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Efficacy and Safety of Induction Therapy With Calcineurin Inhibitors in Combination with Vedolizumab in Patients With Refractory Ulcerative Colitis

Short title: cyclosporine in combination with vedolizumab in ulcerative colitis

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Abbreviations:

UC: ulcerative colitis

ASUC: acute severe ulcerative colitis

TNF: tumor necrosis factor

UCEIS: ulcerative colitis endoscopic index of severity

CRP: C-reactive protein

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GP, DL: study conception and design, study investigator, data interpretation, statistical analysis, drafting and critical revision of the manuscript.

CS, FC, LPB, XR, CA, MN, SN, JF, RA, HB and GF: generation and collection of data.

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Abstract

Background & Aims: Vedolizumab is used to treat patients with ulcerative colitis (UC), although there is a delay before it is effective. Induction therapy with a calcineurin inhibitor (cyclosporine or tacrolimus) in combination with vedolizumab as maintenance therapy could be an option for patients with an active steroid-refractory UC. We assessed the efficacy and safety of this combination.

Methods: We performed a retrospective observational study, collecting data from 12 referral centers in France that were included in the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif. We collected information on 39 patients with an active steroid-refractory UC (31 with active severe UC and 36 failed by treatment with a tumor necrosis factor antagonist) who received a calcineurin inhibitor as an induction therapy along with vedolizumab as a maintenance therapy. Inclusion date was the first vedolizumab infusion. The outcomes were survival without colectomy, survival without vedolizumab discontinuation, and safety.

Results: After a median follow-up period of 11 months, 11 patients (28%) underwent colectomy. At 12 months, 68% of the patients survived without colectomy (95% CI, 53%–84%) and 44% survived without vedolizumab discontinuation (95% CI, 27%–61%). No deaths occurred and 4 severe adverse events were observed.

Conclusion: In a retrospective analysis of 39 patients with an active steroid-refractory UC (most refractory to a tumor necrosis factor antagonist), we found that initial treatment with a calcineurin inhibitor in combination with vedolizumab allowed more than two-thirds of patients to avoid colectomy. Further studies are needed to assess the safety of this strategy.

Keywords: ulcerative colitis; anti-TNF refractory; GETAID; vedolizumab; cyclosporine;.

Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that always affects the rectum with a retrograde continuous extent into the colon. The two main criteria¹ driving UC treatment are disease extent and severity. Indeed, treatment is mainly based on topical therapy when UC is limited to the rectum, while systemic treatments are needed in a more extensive disease². Approximately 20% of UC patients will experience an acute severe flare during their life. In patients with uncomplicated acute severe UC (ASUC), a standardized rapid step-up medical approach is needed². It is recommended to start with intravenous steroids and to give cyclosporine or infliximab as a second-line medical therapy in steroid-refractory patients^{3,4}. Regarding cyclosporine and due to its long-term toxicity, it is given as a bridging therapy to thiopurine in patients without prior failure to these agents.

During the past decades, thiopurines, cyclosporine and infliximab have been increasingly prescribed in patients admitted in tertiary centers for an active UC⁵. Accordingly, there was a trend towards a decrease in colectomy rates⁶. As a consequence, there an increasing number of ASUC patients loosing response especially to anti-TNF that are now admitted in the referral centers.

Vedolizumab has demonstrated its efficacy in UC, as an induction and maintenance therapy in patients who have been exposed or not to thiopurines and anti-TNF^{7,8}. However, it acts progressively and can takes 14 weeks to reach its full efficacy⁹. Vedolizumab has never been evaluated in the setting of ASUC where a prompt efficacy is needed. Therefore, a strategy combining a calcineurin inhibitor (cyclosporine or tacrolimus) as an induction therapy with vedolizumab as maintenance could be an attractive approach for UC patients who have failed a treatment with thiopurines and anti-TNF or that have a contra-indication to these drugs. The aim of the present study was to assess the efficacy and safety of this combination in patients with steroid and anti-TNF-refractory UC.

