Study title: Comparative efficacy of switch strategy and swap strategy in CD patients after failure of first-line therapy with anti-TNF: a retrospective, observational, multicenter study.

Protocol version: 1.1 **Date: 05/12/2022**

Sponsor: Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)

STUDY SYNOPSIS	
Study title	Comparative efficacy of switch strategy and swap strategy in CD patients after failure of first-line therapy with anti-TNF: a retrospective, observational, multicenter study.
Sponsor	Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)
Principal Investigator	Prof. Flavio Caprioli
Protocol Version and Date	1.1 05/12/2022
Background and rationale	In moderate-to- severe Crohn's disease two therapeutic strategies are currently available after failing of first-line therapy with an anti-TNF agent: to introduce a second anti-TNF alpha agent (the so-called switch strategy) or a biologic agent with a different mechanism of action (the so-called swap strategy). There are currently no published head-to-head studies comparing these two therapeutic strategies and the treatment of choice is primarily based on clinician experience, expert-opinion-based treatment algorithms, patient preference and economic issues. We plan to perform a retrospective, multicentre open-labeled real-life study in order to compare the effectiveness of switch strategy and swap strategy after first anti-TNF alpha failure.

Study objectives	Primary end-point will be clinical remission rates at 52 weeks in the swap vs switch group. Secondary endpoint will be clinical remission at 26 weeks, steroid-free clinical remission at 52 weeks, clinical response at 26 and at 52 weeks, endoscopic remission and response at 52 weeks, radiologic/ ultrasound remission and response at 52 weeks, variations of fecal calprotectin (FC) and/or C-reactive protein (CRP) levels at weeks 26 and 52, rate of adverse events, therapeutic persistence over time.
Study design	Retrospective, observational, multicentre, propensity matched study.

Study population	CD patients in active follow up who match the following inclusion criteria, will be enrolled in the retrospective analysis. ***Inclusion criteria*** • CD diagnosis made according to current guidelines. • Able to understand informed consent. • > 18 years old at the time of the enrollment • Patients who failed a first line therapy with anti-TNF because of primary/secondary failure or intolerance and then started a second biological agent for their intestinal disease. • Patients with at least 12 months of follow-up after starting the second biological agent • All concomitant therapy will be permitted, in order to reflect real world experience. ***Exclusion criteria*** • History of ulcerative colitis. • Presence of ostomy. • Second biological agent started for an indication different from Crohn's disease. • Lack of information regarding the reason of discontinuing first anti-TNF agent therapy

Methodology	All clinical records of CD patients in active follow up in each participating centres will be retrospectively reviewed. Collected data will include gender, age, weight, smoking status, disease duration, disease extent and phenotype (according the Montreal Classification for CD), previous and concomitant CD treatments such as immunomodulators, anti-TNF alpha therapy (including data on primary/ secondary failure and intolerance status) and previous surgery. Data of Infliximab or Adalimumab trough levels and anti-therapeutic antibodies, at the moment of the first anti-TNF agent discontinuation, will be collected if available. Data on disease activity by Harvey Bradshaw Index (HBI) at baseline, 26 weeks (V6) and 52 weeks (V12) will be also collected. Ileocolonoscopy and/or MR/CT enteroclysis and/or small bowel ultrasound performed within 3 months before the beginning of the treatment will be considered as baseline and used to assess objective response/remission at 12 months (± 3months). The comparison between baseline and week 52 will be performed if data obtained from one or more technique will be available at both baseline and week 52. For each patient, FC and CRP levels at baseline, 26 and 52 weeks will be collected and included in the database if available. Side effects and all adverse events will be recorded and analysed.

