Increased incidence of systemic serious viral infections in patients with inflammatory bowel disease associates with active disease and use of thiopurines

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Incidence and risk factors of extra-intestinal serious viral infections in patients with Inflammatory Bowel Disease.

Short title: Serious viral infections in IBD

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BMI, body mass index;

CD, Crohn’s disease;

CI, confidence interval;

CMV, cytomegalovirus;

EBV, Epstein-Barr virus;

HLH, hemophagocytic lymphohistiocytosis;

HR, hazard ratio;

IBD, inflammatory bowel diseases;

PMSI, French hospital discharge database;

SD, standard deviation;

SIR, standardized incidence ratio;

SVI, serious viral infections;

TNF, tumor necrosis factor;

UC, ulcerative colitis;

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ABSTRACT

Background and aims: magnitude and drivers of the risk of serious viral infections (SVI) in Inflammatory Bowel diseases (IBD) are unclear. We aimed to assess the incidence (compared to general population) and risk factors of extra-intestinal SVI in patients with IBD.

Methods: Using MICISTA, an IBD-unit database detailing prospectively characteristics and complications of IBD, we identified between January 2005 and December 2014 patients followed for IBD outside the context of organ transplantation, HIV infection or chronic hepatitis. We estimated incidences of extra-intestinal SVI, defined by need for hospitalization or permanent organ damage. Standardized incidence ratios (SIR) were calculated using the French hospital database. We performed a case-control study nested in MICISTA for assessing the role of exposure to IBD drugs and IBD clinical activity in the risk of developing SVI.

Results: We identified 31 patients with SVI among 2645 patients followed for 15,383 person-years. We observed 13, 10, 5 and 3 cases of CMV, EBV, VZV and HSV infection, respectively. No death occurred. The incidence rate of SVI in patients with IBD was 2.02/1000 person-years, and the SIR was 3.09 (95% CI, 1.98-4.20; *P*=.0002) in the study population. By multivariate analysis, increased risk of SVI was associated with exposure to thiopurines (odds-ratio (OR), 3.48; 95% CI,1.36-8.90; *P*=.009), and clinically active IBD at onset of SVI (OR,3.35; 95% CI,1.23-9.23; *P*=.02).

Conclusions: The incidence of extra-intestinal SVI in patients with IBD is tripled compared to general population. Clinically active IBD and exposure to thiopurines are the main drivers of the risk.

Key words: viral infections, immune-suppressive therapy, thiopurines, cytomegalovirus, Epstein-Barr virus, hemophagocytic lymphohistiocytosis.

Crohns' disease (CD) and ulcerative colitis (UC) are lifetime diseases characterized by continuous or relapsing intestinal inflammation. Most of the patients with IBD are currently exposed for prolonged periods to various immunosuppressive drugs, including small molecules (thiopurines and methotrexate) and biologics, mainly anti-Tumor Necrosis Factor (TNF) agents.[1]

Serious viral, bacterial or fungal infections are usually defined as infections that require hospitalization or result in death or permanent organ damage.[2–4] Focusing to viral infections, patients with IBD may first develop serious viral infections (SVI) that are not related to IBD activity or to immunosuppression due to IBD treatment. They may also develop SVI triggered by inflammatory intestinal lesions, mainly cytomegalovirus (CMV) colitis,[5,6] and Epstein-Barr Virus (EBV) systemic reactivation.[7] Finally, they may develop SVI attributable to the immunosuppressive action of IBD drugs, knowing that the magnitude of this effect may substantially differ among drugs.[4]

Clinical research on extra-intestinal viral infections in IBD has been mainly focused on herpes zoster,[8–10] an easily identified infection that is treated in most cases in an ambulatory setting, and usually does not result in permanent organ damage. The promoting effect of immunosuppressive agents on serious infections, including SVI, has been also repeatedly reported.[10–17] However, in these studies, the respective role of IBD clinical activity and IBD drugs has not been addressed. The aim of this study was to assess the incidence (compared to age and gender-matched general population), and risk factors of extra-intestinal SVI in patients with IBD, followed prospectively with an IBD-specific database in a big IBD unit.

