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Infliximab Induction Strategies in Corticosteroid-Refractory Acute Severe Ulcerative Colitis: A Case Series and Literature Review

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Keywords
Acute severe ulcerative colitis · Accelerated infliximab induction · Intensified infliximab induction

Abstract
Acute severe ulcerative colitis (ASUC) is an emergent medical condition and particularly challenging to treat efficaciously. Infliximab is one of the medical salvage treatment options after corticosteroid refractoriness, but the best induction strategy is not yet defined. With this case series, the authors intend to describe three corticosteroid-refractory ASUC cases with different intensified/accelerated infliximab induction approaches and review the literature on this topic.The first case describes an 18-year-old girl with ASUC at disease onset with rapid progression to toxic megacolon, complicated also with anemia, hypoalbuminemia, and coagulopathy. After corticosteroid failure, both accelerated and intensified (10 mg/kg) infliximab regimen was completed within 11 days, with solid clinical response and colon imaging normalization. Second, we present a 26-year-old male with left-sided ulcerative colitis known for 2 years, under mesalazine, who developed a moderate flare and was started on infliximab after partial and inconsistent response to corticosteroids. During the induction period, he presented this time an ASUC episode, which motivated an early and intensified third dose with good clinical response. Finally, we describe the case of a 78-year-old man with ulcerative proctitis for 12 years presenting ASUC with proximal disease extension as well. After unsatisfactory response to corticosteroids, infliximab was initiated on an accelerated induction regimen, completed in 13 days, with the standard dose, achieving clinical remission. Accelerated or intensified infliximab induction plans are becoming current clinical practice in corticosteroid-refractory ASUC. Current guidelines refer to the possibility of this type of strategies, not determining the optimal regimen due to lack of solid evidence. Literature is mainly based on retrospective studies, not randomized, with heterogeneous groups according to disease severity, and the effect on colectomy rates, mainly on the long term, is not clear. Additional well-supported studies are needed on this subject in order to seek a more widely uniform approach.

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Estratégias de indução de infliximab na agudização de colite ulcerosa grave: uma série de casos e revisão da literatura

Palavras Chave
Agudização grave de colite ulcerosa · Indução acelerada infliximab · Indução intensificada infliximab

Resumo
A agudização grave de colite ulcerosa é uma emergência médica, particularmente difícil de tratar de forma eficaz. O infliximab é uma das opções de tratamento médico de resgate após refractariedade aos corticosteróides, porém a melhor estratégia de indução ainda não está definida. Com este relato de série de casos, os autores pretendem descrever três casos de agudização grave de colite ulcerosa refratária a corticosteróides com diferentes abordagens de indução intensificada/acelerada de infliximab e rever a literatura sobre este tópico. O primeiro caso descreve uma jovem de 18 anos com agudização grave de colite ulcerosa, à apresentação da doença, com rápida progressão para megacólon tóxico, complicada também com anemia, hipoalbuminemia e coagulopatia. Após ausência de resposta a corticosteróides, foi iniciado regime acelerado e intensificado (10 mg/kg) de infliximab, concluído em 11 dias, com resposta clínica e normalização das alterações imagiológicas do cólon. Em segundo lugar, apresentamos um homem de 26 anos com colite ulcerosa esquerda conhecida há 2 anos, sob messalazina, que apresentou uma agudização moderada da doença e iniciou infliximab após resposta parcial e inconsistente aos corticosteróides. Durante o período de indução, apresentou desta vez um episódio de agudização grave, o que motivou uma terceira dose precoce e intensificada com boa resposta clínica. Por fim, descrevemos o caso de um homem de 78 anos com proctite ulcerosa há 12 anos apresentando agudização grave de colite ulcerosa, também com extensão proximal da doença. Após resposta insatisfatória a corticosteróides, foi iniciado infliximab em regime de indução acelerada, completado em 13 dias, com a dose padrão, obtendo remissão clínica. Os esquemas de indução de infliximab acelerados ou intensificados têm vindo a tornar-se prática clínica habitual nos casos de agudização grave de colite ulcerosa refratária a corticosteróides. As diretrizes atuais referem a possibilidade deste tipo de estratégias, não indicando qual o regime ideal por falta de evidência sólida. A literatura baseia-se principalmente em estudos retrospetivos, não randomizados, com heterogeneidade de grupos de estudo de acordo com a gravidade da doença e o efeito nas taxas de colectomia, sobretudo a longo prazo, não é claro. Estudos mais fundamentados são necessários sobre esta matéria de modo a que seja possível uma abordagem amplamente mais uniforme.

