Direct and indirect effects of tofacitinib on work productivity in patients with ulcerative colitis: a mediation analysis between work productivity and the Mayo score

B0410

L Targownik,[1] MC Dubinsky,[2] F Steinwurz,[3] AG Bushmakin,[4] JC Cappelleri,[4] E Tai,[5] S Gardiner,[6] P Hur,[6] J Panés[7]

[1]Division of Gastroenterology and Hepatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada; [2]Susan and Leonard Feinstein IBD Center, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [3]Unit of Inflammatory Bowel Disease, Hospital Israelita Albert Einstein, São Paulo, Brazil; [4]Pfizer Inc, Groton, CT, USA; [5]Pfizer Canada, Kirkland, QC, Canada; [6]Pfizer Inc, New York, NY, USA; [7]Formerly Department of Gastroenterology, Hospital Clínic de Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain

Introduction

- Tofacitinib is an oral small molecule Janus kinase inhibitor for the treatment of UC
- Tofacitinib induction treatment has been shown to improve work productivity in patients with UC. However, it is unknown whether improvements in work productivity are fully explained by changes in disease activity, as measured by the Mayo index, or if other factors not captured by these changes also contribute

Objective

- To evaluate the inter-relationships among treatment, Mayo index components, and WPAI-UC components among patients with UC in the Phase 3 studies evaluating tofacitinib as induction therapy for UC (OCTAVE Induction 1 and 2 [NCT01465763, NCT01458951])

Methods

Endpoints

- The Mayo index[1] measures disease activity; higher Mayo scores indicate more severe disease (**Table**)

Table. Breakdown of IBDQ total score

Total Mayo score (0–12 points)			
Stool frequency (SF) (0–3 points)	Rectal bleeding (RB) (0–3 points)	Mayo endoscopic subscore (MES) (0–3 points)	Physician Global Assessment (PGA) (0–3 points)

- The WPAI-UC[2] is a self-administered six-item survey that generates four components: absenteeism (work time missed), presenteeism (impairment whilst working), work productivity loss (overall work impairment from the combination of absenteeism and presenteeism), and activity impairment (non-work activity impairment)
  - Work productivity loss encapsulates both absenteeism and presenteeism and is thus the most comprehensive WPAI-UC component representing overall work impairment
  - Work productivity loss and activity impairment can be viewed as complementary outcomes covering work and non-work activities, respectively

Statistical analysis

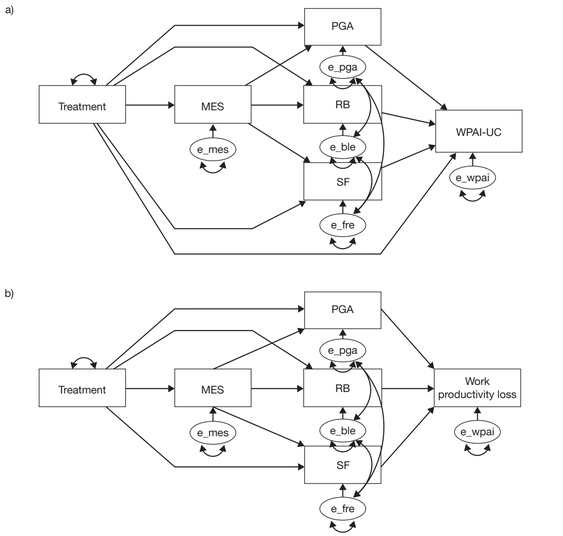
- An initial mediation model used Mayo index components as mediators of the treatment effect on WPAI-UC components as outcomes (**Figure 1a**)
  - Indirect paths represented the paths from treatment to WPAI-UC outcome via the Mayo index components, and the direct path represented the effect of treatment on WPAI-UC outcome by factors not captured by the Mayo index
  - Based on the results of the initial model, the mediation model could be respecified to account for any inconsistences that occurred. The paths represented by non-significant (p>0.05) standardized path coefficients are considered non-meaningful and, as such, could be excluded from the model
- The MES was modeled as a predecessor of RB, SF, and PGA components as these are at least partially impacted by endoscopic inflammation
- Analyses used all available pooled data from Week 8 of OCTAVE Induction 1 and 2 in patients receiving tofacitinib or PBO

Results

Inter-relationships among treatment, Mayo index, and WPAI-UC

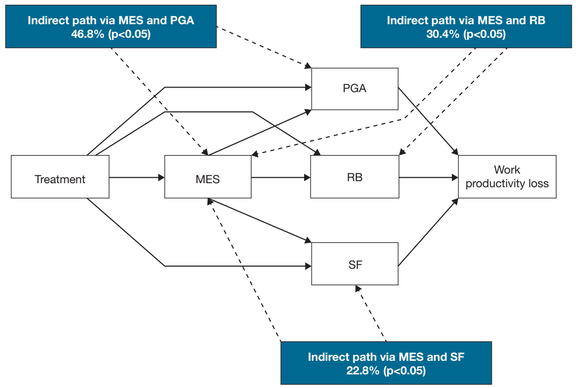
- There were 484 and 1,073 patients available for analysis in the models assessing work productivity loss and activity impairment, respectively
- The initial model evaluating Mayo index components and work productivity loss showed that the standardized path coefficient for the direct path from treatment to work productivity loss was not significant (p>0.05). Based on the initial model results, the model for work productivity loss was respecified to exclude the direct path from treatment to work productivity loss (**Figure 1b**)
- For the model evaluating work productivity loss, 100% of the impact of tofacitinib was mediated through Mayo index components, with the largest effect mediated by MES and PGA (**Figure 2**)
- For the model evaluating the effect of tofacitinib on activity impairment, 26.3% of the effect was mediated through factors not captured by the Mayo index, and 73.7% was mediated through Mayo index components; the largest effect was via MES and a bowel-related symptom, specifically SF (**Figure 3**)