METHODS

Data sources

MICISTA

MICISTA is an IBD-specific prospective electronic-form database dedicated to clinical research created by a senior gastroenterologist (J.C.) in 1994. All patients with a permanent diagnosis of IBD, based on usual clinical, endoscopic, imaging and pathological criteria, and followed in our IBD unit (located in Rothschild hospital from 1994 to December 2002, then in Saint-Antoine hospital from January 2003 up to now) are enrolled in the database at the time of the first face-to-face contact in the IBD unit (outpatient visit or hospitalization). The following items are recorded at entry in the database: socio-demographic details, initial (at diagnosis) and cumulative IBD phenotype according to Montreal classification, smoking status, past history of IBD surgery. The database is then updated prospectively as long as patients are regularly or intermittently followed in our IBD unit.[18] A regular follow-up is defined as at least one face-to-face contact with the patient (visit or hospitalization) per calendar year in our IBD unit. At each contact in the IBD unit, clinical IBD activity is scored as follows: 0, no digestive symptoms; 1, mild symptoms that may be attributable to IBD activity, postoperative functional sequelae or associated irritable bowel syndrome; 2, symptoms that are attributable to IBD and are compatible with usual home and/or professional activities; 3, symptoms that are attributable to IBD and are not compatible with sustained home and/or professional activities; 4, hospitalization for IBD flare; 5, intestinal resection. At every face-to-face contact with the patient at the IBD unit, IBD treatment is

scored as follows: 0, no IBD drug; 1, oral 5-amino-salicylates; 2, low doses of systemic corticosteroids (up to 10 mg a day of prednisone/prednisolone, 8 mg a day of methylprednisolone or 3 mg a day of budesonide); 4, high doses of systemic corticosteroids (more than 10 mg a day of prednisone/prednisolone, 8 mg a day of methylprednisolone or 3 mg a day of budesonide); 4, thiopurines or methotrexate; 5, anti-TNF agent; 6, vedolizumab or ustekinumab. At the end of each calendar year of follow-up, the annual clinical IBD activity of each patient is rated as the highest clinical score recorded within the calendar year, and the annual status of IBD treatment is rated as the highest score of IBD drugs used within the calendar year.

At each face-to-face contact with patients in the IBD unit, physicians are required to fill in the database the date and type of any of the following events that have possibly occurred in the time interval between the last and the current contact: IBD-related surgery, intestinal dysplasia or cancer; extra-intestinal cancer and serious infection, defined as infections that require hospitalization or result in permanent organ damage.

MICISTA database was authorized by the French data protection agency (CNIL, registration number 1 104 603).

French National Hospital Discharge Database

The French National Hospital Discharge Database (Programme de Médicalisation des Systèmes d'Information (PMSI)) covers all public and private hospitals in France. The standardized discharge summary includes: patient's demographics; primary and associated discharge diagnosis codes (WHO International Classification of Diseases, 10th revision (ICD-10)13; medical and surgical procedures performed (French Medical Common Procedure Coding System); length of stay, entry and in-hospital mortality. A unique anonymous identifier allows linking all hospital claims of the patient since

January 2008 and tracking the occurrence and progression of chronic conditions over time.

Patient selection

We considered for enrollment in the study population all patients aged 18 years or older with at least a one-year period of regular follow-up in the MICISTA database between January 1, 2005 and December 31, 2014. We excluded patients with chronic (more than 6 months) replicative infection by Hepatitis B Virus, Hepatitis C Virus or Human Immunodeficiency Virus. In order to focus the study on the role of immunosuppression due to IBD or approved IBD drugs, we excluded organ transplant recipients.

For each individual patient, the observational time started on January 1, 2005 for those patients previously enrolled in the MICISTA database, or the day of entry into the MICISTA database for those patients who were enrolled in the MICISTA database between January 1, 2005 and December 31, 2013. The observational time ended the day of death, the day of first symptoms of extra-intestinal SVI, or the day of end of regular follow-up (i.e. the day of the last face-to-face contact with the patient at the IBD unit followed by a period of more than one year without contact in the IBD unit), or on December 31, 2014).

Definition and selection criteria of extra-intestinal SVI

SVI were defined as viral infections requiring hospitalization or resulting in death or permanent organ damage. In order to exclude isolated intestinal SVI associated with IBD flare, we excluded patients hospitalized for IBD flare associated with CMV colonic infection, defined as follows: intracellular inclusion bodies visualized with standard

haematoxylin and eosin staining (with or without immunohistochemistry with antibodies against pp65) of colon tissue, or detection of CMV DNA in colonic tissue by quantitative PCR; no evidence for extra-intestinal organ damage (lung, retina); no elevation of blood liver tests of more than two times the upper limit of the normal range; no mononucleosis-like syndrome in blood count. We also decided a priori to exclude the possible incident cases of replicative infection by Hepatitis B Virus, Hepatitis C Virus or Human Immunodeficiency Virus.

