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Safety and effectiveness of direct-acting antiviral drugs in the treatment of hepatitis C in patients with inflammatory bowel disease

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ABSTRACT

Background and aims: Hepatitis C virus (HCV) management in Inflammatory Bowel Disease (IBD) is uncertain. The ECCO guidelines 2021 recommended HCV treatment but warn about the risk of IBD reactivation. We aimed to evaluate 1) the effectiveness and safety of direct-acting antivirals (DAAs) in IBD; 2) the interaction of DAAs with IBD drugs.

Methods: Multicentre study of IBD patients and HCV treated with DAAs. Variables related to liver diseases and IBD, as well as adverse events (AEs) and drug interactions, were recorded. McNemar's test was used to assess differences in the proportion of active IBD during the study period.

Results: We included 79 patients with IBD and HCV treated with DAAs from 25,998 IBD patients of the ENEIDA registry. Thirty-one (39.2 %) received immunomodulators/biologics. There were no significant differences in the percentage of active IBD at the beginning (n = 11, 13.9 %) or at the 12-week follow-up after DAAs (n = 15, 19 %) (p = 0.424). Sustained viral response occurred in 96.2 % (n = 76). A total of

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8 (10.1 %) AEs occurred and these were unrelated to activity, type of IBD, liver fibrosis, immunosuppressants/biologics, and DAAs.
Conclusions: We demonstrate a high efficacy and safety of DAAs in patients with IBD and HCV irrespective of activity and treatment of IBD.

1. Introduction

Inflammatory bowel disease (IBD) comprises a series of disorders of unknown cause, such as ulcerative colitis (UC), Crohn's disease (CD) and indeterminate colitis [1–4]. A large majority of these patients are treated with immunosuppressants/biologics, and their chronic use may be associated with an increased rate of infections [5]. The prevalence of hepatitis C virus (HCV) in IBD is similar to general population, with percentages ranging from 1 to 6% in Western countries [6–9]. In the largest studies published to date, the prevalence was 2 % [7]. HCV produces complications such as cirrhosis and hepatocarcinoma; hence, achieving its eradication worldwide is of the great importance [10]. The introduction of direct-acting antivirals (DAAs) in 2011, which have an efficacy greater than 90 % in all patient groups, has meant a very relevant change compared with treatment with classic interferon-based therapies (IFNs). In addition, tolerance of DAAs is significantly better and the duration of treatment shorter than IFNs [11,12].

Currently, the management of HCV infection in patients with IBD is uncertain due to the potential impact of DAAs on disease activity, and there is insufficient evidence on the possible interactions of immunosuppressive and biological medication with DAAs. Data in the medical literature regarding the efficacy and safety of these drugs in patients with IBD and immunosuppressants are very scarce, with only isolated case reports [8,13–16] that are detailed in Supplementary Tables 1. In 2017, an expert opinion proposed three possible HCV treatment strategies in patients with IBD: 1) sequential strategy (initial treatment of active IBD and treatment of HCV infection after achieving remission), 2) concomitant strategy (simultaneous treatment of IBD and HCV with DAAs) and 3) inverted sequential strategy (initial administration of DAA therapy prior to treatment of IBD) [8]. However, the level of evidence supporting this recommendation is very low (grades III and IV and C and D recommendations). Few interactions have been described between DAAs and methotrexate, cyclosporin, or tacrolimus in pharmacokinetic studies performed in non-IBD patients [8,17], but more studies are needed.

The recently published Consensus of the European Crohn's and Colitis Organisation (ECCO) on the management of infections in IBD patients alerts about possible disease exacerbation when patients with IBD are being treated with DAAs and remarks on the lack of information regarding safety and efficacy (essentially, sustained viral response, SVR) in patients under immunosuppression [5]. In the previous ECCO guideline [18], it was not possible to reach a consensus for HCV screening before starting immunomodulators. In contrast, the most recent one [5] recommends performing HCV screening systematically in all patients with IBD, but without clear recommendations regarding treatment once they are diagnosed. Thus, this study is relevant to provide recommendations based on a good level of evidence that contributes to eradicating this infection in patients with IBD.

We aimed to assess the efficacy and safety of HCV treatment with DAAs in patients with IBD, identifying potentially relevant interactions with immunosuppressants/biologics and assessing the impact of DAAs on the course of IBD.

2. Methods

2.1. Study design and data collection system

This is an observational, retrospective, multicentre, nationwide study. Patients were identified from the ENEIDA registry (nationwide study on genetic and environmental determinants of inflammatory bowel disease) [19] of the Spanish Working Group of Crohn's and Colitis (GETECCU), which is a prospectively maintained database set up in 2006 containing demographic, clinical and therapeutic data on patients with IBD. The database has a section dedicated to infections and amongst them the HCV serology is registered. On February 2021, there were 65,604 patients with IBD in the ENEIDA database. Amongst them, 37,332 had been screened for HCV infection at any time (56.9 % of the patients in ENEIDA database) and 388 had anti-HCV positive. Patients were screened for HCV according to criteria of clinicians in charge that probably based their decision on recommendations of previous ECCO guidelines that considered HCV screening non-mandatory [18].

A questionnaire asking for participation was sent to the researchers of 94 centres belonging to the ENEIDA project and 23 agreed to participate. The total number of patients registered in the participant centres was 25,998. Amongst them, 17,497 had been screened for HCV (67.3 %) and 218 were positive for anti-HCV (seroprevalence 1.3 %). Therefore, 218 patients were assessed for eligibility but 139 had some exclusion criteria (see below study criteria and Fig. 1 study flowchart). Investigators of participant hospitals reviewed the medical records of all patients included to ensure that they fulfilled the inclusion/exclusion criteria and to double-check the completeness and accuracy of clinical data. Additional data requested were collected using the online Research Electronic Data Capture (REDCap) [20,21] tools hosted at Asociación Española de Gastroenterología (AEG; www.aegastro.es).

