Title: Practice pattern variability in the management of acute severe colitis: A United Kingdom provider survey

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Contributor Statement

SS, NAK and SS planned the study, JL, SS and NAK developed the questionnaires. AD, AHS, PA, JB, TR, RS, SS, GM, AL contributed to data collection. SS, JS and NC analysed the data. SS, JL drafted the manuscript. All authors reviewed and approved the manuscript.

Practice pattern variability in the management of acute severe colitis: A United Kingdom provider survey

Abstract

Introduction

Lack of comparative trial data on dosing regimens of infliximab in acute severe ulcerative colitis (ASUC) patients failing intravenous (IV) corticosteroids has resulted in variability of rescue regimes in ASUC with potential impact on clinical outcomes. We aimed to evaluate practice variability and physician perspectives in decision making with rescue therapy.

Methodology

An internet-based survey of members of the IBD section of British Society of Gastroenterology (BSG) was conducted. The survey evaluated provider characteristics and general practice in the setting of ASUC, followed by a vignette with linked questions.

Results

The response rate of the survey was 31% (209/682 IBD section members). 134 (78%) reported they would use standard infliximab dose (5 mg/kg) while 37 (22%) favoured a higher front-loading dose of 10 mg/kg citing low albumin, high CRP as their reason for their

preference. IBD specialists chose the higher front-loading dose more often compared to other gastroenterologists (p=0.01)

In the specific case vignette, accelerated induction (AI) was favoured by 51% of the respondents while 25% used the standard induction regime and 19% favoured colectomy. IBD specialists more often favoured AI compared to other gastroenterologists(p=0.03) with main reason being presence of predictors of low infliximab levels (74%). The reasons cited for favouring standard induction (n=57) included lack of evidence for AI (18), their usual practice (11), unlicensed regime (7), and safety concerns (4).

Conclusions

There are significant variations in practice in the use of infliximab rescue therapies with an urgent need for development of care pathways to standardise practice

Keywords: Acute severe colitis, Rescue therapy, Infliximab, Accelerated rescue, provider survey

Abbreviations:

UC: Ulcerative Colitis

ASUC: Acute severe ulcerative colitis

Summary Box

What is already known about this subject?

There is variation in rescue therapy regimens used in steroid refractory acute severe ulcerative colitis (ASUC)

What are the new findings?

This is the first UK survey evaluating clinicians decision making in the choice of rescue therapy in the management of ASUC

How might it impact on clinical practice in the foreseeable future?

Practice protocols with more available data will help in reducing variability and standardising care

Introduction

In population-based studies, patients with ulcerative colitis (UC) have a 15 to 25% life time risk of requiring hospitalization due to acute severe colitis (ASUC) (1,2). More than a third of patients with ASUC fail to respond to first line treatment with intravenous (IV) corticosteroids (3). In these patients rescue therapy using infliximab or ciclosporin has been evaluated as second line medical therapy as an alternative to colectomy (4). Although no difference in relative efficacy between these two agents has been noted in randomised controlled trials (5,6), infliximab is more often used in clinical practice settings owing to safety concerns and challenges with the administration of ciclosporin (7). However, even in the era of rescue therapy for ASUC, one in 5 patients still requires a colectomy within three months of admission (8, 9) indicating the need for further optimisation of therapies.

The dosing schedules used in ASUC were adopted from the original infliximab licencing trials which were in a moderate-severe ambulatory UC cohort. Currently there are no published randomised clinical trials which guide the optimal initial dosing in the setting of ASUC. Disease-related and pharmacokinetic factors may have a role in the response rates to rescue therapy with infliximab (10,11,12,13) with these patients needing more drug at the outset. This has led to the concept of accelerated induction in ASUC using either a higher `front-loading dose` of 10 mg/kg instead of standard 5mg/kg dosing or using more frequent dosing with 5 mg/g given earlier than 2 weeks after the first dose (chaser regime) (14). However, the data on the effectiveness and safety of these strategies are conflicting and are limited to small retrospective observational studies (15,16,17,18). Indeed, a recent meta-analysis did not report any significant difference in short term or long-term colectomy rates with accelerated induction (19). One of the biggest drawbacks of these studies is the potential

for provider bias due to variations in practice by the treating clinician both in relation to regime, dose and timing of initial and subsequent dosing of infliximab.

