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EFFECTIVENESS AND SAFETY OF USTEKINUMAB INTENSIFICATION AT 90 MG EVERY FOUR WEEKS IN CROHN'S DISEASE: A MULTICENTER STUDY

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Abbreviations: CD, Crohn's disease; W, weeks; AEs, adverse events.

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Author Contribution:

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- Analysis and interpretation of data: MF, LPB, MD, XT

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Abstract

Introduction: The approved maintenance regimens for ustekinumab in Crohn's disease (CD) are 90 mg every 8 or 12 weeks. Some patients will partially respond to ustekinumab or will experience a secondary loss of response. It remains poorly known if these patients may benefit from shortening the interval between injections.

Methods: All patients with active CD, as defined by Harvey-Bradshaw score ≥ 4 and one objective sign of inflammation (CRP > 5 mg/L and/or fecal calprotectin > 250 µg/g and/or radiologic and/or endoscopic evidence of disease activity) who required ustekinumab dose escalation to 90mg every 4 weeks for loss of response or incomplete response to ustekinumab 90mg every 8 weeks were included in this retrospective multicenter cohort study.

Results: One hundred patients, with a median age of 35 years (Interquartile Range (IQR), 28 – 49) and median disease duration of 12 (7 – 20) years were included. Dose intensification was performed after a median of 5.0 (2.8 - 9.0) months of ustekinumab treatment and was associated with corticosteroids and immunosuppressants in respectively 29% and 27% of cases. Short-term clinical response and clinical remission were observed in respectively 61% and 31% after a median of 2.4 (1.3 - 3.0) months. After a median follow-up of 8.2 (5.6-12.4) months, 61% of patients were still treated with ustekinumab, and 26% in steroid-free clinical remission. Among the 39 patients with colonoscopy during follow-up, 14 achieved endoscopic remission (no ulcers). At the end of follow-up, 27% of patients were hospitalized, and 19% underwent intestinal resection surgery. Adverse events were reported in 12% of patients, including five serious adverse events.

Conclusion: In this multicenter study, two-thirds of patients recaptured response following treatment intensification with ustekinumab 90 mg every 4 weeks.

Key words: Crohn's disease, ustekinumab, intensification

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Introduction

Ustekinumab (Janssen Biotech, Inc.), a fully human IgG1 monoclonal antibody targeting the IL-12/IL-23 shared p40 subunit, was recently approved for the treatment of Crohn's disease (CD). The UNITI program clearly demonstrated the efficacy of ustekinumab to induce and maintain clinical remission in moderate-to-severe CD, with continuous response for up to 4 years (1). Patients receive a 6 mg/kg intravenous induction therapy, a 90 mg sub-cutaneous administration at 8 weeks and then a ustekinumab 90 mg every 12 weeks [q12w], or ustekinumab 90 mg every 8 weeks [q8w], for maintenance therapy, according to physician's judgement. As observed with anti-Tumor Necrosis Factors (TNFs), about 20 - 35% of patients experienced loss of response to ustekinumab in clinical trials (1-4). In patients treated with anti-TNFs, a dose-response relationship has been demonstrated. An increase in dose or dosing frequency is recommended in patients with loss of response (5,6). In the UNITI program, 20% of patients with loss of response during 90 mg q12W regimen recaptured response after escalation to 90 mg q8W (1).

Real-world effectiveness data provide valuable evidence to support the efficacy observed in randomized controlled trial. Real-world studies include patients representative of the real-world CD population and allow for a variable treatment regimen and optimisation (7). Some real-word studies reported the experience with ustekinumab intensification from 90 mg q8W to q4W and even to q3W (2-4, 8). Recently, the University of Chicago group reported the effectiveness of ustekinumab dose interval shortening from 90 mg q8W to q4W in 51 patients with Harvey-Bradshaw score > 4 (9). They showed that dose escalation resulted in improvement in clinical indices of disease activity.

We aimed to evaluate the effectiveness and safety of intensification from 90 mg q8w to q4W in patients with incomplete or loss of response to ustekinumab in CD in a retrospective multicenter study.

