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Comorbidity, not patient age, is associated with impaired safety outcomes in vedolizumab- and ustekinumab-treated patients with inflammatory bowel disease—a prospective multicentre cohort study

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Summary

Background: Few data are available on the effects of age and comorbidity on treatment outcomes of vedolizumab and ustekinumab in inflammatory bowel disease (IBD).

Aims: To evaluate the association between age and comorbidity with safety and effectiveness outcomes of vedolizumab and ustekinumab in IBD.

Methods: IBD patients initiating vedolizumab or ustekinumab in regular care were enrolled prospectively. Comorbidity prevalence was assessed using the Charlson Comorbidity Index (CCI). Association between age and CCI, both continuously assessed, with safety outcomes (any infection, hospitalisation, adverse events) during treatment, and effectiveness outcomes (clinical response and remission, corticosteroid-free remission, clinical remission combined with biochemical remission) after 52 weeks of treatment were evaluated. Multivariable logistic regression was used to adjust for confounders.

Results: We included 203 vedolizumab- and 207 ustekinumab-treated IBD patients, mean age 42.2 (SD 16.0) and 41.6 (SD 14.4). Median treatment duration 54.0 (IQR 19.9-104.0) and 48.4 (IQR 24.4-55.1) weeks, median follow-up time 104.0 (IQR 103.1-104.0) and 52.0 weeks (IQR 49.3-100.4). On vedolizumab, CCI associated independently with any infection (OR 1.387, 95% CI 1.022-1.883, $P = 0.036$) and hospitalisation (OR 1.586, 95% CI 1.127-2.231, $P = 0.008$). On ustekinumab, CCI associated

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independently with hospitalisation (OR 1.621, 95% CI 1.034-2.541, $P = 0.035$). CCI was not associated with effectiveness, and age was not associated with any outcomes. **Conclusions:** Comorbidity - but not age - is associated with an increased risk of hospitalisations on either treatment, and with any infection on vedolizumab. This underlines the importance of comorbidity assessment and safety monitoring of IBD patients.

1 | INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a chronic immune-mediated disease predominantly affecting the gastrointestinal tract that is characterised by a relapsing and remitting disease course.[1] The presence of IBD associates with an increased risk of comorbidities, such as cardiovascular diseases and diabetes mellitus.[2,3,4] Furthermore, the increase in both incidence and prevalence of IBD and the aging of the general population lead to an increasingly aging IBD patient population with a higher prevalence of comorbidities.[5,6]

In recent years, patient age has been focused on as a potential risk factor for adverse treatment outcomes in immunomodulator or biological therapy.[7-9] A number of these studies have found an increased risk of infections in older patients, especially those treated with biological agents.[7] However, a patients chronological age is an imperfect marker of the reduced physiologic reserve capacity that predisposes patients to an increased risk of adverse treatment outcomes.[10]

The presence of comorbidities could function as a more solid predictor of therapy outcomes as compared to age itself as its presence increases the risk of medication interactions, reduced adherence to treatment and poorer response to treatment.[11] In immunomodulator and anti-TNF-treated IBD patients, an increased risk for infections in patients with comorbidities has been detected.[12,13] For thiopurine treatment, an independent association between cardiovascular risk factors and adverse events was observed.[14]

Vedolizumab, an α4β7 antibody,[15,16] and ustekinumab, a human IgG antibody targeting the p40 subunit of IL-12 and IL-23,[17] were introduced for the treatment of IBD offering an alternative treatment option with a different mechanism of action than, for example, anti-TNF therapy.[18] Both vedolizumab and ustekinumab have displayed a favourable safety profile in the registration trials and observational cohorts.[15-17,19,20] However, in registration trials, both patients of advanced age and those with significant comorbidities failed to meet the strict in- and exclusion criteria, whereas observational cohorts did not evaluate patients with comorbidities. Therefore, it is currently unknown what the impact of the presence of comorbidities is on treatment outcomes of vedolizumab- and ustekinumab-treated IBD patients.

Using data from the Dutch Initiative on Crohn and Colitis (ICC) Registry,[19,20] a nationwide prospective registry for IBD patients starting novel therapies in standard care, this study aims to assess the impact of patient age and comorbidities on safety and effectiveness outcomes in vedolizumab- and ustekinumab-treated IBD patients.

2 | MATERIALS AND METHODS

2.1 | Study design

This is a prospective multicentre cohort study using the Dutch ICC registry, which is a nationwide, observational registry with prospective and systematic follow-up of IBD patients starting IBD treatment in the Netherlands, as previously described in detail.[19,20] Briefly, the ICC registry is used to document the usage, safety and effectiveness of vedolizumab and ustekinumab therapy in IBD patients. Enrolled patients follow a pre-defined schedule of out-patient visits and closely follow regular care. Visits are scheduled at baseline (initiation of therapy), and at weeks 12, 24, 52, 104 or until discontinuation of medication. An electronic case report form (eCRF) is used to collect data.

