Inflammatory bowel disease in older patients: from gut feeling towards evidence-based medicine

Asscher, V.E.R.

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Comorbidity, not patient age, is associated with impaired safety outcomes in vedolizumab- and ustekinumab-treated patients with inflammatory bowel disease

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Vera E.R. Asscher*
Vince B.C. Biemans*
Marieke J. Pierik
Gerard Dijkstra
Mark Löwenberg
Sander van der Marel
Nanne K.H. de Boer
Alexander G.L. Bodelier
Jeroen M. Jansen
Rachel L. West
Jeoffrey J.L. Haans
Willemijn A. van Dop
Rinse K. Weersma
Frank Hoentjen
P.W. Jeroen Maljaars
On behalf of the Dutch Initiative on Crohn and Colitis (ICC)
**Authors contributed equally*

ABSTRACT

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

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

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, hospitalization, 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 was 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). In vedolizumab, CCI associated independently with any infection (OR 1.387, 95% CI 1.022-1.883, p=.036) and hospitalization (OR 1.586, 95% CI 1.127-2.231, p=.008). In ustekinumab, CCI associated independently with hospitalization (OR 1.621, 95% CI 1.034-2.541, p=.035). CCI did not associate with effectiveness, age did not associate with any of the outcomes.

Conclusions Comorbidities, not age, associate with an increased risk of hospitalizations both treatments, and with any infection in vedolizumab treated IBD patients. This study underlines the importance of comorbidity assessment and safety monitoring of IBD patients with multiple comorbidities.

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 characterized 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 leads 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.

MATERIALS AND METHODS

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 outpatient visits and closely follow regular care. Visits are scheduled at baseline (initiation of therapy), and at week 12, 24, 52, 104 or until discontinuation of medication. An electronic case report form (eCRF) is used to collect data.

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 was 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.

Baseline characteristics

Baseline characteristics included age, sex, 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 predefined 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, the presence of a local solid tumor 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.

Outcomes

All outcomes were systematically assessed by following a pre-defined schedule of outpatient visits. To determine safety outcomes, all enrolled patients were analysed. Safety outcomes included: any infection, hospitalizations, 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 (hospitalization or intravenously administrated antibiotics/antiviral medication). Hospitalizations included all-cause hospitalizations 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.

Statistical analysis

Data analyses were performed using IBM SPSS Statistics for Windows, version 23.0. 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-square 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, the maximum number of missing cases per inserted variable was one. Potential confounders were agreed upon beforehand and used in all multivariable binary logistic regression models. These variables included: age, sex, 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 value of <.050 was considered statistically significant.

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.

RESULTS

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, 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 supplementary table 1.

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<.001). Both groups were predominantly female: 60.0% and 56.5%, respectively (p=.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=.460 and 102.4 (52.0-104.0) vs. 102.4 (52.0-104.0), p=.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.

