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THÈSE POUR LE DIPLÔME D'ÉTAT

DE DOCTEUR EN MÉDECINE

Pronostic à long terme après colite aigue grave en centre tertiaire à l'ère des biothérapies : existe-t-il toujours une différence en fonction de la réponse initiale à la corticothérapie intraveineuse ?

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AVERTISSEMENT

La Faculté n'entend donner aucune approbation aux opinions émises dans les thèses : celles-ci sont propres à leurs auteurs.

Short terms

5-ASA : 5-Aminosalicylic Acid

Anti-TNF : Anti-Tumor Necrosis Factor

ASUC : Acute Severe Ulcerative Colitis

CRP : C-Reactive Protein

IBD : Inflammatory Bowel Disease

IFX : Infliximab

IVS : Intravenous steroids

IS : Immunosuppressant

UC : Ulcerative Colitis

UCEIS : Ulcerative Colitis Endoscopic Index of Severity

TABLE DES MATIERES

ABSTRACT

Background & Aims: Long-term prognosis after an acute severe ulcerative colitis has been poorly reported, especially in biologic era. We aim to document long-term outcomes of patients who will respond to a medical therapy for acute severe ulcerative colitis and whether if this prognosis is different depending on the responsiveness to the intravenous steroid therapy.

Methods: Between 2011 and 2019, all patients admitted with Ulcerative Colitis in Lille Hospital for acute severe ulcerative colitis (defined as Lichtiger index equal to or greater than 10) treated with intravenous steroid therapy in first line therapy, who responded to a medical therapy on index hospitalization and followed-up for at least 1 year were included in our monocentric retrospective study. The primary end point was colectomy rate at 1 year.

Results: 97 patients (52% men, median age 30 years (IQR:22-48)) were included: 56 responders to steroids and 41 responders to a rescue therapy by infliximab or ciclosporin after failure of IV steroids. Initial therapy at discharge was 5-aminosalycilates in 23% responders to intravenous steroids
compared to none among non-responders to intravenous steroids (p=0,005). Median follow-up was 27,8 months (IQR:14-57). Long-term colectomy rate was 20% at 1 year and 30% at the end of study period. Recurrence of acute severe ulcerative colitis rate was 18% at 1 year and 29% at the end of study period. 50%, 27% and 16% of patients changed their maintenance therapy at least 1, 2 and 3 times respectively during study period.
No significant differences were found in long-terms outcomes between responders and non-responders to intravenous therapy.

Conclusion: Patients with acute severe ulcerative colitis avoiding colectomy at index hospitalization in the biologic era still have poor long-term prognosis, regardless to the initial responsiveness to intravenous steroid therapy. Prospective studies investigating the best choice of therapy at discharge could modify these results.

RESUME

Introduction : Le pronostic à long terme après colite aigue grave a été peu décrit, particulièrement à l'ère des biothérapies. Les objectifs de notre étude étaient de rapporter les résultats à long terme des patients répondant à un traitement médical pour colite aigue grave, et de rechercher une différence de pronostic en fonction de la réponse initiale à la corticothérapie intraveineuse.

Matériel et méthodes : Nous avons conduit une étude observationnelle monocentrique incluant les patients atteints d'une rectocolite hémorragique admis entre 2011 et 2019 au Centre Hospitalier de Lille pour colite aigue grave (définie par un Lichtiger supérieur ou égal à 10), traités en première ligne par corticothérapie intraveineuse, répondant à un traitement médical lors de l'hospitalisation initiale et suivis au moins 1 ans. Le critère de jugement principal était le taux de colectomie à 1 an.

Résultats : 97 patients (52% d'hommes, âge médian de 30 ans (IQR: 22-48)) ont été inclus : 56 patients ayant répondu à la corticothérapie intraveineuse initiale et 41 patients à un traitement médical de recours par infliximab ou ciclosporine après échec de la corticothérapie. Le traitement de maintenance initial était par 5-aminosalicylates chez 23 % des patients corticosensibles contre 0% des patients corticoresistants (p=0,005). La médiane de suivi était de 27,8 mois (IQR:14-57). Le taux de colectomie était de 20% à 1 an et de 30% à la fin de la période d'étude. Le taux de récidive de colite aigue grave était de 18% à 1 an et de 29% à la fin de la période d'étude. 50%, 27% et 16% des patients auront eu respectivement au moins 1, 2 et 3 modifications de leur traitement de maintenance durant la période d'étude. Aucune différence significative concernant ces résultats à long terme n'était retrouvée entre les patients ayant répondu à la corticothérapie intraveineuse initiale et ceux n'y ayant pas répondu.

Conclusion : Le pronostic à long terme des patients ayant présenté une colite aigue grave et répondant à un traitement médical reste défavorable à l'ère des biothérapies, et ne semble pas dépendre de la réponse initiale à la corticothérapie intraveineuse. Des études prospectives étudiant le choix du meilleur traitement après un premier épisode de colite aigue grave pourraient permettre de modifier ces résultats.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that causes continuous mucosal inflammation and is characterized by an alternation of relapse and remission [1]. 15 to 25 % of patients will experience an acute severe ulcerative colitis (ASUC) in the course of their disease [2]. Breakthroughs in medical therapy benefit the ASUC prognosis, but it remains a life-threatening condition, with an estimated risk of mortality of 1-3 % and emergency colectomy of 30 %[3][4].

ASUC requires a hospital admission with multidisciplinary therapeutic management. First line medical therapy remains intravenous steroids (IVS), with an overall response rate of 67 %, stable since the 1970's [4]. Previous studies into ASUC have focused on steroid refractory patients, investigating the efficacy and safety of either Ciclosporin or Infliximab (IFX) as a rescue therapy, in terms of short and long term colectomy rates [5][6][7].

Data on long term outcomes in patient responding to IVS are scarce, prior to the immunosuppressive era [8] or the modern era, despite the increasingly frequent use of biologic agents as anti-tumor necrosis factor (anti-TNF) agents, anti-integrin and anti-IL-12/23 p40 monoclonal anti body therapies, or small molecules as a JAK inhibitors. It is mainly unknown how these therapies may have influenced the long-term outcomes for patients after an ASUC.

We aim to document the prognosis of patients who will respond to medical therapy for ASUC in the biologic era, and whether if this prognosis is different depending on the responsiveness to the IVS.

PATIENTS & METHODS

STUDY POPULATION

We performed a retrospective cohort study by a systematic review of all consecutive patients hospitalized for ASUC in our tertiary care center in Lille from 2011 to 2019. ASUC was defined by a Lichtiger index equal to or greater than 10 points.

