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Baseline Clearance of Infliximab is Associated with Requirement for Colectomy in Patients with Acute Severe Ulcerative Colitis

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Abstract

Background & Aims: Hospitalized patients with acute severe ulcerative colitis (ASUC) often require surgery. Although the tumor necrosis factor antagonist infliximab is an effective salvage therapy to prevent colectomy in patients with ASUC, optimal dosing is unclear. Calculated infliximab clearance has been associated important outcomes in patients with ulcerative colitis, but its utility in patients with ASUC has not been established. We assessed the relationship between

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calculated baseline infliximab clearance prior to infliximab salvage therapy and requirement for colectomy in patients hospitalized for ASUC.

Methods: We obtained data from hospitalized patients with ASUC who initiated infliximab therapy. We then calculated baseline infliximab drug clearance in these patients based on an existing formula. The primary aim was to compare clearance between patients who required colectomy 6 months later and patients who did not require colectomy. Receiver operating characteristic curve analyses evaluated clearance thresholds for colectomy. Multivariable logistic regression analysis evaluated factors associated with colectomy.

Results: In 39 patients with ASUC, median baseline calculated clearance was higher in patients requiring colectomy at 6 months than in patients without colectomy (0.733 vs 0.569 L/day; *P*=.005). An infliximab clearance threshold of 0.627 L/day identified patients who required colectomy with 80.0% sensitivity and 82.8% specificity (area under the curve, 0.80). A higher proportion of patients with infliximab clearance of 0.627L/day or more underwent colectomy within 6 months (61.5%) than patients with lower infliximab clearance values (7.7%) (*P*=.001). Multivariable analysis identified baseline infliximab clearance as the only factor associated with colectomy. Infliximab dose in hospital was higher in patients who required colectomy. Results were similar at 30 days and 1 y.

Conclusions: In patients hospitalized with ASUC, higher values of calculated infliximab clearance before infliximab administration is associated with higher rates of colectomy. Although patients who required colectomies received higher doses, data on infliximab concentrations are lacking. Infliximab pharmacokinetic models are needed for patients with ASUC, to allow comparative trials on clearance-based vs standard dosing.

Keywords

prognostic factor; response to therapy; outcome; risk

INTRODUCTION:

Ulcerative colitis (UC) is a chronic inflammatory bowel disease. Up to 25% of UC patients will experience an episode of acute severe UC (ASUC).[1] Intravenous corticosteroids are considered first-line management; however, approximately 30% of patients fail therapy[2] and short-term colectomy rates range from 0% to 50% in these patients.[3] Infliximab (IFX), a monoclonal antagonist to tumor necrosis factor-α (TNF), is effective induction and maintenance therapy for UC.[4,5] IFX has been demonstrated to be superior to placebo in randomized controlled trials (RCTs) in ASUC patients.[6, 7] Pooled rates of therapeutic response, 3-month colectomy, and 12-month colectomy in RCT's are 43.8%, 26.6%, and 34.4%, respectively. These rates are considerably better in nonrandomized trials (74.8%, 24.1%, and 20.7%, respectively) and efficacy rates of IFX are similar to cyclosporine; the only other alternative rescue therapy.[8]

While the optimal dosing of cyclosporine is somewhat better delineated, a major knowledge gap exists regarding the optimal IFX dosing required for salvage therapy in hospitalized patients with ASUC. While individual several studies support accelerated dosing, meta analyses do not.[8–11] An exposure response relationship exists for IFX and clinical or

endoscopic outcomes in UC in the ambulatory setting.[5, 12–18] Furthermore, increased IFX clearance likely affects this relationship. In ASUC, drug exposure may be adversely affected by intestinal protein loss leading to hypoalbuminemia and subsequent increased IFX clearance.[21] Observational studies have identified that outpatients with increased IFX clearance have worse clinical outcomes and higher rates of antibodies to infliximab (ATI).[19]

