CO181

Upadacitinib in Moderate-to-Severe Crohn's Disease (CD): A Systematic Review of Remission Outcomes in Adults with Inadequate Response or Intolerance to Biologic Drugs

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Introduction

- Crohn's disease (CD) is a chronic inflammatory bowel condition characterized by inflammation in the digestive tract, potentially affecting any part of it. Typically, it impacts the small intestine and the beginning of the large intestine.
- Symptoms vary based on the location and severity of inflammation and commonly include diarrhea, abdominal cramping, stomach pain, and weight loss.
- Treatment options for newly diagnosed CD include anti-tumor necrosis factor (TNF) agents (like infliximab, adalimumab, certolizumab), corticosteroids (Cs), immunomodulators, or a combination of these drugs. However, high relapse rates pose a significant concern.
- Novel drugs targeting integrins or pro-inflammatory cytokines involved in CD's pathogenesis, such as vedolizumab, ustekinumab, or risankizumab, aim to prevent disease recurrence.
- In 2023, the FDA approved the first orally administered product Rinvoq (upadacitinib) for adults with moderate-to-severe CD who exhibit an inadequate response or intolerance to one or more anti-TNF agents.
- We aimed to evaluate the remission outcomes, particularly Cs-free remission of upadacitinib in anti-TNF therapy experienced patients with CD which can reduce overall cost of treatment.

Objectives

The aim of this systematic review was to assess upadacitinib's efficacy in adults with moderate-to-severe CD who had an inadequate response or intolerance to one or more biologic drugs.

Methods

- Electronic searches were conducted in OVID MEDLINE® (1946 to December 2023), OVID EMBASE® (1974 to December 2023), and google scholar.
- Clinicaltrials.gov was also searched for recently completed trials or supplementary data for potentially eligible RCTs.
- Furthermore, conference proceedings such as American College of Gastroenterology, Digestive Diseases Week, and United European Gastroenterology Week spanning from 2019 to 2023 to pinpoint trials exclusively published in abstract format.
- The bibliographies of all qualifying reviews were searched for any potential studies.
- RCTs were eligible for inclusion if the trial examines the efficacy of upadacitinib against any comparator in adults aged 18 years and above who had prior experience with anti-TNF therapy for CD.

Methods contd.

- Outcomes of interest and their definitions are presented below:

Primary Outcome	Definition
Cs-Free remission	Cs-Free remission among patients receiving glucocorticoids at baseline
Secondary Outcome	**Definition**
CDAI clinical remission	CDAI clinical remission was defined as a CDAI score of less than 150
Endoscopic remission	Simplified Endoscopic Score for CD (SES-CD)<=4 and >=2-point reduction from baseline score, with no subscore >1
SF-APS clinical remission	Average daily very soft/liquid stool frequency [SF] <=2.8 and abdominal pain score [AP] <=1 and both not worse than baseline

Abbreviations: APS - Abdominal pain score; CDAI - Crohn's Disease Activity Index; Cs - Corticosteroid; SES-CD - Simplified Endoscopic Score for CD; SF - Stool frequency

- Two authors independently assessed the eligibility of search results and conference abstracts using pre-defined criteria.
- Data were extracted into Microsoft® Excel spreadsheet by one reviewer as dichotomous outcomes (i.e., remission or no remission). Extracted data were reviewed by an independent author.
- Efficacy was assessed according to the proportion of patients achieving remission in induction or maintenance trials with respect to dose and dosing schedule of active therapy and placebo.
- Two independent reviewers assessed bias using the Cochrane risk-of-bias tool for randomized trials (RoB 2).
- All the disagreements were resolved through consensus

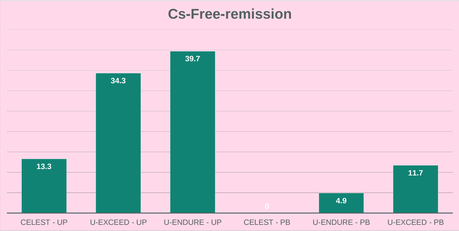
Results

- 205 records were obtained from the searches across all databases. Of them 196 were excluded due to various reasons.
- Finally, nine studies were included reporting four unique RCTs.
- Four RCTs with sample sizes ranging from 36 to 502 were extracted.
- All the trials were placebo controlled.
- Three trials reported primary outcome – Cs-free remission.
- Across three trials, a higher proportion of patients reported Cs-Free remission with upadacitinib (13.3% at week 16 to 39.7% at week 52) compared to the placebo (4.9% at week 52 to 11.7% at week 12).

