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Early Biologic Treatment Decreases Risk of Surgery in Crohn's Disease but not in Ulcerative Colitis: Systematic Review and Meta-Analysis

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Background and Aims: Inflammatory bowel disease (IBD) can lead to long-term complications that significantly impact patients' quality of life and healthcare resource utilization. Prior studies have demonstrated improved short-term outcomes to early exposure of biologics in patients with Crohn's disease (CD) but not in patients with ulcerative colitis (UC). However, there are conflicting data on impact of early intervention on longer-term adverse events. Therefore, we conducted a systematic review and meta-analysis assessing the impact of early biologic treatment on rates of IBD-related surgery.

Methods: A systematic search was conducted in April 2022. Studies were included if biologic initiation was compared between patients starting early (<3 years of diagnosis or top-down treatment) vs later (>3 years of diagnosis or step-up treatment). Studies with <1 year of follow-up were excluded. The outcomes were colectomy and CD-related surgery for patients with UC and CD, respectively. Random-effects analyses were conducted to compare rates of IBD surgery between early and late biologic treatment.

Results: Eighteen studies were included in the meta-analysis. Three studies included patients with UC and 15 studies included patients with CD. In patients with CD, early biologic therapy was associated with lower odds of surgery (odds ratio, 0.63; 95% confidence interval, 0.48-0.84) compared with late treatment. Conversely, in patients with UC, the odds of colectomy were increased (odds ratio, 2.86; 95% confidence interval, 1.30-6.30).

Conclusions: Early biologic treatment is associated with lower rates of surgery in patients with CD. In contrast, early biologic therapy appears to be associated with higher rates of colectomy in patients with UC, which may be confounded by disease severity.

Key Words: ulcerative colitis, Crohn's disease, colectomy, biologic, early

Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is a chronic condition characterized by inflammation of the gastrointestinal tract.

Long-standing transmural inflammation in CD can lead to complications such as strictures, fistulae, and abscesses.[1] Inadequately controlled UC increases the risk of hospitalization and can lead to colectomy and colorectal cancer.[2] Furthermore, long-term complications significantly impact patients' quality of life and healthcare resource utilization.[3]

Introduction of biologics has transformed the landscape of IBD management, and numerous clinical trials have demonstrated their ability to achieve short-term endpoints such as clinical remission.[4-7] Despite the availability of these efficacious medications, the optimal timing of biologic therapy remains uncertain. Management of IBD has conventionally adhered to a step-up approach.[8] However, prior studies have demonstrated improved short-term clinical response rates to biologics in patients with CD who have shorter disease duration but not in patients with UC.[9-11] Furthermore, there is growing interest in the potential disease-modifying impact of early biologic therapy in IBD and its ability to prevent medium- and long-term complications such as need for surgery.[12] In fact, IBD surgery was identified by the International Organization for the Study of Inflammatory Bowel Diseases in the SPIRIT (Selecting-Endpoints for Disease-Modification Trials) consensus as an endpoint to be used in future IBD disease modification trials.[12]

Thus far, data on the impact of early biologic treatment on prevention of surgery have been conflicting. A prospective, longitudinal cohort study of patients with CD in the United States reported that the risk of undergoing surgery was significantly higher in patients who initiated biologic therapy 2 to 5 years after diagnosis compared with earlier initiation.[13] On the other hand, a large study using health administrative data in Ontario, Canada, concluded that introduction of infliximab into the market did not reduce intestinal resection

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Key Messages

What is already known:

- Studies have demonstrated improved short-term clinical response rates to biologics in patients with Crohn's disease (CD) that have shorter disease duration but not in patients with ulcerative colitis.
- Data on the impact of early biologic treatment on prevention of surgery have been conflicting.

What is new here:

- In patients with CD, early biologic therapy was associated with lower odds of surgery (odds ratio, 0.63; 95% confidence interval, 0.48-0.84) compared with late treatment.
- In patients with ulcerative colitis, early biologic therapy was associated with increased odds of colectomy (odds ratio, 2.86; 95% confidence interval, 1.30-6.30). This finding may be confounded by disease severity.

How can this study help patient care:

- In patients with moderate-to-severe CD in whom biologic therapy would be indicated, earlier initiation may be associated with reduction in CD-related surgery.

rates among patients with CD or UC.[14] However, this study did not specifically examine the time between diagnosis and initiation of infliximab. Moreover, the authors postulated that the study results may have been impacted by practice patterns such as using infliximab later in the disease course and infrequent dose optimization.

