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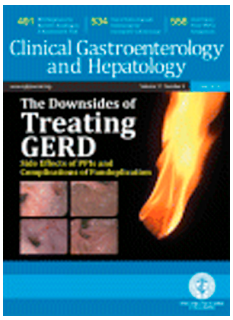

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I-CARE, a European prospective cohort study assessing safety and effectiveness of biologics in inflammatory bowel disease

Short title: Safety and effectiveness of biologics in IBD

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Abbreviations: 5-ASA (5-aminosalycilates), BCG (Bacille Calmette-Guerin), BMI (body mass index), CD (Crohn's disease), CDAI (Clinical Disease Activity Index), CESAME (Cancers Et Surrisque Associé aux Maladies inflammatoires intestinale en France), ECCO (European Crohn's and Colitis Organisation), eCRF (electronic case report form), EFFCA (European Federation of Crohn's and Ulcerative Colitis Associations), GETAID (Groupe d'Etude des Affections Inflammatoires du Tube Digestif), IBD (Inflammatory bowel disease), IBDu (Inflammatory Bowel Disease, unclassified), I-CARE (IBD Cancer and serious infections in Europe), IRB (institutional review board), PRO (patient reported outcomes), TNF (tumor necrosis factor), UC (ulcerative colitis)

Data availability statement

The data underlying this article are available in the article.

Conflict of interest

Laurent Peyrin-Biroulet - personal fees from Galapagos, AbbVie, Janssen, Genentech, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Boerhinger Ingelheim, Pfizer, Index Pharmaceuticals , Sandoz, Celgene, Biogen, Samsung Bioepis, Alma, Sterna, Nestle, Inotrem, Enterome, Allergan, MSD, Roche, Arena, Gilead, Hikma, Amgen, BMS, Vifor, Norgine ; Mylan, Lilly, Fresenius Kabi, Oppilan Pharma, Sublimity Therapeutics, Applied Molecular Transport, OSE Immunotherapeutics, Enthera, Theravance ; Pandion Therapeutics - grants from Abbvie, MSD, Takeda, Fresenius Kabi - stock options : CTMA.

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Authors' Contributions

LPB and LB conceived the study. LPB wrote the article, and created tables and figure. JFR, JK, VA, SS, AA, KK, JG, PB, UH, JB, HY, GD, FM, TM, ML, JH, EZ, HR, CB, FB, and LB critically reviewed the content of the paper and supervised the project. All authors approved the final manuscript.

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*Contributors of the I-CARE Collaborator group are listed in the Appendix.

Abstract

Background and Aims: There is a need to evaluate the benefit-risk ratio of current therapies in inflammatory bowel disease (IBD) patients to provide the best quality of care. The primary objective of I-CARE was to assess prospectively safety concerns in IBD, with specific focus on the risk of cancer/lymphoma and serious infections in patients treated with for anti-tumor necrosis factor and other biologics monotherapy as well as in combination with immunomodulators.

Methods: I-CARE was designed as a European prospective longitudinal observational multicenter cohort study, to include patients with a diagnosis of Crohn's disease, ulcerative colitis or IBD unclassified established at least 3 months prior to enrollment.

Results: A total of 10,206 patients were enrolled between March 2016 and April 2019, including 6,169 (60.4%) patients with Crohn's disease, 3,853 (37.8%) with ulcerative colitis, and 184 (1.8%) with a diagnosis of IBD unclassified. Thirty-two percent of patients were receiving AZA/thiopurines, 4.6% 6-mercaptopurine, and 3.2% methotrexate at study entry. At inclusion, 47.3% of patients were treated with an anti-tumor necrosis factor agent, 8.8% with vedolizumab, and 3.4% with ustekinumab. Roughly one quarter of patients (26.8%) underwent prior IBD related surgery. Sixty-six % of patients had been previously treated with systemic steroids. Three percent of patients had a medical history of cancer prior to inclusion, and 1.1% had a history of colonic, esophageal or uterine cervix high-grade dysplasia.

Conclusion: I-CARE is an ongoing investigator-initiated observational European prospective cohort study that will provide unique information on the long-term benefits and risks of biological therapies in IBD patients.

Keywords: inflammatory bowel disease, biologics, safety, efficacy, I-CARE, cancer, lymphoma

Why I-CARE?

Inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are lifelong, disabling, and incurable chronic inflammatory disorders involving the gastrointestinal tract [1,2]. Over the last decades, biologic therapies have revolutionized the treatment of IBD [3,4]. Precise and individual long-term safety profiles (malignancy, infections) of biologicals, as monotherapy or in combination with immunomodulators are poorly studied.

While the efficacy of immunomodulators in treating IBD was first reported in the 1960s [5], the CESAME (Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales en France) study evaluating the risk of lymphoproliferative disorders in patients receiving thiopurines for IBD was published 50 years later [6]. CESAME was the first nationwide prospective observational cohort which was designed to assess the possible excess risk of cancer in patients with IBD receiving thiopurines [6]. The CESAME cohort study demonstrated that a large cross-sectional observational cohort is able to address accurately and rapidly the long-term major safety issues associated with the prolonged use of thiopurines, with an immediate impact on guidelines [6–8]. Given the incidence of individual malignancies such as lymphomas or colorectal cancer in the general population with the same age-distribution as seen in IBD patients (one case for 1000 patient-years or below), a minimal number follow-up time of 30,000 patient-years is necessary to statistically demonstrate a significant excess risk of cancer associated with exposure to any drug [9–11]. Clinical trials, meta-analyses and safety-dedicated registries, such as TREAT [12] and ENCORE [13] are underpowered to evaluate the impact of IBD therapies on the individual risk of cancer. Of note, IBD phenotype and disease activity may also impact cancer risk. This is well established for colorectal cancer [9] and might be similar for lymphomas. Some nationwide administrative health databases are adequately powered for demonstrating the statistical link between drug exposure and individual cancers [10], but a proper adjustment for

IBD phenotype and disease activity is not possible due to the lack of corresponding data in these studies. Only large statistically powered prospective observational cohort studies with a standardized longitudinal follow-up, including a robust characterization of disease phenotype and a prospective follow-up of IBD activity can evidence based assess the risk-benefit ratio of current therapeutic strategies in the biologic era.

Achieving and maintaining endoscopic remission, prevention of bowel damage and reduction of IBD-related surgeries and hospitalizations have emerged as treatment goals in IBD patients [14,15]. The impact of anti-tumor necrosis factor (TNF) on the natural history of IBD (endoscopic remission, bowel damage, surgeries, and hospitalizations) beyond one year is unknown. The impact of anti-TNF therapy on long-term outcomes cannot be accurately studied using available clinical trial and registry databases. In order to properly assess the risk/benefit ratio of current therapeutic strategies, it was necessary to include all life-threatening events both IBD-related and non-IBD related by collecting all hospitalization reports in these patients.

Real-world data coming from a very large cohort of IBD patients with a long-term follow-up are needed to address these issues [16]. Same duration of follow-up across included patients (as well as a low number of dropout are required to ensure the accuracy of the data. The I-CARE (IBD Cancer and serious infections in Europe) project was initiated in 2010 by capitalizing on the experience of the CESAME cohort study. Limitations of the CESAME study included the lack of information on the dose and duration of treatments exposure as well as no prospective assessment of disease activity and severity. The objective of I-CARE was to assess prospectively the presence and the extent of safety concerns anti-TNF or other biologic agents alone or in combination with thiopurines among IBD patients. In addition, I-CARE represents a unique opportunity to investigate the potential for disease modification as well as health economics assessment. These real-world datas will be used to guide clinicians as well as healthcare Authorities and payers 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 who are candidates for biological therapy.

