Poster D0389

DIFFERENTIAL AND COMBINATORIAL MECHANISM OF ACTION OF GOLIMUMAB AND GUSELKUMAB IN ULCERATIVE COLITIS INDUCTION THERAPY: IL-23 BLOCKADE DRIVES RESTORATION OF NORMAL EPITHELIUM AND MUCOSAL HEALING

Prerak Desai, Patrick Branigan, Dylan Richards,* Marion Vetter, Daniel J. Cua, Thomas Freeman

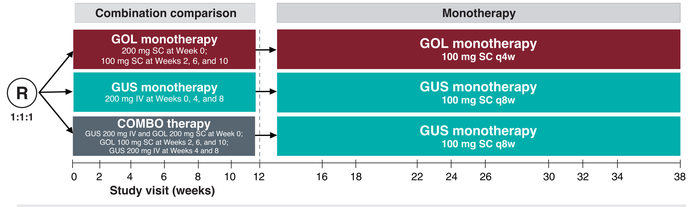
Translational Sciences, Immunology, Janssen Research & Development, LLC, Spring House, PA, USA.

*Presenting author.

BACKGROUND/OBJECTIVE

- In the randomized, phase 2a VEGA clinical trial (**Figure 1**; ClinicalTrials.gov Identifier: NCT03662542), combination induction therapy with GOL, a TNFα antagonist, and GUS, an IL-23 inhibitor, was shown to induce higher rates of clinical remission, endoscopic improvement, and histologic remission than each monotherapy at Week 12 in TNFα-naïve patients with moderately to severely active UC (**Figure 2**)
- Here, we investigated the underlying mechanism of action of GOL, GUS, and the combination of GOL and GUS using colon tissue collected from patients with UC in VEGA

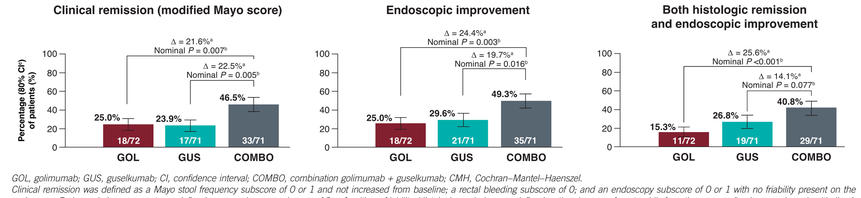
Figure 1. VEGA Phase 2a Study: Combination Induction Therapy With GOL and GUS in Patients With UC



Patient population
- Moderately to severely active UC (Mayo score 6-12, inclusive, and an endoscopy subscore ≥2 by central review)
- Naïve to TNFα, IL-12/23, and IL-23p19 antagonists and have had an inadequate response or intolerance to conventional therapy (immunosuppressants [AZA, 6-MP] and/or corticosteroids)

GOL, golimumab; GUS, guselkumab; UC, ulcerative colitis; R, randomization; SC, subcutaneous; q4w, every 4 weeks; IV, intravenous; q8w, every 8 weeks; COMBO, combination golimumab + guselkumab; TNF, tumor necrosis factor; IL, interleukin; AZA, azathioprine; 6-MP, 6-mercaptopurine.

Figure 2. Combination Therapy With GOL and GUS Induces Higher Rates of Clinical, Endoscopic, and Histo-endoscopic Outcomes Than Monotherapies at Week 12



GOL, golimumab; GUS, guselkumab; CI, confidence interval; COMBO, combination golimumab + guselkumab; CMH, Cochran–Mantel–Haenszel.
Clinical remission was defined as a Mayo stool frequency subscore of 0 or 1 and not increased from baseline; a rectal bleeding subscore of 0; and an endoscopy subscore of 0 or 1 with no friability present on the endoscopy. Endoscopic improvement was defined as an endoscopy subscore of 0 or 1, with no friability. Histologic remission was defined as the absence of neutrophils from the mucosa (lamina propria and epithelium); no crypt destruction; and no erosions, ulcerations, or granulation tissue, according to the Geboes grading system.
[a]The adjusted treatment difference between the combination therapy and monotherapy groups and CI were based on the Wald statistic with the CMH weight.
[b]P value was based on the CMH chi-square test, stratified by corticosteroid use at baseline (yes or no).
[c]The 80% CIs were based on the Wald statistic.