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Methods

Study population

All consecutive adult patients between October 2015 and December 2018 with active CD, as defined by Harvey-Bradshaw score ≥ 4 and at least one objective sign of inflammation (CRP ≥ 5 mg/L and/or fecal calprotectin ≥ 250 µg/g and/or radiologic and/or endoscopic evidence of disease activity) who required ustekinumab dose escalation to 90mg q4W for loss of response (as defined by a loss of response after initial improvement of symptoms, according to physician judgement) or incomplete response (lack of improvement of clinical symptoms) to ustekinumab 90mg q8W in eleven French university hospitals were included in a retrospective multicenter cohort study.

Data collection

The following data were recorded at baseline for each patient: gender, birth date, age at diagnosis, CD phenotype and behavior according to Montreal classification, previous and concomitant medications, smoking status, previous intestinal resection, Harvey-Bradshaw score, CRP, ustekinumab induction regimen, and indication of intensification (loss of response or incomplete response, and luminal and/or perianal CD). Harvey-Bradshaw score, CRP value, adverse events (AEs), concomitant medications, intervals of ustekinumab administration, ustekinumab discontinuation, CD-related hospitalization and intestinal resection were collected at the first clinic visit after dose escalation, at 6 months, at the last visit under ustekinumab, and at the date of the last follow-up. Endoscopic variables were also collected if available. This cohort was declared to the CNIL (Commission nationale de l'informatique et des libertés, declaration n°T196) as national recommendations.

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Outcome measures

Short-term clinical response response was defined by a decrease of Harvey-Bradshaw score ≥ 3 after dose intensification compared to baseline, with a decision to continue the same dose, and was evaluated at the first clinic visit after therapeutic escalation. Clinical remission was defined as a Harvey-Bradshaw score < 4. Endoscopic remission was defined by the absence of ulceration (exclusion of aphtae) and serious AE as an AE-related hospitalization.

Statistical analysis

Quantitative variables were described as medians and interquartile ranges (IQR). Categorical variables were presented as counts and percentages of the cohort. Change from baseline in quantitative variables was evaluated with a paired Student test or a Wilcoxon signed-rank test. The distribution of the delay until ustekinumab withdrawal and surgery were estimated with the non-parametric method of Kaplan Meier. Risk factors for short-term response were assessed using a univariate logistic regression model with odds ratio and a 95% confidence interval; firth penalized likelihood was applied if necessary. Variables with a p <10% value were included in a multivariate logistic regression model. Statistical analyses were performed with SAS® software version 9.4 (SAS Institute, Cary, NC) and survival curves were built using RStudio software Version 1.0.143 – © 2009-2016 RStudio (R.3.4.0 software).

Results

Characteristics of patients

A total of one hundred patients were included. Demographic and baseline disease characteristics at ustekinumab intensification are listed in **Table 1**. Median duration of follow-up was 8.2 (Interquartile Range (IQR), 5.6 – 12.4) months. Fifty-two (52%) of the patients

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were female, the median age was 34.9 years (IQR, 28.1 – 46.3) and the median duration of CD was 11.6 years (IQR, 7.3 – 20.1). According to Montreal classification, one third (n=31, 31%) had ileal location, one third colonic (n=29, 29%) and 40 (40%) had ileo-colonic disease. Most of patients had complicated behaviors (B2—stricturing, 28 (28%) or B3—penetrating, 37 (37%)), 47 (47%) had perianal CD and 34 (34%) extra-intestinal manifestations. All but one were previously exposed to anti-TNF and 55 (55%) to vedolizumab. Half of patients had previous intestinal resection. The median duration of ustekinumab therapy before optimisation was 5.0 (IQR, 2.8 - 9.0) months. At the time of therapeutic escalation, respectively 29 (29%) and 27 (27%) received co-treatment with steroids or immunosuppressants. Incomplete response (74, 74%) and luminal disease (77, 77%) were the main indications for ustekinumab intensification.

