



Real-life burden of adverse reactions to biological therapy in inflammatory bowel disease: a single-centre prospective case series

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Abstract

Background/aim. Biologics represent a key therapeutic option in inflammatory bowel disease (IBD), but are associated with several side effects. Post-marketing surveillance, through a spontaneous adverse drug reactions (ADRs) monitoring system, is essential to assess the safety profile of biologics. The aim of the study was to prospectively evaluate the occurrence of ADRs in IBD patients treated with biologics from a single centre in Southern Italy.

Methods. Data from patients with Crohn's Disease (CD) and Ulcerative Colitis (UC) who underwent biological therapy were prospectively collected. ADRs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA®).

Results. Overall, 68 (54% male, 68% with UC and 32% with CD) biologic-naïve IBD patients underwent biological therapy. Mean follow-up was 11.7 ± 6.2 months. As a results of switches, for 68 patients we obtained 96 biologic prescriptions. Overall, 45 ADRs occurred in 36 (53%) patients, distributed as follows (ADRs/prescriptions): 19/37 with IFX-Remicade, 5/12 with IFX-Remsuma, 8/9 with GOL, 11/26 with ADA, and 2/12 with VDZ. Mild ADRs were 29 (64%), moderate 15 (34%) and 1 (2%) severe. General disorders and administration related reactions were the most frequent ADRs (35%), followed by skin and subcutaneous tissue disorders (20%), infections (15%), musculoskeletal (11%), respiratory (6%) blood (4%), gastrointestinal (4%), and vascular disorders (2%). In 9 cases (20%) the ADRs resulted in definitive discontinuation of biologic therapy.

Conclusion. In a prospective cohort of IBD patients, more than half experienced ADRs during biologic therapy. General disorders and administration related reactions were the most common ADRs, while infections were less common and rarely led to discontinuation of therapy. Findings underline the importance of surveillance in management of IBD patients during biologic therapy and implementing safety protocols with data from real-life settings.

Keywords: inflammatory bowel disease, adverse drug reactions, TNF inhibitors, pharmacovigilance, drug safety, biological therapy

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Introduction

Over the last 20 years, the introduction of biologics represented a breakthrough in the management of inflammatory bowel diseases (IBD), as a fundamental therapeutic option in patients not responding to conventional therapies (mesalamine, steroids and immunosuppressants). The goal of medical therapy is to induce and maintain clinical, endoscopic and histological remission; however, significant challenges remain, including maintaining the long-term therapeutic response, avoiding treatment toxicity and preventing the progression of disease [1].

A tailored therapy is the key for an optimal management of IBD, based on a balance of the risk-benefit profile, clinical judgment and patient preferences [2]. Biological drugs are characterized by improved selectivity compared with conventional therapy, since they act on inflammation mediators, such as TNF- α , and on the binding of lymphocytes to the intestinal epithelium [3]. Besides the clinical benefit, toxicity is the main concern for these drugs and continuous pharmacovigilance programs regarding surveillance for adverse drug reactions (ADRs) from biologics need to be implemented [4]. Clinicians should be aware of potential risks and recognize side effects that may result from the use of these drugs. Clear management strategies in different scenarios are also desirable [5]. The most common ADRs described for biologics are infections, malignancies, immunogenicity, and metabolic disorders [6]. Paradoxical inflammatory effects of TNF- α inhibitors have also been described and include exacerbation or initiation of drug-induced autoimmune diseases, such as psoriasis, systemic lupus erythematosus, vasculitis and uveitis [7]. Most of the data come from clinical trials, which use rigorous inclusion criteria, and thus may not reflect what is found in real clinical practice. Indeed, clinical trials often report short-term clinical outcomes and primary endpoint aims mostly relating to drug effectiveness and not to detailed ADRs description. Research into the long-term safety of biologics needs to be implemented, as well as comparative safety reports for different biologics, and national registries could be used for further relative safety of biologics assessment [8].

The aim of this study was to prospectively describe, in a real-life context, the occurrence and the type of ADRs in a case series of IBD patients from Southern Italy undergoing biological therapy. We considered infliximab, adalimumab, golimumab and vedolizumab since they are used for both Crohn's disease (CD) and ulcerative colitis (UC). A variety of abbreviations for each of the monoclonal antibodies is present in scientific literature, so we chose the most used abbreviation in Italy as follows: IFX for infliximab, ADA for Adalimumab, GOL for Golimumab and VDZ for Vedolizumab.