2.2 | Patients

Patients aged 16 years or older with a confirmed clinical, endoscopic and/or histological diagnosis of CD, UC or IBD-Unclassified (IBD-U) and initiating vedolizumab or ustekinumab in regular care were enrolled at 10 participating centres. Data were collected between August 2014 and June 2019. This study included only CD patients on ustekinumab therapy as ustekinumab has only recently been approved for UC patients in the Netherlands. The decision to start therapy was at the discretion of the treating physician and there were no exclusion criteria other than mentioned in the summary of product characteristics. All eligible patients in the participating centres were approached for participation. When patients changed hospital to continue treatment, the information of subsequent visits would be collected through contact with the respective patient and their new treatment facility. Patients who stopped going to their scheduled hospital visits or their infusions were recorded as discontinued at request of patient, were considered treatment failures and imputed as non-responders in the subsequent visits.

2.3 | Baseline characteristics

Baseline characteristics included age, gender, weight, height, disease duration, behaviour and location according to the Montreal classification (maximum extent at inclusion), previous medication and prior

intestinal resections. Disease severity was measured by the Harvey Bradshaw Index (HBI) for CD patients and the Simple Clinical Colitis Activity Index (SCCAI) for UC and IBD-U patients. The use of concomitant immunosuppressive medication was also registered.

The Charlson Comorbidity Index (CCI) was used to identify the prevalence of comorbidities prior to initiation of vedolizumab or ustekinumab therapy. The CCI is a weighted index taking into account the number and severity of 16 pre-defined comorbidities and is validated for stratifying risk of comorbid conditions in longitudinal studies.[21] For example, the presence of uncomplicated diabetes generates a CCI of 1 point and the presence of a local solid tumour generates 2 points. Age is not included in this index. Theoretically, the CCI could range from a minimum of zero to a maximum of 33 points. In all included patients, the presence of comorbidities was assessed prior to starting therapy and verified using the electronical medical record.

2.4 | Outcomes

All outcomes were systematically assessed by following a pre-defined schedule of out-patient visits. To determine safety outcomes, all enrolled patients were analysed. Safety outcomes included: any infection, hospitalisations, treatment-related adverse events and adverse events resulting in discontinuation of IBD treatment. Infections were classified as mild (no use of antibiotics or antiviral mediation necessary), moderate (oral antibiotic or antiviral medication) or severe (hospitalisation or intravenously administrated antibiotics/antiviral medication). Hospitalisations included all-cause hospitalisations and were further specified in IBD related, infection or malignancy related, or other. Medication-related adverse events were classified as not related, possibly or probably related. Only adverse events that were possibly or probably related are reported in this study. Adverse events requiring discontinuation of therapy were reported separately. In addition, malignancies occurring during treatment and mortality were noted.

To determine effectiveness outcomes, patients with clinical disease activity at baseline (defined by HBI >4 or SCCAI >2 points) were analysed. Effectiveness outcomes included: clinical response, clinical remission, corticosteroid-free clinical remission and clinical remission combined with biochemical remission. Clinical response was defined as a reduction of at least 3 points in HBI or 3 points in SCCAI compared to baseline. Clinical remission was defined as HBI ≤4 or SCCAI ≤2 points. Biochemical remission was defined as a C-reactive protein (CRP) ≤5 mg/L and a faecal calprotectin (FCP) level ≤250 μg/g (when available). All effectiveness outcomes were measured at week 52.

2.5 | Statistical analysis

Data analyses were performed using IBM SPSS Statistics for windows, version 25.0. Continuous variables are presented as mean with standard deviation (SD) or as median with interquartile range (IQR) depending on the normality of the underlying distribution. Variables are compared using an independent *T* test or Mann Whitney *U* test. Categorical variables are presented as counts and percentages and compared by using the chi-squared test. Multivariable binary logistic regression was used to assess the association between comorbidities and outcomes of interest. The regression analyses were performed as complete case analyses and the maximum number of missing cases per inserted variable was 1. Potential confounders were agreed upon beforehand and used in all multivariable binary logistic regression models. These variables included: age, gender, IBD type, disease duration and concurrent medication at baseline (no concurrent medication, steroid or immunomodulator use, steroid and immunomodulator use). In the safety analysis with the outcome *adverse events requiring treatment discontinuation*, multivariable analysis including only age and CCI was performed due to the small number of outcomes. To account for differences in treatment duration in the safety analyses, treatment duration was added as a variable in the regression model. When statistical significance was reached in the 'all patients' analysis, we performed an additional multivariable analysis with CCI as categorical variable (categories 0, 1, 2 or ≥3) in the model. To assess the impact of CCI on drug survival, a multivariable Cox proportional hazards model was used with the above-mentioned confounders, using treatment duration as time and treatment cessation as outcome. Patients were analysed on an intention-to-treat basis. A two-sided $P < 0.050$ was considered statistically significant.