In the absence of robust comparative trial data, the variability in this setting highlights the urgent need for a learning network and potential development of care pathways which can be audited for outcomes. This is the focus of ELEVATE ASUC Study programme (ClinicalTrials.gov Identifier: NCT03907631), initiated in the United Kingdom. The aims of the survey, detailed here and included in the ELEVATE ASUC programme, were to evaluate the perspectives, decision making and practices of gastroenterologists managing ASUC and to identify variability in practice among UK gastroenterologists.

Materials and Methods

We created an internet-based survey using Google Docs (Google Inc, Mountain View, CA, USA) in two sections. The first section of the questionnaire evaluated provider characteristics such as place of work (university teaching hospital versus general hospital), subspecialist expertise in relation to inflammatory bowel disease (IBD), years of experience and the average number of patients with ASUC seen per year. We enquired regarding variations in the management of ASUC such as joint care with colorectal surgery, MDT discussion and timing of endoscopic evaluation. We also captured clinical perspectives in relation to the use of rescue therapy, including the choice of therapy and dosing schedule. The second section of the questionnaire was based on a clinical vignette of a patient with ASUC failing IV corticosteroid therapy. A linked-question format allowed the respondents to be directed to the subsequent question and clinical scenario based on their answer to the preceding question. In the initial questions about the case vignette, respondents were asked about their diagnostic and therapeutic approaches to a patient hospitalised with ASUC. In the subsequent part of the vignette, the decision-making process following failure of IVCS after 3 days of admission,

the response to initiation and assessment of rescue therapy were evaluated. Finally, we also used the survey to understand the perspectives of the clinicians on the unmet needs and data gaps which needs to be addressed by future studies on ASUC.

The survey was circulated to all members of the IBD section of the British Society of Gastroenterology. The survey was anonymous and participation was voluntary.

Data were collected on Google Docs and exported for analysis to Microsoft Excel (Microsoft Corp, Redmond, WA, USA). We performed analysis using Microsoft Excel and SPSS version 25 (IBM Corp, Armonk, NY, USA). Response frequencies were tabulated and expressed as percentages of total responses. For quantitative variables, mean and standard deviation were calculated if they had a normal distribution or median and interquartile range otherwise. The responses were compared using Fisher's exact test for categorical variables. A p-value of <0.05 was taken as significant.

Results

A total of 209 responses were received for the survey distributed to 682 IBD section members of the BSG representing a response rate of 31%. The demographics of the respondents are presented in Table 1. Majority of the respondents (91%) declared themselves as IBD specialists or gastroenterologists with specialist interest in IBD. Nearly half of the respondents saw less than 10 patients per year with ASUC.

Table 1: Provider characteristics

Clinicians role (n, %)	IBD specialist	40 (20%)
	Gastroenterologist with special interest in IBD	144 (71%)
	Gastroenterologist with special interest outside IBD	21(10%)
Type of clinician`s institution (n, %)	University Teaching Hospital	82 (40%)
	General Hospitals	126 (60 %)
Years of experience at consultant level (n, %)	< 5 years	60 (29%)
	5-9 years	70 (34%)
	10-19 years	55 (26%)
	>20 years	23 (11%)
Average number of ASUC admissions per year under the care of respondent	<5 patients	15 (7%)
	5-9 patients	83(40%)
	10-19 patients	80 (38%)
	>20 patients	30 (14%)

Process characteristics- Non vignette based

The processes involved in management of hospitalised ASUC patients in the institutions of the respondents are indicated in Table 2.

Table 2: Process characteristics in ASUC management

Primary team for inpatient management of ASUC	Gastroenterologist	180 (87%)
	Colorectal surgeon	0 (0%)
	Joint care with gastroenterologist and colorectal surgeon	26 (12%)
Proportion of ASUC patients discussed at IBD MDT (n, %)	<25%	109 (52%)
	25-49%	22 (11%)
	50-74%	33 (16%)
	75-100%	44 (21%)
Timing of surgical opinion in ASUC patients (n, %)	All patients within 24 hours of admission	160 (11%)
	All patients within 48 hours of admission	43 (21%)
	At failure of first line therapy	106 (51%)
	At the failure of rescue therapy/when surgery is indicated	37 (18%)
Routinely do imaging in ASUC patients (n, %)	Always abdominal X-ray at admission	160 (77%)
	Abdominal CT at admission	2 (1%)
	Abdominal CT only if suspecting complications	13 (6%)

