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ORIGINAL ARTICLE

Prevalence of Self-Reported Venous Thromboembolism and Cardiovascular Risk Factors in Patients with Ulcerative Colitis: The GETAID FOCUS Study

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Abstract

Background and Aims Patients with inflammatory bowel disease have an increased risk of venous thromboembolism (VTE) and cardiovascular disease (CVD). The study aims to determine the prevalence of CVD and VTE risk factors in a large population of patients with ulcerative colitis (UC).

Methods We conducted a cross-sectional study in 33 French and Belgium referral centers. A questionnaire was developed to explore self-reported risk factors for VTE and CVD, based on the latest international guidelines, in consecutive patients with UC.

Results A total of 1071 patients with UC were included. There were 539 women (50.3%), and the median age of patients was 44 years [32; 57]. The median disease duration was 10 years [6; 17]. In the cohort, 36.5% of patients reported no cardiovascular risk factor (CVRF) and 72% had ≤ 1 CVRF. Regarding cardiovascular risk markers (CVRM) 36.9% of patients reported no CVRM and 78% had ≤ 1 CVRM. Of the 1071 patients, 91.3% of patients reported no VTE strong risk factor and 96% had ≤ 1 VTE moderate risk factor.

Conclusion This is the first cohort specifically designed to assess both VTE and CVD risks in patients with UC. More than one third of patients with UC had no CVRF and around three quarters had ≤ 1 CVRF. In addition, more than nine out of ten patients had no VTE strong risk factor and ≤ 1 moderate risk factor. Physicians should be aware of these factors in their patients.

Keywords Ulcerative colitis · Heart disease risk factors · Disease progression · Venous thromboembolism

Introduction

Inflammatory bowel diseases (IBD) are chronic and disabling conditions [1, 2]. A large spectrum of extra-intestinal manifestations and comorbidities can be seen in these patients, including venous thromboembolism (VTE) and cardiovascular disease (CVD) [3]. Patients with IBD have a 2–3 fold higher risk for VTE compared to general population [3–6]. This risk increases up to eightfold during flare period and VTE is increasingly prevalent among hospitalized patients with IBD [4, 7], justifying a prophylaxis for all patients with IBD admitted to hospital [3, 8]. Patients with IBD can also develop CVD, including pericarditis, myocarditis, ischemic heart disease, heart failure, arrhythmias and arterial thromboembolism (e.g., stroke, mesenteric ischemia) [3, 9–11]. Indeed, patients with IBD have an increased risk of atherosclerosis and early atherosclerosis [3, 12, 13], as active inflammation is altering the balance between physiological procoagulants and anticoagulants and inducing a state of hypofibrinolysis [14]. Meta-analyses did not find association between IBD and CVD mortality [15–18].

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Since 2018, tofacitinib was approved in UC for moderate to severe disease [19]. Recommended dosage is 10 mg twice daily for at least 8 weeks, then 5 or 10 mg twice daily depending on therapeutic response. A safety signal came from the European Medicines Agency (EMA) in 2019 about an increased risk of blood clots in lungs and death with high dose of tofacitinib (10 mg twice daily) in patients with rheumatoid arthritis [20]. However, data about VTE risk with tofacitinib are contradictory in patients with immune-mediated inflammatory diseases like IBD or rheumatoid arthritis [21]. Hence, the EMA and the U.S. Food and Drug Administration (FDA) recommend to use tofacitinib with caution and to consider the benefits and risks when deciding whether to prescribe or continue therapy, especially in case of high risk of VTE or CVD [22, 23]. No study investigated the prevalence of both CVD and VTE risk factors in patients with IBD. The aim of the present cross-sectional study was to determine the prevalence of CVD and VTE risk factors in a large cohort of consecutive patients with UC treated in GETAID centers.