2.6 | Ethical consideration

The study was reviewed and approved by the Committee on Research Involving Human Subjects at the Radboudumc (Institutional Review Board: 4076). All patients gave their informed consent prior to inclusion in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

3 | RESULTS

3.1 | Baseline characteristics

In the ICC Registry, 410 cases (203 vedolizumab and 207 ustekinumab) were enrolled and assessed on the presence of comorbidities using the CCI. Ninety-five patients had one or more comorbidities, of which 49 (51.6%) received vedolizumab treatment and 46 (48.4%) received ustekinumab. Sixty-three (15.4%) patients were aged 60 years or older, 140 (34.1%) between 40 and 60 years and 206 (50.2%) <40 years, 36 patients aged 60 years or older were treated with vedolizumab and 27 patients aged 60 years or older with ustekinumab. Baseline characteristics are presented in Table 1 comparing patients with and without comorbidities. An additional table comparing baseline characteristics of vedolizumab- and ustekinumab-treated patients is presented separately in Table S1.

Mean age in patients with comorbidities was 50.1 years (SD 16.1) and mean age in patients without comorbidities 39.4 years (SD 14.0, $P < 0.001$). Both groups were predominantly women: 60.0% and 56.5% respectively ($P = 0.546$). In patients with comorbidities, 71 patients (74.7%) were diagnosed with CD and 23 patients (24.2%) with UC. Median treatment duration and median follow-up time did not differ between patients with and without comorbidities (51.9 weeks [23.0-101.4] vs 48.9 weeks [23.5-94.3], $P = 0.460$ and 102.4 [52.0-104.0] vs 102.4 [52.0-104.0], $P = 0.427$ respectively). Montreal classification did not differ between groups, except for age at diagnosis, which was higher in patients with comorbidities. Disease duration was comparable between the two groups (12.4 years [4.9-19.9] vs 11.0 years [5.8-18.8]). Clinical disease activity and medication use at baseline did not differ between patients with and without comorbidities, although patients with comorbidity reported less biological use in their medical history compared to patients without comorbidity.

3.2 | Baseline comorbidity prevalence

Prevalence of comorbidities at baseline is presented in Table 2. The most prevalent comorbidities were cardiovascular disease (congestive heart failure, myocardial infarction, peripheral vascular disease and cerebrovascular accident [CVA] or transient ischemic attack [TIA]), connective tissue disease, pulmonary disease (chronic obstructive pulmonary disease [COPD] or asthma) and diabetes. The prevalence of comorbidities was numerically but not statistically significantly higher in vedolizumab-treated patients. However, more cardiovascular and pulmonary diseases were present in the vedolizumab-treated group (cardiovascular: 20 [9.9%] vs 7 [3.4%], $P = 0.031$ and pulmonary: 16 [7.9%] vs 7 [3.4%], $P = 0.048$).

3.3 | Age, comorbidity and safety outcomes

3.3.1 | Infections

Infections, classified as mild, moderate and severe, are presented in Table S2a. The most frequently observed infections were related to the upper respiratory tract and flu-like symptoms. In total, 4.5 infections of any classification per 10 patient years of exposure occurred during follow-up, 6.4 infections in patients with comorbidities and 3.9 in patients without comorbidities. 5.9 infections of any classification per 10 patient years of exposure occurred in patients aged ≥60 years, compared to 3.1 in patients aged between 40 and 60 years and 5.0 in patients aged <40 years.

2.1 severe infections per 10 patient years of exposure occurred in patients with comorbidities and 0.6 in patients without comorbidities. In patients aged 60 years or older, 1.2 severe infections per 10 patient years of exposure occurred in patients aged 60 years or older, 0.4 in patients aged between 40 and 60 years and 1.4 in patients younger than 40.

The CCI was not associated with the occurrence of any infection during treatment in all patients (OR 1.277, 95% CI 0.998-1.634, $P = 0.052$). However, in vedolizumab-treated patients the CCI was significantly associated with the occurrence of any infection during treatment (OR 1.387, 95% CI 1.022-1.883, $P = 0.032$), which was independent of age, gender, IBD type, disease duration, concurrent medication and treatment duration. No significant association between the CCI and any infection was observed in ustekinumab-treated patients (Table 3).

Age at baseline was not associated with the occurrence of any infection during treatment in all patients (OR 0.984, 95% CI 0.966-1.003, $P = 0.109$), or in vedolizumab- (OR 0.985, 95% CI 0.961-1.009, $P = 0.219$) and ustekinumab- (OR 0.987, 95% CI 0.956-1.018, $P = 0.397$) treated patients separately (Table 3).

3.3.2 | Hospitalisations

A total of 138 hospitalisations occurred during treatment, 5.0 per 10 patient years of exposure in patients with comorbidities and 2.7 in patients without comorbidities. 3.4 hospitalisations per 10 patient years of exposure occurred in patients aged ≥60 years, 2.9 in patients aged between 40 and 60 years and 3.5 in patients aged younger than 40 years. The majority of hospitalisations were IBD related (78 hospitalisations, 56.5%) or infection or malignancy related (35 hospitalisations, 25.4%). Fourteen hospitalisations (10.1%) were classified as other and 15 (8.0%) as unknown. Hospitalisations are presented in Table S2b.

