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ORIGINAL ARTICLE

Safety profiles of biologic agents for inflammatory bowel diseases: a prospective pharmacovigilance study in Southern Italy

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ABSTRACT

Introduction: Inflammatory bowel diseases (IBDs) are a public health issue with over 3.5 million patients in Europe, but the advent of several biologic agents has completely changed their management. Pharmacovigilance is needed to early detect expected/unexpected adverse events (AEs) to assess the safety of drugs in a real-world setting. Aim of this prospective pharmacovigilance study was to evaluate the occurrence of AEs in patients treated with biologic drugs in gastroenterology units in Southern Italy.

Methods: All consecutive patients treated with one biologic drug during a 2-years period (2017–2018) in six gastroenterology tertiary units and satisfying inclusion criteria were enrolled. Demographic and clinical characteristics of patients, type of treatment used, therapy discontinuation, failures, switch/swap to another biologic, and possible onset of AEs were collected. Adverse events have been compared to the number of AEs reported in the same centres in the two years before the protocol.

Results: Overall, 623 patients (253 females) with Crohn's disease (352; 56.5%) or ulcerative colitis (271; 43.5%) have been included. Infliximab (IFX) was the most commonly used (308, 49.4%), followed by adalimumab (ADA; 215, 34.5%), vedolizumab (VED; 73, 11.7%), golimumab (GOL; 26, 4.2%) and ustekinumab (UST; 0.2%). Ninety-two patients have experienced AEs (14.8%) and 10 serious adverse events (SAEs) (1.6%) were recorded. Adverse events and SAEs have been reported with GOL (7/26; $p = .88$), IFX (51/308; $p = .54$), ADA (28/125; $p = .40$) and VED (6/73; $p = .11$), no AEs occurred with UST (0/1).

Conclusion: Overall, considering the low rate of AEs reported and discontinuation from therapy, our data seems to confirm the positive beneficial/risk ratio of biologic treatment for IBDs and provide useful data on biologic drugs in gastroenterology.

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Adverse events; biologics; inflammatory bowel diseases; pharmacovigilance

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory bowel diseases (IBDs) characterized by chronic gastrointestinal inflammation and immune-mediated pathogenesis[1], leading often to hospitalisation, surgery and overall impaired quality of life[2].

In the past decade, IBDs have emerged as a public health issue worldwide[3]. In Europe, over 1.5 million and two million people are affected by CD and UC, respectively[4]. In Italy, it has been estimated that there are over 200,000 patients with IBDs (approximately 80,000 with CD and 120,000 with UC)[5], even though no reliable national epidemiological data provide an accurate estimate.

Due to their increasing incidence and their chronic features, IBDs entail considerable individual and social expenses, subdivided in the direct costs incurred by the National health care (e.g. pharmacological therapies, hospitalizations, surgical procedures) and indirect costs (e.g. job days lost by patients and their relatives, reduction of job opportunities).

Several topical and systemic treatments are currently available for treating IBDs: amino salicylates, systemic and topical corticosteroids (budesonide; beclomethasone dipropionate), and antibiotics. Other drugs utilized in IBDs include immunomodulators, thiopurines (azathioprine, 6-mercaptopurine), methotrexate and cyclosporine A[6–8]. The past decade has been characterized by substantial advances in the management of IBDs due to the introduction of several biologic agents[5].

Biologic therapies include monoclonal antibodies anti TNF-α and their related biosimilars (infliximab [IFX] and adalimumab [ADA] approved both for CD and UC, golimumab

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[GOL] for UC[6,9–12]) and agents targeting leukocyte trafficking (the anti-integrin $\alpha_4\beta_7$ vedolizumab [VED] approved for CD and UC[13]) Recently, ustekinumab (UST), a monoclonal antibody binding the p40 subunit of the pro-inflammatory interleukins (IL)-12 and −23[14] have been approved for CD and tofacitinib, an orally administered small molecule that is a nonselective inhibitor of the Janus kinase enzyme, for UC[7].

These new therapeutic approaches have led to an improvement in the quality of life, as well as in reducing hospitalizations and surgical interventions, inducing remission and response rates never achieved before with previous therapies[15,16].

