Poster # 117

Drug-Drug Interaction Risk Assessment Strategies for Protein Therapeutics in Inflammatory Bowel Disease: A Literature-Based Evidence Review

Claire Steinbronn*[1]; Susan Stanley[1]; Sihem Bihorel[1]; Tjerk Bueters[1]
Corresponding and presenting author; [1]Merck & Co., Inc., Rahway, NJ, USA

Background

- In vitro evidence suggests that cytokines implicated in the pathology of immune diseases may impact expression and/or function of drug-metabolizing enzymes and transporters (DMET)
- In ulcerative colitis (UC) and Crohn's disease (CD), elevations of IL-1β, IFN-γ, TNF-α, IL-6, and IL-10 are theorized to cause DMET modulation that may lead to drug-drug interactions (DDI) in vivo[1-3]
- Therapeutic protein (TP) therapy is a mainstay in the treatment of both UC and CD and may lead to normalization of DMET due to the reduction of cytokine concentrations[4-6]
- It is not clear if in vitro assessments quantitatively translate to in vivo DDI risk and to what degree drug clearance may change after introduction of anti-inflammatory therapies
- Agency recommendations for DDI assessment for therapeutic proteins are vague; while there is a published workflow to assess TP DDI potential, there is no consensus on risk assessment strategies[7]

Objectives

- Determine what evidence exists regarding potential in vivo DDIs in inflammatory bowel disease (IBD), specifically UC and CD
- Determine how sponsors conducted DDI risk assessment for anti-inflammatory TPs and assess FDA-approved labeling language to understand if/how the DDI risk is communicated
- Investigate potential mechanisms that may explain exposure differences in observed in vivo DDIs in UC and CD patients due to physiological changes caused by disease

Conduct comprehensive literature search

- Collected studies reporting drug exposure in IBD vs healthy subjects
- Identified DDI studies conducted with anti-inflammatory therapies

Review regulatory packages for approved therapies for UC and CD

- Reviewed the FDA-approved labeling and the clinical pharmacology reviews submitted as part of the NDA package
  - Accessed on the public domain via Drugs@FDA

Analyze DDI reports in IBD to determine potential mechanisms of drug exposure changes

- Reviewed absorption/elimination pathways of victim drug
- Determined degree of change observed in observed DDI
- Proposed potential mechanism of observed DDI

IL-6 levels in inflammatory bowel disease[8]

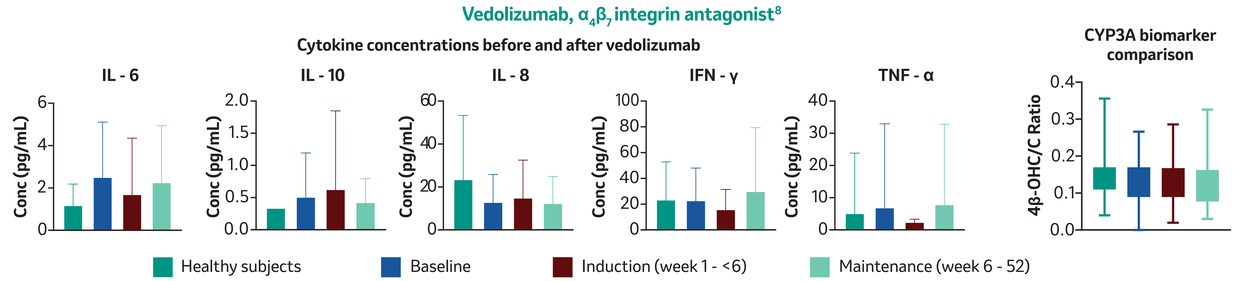
	Baseline serum IL-6 level			
Study citation	N	UC	CD	Healthy subjects
Holtkamp et al.	15	10 +/- 4*	36 +/- 8*	7.3 +/- 1.2
Szkaradkiewicz et al.	20	8.63 +/- 2.14*	8.24 +/- 1.75*	1.59 +/- 0.9
Martinez-Fierro et al.	23	14.4 +/- 3.4	18.1 +/- 1.6	14.4 +/- 10.7
Korolkova et al. (median/IQR)	25	0 (0-1.49)*	1.53 (0-4.85)*	0 (0-0.97)
Ciecko-Michalska et al. (median/IQR)	35	19.6 (21)*	10.8 (7.6)*	3.2 (1.6)
Biesiada et al.	50	8.03 +/- 0.7*	n/a	5.13 +/- 0.40

**Statistically significant difference demonstrated between diseased and healthy controls*

- IL-6 has the most evidence of DDI potential based on clinical data, but the translation of DDI potential from in vitro assays for other cytokines is inconclusive
- Although serum levels of IL-6 are higher in UC and CD patients compared to healthy comparators, it is not clear what threshold of IL-6 elevation indicates in vivo DDI potential in IBD
- Evidence of IL-6-mediated DDIs in other indications, such as acute inflammation following surgery and infection in addition to rheumatoid arthritis patients, is relatively mild (exposure and DMET changes within two-fold)[9]

Selected case examples

Figure 1. Findings of cytokine and 4β-OHC/C ratio assessment in CD patients in various stages of treatment vs healthy subjects



- Concentrations of cytokines in CD patients before and after vedolizumab therapy compared to healthy volunteer data. 4βhydroxycholesterol (4β-OHC) was taken in ratio to cholesterol (C) and suggested no impact on CYP3A activity in CD vs healthy subjects

Selected reports of drugs with altered exposure in IBD[10,11]

Drug	Elimination pathway(s)	Total clearance	Observed change in IBD vs healthy
Midazolam	CYP3A (f_m=0.96), f_e<0.005	0.29-0.63 L/min	↑ 5-fold exposure ↓ 5-fold clearance
Alfentanil	CYP3A (f_m=0.97), f_e=0.01	0.23 L/min	↔ Clearance
Budesonide	CYP3A (f_m=0.76), P-gp	1.0 L/min	Mixed reports
Cyclosporine	CYP3A (f_m=0.79), P-gp, f_e=0.01	0.39 L/min	↔ Exposure
Verapamil	CYP2C8, CYP3A, P-gp	R – 0.66 L/min S – 2.86 L/min	↑ Total exposure (~10-fold S, ~2-fold R); ↔ unbound exposure
Prednisolone	f_e=0.98, CYP3A	0.14 L/min	Mixed reports

Conclusions

- IBD is a group of complex diseases with physiological changes that could alter the pharmacokinetic profile of coadministered medications
- Therapeutic proteins are used to treat UC and CD and may lead to normalization of DMET due to reductions in cytokine levels
- Although IL-6 has the most evidence of clinical DDI potential, it is not clear what levels indicate DDI risk
- Most therapeutic modalities approved for UC and CD contain a generic warning label for CYP substrates, but some drugs, such as vedolizumab, proposed DDI risk assessment to measure cytokine levels and a CYP3A biomarker, 4β-OHC, to demonstrate no DDI potential
- Small-molecule drugs demonstrated differences in exposure in IBD vs healthy comparators, but the provided evidence suggests that the mechanism of exposure change is unclear and may be multifaceted
- This analysis demonstrates the need for more work to understand DDIs following cytokine-modulating therapy

Disclosures

All authors are employed by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may own stock in Merck & Co., Inc., Rahway, NJ, USA.

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