The CCI was independently associated with the occurrence of one or more all-cause hospitalisations during treatment in all patients (OR 1.450, 95% CI 1.119-1.879, $P = 0.005$) and in both vedolizumab- (OR 1.586, 95% CI 1.127-2.231, $P = 0.008$) and ustekinumab-treated patients (OR 1.623, 95% CI 1.035-2.546, $P = 0.035$) separately (Table 4). Patients using concurrent immunosuppressive medication at baseline were also at a higher risk of hospitalisation during both vedolizumab and ustekinumab treatment (steroid or immunomodulator use: OR 1.928, 95% CI 1.123-3.311, $P = 0.017$, steroid and immunomodulator use: OR 3.684, 95% CI 1.650-8.229, $P = 0.001$). A CCI of 3 points or higher was significantly and independently associated with hospitalisation during treatment (OR 4.943, 95% CI 1.778-13.738, $P = 0.002$) when analysing the CCI as a categorical variable (categories 0, 1, 2 or ≥3) in all patients. Furthermore, we observed a strong and independent impact of cardiovascular disease (comprising the CCI categories myocardial infarction, congestive heart failure, peripheral vascular disease and CVA/TIA) on all-cause hospitalisations in vedolizumab-treated patients (OR 3.954, 95% CI 1.048-14.924, $P = 0.042$). Age at baseline was not associated with the occurrence of one or more hospitalisations during treatment in all patients (OR 0.986, 95% CI 0.965-1.008, $P = 0.204$), or in vedolizumab- (OR .986, 95% CI .958-1.014, $P = 0.313$) and ustekinumab

TABLE 1 Baseline characteristics

	One or more comorbidities (n = 95)	No comorbidity (n = 315)	*P*-value
Treatment, N (%)			
Vedolizumab	49 (51.6)	154 (48.9)	0.646
Ustekinumab	46 (48.4)	161 (51.1)	
Age (years), mean (SD)	50.1 (16.1)	39.4 (14.0)	<0.001
Gender—female, N (%)	57 (60.0)	178 (56.5)	0.546
Body mass index, Mean (SD)	25.2 (5.0)	23.7 (4.5)	0.029
IBD type, N (%)			
Crohn's disease	71 (74.7)	256 (81.3)	0.375
Ulcerative colitis	23 (24.2)	57 (18.1)	
IBD unclassified	1 (1.1)	2 (0.6)	
Disease duration (y), Median (IQR)	12.4 (4.9-19.9)	11.0 (5.8-18.8)	0.697
Treatment duration (wk), Median (IQR)	51.9 (23.0-101.4)	48.9 (23.5-94.3)	0.501
Follow-up time (wk), Median (IQR)	102.4 (52.0-104.0)	102.4 (52.0-104.0)	0.427
Montreal classification			
Age at diagnosis (y), N (%)			
≤16	7 (7.4)	71 (22.5)	<0.001
17-40	57 (60.0)	204 (64.8)	
>40	31 (32.6)	40 (12.7)	
Disease location (CD)[a] , N (%)			
Ileum	21 (29.6)	80 (31.4)	0.845
Colon	26 (36.6)	84 (32.9)	
Ileocolonic	24 (33.8)	91 (35.7)	
Upper GI involvement (CD)[a], N (%)	5 (7.0)	18 (7.1)	0.996
Disease behaviour (CD)[a], N (%)			
Inflammatory	37 (52.1)	135 (52.9)	0.348
Stricturing	22 (31.0)	65 (25.5)	
Penetrating	9 (12.7)	50 (19.6)	
Unknown	3 (4.2)	5 (2.0)	
Peri-anal disease (CD)[a], N (%)	8 (11.3)	49 (19.4)	0.117
Disease location (UC/IBD-U)[a], N (%)			
Proctitis	2 (8.3)	4 (6.8)	0.892
Left-sided colitis	11 (45.8)	25 (42.4)	
Pancolitis	10 (41.7)	28 (47.5)	
Unknown	1 (4.2)	2 (3.4)	
Prior intestinal resections, N (%)	43 (45.3)	148 (47.0)	0.768
Prior anti-TNF therapy (ever use anti-TNF), N (%)	85 (89.5)	311 (98.7)	<0.001
Prior VEDO therapy, N (%)	10 (21.7)	72 (44.7)	0.005
Prior USTE therapy, N (%)	1 (2.0)	6 (3.9)	0.535
Clinical disease activity, median (IQR)			
HBI	8.0 (5.0-10.0)	7.0 (5.0-10.0)	0.079
SCCAI	5.0 (3.0-7.0)	6.0 (3.5-9.0)	0.519
Biochemical disease activity, median (IQR)			
CRP (mg/L)	6.0 (3.0-16.0)	8.0 (2.0-21.0)	0.319
FCP (μg/g)	552.0 (197.5-1223.8)	932.5 (296.8-1999.5)	0.044