The impact of early biologic therapy in individuals with IBD remains a matter of debate, with a need for further clarity in this area. Hence, we conducted a systematic review and meta-analysis to assess the impact of early biologic treatment on rates of IBD-related surgery in CD and UC.

Methods

This systematic review and meta-analysis is reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[15]

Search Strategy

A literature search was designed and conducted by a medical librarian (S.W.) using relevant keywords and subject headings on Ovid Medline, Ovid Embase, Cochrane Library (Wiley), and Web of Science Core Collection databases. Complete search language for all databases is available in Supplementary Appendix A. Searches were run on April 18, 2022, and all results were imported into the Covidence software (Veritas Health Innovation) and de-duplicated.

Eligibility and Selection Criteria

Studies were included if timing of biologic initiation (early vs late) was compared between patients with IBD. Early biologic therapy was defined as within 3 years of diagnosis to maximize the number of studies included. Studies in which earlier biologic use (top down) was compared with conventional (step up) strategy were also included. While the search language was broad, only articles reporting rate of colectomy were included. Studies involving pediatric and adult patients were included. Studies with <1 year of follow-up were excluded.

Randomized controlled trials (RCTs), non-RCTs, prospective cohort studies, retrospective cohort studies, case-control studies, and cross-sectional studies were eligible for inclusion. Meta-analyses, case series, and case reports were excluded. Manuscripts and abstracts were considered for inclusion to maximize data available for analysis as long as abstract data included the outcomes of interest and clearly adhered to the selection criteria. In instances in which both published manuscripts and abstracts representing the same data were available, manuscript data were only included.

Three investigators (C.L., B.T., and S.L.) independently screened the titles and abstracts identified by the literature search. Potentially relevant articles were reviewed in full to determine eligibility for inclusion. Any disagreements were resolved through evaluation by a fourth investigator (R.C.U).

Data Extraction and Outcomes

The primary outcomes of interest were colectomy for patients with UC- and CD-related surgery, including perianal surgery for patients with CD. Subgroup analyses were performed with studies including pediatric and adult patients only.

Two investigators (C.L. and B.T.) performed data extraction independently. The data included (1) study characteristics such as primary author, year of publication, article/abstract, and study design; (2) patient and IBD disease characteristics including age (pediatric/adult), IBD subtype, number of patients, and biologic used; and (3) outcome assessment including length of the follow-up period and rate of surgery.

Quality Assessment

Quality assessment was performed using the CLARITY Group risk of bias assessment tools (Tool to Assess Risk of Bias in Cohort Studies, Tool to Assess Risk of Bias in Randomized Controlled Trials; https://www.clarityresearch.ca/). Separate versions of the tool were used for cohort studies and RCTs. The tool for cohort studies evaluated characteristics such as whether the exposed and nonexposed cohorts were drawn from the same population, if one can be confident in the assessment of exposure, and if one can be confident that the outcome of interest was not present at the start of the study. The CLARITY tool for RCTs assessed features such as the method allocation sequence generation, concealment of allocation, and adequacy of blinding.

Statistical Analysis

Data were analyzed using ReviewManager 5.4 (Cochrane Collaboration). Random-effects analyses were conducted to compare rates of IBD surgery between early biologic treatment (<3 years of disease duration or top-down treatment strategy) and late treatment (biologic use after >3 years of disease duration or step-up treatment). Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Subgroup analyses were performed of only studies including adult patients. A sensitivity analysis was completed to assess if a 2-year cutoff defining early vs late biologic treatment resulted in significantly different outcomes. A second sensitivity analysis was conducted without data collected from

abstract sources. Heterogeneity was assessed by calculating the I^2 statistic. I^2 values of >50% were considered to indicate substantial heterogeneity. Publication bias was assessed via visual inspection of funnel plots.

Results

Search Results

The literature search identified 3833 citations. After duplicates were removed, 2986 studies remained for screening. A total of 2789 were excluded after review of the titles and abstracts. We retrieved the full text of the remaining 184 studies. Of these, 18 studies were included in the review (Figure 1).

