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Évaluation à long terme de l'efficacité et de la tolérance de l'ustekinumab dans la maladie de Crohn réfractaire

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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.

LISTE DES ABREVIATIONS

UST	Ustekinumab
CD	Crohn disease
CRP	C-Réactive Protéine
Mg	Milligrammes
IQR	Interquartile range
IC	Confidence interval
TNF	Tumor necrosis factor
HBI	Harvey-Bradshaw index
IS	Immunosuppresseurs

TABLE DES MATIERES

RESUME

Contexte : Ustekinumab is a human IgG1 kappa monoclonal antibody that targets the p40 subunit of interleukin IL-12 and IL-23 and inhibits T helper 1 and T helper 17 pathways implicated in the pathogenesis of CD. Aims of the study were to evaluate the long-term efficacy and safety of ustekinumab and identify predictive factors of ustekinumab failure-free survival in a cohort of anti-TNF refractory CD patients.

Méthods : From June 2016 to December 2018, We performed a retrospective observational study in the tertiary referral centre of the Claude Huriez Hospital in Lille, France, including all consecutive refractory CD patients who had an intravenous induction of ustekinumab. We observed the clinical, biological, endoscopical and morphological effect. We studied the predictive factors of clinical failure, discontinuation or maintenance with corticosteroids at one year following a Kaplan Meier analysis.

Résults: One hundred and one CD patients beginning ustekinumab between June 2016 to December 2018. Median time of follow-up was 77.1 weeks (IQR: 56.3-107.7). Ustekinumab failure-free survival was 90% at 12 months, 75% at 24 months and 67% at 36 months after inclusion. After one year of treatment, clinical, biological response were observed for respectively 59 (81.9%) patients, 55 (83.2%) patients. At last news, 61.4% of patients were in endoscopic and/or morphologic response. No predictive factor of ustekinumab failure, discontinuation or maintenance with corticosteroids were identified at one year. Optimization of treatment was necessary for 42% of patients with a clinical response in 80%. During follow-up, one severe adverse event was observed (dental abscess).

Conclusion : ustekinumab was effective in inducing and maintening a clinical and biological remission at short, medium and long-term (nearly fourth-fifth of patients). Ustekinumab was also effective for achieving long term endoscopical and morphological response. Ustekinumab should be considered to be an interesting, extended and safe therapeutic option in CD patients who are refractory to anti-TNF treatment.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disorder alternating between periods of disease activity and clinical remissions. It is essential to obtain long term deep remission to prevent complications and irreversible intestinal damage and disability (1–4) . Anti tumor necrosis factor (anti-TNF) agents such as infliximab and adalimumab have revolutionized the management of patients with moderate to severe CD after failure of conventional immunosuppressants (thiopurines and methotrexate). However, two-thirds of CD patients treated with anti-TNF agents will develop primary non response, loss of response or intolerance and required other treatment with different mechanism of action (5–9).

Ustekinumab is a human IgG1 kappa monoclonal antibody that targets the p40 subunit of interleukin IL-12 and IL-23 and inhibits T helper 1 and T helper 17 pathways implicated in the pathogenesis of CD. Ustekinumab was shown to be effective in inducing and maintaining a clinical response in CD patients who have failed anti-TNF (infliximab, adalimumab), and also in anti-TNF-naive patients in phase III placebo-controlled trials (UNITI trials) (9). Ustekinumab obtained a European Marketing Authorization in November 2016 for the treatment of CD with an intravenously induction followed by a subcutaneous maintenance treatment every 8 to 12 weeks.

The aim of the present study was to evaluate the long term of clinical, endoscopic and morphologic efficacy to ustekinumab in a large real-life monocentric cohort of CD patients, and to identify predictive factors of ustekinumab failure.

MATERIELS AND METHODS

I. Study design and patient population

We performed a retrospective and observational study in the tertiary referral centre of the Claude Huriez Hospital in Lille, France. Patients were included if they met the following criteria: (a) patients >18 years of age, (b) with a diagnosis of CD according to ECCO guidelines, (c) who received at least one intravenous injection of ustekinumab between June 2016 and December 2018, (d) and were followed at least three months. All the patients included in the study had an intravenous induction with a dose according to body weight (≤ 45kg: 130mg, >45kg to ≤ 55kg: 260mg, > 55kg to ≤ 85kg: 390mg and > 85 kg: 520mg), followed by 90mg subcutaneously every 8 or 12 weeks.