Despite these significant improvements, treatment with biologics is not effective in all patients and many of them lose clinical response overtime. It has been estimated that patients treated with anti-TNF-α almost 30% do not achieve clinical response (primary failure) and up to 40% lose the clinical response (secondary failure).

Moreover, due to their rapid development, the risk/benefit profile of these therapies is still not completely defined and the adverse events (AEs) usually reported are associated with their specific mechanisms of action or excessive immune response, which require strictly monitoring[15]. In different clinical settings, spontaneous reporting has been demonstrated to underestimate the effective number of AEs[17] and an implementation of these activities is needed[18].

Indeed, active post-marketing surveillance programs (namely pharmacovigilance) are crucial to improve the early detection of expected and unexpected AEs and serious adverse events (SAEs), representing a powerful tool to better define brief and long term safety profiles of already marketed drugs and to determine related risk factors[19].

Aim of the present multicentre and multiregional (Calabria and Sicily, Italy) prospective pharmacovigilance study was to evaluate the occurrence of AEs in patients treated with biologic drugs in gastroenterology units in Southern Italy.

Materials and methods

Study protocol and data collection

The Calabria Biologics Pharmacovigilance Program (CBPP) is a multicentre pharmacovigilance project started in 2016 to improve the monitoring of safety of biologic agents in clinical practice in different fields of medicine including rheumatology, gastroenterology and dermatology as previously described[18]. This multiregional, active and prospective pharmacovigilance study was conducted between 1 January 2017 and 31 December 2018, for the evaluation of safety of biologics treatments in five gastroenterology tertiary centres in Calabria (*Azienda Ospedaliera "Pugliese-Ciaccio," Catanzaro, Italy; Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli," Reggio Calabria, Italy; Azienda Ospedaliera "Mater Domini," Catanzaro, Italy; Azienda Ospedaliera Provinciale "San Giovanni di Dio," Crotone, Italy; Azienda Ospedaliera "SS Annunziata," Cosenza, Italy*) and one gastroenterology tertiary centre in Sicily (*Azienda Ospedaliera Universitaria Policlinico "G. Martino," Messina, Italy*). A monitor, specialist in clinical pharmacology and who received specific training of pharmacovigilance, was assigned for each gastroenterology ward. All the consecutive patients treated with a biologic drug and satisfying inclusion criteria (see below) have been enrolled and followed for a maximum of two years.

Inclusion criteria were:

1. Age ≥18 years;
2. Confirmed diagnosis of moderate to severe CD or UC;
3. Treatment with one biologic drug (both monotherapy and co-administration with non- biologic therapy).

A patient encrypted code was used to maintain anonymity. Collected data were entered into an ad hoc developed database. Demographic and clinical data including age, sex, diagnosis (CD or UC), disease duration, current or prior use of other drugs, discontinuation or switch/swap to another drug with reason, and AEs have been collected. The date of the first biologic prescription during the study period represented the "index date" for each patient.

Patients were considered to have discontinued treatment whether the drug is not continued at the first visit after the 3 months follow-up or before. The causes for treatment discontinuation were classified as inefficacy or occurrence of AEs. Moreover, patients were considered to have switched if they have started treatment with a biologic drug other than the one reported on the index date during the study follow-up period.

For the evaluation of AEs, a periodic call has been performed by a clinical pharmacologist to investigate any AE in progress and to improve and stimulate minor AEs reports also during follow-up visits. Specifically, patients received the first call one week after the first administration and monthly thereafter. Moreover, patients were given a diary in order to take note of the eventually occurring AEs that were then reported during the monthly call. For each AE observed, the investigator (physician or pharmacist) recorded a detailed description, including time to onset and recovery, seriousness, outcome and codifying the AE according to the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) and System Organ Class (SOC) levels. An AE was defined as serious if was life-threatening or fatal, required hospitalization (or prolonged existing hospitalization), resulted in persistent or significant disability or in a congenital anomaly/birth defect or was another medically important condition (European Medicines Agency, 2017). Drugs' SmPC and *EudraVigilance* have been checked to assess previous reports.