Table 1. Baseline characteristics

		One or more comorbidities (n=95)	No comorbidity (n=315)	P-value
Treatment				.646
Vedolizumab	N (%)	49 (51.6)	154 (48.9)	
Ustekinumab	N (%)	46 (48.4)	161 (51.1)	
Age (years)	Mean (SD)	50.1 (16.1)	39.4 (14.0)	<.001
Sex - female	N (%)	57 (60.0)	178 (56.5)	.546
Body Mass Index	Mean (SD)	25.2 (5.0)	23.7 (4.5)	.029
IBD Type				.375
Crohn's Disease	N (%)	71 (74.7)	256 (81.3)	
Ulcerative Colitis	N (%)	23 (24.2)	57 (18.1)	
IBD-Unclassified	N (%)	1 (1.1)	2 (0.6)	
Disease duration (years)	Median (IQR)	12.4 (4.9-19.9)	11.0 (5.8-18.8)	.697
Treatment duration (weeks)	Median (IQR)	51.9 (23.0-101.4)	48.9 (23.5-94.3)	.501
Follow-up time (weeks)	Median (IQR)	102.4 (52.0-104.0)	102.4 (52.0-104.0)	.427
Montreal classification				
Age at diagnosis				<.001
≤16 years	N (%)	7 (7.4)	71 (22.5)	
17-40 years	N (%)	57 (60.0)	204 (64.8)	
>40 years	N (%)	31 (32.6)	40 (12.7)	
Disease location (CD)¶				.845
Ileum	N (%)	21 (29.6)	80 (31.4)	
Colon	N (%)	26 (36.6)	84 (32.9)	
Ileocolonic	N (%)	24 (33.8)	91 (35.7)	
Upper GI involvement (CD)¶	N (%)	5 (7.0)	18 (7.1)	.996
Disease behaviour (CD)¶				.348
Inflammatory	N (%)	37 (52.1)	135 (52.9)	
Stricturing	N (%)	22 (31.0)	65 (25.5)	
Penetrating	N (%)	9 (12.7)	50 (19.6)	
Unknown	N (%)	3 (4.2)	5 (2.0)	
Peri-anal disease (CD)¶	N (%)	8 (11.3)	49 (19.4)	.117
Disease location (UC/IBD-U)¶				.892
Proctitis	N (%)	2 (8.3)	4 (6.8)	
Left-sided colitis	N (%)	11 (45.8)	25 (42.4)	
Pancolitis	N (%)	10 (41.7)	28 (47.5)	
Unknown	N (%)	1 (4.2)	2 (3.4)	
Prior intestinal resections	N (%)	43 (45.3)	148 (47.0)	.768
Prior anti-TNF therapy (ever use anti-TNF)	N (%)	85 (89.5)	311 (98.7)	<.001
Prior vedo therapy	N (%)	10 (21.7)	72 (44.7)	.005
Prior uste therapy	N (%)	1 (2.0)	6 (3.9)	.535
Clinical disease activity				
HBI	Median (IQR)	8.0 (5.0-10.0)	7.0 (5.0-10.0)	.079
SCCAI	Median (IQR)	5.0 (3.0-7.0)	6.0 (3.5-9.0)	.519
Biochemical disease activity				
CRP, mg/L	Median (IQR)	6.0 (3.0-16.0)	8.0 (2.0-21.0)	.319
FCP, µg/g	Median (IQR)	552.0 (197.5-1223.8)	932.5 (296.8-1999.5)	.044

Table 1. Continued.

		One or more comorbidities (n=95)	No comorbidity (n=315)	P-value
Concomitant medication				.953
No immunosuppressants	N (%)	44 (46.3)	142 (45.2)	
Corticosteroid or immunomodulator	N (%)	42 (44.2)	139 (44.3)	
Both corticosteroid and immunomodulator	N (%)	9 (9.5)	33 (10.5)	

SD; Standard Deviation, N; Number, IBD; Inflammatory Bowel Disease, IQR; interquartile range, CD; Crohn's disease, GI; gastrointestinal, UC; ulcerative colitis, IBD-U; IBD-Unclassified, anti-TNF; anti-tumor necrosis factor, HBI; Harvey Bradshaw Index, SCCAI; simple clinical colitis activity index, CRP; c-reactive protein, FCP; fecal calprotectin. 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 ¶maximum extent until exclusion.

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 significant higher in vedolizumab treated patients. However, more cardiovascular and pulmonary diseases were present in the vedolizumab treated group (cardiovascular: 20 (9.9%) versus 7 (3.4%), p=.031 and pulmonary: 16 (7.9%) versus 7 (3.4%), p=.048).

Age, comorbidity and safety outcomes

Infections

Infections, classified as mild, moderate, and severe, are presented in supplementary table 2a. 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 years 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.

Table 2. Baseline comorbidity prevalence

		Vedolizumab (n=203)	Ustekinumab (n=207)	P-value
Charlson Comorbidity Index	N(%)			0.247
0		154 (75.9)	161 (77.8)	
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 Tumor				
Localized (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

AIDS; acquired immune deficiency syndrome, CVA; cerebrovascular accident, TIA; transient ischemic attack. Numbers next to each comorbidity represent number of points given according to CCI. Categories of CCI were compared between groups by using chi square test, total number of comorbidities by using Mann-Whitney U Test.

The CCI was not associated with the occurrence of any infection during treatment in all patients (OR 1.277, 95% CI .998-1.634, p=.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=.032), which was independent of age, sex, 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 3a).

Age at baseline was not associated with the occurrence of any infection during treatment in all patients (OR .984, 95% CI .966-1.003, p=.109), or in vedolizumab (OR .985, 95% CI .961-1.009, p=.219) and ustekinumab (OR .987, 95% CI .956-1.018, p=.397) treated patients separately (table 3a).