II. Data collection

The date of inclusion corresponded to the first administration of ustekinumab. Patient's demographic, clinical, biological, endoscopic and morphologic data were prospectively collected in the medical records "Sillage", and retrospectively reviewed.

The following characteristics were collected for each patient: gender, age at diagnosis, age at inclusion, disease duration, smoking status, Body Mass Index (BMI), CD location and phenotype, previous intestinal resections and prior exposure to CD treatment including conventional immunosuppressants (thiopurines, methotrexate), biologics: anti-TNF agents (infliximab, adalimumab, golimumab, certolizumab) and vedolizumab.

Concerning ustekinumab treatment: induction and maintenance doses, duration of ustekinumab treatment, association with an immunosuppressant or steroids at inclusion, biologic, endoscopic or morphologic findings at inclusion and during the follow up were also collected.

III. Outcome and definitions

Mains objectives were to evaluate (1) ustekinumab failure-free survival, (2) response to ustekinumab treatment (clinical, biological) at 8 weeks, 6 months, one year and at last news, , (3) predictive factors of failure to ustekinumab treatment at one year, (4) rate of endoscopic and/or morphologic response (5) failure of ustekinumab defined by the occurrence of surgery, hospitalisation and/or discontinuation therapy, (6) rate of ustekinumab optimization (dose adjustment, adjunction of an immunosuppressants or steroids), (7) ustekinumab safety (adverse events and severe adverse events occurred from the date of inclusion to the last news were recorded).

Clinical response and remission were defined in accordance with the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) definitions. Clinical response was defined by decrease in Harvey Bradshaw Index (HBI) of ≥3 points compared to baseline and clinical remission was defined by an HBI score of ≤4 points. Biological response was defined by a decrease of CRP and remission by a normalization of CRP level below 5mg/l, endoscopic response was defined by the resolution of deep ulcerations and endoscopic remission by the complete normalisation, except for residual apthous ulcers), morphologic response was defined by improvement in bowel wall thickness, inflammatory fat, mural blood flow and hyperenhancement compared to baseline imaging by physician global assessment and

morphological remission was defined by transmural healing (defined by normalisation of bowel wall thickness (BWT) of all inflamed segments by MR enterography).

IV. Statistical analysis

Descriptive data were presented as percentage for discrete data and medians with interquartile range (IQR) for continuous data. The Kaplan-Meier method was used to assess cumulative ustekinumab failure-free survival at 8 weeks, 6 months, one year and at the end of follow-up. Univariate analysis was performed to identify independent predictive factors of ustekinumab clinical failure and discontinuation or maintenance with corticosteroids at one year described by the odds ratio (OR) and 95% confidence interval (95%CI). $P<0.05$ was considered to be significant.

RESULTS

I. Baseline patient characteristics

From June 2016 to December 2018, 101 CD patients receiving ustekinumab induction were included. The baseline demographic and clinical characteristics are presented in Table 1. Sixty-six (65.3%) patients were woman, the median age at inclusion was 34.4 years old (IQR: 25.8-44.2) and the median duration from CD diagnosis to inclusion was 12.3 years (IQR: 6.3-17.7). The median BMI was 21.3 kg/m2, with 8 (8.8%) patients with a BMI over 30 Kg/m2 and 19 (20.9%) patients lower than 18 kg/m2. Most patients had ileocolonic CD (63/101, 62.4%) with a B2 or B3 phenotype (57/101, 56.4%). Forty-five (44.6%) patients had undergone prior intestinal resection. Eighty-three (82.2%) patients were previously exposed to thiopurines or methotrexate. All patients, except one, failed at least to one treatment anti TNF agent and 80 (80%) patients had failed at least two biological therapies. Thirty (29.7%) patients had previous exposure to vedolizumab. At inclusion, concomitant immunosuppressants (IS) were associated with ustekinumab in 46 patients (45.5%), concurrent steroids were used in 21 patients (20.8%). Twelve (11.9%) patients received both IS and steroids at inclusion. Ustekinumab was given for luminal CD in 77 (76.2%) patients, for perianal disease in 6 (5.9%) patients and 18 (17.9%) patients for both of them. All the patients in the study had an intravenous induction with a dose adapted to the weight: 130 mg: 2 (2%), 260 mg: 29 (28.7%), 390 mg: 62 (61.4%), 520 mg: 7 (7.9%). The patients were then treated according to 90 mg regimen every 8 weeks except for 2 (1.9%) every 12 weeks