Statistical plan	A descriptive analysis will be performed on the collected data. The categorical variables will be described as absolute frequency and percentage. The continuous variables with normal distribution will be described as mean and standard deviation (SD), whereas the continuous variables without normal distribution will be given as median and range. D'Agostino-Pearson omnibus normality test will be used to check for normality of continuous variables. Comparisons between treatment group will be performed by Mann-Whitney test or Student's t-test for continuous variables, and by Chi-square or Fisher's exact tests for categorical variables. The rate of therapy discontinuation over time will be calculated separately for each treatment group by computing the Kaplan Meier survival curves. Propensity scores will be used to create a cohort of matched patients with equal distribution of baseline variables in order to reduce the effect of treatment-selection bias. An univariate analysis and then eventually a multivariate analysis will be performed in order to identify predictor factors of response. P-values less than 0.05 will be considered to be statistically significant. We estimate that to find an absolute difference of 20% between two groups with statistically significant difference ($p<0.05$), a sample size of 194 patients (97 Switch vs 97 Swap) will be necessary to obtain a study power of 80%, assuming an expected remission rate of 43% at 52 weeks in patients treated with switch strategy.

Ethical considerations	The study will be conducted in accordance with the Standards of Good Clinical Practice, with the ethical principles deriving from the Helsinki Declaration and the current legislation on observational studies. The observational study and the related documentation will be presented to the competent Ethical Committee of each center
Study timeline	Project start date: 1/2023 Completion date of patients' enrollment: 04/2023 Data collection completion date:06/2023 Data analysis:09/2023 Presentation of the scientific report: 12/2023

ROLES AND RESPONSIBILITIES

Principal Investigator and Study Coordinator	Prof. Flavio Caprioli Phone: 0255033368 e-mail: flavio.caprioli@unimi.it
Steering Committee:	
Trial Manager:	Nadia Trobia Phone: 0255032141 e-mail: nadia.trobia@policlinico.mi.it
Statistician:	Daniele Noviello Phone: 0255034591 e-mail: daniele.noviello@unimi.it

Sub-investigators:

Francesco Conforti
Phone: 0255034591
e-mail: francesco.conforti@policlinico.mi.it

Nicole Piazza O Sed
Phone: 0255034591
e-mail: Nicole.piazza@policlinico.mi.it

AUTHORIZATIONS AND SIGNATURES

Study Title

Comparative efficacy of switch and swap strategy in CD patients after failure of first-line therapy with anti-TNF: a retrospective, observational, multicenter study.

AGREEMENT

This document is confidential and belongs to the Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). The information is confidential and is to be used only in connection with matters authorized IG-IBD, and no part of it is to be disclosed to others without prior written permission from the IG-IBD.

This document, however, can be made known to the designated Ethics Committee, or representatives authorized by the Investigator or the Health Authority provided that they are bound to its confidentiality.

The Principal Investigator's signature below confirms his agreement to this protocol and provides the necessary guarantees that:

1.This study will be conducted following all the clauses of the protocol and in accordance with the Helsinki declaration (Edinburgh 2000 with Explanatory note paragraph 29 from Washington 2002 and paragraph 30 from Tokyo 2004) and current legislation regarding clinical studies.

2. No partial or final data (written or verbal) will be published without prior agreement between the Investigator and the IgIBD

PRINCIPAL INVESTIGATOR SIGNATURE

Printed name: Prof. Flavio Caprioli

Institution: Department of Pathophysiology and Transplantation, Università degli Studi di Milano - Unit of Gastroenterology and Endoscopy, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico di Milano

Signature _____ Date

TITLE

Comparative efficacy of switch and swap strategy in CD patients after failure of first-line therapy with anti-TNF: a retrospective, observational, multicenter study.

INTRODUCTION

BACKGROUND/RATIONALE

In the last decades the increasing use of biological therapies as anti-tumor necrosis factor (TNF)-alpha agents radically changed clinical management of Crohn's disease.

Anti-tumour necrosis factor (TNF)-alpha agents (infliximab and adalimumab) still constitute the first-line biologic therapy for the management of most patients with moderate-to-severe CD refractory to conventional therapy. As known, these agents are able to induce and maintain clinical and endoscopic remission, may lead to a reduction of risk of surgery, hospitalization and disease-related complications (e.g. abscess, fistulas and stenosis). However, above one third of patients may not respond to anti-TNF therapy and 30-40 % could have to withdraw anti-TNF therapy due to lose of response or intolerance (1). It has been demonstrated that a proportion of these patients may recover clinical response and remission following switch of antiTNF drug (from adalimumab to infliximab or from infliximab to adalimumab) (see below).

