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Scientific paper: Body composition profile is associated with response to anti-TNF therapy in Crohn's disease and may offer an alternative dosing paradigm.

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Abbreviations:

BMI – body mass index

TNF – tumour necrosis factor

CT – computer tomography

CD – Crohn's disease

IBD – inflammatory bowel disease

LBM – lean body mass

Authorship Statement:

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(ii) Specific author contributions:

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Author Contributions

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Abstract

Background: Anti-tumour necrosis factor(TNF)s form a major part of therapy in Crohn's disease and have a primary non-response rate of 10-30% and a secondary loss of response rate of 5% per year. Myopenia is prevalent in Crohn's disease and is measured using body composition analysis tools.

Aim: To test the hypothesis that body composition can predict outcomes of anti-TNF primary non-response and secondary loss of response.

Methods: Between January 2007 to June 2012, 106 anti-TNF naïve patients underwent anti-TNF therapy for Crohn's disease with body composition parameters analysed using CT scans to estimate body fat-free mass. The outcome measures were primary non-response and secondary loss of response. COX-regression analysis was used with three-year follow-up data.

Results: 106 patients were included for analysis with 26 (24.5%) primary non-responders and 29 (27.4%) with secondary loss of response to anti-TNF therapy. Sex-specific cut-offs for muscle and fat were ascertained by stratification analysis. On univariate analysis, primary non-response was associated with low albumin (OR 0.94;0.88-0.99,p=0.04) and presence of myopenia (OR4.69;1.83-12.01,p=0.001) when taking into account patient's medical therapy, severity of disease and body composition. On multivariate analysis, presence of myopenia was associated with primary non-response (OR 2.93;1.28-6.71,p=0.01). Immunomodulator therapy was associated with decreased secondary loss of response (OR 0.48;0.23-0.98,p=0.04). BMI was poorly correlated with lean body mass ($r^2=0.15$, $p=0.54$).

Conclusion: In this cohort study, body composition profiles did not correlate well with BMI. Myopenia was associated with primary non-response with potential implications for dosing and serves as an explanation for pharmacokinetic failure.

Keywords

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Crohn's disease, anti-TNF, Computer tomography imaging, medical therapy, treatment outcomes, prediction.

Introduction

Crohn's disease (CD) is a chronic relapsing inflammatory bowel disease (IBD) of multifactorial aetiology. It has long been identified that patients with IBD have altered body composition during various disease states.¹⁻³ This may be due to a multitude of factors such as malnutrition, a catabolic state and malabsorption which alters body composition.^{4,5} Decreased muscle mass or myopenia is prevalent in patients with CD who are in clinical remission.¹ Furthermore, recent studies have shown that body composition influences outcomes in Crohn's patients with surgery, attracting more post-operative complications.^{6,7} CD phenotype may also play a role in a patient's body composition with luminal CD contributing to decreased lean body mass.⁸

Anti-TNF therapy forms the backbone of treatment in patients with moderate to severe Crohn's disease. However, it has a primary non-response rate of 10-30% in clinical practice and secondary loss of response rate of about 5% per patient-year,^{9,10} potentially exposing patients to side-effects with minimal therapeutic benefit. This article is protected by copyright. All rights reserved

benefit. BMI has been linked to primary non-response in observational cohort studies and may be due to pharmacokinetic effects on drug levels.¹¹ Skeletal muscle and adipose tissue have demonstrated either pro or anti-inflammatory properties through the release of cytokines¹². The recent discovery of the role of creeping fat in IBD via Substance P by releasing Il-17 in pre-adipocytes and increasing Il-17A receptors in the IBD colon, has shown the important role of visceral adiposity in the development of inflammatory bowel disease.¹³ It has been observed that inter-patient variability of anti-TNF levels was poorly associated with BMI, but intra-patient anti-TNF levels were stable.¹⁴ However, in a small population of anti-TNF naïve patients, the body composition parameters that correlated with anti-TNF trough levels were body surface area, fat-free mass index (FFMI) and skeletal muscle index (SMI).¹⁵ Therefore, we hypothesized that the composition of a patient's body mass may demonstrate a more refined method of analysis and provide better understanding of the causes of primary non-response and secondary loss of response.