(Continues)

TABLE 1 (Continued)

	One or more comorbidities (n = 95)	No comorbidity (n = 315)	*P*-value
Concomitant medication, N (%)			
No immunosuppressants	44 (46.3)	142 (45.2)	0.953
Corticosteroid or immunomodulator	42 (44.2)	139 (44.3)	
Both corticosteroid and immunomodulator	9 (9.5)	33 (10.5)	

Missing data: age 1 missing; BMI 134 missing; disease duration 1 missing; treatment duration 1 missing; follow-up time 1 missing; disease location (CD) 1 missing; upper GI involvement 1 missing; perianal disease 3 missing; HBI 10 missing; SCCAI 2 missing; CRP 87 missing; FCP 180 missing; concomitant medication 1 missing.

Abbreviations: anti-TNF, anti-tumor necrosis factor; CD, Crohn's disease; CRP, C-reactive protein; FCP, fecal calprotectin. ; GI, gastrointestinal; HBI, Harvey Bradshaw Index; IBD, inflammatory bowel disease; IBD-U, IBD-Unclassified; IQR, interquartile range; N, number; SCCAI, simple clinical colitis activity index; SD, standard deviation; UC, ulcerative colitis.

[a]Maximum extent until exclusion.

(OR .986, 95% CI .951-1.021, $P = 0.418$) treated patients separately (Table 4).

Next, safety analyses for hospitalisations were performed while including only the IBD-related and infection or malignancy-related hospitalisations as an outcome. We found that in all patients (OR 1.349, 95% CI 1.007-1.806, $P = 0.045$) and in ustekinumab patients (OR 1.625, 95% CI 1.002-2.634, $P = 0.049$), the CCI was associated with IBD- and infection- or malignancy-related hospitalisations. We did not find this association in vedolizumab patients separately (OR 1.388, 95% CI 0.933-2.066, $P = 0.105$).

3.3.3 | Adverse events

Adverse events are listed in Table S2c and are classified as possibly or probably related to treatment. 3.4 adverse events per 10 patient years of exposure were reported in patients with comorbidities and 2.7 in patients without comorbidities. 2.9 adverse events per 10 patient years of exposure were reported in patients aged ≥60 years, 3.4 in patients aged 40-60 years and 2.5 in patients <40 years. There was no significant association among age, the CCI and occurrence of adverse events in all patients and in vedolizumab- or ustekinumab-treated patients when analysed separately (Table S3).

In total, 0.3 adverse events per 10 patient years of exposure were classified as a reason for treatment discontinuation, 0.8 in patients with comorbidities and 0.2 in patients without comorbidities (Table S4). In patients aged ≥60 years, 0.1 adverse event per 10 patient years of exposure was classified as a reason for treatment discontinuation, in patients aged 40-60 years 0.5 and in patients aged <40 years 0.3.

The CCI was not associated with these adverse events that led to treatment discontinuation (Table S5). Two patients with comorbidities were diagnosed with a malignancy and discontinued medication: one patient on vedolizumab aged ≥60 years had a peritonitis carcinomatosa originating from the digestive tract and one patient aged between 40 and 60 years on ustekinumab had a peritoneal carcinoma. Three patients without comorbidities were diagnosed with a malignancy; one died (see below) and two patients discontinued treatment: one patient aged 40-60 years on vedolizumab had progression of a known anaplastic oligodendroglioma and one patient on ustekinumab aged ≥60 years was diagnosed with an unknown malignancy. Two patients without comorbidities died during treatment, both aged between 40 and 60 years: one patient on vedolizumab due to a thrombosis in the basilar artery and one patient on ustekinumab due to an abdominal sepsis after colonoscopic perforation after diagnosis of peritoneal carcinoma.

3.4 | Age, comorbidity and effectiveness outcomes

Patients with active disease (HBI >4 or SCCAI >2) at baseline were included in the effectiveness analyses. The CCI was not associated with effectiveness outcomes (clinical remission, clinical response, corticosteroid-free clinical remission and combined biochemical and clinical remission) in all included patients. However, in ustekinumab-treated patients, a higher age at baseline was independently associated with a mildly higher rate of combined biochemical and clinical remission (OR 1.043, 95% CI 1.003-1.085, $P = 0.036$). Results are presented in Tables S6a–d.

Age and the CCI were not associated with drug survival in all patients (age: HR 0.991, 95% CI 0.977-1.004, $P = 0.985$ and CCI: HR 1.002, 95% CI 0.847-1.184, $P = 0.985$), or in vedolizumab- or ustekinumab-treated patients separately (age: HR 0.996, 95% CI 979-1.013, $P = 0.617$ and CCI: HR 0.899, 95% CI 0.725-1.115, $P = 0.333$ and age: HR 0.977, 95% CI 0.955-1.000, $P = 0.054$ and CCI: HR 1.349, 95% CI 0.998-1.823, $P = 0.051$).

