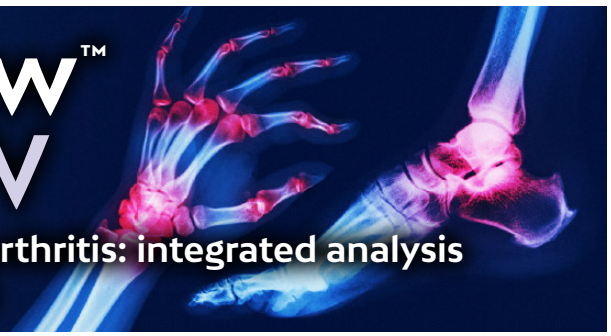
Research Review™
STUDY REVIEW

Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme



Making Education Easy 2022

Independent commentary by Professor Paul Bird
FRACP, PhD, Grad Dip MRI

Professor Paul Bird is a Rheumatologist in private practice and Conjoint Professor at the University of New South Wales. In addition to his clinical duties, he is the Director of Optimus Clinical Research, a clinical research center undertaking Phase 2, 3 and 4 trials of novel agents for the treatment of rheumatic diseases. He has completed a Post Graduate Diploma in Magnetic Resonance Imaging (RMIT University) and his PhD thesis (University of NSW) examined the feasibility, reliability and validity of MRI as an outcome measure in patients with rheumatoid arthritis. He maintains ongoing participation in research projects examining the application of Magnetic Resonance Imaging (MRI) in inflammatory arthritis and is co-chair of the OMERACT international MRI imaging group.

Publication overview

Oral Janus kinase inhibitors (JAKis) provide an alternative treatment option to biologic disease-modifying antirheumatic drugs (bDMARDs) in patients with moderately to severely active rheumatoid arthritis (RA) who are intolerant to or have an inadequate response (IR) to conventional synthetic DMARDs (csDMARDs).[1]

The phase III SELECT clinical trial programme for upadacitinib included five randomised controlled trials: SELECT-NEXT,[2] SELECT-BEYOND,[3] SELECT-MONOTHERAPY,[4] SELECT-COMPARE[5] and SELECT EARLY.[6]

This publication is an integrated safety analysis from these five studies, and presents a report of safety data from both doses of upadacitinib studied (15mg and 30mg once daily).[1]

Updated data are also presented, which include an additional study (SELECT-CHOICE),[7] and up to 4.5 years of upadacitinib exposure.[8]

Introduction

Upadacitinib (RINVOQ®, Product Information) is a selective and reversible JAKi engineered to more potently inhibit JAK1 compared to JAK2 and JAK3.[10] JAKs are important intracellular enzymes that transmit cytokine or growth factor signals involved in a broad range of cellular processes, including inflammatory responses (JAK1), haematopoiesis (JAK2), immune surveillance and lymphocyte function (JAK3).[10] In cellular potency assays that correlated with the *in vivo* pharmacodynamic responses, upadacitinib demonstrated 33-197-fold greater selectivity for JAK1-associated signalling over JAK2-JAK2 signalling.[10] In enzyme assays, upadacitinib had >50-fold selectivity for JAK1 over JAK3.[10]

For RA, RINVOQ is formulated as 15mg modified release tablets designed for once daily oral administration.[10] The recommended dose of RINVOQ is 15mg once daily.[10] As such, only results for the 15mg dose will be presented in this Study Review.[10]

Study background

The safety and efficacy of upadacitinib has been evaluated in a broad phase III clinical development programme, including at least six 'SELECT' trials.[2–7]

Data were pooled from five of these trials (SELECT-NEXT, -BEYOND, -MONOTHERAPY, -COMPARE and -EARLY) for the 2020 *Ann Rheum Dis* publication by Cohen et al,[1] in which upadacitinib was administered with or without background csDMARDs in patients with moderately to severely active RA. These studies included methotrexate-naïve patients and patients with an IR or intolerance to one or more csDMARDs or bDMARDs.[1]

Cohen et al presented an updated analysis as a poster at the European Congress of Rheumatology 2021 Virtual Congress, with an additional trial (SELECT-CHOICE) included,[7] in which upadacitinib was compared with abatacept in patients with an IR to bDMARDs.[8] The analysis provided up to 4.5 years of exposure data for upadacitinib.[8] (**Table 1**)

Expert comment

The SELECT study trials provide a comprehensive set of data examining upadacitinib, in a wide range of different rheumatoid patient populations. Noteworthy is the SELECT-COMPARE study which assessed superiority of upadacitinib versus adalimumab. The efficacy and safety data are wide-ranging, and provides a valuable insight into the practical management of this molecule in RA population.