Introduction

Ulcerative colitis (UC) is a lifelong disease characterized by chronic and continuous inflammation of the colon and rectum. Acute severe ulcerative colitis (ASUC) is a particular disease setting in inflammatory bowel disease [1] and is diagnosed according to the Truelove and Witts [2] criteria, combining signs of clinical disease severity and systemic toxicity. Despite the recent advances in inflammatory bowel disease management, it still constitutes a clinical and therapeutic challenge, with a 10–20% risk of early colectomy [3–5].

Corticosteroid therapy is the mainstay of ASUC treatment, which is successful in around two-thirds of patients. In steroid-refractory patients, infliximab (IFX) is well established as a second-line treatment in ASUC management [1, 6, 7].

Several pathophysiologic characteristics, namely, high inflammatory burden, low albumin levels, and increased IFX clearance, suggest that higher IFX dosages would be required in this context [8, 9]. Thus, intensification regimens with higher induction doses or shorter intervals have been proposed and attempted in order to increase therapeutic success [10]. Their role, however, is not clearly established due to controversial findings and lack of well-designed randomized control trials. Nevertheless, the most recent British Society of Gastroenterology guidelines recommend accelerated regimens in patients who fail to respond to IFX standard dose after 3–5 days [6]. We present 3 cases of ASUC treated with IFX intensified/accelerated regimens and discuss the evidence for and against this strategy.

Case Presentation

First, we present the case of an 18-year-old female with past medical history of asthma under inhaled corticosteroids. She presented in the emergency department with bloody diarrhea (>6 bowel movements/day), associated with 12% bodyweight loss, severe abdominal pain, and vomiting for 3 weeks. On physical examination, she was feverish (38.5°C), with increased heart rate

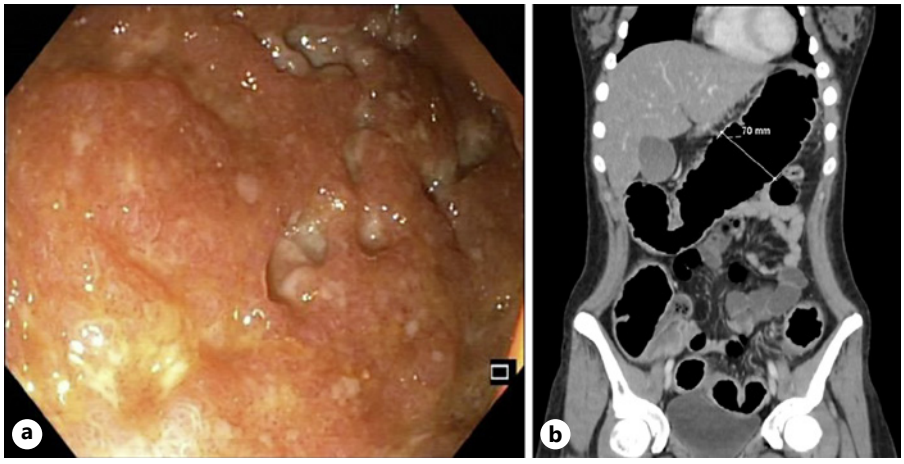

Fig. 1. a Proctosigmoidoscopy showing deep mucosal ulceration in the sigmoid (case 1). **b** Abdomen CT revealing transverse colon dilation, consistent with toxic megacolon (case 1).