All patients (1) with a confirmed diagnosis of UC according to ECCO guidelines; (2) over 16 years of age; (3) treated with IVS in first line therapy; (4) who responded to a medical therapy on index hospitalization avoiding colectomy; and (5) with a follow-up of at least 1 year after hospitalization were included. Patients with Crohn's disease or with unclassified inflammatory bowel disease, treated by a anti-TNF or ciclosporin before the use of IVS, or who underwent a colectomy during index hospitalization were excluded. Patients were identified from the standardized hospital dataset by searching ICD-10 codes for Ulcerative Colitis (UC).

DATA COLLECTION

Demographic, clinical, biological, endoscopic and therapy data patients were collected by reviewing medical records.

Demographic data included date of birth, sex, and smoking status at admission. Clinical data included previous appendicectomy, extra-intestinal manifestation, date of UC diagnosis, disease extent defined by Montreal Classification, and previous therapy exposure (including use of 5-aminosalycilic (5-ASA), oral corticosteroids, thiopurine, methotrexate, anti-TNF, Vedolizumab, Tofacitinib, and Ustekinumab). Data on ASUC included date of admission, Lichtiger index score, number of stools, biological parameters (hemoglobin levels, white cells count, platelet count, CRP and albumin levels), endoscopic activity if available (UCEIS and Endoscopic Mayo Clinic subscore), the presence of any co-infection

(CMV or Clostridium Difficile), treatment exposures during hospitalization (drug classes, date of introduction and withdrawal, responsiveness), whether a colectomy occurred and therapy at hospital discharge. After discharge we assessed the occurrence of treatment modifications, and the recurrence of ASUC. We recorded colectomy rates, death rates, and the date of the patient's last visit to hospital.

All patients received IVS with 0,8-1mg/kg methylprednisolone, as recommended. Refractoriness to steroids was defined by the need for either rescue medical therapy (cyclosporine or infliximab) or colectomy at index hospitalization after IVS. In our study, the term "patients non responders to IVS" will be used instead of the term "patients non responders to IVS but responders to a rescue therapy" for ease, as we have said previously that patients undergoing colectomy at index hospitalization were excluded from our study.

Short term colectomy was defined as surgery performed during index hospitalization. Long-term colectomy was defined as surgery performed any time after hospital discharge. Treatment modifications collected were: additional drug therapies (introduction of an immunosuppressant (IS) as monotherapy, introduction or switch of a biologic agent) due to disease flare, failure or intolerance of IS or biologic agent. Data on the introduction of IS for patients already under biologic agents and changes of IS were not collected, on the basis that this was not a change of therapeutic line.

Patients were followed-up from the date of hospital admission for ASUC until their (1) death, (2) colectomy or (3) last visit, whichever occurred first. The study was approved by the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé.

OUTCOMES MEASURES

The primary outcome was colectomy within one year after hospital discharge. Secondary outcomes included colectomy at the end of follow up, recurrence of ASUC and treatment modification within one year after hospital discharge and at the end of follow up.

STATISTICAL ANALYSIS

All patients were evaluated from the date of hospital discharge to the end of follow-up period. Quantitative data were expressed as median (interquartile range) and compared with the Wilcoxon-Mann-Whitney test. Qualitative data were expressed as a number (%) and compared with the Chi-square or Fisher's test. Colectomy-free, recurrence of ASUC-free and treatment modification-free survivals during the study period were presented using the Kaplan-Meier method. The survival distributions were compared using the log-rank test. P-values <0,05 were considered significant.

RESULTS

STUDY POPULATION

From January 2011 to December 2019, 180 patients were hospitalized for acute ulcerative colitis. 41 underwent a non-severe attack (defined by a Lichtiger index of less than 10), 9 were treated first line by anti-TNF or ciclosporin without IV steroids, and 12 underwent immediate colectomy.

Of the 118 remaining patients, 56 (47%) responded to IVS, and 62 (53%) did not. Among non-responders to IVS, first line of rescue therapy had been IFX for 17/41 (41%) patients and Ciclosporin for 24/41 (59%) patients. 21 patients underwent colectomy after rescue therapy failure, leaving to final analysis 56/118 (47%) responders to IVS and 41/118 (35%) non responders to IVS but responders to rescue therapy (Figure 1).

Characteristics at admission are presented in Table 1. 51 (52%) patients were men, median age at inclusion was 30 years (IQR: 22-48), median duration from UC diagnosis to admission was 21 months (IQR:5-80) and 55 (56%) presented an extensive colitis at diagnosis. Regarding previous therapy, 9 (9%) had none, 39 (40%) had 5-ASA and 49 (50%) had immunosuppressant and/or biologic agents. In non-responders to IVS, disease activity at admission was slightly but significantly more severe than in responders to IVS, for clinical data (Lichtiger index at 13 vs 12, p=0,0298) and endoscopic data (UCEIS at 6 vs 5, p=0,0141 and Endoscopic MAYO Clinic subscore at 3 vs 2, p=0,009). Concerning therapy at discharge, 13/56 (23%) were treated by 5-ASA among responders to IVS and none in the non-responders to IVS group, which was a significant difference (p=0,005). A total of 82/97 (85%) had IS and/or biologic agents (21 IS only, 43 anti-TNF and 18 Vedolizumab). Otherwise, both groups were similar at the time of admission. All patients were followed-up for at least 1 year. The median follow-up was 27,8 months (IQR:14-57).

COLECTOMY

Within 1 year of discharge, 19 of 97 patients (20%) underwent a colectomy. There was no significant difference between responders and non-responders to IVS (17% vs 21%, p=0,6165, Tab 2). Of the remaining 78 patients (80%), 10 underwent a colectomy more than 1 year after discharge.

Overall, during the study period 29 of 97 patients (30%) had a colectomy. No significant difference was found in colectomy-free survival between responders and non-responders to IVS (p=0, 4197, Fig 2). The median time from index admission to colectomy was 9 months (IQR:3-14). In responders and non-responders to IVS, the median time from index admission to colectomy was respectively 9 months (IQR:2-20) and 7 months (IQR:5-14).

Among the 29 patients who underwent a colectomy, 20 (69%) experienced a recurrence of ASUC. By comparison, among the 68 patients who did not undergo a colectomy, only 8 (11%) experienced a recurrence of ASUC.