Calculation of incidence and SIRs of extra-intestinal SVI

The date of the event of SVI was defined as the date of the first symptoms attributable to SVI. To avoid selection bias, patients who had symptoms attributable to SVI at the time of entry into the observational period were not considered as incident cases in the analysis. For determination of incidence of SVI according to exposure to IBD drugs, we considered the number of events related to the cumulative numbers of calendar years that were individually rated by the highest score of IBD drugs used within calendar years of follow-up. For subgroup analyses, age at entry into the observational period was grouped as older than 18 years and less than 35 years, 35-65 years, and older than 65 years.

Data for calculating the incidence of extra-intestinal SVI in general population were obtained from the national French hospital discharge database (PMSI) between 2009 and 2013. Cases of hospital stays associated with a hospitalization ICD-10 code of extra-intestinal SVI (see the list in Supplementary Table 1) were identified in the PMSI database. The general population at risk was defined as all adults residing in France according to the National Vital Statistics compiled in January of each year. As in our

study population, we excluded patients with chronic (more than 6 months) replicative infection by Hepatitis B Virus, Hepatitis C Virus or Human Immunodeficiency Virus, and organ transplant recipients. We obtained the expected number of cases of SVI in the general population by multiplying the person-years at risk in each 10-year age group by the corresponding sex-specific and age-specific incidence rate for each year between 2009 and 2013. The cases of SVI that required hospitalization and were identified in the MICISTA database were then divided by the expected number of cases to determine the SIRs. Confidence intervals for SIRs were calculated with an exact method based on the Poisson distribution.

Characterization of the cases of extra-intestinal SVI identified in the MICISTA database

A specific case report form was constructed for all patients diagnosed with extra-intestinal SVI. Data were extracted by a junior gastroenterologist (A.W) and a senior gastroenterologist (L.B.) from review of medical files in patients managed for extra-intestinal SVI in our hospital. In the remaining patients, data were extracted from hospitalization or out-visit reports associated with SVI that were specifically requested to patients treating physicians for the purpose of the study.

We considered the exposure to IBD drugs and clinical activity of IBD on the first day of symptoms attributable to extra-intestinal SVI. Clinically active IBD was defined by the presence of symptoms clearly attributable to IBD (which corresponds to values 2 to 5 of the MICISTA score).

Nested case-control study and statistical analysis

To assess the respective roles of exposure to drugs and clinical IBD activity on the risk of extra-intestinal SVI, we performed a 4:1 case-control study. The selection process was performed in the MICISTA database: patients were matched for age (up to 5 years older or younger), gender, and IBD subtype (Crohn's disease on one side, ulcerative colitis or IBD unclassified on the other).

We included the following patient characteristics, on the first day of SVI or at the matched observation time in controls, in univariate conditional regression: exposure to IBD drugs and clinical activity of IBD, smoking status, patient Body Mass Index (BMI), level of education, Montreal localization of disease, prior intestinal surgery, clinically active perianal lesions. Items of interest in controls were extracted by a junior gastroenterologist (A.W) and a senior gastroenterologist (L.B.) from review of medical files of patients selected in the MICISTA database. Variables significant at $P < 0.20$ were entered into a multivariate logistic regression model with a backward variable elimination procedure to assess the strength of the associations while controlling for possible confounding variables.

For all subgroup comparisons of the study, proportions were compared using Fisher exact test, and continuous outcomes were compared using the Kruskal-Wallis test. All tests were 2-tailed at a 5% significance level.

RESULTS

Selection, baseline characteristics and follow-up time of the study population

We identified in the MICISTA database 2821 patients over the age of 18 with at least a one-year period of regular follow-up between January 1, 2005 and December 31, 2014 (Figure 1). Among then, we excluded 176 patients who were transplant recipients or

chronically (more than 6 months) infected with Hepatitis B Virus, Hepatitis C Virus or Human Immunodeficiency Virus.

The study population eventually included 2645 patients (44.3% males, 68.6% with Crohn's disease), followed for a total number of 15,383 person-years. Median follow-up time was 6.1 years (interquartile range (IQR), 2.9-9.4). Patient characteristics at entry into the observation period are provided in Table 1. Median age of patients at entry into the observation period was 34.4 years (IQR, 25.2–46.8). Median time interval between the diagnosis of IBD and the entry into the observation period was 6.3 years (IQR, 1.5-13.5).

Incidence and SIR of extra-intestinal SVI

No patients had symptoms attributable to SVI at the time of entry into the observational period. Among the 50 patients who developed acute SVI during the observation period, we excluded 19 patients who developed CMV colitis associated with IBD flare without systemic manifestations (Figure 1). No patent developed infection by Hepatitis B Virus, Hepatitis C Virus or Human Immunodeficiency Virus during the observation period. Finally, we identified 31 patients who developed 31 cases of extra-intestinal SVI during the observation period. Median age of patients at time of SVI diagnosis was 40.8 (30.5-53.3) years and duration of IBD prior to diagnosis of SVI was 12.6 (7.1-20.8) years.

