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## **SELECTIVE JAK1 INHIBITION USING UPADACITINIB FOR THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASES: THE POWERFUL PILL**

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Dr. Hasan Hamam presently serves as a Research Fellow at McMaster University and Hamilton Health Sciences, focusing his expertise on the field of Inflammatory Bowel Diseases (IBD). His academic journey began with achieving a Master of Science degree in molecular genetics from York University in Toronto, Ontario, and then the attainment of a Doctor of Medicine from the Lebanese American University in Beirut, Lebanon. During his time at York University, he demonstrated remarkable dedication, culminating in the publication of several peer-reviewed articles.

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# SELECTIVE JAK1 INHIBITION USING UPADACITINIB FOR THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASES: THE POWERFUL PILL

## Introduction

Inflammatory bowel disease (IBD) is a chronic disorder characterized by inflammation of the gastrointestinal tract, with two main subtypes: ulcerative colitis (UC) and Crohn's disease (CD). The cause of IBD is not fully understood, but it involves a complex interaction between genetics and environmental factors that trigger an abnormal immune response in the gut.<sup>1</sup> The immune system plays a central role in IBD, with an imbalance between pro- and anti-inflammatory mediators leading to an exaggerated immune response and infiltration of immune cells into the mucosa.<sup>2</sup> This infiltration triggers the release of cytokines, interleukins and interferons, activating signalling pathways that damage the mucosal barrier.<sup>3</sup>

Despite the presence of several treatment choices for individuals with inflammatory bowel diseases (IBDs), there still remain significant challenges. The symptoms associated with the disease have a detrimental impact on individuals' quality of life, and uncontrolled inflammation can lead to complications of disease requiring surgery, further emphasizing the need for improved treatment to achieve disease control and enhance overall well-being.

The involvement of the Janus kinase inhibitor (JAK) family of enzymes in the signalling pathways of several pro-inflammatory cytokines plays an important role in the pathogenesis of IBD, which makes it a potential therapeutic target. Tofacitinib, a nonselective pan-JAK inhibitor, was the first JAK inhibitor treatment approved for moderate-to-severe cases of UC.<sup>4,5</sup> However, long-term studies on rheumatoid arthritis (RA) patients treated with tofacitinib have highlighted safety concerns including potentially higher risk of major adverse cardiovascular (CV) events and venous thromboembolism.<sup>6,7</sup> The second generation of JAK inhibitors include selective JAK1 therapies, such as upadacitinib.<sup>6,7</sup> Upadacitinib is a selective and reversible JAK inhibitor approved for treating UC; RA; psoriatic arthritis; ankylosing spondylitis (AS); and atopic dermatitis, and approval for Crohn's disease is expected in the near future.<sup>8</sup> This review intends to describe the mechanism of upadacitinib, evaluate the current clinical evidence of its effectiveness in treating IBD, and discuss safety considerations.

## Pharmacology

Upadacitinib is a small non-protein molecule available in three doses: 15 mg, 30 mg and 45 mg extended-release tablets. It is administered as an oral tablet which differentiates it from the most advanced therapies available for IBD. Given its simple and small structure, it is typically not immunogenic.<sup>9,10</sup>

## Mechanism of Action

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway constitutes the hinge in many essential cellular pathways including cell growth, proliferation, differentiation, and regulatory immune functions.<sup>21</sup> In addition to their crucial roles in cellular activities, the JAK/STAT pathway plays an important role in the pathogenesis of inflammatory diseases such as IBD.<sup>21</sup> The JAK family are non-receptor tyrosine kinases that bind to the cytoplasmic domains of cytokine receptors. It includes four members: JAK1, JAK2, JAK3, and tyrosine kinase 2 (Tyk2).<sup>11</sup> STATs are transcription factors found in the cytoplasm of the cell. There are seven types: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6.<sup>12</sup>

The binding of the cytokine to its receptor leads to conformational changes, enabling receptor subunit dimerization and JAK monomer alignment (**Figure 1**). This allows for phosphorylation of tyrosine residues, activating the JAK. Upon activating JAKs, further phosphorylation of the receptor occurs, creating docking sites for STATs. When recruited to these sites, STATs are phosphorylated by JAKs, leading to their activation and the formation of STAT dimers. These activated dimers will migrate to the nucleus and bind to the DNA promoting the transcription of inflammatory genes and upregulating pro-inflammatory cytokine production. JAKs act as effective tyrosine kinases by transferring phosphate groups from adenosine triphosphate (ATP) to tyrosine. JAK inhibitors, small molecules that compete with ATP, prevent JAKs from phosphorylating their substrates (**Figure 1**). Consequently, STAT activation is inhibited, preventing downstream gene transcription and production of inflammatory cytokines.