We aim to demonstrate that using a validated tool for assessing body composition, we can predict primary non-response or secondary loss of response in patients receiving anti-TNF therapy with moderate to severe Crohn's disease using a patient's muscle and fat content.

Methods

Patient Population

A total of 650 consecutive anti-TNF naïve patients undergoing anti-TNF therapy at St Mark's Hospital, London, between January 2007 and June 2012 were identified from a database. Patients were selected if: an abdominal CT scan was performed within 6 months of commencement of anti-TNF therapy for moderate to severe luminal Crohn's disease and images retrievable in an electronic format; at least 3-year follow-up data on therapy outcomes was available; patient height and weight data were recorded. Patients were excluded if the indication for their initial anti-TNF application was perianal fistulising disease.

Demographics including age, sex and BMI were collected. Patient's Montreal classification at diagnosis was identified and severity of disease was assessed with levels of CRP and albumin at time of induction therapy. An albumin level less than 30g/L was considered to be low. Primary non-response was defined as

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cessation of anti-TNF within 6 months of first administration as deemed by their treating gastroenterologist using global physician assessment. Patient who had cessation of therapy due to drug intolerance were not included as primary non-responders. Secondary loss of response was defined as a recurrence of patient's symptoms after a period of improvement with subsequent need for cessation or switch of anti-TNF therapy. At the time, therapeutic drug monitoring was not routine practice. Endpoints for analysis were primary non-response and secondary loss of response. To demonstrate the wide variations in potential drug levels due to inter-patient variability in body composition, a hypothetical dose of 5mg/kg of infliximab was given with calculated drug levels from fat free mass.

Computed Tomography Image Analysis

Images were retrieved from digital storage in the Picture Archiving and Communication System. Computed tomographic image analysis was performed using Slice-O-Matic V4.3 software (Tomovision, Montreal, Canada) as described previously.¹⁶ The study was limited to CT given it was the predominant modality during the study period with Slice-o-Matic being validated for use in CT and MRI imaging. Briefly, total skeletal muscle and adipose tissue surface area (cm²) were evaluated on a single image at the third lumbar vertebra (L3) level as per previous validated data¹⁷ using Hounsfield unit (HU) thresholds of -29 to 150 for skeletal muscle, -150 to 50 for visceral and subcutaneous adipose tissue (See Supplementary Figure 1). Visceral, subcutaneous fat area (VFA, SFA), and skeletal muscle area (SMA) or skeletal muscle index form the taxonomies used. The sum of skeletal cross-sectional muscle areas were normalized for stature (m²) and reported as lumbar skeletal muscle index (LSMI) (cm²m²). Muscle attenuation (MA) in HUs was reported for the whole muscle area. Reduced LSMI (myopenia) and low MA (myosteatosi) were defined. The database is registered with the UK National Research Ethics Committee (reference number: 14/LO/2010).

Statistical Analysis

SPSS v19.0 (IBM SPSS Statistics, Ontario, Canada) was used for statistical analysis. This article is protected by copyright. All rights reserved

analysis. Body composition parameters are presented as median values and interquartile ranges (IQR) and are categorized into sex-specific groups. The definition of myopenia and myosteatosi s were the lowest quartiles of LSMI and MA, while visceral obesity was defined as the highest quartiles of VFA. This is a validated method from previous work without a reference cohort, performed in previous cancer populations.¹⁷⁻¹⁹ Mann-Whitney and Fisher exact tests were used to test for differences in continuous and categorical variables, respectively. Univariate and multivariate logistic regression were used to assess the relationship between muscle depletion and myosteatosi s and multiple categorical variables with the dichotomous outcomes of primary non-response and secondary loss of response.

Results

650 patients who were administered their first dose of anti-TNF therapy were included with 250 patients having CT studies prior to their first dose. Of these, 106 patients had CT studies within 6 months of anti-TNF commencement (Figure 1).

47 of 106 (44%) were male with a median age of 44.8 years (Interquartile range (IQR) 34.2-53.6) and 13 of 106 (12.3%) were considered obese (BMI> 30). Primary non-response occurred in 26 (24.5%) patients with secondary loss of response in 29 (27.4%) and continued usage at the time of census in 50 patients (47.2%). Study cohort details including Montreal classification, baseline biochemistry data and medical therapy are summarized in Table 1. The median duration of anti-TNF therapy was 22.7 months (range 6.1-37.7). There were 65 (61.3%) patients on combination therapy with immunomodulator at time of induction of anti-TNF.