Included Studies

Sixteen of the included studies were observational studies and 2 studies were post hoc analyses of RCTs. Of these, 5 included pediatric patients and 13 included adult patients. Three studies included patients with UC, while the rest included patients with CD. Most authors focused on early tumor necrosis factor inhibitor therapy. Two articles explored early vedolizumab therapy, while one did not specify the type of biologic. Several definitions of early biologic therapy were used by the studies, and they are summarized in Table 1. All the CD studies used a cutoff of 2 years or less to define early vs late therapy, whereas one study on UC patients[16] used a 3-year cutoff. The mean follow-up period ranged from 12 months to 103 months.

Rate of Surgery

In CD patients, the pooled OR for CD-related surgery in patients who received early vs late biologic therapy was 0.63 (95% CI, 0.48-0.84), with little heterogeneity (I^2 = 22%) (Figure 2). When only data from RCTs were analyzed, the pooled OR for CD-related surgery was 0.75 (95% CI, 0.46-1.23). Among patients with UC, the OR for colectomy was 2.86 (95% CI, 1.30-6.30), with an I^2 of 0%. Subgroup analyses were performed of only studies including adult patients. The results remained similar for CD-related surgery (OR, 0.67; 95% CI, 0.51-0.90). No difference in risk of colectomy was found in patients with UC treated with earlier biologic therapy vs conventional therapy when only studies involving adult patients were analyzed (OR, 2.40; 95% CI, 0.87-6.62). A sensitivity analysis of studies including UC patients with a definition of early biologic