Methods

Study design

I-CARE is a European prospective longitudinal observational multicenter cohort study. A total of 15 countries participated: Belgium, Denmark, France, Germany, Greece, Hungary, Ireland, Israel, Italy, The Netherlands, Poland, Portugal, Spain, Sweden, and United Kingdom. All investigators are European gastroenterologists participating in the study on a voluntary basis. This project is centralized, sponsored, and coordinated by the GETAID (Groupe d'Etude des Affections Inflammatoires du Tube Digestif), and supported by ECCO (European Crohn's and Colitis Organisation) and EFFCA (European Federation of Crohn's and Ulcerative Colitis Associations).

Patient ≥ 18 years with an established diagnosis of CD, UC, or IBD unclassified (UBDu) since ≥ 3 months were included. The diagnosis of IBD was based on internationally accepted endoscopic, radiological, and/or histological criteria. After obtaining an informed consent, information about personal details (mobile and home phone number, email address) was recorded and the patient informed about how record data, using his/her private mobile, computer or other electronic device during the study period. Exclusion criteria were patients unable or refusing to sign the informed consent form, or with no regular access to internet, or receiving treatment at entry in the study with an immunomodulator other than thiopurines and methotrexate (e.g. cyclosporine, tacrolimus, mycophenolate mofetil), and those currently or previously 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).

Each investigator could enroll up to 130 patients (not mandatory) who were divided into 6 pre-defined groups at inclusion based on ongoing IBD-related treatment at inclusion; Group 1: patients without IBD-related treatment or treated with any 5-aminosalycilates (5-ASA) and/or

steroids formulations, Group 2: patients receiving thiopurines/methotrexate alone, Group 3: patients treated with anti-TNF therapy monotherapy (without any concomitant immunosuppressant), Group 4: patients treated with anti-TNF therapy in combination with thiopurines or methotrexate, Group 5: patients treated with vedolizumab with or without any concomitant medications, Group 6: patients treated with ustekinumab with or without any concomitant medications.

The primary objective of I-CARE is to assess prospectively the presence and the extent of safety concerns (cancers (especially lymphoma) and serious infections risks) for anti-TNF or other biologic alone or in combination with thiopurines among IBD patients. The safety profile of all steroid formulations is also analyzed. The four main secondary objectives of the I-CARE project are 1) to investigate prospectively the impact of anti-TNF or other biologic based strategies on the natural history of IBD and their potential for disease modification by collecting validated surrogate markers such as endoscopic remission and disease complications such as bowel damage (strictures, fistulas, abscess), surgeries, and hospitalizations, 2) to assess the evolution of PROs on a yearly basis and the impact of anti-TNF agents or other biologic on PROs in IBD, 3) to evaluate the benefit-risk ratio of strategies based on an earlier and wider use of anti-TNF or other biologic therapy for IBD, and 4) to assess the direct healthcare costs and cost-efficacy of current therapeutic strategies in IBD.

Data collection

Each investigator selected and consented the patient, and entered the baseline demographic and disease characteristic data of the patient in the electronic case report form (eCRF). The gastroenterologist who completed the e-summary form was also requested every year to validate and, if necessary, correct the information prospectively entered by the patients on a

monthly basis. The gastroenterologist was also requested to evaluate yearly available endoscopic and imaging disease activity reports using a predefined and simplified scoring system.

A dedicated web-based tool was built by SANOIA, a service provider with experience in patient e-Diary and e-PRO to capture the information coming from the patients. SANOIA also ensured adequate reminder electronic messages to be send to the patients for timely completion of the e-Diary and e-PRO. Patients completed the e-Diary on a monthly basis including e-PRO, hospitalizations, surgeries and cancer diagnosis. Lifestyle factors such as smoking status and alcohol consumption were recorded at enrollment. Patients who reported hospitalization were requested to provide the related hospitalization report. Patients who reported a cancer or a high-grade dysplasia were instructed to provide the related diagnostic pathology report. An alert system was set up to inform study coordinators and project managers of incomplete data or report of hospitalization, surgery, infection or cancer diagnostic to allow timely tracking of the pertinent documents to upload on the Web Portal. All hospitalization reports collected were coded by a dedicated expert coding group using the ICD-10 classification. Details on the coding methodology will be provided in a separate paper.

As the implementation of the I-CARE project across Europe at the national level was anticipated to be challenging, due to differences in language, regulatory, and practical aspects, healthcare systems, and patients' journey, we gathered a core group of national coordinators (1-3 gastroenterologists per country). Their roles were to identify potential investigators, to disseminate information about logistics and scientific aspects of I-CARE, to translate all patients' documents and questionnaires in local language, to motivate investigators, to get institutional review board (IRB) approval, and to interact with study coordinators on a regular basis.

Cohort size calculation

Calculation of cohort size was made based on the primary objective of I-CARE. We estimated, based on the CESAME lymphoma incidence rates [6], that a minimum of 47,000 patient-years was needed for the study to have a statistical power of 80% to detect a lymphoma hazard ratio of at least 3.5 in the groups of patients receiving thiopurines, either alone or in combination with anti-TNF, vedolizumab or ustekinumab, relative to patients not receiving thiopurines (i.e. receiving anti-TNF alone or no immunosuppressor).

Results

Patient characteristics

From March 2016 to April 2019, 13,262 patients gave informed consent to participate in this study. Among these patients, one was secondarily detected as not fulfilling eligibility criteria, 2150 did not confirm their participation by not activating the e-PRO digital system, 445 activated the e-PRO digital system but did not complete any e-PRO questionnaire, 434 completed only one-PRO questionnaire, thus generating no follow-up time, and 26 withdraw secondarily their consent to the use of their data. Ultimately, 10,206 patients were included in the I-CARE study by 508 investigators from 15 countries (Figure 1). Clinical characteristics of the patients are summarized in Table 1, Table 2, Supplementary table 1 and Supplementary table 2. Among the 10,206 patients, 6,169 (60.4%) had CD, 3,853 (37.8%) had UC, and 184 (1.8%) had IBDu. There was a female preponderance in the cohort (52.8%). The majority of patients had never smoked (54.8%). Mean body mass index (BMI) at inclusion was 24.8 (4.8) $kg.m^2$. Approximately 75% of patients had a job, 6.8% were retired, and 9.2% were students.

A total of 1,141 (11.9%) patients had a family history of IBD (11.0% for UC and IBDu patients and 12.5% for CD patients, p=0.03). Age at diagnosis of IBD was ≤ 16 years in 1,182 (11.6%) patients, between 17 and 40 years in 7,314 (71.7%) patients, and > 40 years in 1,710 (16.8%) patients. Mean age at inclusion was 39.8 (13.1) years. Mean disease duration at inclusion was 10.6 (8.9) years (9.8 (8.5) years for UC and IBDu patients and 11.2 (9.1) years for CD patients, p<0.0001). Location of disease at diagnosis according to Montreal classification was mainly ileocolonic in CD (42.9%), and extensive colitis in UC (45.5%). CD behavior at enrollment was inflammatory in 52% of the cases. Perianal disease was present in 27.9% of CD patients. One hundred and seventy-four (1.8%) had concomitant primary sclerosing cholangitis (2.3% of both the UC and IBDu patients, and 1.5% of the CD patients).

At inclusion about a quarter of patients (26.8%) underwent previous IBD-related surgery (41.7% of the CD patients, and 4.0% of the UC and IBDu patients, p<0.0001). The most frequent surgical procedures were ileocecal resection in 24.4% (1,504/6,169) of CD patients, and perianal surgery in 13.9% (806/6,169) of CD patients.

