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Abbreviations: Crohn's disease: CD; ulcerative colitis: UC; inflammatory bowel disease: HBI: Harvey-Bradshaw index; CRP: C-reactive protein; PSC: primary sclerosing cholangitis.

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ABSTRACT

Introduction: It is unclear whether vedolizumab therapy can be discontinued in patients with inflammatory bowel disease (IBD) after achieving steroid-free clinical remission.

Aim: To assess the risk of relapse after vedolizumab therapy was discontinued.

Patients and Methods: Retrospective observational study, collecting data from 21 tertiary centres affiliated with the GETAID from January 2017 to April 2019. Consecutive patients with IBD who were in steroid-free clinical remission for at least three months and were treated with vedolizumab for at least six months were included at the time of vedolizumab discontinuation.

Results: Ninety-five patients (58 with Crohn's disease) discontinued vedolizumab after a median duration of therapy of 17.5 [10.6-25.4] months. After a median follow-up period of 11.2 (5.8-17.7) months, 61 (64%) patients experienced disease relapse. The probabilities of relapse-free survival were 83%, 59% and 36% at 6, 12 and 18 months, respectively. According to the multivariate analysis, a CRP level less than 5 mg/L at vedolizumab discontinuation (HR=0.56, 95% CI [0.33-0.95], p=0.03) and discontinuation due to patients' elective choice (HR=0.41, 95% CI [0.21-0.80], p=0.009) were significantly associated with a lower risk of relapse. Re-treatment with vedolizumab was noted in 24 patients and provided steroid-free clinical remission in 71% and 62.5% at week 14 and after a median follow-up of 11.0 [5.4-13.3] months, respectively, without any infusion reactions.

Conclusion: In this retrospective study, two-thirds of patients with IBD treated with vedolizumab experienced relapse within the first year after vedolizumab discontinuation. Re-treatment with vedolizumab was effective in two-thirds of patients.

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Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic and disabling diseases characterized by a sequence of flares and remission[1,2]. The advent of biological agents has changed the way we treat patients with IBD, resulting in dramatic improvements in the goals of treatment and the benefits to patients[3,4]. However, once patients achieve stable steroid-free clinical remission, there is no clear recommendation regarding treatment discontinuation[5]. Cessation of biological agents may be considered due to long-term safety issues, economic burden and the desire of patients to discontinue medication. However, concerns about the discontinuation of biological agents rely on the risk of relapse, impairment of previous efficacy after the drug has been restarted and adverse events at re-treatment.

In a prospective multicentre cohort study, Louis et al. provided the first experience of infliximab discontinuation in patients with CD who were in prolonged remission longer than 6 months[6]. After one year, the rate of relapse was 44%. Recently, a large retrospective study that included more than 1000 patients showed a yearly risk of relapse after adalimumab and infliximab discontinuation of 18% per patient-year[7]. In this study, predictors of relapse were younger age, adalimumab vs. infliximab, discontinuation due to safety issues and/or patients' elective choice and the absence of a maintenance immunomodulator after anti-TNF discontinuation.

Vedolizumab is an anti-α4β7 integrin monoclonal antibody that inhibits the recruitment of inflammatory cells in the intestine[8]. The efficacy and safety of vedolizumab have been demonstrated in patients with UC and CD in clinical trials and observational studies[9–14]. There are currently no data on vedolizumab discontinuation in patients in clinical remission.

The aim of the present study was to determine the risk of relapse after vedolizumab discontinuation and the effectiveness of re-treatment with vedolizumab.

Patients and Methods

Study population

The present study was an observational, multicentre, retrospective cohort study conducted at 21 French tertiary centres affiliated with the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives (GETAID).

The study population comprised consecutive patients with IBDs, either CD or UC, who had been treated with vedolizumab for at least six months and who discontinued vedolizumab after at least three months of stable steroid-free clinical remission, from January 2017 to April 2019[5–7]. Reasons for vedolizumab discontinuation were either patient's elective choice, pregnancy, safety issues or reimbursement issues. Patients who had been treated with vedolizumab for less than six months, those with evidence of disease activity or oral steroids during the last three months before discontinuation and those who initiated any new IBD treatment after vedolizumab discontinuation were excluded.

