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Influence of disease location on Vedolizumab effectiveness in inflammatory bowel diseases: a real-life multicenter experience

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**Influence de la localisation des maladies
inflammatoires chroniques de l'intestin sur
l'efficacité du Védolizumab :
une étude multicentrique**

THÈSE

PRÉSENTÉE POUR L'OBTENTION DU DOCTORAT EN MÉDECINE

DIPLÔME D'ÉTAT

Mademoiselle Sandie PESTOUR

[Données à caractère personnel]

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Président du jury : Monsieur le Professeur Vincent LEROY

Membres :

Monsieur le Professeur Bruno BONAZ

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Monsieur le Docteur Nicolas MATHIEU

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Résumé

Influence de la localisation des maladies inflammatoires chroniques de l'intestin sur l'efficacité du Védolizumab : une étude multicentrique

Objectif: déterminer si la localisation des maladies inflammatoires chroniques de l'intestin (MICI) est un facteur prédictif de rémission clinique sans corticoïdes (RCSCS) à 24 semaines sous Védolizumab.

Méthodes: tous les patients avec MICI modérées à sévères traités par Védolizumab sur la période 2014-2017 dans deux centres de référence (Grenoble et Lyon-Sud) ont été inclus dans une étude rétrospective. La RCSC était définie par un Index Harvey-Bradshaw (HBI) ≤ 4 (MC) ou un score Mayo Partiel (PMS) ≤ 2 sans sous-score >1 (RCH), avec arrêt des CS depuis au moins 1 mois.

Résultats: 133 Maladies de Crohn (MC) et 90 Rectocolites Hémorragiques (RCH) ont été incluses. A 24 semaines, la RCSC était obtenue chez 33.1 % (n=44/133) des patients MC et chez 33.3% (n=30/90) des patients RCH. Dans la MC, la RCSC était de 33%, 36% et 35%, respectivement pour les localisations iléales (L1), coliques (L2) et iléocoliques (L3) selon la classification de Montréal (p=0.906), sans différence entre les maladies L2 versus L1-L3 (p=0.928). Dans la RCH, la RCSC était de 37% pour les localisations distales (E1, E2) et 31% pour les pancolites (E3), (p=0.594). La RCSC à 24 semaines était obtenue chez 17% des patients MC avec localisation périnéale active versus 42% des patients MC sans localisation périnéale active (p=0.037).

Conclusion: la RCSC à 24 semaines sous Védolizumab n'apparaît pas associée à la localisation de la MICI, exceptée pour la MC périnéale active. Une étude prospective, avec caractérisation rigoureuse des localisations de la maladie est nécessaire.

Influence of disease location on Vedolizumab effectiveness in inflammatory bowel diseases: a real-life multicenter experience.

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ABSTRACT

Background - The influence of inflammatory bowel disease (IBD) location on Vedolizumab effectiveness is unclear.

Objective - Our goal was to determine if IBD location was a predictive factor of steroid-free clinical remission (SFCR) at week 24 under Vedolizumab.

Methods - We included in a retrospective multicenter study all patients with moderate to severe Crohn's disease (CD) and Ulcerative Colitis (UC) receiving Vedolizumab, in the Grenoble and Lyon-Sud University Hospitals, from 2014 to 2017. SFCR was defined by a Harvey-Bradshaw Index (HBI) ≤ 4 for CD and a Partial Mayo Score (PMS) ≤ 2 with each sub-score of 1 or less for UC, with corticosteroids withdrawn for at least 1 month. The disease location was defined according to the Montreal classification.

Results - 133 CD and 90 UC patients were included. SFCR was achieved in 33.1% (n=44/133) CD patients and 33.3% (n=30/90) UC patients at week 24. SFCR rates for CD were 33%, 36% and 35%, respectively for L1, L2, and L3 disease locations (p=0.906), with no difference when isolated colonic disease (L2) was compared to ileal disease (L1 and L3), (p=0.928). SFCR for UC rates were 37% and 31%, respectively for distal UC (E1, E2) and pancolitis (E3), (p=0.594). SFCR at week 24 was achieved in 17% of CD patients with active perineal disease versus 42% of CD patients without active perineal disease (p=0.037).

Conclusion - SFCR at week 24 under Vedolizumab was not associated with IBD location except for active perineal CD. A prospective study, with stringent assessment of disease and flare locations is required.

KEYWORDS

Crohn's Disease; Ulcerative colitis; ileal location; colonic location; extensive colitis

ABBREVIATIONS

AUROC: area under the receiver operative characteristics curve

BMI: Body Mass Index

CD: Crohn's Disease

CR: clinical remission

CRP: C Reactive Protein

CS: corticosteroids

HBI: Harvey-Bradshaw Index

IBD: Inflammatory bowel disease

MadCAM1: Mucosal Addressin Cell Adhesion Molecule 1

PMS: Partial Mayo Score

pCD: perineal Crohn Disease

NPV: negative predictive value

PPV: predictive positive value

ROC: Receiver Operative Characteristic

TNF: Tumor Necrosis Factor

UC: Ulcerative Colitis

SD: standard deviation

Se: sensitivity

Sp: specificity

VDZ: Vedolizumab

Yrs: years

INTRODUCTION

Inflammatory Bowel Diseases (IBD), Crohn's Disease (CD), and Ulcerative Colitis (UC), are characterized by a chronic and excessive inflammation located in the gastro-intestinal tract. In UC, lesions are localized exclusively in the rectum and colon whereas in CD, all parts of the digestive tract can be involved (ileocaecal location most frequently). IBD have a chronic evolution, with an alternation of remission periods and flares [1].

Owing to early life beginning, chronic evolution, and disabling digestive symptoms during flares, IBD induce a high morbidity rate leading to an impaired quality of life [2; 3]. Moreover, although the impact of IBD on global mortality is low, complications such as acute severe colitis, occlusion, perforation, infection, abscess, and malnutrition can occur and be life-threatening for the patient [4].

The IBD incidence (CD, 12.7 per 100,000 person-years / UC, 24.3 per 100,000 person-years in Europe) and prevalence (CD, 322 per 100,000 / UC, 505 per 100,000 in Europe) are increasing worldwide, resulting in a heavy social and economic burden for healthcare systems. This is due firstly to possible disease complications (hospitalization, surgery) and secondly because of the use of strong, costly, and long-term therapies [5; 6]. Therefore, the management of available therapies is a real public health issue, in particular for moderate to severe disease forms. Current therapies include corticosteroids (CS), immunosuppressant drugs (azathioprine, mercaptopurine, methotrexate), and tumor necrosis factor (TNF) antagonists (infliximab/adalimumab/golimumab/certolizumab pegol). CS are effective when used to induce remission but not as a maintenance therapy. Immunosuppressants are slow-acting drugs that are not able to induce remission. TNF antagonists can induce and maintain remission but not in the long term for most (more than 50% of secondary loss of response at 1 year) [1; 4]. Current therapies have been reported to induce several systemic and potentially disabling adverse effects. That is why there is an increasing interest for emerging drugs with more selective mechanism of action, such as anti-migration therapies.

Vedolizumab (VDZ) is a fully humanized immunoglobulin G₁ monoclonal antibody which specifically targets the $\alpha_4\beta_7$ -integrin on activated leukocytes and inhibits its ability to bind with Mucosal Addressin Cell Adhesion Molecule (MadCAM-1) localized in the digestive endothelium. By blocking $\alpha_4\beta_7$ -integrin, VDZ prevents translocation of leukocytes, especially gut-homing T lymphocytes, from the blood to inflamed intestinal tissue, and then selectively downregulates gut inflammation. Such a mechanism of action, restricted to the gastrointestinal tract, should not affect the whole systemic immune responses, allowing to reduce the risk of infection and to minimize adverse effects of systemic usual IBD immunosuppressive therapies. VDZ can induce and maintain remission both in CD and UC as demonstrated in 3 pivotal phase 3 clinical trials [7-9].

Identifying the predictive factors of therapeutic response is crucial since it allows choosing more personalized therapeutic strategies for each patient, in particular in terms of cost-effectiveness. Various factors associated with a pejorative response to VDZ in IBD patients have been identified, including smoking history, prior TNF antagonist therapy, active perineal disease for CD, elevated C-Reactive Protein (CRP) in UC, severe activity of IBD, and also trough levels of VDZ during the induction regimen [7; 8; 10-12]. Moreover, albumin serum level and body weight values have been reported to impact drug clearance [13].

