

Original Article

Early Intervention With Vedolizumab and Longer-term Surgery Rates in Crohn's Disease: Post Hoc Analysis of the GEMINI Phase 3 and Long-term Safety Programmes

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Abstract

Background: Crohn's disease [CD] is a chronic inflammatory bowel disease that, with progression, may require surgical intervention.

Aim: To determine whether vedolizumab treatment of CD earlier in the disease course [≤ 2 or ≤ 5 years of disease duration] influences risk of CD-related surgery after accounting for probability of response.

Methods: Post hoc analyses of data from CD patients treated with vedolizumab in the GEMINI 2, GEMINI 3, and GEMINI LTS trials [$N = 1253$] evaluated CD-related surgery [bowel resection or colectomy] with stratification by probability of response to vedolizumab [low/intermediate or high]. Analyses used a previously validated clinical decision support tool and both logistic regression and Cox proportional hazard analyses.

Results: In total, 113 [9.0%] vedolizumab-treated patients required CD-related surgery. Surgical rates were 6.1% and 9.8% for the high and low/intermediate probability of response groups, respectively. Risk of surgery was lower for patients with a high probability of response versus those with a low/intermediate probability of response (hazard ratio [HR] 0.50, 95% confidence interval [CI] 0.29 to 0.85). For patients with a low/intermediate probability of vedolizumab response, there was a consistent trend for association between earlier treatment [≤ 2 or ≤ 5 years since diagnosis] and a lower risk of surgery relative to later treatment (≤ 2 years versus > 2 years: odds ratio [OR] 0.77, 95% CI 0.38 to 1.58; ≤ 5 years versus > 5 years: OR 0.61, 95% CI 0.37 to 1.00).

Conclusions: Earlier intervention with vedolizumab may be associated with lower rates of surgery. Use of the clinical decision support tool may help identify patients most likely to benefit from earlier intervention with vedolizumab.

Key Words: Crohn's disease; therapy; vedolizumab

1. Introduction

Crohn's disease [CD] is a chronic, inflammatory, progressive disease of the gastrointestinal tract, characterised by symptoms including abdominal pain, diarrhoea, weight loss, and fatigue.¹ A substantial proportion of patients with CD develop serious complications such as strictures and fistulae, which often lead to hospitalisation and surgery.² Earlier disease intervention with disease-modifying agents may prevent irreversible tissue damage and help preserve quality of life.^{3–5}

Randomised clinical trials [RCTs] with immunosuppressants and tumour necrosis factor antagonists [anti-TNFs] demonstrated that treating patients early [within the first ≤ 2 years of their diagnosis] significantly increases the likelihood of remission and reduces the risk for complications.^{6–8} Some evidence exists to suggest that treating with vedolizumab earlier in the disease course may similarly have added benefit. A post hoc analysis of the GEMINI 2 and 3 studies identified CD duration of < 2 and < 5 years as significant predictors for achieving a Week 2 composite score of abdominal pain ≤ 1 and loose stool frequency ≤ 3 in the patient-reported components of the Crohn's Disease Activity Index [CDAI].⁹ A subgroup analysis of the GEMINI 2 study observed higher clinical remission rates in patients with < 7 years disease duration versus those with longer disease duration.^{10,11} In a real-world study, vedolizumab initiated within 2 years of CD diagnosis was associated with fewer flares and longer median time to first flare compared with when treatment was initiated ≥ 2 years following diagnosis.¹² In a recently published retrospective observational cohort study using the VICTORY Consortium registry, patients with CD disease duration of ≤ 2 years were significantly more likely than those with longer disease duration to achieve clinical remission, corticosteroid-free remission, and endoscopic remission when treated with vedolizumab.¹³

Although these studies help support the potential benefit of early disease intervention with vedolizumab, no studies to date have evaluated the effect of early vedolizumab treatment on CD-related surgery rates in the longer term. Furthermore, substantial differences exist in patient characteristics when classified according to disease duration, and these characteristics have been known to affect response to treatment and the natural history of the disease. Thus, assessment of the impact of early disease intervention requires integration of a patient's baseline probability of response to treatment and natural history of disease. We evaluated whether a previously validated clinical decision support tool [CDST] capable of predicting the probability of response to vedolizumab treatment in patients with CD could predict the risk of CD-related surgery, and whether benefits derived from early disease intervention were influenced by probability of response.