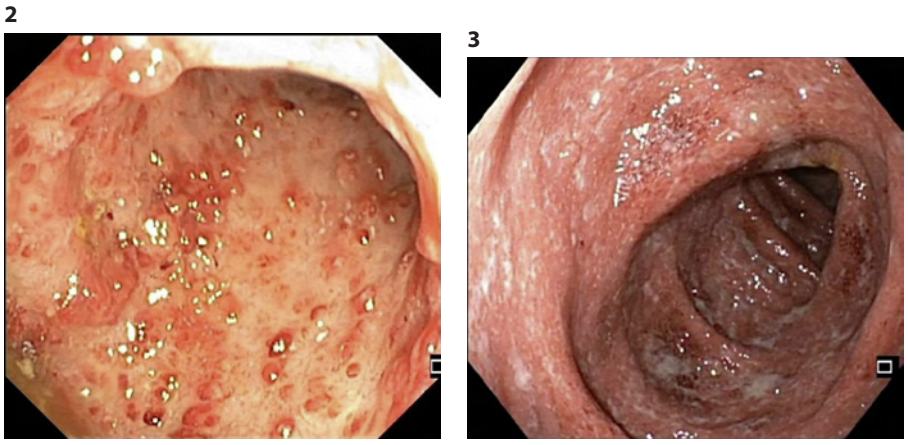

Fig. 2. Colonoscopy showing diffuse descendent colon ulceration and friable mucosa (case 2).
Fig. 3. Endoscopic appearance of the transverse colon, compatible with Mayo score of 3 (case 3).

(108 bpm) and diffuse abdominal tenderness with no signs of peritonitis. From blood analysis, severity signs were present, from which microcytic anemia (hemoglobin 11.9 g/dL), hypoalbuminemia (3.0 g/dL), and high C-reactive protein (CRP; 224 mg/dL) stood out. Hematological involvement with severe coagulopathy was also identified (INR 4.1). Proctosigmoidoscopy revealed the presence of deep ulcers throughout the visualized length (shown in Fig. 1a) compatible with severe UC, which biopsies confirmed. The patient underwent an abdominal computed tomography (shown in Fig. 1b) which revealed toxic megacolon and was then hospitalized under intravenous corticosteroids (1 mg/kg/day), after surgical team consultation.

At day 3 and 5, she showed only mild clinical response and our decision was to start IFX on a 10 mg/kg dosage. After first infusion, she had a good clinical response; however, this improvement only lasted for 3 days. Decision was agreed toward an accelerated induction regimen with this high-dose strategy and a new infusion was administered 5 days after the first. The temporary clinical improvement scenario repeated itself and the third infusion was taken after 6 days, completing the induction phase in just 11 days. IFX blood levels measured 3 days after drug induction conclusion were high (>20 μg/mL). This time and still under i.v. corticosteroids as adjuvant therapy, the clinical response got lasting and progressive, also with radiological normalization of colon diameter and metabolic correction of biomarker alterations and deficits, such as in iron and vitamin K. She was discharged with a 6/6 weeks IFX plan under proactive therapeutic drug monitoring (TDM), corticosteroid tapering, and plan to start combined therapy with immunosuppression on the short term. No drug-related events were recorded and 1 year after the hospitalization patient remains in remission with this strategy.

In second place, we present the case of a 26-year-old male diagnosed with left-sided UC for 2 years, under oral and topical mesalazine. He presented clinical deterioration for 3 months before being hospitalized. Workup revealed elevated CRP (83 mg/dL), hypoalbuminemia (1.9 g/dL), severe anemia (hemoglobin 8.3 g/dL), and an endoscopic Mayo score of 3 in the left colon (shown in Fig. 2). After partial clinical response to i.v. corticosteroids, symptomatic worsening was observed on day 4, when tapering was started, and IFX was initiated on the standard dose (5 mg/kg). He then maintained good clinical improvement and was discharged with corticosteroid tapering plan and a new scheduled IFX infusion in 2 weeks.

Two weeks after the second dose, he presented with an ASUC episode back in our institution and was hospitalized with i.v. corticosteroid resume and a new IFX infusion, this time at 10 mg/kg,

when TDM revealed unmeasurable trough levels and no antibodies. During hospitalization, by reason of severe weight loss and poor nutritional status, partial parenteral nutrition was initially used and progressively withdrawn until the time patient was discharged, when clinically stable, with IFX 10 mg/kg regimen every 4 weeks. Treatment with azathioprine was included on the last days of hospitalization and the patient remains now, 2 years after this episode, on remission under combined therapy, with IFX standard dosage, after tapering driven by TDM.