In UC, extensive colitis (pancolitis) usually has a more pejorative prognosis, with a higher risk of colectomy, than distal location [14]. In CD, ileal and perineal locations are more severe than colonic locations, probably owing to the subsequent associated complications such as fistula and strictures which occur more frequently, whereas the colonic involvement exhibits a preferential association with the inflammatory phenotype of the disease [15]. Moreover, the authors of several cohort studies have also assessed colonic CD as predictor of better response to anti-TNF therapy [15-18]. The mechanisms remain unclear and a genetic influence is suspected [18; 19]. Thereby, recent evidence has suggested that CD with ileal involvement (ileal and ileocolonic) and isolated colonic CD should be considered as separate conditions [18]. Up to now, the contribution of IBD location on the response to VDZ remains unclear.

In the pivotal clinical randomized trials on VDZ in CD (GEMINI II study), there was no significant difference in term of effectiveness in isolated colonic disease compared with other disease locations [8; 18].

Nevertheless, the authors of a recent study reported that clinical response in CD was higher in isolated and moderately active ileal disease location, compared to isolated colonic and ileocolonic location. Concerning UC, higher clinical response has been observed in less extensive locations than in pan UC [20].

These poorly consistent results and the huge lack of evidence regarding the role of IBD disease location on therapeutic response to VDZ therapy justified carrying out our study.

Our goal was to determine whether a colonic location (*versus* ileal) for CD and a distal location (*versus* extensive) for UC were predictive factors of steroid-free clinical remission at 6 months, under VDZ therapy, in real world settings.

PATIENTS AND METHODS

Study population

All adult IBD patients having received a VDZ induction therapy between October 2014 and June 2017 in 2 IBD referral centers (Grenoble and Lyon-Sud University Hospital) were included. The patient's charts were retrospectively reviewed from medical records.

The Patient's demographic and clinical characteristics were collected, including age, gender, Body Mass Index (BMI), smoker status, disease duration, previous IBD related surgeries, CD disease location and behavior, and UC extent according to the Montreal classification [21]. Moreover, previous and current concomitant medications such as steroids including budesonide, immunomodulators (azathioprine, mercaptopurine, methotrexate, tacrolimus and cyclosporine), and prior exposure to anti-TNF antibodies (infliximab, adalimumab, golimumab, certolizumab) were recorded. Laboratory levels of CRP, serum albumin, and fecal calprotectin were collected.

The Harvey-Bradshaw index (HBI) for CD [22] and the partial Mayo clinic score (PMS) for UC [23] were used to assess disease activity. Active disease was defined as a HBI > 4 for CD and a PMS>1 for UC and/or concomitant CS medication. [23-27].

Clinical assessment and end points

The primary outcome measure was the percentage of patients in steroid-free clinical remission (CR) at week 24 for both CD and UC. Steroid-free CR was defined as an HBI score ≤ 4 for CD patients and a PMS ≤ 2 with each sub-score of 1 or less for UC [23-27]. CS had to be stopped at least 1 month before the evaluation to consider the CR as steroid-free. When HBI scoring was impossible (stoma, pouch), evaluation of clinical remission was performed by stoma emptying count and/or physician global assessment.

Patients having discontinued VDZ therapy whatever the reason during the 6 first months as well as patients referred to surgery and patients lost to follow up before week 24 were considered as failure to VDZ therapy and classified in the group of patients having failed to achieve steroid free clinical remission.

Disease location

The disease location was defined from recorded patient medical charts, according to the Montreal classification and was assessed by endoscopy and/or bowel imaging (MRI, CT) at diagnosis and during disease history. In CD, inflammatory lesions can be isolated to ileum (L1: ileal) or colon (L2: colonic) or both (L3: ileocolonic). In UC, inflammation can be limited to the rectum (E1: ulcerative proctitis), to a proportion of the colorectum distal to the splenic flexure (E2: Left sided UC) or extended to the proximal colon above the splenic flexure (E3: extensive UC) [28].

Active perianal CD was defined as simple or complex perianal fistula and/or ulcerations and anal stenosis. All patients underwent clinical examinations, magnetic resonance imaging (MRI) to classify the type of fistula, and also endoscopy for the evaluation of rectal inflammation. Complex fistulas were defined as high (high intersphincteric, high transsphincteric, suprasphincteric, or extrasphincteric) with either multiple external openings associated with such pain or fluctuation suggesting a perianal abscess, or with a rectovaginal fistula or anorectal stricture. The therapeutic management of perianal CD was made by the physician but fistula tracks were systematically treated by curettage, irrigation with saline, and apposition of loose seton to facilitate drainage; the seton drain was removed after VDZ induction if sepsis was not present. If there was no response, the seton was left in place [29].

Statistical analysis

All included patients were evaluated at week 24 and analyzed on an intent-to-treat basis in our study.

Categorical variables were expressed as a number (%) and compared using a Chi-square test whereas continuous variables were expressed as a mean +/- the standard deviation (SD) and compared, using Student's t tests. *P* values inferior to 0.05 were considered significant. Receiver operative characteristic (ROC) curves analyses were performed to identify the best cut-off points of clinical scores and biological parameters which could predict a steroid-free clinical remission at 6 months. When a relative risk (RR) was determined, the associated sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) were reported.

All statistical evaluations were performed with the SPSS software. All authors had access to the study data and reviewed and approved the final article.

RESULTS

Study population

Two hundred and twenty five IBD patients (133 CD, 92 UC), with moderate to severe disease, mainly refractory to anti-TNF therapy and exposed to VDZ therapy, were recorded between 2014 and 2017. Two UC patients were excluded from the study: one presenting with undetermined colitis and one with pouchitis. Ninety UC patients treated with VDZ were finally analyzed. Among those 90 UC patients, 2 patients were lost to follow up during the study period and were considered as failure to VDZ therapy.

VDZ was administered intravenously, according to the standard recommendations, and all IBD patients received an infusion of VDZ 300 mg at week 0, 2, 6 (induction regimen), and then once every 8 weeks thereafter (maintenance regimen). If there was no clinical response at week 6, patients received an additional infusion of 300 mg VDZ at week 10, and then once every 4 weeks (intensification dose) according to daily practice.

The demographic, clinical, biological, and endoscopic characteristics, as well as medication history and concomitant therapies are summarized in tables 1 and 2., The ileocolonic location (L3) was the most frequent (67%) in CD patients whereas isolated ileal location (L1) and isolated colonic location (L2) accounted for 22% and 11% of patients, respectively. Proctitis (E1), left sided colitis (E2), and extensive disease (E3) were reported in 3%, 31%, and 66% of UC patients, respectively.

The mean disease duration in CD patients was 14.2 ± 0.9 years (yrs) and in UC patients 8.7 ± 0.8 yrs. Seventy two CD patients (54%) underwent an intestinal resection. One hundred and seven CD patients (98%) and 85 UC patients (95%) had received at least one (and most several) prior lines of anti-TNF therapies. Among these, 64% of CD patients and 43% of UC patients had received at least 2 anti-TNF agents. The few IBD patients who had not received any anti-TNF agents were those for whom these were contraindicated.

At week 0, only 37 CD patients (29%) and 25 UC patients (28%) were under VDZ monotherapy whereas VDZ was given at the onset of therapy with concomitant corticosteroid therapy for most of them (74 CD (57%) and 48 UC (54%)). An immunosuppressant was associated to VDZ in 40 CD (31%) and in 28 UC (31%) patients. Finally, 20 CD (20%) and 21 UC (24%) patients received concomitant immunosuppressive therapy for more than 3 months in addition to VDZ infusion.

At baseline (week 0), the mean HBI score was 8.3 ± 0.5 points in CD patients and the mean PMS was 6.0 ± 0.2 points in UC patients.

Steroid-free clinical remission at week 24

At 6 months (week 24), steroid-free CR was achieved in 33.1 % (n=44/133) CD patients and 33.3% (n=30/90) UC patients.

VDZ was discontinued in 19 CD patients (14%) (lack of efficacy, n = 16; drug-intolerance, n = 3) who were switched to an alternative therapy, whereas 4 patients (3%) were referred to surgery before week 24. VDZ was discontinued in 5 UC patients (6%) for lack of efficacy (no case of drug-intolerance) whereas 7 patients (8%) were referred to surgery before week 24 for VDZ refractory disease. All those patients were considered as having failed to achieve steroid-free CR.

The characteristics of patients having achieved steroid-free CR at week 24 compared to those having failed are summarized in tables 3 and 4.