RECURRENCE OF ASUC

Within 1 year of discharge, 17 of 97 patients (18%) experienced a recurrence of ASUC. At the end of study period, it happened to 28 of 97 patients (29%). There was no significant difference between responders and non-responders to IVS at 1 year (16 % vs 19%, p=0,7882, Tab 2) or in recurrence of ASUC-free survival during study period (p=0,1700, Fig 3). The median time to recurrence of ASUC after index admission was 6 months (IQR:3-16), respectively 4 months (IQR:2-13) for responders to IVS and 9 months (IQR:3-16) for non-responders to IVS.

Overall, in the group of patients experiencing a recurrence of ASUC, 20/28 (71%) will have a colectomy.

TREATMENT MODIFICATION

At 1 year, 34%, 9% and 4 % of patients changed their maintenance therapy at least 1, 2 and 3 times respectively. No significant difference was found according to responsiveness to IVS (Tab 2).

During the study period, 49 (50%), 27 (27%) and 16 (16%) of patients changed their maintenance therapy at least 1, 2 and 3 times respectively. Treatment modification-free survivals show no significant difference between responders and non-responders to IVS (Fig 4). Median time to first treatment modification was 6 months (IQR:4-13), which was an equal median time for responders and non-responders to IVS.

Treatment modification occurred in 7/13 (55%), 13/21 (62%) and 29/61 (47%) of patients treated with 5-ASA, immunosuppressant and biologic agents at discharge therapy respectively.

In the 13 patients treated by 5-ASA at discharge, 7/13 (55%) had a change of maintenance therapy (6 in the first year), 3 experienced a recurrence of ASUC (2 in the first year) and 3 underwent a colectomy.

DISCUSSION

The aim of our study was to report real-life long-term data from a tertiary center with a cohort of patients with ASUC in the biologic era. The question that matters at discharge hospital for either doctor or patient being first the likelihood of colectomy, it seems clinically relevant to only analyze patients avoiding colectomy at index hospitalization.

As our center is a tertiary care center, patients are referred from other clinics or hospitals for expert advice, both in the gastroenterological and in the surgical field, for patients with medical history of refractory disease, severe disease and/or important comorbidities. It influences our findings, as it can be seen for our short term colectomy rate of 24,7%. It is closer to the 27% rate reported by Turner et al in a meta-analysis from 1974 to 2006 where cyclosporine was not frequently used [4] rather than the 9,4% described recently in the biologic era [9]. It is important to notice that among the 33 patients who underwent colectomy during initial hospitalization, 12 were referred to our center to discuss immediate colectomy.

More interestingly, our study confirms persistent poor long-term outcomes after an ASUC in the biologic era.

The long-term colectomy rate is 30% and will occur in the first year after hospital discharge for more than half of patients. Among studies on prognosis after an ASUC, we found heterogeneity in definition of severity, number of patients included in the study, study design, therapy era and definition of colectomy rate (short, early, long-term and overall colectomy rate). In literature, the range of long-term colectomy goes from 15% to 33% [8][9][10][11][12][13]. Our long-term colectomy rate is similar at the 33 % rate described in a French bi-center cohort study in the biologic era [10]. An Italian study involving 14 centers from 2005 to 2017 with a total of 372 patients reported a 19,4% long-term colectomy rate [9]. In this study, “long-term colectomy rate” was defined as any colectomy occurring more than 3 months after hospital discharge, rather than any colectomy occurring after hospital

discharge. This could explain the difference in results, given that 7 of our 29 patients underwent a colectomy within 3 months of discharge in our study.

Overall, almost one third of patients experienced a recurrence of ASUC, half of them in less than 6 months. Among them, over 70% underwent a colectomy. No recent studies were found about recurrence of ASUC rate, outcomes as flare and/or rehospitalization being preferred, with various definitions. To our knowledge Dinesen et al. described it last, reporting in a large cohort from 1950 to 2000 a 36% rate of recurrence of ASUC, stable over decades. This rate is consistent with our findings, as well as the increase colectomy rate after recurrence of ASUC [14]. Being known that the main indication for colectomy is ASUC [14], our recurrence of ASUC rate is coherent with our long-term colectomy rate.

In our study, half of the patients will have at least 1 treatment modification, in a median time of 6 months (IQR=4-13). This is consistent with recent studies at biologic era. Salameh found in a population of responders to IVS a 60% rate of patients experiencing a clinical relapse due to the failure of the chosen maintenance therapy [15]. A 59% escalation of therapy rate during follow-up is described in Festa's cohort [9]. Treatment modification is a recently used outcome in studies, appropriate in view of the increase of therapeutic lines in the past years. For patients, it might affect their quality of life. Patient-Reported Outcomes (PROs) in Inflammatory Bowel Disease are tools which try to assess disease burden for patients in their social and professional life from their own perception [16]. This burden has been evaluated as "very high" in a French Nationwide survey of IBD patients in 2014 [17]. Treatment modification could be a relevant end-point, both from the clinician's and the patient's perspective.

Prognosis of patient responders to IVS has not been found statistically different from the non-responders to IVS in our study, contrary to what has previously been reported in literature.

Although the first descriptions of better long-term outcomes for patient responders to IVS were made before rescue therapy use, or at a time where cyclosporine place needed to be defined [18][19], these descriptions were later confirmed at the IS era [20][21]. Festa's cohort suggests that steroid refractoriness is still a predictive factor for poor prognosis in the biologic era, with a higher long-term colectomy rate in this population [9]. Our patient's characteristics at admission were almost similar in responders and non-responders to IVS. The only differences we found between them which may have act as confounding factors are Lichtiger Index, endoscopic scores and therapy at discharge. We argue that both (1) a Lichtiger index of 12 versus 13, and (2) an UCEIS score of 5 versus 6, lack clinical relevance. For MAYO endoscopic subscore, although retrospective studies [22][23] reported an association between endoscopic lesion severity and risk of colectomy, a randomized controlled trial did not confirm it [6]. At discharge, a quarter of responders to IVS was put on 5-ASA, and responders to IVS were half as numerous under anti-TNF as non-responders to IVS, even if it did not reach significant difference. The impact of therapy at discharge on long-term outcomes is harder to investigate, and in our opinion should not be underestimated.

ECCO statement highlights the need for maintenance therapy in UC for several years, based on studies showing an increase in long-term remission rates under treatment. In a retrospective study on patients responding to IVS after ASUC, a significantly lower rate of relapse was found in patients treated with anti-TNF compared to 5-ASA and IS [15]. In the Festa cohort, despite a significant difference in maintenance therapy between responders and non-responders, it did not affect the long-term colectomy rate. It was emphasized that treatment differences were quickly reduced over time between groups due to the high rate of treatment modification [9]. A recent ECCO statement based on a low level of evidence recommend that thiopurines-naïve patients with severe colitis responding to steroids or ciclosporin should be treated by thiopurines, while thiopurine-refractory patients should be

treated by infliximab [24]. In a recent study, the lack of a reduction in the risk of colectomy at 1 year from discharge in steroid responders despite ECCO statement, possibly due to absence of drug randomization and/or monitoring [25], advocate for randomized prospective comparing systematic anti-TNF therapy versus thiopurines for ASUC responding to IV steroids (as the ACTIVE TRIAL from the GETAID).