JAK1 participates in the signalling pathways of both Type I and Type II interferons (IFN  $\alpha/\beta$  and IFN  $\gamma$ ),<sup>13,14</sup> as well as gamma chain ( $\gamma_c$ ) cytokines: IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21.<sup>15</sup> Moreover, JAK1 regulates the signalling of IL-6 and oncostatin M (OSM).<sup>16</sup> By selectively blocking JAK1, upadacitinib may produce anti-inflammatory effects without the unwanted consequences that can occur from blockade of JAK2 and JAK3, a potential advance compared to pan-JAK inhibitors.<sup>17</sup> This can be achieved by selectively targeting JAK1, which is primarily associated with the signalling pathways of cytokines involved in inflammation, and avoiding JAK2 and JAK3 which are involved in hematopoiesis and immune cell development.<sup>18</sup>

## Clinical Efficacy

### Phase 3 studies for UC

To test for the efficacy of upadacitinib in treating UC, two Phase 3 induction studies (U-ACHIEVE induction and U-ACCOMPLISH) and one Phase 3 maintenance study (U-ACHIEVE maintenance) were conducted.<sup>19</sup> U-ACHIEVE induction had 474 patients and U-ACCOMPLISH had 522 patients with each receiving either upadacitinib 45 mg or a placebo once daily for eight weeks.<sup>19</sup> The primary endpoint for both studies was achieving clinical remission by week eight as per the adapted Mayo score. More than half of the patients enrolled in the induction studies (U-ACHIEVE induction and U-ACCOMPLISH) and placebo groups had failed previous biological therapy (53% vs 51%; 50% vs 51% respectively).<sup>19</sup> Patients were stratified based on history of biologic exposure, baseline corticosteroid use and baseline Adapted Mayo score.

In the induction studies U-ACHIEVE induction and U-ACCOMPLISH, clinical remission was attained by significantly more patients treated with upadacitinib 45 mg daily vs placebo; 26% (83/319) vs 5% (7/154) in U-ACHIEVE induction; 33% (114/341) vs 4% (7/174) in U-ACCOMPLISH ( $P < 0.0001$ ).<sup>19</sup> Additionally, patients who received upadacitinib 45 mg demonstrated higher rates in the secondary endpoints, such as clinical response and endoscopic improvement vs those who received placebo (**Figure 2a**).

The U-ACHIEVE maintenance study enrolled patients who had achieved a clinical response during induction with upadacitinib. The 451 patients from the induction studies were re-randomized to receive either upadacitinib 15 mg, upadacitinib 30 mg or placebo daily for 52 weeks. The primary endpoint of the maintenance study was to assess clinical remission by 52 weeks using the adapted Mayo score.<sup>19</sup> The results showed that a higher percentage of patients

receiving upadacitinib achieved clinical remission vs those on placebo. Specifically, 42% of patients on upadacitinib 15 mg (63/148) and 52% on upadacitinib 30 mg (80/154) achieved clinical remission, while only 12% on placebo (18/149) achieved the same outcome ( $P < 0.0001$ ).<sup>19</sup> Furthermore, a greater proportion of patients on upadacitinib 15 mg and 30 mg achieved corticosteroid-free clinical remission (57% [27/47] and 68% [39/58]) vs those on placebo (22% [12/54]) ( $P < 0.0001$ ).<sup>19</sup> Upadacitinib, at doses of 15 mg and 30 mg, demonstrated a higher likelihood of achieving the secondary endpoints, specifically endoscopic improvement (Mayo endoscopic sub-score 0/1) and histological improvement indicated by a decrease in the mucosal inflammation baseline score (Geboes score),<sup>25,26</sup> when compared to placebo (**Figure 2b**).

### Phase 3 studies for CD

The efficacy of upadacitinib in CD was assessed in two Phase 3 induction trials (U-EXCEL and U-EXCEED) in which 526 and 495 patients respectively were randomly assigned to receive either 45 mg of upadacitinib or placebo once daily for 12 weeks.<sup>20</sup> Concomitant methotrexate or glucocorticoid use was permitted, but at four weeks into the study, patients who were receiving glucocorticoids began protocol-specified tapering.<sup>20</sup> Patients were stratified based on baseline glucocorticoid use, severity of endoscopic disease and number of failed biological therapies. The co-primary endpoints were clinical remission, defined as average daily liquid or very soft stool frequency (SF)  $\leq 2.8$  and average daily abdominal pain score (APS)  $\leq 1$ , neither worse than baseline (SF/APS clinical remission). Endoscopic response was defined as a decrease in SES-CD  $> 50\%$  from baseline (or for patients with baseline SES-CD of 4, at least a 2-point reduction from baseline), per central reader.<sup>20</sup>

A significantly higher percentage of patients who received 45 mg upadacitinib achieved SF/APS clinical remission and endoscopic response vs those who received placebo (**Figure 2c**). In addition, more patients who received upadacitinib and were using corticosteroids at baseline were able to achieve glucocorticoid-free SF/APS clinical remission vs placebo at 12 weeks (U-EXCEL 44.4% vs. 12.5%; U-EXCEED 37.0% vs. 6.7%;  $P < 0.001$ ).<sup>20</sup>

In the U-ENDURE maintenance study, 502 patients who responded to upadacitinib during the induction studies were re-randomized to receive either 15 mg upadacitinib, 30 mg upadacitinib or placebo daily.<sup>20</sup> The co-primary endpoints were SF/APS clinical remission and endoscopic response at 52 weeks. A higher percentage of patients had SF/APS clinical remission with 15 mg upadacitinib (35.5%)

or 30 mg upadacitinib (46.4%) than with placebo (14.4%) at 52 weeks. Similarly, a higher percentage had an endoscopic response with 15 mg upadacitinib (27.6%) or 30 mg upadacitinib (40.1%) than with placebo (7.3%).<sup>20</sup> In addition, the 15 mg and 30 mg upadacitinib groups were superior to placebo in achieving all secondary endpoints including endoscopic remission and glucocorticoid-free SF/APS clinical remission at week 52 (**Figure 2d**).