Relationship between disease location and steroid-free clinical remission at week 24 under VDZ therapy

Steroid-free CR assessed at week 24 under VDZ therapy was achieved in 33%, 36%, and 35% of CD patients, respectively for L1, L2, and L3 disease locations (p=0.906) (Fig.1A). Furthermore, the rate of patients in steroid-free clinical remission was quite similar when isolated colonic disease (L2) was compared to ileal disease (L1 and L3) (p=0.928) (Fig.1B).

Twenty-nine out of the 133 CD patients (22%) presented with an active perianal disease at the initiation of VDZ therapy (week 0). Most presented with a

simple or complex perianal fistulizing disease, isolated in most cases (n= 18; 67%), associated with anal stenosis (n= 4; 15%), associated with anal ulcers (n= 3; 11%), and associated with anal stenosis and ulcer (n=2; 7%). Perianal abscesses were observed in 8/27 cases (30%) before or at baseline. At week 0, 5 out of 29 patients with perianal disease (17%) were already in stoma for discharge. A significantly lower rate of patients with active perianal CD achieved steroid-free CR at week 24 when compared to CD patients who do not exhibit active perianal disease (17% versus 42%) (p= 0.037) (Fig.2B). The rate of patients under combination therapy with an immunosuppressant drug was similar in both active perianal disease and patients without active perianal disease (p= 0.528).

Steroid-free CR at week 24 was achieved in 37% of UC patients with distal locations (E1 or E2) and in 31% of those with extensive diseases (E3), p=0.594 (Fig.3).

Relationships between baseline disease clinical activity, CRP, serum albumin, and fecal calprotectin, and the occurrence of steroid-free clinical remission at week 24

The baseline mean HBI score measured at the onset of VDZ was significantly lower in CD patients having achieved steroid-free CR at week 24 (6.4 ± 0.6 points) compared to that of patients who had failed (9.4 ± 0.6 points), (p=0.005). A baseline HBI score ≥ 10 points was associated with a high risk of failure to achieve steroid-free CR assessed at week 24 (RR = 1.45, 95%CI [1.15-1.84], Se = 36%, Sp = 87%, PPV = 84%, NPV = 42%).

No significant difference was observed for serum CRP, serum albumin and fecal calprotectin levels measured at the onset of VDZ therapy in CD patients who had achieved steroid-free CR at week 24 when compared with those who had failed.

The baseline mean PMS was significantly lower in UC patients who had achieved steroid-free CR at week 24 (5.5 ± 0.3 points) compared to that of patients who had not (6.3 ± 0.2 points), (p=0.033). A PMS score ≥ 7 points was associated

with high risk of failure to achieve steroid-free CR at week 24 (RR = 1.34, 95%CI = [1.02-1.77], Se = 83%, Sp = 38%, PPV = 25%, NPV = 90%).

A significant difference in serum CRP levels at week 0 was observed in UC patients having achieved steroid-free CR at week 24 (11.2 ± 2.8 mg/l) compared with those of patients who had not (21.5 ± 3.4 mg/l). A baseline serum CRP >20 mg/l was predictive of failure to achieve steroid-free CR at week 24 (RR = 1.29, 95%CI = [0.97-1.70], Se = 81%, Sp = 37 %, PPV = 28%, NPV = 86%).

But we failed to detect any difference in baseline serum albumin and fecal calprotectin levels between patients who had achieve steroid-free CR at week 24 under VDZ compared with those who had not.

Figures 4 and 5 are the ROC curves illustrating the respective performances of the clinical disease activity scores (HBI for CD patients and PMS for UC patients) and the baseline serum CRP level in UC patients to predict steroid-free CR at week 24 under VDZ therapy (AUROC= 0.68, 0.64 and 0.64, respectively).

Relationships between disease clinical activity, CRP, serum albumin, and fecal calprotectin measured at week 14 after VDZ initiation and the occurrence of steroid-free clinical remission at week 24

A significantly lower HBI score was recorded at week 14 in CD patients having achieved steroid-free CR at week 24 (1.9 ± 0.3 points) compared to those who had failed (7.6 ± 0.6 points), ($p < 0.001$). As illustrated in Figure 6.A, the optimal threshold for HBI score allowing to identify accurately remitted patients from non-remitted patients assessed at week 24, was 4 points, with RR=2.82, 95%CI [1.91-4.17], Se=73%, Sp=88%, PPV=90%, NPV=68% (AUROC=0.88). Indeed, 88% of patients with an HBI score ≤ 4 points at week 14 had reached steroid-free CR at week 24 compared to 11% with an HBI score > 4 points ($p < 0.001$).

The CRP level was significantly lower in CD patients having achieved steroid-free CR at week 24 compared with those who had not (7.9 ± 1.7 mg/l vs 15.1 ± 2.2 mg/l), ($p < 0.001$). Figure 6.B is the ROC curve illustrating the

performance of CRP level at week 14 to predict steroid-free CR at week 24 in CD (AUROC=0.65).

A significantly lower PMS (1.9 ± 0.3 points) at week 14 was found in UC patients having achieved steroid-free CR at week 24 compared with those who had failed (4.5 ± 0.3 points), ($p < 0.001$). As illustrated in Figure 7, a threshold at 2 points for PMS calculated at week 14 allowed prediction of steroid-free CR at week 24 with RR= 2.83, 95%CI [1.73-4.64], Se=80%, Sp=85%, PPV=92%, NPV=67% (AUROC= 0.85).

The levels of serum CRP, serum albumin, and fecal calprotectin measured at week 14 were quite similar in both groups of UC patients who achieved or not steroid-free CR at week 24.

Relationship between prior and concomitant therapies in addition to VDZ and the occurrence of steroid-free clinical remission at week 24

An immunosuppressant was associated to VDZ therapy in 13/44 CD patients (29%) having achieved steroid-free clinical remission at 6 months and in 27/89 patients (33%) who had not ($p=0.697$).

There was no statistical difference in the rate of UC patients under combotherapy (VDZ and concomitant immunosuppressants) having achieved steroid-free CR at week 24 and those who had not: 8/29 (28%) and 20/61 (34%), respectively ($p=0.55$).

Only 25% of patients having achieved steroid-free CR at week 24 were under steroids at week 0 compared to 49% in non-remitted patients ($p=0.005$).

We further address the potential impact of the previous number of lines of anti-TNF on the probability to reach steroid free clinical remission: there was no difference in steroid-free CR at week 24 in patients who had received 0 or 1 anti-TNF compared to patients who had received 2 or more anti-TNF drug before VDZ, and this was the case for CD patients ($p = 0.273$) as for UC patients ($p = 0.253$).

Relationship between disease duration and the occurrence of steroid-free clinical remission at week 24 under VDZ therapy

CD duration at onset of VDZ therapy was around 14.7 ± 1.8 yrs in patients having achieved steroid-free CR at week 24 and 13.7 ± 1.1 yrs in patients who had not ($p=0.605$). The disease duration was also similar in both UC groups, respectively: 9.4 ± 1.3 yrs and 8.6 ± 1.0 yrs ($p=0.77$). In addition, the rate of steroid-free CR at week 24 was similar in patients with early CD or UC (diagnosis < 2 years) and in patients with longer disease duration ($p = 0.591$ in CD; $p=0.227$ in UC)).

DISCUSSION

This retrospective study performed in a real life setting, highlights several key clinical observations on VDZ therapy in moderate to severe IBD patients, refractory to anti-TNF for the vast majority. The primary endpoint was steroid-free CR assessed 6 months after VDZ onset, which represents the ultimate clinical goal in IBD outcome [24]. We investigated the influence of various clinical and laboratory parameters measured at baseline and at the end of the induction regimen (week 14) on the occurrence of steroid-free CR at week 24. The effectiveness of VDZ therapy to induce steroid-free CR at 6 months in our study was similar in CD (33.1 %) and in UC patients (33.3%). Our findings correlate to those of pivotal studies. Indeed, in the GEMINI clinical trials, respectively 31% of CD patients and 45.2% of UC patients achieved steroid-free CR at 1 year [7; 8]. The data obtained in the whole prospective and retrospective “real-world” studies conducted later was consistent with GEMINI results since the steroid-free CR rates under VDZ maintenance regimen ranged from 27 to 34% in CD and around 41% in UC at 1 year [10; 30].

Based on these results and on the data of clinical response at weeks 6 (31.4% for CD and 47.1 for UC patients) in the GEMINI trials, it was initially considered that the benefits of VDZ were more marked in UC patients than in CD patients [7; 8; 11; 31]. It was suggested that the transmural inflammatory lesions and systemic inflammatory burden in CD could limit the efficacy of VDZ therapy [11; 31; 32].