Results

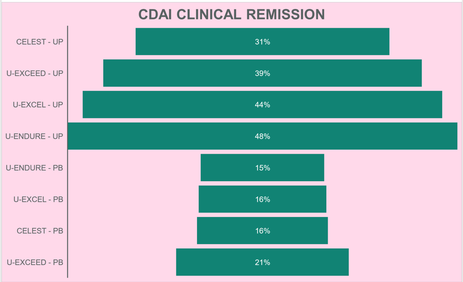
Trial	Intervention	Time-point*	Patients reporting Cs-Free remission	
			Total N	%
U-EXCEED; NCT03345836	Upadacitinib 45 mg QD	12 weeks	108	34.30%
	Placebo		60	11.70%
U ENDURE; NCT03345823	Upadacitinib 15 mg QD	52 weeks	63	39.70%
	Upadacitinib 30 mg QD		63	39.70%
	Placebo		61	4.90%
CELEST; NCT02365649	Upadacitinib 24 mg BID	16 weeks	15	13.3%
	Placebo		13	0

*time point means time at which outcomes were measured



Abbreviations: PB - Placebo; UP - Upadacitinib

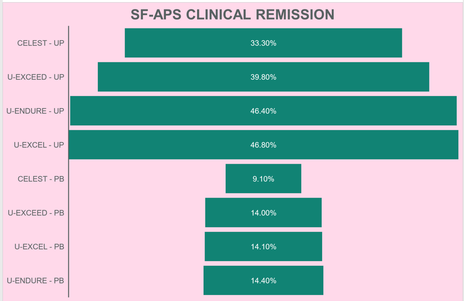
- Similarly, upadacitinib demonstrated favorable secondary outcomes compared to the placebo.
- Four trials documented clinical remission based on the Crohn's Disease Activity Index (CDAI), showing remission rates ranging from 31% at week 16 to 47.6% at week 52 among those treated with upadacitinib.
- While 15% to 21% of patients achieved CDAI remission at week 12.



Abbreviations: PB - Placebo; UP - Upadacitinib

Results contd.

- Four trials reported stool frequency (SF)- abdominal pain score (APS) clinical remission.
- From weeks 12 to 52, SF-APS clinical remission was noted in 33.3% to 46.8% of patients who received upadacitinib treatment.
- Whereas placebo arm achieved SF-APS clinical remission among 9% to 14.4% of patients



Abbreviations: PB - Placebo; UP - Upadacitinib

- Three trials reported endoscopic remission in 28.6% vs 5.5% (upadacitinib vs placebo) at week 52 to 34.6% vs 3.5% (upadacitinib vs placebo) at week 12.

Trial	Intervention	Time-point*	Patients achieving remission outcomes, %			
			Total N	CDAI clinical remission	SF–APS clinical remission	Endoscopic remission
U-EXCEED; NCT03345836	Upadacitinib 45 mg QD	12 weeks	324	38.90%	39.80%	34.60%
	Placebo		171	21.10%	14%	3.50%
U ENDURE; NCT03345823	Upadacitinib 15 mg QD	52 weeks	169	37.30%	35.50%	19.10%
	Upadacitinib 30 mg QD		168	47.60%	46.40%	28.60%
	Placebo		165	15.10%	14.40%	5.50%
U EXCEL; NCT03345849	Upadacitinib 45 mg QD	12 weeks	-	43.90%	46.80%	-
	Placebo		-	15.60%	14.10%	-
CELEST; NCT02365649	Upadacitinib 24 mg BID	12-16 weeks	36	31%	33.30%	30.8%**
	Placebo		37	16%	9.10%	0***

APS – Abdominal pain score; CDAI - Crohn's Disease Activity Index; SF - Stool frequency
*time point at which outcomes were measured
**N=26
***N=15

Limitations

- The review comprised two induction trials: U-EXCEL (conducted from December 2017 to January 2022) and U-EXCEED (conducted from November 2017 to August 2021), along with one ongoing maintenance trial, U-ENDURE (commenced in March 2018).
- Although the CELEST study reported results for both induction and maintenance phases, only the induction phase results were considered due to the unavailability of subgroup data. The remission outcomes reported in the review primarily focused on induction phase results, except for those from the U-ENDURE trial.

Conclusions

While upadacitinib demonstrated superior efficacy in achieving remission compared to a placebo, additional trials involving active drug comparators currently available in the market are necessary to establish its effectiveness in CD patients with inadequate response or intolerance to biologics.

Results contd.

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