Patients with High Visceral Adipose Tissue Burden Have a Higher Target Therapeutic Infliximab Concentrations: Should We Be Filling the VAT?

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Introduction

- In patients with Crohn's disease (CD) or ulcerative colitis (UC), body composition (BC) and specifically visceral adipose tissue (VAT) has been associated with worse response to infliximab (IFX).
- The mechanisms of these observations are unknown, but VAT could potentially play a role in drug clearance and volume distribution.
- VAT may also explain heterogenicity in target trough levels of IFX (TLI) associated with favorable outcomes.

Aims

- The aim of this study was to assess whether TLI cutoffs linked to efficacy in patients with CD/UC receiving IFX vary based on VAT burden.

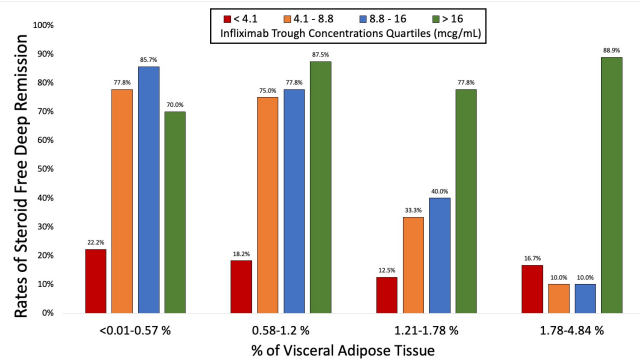
Methods and Materials

- **Design:** prospective cross-sectional study including patients with CD or UC receiving maintenance IFX therapy (≥ 22 weeks).
- Variables collected at enrollment included disease phenotype, inflammation biomarkers (c-reactive protein [CRP] and fecal calprotectin [FCal]), Harvey Bradshaw Index (HBI) and simple endoscopic score (SES-CD) in CD, partial and endoscopic Mayo score (PMS and EMS) in UC.
- TLI and anti-drug antibodies (ADA) were measured using a drug-tolerant assay.
- **BC parameters were measured using a GE Lunar iDXA scan**
- **Primary outcome** was steroid-free deep remission (SFDR) defined as HBI <5 in CD and PMS<2 in UC and a normal CRP and FCal while off corticosteroids.
- **Secondary outcome** was endoscopic remission (EMS≤1 in UC or SES-CD≤2) when colonoscopy was done within 12 weeks of index visit.
- Optimal ITL cutoffs for SFDR by VAT% (VAT/total body mass) were determined using the Youden J statistics (J).

RESULTS

- 142 patients were enrolled.
- Of those, 110 had endoscopic assessment done.
- Differences between patients by SFDR status are shown in **Table 1**.
- An exposure-response association was identified across all VAT%, with higher ITL thresholds associated with higher VAT% (**Figure 1**).
- The optimal ITL cutoffs associated with SFDR and endoscopic remission were 3.9 mcg/mL (J: 0.52) and 4.9 mcg/mL (J: 0.56) for patients in the lowest two VAT% quartiles (<1.2%)
- Optimal ITL cutoffs associated with SFDR and endoscopic remission for those patients in the highest two VAT% quartiles were 15.3 mcg/mL (J: 0.63) and 13.6 mcg/mL (J: 0.57), respectively.

Figure 1



Infliximab trough levels associated with treatment efficacy were higher on those patients with a higher visceral adipose tissue burden

Table 1

	Active Disease	Steroid-Free Deep Remission	P value
Female gender [n (%)]	40 (55.6)	39 (55.7)	0.99
Age [mean in years (SD)]	43 (17)	39 (17)	0.10
Hispanic ethnicity [n (%)]	3 (4.2)	3 (4.3)	0.97
Disease Type [n (%)]			0.47
Crohn's disease	42 (58.3)	45 (64.3)	
Ulcerative colitis	30 (41.7)	25 (25.7)	
Active smoker at baseline [n (%)]	5 (6.9)	9 (12.86)	0.24
Years with IBD [Median in years (IQR)]	2 (1-8)	1 (1-5)	0.10
Body Composition Assessment			
Total Mass [Mean in Kg (SD)]	84.0 (21.3)	78.0 (19.2)	0.081
Body Mass Index [Mean in Kg/m^2 (SD)]	28.8 (6.3)	26.8 (6.3)	0.07
Percentage of Body Fat [Mean in % (SD)]	48.9 (11.0)	48.0 (10.6)	0.62
Total VAT[1] Mass [Mean in gr (SD)]	1417.8 (1116.0)	893.1 (769.0)	0.0014*
VAT[1] percentage of total body mass [Mean in % (SD)]	1.54 (0.96)	1.04 (0.75)	0.0007*
VAT[1] percentage of total fat mass [Mean in % (SD)]	29.3 (15.3)	20.9 (14.2)	<0.001*
Percentage of lean mass [Mean in Kg (SD)]	59.3 (9.1)	62.8 (1.3)	0.04*
Lean mass [Mean in Kg (SD)]	48.9 (11.0)	48.0 (10.6)	0.62
Previous Use of Biologic [n (%)]	16 (22.2)	8 (11.4)	0.086
Use 5-aminosalicilates [n (%)]	7 (9.7)	5 (7.1)	0.58
On combination therapy with immunomodulator [n (%)]	30 (41.7)	43 (61.4)	0.019*
Combination therapy with immunomodulator [n (%)]			0.013*
None	42 (58.3)	28 (40.0)	
Methotrexate	6 (8.3)	11 (15.7)	
Azathioprine	23 (31.9)	28 (40.0)	
Mercaptopurine	1 (1.4)	3 (4.3)	
Simple Endoscopic Score-CD[2,5] [Median (IQR)]	8 (4-10)	0 (0-1)	<0.0001*
Endoscopic Mayo Score[3,5] [n (%)]			0.001*
0	None	7 (38.9)	
1	1 (3.6)	2 (11.1)	
2	14 (50.0)	4 (22.2)	
3	13 (46.4)	5 (27.9)	
SIBDQ[5] [Mean (SD)]	50 (12.4)	53 (12.5)	0.271
Infliximab trough concentration [Median in µg/mL (IQR)]	5.7 (2.6-10.7)	14.4 (6.3-20.6)	<0.0001*
Detectable anti-infliximab antibodies [n (%)]	4 (5.6)	2 (2.7)	0.42

(1) VAT: Visceral Adipose Tissue Mass.
(2) Only patients with Crohn's disease.
(3) Only patients with ulcerative colitis
(4) Patients with endoscopic assessment
(5) SIBDQ: Simple Inflammatory Bowel Disease Questionnaire
(*) Statistically significant

Conclusions

- Patients with a higher visceral adipose tissue burden may require higher infliximab trough levels to achieve remission.
- Clinicians should therefore consider visceral adipose tissue burden when performing therapeutic drug monitoring of infliximab.