Our study has several limitations. First, it is a retrospective observational study. Second, it is a monocentric study, and thus considers a smaller number of patients than most of the other studies available. Third, it is a tertiary center study: it could introduce biases in patient's recruitment, such as responders to IVS not referred to us or lack of follow-up for patients re-addressed to their former care center. Our study has also strengths. To our knowledge, it is one of the first available on long term-outcomes in biologic era, especially on the recurrence of ASUC. New outcomes are explored, as treatment modification. The monocentric design allows a homogeneous practice. It gives results to real-world patient populations.

CONCLUSION

Our study confirms the persistence of a poor long-term prognosis after ASUC in the biologic era with a third of patients undergoing a colectomy, mainly after recurrence of ASUC.

Treatment modification also appears as a frequent event in a patient's life after ASUC, which could be an interesting end-point both from the clinician's and the patient's perspective.

Contrary to what has been described previously in literature, responsiveness to intravenous steroids did not influence long-term prognosis in our study. The role of therapy at discharge in this finding is hard to investigate and argues in favor of a prospective randomized trial on maintenance therapy after ASUC.

REFERENCES

[1] F. C. Edwards and S. C. Truelove, “THE COURSE AND PROGNOSIS OF ULCERATIVE COLITIS,” *Gut*, vol. 4, pp. 299–315, Dec. 1963, doi: 10.1136/gut.4.4.299.

[2] M. Cesarini *et al.*, “Predicting the Individual Risk of Acute Severe Colitis at Diagnosis,” *J Crohns Colitis*, vol. 11, no. 3, pp. 335–341, Mar. 2017, doi: 10.1093/ecco-jcc/jjw159.

[3] G. G. Kaplan *et al.*, “Decreasing colectomy rates for ulcerative colitis: a population-based time trend study,” *Am J Gastroenterol*, vol. 107, no. 12, pp. 1879–1887, Dec. 2012, doi: 10.1038/ajg.2012.333.

[4] D. Turner, C. M. Walsh, A. H. Steinhart, and A. M. Griffiths, “Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression,” *Clin Gastroenterol Hepatol*, vol. 5, no. 1, pp. 103–110, Jan. 2007, doi: 10.1016/j.cgh.2006.09.033.

[5] S. Lichtiger *et al.*, “Cyclosporine in severe ulcerative colitis refractory to steroid therapy,” *N Engl J Med*, vol. 330, no. 26, pp. 1841–1845, Jun. 1994, doi: 10.1056/NEJM199406303302601.

[6] G. Järnerot *et al.*, “Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study,” *Gastroenterology*, vol. 128, no. 7, pp. 1805–1811, Jun. 2005, doi: 10.1053/j.gastro.2005.03.003.

[7] J. G. Williams *et al.*, “Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed methods, open-label, pragmatic randomised trial,” *Lancet Gastroenterol Hepatol*, vol. 1, no. 1, pp. 15–24, Sep. 2016, doi: 10.1016/S2468-1253(16)30003-6.

[8] A. Gustavsson, J. Halfvarson, A. Magnuson, H. Sandberg-Gertzén, C. Tysk, and G. Järnerot, “Long-term colectomy rate after intensive intravenous corticosteroid therapy for ulcerative colitis prior to the immunosuppressive treatment era,” *Am J Gastroenterol*, vol. 102, no. 11, pp. 2513–2519, Nov. 2007, doi: 10.1111/j.1572-0241.2007.01435.x.

[9] S. Festa *et al.*, “Long-term outcomes of acute severe ulcerative colitis in the rescue therapy era: A multicentre cohort study,” *United European Gastroenterol J*, vol. 9, no. 4, pp. 507–516, Feb. 2021, doi: 10.1177/2050640620977405.

[10] G. Le Baut *et al.*, “A Scoring System to Determine Patients’ Risk of Colectomy Within 1 Year After Hospital Admission for Acute Severe Ulcerative Colitis,” *Clin Gastroenterol Hepatol*, vol. 19, no. 8, pp. 1602-1610.e1, Aug. 2021, doi: 10.1016/j.cgh.2019.12.036.

[11] S. Jain *et al.*, “Predictors of long-term outcomes in patients with acute severe colitis: A northern Indian cohort study,” *J Gastroenterol Hepatol*, vol. 33, no. 3, pp. 615–622, Mar. 2018, doi: 10.1111/jgh.13921.

[12] H.-S. Lee *et al.*, “Short- and Long-Term Outcomes of Acute Severe Ulcerative Colitis in Korea: The 1999-2005 Cohort,” *Inflamm Bowel Dis*, vol. 21, no. 8, pp. 1825–1831, Aug. 2015, doi: 10.1097/MIB.0000000000000447.

[13] J. Allison, L. J. Herrinton, L. Liu, J. Yu, and J. Lowder, “Natural History of Severe Ulcerative Colitis in a Community-Based Health Plan,” *Clinical Gastroenterology and Hepatology*, vol. 6, no. 9, pp. 999–1003, Sep. 2008, doi: 10.1016/j.cgh.2008.05.022.

[14] L. C. Dinesen *et al.*, “The pattern and outcome of acute severe colitis,” *J Crohns Colitis*, vol. 4, no. 4, pp. 431–437, Oct. 2010, doi: 10.1016/j.crohns.2010.02.001.

[15] R. Salameh *et al.*, “Long-term outcome of patients with acute severe ulcerative colitis responding to intravenous steroids,” *Alimentary Pharmacology & Therapeutics*, vol. 51, no. 11, pp. 1096–1104, 2020, doi: 10.1111/apt.15751.