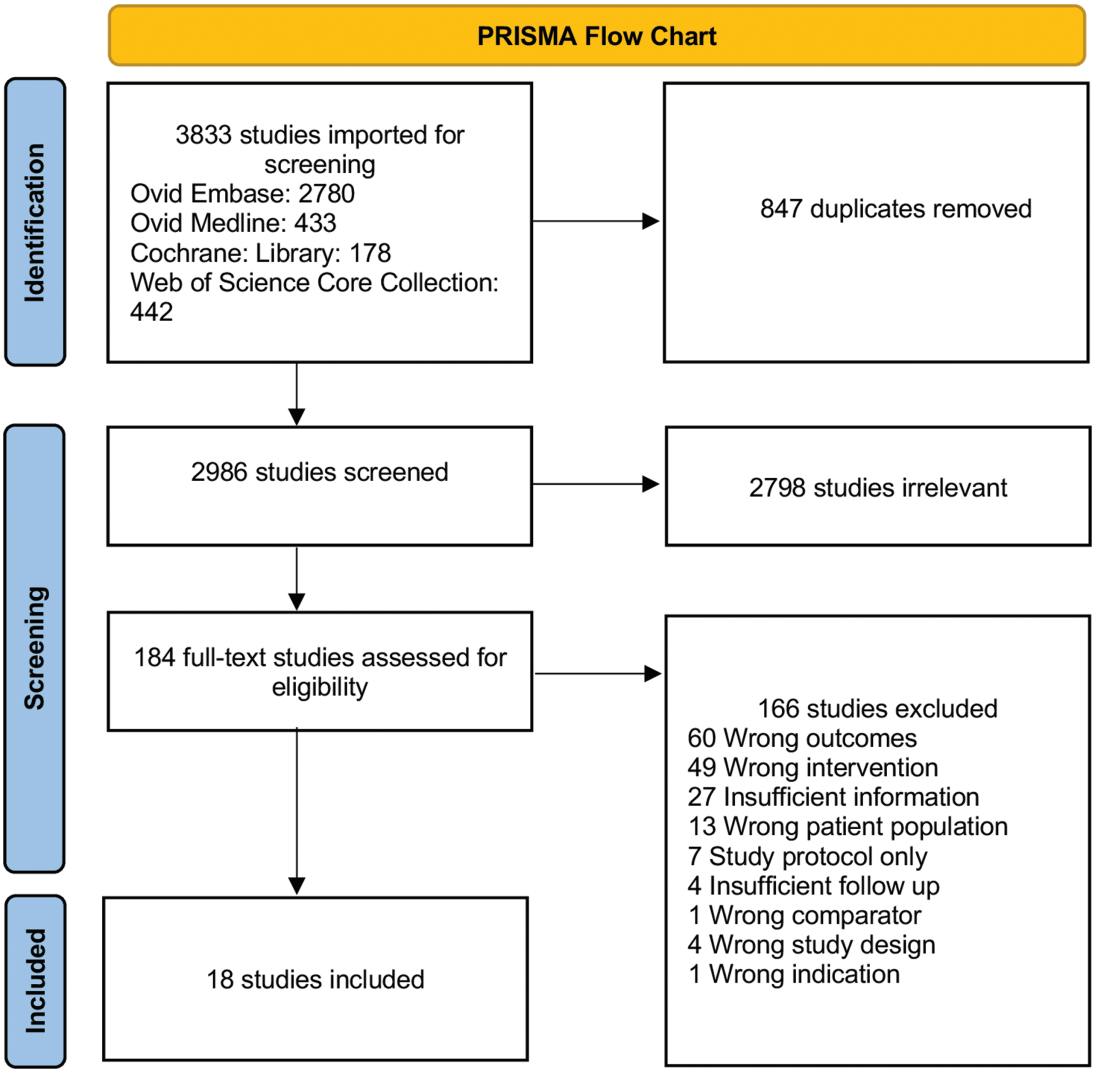

Figure 1. Flowchart of the search strategy for the systematic review. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Study characteristics.

Author and year	Article/ abstract	Study type	Age	IBD type	Total number of patients	Intervention(s)	Disease duration definition for early biologic use	Length of follow-up
De Caro 2015[17]	Abstract	Observational	Pediatric	CD	33	Infliximab or adalimumab	Top down vs step up	24 mo
Pineton de Chambrun 2015[18]	Abstract	Observational	Adult	CD	153	Infliximab	<18 m	Mean of 49 mo in early biologic group, mean of 172 mo in comparison group
Dulai 2021[19]	Article	Post hoc of RCT	Adult	CD	1253	Vedolizumab	<2 y	84 mo
Han 2020[20]	Article	Observational	Adult	UC	698	Infliximab, adalimumab, or golimumab	<2 y	Up to 84 mo
Hoekman 2018[21]	Article	Post hoc of RCT	Adult	CD	119	Early combined immunosuppression (Infliximab with azathioprine) vs Conventional management	Top down vs step up	96 mo
Jung 2020[22]	Article	Observational	Adult	CD	1207	Infliximab or adalimumab	<1 y	Up to 72 mo
Ma 2016[16]	Article	Observational	Adult	UC	115	Infliximab or adalimumab	<3 y	Mean of 153 wk in early biologic group, mean of 168 wk in comparison group
Ma 2016[23]	Article	Observational	Adult	CD	190	Infliximab or adalimumab	<2 y	Mean of 183 wk in early biologic group, mean of 175 wk in comparison group
Mantzaris 2021[24]	Article	Observational	Adult	CD	171	Adalimumab	<2 y	Median of 45 mo in early biologic group, mean of 148 mo in comparison group
Markowitz 2012[25]	Abstract	Observational	Pediatric	CD	108	Infliximab	<30 d	30 mo
Minhas 2010[26]	Abstract	Observational	Pediatric	CD	16	Biologic agent (did not provide more details)	Top down vs step up	12 mo
Mir 2014[27]	Article	Observational	Pediatric	UC	47	Infliximab	<20 mo	12 mo
Oh 2017[28]	Article	Observational	Adult	CD	670	TNF inhibitors	<2 y	Mean follow-up 103 mo
Patel 2018[29]	Abstract	Observational	Adult	CD	122	Vedolizumab	<2 y	12 mo
Schnitzler 2021[30]	Article	Observational	Adult	CD	242	Infliximab	<2 y	24 mo
Seitz 2018[31]	Abstract	Observational	Adult	CD	242	TNF inhibitor (Infliximab or adalimumab)	<2 y	24 mo
Singh 2021[32]	Article	Observational	Pediatric	CD	70	Infliximab	<1 y	24 mo
Zhu 2020[33]	Article	Observational	Adult	CD	154	Infliximab	<18 mo	Mean follow-up 17 mo

Abbreviations: CD, Crohn's disease; RCT, randomized controlled trial; UC, ulcerative colitis.