Drug clearance has been associated with important clinical and endoscopic outcomes in RCT's of ambulatory patients with moderately to severely active UC.[20, 21] Furthermore, increased drug clearance during induction has been associated with subtherapeutic drug exposure and negative long-term clinical outcomes in hospitalized ASUC patients receiving standard IFX induction dosing.[22] However, specifics on pharmacokinetic models for IFX in ASUC are lacking and no threshold IFX drug clearance associated with colectomy has been reported. Currently, no method exists to predict which ASUC patients will A) respond to standard IFX dosing, B) require accelerated IFX dosing to improve or C) respond to neither. Thus, a major knowledge gap exists on predicting the required IFX induction dose on an individualized basis (clearance-based dosing), and whether meeting this minimum required dose alters outcomes. In patients with ASUC requiring infliximab rescue therapy, this study assessed the relationship between induction IFX drug clearance and colectomy rates.

METHODS

Patients and study design

Data were extracted retrospectively from patient records at from the University of California, San Diego (UCSD). Eligible patients were adults (>18 years) with a diagnosis of UC (confirmed by clinical, laboratory, endoscopic, histologic, and radiographic information) receiving infliximab as rescue therapy for ASUC during hospitalization from July 2014-May 2018. The diagnosis of included patients was confirmed using chart review demonstrating documentation by expert IBD physicians stating a diagnosis of acute severe ulcerative colitis. Furthermore, patients were subsequently initiated on infliximab as rescue therapy for this condition. Truelove and Witts criteria was met for 89.7% of patients and remaining patients met either clinical or laboratory features of the severity criteria and all had both the highest category of the Mayo clinic stool frequency subscore (3) and significant endoscopic disease.

Endpoints and definitions:

Requirement for a colectomy was assessed at 30 days, 6 months and 1 year. Albumin and C-reactive protein (CRP) were recorded on admission and immediately prior to the first administration of IFX. IFX clearance (CL) was calculated using a previously published formula as follows: $CL=0.407*(ALB/4.1)^{-1.54}*(1.471)^{ATI}*(0.764)^{sex}$ where CL is the calculated baseline infliximab clearance (L/day), ALB is the albumin concentration (g/dL) at baseline, antibody to infliximab (ATI) status is 0 at baseline, and sex = 1 for females and 0 for males.[20, 21] Data closest to the infliximab infusion was used to calculate clearance. The primary aim compared CL between patients requiring colectomy at 6 months to those without colectomy. Additionally, requirement for re-hospitalization related to UC disease activity was assessed within 6 months of initial hospitalization. Available serum drug

concentrations and ATI (drug tolerant homogeneous mobility shift assay, Prometheus Biosciences, San Diego, CA) within 45 days of the first infliximab dose were also recorded to explore the utility of drug level measurements in ASUC.

Statistical analysis

Data analysis included descriptive statistics computed for continuous variables (mean and standard deviation [sd] for normally distributed data, median with interquartile rage [IQR] for non-normally distributed data). Percentages were used for categorical variables. Between-groups comparisons were performed using Fishers exact test or Wilcoxon rank sums test, as appropriate. Characteristics of test procedure (sensitivity, specificity, likelihood ratios, receiver–operating characteristic (ROC) curve and the area under the curve (AUC)) were used to evaluate optimal cutoff values for IFX clearance for colectomy using the Youden index. Multivariable logistic regression was performed to determine factors associated with colectomy at 6 months. On the basis of clinical relevance, calculated baseline infliximab clearance and CRP were included.

Further variables were not included to ensure adequate fit with the given number of events. An exploratory multivariable analysis additionally included concomitant immunosuppressant use, age, disease duration and body mass index (BMI) in the multivariable model. Backwards elimination was preferred using Aikaike's information criterion and variables with $p \leq 0.2$ selected for inclusion in the final model. The likelihood chi squared test was used to assess for model fit. P-values ≤ 0.05 were considered significant. All statistical analyses were done using STATA SE 15.1 (StataCorp, College Station, TX, USA).

Ethics

All authors had access to study data, reviewed and approved the final manuscript. Study protocol and materials were approved by the institutional review board at UCSD. All patients provided written informed consent.