Material and methods

Patients

In the period between February 2017 and January 2020, consecutive biologic naïve patients with CD and UC, who were candidates for biological therapy at the Digestive Physiopathology Unit of the "Mater Domini" University Hospital, were enrolled prospectively in order to obtain a case series. Diagnosis of UC and CD was established according to clinical, endoscopic and histological criteria [9]. Patient characteristics, medical history, and concomitant medications were extracted from the patients' medical records and confirmed with the patient during their on-site visit. The following data were collected: age, sex, type and duration of disease, current medication, previous use of anti TNF- α agent or other biologic drugs, and presence of other relevant co-morbidities. Patients with previous use of biologic for IBD or any other medical condition were excluded.

Pre-biological screening

Before biologic therapy began, all patients in the study population underwent a pre-biological screening, according to an internal protocol. Each patient for biological therapy was subjected to routine serological tests, such as complete blood count, chemistry panel and coagulation parameters. All patients underwent microbiological (IGRA test) and radiological (chest X-ray) tests to rule out the presence of latent tuberculosis infection. Virologic tests were performed to rule out the presence of latent viral infections (Table I). Pregnancy status in women of childbearing potential was assessed by measuring the β -HCG hormone in urine and serum.

Table I. Virological panel for pre-biological screening performed in the study population.

Virus	Test
HBV	HBsAg, Anti HBs, Anti HBc
HCV	Anti HCV antibodies
Rubella	IgM antibodies IgG antibodies
CMV	Anti CMV IgM antibodies Anti CMV IgG antibodies
Herpes Virus	Anti Herpes simplex 1+2 IgM antibodies Anti Herpes simplex 1 + 2 IgG antibodies
Varicella Zoster Virus	Anti Varicella Zoster virus IgM antibodies Anti Varicella Zoster virus IgG antibodies
Measles	Anti Measles IgM antibodies Anti Measles IgG antibodies
EBV	Anti EBV-VCA IgM antibodies Anti EBV-VCA IgG antibodies
HIV	Anti HIV 1/2 P24 Antigen

HBV= Hepatitis B Virus; HCV= Hepatitis C Virus; CMV= Cytomegalovirus; EBV = Epstein Barr Virus; HIV = Human Immunodeficiency Virus.

Method of administration

Infliximab (IFX-Remicade or IFX-Remsima) was administered as an intravenous infusion at the dose of 5 mg/kg, followed by an additional infusion of 5 mg/kg 2 weeks later and 4 weeks later, during the induction phase. During the maintenance phase, an infusion of 5 mg/kg of IFX was performed every 8 weeks. Adalimumab (ADA) was administered subcutaneously at the standard dose of 160 mg followed by a dose of 80 mg after 2 weeks, during the induction phase, and then the patient received 40 mg every other week during the maintenance phase. Golimumab (GOL) was administered subcutaneously at an initial 200 mg dose, followed by 100 mg at week 2 in the induction phase. During maintenance phase, patients received 100 mg or 50 mg every 4 weeks, as per their body weight \geq or $<$ 80 kg, respectively. Vedolizumab (VDZ) was administered intravenously in a dose of 300 mg, followed by an additional infusion of the same dose 2 weeks later and 4 weeks later, during the induction phase. In the maintenance phase, patients underwent infusions at 300 mg dose every 8 weeks. Intravenous administration was performed on site, while subcutaneous administration was managed by the patients after nursing training at the site. Patients' vital signs including blood pressure, cardiac frequency and body temperature were obtained prior to, during, and at completion of infusion. After infusion, patients were monitored by an experienced nurse for a minimum of 60 minutes after the first 3 infusions and a minimum of 30 minutes after each maintenance infusion. The nurse was trained to observe for any infusion-related adverse events and to seek medical attention if any ADR occurred, as well as to manage the situation according to the internal protocol. For IFX only, an oral pre-medication with loratadine (10 mg) was administered to the patient. No dose adjustment was performed other than that described above in any of the patients.