Prior and current medications

IBD-related medications at study entry are summarized in Table 3 and Table 4. Previous treatments before inclusion are summarized in Supplementary table 3, Supplementary table 4, and Supplementary table 5.

5-ASA/ mesalazine

A total of 3,413 (36.4%) patients received previous treatment with oral 5-ASA (mesalazine), and 2,229 (23.6%) with topical 5-ASA. The majority of patients who were previously treated with topical 5-ASA had UC or IBDu (p<0.0001). At study entry, 3,568 (35%) were receiving oral 5-ASA, and 1,010 (9.9%) patients topical 5-ASA. They were more likely to suffer from UC (p<0.0001).

Corticosteroids

A large majority of patients (65.9%) were previously treated with systemic steroids. Budesonide was previously used in 1,990 (21%) patients (7.2% in UC patients and 30.1% in CD patients, p<0.0001), and budesonide MMX in 106 (1.1%) patients. At enrollment, 569 (5.6%) patients were receiving systemic corticosteroids (oral or intravenous). Budesonide was prescribed in 148 (1.5%) patients, and budesonide MMX in 28 patients (0.3%).

Immunosuppressants/ immunomodulators

30.7% (3136/10,206) of patients reported previous treatment with azathioprine, 6.3% (638/10,206) with methotrexate, and 4.7% (478/10,206) with 6-mercaptopurine. Among 30.7% of patients who received azathioprine prior to study entry, almost half of them (48.4%) were exposed for less than one year.

At enrollment, 3,294 (32.3%) patients were receiving thiopurines, 4.6% (468/10,206) 6-mercaptopurine, and 3.2% (325/10,206) methotrexate. Patients receiving azathioprine or methotrexate were more likely to have CD compared to patients not receiving methotrexate ($p<0.0001$).

Biologics

A total of 1,690 (17.8%) patients had received infliximab before entering the study. Of the enrolled patients, 1,334 (14.0%) had prior use of adalimumab, 141 (1.5%) golimumab, and 60 (0.6%) certolizumab pegol. Concerning other biologics than anti-TNF, 147 (1.5%) had prior use of vedolizumab, and 38 (0.4%) ustekinumab.

At study entry, 2,725 (26.7%) patients were receiving infliximab, 1,937 (19%) adalimumab, 149 (1.5%) golimumab, 9 (0.1%) certolizumab pegol, 894 (8.8%) vedolizumab, and 343 (3.4%) ustekinumab.

History of cancer or dysplasia

Among all included patients, 298 (2.9%) patients had a prior history of any-type of cancer, including 135 UC or IBDu and 163 CD patients, (Supplementary table 6). Moreover, 108 patients (1.1%) had a medical history of high-grade dysplasia: 20 patients had colonic high-grade dysplasia, 3 esopheal high-grade dysplasia, and 71 uterine cervix high-grade dysplasia. There was no difference between UC and CD patients. A total of 1,085 (11.3%) patients had a

family history (first degree relative) of any of the following cancer: lymphoma, colorectal cancer, melanoma or breast cancer (Supplementary table 1).

History of vaccination and infection

Vaccination rate was 6.2% for human papillomavirus vaccine, 56.5% for hepatitis B vaccine, 35.1% for pneumococcus vaccine, and 53.9% for Bacille Calmette-Guerin (BCG) vaccine (Supplementary table 7). A confirmed history of symptomatic mononucleosis infection was reported in 376 patients (5%), including 140 UC or IBDu, and 236 CD patients before inclusion.

Discussion

I-CARE is the first prospective cohort study that is specifically designed to assess the risk-benefit ratio of current therapeutic strategies in the biologic era in patients with IBD. I-CARE is a European collaborative effort involving 15 countries. A total of 10,206 IBD patients were enrolled between March 2016 and April 2019.

To reach the I-CARE objectives, we developed innovative tools like a dedicated web-based tool to capture the information (e-Diary and e-PRO) coming from the patients, and a second platform to house the investigators database and eCRF completed by the investigators (Supplementary Figure 1). An interface was built between these two systems to allow enrollment of patients after the investigators completed their contact information on the eCRF, and investigators to have a summary of data entered by their patients for validation.

One of the strengths of the I-CARE project was the quality of data collection (Table 5). The patient had a central role in the investigation. However, patient data were annually reviewed and validated by their gastroenterologist. For cancer, dysplasia, any IBD related and IBD non-related hospitalizations, surgeries, the corresponding hospitalization and histological reports were collected. Collected comorbidities are alcohol, smoking, BMI. From the hospitalization reports, we will be able to collect other comorbidities, and perform a nested case control study.

The majority of patients had a CD diagnosis in ICARE (60.4%), this rate was similar to the CESAME study (60.3%) [7]. Age at diagnosis of IBD was similar to the previous study, with a large majority of patients diagnosed between 17 and 40 years of age [17]. Concerning the Montreal classification and the presence of perianal lesions, our data were consistent with literature [18]. As expected, in I-CARE, patients were more likely to be treated with biologics than in other databases [19,20]. Even though I-CARE is not a population-based study because of a large sample

size, baseline characteristics are those commonly observed in European studies underscoring its validity and representativeness [19,20].

The primary focus of I-CARE was to address the lymphoma risk, including other malignancies, as well as serious infections in IBD patients exposed to biologics. Based on CESAME experience, to minimize potential bias and confounding effects for evaluation of the effect of each treatment exposure on the occurrence of severe infection, cancer and hospitalization, propensity score (using all details of IBD phenotype and history) for each treatment will be/ was calculated using logistic regression models. To overcome the main limitations of the CESAME project, we prospectively assessed clinical disease activity in IBD patients through prospective monthly assessments (HBI (Harvey-Bradshaw Index) for CD and SCCAI (Simple Clinical Colitis Activity Index) for UC), and disease activity/severity through a scoring system of imaging and endoscopic reports. To this end, we were able to adjust for IBD activity the relationship between drug exposures and outcomes. We also recorded and quantified the exposure to IBD drugs of interest from IBD diagnosis, prior to the enrollment into the cohort, in order to be able to address the potential link between the cumulative dose of drug exposure and the late occurrence of malignancies. For the first time, we have collected all IBD treatments received since IBD diagnosis (every course, every drug class, every date of start and duration of treatment). Only the precise dose was not collected before I-CARE entry. Finally, we recorded family histories of lymphoma, colorectal cancer, melanoma and breast cancer that have been shown to have a key role in the individual cancer risks. The statistical power and granularity of ICARE will provide unique information on the relationships between IBD drugs and efficacy and safety outcomes in the biologics era.

Regarding the obstacles encountered during the I-CARE project, it was necessary to convince countries with existing national cohort to participate in the I-CARE project, obtain regulatory approval across countries, develop authorship rules, organize regular meetings at international

conferences to inform and motivate collaborators, and define a precise task distribution given the number of people involved in this project.

Future findings from I-CARE and sub-studies will likely be implemented in IBD guidelines and used to guide the decision-making process in daily practice.

Regulatory

Master ICARE Protocol received an approval from Saint Louis Ethic Committee on 15/05/2015 and CNIL approval on 27/10/2015.

Each country participating to ICARE had the responsibility to submit the protocol and the amendments in agreement with their own local regulation.

I-CARE Eudract Number : 2014-004728-23

Clinical Trial.gov – Register number : NCT 02377258

N° INDS : TP305083

CEREES approval on 20 Feb 2019

*Members of the I-CARE collaborator group are listed in the Apprendix.