Finally, the third case is a 78-year-old male, previously followed for an ulcerative proctitis for 12 years, under oral mesalazine, as he refused long-term topical therapy. He came to the emergency department due to new onset of bloody diarrhea (>20 episodes/day) and tenesmus for 1 month. At clinical examination, he presented with severe dehydration (blood pressure of 94/52 mm Hg and heart rate of 150 bpm). Blood analysis revealed high CRP (18 mg/dL), hypoalbuminemia (2.6 g/dL), and hyperlactacidemia (4.7 mmol/L). He underwent a colonoscopy that revealed an extensive UC with diffuse deep ulcerations (Mayo score 3, shown in Fig. 3), mainly in the sigmoid and rectum. He started high-dose i.v. corticosteroids with no satisfactory response at day 3 and day 5. It was then decided to start IFX at the standard dose (5 mg/kg) that was reinfused at the same dose after 6 days due to clinical worsening. During the remaining 7 days of hospitalization, he achieved clinical response, in association with partial parenteral nutrition support, completing the induction phase in 13 days. Three years after this episode, he remains in disease remission under IFX standard maintenance plan.

Discussion/Conclusion

In this case series, we aim to illustrate 3 different types of patients and settings according to presentation and disease duration where ASUC is possible. Also, due to the absence of formal guidelines for IFX accelerated or intensified dose regimens, different strategies were considered depending on the episode's and individual's characteristics. Both accelerated and dose-intensified approach was used for the most severe case where it was observed rapid progression to toxic megacolon in a young female. On the other hand, a more cautious plan with standard dose acceleration was chosen for the older patient. It should be underlined that, although cyclosporine provides similar short-term outcomes compared to IFX, it is our institution current practice to prefer the anti-tumor necrosis factor (TNF) drug over the calcineurin inhibitor because of its easiness of use, the transition to the maintenance phase, and the less complex adverse event's profile.

ASUC is a medical emergency and a potential life-threatening condition. Approximately 1 in 5 patients with UC will face an acute exacerbation that requires hospitalization, often at the time of disease onset [11]. As the Truelove and Witts criteria remain the current severity stratification tool over time, also corticosteroids keep their role for decades as the cornerstone treatment for ASUC with response rates around 67% [12]. For the remnant portion of patients, in the absence of clinical improvement, although surgery must be taken into consideration, medical rescue treatments, including cyclosporine and IFX, can be used with proved efficacy [5].

In this setting of patients, IFX is reported to achieve response rates of 44–75%, although early colectomy rates remain relatively high, between 24% and 48% [13–15]. As previously mentioned, the best IFX induction regimen for salvage therapy is not yet well determined due to lack of supporting literature comparing different strategies, although accelerated regimens seem superior taking into account early colectomy-free survival [5]. Therefore, the approach chosen by each healthcare provider team still depends on the institution experience and some of the patient's characteristics and perceived risks.

There are some pathophysiological and pharmacokinetic factors that provide a rationale for the use of intensified or accelerated strategies in these severe cases. High inflammatory burden, or by other words disease severity, in ASUC translates into high TNF circulating levels. The clearance of IFX is directly associated with TNF in the systemic circulation, mainly due to the formation of immune complexes and consequent faster proteolytic degradation by the reticuloendothelial system [10]. Additionally, a study by Brandse et al. [16] clearly showed that high levels of IFX in stools of patients with UC were associated with nonresponse to treatment, especially in the severe cases, suggesting a role for repeated infusions to counterbalance monoclonal antibodies fecal loss. The damage of the intestinal epithelial barrier due to extensively ulcerated mucosa is also known for being responsible for protein loss and high incidence of hypoalbuminemia; therefore, it is reasonable to use albumin as a biomarker of drug clearance. The serum level of albumin and C-reactive protein (CRP) reflect the inflammatory status in daily practice, being associated with poorer outcomes, such as early and late colectomy [17], and recently a unicenter-based group proposed a protocol based on CRP/albumin ratio at presentation for the decision of intensified dose use and CRP at day 3 for accelerating dosing [18].