The protocol was approved by an ethics committee (CCTIRS N° 15.403). All authors had access to the study data and reviewed and approved the final manuscript.

Data collection

The inclusion date corresponds to the date of the last infusion of vedolizumab. Baseline patient demographic, clinical and endoscopic characteristics were collected from medical records and included age, sex, smoking habits, extraintestinal manifestation, familial history

of IBD, history of medical and surgical treatment of IBD, date of diagnosis, and behaviour of disease according to the Montreal classification.

Disease activity and safety were assessed at various time points: at the first infusion of vedolizumab, at inclusion, every 6 months until 24 months after the discontinuation of vedolizumab and at the end of follow-up. At each time point, clinical activity was assessed using the Harvey Bradshaw index (HBI) for patients with CD and the partial Mayo Clinic score for patients with UC. Biological activity was assessed using haemoglobin, CRP, albuminemia and faecal calprotectin. Endoscopic activity was assessed using the Mayo Clinic endoscopic subscore and ulcerative colitis endoscopic index of severity (UCEIS) for patients with UC. Endoscopic assessment of CD activity was not mandatory and was at the investigator's discretion. Severe adverse events were defined as the occurrence of treatment interruption, hospitalization, disability, persistent damage, colectomy or death.

The concomitant use of 5ASA and/or immunomodulators for IBD at the time of discontinuation of vedolizumab therapy was allowed according to the investigator's decision and was recorded at the time of discontinuation of vedolizumab therapy and thereafter until the end of follow-up.

Patients experiencing relapse were assessed for response and safety at week 14 after vedolizumab was reintroduced or after another IBD treatment was started and at the end of the follow-up period.

Outcome measures

Clinical remission was defined as an HBI < 4 for patients with CD and a partial Mayo Clinic score < 3 for patients with UC with a combined stool frequency and rectal bleeding subscore of 1 or less for UC. Relapse was defined by active disease according to an HBI ≥ 4

and the introduction of any specific systemic IBD treatment, IBD-related hospitalization and/or surgery. The effectiveness and safety of re-treatment with vedolizumab were also assessed.

Mucosal healing was defined as the absence of any ulcer for patients with CD and as a Mayo Clinic endoscopic subscore of 0 or 1 for patients with UC.

Severe adverse events were defined as the occurrence of treatment interruption, hospitalization, disability, persistent damage, colectomy or death.

Statistical analysis

Quantitative data are expressed as the mean and standard deviation (SD) or median [interquartile range], whereas qualitative data are expressed as a number (%). Hazard ratios (HRs) are given with their 95% confidence intervals (CIs). Relapse-free survival was studied using the Kaplan-Meier method. Patients who restarted vedolizumab without any evidence of clinically active disease were censored at the time of vedolizumab reintroduction. To identify predictors of relapse, the survival distributions were studied using the log-rank test for the univariate analysis and then using Cox proportional hazard models for the multivariate analysis. Furthermore, p-values less than 0.10 in the univariate analysis were considered significant and allowed for inclusion in the multivariate analysis, whereas p-values less than 0.05 were considered significant for other analyses. All of the statistical evaluations were performed using SPSS statistical software (SPSS Inc., v23, Chicago, IL, USA).

RESULTS

Characteristics of the study population

Ninety-five patients (24 males; median age: 32.5 [IQR 27.3-42.4] years) from 21 GETAID centres who discontinued vedolizumab therapy from January 2017 to April 2019 were included. The baseline demographic and clinical characteristics are presented in Table 1. Briefly, 58 (61%) patients had CD with a mean HBI of 1.7 ± 1.4 at inclusion, and 37 (39%) had UC with a mean partial Mayo Clinic score of 0.7 ± 1.1 at inclusion. At baseline, mucosal healing was observed in 22/38 (58%) patients with CD and 19/26 (73%) patients with UC.

At baseline, the median duration of vedolizumab therapy was 14.5 [8.2-21.5] months. Patients were treated either every 8 weeks in 68 (72%) patients or every four weeks in 27 (28%). The reasons for vedolizumab discontinuation were pregnancy in 37 (39%), safety issues in 26 (28%), patients' elective choice in 24 (25%) and reimbursement issues in 8 (8%). At baseline, only 7 (7%) patients were treated concomitantly with immunosuppressants and 21 (22%) with aminosalicylates.