2.2. Study population and antiviral treatment

We identified all patients diagnosed with chronic HCV infection (defined as positive anti-HCV and detectable HCV-RNA) treated with DAAs and/or IFN registered in the ENEIDA database. The study period ranged from January 1, 2011, to February 28, 2021. UC and CD patients infected with HCV (population evaluated for eligibility) were included if they were treated with DAAs during the study period (inclusion criteria). The evaluation period for every patient ranged from 15 days before DAA administration to 12 weeks follow-up after DAA administration. The exclusion criteria were spontaneous cure of HCV without treatment, HCV treated with IFN-based therapies, lost to follow-up before DAAs initiation, incomplete data in clinical records, non-acceptance of DAAs treatment and treatment of HCV outside the study period.

The type of DAAs was decided by consensus for every case by the committee comprising the hepatologist in charge, the "IBDologist" and/or the pharmacy department and was based on the availability and recommendations at different time points.

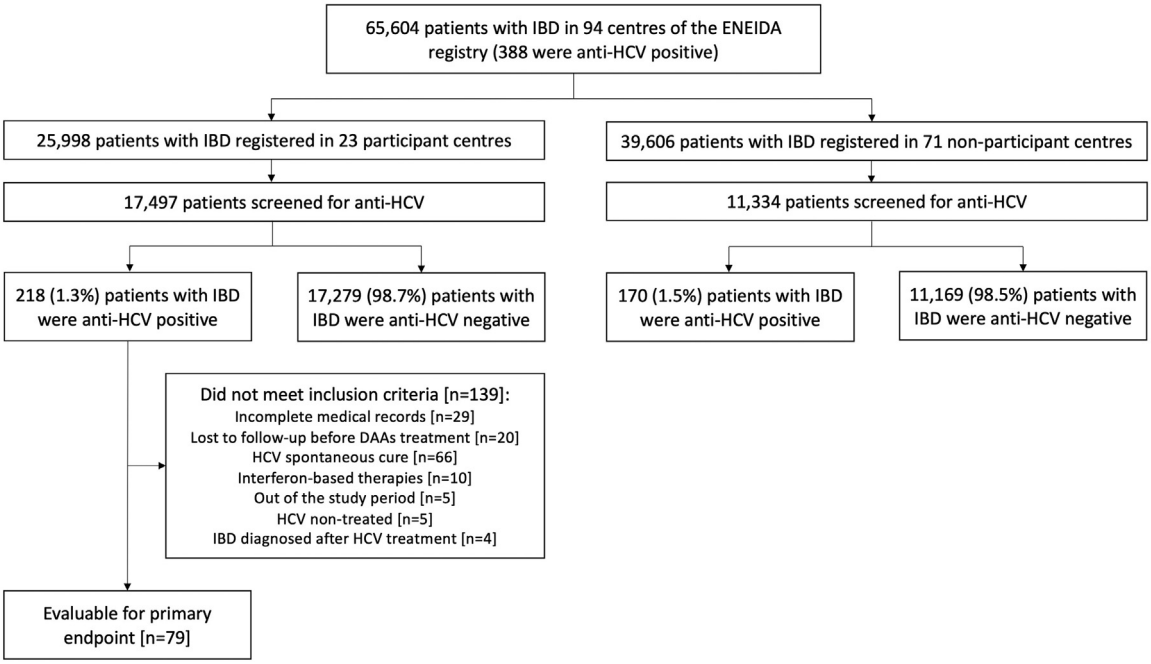

Fig. 1. Patient selection flowchart.

2.3. Clinical variables

The following clinical variables were recorded before DAAs starting: age, sex, surgical procedures, location, extent, and phenotype of IBD according to the Montreal classification. Clinical activity was evaluated using the Partial Mayo Score (PMS) [22] (cut-off values: <2, remission; 2–4, mild activity; 5–7, moderate activity; and >7, severe activity) in UC or the Harvey–Bradshaw Index (HBI) [23] (cut-off values: <5, remission; 5–7, mild activity; 8–16, moderate activity; and >16, severe activity) in CD. Clinical indices were calculated during the evaluation period (within 2 weeks before DAA initiation, at the end of DAA treatment and at the 12-week follow-up). The endoscopic activity was evaluated when available in patients with active disease using the Mayo Endoscopic Subscore (MES) [22] (cut-off values: Mayo 0, normal mucosa or inactive disease; Mayo 1, mild activity; Mayo 2, moderate activity; and Mayo 3, severe activity) for UC or by the Simple Endoscopic Score for CD (SES-CD) [24] (cut-off values: 0–2, remission; 3–6, mild endoscopic activity; 7–15, moderate endoscopic activity; and >15, severe endoscopic activity). The therapeutic regimen for IBD was recorded at the beginning and at the end of DAA treatment and at 3 months of follow-up. In patients with liver cirrhosis, the specific treatment (diuretics, B-blockers, antibiotics, etc.) administered during DAA therapy was also registered. To rule out possible confounding factors triggering IBD outbreaks or worsening liver function, smoking, alcohol consumption, concomitant infection with hepatitis B virus (HBV) and human immunodeficiency virus (HIV) were recorded. Risk of alcohol consumption was defined according to the criteria of the World Health Organization (regular daily consumption of ≥20 to 40 gs of alcohol in women and ≥40 to 60 gs in men).