RESULTS:

Of the 39 patients with ASUC identified, 97.4% had left sided or extensive endoscopic disease extent and 100% had moderate to severe endoscopic activity documented (Table 1). The median length of hospitalization was 9.0 days (5.5–13.5), a median of 50 mg (50–75) of prednisone equivalents were administered at baseline, and 46.2% of patients received concomitant immunosuppressants. The median baseline clearance was 0.592 L/day (0.491–0.688). A total of 12.8% of patients required colectomy within 30 days, 25.6% required colectomy within 6 months, and 30.8% of patients required colectomy within 1 year. Additionally, 41.0% of patients required re-hospitalization within 6 months.

Infliximab Dose in Hospitalization and Colectomy

Patients received a median IFX dose of 10.7 mg/kg (10.0–20.1) during their hospitalization over a mean of 1.5 doses (+/−0.64). In all patients, the median first infliximab dose was 10.1mg/kg (9.7–10.5mg/kg). A total of 13 patients (33.3%) received exactly 2 infliximab

doses. In these patients, the median first infliximab dose was 10.1mg/kg (9.7–10.6 mg/kg) and the median second infliximab dose was 10.1mg/kg (9.7–10.4mg/kg) at a median of 4 days (3–5) from the first dose. Additionally, 3 patients (7.7%) received exactly 3 infliximab doses. In these patients, the median first infliximab dose was 10.2 mg/kg (10.0–10.7 mg/kg) and the median second infliximab dose was 10.1mg/kg (9.9–10.2mg/kg) at a median of 3 days (3–3) from the first dose. The median third infliximab dose was 10.3 mg/kg (10.2–10.4 mg/kg) at a median of 5 days (3.5–5) from the second dose.

The total infliximab dose administered was higher in patients requiring colectomy at 6 months than those not requiring colectomy (20.6 mg/kg (18.0–22.0) vs. 10.4 mg/kg (9.9–18.6), p=0.003). This was consistent for colectomy at 30 days (21.8mg/kg (18.4–22.0) vs.10.6 mg/kg (9.9–19.7), p=0.01), and 1 year (19.2 mg/kg (11.0–21.9) vs. 10.4 (9.9–19.0), p=0.02). The relationship between the dose administered and colectomy rates were not affected by length of hospitalization (supplementary Table 1).

Calculated Baseline Infliximab Clearance in Hospital and Colectomy

The median calculated infliximab clearance prior to inpatient infliximab administration was higher in patients requiring colectomy at 6 months (0.733 L/day (0.637–0.859) vs. 0.569 L/day (0.458–0.596), p=0.005) compared to those not requiring colectomy. Similar findings existed for colectomy at 30 days (0.757L/day (0.709–0.821) vs. 0.569L/day (0.477–0.627), p=0.07) and at 1 year (0.688 L/day (0.605–0.833) vs. 0.569 L/day (0.452–0.604), p=0.02).

An AUROC analysis revealed a threshold clearance of 0.627 L/day or greater had an 80.0% sensitivity and 82.8% specificity to predict requirement of colectomy at 6 months (AUC=0.80, 95% CI 0.64–0.96, Figure 1, supplementary Table 2). AUC's were similar for 30-day (0.76, 95% CI 0.51–1.0) and 1-year (0.76, 95% CI 0.59–0.92) colectomy (supplementary Tables 3 and 4, Supplementary Figures 1 and 2). Patients with a clearance of 0.627L/day or greater had higher rates of colectomy at 6 months (61.5% vs. 7.7%, p=0.001, Figure 2). This was also observed at 30 days (30.7% vs. 3.8%, p=0.04), and 1 year (61.5% vs. 15.4%, p=0.005) compared to patients with lower clearance (Table 2). Additionally, patients with a clearance of 0.627L/day or greater had numerically higher re-hospitalization rates within 6 months (61.5% vs. 30.8%, p=0.07). Furthermore, the AUROC of baseline calculated infliximab clearance was greater than that of baseline CRP (0.57, 95% CI 0.37–0.77) for predicting colectomy at 6 months (p=0.03, supplementary Figure 3).