At the time of ustekinumab introduction, median HBI score was 6 (IQR : 3.8-10) , median C-reactive protein was 12 mg/l (IQR : 5.7-22), twenty four (25.8%) patients had a CRP lower than 5mg/l and 69 (74.2%) had a CRP higher than 5mg/l.

Sixty-four (63.4%) patients had a colonoscopy in the year preceding ustekinumab induction and active endoscopic lesions were observed in 60 (63.4%) patients , including 41 with ulcerations and 19 with an inflammatory stricture. Sixty-one (60.4%) patients had an MR enterography: 40 (65.5%) had signs of inflammation and 11 (18.1%) patients a stricture.

Table 1: Demographic and clinical characteristics of included patients N = 101

Male, n (%)	35 (34.7)
Median age at the time of UST induction (years, IQR)	34.4 (25.8-44.2)
Median disease duration before UST (years, IQR)	12.3 (6.3-17.7)
Median weight, (IQR)	62.0 (53-74.3)
Median BMI (IQR), (Kg/m2)	21.3 (18.4-24.4)
BMI > 30 kg/m2, n (%)	8 (8.8)
BMI > 25 kg/m2, n (%)	17 (18.7)
BMI < 18 kg/m2, n (%)	19 (20.9)
Smoker status, n (%)	
Current smoker	28 (29.8)
Former smoker	9 (9.6)
Never smoker	57 (60.6)
Disease location (Montreal classification), n (%)	
L1	26 (25.7)
L2	12 (11.9)
L3	63 (62.4)
L4	17 (16.8)
Disease phenotype (Paris classification), n (%)	
B1	44 (43.6)
B2	21 (20.8)
B3	36 (35.6)
P	37 (36.6)
Previous intestinal resections, n (%)	45 (44.6)
Previous CD treatment, n (%)	
Immunomodulator therapy	
Thiopurines	77 (76.2)
Methotrexate	36 (35.7)
Biologic therapy	100 (99)
Infliximab	84 (83.2)
Adalimumab	89 (88.1)
Certolizumab	13 (12.9)
Golimumab	5 (5)
Vedolizumab	30 (29.7)
protocol	3 (3)
Previous biologic failure criteria, n (%)	
Primary non response	40 (39.6)
Secondary loss of response	91 (90)
Adverse effect/intolerance	51 (50.5)
Number of lines of biologic, n (%)	

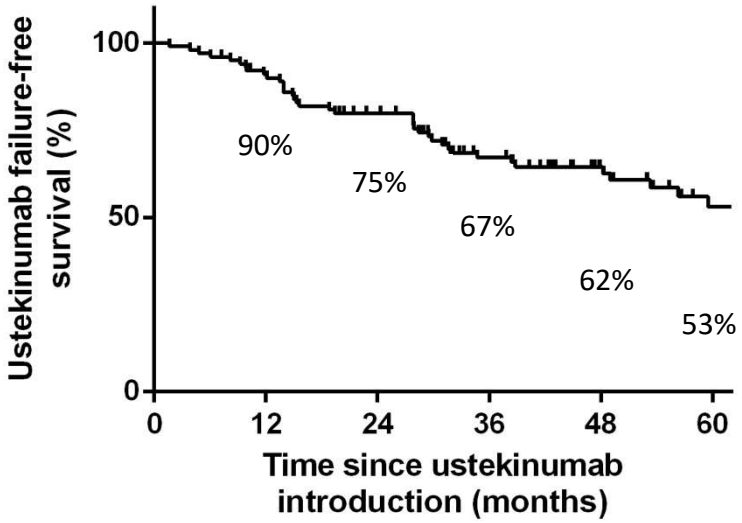
1, n(%)	19 (19)
2, n (%)	49 49)
>2, n(%)	32 (32)
Median C-reactive protein (mg/l, IQR) at UST introduction	12 (5.7-22)
CRP < 5mg/l n(%)	24 (25.8)
CRP > 5mg/l n(%)	69 (74.2%)
Median Harvey Bradshaw Index (IQR) at UST introduction	6 (3.8-10)
Concomitant immunosuppressant at inclusion, n (%)	46 (45.5)
Thiopurines	28 (60.9)
Methotrexate	17 (30.4)
Ciclosporine	1 (8.7)
Concomitant corticosteroids at inclusion, n (%)	21 (20.8)
Concomitant immuosuppressant and steroids at inclusion, n (%)	12 (11.9)
UST IV dosing, n (%)	
130 mg	2 (2)
260 mg	29 (28.7)
390 mg	62 (61.4)
520 mg	7 (7.9)
Median follow-up per patient, weeks (IQR)	77.1 (53.6-107.7)

