Anti-tumor Necrosis Factor-alpha Exposure Impacts Vedolizumab Mucosal Healing Rates in Pediatric Inflammatory Bowel Disease

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ABSTRACT

Background: Vedolizumab (VDZ) is effective for treating both adult and pediatric onset inflammatory bowel disease (IBD). Clinical outcomes, however, have been reported to be superior in patients naïve to anti-tumor necrosis factor (TNF). With the growing interest in endoscopic endpoints, we aimed to describe rates of mucosal healing in pediatric patients being treated with VDZ and examine the influence of anti-TNF on outcomes.

Methods: We conducted a retrospective review of all IBD patients ≤21 years of age who initiated VDZ and underwent endoscopy. Primary outcome was mucosal healing (composite of endoscopic [SES-CD] and Mayo score UC) and histological remission [Nancy index-UC and Crohn disease (CD) histologic activity]. Descriptive statistics summarized the data. Comparisons were made for endpoints based on anti-TNF exposure using univariate testing.

Results: Sixty-eight patients were included in the final analysis; 35 with UC and 33 with CD. Thirty-two patients (22 UC and 10 CD) were anti-TNF-naïve and 36 patients (13 UC and 23 CD) were anti-TNF-exposed. The median duration on VDZ before endoscopic assessment was 49 (IQR 32–73) weeks. A total of 38% (25/66) of patients met the primary outcome of mucosal healing and did not differ between anti-TNF-naïve or anti-TNF-exposed. Endoscopic remission was achieved by 51% with significantly more anti-TNF naïve patients reaching this endpoint (66% vs 40%, $P = 0.03$). Histologic remission was achieved by 42% of patients with a nonsignificant trend towards improved histologic remission rates in anti-TNF-naïve patients (52% vs 33%, $P = 0.13$).

Conclusions: VDZ is associated with mucosal healing in pediatric IBD. Anti-TNF exposure significantly impacted endoscopic remission, but not histologic remission in children on VDZ.

Key Words: inflammatory bowel disease, mucosal healing, pediatrics, vedolizumab

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What Is Known

- Vedolizumab is known to induce clinical remission in both adult and pediatric patients with inflammatory bowel disease.
- Mucosal healing is recognized as an important target in the treatment of inflammatory bowel disease.
- Differences in response to vedolizumab have been described between anti-tumor necrosis factor-alpha-naïve and -exposed cohorts.

What Is New

- Vedolizumab induces both endoscopic and histologic healing in pediatric inflammatory bowel disease.
- Rates of mucosal healing are higher in those who have no prior anti-tumor necrosis factor-alpha exposure.

Vedolizumab (VDZ) is an anti-$\alpha4\beta7$ integrin monoclonal antibody approved for the treatment of Crohn disease (CD) and ulcerative colitis (UC) in patients 18 years of age and older (1,2). It interferes with the binding of $\alpha4\beta7$-integrin-positive leukocytes with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and disrupts leukocyte trafficking to areas of intestinal inflammation.

On the basis of the GEMINI induction data, 47.1% and 16.9% of UC patients and 31.4% and 14.5% of CD patients experienced clinical response and remission, respectively. Week 52 remission rates were 45% in UC and 39% in CD in those who responded at week 6. Beyond just clinical remission, these pivotal studies also established the ability of VDZ to induce endoscopic healing (1–4). A phase 3b study in CD (VERSIFY) has more recently demonstrated endoscopic healing in patients on VDZ with an emphasis on the distinction between those with and without prior anti-TNF exposure (5). Real world studies are now reporting on histological outcomes with remission rates varying from 21% in CD and up to 55% in UC (4,6).

There have been many studies examining factors that are associated with vedolizumab efficacy both clinically and endoscopically (7–9). As shown in the GEMINI studies, prior anti-TNF exposure continues to influence vedolizumab outcomes, especially in CD in real world studies (1–3,5,7,9–12). There remains a debate as to whether there is a physiologic mechanism for these observed differences with down-regulation of MAdCAM-1 by anti-TNF (13), or if the exposed population represents a more refractory disease phenotype (14). Anti TNF-exposed CD patients in GEMINI 3 had a

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longer duration of disease, greater number of surgeries, and a higher prevalence of fistulizing disease.

The favorable safety profile and gut specificity makes VDZ an ideal therapeutic choice for pediatric IBD and has resulted in significant off-label use (15–18). Pediatric experiences with VDZ have described good clinical effectiveness with remission rates in UC and CD reaching as high as 76% and 42%, respectively (15–18).

Similar to what is seen in adult cohorts, the impact of anti-TNF exposure on VDZ outcomes has also been reported in children (15,16). Week 22 remission rates were much higher in anti-TNF-naïve pediatric patients compared with those with exposure (100% vs 45%) (15).

Despite the increasing evidence of symptom improvement in pediatric VDZ-exposed patients, there is little data available on endoscopic, and none on histological outcomes (17). We aimed to describe the endoscopic and histologic outcomes and how anti-TNF exposure impacts these outcomes in pediatric patients treated with VDZ.