We failed to detect any difference in the rate of steroid-free CR for CD and UC patients. Several hypotheses may be raised: firstly, our very selected and complex IBD cohort was characterized by a long disease duration (mean 14.2 ± 0.9 yrs) for CD and 8.7 ± 0.8 yrs for UC) and several previous therapeutic lines, especially anti-TNF antagonists (at least 2 prior anti-TNF agents in most CD and UC patients) that could reflect long-lasting and refractory diseases unlikely to be easily controlled by medical therapy. Moreover, the baseline high clinical score as well as a high inflammatory burden highlighted by elevated serum CRP were

associated with high risk of therapeutic failure under VDZ maintenance therapy in UC patients.

In the literature, steroid-free CR rates at week 14 were reported to be similar in CD and UC patients: from 18.8 to 31% in CD patients, and 19.1 to 36% in UC patients [11; 33-36]. The remission rates improve progressively between 3 months and 1 year since an incremental benefit with ongoing VDZ therapy has been suggested [10].

Steroid-free CR at 6 months had never been evaluated for UC patients and only one study is available for CD patients: the US Victory Consortium study [10] whose authors reported steroid-free CR rates of 18% at 6 months and 34% at 1 year, indicating cumulative remission rates during a continuous treatment with VDZ between 6 and 12 years. In this study, the median time to achieve remission ranged around 25 weeks. Therefore, a minimum of 6 months of treatment should be achieved before evaluating clinical remission and guiding the decision to optimize VDZ in case of insufficient efficacy.

The CD location (L1, L2 or L3), did not influence steroid-free CR at 6 months. In addition, no difference was observed when isolated colonic disease was compared to ileal location (isolated or associated with colonic location). On the other hand, no influence of UC location (distal versus extensive) was highlighted. Such insignificant results could be explained by the lack of statistical power since only 14/133 patients (11%) presented with an isolated colonic CD, and since distal disease accounted for only 1/3 of the UC population (31/90 patients). Moreover, our study had limitations, especially because of its retrospective design. Furthermore, it could be supposed that the primary endpoint and/or the timing of disease outcome were not the most appropriate to assess the impact of disease location on VDZ effectiveness. Finally, the characteristics of IBD patients may explain this absence of difference between locations: the frequent clinical and endoscopic severity for UC patients, even for distal locations, the frequent aggressive behavior of the disease (stricturing and/or fistulizing in 71% of CD patients), and the frequent gut anatomy modifications due to multiple IBD surgeries (more than 80% of the CD patients had a past history of surgery). It is assumed that CD location is closely correlated with the course of the disease and age at onset [15; 18]. That is why the association observed between colonic CD

and response to induction of anti-TNF therapies could result more from the global disease characteristics than from the exclusive contribution of the disease location.

Even if a role of the $\alpha_4\beta_7$ -integrins has been established, the precise mechanisms controlling homing of T effector and T regulator lymphocytes to the inflamed gut in CD and UC remain unclear from a pathophysiologic point of view. As suggested by a study on in vitro and in vivo models, T effector lymphocyte homing mechanisms, in particular involvement of $\alpha_4\beta_1$ -integrins, were reported distinct between ileal and colonic inflamed intestinal mucosa [37]. However, more studies are required to understand these potential consequences on VDZ efficacy. On the other hand, an influence of gut microbiome on the response to VDZ has been recently suggested in CD and UC patients. Indeed, associations between taxonomic composition and function at baseline and clinical remission at week 14 were identified [38].

Nevertheless, even if luminal CD location did not seem to have an impact on the clinical remission rate, active pCD appeared to be correlated with treatment failure. It was a fistulizing disease in 67% of the cases, isolated or associated with stenosis or ulcers. About half of the pCD patients had undergone surgery at week 0 or before. Our study confirms the role of active perineal disease as a baseline predictor of failure to achieve clinical remission [10].

According to our results, an active pCD associated with clinical severity according to the HBI score at week 0 in CD patients and clinical severity according to the partial Mayo score with a high systemic inflammatory burden at week 0 in UC patients seemed to be associated with less chance to achieve clinical remission at 6 months. Indeed, an HBI threshold of 10 and more and a partial clinical Mayo score of 7 and more seemed predictive of treatment failure, but with weak performances. Evidence has identified an HBI ≥ 10 and a global Mayo score ≥ 9 as factors associated with a pejorative response [11]. It must be noted that clinical scores and CRP levels at week 0 in our study should be interpreted with caution because of the frequent concomitant use of corticosteroids which can alter

these parameters. A higher rate of patients receiving CS at week 0 was observed in the non remission group, reflecting the initial clinical severity in this group.

The HBI score and partial clinical Mayo score were predictive factors for steroid-free clinical remission, among clinical and biological parameters at the end of the induction period. An HBI score > 4 for CD patients and a partial Mayo clinic score > 2 (absence of clinical remission) at week 14 predicted the absence of steroid-free CR at week 24, with relevant performances (Fig. 6 and 7). CRP also appeared as a potential predictive factor in CD patients, but to a lesser extent since the analysis of performances was less convincing (Fig.6B). These results are consistent with previous results showing that the absence of clinical remission at week 14 in CD patients and the absence of clinical response in UC patients indicated a low likelihood of clinical remission at 1 year, and that lower CRP levels at week 14 was a predictor of clinical remission at 1 year in CD and UC patients [39]. In another study, an early clinical response (week 6) was also found to be a predictor of steroid-free clinical remission [30].

No benefit of combination therapy with a concomitant immunosuppressive drug for steroid-free clinical remission was observed. This correlates with data of clinical trials and real world cohorts [7-11; 34; 39]. In contrast, the benefit of concomitant immunosuppressive therapy was reported for anti-TNF antagonists in several trials [11; 40-42] and was secondary to a decrease of immunogenic mechanisms. The low rate of antibody formation with VDZ (3.7-4.1% of patients in the GEMINI studies) could explain this absence of benefit [7-9; 12]. Nevertheless, contradictory results have been reported in a retrospective study with a seeming predictive character of combination therapy for clinical response or remission at 1 year. However, these results were obtained in a selected population of patients who demonstrated an initial response to VDZ induction and should be confirmed by prospective studies [43].

The main limitation of our study was the retrospective data collection from 2 different centers, with missing or imprecise data for some parameters. Moreover, even if patient populations were supposed to be similar in terms of demographic characteristics and disease severity, some differences in clinical practice between

the 2 medical centers remained (evaluation of clinical and endoscopic remission, optimization during and after induction period). Although we tried to overcome these limitations by using objective parameters for outcomes measurements, the bias related to our study design may have influenced the results.

However, in spite of its limitations, a “real-life” assessment of effectiveness, safety, and predictors of remission seemed very important since it had previously been established that many IBD patients were not eligible for clinical trials assessing biological therapies (such as patients with an ostomy or an ileo-anal pouch for instance). Thus, because of the stringent selection criteria, patients enrolled in clinical trials are not entirely representative of those managed in routine clinical practice settings and generalization of the trial results to the whole IBD community could be discussed [34; 44].

In conclusion, in our study, the disease location did not appear to influence the VDZ effectiveness, except from active pCD which was associated with a lower remission rate at 6 months. A prospective study, based on the rigorous assessment of disease and flare locations thanks to endoscopic and radiologic evaluations should be made.

At week 14, clinical and biological predictors of steroid-free clinical remission at 6 months were identified.

Finally, an earlier initiation of VDZ for some patients (short disease duration, no more than 1 anti-TNF antagonist) could be appropriate: however, the strategies to appropriately select these patients need to be clarified.