	Not routinely image, only in selected patients	33 (16%)
Routinely do sigmoidoscopy in ASUC patients (n, %)	Yes as soon as possible but within 48 hours of admission	88 (43%)
	Yes as soon as possible but may be >48 hours after admission	91 (44%)
	Not routinely, only if no response to steroids	27 (13%)
Routinely check for CMV in ASUC patients (n, %)	Yes, both in biopsies and serology	53 (26%)
	Yes, only in biopsies	100 (49%)
	Rarely check	50 (25%)
	Never check	1 (0.5%)
Offer colectomy as alternative option to intravenous steroids	No	176 (85 %)
	Yes	32 (15%)
Offer rescue therapy in steroid non-responsive	Yes	204 (99 %)
	No	2 (1%)
Drug used in rescue therapy	Infliximab	123 (60 %)
	Ciclosporin	2 (1%)
	Either infliximab or ciclosporin	81 (39%)
Local colorectal team offer laparoscopic colectomy in the setting of ASUC	Yes, often	81 (38 %)
	No	86 (41%)
	Occasionally	25 (12%)
	Unsure	16 (8%)

Number of days of IV steroids before considering rescue therapy	2 days	4 (2%)
	3 days	165 (79%)
	5 days	28 (13%)
	7 days	11 (5%)

The majority of the hospitalised ASUC patients (88%) were admitted and managed primarily under gastroenterologists with only 12% respondents indicating joint care with colorectal surgeons and none indicating colorectal surgery as the primary team for initial management. Only 20% of respondents indicated they routinely held a multidisciplinary team meeting discussion for patients with ASUC, and over half of the respondents reported MDT discussion in less than a quarter of their admissions with ASUC. Nevertheless, 31% of respondents sought a colorectal surgical opinion for their patients within 48 hours of admission with ASUC while 51% and sought a colorectal surgical opinion after failure of first line therapy with intravenous steroids and 18% sought one at the point when no further medical therapy is feasible. Three quarters of the respondents routinely performed an abdominal x-ray at admission while 7% performed an abdominal CT scan. 87% organised a flexible sigmoidoscopy during the admission of an ASUC patient with over half of these performed within 24 hours after admission while the remaining 13% only performed sigmoidoscopy if there was lack of response to initial medical therapy. Presence of cytomegalovirus (CMV) was routinely checked in biopsies in 49% of respondents and by biopsies plus serology and 26% of the respondents.

Medical therapy was the initial approach to an admitted patient with ASUC for 85% of respondents with almost 90 % favouring intravenous hydrocortisone while 15% felt that colectomy should be offered as an alternative to medical therapy at admission. Three days of intravenous steroids was the timepoint for assessing response was favoured by 79% of the

respondents while 13% and 5% preferred to wait 5 and 7 days respectively to assess response. Ninety nine percent of respondents will consider offering rescue therapy following failure of intravenous steroids while two respondents favoured colectomy in the setting of steroid failure. The factors taken into account by the respondents before consideration of rescue therapy are depicted in Figure 1.

Majority (60%) will only consider infliximab for rescue therapy while 39% will consider either infliximab or ciclosporin as their rescue therapy drug. Laparoscopic colectomy was not available from colorectal surgeons as an option in the setting ASUC in the sites of the 41% of the respondents.

Case Vignette based practice characteristics

Initial management

Upon admission of a patient with ASUC, 91% of the respondents indicated they would promptly initiate intravenous corticosteroids without waiting for the result of the stool cultures for enteric pathogens, while 8% of the respondents preferred to wait for the results of cultures before initiating IV steroids. Only two respondents (1%) favoured starting infliximab along with steroids. Both these respondents reported the reason for choosing infliximab at admission along with steroids to be the severity of presentation, noting low albumin, very high stool frequency and low haemoglobin. None of the respondents favoured colectomy at presentation. Routine antibiotic use was not favoured by the majority, while 17% would initiate antibiotics along with IV steroids. Flexible sigmoidoscopy with and without bowel preparation would be performed by 16.5% and 76% respectively while 8% preferred to delay endoscopic evaluation. The majority of respondents (77%) indicated they would assess their

patient for response to steroids on Day 3 and 7% preferred an earlier evaluation on Day 2 after admission.

Management following failure of intravenous steroids Day 3

A pictorial summary of the therapeutic decision making in case vignette is depicted in Figure 2:

On failure of response to intravenous steroids by day 3, 83% of respondents elected to start infliximab rescue therapy while 10% elected to persevere with steroids. Ciclosporin was chosen for rescue therapy by 6% and 3 respondents (1.5%) favoured colectomy to rescue therapy. Of the 19 respondents who favoured the continuation of steroids for more than 3 days before decision, all but one favoured initiation of standard dose (5 mg/kg) of infliximab rescue when asked to review their treatment decision in the context of persistent IV steroid failure at 5-7 days. Among the respondents initiating on infliximab rescue therapy (171 respondents), 78% favoured standard dose rescue while a higher front-loading dose of 10 mg/kg was preferred by 37 (22%) respondents. The higher dose was preferred by IBD specialists compared with other clinicians ($p= 0.01$) and by those working in university teaching hospitals ($p= 0.04$). The main reasons cited for higher dose included very low albumin (38%) very high CRP (32%) and severity of symptoms (16%), while higher dose was reported as their normal practice by 15% of respondents.