The sex-specific cut-offs for L3 skeletal muscle index ascertained by the lowest quartile were 31.0 cm²/m² for men and 32.37 cm²/m² for women with patients below these values being classified as having myopenia. Lumbar visceral fat index (LVFI) was calculated with cut-offs being the 75th centile (40.7 for males and 31.8 for females) with values above this being classified as visceral obesity. Muscle attenuation (MA) was measured in Hounsfield units (HU) with cut-offs being the 25th centile (31.0 for males, 29.5 for females), which was defined as myosteatosi s.

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Primary non-response

There were 26 patients (24.5%) who experienced primary non-response. Of these, 15 (57.7%) were myopenic. There were 6 (25%) patients with nonvisceral obesity and 5(25%) with myosteatosiis.

On univariate analysis, presence of myopenia [Odds ratio (OR) 4.69;1.83-12.01,p=0.001] and albumin (OR 0.94;0.88-0.99,p=0.04) predicted primary non-response. When myopenia and albumin were entered into multivariable analysis, only presence of myopenia was significant (OR 2.93;1.28-6.71,p=0.01) (Figure 2). No other factors, including BMI or inflammatory markers (C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)) at induction were shown to be significant (Table 2). There were no statistical differences between patients who were myopenic and non-myopenic in regard to their demographics (disease duration, phenotype, age or biochemical markers of severity). The rates of primary non-response with each quartile of lumbar skeletal muscle index (LSMI) correlated with the lowest quartile of lumbar skeletal muscle index (myopenic patients). The rate of primary non response in the lowest quartile was 11 (40.7%) and decreased to 7 (25.9%) in the 2nd quartile, 3(11.5%) in the 3rd quartile and 5(19.2%) in the fourth quartile. (Table 3)

Secondary loss of response

In our cohort, 29 (27.4%) patients had secondary loss of response. The reason for the switch or cessation of anti-TNF therapy was due to recurrence in symptoms after a period of clinical remission. Of the patients that had secondary loss of response, 7 (24.1%) were myopenic, 8 (27.6%) had visceral obesity and 5 (17.3%) had myosteatosiis. On univariate analysis (Table 4), the use of immunomodulator was protective for secondary loss of response (OR 0.48;0.23-0.98,p=0.04) (See Figure 3). However, none of the body composition factors or biochemistry at induction were associated with secondary loss of response.

Obesity

BMI > 30, defined obesity, did not predict for primary non-response or secondary loss of response and was poorly correlated with all composite markers of body composition (LSMI, LVFI and MA). There were 13 (12.3%)

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patients who were classified as obese (BMI > 30) and 31 (29.2%) being underweight (BMI < 20). Of the obese patients, only 5 did not meet criteria for having visceral obesity.

Pharmacokinetic sub-study

The association between estimated total body fat-free mass and BMI was poor ($r^2=0.15$; $p=0.54$). A consequence of high fat mass or low fat free mass would be a larger volume of distribution of anti-TNF therapy. This effectively means higher doses are required to obtain a particular drug level. A simulated hypothetical dose of anti-TNF at 5 mg/kg of body weight was used to calculate the variation in the resulting anti-TNF per kg estimated fat-free mass. The overall distribution of estimated anti-TNF per kg fat-free mass varied greater than six-times (range 14.36– 97.92 mg anti- TNF per kg) (Figure 4a).

Men were more likely to have a lower fat-free mass in proportion to their BMI than women ($p=0.05$), and thus a larger proportion of men than women were in the highest ranges of anti-TNF per kg fat-free mass. This is demonstrated in Figure 4b.