Methods

Study Design and Study Population

We conducted a cross-sectional study in IBD 33 referral centers in France and Belgium affiliated to the GETAID (Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif) between September 2020 and October 2020. Among the 58 GETAID centers invited, 33 agreed to participate (56.9%). All consecutive patients attending a consultation or a day outpatient hospitalization (for intravenous biologic treatment), older than 18 years, followed for a confirmed diagnosis of UC for at least 3 months and able to receive information were systematically invited to fill out the "FOCUS" questionnaire (*Supplementary Document*). It was decided that patients from day hospitalization for biologic infusion should not exceed 50% of all participants.

Data Collection

The FOCUS study was conducted via a self-administered questionnaire that was developed based on the latest international guidelines on CVD and VTE [24, 25]. The questionnaire first investigated information about patients' characteristics [age, sex, height, weight and body mass index (BMI)] and about disease characteristics (year of diagnosis, location, disease activity, ongoing treatments, history of colectomy). The second part of the questionnaire was about patients' life habits (smoking status, sport activity, consumption of fruits and vegetables, alcohol consumption) and about all their medical history related to cardiovascular and VTE risk (e.g., cardiovascular heredity, hypertension, diabetes, history of previous VTE, malignancy/chemotherapy, thrombophilia…). After their completion, questionnaires were returned to the head office of the GETAID.

Cardiovascular and VTE Risk Factors

Based on the latest European guidelines on CVD [24], the cardiovascular assessment can be separated in risk factors and risk markers. Cardiovascular risk factors (CVRF) are the following items: man older than 45 years, woman older than 55 years, family history of premature cardiovascular disease in first-degree relatives (before 55 years in men and 65 years of age in women), active or withdrawn smoking for less than 3 years, hypertension, diabetes, dyslipidemia and BMI ≥ 30; while CV risk markers (CVRM) are: absence of sports activity, alcohol > 7 drinks/week, absence of fruit and vegetable consumption and obstructive sleep apnea syndrome.

According to the latest European guidelines for the diagnosis and management of acute pulmonary embolism [25], predisposing factors of VTE can be separated in strong (Odds Ratio (OR) > 10), moderate (OR 2–9) and weak risk factors (OR < 2). Strong risk factors of VTE are: previous VTE, fracture of lower limb/hip or knee replacement/spinal cord injury/major trauma, hospitalization for heart failure or atrial fibrillation/flutter within previous 3 months and myocardial infarction within previous 3 months; while moderate risk factors are: Estrogen-containing oral contraceptive/hormone replacement therapy, previous superficial vein thrombosis, cancer/chemotherapy, congestive heart failure/respiratory failure, autoimmune diseases, paralytic stroke, post-partum period, in-vitro fertilization, thrombophilia, blood transfusion, human immunodeficiency virus (HIV) infection, central venous lines/intravenous catheters and arthroscopic knee surgery. Of note, IBD are also a moderate risk factor for VTE, but in the present study it was not taken into account in the total number of these risk factors.

Statistical Analysis

Data were entered into a secured case report form (Microsoft Office Excel®) and were expressed as percentages for categorical variables or median [$Q1$–$Q3$] for quantitative variables. Only descriptive statistics were performed.

Results

Patients' Characteristics and Treatments

A total of 1084 consecutive patients with UC were included in the FOCUS study. Among them, 1071 patients fully completed the questionnaire. The median number of

included patients per center was 23 [17; 39]. The Table 1 summarizes the main characteristics of the study population. Among the respondents, there were 539 women (50.3%), and the median age of patients was 44 years [32; 57]. The median disease duration was 10 years [6; 17].

The distribution of treatments is exposed in Table 1. For UC treatment, the three most used drugs at the time of the study were infliximab ($n = 329$, 30.7%), 5-aminosalicylic acid ($n = 305$, 28.5%) and vedolizumab ($n = 265$, 24.7%). Among respondents, 129 patients (12%) had taken anticoagulant or antiplatelet agent during the past 12 months. Of these 129 patients, 5 were treated with an anti-vitamin K (3.9%), 24 with direct oral anticoagulant (18.6%), 36 with heparin (27.9%), 46 with platelet-aggregation inhibitor (35.7%), 2 with another drug (1.5%) and 16 did not know (12.4%).