4 | DISCUSSION

This study aimed to assess the impact of age and comorbidities on safety and effectiveness outcomes in vedolizumab- and ustekinumab-treated IBD patients using data from the Dutch ICC Registry. In contrast to age, the presence of comorbidities was independently associated with impaired safety outcomes in both vedolizumab- and ustekinumab-treated patients. Comorbidities were independently associated with the occurrence of any infection during vedolizumab

TABLE 2 Baseline comorbidity prevalence

	Vedolizumab (n = 203)	Ustekinumab (n = 207)	*P*-value
Charlson comorbidity index, N (%)			
0	154 (75.9)	161 (77.8)	0.247
1	26 (12.8)	33 (15.9)	
2	8 (3.9)	6 (2.9)	
≥3	15 (7.4)	7 (3.4)	
Diabetes			
Uncomplicated (1)	7 (3.4)	8 (3.9)	
End-organ damage (2)	2 (1.0)	0 (0.0)	
Liver disease			
Mild (1)	0 (0.0)	2 (1.0)	
Moderate to severe (3)	4 (2.0)	2 (1.0)	
Solid tumour			
Localised (2)	3 (1.5)	1 (0.5)	
Metastatic (6)	0 (0.0)	0 (0.0)	
Leukaemia (2)	0 (0.0)	0 (0.0)	
Lymphoma (2)	2 (1.0)	1 (0.5)	
AIDS (6)	0 (0.0)	0 (0.0)	
Chronic kidney disease (2)	8 (3.9)	5 (2.4)	
Congestive heart failure (1)	6 (3.0)	1 (0.5)	
Myocardial infarction (1)	9 (4.4)	3 (1.4)	
Pulmonary disease (1)	16 (7.9)	7 (3.4)	
Peripheral vascular disease (1)	1 (0.5)	1 (0.5)	
CVA or TIA (1)	4 (2.0)	2 (1.0)	
Dementia (1)	1 (0.5)	0 (0.0)	
Hemiplegia (2)	0 (0.0)	0 (0.0)	
Connective tissue disease (1)	11 (5.4)	21 (10.1)	
Peptic ulcer (1)	2 (1.0)	4 (1.9)	
Total number of comorbidities	76	58	0.523

Categories of CCI were compared between groups by using chi-squared test, total number of comorbidities by using Mann-Whitney *U* Test. Numbers next to each comorbidity represent number of points given according to CCI.

Abbreviations: AIDS, acquired immune deficiency syndrome; CVA, cerebrovascular accident; TIA, transient ischemic attack.

treatment, and with all-cause hospitalisation during both vedolizumab and ustekinumab treatment. No association among age, comorbidities and impaired effectiveness outcomes was found.

Clinical trials frequently follow strict exclusion criteria regarding advanced age and the presence of comorbidities such as biochemic abnormalities, the presence of an unstable or uncontrolled medical disorder[15] or a history of cancer.[17] In our real-life cohort, 15.4% of the included patients were aged 60 years or older. The prevalence of comorbidities according to the CCI was 24.1% in vedolizumab- and 23.7% in ustekinumab-treated patients. Most of these patients would have been excluded from clinical trials. As a result, little data on comorbidities and their prevalence and especially relevance in IBD are available.[11] The prevalence of comorbidities found in our prospective cohort is comparable to a retrospective study by Khan et al in which 63.759 IBD patients who initiated corticosteroids, immunomodulators or biologic therapy were analysed. In this study, 25.7% of the overall cohort had one or more comorbidities according to the CCI.[22] However, other studies using the same CCI have shown a wide range of comorbidity prevalence. In these studies, the prevalences ranged from less than one fifth to more than two thirds of the included patients with one or more comorbidities.[12,23]

In our study, we found no association between age and safety outcomes. This finding is comparable with a recently published meta-analysis by Piovani et al which found no evidence of an increased risk of any infection in older IBD patients treated with biologics[9] but in contrast to a meta-analysis published last year in older patients exposed to biologics.[7] However, next to age, we also assessed the presence of comorbidities. In our study, comorbidities were independently associated with safety outcomes in both vedolizumab- and ustekinumab-treated patients. In both treatment groups, an increase in the CCI was significantly associated with all-cause hospitalisation during treatment. Analysing the CCI as a categorical variable (categories 0, 1, 2 or ≥3), the presence of 3 points or higher was significantly associated with all-cause hospitalisation during treatment. Furthermore, we performed safety analyses regarding hospitalisations including only IBD- and infection- or malignancy-related hospitalisations as an outcome. In this analysis we found the CCI to be significantly associated with IBD- and infection- or malignancy-related hospitalisations in all patients and in ustekinumab patients, but not in vedolizumab patients. An increase in CCI was associated with any infection during treatment in vedolizumab (OR 1.387, 95% CI 1.022-1.883, $P = 0.036$), but not in ustekinumab-treated patients (OR 0.998, 95% CI 0.611-1.630, $P = 0.994$). While earlier studies showed an association between comorbidities and adverse events for immunomodulators,[14] this association was not found for vedolizumab or ustekinumab in our study.