[16] N. Williet, W. J. Sandborn, and L. Peyrin-Biroulet, “Patient-reported outcomes as primary end points in clinical trials of inflammatory bowel disease,” *Clin Gastroenterol*

Hepatol, vol. 12, no. 8, pp. 1246-1256.e6, Aug. 2014, doi: 10.1016/j.cgh.2014.02.016.
[17] N. Williet *et al.*, “Patient-reported Outcomes in a French Nationwide Survey of Inflammatory Bowel Disease Patients,” *J Crohns Colitis*, vol. 11, no. 2, pp. 165–174, Feb. 2017, doi: 10.1093/ecco-jcc/jjw145.
[18] S. C. Truelove and D. P. Jewell, “Intensive intravenous regimen for severe attacks of ulcerative colitis,” *Lancet*, vol. 1, no. 7866, pp. 1067–1070, Jun. 1974, doi: 10.1016/s0140-6736(74)90552-2.
[19] S. P. Travis *et al.*, “Predicting outcome in severe ulcerative colitis,” *Gut*, vol. 38, no. 6, pp. 905–910, Jun. 1996, doi: 10.1136/gut.38.6.905.
[20] D. Bojic, Z. Radojicic, M. Nedeljkovic-Protic, M. Al-Ali, D. P. Jewell, and S. P. L. Travis, “Long-term outcome after admission for acute severe ulcerative colitis in Oxford: the 1992-1993 cohort,” *Inflamm Bowel Dis*, vol. 15, no. 6, pp. 823–828, Jun. 2009, doi: 10.1002/ibd.20843.
[21] T. Molnár, K. Farkas, T. Nyári, Z. Szepes, F. Nagy, and T. Wittmann, “Response to First Intravenous Steroid Therapy Determines the Subsequent Risk of Colectomy in Ulcerative Colitis Patients,” *Journal of Gastrointestinal and Liver Diseases*, vol. 20, no. 4, Art. no. 4, Dec. 2011.
[22] “Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity - PubMed.” https://pubmed.ncbi.nlm.nih.gov/8026269/ (accessed Mar. 19, 2022).
[23] W. Cacheux *et al.*, “Predictive factors of response to cyclosporine in steroid-refractory ulcerative colitis,” *Am J Gastroenterol*, vol. 103, no. 3, pp. 637–642, Mar. 2008, doi: 10.1111/j.1572-0241.2007.01653.x.
[24] M. Harbord *et al.*, “Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management,” *Journal of Crohn’s and Colitis*, vol. 11, no. 7, pp. 769–784, Jul. 2017, doi: 10.1093/ecco-jcc/jjx009.
[25] A. Vedamurthy *et al.*, “Long-Term Outcomes of Immunosuppression-Naïve Steroid Responders Following Hospitalization for Ulcerative Colitis,” *Dig Dis Sci*, vol. 63, no. 10, pp. 2740–2746, Oct. 2018, doi: 10.1007/s10620-018-5176-3.

FIGURES

Figure 1. Flow chart of study

Figure 2. Kaplan-Meier curves of long-term colectomy free-survival in ASUC patients who avoided colectomy at index hospitalization for responders and non-responders to IVS during study period

Figure 3. Kaplan-Meier curves of recurrence of ASUC-free survival in ASUC patients who avoided colectomy at index hospitalization for responders and non-responders to IVS during study period

Figure 4, 5, 6. Kaplan-Meier curves of treatment modification-free survival in ASUC patients who avoided colectomy at index hospitalization for responders and non-responders to IVS during study period

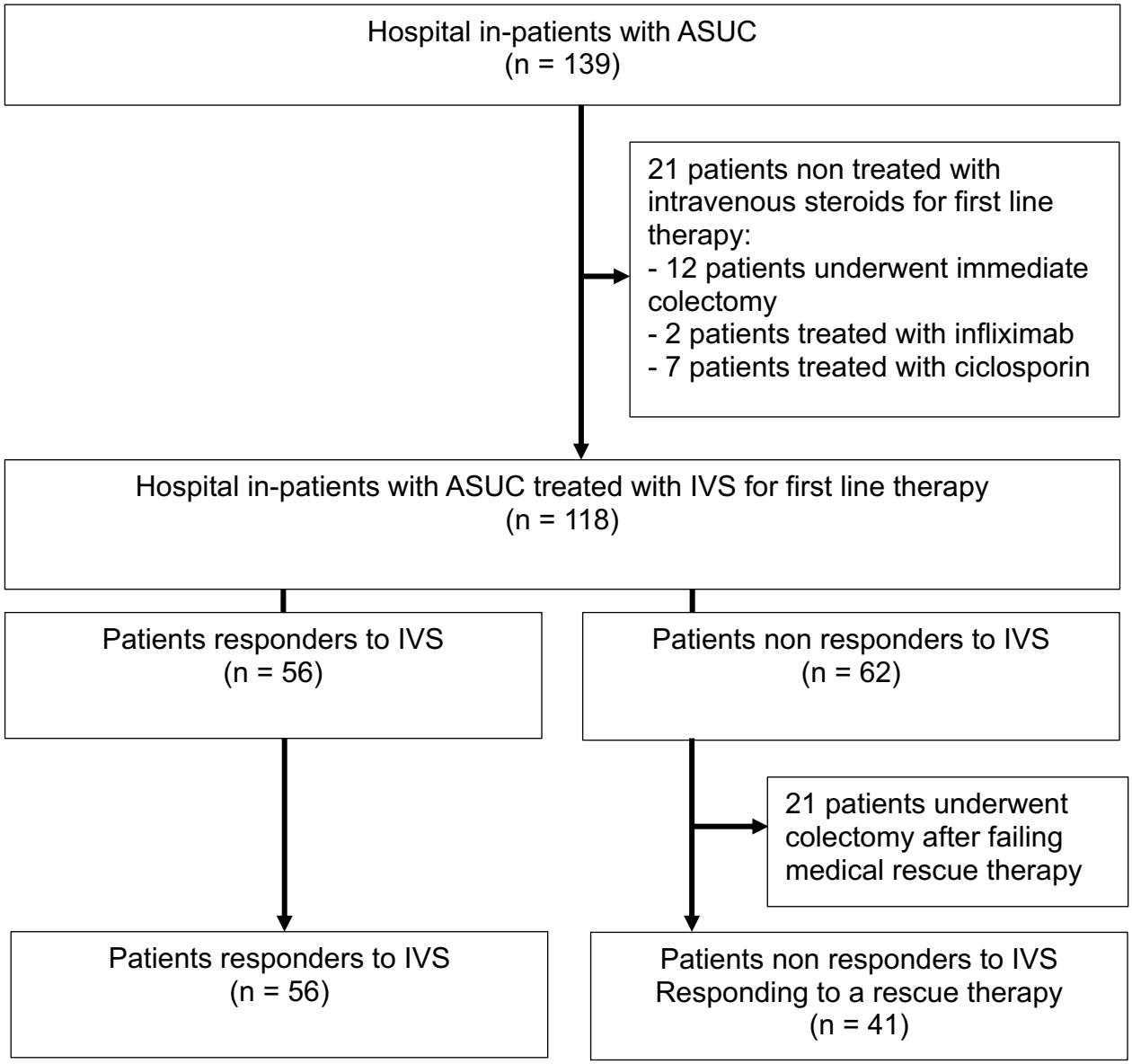

Figure 1. Flow chart of study

ASUC : acute severe ulcerative colitis; IVS: intravenous steroid.