Cardiovascular Risk Factors and Markers

Apart from age and gender, the four most common CVRFs were active or past smoking (16.6%), heredity (12.7%), hypertension (12.4%) and BMI > 30 kg/m^2 (12.4%) (Table 2). Dyslipidemia and diabetes were found in 11% and 4.8%, respectively. In the cohort, 36.5% of patients had no CVRF and 72% had ≤ 1 CVRF (Fig. 1A). By stratifying on age, among patients under 45 s, 65.5% (355/542) had no CVRF, 28.4% (152/542) had 1 CVRF and 6.1% (33/542) had ≥ 2 CVRFs. In the age group of 45-65 s, 44.9% (173/385) had no CVRF, 33.3% (128/385) had 1 CVRF and 21.8% (84/385) had ≥ 2 CVRFs. In patients older than 65 s, 34.7% (50/144) had no CVRF, 27.1% (39/144) had 1 CVRF and 38.2% (55/144) had ≥ 2 CVRFs. By stratifying on sex, in female patients, 45.1% (243/539) had no CVRF, 34.9% (188/539) had 1 CVRF, 11.7% (63/539) had 2 CVRFs and 8.3% (45/539) had ≥ 3 CVRFs. In male patients, 27.8% (148/532) had no CVRF, 36.1% (192/532) had 1 CVRF, 19.4% (103/532) had 2 CVRFs and 16.7% (89/532) had ≥ 3 CVRFs.

Absence of sport activity (52.7%) and absence of fruits and vegetable consumption (21.5%) were the two most common CVRMs (Table 2). Consumption of > 7 glasses/week of alcohol and obstructive sleep apnea syndrome were found in 8.2% and 6.7%, respectively. In the cohort, 36.9% of patients had none and 78% had ≤ 1 (Fig. 1B). By stratifying on age, among patients under 45 s, 42.8% (232/542) had no CVRM, 40.6% (220/542) had 1 CVRM and 16.6% (90/542) had ≥ 2 CVRMs. In the age group of 45–65 s, 32.7% (126/385) had no CVRF, 43.1% (166/385) had 1 CVRM and 24.2% (93/385) had ≥ 2 CVRMs. In patients older than 65 s, 25.7% (37/144) had no CVRM, 38.2% (55/144) had 1 CVRM and 36.1% (52/144) had ≥ 2 CVRMs.

Table 1 Patient's characteristics and treatments

	N	%/median	*Q*1	*Q*3
Total	1071			
Sex				
Female	539	50.3		
Median age of responder (years)	1071	44	32	57
Smoking				
Active smoker	130	12.1		
Former smoker	367	34.3		
Non-smoker	574	53.6		
BMI (kg/m^2)				
< 18.5	44	4.1		
18.5–25	582	54.4		
25–30	312	29.1		
> 30	133	12.4		
Montreal A				
A1: ≤ 16 years	91	8.5		
A2: 17–39 years	632	59		
A3: ≥ 40 years	314	29.3		
Montreal E				
E1 (proctitis)	244	22.8		
E2 (left-sided colitis)	273	25.5		
E3 (pancolitis)	378	35.3		
Did not know	176	16.4		
Median disease duration (years)	1037	10	6	17
Disease activity				
Controlled by treatments	783	73.1		
Active	177	16.5		
Did not know	111	10.4		
History of colectomy	77	7.2		
UC treatments				
None	66	6.2		
5-ASA	305	28.5		
Steroids	73	6.8		
Thiopurines	148	13.8		
Methotrexate	38	3.5		
Infliximab	329	30.7		
Adalimumab	62	5.8		
Golimumab	54	5		
Ustekinumab	34	3.2		
Vedolizumab	265	24.7		
Tofacitinib	29	2.7		
Other	58	5.4		
Did not know	41	3.8		
Anticoagulant or antiplatelet agent in the past 12 months	129	12		
Heparin	36	27.9		
Anti-vitamin K	5	3.9		
Direct oral anticoagulant	24	18.6		
Antiplatelet agent	46	35.7		
Other	2	1.5		
Did not know	16	12.4		