Table 3a. Safety analysis – any infection

All patients	**OR**	**95% CI**	**p-value**
CCI	1.277	0.998-1.634	.052
Age at baseline (years)	.984	0.966-1.003	.109
Sex (female)	.930	.586-1.476	.757
Crohn's Disease (ref. UC/IBDU)	.907	.478-1.722	.766
Disease duration (years)	1.011	.986-1.037	.393
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.155	.718-1.856	.552
Steroid and immunomodulator	.809	.361-1.816	.607
Treatment duration (weeks)	1.014	1.007-1.020	.000
Treatment (ustekinumab)	.758	.449-1.282	.301
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	1.387	1.022-1.883	.036
Age at baseline (years)	.985	.961-1.009	.219
Sex (female)	.746	.397-1.401	.362
Crohn's Disease (ref. UC/IBDU)	1.007	.520-1.952	.983
Disease duration (years)	.993	.958-1.030	.720
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.067	.550-2.070	.849
Steroid and immunomodulator	.683	.251-1.857	.455
Treatment duration (weeks)	1.012	1.004-1.019	.002
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	1.134	.720-1.788	.587
Age at baseline (years)	.987	.956-1.018	.397
Sex (female)	1.174	.584-2.363	.652
Disease duration (years)	1.025	.987-1.064	.197
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.187	.594-2.373	.627
Steroid and immunomodulator	.959	.229-4.012	.954
Treatment duration (weeks)	1.017	1.005-1.028	.005

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; UC, Ulcerative Colitis; IBDU, IBD-Unclassified; 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 which 49 reached endpoint. Multivariable binary logistic regression analysis was performed, CCI was analyzed as a continuous variable.

Hospitalizations

A total of 138 hospitalizations occurred during treatment, 5.0 per 10 patient years of exposure in patients with comorbidities and 2.7 in patients without comorbidities. 3.4 hospitalizations 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 hospitalizations were IBD-related (78 hospitalizations, 56.5%) or infection or malignancy

related (35 hospitalizations, 25.4%). Fourteen hospitalizations (10.1%) were classified as other and 15 (8.0%) as unknown. Hospitalizations are presented in supplementary table 2b.

The CCI was independently associated with the occurrence of one or more all-cause hospitalizations during treatment in all patients (OR 1.450, 95% CI 1.119-1.879, p=.005) and in both vedolizumab (OR 1.586, 95% CI 1.127-2.231, p=.008) and ustekinumab treated patients (OR 1.623, 95% CI 1.035-2.546, p=.035) separately (table 3b). Patients using concurrent immunosuppressive medication at baseline were also at a higher risk of hospitalization during both vedolizumab and ustekinumab treatment (steroid or immunomodulator use: OR 1.928, 95% CI 1.123-3.311, p=.017, steroid and immunomodulator use: OR 3.684, 95% CI 1.650-8.229, p=.001). A CCI of three points or higher was significantly and independently associated with hospitalization during treatment (OR 4.943, 95% CI 1.778-13.738, p=.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 hospitalizations in vedolizumab treated patients (OR 3.954, 95% CI 1.048-14.924, p=.042). Age at baseline was not associated with the occurrence of one or more hospitalizations during treatment in all patients (OR .986, 95% CI .965-1.008, p=.204), or in vedolizumab (OR .986, 95% CI .958-1.014, p=.313) and ustekinumab (OR .986, 95% CI .951-1.021, p=.418) treated patients separately (table 3b).

Next, safety analyses for hospitalizations were performed while including only the IBD-related and infection or malignancy related hospitalizations as an outcome. We found that in all patients (OR 1.349, 95% CI 1.007-1.806, p=.045) and in ustekinumab patients (OR 1.625, 95% CI 1.002-2.634, p=.049) the CCI was associated with IBD- and infection or malignancy related hospitalizations. We did not find this association in vedolizumab patients separately (OR 1.388, 95% CI .933-2.066, p=.105).

Adverse events

Adverse events are listed in supplementary table 2c 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 to 60 years and 2.5 in patients <40 years. There was no significant association between age, the CCI and occurrence of adverse events in all patients and in vedolizumab or ustekinumab treated patients when analysed separately (supplementary table 3).

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 (supplementary table 4). 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 to 60 years 0.5 and in patients aged <40 years 0.3.