Methods

Study design and patients

We performed a retrospective multicenter observational study in 12 French tertiary academic centers affiliated to the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID).

From December 2014 to May 2017, patients with an active steroid-refractory UC were consecutively enrolled when they received a calcineurin inhibitor (cyclosporine or tacrolimus) as an induction therapy and vedolizumab as maintenance. Patients were eligible when they were admitted for a refractory UC, that could be an ASUC (defined according to the Truelove and Witts criteria¹⁰) or not, and if they previously did not respond adequately to at least one anti-TNF agent or if it was contraindicated. Baseline corresponded to the date of the first vedolizumab infusion.

Cyclosporine was started by continuous intravenous infusion at an initial dose of 2 mg/kg/d or orally at 4 mg/kg/d. The dose was subsequently adjusted to obtain a cyclosporine concentration between 150 and 250 ng/mL. When response was achieved with intravenous cyclosporine, it was switched to oral drug (Neoral®), given twice a day at 4 mg/kg/d. Tacrolimus was started orally at 0.05-0.1 mg/kg/d secondary adjusted on plasmatic concentration targeting blood concentration of 10–15 ng/mL until week 2 and 5–10 ng/mL thereafter. Choice of calcineurin inhibitor molecule – cyclosporine or tacrolimus – depended on centres routine practice. Both calcineurin inhibitors were given as a bridge therapy to vedolizumab for approximately three months in responders. They were intentionally withdrawn at this time, or previously in case of intolerance or failure.

In France, vedolizumab is licensed only in patients who are in failure of a treatment with anti-TNF or in whom these drugs are contraindicated. Inclusion date was the first vedolizumab infusion.

All patients received treatment according to clinical need. Medications were those currently recommended in UC, according to their licensed or published doses. Patients were informed by written notice of their participation. The French Data Protection Agency (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé, n° of approval 17-037) and investigational review board of each center approved the study. All authors had access to the study data and have reviewed and approved the final manuscript.

Data collection

At inclusion, the following characteristics were recorded for each patient: sex, age, disease duration, smoking status, UC characteristics according to Montreal Classification, extra-intestinal manifestation, prior received treatments (steroids, thiopurine, methotrexate, infliximab, adalimumab and golimumab) and reasons for discontinuation (primary failure, loss of response or intolerance), disease activity according to the partial Mayo and the Lichtiger scores, endoscopic activity measured with the endoscopic Mayo subscore and UC endoscopic index of severity (UCEIS), severe endoscopic lesions, C-reactive protein (CRP), haemoglobin, and albumin levels.

Follow-up

Follow-up started from inclusion up to august 2017.

Vedolizumab 300mg infusions were administered intravenously at weeks 0, 2 and 6, and then every 8 weeks. If needed, vedolizumab could be prescribed every 4 weeks from week 10. Other UC treatments, including calcineurin inhibitors, corticosteroids or thiopurines were given according to clinical need as judged by the physician. Treatment duration of each drug was collected during the follow-up period.

UC clinical activity (according to the partial Mayo score), received treatments and CRP measurements were collected at each vedolizumab infusion – i.e. at least at weeks 2, 6 and 14

– until death, colectomy, vedolizumab discontinuation or end of follow-up. Reasons for vedolizumab withdrawal were collected and investigated. Due to its retrospective design, no standardized endoscopic assessment was performed during the study.

Each adverse event occurring during the follow-up period was collected and investigated.

Objectives

The primary objective was survival without colectomy. Secondary objectives were survival without colectomy according to disease severity, survival without vedolizumab discontinuation, clinical response at weeks 6 and 14, clinical remission at weeks 6 and 14, biochemical remission at weeks 6 and 14, predictive factors of colectomy and safety.

Clinical response was defined by decrease of the partial Mayo score of at least 3 points with decrease of at least 30% and reduction of at least 1 point on the bleeding subscore with subscore of 0 or 1, as compared to inclusion. Clinical remission was defined by partial Mayo score of less than 3, without any of the subscores having a value higher than 1. Biochemical remission was defined by normal CRP level, below 5 mg/L. Adverse effects were classified as severe when they lead to treatment interruption, hospitalization or death.