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Figure legend

Figure 1. Patient's Flowchart

Table legends

Table 1. Baseline characteristics

Table 2. Disease characteristics

Table 3. Ongoing immunomodulators, corticosteroids and 5-ASA treatments at entry

Table 4. Ongoing Biological treatments at entry

Table 5. Strengths of I-CARE

Table 1. Baseline characteristics

	Total N= 10206			Ulcerative colitis or IBD Unclassified N=4037 (39.6%)			Crohn's Disease N=6169 (60.4%)			
	N	%/mean	SD	N	%/mean	SD	N	%/mean	SD	p*
Distribution of patients included by country										<.0001
Belgium	499	4.9		185	4.6		314	5.1		
Denmark	320	3.1		148	3.7		172	2.8		
France	2955	29.0		1007	24.9		1948	31.6		
Germany	481	4.7		208	5.2		273	4.4		
Greece	850	8.3		307	7.6		543	8.8		
Hungary	244	2.4		98	2.4		146	2.4		
Ireland	273	2.7		117	2.9		156	2.5		
Israel	298	2.9		75	1.9		223	3.6		
Italy	861	8.4		404	10.0		457	7.4		
Netherlands	116	1.1		45	1.1		71	1.2		
Poland	80	0.8		22	0.5		58	0.9		
Portugal	267	2.6		99	2.5		168	2.7		
Spain	791	7.8		312	7.7		479	7.8		
Sweden	94	0.9		63	1.6		31	0.5		
United Kingdom	2077	20.4		947	23.5		1130	18.3		
Disease duration at inclusion (years)	10206	10.6	8.9	4037	9.8	8.5	6169	11.2	9.1	<.0001
Gender										<.0001
Female	5385	52.8		2032	50.3		3353	54.4		
Male	4821	47.2		2005	49.7		2816	45.6		
Age at inclusion (years)	10206	39.8	13.1	4037	41.5	13.7	6169	38.7	12.5	<.0001
IBD sub type										<.0001
Crohn's Disease	6169	60.4		0	0.0		6169	100.0		
IBD Unclassified	184	1.8		184	4.6		0	0.0		
Ulcerative Colitis	3853	37.8		3853	95.4		0	0.0		
Working status										<.0001
Having a job	7644	74.9		3048	75.5		4596	74.5		
Unemployed	923	9.0		303	7.5		620	10.1		
Retired	698	6.8		337	8.3		361	5.9		
Student	941	9.2		349	8.6		592	9.6		
Body Mass Index (kg.m²)	9384	24.8	4.8	3728	25.0	4.7	5656	24.7	4.9	0.0001
Smoking status										<.0001
Current	1471	15.5		336	8.9		1135	19.8		
Former	2827	29.8		1199	31.8		1628	28.4		
Never	5204	54.8		2235	59.3		2969	51.8		
Missing	704			267			437			
Alcohol Consumption										<.0001
No	7715	81.0		2917	77.1		4798	83.6		
Yes	1805	19.0		864	22.9		941	16.4		
Missing	686			256			430			

* Chi-square test for qualitative variables, Wilcoxon test for quantitative variables
Abbreviation: IBD (Inflammatory Bowel Disease), SD (Standard Deviation)

Table 2. Disease characteristics

	Total N= 10206			Ulcerative colitis or IBD Unclassified N=4037 (39.6%)			Crohn's Disease N=6169 (60.4%)			
	N	%/mean	SD	N	%/mean	SD	N	%/mean	SD	p*
Age at diagnosis (years)										<.0001
(A1) 16 and below	1182	11.6		325	8.1		857	13.9		
(A2) between 17 and 40 included	7314	71.7		2848	70.5		4466	72.4		
(A3) 41 and above	1710	16.8		864	21.4		846	13.7		
CD Location (L1, L2, L3)										
(L1) ileal, including caecum	2172	37.9					2172	37.9		
(L2) colonic	1100	19.2					1100	19.2		
(L3) ileocolonic	2463	42.9					2463	42.9		
Missing	434						434			
CD Behavior (B1, B2, B3)										
(B1) non-stricturing, non-penetrating	2976	52.0					2976	52.0		
(B2) stricturing	1613	28.2					1613	28.2		
(B3) penetrating	1134	19.8					1134	19.8		
Missing	446						446			
Any perianal disease										
No	4145	72.1					4145	72.1		
Yes	1606	27.9					1606	27.9		
Missing	418						418			
UC involvement (E1, E2, E3)										
(E1) Proctitis	551	14.6		551	14.6					
(E2) Left sided colitis	1501	39.9		1501	39.8					
(E3) Extensive UC	1714	45.5		1715	45.5					
Missing	271			271						
Cumulative estimated microscopic and/or macroscopic extend of the surface of colonic mucosa										<.0001
0%	2321	27.3		436	13.0		1885	36.8		
]0%-50%]	3210	37.8		1396	41.5		1814	35.4		
]50%-100%]	2961	34.9		1533	45.6		1428	27.9		
Missing	1714			672			1042			
Associate confirmed primary sclerosing cholangitis										0.0031
No	9262	98.2		3657	97.7		5605	98.5		
Yes	174	1.8		88	2.3		86	1.5		
Missing	770			292			478			

* Chi-square test

Abbreviation : CD (Crohn's Disease), SD (Standard Deviation), UC (Ulcerative Colitis)

Table 3. Ongoing immunomodulators, corticosteroids and 5-ASA treatments at entry

	Total N= 10206			Ulcerative colitis or IBD Unclassified N=4037 (39.6%)			Crohn's Disease N=6169 (60.4%)			
	N	%/mean	SD	N	%/mean	SD	N	%/mean	SD	p*
Any oral form of 5-ASA (oral)										<.0001
No	6638	65.0		1473	36.5		5165	83.7		
Yes	3568	35.0		2564	63.5		1004	16.3		
Any topical forms of 5-ASA (suppository, foam, enema)										<.0001
No	9196	90.1		3103	76.9		6093	98.8		
Yes	1010	9.9		934	23.1		76	1.2		
Any form of systemic corticosteroids										<.0001
No	9637	94.4		3721	92.2		5916	95.9		
Yes	569	5.6		316	7.8		253	4.1		
Corticosteroids: administration of treatment										0.1963
Intravenous	11	1.9		4	1.3		7	2.8		
Oral	558	98.1		312	98.7		246	97.2		
Budesonide (oral)										<.0001
No	10058	98.5		4018	99.5		6040	97.9		
Yes	148	1.5		19	0.5		129	2.1		
Budesonide MMX (oral)										<.0001
No	10178	99.7		4015	99.5		6163	99.9		
Yes	28	0.3		22	0.5		6	0.1		
Beclometasone (oral)										<.0001
No	10186	99.8		4019	99.6		6167	100.0		
Yes	20	0.2		18	0.4		1	0.0		
Azathioprine										<.0001
No	6912	67.7		2890	71.6		4022	65.2		
Yes	3294	32.3		1147	28.4		2147	34.8		
6-Mercatopurine										0.2819
No	9738	95.4		3863	95.7		5875	95.2		
Yes	468	4.6		174	4.3		294	4.8		
Methotrexate										<.0001
No	9881	96.8		3969	98.3		5912	95.8		
Yes	325	3.2		68	1.7		257	4.2		

* Chi-square test
Abbreviations : 5-ASA (5-aminosalycilates), SD (Standard Deviation)

