Study title: Prospective observational national registry on the safety of biosimilars of anti-TNF in patients with inflammatory bowel disease: a collaborative multicenter IG-IBD study

Study Acronym: ORBIT

Protocol version: Version 1.0 Date: 27.06.2019

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

STUDY SYNOPSIS	
Study title	Prospective observational national registry on the safety of biosimilars of anti-TNF in patients with inflammatory bowel disease: a collaborative multicenter IG-IBD study (ORBIT)
Sponsor	Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD)
Principal Investigator	Gionata Fiorino
Protocol Version and Date	V. 1.0 29/Jun/2019
Background and rationale	Anti-Tumor Necrosis Factor agents (anti-TNF), such as infliximab, adalimumab, and golimumab are currently approved and reimbursed for the treatment of active moderate-to-severe inflammatory bowel disease (IBD), both Crohn's disease (CD) and ulcerative colitis (UC) in Italy. These agents are effective in inducing and maintaining clinical and endoscopic remission, however their use is limited by high costs especially in patients requiring long-term maintenance therapy. Since 2013, the European Medicine Agency (EMA) approved CT-P13, a biosimilar of infliximab (Remsima® and Inflectra®), for the same indications as for the originator. More recently, another biosimilar of infliximab, SB2 (Flixabi®) has been also approved for the same indications, as well as biosimilars of adalimumab. Since the beginning, some concerns arose on the safety of biosimilars in IBD patients, either in those naïve to any biologic or being switched from the originator to a biosimilar. Such concerns have been dramatically overcome by recent data coming from observational studies across the world, demonstrating the clinical equivalence in terms of safety, efficacy and immunogenicity in the short-term9-11. However, the recent Position Paper by the European Crohn's Colitis Organisation (ECCO) still supports the role of

	long-term registries to monitor the safety of biosimilars.
Study objectives	The aim of this study is to collect and analyze data on safety and efficacy of all licensed biosimilars in patients with IBD recruited at the participating centers. The primary objective will be to assess the safety of biosimilars (CT-P13 and SB2, but also new biosimilars eventually approved in the next future) through 5 years since the introduction of biosimilars in the market. The secondary objectives will be: - To assess the adverse events leading to discontinuation through year 5 - To assess the loss of response at year 5 - To assess the treatment persistence at year 5 - To evaluate whether switching, re-switching or cross-switching are associated with significant and relevant adverse events - To identify baseline risk factors for adverse events and loss of efficacy in the study population
Study design	All patients with established diagnosis of Crohn's disease or ulcerative colitis with indication to start, currently on, or previously treated with a biosimilar of infliximab or adalimumab will be eligible for the study.
Study popolation	This will be a prospective long-term nationwide registry. All consecutive IBD patients treated with any biosimilars for any licensed indication will be enrolled. For patients treated with any biosimilar before the starting date, if their consent to manage their data retrospectively and anonymously has been obtained, data can be included in the database. Data will be collected at definite time-points, and all the relevant information will be recorded in the medical report of the patient.

Methodology	All patients included in the study will be evaluated every 6 months, and safety and efficacy endpoints will be evaluated through year 5 since the study initiation.
Statistical plan	Since this is a prospective observational cohort, no calculation of the sample size will be required. Data will be analyzed by a descriptive analysis and a comparison through appropriate parametric and non-parametric tests, where required, will be made for three different groups: - Patients naïve to the originator(any) - Patients previously exposed to the originator (any) - Patients switched from one to another biosimilar/originator while on treatment If required, survival curve analyses will be also performed (Kaplan-Meyer curves with log-rank calculation, and Cox analysis). All differences will be considered statistically significant for $p<0.05$.
Ethical considerations	Data will be handled anonymously according to the Italian regulations, and e-CRF will be used for the data collection. No procedures, investigations, therapies outside the current good clinical practice are required
Study timeline	February 2021: submission to Ethical Committees of the participating Centers March-April 2021: start of the enrollment process March-April 2026: end of enrollment June 2026: data analysis and statistical report December 2026: publication of the results in full-paper Interim analyses will be done at 1 and 3 years since the study initiation.