In the last years novel biological therapies have been approved for the treatment of moderate-to-severe CD, i.e. the anti-integrin alpha-4/beta-7 Vedolizumab (VDZ) and the anti-p40 IL12/IL23 Ustekinumab (UST). These agents

Therefore, after failing of first anti-TNFalpha therapy, two strategies are now possible: to introduce a second anti-TNF alpha agent (the so-called switch strategy) or a biologic agent with a different mechanism of action (the so-called swap strategy).

Effectiveness of a second anti-TNF after failing of a first anti-TNF therapy due to primary/secondary failure or intolerance, was evaluated in a systematic review with meta-analysis, which suggested that effectiveness of second anti-TNF reason may be dependent on the reason of first antiTNF discontinuation. Specifically, remission rates with a second antiTNF are higher when failure of a first antiTNF are due to intolerance with respect to either primary or secondary failure(2). There are network meta-analysis that have tried to indirectly compare indirectly effectiveness of second-line biologic

therapy, either with anti-TNF agent or biologic agent with different mechanism of action, after failing of first anti-TNF agent, without strong recommendations of the best therapeutic strategy in CD patients who failed anti-TNF therapy (3;4).

There are few evidences about the best option for a second-line therapy after failing of first biologic therapy. In particular, the best choice between a second anti-TNF alpha or a biologic agent with a different mechanism of action in the case of failure to anti-TNF alpha remains an open issue.

There are currently no published head-to-head studies comparing these two therapeutic strategies (the so-called switch and swap) and the treatment of choice is primarily based on clinician experience, expert-opinion-based treatment algorithms, patient preference and economic issues.

In the absence of prospective, randomized direct evidences, we plan to perform a retrospective, multicentre open-labeled real-life study in order to compare the effectiveness of switch strategy and swap strategy after first anti-TNF alpha failure.

OBJECTIVES

Objective of the present study is to assess, in an observational retrospective multicenter study, the effectiveness of a second anti-TNF alpha or a biologic agent with a different mechanism of action (e.g. VDZ and UST) in CD patients who failed one anti-TNF alpha as first line of therapy.

End-points

Primary endpoint

- Clinical remission rates at 52 weeks

Secondary endpoints

- Steroid-free clinical remission at 52 weeks.
- Clinical remission rates at 26 weeks
- Clinical response at 26 and at 52 weeks
- Endoscopic remission and response at 52 weeks
- Radiologic/ultrasound remission and response at 52 weeks

- Variations of fecal calprotectin (FC) and/or C-reactive protein (CRP) levels at baseline and week 26 and 52
- Adverse events
- Therapeutic persistence over time

METHODS

STUDY DESIGN

Retrospective, observational, multicentre, propensity matched study.

SETTING

All clinical records of CD patients in active follow up in each participating centers will be retrospectively reviewed.

CD patients, previously failing to one anti-TNF, (including primary and secondary failures and intolerants) and receiving indications to receive a second-line therapy with a second anti-TNF, UST or VDZ as for clinical standard of care, and matching the inclusion/ exclusion criteria will be included in the study.

Demographic and disease characteristic data of the included patients will be collected in a common database. Collected data will include gender, age, weight, smoking status, disease duration, disease extent and phenotype (according the Montreal Classification for CD), previous and concomitant CD treatments such as immunomodulators, and previous surgery.

Data on therapy with first anti-TNF agent will be collected, especially the reason for discontinuation (i.e. primary failure defined as lack of clinical response after induction period, secondary failure defined as a loss of response during maintenance period and intolerance)

Data of Infliximab or Adalimumab trough levels and anti-therapeutic antibodies, at the moment of the first anti-TNF agent discontinuation, will be collected if available.