FIGURES

	Crohn's Disease	Ulcerative colitis
Mean age, yrs (SD)	38.3 (1.1)	43.4 (1.8)
Male gender, n (%)	58 (44)	43 (48)
Body Mass Index, kg/m² (SD)	22.4 (0.5)	23.8 (0.7)
Active smoking status, n (%)	51 (40)	4 (5)
Mean disease duration, yrs (SD)	14.2 (0.9)	8.7 (0.8)
Crohn's disease:		
Disease location, n (%)		
Ileal (L1)	29 (22)	.
Colonic (L2)	14 (11)	.
Ileocolonic (L3)	89 (67)	.
Upper gastrointestinal tract (L4)	11 (8)	.
Perineal disease (p)	63 (47)	.
Associated with L1/L2/L3/L4	62 (98)	.
Isolated	1 (2)	.
Disease phenotype, n (%)		
B1	37 (28)	.
B2	46 (35)	.
B3	49 (37)	.
Harvey-Bradshaw Index, mean score (SD)	8.3 (0.5)	.
Ulcerative Colitis		
Location, n (%)		
Proctitis (E1)	.	3 (3)
Left sided colitis (E2)	.	28 (31)
Extensive colitis (E3)	.	59 (66)
Mayo score, mean score (SD)		
Partial Mayo clinic score (/9)	.	6.0 (0.2)
Partial Mayo endoscopic score (3/)	.	2.6 (0.1)
Global Mayo score (/12)	.	8.7 (0.3)
UCEIS, mean score (SD)	.	4.9 (0.2)

Prior antiTNF therapy, n (%)	127 (98)	85 (95)
One anti-TNF agent	22 (17)	32 (36)
2 anti-TNF agents	83 (64)	39 (43)
3 anti-TNF agents	21 (16)	14 (16)
4 anti-TNF agents	1 (0,8)	0 (0)
Concomitant medications, n (%)		
Corticosteroids	74 (57)	48 (54)
only	52 (72)	36 (75)
with immunosuppressant	20 (28)	12 (25)
Immunosuppressant	40 (31)	28 (31)
only	20(50)	16 (57)
with corticosteroids	20 (50)	12 (43)
Immunosuppressant > 3mois	26 (20)	21 (24)
No corticosteroids or immunosuppressant	37 (29)	25 (28)
Prior Crohn's disease surgery, n (%)	88 (66)	.
Only luminal surgery,	46 (52)	.
Only perineal surgery,	16 (18)	.
Luminal and perineal surgery,	26 (30)	.

Table 1 -

Demographic and disease characteristics, previous and concomitant medication of the 223 IBD patients at baseline (week 0).

Continuous variables are presented as mean +/- standard deviation (SD) and categorical variables are presented as raw number (n) and percentage (%).

	Crohn's Disease	Ulcerative colitis
CRP (mg/l)	12.4 (1.3)	18.0 (2.5)
Serum albumin level (g/l)	35.2 (0.6)	36.5 (0.7)
Fecal Calprotectin (µg/g)	1149 (173)	3180 (322)

Table 2 -
Biological characteristics of the 223 IBD patients at baseline (week 0).
Variables are presented as mean +/- standard derivation (SD).

	Steroid-free clinical remission	No steroid-free clinical remission	
	<i>n</i> = 44	<i>n</i> = 89	<i>p</i> value
Mean age, yrs (SD)	39 (2.0)	38 (1.4)	0.576
Male gender, n (%)	19 (43%)	39 (46%)	0.726
Body Mass Index, kg/m² (SD)	22.9 (0.6)	22.2 (0.6)	0.466
Active smoking status, n (%)	14 (32%)	34 (41%)	0.312
Disease duration, yrs (SD)	14.7 (1.8)	13.7 (1.1)	0.605
Prior TNF antagonist therapy, n (%)			0.273
0 or 1 anti-TNF agent	11 (25%)	14 (17%)	
≥ 2 anti-TNF agents	33 (75%)	69 (83%)	
Concomitant medications at W0, n (%)			p=0.005*
Only VDZ	20 (46%)	15 (18%)	
VDZ + CS	11 (25%)	40 (49%)	
VDZ + immunosuppressant	8 (18%)	12 (15%)	
VDZ + CS+ immunosuppressant	5 (11%)	15 (18%)	
Disease location, n (%)			0.906
Ileal (L1)	9 (21%)	18 (21%)	
Colonic (L2)	5 (11%)	9 (11%)	
Ileocolonic (L3)	30 (68%)	56 (67%)	
Isolated p location	0	1 (1.0%)	
Perineal disease, n (%)			
Global (active or inactive at week 0)	18 (41%)	42 (50%)	0.328
Active at week 0	5 (28%)	24 (57%)	0.037*
Disease phenotype, n (%)			0.236
B1	16 (36%)	20 (24%)	
B2	11 (25%)	34 (41%)	
B3	17 (39%)	29 (35%)	
Prior Crohn's disease surgery, n (%)			0.860
Only luminal surgery	14 (32)	32 (36)	
Only perineal surgery	5 (11)	11 (12)	
Luminal and perineal surgery	6 (14)	20 (22)	

Harvey-Bradshaw Index, mean score(SD)			
at week 0	6.4 (0.8)	9.4 (0.6)	0.005*
at week 14	1.9 (0.3)	7.6 (0.6)	<0.001*
CRP (mg/l)			
at week 0	12.4 (1.9)	12.7 (1.8)	0.912
at week 14	7.9 (1.7)	15.1 (2.2)	0.022*
Serum albumin level at week 0 (g/l)	36.8 (5.1)	34.5 (5.8)	0.07
Fecal Calprotectin (µg/g)			
at week 0	1401 (487)	1080 (166)	0.425
at week 14	959 (232)	1789 (507)	0.244

Table 3 -

Baseline characteristics of CD patients demonstrating steroid-free clinical remission under VDZ at week 24 compared to those with no steroid-free clinical remission.

Continuous variables are presented as mean +/- standard deviation (SD) and categorical variables are presented as raw number and percentage (%).

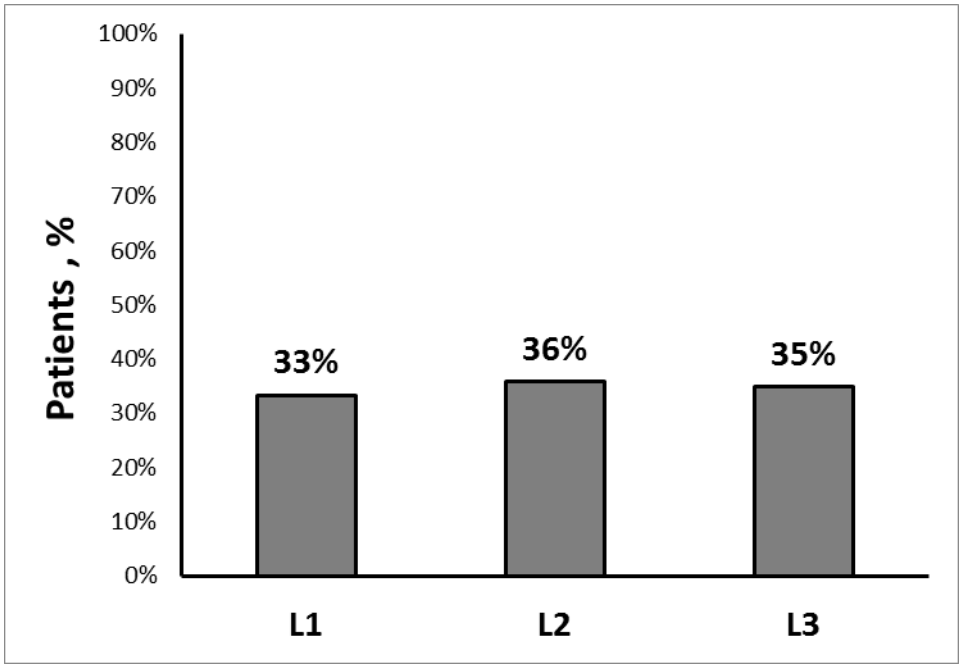
	Steroid-free clinical remission	No steroid-free clinical remission	
	<i>n</i> = 29	<i>n</i> = 61	<i>p</i> value
Mean age, yrs (SD)	44 (3.0)	43 (2.2)	0.704
Male gender, n (%)	14 (48%)	28 (48%)	0.942
Body Mass Index, kg/m² (SD)	24.7 (1.3)	23.4 (0.8)	0.160
Active smoking status, n (%)	0 (0%)	4 (7%)	0.151
Disease duration, yrs	9.1 (1.3)	8.6 (1.0)	0.77
Prior TNF antagonist therapy, n (%)			
0 or 1 anti-TNF agent	14 (48%)	21 (36%)	0.253
≥ 2 anti-TNF agents	15 (52%)	38 (64%)	
Concomitant medications at W0, n (%)			
Only VDZ	10 (35%)	14 (24%)	0.733
VDZ + CS	11 (38%)	25 (42%)	
VDZ + immunosuppressant	5 (17%)	11 (19%)	
VDZ + CS + immunosuppressant	3 (10%)	9 (15%)	
Disease Location, n (%)			0.594
Proctitis (E1) or Left sided colitis (E2)	11 (38%)	19 (32%)	
Extensive colitis (E3)	18 (62%)	40 (68%)	
Mayo score at week 0, n (%)			
Partial Mayo clinic score (/9)	5.5 (0.3)	6.3 (0.2)	0.033*
Partial Mayo endoscopic score (3/)	2.5 (0.2)	2.6 (0.1)	0.558
Global Mayo score (/12)	8.1 (0.5)	9.0 (0.3)	0.079
Mayo score at week 14, mean score (SD)			
Partial Mayo clinic score (/9)	1.9 (0.3)	4.5 (0.3)	<0.001*
UCEIS score, mean score (SD)	4.7 (0.3)	5.0 (0.2)	0.557
CRP (mg/l)			
at week 0	11.2 (2.8)	21.5 (3.4)	0.021*
at week 14	8.2 (2.2)	11.8 (1.8)	0.252
Serum albumin level at week 0 (g/l)	37.6 (0.9)	36.0 (1.0)	0.339