Although the impact of age and comorbidities was analysed for vedolizumab- and ustekinumab-treated patients separately, these analyses do not allow a direct comparison between both treatment groups for safety outcomes due to selection bias. An increase in CCI was associated with IBD-related and infection- or malignancy-related hospitalisations in the ustekinumab group, and with any infection during treatment in the vedolizumab group. In our study, only CD patients, and not UC patients, on ustekinumab were included. Furthermore, ustekinumab-treated patients had a higher percentage of previous anti-TNF therapy, or previously failed on vedolizumab therapy (Table S1). Besides this, since vedolizumab is considered to be a safe treatment option due to its supposed gut-specific mechanism of action, it is likely that patients who were at an increased infection risk were initiated on vedolizumab therapy. This hypothesis is supported by the fact that vedolizumab-treated patients had a higher absolute number of comorbidities and a higher number of patients with a high CCI (a score of 3 or more). Especially a higher

TABLE 3 Safety analysis—any infection

All patients	OR	95% CI	*P*-value
CCI	1.277	0.998-1.634	0.052
Age at baseline (y)	0.984	0.966-1.003	0.109
Gender (female)	0.930	0.586-1.476	0.757
Crohn's disease (ref. UC/IBDU)	0.907	0.478-1.722	0.766
Disease duration (y)	1.011	0.986-1.037	0.393
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.155	0.718-1.856	0.552
Steroid and immunomodulator	0.809	0.361-1.816	0.607
Treatment duration (wk)	1.014	1.007-1.020	0.000
Treatment (ustekinumab)	0.758	0.449-1.282	0.301
Vedolizumab	**OR**	**95% CI**	***P*-value**
CCI	1.387	1.022-1.883	0.036
Age at baseline (y)	0.985	0.961-1.009	0.219
Gender (female)	0.746	0.397-1.401	0.362
Crohn's Disease (ref. UC/IBDU)	1.007	0.520-1.952	0.983
Disease duration (y)	0.993	0.958-1.030	0.720
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.067	0.550-2.070	0.849
Steroid and immunomodulator	0.683	0.251-1.857	0.455
Treatment duration (wk)	1.012	1.004-1.019	0.002
Ustekinumab	**OR**	**95% CI**	***P*-value**
CCI	1.134	0.720-1.788	0.587
Age at baseline (y)	0.987	0.956-1.018	0.397
Gender (female)	1.174	0.584-2.363	0.652
Disease duration (y)	1.025	0.987-1.064	0.197
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.187	0.594-2.373	0.627
Steroid and immunomodulator	0.959	0.229-4.012	0.954
Treatment duration (wk)	1.017	1.005-1.028	0.005

All patients: 409 patients included in analysis of which 119 reached endpoint; VEDO: 203 patients, endpoint: 70 patients; UST: 206 patients included in analysis of whom 49 reached endpoint. Multivariable binary logistic regression analysis was performed and CCI was analysed as a continuous variable.

Abbreviations: CI, confidence interval; CCI, Charlson Comorbidity Index; IBDU, IBD-Unclassified; OR, odds ratio; UC, ulcerative colitis.

number of cardiovascular diseases and pulmonary diseases were observed in these patients.

The association between the presence of comorbidity and impaired safety outcomes found in this study could be explained by the fact that comorbidity is a predictor of impaired immunity and frailty which could lead to impaired safety outcomes.[24] Furthermore, medication interactions due to polypharmacy as a consequence of comorbidity could influence the results. However, the route of metabolism of ustekinumab and the working mechanism of vedolizumab have not fully been characterised.[25-27]

No association among age, comorbidities and impaired effectiveness outcomes was found in our study. In line with this observation, prior studies in IBD patients receiving other biologicals also did not find an association among age, comorbidities and impaired effectiveness outcomes.[8,28] For example, Lobatón et al studied the impact of comorbidities in anti-TNF treated patients, and found no association between comorbidities (CCI>0) and efficacy outcomes.[28] In our study, an independent association between an increasing age and a higher rate of biochemical and clinical remission in ustekinumab-treated patients was observed. This further underlines the fact that the effectiveness of biological therapies is no less in patients of advanced age. Overall, we did not find a significant impact of age and CCI on drug survival, although in ustekinumab patients both age and CCI were borderline significant. With an increasing age, patients tended to have a lower chance of therapy cessation (HR .977, 95% CI .955-1.000,