II. Ustekinumab efficacy

A. Response to ustekinumab during maintenance therapy

One hundred and one CD patients were followed for a median of 77.1 weeks (IQR: 53.6-107.7). Patients were treated with ustekinumab for a median time of 65.9 weeks (IQR: 39-91.4). Ustekinumab failure-free survival in the 101 patients was 90% at one year, 67% at three years and 53% at 5 year after inclusion (Figure 1).

Figure 1: Kaplan-Meier survival curve of ustekinumab failure-free survival



Patients at risk	101	90	75	52	35	19

B. Clinical and biological ustekinumab efficacy

1. Evaluation at 8 weeks

At 8 weeks, clinical data was available for 74/101(73.3%) patients. Response and remission were observed for 13 (17.6%) and 36 (48.6%) patients, respectively. The median improvement in the HBI score was one point (IQR: 0-1).

Biological data was available for 53/101 (52.5%) patients; response and remission were observed for 17 (32.1%) and 26 (49.1%) patients.

2. Evaluation at 6 months

Among patients who were followed at 6 months (data was available for 69/89 (76.4%) patients), response and remission were observed for 6 (8.7%) and 47 (68.1%) patients, respectively. The median improvement in the HBI score was two points (IQR: 0-6).

At 6 months, biological data was available for 55/89 (61.8%) patients; response and remission were observed for respectively 26 (47.3%) and 18 (32.7%) patients.

3. Evaluation at one year

Among patients who were followed at one year (data was available for 72/79 (91.1%) patients), response and remission were observed for respectively three (4.2%) and 56 (77.7%) patients. The median improvement in the HBI score was 3 points (IQR: 0-6).

At one year, biological data was available for 54/79 patients; response and remission were observed for respectively 34 (62.9%) and 11 (20.3%) patient.

In univariate analysis, no predictive factors of ustekinumab maintenance with or without steroids at one year of treatment were identified (Tables 2 and 3).

Table 2: Predictive factors of ustekinumab maintenance at one year

Predictive factors	**Univariate odds ratio (95% CI)**	***p value***
Male	0.98 (0.42-2.38)	0.99
BMI > 30 Kg/m2	2.11 (0.43-10.24)	0.34
age at inclusion	1.21 (0.53-2.75)	0.65
Disease duration	1.55 (0.65-3.59)	0.29
Smoker status	0.95 (0.37-2.44)	0.92
Phenotype (B2-B3)	1,21 (0.49-2.59)	0.79
CD location (L1-L3)	0.86 (0.32-2.28)	0.76
Perineal disease	1.05 (0.45-2.46)	0.91
Previous resection	1.11 (0.49-2.55)	0.80

Concomitant immunosuppressant at time of ustekinumab introduction	1.76 (0.76-4.09)	0.18
Concomitant corticosteroids at time of ustekinumab introduction	0.84 (0.30-2.37)	0.75
C-reactive protein > 5mg/L	0.57 (0.22-1.51)	0.25
Colonoscopy during previous year	0.61 (0.26-1.44)	0.25
Endoscopic stenosis	1.91 (0.60-6.05)	0.26
MRI in previous year	1.51 (0.64-3.55)	0.34
MRI stenosis	0.74 (0.19-2.94)	0.67

Table 3: **Univariate logistic regression analysis of factors predicting ustekinumab maintenance with steroids at one year**

