"Italian real-life study evaluating the long-term effectiveness of Vedolizumab for the treatment of Inflammatory Bowel Disease (IBD)"

Study code	**LIVE (Long-term Italian Vedolizumab Effectiveness)**
Protocol title	**"Italian real-life study evaluating the long-term effectiveness of Vedolizumab for the treatment of Inflammatory Bowel Disease (IBD)"**
Phase of development	**4**
Study Promoter	Prof. Alessandro Armuzzi and Dr Daniela Pugliese Affiliation: UOC Medicina Interna e Gastroenterologia Presidio Columbus Fondazione Policlinico Gemelli Università Cattolica del Sacro Cuore, Roma Tel. +39063503357 Mail: alearmuzzi@yahoo.com ; danipug@libero.it
Study Design	Multicenter, observational, retrospective/prospective
Study Population	All patients, who started Vedolizumab in Italy within June 2017, able to express a written informed consent for this study, are eligible.
Primary endpoints	The primary objectives are to evaluate: - the cumulative Vedolizumab drug persistence, defined through study as discontinuation due to lack of benefit, loss of response or adverse events; - Vedolizumab safety profile
Secondary endpoints	To define the proportion of patients achieving: • Steroid-free clinical remission at 6, 12, 18 and 24 months, stratifying patients according to anti TNF-α previous exposure; • Sustained clinical remission trough study; Endoscopic remission (mucosal healing) during follow-up; To assess: • change in C-reactive protein and faecal calprotectin levels at 6, 12, 18 and 24 months; • rate of surgery through study; • rate of IBD-related hospitalization; To explore needs for:

	• optimization; • steroids bridge therapy; To assess predictors of clinical remission at each timepoints; To explore effectiveness and safety of Vedolizumab in specific subgroups of patients, including aged ones (> 65 years old) and patients with a previous history of cancer.
Investigational product (1)	Vedolizumab 300 mg
Investigational product (2)	All concomitant therapies administered, according to medical judgement
Number of Subjects and centers	1500 patients, 40 centers
Coordinator center	Prof Alessandro Armuzzi UOC Medicina Interna e Gastroenterologia Presidio Columbus Fondazione Policlinico Gemelli Università Cattolica del Sacro Cuore Roma
Ethic committee of coordinator center	COMITATO ETICO INDIPENDENTE UNIVERSITA' CATTOLICA DEL SACRO CUORE FONDAZIONE POLICLINICO GEMELLI

Background

Vedolizumab is a fully human IgG1k monoclonal α4β7antibody, blocking leukocyte trafficking to the gut mucosa, approved for treatment of both moderately-to-severely active Crohn's disease (CD) and Ulcerative Colitis (UC). In the phase III GEMINI program, Vedolizumab demonstrated efficacy in inducing and maintaining remission in both diseases.[1-2] Moreover, Vedolizumab showed a favorable profile with low incidence rates of serious infections, infusion-related reactions and malignancies over a 5 years treatment period.[3-4] Notably, the GEMINI program included (for the first time for clinical trials in IBD with biologics) aged patients (up to 80 years old).

However, patients enrolled in clinical trials are not entirely representative of those encountered in the clinical practice setting. To date, several real-world data series have been published demonstrating efficacy and safety comparable to that reported in the randomized controlled trials. However, most of them included a small number of patients and a limited follow-up. The aim of our study is to evaluate the effectiveness and safety of Vedolizumab in

the largest real-life series, with a follow-up on therapy up to 2 years. Moreover, the long-term safety will be evaluated in a specific subgroup of patients, including aged ones (> 65 years old) and patients with a previous history of cancer.

Study design and patient population

Male and female subjects with a diagnosis of moderately to severely active UC or CD, who started Vedolizumab within June 2017 in Italy, able to express a written informed consent for this study, are eligible.

This observational study includes two phases:

1) Fist phase: retrospective

Physicians will perform a retrospective review of original documents, collecting data from the first Vedolizumab dose to June 2018.

All data will be inserted in a common shared electronic database.

The first deadline for preliminary analysis will be on 15 July 2018.

2) Second phase: prospective

From 01 July 2018 to 30 June 2019 (the end of the study), data will be prospectively collected, using the same database.

The last deadline for inserting data will be on 15 July 2019.

Outcomes

The primary objectives are to evaluate in clinical practice:

1. the cumulative Vedolizumab drug persistence, defined through study as discontinuation due to lack of benefit, loss of response or adverse events;
2. Vedolizumab safety profile

The secondary objectives are:

- To define the proportion of patients achieving:
  - Steroid-free clinical remission at 6, 12, 18 and 24 months, stratifying patients according to anti TNF-α previous exposure

  - Sustained clinical remission trough study;
  - Endoscopic remission (mucosal healing) during follow-up;
- To assess change in C-reactive protein and faecal calprotectin levels at 6, 12, 18 and 24 months;
- To explore needs for:
  - optimization;
  - steroids bridge therapy;
- To assess predictors of clinical remission at each timepoints;
- To explore effectiveness and safety of Vedolizumab in specific subgroups of patients, including aged ones (> 65 years old) and patients with a previous history of cancer.

Definitions and cut-offs

Steroid-free clinical remission is defined as:

- Harvey-Bradshaw index of ≤4 for CD patients without oral steroids for at least 6 months;

- Partial Mayo score of ≤2, with no subscore > 1 for UC patients without oral steroids for at least 6 months.

Sustained clinical remission is defined as clinical remission at 6, 12, 18 and 24 months.