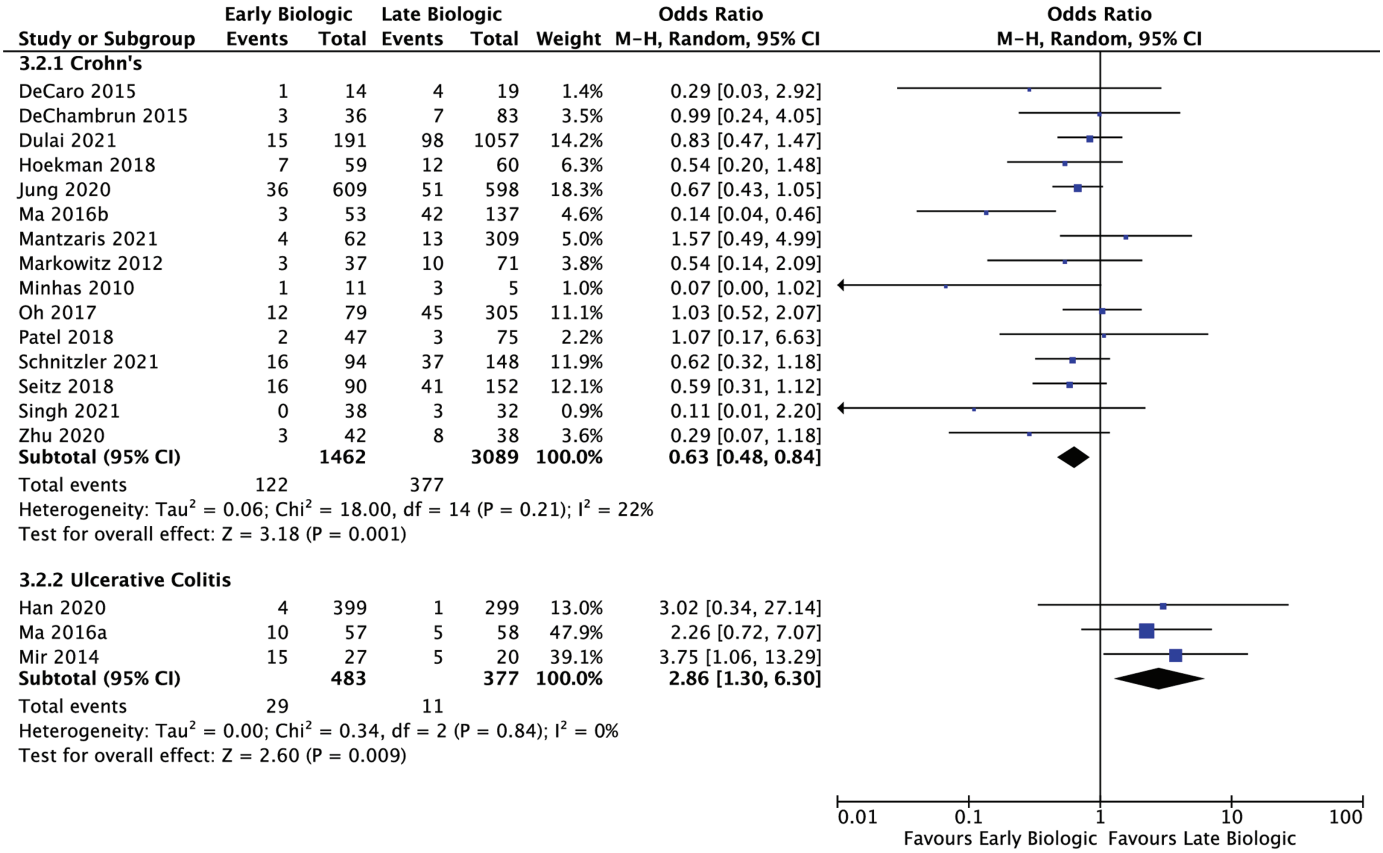

Figure 2. Forest plot demonstrating the risk of inflammatory bowel disease-related surgery among patients with Crohn's disease and ulcerative colitis treated with early vs late biologic therapy. CI, confidence interval; 2M-H, Mantel-Haenszel.

therapy within 2 years of diagnosis resulted in similar findings with an OR of 3.55 (95% CI, 1.19-10.36). Another sensitivity analysis excluding data obtained from abstracts revealed an OR of 0.64 (95% CI, 0.44-0.92) for CD-related surgery. All included studies pertaining to colectomy in UC were manuscripts.

Quality Assessment and Publication Bias

Study quality was assessed using the CLARITY Group risk of bias tools for RCTs and cohort studies. Details of the quality assessment for the included articles can be found in Supplementary Appendix B.

Discussion

While a number of meta-analyses have examined the impact of early biologic therapy on short-term outcomes such as clinical remission,[9,11] long-term outcomes are less studied. To our knowledge, this is the first meta-analysis to specifically explore the impact of early biologic therapy on risk of surgery. This study demonstrates that early biologic therapy is associated with a statistically lower risk of IBD-related surgery in patients with CD but not in patients with UC. In fact, risk of surgery appeared higher in patients with UC who were treated with biologics early in the disease course.