Short-term response and remission

After a median of 2.4 (IQR, 1.3 –3 .0) months following ustekinumab intensification, 61 patients (61%) experienced a clinical response. In addition, 31 (31%) and 27 (27%) of the patients achieved clinical remission and steroid-free clinical remission, respectively (**Figure 1**). The median value of Harvey-Bradshaw index significantly dropped from 8.0 at baseline (IQR, 5.0 – 11.2) to 5.0 (IQR, 3.0–7.0) (p = 0.001). Ten patients of 29 (35.5%) receiving steroids at inclusion were weaned before the first visit after ustekinumab escalation. In general, systemic steroid was tapered according to ECCO guidelines. The median CRP level decreased from 12.3 mg/L (IQR, 5.0 – 30.5) to 9.6 mg/dL (IQR, 3.2–18.0) (p =0.2). Among the baseline factors evaluated in the univariate analysis (**Table 2**), loss of response to ustekinumab (vs. incomplete response) was associated with short-term clinical response (odds Ratio (OR), 3.03, CI95% [1.03 ; 8.91], p=0.044) as well as duration of ustekinumab therapy before dose intensification (OR, 1.11, CI95% [1.00 ; 1.22], p=0.051). However, no

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factors were independently associated with short-term clinical response in multivariate analysis probabily due to multicollinearity.

Long-term outcomes

Follow-up information at 6 months was available for 69 of 100 patients. Of those, 34 (49%) were in steroid-free clinical remission. The median Harvey-Bradshaw score was 4 (2.5 – 6.0) and the median CRP level was 8.5 (2.25 – 17.3) mg/L. Among the 35 non-responders to ustekinumab 90 mg q4W in the short term, 6 (17.1%) achieved clinical remission at 6 months.

The median Harvey-Bradshaw score of the 65 short-term responders decreased from 7 (IQR, 5 - 10) at baseline to 3.5 (IQR, 2 - 5) at month 6 ($P < 0.001$), and the CRP level dropped from 9.3 mg/L (IQR, 3.2 – 21.1) at baseline to 4 mg/L (IQR, 1.2 – 10.2) at month 6 ($P = 0.02$).

After a median follow-up of 8.2 (5.6 – 12.4) months, 61 (61%) were still treated with ustekinumab. The cumulative probabilities of ustekinumab persistence were 81% at 6 months and 51% at 12 months (**Figure 2**). At the end of follow-up, 26 (26%) patients were in steroid-free clinical remission. Reasons for ustekinumab withdrawal were the absence of response to optimisation, loss of response and pregnancy in 23 (38%), 13 (21%) and 3 (5%) patients, respectively. Nine patients could de-escalate ustekinumab, seven to 90 mg q8W and two to 90 mg q6W after a median time of 7.4 (IQR, 5.5 – 13.2) months since optimisation. Thirty-nine patients had colonoscopy after a median interval of 5.9 (2.4 – 7.8) months after ustekinumab intensification. Endoscopic remission was observed in 14 patients (35.9%).

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Sixteen (16%) patients had ustekinumab intensification for perianal disease and 7 (7%) for both perianal and luminal CD. Among them, 14/23 (61%) experienced an immediate response according to physician judgment. Closure of perianal fistula was observed in 5/23 (22%) patients at last news. Conversely, four patients experienced perianal CD worsening needing perianal surgery during follow-up.

Surgery and hospitalization

After a median follow-up of 8.2 (IQR, 5.6–12.5) months, 27 (27%) patients needed CD-related hospitalization. Major abdominal surgery was required for 19 (19%) patients. Of these, 11 did not respond to ustekinumab intensification, whereas eight had a secondary loss of response to ustekinumab 90 mg q4W. Cumulative risks of hospitalization and surgery are highlighted in the **Supplementary Figures 1 and 2**.

Adverse event

During the follow-up period, there were no death or malignancy. Thirteen adverse events were reported in 12 patients (12%), including eight infections (**Table 3**). Five patients experienced severe adverse events including two pyelonephritis, one nasopharyngitis with epiglottitis, one pneumonitis, and one infectious colitis. None of these AEs had led to definitive ustekinumab withdrawal.