In the case vignette, the patient went on to have a suboptimal response to the first dose of infliximab rescue. In this context, 75/171 respondents favoured a further dose within 5-7 days (44%). However only 16% of the respondents giving an initial 10 mg/kg dose gave a further dose within 7 days; the rest favoured colectomy as the next step. In contrast, 52% of those starting 5 mg/kg dose opted to give a further dose. The reasons for favouring accelerated

induction (both higher initial dosing or second dose within 7 days) are depicted in Figure 3. IBD specialists favoured accelerated induction more often than other gastroenterologists (p=0.03).

Among those preferring standard first dose, 19% favoured colectomy while 25% elected to monitor and give a further dose after 2 weeks. The reasons for not giving accelerated induction and for favouring colectomy after lack of response to first dose infliximab are detailed in Figure 4 and Figure 5.

Forty percent of respondents based the interval between the first and second doses on the clinical response of the patient, while 25% preferred to always give the second dose within 5 days after the first. Following response to accelerated induction, the third dose was given two weeks after the second by 85% of the respondents while 12% indicated they would wait for drug levels to make this decision. Eighty percent of respondents said they would continue infliximab maintenance until loss of response following successful rescue therapy.

Perspectives of gaps in data

The main barriers for using accelerated induction regimes in ASUC patients reported by 163 respondents included the lack of reliable studies (80/163, 49%), safety concerns (63/163, 39%) and the absence of predictive markers of non-response (44/163, 27%). Recommended aspects to be evaluated in future trials on rescue therapy in ASUC include identifying the best initial dose of infliximab (89% of respondents), identifying the biomarkers to identify

response (56% of respondents) , the value of drug level monitoring in clinical practice (40% of respondents) and determining the best maintenance strategy in patients receiving rescue therapy (56% of respondents). (See Figure 6)

Discussion

There is growing evidence from pharmacokinetic and pharmacodynamic studies that infliximab clearance is more rapid in ASUC and this may potentially impact outcomes (21). Based on the solid theoretical underpinning of this concept, the community of IBD experts appear to have moved towards use of accelerated infliximab regimes in ASUC patients without waiting for definitive evidence. However, the data from uncontrolled and retrospective studies show conflicting results, and our recent meta-analysis (19) also casts doubts on the evidence for such practice. Majority of the current recommendations and guidelines (22,23) do not support the use of accelerated induction in the algorithm for patients with steroid-refractory ASUC although the recent BSG guidelines (24) support its use after a colorectal surgical review to determine whether emergency colectomy is required.

Our survey provides evidence for the significant variations in management practices in the real world setting among gastroenterologists caring for hospitalised patients with ASUC, particularly in the scenario of rescue therapy. In contrast to the best practice guidelines (22,23), the majority of our admitted patients do not have the benefit of joint care with colorectal surgery from the first day of admission with ASUC. Only one fifth of these severely ill patients are discussed at MDT meetings in a prospective contemporaneous manner. When treating steroid-refractory patients, despite the equal efficacy of ciclosporin

and infliximab in IV-steroid-refractory ASUC, the majority of clinicians prefer the use of infliximab over ciclosporin. This is consistent with the results of a nested study in the CONSTRUCT Trial (7), where ease of use, perceived better adverse effect profile and less intensive monitoring regimes made clinicians favour infliximab. Furthermore, only a very small proportion of our respondents (2%) chose colectomy in the setting of IV steroid failure, despite the lack of randomised trials comparing colectomy to medical therapy and the high failure rates of rescue therapy in the literature (5,6,8).

The most marked variability in our survey was in the choice of dosing regimens of infliximab rescue therapy in the case vignette. The vignette included a number of variables proven to be determinants of altered pharmacokinetics and higher clearance of infliximab such as extensive disease, elevated CRP and low albumin (10). Yet only one in 5 respondents favoured a higher initial dose of infliximab for rescue. There was also variability in considering a second dose following suboptimal response. Only half the respondents suggested they would give an additional dose within 7 days, the rest favouring the standard regime or suggesting colectomy. There are currently no prospective trials which have clearly indicated improved efficacy and safety of accelerated dosing regimens in the hospitalised patients with ASUC, and this was once of the main reasons indicated by over 50% our respondents for their reluctance to choosing accelerated induction regimes. Nevertheless, half of our respondents felt confident in using higher dosing schedule in their patients.