Study design and methods

Patients and treatment

Eligible patients were aged ≥18 years with active RA (≥6 swollen and ≥6 tender joints, and high-sensitivity C-reactive protein (CRP) ≥3 mg/L (NEXT, BEYOND, SELECT and CHOICE) or ≥5 mg/L (EARLY, COMPARE) at screening), and who met the 2010 American College of Rheumatology / European League Against Rheumatism classification criteria.[1]

In SELECT-EARLY and SELECT-COMPARE, additional inclusion criteria were erosive joint damage and/or seropositivity for autoantibodies.[1]

Exclusion criteria across the studies included: cerebrovascular accident or myocardial infarction within the past 6 months, most malignancies, gastrointestinal perforation or diverticulitis, active infection requiring parenteral anti-infectives within 30 days, or oral anti-infectives within 14 days prior to the study, elevated liver transaminases, reduced kidney function, and low cell counts.[1] All of the SELECT studies excluded patients who had prior exposure to a JAKi.[2-7] In the SELECT-NEXT, -BEYOND, -MONOTHERAPY, -COMPARE and -EARLY studies, patients were excluded if they had prior IR to bDMARDs.[2-6] In SELECT-NEXT and -COMPARE, the protocols allowed for up to 20% of patients to be included if they had prior intolerance or <3 months' exposure to bDMARDs.[2,5]

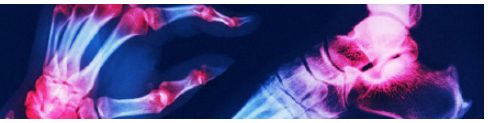


Table 1. **Characteristics of the studies and treatment arms included in the pooled analyses.**[1,8]

Trial	SELECT-EARLY (NCT02706873)		SELECT-NEXT (NCT02675426)		SELECT-COMPARE (NCT02629159)		SELECT-MONOTHERAPY (NCT02706951)		SELECT-BEYOND (NCT02706847)		SELECT-CHOICE (NCT03086343)	
Patients	MTX-naïve N=945		csDMARD-IR n=661		MTX-IR N=1629		MTX-IR N=648		bDMARD-IR n=498		bDMARD-IR n=612	
Comparators	MTX		Placebo		Placebo, adalimumab		Placebo continued prior to MTX		Placebo		Abatacept	
Background treatment	N/A		csDMARDs		MTX		N/A		csDMARDs		csDMARDs	
	Cut-off date SELECT											
Primary publication (Data-set 1)[1]	16 August 2018		22 March 2018		6 July 2018		25 May 2018		16 April 2018		–	
Congress update (Data-set 2)[8]	30 June 2020		30 June 2020		30 June 2020		30 June 2020		30 June 2020		30 June 2020	
Treatment arm description												
Included in data-set	1	2	1	2	1	2	1	2	1	2	1	2
Placebo pooled (short-term)			✓		✓				✓			
MTX monotherapy	✓	✓					✓					
Adalimumab					✓	✓						
Upadacitinib 15mg pooled	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	n/a	✓
Upadacitinib 30mg pooled	✓	✓	✓	✓			✓	✓	✓	✓		

bDMARD = biologic disease-modifying antirheumatic drug; **csDMARD** = conventional synthetic disease-modifying antirheumatic drug; **IR** = inadequate response; **MTX** = methotrexate; **N** = number; **N/A** = not applicable.

Across the five SELECT studies in the initial analysis, patients received either modified release upadacitinib (15mg or 30mg once daily), placebo, methotrexate or subcutaneous adalimumab (40mg every other week), as monotherapy or in combination with background csDMARDs. Methotrexate-naive patients randomised to methotrexate were started at a dose of 10 mg/week (or 7.5 mg/week in China and Japan), which was titrated up to a maximum of 20 mg/week (or 15 mg/week in China and Japan), depending on tolerability. Switching between upadacitinib doses was not permitted. The data-cuts for the analysis ranged from March to August 2018.[1] (**Table 1**)

An updated integrated safety analysis was presented at the European Congress of Rheumatology meeting, 2 – 5 June, 2021, with up to 4.5 years of upadacitinib treatment and a data-cut of 30 June 2020.(**Table 1**)[7,8] The updated included the five studies from the original analysis, plus the SELECT-CHOICE trial, which compared upadacitinib with abatacept in bDMARD-IR patients.

