Indirect effects of tofacitinib on work productivity in patients with ulcerative colitis: a mediation analysis between work productivity and the Inflammatory Bowel Disease Questionnaire

B0411

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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, IBDQ domains, 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 IBDQ[1] measures HRQoL; higher IBDQ scores indicate better HRQoL (**Table**)

Table. Breakdown of IBDQ total score

IBDQ total score (32–224 points)			
Bowel domain (10–70 points)	**Emotional domain (12–84 points)**	**Social domain (5–35 points)**	**Systemic domain (5–35 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

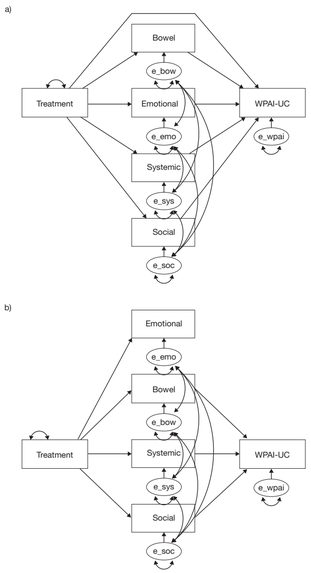
- An initial mediation model used IBDQ domains as mediators of the treatment effect on WPAI-UC components as outcomes (**Figure 1a**)
  - Indirect paths represented the paths from treatment to WPAI-UC outcome via the IBDQ domains, and the direct path represented the effect of treatment on WPAI-UC outcome by factors not captured by the IBDQ
  - 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 were considered non-meaningful and, as such, could be excluded from the model
- 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, IBDQ, and WPAI-UC

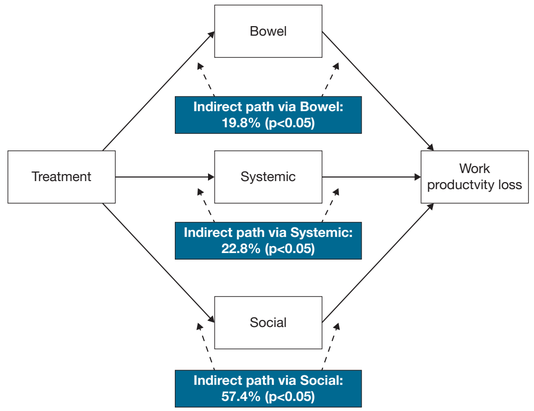
- There were 490 and 1,083 patients available for analysis in the models assessing work productivity loss and activity impairment, respectively
- The initial models showed that the standardized path coefficient for the direct path from treatment to either WPAI-UC outcome was not significant (p>0.05). The path from the Emotional domain to either WPAI-UC outcome was also not significant (p>0.05). Based on the initial model results, the models were respecified to exclude the direct path from treatment to WPAI-UC outcome and the path from the Emotional domain to WPAI-UC outcome (**Figure 1b**)
- The impact of tofacitinib via the IBDQ Emotional domain affected WPAI-UC components implicitly through relationships with other IBDQ domains (**Figure 1b**)
- For the models evaluating work productivity loss (**Figure 2**) and activity impairment (**Figure 3**), the effects of tofacitinib were fully mediated via IBDQ domains; the largest effects were via the IBDQ Social domain
- The IBDQ Bowel domain contributed more to the effect of tofacitinib on activity impairment than work productivity loss (**Figure 2** and **Figure 3**)

Figure 1. a) Initial and b) respecified mediation model depicting the inter-relationships among treatment, IBDQ domains, and a WPAI-UC component



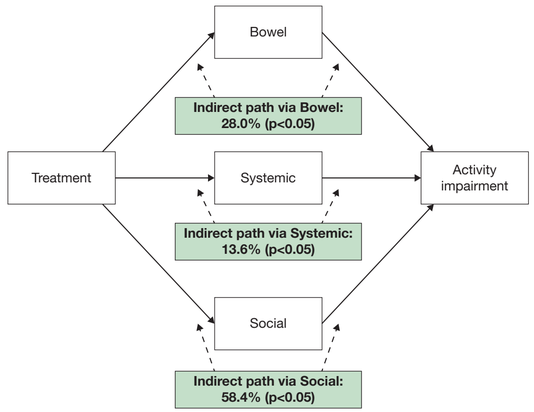
Treatment represents tofacitinib vs PBO

Figure 2. Summary of indirect (mediated through IBDQ domains) 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 indirect (mediated through IBDQ domains) 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 induction therapy on work productivity loss and activity impairment in patients with UC were fully mediated via the IBDQ Bowel, Social, and Systemic domains**
- **Bowel symptoms may be more important in a non-working vs working environment, which may be due to having sufficient accessibility and proximity to bathroom facilities in modern work environments**
- **These findings provide important insights into the inter-relationships among IBDQ domains and the WPAI-UC, and targeting IBDQ domains alone may reduce the impact of UC therapies on patients' work and leisure activities**

Abbreviations

e_bow, error bowel; **e_emo**, error emotional; **e_soc**, error social; **e_sys**, error systemic; **e_wpai**, error WPAI; **HRQoL**, health-related quality of life; **IBDQ**, Inflammatory Bowel Disease Questionnaire; **PBO**, placebo; **UC**, ulcerative colitis; **WPAI-UC**, Work Productivity and Activity Impairment-Ulcerative Colitis.

References

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3. DeTora LM et al. Ann Intern Med 2022; 175: 1298-1304.

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Reference to other presentations

The inter-relationships among treatment, Mayo index components, and WPAI-UC have also been assessed in patients with UC from OCTAVE Induction 1 and 2. These data are presented in B0410.

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.

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