2. Methods

2.1. Patient population

This post hoc analysis was conducted on individual participant data from patients diagnosed with moderately to severely active CD who were treated with vedolizumab [irrespective of dosing regimen] after enrolment to studies GEMINI 2, GEMINI 3, and/or GEMINI long-term safety [LTS]. GEMINI 2 [NCT00783692] was a phase 3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of vedolizumab treatment in moderately to severely active CD.¹⁰ GEMINI 3 [NCT01224171] was a phase 3, randomised, double-blind, placebo-controlled study to determine the effect of vedolizumab induction on clinical remission at Week 6

among patients with CD and previous anti-TNF failure.¹⁴ GEMINI LTS [NCT00790933] was a single-arm, open-label, phase 3 study of the safety of long-term vedolizumab treatment in moderately to severely active CD and ulcerative colitis.^{15–17} Patients who completed GEMINI 2 or GEMINI 3 were eligible for entry into GEMINI LTS. The eligibility criteria for *de novo* GEMINI LTS patients [ie, patients who were not previously enrolled and treated with vedolizumab in GEMINI 2 or GEMINI 3] were similar to those for GEMINI 2.¹⁷ In the current analysis, only GEMINI LTS patients with CD who had rolled over from GEMINI 2 or GEMINI 3, or *de novo* GEMINI LTS patients with CD, were considered. The data included represent a follow-up of up to 7 years after initiation of vedolizumab treatment. Patients for whom any of the five CDST baseline parameters to calculate the probability of response were missing were excluded from the analysis.

2.2. Patient consent for publication

As part of the original GEMINI studies, all patients provided written informed consent, and the trials were approved by the institutional review board of each participating institution. Because the current post hoc analyses used existing data from the primary studies, additional consent was not required.

2.3. Outcome measures

The outcomes of interest were to determine if early disease intervention with vedolizumab was associated with higher rates of clinical remission and corticosteroid-free remission and lower rates of CD-related surgery, and if any observed associations were influenced by a patient's baseline probability of response. A previously validated CDST, originally developed to predict and classify a patient's probability of response to vedolizumab treatment as high, intermediate, or low, was employed for risk stratification.¹⁸ The CDST is composed of five variables associated with probability of remission to vedolizumab: previous bowel surgery, previous anti-TNF use, previous fistulising disease, baseline albumin, and baseline C-reactive protein.¹⁸ The *a priori* hypothesis based on biological plausibility was that patients with a high probability of response would be at lower risk for surgery, which would be less likely to be modifiable by earlier disease intervention, whereas patients with a low to intermediate probability of response would have higher risk for surgery, which might be modifiable by earlier disease intervention. For the analyses only the first CD-related surgery and the time to this first CD-related surgery were considered. CD-related surgery was considered a surrogate for disease progression.

2.4. Definitions

Clinical remission was defined as a CDAI score ≤ 150 points at Week 52, and corticosteroid-free clinical remission was defined as clinical remission at Week 52 without corticosteroid treatment in the subset of patients with concomitant corticosteroid use at treatment initiation. Patients with missing data for determination of clinical remission status were categorised as not having clinical remission. CD-related surgery was defined as either a colectomy or a bowel resection after treatment initiation and was assessed over a 7-year time horizon. The definition of 'earlier versus later' disease was examined using cutoffs of 2 and 5 years, and patients were accordingly classified into earlier versus later disease categories, as measured by time since CD diagnosis.

2.5. Statistical analysis

To account for baseline probability of response while evaluating the effect of earlier disease intervention with vedolizumab in patients with CD, analyses were stratified by each individual patient's baseline probability of clinical response to vedolizumab, classified as low/intermediate or high, using the CDST. Within each probability of response group, patients were further stratified based on disease duration at initiation of vedolizumab using two definitions for early disease: ≤ 2 years since CD diagnosis and ≤ 5 years since CD diagnosis. In addition, a further stringent definition of early disease, defined as ≤ 5 years since diagnosis with no previous history of CD-related surgery and no fistulising disease, was evaluated.

The rates of clinical remission and corticosteroid-free clinical remission [in the subset of patients with concomitant corticosteroid use at treatment initiation] were calculated for each probability of response category and stratified by duration of disease; odds ratios [ORs] and 95% confidence intervals [CIs] were calculated. CD-related surgery rates were calculated for the probability of response and disease duration stratified subgroups and compared using Cox proportional hazard and logistic regression models. Cox proportional hazard models and time-to-event analyses were used to compare the risk of CD-related surgery across CDST-predicted probability of response groups, to account for any time-dependent

response differences between groups. For the comparison of subgroups stratified by disease duration, logistic regression models were used due to the non-proportional hazard of events over time between disease duration-stratified subgroups within the CDST-stratified probability of response groups. Results are reported in hazard ratios [HRs] and ORs with accompanying CIs. Kaplan-Meier plots were generated to determine the relationships between response probability and disease duration with time to CD-related surgery.