The incidence rate of extra-intestinal SVI in patients with IBD was 2.02 per 1000 (95% CI, 1.95-2.08) person-years in the total study population. Incidence rates of extra-intestinal SVI by age class, gender, IBD subtype, and exposure to IBD drugs are detailed in Supplementary Table 2. The SIR of extra-intestinal SVI in patients with IBD was 3.09 (95% CI, 1.98-4.20, P = 0.002) in the total study population. The SIR of extra-

intestinal SVI by age class, gender, IBD subtype, and exposure to IBD drugs are shown in Table 2. Among age classes, the highest SIR was observed in patients under 35 years. The SIR of extra-intestinal SVI was higher in patients with UC or IBD unclassified than in patients with CD. Regarding IBD drugs, the highest SIR was observed in patients exposed to immunomodulators within the calendar year of occurrence of SVI.

Characteristics of SVI

Distribution of SVI according to pathogens and clinical expression is shown in Table 3. Among the 31 patients who developed SVI, 15 had CMV systemic infection, 8 had EBV infection, 3 had herpes simplex virus (HSV) infection and 5 had varicella zoster virus (VZV) infection.

Characteristics of incident SVI are shown in Table 4. All but one (97%) patients required hospitalization, while the remaining patient who developed permanent HSV facial nerve paralysis was treated in an ambulatory setting. IBD was clinically active at clinical onset of SVI in 35% of patients. Five of the 10 patients with CMV primary infection and 4 of the 5 patients with reactivation of CMV infection had clinically active IBD at clinical onset of SVI. None of the 5 patients with EBV primary infection and 1 of the 3 patients with reactivation of EBV infection had clinically active IBD at clinical onset of SVI. EBV-induced hemophagocytic lymphohistiocytosis (HLH) was observed in 3 patients. These 3 patients were exposed to thiopurines and one of them had clinically active IBD at onset of symptoms attributable to extra-intestinal HLH. Among the 3 patients with HLH, one patient received corticosteroids, immunoglobulins, etoposide and rituximab, while the others had spontaneous resolution of the disease.

Anti-viral therapy was administered in 61% of patients, including 13 of the 15 patients who developed extra-intestinal CMV infection. Twenty (65%) of the 31 patients who developed SVI were exposed to thiopurines at clinical onset of SVI. Seven (88%) of the eight patients who developed EBV infection were exposed to thiopurines at clinical onset of SVI. SVI occurrence led to transient suspension (drug withheld until SVI resolution) of immunosuppressive therapy in 58% of cases, and permanent drug withdrawal for the rest of the follow-up in 35% of cases. No permanent end-organ damage or death was reported.

Risk factors of extra-intestinal SVI in the study population

Nested case-control study for assessing risk factors of SVI included 31 cases and 124 controls. Non-matched characteristics of IBD were not significantly differently distributed between cases and controls (Supplementary Table 3). Among the 13 factors that were entered in the univariate analysis, only two factors, clinically active IBD at clinical onset of SVI and exposure to thiopurines at clinical onset of SVI, reached the eligibility level (P <0.20) for being entered in the multivariate model. By multivariate analysis, increased risk of SVI was associated with exposure to thiopurines (odds-ratio (OR), 3.48; 95% CI, 1.36-8.90; P = .009), and clinically active disease (OR, 3.35; 95% CI, 1.23-9.23; P = .02) at clinical onset of SVI. Values of odds-ratio associated with IBD clinical activity and exposure to IBD drugs at clinical onset of SVI, by univariate and multivariate analysis, are shown in Table 5.

DISCUSSION

We have shown that the risk of extra-intestinal SVI is tripled in patients with IBD followed in IBD units, compared to age and gender-matched individuals of general population. The excess risk is mainly related to IBD clinical activity and chronic exposure to thiopurines. Excess hospitalizations due to SVI contribute to the human and financial burden associated with management of IBD.[19]

The main limitation of this study is the recruitment of patients restricted to a tertiary IBD center, which is associated with an over-representation of severe forms of IBD. However, patients followed in IBD units pose the most difficult problems in balancing risks versus benefits of immunosuppressive drugs.[2] A significant strength of our study was to integrate in the analysis of risks factors of SVI the prospective monitoring of IBD clinical activity, which allowed a partial distinction between complications of IBD drugs and complications of IBD itself. This causality assessment is not possible with the same level of precision in studies using medico-administrative databases.[3,4]