Statistical analysis

Continuous variables were reported as median and range. They were compared with the Student t-test or Mann–Whitney–Wilcoxon test for variables with abnormal distribution, and categorical variables with Pearson’s chi-square or Fisher's exact tests where appropriate. Regarding assessments at weeks 6 and 14, patients who underwent colectomy or vedolizumab discontinuation since inclusion were considered as failure.

For the survival analysis, a Kaplan-Meier curve and a log-rank test were used. Because there were no deaths in our study population, there was no need for considering competitive risk. Cox proportional hazard models were used to identify predictors of surgery. Variables associated with colectomy with a $p < 0.30$ in univariate analysis were included in the

multivariate model. ASUC is a well-known risk factor for colectomy and then was forced into the multivariate model, whatever the result of the univariate analysis. The final cox model was obtained by a backward stepwise selection of variables with a p value < 0.05 . SAS Software 9.4 and R were used for statistical analysis.

Results

Patient characteristics

Thirty-nine UC patients were included in 12 centres during the study period. Their main characteristics are shown in Table 1. To summarize, 23 patients (59%) were women, with a median age of 32 (range: 17–73) years. None underwent prior liver transplantation. Median disease duration was 4.0 (0.2–23.9) years and 31 patients (79%) were admitted for an ASUC. Thirty-three patients (85%) had been previously exposed to thiopurines, 1 (%) to methotrexate and 36 (92%) to at least one anti-TNF agent. Three (8%) other patients had a contraindication to anti-TNF agents due to multiple sclerosis (1), recent malignancy (1) or tuberculosis (1). Twenty-six (67%) patients received an anti-TNF agent in the three previous months, and 13 (33%) in the last month. Median interval between the last anti-TNF administration and first vedolizumab infusion was 43 days (7–3230 days). Thirty (77%) patients received corticosteroids at baseline.

Regarding calcineurin inhibitor, 37 (95%) patients received cyclosporine and 2 (5%) tacrolimus. Vedolizumab was started after a median interval of 7 (0–180) days after the calcineurin inhibitor (one patient received cyclosporine for 180 days waiting for vedolizumab approval in France). Thirty-six (92%) patients started calcineurin inhibitors before vedolizumab. The remaining three patients started calcineurin inhibitor during the vedolizumab induction regimen, within a median interval of 30 days. Calcineurin inhibitor was continued for a median duration of 80 (5–384) days since inclusion.

Efficacy

The median duration of follow-up was 10.8 (0.4–30.2) months. No deaths occurred and no patient was lost to follow-up.

Eleven (28%) patients underwent colectomy after a median duration of 112 (11 – 344) days. Six of them underwent early surgery, before week 14. The survival rate without colectomy was 68% at one year (95% confidence interval – 95%CI: 53-84%) (Figure 1A).

At one year, rates of survival without colectomy were 64% (IC95%: 46-83%) in patients with ASUC and 87% (IC95%: 65-100%) in those without ASUC (p=0.32) (Figure 1B).

Nineteen (49%) patients stopped vedolizumab during the study period: 18 due to lack of efficacy and one due to intolerance (depression). After one year of follow-up 44% (IC95%: 27-61%) of patients were still treated with vedolizumab (Figure 2). Vedolizumab was intensified every 4 weeks in 26 (67%) patients (in 19 patients at week 10 and 7 after week 14). Among the 19 optimised patients at week 10, 9 (47%) were in clinical remission at week 14. Regarding the 18 patients who did not respond to vedolizumab, 11 underwent colectomy and 7 were treated with another medical treatment (combotherapy with infliximab and thiopurines for two patients, inclusion in a clinical trial for three - tofacitinib (2) and fecal microbiota transplantation (1) -, allopurinol plus thiopurine for one and oral tacrolimus for one).