Table 4. Ongoing Biological treatments at entry

	Total N= 10206			Ulcerative colitis or IBD Unclassified N=4037 (39.6%)			Crohn's Disease N=6169 (60.4%)			
	N	%/mean	SD	N	%/mean	SD	N	%/mean	SD	p*
Biological treatments										<.0001
Adalimumab	1937	19.0		262	6.5		1675	27.2		
Certolizumab Pegol	9	0.1		1	0.0		8	0.1		
Golimumab	149	1.5		137	3.4		12	0.2		
Infliximab	2725	26.7		853	21.1		1872	30.3		
None	4149	40.6		2280	56.5		1869	30.3		
Ustekinumab	343	3.4		12	0.3		331	5.4		
Vedolizumab	894	8.8		492	12.2		402	6.5		
Infliximab: Estimated duration of treatment before entry in I-CARE (years)										.
<1 year	780	28.6		303	35.5		477	25.5		
1 year	363	13.3		129	15.1		234	12.5		
2 years	353	13.0		117	13.7		236	12.6		
3 years	260	9.5		72	8.4		188	10.0		
4 years	217	8.0		66	7.7		151	8.1		
5 years	162	5.9		43	5.0		119	6.4		
6 years	143	5.2		36	4.2		107	5.7		
7 years	113	4.1		25	2.9		88	4.7		
8 years	80	2.9		22	2.6		58	3.1		
9 years	70	2.6		16	1.9		54	2.9		
10 years	56	2.1		10	1.2		46	2.5		
11 years	44	1.6		5	0.6		39	2.1		
12 years	32	1.2		3	0.4		29	1.5		
13 years	18	0.7		2	0.2		16	0.9		
14 years	10	0.4		2	0.2		8	0.4		
15 years	9	0.3		2	0.2		7	0.4		
16 years	9	0.3		0	0.0		9	0.5		
17 years	1	0.0		0	0.0		1	0.1		
18 years	1	0.0		0	0.0		1	0.1		
19 years	1	0.0		0	0.0		1	0.1		
20 years	1	0.0		0	0.0		1	0.1		
Missing	2			0			2			
Adalimumab: Estimated duration of treatment before entry in I-CARE (years)										.
<1 year	564	29.1		109	41.6		455	27.2		
1 year	297	15.3		47	17.9		250	14.9		
2 years	319	16.5		40	15.3		279	16.7		
3 years	211	10.9		19	7.3		192	11.5		
4 years	183	9.4		21	8.0		162	9.7		
5 years	97	5.0		9	3.4		88	5.3		
6 years	81	4.2		6	2.3		75	4.5		
7 years	75	3.9		3	1.1		72	4.3		
8 years	41	2.1		4	1.5		37	2.2		
9 years	28	1.4		1	0.4		27	1.6		
10 years	24	1.2		3	1.1		21	1.3		
11 years	8	0.4		0	0.0		8	0.5		
12 years	2	0.1		0	0.0		2	0.1		
13 years	2	0.1		0	0.0		2	0.1		
14 years	1	0.1		0	0.0		1	0.1		
Missing	4			0			4			
Certolizumab Pegol: Estimated duration of treatment before entry in I-CARE (years)										0.6667
<1 year	2	22.2		1	100.0		1	12.5		
1 year	3	33.3		0	0.0		3	37.5		
2 years	1	11.1		0	0.0		1	12.5		
3 years	1	11.1		0	0.0		1	12.5		
4 years	1	11.1		0	0.0		1	12.5		
7 years	1	11.1		0	0.0		1	12.5		
Golimumab: Estimated duration of treatment before entry in I-CARE (years)										0.1842
<1 year	76	51.0		71	51.8		5	41.7		
1 year	36	24.2		34	24.8		2	16.7		

	Total N= 10206			Ulcerative colitis or IBD Unclassified N=4037 (39.6%)			Crohn's Disease N=6169 (60.4%)			
	N	%/mean	SD	N	%/mean	SD	N	%/mean	SD	p*
2 years	25	16.8		23	16.8		2	16.7		
3 years	10	6.7		7	5.1		3	25.0		
4 years	2	1.3		2	1.5		0	0.0		
Vedolizumab: Estimated duration of treatment before entry in I-CARE (years)										0.3220
<1 year	576	64.5		325	66.1		251	62.6		
1 year	187	20.9		93	18.9		94	23.4		
2 years	97	10.9		57	11.6		40	10.0		
3 years	24	2.7		11	2.2		13	3.2		
4 years	7	0.8		5	1.0		2	0.5		
5 years	1	0.1		1	0.2		0	0.0		
8 years	1	0.1		0	0.0		1	0.2		
Missing	1			0			1			
Ustekinumab: Estimated duration of treatment before entry in I-CARE (years)										0.0950
<1 year	237	69.1		10	83.3		227	68.6		
1 year	55	16.0		0	0.0		55	16.6		
2 years	36	10.5		0	0.0		36	10.9		
3 years	8	2.3		2	16.7		6	1.8		
4 years	2	0.6		0	0.0		2	0.6		
5 years	2	0.6		0	0.0		2	0.6		
6 years	1	0.3		0	0.0		1	0.3		
7 years	1	0.3		0	0.0		1	0.3		
8 years	1	0.3		0	0.0		1	0.3		

* Chi-square test or Fisher's exact test

Abbreviation : SD (Standard Deviation)

Table 5. Strengths of I-CARE

1. Large statistically powered prospective observational cohort study
2. Real-world data
3. Standardized longitudinal follow-up
4. Long-term follow-up
5. Quality of data collection
6. Primary objective: to assess prospectively the presence and the extent of safety concerns (cancers (especially lymphoma) and serious infections risks) for anti-TNF or other biologic alone or in combination with thiopurines
7. Secondary objectives: - To investigate prospectively the impact of anti-TNF or other biologic based strategies on the natural history of IBD and their potential for disease modification - To assess the evolution of PROs on a yearly basis and the impact of anti-TNF agents or other biologic on PROs in IBD - To evaluate the benefit-risk ratio of strategies based on an earlier and wider use of anti-TNF or other biologic therapy for IBD - To assess the direct healthcare costs and cost-efficacy of current therapeutic strategies in IBD

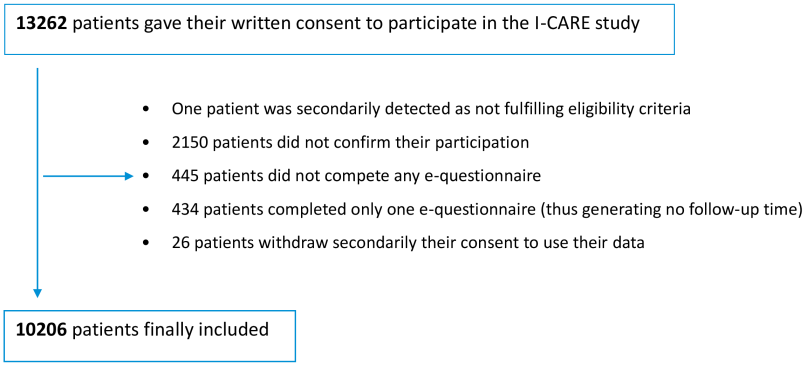

Figure 1 : Patient 's Flowchart

Appendix: I-CARE Collaborator Group

Investigators, listed by decreasing number of patients enrolled:

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Supplementary table legends

Table 1. Family History of inflammatory bowel disease or cancer

Table 2. Previous surgeries

Table 3. Previous 5-ASA and corticosteroids treatments

Table 4. Previous Immunomodulators treatments

Table 5. Previous Biological treatments

Table 6. History of cancer

Table 7. History of vaccination and infection

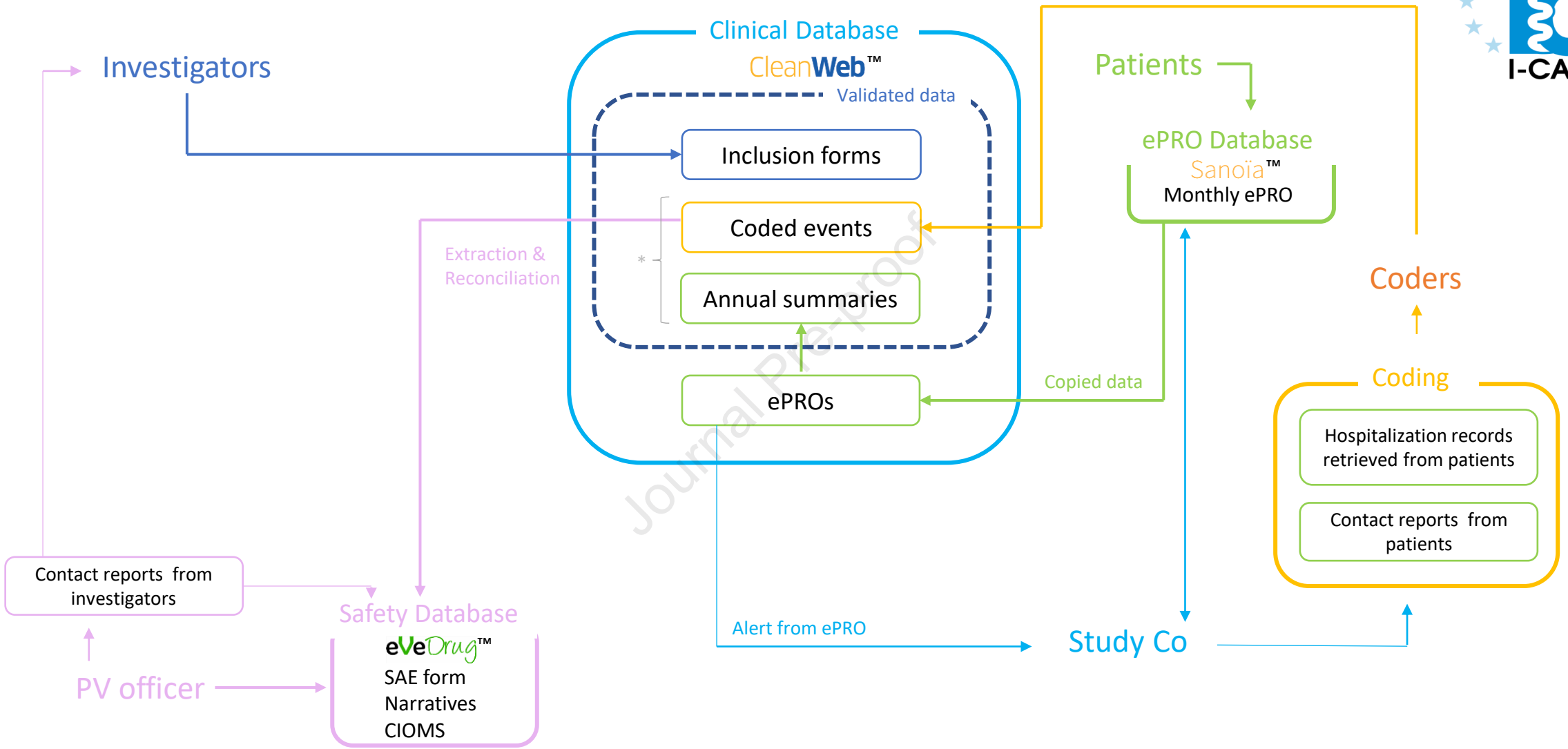

Figure 1a:ICARE Dataflow

* Reconcilation at the end of the study

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Figure 1b: I-Care contributors

Nov. 2009
First draft (Laurent Beaugerie): concept of a CESAME-type cohort of highest quality and at the European level to better understand the relationships between cancers, IBD and biologics

June 2010
Founding meeting of the project with Laurent Beaugerie, Marc Lémann and Laurent Peyrin-Biroulet (designated as PI)

UEG 2010
Participation of Severine Vermeire and Jean-François Rahier
Decision to extend the major events of interest to serious infections

DDW 2014
Searching for funding with industrial partners

Oct. 2014
Signing of the first funding agreement

Oct. 2014
Release of Icare Publication Rules

UEGW 2014
First Nat coord meeting

Nov. 2014
Start of the database implementation

Jan. 2015
French Ethics committee approval

Nov. 2015
End of the database implementation

March 2016
First Patient In

April 2017
Adding the ustekinumab group

Sept. 2018
Extension of the patient participation up to 6 years

Nov. 2018
Training of the coders

Jan. 2019
Implementation of the Annual Summaries

Mar. 2019
Last Patient In

Mar. 2020
Implementation of the COVID 19 infection in the ePRO

Aug. 2020
Implementation of baseline characterics queries in the database

Jan. 2021
Database lock and baseline caracteristics extraction of the database

May 2022
Last ePRO completed

Submission on the first abstract on the I-Care Cohort

Figure 1c: Some history of I-Care

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Supplementary Table 1. Family History of inflammatory bowel disease or cancer

	Total N= 10206			Ulcerative colitis or IBD Unclassified N=4037 (39.6%)			Crohn's Disease N=6169 (60.4%)			
	N	%/mean	SD	N	%/mean	SD	N	%/mean	SD	p*
Family history of IBD										0.0263
No	8442	88.1		3382	89.0		5060	87.5		
Yes	1141	11.9		418	11.0		723	12.5		
Missing	623			237			386			
Family history of lymphoma, colorectal cancer, melanoma, breast cancer										0.0201
No	8485	88.7		3333	87.7		5152	89.1		
Yes	1085	11.3		466	12.3		619	10.7		
Missing	636			238			398			

* Chi-square test
Abbreviation : IBD (Inflammatory Bowel Disease), SD (Standard Deviation)

Supplementary Table 2. Previous surgeries

	Total N= 10206			Ulcerative colitis or IBD Unclassified N=4037 (39.6%)			Crohn's Disease N=6169 (60.4%)			
	N	%/mean	SD	N	%/mean	SD	N	%/mean	SD	p*
Previous surgery										<.0001
No	7473	73.2		3877	96.0		3596	58.3		
Yes	2733	26.8		160	4.0		2573	41.7		
Proximal small bowel resection										<.0001
No	10004	98.0		4036	100.0		5968	96.7		
Yes	202	2.0		1	0.0		201	3.3		
Ileocaecal or ileal resection										<.0001
No	8699	85.2		4034	99.9		4665	75.6		
Yes	1507	14.8		3	0.1		1504	24.4		
Stricturoplasty										<.0001
No	10082	98.8		4036	100.0		6046	98.0		
Yes	124	1.2		1	0.0		123	2.0		
Segmental colectomy										<.0001
No	9855	96.6		4025	99.7		5830	94.5		
Yes	351	3.4		12	0.3		339	5.5		
Subtotal colectomy with ileorectal anastomosis										<.0001
No	10039	98.4		4015	99.5		6024	97.6		
Yes	167	1.6		22	0.5		145	2.4		
Total proctocolectomy with ileoanal anastomosis										0.7557
No	10119	99.1		4004	99.2		6115	99.1		
Yes	87	0.9		33	0.8		54	0.9		
Surgical drainage of abdominal abscess										<.0001
No	10038	98.4		4028	99.8		6010	97.4		
Yes	168	1.6		9	0.2		159	2.6		
Permanent stoma										<.0001
No	10085	98.8		4036	100.0		6049	98.1		
Yes	121	1.2		1	0.0		120	1.9		
Perianal surgery										<.0001
No	9345	91.6		3982	98.6		5363	86.9		
Yes	861	8.4		55	1.4		806	13.1		