The results of this last single-center retrospective study did not detect a significant difference on early colectomy rates in those exposed to accelerated and standard strategies; however, the cohort for the first group had higher CRP levels at IFX start. This tendency is corroborated by a meta-analysis by Nalagatla et al. [19], where no associa-

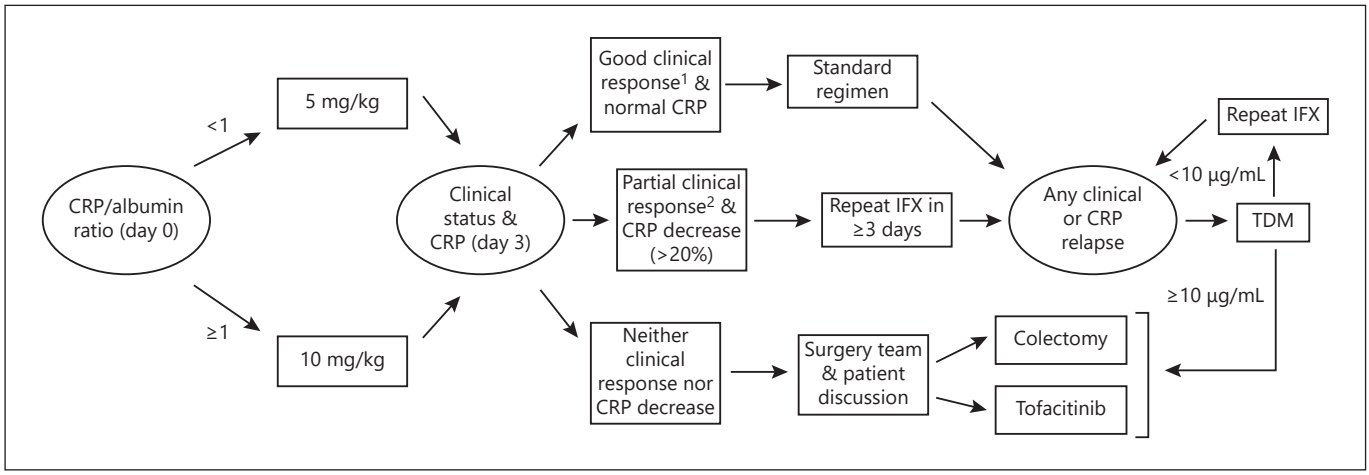

Fig. 4. Proposed decision algorithm for steroid-refractory acute severe colitis. [1]<4 bowel movements/day and no rectal bleeding. [2]Significant improvement on number of bowel movements/day and resolution of rectal bleeding. CRP, C-reactive protein; IFX, infliximab; TDM, therapeutic drug (IFX) monitoring.

tion is found between accelerated IFX induction therapy and lower rates of colectomy; however, as a retrospective study, the possible bias of different disease severity in both groups might play a role in the final results. Additionally, another systematic review and meta-analysis examining the impact on colectomy-free survival of different IFX induction dosages in ASUC conclude that the results were not statistically different between the standard induction group versus the accelerated or intensified induction dose groups, but again the meta-regression performed revealed higher CRP and lower albumin levels in the intensified group, both of these two prognostic factors being associated with higher risk of colectomy [20]. Partially pointing in an opposite direction, Gibson et al. [9] performed a retrospective analysis of a small group of patients with ASUC, showing that an accelerated induction may bring benefits in the shorter term with lower colectomy rates during induction, although no differences in colectomy during follow-up were seen.

As it becomes clear, there is much need for a robust randomized clinical trial that could unveil the beneficial outcomes of an accelerated or intensified induction strategy, currently used in a heterogeneous and irregular manner, comparing to standard regimens originated from pivotal studies (Table 1). Thus, we are eagerly looking forward to the results of the PREDICT-UC (Clinicaltrials.gov: NCT02770040), the only controlled trial of IFX dosing in ASUC, knowing that some questions will remain unanswered. Other aspects like identification of IFX induction levels threshold or additional clinical predictors which could indicate the need for either accelerated or intensified strategies should also be pursued. To date, there are still insufficient data to indicate what is the target trough level during ASUC treatment and consequently the role for TDM becomes unclear. A single study identified IFX serum concentrations of <16.5 and <5.3 µg/mL at week 2 and 6, respectively, as independent predictors for colectomy [21]. Curiously, it was also shown by Ungar et al. [22] that primary nonresponders did not have lower IFX levels compared to responders at week 2; however, a significant difference was seen at week 6. This points to the fact that pharmacokinetics is not the only driver for induction and that TDM role is limited to auxiliate on the assumption of treatment failure, when no clinical improvement is registered despite high IFX serum concentrations, rather than being a tool to pursuit a optimal value.