Furthermore, in order to evaluate the association between AEs and drug treatment, the Naranjo Adverse Probability Scale[20] was applied, which is a method to assess whether there is a causal relationship between an identified untoward clinical event and a drug using a simple questionnaire to assign probability scores. For each AE reported, except for local AEs that are obviously linked to the injection of the active substance, clinical pharmacologist validated the causal link using the Naranjo algorithm and assigned a score to classify AE in certain (>8) probable (5–8) possible (1–4)

doubtful (0). During this quality control process, AEs were reviewed by a clinical pharmacist and reported to the National Pharmacovigilance Center.

Moreover, to compare the effectiveness of our active pharmacovigilance program, the number of AEs spontaneously reported for biologics in the same tertiary centres only of the Calabria region 24 months before starting the protocol (1 January 2015 to 31 December 2016) have been reported.

The study protocol was approved by the local Ethics Committee (*Comitato Etico Regionale Calabria*, Italy), protocol number 278/2015. All procedures were performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

Statistical analysis

Demographic and baseline characteristics were summarized using descriptive statistics. Continuous data are presented as mean ± standard deviation (SD) or median (25–75 percentile) as appropriate, while ordinal data are expressed as number (percentage). The Fisher's exact test or the Pearson chi-squared test for qualitative variables was used to compare cohorts with or without AEs/inefficacy to treatment. Student t-test was used for continuous variables. The significance level was set at a p value $\leq$ .05. SPSS 22.0 software (Chicago, IL) was used for statistical and data analysis.

Results

General characteristics of study cohort

Overall, 623 patients (253 females; mean age: 45.2 ± 15.9 years) with a diagnosis of active CD (352; 56.5%) or UC (271; 43.5%) started a treatment with a biologic drug and have been enrolled. All demographic and clinical information of the study population are summarized in Table 1.

Infliximab was the most commonly administered biologic drug at the index date (308; 49.4%), followed by ADA (215; 34.5%), VED (73; 11.7%), GOL (26; 4.2%) and only one patient with UST (0.2%); data subdivided *per* drugs are reported in Table 2.

Furthermore, 478 patients (76.7%) received concomitant treatment with one or more immunomodulatory drugs, non-steroidal anti-inflammatory drug (NSAIDs) or corticosteroids (CCS).

At the index date, 250 patients (40.1%) were naïve to biologic treatment; the remaining represent a prevalent population of patients already on treatment with one or more previous biologic drugs (number of previous biologic drugs range: 1–2; mean (±SD) therapy duration at study entry was 34.8 months ± 26.4).

Data reported in Table 3 refer to switches occurred during study period for AEs or treatment ineffectiveness (see Table 3 for switches details).

Table 1. Characteristics of the study cohort.

	Overall patients ($n = 623$)
Age, years	45.2 ± 15.9
Female sex, *n* (%)	253 (40.6)
Follow up, months	19.5 ± 1.5
Age first biologic therapy, years	42.6 ± 16.3
Naïve, *n* (%)	250 (40.1)
Diagnosis	
Crohn's disease, *n* (%)	352 (56.5)
Ulcerative colitis, *n* (%)	271 (43.5)
Biologic drugs prescribed	
IFX, *n* (%)	308 (49.4)
ADA, *n* (%)	215 (34.5)
GOL, *n* (%)	26 (4.2)
UST, *n* (%)	1 (0.2)
VED, *n* (%)	73 (11.7)
Concurrent treatments	478 (76.7)
MTX, *n* (%)	55 (8.8)
CyA, *n* (%)	1 (0.2)
AZA, *n* (%)	306 (49.1)
SSZ, *n* (%)	7 (1.1)
CCS, *n* (%)	102 (16.4)
NSAIDs, *n* (%)	214 (34.3)
CP, *n* (%)	1 (0.2)
6-MP, *n* (%)	34 (5.5)
Switched, *n* (%)	172 (27.6)
Adverse events	
AEs, *n* (%)	92 (14.8)
SAEs, *n* (%)	10 (1.6)

Abbreviations. IFX: infliximab; ADA: adalimumab; GOL: golimumab UST: ustekinumab; VED: vedolizumab; MTX: methotrexate; CyA: cyclosporin A; AZA: azathioprine; SSZ: sulfasalazine; CCS: corticosteroids; NSAIDs: Nonsteroidal anti-inflammatory drugs; CP: cyclophosphamide; 6-MP: 6-mercaptopurine; AEs: adverse events; SAEs: serious adverse events.