Median partial Mayo score were 7 at baseline, 2 at week 6 and 3 at week 14, respectively. Clinical response and clinical remission, were achieved in 25/39 (64%) and 18/39 (46%) patients at week 6 and, in 22/39 (56%) and 15/39 (38%) at week 14, respectively (Figure 3). Among the 30 patients receiving corticosteroids at baseline, steroid free remission was achieved in and 7/30 (23%) at week 6, and 12/30 (40%) at week 14. Proportions of patients still receiving the calcineurin inhibitor were 25/39 (64%) at week 6, and 8/39 (21%) at week 14.

There were 9/32 (28%) patients in biochemical remission (CRP <5mg/L) at week 6 and 8/34 (24%) patients at week 14. Median CRP was 6 mg/L at week 6, and 7.8 mg/L at week 14.

In multivariate analysis, four baseline factors were associated with colectomy during the follow-up period: female gender (HR: 10.5; 95%CI: 2.05-54.33; p=0.004), age more than 31 years (HR: 13.16; 95%CI: 2.27–76.26), concomitant immunosuppressant (HR: 9.59; 95%CI: 1.13–81.60) and haemoglobin more than 11.2 g/dL (HR: 1.93; 95%CI: 0.59-6.32).

Safety

Eleven (28%) patients experienced at least one adverse event during the study. They are summarized in the table 2. Four of them were severe: three patients developed mild and transient renal failure, leading to cyclosporine withdrawal in one case and, one patient developed a *Campylobacter jejuni* colitis while treated with vedolizumab and tacrolimus that completely recovered with antibiotics. No opportunistic infection or malignancy was observed. One patient in clinical remission decided to stop vedolizumab due to a depression that was thought to be due to the drug.

Discussion

In the present multicentre cohort of patients admitted for a steroid-refractory UC with prior anti-TNF failure, a combination between a calcineurin inhibitor with vedolizumab could avoid colectomy in approximately two out of three patients within one year, whatever disease severity, with a good safety profile. As far as we know, this study is the largest to investigate this association in a cohort of highly selected patients with refractoriness to all current licensed drugs in UC ^{11,12}.

The number of UC anti-TNF refractory patients is *de facto* increasing in parallel with the growing use of these drugs. Currently, these patients are candidates to either vedolizumab or colectomy. Until now, vedolizumab has not been evaluated in patients with ASUC who were excluded from the pivotal trials. In addition, physicians are reluctant to use vedolizumab in this setting, because of its delayed efficacy ^{7,9}. However, and as a parallel with the bridging strategy combining cyclosporine and thiopurine in the management of patients with steroid-refractory UC before the anti-TNF era ¹³, it could be attractive to combine a calcineurin inhibitor as induction therapy with vedolizumab as maintenance in these patients.

Although patients recruited in the present cohort were more severe, the efficacy of vedolizumab was similar with that reported in the literature in UC. Published clinical response and remission rates at week 14 were 43-57% and 23-39% respectively, as compared to 56% and 38% in our cohort. In addition, reported vedolizumab failure rates within the first year of treatment were of 35-48% in previous series ¹⁴⁻¹⁶, and 49% in our cohort.

However, as vedolizumab was given as a last-chance drug before surgery in the present cohort, the absence of colectomy during the follow-up does not necessarily mean that the drug was efficient. Indeed, half of patients discontinued vedolizumab within one year, while approximately one third were operated on. Moreover, some patients continued the drug

despite partial efficacy. This illustrates the impact of a limited therapeutic choice on drug persistence.

In ASUC patients from the present cohort, the 36% one-year colectomy rate was similar to those reported with cyclosporine (29%) or infliximab (31%) when combined with azathioprine after intravenous steroid failure¹⁷.

As observed in controlled trials and observational studies, vedolizumab appears to have a good safety profile⁸. Yet, concomitant use of calcineurin inhibitor was not allowed in the GEMINI trial and the experience of combining an anti-integrin with a calcineurin inhibitor is very limited in UC as well as in multiple sclerosis. A prior study conducted in 9 patients with Crohn's disease and 11 with UC did not observe additional safety events than those related to calcineurin inhibitors alone. Adverse events observed in the present cohort were mostly related to calcineurin inhibitors except one case of *Campylobacter jejuni* colitis associated with vedolizumab. No other case of opportunistic infection or malignancy was observed.

