Safety of new medications in inflammatory bowel diseases: A French prospective nationwide study

I-CARE II study

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BACKGROUND

Inflammatory bowel disease (IBD), encompassing Crohn's Disease (CD) and Ulcerative Colitis (UC), is a chronic, disabling, incurable condition affecting 250,000 people in France. Current therapeutic options are limited and comprise 5ASA, immunosuppressant (IS), anti-TNF (infliximab, adalimumab, certolizumab pegol, and golimumab) and more recently vedolizumab (anti-integrins), ustekinumab (anti IL12/23), and tofacitinib (Janus kinase inhibitors). However, a great proportion of patients experience primary non-response (31–53%) or secondary loss of response (43–70%) to these currently approved medications.

Hence, new drugs with other mechanisms of action acting on different inflammatory pathways involved in the pathogenesis of IBD are currently incorporated in clinical practice and some are still under development. Small oral molecules targeting simultaneously multiple cytokines as janus kinase inhibitors (tofacitinib, filgotinib and upadacitinib) or interfering with inflammatory cell migration [e.g. sphingo-sine-1- phosphate (S1P) receptor modulators: ozanimod, etrasimod], as well has been developed in both CD and UC. Small-molecule drugs have low molecular weights and diffuse easily through cell membranes, associated with some advantages over more complex biological agents in terms of route of administration, pharmacokinetic features, and formation of anti-drug antibodies related to immunogenicity. On the other hand, understanding the pathogenic role of IL-23 in IBD has led to the development of new molecules that may be a valid alternative to anti-TNF drugs. Ustekinumab, a monoclonal antibody against the shared p40 subunit of IL-12 and IL23, was the first anti-IL12/IL23 approved. Because IL23 involvement and not IL12 seems pivotal in IBD pathogenesis, a more selective generation of antibodies towards IL23 p19 is under investigation (mirikizumab, risankizumab, brazikumab, and guselkumab). Preliminary data on anti-IL-23 agents show promising results in terms of efficacy and safety but more data are needed on the long-term outcomes to understand the best positioning of those agent in the therapeutic algorithm.

The development of biologics and small molecules revolutionize the management of IBD patients. Many new drugs will soon be available for both CD and UC patients, expanding the therapeutic alternatives. Although this represents an undoubted positive aspect, it raises new unsolved questions, as the long-term and real-life safety and effectiveness of these drugs. Safety being one of the main drivers of choice of a drug, this data will be unvaluable to position these molecules in the therapeutic algorithm of IBD patients. The efficacy and safety of JAKi and IL23 have been assessed in a large number of pivotal studies in both UC and CD. To date, tofacitinib (anti-JAK 1 and 3) has been approved and reimbursed for the treatment of UC. This should be the case in France for the other molecules mentioned above between 2022 and 2023. Pivotal clinical trials on tofacitinib have yielded the first data on the tolerance of JAKi. The main side effects were the onset of dyslipidemia with an increase in LDL and HDL cholesterol. Infections were numerically, but not significantly, more frequent with JAKi than with placebo (upper airway, urinary tract, influenza infections). Reactivation of varicella-zoster virus infections was observed significantly more frequently than with placebo. Recently, a clinical trial in RA patients at high cardiovascular risk showed an increased risk of major adverse cardiovascular events and malignancies with tofacitinib compared to TNF blockers. This has resulted in restrictions on the use of this molecule in certain populations at risk. The results of phase III study in UC for upadacitinib and filgotinib have been recently

presented. These more selective molecules could be associated to a different tolerance profile. To date, excepting ustekinumab, data on the safety profile of monoclonal antibodies targeting IL23 is limited. In current phase II and phase III available no signal in terms of malignancies, infections or vascular events occurred.

Given these data, we must urgently address safety concerns for these new medications. Clinical trials are insufficient to accurately assess the tolerance and long-term effectiveness of a drug. Indeed, the latter target very specific populations not representative of the general population. Likewise, the numbers of these studies are determined in order to be able to obtain the power necessary to demonstrate a difference in terms of short-term efficacy, but not in terms of safety. The time horizon of the trials is generally insufficient to observe long-term impacts that prolonged real-life monitoring can detect. It is therefore widely accepted that when it comes to safety, or disease natural history real-life observations are essential in addition to clinical trials. Several factors can influence the safety profile of a drug in IBD such as phenotype, treatment duration as well as disease activity and severity or comorbidities. The CESAME and I-CARE-I demonstrated that a huge cross-sectional observational cohort is able to address accurately and rapidly the long-term major safety issues associated with the prolonged use of thiopurines and anti-TNF with an immediate impact on national and international guidelines.