Patients with silent chronic CMV infection may develop intestinal viral replication or CMV-mediated colitis, without extra-intestinal manifestations of CMV infection, in the context of IBD flare.[6] Conversely, we observed that half of the patients with extra-intestinal CMV primary infection had intestinal manifestations considered as clinically active IBD at clinical onset of SVI, suggesting that primary CMV infection may provoke or worsen intestinal inflammation. Most of the patients with extra-intestinal signs of reactivation of CMV infection had clinically active IBD at clinical onset of SVI, suggesting at least a partial role of IBD activity in the pathogenesis of infection. EBV primary infection was never associated with digestive symptoms, but IBD was clinically active at clinical onset of symptomatic reactivation of EBV infection in one patient. In relation with this latter observation, it had been previously observed in a study with prospective

monitoring of systemic EBV viral load in patients with IBD that significant increase of viral load may occur in the context of severe IBD flare,[7] before the initiation of immune-suppressive therapy.

It is now clear that thiopurines promote both symptomatic primary viral infections[20] and symptomatic reactivation of latent chronic infection.[9] The overall absolute risk of SVI reaches 4/1000 PY in patients exposed to thiopurines, which corresponds to a 4% risk for a 10-year period of treatment. Severe or fatal forms of primary VZV[21] and EBV primary infection [20] represent the most challenging problem for clinicians in the management of SVI in patients exposed to thiopurines. Severe forms of varicella are not associated with HLH and can be prevented by vaccinating patients against VZV before starting immunosuppressive therapy. Severe forms of HLH that occur in patients with IBD are mainly due, in our study like in others,[20,22] to EBV primary infection, and are almost exclusively observed in patients exposed to thiopurines.[20] This specific risk, together with the risk of fatal post-mononucleosis lymphoproliferation,[23,24] can be reduced by limiting the use of thiopurines in EBV-seronegative patients.[25] In EBV-seronegative patients exposed to thiopurines, clinicians should measure EBV viral load and look at biological signs of HLH as soon as possible in case of unexplained fever, splenomegaly or bicytopenia. Prompt consultation with a hematologists may lead to early treatment of HLH, including increasingly rituximab.[26,27]

In an ideal word, the risk of SVI in patients with IBD could get closer to that of the general population with the use of IBD drugs that prevent IBD-related SVI by way of maintained mucosal healing, whilst not promoting SVI via immunosuppressive effects. We are far from these goals because mucosal healing is currently achieved in a minority of patients and all immunosuppressive drug classes that are currently used promote

serious infections in general, and SVI in particular, at various extents. Thiopurines promote more SVI than anti-TNF agents,[4,9] but the converse is true for opportunistic bacterial infections.[4]

In conclusion, our study provides a comprehensive snapshot in the field of SVI caused by IBD and IBD drugs prior to the arrival of new small oral molecules, keeping in mind that one of them, tofacitinib, is associated with a marked excess risk of herpes zoster.[10]

Figure legends

Figure 1: Flow diagram for study population selection and identification of extra-intestinal serious viral infections

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Table 1. Characteristics of the study population at entry into the observation period

Patients, n	2645
Median age, years (IQR)	34.4 (25.2-46.8)
Median time from diagnosis of IBD, years (IQR)	6.3 (1.5-13.5)
Male sex, n (%)	1172 (44.3)
Median BMI (IQR)	21.9 (19.6-24.6)
BMI<18.5, n (%)	394 (14.9)
BMI≥30, n (%)	148 (5.6)
Active smokers, n (%)	673 (25.4)
Crohn's disease, n (%)	1814 (68.6)
Segments ever involved[a]	
L1, n (%)	493 (27.2)
L2, n (%)	488 (26.9)
L3, n (%)	813 (44.8)
L4, n (%)	20 (1.1)
perineal disease, n (%)	430 (23.7)
Ulcerative colitis or IBD unclassified, n (%)	831 (31.4)
Segments ever involved[a]	
E1, n (%)	89 (10.7)
E2, n (%)	356 (42.8)
E3, n (%)	386 (46.5)

IQR, interquartile range; IBD, inflammatory bowel disease; BMI, body mass index
[a] according to Montreal classification.