### **Impact of biologic experience on efficacy of upadacitinib**

Within both UC and CD trials, comparable clinical efficacy rates were observed for both patients with no prior biologic treatment failure and biologic-experienced patients after completion of induction with upadacitinib 45 mg daily (**Figure 3**). Although the numerical rate of clinical remission was slightly lower in patients with biologic experience, the treatment difference between upadacitinib and placebo remained consistent for both biologic-naïve and biologic-experienced patients. This suggests that upadacitinib demonstrated significant efficacy in both patient groups, irrespective of patients' prior biologic treatment history.

### **Safety**

JAK inhibitors were issued a black box warning by the FDA due to the results of the ORAL Surveillance trial, a study of older RA patients using tofacitinib.<sup>22,23</sup> All patients were older than 50 years of age with an additional CV risk factor and received either tofacitinib 5 mg or 10 mg two times daily or a TNF inhibitor.<sup>23</sup> It was found that the risk of major adverse cardiovascular events (MACE), cancer, venous thromboembolic events (VTE), and infections was higher in patients who received tofacitinib compared to that of TNF inhibitors, particularly at the 10 mg twice daily dose.<sup>23</sup> Although this led to a black box warning across all JAK inhibitors, it is unclear whether or not these signals exist for selective JAK1 inhibitors. A long-term safety and efficacy study of upadacitinib vs adalimumab in patients with RA rendered comparable adverse event rates in both therapies for MACE, VTE and malignancy.<sup>24</sup> In the CD and UC phase 3 trials, only one major CV event was reported from the CD induction studies (placebo group in U-EXCEL study), and one case was reported in the UC maintenance study (placebo group in U-ACHIEVE maintenance study) (**Table 1**). With respect to VTE, only one case was reported in the UC induction studies (placebo group of U-ACCOMPLISH study), and two cases were reported in the UC maintenance study, both in the 30 mg upadacitinib arm of U-ACHIEVE maintenance (**Table 1**). In addition, seven cases of malignancies were seen in the maintenance

groups of both trials (**Table 1**). No deaths were reported in either clinical trial.<sup>19,20</sup>

Overall, there were no new safety signals observed during the upadacitinib Phase 3 clinical trial programs for IBD. The most common adverse event was nasopharyngitis, worsening of UC or CD diseases, upper respiratory tract infections, and headache.<sup>19,20</sup> Opportunistic infections were rarely reported, with one case of pneumocystis jirovecii pneumonia and two cases of cytomegalovirus infections.<sup>19,20</sup> There were 38 cases of herpes zoster in the CD clinical trial and 15 cases in the UC clinical trial (including induction, maintenance and placebo groups in both clinical trials)<sup>19,20</sup> (**Table 1**). The number of patients with herpes zoster infection was numerically higher with upadacitinib in both studies vs placebo-treated patients (**Table 1**).

In general, the rates of infection with upadacitinib are acceptable and consistent with previous data on JAK inhibitors.<sup>19,20</sup> However, vaccination against herpes zoster is recommended, with a non-live vaccine available in most jurisdictions for those who are on therapy or needing to initiate therapy soon. Before initiation of upadacitinib, patients should be screened for tuberculosis and viral hepatitis, and females should be queried about plans for pregnancy. A baseline complete blood count, liver enzymes and lipid profile should be assessed and monitored periodically.<sup>22,23</sup>

**Table 2** provides a summary of considerations for initiating and monitoring patients on upadacitinib.

### **Conclusion**

Upadacitinib is an effective medication for the induction and maintenance of both CD and UC.<sup>19,20</sup> The advantage of upadacitinib lies in its oral route with once-daily dosing, providing convenience and flexibility, and low risk of immunogenicity due to its JAK1 selectivity. It can be used for the treatment of biologic-naïve patients or those with multiple treatment failures.<sup>19,20</sup> Various doses available for maintenance therapy permit some flexibility for clinicians to lower doses in selected patients.

Although some safety concerns remain with regard to the black box warning issued by the FDA for JAK inhibitors and an association with MACE and VTEs, a similar study to ORAL surveillance enriched with high-risk patients for cardiovascular outcomes has not been conducted with upadacitinib. From the observed safety profile to date across numerous other disease indications,<sup>29-32</sup> a similar signal for MACE and VTE has yet to be observed. However, longer-term studies are needed to confirm the safety profile for upadacitinib.