Discussion

Myopenia is associated with primary non-response to anti-TNF therapy in patients with moderate to severe luminal Crohn's disease. This study also demonstrates that there is wide variation in body composition profile, thus tailoring medication to each patient is important. This may be due to a multitude of factors including underlying luminal disease causing malabsorption^{1,5,20,21} and the interplay between pro-inflammatory and anti-inflammatory cytokines released by adipocytes or muscle.^{22,23} Body composition is important in determining the volume of distribution of medications such as anti-TNF therapy and it is plausible that this contributes to pharmacokinetic failure due to inadequate dosing.²⁴

The mechanisms of primary non-response as laid out in a review by Ding et al include pharmacokinetic, pharmacodynamic or immunogenic failure.¹⁰ Following administration, anti-TNF is distributed centrally to extracellular fluid with a volume of distribution of about 0.11/kg.^{25,26} The most likely explanation for non-

response due to myopenia would be inadequate dosing due to increased clearance or decreased uptake resulting in pharmacokinetic failure. Unfortunately, drug levels were not available at the time of this study but would be an area of future research. Furthermore, taking into account patient's disease phenotype and severity at time of induction, myopenia was associated with primary non-response to anti-TNF therapy. However secondary loss of response was not associated with any of the body composition factors. Rather, combined immunomodulator at time of induction was protective of secondary loss of response as shown in Figure 3, which complements the existing literature.^{27,28} The lack of association may be due to anti-TNF therapy improving inflammatory myopenia after induction therapy as demonstrated in a prospective observational study.²⁹ The finding that combination therapy with an immunomodulator and anti-TNF is protective of secondary loss of response demonstrates that this may prevent immunogenic failure through the inhibition of antibody formation.²⁷

Intra-individual variation in anti-TNF level is dramatic given that anti-TNF therapy is absorbed and distributed centrally throughout the body.³⁰ Data from oncology utilising a similar pharmacokinetic study with FFM as the volume of distribution of chemotherapy drugs rather than body-surface area, showed similar variations in drug level within the cohort.¹⁹ Therefore, the composition of an individual's mass is important in determining correct dosing. Body surface area has been shown to have a negative correlation with adalimumab trough levels and is correlated to muscle content (FFMI: $r=-0.494$, $p=0.045$), but not with fat parameters (BFMI: $r=-0.099$ $p=0.708$).¹⁵ Our study in this large cohort confirms these findings, as pharmacokinetic failure may result from myopenia, but no correlation was identified with visceral obesity. The median albumin in our cohort was 37 g/L (IQR 37-40). Our finding that albumin (less than 30g/L) was associated with primary non-response on univariate analysis (OR 0.94;0.88-0.99, $p=0.04$) also supports the current literature and demonstrates that patients with severe disease may require higher doses to induce remission.¹¹

A consistent finding is that there is loss of lean mass with preserved fat mass.³ Other possible causes of pharmacokinetic failure may be due to increased drug clearance in patients with higher (>120kg) and low (<40kg) body weight.³¹ Our hypothetical scenario of anti-TNF infusion at a dose of 5mg/kg when taking into
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account patient's lean body mass revealed six-fold variation in anti-TNF per kg fat-free mass.

The wide variation in body composition profiles of patients with Crohn's disease and the additional data that can be obtained from CT images can be used in personalizing medical therapy. Within our cohort, there were 33 (31.1%) patients who had myopenia and 24(22.6%) with visceral obesity. BMI did not predict for primary non-response or secondary loss of response. Furthermore, BMI was poorly correlated with lean body mass ($r=-0.15$, $p=0.54$). It is important to note that patients who are obese have a wide variation in body composition profile and 38.5% of those who had BMI> 30 did not have visceral obesity.

A large proportion of patients with Crohn's disease are also affected by sarcopenia or the functional loss of muscle with rates of up to 60% as demonstrated in a study of those in clinical remission.¹ Infliximab has been shown to reverse inflammatory sarcopenia in Crohn's disease in a recent publication.²⁹ This study demonstrated that those receiving infliximab had increased muscle volume at the right quadriceps femoris from 1505 cm³ at baseline to 1607 cm³ ($p=0.012$) following induction at week 16. There was a coinciding increase in muscle strength with a reduction in pro-inflammatory cytokine Il-6 from 4.195ng/ml at week 1 to 0.175ng/ml at week 25 ($p=0.037$). These findings suggest that patients with Crohn's have loss of muscle mass and that subsequent treatment with anti-TNF therapy may possibly reverse this.

