Italian real-life study on effectiveness and safety of Ustekinumab compared to Vedolizumab in elderly patients with Crohn's disease (CD)

Study code	
Protocol title	**Italian real-life study on effectiveness and safety of Ustekinumab compared to Vedolizumab in elderly patients with Crohn's disease (CD)**
Phase of development	**4**
Study Promoter	Prof. Walter Fries and Dr Anna Viola Affiliation: UOSD Malattie Intestinali Croniche AOU Policlinico G.Martino, Via Consolare Valeria 1, 98127, Messina Tel. +390902212387 Mail: fwalter@unime.it ; annaviola88@gmail.com
Study Design	Retrospective case-control study
Study Population	**Group 1.** All patients with CD aged ≥65 years who started Ustekinumab in Italy within May 2019 able to express a written informed consent for this study, are eligible. **Group 2 (control group).** All patients with CD aged < 65 years who started Ustekinumab in Italy within May 2019 able to express a written informed consent for this study, are eligible. Patients of control group are matched 1:2 for sex, disease duration and side, disease activity and number of previous therapies. **Group 3 (control group).** Patients with CD aged > 65 years treated with Vedolizumab and matched 1:2 for sex, disease duration and side and disease activity.
Primary endpoints	• Persistence on therapy of the two groups • Ustekinumab safety profile (incidence of adverse events, AEs)
Secondary endpoints	• Steroid-free clinical remission at week 12, 24 and 52 • Clinical and biochemical response at 12, 24 and 52 weeks; • Endoscopic remission (mucosal healing) during follow-up;

	• rate of surgery through study; • rate of IBD-related hospitalization; • predictors of clinical response, clinical and endoscopic remission at each timepoints; • predictors of treatment discontinuation
Investigational product (1)	Ustekinumab 90 mg ev/sc
Investigational product (2)	Vedolizumab 300 mg ev All concomitant therapies administered, according to medical judgement
Number of Subjects and centers	
Coordinator center	Prof. Walter Fries and Dr Anna Viola Affiliation: UOSD Malattie Intestinali Croniche AOU Policlinico G.Martino, Via Consolare Valeria 1, 98127, Messina
Ethic committee of coordinator center	COMITATO ETICO AOU POLICLINICO G. MARTINO

Background.

Ustekinumab (Stelara®, Janssen Biotech Inc., Horsham, PA, USA) is a monoclonal antibody targeting the p40 subunit of interleukin (IL)-12 and IL-23. It has been recently approved and used to treat moderate to severe active Crohn's disease (CD) in adult patients unresponsive or intolerant to

anti-TNFα agents or patients in which these biologic agents are contraindicated. It was available in 2016 in the United States and 2017 in Europe. The phase IIb trial CERTIFY showed short-term clinical response in a cohort of anti-TNFs experienced patients. The following three phase III trials (UNITI -1, UNITI-2 and IM-UNITI) showed effectiveness of Ustekinumab in induction and maintenance of remission in anti-TNF refractory and anti-TNF naive CD patients.(1-4) However, patients enrolled in clinical trials are not entirely representative of those treating in real life and elderly patients are often underrepresented in RCTs. In the last years several observational real-life studies from Europe confirmed external validity of RCTs with a good effectiveness and safety of Ustekinumab in refractory CD population.(5) However real-life data on Ustekinumab in elderly patients are scarce. A recent work, available only as abstract form, showed a good safety and effectiveness of Ustekinumab in elderly patients (patients aged over 65 years was compared with younger) but a delayed time to response compared to younger patients. (6) The aim of the present study is to assess effectiveness and safety of Ustekinumab in elderly patients with CD compared with younger and compared with patients treated with Vedolizumab.

Study design and patient population.

Male and female subjects with a diagnosis of moderately to severely active CD, who started Ustekinumab within June 2019 in Italy, able to express a written informed consent for this study, are eligible. Physicians will perform a retrospective review of original documents, collecting data from the first Ustekinumab dose to June 2020. All data will be inserted in a common shared electronic database. For each patient aged over 65 years, data of two patients younger matched for sex, disease duration and side, disease activity and number of previous therapies will be collected togheter with data of two patients treated with Vedolizumab.

Outcomes.

