DOP Session 8: Diagnostics, Biomarkers and Monitoring II

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DOP066
Pharmacokinetics and transcriptomic analysis reveal the molecular signature of mucosal healing in patients with Acute Severe Ulcerative Colitis treated with infliximab (PROTOS)

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Background: Infliximab (IFX), a monoclonal antibody targeting tumour necrosis factor-α, is utilised as a rescue therapy in acute severe ulcerative colitis (ASUC). The relationships between IFX concentrations in serum and colonic mucosa and the pharmacodynamic changes underlying mucosal healing are not well defined.

Methods: We conducted an open-label, prospective, observational study in hospitalised patients with ASUC requiring rescue IFX to characterise the pharmacokinetics (PK) of IFX in serum and colonic mucosa, and to assess the relationships between IFX exposure, molecular signatures, and treatment response. Patients were followed for up to 22 weeks (wks), with longitudinal collection of serum samples (wks 0-22) and biopsies (day 2 and between wk 1622). Serum and tissue IFX concentrations were compared between endoscopic remitters (ERs; Mayo endoscopic subscore of 0 or 1 at wk 22 without an interim UC-related hospitalisation or colectomy) and non-remitters (NRs). RNA sequencing was performed on colonic biopsies to analyse differential gene expression and pathways between ERs and NRs.

Results: 14 patients (7 ERs and 7 NRs) completed the study. PK analysis demonstrated that ERs maintained significantly higher median dose-normalised serum IFX area under the curve than NRs during early induction (wk 0-2: 0.943 vs 0.402 μg*day/mL/mg, p = 0.007), induction (wk 014: 2.053 vs 1.223, p = 0.007), and maintenance therapy (wk 15-22: 0.823 vs 0.188, p = 0.007) (Figure 1A). In contrast, tissue IFX concentrations were similar, regardless of inflammation status or response outcome (Figure 1B).

Transcriptomic profiling showed similar gene expression on day 2 between ERs and NRs. However, at end of study, profound transcriptional changes were observed in ERs, with 382 genes upregulated and 2,536 genes downregulated (Figure 2A). NRs showed only 1 end-of-study differentially expressed gene (DEG) compared to day 2 (Figure 2B). Pathway analysis of the DEGs in ERs indicated a significant decrease in both innate and adaptive immune responses. This was accompanied by a concomitant upregulation of metabolic processes, reflecting the molecular hallmarks associated with mucosal healing.

Conclusion: Endoscopic remission in ASUC was strongly associated with high systemic IFX exposure across all treatment phases. Transcriptomic profiling showed a profound molecular differentiation, characterised by widespread suppression of inflammatory pathways and upregulation of metabolism in ERs, despite similar tissue IFX concentrations to NRs. Our study was the first to demonstrate the tissue transcriptional pharmacodynamics of IFX in ASUC while controlling for colonic drug exposure.

Conflict of interest:

Battat, Robert: Speaker/consulting/moderator: Bristol Myers Squibb, Johnson and Johnson Innovative Medicine, AbbVie, Takeda, Ferring, Celltrion, Pfizer, Merck, Eli Lilly Advisory boards: Celltrion, AbbVie, Pfizer, Janssen, Bristol Myers Squibb, Takeda, Merck, Eli Lilly Educational grants and educational sponsorships: Abbvie, Johnson and Johnson Innovative Medicine, Pfizer, Eli Lilly, Amgen, Pendopharm, Kye Pharma, Merck, Celltrion, Organon, Takeda Travel support: Pfizer, Celltrion, Johnson and Johnson Innovative Medicine, Abbvie.

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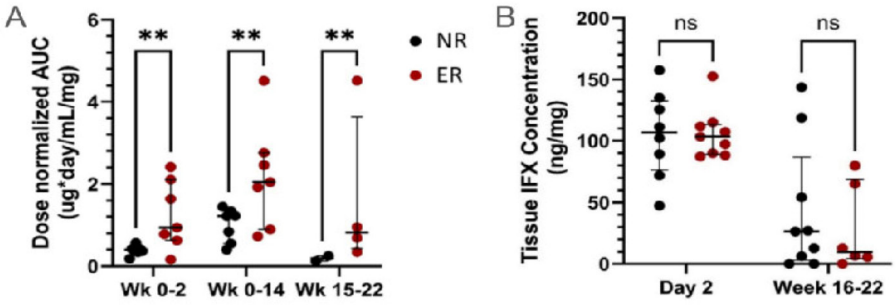
Figure(s)/Table(s): see next page

Figure 1. Serum (A) and Colonic (B) Infliximab Exposure



**p<0.01. AUC, area under the curve; ER, endoscopic remitter; IFX, infliximab; NR, non-remitter; ns, nonsignificant; wk, week.

Figure 2. Differential gene expression between end of study and day 2 in endoscopic remitters (A) and non-remitters (B)