21A102

Integrated Laboratory Abnormality Profiles of Upadacitinib With Up to 4.5 Years of Exposure in Patients With Rheumatoid Arthritis Treated in the SELECT Phase 3 Program

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Irish Society of Rheumatology 30th of September to the 1st of October 2021

OBJECTIVE

To describe the long-term laboratory profiles associated with exposure to UPA, ADA, and MTX in patients with RA treated in the SELECT trials

BACKGROUND

Safety and efficacy of Upadacitinib (UPA), an oral Janus kinase inhibitor approved for rheumatoid arthritis (RA), was evaluated across a spectrum of patients (pts) with RA in the phase 3 SELECT clinical program.[1,2,3]

METHODS

Laboratory data from 6 randomized controlled UPA RA trials were analysed (Table 1).
The proportions of pts experiencing potentially clinically significant changes (single time-point) were summarised for the following1,2:

- pooled UPA 15 mg once daily (QD) (UPA15; 6 trials),
- pooled UPA 30 mg QD (UPA30; 4 trials),
- ADA 40 mg every other week (1 trial),
- MTX monotherapy (1 trial).

Pts received UPA with/without background conventional synthetic disease-modifying antirheumatic drugs.
Treatment-emergent adverse events are reported as exposure-adjusted event rates (events/100 pt-years [E/100PY]).
Toxicity was graded per OMERACT criteria, or NCI CTCAE for creatine phosphokinase (CPK) and creatinine.

Table 1. Overview of UPA Phase 3 clinical program

Overview of UPA Phase 3 clinical program[1]

Cut-off date: June 30, 2020	MTX monotherapy (n=314)	ADA 40 mg EOW + MTX (n=579)	UPA 15 mg QD pooled (n=3209)	UPA 30 mg QD pooled (n=1204)
MTX-naïve (n=945)	✓		✓	✓
csDMARD-IR (n=661)			✓	✓
MTX-IR (n=648)			✓	✓
MTX-IR (n=1629)		✓	✓	
bDMARD-IR (n=498)			✓	✓
bDMARD-IR (n=612)			✓	
Exposure				
PY	637.4	1051.8	7023.8	3091.6
Mean (SD), weeks	106 (67)	95 (70)	114 (64)	134 (66)
Median (range), weeks	144 (1, 221)	118 (2, 231)	136 (0, 232)	160 (0, 231)

ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EOW, every other week; IR, inadequate responder; MTX, methotrexate; PY, patient-years; QD, once daily; RA, rheumatoid arthritis; SD, standard deviation; UPA, upadacitinib

RESULTS

CPK elevations were more frequent with UPA compared with MTX monotherapy and ADA 40 mg EOW + MTX (Figure 1)

Most events were asymptomatic, and one case of rhabdomyolysis in a patient receiving UPA 30 mg QD was considered not related to study drug (attributed to influenza) (Figure 1)

Rates of anaemia, as reported by the investigator, were comparable between UPA 15 mg QD, ADA and MTX groups (Figure 1)

Discontinuations as a result of anaemia, lymphopenia, neutropenia, creatinine elevations, and CPK elevations, were low (≤0.2%) in all arms (Table 3)

Incidence of Grade 3 or 4 laboratory parameters with UPA 15 mg QD was similar to or less than MTX monotherapy or ADA 40 mg EOW + MTX, with the exception of CPK elevations (Table 4)

Over the first 24-month period, incidence of Grade 3/4 hemoglobin levels was lower in UPA 15 mg QD and ADA 40 mg EOW + MTX treatment arms compared with UPA 30 mg QD or MTX monotherapy arms (Figure 4)

Over any 12-month period, incidence of Grade 3/4 CPK elevations was higher in UPA treatment groups compared with ADA 40 mg EOW + MTX or MTX monotherapy (Figure 3)

Over any 12-month period, incidence of Grade 3/4 neutrophil levels was higher in the UPA 30 mg QD treatment group compared with UPA 15 mg QD, ADA 40 mg EOW + MTX, and MTX monotherapy (Figure 5)

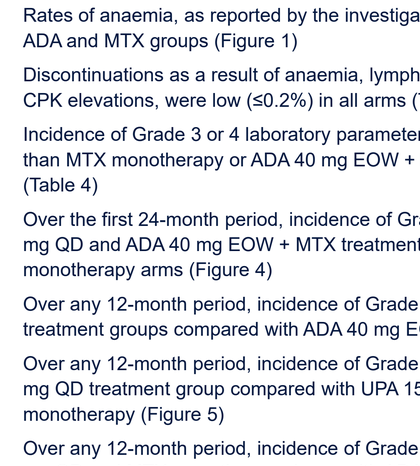
Over any 12-month period, incidence of Grade 3/4 lymphocyte levels was similar with UPA 15 mg QD and MTX monotherapy, lower with ADA 40 mg EOW + MTX, and highest with UPA 30 mg QD (Figure 6)

