# TITLE: “Risk of relapse and retreatment success after vedolizumab discontinuation in IBD patients in long-standing remission”

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## ABSTRACT

AIMS: to investigate the risk of relapse and retreatment success in IBD patients that discontinue vedolizumab due to sustained steroid-free remission.

METHODS: this will be a prospective observational study in which two groups of patients in sustained remission will be formed, i.e., patients stopping vedolizumab and patients continuing the treatment. Differences regarding rates of disease flares, IBD-related hospitalisations and surgeries will be analysed. The rate of retreatment success in patients presenting a flare after discontinuation will also be recorded. In addition, potential predictive factors of disease relapse will be investigated to provide future guidance on the patient profile that might benefit the most from intermittent VDZ treatment. The study will last 3 years in total, with the first year dedicated to patient inclusions.

ANTICIPATED IMPACT: only few data are currently available regarding intermittent treatment with vedolizumab. Therefore, this study may provide insights on when to interrupt this biologic with high probability of maintaining remission, while also showing high-risk features that would suggest against stopping the treatment. The use of treatment cycles may represent an impactful cost reduction for our healthcare systems as well as a decrease of potential side effects that are an inevitable consequence of years of immunosuppression.

## INTRODUCTION

An increasing number of biological agents and small molecules are available for the treatment of inflammatory bowel disease (IBD). The chronic nature of IBD and the fear of severe relapses in case of biological discontinuation has pushed the duration of immunosuppressive therapies to many years. On the other hand, the concerns about potential side effects and the costs for the healthcare society should also be considered

and treatment discontinuation suggested in selected patients with sustained deep remission.

It is currently known that stopping anti-TNFs after a period of sustained remission leads to disease flare in about half of the patients after one year,[1,2] and that primary non-response to anti-TNFs is associated with inferior response rates to second-line biological agents.[3] However, some evidence has shown that as high as 88% of patients may regain disease control when retreated with the same drug.[4] Focusing on "treatment cycles", in the last few years the BIOCYCLE Team has explored the field of intermittent use of either anti-TNFs or immunosuppressants in Crohn's disease (CD) patients that were treated with combination therapy (HORIZONE 2020 Grant, https://cordis.europa.eu/project/id/633168) with the aim of investigating the short- and long-term outcomes of treatment de-escalation. In their landmark trial, the authors showed that withdrawal of immunosuppressant should be considered as a preferable strategy over infliximab discontinuation in case of treatment de-escalation.[5]

To date, none or scarce data are available for biological agents other than anti-TNFs. Vedolizumab (VDZ), the first non-anti-TNF agent approved for the treatment of IBD, is being used since 2014 but only two recent papers have evaluated the effect of its discontinuation. The GETAID-Vedo-STOP study is a retrospective study on 95 IBD patients who discontinued VDZ after achieving at least 3 months of steroid-free clinical remission: in this cohort, 64% of these patients experienced a relapse after less than a year[6]. However, remission was not the only reason for drug withdrawal in many patients, as pregnancy accounted for 39% of discontinuations and safety concerns were present in approximately one fourth of patients. Interestingly, VDZ retreatment was effective in 71% of flares.[6] The POLONEZ study is a prospective study conducted in Poland, in which 100 patients with active ulcerative colitis (UC) were treated with VDZ for 54 weeks; the biological treatment was then stopped due to national reimbursement regulations and patients followed thereafter.[7] Among patients who achieved clinical remission by week 54 (n = 61), as high as 37% relapsed within 26 weeks after discontinuation.[7] These small cohorts represent very limited data to draw conclusions and the recently published ECCO Topical Review on the matter also concluded that "the risk of relapse and re-treatment success after ustekinumab or vedolizumab discontinuation in patients with Crohn’s disease is relatively unknown".[8] Therefore, more data are needed on this subject with prospectively conducted studies and larger groups of patients.