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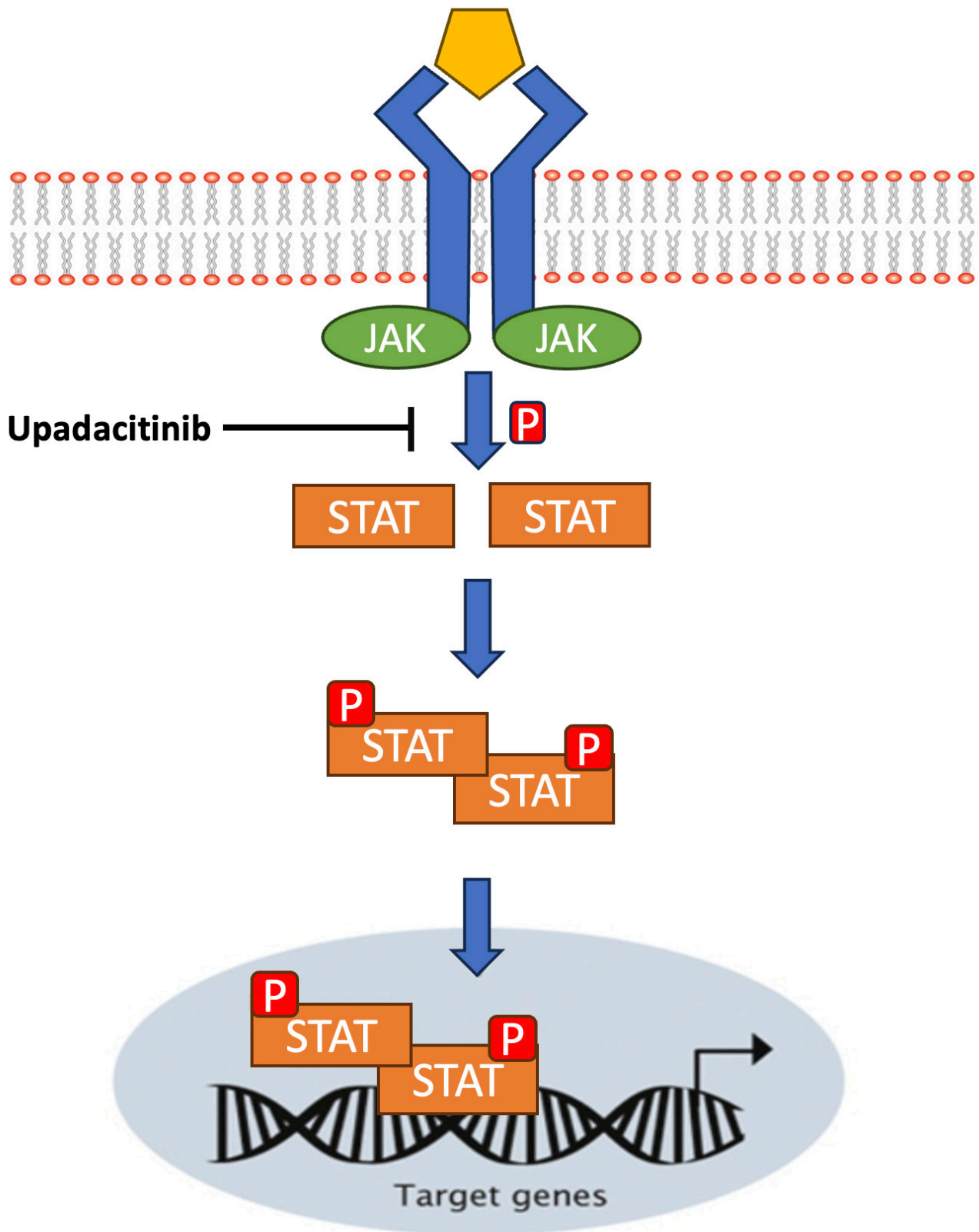
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