ROLES AND RESPONSIBILITIES	
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Trial Manager:	Name Surname Phone: Fax: e-mail:
Statistician:	Name Surname Phone: Fax: e-mail:

AUTHORIZATIONS AND SIGNATURES

Prospective observational national registry on the safety of biosimilars of anti-TNF in patients with inflammatory bowel disease: a collaborative multicenter IG-IBD study (ORBIT)

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: GIONATA FIORINO

Institution: Gastroenterologist, IBD Center, Humanitas Clinical and Research Institute

Signature _____ Date

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TITLE

Prospective observational national registry on the safety of biosimilars of anti-TNF in patients with inflammatory bowel disease: a collaborative multicenter IG-IBD study (ORBIT)

BACKGROUND/RATIONALE

Anti-Tumor Necrosis Factor agents (anti-TNF), such as infliximab, adalimumab, and golimumab are currently approved and reimbursed for the treatment of active moderate-to-severe inflammatory bowel disease (IBD), both Crohn's disease (CD) and ulcerative colitis (UC) in Italy[1]. These agents are effective in inducing and maintaining clinical and endoscopic remission[2], however their use is limited by high costs especially in patients requiring long-term maintenance therapy[3]. Since 2013, the European Medicine Agency (EMA) approved CT-P13, a biosimilar of infliximab (Remsima® and Inflectra®), for the same indications as for the originator[4,5]. More recently, another biosimilar of infliximab, SB2 (Flixabi®) has been also approved for the same indications[6]. More recently, also biosimilars of adalimumab have been approved for the treatment of IBD. Since the beginning, some concerns arose on the safety of biosimilars in IBD patients, either in those naïve to any biologic or being switched from the originator to a biosimilar[3,7,8]. Such concerns have been dramatically overcome by recent data coming from observational studies across the world, demonstrating the clinical equivalence in terms of safety, efficacy and immunogenicity in the short-term[9-11]. However, the recent Position Paper by the European Crohn's Colitis Organisation (ECCO) still supports the role of long-term registries to monitor the safety of biosimilars[12].

There are no long-term data on safety and effectiveness of biosimilars in large populations of IBD patients, especially in the long-term.

OBJECTIVES

General objectives

The primary objective of this study is to collect and analyze data on safety and efficacy of all licensed biosimilars in patients with IBD recruited at the participating centers.

The primary objective will be to assess the safety of biosimilars (CT-P13 and SB2, biosimilars of adalimumab, but also new biosimilars eventually approved in the next future) through 5 years since the introduction of biosimilars in the market.

The secondary objectives will be:

- To assess the adverse events leading to discontinuation through year 5

- To assess the loss of response at year 5

- To assess the treatment persistence at year 5

- To evaluate whether switching, re-switching or cross-switching are associated with significant and relevant adverse events

- To identify baseline risk factors for adverse events and loss of efficacy in the study population

End-points

Primary endpoint

Rate of any adverse event related to the biosimilars of infliximab and adalimumab through the study period.

Secondary endpoints

- Rate of adverse events leading to discontinuation through year 5

- Rate of loss of response at year 5

- Rate of treatment persistence at year 5

- To evaluate whether switching, re-switching or cross-switching are associated with significant and relevant adverse events, defined as the rate of adverse events in the study population by biosimilar

- To identify baseline risk factors for adverse events and loss of efficacy in the study population, including age, gender, disease duration, disease classification, previous and

concomitant IBD-related drug exposure, switching from originator to any biosimilar, or switching from a biosimilar to another biosimilar of the same molecule.

METHODS

STUDY DESIGN

This will be a prospective long-term nationwide registry of patients exposed to biosimilars.

All consecutive IBD patients treated with any biosimilars for any licensed indication will be enrolled. For patients treated with any biosimilar before the starting date, if their consent to manage their data retrospectively and anonymously has been obtained, data can be included in the database. Each patient will be followed-up for 5 years since the inclusion or the start of the last biosimilar.

Data will be collected at definite time-points (every 6 months), and all the relevant information will be recorded in the medical report of the patient.

Data will be handled anonymously according to the Italian regulations, and e-CRF will be used for the data collection.

PATIENT SELECTION CRITERIA

Inclusion criteria

- Patients with established diagnosis of Crohn's disease or ulcerative colitis (confirmed by clinical, endoscopic, histological and/or radiological evaluation)
- Any age and gender
- Indication to be treated with infliximab or adalimumab biosimilar OR currently treated with a biosimilar of infliximab or adalimumab OR previous treatment with any biosimilar of infliximab or adalimumab
- Naïve to any treatment with biosimilar of infliximab or adalimumab OR previously treated with any infliximab or adalimumab OR switched from infliximab or adalimumab originator to a biosimilar of the same molecule OR switched from a biosimilar to another biosimilar of the same molecule OR switched from a biosimilar to the respective originator.