The variables related to HCV infection or of its induced liver disease were genotype, viral load at baseline and at the end of HCV treatment, SVR, hepatic fibrosis and Child–Pugh scale of liver cirrhosis. SVR is defined as undetectable viral load 3 months after the end of DAA treatment [12]. Hepatic fibrosis was measured by transient elastography [25]. Tissue stiffness is expressed in kilopascals (kPa) and the METAVIR equivalent score (F0 to F4), which incorporates five stages of fibrosis [26]: F0, no fibrosis; F1 (1–7 kPa), portal fibrosis without septa or minimal fibrosis; F2 (7–9 kPa), portal fibrosis with a few septa, moderate fibrosis or clinically significant fibrosis; F3 (9–14 kPa), septal fibrosis with many septa but no cirrhosis or severe fibrosis; and F4 (>14 kPa), cirrhosis. The presence of chronic liver disease complications before the start of DAA or the appearance during DAAs were recorded.

2.4. Adverse events and adherence to DAAs

The adverse events (AEs) and/or pharmacological interactions potentially associated with DAAs were recorded and classified according to severity. The causality of the drug on the AE was classified as not related to the medication, possibly related, or probably related at the discretion of the investigator. The degree of association with the drug is greater for those considered probable than those considered possible [27].

DAAs are completely financed by the public health system in Spain and are dispensed at the hospital pharmacy. Patients collected the medication monthly, and adherence was recorded by the number of tablets administered and returned, depending on the treatment schedule. The adherence was considered good when more than 90 % of the prescribed drug was taken by the patient [28]. In Supplementary Tables 2 and 3, we provide the active drugs, trade names, and doses of the commonly used DAAs marketed in Spain.

2.5. Statistical analysis

Qualitative variables are expressed as percentages and 95 % confidence intervals (CIs), and quantitative variables are expressed as medians and interquartile range. Patients with UC and CD were analysed separately to assess whether DAAs could have a differential impact on the evolution of the two diseases and on the occurrence of AE. To compare differences in the proportions between groups, the chi square test or Fisher's exact test was used. McNemar's test was applied to ascertain whether there were differences in the proportion of active patients at the beginning, at the end of DAA treatment and at the end of the follow-up period in both UC and CD. The statistical package used to process and analyse the

Table 1
Baseline characteristics of patients with inflammatory bowel disease at starting of direct-acting antivirals.

Crohn's disease, *n* (%)	42 (100)	**Ulcerative colitis, *n* (%)**	37 (100)
Male gender, *n* (%)	23 (54.8)	Male gender, *n* (%)	26 (70.3)
Age (years), mean +/- SD	55.69 +/- 12.89	Age (years), mean +/- SD	51.95 +/- 12.27
Disease duration (years), median (IQR)	8 (2–22)	Disease duration (years), median (IQR)	10 (4–17)
Location		**Extent**	
L1 ileal, *n* (%)	26 (61.9)	E1 proctitis, *n* (%)	11 (29.7)
L1 ileal + L4, *n* (%)	1 (2.4)	E2 left-sided colitis (*n* (%)	10 (27.0)
L2 colonic, *n* (%)	6 (14.3)	E3 extensive colitis, *n* (%)	16 (43.2)
L2 colonic + L4, *n* (%)	0 (0)		
L3 ileocolonic, *n* (%)	8 (19.0)		
L3 ileocolonic + L4, *n* (%)	1 (2.4)		
Behaviour			
B1 non-stricturing, non-penetrating, *n* (%)	17 (40.5)		
B1 non-stricturing, non-penetrating + P, *n* (%)	5 (11.9)		
B2 stricturing, *n* (%)	10 (23.8)		
B2 stricturing + P, *n* (%)	1 (2.4)		
B3 penetrating, *n* (%)	6 (14.3)		
B3 penetrating + P, *n* (%)	3 (7.1)		
Previous intestinal resection, *n* (%)	17 (40.5)	Colectomy, *n* (%)	4 (10.8)
Smoking, *n* (%)	12 (28.6)	Smoking, *n* (%)	8 (21.6)
Therapeutic requirements			
No treatment, *n* (%)	11 (26.2)	No treatment, *n* (%)	6 (16.2)
Salicylates, *n* (%)	8 (19.0)	Salicylates, *n* (%)	19 (51.4)
Azathioprine, *n* (%)	7 (16.6)	Azathioprine, *n* (%)	2 (5.4)
Methotrexate, *n* (%)	1 (2.4)	Methotrexate, *n* (%)	0 (0)
Corticosteroids, *n* (%)	1 (2.4)	Corticosteroids, *n* (%)	0 (0)
AntiTNF, *n* (%)	8 (19.0)	AntiTNF, *n* (%)	0 (0)
Salicylates, corticosteroid, *n* (%)	1 (2.4)	Salicylates, corticosteroid, *n* (%)	2 (5.4)
Salicylates, azathioprine, *n* (%)	1 (2.4)	Salicylates, azathioprine, *n* (%)	5 (13.5)
Azathioprine, antiTNF, *n* (%)	1 (2.4)	Azathioprine, antiTNF, *n* (%)	0 (0)
Azathioprine, ustekinumab, *n* (%)	2 (4.8)	Azathioprine, ustekinumab, *n* (%)	0 (0)
Vedolizumab, *n* (%)	1 (2.4)	Vedolizumab, *n* (%)	0 (0)
Salicylates, vedolizumab, *n* (%)	0 (0)	Salicylates, vedolizumab, *n* (%)	1 (2.7)
Salicylates, azathioprine, antiTNF, *n* (%)	0 (0)	Salicylates, azathioprine, AntiTNF, *n* (%)	1 (2.7)
Salicylates, azathioprine, apheresis, *n* (%)	0 (0)	Salicylates, azathioprine, Apheresis, *n* (%)	1 (2.7)
Total of patients with CD that received immunomodulators/biologics, *n* (%)	21 (50)	Total of patients with UC that received immunomodulators/biologics, *n* (%)	10 (27)
Frequency of treatments			
Corticosteroids, *n* (%)	2 (4.8)	Corticosteroids, *n* (%)	2 (5.4)
Immunomodulators, *n* (%)	12 (28.6)	Immunomodulators, *n* (%)	9 (24.3)
Biologics, *n* (%)	12 (28.6)	Biologics, *n* (%)	2 (5.4)

Abbreviations: IBD: inflammatory bowel disease; P: perianal disease; L4: upper disease involvement; SD: standard deviation; IQR: interquartile range; CD: Crohn's disease; UC: ulcerative colitis.

data was SPSS Statistics version 25 for Mac OS. Graphics were generated using GraphPad Prism Version 9.4.0 for Mac OS.