This study's findings are consistent with previous studies that have reported the benefit of early biologic therapy in CD but not in UC.[9,10,34] It is plausible that CD and UC respond differently to biologic therapy. As previously noted, a meta-analysis by Ungaro et al[9] demonstrated that early intervention in CD improves short-term response rates, but not in UC, and the same could be true of long-term response.

While statistically significant, our finding of a higher risk of colectomy in patients UC patients treated with early biologic therapy may be confounded by several factors. First, results are limited by the modest number of studies. Second, when a study involving pediatric patients was removed for subgroup analysis, the result became nonsignificant. Perhaps response to biologics in children may be different than in adults. Nevertheless, it is unlikely that early biologic therapy would hasten the need for colectomy, but it is more likely that this represents a bias by indication, considering that the UC studies were all observational in nature. Few studies controlled for disease severity at baseline; the findings may be confounded by the number of patients presenting with acute severe UC at the time of diagnosis, which is associated with a high rate of colectomy.[35]

Similarly, the lower risk of IBD-related surgery in patients with CD must also be viewed in light of the preponderance of observational studies included. When observational studies were excluded from the analysis, the result became non–statistically significant. However, as only 2 RCTs met the inclusion criteria, the ability to draw firm conclusions is limited. The inclusion of observational studies also raises the possibility of confounders related to disease severity, duration, management, and other unmeasured factors. It is not known how long patients were symptomatic before they received a diagnosis of IBD. Diagnostic delay is more common in IBD,[36] more so in CD than in UC, and would attenuate the benefit of early biologic treatment. Studies in this meta-analysis either

involved treatment with tumor necrosis factor inhibitors or vedolizumab, so the findings may not be generalizable to other drugs such as anti-interleukins and small molecules. Also, it was not always clear if biologics were used in combination with other medications, if doses were optimized, and if there were interruptions or delays in their administration. Last, a variety of definitions of early biologic therapy were used in studies. Most authors defined early biologic therapy as within 2 years of diagnosis of IBD. However, in studies in which top-down and step-up strategies were compared, it is not known exactly when biologics were started for each patient.

A broad search strategy was used in this study. During the screening process, we noted that few studies reported rates of mortality, permanent stoma, and short bowel syndrome. These are long-term outcomes identified by the SPIRIT consensus, and this information would be of interest and value to clinicians and patients. Future research should consider reporting of these rare but important outcomes.

Conclusions

This systematic review and meta-analysis provides insight into the relationship between early biologic therapy in IBD and need for surgery. Early intervention in UC was not associated with reduced risk of colectomy, potentially related to confounding by indication but a finding that may also reflect the limited data supporting increased efficacy in earlier disease in UC patients. In contrast, earlier use of biologics in CD patients is associated with lower risk of surgery, highlighting the potential of early intervention strategies to modify the disease course. Interpretation of these findings should take into account the modest sample size and preponderance of observational studies.

Supplementary Data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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Conflicts of Interest

N.N. has received honoraria for serving on the speakers bureau or advisory board from Janssen, AbbVie, Takeda, Pfizer, Organon, Sandoz, Novartis, Mylan, Fresenius Kabi, Innomar Strategies, Iterative Health, Amgen, and Ferring. J.-F.C. has received research grants from AbbVie, Janssen Pharmaceuticals, Takeda, and Bristol Myers Squibb; has received payment for lectures from AbbVie and Takeda; has received consulting fees from AbbVie, Amgen, AnaptysBio, Allergan, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Celgene Corporation, Celltrion, Eli Lilly, Ferring Pharmaceuticals, Galmed Research, Glaxo Smith Kline, Genentech (Roche), Janssen Pharmaceuticals, Kaleido Biosciences, Immunic, Iterative Scopes, Merck, Landos, Microba Life Science, Novartis, Otsuka Pharmaceutical, Pfizer, Protagonist Therapeutics, Sanofi, Takeda, TiGenix, and Vifor; and holds stock options in Intestinal Biotech Development. R.C.U. has served as a consultant for or received speaker fees from AbbVie, Bristol Myers Squibb, Janssen, Lilly, Pfizer, and Takeda; and received research support from AbbVie, Boehringer Ingelheim, Lilly, and Pfizer.

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