Endpoints and analyses

The placebo-controlled analysis set included short-term data from SELECT-NEXT, -COMPARE and -BEYOND.[1] The adalimumab-controlled analysis set included data for patients who were randomised or rescued to adalimumab in SELECT-COMPARE.[1] In the updated analysis, placebo and abatacept (in SELECT-CHOICE) were excluded.[8]

The methotrexate-controlled analysis set included pooled data from SELECT-EARLY and SELECT-MONOTHERAPY, which were censored at the time of rescue (i.e. the addition of upadacitinib).[1]

In the updated analysis, only methotrexate monotherapy data from SELECT-EARLY were included.[8]

Upadacitinib 15mg data were pooled from all five studies, and 30mg data were pooled from four studies (excluding SELECT-COMPARE) (**Table 1**).[1] In the updated analysis, upadacitinib 15mg data were pooled from all six studies, the 30mg data from the original four studies.[8]

Adverse events (AEs) were assessed using Outcome Measures in Rheumatology (OMERACT) criteria. Alterations in laboratory values were determined by OMERACT criteria, except for changes in creatine phosphokinase (CPK) and serum creatinine, which were graded using the National Cancer Institute's Common Toxicity Criteria v4.03.[1]

Treatment-emergent AEs (TEAEs) were defined as an AE with onset on or after the first dose of study drug and no more than 30 days after the last dose of study drug (70 days for adalimumab). They were summarised using the Medical Dictionary for Regulatory Activities (MedDRA) v19.1 system organ class and preferred term.[1]

Exposure-adjusted event rates (EAERs) per 100 patient-years (PY) were calculated as events based on the treatment received at the time of each AE; each patient could have more than one AE, and this was included in the numerator.[1] Any statistical comparisons between upadacitinib and comparator arms should be interpreted with caution due to inherent limitations of the analysis.[1] Many of the AEs of special interest evaluated were rare events and the limited sample size or exposure may bias the result. In addition, upadacitinib data may be over-represented due to differences in sample size and exposure time between upadacitinib and comparator arms.[1] For full details, please refer to the Supplementary Appendix here.[1]

Study results

Patient characteristics

In the initial analysis, data were pooled for 3,834 patients who had received at least one dose of upadacitinib, either 15mg (n=2,630) or 30mg (1,204) once daily; this provided 4,020.1 PY of exposure data (2,655.1 PY upadacitinib 15mg and 1,365.0 PY upadacitinib 30mg).[1]

A 4.5-year pooled analysis included an additional study (SELECT-CHOICE) and data for 3,209 patients who received 15mg of upadacitinib; the pooled data for the number of patients who received 30mg were unchanged. The total number of patients who received at least one dose of upadacitinib was 4,413, providing 10,115.4 PY of exposure data (7,023.8 PY upadacitinib 15mg and 3,091.6 PY upadacitinib 30mg).[8]

Pooled data were available for 314 and 579 patients who received MTX monotherapy or adalimumab plus MTX, respectively, in the 4.5-year analysis.[8]

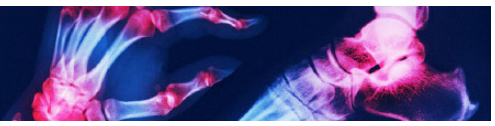
The baseline characteristics were generally similar across the treatment groups in the 4.5-year analysis (**Table 2**).[8]

Table 2. **Baseline characteristics of patients included in the 4.5-year pooled analysis**[8]