Table 2. Baseline Characteristics

Mean (SD), unless otherwise stated	MTX monotherapy (n=314; 637.4 PY)	ADA 40 mg EOW + MTX (n=579; 1051.8 PY)	UPA 15 mg QD pooled (n=3209; 7023.8 PY)	UPA 30 mg QD pooled (n=1204; 3091.6 PY)
Age, years	53.3 (12.9)	54.1 (11.7)	54.3 (12.0)	55.3 (11.9)
Female, n (%)	240 (76.4)	470 (81.2)	2581 (80.4)	948 (78.7)
Time since RA diagnosis, years	2.6 (5.1)	8.2 (8.0)	8.5 (8.4)	7.0 (8.3)
Concomitant csDMARDs, n (%)	N/A	578 (99.8)	2548 (79.4)	561 (46.6)
Concomitant steroids, n (%)	162 (51.6)	349 (60.3)	1761 (54.9)	570 (47.3)
Prior bDMARD use, n (%)	0	57 (9.8)	979 (30.5)	281 (23.3)
Seropositive (RF or ACPA), n (%)	255 (81.2)	497 (85.8)	2707 (84.4)	948 (78.7)
CRP, mg/L	21.2 (22.1)	14.2 (20.5)	17.8 (21.6)	15.9 (19.8)
DAS28-CRP[a]	5.9 (1.0)	5.2 (1.3)	5.8 (1.0)	5.4 (1.2)
History of CV event[b], n (%)	27 (8.6)	62 (10.7)	383 (11.9)	144 (12.0)
History of tobacco/nicotine use (current + former)	120 (38.2)	199 (34.4)	1221 (38.0)	509 (42.3)
Statin use	26 (8.3)	55 (9.5)	369 (11.5)	169 (14.0)
Hemoglobin[c], g/L	130.5	130.0	129.8	130.3
Neutrophils[d], 10^9/L	5.9	5.9	5.5	5.4
Lymphocytes[d], 10^9/L	1.9	1.8	1.8	1.8
CPK[e], U/L	75.5	67.6	84.8	83.8

[a]n=577 (ADA + MTX); n=3194 (UPA 15 mg); n=1199 (UPA 30 mg). [b]This includes any CV events (both MACE and other CV events). [c]n=312 (MTX); n=325 (ADA + MTX); n=3201 (UPA 15 mg); n=1193 (UPA 30 mg). [d]n=312 (MTX); n=325 (ADA + MTX); n=3201 (UPA 15 mg); n=1192 (UPA 30 mg). [e]n=312 (MTX); n=326 (ADA+ MTX); n=3199 (UPA 15 mg); n=1196 (UPA 30 mg).
ACPA, anti-citrullinated protein antibody; CPK, creatine phosphokinase; CRP, C-reactive protein; CV, cardiovascular; DAS28-CRP, 28-joint Disease Activity Score using C-reactive protein; MACE, major adverse cardiovascular event; RF, rheumatoid factor; SD, standard deviation

Figure 1: TEAE'S OF Special Interest in Patients Treated with UPA, MTX, and ADA



UPA 15 mg: n=3209, PY=7023.8; UPA 30 mg: n=1204, PY=3091.6; ADA + MTX: n=579, PY=1051.8; MTX monotherapy: n=314, PY=637.4. Laboratory-related AEs of special interest were defined using standardized MedDRA query or company MedDRA query search criteria and reported per investigator's judgment.
AE, adverse event; CI, confidence interval; E/100 PY, event per 100 patient-years; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

RESULTS continued

Table 3. Patients Who Discontinued UPA, ADA, or MTX Due to Abnormal Laboratory Parameters

Discontinuations due to abnormal laboratory parameters, %	MTX monotherapy (n=314; 637.4 PY)	ADA 40 mg EOW + MTX (n=579; 1051.8 PY)	UPA 15 mg QD pooled (n=3209; 7023.8 PY)	UPA 30 mg QD pooled (n=1204; 3091.6 PY)
Any AE	2.2	0.7	0.8	2.0
Hemoglobin decreased	0	0.2	0.1	0.2
WBC count decreased	0	0	0	<0.1
Neutrophil count decreased	0	0	0	<0.1
AST increased	1.3	0.3	0.3	0.6
ALT increased	1.3	0.3	0.3	0.8
Blood creatinine increased	0	0	0.2	0.2
Blood CPK increased	0	0	<0.1	0.2