BMI body mass index, *N* number, *Q* quartile, *UC* ulcerative colitis, *5-ASA* 5-aminosalicylic acid

Table 2 Cardiovascular risk factors and markers in the population

CV risk factors	
♀ > 55 years old	24.7%
♂ > 45 years old	55.1%
Heredity*	12.7%
Active or withdrawn smoking < 3 years	16.6%
Hypertension	12.4%
Dyslipidemia	11%
Diabetes	4.8%
BMI > 30 (kg/m^2)	12.4%
CV risk markers	
Absence of sports activity	52.7%
Alcohol > 7 glasses/week	8.2%
Absence of fruits and vegetables consumption	21.5%
Obstructive sleep apnea syndrome	6.7%

BMI body mass index, *CV* cardiovascular

*Family history of premature cardiovascular disease in first-degree relatives, before 55 years in men and 65 years in women;

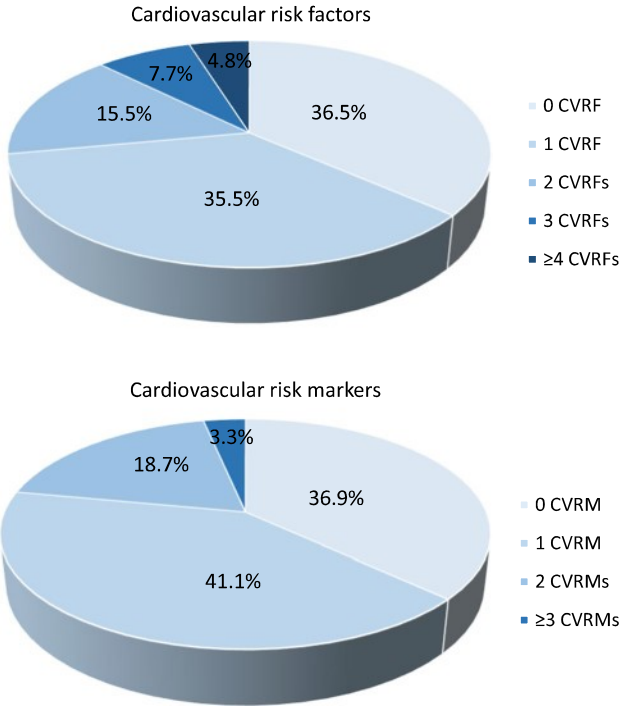

Fig. 1 Cardiovascular risk factors and markers. **A** Proportion of cardiovascular risk factors in the study population. **B** Proportion of cardiovascular risk markers in the study population. CVRF, cardiovascular risk factor; CVRM, cardiovascular risk marker

Venous Thromboembolism Risk Factors and Markers

A previous VTE event (4.4%) and a previous fracture of lower limb, hip or knee replacement, spinal cord injury or major trauma (3.2%) were the most common strong risk factors for VTE (Table 3). In the cohort, 91.3% of patients had no VTE strong risk factor and almost all patients (99.5%) had ≤ 1 VTE strong risk factor (Fig. 2A). By stratifying on age, among patients under 45 s, 96% (520/542) had no VTE strong risk factor and 4% (22/542) had only 1 VTE strong risk factor. In the age group of 45–65 s, 88.1% (339/385) had no VTE strong risk factor, 11.2% (43/385) had 1 VTE strong risk factor and 0.7% (3/385) had 2 VTE strong risk factors. In patients older than 65 s, 81.9% (118/144) had no VTE strong risk factor, 16% (23/144) had 1 VTE strong risk factor and 2.1% (3/144) had 2 VTE strong risk factors.

