

BACKGROUND

- Tofacitinib is the 1st in class Janus Kinase (JAK) inhibitor, approved for moderate-to-severely active ulcerative colitis (UC).
- In contrast to monoclonal antibodies, very little is known about pharmacokinetic-pharmacodynamic profile of small molecules.

AIM:

- To assess pharmacokinetic-pharmacodynamic changes in tofacitinib (TFC) treated UC patients
- To assess the potential of STAT3 phosphorylation as predictive / monitoring tool, as it has been proposed as a marker of efficacy mechanistically

METHODS

- 30 consecutive UC patients with active endoscopic disease (Mayo endoscopic subscore 2-3) initiating TFC were recruited at the University Hospitals Leuven (Belgium) and the Amsterdam UMC (The Netherlands) (Table 1)

Sex, women, n (%)	17 (56.7)
Age at initiation of tofacitinib, y, median [IQR]	47.1 (28.2 – 53.7)
Disease duration, y, median [IQR]	7.5 (3.1 – 15.4)
Faecal calprotectin, mg/g, median [IQR]	1718.6 (1446.8 – 1800)
Serum albumin, g/L, median [IQR]	41.7 (40.8 – 44.2)
Partial Mayo score, median [IQR]	10.0 (9.0 – 11.0)
Endoscopic scoring	
- Mayo endoscopic sub-score, median [IQR]	3.0 (2.0 – 3.0)
- Ulcerative colitis index of severity, median [IQR]	5.0 (4.0 – 6.0)
Histologic scoring	
- Nancy index, median [IQR]	3.0 (3.0 – 3.0)
Disease extent, n (%)	
- Proctitis E1	4 (13.3)
- Left-sided colitis E2	14 (40.0)
- Extensive colitis E3	12 (46.7)
Concomitant medication, n (%)	
- Corticosteroids	
• Topical	7 (23.3)
• Systemic	8 (26.7)
- Immunomodulators	0 (0.0)
Smoking status, n (%)	
- Active smoking	4 (13.3)
- Previously smoking	10 (33.3)
- Never smoked	16 (53.3)

Table 1: Baseline features

- Patients initiated TFC 10mg BID till week 8, with subsequent de-escalation to 5mg BID upon discretion of the treating physician
- Patients were prospectively monitored, with sampling (colonic tissue and serum) at baseline and 8-16 weeks after TFC initiation (Figure 1).
- Endoscopic improvement was defined as a Mayo endoscopic subscore 0-1.

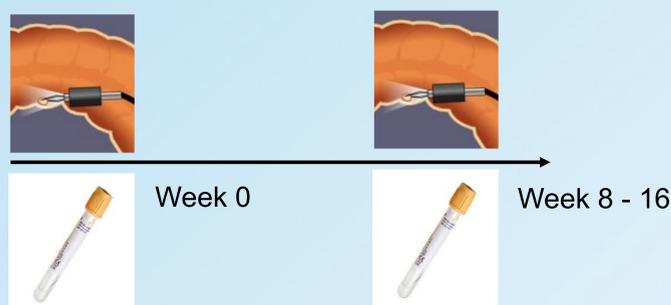


Figure 1: Sampling strategy and prospective monitoring

- TFC was extracted from tissue using acetonitrile, dried down and quantitated using mass spectrometry. Both total as well as phosphorylated STAT3 were measured in lysed tissue using specific antibodies with an ultrasensitive luminescent oxygen channelling assay.

RESULTS

- TFC tissue and serum concentrations correlated significantly ($r=0.92$, $p<0.001$), though were significantly higher in tissue (median 520.19ng/g vs 17.35ng/mL, $p<0.001$) (Figure 2).