2.6. Ethical statement

This was an observational study performed in accordance with the Declaration of Helsinki. The study was approved by the scientific committee of ENEIDA (GETECCU Research Board) in October 2020 and the local ethics committees of the participating centres (Comitè Ètic d'Investigació Clínica, Hospital Universitari Mútua Terrassa, code O/21–052, 29 April 2021). This study was registered at ClinicalTrials.gov (NCT05452187). Written informed consent to participate in the ENEIDA registry was obtained from all patients before their inclusion.

3. Results

3.1. Clinical characteristics of the study population

Seventy-nine patients with HCV infection met the inclusion criteria and received treatment with DAAs (mean age +/- standard deviation [years] at the time of DAA treatment was 54+/−12; 62 % male gender). Thirty-one patients (39.2 %) received immunomodulators (azathioprine or methotrexate) or biologics (antiTNF, vedolizumab or ustekinumab) for IBD. Table 1 shows the patients' baseline characteristics of IBD and therapeutic requirements before DAAs. Table 2 shows the liver disease characteristics and DAA therapies. Approximately half of the cohort had UC (n = 37; 46.8 %), and the rest had CD (n = 42; 53.2 %). The majority of UC patients had left-sided or extensive colitis, and only 4 (10.8 %) were colectomised. Amongst patients with CD, more than 50 % had B1 non-stricturing, non-penetrating behaviour, and 17 patients (40.5 %) had previous intestinal resections. A similar proportion of active smokers at the time of DAA treatment was detected amongst CD (n = 12; 28.6%) and UC (n = 8; 21.6%).

Twenty-five patients (31.6%) had Child–Pugh A liver cirrhosis - significant fibrosis, whereas the remaining patients did not present significant fibrosis. HCV genotype 1 was predominant, accounting for 61 cases (77.2 %). Six patients (7.6%) in the cohort had significant alcohol intake, which could contribute to liver cirrhosis in some patients.

3.2. Efficacy of DAA therapy

The most frequent DAA therapeutic schedules were sofosbuvir plus ledipasvir and glecaprevir plus pibrentasvir (n = 26 [32.9 %] and n = 13 [16.4 %], respectively). In Supplementary Table 4, we provide a detailed description of the DAA regimens and the concomitant therapies for IBD. DAAs were generally administered for 8 or 12 weeks (n = 29 [37 %] and n = 45 [57 %], respectively). SVR was achieved in 76 patients (96.2 %). Only one patient with UC had viral load persistence at 3–6 months despite good adher-

Table 2
Baseline characteristics of the hepatitis C and direct-acting antivirals schedule.

Characteristics of the underlying chronic liver disease	
Nonsignificant fibrosis (F0-F1-F2), *n* (%)	51 (64.6)
Significant fibrosis (F3-F4), *n* (%)	25 (31.6)
Fibrosis not assessed, *n* (%)	3 (3.8)
HCV viral load (UI/mL), median (IQR)	1555,437 (647,613–3037,243)
Genotype 1 HCV, *n* (%)	61 (77.2)
Genotype 2 HCV, *n* (%)	5 (6.3)
Genotype 3 HCV, *n* (%)	10 (12.7)
Genotype 4 HCV, *n* (%)	3 (3.8)
Alcohol intake of risk, *n* (%)	6 (7.6)
HBV, *n* (%)	1 (1.3)
HIV, *n* (%)	7 (8.9)
DAA therapies	
Sofosbuvir, ledipasvir, *n* (%)	26 (32.9)
Glecaprevir + pibrentasvir, *n* (%)	13 (16.4)
Parietaprevir + ritonavir + ombitasvir, dasabuvir, *n* (%)	9 (11.3)
Sofosbuvir, velpatasvir, *n* (%)	8 (10.0)
Sofosbuvir, daclatasvir, *n* (%)	7 (8.8)
Parietaprevir + ritonavir + ombitasvir, dasabuvir, ribavirin, *n* (%)	5 (6.3)
Grazoprevir + elbasvir, *n* (%)	3 (3.9)
Parietaprevir + ritonavir + ombitasvir, *n* (%)	2 (2.6)
Sofosbuvir, ledipasvir, ribavirin, *n* (%)	2 (2.6)
Sofosbuvir, simeprevir, *n* (%)	1 (1.3)
Sofosbuvir, ribavirin, *n* (%)	1 (1.3)
Sofosbuvir, daclatasvir, ribavirin, *n* (%)	1 (1.3)
Sofosbuvir, *n* (%)	1 (1.3)

Abbreviations: HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IQR: interquartile range.

ence to DAAs, and in two patients SVR (HCV viral load) was not available 3–6 months after DAAs treatment.

3.3. Safety and tolerance of DAAs

AEs occurred in 8 patients (10.1 %), 5 (6.3 %) possibly/probably related to DAAs, and all of them were mild. Three more AEs (3.8 %) were considered unrelated to DAAs: 1 mild pancytopenia that recovered after azathioprine withdrawal, another mild hepatotoxicity resolved after azathioprine withdrawal, and 1 death by suicide in a patient with a severe underlying psychiatric disorder. No DAA regimens had to be withdrawn due to intolerance or clinically relevant interactions with salicylates or immunosuppressants/biologics. The AEs, the type of DAAs and IBD therapy are detailed in Table 3. The AEs were not related to the activity of IBD, type of IBD, presence of liver fibrosis, use of immunosuppressants/biologics, or DAA regimen. Tolerance to DAAs was optimal, achieving adherence to the treatment in 76 patients (96.2 %). Two patients did not return the tablets to the hospital pharmacy service; therefore, adherence could not be confirmed in these two cases. One patient was cured despite insufficient adherence to DAAs (<90 % of prescription), presenting an SVR at 3 months.