Fecal Calprotectin ($\mu\text{g/g}$)			
at week 0	2626 (428)	3511 (434)	0.201
at week 14	1586 (857)	3169 (812)	0.258

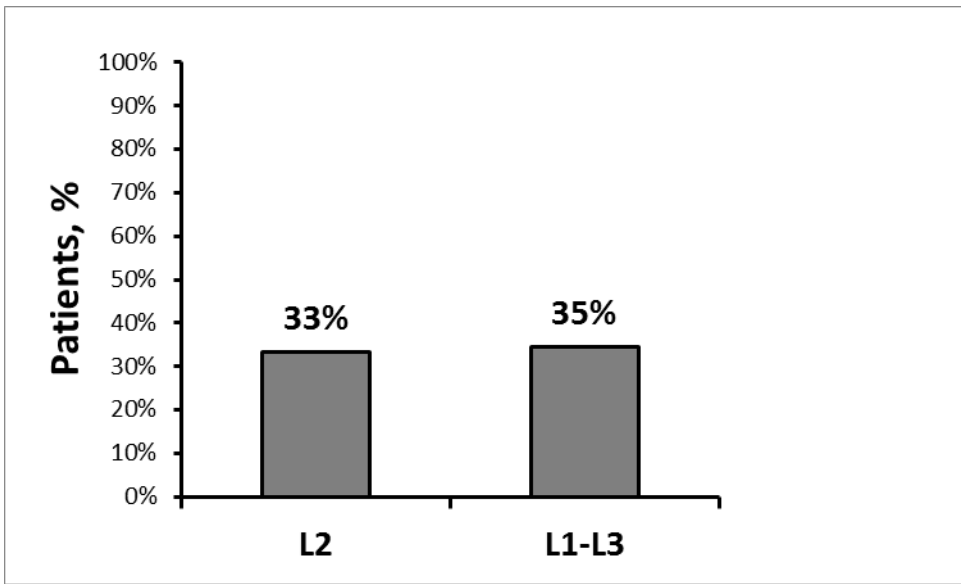
Table 4 -

Baseline characteristics of UC patients demonstrating steroid-free clinical remission under VDZ at week 24 compared to those with no steroid-free remission.

Continuous variables are presented as mean +/- standard deviation (SD) and categorical variables are presented as raw number and percentage (%).



A.



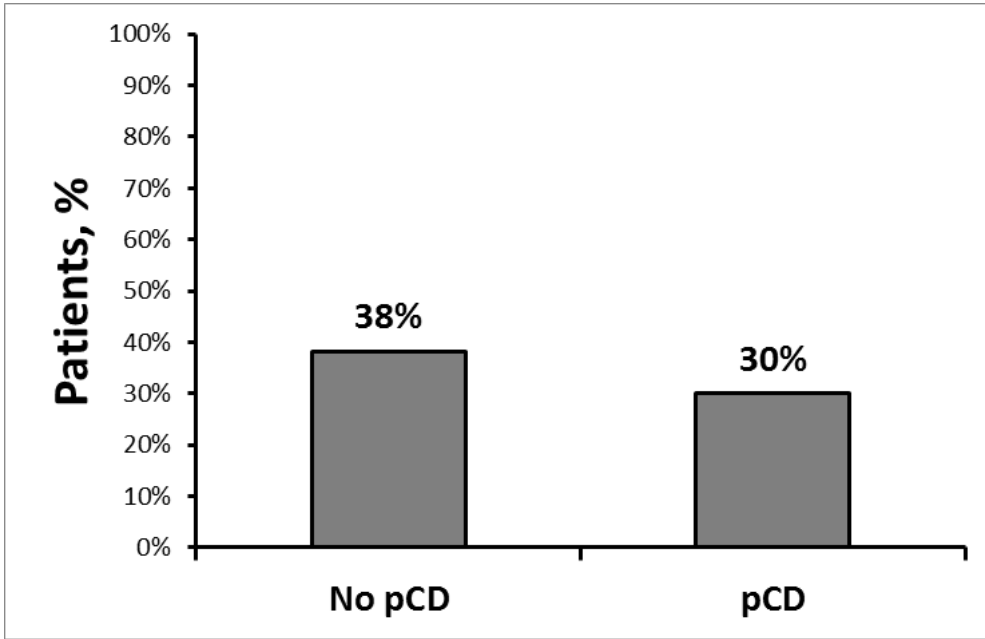
B.

Figure 1

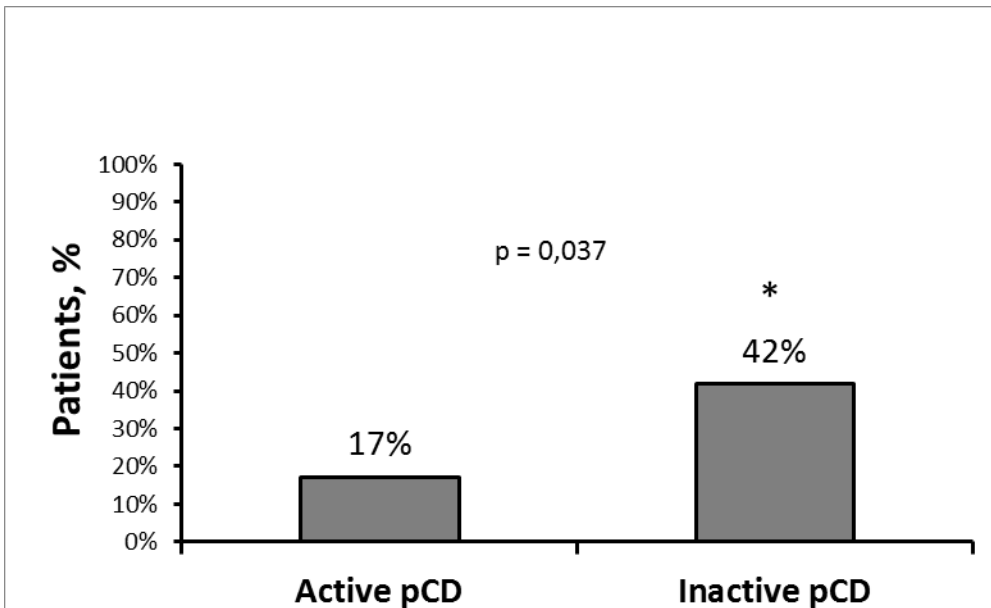
Steroid-free clinical remission at week 24 in CD patients according to luminal disease location.

A. Comparison between L1 (ileal), L2 (colonic) or L3 (ileocolonic) location.

B. Comparison between L2 (isolated colonic) versus L1 (isolated ileal) and L3 (ileocolonic) location.



A.



B.

Figure 2 -

Steroid-free clinical remission at week 24 in patients with perineal CD (pCD):

A. History versus no history of pCD.

B. Active versus inactive perineal CD (pCD) at week 0.

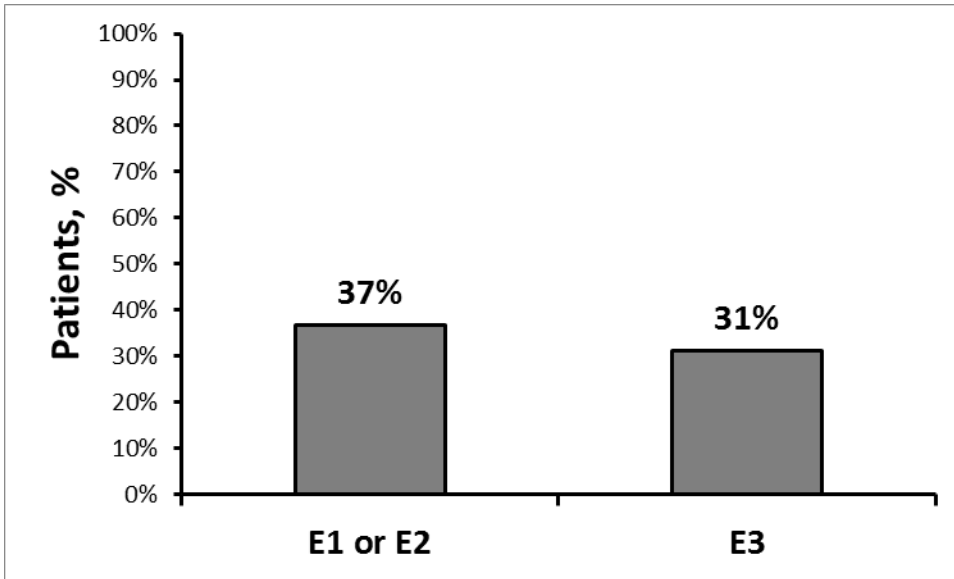


Figure 3 - Steroid-free clinical remission at week 24 in UC patients according to disease location.
Comparison between distal (E1, E2) and extensive (E3) UC.