Endoscopic remission (mucosal healing) is defined as:

- SES-CD ≤2 for CD patients;

- endoscopic Mayo subscore ≤1 for UC patients.

The cut-offs of normal CRP and FC concentration are 5 mg/L and 50 mg/Kg, respectively.

Optimization is defined as the reduction of the interval between infusions from 8 to 4 weeks because of loss of response.

For CD patients, rate of extra-infusion at week 10 was also recorded.

Bridge therapy is defined as a concomitant steroidal therapy, maintained through the induction period.

Data collection

Baseline data collected include: gender, date of birth, weight, smoking status, type of disease (CD and UC), date of diagnosis, extension of disease (according to Montreal classification),

clinical activity (partial Mayo Score and Harvey-Bradshaw), endoscopic activity, previous and concomitant therapies, extra-intestinal manifestations, date of starting Vedolizumab, CRP and FC.

Follow-up CRP and FC data were collected, when available, according to each routine clinical practice.

Materials and methods

For all eligible patients, physicians will perform a retrospective review of medical records. Collected data will be inserted in a common shared database (Appendix 1). All data are collected anonymously.

Statistical analysis

Baseline characteristics will be analysed with standard descriptive statistics. The Kaplan-Meier method was used to assess Vedolizumab drug continuation over time. The proportions of patients in steroid-free clinical remission at each time-point and endoscopic remission were computed using the Pearson chi-squared test. Univariate and multivariate logistic regression analyses will be performed to identify factors predictive of steroid-free clinical remission at each time-point.

Expected results

This study could represent the largest cohort of patients outside of the registry trials treated with vedolizumab and hence could provide real-world context to the use of vedolizumab in clinical practice. Furthermore, the analysis of potential predictive factors of durability of

vedolizumab treatment could improve appropriate positioning of it in the treatment algorithms

References

1) Feagan BG, Rutgeerts P, Sands BE, et al.; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013 Aug 22;369(8):699-710. doi: 10.1056/NEJMoa1215734. PubMed PMID: 23964932.
2) Sandborn WJ, Feagan BG, Rutgeerts P,et al.; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013 Aug 22;369(8):711-21. doi:10.1056/NEJMoa1215739. PubMed PMID: 23964933.
3) Bye WA, Jairath V, Travis SPL. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. Aliment Pharmacol Ther. 2017 Jul;46(1):3-15. doi: 10.1111/apt.14075. Epub 2017 Apr 27. Review. PubMed PMID:28449273.
4) Colombel JF, Sands BE, Rutgeerts P, et al.The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut. 2017 May;66(5):839-851. doi: 10.1136/gutjnl-2015-311079.

Appendix 1

BASELINE

Center	Sequential number
Patient code	Sequential number
Gender	0 F 1 M
Date of birth	dd/mm/year
Type of disease	0 CD 1 UC
Date of diagnosis	mm/year
Extension/localization of disease	according to Montreal classification
Weight	Kg
Smoking status	0 never 1 current/ex
Extra-intestinal manifestations	0 no 1 skin 2 arthritis 3 ocular 4 other
Previous exposure to IMM	0 no 1 yes
Previous exposure to anti TNF-alpha	0 no 1 yes
Date of starting Vedolizumab	dd/mm/year
Clinical activity	According to partial Mayo Score and Harvey-Bradshaw
Endoscopic activity	According to endoscopic Mayo Score and SES-CD
Concomitant therapies	0 none, 1 5-ASA, 2 IMM
Steroidal bridge therapy	0 none 1 yes
CRP	mg/l
FC	g/Kg

6 MONTHS

Clinical activity	According to partial Mayo Score and Harvey-Bradshaw
Endoscopic activity	According to endoscopic Mayo Score and SES-CD
Concomitant therapies	0 none, 1 5-ASA, 2 IMM 3 steroids
CRP	mg/l
FC	g/Kg
Optimization	0 no 1 yes
Adverse events	0 no 1 yes
Type of AEs	description
Surgery	0 no 1 yes
Hospitalization	0 no 1 yes

12 MONTHS

Clinical activity	According to partial Mayo Score and Harvey-Bradshaw
Endoscopic activity	According to endoscopic Mayo Score and SES-CD
Concomitant therapies	0 none, 1 5-ASA, 2 IMM 3 steroids
CRP	mg/l
FC	g/Kg
Optimization	0 no 1 yes
Adverse events	0 no 1 yes
Type of AEs	description
Surgery	0 no 1 yes
Hospitalization	0 no 1 yes

18 MONTHS

Clinical activity	According to partial Mayo Score and Harvey-Bradshaw
Endoscopic activity	According to endoscopic Mayo Score and SES-CD
Concomitant therapies	0 none, 1 5-ASA, 2 IMM 3 steroids
CRP	mg/l
FC	g/Kg
Optimization	0 no 1 yes
Adverse events	0 no 1 yes
Type of AEs	description
Surgery	0 no 1 yes
Hospitalization	0 no 1 yes

24 MONTHS

Clinical activity	According to partial Mayo Score and Harvey-Bradshaw
Endoscopic activity	According to endoscopic Mayo Score and SES-CD
Concomitant therapies	0 none, 1 5-ASA, 2 IMM 3 steroids
CRP	mg/l
FC	g/Kg
Optimization	0 no 1 yes
Adverse events	0 no 1 yes
Type of AEs	description
Surgery	0 no 1 yes
Hospitalization	0 no 1 yes