Table 3b. Safety analysis - hospitalization

All patients	**OR**	**95% CI**	**p-value**
CCI	1.450	1.119-1.879	.005
Age at baseline (years)	.986	.965-1.008	.204
Sex (female)	1.521	.903-2.561	.115
Crohn's disease (ref. UC/IBDU)	2.655	1.245-5.663	.012
Disease duration (years)	1.006	.978-1.035	.675
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.928	1.123-3.311	.017
Steroid and immunomodulator	3.684	1.650-8.229	.001
Treatment duration (weeks)	.999	.992-1.006	.857
Treatment (ustekinumab)	.580	.336-1.004	.052
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	1.586	1.127-2.231	.008
Age at baseline (years)	.986	.958-1.014	.313
Sex (female)	1.558	.759-3.200	.227
Crohn's disease (ref. UC/IBDU)	3.468	1.523-7.897	.003
Disease duration (years)	.969	.927-1.012	.156
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.618	.737-3.550	.230
Steroid and immunomodulator	4.503	1.551-13.071	.006
Treatment duration (weeks)	.996	.987-1.004	.329
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	1.623	1.035-2.546	.035
Age at baseline (years)	.986	.951-1.021	.418
Sex (female)	1.427	.652-3.122	.374
Disease duration (years)	1.042	.999-1.086	.054
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	2.269	1.051-4.901	.037
Steroid and immunomodulator	1.861	.436-7.945	.402
Treatment duration (weeks)	1.008	.996-1.021	.179

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; UC, Ulcerative Colitis; IBDU, IBD-Unclassified; All patients: 409 patients included in analysis of which 90 reached endpoint; VEDO: 203 patients, endpoint: 51 patients; UST: 206 patients included in analysis of which 39 reached endpoint. Multivariable binary logistic regression analysis was performed, CCI was analyzed as a continuous variable

The CCI was not associated with these adverse events that led to treatment discontinuation (supplementary table 5). 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 to 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 to 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.

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=.036). Results are presented in supplementary tables 6a, 6b, 6c and 6d.

Age and the CCI were not associated with drug survival in all patients (age: HR .991, 95% CI .977-1.004, p=.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 .996, 95% CI ,979-1.013, p=.617 and CCI: HR 0.899, 95% CI 0.725-1.115, p=0.333 and age: HR .977, 95% CI .955-1.000, p.054 and CCI: HR 1.349, 95% CI 0.998-1.823, p=0.051).

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 treatment, and with all-cause hospitalization during both vedolizumab and ustekinumab treatment. No association between 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 was 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 is 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 hospitalization during treatment. Analysing the CCI as a categorical variable (categories 0,1,2 or ≥3), the presence of three points or higher was significantly associated with all-cause hospitalization during treatment. Furthermore, we performed safety analyses regarding hospitalizations including only IBD- and infection or malignancy related hospitalizations as an outcome. In this analysis we found the CCI to be significantly associated with IBD- and infection or malignancy related hospitalizations 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=.036), but not in ustekinumab treated patients (OR 0.998, 95% CI 0.611-1.630, p=.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 hospitalizations 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 (supplementary table 1). 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 three or more). Especially a higher number of cardiovascular diseases and pulmonary diseases was 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 characterized. [25-27]

No association between age, comorbidities and impaired effectiveness outcomes was found in our study. In line with this observation, prior studies in IBD patients receiving other biologicals, did also not find an association between 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, p=.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 three points or higher and the presence of cardiovascular disease were associated with impaired safety outcomes (all-cause hospitalization). This sub analysis 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 hospitalization 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 used, 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 hospitalizations in vedolizumab treated IBD patients and hospitalizations 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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Supplementary table 1. Baseline characteristics vedolizumab and ustekinumab treated patients