In multivariable logistic regression that included baseline clearance and CRP, only baseline clearance was associated with associated with 6-month colectomy (OR 651.5, 95% CI 4.0–104824.6, p=0.01). Additionally, an exploratory multivariable analysis was performed to determine if other factors were associated with colectomy. After stepwise regression, IFX clearance, age and disease duration were retained in the multivariable model. The likelihood chi squared test revealed a good model fit (p=0.001). The only factor on multivariable analysis associated with 6-month colectomy was baseline clearance (OR 543.9, 95% CI 2.3–123306.1, p=0.02, Supplementary Figure 4). Similar findings existed for clearance and 1 year colectomy (OR 125.7 95% CI 1.8–8933.9, p=0.02). Conclusions were identical for univariable analyses (supplementary Table 5).

Within patients with higher clearance (≥0.627 L/day), the doses of infliximab administered was similar between those requiring colectomy at 6 months and those not requiring colectomy (19.2mg/kg (16.1–24.1) vs. 20.8 mg/kg (10.3–21.0), p=0.66). This was consistent at 30 day (p=0.44) and 1 year (p=0.66). In patients without higher clearance (<0.627 L/day), patients requiring colectomy at 6 months still received higher doses than those not requiring colectomy (p=0.02, supplementary Table 6) and similar trends for higher dose administration were found for colectomy at 30 days (p=0.10) and 1 year (p=0.18).

Early Infliximab Drug Monitoring:

Amongst the 5 patients requiring a colectomy within 30 days, 4 patients had 5 drug levels performed at a median of 8.4 days (6.4–8.4), all of which were >34 ug/mL (above limit of detection: ALOD). Amongst the 35 patients not requiring a colectomy within 30 days, 12 patients had 15 drug levels performed at a median time of 15.6 days (7.4–27.5), 11 of which were >34 ug/mL (ALOD), 3 patients had infliximab concentrations ranging from 15.9–26.6 ug/mL at 20–33 days. In this group, only one patient had detectable antibodies (10.2) at 15.6 days with undetectable drug levels. This patient required a colectomy within 6 months (135 days after the first infliximab dose).

DISCUSSION

Hospitalization for acute severe UC occurs in significant proportions of UC patients and often requires colectomy. Although infliximab is effective to avoid this outcome, clinical tools are needed to identify ASUC patients at high risk for IFX therapy failure. To date, limited data exists on the effect of baseline clearance on outcomes in ASUC.

Our study demonstrates higher calculated baseline IFX clearance in patients requiring colectomy. The only factor on multivariable analysis associated with colectomy was baseline IFX clearance. Additionally, infliximab clearance had excellent diagnostic accuracy to predict requirement of colectomy at 6 months, and performed similarly for 30-day and 1-year colectomy. In patients with a calculated baseline IFX clearance of 0.627L/day or greater, higher proportions required colectomy at 30 days, 6-months and 1-year. Lastly, baseline clearance demonstrated greater accuracy in predicting colectomy than CRP.

A population pharmacokinetic model based on the ACT trials in UC has been previously derived to calculate baseline IFX clearance in individual patients.[21] This predicted increased IFX clearance prior to IFX initiation, which would lead to sub-therapeutic drug concentrations. Using this model, calculated clearance of less than 0.397L/day in outpatients with UC was associated with improved endoscopic outcomes.[20] Due to a higher inflammatory burden in patients with ASUC, other factors in addition to body weight and serum albumin concentration may contribute to increased drug clearance. Due to this, current models may be inadequate to predict the required doses to achieve adequate trough concentrations in hospitalized patients with ASUC.[20–22]

A previous study identified increased clearance in induction was associated with worse outcomes in ASUC.[22] Although an undisclosed population pharmacokinetic model was developed, it was based on both UC and Crohn’s disease patients, lacked dosing

heterogeneity, and applied to a group of UC patients that were not universally hospitalized. The current study in hospitalized patients with ASUC is the first to provide a threshold clearance as a predictive factor, provides the strength of having a range of IFX dosing and uses an important outcome –colectomy– as the endpoint of interest.