One possible explanation for lower muscle mass in CD patients is poor nutritional status. In CD, selected micro and macro-nutrient deficits, loss of body cell mass and muscle strength are frequent even in remission.⁴ In a recent publication by van Langenberg et al,¹² there was a 54% lower phosphorylated:total Akt ratio in muscle samples ($p<0.05$) showing a key decrease in the hypertrophy signalling pathway. However, there were no differences in the atrophy signalling targets MuRF-1 or atrogin-1 mRNA protein levels.

Therefore, the rate of replacement of muscle protein may not be adequate to meet the rate of muscle proteolysis in an inflammatory state.³² In an in vivo animal model, it was shown that colitis increased albumin synthesis at the expense of muscle protein synthesis in macronutrient-restricted piglets.³³

Demonstrating that myopenia is prevalent in Crohn's patients is important for its functional effects on patients including weakness and quality of life.^{4,34,35} Much of the focus on anti-TNF therapy has been on goals of therapy particularly mucosal healing.^{9,36,37} However, early work by Wiese et al, demonstrated that infliximab improved nutritional indices along with inflammatory markers with possible decrease lipolysis and resultant weight gain.³⁸ Much of this may be attributed to the decrease in inflammatory sarcopenia.²⁹

The main limitation of this retrospective observational study design is the inability to determine causality. Other clinical parameters such as smoking could not be obtained given the retrospective nature of the data. Also, therapeutic drug monitoring was not available during the time of this study and therefore the endpoint of anti-TNF cessation or switch was used as the definition of secondary loss of response. However, myopenia was identified to be a significant factor after adjusting for biomarkers of disease severity such as CRP and albumin. Although albumin may be a marker for chronic disease, this was not seen to be significant on multivariable analysis. Furthermore, this work will lead onto further studies detailing adequate dosage adjustments which may be made with body composition markers as the main determinant rather than body mass index and with the measurement of drug levels, which will have implications for therapy. Potentially, measuring body composition in patients prior to anti-TNF therapy may allow for a more accurate dosing paradigm in personalizing medical therapy.

Conclusion

Body composition is important in analysis of patients with Crohn's disease. Our study has identified myopenia prior to anti-TNF administration was associated with primary non-response of anti-TNF therapy in Crohn's patients. Adjusting dosage and undertaking a holistic management approach with nutrition and muscle-building exercises may improve therapeutic outcomes in patients commencing anti-TNF therapy.

Authors' declaration of personal interests:

(i) Nik Ding has served as a speaker and an advisory board member for Abbvie and Falk

2. Declaration of funding interests:

(i) This study was funded in part by ForCrohn's charity

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Table 1: Background and demographics of study cohort

Demographics

Sex	Male N(%)	47 (44.3)
	Female N(%)	59 (55.7)
Age in yrs (Med (IQR))		44.84 (34.16-53.55)
BMI in kg/m ² (Med (IQR))		22.31 (19.60-(26.87
BMI categories	Obese (BMI >30)	13 (12.3)
	Overweight (BMI 25-30)	23 (21.7)
	Normal (BMI 20-25)	39 (36.8)
	Underweight (BMI<20)	31 (29.2)
Montreal classification N(%)		
	A1	17 (16.0)
	A2	69 (65.1)
	A3	15 (14.1)
	L1 – terminal ileum	7 (6.6)
	L2 - colon	16 (15.1)
	L3 - ileocolonic	87 (82.1)
	L4 – upper GI	0 (0)
	B1 – inflammatory disease	31 (29.2)
	B2 - stricturing disease	21 (19.9)
	B3 – penetrating disease	49 (46.2)
Biochemistry (Med (IQR))		
	CRP (mg/L)	5.0 (1.0-19.7)
	ESR mm/hr	10.5 (3.0-26.3)
	Albumin (g/L)	37 (31-40)
Medical therapy N(%)		
	Immunomodulator	65 (61.3)
Anti-TNF	Infliximab	73 (68.9)
	Adalimumab	33 (31.1)

Outcome N(%)	
PNR	26 (24.5)
SLOR	29 (27.4)
Ongoing	50 (47.2)
Remission	1 (0.9)
Months on anti-TNF (Med (IQR))	22.65 (6.05-37.68)