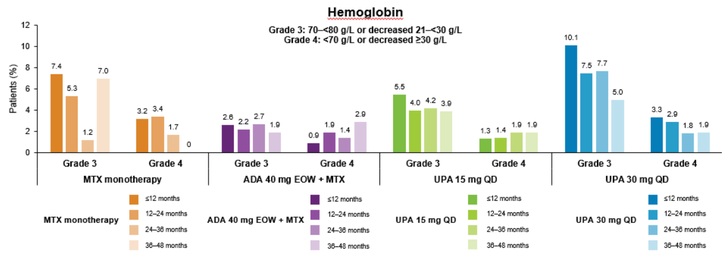
MTX monotherapy includes MTX monotherapy exposure from start and censored at time of rescue to UPA + MTX. Laboratory-related AEs of special interest were defined using standardized MedDRA query or company MedDRA query search criteria and reported per investigator's judgment.
ALT, alanine aminotransferase; AST, aspartate transaminase; WBC, white blood cell

Table 4. Patients with Grade 3/4 Laboratory Parameters

Parameter, %	MTX monotherapy (n=314; 637.4 PY)	ADA 40 mg + MTX EOW (n=579; 1051.8 PY)	UPA 15 mg QD pooled (n=3209; 7023.8 PY)	UPA 30 mg QD pooled (n=1204; 3091.6 PY)
Hemoglobin, g/L				
Gr 3 (70–<80 or decreased 21–<30)	9.0[a]	4.2[b]	7.9[d]	14.2[f]
Gr 4 (<70 or decreased ≥30)	5.1[a]	2.8[b]	3.2[d]	6.5[f]
Neutrophils, 10^9/L				
Gr 3 (0.5–<1.0)	1.0[a]	0.5[b]	1.2[d]	3.1[g]
Gr 4 (<0.5)	0.3[a]	0.2[b]	0.3[d]	0.4[g]
Lymphocytes, 10^9/L				
Gr 3 (0.5–<1.0)	23.7[a]	9.2[b]	25.1[d]	35.5[g]
Gr 4 (<0.5)	1.6[a]	0.5[b]	2.3[d]	3.9[g]
ALT, U/L				
Gr 3 (3.0–8.0 × ULN)	8.3[a]	2.3[c]	4.8[e]	5.9[h]
Gr 4 (>8.0 × ULN)	1.6[a]	0.7[c]	0.8[e]	0.8[h]
AST, U/L				
Gr 3 (3.0–8.0 × ULN)	4.8[a]	1.6[c]	3.2[e]	3.0[h]
Gr 4 (>8.0 × ULN)	0.3[a]	0.9[c]	0.6[e]	0.7[h]
CPK, U/L				
Gr 3 (>5.0–10.0 × ULN)	0.6[a]	0.5[c]	2.0[e]	3.0[i]
Gr 4 (>10.0 × ULN)	0[a]	0.5[c]	0.8[e]	1.3[i]
Creatinine, µmol/L				
Gr 3 (>3.0–6.0 × ULN)	0[a]	0.2[c]	<0.1[e]	0.2[i]
Gr 4 (>6.0 × ULN)	0[a]	0.7[c]	0.3[e]	<0.1[i]

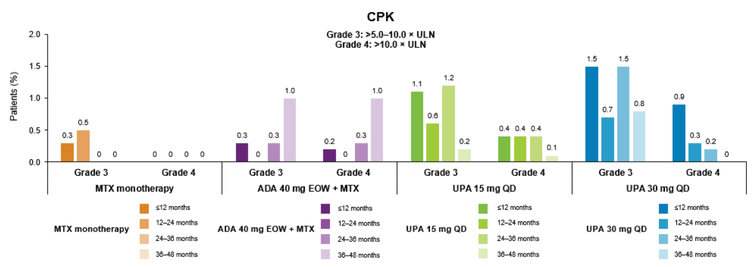
[a]n=312. [b]n=576. [c]n=577. [d]n=3201. [e]n=3199. [f]n=1193. [g]n=1192. [h]n=1195. [i]n=1196. [j]n=1197
Toxicity grading scale is based on OMERACT criteria. For CPK and creatinine, NCI standard CTC grading methodology was used. Post-baseline Grade must be higher than baseline Grade.
CTC, common terminology criteria; Gr, Grade; NCI, National Cancer Institute; ULN, upper limit of normal