3. Results

3.1. Patient population

In total, 1253 patients treated with vedolizumab from the GEMINI 2, GEMINI 3, and GEMINI LTS studies were included in the analysis. The mean (standard deviation [SD]) patient age was 36.5 [12.4] years, with 44.9% male patients. Mean [SD] time since CD diagnosis was 9.6 [8.1] years, and most (1046 [83.5%]) patients had colonic or ileocolonic disease. The majority of patients had failed previous anti-TNF treatment (822 [65.6%]) and more than half were receiving concomitant corticosteroid treatment at vedolizumab initiation (527 [51.6%]) [Table 1]. The overall mean duration of patient follow-up was 2.6 years [Table 1]. According to the CDST, 988

Table 1. Baseline demographics and disease characteristics

	Disease duration				Overall [n = 1253]
	≤ 2 years [n = 191]	> 2 years [n = 1062]	≤ 5 years [n = 453]	> 5 years [n = 800]	
Male, n [%]	104 [54.5]	459 [43.2]	225 [49.7]	338 [42.3]	563 [44.9]
Age [years], mean [SD]	34.1 [12.9]	36.9 [12.2]	33.2 [12.2]	38.3 [12.1]	36.5 [12.4]
HBI score, mean [SD]	10.5 [3.5]	11.2 [3.6]	10.9 [3.6]	11.3 [3.6]	11.1 [3.6]
CD severity, n [%]					
Remission [HBI score < 5]	4 [2.1]	20 [1.9]	11 [2.4]	13 [1.6]	24 [1.9]
Mild activity [HBI score 5–7]	30 [15.7]	99 [9.3]	51 [11.3]	78 [9.8]	129 [10.3]
Moderate activity [HBI score 8–16]	148 [77.5]	862 [81.2]	361 [79.7]	649 [81.1]	1010 [80.6]
Severe activity [HBI score > 16]	9 [4.7]	81 [7.6]	30 [6.6]	60 [7.5]	90 [7.2]
HBI stool score, mean [SD]	5.5 [3.2]	6.2 [3.3]	5.8 [3.4]	6.2 [3.2]	6.1 [3.3]
Time since CD diagnosis [years], mean [SD]	1.2 [0.5]	11.1 [7.8]	2.5 [1.4]	13.6 [7.5]	9.6 [8.1]
Current smoker, n [%]	44 [23.0]	284 [26.8]	108 [23.8]	220 [27.5]	328 [26.2]
Disease location, n [%]					
Ileocolonic	95 [49.7]	621 [58.5]	238 [52.5]	478 [59.8]	716 [57.1]
Colon only	65 [34.0]	265 [25.0]	144 [31.8]	186 [23.3]	330 [26.3]
Ileum only	31 [16.2]	176 [16.6]	71 [15.7]	136 [17.0]	207 [16.5]
Previous bowel surgery, ^a n [%]	28 [14.7]	521 [49.1]	104 [23.0]	445 [55.6]	549 [43.8]
History of fistulising disease, ^a n [%]	46 [24.1]	409 [38.5]	116 [25.6]	339 [42.4]	455 [36.3]
Concomitant oral corticosteroids, ^b n [%]	98 [61.3]	429 [49.8]	197 [53.0]	330 [50.8]	527 [51.6]
Concomitant immunomodulator use, n [%]	79 [41.4]	308 [29.0]	168 [37.1]	219 [27.4]	387 [30.9]
Previous exposure to anti-TNF, ^a n [%]	72 [37.7]	791 [74.5]	229 [50.6]	634 [79.3]	863 [68.9]
Previously failed anti-TNF, n [%]	66 [34.6]	756 [71.2]	214 [47.2]	608 [76.0]	822 [65.6]
C-reactive protein [mg/L], ^a mean [SD]	20.5 [28.7]	20.9 [27.0]	20.8 [29.1]	20.9 [26.2]	20.9 [27.3]
Albumin [g/L], ^a mean [SD]	35.7 [5.9]	34.8 [5.5]	35.5 [5.8]	34.6 [5.4]	34.9 [5.5]
Low/intermediate probability of response, ^c n [%]	113 [59.2]	875 [82.4]	300 [66.2]	688 [86.0]	988 [78.9]
High probability of response, ^c n [%]	78 [40.8]	183 [17.2]	151 [33.3]	110 [13.8]	261 [20.8]
Duration of follow-up in years					
Mean [SD]	2.9 [2.5]	2.5 [2.3]	2.7 [2.4]	2.5 [2.3]	2.6 [2.4]
Median [range]	2.0 [0–8.2]	1.4 [0–8.2]	1.7 [0–8.2]	1.4 [0–8.2]	1.5 [0–8.2]