PNR = Primary Non-response

SLOR = Secondary Loss of Response

Table 2: Univariate and multivariate analysis of patient demographics, medical therapy, biochemistry and body composition factors on outcome of primary non response (PNR) to anti-TNF therapy

Variables		Univariate Analysis		Multivariate Analysis	
		OR 95% CI	p-value	OR 95% CI	p-value
Gender	Male	1			
	Female	1.37 (0.56-3.40)	0.49		
Age	(b=-0.002)	0.99 (0.96-1.03)	0.91		
BMI	BMI < 30	1			
	BMI > 30	0.52 (0.11-2.52)	0.42		
Medical Therapy					
Immunomodulators*	Absent	1			
	Present	0.54 (0.22-1.32)	0.09		

Anti TNF drug					
Infliximab	1	1			
Adalimumab	2	0.32 (0.10-1.02)	0.052		
Biochemistry					
CRP (mean)		1.012 (0.99-1.03)	0.28		
Albumin (mean) #		0.94 (0.88-0.99)	0.04	0.97(0.92-1.01)	0.15
Body composition factors					
Myopenia #	Absent	1		1	
	Present	4.69(1.83-12.01)	0.001	2.93(1.28-6.71)	0.01
Visceral Obesity	Absent	1			
	Present	1.03 (0.36-2.96)	0.95		
Myosteatorsis	Absent	1			
	Present	1.13 (0.33-3.17)	0.92		
Myopenic Obesity	Absent	1			
	Present	0.52 (0.11-2.53)	0.42		

*azathioprine, mercaptopurine or methotrexate

significant at p<0.05 on univariate analysis

Table 3: Primary non response rates to anti-TNF therapy with each quartile of muscle mass with correlation between lean skeletal muscle index and primary non response.

Degree of myopaenia	PNR (%)		Chi-squared, <i>P</i>	Total
	No	Yes		
1 st (<25%)	16 (59.3)	11 (40.7)	0.02 (against no myopaenia)	27
2 nd (25-49%)	20 (74.1)	7 (25.9)	0.25 (against 1 st)	27

			quartile)	
3 rd (50-74%)	23 (88.5)	3 (11.5)	0.02 (against 1 st quartile)	26
4 th (>75%)	21 (80.8)	5 (19.2)	0.09 (against 1 st quartile)	26
No myopaenia (i.e. >25%)	64 (81.0)	15 (19.0)	0.02 (against 1 st quartile)	79
Total	80	26	N/A	106

Table 4: Univariate and multivariate analysis of patient demographics, medical therapy, biochemistry and body composition factors on outcome of secondary loss of response to anti-TNF therapy.

Variables		Univariate Analysis		Multivariate Analysis	
		OR 95% CI	p-value	OR 95% CI	p-value
Gender	Male	1			
	Female	0.80 (0.34-1.90)	0.62		
Age	(b=-0.009)	1.01 (0.98-1.04)	0.59		
BMI	BMI < 30	1			
	BMI > 30	1.80 (0.54-6.02)	0.32		
Medical therapy					
Immunomodulators* #	Absent	1			
	Present	0.48 (0.23-0.98)	0.04		
Anti TNF drug					
Infliximab	1	1			

Adalimumab	2	1.88 (0.77-4.59)	0.165	
Biochemistry				
CRP (mean)		0.97 (0.94-1.01)	0.10	
Albumin (mean)		1.06 (0.99-1.13)	0.10	
Body composition factors				
Myopenia	Absent	1		
	Present	0.62 (0.24-1.65)	0.34	
Visceral Obesity	Absent	1		
	Present	1.45 (0.54-3.88)	0.45	
Myosteatorsis	Absent	1		
	Present	0.86 (0.28-2.63)	0.79	
Myopenic Obesity	Absent	1		
	Present	1.79 (0.54-6.03)	0.34	

*azathioprine, mercaptopurine or methotrexate

significant at p<0.05 on univariate analysis

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Figure 4a: Association between lean body mass and BMI in patients with anti-TNF therapy

Figure 4b: Estimated anti-TNF dose per kg fat-free mass in male and female patients based on 5mg/kg anti-TNF dosing; all patients ranked from lowest to highest anti-TNF dose per kg fat-free mass.

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