This study has several limitations inherent to its retrospective design. Treatments were not standardized as well as outcome measures, especially endoscopic assessments. Patients were selected in few referral centres and most of them were primary responders to calcineurin inhibitors who received vedolizumab only when they responded adequately to the induction therapy. The follow-up was limited to 11 months.

Overall, a strategy combining a calcineurin inhibitor with vedolizumab in patients with steroid-refractory UC and prior anti-TNF failure or contra-indication can avoid colectomy in approximately two thirds of the patients within one year and seems safe. It can be considered in patients with ASUC or non-severe UC when they are refractory to all conventional therapies, including anti-TNF agents. The safety profile of this combination will require further investigation.

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Figure legends:

Figure 1: Survival without colectomy:

A: Among 39 patients with refractory ulcerative colitis treated by a combination between a calcineurin inhibitor and vedolizumab;

B: According to disease severity.

ASUC: acute severe ulcerative colitis

Figure 2: Survival without vedolizumab discontinuation among 39 patients with refractory ulcerative colitis treated with a calcineurin inhibitor and vedolizumab.

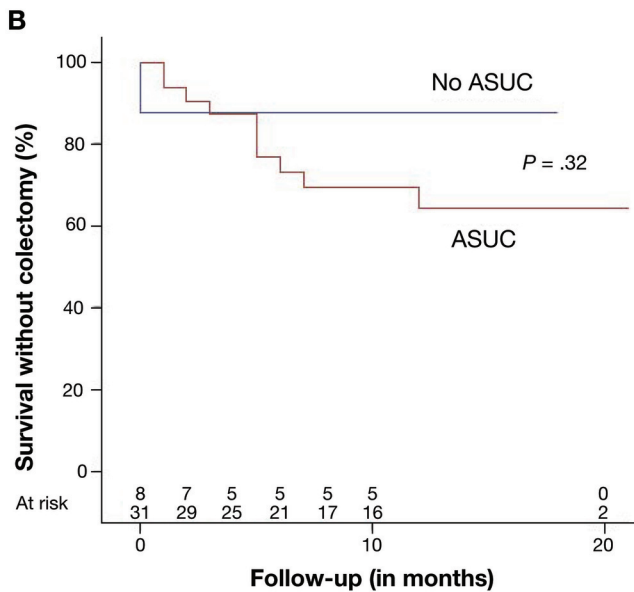
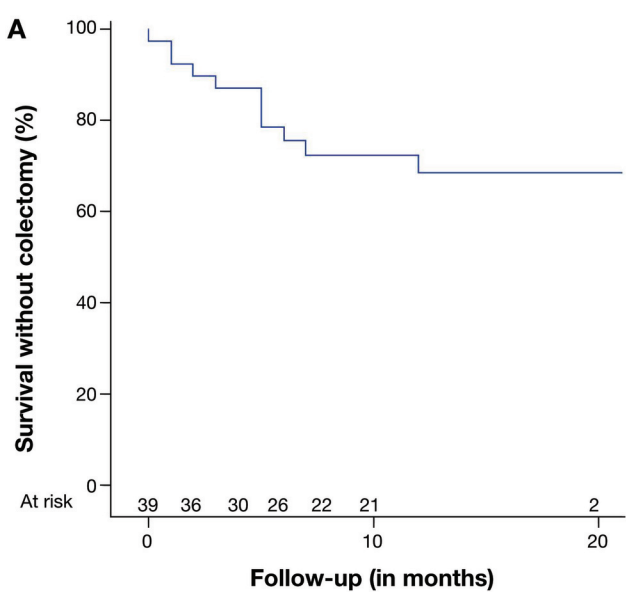
Figure 3: Clinical response, clinical remission and steroid-free remission at weeks 6 and 14 among 39 patients with refractory ulcerative colitis treated by a combination between a calcineurin inhibitor and vedolizumab.