		Vedolizumab (n=203)	Ustekinumab (n=207)	P-value
Age (years)	Mean (SD)	42.2 (16.0)	41.6 (14.4)	.677
Sex - female	N (%)	112 (55.2)	123 (59.4)	.385
Body Mass Index	Mean (SD)	24.1 (4.4)	24.1 (4.9)	.965
IBD Type				NA
Crohn's Disease	N (%)	120 (59.1)	207 (100.0)	
Ulcerative Colitis	N (%)	80 (39.4)	NA	
IBD-Unclassified	N (%)	3 (1.5)	NA	
Disease duration (years)	Median (IQR)	10.2 (4.8-17.6)	12.2 (6.4-20.9)	.051
Treatment duration (weeks)	Median (IQR)	54.0 (19.9-104.0)	48.4 (24.4-55.1)	.005
Follow-up time (weeks)	Median (IQR)	104.0 (103.1-104.0)	52.0 (49.3-100.4)	.000
Montreal classification				
Age at diagnosis				.298
≤16 years	N (%)	34 (16.7)	44 (21.3)	
17-40 years	N (%)	129 (63.5)	132 (63.8)	
>40 years	N (%)	40 (19.7)	31 (15.0)	
Disease location (CD)				.277
Ileum	N (%)	34 (28.3)	67 (32.5)	
Colon	N (%)	37 (30.8)	73 (35.4)	
Ileocolonic	N (%)	49 (40.8)	66 (32.0)	
Upper GI involvement (CD)†	N (%)	12 (10.0)	11 (5.3)	.113
Disease behaviour (CD)				.953
Inflammatory	N (%)	65 (54.2)	107 (51.9)	
Stricturing	N (%)	32 (26.7)	55 (26.7)	
Penetrating	N (%)	21 (17.5)	38 (18.4)	
Unknown	N (%)	2 (1.7)	6 (2.9)	
Peri-anal disease (CD)	N (%)	19 (16.2)	38 (18.4)	.590
Disease location (UC/IBD-U)				NA
Proctitis	N (%)	6 (7.2)	NA	
Left-sided colitis	N (%)	36 (43.4)	NA	
Pancolitis	N (%)	38 (45.8)	NA	
Unknown	N (%)	3 (3.6)	NA	
Prior intestinal resections	N (%)	71 (35.0)	120 (58.0)	.000
Prior anti-TNF therapy (ever use anti-TNF)	N (%)	192 (94.6)	204 (98.6)	.031
Prior vedo/uste therapy	N (%)	7 (3.4)	82 (39.6)	NA
Clinical disease activity				
HBI	Median (IQR)	7.0 (5.0-10.0)	7.0 (5.0-11.8)	.782
SCCAI	Median (IQR)	5.0 (3.0-8.0)	NA	NA
Biochemical disease activity				
CRP, mg/L	Median (IQR)	7.0 (2.0-22.0)	8.0 (3.0-19.5)	.655
FCP, µg/g	Median (IQR)	898.0 (301.0-2016.0)	721.0 (228.5-1780.5)	.294
Concomitant medication				.000
No immunosuppressants	N (%)	74 (36.5)	112 (54.4)	
Corticosteroid or immunomodulator	N (%)	99 (48.8)	82 (39.8)	
Both corticosteroid and immunomodulator	N (%)	30 (14.8)	12 (5.8)	

SD; Standard Deviation, N; Number, IBD; Inflammatory Bowel Disease, NA; not applicable, IQR; interquartile range, CD; Crohn's disease, GI; gastrointestinal, UC; ulcerative colitis, IBD-U; IBD-Unclassified, anti-TNF; anti-tumor necrosis factor, HBI; Harvey Bradshaw Index, SCCAI; simple clinical colitis activity index, CRP; c-reactive protein, FCP; faecal calprotectin.
Montreal classification is reported as maximum extent until exclusion.

Supplementary table 2a. Safety outcomes – any infection

	One or more comorbidities (n=95)	No comorbidity (n=315)	All patients
Mild infections	**25**	**66**	**91**
Gastrointestinal	1	9	10
Upper respiratory tract	13	27	40
Flu like symptoms	5	17	22
Cold sores	0	3	3
Soft tissue	0	4	4
Skin infections - other	2	2	4
Urinary tract	0	1	1
Fever of unknown origin	2	3	5
Other	2	0	2
Moderate infections	**17**	**39**	**56**
Gastrointestinal	2	3	5
Upper respiratory tract	2	11	13
Flu like symptoms	1	2	3
Soft tissue	1	2	3
Skin infections - other	4	2	6
Urinary tract	3	8	11
Fever of unknown origin	0	1	1
Lower respiratory tract	2	4	6
Herpes zoster	1	1	2
Gynaecological	0	1	1
Other	1	2	3
Unknown	0	2	2
Severe infections	**22**	**20**	**42**
Gastrointestinal	7	10	17
Upper respiratory tract	1	0	1
Lower respiratory tract	5	2	7
Herpes zoster	0	1	1
Urinary tract	1	1	2
Skin infections-other	0	1	1
Fever of unknown origin	1	1	2
Other	7	3	10
Unknown	0	1	1
Unknown severity	**2**	**0**	**2**
Urinary tract	1	0	1
Upper respiratory tract	1	0	1
Total infections	**66**	**125**	**191**