Taking in consideration what we found wiser from each protocol of accelerated regimens used in the studies available to date, we propose a possible algorithm of action in the steroid-refractory ASUC setting (shown in Fig. 4). Additionally, we considered as a possible salvage medical treatment option the rapidly acting janus kinase inhibitor, tofacitinib, although it is still controversial and lacking supporting evidence. The biggest retrospective study to date by Berinstein et al. [23] evaluating the effect of high-dose tofacitinib (together with corticosteroids) in biologic-experienced ASUC patients confirmed its beneficial effect on reducing the 90-day colectomy rate. Similarly, a case series published in 2022 revealed that 4 out

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Table 1. Summary of existing studies on intensified or accelerated IFX induction regimens

Author	Year	Type of study	Eligibility for rescue therapy	Sample size	IFX induction dose	IFX accelerated induction strategy	Endpoints	Relevant findings
Gibson et al. [9]	2015	Retrospective, unicentric	IV steroid-refractory ASUC	50	5 mg/kg	3 doses within 24 days	Colectomy rate during induction and follow-up (2 years) period	Standard regimen associated with shorter time to colectomy; rate of colectomy significantly lower during accelerated induction period; colectomy rates similar in both groups during follow-up
Gibson et al. [25]	2018	Retrospective, multicentric	IV steroid-refractory ASUC	145	5 mg/kg	3 doses within 42 days	Time to colectomy; time to IFX discontinuation	Time to colectomy significantly prolonged with use of accelerated dose in those with more severe disease; time to IFX discontinuation was shorter in the standard dose group
Nalagatla et al. [19]	2019	Retrospective, multicentric	IV steroid-refractory ASUC	213	5–10 mg/kg	If partial or nonresponders to first dose, second dose in 3–5 days	Inhospital, 3-, 6-, 12-, and 24-month colectomy rate	No difference between accelerated and standard IFX in need for short- or long-term colectomy; among those in the accelerated induction group, lower inhospital and long-term colectomy rates in the 10 mg/kg group
Chao et al. [17]	2019	Retrospective, multicentric	Mayo score ≥6; Mayo endoscopic score ≥2; IV steroid-refractory ASUC	72	5–10 mg/kg	(No accelerated strategy used for comparison)	3-month colectomy rate	Rate of colectomy at 3 months not significantly different between standard and high-dose IFX; higher need for shortened induction regimen in the 5 mg/kg group, which itself was an independent predictor for early colectomy
Govani et al. [18]	2020	Retrospective, unicentric	IV steroid-refractory ASUC	66	5–10 mg/kg	IFX repeated dose in 3 days if partial CRP response	90-day colectomy rate	No significant colectomy rate difference between the standard and accelerated induction group; 69.7% of those with incomplete response to IFX first dose were able to avoid colectomy with an accelerated strategy

IFX, infliximab; IV, intravenous.

of 5 IFX-refractory ASUC patients responded to high-dose tofacitinib, all remaining colectomy free at day 90 [24]. In the near future, we hope that recognition of inflammatory pathways specific for each patient can modulate therapeutic approaches bringing to clinical practice the goal of personalized medicine.

Statement of Ethics

This case report did not require ethics approval. Informed consent was obtained from the participants for publication of this case series report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

Pedro Bernardes Antunes was responsible for the design of the study, collecting the data, and drafting of the manuscript. Bruno Gonçalves and Bruno Arroja were responsible for the interpretation of the data. Raquel Gonçalves was responsible for critical revision of the work for important intellectual content. Tiago Leal was responsible for design of the study and critical revision of the work for important intellectual content. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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