Regarding VTE moderate risk factors, the most common were autoimmune diseases (14.4%), estrogen-containing oral contraceptive or hormone replacement therapy in women (11.3%, 61/539), previous superficial vein thrombosis (4.9%), congestive heart failure or respiratory failure (4.3%), central venous line or intravenous catheter (1.2%) and cancer or chemotherapy (1.1%) (Table 3). The seven other factors (paralytic stroke, post-partum period, in-vitro fertilization, thrombophilia, blood transfusion, HIV infection and arthroscopic knee surgery) occurred in less than 1% of participants (Table 3). In the cohort, 70.2% of patients had none and 96% had ≤ 1 (Fig. 2B). By stratifying on age, among patients under 45 s, 45.1% (387/542) had no VTE moderate risk factor, 24.2% (131/542) had 1 VTE moderate risk factor and 4.4% (24/144) had ≥ 2 VTE moderate risk factors. In the age group of 45–65 s, 72.7% (280/385) had no VTE moderate risk factor, 25.2% (97/385) had 1 VTE moderate risk factor and 2.1% (8/385) had ≥ 2 VTE moderate risk factors. In patients older than 65 s, 59.7% (86/144) had no VTE moderate risk factor, 33.3% (48/144) had 1 VTE moderate risk factor and 7% (10/144) had ≥ 2 VTE moderate risk factors.

Discussion

Our work evaluated for the first-time the prevalence of CVD and VTE risk factors in a large cohort of consecutive patients with UC. The FOCUS study showed that more than one third (36.5%) of patients with UC had no CVRF and around three quarters (72%) had ≤ 1 CVRF. A UK study included 1875 patients with IBD reported that 39% of patients had one CVRF [26]. Although the study found similar results, it was based on a 5-year follow-up health database and only hypertension, smoking, BMI and cholesterol were taken into account for the assessment of CVRF [26]. A large Danish population-based study, of more than 100,000 individuals including 1203 patients with IBD, demonstrated that CVRF were not increased in IBD [27]. The study including plasma lipids and glucose, BMI and blood pressure to assess the cardiovascular risk. Overall, there is a wide variability for the cardiovascular risk assessment, as well as in the recommended tools between countries [24]. A nationwide French

Table 3 Venous thromboembolism risk factors in the population

Strong VTE risk factors	
Previous VTE	4.4%
Fracture of lower limb/hip or knee replacement/spinal cord injury/major trauma	3.2%
Hospitalization for heart failure or atrial fibrillation/flutter within previous 3 months	1.1%
Myocardial infarction within previous 3 months	0.6%
Moderate VTE risk factors	
Estrogen-containing oral contraceptive/hormone replacement therapy	11.3% (61/539)
Previous superficial vein thrombosis	4.9%
Cancer/chemotherapy	1.1%
Congestive heart failure/respiratory failure	4.3%
Autoimmune diseases	14.4%
Paralytic stroke	0.5%
Post-partum period	0.7% (4/539)
In-vitro fertilization	0.9% (5/539)
Thrombophilia	0.7%
Blood transfusion	0.5%
HIV infection	0.1%
Central venous line/intravenous catheter	1.2%
Arthroscopic knee surgery	0.2%