Mean (SD), unless otherwise stated	MTX monotherapy (N = 314, 637.4 PY)	ADA + MTX (N = 579, 1051.8 PY)	UPA 15 mg pooled (N = 3209, 7023.8 PY)
Age, years	53.3 (12.9)	54.1 (11.7)	54.3 (12.0)
Female, n (%)	240 (76.4)	470 (81.2)	2581 (80.4)
Time since RA diagnosis, years	2.6 (5.1)	8.2 (8.0)	8.5 (8.4)
Concomitant csDMARDs, n (%)	0	578 (99.8)	2548 (79.4)
Concomitant steroids, n (%)	162 (51.6)	349 (60.3)	1761 (54.9)
Prior bDMARD use, n (%)	0	57 (9.8)	979 (30.5)
Seropositive (RF or ACPA), n (%)	255 (81.2)	497 (85.8)	2707 (84.4)
CRP, mg/L	21.2 (22.1)	14.2 (20.5)	17.8 (21.6)
DAS28-CRP[a]	5.9 (1.0)	5.2 (1.3)	5.8 (1.0)
History of HZ, n(%)	4 (1.3)	12 (2.1)	66 (2.1)
History of VTE, n(%)	3 (1.0)	9 (1.6)	53 (1.7)
History of CV event[b], n(%)	27 (8.6)	62 (10.7)	383 (11.9)
CV risk factors at baseline, n (%)			
History of hypertension	112 (35.7)	252 (43.5)	1275 (39.7)
Diabetes mellitus	19 (6.1)	40 (6.9)	255 (7.9)
History of tobacco/nicotine use (current + former)	120 (38.2)	199 (34.4)	1221 (38.0)
Elevated LDL-C[c]	86 (27.5)	170 (29.4)	854 (26.7)
Elevated HDL-C[d]	193 (61.5)	328 (56.6)	1838 (57.3)
Statin use	26 (8.3)	55 (9.5)	369 (11.5)

[a] N=588 (adalimumab + MTX), N=3,194 (upadacitinib 15mg)
[b] Any cardiovascular event (major or otherwise)
[c] ≥3.36 mmol/L (≥129.9 mg/dL); N=313 (MTX), N=3,201 (upadacitinib 15mg)
[d] ≤1.55 mmol/L (≤55.9 mg/dL)

ACPA = anti-citrullinated protein antibody; **ADA** = adalimumab; **bDMARD** = biologic disease-modifying antirheumatic drug; **CRP** = c-reactive protein; **csDMARD** = conventional synthetic disease-modifying antirheumatic drug; **CV** = cardiovascular; **DAS28** = 28-joint Disease Activity Score; **HDL-C** = high-density lipoprotein cholesterol; **HZ** = herpes zoster; **LDL-C** = low-density lipoprotein cholesterol; **MACE** = major adverse cardiovascular event; **MTX** = methotrexate; **N/n** = number; **PY** = patient-years; **RF** = rheumatoid factor; **SD** = standard deviation; **UPA** = upadacitinib; **VTE** = venous thromboembolism.



Safety

Primary publication[1]

The authors note that any statistical comparisons between upadacitinib and comparison arms should be interpreted with caution due to inherent limitations of the analysis.[1] For full details, please refer to the Supplementary Appendix here.[1] The most common TEAEs that occurred at a rate of ≥10 events per 100 PY (E/100 PY) with upadacitinib 15mg included upper respiratory tract infection, nasopharyngitis and urinary tract infections.

The most common serious TEAE (SAE) with upadacitinib 15mg was pneumonia. Overall, the EAER of SAEs with upadacitinib 15mg (15 E/100 PY) was similar to adalimumab (15.6 E/100 PY), but higher than that of MTX (11.9 E/100 PY) (**Table 3**).[1]

Table 3. **TEAEs across treatment arms in the five studies of the primary publication[1]**

				Upadacitinib all phase III long-term*
	Placebo pooled (n=1,042)	MTX pooled (n=530)	Adalimumab (n=579)†	Upadacitinib 15mg (n=2,630)
Events/100 PY (95% CI) (unless otherwise stated)	Short-term data up to 12/14 weeks	Long-term MTX monotherapy; mean exposure 36 weeks	Long-term adalimumab; mean exposure 42 weeks	Long-term upadacitinib monotherapy or in combination with MTX / other csDMARDs; mean exposure 53 weeks (15mg)
Total PY of exposure, years	256.8	368.7	467.8	2,655.1
Median exposure, days (range)	97.0 (1–128)	179.5 (7–865)	257.0 (14–894)	375.0 (2–898)
Any AE	447.4 (421.9, 474.1)	321.7 (303.6, 340.5)	294.8 (279.4, 310.8)	295.7 (289.2, 302.3)
Any SAE	9.3 (6.0, 13.9)	11.9 (8.7, 16.0)	15.6 (12.2, 19.6)	15.0 (13.6, 16.6)
Any AE leading to discontinuation	10.9 (7.2, 15.8)	9.5 (6.6, 13.2)	11.1 (8.3, 14.6)	8.4 (7.4, 9.6)
Deaths‡	0.8 (0.1, 2.8)	0.3 (0.0, 1.5)	0.9 (0.2, 2.2)	0.5 (0.3, 0.8)