Previously identified factors that increase IFX clearance in ambulatory UC include low albumin, elevated CRP, elevated body weight, presence of ATI and lack of immunomodulator use.[23, 24] In the current study, multivariable analysis found that calculated clearance, but no other factors, were associated with colectomy. This is consistent with previous data. A pharmacokinetic model for calculated IFX clearance found gender, albumin and presence of ATI to be significant for inclusion.[21] Furthermore, the current study uniquely analyzed immunomodulator use in the context of drug pharmacokinetics and outcomes in ASUC. Study limitations include a retrospective design and sample size limiting number of events for multivariable analyses. However, conclusions were consistent across analyses, demonstrating clearance was higher in patients requiring colectomy, AUROC analyses with high diagnostic accuracy and similar findings on multivariable analysis. While Truelove and Witts criteria were not used for inclusion, expert IBD physicians documented this diagnosis, baseline laboratory data were consistent with these criteria and baseline endoscopic data and subsequent management was consistent with ASUC. Additionally, a vast majority of patients met Truelove and Witts criteria and remaining patients met either clinical or laboratory features of the severity criteria and all had both the highest category of the Mayo clinic stool frequency subscore (3) and significant endoscopic disease. Lastly, conclusions were unchanged when analyses were performed excluding patients not meeting criteria. There is a possibility that existing models may not be fully adequate to predict the required doses to achieve adequate trough concentrations in ASUC. Nevertheless, despite this possible limitation, we were able to see an important clinical effect with the existing model. Further confirmatory studies are needed to validate the use of this model to calculate infliximab clearance in this population. Infliximab infusion protocols may impact subsequent drug clearance after drug administration. However, results on the effect of baseline calculated clearance prior to any infliximab administration to predict outcomes is likely unaltered by this. Additionally, a majority of patients received only one 10mg/kg dose. Lastly, dosing was standardized for patients requiring multiple doses, with 10mg/kg administered for all subsequent inpatient doses at 3–5 day intervals. A possibility exists that drug discontinuation may occur after patients are rescued from colectomy.[25, 26] However, it has been consistently demonstrated that regardless of subsequent medication changes, a majority of rescued patients avoid subsequent colectomy and early management affects these outcomes. While clinical and endoscopic remission are the current treatment targets, an important objective outcome in ASUC is colectomy. While clinical relapse data was unavailable, need for re-hospitalization was analyzed and represents important data regarding a more severe form of clinical relapse. The findings in this study that overall colectomy rates were similar to pooled data on infliximab for ASUC is reassuring.[8] Moreover, it was promising that 92.3% of patients with infliximab clearance below 0.627L/day avoided colectomy at 6 months with infliximab therapy.

Drug concentrations within 45 days of IFX initiation were available in a significant proportion of patients. However, analyses based on these were limited due to the vast

majority being above limit of quantification at these early timepoints. Additionally, serum infliximab concentrations were not measured in a standardized manner.

In patients with baseline calculated infliximab clearance less than 0.627L/day, over 90% avoided colectomy at 6-months. Thus, the use of this tool at baseline may assist in selecting ASUC patients with high probability of treatment success with infliximab. Additionally, this study demonstrated that higher doses did not necessarily improve outcomes in patients with higher clearance. In these patients, small molecules such as cyclosporine may be preferable rescue agents. Additionally, this serves as a basis to study clearance-based dosing. This may identify that, in patients with higher clearance, doses significantly higher than current standard of care may be needed to observe efficacy for infliximab rescue therapy.

Increased clearance in UC may be caused by various mechanisms. Importantly, two studies have associated the loss of IFX in stool with poor outcomes.[27, 28] However, a knowledge gap still persists for adequate population pharmacokinetic models in patients with ASUC receiving IFX. Establishing these models will require intensive sampling and collection of covariates that could be associated with outcomes in ASUC. Prospective multicenter studies (NCT03765450) are underway to validate these findings, guide infliximab dosing strategies and delineate drug clearance mechanisms.