Figure 2. Patients with Grade 3/4 Hemoglobin Levels by 12-Month Time Intervals



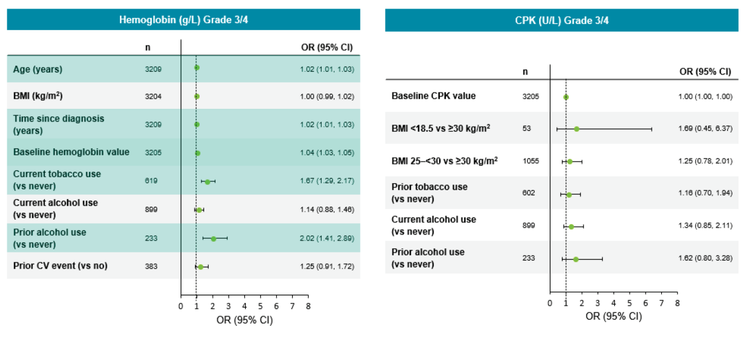
Toxicity grading scale is based on OMERACT criteria. Post-baseline Grade must be higher than baseline Grade

Figure 3. Patients with Grade 3/4 CPK elevations by 12-Month Time Intervals



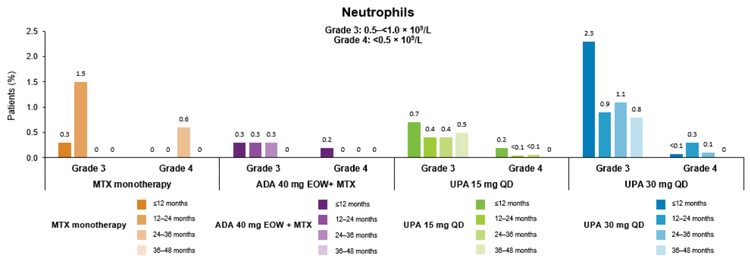
NCI standard CTC grading methodology was used. Post-baseline Grade must be higher than baseline Grade

Figure 4. Risk Factors of Interest for Grade 3/4 Hemoglobin and CPK with UPA 15mg QD



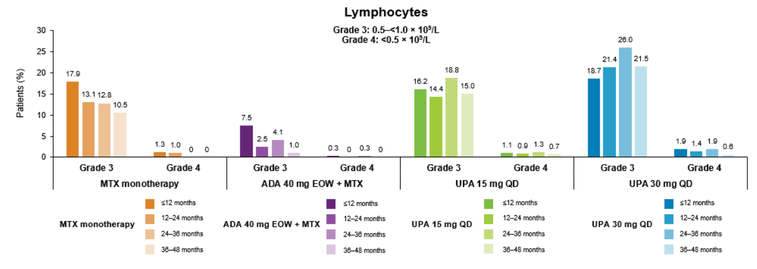
A univariate logistic regression model was used to assess risk factors
BMI, body mass index; OR, odds ratio

Figure 5 Patients with Grade 3/4 Neutrophil Levels by 12-Month Time Intervals



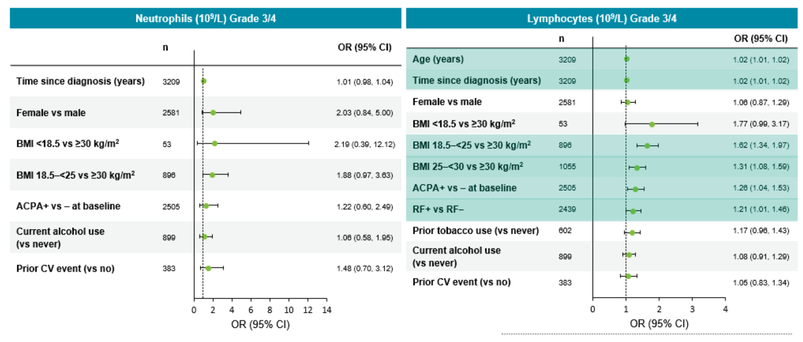
Toxicity grading scale is based on OMERACT criteria. Post-baseline Grade must be higher than baseline Grade