Adverse events classification

Safety was assessed at each treatment visit by ADR evaluation, clinical laboratory tests, and physical examinations, and obviously through prompt reporting of the patient when an ADR occurred. A trained physician filled in the suspected ADR reporting form of the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) recording a detailed description, including time of onset and recovery, severity, and outcome. Pharmacologists' team codified the ADRs according to the Medical Dictionary for Regulatory Activities (MedDRA®, The International Federation of Pharmaceutical Manufacturers & Associations, IFPMA, Geneva, Switzerland), Preferred Term (PT) and System Organ Class (SOC) levels. All those events that occurred in the first 24 hours from administration were defined early, and those that occurred after 24 hours and within 14 days were defined late^[10]. ADRs which caused minimal discomfort and did not interfere with normal daily activities were defined mild, while ADRs that caused discomfort to the patient, hindering the normal course of daily activities,

were defined as moderate. An ADR was defined as serious if it was life-threatening or fatal, or required hospitalization (or prolonged existing hospitalization), or resulted in persistent or significant disability or in a congenital anomaly/birth defect, or consisted of any other medical relevant condition [11]. Infusion-related reactions (IRRs) were considered as those ADRs that occurred during the administration of an intravenous biologic agent or within the following two hours from termination [12].

Protocols adopted in case of infusion-related reactions at site

Since the intravenous administration of biologic agents were performed only on site, all the IRRs were recorded during the procedure, in the presence of the nurse and the medical staff. In mild ADRs, the infusion rate was reduced to 10 mL/h and chlorphenamine (10 mg/1 ml intravenously) and paracetamol (650 mg) were administered, followed by physiological solution for infusion from 500 mL/h to 1000 mL/h. The vital signs were monitored every 10 minutes, until they returned to normal limits. In patients stabilized with the treatment described above, the infusion was resumed at 10 mL/h for 15 minutes, then increased to 20 mL/h for 15 minutes, then 40 mL/h, 80 mL/h, 100 mL/h and finally 125 mL/h every 15 minutes, if tolerated. In moderate ADRs, the infusion was stopped and chlorphenamine (10 mg/1 ml intravenously) and paracetamol (650 mg), were administered followed by physiological solution for infusion from 500 mL/h to 1000 mL/h. In severe ADRs, the infusion was stopped and chlorphenamine (10 mg/1 ml), hydrocortisone (100 mg) or methylprednisolone (20-40 mg) were administered intravenously plus physiological solution for infusion (500-1000 mL/h). Adrenaline (1: 1000) syringe from 0.1 mL to 0.5 mL were available to be used subcutaneously.

Ethical considerations

The study protocol was approved by the local Ethics Committee (Comitato Etico Regionale Calabria, Italy), protocol number 278/2015. Written informed consent was obtained from all patients at the time of enrollment. Patients were informed that medical records utilized for this study will remain anonymous. All procedures were performed in accordance with the 1964 Declaration of Helsinki and its later amendments.

Results

Demographic and clinical characteristics of the study population

During the period of the study, a total of 71 biologic-naïve consecutive patients with IBD underwent biological therapy. Of them, 68 (37 male and 31 female), of which 46 (68%) were UC and 22 (32%) CD patients, accepted to take part in the prospective study. Patients with UC displayed a pancolitis in the majority (n=31, 67.5%) of cases, while CD patients showed an ileo-colonic involvement in 16 (73%) cases. During the study period, 46 patients experienced one

single type of biological drug, while for 18 patients it was necessary to switch to a second type of biologic (5 patients withdrew drug because of ADRs, 13 because of loss of response), and in 5 patients, it was necessary to use a third type after the failure of the two previously used. Therefore, for 68 patients we registered 96 biologic prescriptions and we considered this number for the analysis of the ADRs. No patient had significant heart failure, neurological pathologies, chronic liver diseases or a clinical history of lymphoproliferative diseases. No patient had previously been treated with biologics, nor had been taking thiopurines or steroids when initiating biologics. All patients had been on a stable dose of oral mesalazine for at least 6 months.

The demographic and clinical characteristics of the patients, according to biologic therapy, are shown in table II.