METHODS

- Colon biopsies were obtained at screening and at Week 12 in patients who received GOL (n = 48), GUS (n = 52), or the combination of GOL and GUS (n = 50)
- Tissue transcriptional profiles at Week 12 versus baseline were determined with RNA-seq (**Table 1**)

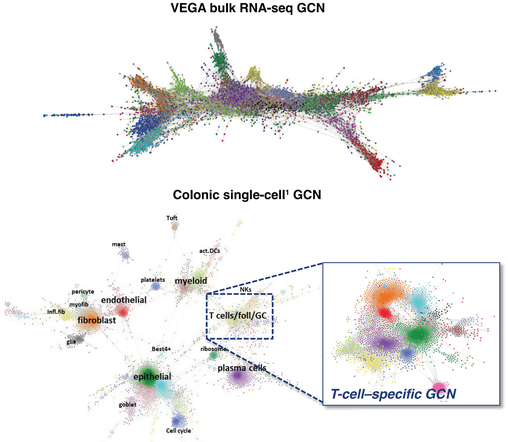
Table 1. Colon Biopsy RNA-seq Samples

	GOL	GUS	COMBO
Baseline	55	57	66
Week 12	52	58	58
Number of paired samples	**48**	**52**	**50**

RNA-seq, RNA sequencing; GOL, golimumab; GUS, guselkumab; COMBO, combination golimumab + guselkumab.

- Significant differences were interpreted in the context of cell-type–specific transcriptional modules by leveraging (**Figure 3**):
  - Gene correlation networks (GCNs)
  - Colonic single-cell data
- Gene module scores (from gene set variation analysis [GSVA]) were used to quantitatively assess pharmacodynamics (PD) and response-related biology

Figure 3. GCNs Used to Analyze Differentially Expressed Genes

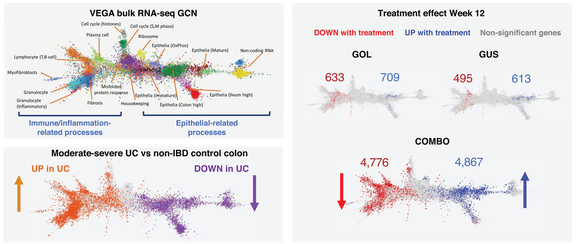


GCN, gene correlation network; RNA-seq, RNA sequencing; act.DC, activated dendritic cell; NK, natural killer T cell; myofib, myofibroblast; Infl.fib, inflammatory fibroblast; foll, follicular cell; GC, germinal center; Basti+, bestrophin 4+. Each cluster of genes (nodes with similar color) represent co-expressed genes that arise due to their association with a particular cell type or pathway.

RESULTS

Combination therapy with GOL and GUS reverses the disease transcriptomic profile more than monotherapies (Figure 4)

Figure 4. VEGA Bulk RNA-seq GCN With Disease and Treatment

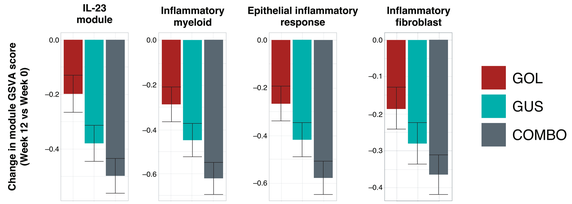


RNA-seq, RNA sequencing; GCN, gene correlation network; OxPhos, oxidative phosphorylation; UC, ulcerative colitis; IBD, inflammatory bowel disease; GOL, golimumab; GUS, guselkumab; COMBO, combination golimumab + guselkumab.
Significant genes defined as adjusted P <0.05.