Figure 6. Patients with Grade 3/4 Lymphocyte Levels by 12-Month Time Intervals



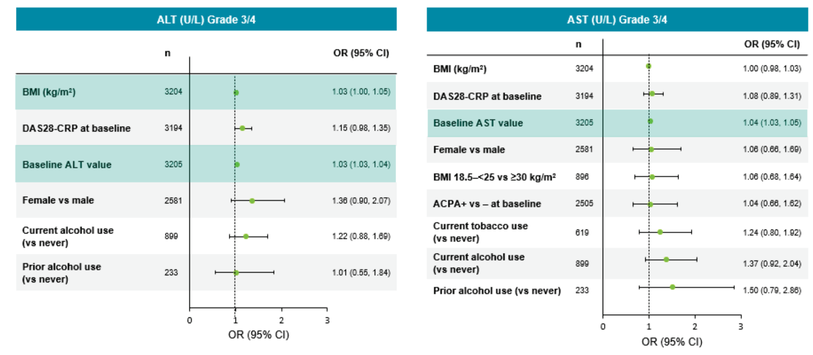
Toxicity grading scale is based on OMERACT criteria. Post-baseline Grade must be higher than baseline Grade

Figure 7. Risk Factors of Interest for Grade 3/4 Neutrophils and Lymphocytes with UPA 15mg QD



A univariate logistic regression model was used to assess risk factors

Figure 8. Factors of Interest for Grade 3/4 ALT and AST with UPA 15 mg QD



CONCLUSIONS

- This long-term analysis of UPA-treated patients with RA showed dose-dependent relationships for several laboratory abnormalities; incidences of these with UPA 15 mg QD were similar to MTX monotherapy, but typically higher than with ADA 40 mg EOW + MTX
- EAERs of lymphopenia, neutropenia, and anaemia were similar between UPA 15 mg QD, MTX monotherapy, and ADA 40 mg EOW + MTX; hepatic disorders were most common with MTX monotherapy
- Treatment discontinuations as a result of abnormalities in laboratory parameters were uncommon (≤1.3%)
- Proportions of patients with Grade 3/4 lymphocytes, neutrophils, hemoglobin, and ALT were numerically greater with UPA 15 mg QD compared with ADA 40 mg EOW + MTX
  - CPK elevations (EAER and incidence of Grade 3/4 elevations) were higher with both doses of UPA than with MTX monotherapy and ADA 40 mg EOW + MTX
- Incidence of Grade 3/4 laboratory abnormalities was generally low over any 12-month period, and there was no temporal pattern to their occurrence

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ACKNOWLEDGEMENTS

AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, review, and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship. Medical writing support was provided by Alex Watson, MSc, of 2 the Nth (Cheshire, UK), and was funded by AbbVie

DISCLOSURES

Charles-Schoeman C: Research grants from AbbVie, Bristol-Myers Squibb, and Pfizer; and consulting fees from AbbVie, Gilead, Pfizer, and Sanofi/Regeneron
Giles JT: Research grants from Pfizer; and consulting fees from AbbVie, Bristol-Myers Squibb, Eli Lilly, Gilead, Pfizer, and UCB
Lane NE: Consulting fees from Amgen, Mallinckrodt, Pfizer, and Roche
Choy E: Research grants from Bio-Cancer, Biogen, Novartis, Pfizer, Roche, Sanofi, and UCB; consulting fees from AbbVie, Amgen, Biocon, Biogen, Chugai, Eli Lilly, Gilead, Janssen, Merck Serono, Novartis, Pfizer, Regeneron, Roche, R-Pharm, and Sanofi; and speaker fees from AbbVie, Amgen, Bristol-Myers Squibb, Chugai, Eli Lilly, Galapagos, Gilead, Janssen, Novartis, Pfizer, Regeneron, Roche, Sanofi, and UCB
Furst D: Research grants from Actelion, Amgen, Bristol-Myers Squibb, Corbus, Galapagos, GSK, NIH, Novartis, Pfizer, Roche/Genentech, and Sanofi; and consulting fees from AbbVie, Actelion, Amgen, Bristol-Myers Squibb, Corbus, Galapagos, Novartis, and Pfizer; speaker fees from AbbVie, Continuing Medical Education, and Novartis
Vencovský J: Consulting fees from AbbVie, Boehringer Ingelheim, Eli Lilly, Gilead, and Octapharma; and speaker bureau fees from AbbVie, Biogen, MSD, Pfizer, Roche, Sanofi, and UCB
Wilson AG: Nothing to disclose
Burmester GR: Consulting fees and speaker bureau fees from AbbVie, Eli Lilly, Gilead, Janssen, MSD, Pfizer, Roche, and UCB
Shaw T, Song Y, Camp HS, Khan N, Yee JB, and **Anyanwu SI:** Employees of AbbVie and may own stock or options
McInnes IB: Research grants from Celgene, Janssen, Novartis, Pfizer, Roche, and UCB; and consulting fees from AbbVie, Celgene, Janssen, Novartis, and UCB