***** Included patients originally assigned to placebo, MTX or adalimumab, but who were switched to upadacitinib
† Included patients switched from upadacitinib to adalimumab post-switch (i.e. from the start of adalimumab)
‡ Included non-treatment-emergent deaths occurring >30 days after the last dose of study drug (upadacitinib 15mg (n=3) and adalimumab (1); when non-treatment-emergent deaths are included, PY of exposure for upadacitinib increased to 2925.0 PY for 15mg
AE = adverse event; **csDMARDs** = conventional synthetic disease-modifying antirheumatic drugs; **MTX** = methotrexate; **PY** = patient-years; **SAE** = serious adverse event; **TEAE** = treatment-emergent adverse events.

In terms of adverse events of special interest (AESI), the EAER for serious infections was similar between upadacitinib 15mg (3.8 E/100 PY) and adalimumab (4.3 E/100 PY), which was higher than that of MTX (2.7 E/100 PY). The serious infection EAER in the upadacitinib 15mg group did not increase over time. The EAERs of opportunistic infections were similar across treatment groups.[1]

EAERs of HZ were greater with upadacitinib than with placebo, MTX or adalimumab, with an E/100 PY of 3.7; at this dose, 96% of cases were classified as non-serious, and 74% involved a single dermatome. In the 15mg group, there was one serious event of disseminated HZ, two non-serious ophthalmic HZ events, and five non-serious post-herpetic neuralgia events; Asian patients, patients aged ≥50 years, or those with a history with HZ were found to have a higher risk of HZ in this dose group.[1]

Active/latent TB EAERs were similar between the active treatment groups, with no events reported with placebo.[1]

The EAERs of NMSC and malignancies excluding NMSC (i.e. non-NMSC) were generally similar across treatment groups.

Five potential GI perforations were reported with upadacitinib 15mg, occurring at 73–341 days after the initiation of treatment. These were assessed as GI perforations by the sponsor in 2/5 cases, giving an EAER of <0.1/100 PY.[1]

Rates of adjudicated major adverse cardiac events (MACE) and venous thromboembolism (VTE) were similar across treatment groups. Although levels of total, LDL and HDL cholesterol increased with upadacitinib treatment, LDL-C/HDL-C ratios remained consistent and there was no apparent association of LDL-C levels with the occurrence of MACE.[1]

Elevations in CPK were observed with upadacitinib 15mg and were more frequent than with placebo, MTX or adalimumab. The greatest rise in levels occurred at week 4, after which levels rose less markedly and plateaued around weeks 36–48.[1]

Congress update[8]

With 4.5 years' follow up, the most common AEs were reported as ≥5 events per 100 PY, and included upper respiratory tract infections, nasopharyngitis, and urinary tract infections as previously observed, in addition to bronchitis.[8]

Compared with the primary publication, the EAERs for SAEs were slightly lower across all treatments; it was similar with upadacitinib 15mg (13.0 E/100 PY) and adalimumab (13.3 E/100 PY), which was higher than MTX (10.4 E/100 PY). The most common SAE with upadacitinib was also as previously observed – pneumonia – with an E/100 PY of 0.7 at the 15mg dose.[8]

The rates of serious infections and opportunistic infections at the upadacitinib 15mg dose were similar to those observed with MTX and adalimumab.[8] (**Table 4**)

The EAERs for HZ remained higher for upadacitinib, compared with MTX and adalimumab. Similar to the previous report, most HZ events at the 15mg dose were non serious (>90%), with almost three quarters involving a single dermatome; 13–17% were recurrent HZ events.[8]

EAERs for NMSC were numerically higher in the upadacitinib group, compared with MTX and adalimumab – no patients in the 15mg group had a recurrent NMSC event.[8]

The EAERs for malignancies excluding NMSC (i.e. non-NMSC) were similar across treatment groups.