Table 2. Standardized incidence ratios (SIR) of extra-intestinal SVI according to age, gender, IBD subtype and exposure to IBD drugs

	Person-years	Reported cases[a]	Expected cases	SIR	95% CI	*P* value
All patients	15,383	30	9.7	3.09	1.98-4.20	.0002
Age class[b]						
At least 18 and less than 35 years	6311	19	3.7	5.10	2.81-7.40	.0005
35 to 65 years	7833	9	4.5	1.98	0.69-3.28	.14
More than 65 years	1238	2	1.5	1.32	0-3.15	.73
Gender						
Male	6720	14	4.3	3.23	1.54-4.92	.01
Female	8663	16	5.4	2.98	1.52-4.44	.008
IBD subtype						
Crohn's disease	10,893	17	6.8	2.51	1.32-3.70	.03
Ulcerative colitis or IBD, unclassified	4490	13	2.9	4.44	2.03-6.85	.005
Exposure to IBD drugs[c]						
No treatment or 5-amino-salicylates	5,773	4	3.9	1.03	0.02-2.05	.95
Systemic corticosteroids	934	1	0.6	1.61	0.00-4.76	.71
Immunomodulators[d]	4,836	19	3.0	6.43	3.54-9.32	.0002
Anti-TNF agents	3,840	6	2.3	2.65	0.53-4.78	.13

IBD, inflammatory bowel disease; SVI, serious viral infection; TNF, tumor necrosing factor;
[a]Analysis restricted to SVI requiring hospitalization (30 out of 31)
[a]At entry into the observation period
[b]Maximal treatment, according to MICISTA IBD drug scale (see Method section) during the calendar year of occurrence of SVI
[c]Thiopurines or methotrexate

Table 3. Characteristics of extra-intestinal SVO according to pathogens and clinical expression

Pathogen	n	Subgroups	n	Specific presentation	n
CMV	15	Primary infection	10	Mononucleosis syndrome	8
				isolated	2
				with hepatitis	3
				with pericarditis	1
				with cutaneous manifestations	1
				with hepatitis and pneumonitis	1
				Isolated hepatitis	1
				IBD flare with high viremia and without colitis	1
		Reactivation	5	IBD flare	4
				with hepatitis	2
				with haemolytic anemia	1
				with high viremia and without colitis	1
				CMV colitis and CMV induced-hepatitis	1
EBV	8	Primary infection	5	Mononucleosis syndrome	4
				isolated	1
				with severe neutropenia	2
				with hepatitis	1
				Hemophagocytic lymphohistiocytosis	1
		Reactivation	3	Hemophagocytic lymphohistiocytosis	2
				IBD flare with EBV-induced hepatitis	1
HSV	3		3	Severe esophagitis	1
				Facial nerve paralysis	1
				Severe cutaneous lesions	1
VZV	5	Varicella	3	Severe cutaneous manifestation	2
				With hepatitis	1
		Herpes zoster	2	Multidermatomal	2

CMV, cytomegalovirus; EBV, Epstein-Barr virus; VZV, varicella zoster virus; HSV, herpes simplex virus.