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Discussion

This national retrospective multicenter observational cohort study assessed the effectiveness and safety of ustekinumab dose escalation in CD. Two-thirds of patients recaptured response and about half of them had steroid-free clinical remission at 6 months. Importantly, most patients were candidates for surgery or inclusion in a clinical trial, as many had a previous exposure to anti-TNFs therapy and vedolizumab, with active disease as indicated by objective signs of inflammation despite ustekinumab therapy. In this refractory population, 20% of patient needed major abdominal surgery at the end of follow-up.

Secondary loss of response is frequent in patients treated by ustekinumab, ranging from 20% of patients in IM-UNITI to 35% in real world observational studies (1-4). To date, no prospective study has evaluated the management of loss of response during ustekinumab therapy. Randomized prospective studies evaluating the efficacy and safety of ustekinumab therapy in CD have not specifically evaluated the response to ustekinumab dose escalation. In the IM-UNITI trial, among 29 patients randomized to the ustekinumab 90mg q12w group who lose response with therapeutic escalation to 90mg q8w, 41% achieved clinical remission and 55% clinical response (1). Some real-world retrospective studies reported optimisation to ustekinumab 90 mg q4W. Dose escalation (90 mg q4W or q6W) effectively recaptured clinical response in 9/17 (53%) patients in the Canadian study of Ma and

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colleagues (4). The GETAID reported the long-term outcome in 88 patients treated by 10 various regimens of ustekinumab (2). Thirty-two patients required a dose intensification of ustekinumab during follow-up, among them 12 patients received 90 mg q4W. This strategy was effective in 18 (56%) including a dose increase in two patients, interval reduction in seven, and both in nine. In a Dutch study including 221 patients treated with ustekinumab, 11 patients were on a q4w interval and 70% were in corticosteroid-free clinical remission (10). Another Canadian cohort recruited 62 patients with CD treated with 90 mg of ustekinumab subcutaneously at weeks 0, 1, and 2 during induction and 90 mg every 4 (n=48) or 8 (n=14) weeks during maintenance (3). Clinical and endoscopic outcomes were not different between the two maintenance regimens. Some studies reported outcomes after a combination of intravenous reinduction with a dose escalation strategy, with an effectiveness in about half of patients (3,10). More recently, the Chicago group had reported the effectiveness of ustekinumab dose escalation to q4W in 110 patients with CD followed with a median time of 9 months (9). Clinical response as defined by Harvey-Bradshaw score improvement was observed in 42% of the 78 patients with available data. During the follow-up period, clinical remission following interval shortening was achieved in 28% of the 51 patients with Harvey-Bradshaw score > 4 before interval shortening. In this single-center center only a limited subset (n=11) of patients had endoscopic evaluation following dose escalation. In the study reported here, we included only patients with clinically active CD, and at least one objective sign of inflammation, with a standardized follow-up in 11 different centers. Our results are in line with those from Chicago, reporting clinical remission in one third of patients. In our cohort, endoscopic data were available in 39 patients and endoscopic remission was observed in 14 of them.

Currently, no data exists to identify which patients are more likely to benefit from dose escalation, and management of attenuated response is based on clinical judgment. As for anti-TNF therapy, therapeutic drug monitoring with incorporation of pharmacokinetic data in developing a management algorithm for primary and secondary failure will likely become a

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mainstay of therapy, identifying appropriate patients needing a rescue dose (11-13). In the UNITI program, serum concentrations of ustekinumab were proportional to dose, and associated with clinical efficacy (1,14). Also limited real-life data suggested better outcomes with higher exposure. Verstockt et al. demonstrated that a clear exposure-response relationship exist, both during induction as during maintenance therapy, with different thresholds depending on the targeted outcome (15). Ustekinumab serum concentrations were higher in endoscopic responders at every time point. At week 8, ustekinumab through level lower than 5.0 µg/mL at W8 almost ruled out endoscopic response later. During maintenance, thresholds of 2.3 µg/mL at W16 and 1.9 µg/m at W24 were identified as the minimal exposure needed to achieve endoscopic response after 6 months. In a retrospective study, Battat et al. reported that maintenance trough concentrations of ustekinumab above 4.5 µg/mL were associated with biomarker reduction and endoscopic response (16). However, 42 out of their 56 included patients had been dose-escalated to q4w maintenance in order to achieve these high maintenance levels. Three ongoing randomized clinical trial (Rescue trial, EudraCT number 2018-004269-14, The Power trial NCT03782376 and STARDUST trial, NCT03107793) will address this issue and assess whether ustekinumab dose-optimisation may improve endoscopic remission rates by rescuing patients who quickly lost response after sub-cutaneous maintenance and if a treat to target approach on endoscopic remission and ustekinumab trough level may improve long-term outcomes.