Adjudicated GI perforations were uncommon.[8]

Rates of MACEs and VTEs remained similar across treatment arms, with no apparent imbalances in the types of MACE reported in any treatment group. Overall, patients who experienced a MACE or VTE whilst on treatment with upadacitinib had ≥1 cardiovascular risk at baseline.[8]

With longer-term follow-up, CPK elevations continued to occur more commonly with upadacitinib than with MTX or adalimumab, but were mostly asymptomatic; elevations leading to treatment discontinuation were rare (<0.1 E/100 PY).[8]

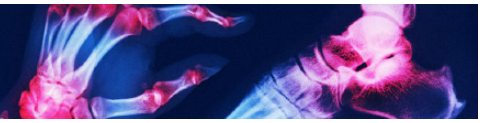


Table 4. AEs in the integrated safety analysis across six Phase 3 studies with up to 4.5 years exposure[8]

Adverse events E/100 PY (95% CI) unless otherwise stated	Upadacitinib 15mg pooled (n=3209, 7023.8 PY)	Adalimumab + MTX (n=579, 1051.8 PY)	MTX monotherapy (n=314, 637.4 PY)
Any AE	**230.7** (227.2–234.3)	**216.6** (207.8–225.7)	**227.8** (216.2–239.8)
Any serious AE	**13.0** (12.2–13.9)	**13.3** (11.2–15.7)	**10.4** (8.0–13.2)
AE leading to discontinuation	**5.6** (5.0–6.1)	**6.8** (5.3–8.5)	**6.3** (4.5–8.5)
Serious infection	**3.3** (2.9–3.7)	**3.1** (2.2–4.4)	**2.4** (1.3–3.9)
Herpes zoster	**3.3** (2.9–3.8)	**1.1** (0.6–2.0)	**0.8** (0.3–1.8)
Active TB	**<0.1** (0.0–0.2)	**0.2** (0.0–0.7)	**0.0** (0.0–0.6)
Opportunistic infection[a]	**0.3** (0.2–0.4)	**0.2** (0.0–0.7)	**0.2** (0.0–0.9)
Anaemia	**3.4** (3.0 3.9)	**3.1** (2.2–4.4)	**3.3** (2.0–5.0)
Neutropaenia	**2.3** (2.0–2.7)	**2.1** (1.3–3.2)	**2.0** (1.1–3.5)
Lymphopaenia	**1.7** (1.4–2.0)	**1.0** (0.5–1.7)	**3.5** (2.2–5.2)
Hepatic disorder	**11.7** (10.9–12.5)	**8.6** (6.9–10.5)	**13.3** (10.7–16.5)
GI perforation (adjudicated)	**<0.1** (0.0–0.2)	**0.0** (0.0–0.4)	**0.0** (0.0–0.6)
Elevated CPK	**4.9** (4.4–5.4)	**1.6** (0.9–2.6)	**1.7** (0.9–3.1)
Malignancy (excluding NMSC)	**0.8** (0.6–1.1)	**0.8** (0.3–1.5)	**0.9** (0.3–2.0)
MACE, adjudicated	**0.4** (0.3–0.6)	**0.3** (0.1–0.8)	**0.0** (0.0–1.1)
VTE, adjudicated	**0.5** (0.3–0.6)	**0.5** (0.2–1.1)	**0.3** (0.0–1.1)
Treatment-emergent deaths	**0.4** (0.3–0.6)	**0.4** (0.1–1.0)	**0.2** (0.0–0.9)

[a] Excluding TB, oral candidiasis, and HZ; the most common opportunistic infections reported with upadacitinib were oesophageal candidiasis and oral fungal infections
[b] CV death, non-fatal myocardial infarction, and non-fatal stroke
[c] Deep-vein thrombosis and pulmonary embolism
AE = adverse event; **CI** = confidence interval; **CPK** = creatine phosphokinase, **CV** = cardiovascular; **E** = event; **GI** = gastrointestinal; **HZ** = herpes zoster; **IR** = inadequate response; **MACE** = major adverse cardiovascular event = **MTX** = methotrexate; **n** = number; **NMSC** = non-melanoma skin cancer; **PY** = patient-years; **TB** = tuberculosis; **VTE** = venous thromboembolism.

Expert comment

The safety data are reassuring for the 15mg formulation which is currently available in Australia.

Serious infectious events: It should be noted that in terms of AESI, the EAER for serious infections was similar between upadacitinib 15mg (3.8 E/100 PY) and adalimumab (4.3 E/100 PY), which was higher than that of MTX (2.7 E/100 PY). Upadacitinib 15mg was not associated with a significant increase in the risk of serious infections, which was similar to adalimumab, or opportunistic infections, which were similar across treatments.