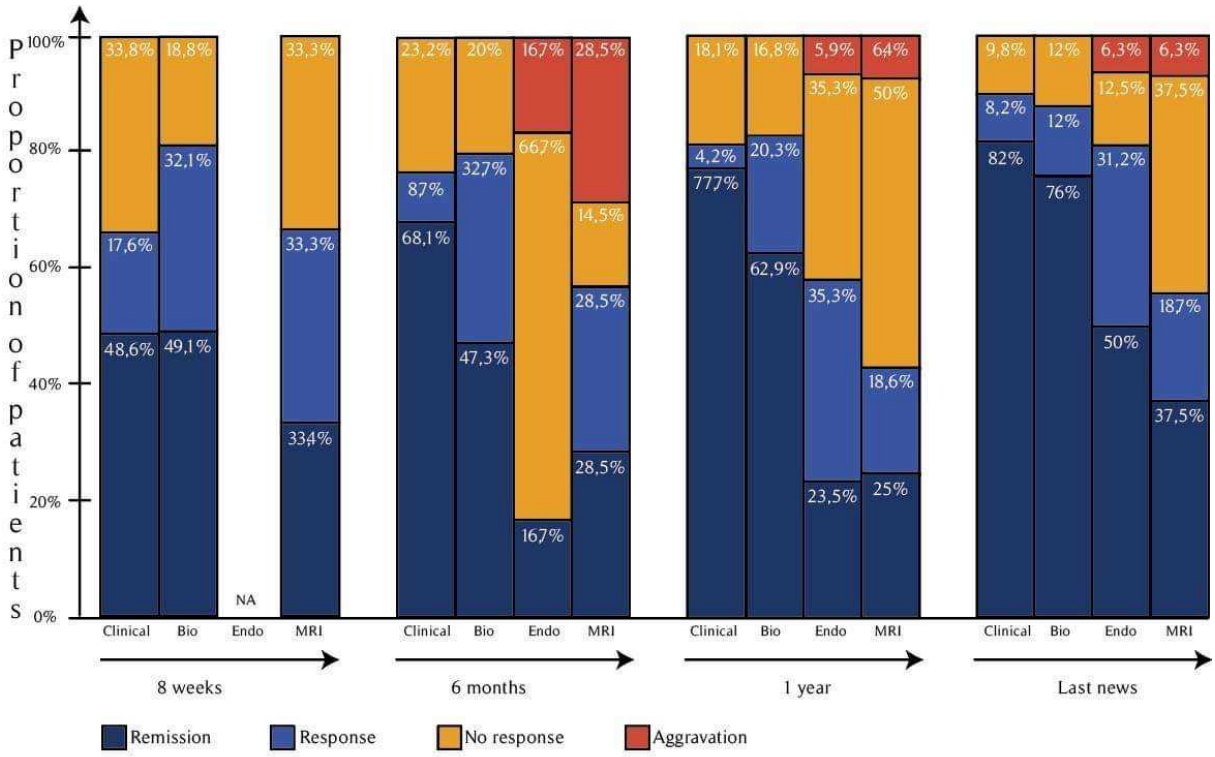
Predictive factors	**Univariate odds ratio (95% CI)**	***P value***
Male	0.83 (0.31-2.20)	0.71
BMI > 30	2.25 (0.45-11.13)	0.30
Age at inclusion	0.78 (0.31-1.97)	0.61
Disease duration	1.29 (0.51-3.23)	0.59
Smoker status	0.95 (0.34-2.65)	0.92
Phenotype (B2-B3)	1.13 (0.45-2.88)	0.79
CD location (L1-L3)	1.24 (0.40-3.82)	0.71
Perineal disease	1.84 (0.72-4.72)	0.19
Previous resection	0.63 (0.24-1.62)	0.33
Concomitant immunosuppressant at time of ustekinumab introduction	1.15 (0.46-2.89)	0.76
Concomitant corticosteroids at time of ustekinumab introduction	1.31 (0.44-3.91)	0.63
C-reactive protein > 5mg/L	1.32 (0.42-4.12)	0.63
Colonoscopy during previous year	0.51 (0.20-1.31)	0.15
Endoscopic stenosis	1.73 (0.47-6.37)	0.40
MRI during previous year	1.34 (0.52-3.47)	0.54
MRI stenosis	0.95 (0.22-4.21)	0.95

4. Evaluation at last news

Clinical data was available for 61/64 (95.3%) patients; response and remission were observed for respectively 5 (8.2%) and 50 (82%) patients. The median improvement in the HBI score was 4.5 points (IQR: 1-6).