Anti-TNF, tumour necrosis factor antagonist; CD, Crohn's disease; HBI, Harvey-Bradshaw Index; SD, standard deviation.

^aClinical decision support tool parameter.

^bValues are based on patients from GEMINI 2 and GEMINI 3 only.

^cFour patients were excluded from the analysis by response probability due to ≥ 1 missing clinical decision support tool variables.

patients had a low/intermediate probability of response (352 low [28.1%]; 636 intermediate [50.8%]), and 261 [20.8%] had a high baseline probability of response. Notable differences in baseline disease characteristics with higher rates in later disease groups across disease duration subgroups were mean disease duration, previous bowel surgery, history of fistulising disease, previous exposure to anti-TNF, and previous anti-TNF failure [Table 1].

3.2. Clinical remission and corticosteroid-free clinical remission

Compared with the high probability of response group, the low/intermediate probability of response group was significantly less likely to achieve clinical remission [OR 0.44, 95% CI 0.33 to 0.58] and corticosteroid-free clinical remission [OR 0.31, 95% CI 0.19 to 0.52], irrespective of disease duration. Within each probability of response group specifically, there were trends towards higher

rates of clinical remission when vedolizumab was used earlier in the disease course, but a statistically significant difference was only observed in the high probability of response subgroup using the 2-year definition for early disease [OR 1.74, 95% CI 1.02 to 2.97] [Figures 1 and 2]. Similar trends were observed for higher rates of corticosteroid-free clinical remission when vedolizumab was used earlier in the disease course, but none of the comparisons were statistically significant.

3.3. CD-related surgery

A total of 113 [9.0%] patients required CD-related surgery during the 7-year follow-up period, with 66 [58.4%] requiring a bowel resection and 47 [41.6%] requiring a colectomy as their initial surgery. Overall, 97 [9.8%] patients in the low/intermediate probability and 16 [6.1%] patients in the high probability of response groups required CD-related surgery.

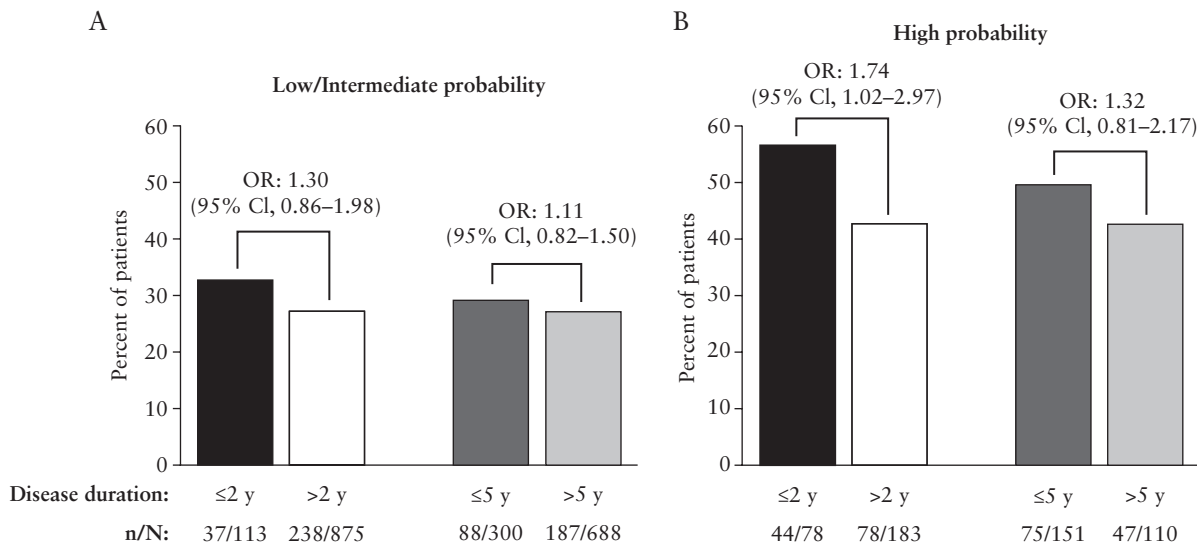


Figure 1. Odds of clinical remission at Week 52 by disease duration and probability of response.