3.4. IBD flare-ups and liver disease evolution during DAAs

There were no significant differences in the percentage of CD patients who were active at the beginning of the DAA treatment (n = 9, 21.4 % [95 % CI 11.7−35.9 %]) *vs.* at the end of the 12-week follow-up (n = 8, 19.1 % [95 % CI 10.0−33.3 %]) (p = 1.00). There were no significant differences in the percentage of UC patients who were active at the beginning of DAA treatment (n = 2, 5.4 % [95 % CI 1.5−17.7 %]) *vs.* at the end of the 12-week follow-up (n = 7, 18.9 % [95 % CI 9.5−34.2 %]) (p = 0.063).

Overall, amongst all IBD patients, there were also no significant differences in the percentage of patients active at the beginning of DAAs (n = 11, 13.9 % [95 % CI 8.0−23.2 %]) *vs.* at the end of the 12-week follow-up (n = 15, 19.0 % [95 % CI 12.0−29.0 %]) (p = 0.424). Six patients (7.6%) maintained the inflammatory activity from the beginning to the end of the 12-week follow-up.

Fig. 2 summarizes the outcome of the activity of the whole IBD cohort and separately for CD and UC during the entire evaluation period. Adjustments in the therapeutic management of IBD due to changes in disease activity before, during DAA administration and at the 12-weeks of follow-up are detailed in Table 4. In 14 (17.7 %) patients, IBD treatment had to be intensified and the treatment remained unchanged in 63 (79.8 %) patients during the evaluation period. There was no relationship between the development of inflammatory activity and any DAA regimen. No complications due to liver disease occurred before DAA administration, during treatment or 12 weeks afterwards.

4. Discussion

We report herein the results of the first cohort of patients with IBD infected with HCV treated with DAAs. The study demonstrated that DAAs are effective and safe therapies for the treatment of HCV in patients with IBD.

The efficacy of DAAs in the present cohort, with an SVR of 96.2 %, is similar to that previously reported regardless of the therapeutic schedule used [12,29,30].

In contrast, the clinical characteristics of IBD apparently do not impact the efficacy of DAAs. The high percentage of SVR achieved, irrespective of the location of CD, behaviour extent and activity of the disease, gives support to this assertion. These results are important because extensive small bowel involvement could have theoretically impacted the absorption [17,31]. The intestinal distribution of drug transporters is not homogenous, and each segment of the gastrointestinal tract possesses a specific set of transporters that determine functional diversity, affecting, *e.g.*, drug absorption [31]. Despite this information, a high efficacy of DAAs was also obtained in CD patients with intestinal resection (40.5 % of the CD cohort) and in colectomised UC patients (10.8 % of the UC cohort). Thus, the high effectiveness of DAAs and the wide distribution of drug carriers in the gastrointestinal tract allow correct absorption and high SVR despite the presence of intestinal resections or inflamed intestinal segments.

One patient in our cohort achieved SVR despite insufficient adherence. The impact of adherence on SVR has been assessed in populations with a high risk of inadequate adherence. Cunningham et al [28]. reported good efficacy of two regimens (sofosbuvir/velpatasvir or paritaprevir/ritonavir/ombitasvir and dasabuvir with or without ribavirin), even in nonadherent patients (<90 % adherence).

In the present series, only one serious AE (suicide) was reported, and it was considered unrelated to sofosbuvir plus velpatasvir, the DAA that this patient was receiving. In the era before DAAs, the management of psychiatric symptoms induced or aggravated by IFN-based therapies was a major problem in the management of hepatitis C occurring in approximately 5 % of IFN-treated cases [32–35]. Cases of death due to suicide were occasionally reported in clinical trials with DAA schedules and even in a recent phase II trial with a combination of sofosbuvir plus velpatasvir [36]. All cases were considered unrelated to this antiviral therapy. However, considering that comorbid conditions can induce suicide in HCV patients, this eventuality should be considered in at-risk patients. AEs, possibly related to DAAs, were mild and occurred in 6.3 % (n = 5) of the cases, although causality could not be completely established. Fatigue and headache were the most common AEs described in clinical trials [12], similar to those found in this cohort. The safety of DAAs in IBD patients was excellent and similar to that described elsewhere [12].

Table 3
Adverse events recorded during direct-acting antiviral treatment.

Montreal Classification	Degree of IBD activity before DAAs	Degree of hepatic fibrosis	DAA treatment and duration (weeks)	IBD treatment	Type of AE	Severity of AE, n (%)	Causality
CD (L3 + B1)	HBI: Remission	F4	Sofosbuvir + daclatasvir (24)	No treatment	Flu-like syndrome (asthenia, myalgias, headache, low-grade fever, nausea)	Mild, 5 (6.3)	Possibly related
UC (E2)	PMS: Remission	F4	Sofosbuvir + ledipasvir + ribavirin (12)	Salicylates			
UC (E1)	PMS: Remission	F2	Sofosbuvir + ribavirin (12)	Salicylates			
UC (E1)	PMS: Remission	F4	Sofosbuvir + simeprevir (12)	Salicylates	Eczema		
UC (E2)	PMS: Remission	F2	Paritaprevir + ritonavir + Ombitasvir + dasabuvir + Ribavirin (12)	No treatment	Hypotension		
CD (L3 + L4 + B2)	HBI: Mild SES-CD: Mild	F2	Sofosbuvir + daclatasvir (12)	Azathioprine	Hepatotoxicity	Mild, 2 (2.5)	Not related
UC (E1)	PMS: Remission	F1	Sofosbuvir + ledipasvir (12)	Salicylates and azathioprine	Pancytopenia		
UC (E2)	PMS: Mild MES: Mild	F2	Sofosbuvir + velpatasvir (12)	Salicylates and corticosteroids	Suicide	Severe, 1 (1.3)	