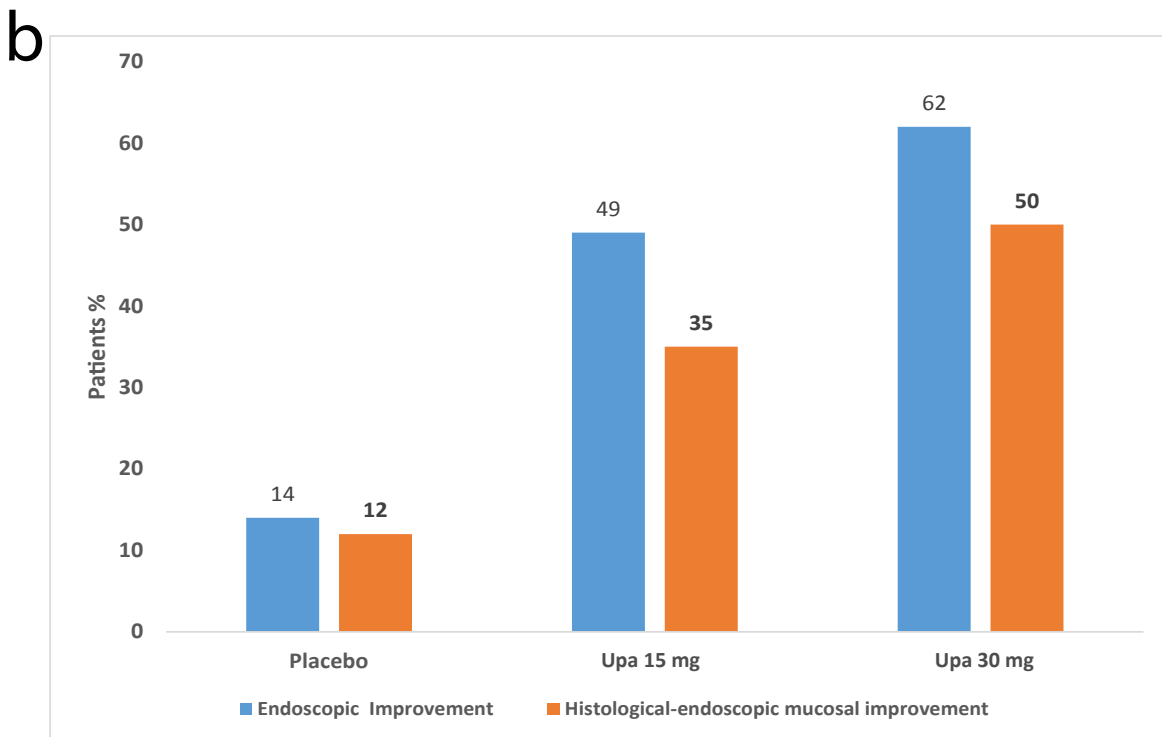
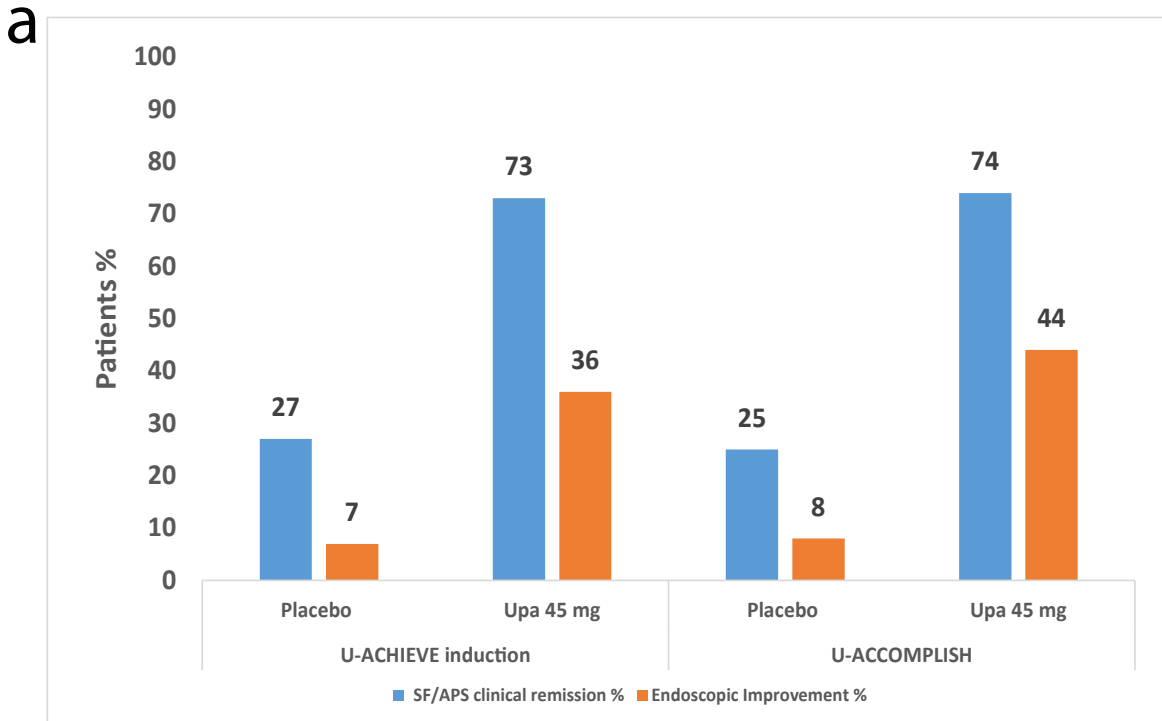
**H.H.** None to report