Key single-cell–derived transcriptional modules were identified as proximal markers of the IL-23 pathway and patient response (Figures 5 and 6)

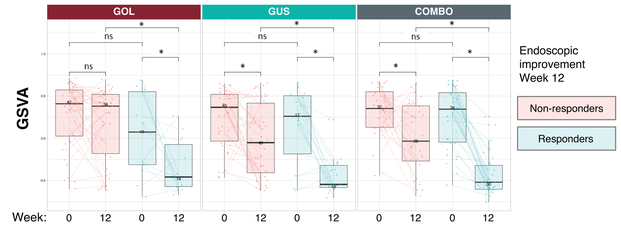
- The **IL-23 module** (23 genes) derived from the colonic T-cell single-cell co-expression graph reflects an inflammatory transcriptional Th17-like state (including genes *IL-22*, *IL-17A*, *IL-12Rβ1*, and *RAR-related orphan receptor C*; **Figure 5**)
- **Marker for IL-23 biology:** Significant decreases in GUS and combination therapy non-responders but not in GOL non-responders (**Figure 6**)
- A predictive cell signaling algorithm (NicheNet) supported IL-23 as the main driver of this biology[1]

Figure 5. Change in Single-cell–derived Transcriptional Modules With Treatment



GSVA, gene set variation analysis; IL, interleukin; GOL, golimumab; GUS, guselkumab; COMBO, combination guselkumab + golimumab therapy.

Figure 6. Change in IL-23 Module GSVA Score With Treatment in Non-responders and Responders

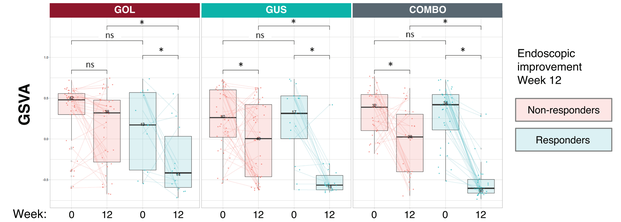


IL, interleukin; GSVA, gene set variation analysis; GOL, golimumab; GUS, guselkumab; COMBO, combination guselkumab + golimumab therapy; ns, non-significant. Responders defined as those patients with an endoscopic improvement subscore of 0 or 1.
**P <0.05.*

Key single-cell–derived transcriptional modules identified IL-22 as a mechanistic link to epithelial restitution (Figures 5 and 7)

- The **epithelial inflammatory module** (132 genes) derived from the colonic epithelial single-cell co-expression graph reflects an inflammatory transcriptional state (including genes *chemokine C-C motif ligand 20*, *signal transducer and activator of transcription 3*, *C-X-C motif chemokine ligand 1*, and *dual oxidase*; **Figure 5**)
- **Proximal to GUS mechanism:** Decreases more in GUS and combination therapy non-responders than in GOL (**Figure 7**)
- **IL-22 was a top-ranked ligand predictive of changes in this module expression** (part of the IL-23 module)
- **Crypt destruction histological subscore** was significantly lower at Week 12 in GUS and combination therapy but not in GOL treatment group (*data not shown*)

Figure 7. Change in Epithelial Inflammatory Response Module GSVA Score With Treatment in Non-responders and Responders



GSVA, gene set variation analysis; GOL, golimumab; GUS, guselkumab; COMBO, combination guselkumab + golimumab therapy; ns, non-significant. Responders defined as those patients with an endoscopic improvement subscore of 0 or 1.
**P <0.05.*

CONCLUSIONS

- **Combination induction therapy with golimumab (GOL) and guselkumab (GUS) induces higher rates of clinical remission, endoscopic improvement, and histologic remission than each monotherapy in tumor necrosis factor (TNF)α–naïve patients with moderately to severely active ulcerative colitis (UC)**
- **Combination therapy with GOL and GUS reverses the disease transcriptomic profile more than each monotherapy**
- **Leveraging relevant colonic single-cell–derived transcriptional modules provides a view into the mechanistic distinctions among treatments**
- **Key single-cell–derived transcriptional modules were identified as proximal markers of the interleukin (IL)-23 pathway and patient response**
- **IL-22 was identified as a mechanistic link to epithelial restitution**
- **Exploration into combinatorial molecular mechanisms and analysis of Week 38 data are ongoing**

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Disclosures
PD was an employee of Janssen Research & Development, LLC (a wholly owned subsidiary of Johnson & Johnson) at the time of the study. PB, DR, MV, DJC, and TF are employees of Janssen Research & Development, LLC (a wholly owned subsidiary of Johnson & Johnson) and may own Johnson & Johnson stock or stock options.

Reference
1. Smillie CS, et al. *Cell.* 2019;178(3):714-730.e22.

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