TABLE 4 Safety analysis—hospitalisation

All patients	OR	95% CI	*P*-value
CCI	1.450	1.119-1.879	0.005
Age at baseline (y)	0.986	0.965-1.008	0.204
Gender (female)	1.521	0.903-2.561	0.115
Crohn's disease (ref. UC/IBDU)	2.655	1.245-5.663	0.012
Disease duration (y)	1.006	0.978-1.035	0.675
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.928	1.123-3.311	0.017
Steroid and immunomodulator	3.684	1.650-8.229	0.001
Treatment duration (wk)	0.999	0.992-1.006	0.857
Treatment (ustekinumab)	0.580	0.336-1.004	0.052
Vedolizumab	**OR**	**95% CI**	***P*-value**
CCI	1.586	1.127-2.231	0.008
Age at baseline (y)	0.986	0.958-1.014	0.313
Gender (female)	1.558	0.759-3.200	0.227
Crohn's disease (ref. UC/IBDU)	3.468	1.523-7.897	0.003
Disease duration (y)	0.969	0.927-1.012	0.156
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.618	0.737-3.550	0.230
Steroid and immunomodulator	4.503	1.551-13.071	0.006
Treatment duration (wk)	0.996	0.987-1.004	0.329
Ustekinumab	**OR**	**95% CI**	***P*-value**
CCI	1.623	1.035-2.546	0.035
Age at baseline (y)	0.986	0.951-1.021	0.418
Gender (female)	1.427	0.652-3.122	0.374
Disease duration (y)	1.042	0.999-1.086	0.054
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	2.269	1.051-4.901	0.037
Steroid and immunomodulator	1.861	0.436-7.945	0.402
Treatment duration (wk)	1.008	0.996-1.021	0.179

All patients: 409 patients included in analysis of whom 90 reached endpoint; VEDO: 203 patients, endpoint: 51 patients; UST: 206 patients included in analysis of whom 39 reached endpoint. Multivariable binary logistic regression analysis was performed and CCI was analysed as a continuous variable.

Abbreviations: CI, confidence interval; CCI, Charlson Comorbidity Index; IBDU, IBD-Unclassified; OR, odds ratio; UC, ulcerative colitis.

$P = 0.054$) and with increasing points on the CCI patients tended to have a higher chance of therapy cessation (HR 1.349, 95% CI 0.998-1.823, $P = 0.051$).

The results of our study have several clinical implications. First, although age in itself was not associated with impaired safety outcomes, patients with comorbidities were older. Therefore, we advise treating gastroenterologists to be aware of this higher prevalence of comorbidities in older IBD patients and, when comorbidity is suspected, to perform adequate screening and referral as deemed necessary. Second, in particular a CCI of 3 points or higher and the presence of cardiovascular disease were associated with impaired safety outcomes (all-cause hospitalisation). This subanalysis identified a group of patients with an especially elevated risk for impaired safety outcomes which should be monitored closely. Third, concomitant immunosuppressive medication use at baseline was associated with hospitalisation during vedolizumab and ustekinumab therapy in our study and with infections in other studies.[29] Prior studies have shown no significant differences in effectiveness rates when comparing vedolizumab or ustekinumab monotherapy to vedolizumab or ustekinumab therapy combined with immunosuppressive medication.[19,20] Therefore, we discourage concomitant immunosuppressive medication use in patients in which multiple comorbidities are present as well.

Our study has several strengths. This is the first study assessing the impact of comorbidities next to age on therapy outcomes in vedolizumab- and ustekinumab-treated IBD patients. The ICC

Registry is a large prospective real-life cohort without restricting in- and exclusion criteria and a nationwide coverage. Hence, the included patients are a representative cohort from non-academic and academic centres, reflecting daily IBD care. Finally, comorbidity was assessed systematically, using a validated comorbidity index that allows external validity.

However, since this is an ongoing registry, not all patients were followed for the same time period. We intended to limit this by correcting for follow-up duration in safety analyses. It is possible that results of our study are subjected to ascertainment bias: patients with comorbidities generally have more hospital visits or physician contacts, and therefore, a safety outcome, such as infection, could be noted more frequently in this group. However, to limit this type of bias, the ICC registry applies scheduled visits with automated reminders for strict adherence to protocol in all patients. The comorbidity index, the CCI, is a commonly used index to assess the number and severity of comorbidities but is not specifically validated for IBD patients. Furthermore, not all comorbidities, such as neurological conditions, are accounted for in this index. An IBD-validated comorbidity index is, therefore, needed.[11] Finally, the number of old or very old patients was low in this study, which could have led to an underestimation of the effect of old age or CCI on treatment safety.

In conclusion, this study demonstrates that comorbidities, and not age, are independently associated with any infection and hospitalisations in vedolizumab-treated IBD patients and hospitalisations in ustekinumab-treated IBD patients. Effectiveness of both treatments was not impaired by presence comorbidities or a higher age. These results underline the importance of assessing comorbidity status instead of age prior to initiating vedolizumab and ustekinumab therapy, in order to discuss additional safety risks and need for close monitoring in IBD patients with multiple comorbidities.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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APPENDIX 1.

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