<u>Primary outcomes</u>

- Persistence on therapy of the four groups at 12 months

<u>Secondary outcomes</u>

- Ustekinumab safety profile (incidence of adverse events, AEs)
- Steroid-free clinical remission at week 12, 24 and 52
- Clinical and biochemical response at 12, 24 and 52 weeks;

- Endoscopic remission (mucosal healing) at 12 months;
- rate of surgery through study;
- rate of optimization
- rate of IBD-related hospitalization;
- predictors of clinical response, clinical and endoscopic remission at each timepoints;
- predictors of treatment discontinuation

Definitions.

Clinical activity is evaluated using Harvey Bradshaw index (HBI) with classification of CD activity into remission (HBI <5), mild (HBI 5-7), moderate (HBI 8-16) and severe (HBI>16).

Clinical response in defined a reduction of Harvey-Bradshaw Index (HBI) ≥ 3 compared with baseline.

Steroid free remission is defined as a clinical disease activity with an HBI ≤ 5 points without any kind of steroids.

Loss of response (LOR) is defined as worsening of patient's symptoms together with serologic evidence of inflammation and/or endoscopic findings

Primary failure (PF) is defined as the persistence of patient's symptoms together with serologic evidence of inflammation at the end of induction period.

Endoscopic activity is evaluated using SES-CD score (≤2 remission, 3-6 mild activity, 7-15 moderate activity, > 15 severe activity). Endoscopic remission will be evaluated only for patients with baseline endoscopic (window for both asssessment ± 3 months).

Optimization is defined as the introduction of immunomodulators (azathioprine, 6-mercapthopurine or methotrexate) because of loss of response or the optimization of UST dose from 90 mg every 12 wks to 8 wsk. Optimization for Vedolizumab is defined as the introduction of immunomodulators or reduction of dose interval.

For patients with concomitant spondiloarthritis we defined:

1) Absence of response: no improvement or worsening of symptoms

2) Response: absence of all clinical symptoms.

Data collection.

At baseline the following data will be collected for all groups: gender, age at start of treatment, age at diagnosis, BMI, smoking status, date of diagnosis, extension of disease (according to Montreal classification), CD phenotype, perianal disease, clinical activity , endoscopic activity , previous and concomitant therapies, extra-intestinal manifestations, previous history of CD-related surgery, numbers and type of previous biologics (including reason for discontinuation). Concomitant diseases were assessed for each patient and expressed as the Charlson comorbidity index (CCI). (7) Data on previous history of cancer will be also collected.

Follow-up data including HBI, response and steroid-free remission, SES-CD, CRP and FC data were collected, when available, according to each routine clinical practice. All adverse events (AEs) were recorded together with causes of discontinuation.

Statistical analysis.

Descriptive statistics will include the calculation of mean values with standard deviation, (SD) or of median value with interquartile ranges (IQR) for all continuous variables. The categorical variables will be summarized using absolute frequencies and percentages. The Kaplan-Meier method will be used to assess persistence on treatment. Proportional Cox risk models will be estimated to assess independent predictors for treatment discontinuation. Univariate and multivariate logistic regression analyses will be performed to identify factors predictive of steroid-free clinical and endoscopic remission at each time-point.

Expected results.

To our knowledge this is the first study on Ustekinumab compared to Vedolizumab in elderly CD population in Italy. We expected to provide a good safety profile in this setting of patients compared to younger population. The assessment of risk factor for treatment discontinuation and for lack of remission could help to understand the better position on treatment algorithm of this drug.

Data

Baseline

Center	Sequential number
Patient code	Sequential number
Gender	1F 2 M
Date of birth	dd/mm/year
Age	Years
BMI	Kg/m
Date of diagnosis	dd/mm/year
Age at diagnosis	Years
Smoking status	0 never 1 current 2 former
Extension/localization of disease	according to Montreal classification
CD phenotype	1 B1 2 B2 3 B3
Perianal disease	0 no 1 yes
Concomitant disease	According to Charlson Comorbidity Index
Previous history of cancer	0 no 1 yes (free text)
Concomitant medications	Free text
Extension/localization of disease	according to Montreal classification
Extra-intestinal manifestation	0 no 1 skin 2 spondiloarthritis 3 ocular 4 other
Spondiloarthritis	1 axial active 2 active peripherals 3 axial/peripherals inactive
Disease Duration	Years
Previous CD surgery	0 no 1 yes
Number of previous biologics	Sequential number
Type of previous biologics	1 Infliximab 2 Adalimumab 3 Vedolizumab
Reason for stop 1st anti-TNF	1 Adverse event 2 Primary failure 3 secondary failure
Reason for stop 2nd anti-TNF	1 Adverse event 2 Primary failure 3 secondary failure
Reason for stop Vedolizumab	1 Adverse event 2 Primary failure 3 secondary failure