* Chi-square test
Abbreviation : SD (Standard Deviation)

Supplementary Table 3. Previous 5-ASA and corticosteroids treatments

	Total N= 10206			Ulcerative colitis or IBD Unclassified N=4037 (39.6%)			Crohn's Disease N=6169 (60.4%)			
	N	%/mean	SD	N	%/mean	SD	N	%/mean	SD	p*
Any oral form of 5-ASA										<.0001
No	5967	63.6		2679	72.2		3288	58.0		
Yes	3413	36.4		1034	27.8		2379	42.0		
Missing	826			324			502			
Foam, suppositories or enema form of 5-ASA										<.0001
No	7223	76.4		2086	55.5		5137	90.2		
Yes	2229	23.6		1670	44.5		559	9.8		
Missing	754			281			473			
Any form of systemic corticostetoids										0.0063
No	3223	34.1		1344	35.7		1879	33.0		
Yes	6237	65.9		2420	64.3		3817	67.0		
Missing	746			273			473			
Budesonide										<.0001
No	7474	79.0		3496	92.8		3978	69.9		
Yes	1990	21.0		270	7.2		1720	30.1		
Missing	742			271			471			
Budesonide MMX										<.0001
No	9383	98.9		3701	98.2		5682	99.4		
Yes	106	1.1		69	1.8		37	0.6		
Missing	717			267			450			
Beclometasone										<.0001
No	9057	95.4		3425	90.9		5632	98.4		
Yes	434	4.6		344	9.1		90	1.6		
Missing	715			268			447			

* Chi-square test
Abbreviations : 5-ASA (5-aminosalycilates), SD (Standard Deviation)

Supplementary Table 4. Previous Immunomodulators treatments

	Total N= 10206			Ulcerative colitis or IBD Unclassified N=4037 (39.6%)			Crohn's Disease N=6169 (60.4%)			
	N	%/mean	SD	N	%/mean	SD	N	%/mean	SD	p*
Azathioprine										<.0001
No	7070	69.3		3161	78.3		3909	63.4		
Yes	3136	30.7		876	21.7		2260	36.6		
Azathioprine: Estimated duration of treatment before entry in I-CARE (years)										.
<1 year	1488	48.4		473	55.1		1015	45.8		
1 year	302	9.8		76	8.8		226	10.2		
2 years	309	10.1		79	9.2		230	10.4		
3 years	182	5.9		45	5.2		137	6.2		
4 years	163	5.3		45	5.2		118	5.3		
5 years	128	4.2		34	4.0		94	4.2		
6 years	119	3.9		28	3.3		91	4.1		
7 years	81	2.6		25	2.9		56	2.5		
8 years	57	1.9		12	1.4		45	2.0		
9 years	42	1.4		5	0.6		37	1.7		
10 years	47	1.5		8	0.9		39	1.8		
11 years	37	1.2		9	1.0		28	1.3		
12 years	36	1.2		4	0.5		32	1.4		
13 years	23	0.7		5	0.6		18	0.8		
14 years	11	0.4		4	0.5		7	0.3		
15 years	9	0.3		1	0.1		8	0.4		
16 years	13	0.4		1	0.1		12	0.5		
17 years	9	0.3		0	0.0		9	0.4		
18 years	4	0.1		1	0.1		3	0.1		
20 years	5	0.2		1	0.1		4	0.2		
21 years	2	0.1		0	0.0		2	0.1		
22 years	1	0.0		1	0.1		0	0.0		
24 years	1	0.0		0	0.0		1	0.0		
25 years	1	0.0		1	0.1		0	0.0		
26 years	1	0.0		0	0.0		1	0.0		
29 years	1	0.0		0	0.0		1	0.0		
>30 years	1	0.0		1	0.1		0	0.0		
Missing	63			17			46			
6-Mercatopurine										<.0001
No	9728	95.3		3890	96.4		5838	94.6		
Yes	478	4.7		147	3.6		331	5.4		
6-Mercaptopurine: Estimated duration of treatment before entry in I-CARE (years)										.
<1 year	330	70.5		100	68.5		230	71.4		
1 year	44	9.4		15	10.3		29	9.0		
2 years	24	5.2		7	4.8		17	5.3		
3 years	20	4.3		4	2.7		16	5.0		
4 years	10	2.1		5	3.4		5	1.6		
5 years	6	1.3		3	2.1		3	0.9		
6 years	8	1.7		4	2.7		4	1.3		
7 years	6	1.3		3	2.1		3	0.9		
8 years	6	1.3		3	2.1		3	0.9		
9 years	4	0.9		1	0.7		3	0.9		
10 years	2	0.4		0	0.0		2	0.6		
11 years	2	0.4		1	0.7		1	0.3		
12 years	2	0.4		0	0.0		2	0.6		
14 years	1	0.2		0	0.0		1	0.3		
15 years	1	0.2		0	0.0		1	0.3		
16 years	1	0.2		0	0.0		1	0.3		
18 years	1	0.2		0	0.0		1	0.3		
Missing	10			1			9			
Methotrexate										<.0001
No	9568	93.7		3931	97.4		5637	91.4		
Yes	638	6.3		106	2.6		532	8.6		
Methotrexate: Estimated duration of treatment before entry in I-CARE (years)										.

	Total N= 10206			Ulcerative colitis or IBD Unclassified N=4037 (39.6%)			Crohn's Disease N=6169 (60.4%)			
	N	%/mean	SD	N	%/mean	SD	N	%/mean	SD	p*
<1 year	316	51.2		59	57.8		257	49.9		
1 year	99	16.0		15	14.7		84	16.3		
2 years	86	13.9		14	13.7		72	14.0		
3 years	33	5.3		6	5.9		27	5.2		
4 years	28	4.5		4	3.9		24	4.7		
5 years	14	2.3		0	0.0		14	2.7		
6 years	13	2.1		0	0.0		13	2.5		
7 years	10	1.6		2	2.0		8	1.6		
8 years	7	1.1		0	0.0		7	1.4		
9 years	3	0.5		0	0.0		3	0.6		
10 years	5	0.8		1	1.0		4	0.8		
12 years	1	0.2		1	1.0		0	0.0		
14 years	1	0.2		0	0.0		1	0.2		
15 years	1	0.2		0	0.0		1	0.2		
Missing	21			4			17			

* Chi-square test
Abbreviation : SD (Standard Deviation)