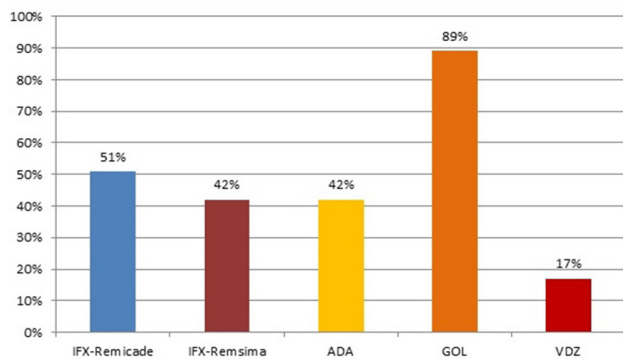


Figure 1. Incidence rate of the ADRs according to the number of prescriptions for each drug (19/37 with IFX-Remicade, 5/12 with IFX-Remsima, 8/9 with GOL, 11/26 with ADA, and 2/12 with VDZ).

Occurrence of the adverse drug reactions

Among the 96 prescribed treatments, a total of 45 ADRs occurred in 36 (53%) patients, as follows: 19 ADRs

with IFX-Remicade, 5 with IFX-Remsima, 8 with GOL, 11 with ADA, and 2 with VDZ. Considering that the 96 prescriptions were differently distributed (IFX-Remicade N=37, IFX-Remsima N=12, ADA N=26, GOL N=9, VDZ N=12), we evaluated the incidence rate of ADRs for each drug, comparing the number of ADRs that occurred for each biologic with the corresponding number of treatments for that biologic. Although in terms of absolute numbers the majority of the ADRs occurred during IFX-Remicade, GOL showed the worst safety performance, as for 9 prescriptions there were 8 ADRs (Figure 1).

Description of the adverse drug reactions

Among the 45 ADRs, 16 (36%) were early and 29 (64%) late ADRs, while according to severity we found 29 (64%) mild ADRs, 15 (34%) moderate ADRs and only 1 (2%) severe ADR. Among the early ADRs, the most common were the IRRs (N=9, 20%), which occurred with heterogeneous symptoms and signs, such as flushing, dyspnea, cough, bronchospasm, sense of chest constriction, hypertensive spikes, nausea, headache, rash, and dizziness. Such reactions were reported in 7 patients taking IFX-Remicade and 2 patients taking IFX-Remsima, while no VDZ infusion was accompanied by IRRs. Of the IRRs, 4 occurred in the induction phase, and 5 between the fourth and tenth administration, over an average period of 8 months. In 3 cases, the occurrence of IRRs made it necessary to discontinue the infusion. Relevant late ADRs were infections, represented by 7 ADRs and including bacterial and fungal infections as well as herpes virus reactivation. Of note, 2 cases of leukopenia occurred, one following the fifteenth administration of ADA, and one after the fourth administration of IFX-Remsima. Both these ADRs led to the definitive discontinuation of the drug. Detailed information of the ADRs, provided as a MedDRA® compliant description, are summarized in table III.

Table II. Clinical and demographic characteristics of the 68 patients with IBD according to each biologic drug used (N=96 prescriptions*).

	IFX/RC	IFX/RS	ADA	GOL	VDZ	Total
Prescriptions	N=37	N=12	N=26	N=9	N=12	N=96
Age at starting therapy, years (mean ± SD)	41.6 ± 13.9	44.1±12.1	43.5±13.5	40 ± 10.8	43.4 ± 18.4	43 ± 13.7
Sex (M/F)	18/19	8/4	10/16	5/4	5/7	46/50
Type of disease						
UC	24	9	12	9	10	64
CD	13	3	14	0	2	32
Duration of disease at starting therapy, years (mean ± SD)	13.2 ± 7.4	11.1 ± 8.5	14.6±7.4	12.3±7.7	12.1 ± 7.2	12.9 ± 7.3
Duration of therapy or last follow-up, months (mean ± SD)	11.8 ± 7.2	8.7 ± 5.1	13.6 ± 8	12.7±6.6	7.8 ± 4.2	11.7 ± 6.2

*N=23 patients underwent therapy with more than one biological drug

SD= standard deviation, UC= ulcerative colitis, CD= Crohn disease, IFX/RC= Infliximab Remicade, IFX/RS= Infliximab Remsima, ADA= Adalimumab, GOL= Golimumab, VDZ= Vedolizumab

In total, 9 (20%) ADRs resulted in definitive discontinuation of the drug in 9 patients. Except for one, classified as severe IRR which required hospitalization of the patient, the remaining 8 were of a moderate type

(Table IV). No ADRs resulted in the patient's death or the occurrence of permanent disabilities. Furthermore, there have been no cases of malignancy during the observed period.