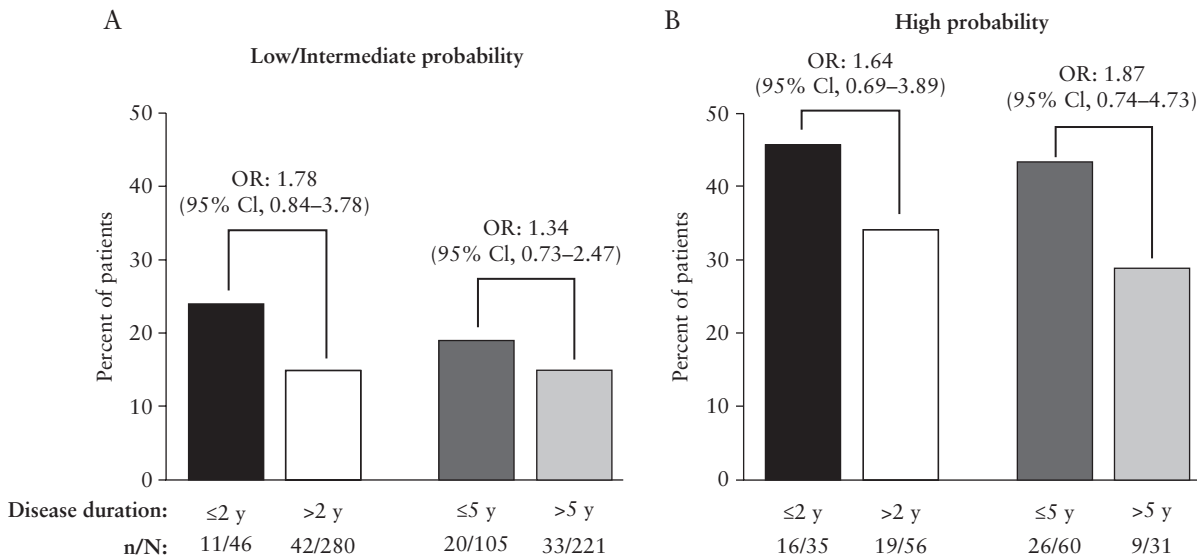


Figure 2. Odds of corticosteroid-free clinical remission at Week 52 by disease duration and probability of response.

Patients with a high probability of response at baseline had half the risk of CD-related surgery compared with patients with a low/intermediate probability of response at baseline [HR 0.50, 95% CI 0.29 to 0.85] [Figure 3A]. The data supported a trend for higher risk of CD-related surgery among patients treated with vedolizumab later in the disease course; however, this was statistically significant only when using the 5-year cut-off for defining early disease [HR 1.73, 95% CI 1.13 to 2.64] [Figure 3B–D].

For the low/intermediate probability of response group specifically, patients with a disease duration of ≤ 5 years had lower odds of requiring CD-related surgery compared with low/intermediate probability of response patients with disease duration > 5 years [OR 0.61, 95% CI 0.37 to 1.00]. No such difference was observed in the high probability of vedolizumab response group [Figure 4]. In a subgroup analysis comparing patients with ≤ 5 years disease duration with no previous bowel surgery and no history of fistulising disease with patients who did not fit those criteria, similar trends were observed supporting an impact of earlier treatment on risk of CD-related surgery for low/intermediate probability of response patients, but not for high probability of response patients [Figure 5].

4. Discussion

In this post hoc analysis of the GEMINI phase 3 and long-term safety programmes, we made several notable observations. The previously validated CDST capable of predicting probability for

achieving clinical remission, corticosteroid-free remission, and mucosal healing was able to predict differences in rates of CD-related surgery when receiving vedolizumab therapy up to a 7-year time horizon.¹⁸ After accounting for an individual's probability of response to vedolizumab treatment using this CDST, treatment with vedolizumab earlier in the disease course was most impactful in reducing the risk of CD-related surgery among those classified as having a low/intermediate baseline probability of response to therapy. Rates of clinical remission, however, were not as substantially influenced by early disease intervention in this same patient population. Conversely, earlier disease intervention significantly influenced clinical remission in patients with a high baseline probability of response to vedolizumab, but early disease intervention did not have a substantial impact on risk of CD-related surgery in this patient population.