Clinical relapse

After a median follow-up of 11.2 (5.8-17.2) months, 61 (64%) patients experienced relapse. The median time to relapse was 13.2 (10.8-15.6) months. The probabilities of relapse-free survival were 83%, 59% and 36% at 6, 12 and 18 months, respectively.

Based on the univariate analysis, a CRP level < 5 mg/L at inclusion, vedolizumab discontinuation as an elective choice, an HBI or a partial Mayo Clinic score at the time of vedolizumab discontinuation ≤ 1, mucosal healing and a leukocyte count < 8000 /mm^3 were associated with a lower risk of relapse, whereas reimbursement issues and steroids at the time of vedolizumab introduction were associated with a higher risk of relapse. No difference was

found between patients with CD and UC in relapse-free survival (p = 0.40, Figure 2). Based on the multivariate analysis, patients with a CRP level < 5 at the time of vedolizumab discontinuation (HR = 0.56, 95% CI [0.33-0.95], p = 0.03) and those who discontinued vedolizumab as an elective choice (HR = 0.41, 95% CI [0.21-0.80], p = 0.009) were less likely to experience relapse (Figure 2).

Outcome of vedolizumab re-treatment

Among the 61 patients who experienced a relapse, vedolizumab was re-introduced in 24 (39%). Re-treatment consisted of a standard induction regimen with three 300-mg infusions at weeks 0, 2 and 6 in all cases. The rate of steroid-free clinical remission after vedolizumab re-treatment at week 14 was 71%. After a median follow-up of 11.0 [5.4-13.3] months after vedolizumab re-treatment, 15 (62.5%) patients were still in clinical remission on vedolizumab therapy. No infusion reaction was noted after vedolizumab re-treatment during the induction phase and thereafter.

Among patients who relapsed, 37 (60.7%) were not re-treated with vedolizumab. Rescue therapy included ustekinumab (n=15), surgery (n=7), prolonged steroids (n=7), additional anti-TNF (n=3), 5-ASA (n=3) cyclophosphamide (n=1) and tofacitinib (n=1). Prolonged steroid therapy was chosen in seven patients due to the patients' choice (n=3), pregnancy (n=2), multiple sclerosis (n=1) and concomitant breast cancer (n=1).

DISCUSSION

Whether a drug should be continued when clinical remission has been achieved is highly controversial. Indeed, the likelihood of relapse after discontinuing treatment may be as high as 30-40% in patients treated with anti-TNF, and the re-introduction of the same

treatment is often but not always as efficient as before[5]. On the other hand, socio-economic issues, the cumulative risk of serious adverse events over time and other circumstances, including pregnancy and the will of patients, promote discontinuation[15]. Herein, we provide the first data on vedolizumab discontinuation in patients who achieved steroid-free clinical remission. Clinical relapse occurred in 64% of patients after 18 months of discontinuation. Clinical relapse was even more frequent when discontinuation occurred in patients with a CRP level > 5 mg/L and when discontinuation occurred as an incidental event rather than as an elective choice. In the case of vedolizumab reintroduction, steroid-free clinical remission was achieved in two-thirds of patients at week 14 and during the 11-month follow-up period.

Evidence from clinical trials and observational studies has identified differences in the modes of action between vedolizumab and anti-TNF agents[14,16–18]. Although vedolizumab has been used frequently after anti-TNF failure, it has often been characterized by a slow action during the induction phase and has stable effectiveness over time. Cycling therapy has been proposed in IBD to prevent incidental adverse events[2,15]. In patients who discontinued anti-TNF, mostly infliximab, after a period of remission, the risk of relapse was 40% at 12 months for patients with CD and 28% for those with UC, according to a meta-analysis of 27 studies[19]. In the present series, we provide the first data of patients discontinuing vedolizumab after achieving steroid-free clinical remission. After a follow-up period of 11.2 months, the risk of relapse was 59% at 12 months. A direct comparison between anti-TNF and vedolizumab after treatment discontinuation is questionable. Indeed, most of the patients in the present series had been previously treated with immunomodulators (87% of the patients) and anti-TNF (91%), which was not the case for data from patients discontinuing anti-TNF. Further prospective studies should assess the risk of relapse in patients with vedolizumab to improve decision making when discontinuation is discussed with patients.