Table III. MedDRA® compliant description of adverse drug reactions.

	ADA N=11	GOL N=8	IFX/RC N=19	IFX/RS N=5	VDZ N=2	Total N=45 (%)
SOC – General disorders and administration site conditions	2	3	8	3		16 (35)
PT – Pyrexia	1/1*	2/1*	1/2*	1		9
PT1 – Administration related reaction			5*°	1*°/1*†°		7
SOC – Skin and subcutaneous tissue disorders	2	3	4			9 (20)
PT – Subcutaneous abscess			1			1
PT1 – Eczema	1					1
PT2 – Dermatitis atopic		1	1			2
PT3 – Injection site erythema	1*	1				2
PT4 – Rash			1*			1
PT5 – Dermatitis psoriasiform			1			1
PT6 – Urticaria		1				1
SOC – Infections and infestations	4		2		1	7 (15)
PT – Tooth abscess			1			1
PT1 – Herpes virus infection	1					1
PT2 – Herpes zoster	1					1
PT3 – Tinea versicolour					1	1
PT4 – Anal abscess	1		1			2
PT5 – Pilonidal cyst	1					1
SOC – Musculoskeletal and connective tissue disorders	1	1	2	1		5 (11)
PT – Arthralgia	1		2	1		4
PT1 – Myalgia		1				1
SOC – Respiratory, thoracic and mediastinal disorders			3			3 (6)
PT – Bronchospasm			1*°			1
PT1 – Bronchitis			1			1
PT2 – Cough			1*°			1
SOC – Blood and lymphatic system disorders	1			1		2 (4)
PT – Leukopenia	1			1		2
SOC – Gastrointestinal disorders	1				1	2 (4)
PT – Aphthous ulcer					1	1
PT – Abdominal pain	1					1
SOC – Vascular disorders		1				1 (2)
PT12 – Presyncope		1*				1

* Classified as early ADRs (Adverse drug reactions that occurred within 24 hours of drug administration);

° Classified as Infusion-related reactions;

† Classified as serious ADRs;

SOC = System Organ Class; PT = preferred term; Discontinuation of Biologic therapy.

Table IV. Adverse drug reactions that led to discontinuation of therapy.

ADRs (case)	Characteristics of the patient	ADR type	Drug	Duration therapy at the time of the ADR, months
1	male; UC; 17 years	IRR	Remicade	1.5
2	male; CD; 35 years	IRR	Remicade	0.5
3	male; UC; 25 years	IRR	Remsima	8
4	female; UC; 47 years	Vasovagal syncope	Golimumab	0
5	female; UC; 62 years	Herpetic dermatitis	Adalimumab	22
6	female; CD; 33 years	Skin abscess	Remicade	16
7	female; CD; 27 years	Skin abscess	Adalimumab	13
8	female; UC; 36 years	Leukopenia	Adalimumab	8
9	male; CD; 50 years	Leukopenia	Remsima	12

UC = ulcerative colitis; CD = Crohn disease; IRR = infusion-related reaction.

Discussion

Biological drugs have radically changed the management of patients with CD and UC. Beyond their proven effectiveness, however, doubts remain regarding their safety profile and the optimization of their use, especially in relation to an individualization of the therapy [13]. In our case series, the occurrence of ADRs during biological therapy was assessed in 68 consecutive patients with IBD, during a two-year period. We registered 45 ADRs out of a total of 96 treatments. This result is substantially in line with current literature, although it is not easy to obtain an estimate of the incidence of ADRs as the studies are conditioned by the characteristics of the population under consideration, by the study design, as well as by the classification criteria of the ADRs [14].