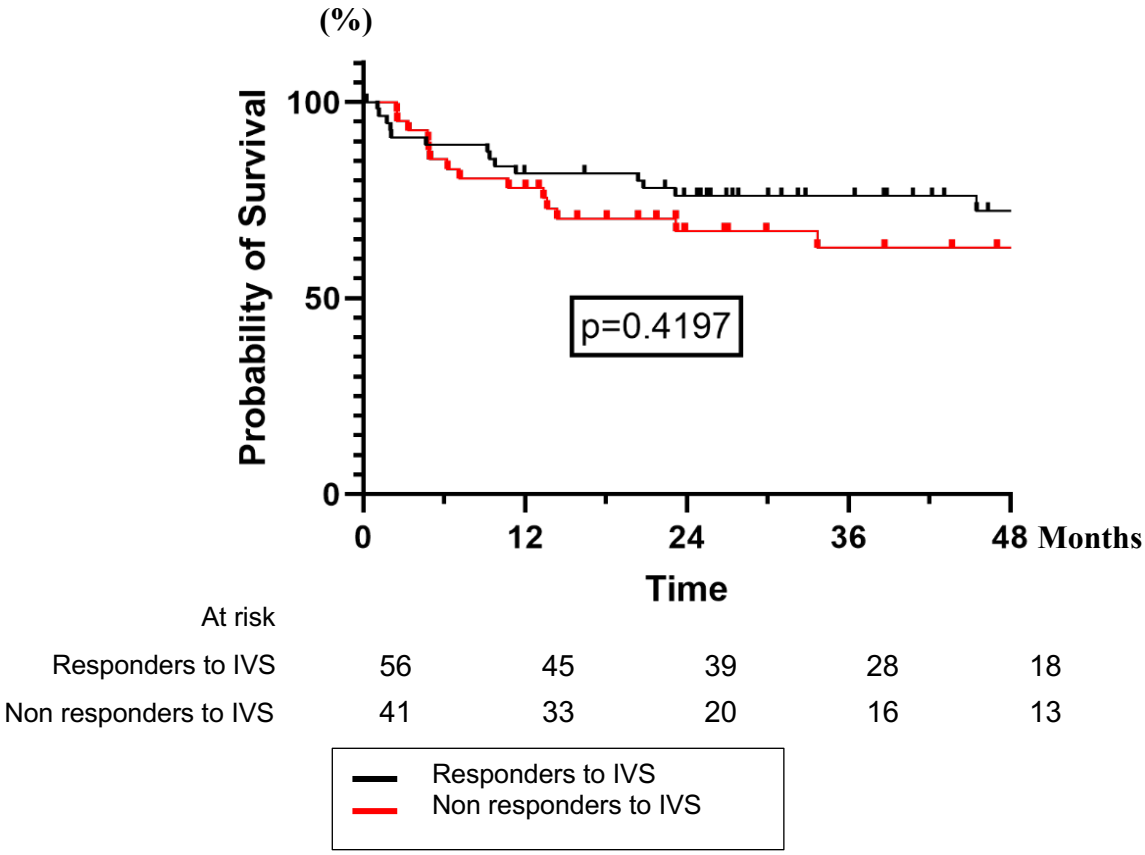

Figure 2. Kaplan-Meier curves of long-term colectomy free-survival in ASUC patients who avoided colectomy at index hospitalization for responders and non-responders to IVS during study period.

ASUC: acute severe ulcerative colitis; IVS: intravenous steroid.

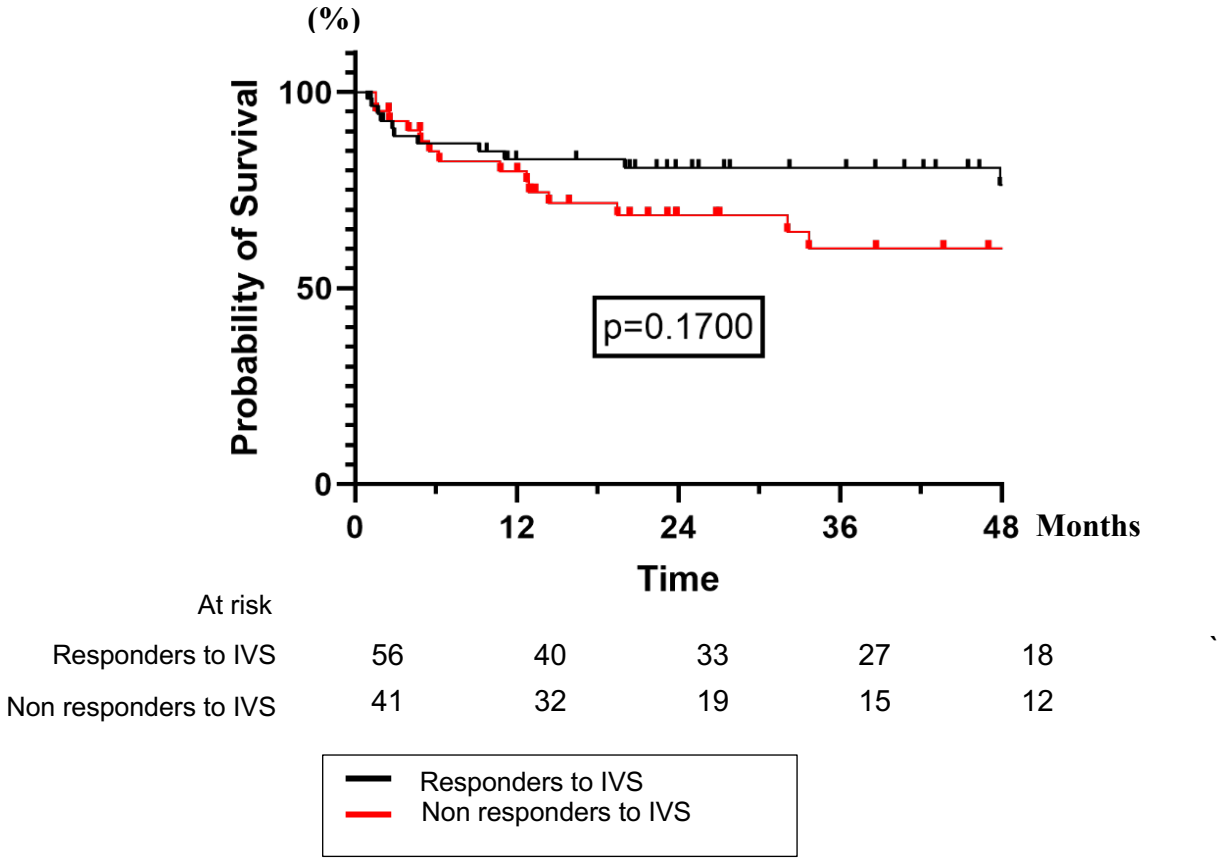

Figure 3. Kaplan-Meier curves of recurrence of ASUC-free survival in ASUC patients who avoided colectomy at index hospitalization for responders and non-responders to IVS during study period