Regarding safety, no death was observed. Five patients required hospitalization for infectious AEs. The interpretation of these results is limited by the relatively small sample and short follow-up period of the cohort. The ongoing I-CARE study, European prospective cohort study assessing long-term safety of inflammatory bowel diseases therapies (NCT02377258), should answer this question.

Our study has some limitations. The pharmacokinetics of ustekinumab could not be assessed, since this is not routinely performed in France. However, we used objective

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measures of effectiveness as steroid-free clinical remission and mucosal healing. Strengths of the study include its multicenter national study design including all consecutive CD patients treated with ustekinumab 90mg q4W in 11 academic centers. Only patients with objective signs of inflammation and with a standardized follow-up, including Harvey-Bradshaw index and CRP levels measurements, were included.

In conclusion, ustekinumab 90 mg q4W was effective to recapture response and to induce clinical remission in a subset of patients with CD with loss of response or incomplete response under 90 mg q8W therapy. Our findings suggest that ustekinumab intensification may be considered in routine practice in CD patients who experience loss of response or insufficient response. Large prospective studies with ustekinumab serum monitoring are warranted to elucidate the best approach for optimizing drug therapy and to confirm the long-term safety and efficacy of this strategy.

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Table 1. Characteristics of the population at diagnosis. IQR, InterQuartile Range.

	Patients (n=100)
Female (n, %)	52 (52%)
Age, years (median, IQR)	34.9 (28.1-49.3)
Disease duration, years (median, IQR)	11.6 (7.3-20.2)
Smoking (n, %)	25 (25%)
Localization (Montreal) (n, %)	
Ileal (L1)	31 (31%)
Colonic (L2)	29 (29%)
Ileo-colonic (L3)	40 (40%)
Behavior (Montreal) (n, %)	
Inflammatory (B1)	35 (35%)
Stricturing (B2)	28 (28%)
Penetrating (B3)	37 (37%)
Perianal Crohn's disease (Montreal) (n, %)	47 (47%)
Extra-intestinal manifestation (n, %)	34 (34%)
Previous therapy (n, %)	
Thiopurines	91 (91%)
Methotrexate	51 (45%)
Anti-TNF	99 (99%)
1 anti-TNF	14 (14%)
2 Anti-TNF	70 (70%)
3 anti-TNF	14 (14%)
4 anti-TNF	1 (1%)
Vedolizumab	55 (55%)
Previous intestinal resection (n, %)	49 (49%)
Induction regimen (n, %)	
6 mg/kg IV	84 (84%)
Others	16 (16%)
Duration of therapy before intensification, months (median, IQR)	5.0 (IQR, 2.8 - 9.0)
Indication of intensification (n, %)	
Incomplete response	74 (74%)
Loss of response	26 (26%)
Luminal disease	77 (77%)
Perianal disease	16 (16%)
Both luminal and perianal disease	7 (7%)
Co-immunosuppressant (n, %)	27 (27%)
Steroids (n, %)	29 (29%)
Harvey-Bradshaw (median, IQR)	8 (5.0-11.2)
CRP, mg/L (median, IQR)	12.3 (5.0-30.5)

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Table 2. Adverse events outcome. AE, adverse event.