The incidence of the ADRs in our case series have confirmed that the safety of IFX-Remsuma is comparable to that of the originator, as previously reported [15]. Accordingly, VDZ seemed to display the better safety profile in our cohort, as demonstrated in other multicenter experience [16]. Of note was the number of ADRs observed with GOL (8 among 9 treatments), although they did not determine discontinuation of the drug. GOL was recently the subject of an Italian multicenter prospective study that assessed its efficacy and safety in a real-life context, and the final analysis showed that the ADRs caused by GOL were 4% and all were dermatological reactions occurring at the injection site [17]. Our data were probably affected by the very small number of patients under GOL treatment.

General disorders and administration site conditions, such as acute hypersensitivity reactions (the so-called IRRs), injection site swelling and induration, and fever, are among the most frequent ADRs observed during biological therapy in patients with IBD [18]. In our series, these ADRs were the most common (35%), but only one was classified as severe and required hospitalization of the patient. All patients treated with IFX (both IFX-Remicade and IFX-Remsuma) received loratadine (10 mg) before infusion, but nonetheless 9 IRRs occurred under IFX, representing 20% of overall ADRs. These types of reactions related to the administration of biological drugs are still being studied, as often in randomized controlled trials they are investigated as a secondary outcome, and therefore are not detailed in the final analysis of the safety profile [12].

Although the action of the biological drugs on the immune system may predispose to a greater susceptibility towards infectious agents, in our case series no severe infections were recorded. These data agree with a recent meta-analysis that evaluated 44 trials conducted on the use of biological drugs in IBD, not showing a significant association with the risk of developing severe infections [19]. These data were further confirmed by another recent meta-analysis which assessed the efficacy and safety of ADA in UC patients [20]. A Spanish study conducted on 152 patients treated with IFX for IBD, with a 9-year

follow-up, revealed only 11 cases of viral and/or bacterial infections that required hospitalization [21]. Another monocentric study involving 734 patients with IBD treated with IFX did not reveal statistically significant differences in infection rate compared with 666 IBD controls not treated with biologics. The authors found that the only independent factor for the greatest susceptibility to infections was the concomitant steroid therapy [22]. In our series, no patient was on concomitant steroid treatment and this could explain the absence of severe infections. A Korean study including 175 patients being treated with biologics, of which 54 were suffering from IBD, showed a 6% rate of severe infections, without observing differences compared to the use of IFX or ADA [23]. Data from Australia and New Zealand on over 5,000 patients identified a severe infection rate of 2.2%, including two cases of primary Varicella Zoster infection, thus emphasizing the importance of elective vaccination of *naïve* patients before starting the biological therapy [24]. Of note, in our series GOL did not cause any infections, in agreement with a Spanish study of a cohort of 33 UC patients followed prospectively for one year [25]. It is acknowledged that exposure to biological agents significantly increases the risk of opportunistic infections in patients with IBD [19]. Three patients developed herpes virus reactivation, varicella zoster infection and fungal infection, respectively, which are considered as opportunistic infections. Despite the evidence of a dysregulation of the mucosal immune response in patients with IBD, there is no strong evidence of a systemic immune deficiency in the absence of concomitant therapy with immunomodulatory drugs [26]. None of the three above-mentioned patients was taking steroids or thiopurines. There are few epidemiological data on the predisposing factors for the development of opportunistic infections in patients with IBD, and the variables mainly involved seem to be older age, malnutrition, associated comorbidities, total parenteral nutrition and intestinal surgery [27]. A recent Italian multicentric study documented 2 cases of fungal pneumonia and 2 herpes zoster reactivation among 136 IBD patients treated with VDZ [28]. An increased risk of developing herpes zoster and pneumonia in patients with IBD has been widely described in patients treated with anti-TNF α , especially when in combination with steroids and thiopurines [29,30]. None of our patients developed tuberculosis, nor did they show a positivity at screening for contact with mycobacterium as assessed according to the guidelines [31].

