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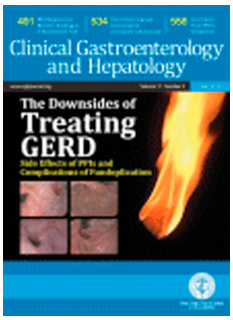

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Efficacy of induction therapy with calcineurin inhibitors in combination with ustekinumab for acute severe ulcerative colitis.

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Conflict of interest : PV was a speaker for Abbvie, Vifor Pharma, Janssen, Sanofi, GP declare fees from Pfizer, D L declares counseling, boards, transports or fees from Abbvie, Biogaran, Biogen, Ferring, HAC-pharma, Janssen, MSD, Novartis, Pfizer, Prometheus, Roche, Takeda, Theradiag, Tillots. MN received board membership, consultancy, or lecture fees from Abbvie, Adacyte, Amgen, Arena, Biogen, CTMA, Celltrion, Ferring, Fresenius-Kabi, Janssen, Mayoli-Spindler, MSD, Pfizer, Takeda, PJ was a consulting/Board/speaker: AbbVie, Arena, Amgen, BMS, Ferring, Gilead, Janssen, Lilly, MSD, Pfizer, Pierre Fabre, Roche, Sandoz, Takeda, Tillots, UCB Pharma, XR was a speaker for MSD, Abbvie, and Takeda and participated as an advisory board member for MSD, Takeda, Janssen, and Pfizer, MF, MA and SN declares no conflict of interest.

Author's contribution: XR and PV: conception and supervision of the study, interpretation of data and critical review of the manuscript; PV, XR, DL: wrote the paper; All of the authors participated in data collection; All of the authors approved the final version of the manuscript.

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Ulcerative colitis (UC) is a chronic inflammatory bowel disease. Approximately 20% of patients will experience an acute severe attack during their life. In acute severe UC (ASUC), first line therapy is intravenous (IV) steroids. In the absence of clinical improvement, two medical options can be considered: ciclosporin or infliximab.[1] In ASUC, ciclosporin is commonly used as a bridging therapy for thiopurines. Pellet et al found that the same bridge strategy with vedolizumab was effective and can avoid colectomy. [2] Given that an increasing number of patients with ASUC have been exposed to thiopurines, vedolizumab and anti-TNF biologic therapies, newer approaches are needed in these patients as tofacitinib or ustekinumab. Ustekinumab, an antagonist of the p40 subunit of interleukin-12 and interleukin-23, has shown is efficacy in UC and can be given in this indication. [3] In this retrospective study, we aimed to evaluate the efficacy and safety of a bridge from calcineurin inhibitor to ustekinumab in patients with ASUC.

We conducted a retrospective study by questioning 50 IBD centers affiliated to the GETAID. Patients were included at their admission for an ASUC defined by Truelove-Witts criteria[4], refractory to IV corticosteroid at recommended dosage (0.8-1mg/kg) defined by a Lichtiger[5] score that did not decrease below 10, when they started a sequential treatment by calcineurin inhibitor (ciclosporin, tacrolimus) followed by ustekinumab, in the 60 days thereafter. Patients non-responding to calcineurin inhibitor or requiring emergent colectomy were excluded. Inclusion date corresponded to the first day of calcineurin inhibitor. Patients were all treated with an initial infusion of ustekinumab (6mg/kg), followed by 90mg SC every 8 weeks. After 7 days of intravenous calcineurin inhibitor (ciclosporin dose of 2mg/kg/d at beginning, targeting a blood concentration between 150 to 250 ng/ml, tacrolimus at 0.05mg/kg), clinical responders were switched orally targeting the same blood concentration. Calcineurin inhibitor given as a bridge therapy were withdrawn within the first three months after inclusion.
Endpoints were clinical response (decrease of the partial Mayo score of at least 3 points, with a decrease of at least 30% and a reduction of at least 1 point on the bleeding subscore with a subscore of 0 or 1, as compared with inclusion), clinical remission (partial Mayo score of less than 3, without any of the subscores having a value higher than 1) and biochemical remission (CRP <5 mg/L) at 6 months after inclusion, colectomy free-survival, survival without ustekinumab discontinuation and safety. All adverse events were collected. Continuous variables were reported as medians and ranges. They were compared with the Student t test or Mann–Whitney–Wilcoxon test for variables with abnormal distribution.