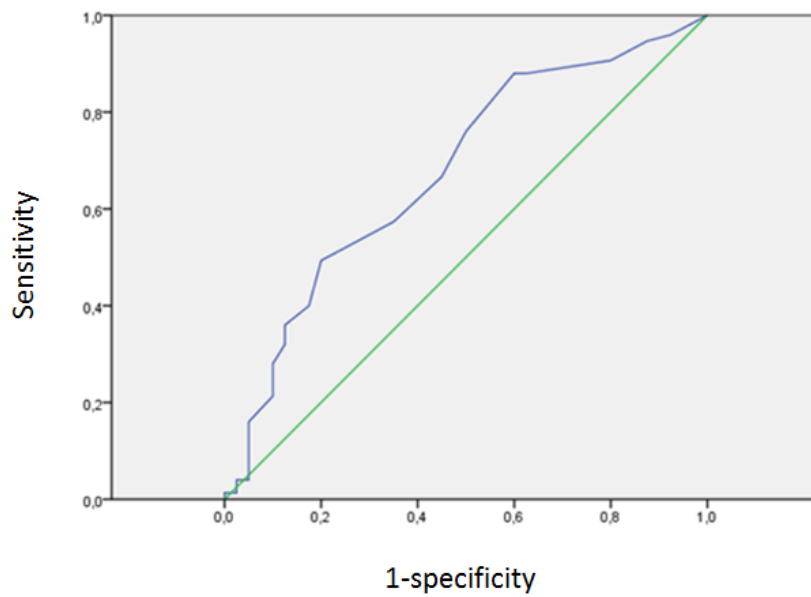
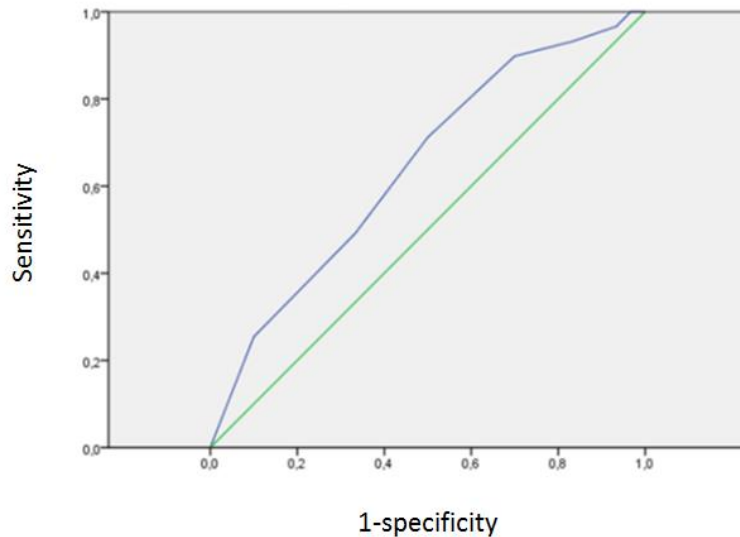
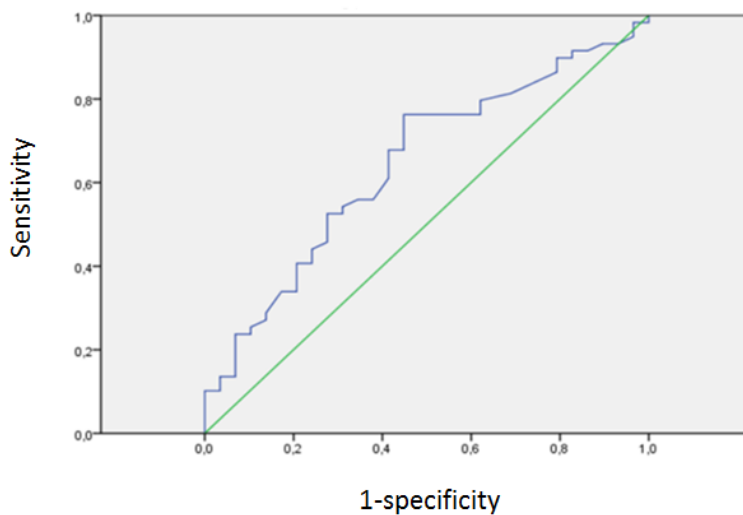


Figure 4 -
Performances of the HBI score at week 0 in CD patients for the prediction of steroid-free clinical remission at week 24. AUC = 0.68.
A score ≥ 10 was associated with failure to achieve steroid-free clinical remission at week 24 with RR = 1.45, 95%CI = [1.15-1.84], Se = 36%, Sp = 87%, PPV = 84%, NPV = 42%.



A.



B.

Figure 5 -

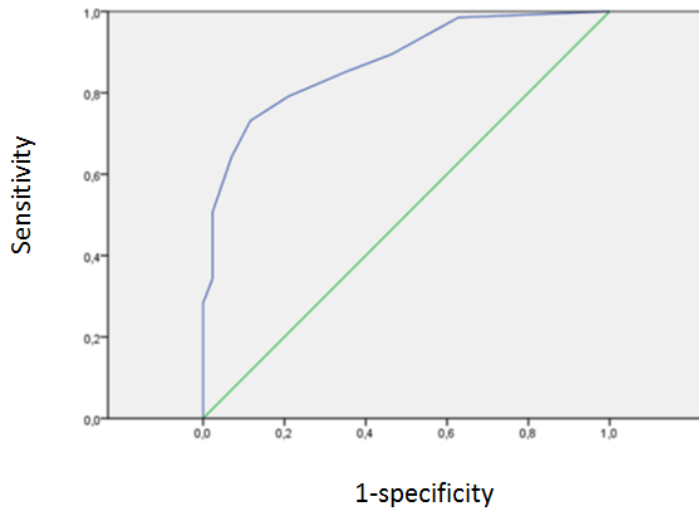
Performances of Partial Mayo clinic score and CRP level (mg/l) at week 0 in UC patients for the prediction of steroid-free clinical remission at week 24.

A. Partial Mayo Clinic score at week 0 in UC patients: AUC = 0.64

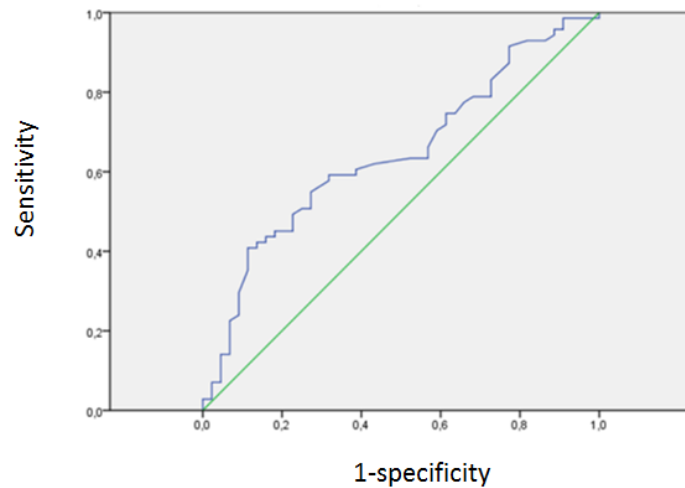
A score ≥ 7 was associated with failure to achieve steroid-free clinical remission at week 24 with RR = 1.34, 95%CI = [1.02-1.77], Se = 83%, Sp = 38%, PPV = 25%, NPV = 90%

B. CRP level (mg/l) at week 0 in UC patients: AUC = 0.64

CRP > 20 mg/l was associated with failure to achieve steroid-free clinical remission at week 24 with RR = 1.29, 95%CI = [0.97-1.70], Se = 81%, Sp = 37%, PPV = 28%, NPV = 86%.



A.



B.

Figure 6 -

Performances of HBI score and CRP level (mg/l) at week 14 in CD patients for the prediction of steroid-free clinical remission at week 24.