Venous thromboembolism and MACE: Reassuring data for upadacitinib 15mg. Rates of adjudicated major adverse cardiac events (MACE) and venous thromboembolism (VTE) were similar across treatment groups. Although there were increases in total, LDL and HDL cholesterol with upadacitinib treatment, LDL-C/HDL-C ratios remained consistent and there was no apparent association of LDL-C levels with the occurrence of MACE.

Herpes Zoster: As expected there is a consistent zoster signal for JAK inhibitors, but reassuringly the majority of events were uni-dermatomal with a low incidence of post herpetic neuralgia. The EAERs for HZ remained numerically higher for upadacitinib, compared with MTX and adalimumab. Similar to the previous report, most HZ events were non serious (>90%), with almost three quarters involving a single dermatome; 13–17% were recurrent.

CPK elevation: CPK elevation is an interesting effect noted in these trials. The elevation is not associated with muscle injury nor worsening over time. The putative mechanism from *in vitro* studies is that in active disease, gp130-mediated cytokine oncostatin M blocks myoblast differentiation into myotubules resulting in a decrease in CPK expression.[10] Oncostatin M is highly expressed in RA synovium and other inflammatory milieu and may be one mechanism driving sarcopenia in RA. JAK inhibition restores muscle differentiation and increased CPK expression.

Study interpretation

Based on this integrated safety analysis of five phase III clinical trials, the overall safety and tolerability of upadacitinib appears to be acceptable, with no new or unexpected safety signals identified at the approved dose of 15mg once daily in patients with moderately to severely active RA[1]

A stated limitation of the data at the time of publication was exposures to date.[1] To this end, the authors published a longer-term follow-up with up to 4.5 years of exposure; with this, the safety profile of upadacitinib remained consistent with previous analyses.[8]

Take home messages

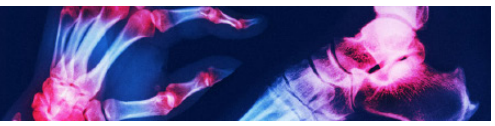
- Upadacitinib 15mg once daily has an acceptable safety profile in patients with moderately to severely active RA
  - It is associated with an increased risk of HZ and CPK elevations, compared with MTX and adalimumab plus MTX
  - It has similar rates of serious infection, MACEs, VTE and malignancies excluding NMSC to adalimumab plus MTX
- Follow-up of patients will continue in long-term extensions of clinical trials and post-marketing studies.

Expert's concluding remarks

Encouraging safety data from the SELECT trials but very important that we continue to be vigilant in pursuing post-trial data and examining the increasingly available evidence from real-world databases.

References

1. Cohen SB, et al. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. Ann Rheum Dis. 2020;80(3):304–11.
2. Burmester GR, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391(10139):2503–12.
3. Genovese, MC et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet. 2018;391(10139):2513–24.
4. Smolen, JS et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study. Lancet. 2019;393(10188):2303–11.
5. Fleischmann, R et al. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. Arthritis Rheumatol. 2019;71(11):1788–1800.



6. van Vollenhoven, R et al. Efficacy and safety of upadacitinib monotherapy in methotrexate-naive patients with moderately-to-severely active rheumatoid arthritis (SELECT-EARLY): A multicenter, multi-country, randomized, double-blind, active comparator-controlled trial. Arthritis Rheumatol. 2020;72(10):1607–1620.
7. Rubbert-Roth, A et al. Trial of upadacitinib or abatacept in rheumatoid arthritis. N Engl J Med. 2020;383(16):1511–21.
8. Cohen, SB et al. Integrated safety profile of upadacitinib with up to 4.5 years of exposure in patients with rheumatoid arthritis. Ann Rheum Dis. 2021;80(Suppl 1):328.
9. AbbVie Pty Ltd. RINVOQ® (upadacitinib modified release tablets) Product information. Available from: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2020-PI-01075-1&d=202107091016933. Accessed February 2022.
10. Queeney, K et al. Elucidating the mechanism underlying creatine phosphokinase upregulation with upadacitinib. Ann Rheum Dis. 2019;78:734-5.

Company Commissioned Article

This publication has been commissioned by AbbVie Pty Ltd. The content is authored by Research Review and based on published studies and the authors' opinions. It may not reflect the views of AbbVie. Please review the full Rinvoq® Australian Product Information, and also review the full Product Information for any other product mentioned in this review via the TGA website https://www.ebs.tga.gov.au before prescribing. Treatment decisions based on these data are the full responsibility of the prescribing physician. AU-RNQR-210263. Date of preparation: February 2022.