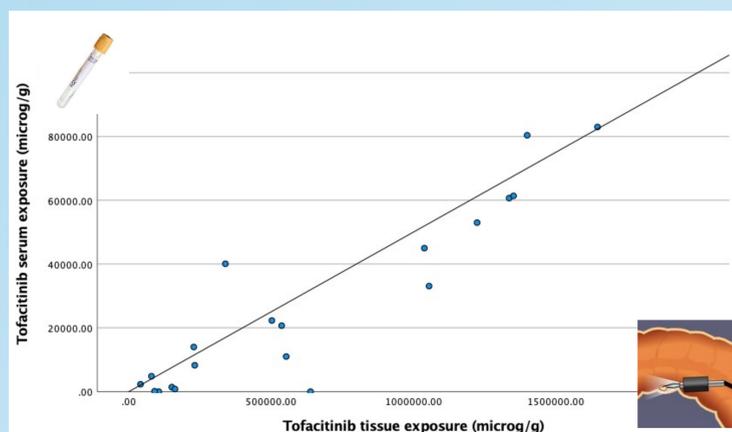


Figure 2: Correlation between TFC tissue and serum concentration

- In contrast to TFC serum exposure ($p=0.26$), TFC tissue exposure at the end of induction was associated with endoscopic improvement by week 16 ($p=0.04$) (Figure 3).

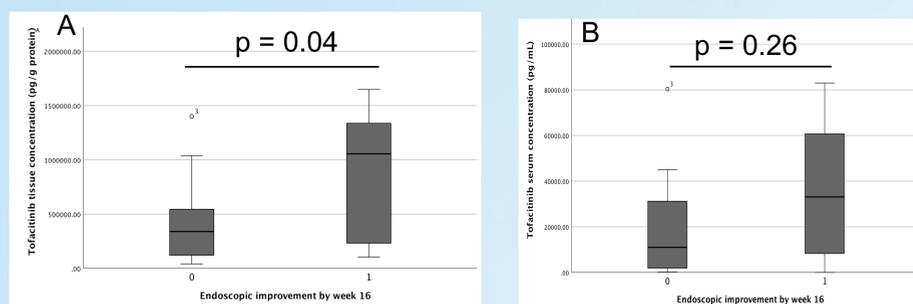


Figure 3: Comparison in tofacitinib tissue (A) or serum (B) exposure between (non-)responders by week 16

- In TFC responders ($n=14$), TFC tissue exposure exceeded the concentration required to block 90% of the target (IC90) reported in literature (median tissue exposure 1,055.00ng/g; IC90 823ng/g). TFC tissue exposure in non-responders ($n=16$) was lower, but clearly exceeded the IC50.
- Although IL-6 was not significantly downregulated after TFC induction, a significant decrease in the ratio of mucosal IL-6 driven phosphorylated STAT3 over total STAT3 ($pSTAT3/STAT3$) was observed in responders ($p=0.05$), but not in non-responders ($p=0.88$) (Figure 4).

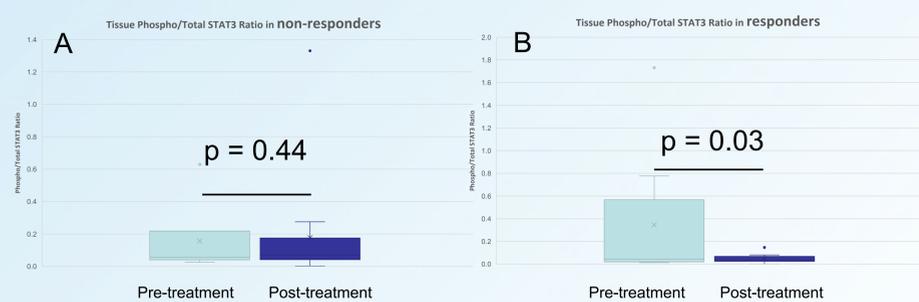


Figure 4: Tissue phospho/total STAT3 before and after TFC therapy in non-responders (A) and responders (B)

- The $pSTAT3/STAT3$ ratio also correlated significantly with faecal calprotectin ($r=0.35$, $p=0.05$), but only weakly with the Mayo endoscopic sub score ($r=0.22$, $p=0.13$).
- Baseline mucosal $pSTAT3/STAT3$ did not differ significantly between future responders and non-responders.

CONCLUSIONS

- We demonstrated for the first time a mucosal exposure-response relationship with tofacitinib in UC
- $pSTAT3/STAT3$ ratio is a potential molecular marker to track response, directly linked to the MOA of tofacitinib
- Can an increased local dose of tofacitinib result in better efficacy without compromising safety? UC induction trial with PGN-600 (topical tofacitinib) soon to be expected.