ASUC : acute severe ulcerative colitis; IVS: intravenous steroid.

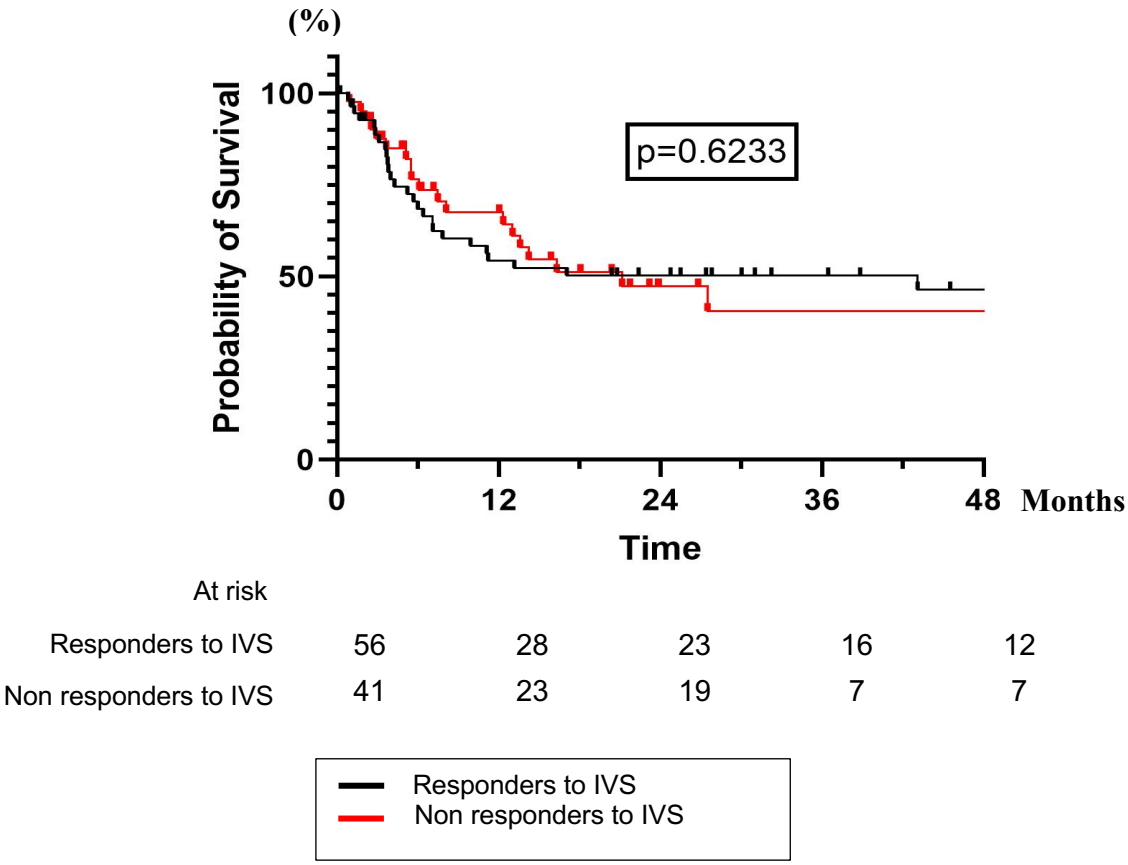

Figure 4. Kaplan-Meier curves of first treatment modification-free survival in ASUC patients who avoided colectomy at index hospitalization for responders and non-responders to IVS during study period

ASUC : acute severe ulcerative colitis; IVS: intravenous steroid.

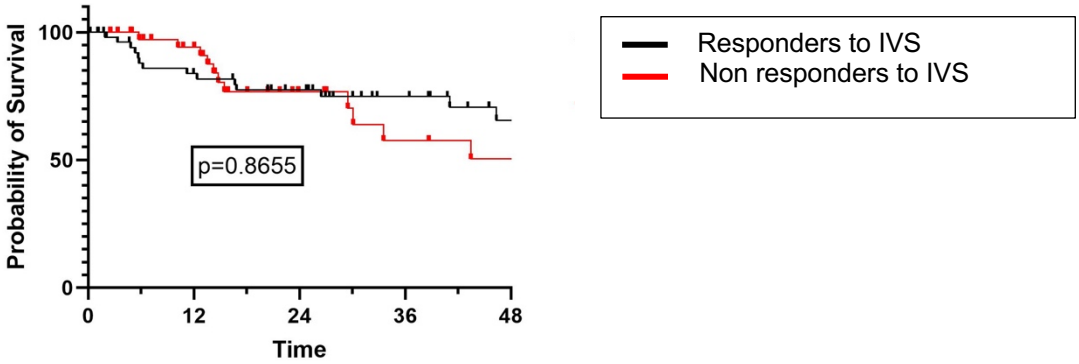

Figure 5. Kaplan-Meier curves of second treatment modification-free survival in ASUC patients who avoided colectomy at index hospitalization for responders and non-responders to IVS during study period

ASUC : acute severe ulcerative colitis; IVS: intravenous steroid.