Concomitant immunomodulators	0 no 1 AZ 2 6MP 3 MTX
Data start Ustekinumab	dd/mm/year
Data start Vedolizumab	dd/mm/year
Steroidal bridge therapy	0 none 1 yes
Clinical activity	According to Harvey-Bradshaw
Endoscopic activity	According to endoscopic SES-CD
CRP	mg/l
Faecal calprotectin	g/Kg

Week 8/12

Steroid free remission	0 no 1 yes
Response	0 no 1 yes
Steroidal therapy	0 no 1 yes
Clinical activity	According to Harvey-Bradshaw
Endoscopic activity	According to endoscopic SES-CD
CRP	mg/l
Faecal calprotectin	g/Kg
Adverse events	0 no 1 yes
Type of AE	Free text
IBD related surgery	0 no 1 yes
Optimization with IMM	0 no 1 yes
Concomitant immunomodulators	0 no 1 AZ 2 6MP 3 MTX
Treatment discontinuation	0 no 1 yes
Reason for discontinuation	1 primary failure 2 secondary failure 3 adverse events 4 lost to follo-up 5 other
Spondiloarthritis	1 response 0 no response

Week 24

Steroid free remission	0 no 1 yes
Response	0 no 1 yes
Steroidal therapy	0 no 1 yes
Clinical activity	According to Harvey-Bradshaw
CRP	mg/l
Endoscopic activity	According to endoscopic SES-CD
Faecal calprotectin	g/Kg
Adverse events	0 no 1 yes
Type of AE	Free text
IBD related surgery	0 no 1 yes
Optimization with IMM	0 no 1 yes
Concomitant immunomodulators	0 no 1 AZ 2 6MP 3 MTX
Treatment discontinuation	0 no 1 yes
Reason for discontinuation	1 primary failure 2 secondary failure 3 adverse events 4 lost to follo-up 5 other
Spondiloarthritis	1 response 0 no response

Week 52

Steroid free remission	0 no 1 yes
Response	0 no 1 yes
Steroidal therapy	0 no 1 yes
Clinical activity	According to Harvey-Bradshaw
CRP	mg/l
Endoscopic activity	According to endoscopic SES-CD
Faecal calprotectin	g/Kg
Adverse events	0 no 1 yes
Type of AE	Free text
IBD related surgery	0 no 1 yes
Concomitant immunomodulators	0 no 1 AZ 2 6MP 3 MTX
Optimization with IMM	0 no 1 yes
Treatment discontinuation	0 no 1 yes
Reason for discontinuation	1 primary failure 2 secondary failure 3 adverse

	events 4 lost to follo-up 5 other
Spondiloarthritis	1 response 0 no response

End follow-up

Optimization	0 no 1 yes
Response	0 no 1 yes
Endoscopic activity	According to endoscopic SES-CD
Mucosal healing	0 no 1 yes
Data end follow-up	Dd/mm/year
Lost to follow-up	0 no 1 yes
Death	0 no 1 yes

References.

1. Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med. 2012;367(16):1519-28.

2. Sandborn WJ, Feagan BG, Fedorak RN, Scherl E, Fleisher MR, Katz S, et al. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. Gastroenterology. 2008;135(4):1130-41.

3. Simon EG, Ghosh S, Iacucci M, Moran GW. Ustekinumab for the treatment of Crohn's disease: can it find its niche? Therap Adv Gastroenterol. 2016;9(1):26-36.

4. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease. N Engl J Med. 2016;375(20):1946-60

5. Macaluso FS, Maida M, Ventimiglia M, Cottone M, Orlando A. Effectiveness and safety of Ustekinumab for the treatment of Crohn's disease in real-life experiences: a meta-analysis of

observational studies. Expert Opin Biol Ther. 2020;20(2):193–203. doi:10.1080/14712598.2020.1707800

6. Garg R, Aggarwal M, Regueiro MD, Click BH, Ustekinumab is safe in elderly Crohn's disease patients. Sa1841; DDW 2020

7. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.