Figure 1. a) Initial mediation model depicting the inter-relationships among treatment, Mayo index components, and a WPAI-UC component, and b) respecified mediation model depicting the inter-relationships among treatment, Mayo index components, and work productivity loss



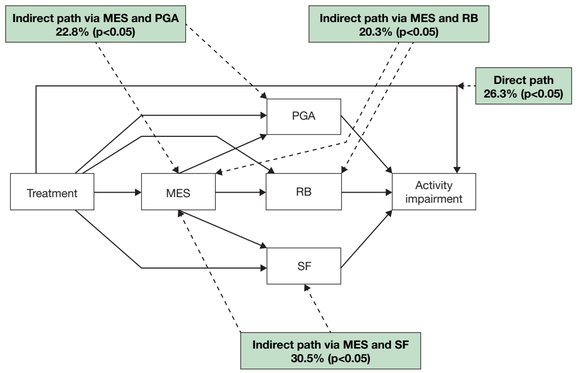
Treatment represents tofacitinib vs PBO

Figure 2. Summary of indirect (mediated through Mayo index components) effects of tofacitinib on work productivity loss, as a percentage of the total treatment effect



Treatment represents tofacitinib vs PBO
White boxes represent model variables and blue shaded boxes represent model results

Figure 3. Summary of direct and indirect (mediated through Mayo index components) effects of tofacitinib on activity impairment, as a percentage of the total treatment effect



Treatment represents tofacitinib vs PBO
White boxes represent model variables and green shaded boxes represent model results

Limitations

- Mediation models in general cannot prove causation, but are rather used to generate hypotheses. As such, the purpose of these mediation modeling analyses was: (1) to determine whether our hypothesized causal inferences were appropriate based on the data; and (2) to confirm the validity of the assumptions
- The WPAI-UC is designed in a way that allows for the patient to skip certain questions; this can result in a different number of available observations for modeling, depending on the type of WPAI component
  - The WPAI-UC is based on how the patient felt during the 7 days prior to completion of the questionnaire, and there are restrictions on what can be interpreted from a single question
- This analysis was post hoc in nature and its results would therefore benefit from being replicated in a prospectively defined study
- The results from these clinical trial studies may not be generalizable to clinical practice

Conclusions

- **This analysis suggests that the effects of tofacitinib on work productivity loss in patients with UC were fully mediated by Mayo index components, whereas the effects on activity impairment were only partially mediated by these components**
- **MES and SF had the largest indirect effect in non-work environments and the smallest indirect effect on work productivity loss. This may be due to improved accessibility and proximity to bathroom facilities in modern work environments, resulting in decreased concern and anxiety about symptom management for patients with UC**
- **These findings provide important insights into the inter-relationships among Mayo index components and the WPAI-UC, and targeting Mayo index components alone may reduce the impact of UC therapies on patients' work and leisure activities**

Abbreviations

e_ble, error rectal bleeding; **e_fre**, error stool frequency; **e_mes**, error MES; **e_pga**, error PGA; **e_wpai**, error WPAI; **HRQoL**, health-related quality of life; **IBDQ**, Inflammatory Bowel Disease Questionnaire; **MES**, Mayo endoscopic subscore; **PBO**, placebo; **PGA**, Physician Global Assessment; **RB**, rectal bleeding; **SF**, stool frequency; **UC**, ulcerative colitis; **WPAI-UC**, Work Productivity and Activity Impairment-Ulcerative Colitis.

References

1. Schroeder KW et al. N Engl J Med 1987; 317: 1625-1629.
2. Yarlas A et al. J Patient Rep Outcomes 2018; 2: 62.
3. DeTora LM et al. Ann Intern Med 2022; 175: 1298-1304.

Acknowledgments

These studies were sponsored by Pfizer. The authors would like to thank the patients, investigators, and study teams involved in the tofacitinib UC clinical program. Medical writing support, under the direction of the authors, was provided by Caitlin Duncan, PhD, CMC Connect, a division of IPG Health Medical Communications, and was funded by Pfizer, New York, NY, USA, in accordance with Good Publication Practice (GPP 2022) guidelines.[3]

Reference to other presentations

The inter-relationships among treatment, IBDQ domains, and WPAI-UC have also been assessed in patients with UC from OCTAVE Induction 1 and 2. These data are presented in B0411.

The relationship between HRQoL and WPAI-UC has also been assessed in patients with UC from OCTAVE Induction 1 and 2 and OCTAVE Sustain. These data are presented in B0412.

Disclosures

L Targownik has received research funding and has been an advisory board member for Pfizer Canada. MC Dubinsky has received consulting fees from Pfizer Inc. F Steinwurz has been an advisory board member for Pfizer Inc. AG Bushmakin, JC Cappelleri, E Tai, S Gardiner, and P Hur are employees and stockholders of Pfizer Inc. J Panés reports personal fees and has received grant support from Pfizer Inc.

Poster presented at ACG Annual Scientific Meeting, Charlotte, North Carolina and Virtual, October 21–26, 2022