Biological data was available for 50/64 patients: response and remission were observed for respectively 6 (12%) and 38 (76%) patients.

Figure 2: Rate of clinical, biological, endoscopical and morphological response observed at 8 weeks, 6 months, one year and at last news.



C. Endoscopic and morphologic ustekinumab efficacy

At the end of follow-up, 57 (56.4%) patients in the cohort had either endoscopic or morphologic evaluation of disease with a median time of 43.9 weeks (IQR: 28.7-101.6). Approximately 2/3 of patients (61.6%) achieved objective response and among them, 36.8% were in objectively defined remission.

III. Ustekinumab failure

Thirty-eight (37.6%) patients stopped ustekinumab treatment during follow-up: 31 (81.5%) for treatment failure, two (5.3%) for adverse event (one dental abscess and one unknown gynecological disease) one for remission and 4 for pregnancy. Among the 31 patients with ustekinumab failure, 19 (61.3%) patients required a hospitalization with a median time of 33.4 weeks (IQR: 12.8-64.9) and among them, 12 required a surgery with a median time of 30 weeks (IQR: 24-68). Nine (69.2%) patients had a resection and 4 (30.8%) patients had an anal drainage. No postoperative complications at 2 months was reported.

IV. Ustekinumab optimization

Forty-three patients (42.6%) required a dose intensification of ustekinumab during follow-up due to an initial lack of efficacy or a secondary decrease in efficacy. Forty (93%) patients were optimized to 90 mg per 4 weeks, one to 90 mg per 6 weeks and two were optimized to 90 mg per 8 weeks (initial dose to 90 mg per 12 weeks). The median optimization time was 20.4 weeks. The median time between optimization and clinical evaluation was 14 weeks; response and remission were observed for 6 (14%) and 29 (67.4%) patients, respectively. Biological data was available for 34 patients; response and remission were observed for 10 (30%) and 15 (44.1%) patients, respectively. Endoscopic data was

available for 14 patients; response and remission were observed for respectively 5 (35.7%) and three (21.4%) patients whereas 4 (28.4%) patients were in no endoscopic response and 2 (14.5%) in endoscopic aggravation. Morphologic data was available for 10 patients; response and remission were observed for three (30%) and three (30%) patients respectively, whereas 4 (40%) patients were in morphologic no response.

During the follow up, an immunosuppressant was introduced for 13 patients with a median time of 44 weeks (IQR: 27.5-62) after introduction of ustekinumab. for a lack of response. Introduction of immunosuppressant recaptured clinical response and remission for respectively one (7.7%) and 9 (69.2%) patients. Biological response and remission were observed for 3 (30%) and 6 (60%) patients. Only one of the two patients who subsequently had an endoscopy was in response. Two patients had a morphological evaluation after introduction of immunosuppressant with a response in both patients. Steroids are needed 11 patients with a median time of 28.3 weeks (IQR: 12.8-64.9).

V. Safety of ustekinumab treatment

An adverse event occurred in 11 patients (10.6%) (Table 4). Arthralgia and headache were the most frequent events, observed respectively for 5 and three patients. One patient presented with an allergic reaction (rash). Two other patients developed myalgia. Two patients stopped ustekinumab due adverse event (dental abscess and unknown gynecological disease).

No malignancies or deaths were reported during follow-up. No injection site reaction was observed.

Table 4: Adverse events

Adverse events related to ustekinumab among all treated patients n (%)	**n = 101**
Arthralgia	5 (4.9)
Headache	3 (2.9)
Allergic reaction	1 (0.99)
Patients with adverse event leading to UST withdrawal	2 (1.8)
Dental abscess	1 (0.99)
Unknown gynecological causes	1 (0.99)

DISCUSSION

This study reports the real-life experience of ustekinumab efficacy in a large cohort of 101 anti-TNF refractory CD patients, with a median time under treatment of almost 2 years. No predictive factors of ustekinumab efficacy at one year was identified with a long median of follow-up, 77.1 weeks (IQR: 53.6-107.7). We observed a high proportion of patients achieving clinical and biological response with a safe and well tolerated profile of ustekinumab. Sixty-one percent of patient achieving endsocpic and/or morphologic response at last news. More than 1/3 (43.6%) of patients required optimization treatment allowing a clinical and biological response in 80%.

