Pharmacokinetic stratification of cytokine profiles during anti-TNF induction treatment in moderate-to-severe UC

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Background

It remains unclear why up to 30% of patients with ulcerative colitis (UC) do not respond to anti-TNF treatment. Moreover, it is unclear whether cytokine profiles are correlated to pharmacokinetics, pharmacodynamics, or simply reflect overall disease severity.

Aim

To explore multi compartment cytokine and anti-TNF concentrations in peripheral blood (PB), faeces (F) and colonic tissue (T) before, during and after anti-TNF induction treatment in UC and to stratify for PK status.

Methods

Main inclusion criteria: Moderate-severe UC (Mayo endoscopic score (MES) 2-3) AND Induction treatment with infliximab (IFX) OR adalimumab (ADA).
Study design: multi-center prospective cohort study.
Baseline assessment: clinical & endoscopic assessment. Peripheral blood (PB), faeces (F) and colonic tissue (T) sampling.
Follow-up assessment: Endoscopic assessment. T sampling: first endoscopy at follow-up. PB and F sampling: first endoscopy at follow-up and optionally at day 3, 7, 14, 28.

Response (R) = Mayo endoscopic score of 0 or 1 at follow-up (blinded independent reading) AND subsequent anti-TNF therapy > 1 year, **Non-Response (NR)** = all other patients.

Outcomes: TNF, IL6, IL10 and anti-TNF levels in all compartments. OSM and IL12p40 in T (F anti-TNF with ELISA and cytokines and PB and T anti-TNF with a bead-based immunoassay). T levels were normalized for gram of protein (gop). To differentiate pharmacokinetic (PK) from pharmacodynamic (PD) failures, we calculated T anti-TNF/TNFα and classified values above the median as sufficient PK (Good PK) and values below as insufficient PK (Bad PK).

Results

Table 1. Baseline characteristics

	Responders	*Non-responders*	*p-value*
n (patients)	39	52	
Gender [Male (%)]	15 (38.5)	29 (55.8)	0.155
age (median [IQR])	31.00 [24.50, 43.00]	36.00 [30.75, 46.00]	0.114
anti-TNF [IFX (%)]	33 (63.5)	31 (79.5)	0.154
MES at baseline = 3 (%)	29 (74.4)	30 (57.7)	0.154
Extent baseline = E3 (%)	14 (42.4)	23 (54.8)	0.318
CRP (median [IQR])	9.85 [2.40, 45.70]	5.80 [1.60, 25.00]	0.404
Albumin (median [IQR])	39.60 [34.00, 43.72]	42.25 [38.00, 45.00]	0.08

Sample collection: T, PB and F samples were collected from 71 (31 R, 40 NR), 91 (39 R, 52 NR) and 27 (9 R, 18 NR) patients, respectively.

Outcomes

At Baseline, cytokine levels were similar in all compartments.
At follow-up, PB IL6 was lower in R (p=0.045). All F cytokines were significantly higher in R (TNFα: p<0.001; IL6: p<0.001; IL10: p<0.001). In T, IL6 and OSM were lower and IL12p40 higher in R (IL6: p=0.004; OSM: p=0.01; IL12p40: p=0.021).

Stratification for PK in Tissue samples

T anti-TNF/TNFα was calculated (median: 2.5061, range: 0.59 - 11.34). A trend towards lower values in R vs NR was observed (median 4.30 vs 7.73, p=0.568).

After stratification for PK (fig. 1), T IL6 was highest in Good PK NR vs Good PK R (6905 vs 2980 pg/gop, p=0.002) and OSM was lowest in R vs NR groups (2466 vs 36111 pg/gop in Good PK R vs Good PK NR, p=0.002). Trends were observed towards highest IL10 in Bad PK R and Highest IL12p40 in Good PK R, although not significant. PB and F concentrations were similar.