Data on disease activity by Harvey Bradshaw Index (HBI) at baseline, 26 weeks (V6) and 52 weeks (V12) will be also collected. Ileocolonoscopy and/or MR/CT enteroclysis and/or small bowel ultrasound performed within 3 months before the beginning of the treatment will be considered as baseline objective evaluation of disease activity and used to assess objective response/remission (see definition of variables) at 12 months (±

3months). The comparison between baseline and week 52 will be performed if data obtained from one or more technique will be available at both baseline and week 52. For each patient, FC and CRP levels at baseline, 26 and 52 weeks will be collected and included in the database if available.
Side effects and all adverse events will be recorded and analysed.

PARTICIPANTS

CD patients in active follow up who failed one anti TNF-alpha and match the following inclusion criteria, will be enrolled in the retrospective analysis.

Inclusion criteria

- CD diagnosis made according to current guidelines.
- Able to understand informed consent.
- > 18 years old at the time of the enrollment
- Patients who failed a first line therapy with anti-TNF because of primary/ secondary failure or intolerance and then started a second biological agent for their intestinal disease.
- Patients with at least 12 months of follow-up after starting the second biological agent
- Previous exposure to a single antiTNF agent (both primary and secondary failure and intolerant).
- All concomitant therapy will be permitted, in order to reflect real world experience.

Exclusion criteria

- History of ulcerative colitis.
- Presence of ostomy during follow up period.
- Second biological agent started for an indication different from Crohn's disease.
- Lack of information regarding the reason of discontinuing first anti-TNF agent therapy

VARIABLES

Definition of the variables:

Clinical remission: Harvey Bradshaw Index (HBI) ≤ 4.

Clinical response: Reduction of HBI ≥3 points from the baseline value.

Endoscopic response will be defined by a decrease in SES-CD of > 50 % from the baseline

Endoscopic remission will be defined by a SES-CD

Radiologic response will be defined by improvement in at least one or more features of bowel wall thickness, inflammatory fat, mural blood flow and hyperenhancement compared to baseline imaging. (5)

Radiologic remission will be defined by complete normalization of inflammatory parameters on cross-sectional imaging. (5)

Ultrasound response will be defined by improvement of bowel wall thickness defined as reduction of BWT (mm) as compared to baseline.

Ultrasound remission will be defined by bowel wall thickness will be considered normal if ≤3 mm. (6)

Route of Administration:

For UST as in standard practice, Intravenous (IV) for the induction, subcutaneously (SC) in the maintenance phase.

Dose: for UST a weight-range-based dose (260 mg if weight < 55 Kg, 390 mg if weight > 55 Kg and < 85 Kg, 520 mg if weight > 85 Kg) will be administered in the induction followed by maintenance with UST 90 mg SC every 12 or 8 weeks according to standard clinical practice.

For VDZ as in standard practice, IV route for induction and maintenance phases.

Dose: VDZ will be administered 300mg IV at 0, 2 and 6 weeks for the induction. Additional 300mg VDZ infusion can be given at week 10 based on clinical judgment. VDZ 300mg IV every 8 weeks will be given as maintenance. Intensification dose every 6 or 4 weeks will be accepted, according to standard practice.

For ADA as in standard practice subcutaneous route for induction and maintenance phase.

Dose: ADA will be administered 160 mg at 0 weeks, 80 mg at 2 weeks and followed by 40 mg each other week for maintenance. Interval between administration shortened to every week or therapeutic dose increased to 80 mg eow will be accepted, according to standard practice.

For IFX as in standard practice, IV route for induction and maintenance phases.

Dose: IFX will be administered 5mg/kg IV at 0, 2 and 6 weeks for the induction. IFX 5mg/ Kg IV every 8 weeks will be given as maintenance. Interval between administration shortened to 6 or 4 weeks or therapeutic dose increased to 10mg/Kg will be accepted, according to standard practice.

DATA SOURCES/ MEASUREMENT

Data from the clinical chart will be recorded anonymously in a common database.

STUDY SIZE

Considering the efficacy data from a meta-analysis assessing clinical response and remission of a second anti-TNF after failing of first anti-TNF therapy in CD patients, we expect a remission rate of 43% at 52 weeks in patients treated with switch strategy. Therefore, we estimate that to find an absolute difference of 20% between two groups with statistically significant difference ($p<0.05$), a sample size of 194 patients (97 Switch vs 97 Swap) will be necessary to obtain a study power of 80%.