HIV human immunodeficiency virus, *VTE* venous thromboembolism

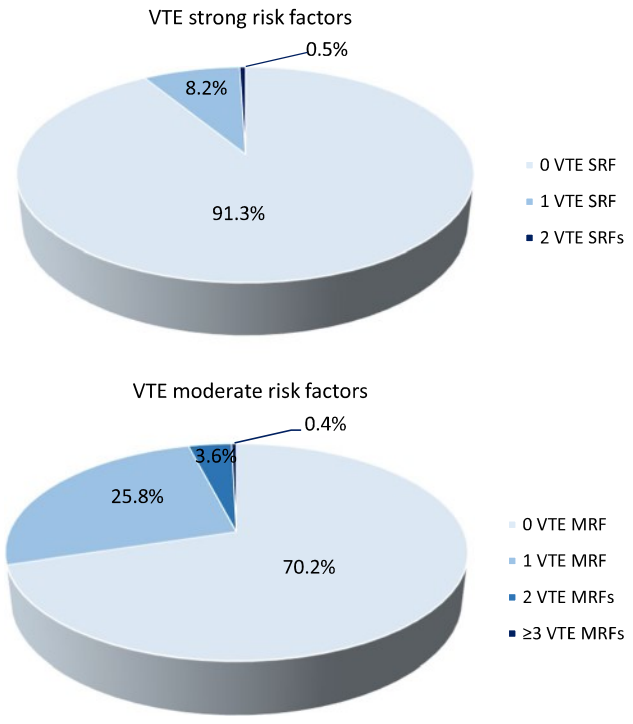

Fig. 2 Venous thromboembolism risk factors. **A** Proportion of venous thromboembolism strong risk factors in the study population. **B** Proportion of venous thromboembolism moderate risk factors in the study population. MRF, moderate risk factor; SRF, strong risk factor; VTE, venous thromboembolism

administrative database of 112,454 patients with UC showed a statistically significant overall increased risk of acute arterial events (ischemic heart disease, cerebrovascular disease, peripheral artery disease) in patients with UC (standardized incidence ratio 1.10; 95 CI 1.06–1.13) [28]. The authors found similar prevalence for hypertension (15%) and diabetes (5.5%), whereas smoking (4.4%), dyslipidemia (6%) and obesity (5.7%) that differed from our results. In a second publication of 177 827 patients with IBD from the same study group, but this time based also on outpatient data, authors found similar prevalence for dyslipidemia (9.5%) and diabetes (4.5%) compared to our results [29]. A recent American observational study reported that incidence of acute coronary events did not show a statistically significant difference compared to the matched cohort [30]. However, the study included only 6658 patients with UC compared to the French work. But the studies' population differ largely between these two countries, hence it is difficult to balance results.

To the best of our knowledge, our study is the only one that assessed the prevalence of VTE and CVD risk factors in a comprehensive manner and using definitions for these risk factors available in the most recent international guidelines using a large multicenter cohort of patients with UC. We showed that nine out of ten patients had no strong risk factor for VTE (91.3%) and ≤ 1 moderate risk factor (96%). It is well known that patients with IBD have an increased risk of VTE compared to general population [3–6], especially during flare periods [4, 7]. In addition, according to the latest European guidelines, IBD is one of

the moderate risk factors for VTE [25]. Accordingly, all patients should be considered as having one more moderate risk factor for VTE, and a special attention should be paid during flare-ups. Additional risk factors specifically related to IBD have been reported, as older and younger patients, those having increased length of stay or a major surgical procedure [31, 32]. An increase of the incidence of VTE was reported after surgical procedure in patients with UC, and during or after hospitalization for patients with IBD [31, 33]. In a cohort of 654 patients with Crohn's disease and 439 patients with UC, authors showed a prevalence of 5.1% of thrombosis and half of them occurred in the outpatient setting [34]. Assessment of risk factors for CVD and VTE is critical for IBD management, especially before the initiation of Janus kinase inhibitors [31]. According to the latest safety data (e.g., major adverse cardiovascular events, pulmonary embolism) [20, 35], the use of tofacitinib in UC appears to be one of the treatments for which this evaluation is decisive. A systematic review with an indirect meta-analysis reported contradictory findings about the VTE risk and the dose-dependent risk [21]. Physicians should use high dose of tofacitinib with caution in patients with CVD or VTE risk factors, especially in the long term, even though pooled analyses were negative so far in UC [36]. In a recent international consensus on the prevention of venous and arterial thrombotic events in IBD, the screening of CVD and VTE risk factors was recommended by experts [37]. The expert panel also stated that no increased in the risk of VTE or major adverse cardiovascular events has been observed in the overall UC population treated with tofacitinib [37].