- ability to give informed consent according to *ICH/EU GCP,* and national/local regulations.

Exclusion criteria

Some possible criteria are reported as example

- Patients with diagnosis of undefined IBD (IBD-U)
- Patients with active diverticulitis, infectious colitis, confirmed colonic dysplasia at the time of inclusion
- Any contraindication to be treated with a biosimilar according to the summary of characteristics of product

STATISTICAL METHODS

Sample size

Since this is a prospective observational cohort, no calculation of the sample size will be required.

Analysis

For each statistical comparison to be made specify

Data will be analyzed by a descriptive analysis and a comparison through appropriate parametric and non-parametric tests, where required, will be made for three different groups:

- Patients naïve to the originator(any)

- Patients previously exposed to the originator (any)

- Patients switched from one to another biosimilar/originator while on treatment

In particular, if time of exposure to biosimilars and/or the time of follow-up will be different between patients and groups, the calculation of Incidence Rate Ratio (IRR) and treatment persistence will be performed.

If required, survival curve analyses will be also performed (Kaplan-Meyer curves with log-rank calculation, and Cox analysis). All differences will be considered statistically significant for $p<0.05$.

An interim analysis is planned at year 1 and year 3 after the study initiation.

WITHDRAWAL OF SUBJECTS

Since this is an observational study, patients can be withdrawn from the study at any time they will revoke their consent to participate into this study.

The patients will be also be withdrawn in case of discontinuation of the current therapy, if they will be treated with another molecule other than infliximab or adalimumab

REGULATORY AND ETHICAL CONSIDERATIONS

Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country.

The protocol has been written, and the study will be conducted according to the ICH Guideline for Good Clinical Practice

The protocol and its annexes are subject to review and approval by the competent Independent Ethics Committee(s) ("IEC").

Subject identification – Personal Data protection

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, not be made publicly available. The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the study. This number will identify the patient and must be included on all case report forms.

Any and all patient information or documentation pertaining to a clinical trial, to the extent permitting, through a "key" kept anywhere, regardless of whether such key is supplied along with the information or documentation or not, must be considered as containing sensitive personal data of the patient, and is therefore subjected to the provisions of applicable data protection ("privacy") regulations. The study coordinator and all the investigators are aware that a breach of such regulations may result in administrative or even criminal sanctions.

An information sheet prepared according to such regulations and a form to evidence the consent of patients to the processing of such data will accompany the informed consent administered to the patient. Such information (i) identify the roles of the holder ("titolare")

and processor (“responsabile”, appointed by the holder) of the patient personal data (also if not directly identifying the patient), as well as the purposes of the personal data collection and processing (medical treatment and related/unrelated scientific research), (ii) adequately describe the flows of communication involving them, particularly if third parties should become involved, and (iii) seek the patient’s prior and specific consent to such processing.

In addition, anonymized data may be uploaded, with explicit consent, on a single database protected by password that can be accessed through the platform of the IGIBD database. The members of the IG-IBD Scientific and Steering Committee and the Investigators who coordinate this study will have access to the database; access and consultation of the data will be carried only for scheduled review or on the specific mandate of the IGIBD Scientific Committee for the timely assessment of specific variables.

Informed consent

All patients will be informed of the aims of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician. An example of a patient informed consent statement is given as an appendix to this protocol.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient’s subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered at the Data Center. This will be done in accordance with the national and local regulatory requirements.

The informed consent procedure will conform to the ICH guidelines on Good Clinical Practice. This implies that “the written informed consent form should be signed and personally dated by the patient or by the patient’s legally acceptable representative”.

A copy of Informed consent will be attached to this Protocol Template.

CONFLICT OF INTEREST

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) will fully disclose the nature of the conflict of interest.

DATA OWNERSHIP

According to the ICH Guidelines on Good Clinical Practice the Sponsor of this study will be the owner of the data resulting therefrom. All centers and investigators participating in the study should be made aware of such circumstance and invited not to disseminate information or data without the Institution's prior express consent.

PUBLICATION 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.

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