Supplementary table 2b. Safety outcomes - hospitalizations

	One or more comorbidities (n=95)	No comorbidity (n=315)	All patients
IBD-related hospitalizations	**21**	**57**	**78**
Worsening of IBD	10	28	38
Ileus	1	13	14
Fistula or abscess	2	6	8
Surgical resection	8	10	18
Infection or malignancy related hospitalizations	**18**	**17**	**35**
Infection:	**17**	**16**	**33**
-Gastrointestinal infection	5	6	11
-Respiratory tract infection	3	2	5
-Urinary tract infection	1	1	2
-Fever of unknown origin	2	1	3
-Infected CVC line	6	1	7
-Infection or abscess after surgery	0	3	3
-Appendicitis with phlegmon	0	1	1
-Diarrhoea during antibiotic use	0	1	1
Malignancy:	**1**	**1**	**2**
-Peritonitis carcinomatosis originating from gastrointestinal tract	1	1	2
Other hospitalizations	**10**	**4**	**14**
Laparoscopic cholecystectomy	2	0	2
Cholecystitis	0	1	1
ERCP	1	0	1
Pulmonary embolism	0	1	1
Endoscopic submucosal dissection	0	1	1
CVC for parenteral nutrition	0	1	1
Postoperative pain after surgery	1	0	1
Mamma puncture	1	0	1
Osteonecrosis	1	0	1
Diverticulitis	1	0	1
Variceal bleeding	1	0	1
Suspected pancreatitis	1	0	1
Lumbago	1	0	1
Unknown	**6**	**9**	**15**
Total hospitalizations	**52**	**86**	**138**

CVC; central venous catheter, ERCP; endoscopic retrograde cholangiopancreatography. Four hospitalizations were categorized as both worsening of IBD and infection.

Supplementary table 2c. Safety outcomes - adverse events

	One or more comorbidities (n=95)	No comorbidity (n=315)	All patients
Possibly related adverse event	**32**	**75**	**107**
Skin and subcutis	13	20	33
Musculoskeletal or connective tissue	4	5	9
Vascular disorders	0	5	5
Eye disorders	1	3	4
Kidneys and urinary tract	1	1	2
Gastrointestinal	1	3	4
Worsening of IBD	0	1	1
Neoplasia (benign, malignant, including cysts and polyps)	2	0	2
Respiratory, thoracic and mediastinal disorders	0	1	1
Cardiac disorders	1	0	1
Hepatobiliary disorders	1	0	1
Nervous system disorder	0	2	2
Psychiatric disorder	0	1	1
Result of medication administration: infusion reaction	0	1	1
Result of medication administration: other	3	3	6
Other	5	29	34
Probably related adverse event	**3**	**12**	**15**
Skin and subcutis	1	3	4
Nervous system disorder	0	1	1
Result of medication administration: delayed hypersensitivity	0	1	1
Result of medication administration: infusion reaction	0	2	2
Result of medication administration: other	1	1	2
Other	1	4	5
Total adverse events	**35**	**87**	**122**

Supplementary table 3. Safety analysis – adverse events

All patients	**OR**	**95% CI**	**p-value**
CCI	1.228	.963-1.567	.098
Age at baseline (years)	1.008	.988-1.028	.426
Sex (female)	1.924	1.145-3.234	.013
Crohn's Disease (ref. UC/IBDU)	1.104	.526-2.317	.794
Disease duration (years)	.992	.966-1.019	.568
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.750	.452-1.243	.264
Steroid and immunomodulator	.428	.154-1.188	.103
Treatment duration (weeks)	1.006	.999-1.013	.090
Treatment (ustekinumab)	1.250	.702-2.226	.449
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	1.239	.908-1.692	.177
Age at baseline (years)	0.992	.964-1.021	.587
Sex (female)	1.931	.903-4.131	.090
Crohn's Disease (ref. UC/IBDU)	1.024	.475-2.209	.951
Disease duration (years)	1.014	.973-1.057	.510
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	0.835	.387-1.801	.646
Steroid and immunomodulator	0.834	.262-2.653	.759
Treatment duration (weeks)	1.012	1.003-1.021	.009
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	1.181	.779-1.789	.435
Age at baseline (years)	1.022	.993-1.051	.133
Sex (female)	2.337	1.108-4.927	.026
Disease duration (years)	.979	.945-1.014	.235
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.749	.376-1.492	.411
Steroid and immunomodulator	.000	.000	.999
Treatment duration (weeks)	.996	.984-1.008	.531

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; UC, Ulcerative Colitis; IBDU, IBD-Unclassified; All patients: 409 patients included in analysis of which 90 reached endpoint; VEDO: 203 patients, endpoint: 41 patients; UST: 206 patients included in analysis of which 49 reached endpoint. Multivariable binary logistic regression analysis was performed, CCI was analyzed as a continuous variable.