In summary, baseline drug clearance was a strong predictive factor for colectomy in hospitalized patients with ASUC receiving IFX salvage therapy. Understanding differences in inter-individual drug clearance may explain the previous lack of support for accelerated dosing; the proportion of patients with accelerated clearance may confound results. In the current study, patients requiring colectomy received higher IFX doses. However, no data exists on whether accelerated dosing was sufficient to achieve adequate drug concentrations. There is therefore an urgent need for pharmacokinetic models to personalize dosing based on baseline clearance, and trials must compare the efficacies of clearance-based and standard dosing in ASUC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ASUC	acute severe ulcerative colitis

ALB	albumin
ATI	antibodies to infliximab
AUC	area under the curve
BMI	body mass index
CRP	C-reactive protein
CL	clearance
IFX	infliximab
IQR	interquartile rage
RCT	srandomized controlled trials
ROC	receiver–operating characteristic
TNF	tumor necrosis factor-α
UC	ulcerative colitis
UCSD	University of California, San Diego

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What You Need to Know

Background

- Infliximab is an effective salvage therapy to avoid colectomy in acute severe ulcerative colitis (ASUC).
- Infliximab drug concentrations relate to outpatient outcomes, but data is lacking on personalized dosing to achieve these levels in ASUC.

Findings

- A baseline infliximab clearance was calculated using a simple formula.
- Clearance of ≥ 0.627 L/day predicted colectomy with high diagnostic accuracy.
- Baseline clearance was the only factor on multivariable analysis associated with colectomy

Implications for Patient Care:

- Patients with a clearance ≥ 0.627 L/day were at higher risk for colectomy, whereas below this threshold, infliximab was highly effective and resulted in 6-month colectomy free survival rates above 90% in ASUC.
- Further studies are needed to determine the required dose on an individualized basis to avoid colectomy.