Adverse events and their prevalence before and after the study

Overall, we reported a total of 102 AEs; in particular, 92 patients have experienced AEs (14.8%) and 10 SAEs (1.6%). Naranjo probability scale documented a probable association (Naranjo Score value 6–8) for all AEs detected.

In our cohort, for each drug, AEs have been reported with GOL (7/26; $p = .88$), IFX (51/308; $p = .54$), ADA (28/125; $p = .40$) and VED (6/73; $p = .11$), no AEs have been occurred with UST (0/1) (Figure 1). Regarding severity, we reported six SAEs by IFX, 3 by ADA and 1 by VED, no statistical significance has been highlighted. Statistical difference in the frequency of AEs between naïve and previously exposed patients (65; 70.7% versus 27; 29.3%; $p = .022$, respectively) has been reported. On the other hand, any statistical difference between the two groups (naïve [4; 40%] versus non naïve [6; 60%], $p = .196$) regarding SAE has been found. The most common adverse events were skin and subcutaneous tissue disorders and general disorders and administration site conditions. All the AEs and SAEs, categorized according to the MedDRA dictionary, are detailed in Table 4.

No significant difference in the number of AEs/SAEs between CD ($n = 56$) and UC ($n = 44$) groups have been reported ($p = .67$ and $p > 1.00$, respectively for AEs and SAEs).

Ten patients experiencing SAEs were reported during the study period: one case of myocardial infarction and pulmonary embolism (both with infliximab), one case of nephrolithiasis (adalimumab), a case of severe pneumonia leading to

Table 2. Characteristics of the study cohort *per* drugs.

	IFX ($n = 308$)	ADA ($n = 215$)	GOL ($n = 26$)	UST ($n = 1$)	VED ($n = 73$)
Age, years	42.0 ± 14.7	44.1 ± 14.3	48.1 ± 14.5	45.2	61.0 ± 16.9
Male sex, *n* (%)	196 (63.4)	121 (56.3)	13 (50.0)	0	40 (54.8)
Follow up, months	21.1 ± 2.4	19 ± 1.7	19.3 ± 1.1	20.2	18 ± 2.5
Age first biologic therapy, years	39.2 ± 14.6	41.7 ± 14.7	46.3 ± 14.1	42.6	60.1 ± 17.2
Naïve, *n* (%)	120 (38.9)	72 (33.5)	6 (23.0)	0	60 (82.2)
Diagnosis					
Crohn's disease, *n* (%)	129 (41.9)	193 (89.8)	0	1 (100)	29 (39.7)
Ulcerative colitis, *n* (%)	179 (58.1)	22 (10.2)	26 (100)	0	44 (60.3)
Concurrent treatments	237 (76.9)	167 (77.7)	22 (84.6)	0	52 (71.2)
MTX, *n* (%)	15 (4.9)	26 (12.1)	1 (3.8)	0	27 (36.9)
CyA, *n* (%)	1 (0.3)	0	0	0	0
AZA, *n* (%)	152 (49.3)	113 (52.5)	14 (53.8)	0	1 (1.4)
SSZ, *n* (%)	2 (0.6)	5 (2.3)	0	0	0
CCS, *n* (%)	91 (29.5)	15 (6.9)	11 (42.3)	0	4 (5.5)
NSAIDs, *n* (%)	111 (36.0)	65 (30.2)	10 (38.5)	0	28 (38.3)
CP, *n* (%)	1(0.3)	0	0	0	0
6-MP, *n* (%)	18 (5.8)	14 (6.5)	0	0	2 (2.7)
Switched, *n* (%)	92 (29.9)	59 (27.4)	6 (23.1)	1 (100)	14 (19.2)
Adverse events					
AEs, *n* (%)	51 (16.6)	28 (13.0)	7 (26.9)	0	6 (8.2)
SAEs, *n* (%)	6 (1.9)	3 (1.4)	0	0	1 (1.4)