Little is known about the optimal duration of therapy with a biological agent for patients with IBD before discontinuation may be considered. In patients discontinuing thiopurine, the risk of relapse was reduced when patients were treated for more than four years[20]. Indeed, although patients are deemed to relapse due to genetic predisposition, environmental factors, the gut microbiome and underlying impairments of intestinal immunity, a longer duration of remission may be associated with a more profound restoration of intestinal immunity that could be beneficial to better maintain remission after discontinuing a drug[21,22]. Evidence that a longer duration of anti-TNF therapy until its discontinuation favours a lower risk of relapse has not yet been demonstrated. This concept has been supported by early experience with infliximab with a poorer long-term outcome in patients treated with only three infliximab induction infusions[23]. The majority of the study assessing the risk of relapse after anti-TNF discontinuation included patients treated for at least 2 years with anti-TNF. In a recent multicentre observational study that included 1,055 patients with IBD, Casanova et al showed that a top-down strategy with early discontinuation of anti-TNF was associated with a lower risk of relapse than elective discontinuation or discontinuation for safety issues[7]. In our study, elective discontinuation (vs. safety issues, pregnancy or reimbursement issues) was associated with a lower risk of relapse but not a longer duration of vedolizumab therapy. The fact that very few patients had taken concomitant immunomodulators may be an explanation, but the majority of patients had been treated previously with at least one immunomodulator and had experience with failure or intolerance to the drug. It is not also conceivable that elective discontinuation reflects a more deep remission compared with unscheduled events such as pregnancy, safety issues or reimbursement issues.

The combination of steroid-free clinical remission and mucosal healing is now recommended in clinical trials and in daily practice in a treat-to-target manner[4,24]. Indeed, the

achievement of mucosal healing was associated with a reduced risk of relapse, fewer hospitalizations and fewer surgeries in mostly retrospective studies[1,2]. In the CALM study, Colombel et al demonstrated with a prospective trial the benefits of targeting mucosal healing assessed with faecal calprotectin compared with a symptom-based strategy[24]. In the present study, patients with mucosal healing had a lower probability of relapse after vedolizumab discontinuation according to the univariate analysis (22% vs 39% at 12 months; OR = 0.57 [0.25-0.89], p = 0.002). The presence of mucosal healing is a major issue when considering the discontinuation of a biologic, even if its predictive value was not confirmed in our multivariate, probably due to a lack of endoscopic assessment before discontinuation in one-third of patients (31 out of 95). However, we showed evidence that residual systemic inflammation characterized by a CRL level > 5 mg/L at the time of discontinuation was a predictor of relapse according to the multivariate analysis.

In the present study, 24 out of 61 patients who experienced clinical relapse were retreated with vedolizumab with a 14-week steroid-free clinical remission rate of 71%. These results are in line with similar experiences with thiopurine and anti-TNF. Indeed, two studies have reported similarly successful re-introduction of thiopurines after discontinuation in 85% of patients with IBD[25,26]. A recent meta-analysis reported that re-treatment with anti-TNF after discontinuation induced clinical remission in 80% of patients with IBD[19]. A high proportion of patients (60.7%) were not re-treated with vedolizumab after relapse. Some were referred for surgery (n = 7) because of bowel complications at the time of relapse, and seven decided to remain on steroids (n = 7) for various reasons (own decision, contraindication to any anti-TNF or patient's decision). Some were treated with other biological agents, mostly ustekinumab, for reasons we could only extrapolate, safety issues leading to discontinuation, benefits of 8-12 weekly subcutaneous injections compared to 4-8 weekly intravenous infusions and the lack of data considering vedolizumab re-introduction.