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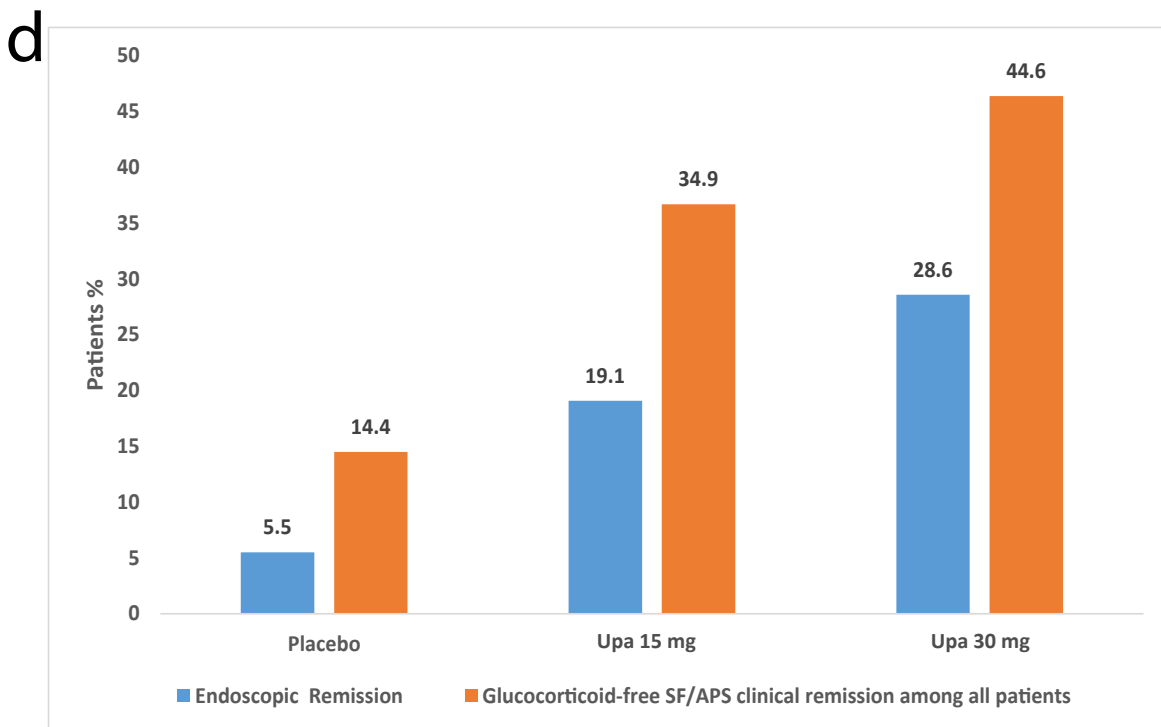
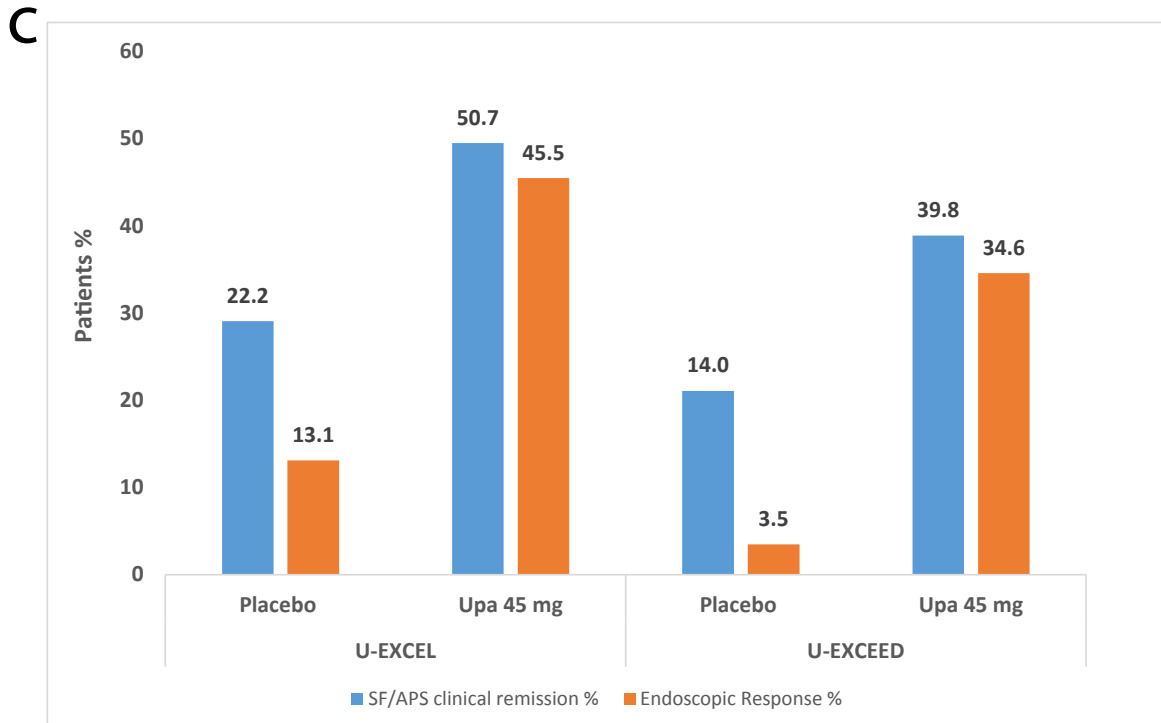