Abbreviations. IFX: infliximab; ADA: adalimumab; GOL: golimumab; UST: ustekinumab; VED: vedolizumab; MTX: methotrexate; CyA: cyclosporin A; AZA: azathioprine; SSZ: sulfasalazine; CCS: corticosteroids; NSAIDs: Nonsteroidal anti-inflammatory drugs; CP: cyclophosphamide; 6-MP: 6-mercaptopurine; AEs: adverse events; SAEs: serious adverse events.

Table 3. Details on switches related to inefficacy or switches related to AEs (in blankets) between biologic drugs.

		Switch to				
Switch from		IFX	ADA	GOL	UST	VED
	IFX		27 (6)	9 (1)	(2)	38 (8)
	ADA	12 (5)		1	21 (4)	18 (2)
	GOL	3	1		/	7
	UST	1	1	/		/
	VED	6	1	3 (1)	6	

On blankets switches related to AEs; Abbreviations. IFX: infliximab; ADA: adalimumab; GOL: golimumab; UST: ustekinumab; VED: vedolizumab.

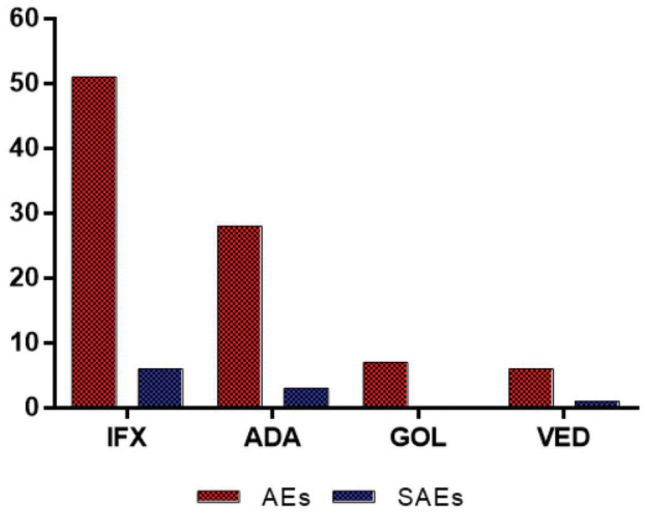

Figure 1. Patients with adverse events (AEs) and serious adverse events (SAEs). *No adverse events for ustekinumab. IFX: infliximab; ADA: adalimumab; GOL: golimumab; VED: vedolizumab; AEs: adverse events; SAEs: serious adverse events.

hospitalization (adalimumab), a case of pyelonephritis (infliximab), three cases of malignant neoplasm (i.e. one colorectal and a skin cancer with vedolizumab and one lung adenocarcinoma with adalimumab), a case of severe anemia leading to blood transfusion (infliximab) and an anaphylactoid reaction (infliximab). During the follow-up, none of the SAEs had a fatal outcome.

In the previous 2 years (2015–2016) before our active program, the same tertiary centres in Calabria reported overall only 35 patients experiencing AEs and the majority only with infliximab (29 with IFX, five with ADA and one with GOL) and none SAE related with biologic therapy in gastroenterology. No statistically significant differences in demographic or clinical features have been evidenced between the group with reported AEs and patients without.

Discussion and conclusion

The management of IBDs has been deeply changed by the introduction in clinical practice of biologic agents. These drugs, including monoclonal anti-TNFα (ADA, GOL, IFX), integrins (VED) and IL12/23 (UST), target mediators involved in the development and maintenance of inflammation in immunomediated diseases and are associated to high remission and response rates not achieved by other therapies before[15]. Efficacy and safety of these drugs in IBDs have been demonstrated in many clinical trials[21–27], but detecting rare, uncommon or long-term AEs is a limitation of clinical trials, due to relative brief follow-up period and a strictly selected population, not representing a real-world population. Therefore, to early detect known and still unknown AEs in clinical practice, active pharmacovigilance programs have gained a rising importance. Spontaneous reporting of suspected AEs represents the cornerstone of pharmacovigilance, but it is limited by an high rate of under-reporting, as demonstrated in[28].