Abbreviations: IBD: inflammatory bowel disease; DAAs: direct-acting antivirals; CD: Crohn's disease; UC: ulcerative colitis; HBI: Harvey–Bradshaw index; PMS: partial Mayo score; MES: Mayo endoscopic subscore; SES-CD: Simple Endoscopic Score for Crohn's disease; L1: ileal location; L2: colonic location; L3: ileocolonic location; L4: upper disease involvement; B1: inflammatory behaviour; B2: stenosing behaviour; B3: penetrating behaviour; P: perianal disease; E1: ulcerative proctitis; E2: left-sided UC (distal UC); E3: extensive UC (pancolitis); antiTNF: antitumour necrosis factor therapies.

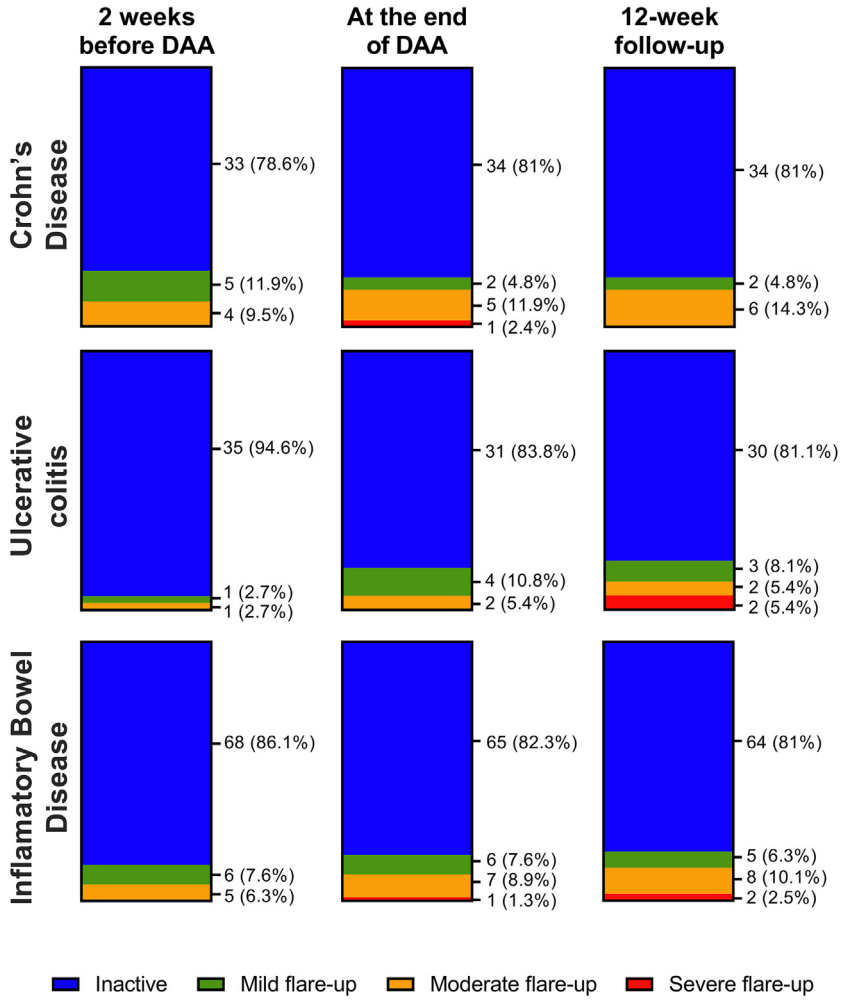

Fig. 2. Evolution of the activity of CD (measured by the Harvey–Bradshaw Index), UC (measured by Partial Mayo Score) and IBD overall associated with DAAs administration during the evaluation period.

Table 4
Evolution of disease activity and therapeutic adjustments in patients who developed activity during the evaluation period.