**Figure 1:** JAK/STAT pathway leads to the activation of transcription of pro-inflammatory genes blocked by JAK inhibitor (upadacitinib). JAK: Janus kinase. STAT: Signal transducer and activator of transcription. P: phosphorus from ATP. Upadacitinib: Selective JAK inhibitor; courtesy of Neeraj Narula, MD and Hasan Hamam, MD

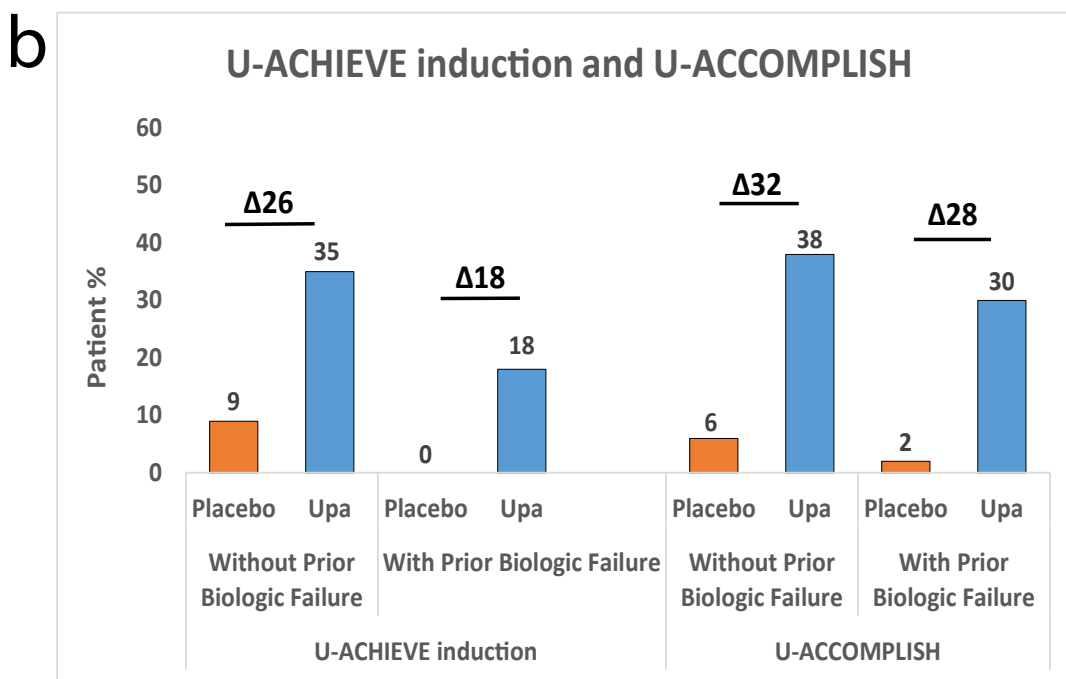
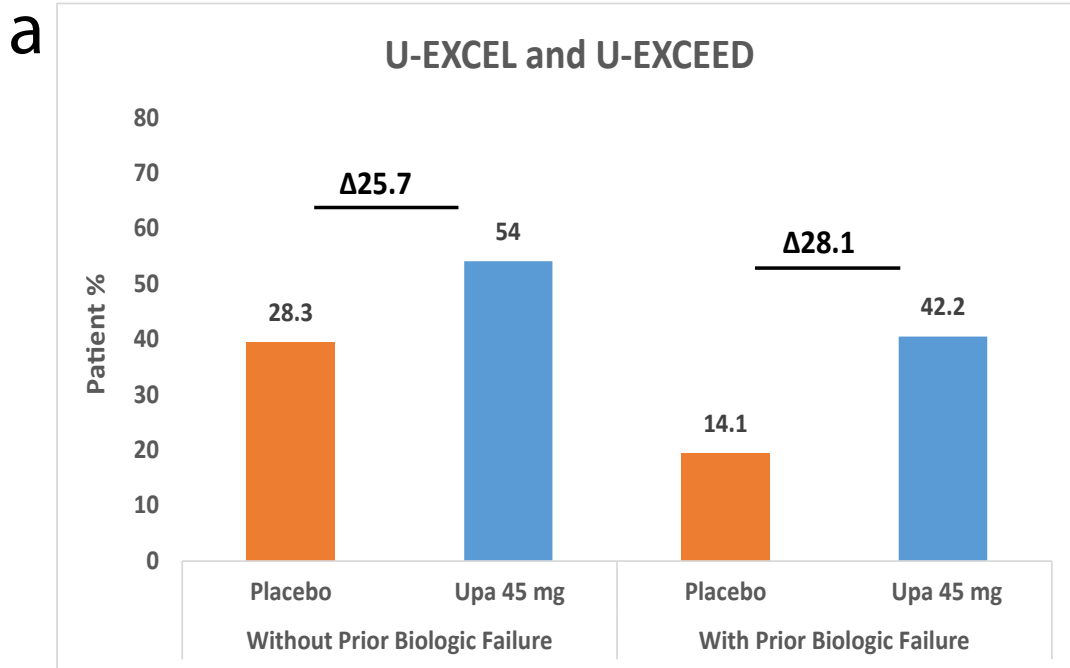


**Figure 2: a)** Clinical response and endoscopic improvement at week 8 induction studies in UC study (U-ACHIEVE induction and U-ACCOMPLISH) with upadacitinib 45 mg (upa 45 mg),  $P$  value  $<0.0001$ . **b)** Secondary endpoint outcomes of the U-ACHIEVE maintenance of the UC clinical trial at week 52 using upadacitinib 15 mg, 30 mg or placebo (endoscopic improvement and histological-endoscopic mucosal improvement); courtesy of Neeraj Narula, MD and Hasan Hamam, MD





**Figure 2: c)** Primary endpoints: SF/APS clinical remission and endoscopic response at week 12 of induction studies in CD study (U-EXCEL and U-EXCEED) with upadacitinib 45 mg (upa 45 mg). **d)** Secondary endpoint outcomes of the U-ENDURE maintenance group of the CD clinical trial with upadacitinib 15 mg, 30 mg, or placebo (endoscopic remission and glucocorticoid-free SF/APS clinical remission among all patients); courtesy of Neeraj Narula, MD and Hasan Hamam, MD