	AE	Hospitalisation	Treatment	Outcome of AE	Ustekinumab outcomes
Non-infectious	Urticaria	No	anti-histaminic	Resolution	90 mg q4W continued
	Hair loss	No	/	Stabilization	90 mg q4W continued
	Asthenia	No	/	Resolution	90 mg q4W continued
	Headache	No	Paracetamol	Resolution	90 mg q4W continued
	Skin Rash	No	/	Resolution	90 mg q4W continued
Infectious	Infectious colitis	Yes	antibiotics	Resolution	90 mg q4W continued
	Otitis	No	antibiotics	Resolution	90 mg q4W continued
	Pneumonitis	Yes	antibiotics	Resolution	90 mg q4W continued
	Pharyngitis/Epiglotitis	Yes	antibiotics/steroids	Resolution	90 mg q4W continued
	Pyelonephritis	Yes	antibiotics/double-J stent	Resolution	90 mg q4W continued
	Pyelonephritis	Yes	antibiotics	Resolution	90 mg q4W continued
	Angina	No	antibiotics	Resolution	90 mg q4W continued
	Sinusitis	No	antibiotics/steroids	Resolution	90 mg q4W continued

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Table 3. Factors associated with short term clinical response.

*Firth penalized likelihood was applied because of sparse data

	Univariate analysis		Multivariate analysis	
	OR (95%CI)	pvalue	OR (95%CI)	pvalue
Age	0.92 [0.96 ; 1.02]	0.642	-	
Disease duration	0.99 [0.94 ; 1.04]	0.649	-	
Localisation*			-	
Ileal (L1)	1			
Colonic (L2)	2.19 [0.73 ; 6.66]	0.332		
Ileo-colonic (L3)	1.08 [0.42 ; 2.77]	0.135		
Montreal Behavior*			-	
Inflammatory (B1)	1			
Stricturing (B2)	0.71 [0.25 ; 2.00]	0.496		
Penetrating (B3)	0.76 [0.29 ; 2.00]	0.668		
Duration of therapy before intensification	1.11 [0.99 ; 1.22]	0.051	-	
Indication intensification (loss response vs incomplete response)	**3.03 [1.03 ; 8.91]**	**0.044**	-	
Indication intensification 2 (luminal vs perianal)	0.59 [0.24 ; 1.43]	0.242	-	
immunosuppressant combination			-	
Azathioprine	1.95 [0.40 ; 9.57]	0.102		
Methotrexate	0.72 [0.14 ; 3.86]	0.239		
Steroids combination	0.59 [0.24 ; 1.43]	0.242	-	
Anti-TNF exposure ≥ 2	1.47 [0.50 ; 4.37]	0.482	-	
Vedolizumab exposure	1.15 [0.51 ; 2.61]	0.737	-	

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Figures

Figure 1. Short-term effectiveness of ustekinumab intensificationfrom 90mg q8W to q4W

Figure 2. Kaplan-Meier analysis of persistence of ustekinumab after intensification.