Montreal Classification	Degree of IBD activity			IBD treatment			IBD therapeutic adjustments	DAA treatment and duration (weeks)
	2 weeks before DAA treatment	At the end of DAA treatment	At the 12-week follow-up	At DAA initiation	At the end of DAA treatment	At the 12-week follow-up		
CD (L1 + B2)	HBI: Moderate SES-CD: Moderate	HBI: Moderate	HBI: Remission	AntiTNF	AntiTNF	AntiTNF	Unchanged	Sofosbuvir + velpatasvir (12)
CD (L2 + B1 + p)	HBI: Moderate SES-CD: Mild	HBI: Moderate	HBI: Mild	No treatment[a]	No treatment[a]	No treatment[a]	Unchanged	Sofosbuvir + velpatasvir (12)
CD (L3 + B1 + p)	HBI: Mild	HBI: Remission	HBI: Remission SES-CD: Remission	Azathioprine + ustekinumab	Azathioprine + ustekinumab	Azathioprine + ustekinumab	Unchanged	Glecaprevir + pibrentasvir (8)
UC (E3)	PMS: Moderate	PMS: Moderate	PMS: Severe MES: Severe	Salicylates + azathioprine + antiTNF (adalimumab)	Salicylates + azathioprine + antiTNF (switching from adalimumab to infliximab)	Salicylates + corticosteroids + vedolizumab	Intensified	Sofosbuvir + ledipasvir (12)
UC (E2)	PMS: Mild MES: Mild	PMS: Mild	PMS: Moderate	Salicylates + corticosteroids	Salicylates	Azathioprine + corticosteroids	Intensified	Sofosbuvir + velpatasvir (12)
CD (L3 + L4 + B2)	HBI: Mild SES-CD: Mild	HBI: Remission	HBI: Moderate	Azathioprine	No treatment (azathioprine withdrawn due to hepatotoxicity)	No treatment	Changed due to AE	Sofosbuvir + daclatasvir (12)
CD (L1 + B3)	HBI: Moderate SES-CD: Moderate	HBI: Moderate	HBI: Remission	Salicylates + azathioprine	Salicylates + azathioprine + antiTNF	Salicylates + antiTNF	Intensified	Sofosbuvir + ledipasvir (8)
CD (L3 + B1)	HBI: Mild SES-CD: Moderate	HBI: Remission SES-CD: Mild	HBI: Remission	Salicylates	Salicylates	Salicylates	Unchanged	Grazoprevir + elbasvir (16)
CD (L1 + B2)	HBI: Mild SES-CD: Moderate	HBI: Moderate SES-CD: Moderate	HBI: Moderate	Salicylates + corticosteroids	Corticosteroids + azathioprine + antiTNF	Azathioprine + antiTNF	Intensified	Sofosbuvir (8)
CD (L2 + B3 + p)	HBI: Mild SES-CD: Mild	HBI: Mild	HBI: Moderate	No treatment	No treatment	Azathioprine + antiTNF	Intensified	Sofosbuvir + ledipasvir (8)
CD (L1 + B3)	HBI: Moderate	HBI: Severe	HBI: Remission	No treatment	Surgery + preventive azathioprine	Azathioprine	Intensified	Sofosbuvir + daclatasvir (12)
UC (E3)	PMS: Remission	PMS: Moderate	PMS: Remission	Azathioprine	Azathioprine + beclomethasone + topical salicylates	Azathioprine + salicylates	Unchanged	Grazoprevir + elbasvir (12)
UC (E1)	PMS: Remission	PMS: Mild MES: Mild	PMS: Mild	Salicylates	Salicylates	Salicylates	Unchanged	Sofosbuvir + ledipasvir (8)
CD (L3 + B3 + p)	HBI: Remission	HBI: Moderate	HBI: Remission	Vedolizumab	Ustekinumab	Ustekinumab	Intensified	Glecaprevir + pibrentasvir (8)
CD (L1 + B1)	HBI: Remission	HBI: Mild SES-CD: Mild	HBI: Moderate	No treatment	No treatment	Corticosteroids	Intensified	Paritaprevir + ritonavir + pmbitasvir + dasabuvir (8)
UC (E2)	PMS: Remission	PMS: Mild MES: Mild	PMS: Mild MES: Moderate	Salicylates	Salicylates + corticosteroids + azathioprine	Azathioprine + antiTNF	Intensified	Sofosbuvir + ledipasvir (8)
UC (E1)	PMS: Remission	PMS: Mild MES: Mild	PMS: Remission	Salicylates + azathioprine	Budesonide (azathioprine withdrawn due to pancytopenia)	Budesonide	Changed due to AE	Sofosbuvir + ledipasvir (12)
UC (E2)	PMS: Remission	PMS: Remission	PMS: Severe MES: Severe	Salicylates	Salicylates	AntiTNF	Intensified	Sofosbuvir, ledipasvir (24)
UC (E3)	PMS: Remission	PMS: Remission	PMS: Mild	Salicylates, azathioprine	Salicylates, azathioprine	Doses of salicylates were increased, azathioprine	Unchanged	Parietaprevir + ritonavir + ombitasvir, dasabuvir, ribavirina (12)
UC (E2)	PMS: Remission	PMS: Remission	PMS: Moderate MES: Severe	Salicylates	Salicylates	Salicylates + corticosteroids	Intensified	Sofosbuvir, ledipasvir (8)
CD (L1 + B2)	HBI: Remission	HBI: Remission	HBI: Mild	Azathioprine	Azathioprine	Corticosteroids, azathioprine	Intensified	Glecaprevir + pibrentasvir (8)
CD (L1 + B2)	HBI: Remission	HBI: Remission	HBI: Moderate	Salicylates	Salicylates	Azathioprine	Intensified	Sofosbuvir, ledipasvir (12)
CD (L2 + B1 + p)	HBI: Remission	HBI: Remission	HBI: Moderate SES-CD: Moderate	No treatment	No treatment	Infliximab + azathioprine	Intensified	Sofosbuvir, velpatasvir (12)

[a] This patient was treated with DAAs in a drug addiction unit, and he did not attend the IBD clinic until the DAA therapy was finished; this was why he did not receive IBD treatment despite evident disease activity.
Abbreviations: IBD: inflammatory bowel disease; DAAs: direct-acting antivirals; CD: Crohn's disease; UC: ulcerative colitis; HBI: Harvey–Bradshaw index; PMS: partial Mayo score; MES: Mayo endoscopic subscore; SES-CD: Simple Endoscopic Score for Crohn's disease; L1: ileal location; L2: colonic location; L3: ileocolonic location; L4: upper disease involvement; B1: inflammatory behaviour; B2: stenosing behaviour; B3: penetrating behaviour; P: perianal disease; E1: ulcerative proctitis; E2: left-sided UC (distal UC); E3: extensive UC (pancolitis); antiTNF: antitumour necrosis factor therapies; AE: adverse events.

Regarding the evolution of liver disease, there were also no liver-related complications during DAA administration or during follow-up. An SVR is generally associated with normalization of liver enzymes, improvement or regression of liver necroinflammation and fibrosis, and improvement in liver function. Moreover, the risk of HCC and liver-related mortality is significantly reduced but not eliminated depending on the degree of initial liver fibrosis before DAAs [12].