We acknowledge several limitations of this study, including its retrospective design, the lack of a mucosal healing assessment or faecal calprotectin measurement, the absence of therapeutic drug monitoring at the time of vedolizumab discontinuation and the absence of a detailed follow-up protocol. However, this study also has several strengths. First, we provide original data in the field of discontinuing vedolizumab after achieving steroid-free clinical remission. Second, the sample size for each patient population is considered clinically relevant. Third, patients were recruited in GETAID centres allowing high experience and compliance to ECCO guidelines for the management of patients with IBD.

In conclusion, two-thirds of patients experienced clinical relapse after vedolizumab discontinuation at the time of steroid-free clinical remission. Further studies are warranted to confirm our data and determine whether longer durations of vedolizumab therapy and deep remission could afford the opportunity for this strategy. Overall, our findings are not in favour of vedolizumab discontinuation with the exception of indisputable reasons such as pregnancy or safety issues.

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FIGURE LEGENDS

Figure 1: Kaplan–Meier relapse-free survival curve after vedolizumab therapy was discontinued in 95 patients with inflammatory bowel disease with steroid-free clinical remission for at least three months and vedolizumab therapy for at least six months

Figure 2: Kaplan–Meier relapse-free survival curve after vedolizumab therapy was discontinued according to the CRP level at the time of discontinuation (Panel A) and reason for discontinuation (Panel B)

TABLE LEGENDS

Table 1: Demographics, disease characteristics and medication histories of 95 patients with inflammatory bowel disease with steroid-free clinical remission for at least three months and vedolizumab therapy for at least six months, at the time of vedolizumab discontinuation

Table 2: The predictors associated with clinical relapse after discontinuation of vedolizumab in 95 patients with inflammatory bowel disease in steroid-free clinical remission for at least three months, treated with vedolizumab therapy for at least six months.

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Table 1: Demographics, disease characteristics and medication histories of 95 patients with inflammatory bowel disease with steroid-free clinical remission for at least three months and vedolizumab therapy for at least six months, at the time of vedolizumab discontinuation

Characteristic	**Crohn's disease (n = 58)**	**Ulcerative colitis (n = 37)**
Median age at IBD diagnosis, years	32.5 [27.3-42.4]	
Male gender, no (%)	24 (25%)	
Body mass index, kg/m²	22.5 ± 4.4	
Median duration of IBD, years	12.3 [6.7-17.3]	7.7 [5.3-12.9]
Age at diagnosis – Montreal classification **A1** **A2** **A3**	 14 (15%) 71 (75%) 10 (10%)	
Median duration of vedolizumab therapy, years	14.5 [8.2-21.5]	
Current smoker, no (%)	19 (33%)	3 (8%)
Clinical disease activity scoring at the time of the last vedolizumab infusion	Harvey-Bradshaw Index 1.7 ± 1.4	Mayo Clinic score 1.3 ± 1.7 Partial Mayo Clinic score

		0.7 ± 1.1
Disease location – Montreal classification	L1 : 14 (24%) L2 : 16 (28%) L3 : 26 (45%) L4 : 5 (9%)	E1 : 3 (8%) E2 : 11 (30%) E3 : 23 (62%)
Disease phenotype – Montreal classification	B1: 33 (57%) B2: 16 (28%) B3: 9 (15%) p: 21 (22%)	- - - -
History of intestinal resection, no (%)	21 (36%)	2 (5%)
History of IBD treatment, no (%)		
aminosalicylates	62 (83%)	
steroids	73 (97%)	
thiopurine	78 (82%)	
methotrexate	29 (31%)	
any immunomodulator	83 (87%)	
anti-TNF therapy	68 (91%)	
≥ 2 anti-TNF	57 (60%)	
Ustekinumab	3 (3.2%)	
Reason for vedolizumab discontinuation		

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Patient's elective choice	24 (25%)	
Pregnancy	37 (39%)	
Safety issue	26 (28%)	
Reimbursement issue	8 (8%)	
Biologic variables at the time of the last vedolizumab infusion		
serum albumin, g/L	37.1 ± 5.3	
leukocytes count, /mm3	7793 ± 2227	
haemoglobin, g/dL	13.3 ± 1.4	
Platelets count, 10^9/L	297 ± 88	
CRP level, mg/L	5.7 ± 9.2	
Concomitant medications		
Aminosalicylates	1 (2%)	20 (54%)
Immunosuppressants	4 (7%)	3 (8%)
Mucosal healing	22/38 (58%)	19/26 (73%)

CRP: high sensitivity C-reactive protein; IBD: inflammatory bowel disease.

