pts randomized to UPA15 or 30 continued their initial treatment. No dose adjustments for UPA were allowed. Starting at Wk26, for pts who did not achieve CDAI ≤10, background csDMARDs could be initiated. Efficacy data up to the Wk48 visit are reported “As Observed”. Adverse events (AE) per 100 pt yrs (PYs) are summarized up to May 25 2018.

Results: Of 648 pts randomized at BL, 598 (92%) completed 14 wks and continued on to the extension period. By May 25 2018, 16% discontinued study drug; 5% due to AE, 0.5% due to lack of efficacy, 4% withdrew consent, 1% were lost to follow-up, and 6% due to other reasons. Cumulative exposures to UPA15 and UPA30 were 336.0 PYs and 337.1