In this multicentre, inter-regional and real-world setting study, we have provided and analysed data of our study to improve the quality and the quantity of AEs reporting associated with biologics in IBDs. Infliximab, as expected, was the biologic agent most prescribed, whereas GOL was associated

Table 4. MedDRA- compliant description of adverse events (AEs).

	IFX	ADA	GOL	VED	Total
SOC – General disorders and administration site conditions	**14**	**5**	**2**		**21**
PT – Pyrexia			1		1
PT1 – Asthenia	3	2			5
PT2 – Hot flush	4				4
PT3 – Pallor		1			1
PT4 – Administration site reactions	1	1	1		3
PT5 – Peripheral oedema	2				2
PT6 – Chest pain	1	1			2
PT7 – Hyperhidrosis	3				3
SOC – Cardiac disorders	**4**	**1**			**5**
PT – Tachycardia	3	1			4
PT2 – Myocardial infarction	1*				1
SOC – Skin and subcutaneous tissue disorders	**18**	**8**	**1**	**1**	**28**
PT – Folliculitis		1			1
PT1 – Rash	3				3
PT2 – Pruritus	5	1	1		7
PT3 – Erythema	8				8
PT4 – Psoriasis		2			2
PT5 – Parapsoriasis		3			3
PT6 – Urticaria	1	1			2
PT7 – Pityriasis	1				1
PT8 – Purpura				1	1
SOC – Ear and labyrinth disorders	**1**				**1**
PT – Vertigo	1				1
SOC – Nervous system disorders	**8**				**8**
PT – Headache	5				5
PT1 – Drowsiness	1				1
PT2 – Confusional state	1				1
PT3 – Paraesthesia	1				1
SOC – Infections and infestations	**1**	**9**	**2**	**4**	**16**
PT – Cytomegalovirus infection		1	1		2
PT1 – Herpes virus infection	1	5		1	7
PT2 – Pyelonephritis	1*				1
PT3 – Subcutaneous abscess			1		1
PT4 – Abscess oral		2			2
PT5 – Cystitis				1	1
PT6 – Clostridia infections				1	1
PT7 – Tinea versicolour				1	1
SOC – Respiratory, thoracic and mediastinal disorders	**10**	**5**	**1**	**2**	**18**
PT – Pneumonia		1 (1*)			2
PT1 – Asthma		1			1
PT2 – Nasopharyngitis			1		1
PT3 – Tonsillitis	1				1
PT4 – Dyspnoea	8	2		1	11
PT5 – Laryngospasm				1	1
PT6 – Pulmonary embolism	1*				1
SOC – Blood and lymphatic system disorders	**4**	**3**	**1**		**8**
PT – Leucocytosis	1				1
PT1 – Leukopenia		1			1
PT2 – Anaemia	1*				1
PT3 – Neutropenia		1			1
PT4 – Lymphadenopathy	2				2
PT5 – Lymphadenitis		1			1
PT6 – White blood cell disorder			1		1
SOC – Gastrointestinal disorders	**6**				**6**
PT – Vomiting	1				1
PT1 – Gingivitis	1				1
PT2 – Nausea	1				1
PT3 – Tooth loss	1				1
PT4 – Abdominal pain	1				1
PT5 – Dyspepsia	1				1
SOC – Immune system disorders	**2**	**1**			**3**
PT – Allergic reaction	1	1			2
PT1 – Anaphylactoid reaction	1*				1
SOC – Renal and urinary disorders		**1**			**1**
PT – Nephrolithiasis		1*			1
SOC – Neoplasms benign, malignant and unspecified	1	**1**		**1**	**3**
PT – Colorectal cancer	1*				1
PT1 – Skin cancer				1*	1
PT2 – Lung adenocarcinoma		1*			1
SOC – Musculoskeletal and connective tissue disorders	**17**			**1**	**18**
PT – Myalgia	3				3
PT2 – Limb discomfort	2				2
PT3 – Back pain	1				1

(*continued*)

Table 4. Continued.