Variables are presented as n (%), mean ± standard deviation or median (interquartile range).

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Table 2: The predictors associated with clinical relapse after discontinuation of vedolizumab in 95 patients with inflammatory bowel disease in steroid-free clinical remission for at least three months, treated with vedolizumab therapy for at least six months.

Risk factors	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
CRP level at discontinuation < 5 mg/L	0.53 [0.31-0.90]	0.02	0.56 [0.33-0.95]	0.03
Patient's elective decision	0.40 [0.20-0.76]	0.006	0.41 [0.21-0.80]	0.009
HBI or partial Mayo Clinic score ≤ 1	0.65 [0.39-1.08]	0.09	-	NS
Mucosal healing	0.47 [0.25-0.89]	0.02	-	NS
Leukocytes count > 8000 /mm^3	0.47 [0.25-0.90]	0.02	-	NS
Concomitant steroids at the time of vedolizumab introduction	2.08 [1.22-3.57]	0.007	-	NS
Reimbursement issue	4.35 [2.04-9.09]	<0.001	-	NS
Crohn's disease	1.26 (0.74-2.14)	0.40	-	NS

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CRP: high sensitivity C-reactive protein; HBI: Harvey-Bradshaw Index; HR: hazard ratio; CI: confidence interval. Hazard ratio (HR) with 95% confidence interval (CI) was estimated using Cox models