Table 4. Characteristics of incident cases of extra-intestinal SVI

Patient number	Sex	IBD type	Age at diagnosis of IBD	Age at clinical onset of SVI	Virus	Infection type	Exposure to IBD drugs at clinical onset of SVI	Mononucleosis syndrome or systemic symptoms	Clinical or biological expression	Clinically active IBD at clinical onset of SVI	IBD treatment prior to SVI suspended	Antiviral treatment
1	M	CD	20	22	CMV	Primary Infection	Anti-TNF agent	Yes	Mononucleosis Syndrome	Yes	Yes	IV
2	F	UC	21	22	CMV	Reactivation	5-ASA	No	Hepatitis	Yes	Yes	IV
3	F	UC	19	23	CMV	Primary infection	MTX	Yes	Pneumonitis, Hepatitis	No	Yes	IV
4	M	UC	13	27	CMV	Primary infection	AZA	Yes	Mononucleosis syndrome	No	No	No
5	F	CD	22	29	CMV	Primary infection	AZA	Yes	Hepatitis	Yes	Yes	Oral
6	F	UC	19	30	CMV	Primary infection	5-ASA, AZA	Yes	Cutaneous	Yes	Yes	IV
7	F	UC	19	34	CMV	Primary infection	AZA, Anti-TNF agent	Yes	Hepatitis	No	Yes	No
8	M	CD	20	35	CMV	Reactivation	5-ASA	No	Hemolytic anemia	Yes	Yes	IV
9	M	CD	25	36	CMV	Primary infection	AZA	Yes	Mononucleosis syndrome	No	Yes	IV
10	F	UC	22	37	CMV	Primary infection	AZA	Yes	Pericarditis	No	Yes	IV
11	F	UC	37	39	CMV	Reactivation	5-ASA, AZA	No	Hepatitis	Yes	Yes	IV
12	F	CD	21	42	CMV	Primary infection	AZA	Yes	Hepatitis	Yes	Yes	IV
13	F	UDC	22	45	CMV	Primary infection	AZA	Yes	Mononucleosis syndrome	Yes	Yes	IV
14	M	UC	48	51	CMV	Reactivation	Corticosteroids Anti-TNF agent,	No	Hepatitis	No	Yes	Oral
15	M	UC	50	79	CMV	Reactivation	5-ASA, MTX, Corticosteroids	Yes	Mononucleosis syndrome	Yes	Yes	IV
16	F	CD	8	20	EBV	Primary infection	AZA	Yes	Neutropenia	No	Yes	No
17	M	CD	5	20	EBV	Primary infection	AZA, Anti-TNF agent	Yes	Mononucleosis	No	Yes	No
18	F	CD	15	21	EBV	Primary infection	5-ASA, AZA	Yes	HLH	No	Yes	No
19	F	UC	22	23	EBV	Reactivation	5-ASA, Corticosteroids	No	Hepatitis	No	Yes	No
20	M	CD	14	24	EBV	Primary infection	5-ASA, AZA	Yes	Hepatitis	No	Yes	No
21	F	CD	20	25	EBV	Primary infection	5-ASA, AZA	Yes	Neutropenia	No	Yes	No
22	M	CD	37	43	EBV	Reactivation	AZA	Yes	HLH	Yes	Yes	No
23	F	CD	19	53	EBV	Reactivation	AZA	Yes	HLH	No	Yes	No
24	M	CD	18	19	HSV	Primary infection	Corticosteroids	No	Esophagitis	Yes	Yes	IV
25	M	CD	25	32	HSV	Reactivation	MTX, Anti-TNF agent	No	Severe labial lesions	No	Yes	IV
26	F	CD	27	36	HSV	Primary infection	AZA	No	Facial paralysis	No	Yes	IV
27	F	CD	17	18	VZV	Reactivation	AZA, Anti-TNF agent	No	Multidermatomal shingles	No	Yes	Oral
28	M	UC	8	22	VZV	Primary infection	5-ASA, AZA	No	Varicella, Hepatitis	No	Yes	No
29	M	CD	23	23	VZV	Reactivation	AZA	No	Multidermatomal shingles	No	Yes	Oral
30	F	CD	6	28	VZV	Primary infection	MTX	No	Varicella	No	No	No
31	M	UC	56	78	VZV	Primary infection	None	No	Varicella	No	Yes	IV

IBD, inflammatory bowel disease; SVI, serious viral infections; M, male; F, female; CD, Crohn's disease; UC, ulcerative colitis; TNF, tumor necrosis factor; IV, intravenous; 5-ASA, 5-amino-salicylates; MTX, methotrexate; AZA, azathioprine; HLH, hemaphagocytic lymphohistiocytosis

Table 5. Impact of IBD clinical activity and exposure to IBD drugs at clinical onset of SVI in cases on the risk of SVI.

	Cases of SVI (n=31)	Controls (n=124)	Univariate analysis			Multivariate analysis		
	n (%)	n (%)	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Clinically active disease	13 (41.9)	23 (18.6)	3.86	1.46-10.17	.006	3.35	1.23-9.23	0.02
5-ASA	10 (32.3)	53 (42.7)	0.62	.26-1.46	.27	--	--	--
Corticosteroids	3 (9.7)	12 (9.7)	1.00	.25-4.00	1	--	--	--
Methotrexate	4 (12.9)	11 (8.9)	1.53	.44-5.21	.50			
Azathioprine or 6-mercaptopurine	20 (64.5)	42 (33.9)	3.94	1.55-10.02	.004	3.48	1.36-8.90	.009
Anti-TNF agent	6 (19.4)	21 (16.9)	1.18	.43-3.25	.75	--	--	--
Combination therapy[a]	4 (12.9)	11 (8.9)	1.47	.45-4.75	.51	--	--	--

IBD, inflammatory bowel disease; SVI, serious viral infection
[a]anti-TNF agent and azathioprine, 6-mercaptopurine or methotrexate