**Figure 3: Clinical remission with upadacitinib treatment among patients with and without prior biologic failure in UC and CD clinical trials.** Upa: upadacitinib 45 mg induction.  $\Delta$ : Difference between placebo and Upa clinical remission rates. a) CD Clinical Trial: U-EXCEL: Patients without prior biologic failure (placebo: 99, upadacitinib 45 mg: 189). U-EXCEED: All patients had prior biologic failure (placebo: 171, upadacitinib: 324). "With prior biologic failure" bars combined data from both studies (placebo: 248, upadacitinib: 485). b) UC Clinical Trial: U-ACHIEVE Induction: Without prior biologic failure (placebo: 7, upadacitinib: 53), with prior biologic failure (placebo: 0, upadacitinib: 30). U-ACCOMPLISH: Without prior biologic failure (placebo: 5, upadacitinib: 63), with prior biologic failure (placebo: 2, upadacitinib: 51); courtesy of Neeraj Narula, MD and Hasan Hamam, MD

Induction Studies	U-ACHIEVE INDUCTION		U-ACCOMPLISH		U-EXCEL		U-EXCEED	
Adverse Event	Placebo (n=155)	Upa 45 (n=319)	Placebo (n=177)	Upa 45 (n=344)	Placebo (n=176)	Upa 45 (n=350)	placebo (n=171)	Upa 45 (n=324)
Opportunistic infections	0	1	0	2	0	0	0	2
Herpes zoster	0	1	0	2	0	10	0	5
MACE	0	0	0	0	1	0	0	0
VTE	0	0	1	0	0	0	0	0
Malignancy	0	0	0	0	0	0	0	0

Maintenance studies	U-ACHIEVE UC maintenance				U-ENDURE CD maintenance			
Adverse event	Placebo (n=149)	Upa 15 (n=148)	Upa 30 (n=154)		Placebo (n=223)	Upa 15 (n=221)	Upa 30 (n=229)	
Opportunistic infections	0	1	0		0	1	1	
Herpes zoster	0	6	6		5	6	12	
MACE	1	0	0		0	0	0	
VTE	0	0	2		0	0	0	
Malignancy	1	1	2		0	1	2	

**Table 1.** Selected adverse events in the induction and maintenance studies of UC and CD clinical trials. UC induction studies: U-ACHIEVE induction and U-ACCOMPLISH. CD induction studies: U-EXCEL, U-EXCEED. Upa 45: Upadacitinib 45 mg administered in the induction studies. UC maintenance study: U-ACHIEVE maintenance. CD maintenance study: U-ENDURE maintenance. Upa 15: Upadacitinib 15 mg, Upa 30: Upadacitinib 30 mg. MACE: Major adverse cardiovascular event. VTE: Venous thromboembolic event. Opportunistic infections excluded tuberculosis and herpes zoster infections; courtesy of Neeraj Narula, MD and Hasan Hamam, MD

<b>Before starting</b>	<ul style="list-style-type: none"> <li>TB, Hep B</li> <li>Stop immunomodulators</li> <li>Shingles vaccination</li> <li>Screen for VTE / MACE risk factors</li> </ul>	<ul style="list-style-type: none"> <li>Don't delay therapy for vaccination (Shingrix)</li> <li>Personal/fam hx, immobility, smoking, etc.</li> </ul>
<b>Induction</b>	<ul style="list-style-type: none"> <li>Upadacitinib 45 mg daily po</li> </ul>	<ul style="list-style-type: none"> <li>8 weeks UC, 12 weeks CD</li> <li>Consider extended induction if slow to respond</li> </ul>
<b>Maintenance</b>	<ul style="list-style-type: none"> <li>Upadacitinib 15 mg or 30 mg daily</li> </ul>	<ul style="list-style-type: none"> <li>Consider de-escalation to 15 mg in stable biologic naïve patients</li> </ul>
<b>Monitoring</b>	<ul style="list-style-type: none"> <li>CBC</li> <li>Liver enzymes</li> <li>Lipid profile</li> <li>Women of childbearing age</li> </ul>	<ul style="list-style-type: none"> <li>Baseline, 2 months, then every 3-6 months</li> <li>Long-acting contraception (e.g., IUD)</li> </ul>
<b>Assessment of Efficacy</b>	<ul style="list-style-type: none"> <li>Symptoms at 2-4 weeks</li> <li>Calprotectin at baseline/week 6 or 8</li> </ul>	<ul style="list-style-type: none"> <li>Could consider flex sig in UC at 8-12 weeks before deciding on maintenance dosing</li> </ul>

**Table 2.** Recommendations for initiating and monitoring patients using upadacitinib for CD and UC.

TB: Tuberculosis. Hep B: Hepatitis B virus. VTE: Venous thromboembolic events. MACE: Major Adverse Cardiovascular Event. CD: Crohn's Disease. UC: Ulcerative Colitis. Hx: History. CBC: Complete Blood Count. IUD: Intrauterine Device; courtesy of Neeraj Narula, MD and Hasan Hamam, MD

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