STATISTICAL METHODS

A descriptive analysis will be performed on the collected data. The categorical variables will be described as absolute frequency and percentage. The continuous variables with normal distribution will be described as mean and standard deviation (SD), whereas the continuous variables without normal distribution will be given as median and range. D'Agostino-Pearson omnibus normality test will be used to check for normality of continuous variables. Comparisons between treatment group will be performed by Mann-Whitney test or Student's t-test for continuous variables, and by Chi-square or Fisher's exact tests for categorical variables.

The rate of therapy discontinuation over time will be calculated separately for each treatment group by computing the Kaplan Meier survival curves.

We will perform an univariate analysis and then eventually a multivariate analysis in order to identify predictor factors of response.
Propensity scores will be used to create a cohort of matched patients with equal distribution of baseline variables in order to reduce the effect of treatment-selection bias.
P-values less than 0.05 will be considered to be statistically significant.

REGULATORY AND ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the Standards of Good Clinical Practice, with the ethical principles deriving from the Helsinki Declaration and the current legislation on observational studies. The observational study and the related documentation will be presented to the competent Ethical Committee of each center. The study will start only after receiving the required authorizations according to the institution's internal procedures. The Ethical Committee must also approve any modification to the protocol and the advertising used to recruit subjects for the study, according to local regulations.
Given the observational nature of the proposed studies, additional insurance policies are not required compared to those already provided for normal clinical practice.

INFORMED CONSENT/ASSENT AND DATA PROCESSING

It is the responsibility of the physicians to obtain a consent to the informative note through the privacy consent with date and signature by each patient before the beginning of the data collection. The signature confirms the understanding of the consent form and the information contained therein. Furthermore, the investigator must sign and date the informed consent form. The signed documents must be archived by the investigator, while a copy must be given to the patient.

CONFLICT OF INTEREST

No conflict of interest

PUBLICATION/DATA SHARING POLICY

After completion of the study, the project coordinator will prepare a draft manuscript containing final results of the study on the basis of the statistical analysis. The manuscript will be derived to the co-authors for comments and after revision will be sent to a major scientific journal.

All publications, abstracts, presentations, manuscripts and slides including data from the present study will be submitted to and reviewed by the Study Coordinator for coordination and homogeneity purposes. The timing of publications (in the event several Centers should be participating in the Study) will be set according to the MoH's Decree of May 12, 2006, since investigators cannot be precluded from or limited in publishing the results of their studies.

The Study Coordinator will be the Senior Author and the Corresponding Author of the relevant publications. The Authors' list will include all the investigators (up to the maximum required by the Journal to whom the article will be submitted) in a decreasing order of patients included into the final analysis for the primary outcome.

LITERATURE REFERENCES

1. Berns M, Hommes DW. Anti-TNF-α therapies for the treatment of Crohn's disease: the past, present and future. Expert Opin Investig Drugs. 2016;25(2):129-43.
2. Gisbert JP, Marín AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. Aliment Pharmacol Ther. 2015 Apr;41(7):613-23.
3. Pagnini C, Siakavellas SI, Bamias G. Systematic Review with Network Meta-Analysis: Efficacy of Induction Therapy with a Second Biological Agent in Anti-TNF-Experienced Crohn's Disease Patients. Gastroenterol Res Pract. 2018 Jul 17;2018:6317057
4. Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review and network meta-analysis: first- and second-line biologic therapies for moderate-severe Crohn's disease. Alimentary pharmacology & therapeutics. 2018;48(4):394-409.
5. Carucci LR, Levine MS. Radiographic imaging of inflammatory bowel disease. Gastroenterology clinics of North America. 2002;31(1):93-117, ix.
6. Castiglione F, Imperatore N, Testa A, et al. One-year clinical outcomes with biologics in Crohn's disease: transmural healing compared with mucosal or no healing. Alimentary pharmacology & therapeutics. 2019;49(8):1026-1039.