Previous observational studies and post hoc analyses have predominately focused on the association between early disease intervention with vedolizumab and clinical outcomes such as improvements in symptoms and achievement of clinical remission.^{9–13,19} We observed that when early disease intervention with vedolizumab affected remission outcomes, as with the high probability of response group, this did not translate into meaningful effects on disease-related complications [surgery]. When early disease intervention with vedolizumab did significantly impact CD-related surgery outcomes, as with the low/intermediate probability of response group, an effect on remission outcomes was not observed. This is in keeping with the REACT clinical trial programme where

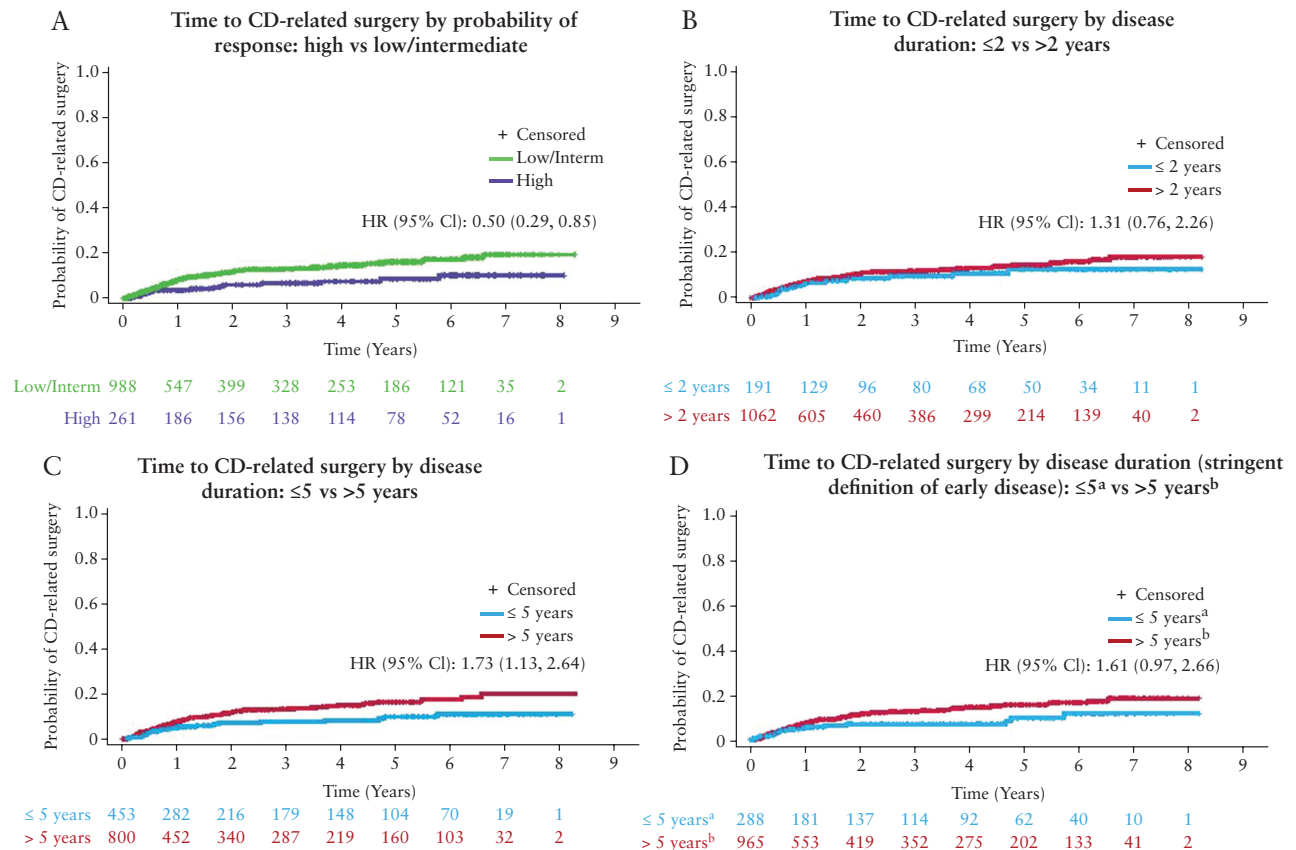


Figure 3. Time to CD-related surgery based on probability of response and disease duration. ^aPatients with ≤ 5 years disease duration with no previous bowel surgery and no history of fistulising disease. ^bPatients who did not meet criteria for ≤ 5 years disease duration with no previous bowel surgery and no history of fistulising disease. CD, Crohn's disease.