Taking the opportunity of the experience of the I-CARE-I study, we design an innovative study based on researcher patient in network with physicians. We designed a nationwide prospective longitudinal observational multicenter cohort study with a data linkage to the French National Health Data System to evaluate the real-life safety as well as the potential for disease modification of JAK1, anti-IL23p19 and S1p modulators in IBD.

STUDY OBJECTIVES

The primary objective of I-CARE II is to assess prospectively the presence and the extent of safety concerns (**cancer, serious infections, arterial and venous thrombotic events**) in patients treated with JAKi, anti-IL23p19, and S1p modulators.

We will stratify the risk of cancers, serious infections and vascular events according to IBD phenotype, disease activity (clinical, radiologic and endoscopic) and main comorbidities at baseline.

The five main secondary objectives of the I-CARE II project are:

- To assess the presence and the extent of safety concerns in patients treated with JAKi, anti-IL23p19, and S1p modulators for **each outcome of interest separately** (cancer, serious infections, arterial and venous thrombotic events).

- To investigate prospectively the impact of JAKi, anti-IL23p19 and S1p modulators strategies on the **natural history** of IBD and their **potential for disease modification** by collecting validated surrogate markers such as mucosal healing and disease complications such as bowel damage (strictures, fistulas, abscess), surgeries, and hospitalizations

- To assess the evolution of **ePROs** on a trimester basis and the impact of JAKi, anti-IL23p19, and S1p modulators on ePROs in IBD

- To evaluate the **benefit-risk ratio** of strategies based on a wider use of JAKi, anti-IL23p19, and S1p modulators therapy for IBD

- To assess **the healthcare costs and cost-efficacy** of current therapeutic strategies in IBD.

STUDY DESIGN

This is a French prospective longitudinal observational multicenter cohort study. Every gastroenterologist located throughout France will be able to participate based on a voluntary basis, including gastroenterologists in full-time hospital practice, mixed public/private practice, or full-time private practice. All members of ANGH (general hospital) and CREGG (private practice), as well as the GETAID (academic center) will be notably invited to participate. We aim to include a minimum of 250 gastroenterologist investigators.

Study duration: 7 years
- Three-and-a-half-year inclusion period (January 2023 to July 2026)
- At least four-year follow-up period for all patients. All patients included will be followed until the end of the study (2030).

Sample size, number of investigators, number of patients per investigator, participating centers

Calculation of sample size was made based on the primary objective of I-CARE II. We estimated that a minimum of 20,000 persons years (i.e one person followed for one year) is needed for the study to have a statistical power of 80% to detect a theoretical relative risk (drug class of interest versus anti-TNF) of 0.74 for anti-integrins, 0.69 for JAKi and 0.77 for IL12/23. The final patient population will be at least 6,000 and the follow-up duration for each patient will be at least 4 years, in order to have at least 20,000 person-years, assuming a mean completion rate of 85% based on I-CARE I findings. Of note, we are expecting treatment switch to other treatment of interest during follow-up, which will be included in the analysis to achieve the adequate statistical power.

Investigators will be all French gastroenterologists (either full-time hospital practice, mixed public/private practice, and full-time private practice) voluntary for participating in the study on an unpaid basis, and accepting to provide phone number and e-mail address for the purpose of the study.

Each investigator will include inpatients or outpatients that he personally manages for IBD, matching the inclusion criteria and stratified according to the exposure to medications of interest at inclusion. According to a new user design, patients will be included from the time of treatment initiation, to capture pretreatment characteristics as well as all events occurring anytime during follow-up.

Cohort entry will be **allowed up to one month after treatment initiation**, which will allow to assess disease activity from the time of treatment initiation.

Treatment of interest:
- Group 1: anti-IL23p19 (risankizumab, guselkumab, mirikizumab, brazikumab)
- Group 2: Jak inhibitors (tofacitinib, upadacitinib, filgotinib)
- Group 3: S1P modulators (ozanimod, etrasimod)
- Group 4: anti-TNF (infliximab, adalimumab, golimumab) (with a maximal proportion of 25% as 1st first line biologic after conventional treatment (aminosalicylates, corticosteroids, thiopurines, methotrexate)
- Group 5: anti-integrins
- Group 6: anti-IL12/23 (ustekinumab)

Patients starting anti-TNF, anti-integrins or ustekinumab (Groups (4, 5 and 6) will be included to increase the validity of the findings reported for the treatment of interest (Groups 1 to 3). First, in the subgroup of patients included after anti-TNF, anti-integrin or ustekinumab initiation and starting a treatment of interest during follow-up, previous exposure to biologics will be comprehensively assessed during follow-up, which will allow to better adjust for this key covariate. Second, findings in these groups (Groups 4 to 6) will allow to assess the robustness of the design and notably of the outcome identification process, as incidence rates of the outcomes of interest are known for these treatment groups, and findings in the literature could be compared with the incidence rates observed in I-CARE II.