## OBJECTIVES

Considering the limited evidence on the topic, the objective of this project is to investigate the risk of relapse and retreatment success after VDZ discontinuation in IBD patients who achieved sustained steroid-free remission. Particularly, this strategy will be compared to a control group of patients continuing VDZ treatment to assess any differences regarding rates of disease flares, IBD-related hospitalisations and surgeries. In addition, potential predictive factors of disease flares will be investigated to provide future guidance on the patient profile that might benefit the most from intermittent VDZ treatment with lower risk of disease relapse.

## METHODOLOGY

This will be a multicentre prospective observational study to be conducted in the Italian Centres affiliated to the "*Italian Group for the study of Inflammatory Bowel Disease*" (IG-IBD). An open call will be sent out through the IG-IBD platform for local recruitments in Italy, with the possibility to extend the study to the other European IBD Societies whose Centres want to contribute to the study. The full duration of the project is supposed to be 3 years: patient inclusions will be possible during the first year, allowing for a minimum follow-up of (ideally) 24 months with constant and periodic updates during the study period.

### 1. Study population

IBD patients treated with VDZ who achieved *sustained remission** (as specified below) will be included.

Inclusion criteria will be the following:

1. Established diagnosis of CD or UC.
2. ***Sustained remission**** with no flare of symptoms for the previous 6 months
3. Stable VDZ maintenance dose (every 8 weeks intravenously or every 2 weeks subcutaneously) in the last 6 months with no need of treatment adjustments
4. Steroid-free remission for the last 6 months before inclusion

Exclusion criteria will be the following:

1. Patients younger than 18 years of age.
2. Need for treatment optimisation or any steroid (systemic or topical) treatment in the last 6 months.
3. Primary non-response or secondary loss of response as reasons for VDZ discontinuation.
4. Discontinuation for reasons different from sustained clinical remission: pregnancy, patient's choice, safety concerns, reimbursement issues etc...
5. Isolated (proximal) small bowel CD that cannot be assessed with endoscopy
6. Treatment started for prevention of CD postoperative recurrence and chronic pouchitis

****Sustained remission*** is defined as the combination of clinical remission (without the need for VDZ optimisation or steroids in the previous 6 months) + evidence of endoscopic remission at last endoscopic evaluation

Patients meeting the inclusion criteria will then be divided in 2 groups:

- **"Discontinuation" group**: patients in *sustained remission* who discontinue VDZ treatment as per physician's decision.

- **"Control" group**: patients in *sustained remission* who continue the scheduled treatment

The observation period will start from the date of the last VDZ infusion/injection for the "discontinuation" group, whereas it will begin at the first visit meeting the definition of sustained remission for the "control" group (based on whichever is closer among the endoscopic evaluation and the 6-month clinical remission).

Data about clinical activity (see below) and safety will be assessed at baseline, then every 6 months for the first 24 months, and at the last follow-up visit. Levels of C-reactive protein and faecal calprotectin will be recorded whenever available according to the clinical practice of each participating Centre, preferably at baseline and then every 6 months for the first 24 months. Use of immunomodulators in combination with VDZ or as maintenance at its discontinuation will be at physicians' discretion and will be recorded as separate covariate.

## 2. Endpoints, co-variates, and variables

Primary outcome: to compare the incidence rate of clinical relapse between the 2 study groups.

Secondary outcomes will be the following:

a) To assess the rates of IBD-related hospitalisation and surgery (colectomy for UC, any intestinal resection for CD) after VDZ discontinuation;

b) To assess the rates of clinical response, clinical remission, and the occurrence of adverse events in patients in the "discontinuation" group who re-initiated VDZ due to a flare;

c) To compare the relative effectiveness of different maintenance therapeutic strategies after VDZ discontinuation;

d) To assess the potential predictive factors of primary and secondary outcomes

e) To assess the occurrence of perianal CD after VDZ discontinuation

Patient phenotype will be determined according to the Montreal classification[9].