Long term data on the outcome of ustekinumab efficacy are scarce. Previous long-term retrospective study on ustekinumab response in CD had a follow-up of 26.6 months. (4) The cumulative probability of ustekinumab maintenance was 80% at 12 months, 67% at 24 months and 59% at 36 months. In our study, we reported that ustekinumab treatment was maintained without loss of response or surgery in 90% of CD patients at one year, 67% at three years and 53% at 5 years. These higher rate of response to ustekinumab can be explained by the high proportion of patients refractory to previous biologic agents in the GETAID cohort (90% of patients were failed to two biologics versus 80% in our cohort). Two other retrospective studies also assessed the efficacy of ustekinumab in real-life practice in a cohort of 45 and 116 CD patients with a clinical response to ustekinumab in approximately 40% and a median follow-up with ustekinumab of 12 months and 10 months respectively (10,11) Preliminary results of the long-term extension phase of prospective studies showed clinical remission at weeks 92 in 74% of the patients receiving subcutaneous ustekinumab every 8 weeks. Our study reports the second longest follow-up period after the GETAID cohort with ustekinumab in CD patients with a median treatment duration of 16.5 months

(IQR: 9.8-22.9) with a composite assessment of response (clinical, biologic, endoscopic and morphologic) and showed that the clinical benefit of ustekinumab was associated with a biologic response in most patients. At one year, there was a clinical improvement in more than 4/5 of the patients who maintained ustekinumab with high rates of biological response (83.2%). In another cohort of 97 Spanish patients with CD responding to ustekinumab induction, Khorrami et al reported the cumulative probability for maintained clinical benefit to ustekinumab was 74% at 12 months, versus 81.9% in our studies (11).

The short and intermediate endoscopic and morphologic efficacy of ustekinumab has already been evaluated in CD but sufficient long-term data on the outcome of ustekinumab treatment in patients with refractory CD are lacking. Rutgeerts et al (12) have reported the evidence for the efficacy of ustekinumab for inducing endoscopic healing. Another study from Verstockt et al (13) reported a proportion of patients achieving endoscopic response (20.5%) or endoscopic remission (7.1%) were low at 24 weeks. We observed in our study a similar poor endoscopic remission in 16.7% of patients at 6 months. Only one retrospective study (14) assess the endoscopic and morphologic response to ustekinumab in CD with 69.6% and 21.7% of response respectively at one year (versus 58.8% and 43.6% at one year in our studies). Finally, we observed high rate of endoscopic and/or morphologic response to ustekinumab, over 60% after a median of follow-up of more than 65 weeks.

Only one study shown that concomitant immunosuppressant was associated with a clinical benefit to ustekinumab at 3 months. (15) Only a few studies have evaluated association between clinical response and patients BMI in CD. Wong et al reported, in a cohort of 254 CD patients (38/254; 14.9%; with a BMI > 30kg/m2) that BMI impacts ustekinumab drug levels, but no impacts clinical ustekinumab efficacy (16). In our study, ustekinumab was introduced in 8 (8.8%) patients with obesity (BMI > 30 kg/m2) and this factor was no associated with ustekinumab failure.

During follow-up, only 30% of patients stopped treatment due to loss of response. Among patients who stopped the treatment, we observed 60% of hospitalization, and among them, two-third required a surgery with a median time of 30 weeks (IQR: 24-68). This result highlight the effectiveness of ustekinumab but also the interest of optimizing treatment earlier. Two studies have reported that increasing the dose of ustekinumab was successful in two-thirds of patients with CD who lost response (17,18). In our studies, 43 (42.6%) patients were optimized with a median time evaluation after optimization of 14 weeks We observed a clinical response in 80% of patients including two-thirds of patients in remission. Currently, no data exists to identify which patients are more likely to benefit from dose escalation, and management of attenuated response is based on clinical judgment.