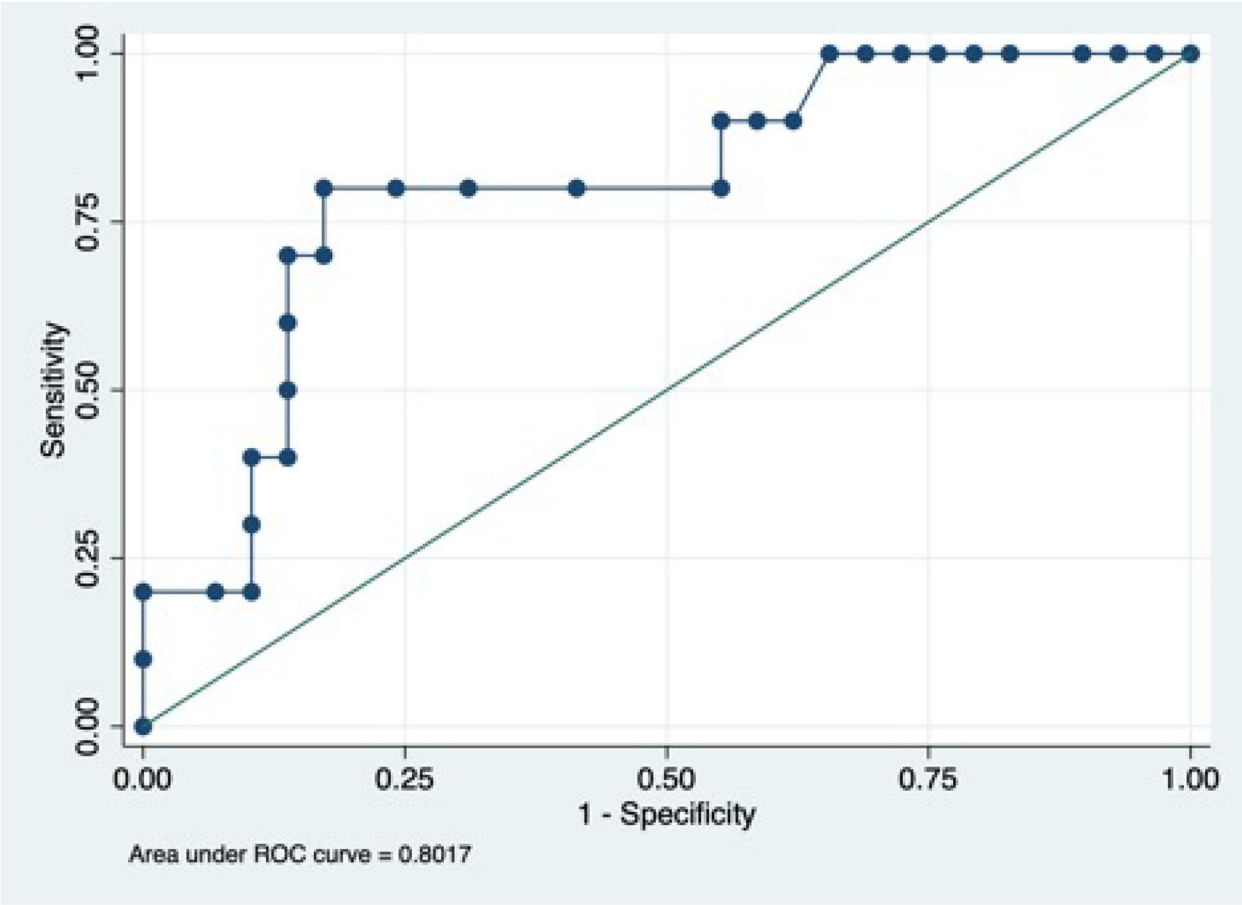

Figure 1:
The relationship between infliximab drug clearance and 6-month colectomy rates: Receiver operator characteristic curve analysis