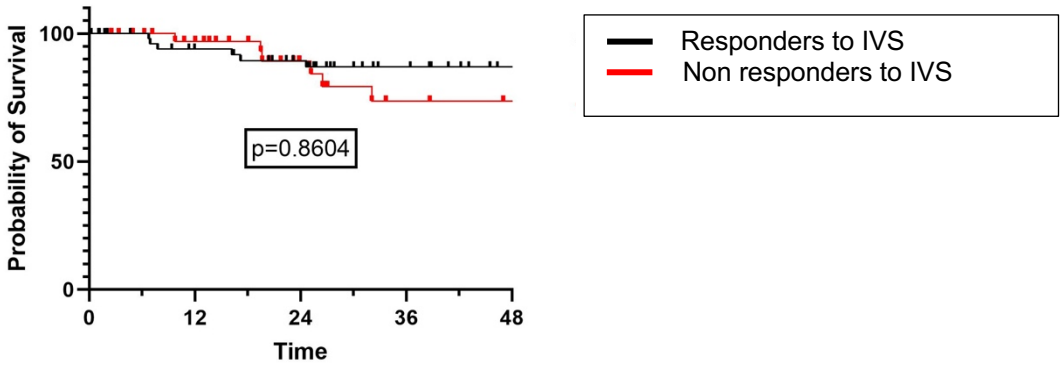

Figure 6. Kaplan-Meier curves of third treatment modification-free survival in ASUC patients who avoided colectomy at index hospitalization for responders and non-responders to IVS during study period

ASUC : acute severe ulcerative colitis; IVS: intravenous steroid.

Table 1: Characteristic at admission

	Responders to IVS (n=56)	Non responders to IVS (n=41)	p
Female gender, n (%)	26 (46%)	20(49%)	0,8397
Age at admission, y	29 (21-49)	30 (23-45)	0,9797
Disease duration at admission, months	25 (4-77)	17 (6-94)	0,7643
Extension of disease at diagnosis			
Proctitis	8 (14%)	7 (17%)	0,7076
Left sided colitis	15 (27%)	12 (29%)	0,7876
Extensive colitis	33 (59%)	22 (54%)	0,6048
Extra intestinal manifestation	8 (14%)	2 (5%)	0,1830
Active smoker, n (%)	2 (4%)	4 (10%)	0,2377
Previous appendectomy	4 (7%)	0 (0%)	0,1352
Previous therapy (past and/or current exposure)			
No treatment	7 (12%)	2 (5%)	0,2945
5-ASA only	21 (38%)	18 (44%)	0,8335
IS and/or biologic agent	28 (50%)	21 (51%)	0,999
Disease activity			
Lichtiger index	12 (10-14)	13 (11-15)	**0,0298**
Endoscopic Mayo Clinic subscore	2 (2-3)	3 (3-3)	**0,0009**
UCEIS	5 (4-6)	6 (5-6)	**0,0141**
Biologic variables			
Hemoglobin level, g/dL	11,6 (10,2-13,3)	12,3 (11,2-13,9)	0,1039
Serum Albumin, g/L	34 (27-37)	32 (27-37)	0,2794
CRP level, mg/L	39	50	0,8287
Therapy at discharge			
5-ASA only	13 (23%)	0 (0%)	**0,005**
IS only	9 (16%)	12 (29%)	0,1190
Biologic agent*			
Anti TNF therapy	20 (35%)	23 (56%)	0,0627
Vedolizumab	13 (23%)	5 (12%)	0,1957

**It includes biologic agents with or without IS*
IVS: Intravenous steroids; IS: Immunosuppressant

Table 2:
Colectomy, recurrence of ASUC and treatment modification incidences within 1 year of follow up according to responsiveness to IVS

	Responders to IVS (n=56)	Non responders to IVS (n=41)	p
Colectomy	10 (17%)	9 (21%)	0,6165
Recurrence of ASUC	9 (16%)	8 (19%)	0,7882
Treatment modification			
At least 1	20 (35%)	13 (31%)	0,8286
At least 2	7 (12%)	2 (4%)	0,1632
At least 3	3 (5%)	1 (2%)	0,6355

ASUC: Acute Severe Ulcerative Colitis; IVS: Intravenous steroids

AUTEUR : Nom : LAIB **Prénom : Mathilde**

Date de soutenance : 08/04/2022

Titre de la thèse : Pronostic à long terme après Colite Aigue Grave en centre tertiaire à l'ère des biothérapies : existe-t-il toujours une différence en fonction de la réponse initiale à la corticothérapie intraveineuse ?

Thèse - Médecine - Lille 2022

Cadre de classement : *gastro-entérologie*

DES : hépato-gastro-entérologie

Mots-clés : Colite aigue grave, pronostic, colectomie, biothérapies

Introduction : Le pronostic à long terme après colite aigue grave a été peu décrit, particulièrement à l'ère des biothérapies. Les objectifs de notre étude étaient de rapporter les résultats à long terme des patients répondant à un traitement médical pour colite aigue grave, et de rechercher une différence de pronostic en fonction de la réponse initiale à la corticothérapie intraveineuse.

Matériel et méthodes : Nous avons conduit une étude observationnelle monocentrique incluant des patients atteints d'une rectocolite hémorragique admis entre 2011 et 2019 au Centre Hospitalier de Lille pour colite aigue grave (définie par un Lichtiger supérieur ou égal à 10), traités en première ligne par corticothérapie intraveineuse, répondant à un traitement médical lors de l'hospitalisation initiale et suivis au moins 1 ans. Le critère de jugement principal était le taux de colectomie à 1 an.

Résultats : 97 patients (52% d'hommes, âge médian de 30 ans (IQR: 22-48)) ont été inclus : 56 patients ayant répondu à la corticothérapie intraveineuse initiale et 41 patients à un traitement médical de recours par infliximab ou ciclosporine après échec de la corticothérapie. Le traitement de maintenance initial était par 5-aminosalicylates chez 23 % des patients corticosensibles contre 0% des patients corticoresistants (p=0,005). La médiane de suivi était de 27,8 mois (IQR:14-57). Le taux de colectomie était de 20% à 1 an et de 30% à la fin de la période d'étude. Le taux de récidive de colite aigue grave était de 18% à 1 an et de 29% à la fin de la période d'étude. 50%, 27% et 16% des patients auront eu respectivement au moins 1, 2 et 3 modifications de leur traitement de maintenance durant la période d'étude. Aucune différence significative concernant ces résultats à long terme n'était retrouvée entre les patients ayant répondu à la corticothérapie intraveineuse initiale et ceux n'y ayant pas répondu.

Conclusion : Le pronostic à long terme des patients ayant présenté une colite aigue grave et répondant à un traitement médical reste défavorable à l'ère des biothérapies, et ne semble pas dépendre de la réponse initiale à la corticothérapie intraveineuse.

Composition du Jury :

Président : Professeur Pierre DESREUMAUX

Assesseurs : Docteur Nicolas DUVEAU,

Docteur Clémentine LAURIOT DIT PREVOST

Directeur de thèse : Docteur Maria NACHURY