In the present study, ustekinumab was found to be safe and well tolerated with only one serious adverse even (dental abscess) and one unknown gynaecological event leading to ustekinumab withdrawal. These results are consistent with the current safety profile of long-term ustekinumab treatment in patients with psoriasis. The long-term data from randomised controlled trials evaluating tolerance to ustekinumab in patients with psoriasis after up to 5 years of follow-up did not report any increased risk of death, severe infection or malignancy (19).

These results clearly underline the sustained efficacy of new molecules in CD such as ustekinumab, providing new medical therapeutic options in refractory patients to change disease course and prevent bowel damage and disability.

Several limitations to our study have to be acknowledged, mainly related to its restrospective evaluation. First, some factors potentially impacted ustekinumab efficacy such as adherence to therapy could not be assessed. Second, the study suffers from a lack of

endoscopical and morphological evaluation since only 31 patients had at least one colonoscopy and 26 at least one MR enterography after ustekinumab introduction. We also failed to identify predictors of long-term efficacy of ustekinumab, maybe due to the limited number included in study. Finally, ustekinumab through level and the rate of antibodies against ustekinumab were not available. However, recent data reported that monitoring of ustekinumab drug concentrations were not associated with clinical outcome but were only associated with biomarker reduction and endoscopic response to ustekinumab with a through concentration above 4.5 μg/mL (20) Along this, monitoring ustekinumab concentration is not currently recommended in practice.

CONCLUSION

In this large unicentric retrospective cohort of refractory CD patients, ustekinumab was effective in inducing and maintaining clinical and biological remission at long-term in nearly 4/5 of patients. Ustekinumab was also effective for achieving long term endoscopical and morphological response. With a very good safety profile, these results underline that ustekinumab represents an efficient therapeutic option at long term in CD patients refractory to anti-TNF treatment.

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Titre de la thèse : Évaluation à long terme de l'efficacité et de la tolérance de l'ustekinumab dans la maladie de Crohn réfractaire

Thèse - Médecine - Lille 2020
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Mots-clés : Maladie de Crohn réfractaire ; ustekinumab ; suivi à long terme

Contexte : L'ustekinumab est un anticorps monoclonal humanisé dirigé contre la sous-unité p40 commune des interleukines 12 et 23 ayant montré son efficacité en traitement d'induction et de maintenance dans la maladie de Crohn (MC) luminale. L'objectif de notre étude était d'évaluer l'efficacité et la tolérance de l'ustekinumab par voie sous-cutanée dans une cohorte de malades atteints de MC réfractaire aux anti-TNF. **Méthodes :** De Juin 2016 à 2018, nous avons mené une étude rétrospective et observationnelle dans le service des maladies de l'appareil digestif du centre hospitalier et universitaire de Lille. Tous les malades ayant reçu au moins une injection d'ustekinumab par voie intra-veineuse pour une MC réfractaire et suivis au moins trois mois ont été inclus. Les objectifs principaux étaient d'évaluer le maintien de l'ustekinumab, la réponse clinique, biologique, endoscopique et morphologique, les facteurs prédictifs de maintien à un an, ainsi que la tolérance à l'ustekinumab.

Résultats: 101 patients ont été inclus dans l'étude avec un suivi médian de 77.1 semaines (IQR: 56.3-107.7). La probabilité cumulée de maintenir une réponse clinique était de 90% à 12 mois, 67% à 3 ans et 53% à 5 ans après introduction. Après un an de traitement, une réponse clinique et biologique était obtenue respectivement chez 59 (81.9%) et 55 (83.2%) patients. Aux dernières nouvelles, une réponse endoscopique et/ou morpholgique était obtenue pour 61.4% des patients. Nous n'avons pas retrouvé de facteurs prédictifs d'échec à l'ustekinumab à un an. L'optimisation a été nécessaire pour 42% des patients, permettant leur amélioration dans 80% des cas. Durant l'étude, un seul événement grave a été déclaré (abcès dentaire).

Conclusion : L'ustekinumab s'est révélé efficace pour induire et maintenir une rémission clinique et biologique à court, moyen et long terme (près de 80% des patients). L'ustekinumab s'est également avéré efficace pour obtenir une réponse endoscopique et morphologique à long terme. L'ustekinumab doit être considéré comme une option thérapeutique intéressante et bien tolérée chez les patients atteints de MC réfractaire au traitement anti-TNF.

Composition du Jury :

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