Ten patients were included among 7 French and one Swiss centers. Baseline characteristics of patients are reported in Table 1. Eight were women, with a median age of 32 years. The median disease duration was 7 years. Nine patients were previously exposed to infliximab and 8 to vedolizumab. At inclusion, median Lichtiger score, partial Mayo score and CRP were 13.5 [IQR, 13-13.6], 8 [IQR, 8-9] and 17.5 mg/L [IQR, 4.1-38.8], respectively. The mean Endoscopic Mayo score was 2.6 +/-0.7. Three patients were steroids dependent before hospitalization. One patient (10%) was treated by tacrolimus and nine (90%) by ciclosporin. Six patients (60%) were switched orally within the first week and four (40%) patients were still under IV therapy. All patients stopped calcineurin inhibitor between two months after initiation of treatment. Median time between beginning of ustekinumab and withdrawal of calcineurin inhibitor was 45 (IQR 45-60) days. The median time between starting calcineurin inhibitor and ustekinumab was 22 (range: 6-60) days. Two patients (20%) initiated ustekinumab in the seven days following admission. (Supplementary Table 2).

At 6 months, none of the patients underwent colectomy. Median partial Mayo score and CRP levels were significantly reduced at 6 months: 10.6 vs 1.0 (p = 0.005) (Supplementary Figure 1) and 17.5 (IQR, 4.1-38.8) mg/L vs 2.3 (IQR, 1.7-3.2) mg /L (p = 0.02), respectively. One patient failed to obtain both clinical response and remission. One patient (10%) was still on steroid at 6 months.
With a median follow-up duration of 9 months (IQR, 5-11), one patient withdrew ustekinumab because of treatment failure (Supplementary Figure 1). Two patients (20%) required ustekinumab dose optimization after three months for lack of efficacy at three months (clinical response with persistence of symptoms). Tolerance to treatment was good with only one case of alopecia described that didn't lead to treatment interruption.

In this retrospective study including mostly patients who previously failed to infliximab and vedolizumab, a sequence combining calcineurin inhibitor with ustekinumab was effective with a significant improvement of clinical Mayo score and avoidance of colectomy.
Currently, steroid-refractory patients with ASUC may receive ciclosporin for a short period, as an induction treatment for a maintenance therapy with thiopurine. A new bridging approach was proposed with vedolizumab as maintenance by Pellet et al. [2], avoiding colectomy in two thirds of the patients. The same findings were found by Ollech et al.[6], in a cohort of 71 patients with ASUC, with rates of colectomy-free survival at 93% at 3 months and 55% at 2 years. Results from the present cohort suggest this bridging approach is also feasible with ustekinumab, providing clinical response and avoiding colectomy with an acceptable safety profile as observed in cohorts of inflammatory bowel disease patients. Indeed, both agents share some common pathways and ustekinumab long-term safety profile is acceptable.[7]
We acknowledge the limited sample of the specific population included in the present retrospective series that recruited patients not requiring emergent colectomy at admission if they responded to calcineurin inhibitor. The follow-up was less than one year.
In this retrospective study including patients hospitalized for steroid-resistant ASUC, the sequence of treatment with induction calcineurin inhibitor followed by maintenance treatment with ustekinumab appears to be effective and well tolerated. These encouraging data have to be confirmed in larger cohorts of patients.

Table 1: baseline characteristics of patients

N=10	
Mean age (range) in years	32 (25.2-37.8)
Female gen,der, n (%)	8 (80)
Disease extension, Montreal Classification	
E1	10% (1 patient)
E2	40% (4 patients)
E3	50% (5 patients)
Active smokers, n (%)	0 (0)
Disease duration (median, IQR) years	7 [IQR 3-8.7]
Prior exposure to treatment	
Infliximab	90% (9 patients)
Adalimumab	20% (2 patients)
Golimumab	18% (2 patients)
Vedolizumab	80%(8 patients)
Median Lichtiger score (IQR)	13.5 [13-14.7]
Median Mayo score (IQR)	10.6 [10-11.7]
Median CRP (IQR) mg/ml	17.5 [(4.1-38.8]
Mean Mayo endoscopic subscore (range)	2.6 (+/-0.7)