Supplementary Table 5. Previous Biological treatments

	Total N= 10207			Ulcerative colitis or IBD Unclassified N=4038 (39.6%)			Crohn's Disease N=6169 (60.4%)			
	N	%/mean	SD	N	%/mean	SD	N	%/mean	SD	p*
Infliximab										<.0001
No	7790	82.2		3286	86.6		4504	79.2		
Yes	1690	17.8		507	13.4		1183	20.8		
Missing	726			244			482			
Infliximab: Estimated duration of treatment before entry in I-CARE (years)										.
<1 year	743	44.8		249	49.8		494	42.6		
1 year	269	16.2		92	18.4		177	15.3		
2 years	247	14.9		62	12.4		185	15.9		
3 years	145	8.7		36	7.2		109	9.4		
4 years	93	5.6		25	5.0		68	5.9		
5 years	55	3.3		12	2.4		43	3.7		
6 years	27	1.6		8	1.6		19	1.6		
7 years	30	1.8		7	1.4		23	2.0		
8 years	11	0.7		2	0.4		9	0.8		
9 years	16	1.0		3	0.6		13	1.1		
10 years	7	0.4		2	0.4		5	0.4		
11 years	4	0.2		1	0.2		3	0.3		
12 years	5	0.3		0	0.0		5	0.4		
13 years	1	0.1		1	0.2		0	0.0		
14 years	2	0.1		0	0.0		2	0.2		
15 years	4	0.2		0	0.0		4	0.3		
17 years	1	0.1		0	0.0		1	0.1		
Missing	30			7			23			
Adalimumab										<.0001
No	8186	86.0		3515	92.3		4671	81.8		
Yes	1334	14.0		292	7.7		1042	18.2		
Missing	686			240			456			
Adalimumab: Estimated duration of treatment before entry in I-CARE (years)										.
<1 year	562	42.9		184	64.1		378	36.9		
1 year	242	18.5		51	17.8		191	18.7		
2 years	185	14.1		27	9.1		158	15.4		
3 years	131	10.0		13	4.5		118	11.5		
4 years	71	5.4		7	2.4		64	6.3		
5 years	44	3.4		2	0.7		42	4.1		
6 years	36	2.7		0	0.0		36	3.5		
7 years	17	1.3		1	0.3		16	1.6		
8 years	10	0.8		0	0.0		10	1.0		
9 years	4	0.3		1	0.3		3	0.3		
10 years	6	0.5		1	0.3		5	0.5		
11 years	2	0.2		0	0.0		2	0.2		
17 years	1	0.1		0	0.0		1	0.1		
Missing	23			5			18			
Certolizumab pegol										<.0001
No	9501	99.4		3805	99.8		5696	99.1		
Yes	60	0.6		6	0.2		54	0.9		
Missing	645			226			446			
Certolizumab: Estimated duration of treatment before entry in I-CARE (years)										.
<1 year	35	59.3		2	33.3		33	62.3		
1 year	14	23.7		2	33.3		12	22.6		
2 years	4	6.8		0	0.0		4	7.5		
3 years	4	6.8		1	16.7		3	5.7		
4 years	1	1.7		0	0.0		1	1.9		
5 years	1	1.7		1	16.7		0	0.0		
Missing	1			0			1			
Golimumab										<.0001
No	9347	98.5		3700	97.1		5717	99.4		
Yes	141	1.5		109	2.9		32	0.6		

	Total N= 10207			Ulcerative colitis or IBD Unclassified N=4038 (39.6%)			Crohn's Disease N=6169 (60.4%)			
	N	%/mean	SD	N	%/mean	SD	N	%/mean	SD	p*
Missing	648			228			420			
Golimumab: Estimated duration of treatment before entry in I-CARE (years)										.
<1 year	95	68.8		74	67.9		21	72.4		
1 year	25	18.1		22	20.2		3	10.3		
2 years	11	8.0		9	8.3		2	6.9		
3 years	6	4.3		4	3.7		2	6.9		
4 years	1	0.7		0	0.0		1	3.4		
Missing	3			0			3			
Vedolizumab										0.0030
No	9392	98.5		3753	98.9		5639	98.2		
Yes	147	1.5		41	1.1		106	1.8		
Missing	667			243			424			
Vedolizumab: Estimated duration of treatment before entry in I-CARE (years)										.
<1 year	91	63.2		29	72.5		62	59.6		
1 year	32	22.2		6	15.0		26	25.0		
2 years	16	11.1		3	7.5		13	12.5		
3 years	4	2.8		2	5.0		2	1.9		
4 years	1	0.7		0	0.0		1	1.0		
Missing	2			1			1			
Ustekinumab										0.0002
No	9518	99.6		3807	99.9		5711	99.4		
Yes	38	0.4		4	0.1		34	0.6		
Missing	650			226			424			
Ustekinumab: Estimated duration of treatment before entry in I-CARE (years)										.
<1 year	28	73.7		3	75.0		25	73.5		
1 year	4	10.5		0	0.0		4	11.8		
2 years	2	5.3		1	25.0		1	2.9		
3 years	1	2.6		0	0.0		1	2.9		
4 years	3	7.9		0	0.0		3	8.8		

* Chi-square test
Abbreviation : SD (Standard Deviation)

Supplementary Table 6. History of cancer

	Total N= 10206			Ulcerative colitis or IBD Unclassified N=4037 (39.6%)			Crohn's Disease N=6169 (60.4%)			
	N	%/mean	SD	N	%/mean	SD	N	%/mean	SD	p*
Personal history of cancer										0.0395
No	9908	97.1		3902	96.7		6006	97.4		
Yes	298	2.9		135	3.3		163	2.6		
DYSPLASIA Colon										0.1574
No	10186	99.8		4026	99.7		6160	99.9		
Yes	20	0.2		11	0.3		9	0.1		
DYSPLASIA Esophagus										0.2827
No	10203	100.0		4037	100.0		6166	100.0		
Yes	3	0.0		0	0.0		3	0.0		
DYSPLASIA Uterine cervix (only CIN 3)										0.1496
No	10135	99.3		4003	99.2		6132	99.4		
Yes	71	0.7		34	0.8		37	0.6		
DYSPLASIA Uterine cervix (only women)										0.0756
No	5314	98.7		1998	98.3		3316	98.9		
Yes	71	1.3		34	1.7		37	1.1		

* Chi-square test or Fisher's exact test
Abbreviation : SD (Standard Deviation)

Supplementary Table 7. History of vaccination and infection

	Total N= 10206			Ulcerative colitis or IBD Unclassified N=4037 (39.6%)			Crohn's Disease N=6169 (60.4%)			
	N	%/mean	SD	N	%/mean	SD	N	%/mean	SD	p*
Human papilloma virus vaccine										0.6856
No	6088	93.8		2443	94.0		3645	93.7		
Yes	404	6.2		158	6.0		246	6.3		
Missing	3714			1436			2278			
Hepatite B vaccine										0.0379
No	2646	43.5		1093	45.1		1553	42.4		
Yes	3441	56.5		1331	54.9		2110	57.6		
Missing	4119			1613			2506			
Pneumococcus vaccine										<.0001
No	4031	64.9		1762	71.6		2269	60.5		
Yes	2184	35.1		700	28.4		1484	39.5		
Missing	3991			1575			2416			
BCG vaccine										0.4242
No	2609	46.1		1074	46.8		1535	45.7		
Yes	3046	53.9		1222	53.2		1824	54.3		
Missing	4551			1741			2810			
Herpes zoster										0.7668
No	5984	97.4		2426	97.5		3558	97.3		
Yes	160	2.6		63	2.5		97	2.7		
Missing	4062			1548			2514			
Confirmed symptomatic mononucleosis										0.2027
No	7178	95.0		2910	95.4		4268	94.8		
Yes	376	5.0		140	4.6		236	5.2		
Missing	2652			987			1665			

* Chi-square test
Abbreviation : BCG (Bacille Calmette-Guerin), SD (Standard Deviation)

What You Need to Know

Background: There is a need to evaluate the benefit-risk ratio of current therapies in inflammatory bowel disease (IBD) patients to provide the best quality of care.

Findings: I-CARE is an ongoing investigator-initiated observational European prospective cohort study that will provide unique information on the long-term benefits and risks of biological therapies in IBD patients.

Implications for patient care: Future findings from I-CARE and sub-studies will likely be implemented in IBD guidelines and used to guide the decision-making process in daily practice.