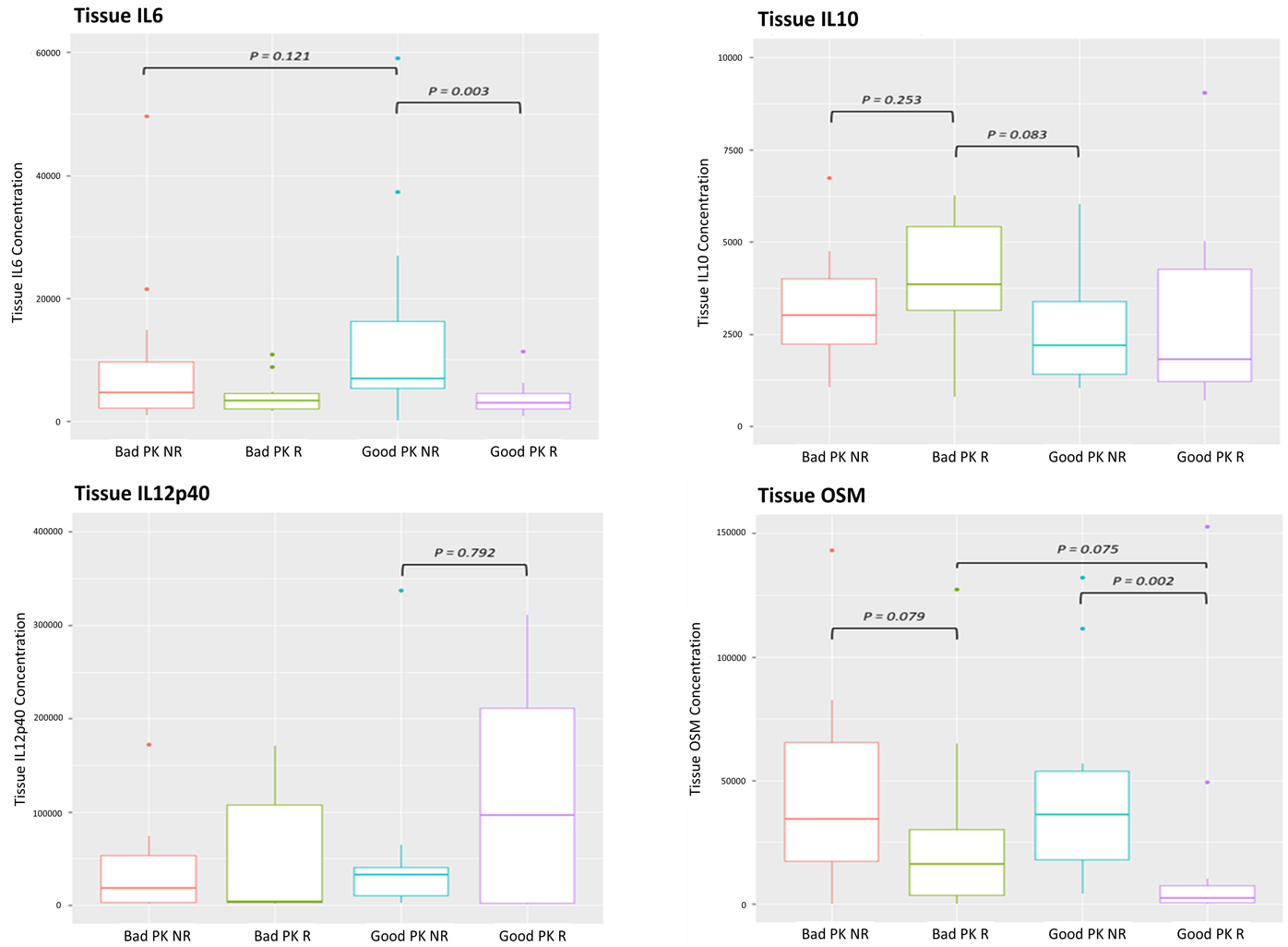

Figure 1. Tissue cytokines in pg / gram of protein (gop). All patients, stratified for response and PK status.

Conclusion

- **Baseline cytokine concentrations in peripheral blood, colonic tissue and faeces did not predict response to anti-TNF induction treatment in UC**
- **At follow-up, responders showed lower OSM and IL6 in R but not in NR despite similar peripheral blood and tissue anti-TNF concentrations**
- **Responders showed higher faecal cytokine shedding**
- **Pharmacodynamic failure (Good PK NR) was characterized by highest tissue IL6, indicating it is a driver to inflammation alternative to anti-TNF**
- **R was characterized by lowest tissue OSM regardless of PK status, indicating OSM mainly reflects disease activity**
- **Combination treatment might improve outcome in Good PK NR**