Supplementary table 4. Safety outcomes – adverse events requiring treatment discontinuation

	One or more comorbidities (n=95)	No comorbidity (n=315)	All patients
Adverse events requiring treatment discontinuation	**8**	**6**	**14**
Skin and subcutis	1	0	1
Musculoskeletal or connective tissue	2	2	4
Nervous system disorder	1	0	1
Result of medication administration: infusion reaction	1	1	2
Result of medication administration: other	0	1	1
Other	3	2	5

Supplementary table 5. Safety analysis – adverse events requiring discontinuation

All patients	**OR**	**95% CI**	**p-value**
CCI	1.444	.920-2.267	.110
Age at baseline (years)	.996	.955-1.038	.843
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	1.189	.603-2.347	.617
Age at baseline (years)	1.005	.947-1.066	.870
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	2.000	.986-4.059	.055
Age at baseline (years)	.984	.926-1.046	.613

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; All patients: 409 patients included in analysis of which 11 reached endpoint; VEDO: 203 patients, endpoint: 5 patients; UST: 206 patients included in analysis of which 6 reached endpoint Multivariable binary logistic regression analysis was performed, CCI was analyzed as a continuous variable.

Supplementary table 6a. Effectiveness analysis – clinical remission

All patients	**OR**	**95% CI**	**p-value**
CCI	.930	.680-1.261	.638
Age at baseline (years)	1.007	.986-1.028	.509
Sex (female)	.846	.500-1.430	.533
Crohn's Disease (ref. UC/IBDU)	1.313	.612-2.816	.485
Disease duration (years)	.977	.949-1.005	.104
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.846	.497-1.442	.540
Steroid and immunomodulator	.930	.400-2.161	
Treatment (Ustekinumab) (ref. vedolizumab)	2.314	1.289-4.153	.005
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	1.048	.726-1.512	.802
Age at baseline (years)	.994	.967-1.023	.695
Sex (female)	1.037	.484-2.220	.926
Crohn's Disease (ref. UC/IBDU)	1.282	.582-2.823	.538
Disease duration (years)	.979	.936-1.023	.339
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.717	.322-1.597	.416
Steroid and immunomodulator	.882	.299-2.601	.819
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	.776	.457-1.317	.347
Age at baseline (years)	1.026	.992-1.060	.132
Sex (female)	.707	.336-1.489	.362
Disease duration (years)	.968	.930-1.008	.115
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.015	.491-2.097	.968
Steroid and immunomodulator	.996	.243-4.076	.996

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; UC, Ulcerative Colitis; IBDU, IBD-Unclassified. All patients: 289 patients included in analysis of which 105 reached endpoint; VEDO: 154 patients, endpoint: 41 patients; UST: 135 patients included in analysis of which 46 reached endpoint. Multivariable binary logistic regression analysis was performed, CCI was analyzed as a continuous variable.

Supplementary table 6b. Effectiveness analysis – clinical response

All patients	**OR**	**95% CI**	**p-value**
CCI	.949	.704-1.278	.730
Age at baseline (years)	.995	.975-1.016	.656
Sex (female)	.985	.585-1.658	.955
Crohn's Disease (ref. UC/IBDU)	.715	.344-1.490	.371
Disease duration (years)	.992	.965-1.021	.594
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.031	.608-1.750	.909
Steroid and immunomodulator	.932	.405-2.145	.868
Treatment (Ustekinumab) (ref. vedolizumab)	2.975	1.652-5.358	.000
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	1.178	.826-1.680	.366
Age at baseline (years)	.982	.954-1.010	.214
Sex (female)	.993	.468-2.104	.985
Crohn's Disease (ref. UC/IBDU)	.711	.331-1.531	.384
Disease duration (years)	.992	.951-1.035	.722
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.104	.501-2.433	.807
Steroid and immunomodulator	.862	.287-2.594	.792
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	.630	.361-1.101	.105
Age at baseline (years)	1.013	.981-1.046	.436
Sex (female)	.984	.468-2.066	.965
Disease duration (years)	.983	.945-1.022	.394
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.995	.481-2.058	.989
Steroid and immunomodulator	1.236	.301-5.072	.768