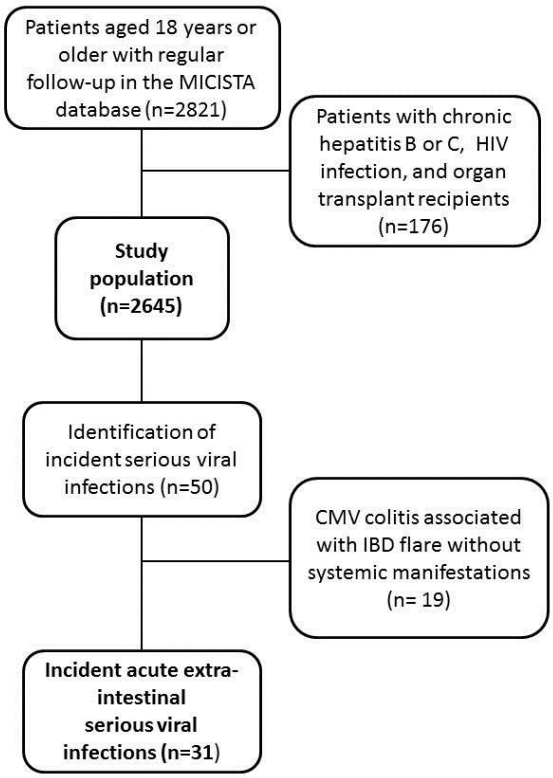
Patients aged 18 years or older with regular follow-up in the MICISTA database (n=2821)
Patients with chronic hepatitis B or C, HIV infection, and organ transplant recipients (n=176)
Study population (n=2645)
Identification of incident serious viral infections (n=50)
CMV colitis associated with IBD flare without systemic manifestations (n= 19)
Incident acute extra-intestinal serious viral infections (n=31)

Figure 1

Supplementary Table 1. Diagnoses of infections with related ICD 10-codes included as viral infections

Diagnoses	ICD-10
Herpes virus	B00-B02
Cytomegalovirus	B25
Epstein–Barr virus	B27
Acute viral hepatitis unspecified	B17.9; B19
Other viral infections of skin, oral tissue and subcutaneous tissue	B03-B09; B26; B30-B34

Supplementary Table 2. Incidence rates of acute extra-intestinal SVI according to age, gender, IBD subtype and exposure to IBD drugs

	Person-years	Observed cases (n)	Incidence rates per 1000 person-years	95% CI
All patients	15,383	31	2.02	1.95-2.08
Age class[a]				
At least18 and less than 35	6311	19	3.01	2.9-3.1
years	7834	10	1.28	1.20-1.35
35 to 65 years	1238	2	1.62	1.41-1.82
More than 65 years				
Gender				
Male	6720	14	2.08	1.99-2.18
Female	8663	17	1.96	1.88-2.05
IBD subtype				
Crohn's disease	10,893	18	1.65	1.58-1.72
Ulcerative colitis or IBD,	4490	13	2.90	2.76-3.03
unclassified				
Exposure to IBD drugs[b]				
No treatment or 5-amino-	5,773	4	0.69	0.63-0.76
salicylates	934	1	1.07	0.87-1.27
Systemic corticosteroids	4,836	20	4.14	4.00-4.27
Immunomodulators[c]	3,840	6	1.56	1.45-1.68
Anti-TNF agents				

IBD, inflammatory bowel disease; SVI, serious viral infection; TNF, tumor necrosing factor;
[a]At entry into the observation period
[b]Maximal treatment, according to MICISTA IBD drug scale (see Method section) during the calendar year of occurrence of SVI
[c]Thiopurines or methotrexate.

Supplementary Table 3. Characteristics of cases and controls in the case-control study nested in the MICISTA database for assessing risk factors for SVI.

	Patients with SVI (n=31)	Control group (n= 124)	*P* value
Male sex, n (%)	14 (45.2)	56 (45.2)	1
BMI (IQR)	21.3 (19.4-23.8)	21.6 (19.7-24.0)	.53
BMI < 18.5 (%)	5 (16.1)	22 (17.7)	1
BMI ≥ 30 (%)	0 (0)	3 (2.4)	1
Smokers, n (%)	7 (22.6)	26 (21.0)	.81
Age at onset of IBD, years (IQR)	20.6 (17.1-25.2)	20.9 (16.9-24.7)	.83
Crohn's disease, n (%)	18 (58.1)	72 (58.1)	1
Segments ever involved[a] n (%)			.50
L1	5 (27.8)	15 (20.8)	
L2	4 (22.2)	22 (24.4)	
L3	8 (44.4)	34 (47.2)	
L4	1 (5.6)	1 (1.11)	
perineal disease, n (%)	7 (22.3)	20 (16.1)	.42
UC or unclassified colitis n (%)	13(41.9)	52(41.9)	1
Segments ever involved[a]			.61
E1	1 (7.6)	3 (5.8)	
E2	6 (46.2)	19 (36.5)	
E3	6 (46.2)	30 (57.7)	

SVI, serious viral infection; BMI, body mass index; IQR, interquartile range; UC, ulcerative colitis

[a] At clinical onset of SVI in cases, according to Montreal classification