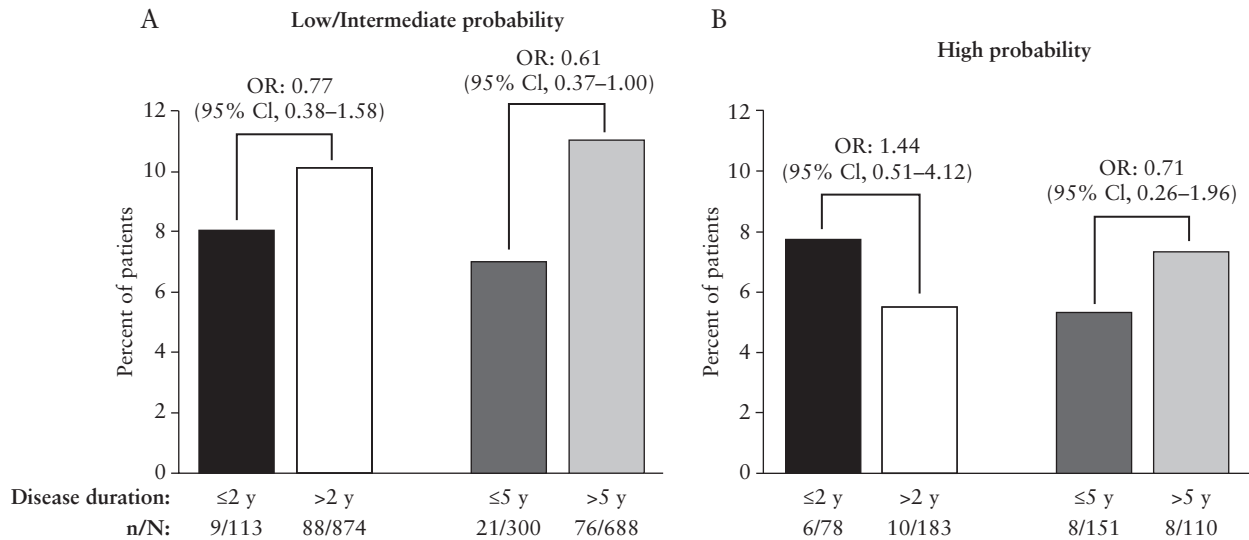


Figure 4. Risk of CD-related surgery stratified by probability of response and disease duration. CD, Crohn's disease.

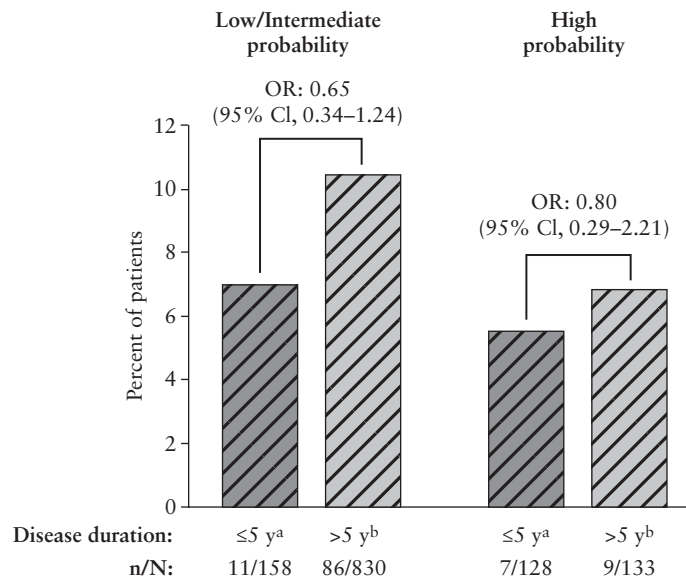


Figure 5. Risk of CD-related surgery stratified by probability of response and disease duration in patients with no previous bowel surgery or history of fistulising disease. ^aPatients with ≤5 years disease duration with no previous bowel surgery and no history of fistulising disease. ^bPatients who did not meet criteria for ≤5 years disease duration with no previous bowel surgery and no history of fistulising disease. CD, Crohn's disease.

early combined immunosuppression significantly reduced the risk of CD-related complications after 2 years, but it had no significant impact on rates of disease remission.²⁰ These findings may in part be explained by limitations of indices used to measure clinical remission in CD, which have poor correlation with objective outcomes of inflammation.^{21–23}

The subgroup that appeared to benefit most from an early disease intervention strategy with vedolizumab for reducing the risk of CD-related surgery was the low/intermediate probability of response group, when early disease was defined using a 5-year cut-off. Point estimates were similar when using more stringent definitions, which included a 2-year cut-off, or a 5-year cut-off with no previous bowel surgery or fistulising disease, thereby demonstrating a consistent signal of benefit for early disease intervention in this subgroup; however, these secondary definitions did not reach statistical significance due to sample sizes.