STUDY POPULATION

Inclusion criteria:

- Patient with an established diagnosis of Crohn's disease, ulcerative colitis or IBD, unclassified based on usual radiological, endoscopic or histological criteria.
- Patient aged 18 and older accepting to sign the informed participating consent form, stating that he accepts to provide personal details (mobile and home phone number, e-mail address), to complete the e-PRO as required and to be contacted by a Study Coordinator and his gastroenterologist for the purpose of the study during the entire study period and during follow up if required.

Exclusion criteria:

- Patient unable to sign the informed consent form
- Patient with no regular access to internet
- Patient refusing to sign the informed consent form
- Patient enrolled in a Randomized Clinical Trial (If the investigational product received was blinded, and if the treatment is unknown at time of enrollment in I-CARE II)

ROLES AND RESPONSIBILITIES

Gastroenterologist investigator

- The gastroenterologist selects and consents the patient and enters the baseline demographic data of the patient in the eCRF. The accuracy of all the information entered by the patient must be validated at least once a year by the gastroenterologist who will complete the e-summary form. She/he will also be requested to confirm treatment switch of treatment of interest during follow-up, to evaluate endoscopic and imaging disease activity based on available reports.

Study Coordinators (SC)

- The accuracy and completeness of the information reported by the patients will bechecked on a quarterly basis by the Study Coordinators working under the responsibility of the National Coordinators and supported by the GETAID Project Manager. The Study Coordinators will ensure that all data are completed on a monthly basis by the patients and will follow up if required.
- For cancer, dysplasia, all hospitalizations, surgeries and thrombotic events, if the patient did not or could not upload the report, SCs will have to get a copy of the corresponding histological, hospitalization report, or imaging report for outpatient venous thrombotic events from the patient, general practitioner, gastroenterologist or other organ specialist, and upload an anonymized copy on the eCRF portal for review and validation by the Gastroenterologist.
- Occurrence of death within the preceding year: this information will be obtained by the patient circle after failure of direct contact, or by the general practitioner, attending gastroenterologist or other organ specialist. Study Coordinators are requested to get reliable information on the cause of the death.

Patients

- Patient will complete the e-Diary on a quarterly basis and the ePRO once a year. In case of treatment switch to a treatment of interest during follow-up, patient will complete the e-Diary at treatment switch and the next e-Diaries will be collected on a quarterly basis from the date of treatment switch.
- Report all hospitalization, surgery, and serious infections, cancer and vascular event diagnosis
- Obtain all hospitalization and surgery summary, as well as pathology and imaging reports from treating physicians and provide to Study Coordinators for upload on the secure server.
- Provide contact information for Study Coordinator to collect the documents necessary for the analysis.

PROJECT MANAGEMENT

The GETAID is the sponsor of the I-CARE II study.

Scientific Committee: The committee oversees the initial construction of the scientific content and logistic architecture of the project, organization and project oversight. The SC decide and control all aspects of the scientific content and production of initial and secondary nested projects

Members include:

- Julien Kirchgesner, PI
- Mathurin Fumery, co-PI
- Laurent Peyrin-Biroulet (GETAID president)
- Charlotte Mailhat (GETAID)- Project Director
- Two Members of ANGH
- Two members of CREGG

Methodologists:

- Team PEPITES of the Pierre Louis Institute of Epidemiology and Public Health (IPLESP), Sorbonne University, Paris.
- Cedric Baumann, PARC / MDS unit, Nancy University Hospital

The linkage to the SNDS will be performed under the supervision of the team PEPITES ate ILPLESP and will allow to assess comorbidities and cotreatment exposure that are not collected in eDiaries.

EXPECTED RESULTS

I-CARE II is the first nationwide observational prospective cohort study at the era of JAKi, anti-IL23p19 and S1P modulators that will provide new and unique information (safety, efficacy/potential for disease modification, risk-benefit ratio, and healthcare costs) on the long-term use of its medication in IBD, using a predefined standardized follow-up. These real-world data will be used to guide clinicians as well as Healthcare authorities to provide the best care for IBD patients by optimizing available therapies. These findings may assist in maximizing benefits and minimizing risks among IBD patients.