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Figure 1

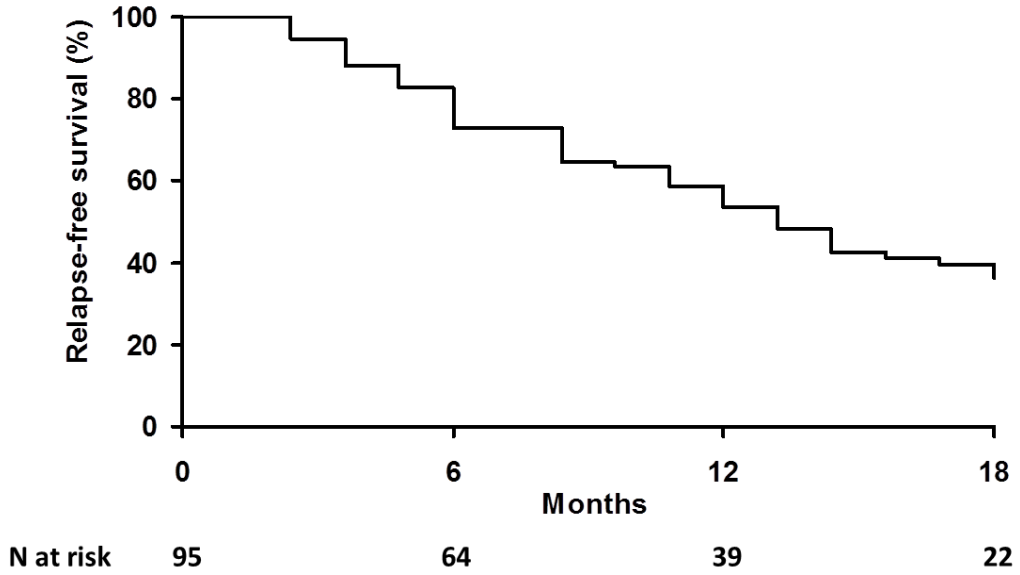

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Figure 2A

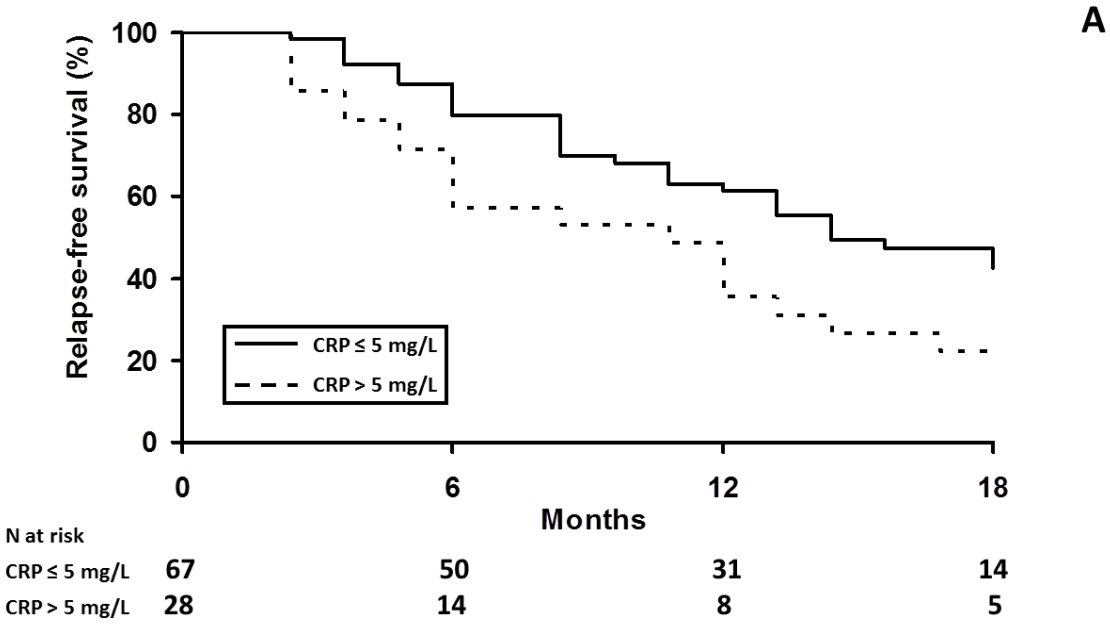

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FIgure 2B

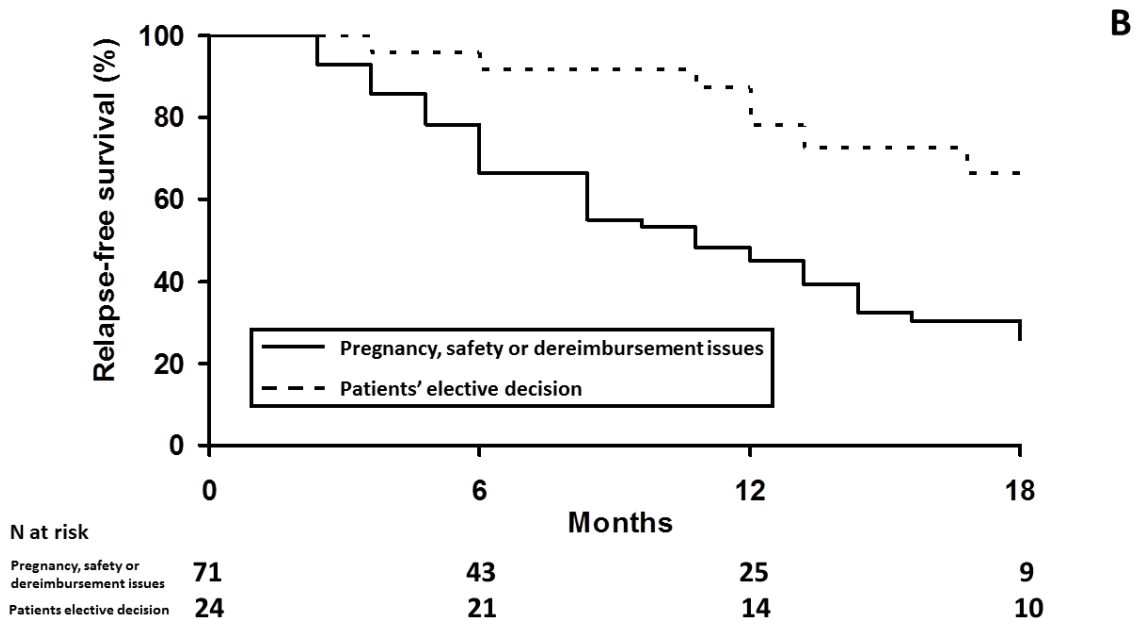

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Figure 2C