The strengths of this study include its size, the use of individual participant data from the original registration trials of vedolizumab for CD, and up to 7 years of long-term follow-up data through the safety extension programmes. These findings are novel, as the potential for anti-integrins to show disease modification in CD is currently unknown. The study also had several limitations that should be acknowledged. First, the GEMINI 2 and GEMINI LTS were designed to evaluate the clinical efficacy and safety of vedolizumab for CD, but the presented analysis was post hoc and the original studies were not primarily designed to evaluate the impact of earlier vedolizumab use on surgical resection rates. Endoscopy was also not routinely performed in these studies, so this post hoc analysis lacked this objective measure of disease severity. Thus, the findings of this analysis should be considered hypothesis-generating and be validated in a disease modification trial specifically addressing this issue. Patient loss to follow-up also limited the number of patients

with data available for analysis. Finally, there were relatively few patients in GEMINI with ≤ 2 years of disease duration at entry ($n = 191$ [15%]) and a relatively low surgical event rate [$<10\%$]. Because most surgeries occurred within 5 years of vedolizumab initiation, further studies are needed on the long-term implications of early vedolizumab use on surgical outcome. Although a trend for association between earlier treatment [≤ 2 or ≤ 5 years since diagnosis] and a lower risk of surgery relative to later treatment [>2 or >5 years since diagnosis] for patients with a low/intermediate probability of vedolizumab response was observed using both cut points, the odds were greatest using the 5-year cut point, and some clinicians may not consider a period of 5 years since disease diagnosis as early disease.

The current CD vedolizumab CDST may have utility in identifying CD patients who are likely to derive the most long-term benefit from early vedolizumab intervention, which could have implications for patient management. Specifically, physicians may be able to use the CDST to assess whether a recently diagnosed patient could benefit from initiating vedolizumab treatment earlier. Early intervention during a window of opportunity may prevent long-term CD complications and thus increase quality of life.²⁴ The results of this post hoc analysis suggest that early disease intervention with vedolizumab should be further examined in the context of long-term outcomes such as surgery.

Data are available upon reasonable request. Anonymised patient-level data for the GEMINI trials are available to researchers with a valid research proposal, via application at <https://search.vivli.org>.

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Conflict of Interest

PSD: consultancy: Takeda, Janssen, Pfizer, AbbVie; research support: Prometheus, Polymedco, Bullmann, Takeda, Janssen, AbbVie; patent: the University of California – San Diego and PSD owns a provisional patent on the vedolizumab clinical decision support tool and modelling discussed. VJ: consultancy: AbbVie, Eli Lilly, GlaxoSmithKline, Arena Pharmaceuticals, Genentech, Pendopharm, Sandoz, Merck, Takeda, Janssen, Robarts Clinical Trials, Topivert, Celltrion, Ferring; lecture fees: Takeda, Janssen, Shire, Ferring, AbbVie, Pfizer. LP-B: personal fees: AbbVie, Janssen, Genentech, Ferring, Tillotts, Pharmacosmos, Celltrion, Takeda, Boehringer Ingelheim, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Alma, Sterna, Nestle, Enterome, Allergan, MSD, Roche, Arena, Gilead, Hikma, Amgen, BMS, Vifor, Norgine, Mylan, Eli Lilly, Fresenius Kabi, Oppilan Pharma, Sublimity Therapeutics, Applied Molecular Transport, OSE Immunotherapeutics, Entera, Therevance; grants: AbbVie, MSD, Takeda; stock options: CTMA. DD: employee of Takeda; holds Takeda stocks or stock options. KL: employee of Takeda; holds relevant Takeda patents. KAH: employee of IQVIA, which received funding from Takeda. DL: employee of Takeda; holds Takeda stock or stock options. HP: employee of Takeda at the time when this research was conducted.

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Author Contributions

All authors contributed to the development of this manuscript; HP, DD, KL secured the funding for this study. DL provided statistical support. All authors helped with the interpretation of study findings. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors approved the final version of the manuscript.

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