Our study assessed for the first time the risk factors for both CVD and VTE in patients with UC in a comprehensive manner. The study was conducted in a large UC population (this sample represents about 1% of the general population of patients with UC) and in a multicenter cohort. The main limitation was that our study enrolled solely patients from tertiary referral centers, which could induce bias due to a higher proportion of severe patients. Another limitation was the data collection as CVD and VTE risk factors were self-reported by patients, including possible memory bias and reporting bias. In addition, few data could not be collected in an optimal way (e.g., lipid profile, blood pressure, sports activity, disease activity).

In conclusion, considering all CVRFs, more than one third of patients with UC had no CVRF and around three quarters had ≤ 1 CVRF. In addition, more than nine out of ten patients had no VTE strong risk factor and ≤ 1 moderate risk factor. Physicians should be aware of these factors in their patients, especially before initiating a new treatment.

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Author's Contribution LG wrote the article. MN, CR, LG and LPB conceived and supervised the study. LG performed the statistical analysis. LPB critically revised the manuscript. The manuscript was approved by all authors.

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Data Availability The data underlying this article are available in the article and in its online supplementary material.

Declarations

Conflict of interest L Guillo declares consulting fees for Abbvie. A Amiot declares counseling, boards, lecture, transports or fees from Abbvie, Hospira, Takeda, Gilead, Biocodex, Janssen, Ferring and MSD. M Serrero declares lecture and consulting fees for Abbvie, Celltrion, Ferring, Janssen, MSD, Takeda and Tillotts. R Altwegg declares counseling, boards, transports or fees from Abbvie, Amgen, Biogen, Ferring, Janssen, MSD, Pfizer, Takeda, Tillotts. A Buisson declares lecture and consulting fees for Abbvie, Amgen, Arena, Biogen, Janssen, MSD, Mayoly-Spindler, Norgine, Pfizer, Roche, Takeda and Tillots. C Le Berre has served as a consultant for Janssen and Gilead; reports receiving payment for lectures from AbbVie, Ferring Janssen, MSD, Pfizer and Takeda. C Reenaers has served as a speaker and advisory board member for Abbvie, Janssen, Pfizer, Takeda, Celltrion. JM Gornet has received personal fees from Amgen, Janssen Cilag, Sanofi,Takeda, Roche and Tillots Pharma. D Laharie declares counseling, boards, transports or fees from Abbvie, Biogaran, Biogen, BMS, Ferring, HAC-pharma, Janssen, Gilead, MSD, Novartis, Pfizer, Prometheus, Roche, Takeda, Theradiag, Tillots. V Abitbol declares counseling, boards, transports or fees from Janssen, Takeda, sandoz, Mylan, Amgen, Fresenius, Tillotts, Celltrion, Gilead, Pfizer. B Caron has received lecture and/or consulting fees from Abbvie, Amgen, Celltrion, Janssen, Takeda. S Nancey declares lecture and consulting fees for Abbvie, Celltrion, Amgen, Biogen, Janssen, Hospira/Pfizer, MSD, HAC, Fresenius, Takeda, Bristol Myers Squibb and Tillotts. L Vuitton has received lecture fees from Abbvie, MSD, Takeda, Ferring, Janssen and Pfizer, and research grants from MSD, Takeda and Pfizer. L Caillo declares lecture and consulting fees for Abbvie, Pfizer, Ferring, Janssen, Amgen, Biogen, Takeda and Tillotts. J Kirchgesner declares lecture and consulting fees from Roche, Pfizer, and Gilead. M Nachury declares lecture and consulting fees for Abbvie, Adacyte, Amgen, Arena, Biogen, CTMA, Ferring, Janssen, Mayoli-Spindler, MSD, Pfizer, Takeda. L Peyrin-Biroulet has served as a speaker, consultant and advisory board member for Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillotts, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, HAC- Pharma, Index Pharmaceuticals, Amgen, Sandoz, For- ward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis, Theravance. The remaining authors have no conflict of interest.

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