**For ulcerative colitis**:

Disease activity will be evaluated with the Mayo clinical subscore[10]. Clinical remission will be defined as a Mayo subscore ≤2, with no rectal bleeding and no other subscore exceeding 1. Endoscopic remission will be defined as a Mayo endoscopic subscore of 0-1. A relapse will be defined as a global Mayo score of 2 or greater, with rectal bleeding and an endoscopic subscore of 2-3. Clinical response will be defined as a decrease from baseline in the partial Mayo score (PMS) of at least 3 points and at least 30%.

**For Crohn's disease**:

Disease activity will be evaluated with the Harvey-Bradshaw index (HBI)[11]. Clinical remission will be defined as HBI <4. Endoscopic remission will be defined as SES-CD <3 or Rutgeerts i0-i1 in case of previous resection. A relapse will be defined as HBI ≥4. Clinical response will be defined as a decrease from baseline in the HBI of at least 3 points or at least 30%.

**COVARIATES**: Other than disease phenotype and activity scores, the following co-variates will be considered during heterogeneity tests and logistic regression analysis: gender; age at diagnosis; age at treatment initiation and discontinuation; disease duration; active smoking; lab results (faecal calprotectin, haemoglobin, leukocytes, platelets, albumin, and C-reactive protein) within 4 weeks before treatment discontinuation, if available; concurrent treatment; immunosuppressants/biologics used after VDZ discontinuation; route of administration (iv vs sc); previous use of biologics (naïve or experienced)

A propensity score-weighted analysis of covariates will be performed to reduce the selection bias effect and simulate that of randomisation[12].

## 3. Statistical methods

Descriptive data will be reported as medians and interquartile ranges (IQR) for continuous variables, whereas frequencies and proportions will be used for categorical variables. Comparisons between categorical variables will be performed with the Chi-square test or the Fisher's exact test for small samples; comparisons between continuous variables will be assessed with the Mann-Whitney U test. Logistic regressions will be used to determine predictors of primary and secondary outcomes among patient characteristics in the different study groups. Variables with significance ($p < 0.05$) in the univariate analysis will be included in the multivariable model.

Three types of events will be considered as endpoints for survival analysis: the occurrence of relapse (primary outcome), IBD-related hospitalisation, and IBD-related surgery. Time to event in such analyses will be defined as the time from the date of VDZ discontinuation (or the date of completion of 12 months of treatment for patients in the control group) until the date of the event. Kaplan–Meier curves and log-rank test will be used to compare groups, and univariable and multivariable Cox proportional hazard (PH) models will be used for the analysis of relevant prognostic factors. In the univariable Cox PH analysis, a criterion of $p < 0.10$ will be used to identify candidate predictors. The hazard ratios (HRs) or relative hazards derived from the Cox PH models will be presented with their 95% confidence intervals (CI) and the respective p values. A ratio higher than 1 implies a higher probability of an event compared with the reference group. P values less than 0.05 will be considered statistically significant. All statistical tests will be 2-sided.

Considering the low amount of data for VDZ discontinuation, it is not possible to adequately calculate the minimum sample size that is needed. However, the goal will be to reach at least 50 CD and 50 UC patients in both groups of patients (for a total of at least 200 patients).

## SIGNIFICANCE AND IMPACT

Since few data are currently available with regard to intermittent treatment with VDZ, this project may contribute to a better understanding of when to interrupt this biological therapy with high probability of maintaining remission. At the same time, it will give a guidance on high-risk features that would suggest against stopping VDZ. Considering the high costs of these medications for the healthcare system, the use of treatment cycles may represent an impactful saving in our economics. In addition, this approach would be beneficial also from patient's perspective, reducing potential side effects and years of immunosuppression. Moreover, a comparison with the findings already present for anti-TNFs could accelerate and extend this approach for other classes of biologicals and small molecules, if the findings will be similar. In the end, the results of this study will help clinicians to increase their confidence on when (and if) to stop biologicals and provide information regarding the short-term and long-term disease history.

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