A. HBI score at week 14 in CD patients: AUC 0.88

A score > 4 was associated with failure to achieve steroid-free clinical remission at week 24 with RR = 2.82, 95%CI = [1.91-4.17], Se = 73%, Sp = 88%, PPV = 90%, NPV = 68%.

B. CRP level (mg/l) in CD patients at week 14: AUC = 0.65

CRP > 5 mg/l was associated with failure to achieve steroid-free clinical remission at week 24 with RR = 1.4, 95%CI = [1.03-1.90], Se = 60%, Sp = 61%, PPV = 72%, NPV = 49%.

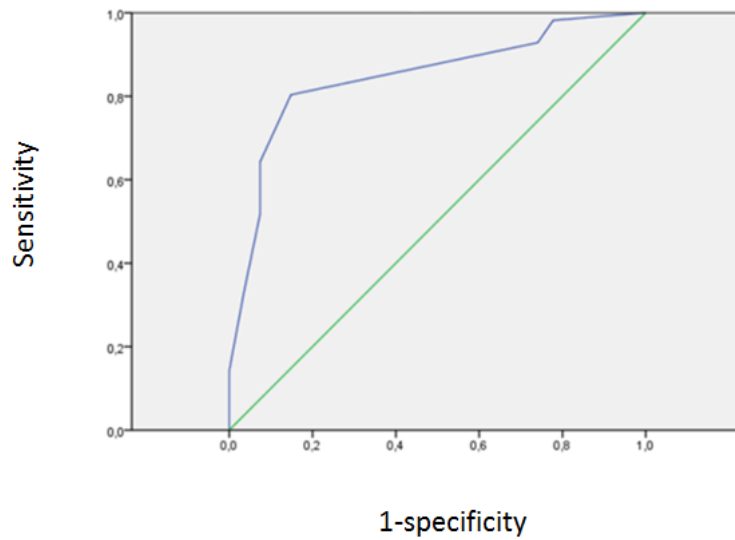


Figure 7 -
Performances of Partial Mayo clinic score at week 14 in UC patients for the prediction of steroid-free clinical remission at week 24. AUC = 0.85
A score > 2 was associated with failure to achieve steroid-free clinical remission at week 24 with RR = 2.83, 95%CI = [1.73-4.64], Se = 80%, Sp = 85%, PPV = 92%, NPV = 67%.

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THESE SOUTENUE PAR : **Sandie PESTOUR**

TITRE :

Influence de la localisation des maladies inflammatoires chroniques de l'intestin sur l'efficacité du Védolizumab : une étude multicentrique

CONCLUSION

Les maladies inflammatoires chroniques de l'intestin (MICI), Maladie de Crohn (MC, prévalence 322 / 100 000 en Europe) et Rectocolite Hémorragique (RCH, prévalence 505 / 100 000 en Europe), sont des maladies graves du sujet jeune, chroniques, invalidantes, responsables d'une morbidité élevée altérant la qualité de vie. Leur prise en charge représente un enjeu de santé publique car leur impact socio-économique est majeur du fait de la nécessité de traitements prolongés et coûteux.

La prise en charge actuelle des MICI est celle d'une médecine de précision, basée sur l'identification de facteurs prédictifs de réponse aux différentes thérapies disponibles dans le but de choisir la stratégie thérapeutique la plus adaptée à chaque patient, en particulier en termes de coût/efficacité. Les thérapies systémiques actuelles (corticostéroïdes, immunosuppresseurs, anti-TNF) n'étant pas dénuées d'effets indésirables potentiellement sévères, de nouvelles molécules aux mécanismes d'action plus ciblés ont été récemment développées. Parmi elles, le Védolizumab (VDZ) est un anticorps monoclonal bloquant spécifiquement l'interaction entre les intégrines $\alpha_4\beta_7$ des lymphocytes T activés circulants et les molécules d'adhésion endothéliales, empêchant ainsi la migration lymphocytaire vers la muqueuse digestive inflammatoire. Cette thérapie anti-migration leucocytaire a démontré son efficacité à induire et maintenir une rémission clinique dans 3 essais cliniques pivots.

Dans différentes études prospectives et rétrospectives, certains facteurs ont été associés à une moins bonne réponse au VDZ, tels que le tabagisme, l'exposition antérieure à un traitement anti-TNF, l'atteinte ano-périnéale et la sévérité clinico-biologique de la maladie. Il existe actuellement très peu de données concernant l'influence de la localisation de l'atteinte inflammatoire de la MICI sur la réponse au VDZ, alors que celle-ci a été identifiée comme facteur prédictif de réponse aux anti-TNF pour la MC et la RCH. L'objectif de ce travail était de déterminer si la localisation colique (versus iléale) pour la MC et distale (versus pancolique) pour la RCH sont des facteurs prédictifs de rémission clinique sans corticostéroïdes à 6 mois.

Pour la MC luminale comme pour la RCH, Il n'a pas été mis en évidence dans cette étude de différence de rémission entre les différentes localisations. L'atteinte colique dans la MC, pourtant considérée comme de phénotype moins agressif et associées à de meilleures chances de rémission avec les anti-TNF, n'apparaît pas ici comme facteur prédictif de réponse au VDZ. Il en est de même pour la RCH étendue (pancolique), habituellement considérée comme un facteur péjoratif associé à un risque plus élevé de colectomie, versus la RCH distale. Pour expliquer ces résultats, nous pouvons supposer d'une part qu'il n'existe effectivement pas d'influence de la localisation sur la rémission sans CS à 6 mois

sous VDZ, ou d'autre part que cette influence n'a pas pu être mise en évidence du fait des limitations de notre étude. En effet, son caractère rétrospectif peut être responsable d'une imprécision d'évaluation des certains paramètres. De même, les patients MICI inclus dans notre étude constituent une population très sélectionnée, suivie en centre spécialisé, présentant des maladies sévères, de longue durée d'évolution et de phénotype agressif, avec antécédents fréquents de résections chirurgicales et traitements médicamenteux multiples, toutes localisations confondues.

Dans la MC, même s'il n'existait pas de différence entre localisation luminale iléale et colique, notre étude a tout de même permis de confirmer l'influence de la maladie ano-périnéale active qui apparait clairement associée à des chances plus faibles de rémission clinique sous VDZ.

Grâce à cette étude menée sur une importante cohorte multicentrique, des résultats intéressants sur les performances prédictives de certains paramètres cliniques et biologiques ont pu être obtenus. En effet, pour la MC comme pour la RCH, il est apparu que l'absence d'obtention d'une rémission clinique (définie selon les scores d'activité validés) à la fin de la phase d'induction, soit à 14 semaines de traitement, était prédictif de l'absence de rémission sans corticostéroïdes à 6 mois. De même, dans la MC, une CRP élevée à la semaine 14 semble être associée à un risque d'échec, mais avec des performances moindres. Ces résultats constituent des outils utiles au clinicien pour apprécier les chances d'efficacité du VDZ dès la fin de la phase d'induction et guider l'adaptation thérapeutique précoce.

En conclusion, la localisation n'apparait pas dans cette étude comme un facteur prédictif d'efficacité du VDZ, en dehors de la localisation périnéale active qui est associée à moins de chances de rémission sans corticostéroïdes à 6 mois. Une étude prospective, avec caractérisation rigoureuse des localisations de la maladie apparait nécessaire pour confirmer ces résultats.

Le rôle du clinicien, aidé de scores validés, reste majeur pour la prédiction des chances de rémission sans corticostéroïdes à 6 mois.

VU ET PERMIS D'IMPRIMER

Grenoble, le

26/09/17

(*) LE DOYEN

Pour la Présidente
par délégation
L. Doyen de Médecine
Pr. Paul ROMANET

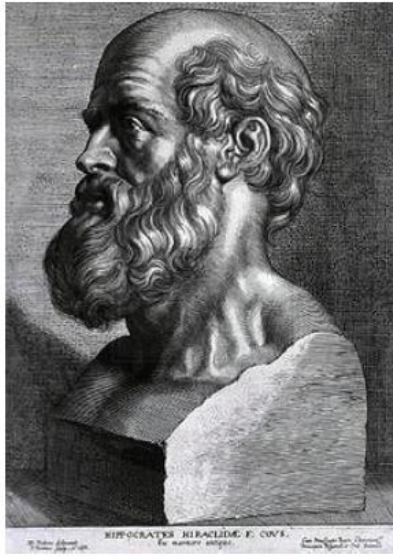
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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerais mes soins gratuitement à l'indigent et n'exigerais jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.