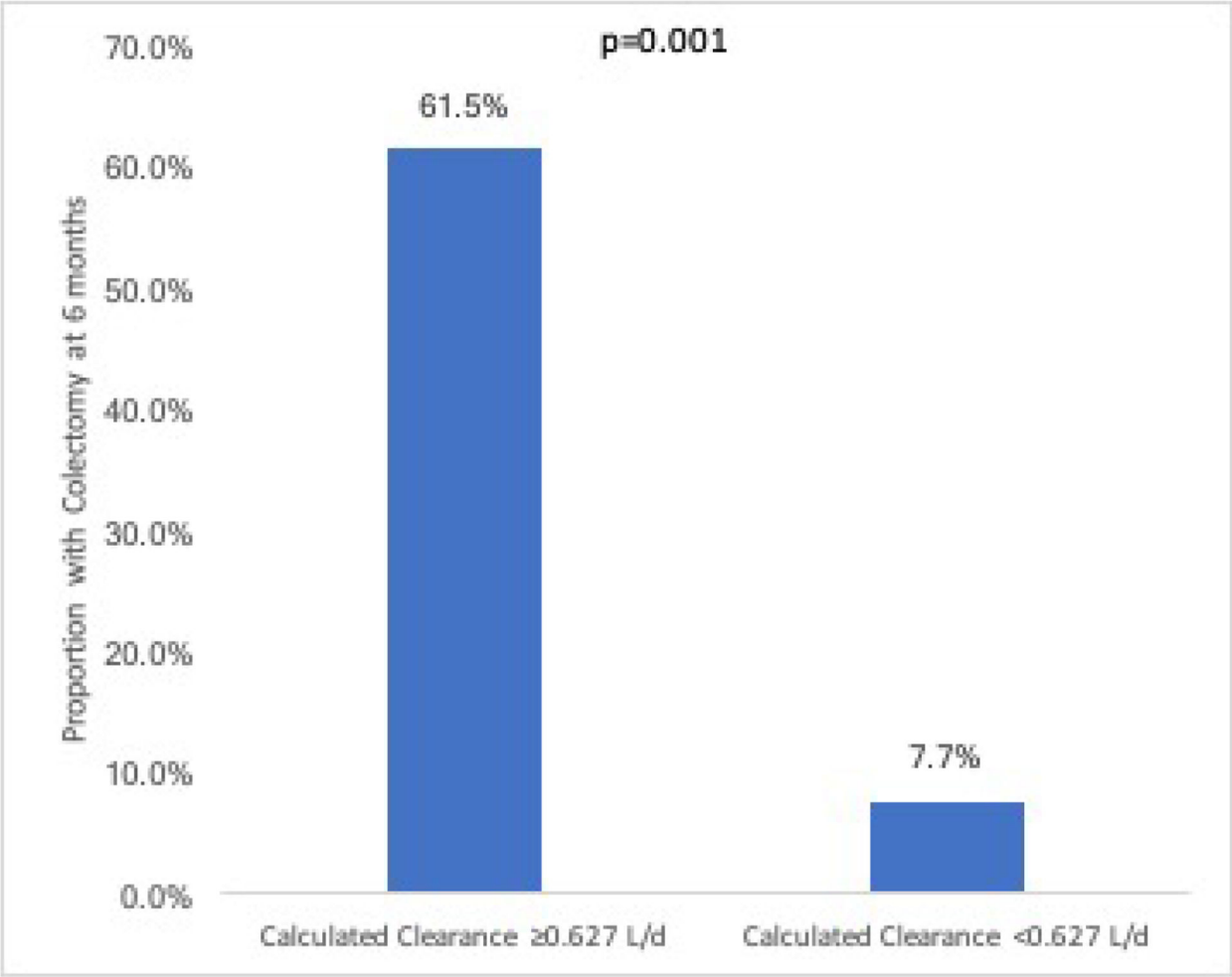

Figure 2: Calculated Baseline Drug Clearance Associated With 6-Month Colectomy Rate

Patients with a calculated baseline infliximab clearance of ≥0.627L/day had higher rates of colectomy at 6 months compared to those with lower baseline clearance.

Table 1:

Baseline Characteristics

Age, years (median (IQR))	31 (20.0–46.5)
Female gender, n (%)	18 (46.2)
Age at diagnosis, n (%)	
<16 years	2(5.1)
16–40 years	28 (71.8)
>40 years	9 (23.1)
Disease duration, years (median (IQR))	2 (0.8–4.5)
Disease Extent, n (%) *	
Proctitis	1 (2.6)
Left sided colitis	22 (57.9)
Extensive colitis	15 (39.5)
Baseline endoscopic activity *	
Mayo 3	11 (28.9)
Mayo 2	2(5.3)
Severe	15 (39.5)
Moderate to Severe	10 (26.3)
Body mass index (median (IQR))	22.5 (20.2–26.1)
CRP, mg/dL (median (IQR))	
On Admission	3.4(1.8–7.9)
Prior to first Infliximab Dose	3.2(1.3–5.8)
Prior to Discharge	1.1 (0.5–2.4)
Albumin, g/dL (median (IQR))	
On Admission	3.3(2.7–3.7)
Prior to first Infliximab Dose	3.1(2.6–3.4)
Prior to Discharge	2.9(2.7–3.2)
Baseline Clearance, L/day (median (IQR))	0.592 (0.491–0.688)
Infliximab Dose in Hospital, mg/kg	
Total Dose (median (IQR))	10.7 (10.0–20.1)
Doses administered (mean (SD))	1.5 (0.64)
Length of Hospitalization, days (median (IQR))	9.0(5.5–13.5)
Baseline Daily Corticosteroid Dose, mg (median (IQR))	50 (50–75)
Concomitant Immunomodulator use, n (%)	18 (46.2)

*One patient with missing endoscopic data

IQR: Interquartile Range

Table 2:

The relationship between baseline infliximab clearance and colectomy rates

	Clearance ≥0.627, n=13	Clearance <0.627, n=26	p value
Colectomy within 30 days, % (n)	30.7 (4)	3.8(1)	0.04
Colectomy within 6 months, % (n)	61.5(8)	7.7 (2)	0.001
Colectomy within 1 year, % (n)	61.5(8)	15.4 (4)	0.005