# Is there an association between improvement of GI symptoms in patients with functional gastrointestinal disorders and alterations of circulating gut homing T cells and pro-inflammatory cytokines in response to a 12 week multidisciplinary treatment approach?

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## INTRODUCTION

•The pathophysiology of functional gastrointestinal disorders (FGIDs) including irritable bowel syndrome (IBS) and functional dyspepsia (FD) is not well understood.

•Previous studies observed increased cytokine profiles and circulating gut homing (α4+β7+CCR9+) T cell levels in FGID patients, consistent with immune activation as compared to healthy controls (1, 2).

## AIMS

To explore the links between symptom improvement and alterations of parameters of immune activation in patients who received 12-week intensive multidisciplinary integrated care clinic treatment (ICCT).

## METHODS

•Patients with severe FGID (Rome III criteria; mostly overlapping IBS and FD) referred by their GP or specialists participating in the ICCT provided blood samples at entry and at the end of the intervention.

•Peripheral blood mononuclear cells (PBMCs) were isolated by density centrifugation. PBMCs were cultured (n=7, 57% female, mean age 41 yrs) for 6h and 24h in the presence of 0.2ng/mL lipopolysaccharide (LPS) and cytokine production (Tumour Necrosis Factor (TNF), interleukin (IL)-6, IL-1B, IL-8) was measured using enzyme-linked immunosorbent assay. Additionally, gut homing (CD4+α4β7+CCR9+ and CD8+α4β7+CCR9+) T-cells populations (n=11, 73% female, mean age 46 years) were quantified using flow cytometry.

• Gastrointestinal (GI) symptom severity was measured at study entry and exit using the Structured Assessment of Gastrointestinal Symptoms scale (SAGIS).

## RESULTS

- GI symptom burden significantly decreased after 12 weeks of therapy compared to baseline (baseline 30±16 vs 12 week 18±14, p<0.01) (Figure 1).

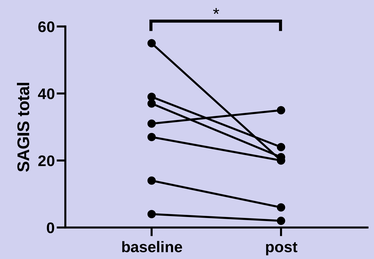


**Figure 1: Symptom score pre and post intervention**

- Comparing baseline with 12 weeks post therapy, there was no significant change in LPS-induced release of TNF (p=0.9), IL-6 (p=0.8), IL-1B (p=0.4), IL-8 (p=0.7; Figure 2).
- Similarly, there was no significant change in circulating gut homing markers (CD4+α4β7+CCR9+ baseline: 1.2%±1.3 vs. post ICCT: 1.2%±1.2; p=0.278, CD8+α4β7+CCR9+ baseline: 0.3%±0.2 vs. post ICCT: 0.3%±0.3; p=0.241) (Figure 3).

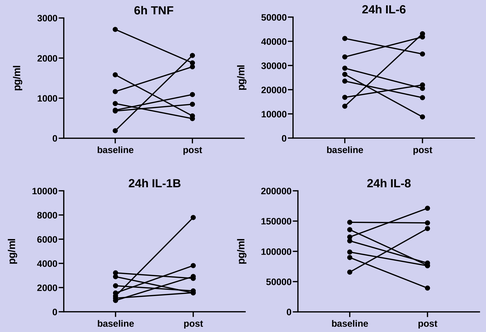


**Figure 2: Cytokine levels from stimulated PBMCs pre and post ICCT**

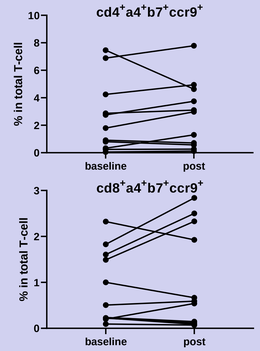


**Figure 3: T-cell populations pre and post ICCT**

## RESULTS

• There was no significant correlation between improvement in symptoms and change in cytokine production (TNF, IL-6, IL-1B or IL-8; Table 1) or change in gut homing T cell populations (CD4+α4β7+CCR9+ or CD8+α4β7+CCR9+; Table 1).

**Table 1: Summary of correlations between symptoms and immune parameters**

| Change in symptoms with: | R | P |
|---|---|---|
| % change in cd4+α4b7+ccr9+ in total T-cell | 0.07 | 0.83 |
| % change in cd8+α4b7+ccr9+ in total T-cell | 0.49 | 0.13 |
| Change in TNF | 0.36 | 0.4 |
| Change in IL-6 | 0.0 | >0.99 |
| Change in IL-1B | 0.29 | 0.56 |
| Change in IL-8 | 0.0 | >0.99 |

## CONCLUSIONS

•While 12-weeks of ICCT resulted in a significant reduction of GI symptoms, these improvements were not significantly correlated with alterations of gut homing T-cells or in vitro cytokine release from PBMCs.

• Our data suggest that symptom improvement in FGID patients can occur irrespective of alterations of immune parameters. Immune activation might be a marker of FGID patients but not necessarily the cause of symptoms.

**References:**

1. Bashashati M et al. Neurogastroenterol Motility. 2014; 26:7.
2. Burns G et a. Am J Gastroenterol. 2018 Nov 14:1.

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