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; UC, Ulcerative Colitis; IBDU, IBD-Unclassified. All patients: 286 patients included in analysis of which 114 reached endpoint; VEDO: 153 patients, endpoint: 45 patients; UST: 133 patients included in analysis of which 69 reached endpoint. Multivariable binary logistic regression was used, CCI was analyzed as a continuous variable.

Supplementary table 6c. Effectiveness analysis – corticosteroid-free clinical remission

All patients	**OR**	**95% CI**	**p-value**
CCI	.922	.673-1.265	.616
Age at baseline (years)	1.003	.982-1.025	.784
Sex (female)	.780	.458-1.327	.359
Crohn's Disease (ref. UC/IBDU)	1.386	.636-3.019	.412
Disease duration (years)	.972	.944-1.000	.054
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.770	.449-1.323	.344
Steroid and immunomodulator	.940	.402-2.195	.886
Treatment (Ustekinumab) (ref. vedolizumab)	2.298	1.270-4.155	.006
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	.992	.671-1.467	.969
Age at baseline (years)	.992	.964-1.022	.607
Sex (female)	1.054	.484-2.295	.894
Crohn's Disease (ref. UC/IBDU)	1.312	.586-2.935	.509
Disease duration (years)	.979	.935-1.025	.368
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.609	.268-1.380	.235
Steroid and immunomodulator	.863	.292-2.551	.789
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	.834	.493-1.412	.449
Age at baseline (years)	1.018	.985-1.052	.291
Sex (female)	.594	.280-1.260	.174
Disease duration (years)	.961	.923-1.001	.056
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	.962	.464-1.995	.916
Steroid and immunomodulator	1.066	.258-4.406	.930

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; UC, Ulcerative Colitis; IBDU, IBD-Unclassified. All patients: 289 patients included in analysis of which 101 reached endpoint; VEDO: 154 patients, endpoint: 39 patients; UST: 135 patients included in analysis of which 62 reached endpoint. Multivariable binary logistic regression analysis was performed, CCI was analyzed as a continuous variable.

Supplementary table 6d. Effectiveness analysis – biochemical and clinical remission

All patients	**OR**	**95% CI**	**p-value**
CCI	1.082	.766-1.528	.656
Age at baseline (years)	1.018	.991-1.045	.184
Sex (female)	1.346	.667-2.715	.407
Crohn's Disease (ref. UC/IBDU)	1.086	.410-2.873	.869
Disease duration (years)	0.980	.946-1.016	.281
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.335	.659-2.704	.423
Steroid and immunomodulator	1.984	.717-5.485	.187
Treatment (Ustekinumab) (ref. vedolizumab)	1.664	.770-3.597	.195
Vedolizumab	**OR**	**95% CI**	**p-value**
CCI	1.035	.642-1.667	.888
Age at baseline (years)	0.997	.961-1.035	.887
Sex (female)	1.541	.553-4.290	.408
Crohn's Disease (ref. UC/IBDU)	0.955	.348-2.622	.929
Disease duration (years)	0.990	.934-1.050	.740
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.232	.412-3.687	.709
Steroid and immunomodulator	2.022	.531-7.695	.302
Ustekinumab	**OR**	**95% CI**	**p-value**
CCI	1.264	.721-2.215	.413
Age at baseline (years)	1.043	1.003-1.085	.036
Sex (female)	1.210	.445-3.288	.709
Disease duration (years)	.974	.929-1.022	.283
Concurrent medication (ref. no concurr. medication)			
Steroid or immunomodulator	1.516	.588-3.912	.389
Steroid and immunomodulator	1.690	.301-9.477	.551

OR, odds ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; UC, Ulcerative Colitis; IBDU, IBD-Unclassified. All patients: 286 patients included in analysis of which 46 reached endpoint; VEDO: 153 patients, endpoint: 21 patients; UST: 133 patients included in analysis of which 25 reached endpoint. Multivariable binary logistic regression analysis was performed, CCI was analyzed as a continuous variable.