The timing of the assessment to consider rescue therapy and reassessment of response also appear to be inconsistent among the responders. The Travis index (25) is the most commonly used index for assessing response to intravenous steroids in ASUC and this recommends reassessment after 3 days of IV steroids. In our survey 20 % of respondents preferred to give a longer interval of up to 5-7 days before considering rescue therapy or colectomy. Similar

variation was also seen in the time to reassess response to first dose of rescue therapy with a quarter reassessing at 5 days, 33% waiting for 7 days and the others variable intervals based on clinical response. The lack of clear biomarkers of response and concerns regarding safety of additional dosing may have contributed to this practice variability.

This is, to the best of our knowledge, the largest survey on practice variations in the setting of the management of acute severe colitis. In a retrospective review of the Veterans Healthcare System in the USA (26) published three years ago, providers differed in their choice of initial therapy for ASUC with 83% providing intravenous steroids but 17% used infliximab as first line therapy at admission. In comparison, all of our respondents used intravenous steroids as initial therapy and only two of our respondents in the clinical vignette started infliximab along with IVCS at admission. In our survey, the majority of the providers in this survey (65%) reported use of standard induction regimen dosing (5 mg/kg) and only one third performed accelerated induction (26). In contrast, in another internet-based survey of the members of the International Organisation for Inflammatory Bowel Disease and Crohn`s and Colitis Foundation Clinical Research Alliance (27), only 24% of respondents used the standard induction regime of 5 mg/kg at 0, 2 and 6 weeks for ASUC. In this survey participants were asked for reasons for giving accelerated dosing of infliximab, and the reasons cited were severity of clinical symptoms, high C-reactive protein, low serum albumin level and endoscopic severity. This survey only included experts in IBD, and the authors did not provide descriptive details such as response rates; both of these may introduce bias in the responses. Significant practice pattern variability is also reported from a high-volume tertiary referral centre survey in Mount Sinai USA (28). This survey, including 30 senior and junior gastroenterologists, suggested a higher proportion of infliximab use as first line therapy (17%) compared to our survey. The use of antibiotics, imaging and sigmoidoscopy practised in this centre was similar to the responses to our survey. In the Mount Sinai study, however, a

higher proportion of respondents used a front-loading dose of 10 mg/kg (35%) compared to our survey where only 22% of respondents used front loading regime. In this study the choice of dosing regime was independent of the level of training. A more recent survey conducted among the members of the Spanish Crohn's Disease and Ulcerative Colitis Working Group (GETECCU) (29), was limited by the low response rate (20%), and like in our survey almost exclusively included gastroenterologists alone. The use of higher front-loading dose of infliximab for rescue therapy (56%) and earlier use of the second dose (75%) was more prevalent among Spanish gastroenterologists compared with our study.

There are some limitations of our study which we acknowledge. Firstly, our survey was sent only to the members of the IBD section of the British Society of Gastroenterology and hence did not capture the perspectives of other members of a multidisciplinary IBD team including colorectal surgeons and IBD nurses. In addition, we did not include trainees in the survey, and in a number of centres trainees may be the first point of contact with an admitted patient with ASUC. However, we feel that decisions pertaining to medical therapy in general and rescue therapies ought to be and often are made by senior gastroenterologists with IBD interest, and in that respect the survey is representative of the clinical practice scenario in the United Kingdom.

The results of our survey highlight the marked variations in management practises for hospitalised ASUC patients, particularly in respect to infliximab rescue therapy. Reduction in variations in care is a key goal of the UK IBD standards (30). Further data from prospective studies are required to fully evaluate the efficacy and safety of different dosing regimens in ASUC. We urgently need early predictors of response to intravenous steroids, which will allow earlier use of rescue therapies in selected patients. Further understanding of factors predictive of response to infliximab rescue therapy in ASUC patients is also required.

In the interim, we would recommend attempts to reduce variability by introducing care bundles or learning networks.

Contributors Statements

SS, NAK and SS planned the study, JL, SS and NAK developed the questionnaires. AD, AHS, PA, JB, TR, RS, SS, GM, AL contributed to data collection. SS, JS and NC analysed the data. SS, JL drafted the manuscript. All authors reviewed and approved the manuscript.

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