The SVR in IBD patients under immunosuppression is largely unknown [5]. But based on our results, achieving an efficacy similar than previously described in non-immunosuppressed cohorts [29], we can affirm that immunosuppressants have no influence on the efficacy of DAAs. The present cohort of patients with IBD and HCV may be considered representative of the whole population of IBD. The clinical characteristics in terms of location, extension, behaviour and activity of the disease are in the line of previously described population-based studies of IBD [37–39]. The proportion of patients under immunosuppressants and/or biologics in our study (39.2 %) is similar to that described in the literature [37,38] except for a lower proportion of patients with CD treated with immunosuppressants (66% reported by Burisch et al [37]., 45 % reported by Chaparro et al [37]. *vs* 24.3 % in the present study). By contrast, a similar use of biologics was observed. We cannot rule out that physicians in charge of these patients, due to the concomitant HCV infection, decided to give less immunosuppressants or deescalate at any time, during the evolution of the disease. Any case, the activity of the disease of patients in our study was quite similar compared to other cohorts [37–39].

We also did not detect clinically relevant drug-to-drug interactions with the immunosuppressants/biologics administered and DAAs. However, our cohort did not include patients treated with cyclosporin, tofacitinib, tacrolimus, or mycophenolate. Nevertheless, the use of mycophenolate is considered safe, and it is administered with the majority of DAA combinations. Some combinations of DAAs and tacrolimus should be administered with caution, and others are disadvised combined with cyclosporin [12].

Our study has strengths and limitations. This is the only large cohort of IBD patients infected with HCV and treated with DAAs providing reliable information about how to manage these patients. The most important limitation is the retrospective nature of some data obtained from the clinical records of patients identified from the ENEIDA database, mainly data regarding therapeutic schedules of DAAs and activity of IBD. In contrast, all the treatments for IBD are prospectively updated in the ENEIDA registry. In addition, the present cohort did not include patients with IBD and advanced hepatic failure (Child B or C) with decompensated liver cirrhosis.

With the results of this study, all the questions raised by the ECCO guidelines [5] can be answered, and better recommendations can be given, enabling the treatment of all patients with IBD and HCV with confidence. In addition, no relevant clinical interactions between immunosuppressants/biologics therapy and DAAs exist in terms of both efficacy and safety. Furthermore, our results demonstrated that any of the strategies empirically proposed for the treatment of HCV in IBD (sequential, concomitant or inverted) can be used [8]. Moreover, considering that the activity of the disease either does not worsen or does so minimally in a low proportion of patients, mainly those with UC, the concomitant treatment of the two entities is a perfectly reasonable option.

In conclusion, treatment with DAAs in patients with IBD is effective and safe. Future ECCO guidelines on the management of infections in patients with IBD should recommend the eradication of HCV with DAAs for all patients with IBD following the same therapeutic schedules of HCV-infected patients without IBD based on international guidelines.

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Author contributions

AMC and ME were involved in the conception and design of the study. AMC, DH, PFD, MV, FM, CRB, MJG, HM, LPN, CSF, MJC, MOD, EP, XC, SJF, CGM, MP, IRL, ES, FBC, NMM, AO, BO, BS, ACG, ED and ME recruited patients, collected the data and conducted the study. AMC performed the statistical analysis, prepared figures, and drafted the manuscript. AMC coordinated the research group and directed the execution of the study. AMC and ME conceived and designed the study and revised, edited, and finalised the manuscript. All authors read and approved the final version of the manuscript, including the authorship list.

Conflict of interest

Dr. A. Martín-Cardona has received financial support for conference attendance, educational activities, and research support from Abbvie, Biogen, Faes Farma, Ferring, Jannsen, MSD, Pfizer, Takeda, Dr. Falk Pharma and Tillotts. Dra. MJ Casanova has received research or education funding from Pfizer, Takeda, Janssen, MSD, Ferring, Abbvie, Biogen, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi and Norgine. Dr. C. González-Muñoza has received financial support for travel and educational activities from Pfizer, Takeda, MSD, Norgine, Janssen, Tillots, and Kern Pharma. Dra. M. Piqueras has served as a speaker or has received research or education funding from Takeda, Abbvie and Janssen. Dr. I. Rodríguez-Lago has received financial support for travelling and educational activities from or has served as an advisory board member for Abbvie, Adacyte, Celltrion, Chiesi, Danone, Dr. Falk Pharma, Ferring, Faes Farma, Janssen, Galapagos, MSD, Otsuka Pharmaceutical, Pfizer, Roche, Takeda, and Tillotts Pharma. Dra. N. Manceñido Marcos has served as a speaker and consultant for or has received financial support for educational activities from Janssen, AbbVie, Pfizer, Takeda, Ferring, Faes Farma, Dr. Falk Pharma and Tillotts Pharma. Dra. B. Sicilia has received research or education funding or advisory fees from Abbvie, FAES, Chiesi, Dr. Falk, MSD, Tillots Pharma, Khern Pharma, Janssen, Pfizer and Takeda. Dr. E. Domènech has served as a speaker or has received research or education funding or advisory fees from AbbVie, Adacyte Therapeutics, Biogen, Celltrion, Galapagos, Gilead, Imidomics, Janssen, Kern Pharma, MSD, Pfizer, Roche, Samsung, Takeda and Tillots. Dra. M. Esteve has received support for conference attendance and research support from Abbvie, Biogen, Faes Farma, Ferring, Jannsen, MSD, Pfizer, Takeda, and Tillotts. The remaining authors report no conflicts of interest related to this manuscript.

Data availability

The data underlying this article are available on reasonable request.

Acknowledgments

The complete list of the affiliations of the ENEIDA-GETECCU investigators is available in the Supplementary Material.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2023.09.004.

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