Supplementary Table 2: Beginning of each treatment during ASUC

Supplementary Figure 1: Evolution of Mayo score and treatment for patient under combining therapy with ciclosporin and ustekinumab

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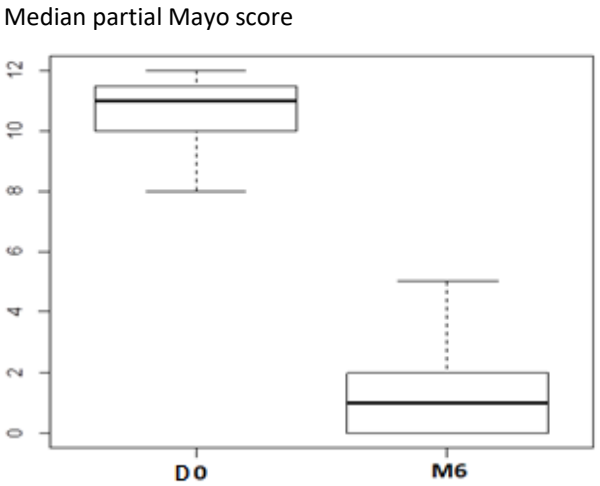
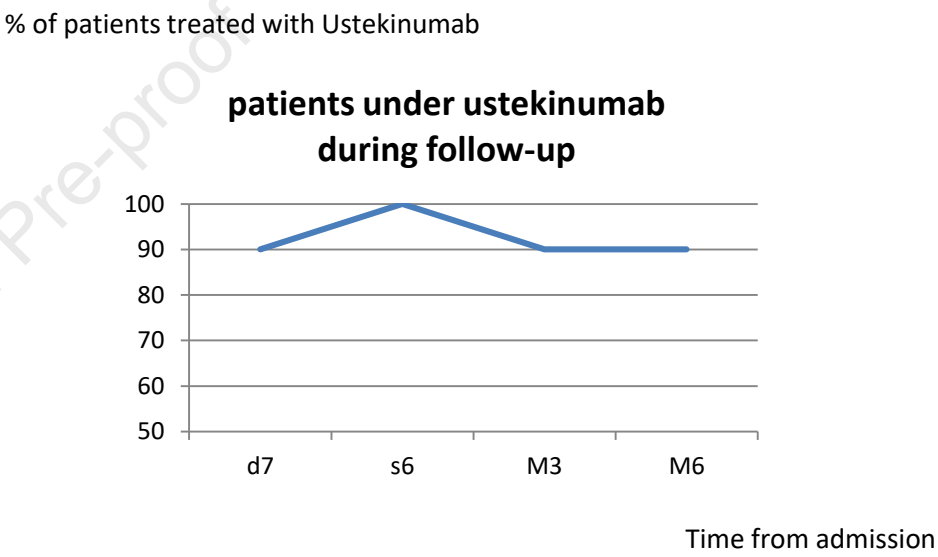
Supplementary Fig 1





Supplementary table 2

Patient	Disease duration (years)	Prior drug failure	Interval between calcineurin inhibitor and ustekinumab (days)	Calcineurin inhibitor	Total Mayo score at inclusion	Lichtiger score at inclusion	CRP at inclusion	Mayo endoscopic subscore at inclusion
1	4	Infliximab Adalimumab vedolizumab	46	ciclosporin	12	13	60	3
2	10	Infliximab vedolizumab	58	ciclosporin	12	11	72	3
3	4	Infliximab vedolizumab	32	ciclosporin	11	12	3,5	3
4	8	None*	7	ciclosporin	11	12	14	3
5	25	Infliximab vedolizumab	6	ciclosporin	11	14	4	3
6	16	Infliximab Adalimumab vedolizumab	23	ciclosporin	10	12	4	2
7	3	infliximab	10	ciclosporin	11	13	42	2
8	9	Infliximab vedolizumab	38	tacrolimus	12	9	4,5	3
9	8	Infliximab vedolizumab	22	ciclosporin	8	11	21	3
10	3	Infliximab vedolizumab	8	ciclosporin	9	11	29,4	2

*: contraindication to anti-TNF