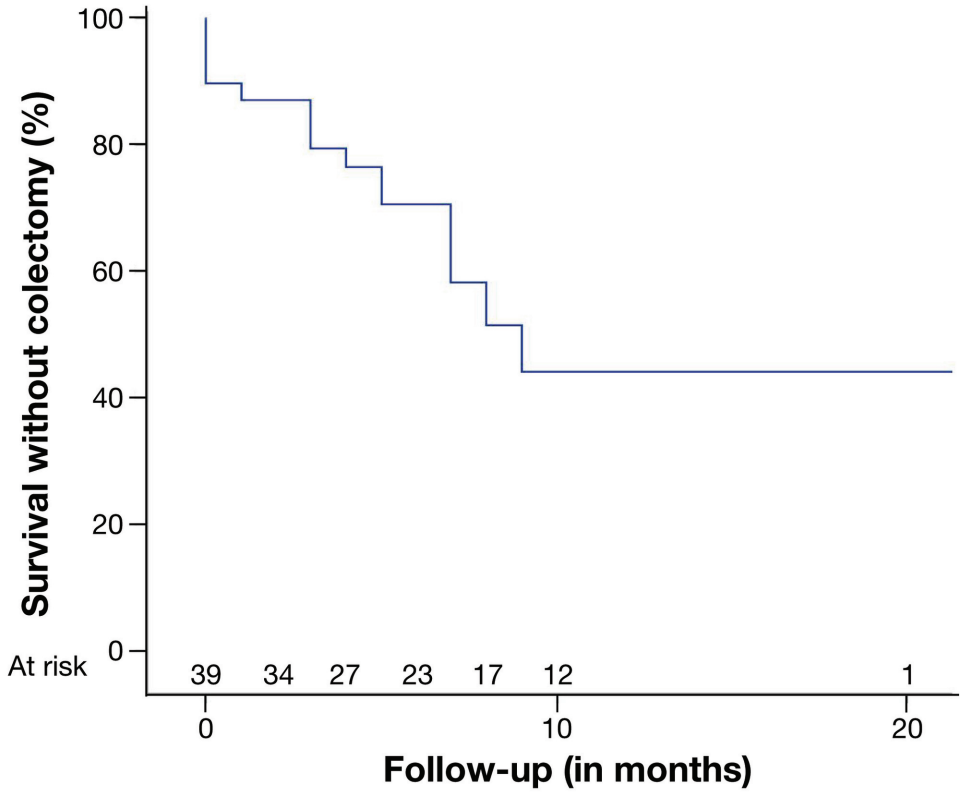
Table 1: Main patients' characteristics at baseline

	N=39 (%)
Female gender	23 (59)
Median age, years (range)	32 (17-73)
Median UC duration, years (range)	4.0 (0.2-23.9)
Prior thiopurine exposure	33 (85)
Prior anti-TNF exposure	36 (92)
1 agent	19 (49)
2 agents	15 (38)
3 agents	2 (5)
Contra-indication to anti-TNF	3 (8)
Acute severe UC	31 (79)
Concomitant steroids	21 (54)
Concomitant thiopurine	3 (8)
Median partial Mayo score (range)	7 (1-9)
Median Mayo endoscopic subscore	3 (1-3)
Median CRP, mg/L (range)	12.8 (0.2-219.0)

Table 2: Adverse events observed during the study

Events	Current treatments given	N (%)
Severe adverse event		
Kidney failure	Cyclosporine + steroids (1), cyclosporine (2)	3 (8)
Campylobacter colitis	Tacrolimus	1 (3)
Non-severe adverse events		
Headache	Cyclosporine + steroids	2
Gingivitis	Cyclosporine	1 (3)
Trichauxis	Cyclosporine	1 (3)
Dry syndrome	Cyclosporine + steroids	1 (3)
Asthenia	Cyclosporine + steroids	1 (3)
Depressive syndrome	Vedolizumab	1 (3)
Oedema	Cyclosporine + steroids	1 (3)
Arthralgia	Cyclosporine + steroids	1 (3)





Clinical response and remission at week 6 and 14