In the context of ADRs induced by biological drugs, dermatological manifestations deserve special attention, as the skin appears to be one of the most frequently involved organs in ADRs occurrence during anti-TNF α therapy in patients with IBD [32]. We documented skin disorders in 20% of cases, including one atopic dermatitis and one psoriasiform dermatitis. There are numerous reports of skin involvement during anti-TNF α therapy, including

new psoriasis onset or exacerbation during therapy, vasculitis or lupus, skin infections and neoplasms, and of course injection-site reactions, both acute and delayed [33]. Nevertheless, the risk factors for adverse skin events have not yet been fully identified in patients with IBD who undergo anti-TNF α therapy, considering that the incidence of cutaneous manifestations is between 2 and 34% as extraintestinal manifestations of the disease [34]. In the large cohort analyzed by a Portuguese study for a period of 10 years, among 732 patients with IBD treated with anti-TNF α agents, 211 (29%) developed at least one dermatological complication [35]. Some patients presented idiosyncratic reactions on an allergic basis, while other dermatological ADRs were a consequence of immunosuppression (for example, infections and cancer), or seemed to be a consequence of the alteration in inflammatory cytokine balance under TNF α inhibition (e.g. in the case of psoriasis) [33]. However, there is little knowledge of the risk factors associated with the development of dermatological complications in patients with IBD treated with anti-TNF α [36].

Five (11%) patients developed ADRs classified as musculoskeletal disorders: 4 patients reported diffuse arthralgias and 1 reported a myalgia. The phenomenon of paradoxical arthritis that arises during anti-TNF α therapy in patients with IBD is of great interest in the scientific community [37]. In fact, joint manifestations are called paradoxes when they occur during treatment with anti-TNF α since this type of medication is approved for their treatment [38]. Up to 10% of patients who develop paradoxical arthritis during anti-TNF α therapy are forced to discontinue therapy [39]. In our case series, none of the 5 patients with development of musculoskeletal disorders discontinued therapy, these ADRs being classified as mild. The mechanisms related to these paradoxical manifestations are still unclear [40].

For 2 patients who developed leukopenia, the discontinuation of the biological drug was necessary; however, hematological values returned to normal a short time after stopping biological therapy. Biological therapies act directly on the inflammatory cascade, therefore their immunosuppressive mechanism can determine alterations in the white blood cell count or myelo-suppression [41]. Although this side effect is more investigated for thiopurine, leukopenia was documented also during anti-TNF therapy [42].

Regarding the risk of lymphoproliferative diseases and neoplasms, the literature data are often conflicting, in part due to heterogeneity of studies [43]. There have been no cases of malignancy in our population during a two-year period. The presence of selection and detection bias is frequently a limiting factor in clinical trials, and this could overestimate the risk of cancer in IBD during biologic therapy. On the contrary, population studies on cohorts of unselected patients are more representative of the real

risk of cancer in patients with IBD and, therefore, lend themselves to the acquisition of prognostic information and risk estimates [44,45]. A recent meta-analysis comprising 23 studies, for a total of 9455 patients, did not reveal a significant increase in cancer risk in patients with IBD treated with anti-TNF α [19]. In a recent Danish cohort study conducted on 56,146 patients with IBD, the use of anti-TNF α was not associated with an increased risk of hematological malignancies [46]. Reassuring data also come from studies conducted on pediatric populations, which show that exposure to IFX is not associated with the development of neoplasms or hematological disorders [47]. Also, with regard to skin tumors, from the data in the literature it can be assumed that biological drugs do not predispose to a greater risk [48]. Although an increased frequency of hematological cancers was reported in a study conducted in Minnesota on 122 patients treated with biologics, the data were not statistically significant [49].

Conclusions

The safety and tolerability of biological drugs in IBD is widely investigated. However, the precise interactions of this class of drugs with the immune system have not yet been fully understood, making it difficult to predict the occurrence and the severity of ADRs. In the cohort of patients with IBD treated with biological drugs, observed in our Unit, ADRs have been frequent, but in most cases were mild. Most ADRs were recorded during the infusion of IFX. However, if we consider the number of patients treated with each drug, GOL was the most frequently associated with the occurrence of ADRs, albeit mild. In contrast, VDZ presented the lowest risk of triggering ADRs. As regards the comparison between the forms of IFX currently on the market, the security of the biosimilar Remsima (CT-P13) is comparable to that of the originator in our series. There were no cases of lymphoproliferative diseases and malignancies in the enrolled patients. Finally, only 9 ADRs made it necessary to permanently discontinue the drug. No ADRs resulted in the death or the occurrence of permanent disabilities. Consequently, it is possible to conclude that the results of our study are in line with the data from the available studies on the safety of biological drugs. Pharmacovigilance programs are important to report the clinical practice experience during the post-marketing phase, thereby providing clinicians with data reflecting a daily reality.

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