	IFX	ADA	GOL	VED	Total
PT4 – Arthralgia	11			1	12
SOC – Eye disorders	**1**	**1**			**2**
PT – Dry eye	1				1
PT1 – Blurred vision		1			1
SOC – Psychiatric disorders	**1**				**1**
PT – Libido decreased	1				1
SOC – Hepatobiliary disorders		**1**			**1**
PT – Cholelithiasis		1			1

Bold values are used to highlight total AEs per SOC.
*Classified as serious adverse event (SAE).
No AEs reported with ustekinumab (not shown).
Abbreviations. IFX: infliximab; ADA: adalimumab; GOL: golimumab; VED: vedolizumab; SOC: system organ class; PT: preferred term.

with the higher rate of AEs. All the AEs reported in our study are consistent with those reported in literature[29–31] and were all known; the most common AEs were skin and subcutaneous tissue disorders followed by general disorders and administration site conditions (from mild to moderate). We documented statistically significant differences of AEs between naïve and non-naïve patients (naïve [65; 70.7%] versus non naive [27; 29.3%] $p = .02$); we can speculate that this may be due to the higher incidence of some AEs between one month to one year after initiating the therapy with a biological agent[32].

Furthermore, we have reported some cases of new onset neoplasms (colorectal, skin and pulmonary cancers) and severe infections (e.g. by Cytomegalovirus, Clostridia and one case of pyelonephritis) leading to treatments withdrawal. Controversial data are reported in literature; in some studies biologics have been associated with increased rates of infections (especially associated with conventional immunomodulatory drugs) and malignancies[33,34] but of note, one meta-analysis on anti-TNF drugs in patients with CD (including 13 randomized controlled trials) demonstrated that these agents decreased the incidence of SAE without an increased risk of malignancy or serious infections[8]. However, while 2 years follow-up is likely enough to look infections insurgence, it is likely too short to evaluate the malignancy risks.

The newly available biologic agents such as VED and UST seem not to show an increased risk of these severe infections compared to anti-TNFα[35], although we observed one case of Clostridia infection in a patient treated with VED, according to data reported also in[36].

Post-marketing surveillance activities play an important role in significantly improving the detection and reporting of AEs and SAEs in a real-life context, providing important data on the safety of numerous treatments. The implementation of CBPP through improving the pharmacovigilance awareness/compliance of physicians and boosting the attitude to report AEs, resulted in a significant increase in number of AEs reported (102 *vs* 35 between comparable populations), providing a greater knowledge of safety and tolerability of biologic agents in clinical practice. Indeed, as observed in this study, even the simple increase of information about pharmacovigilance and related instruments of reporting among healthcare professionals, may be a simple and not expensive approach to overcome the issue of under-reporting rates, as already indicated by some previous studies[37–39]. Before the CBPP, AEs were reported by spontaneous activity with a consequent phenomenon of under-reporting has evidenced by our study. Our project seems to demonstrate that active post-marketing pharmacovigilance studies are a valid strategy to increase awareness on pharmacovigilance culture, reduce underreporting and providing important information on previous unknown AEs/SAEs, resulting in a therapy optimization in clinical practice, also in agreement with a previous study[18].

However, the relatively small sample size has limited further AEs' analysis for each molecule and not all the gastroenterology tertiary centers of Calabria and Sicily have been involved in the study. Moreover, the increase observed in our study, although its statistical value, is lower than that observed in the rheumatologic area of the CBPP (134 *vs* 42), suggesting that further improvements are needed in gastroenterology.

In conclusion, we report data of more than 600 IBDs' patients, treated with biologics, in a real-world setting during a 2-years study period and our results confirm the importance of active pharmacovigilance programs in improving the knowledge of biologics' safety in gastroenterology.

To date, this is the first study assessing biologic drugs safety and use in Calabria and Sicily regions, also providing useful data for future local cost-effectiveness analysis. The AEs reported were all known, generally mild to moderate and no deaths occurred during the follow-up period. In the next years, further studies are mandatory to include all the tertiary centres and the new biologics in progress of marketing for IBDs and to assess long term safety.

Transparency

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