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Figure 1

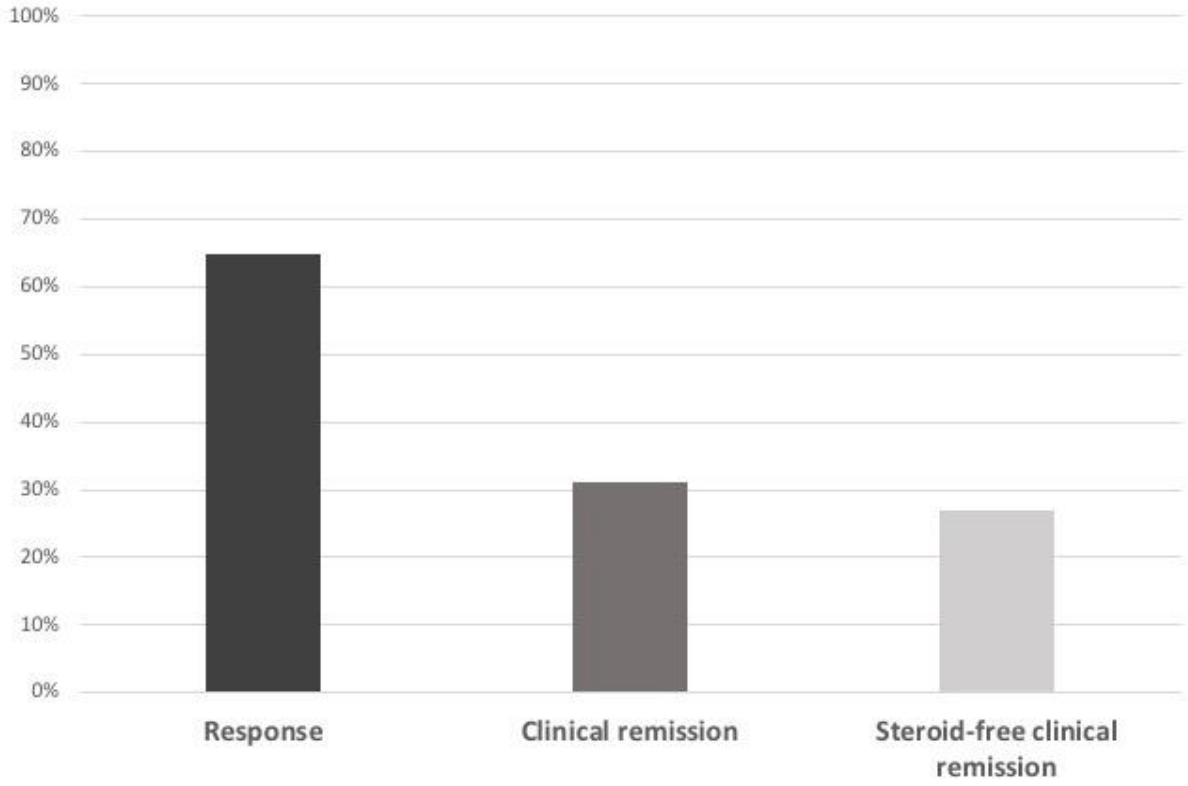

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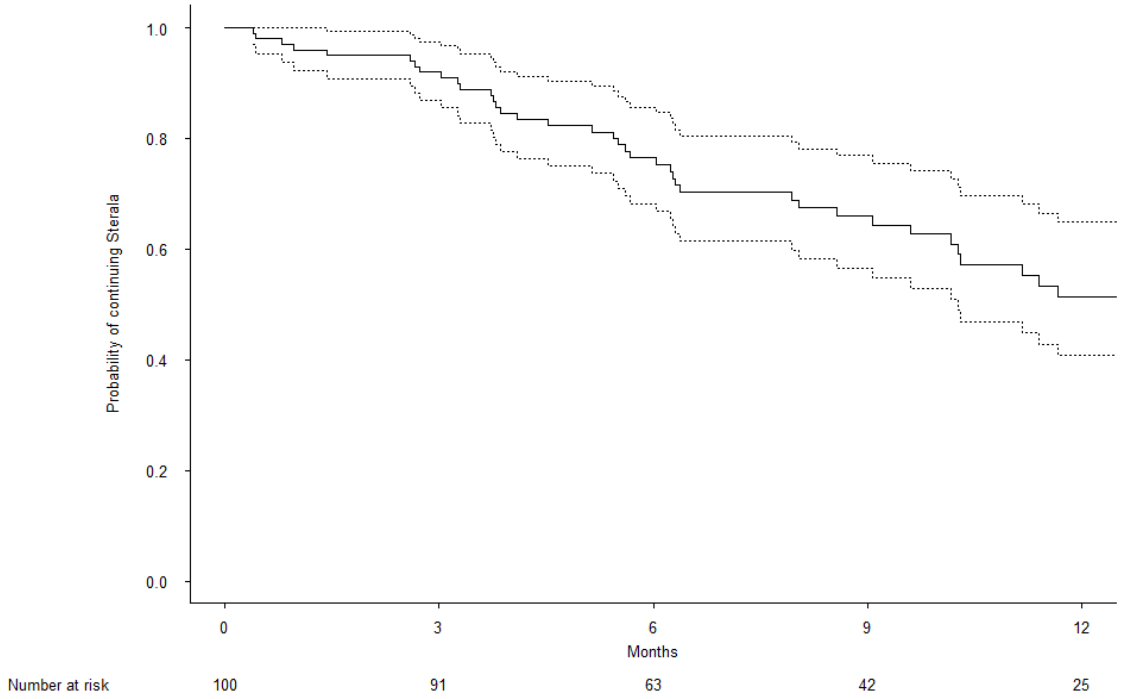
Figure 2



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