METHODS

Study Design and Patient Population

As part of an ongoing observational cohort study of biologic-treated pediatric patients with IBD, we conducted a retrospective review of all patients ≤21 years of age who initiated VDZ for the treatment of IBD and underwent endoscopic assessment as part of either standard of care treat to target colonoscopy or for persistent symptoms while on VDZ. Patients who underwent endoscopy before 8 weeks of VDZ therapy were excluded. The study was conducted between December 2014 and June 2018 at the Susan and Leonard Feinstein Inflammatory Bowel Disease Clinical Center, Icahn School of Medicine, Mount Sinai, NY. The decision to prescribe VDZ was at the discretion of the prescribing physician. The study was approved by our Institutional Review Board (IRB-18–00794).

Data Collection

Electronic medical records were reviewed for demographics, medical and surgical treatment history, including steroid use, previous biologic and immunomodulator exposure, disease location and behavior (Paris classification), disease activity (weighted pediatric Crohn disease activity index [wPCDAI] for CD and partial Mayo score [pMS] for UC), endoscopic scores (SES-CD for CD and Mayo endoscopic subscore for UC), and histology scores (Nancy Index^{-} (19) for UC and a CD histologic activity scale in CD (normal [0], chronic inflammation [1], mildly active, chronic inflammation [2], moderate to severely active chronic inflammation [3]) (20–22). When disease was patchy in CD, the score assigned corresponded to the most inflamed segment. VDZ treatment information included dose, frequency, and duration of therapy before endoscopic assessment. Laboratory data reviewed included complete blood count, albumin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and calprotectin when available.

Outcome Measures

The primary outcome was mucosal healing defined as the composite of endoscopic and histologic remission. Endoscopic remission was defined as a Mayo endoscopic subscore of 0 in UC and an SES-CD score (sum of all segments) of ≤ 2 in CD. Histologic remission was defined as a Nancy Index score ≤1 in UC and a CD histologic activity score ≤1 in every segment. Secondary outcomes included corticosteroid-free clinical remission defined as a weighted PCDAI <12.5, or partial Mayo score <2 and off corticosteroids at the time of endoscopic assessment.

Statistical Analysis

Standard descriptive statistics, including frequency for categorical variables and median (interquartile range [IQR]) for continuous variables were calculated. Univariate analyses were performed to examine associations of clinical and laboratory characteristics with VDZ effectiveness outcomes by chi-square analysis or the Fisher exact test whenever applicable. Two-sided P values of <0.05 were considered statistically significant.

RESULTS

Study Population

One hundred eighteen pediatric patients with IBD being treated with VDZ were evaluated for eligibility. Fifty VDZ-exposed patients were excluded from analysis; 2 who had undergone colectomy, 2 with monogenic etiology for IBD, and 46 who did not have endoscopic evaluation while being treated with VDZ. Sixty-eight patients were included in the final analysis; 35 with UC and 33 with CD. Thirty-two patients (22 UC and 10 CD) were anti-TNF-naïve and 36 patients (13 UC and 23 CD) were anti-TNF-exposed and underwent endoscopic evaluation after a median duration of 49 (IQR 32–73) weeks on VDZ.

Baseline characteristics, at the start of VDZ, were similar between CD and UC patients and between patients who were anti-TNF-naive versus exposed. (Table 1). Median age at VDZ initiation was 16.4 (IQR 13.3–18.2) years. The youngest patient was 3 years 6 months old and 25% were 18 years of age or older at time of VDZ induction. Median disease duration was 2.7 (IQR 0.8–5.2) years. Most CD patients (88%) had nonstricturing, nonpenetrating disease (B1) and 30% had a history of perianal disease. Eighty-nine percentage of UC patients had extensive (E3) disease. Prior anti-TNF failure was more common in CD than in UC (CD 70% vs UC 37%, $P = 0.007$). Concurrent use of corticosteroids (prednisone or oral budesonide) at the time of vedolizumab initiation was present in 65% of patients.

Anti-tumor Necrosis Factor-alpha Exposure History

In the 38 (53%) anti-TNF exposed patients, 2 (5%) had been treated with 3 prior anti-TNF agents, 14 (37%) received 2 prior agents, and the remainder had been treated with 1 prior anti-TNF (58%). Median time between last anti-TNF dose and initiation of VDZ was 7 (IQR 2.2–13) weeks, although 2 patients remained on anti-TNF therapy through VDZ induction. Disease duration did not vary significantly between those with prior anti-TNF exposure versus those without (exposed: 2.8 [IQR 1–7.3] years; naïve: 1.85 [0.5–5] years, $P = 0.35$). Other baseline characteristics including age at diagnosis, age at VDZ start, percentage female sex, CRP, albumin, haemoglobin, and ESR were also not significantly different between those with and without anti-TNF exposure. Corticosteroid use at VDZ start was marginally more common in those who had a history of anti-TNF exposure (69% vs 61%, $P = 0.5$).

Clinical severity scores at baseline were not significantly different between anti-TNF-naïve versus exposed CD patients (wPCDAI: naive 26 [IQR 19–35]; exposed 35 [IQR 25–57.5]; $P = 0.14$); however, anti-TNF-naïve UC patients had lower pMayo scores compared with those who were exposed (naïve: 3.5 [IQR 2–5]; exposed: 6 [IQR 3–6.5]; $P = 0.047$).

TABLE 1. Baseline demographics and clinical characteristics

	Crohn disease			Ulcerative colitis		
	Anti-TNF-naïve, N = 10	Anti-TNF-exposed, N = 23	*P* value	Anti-TNF-naïve, N = 10	Anti-TNF-exposed, N = 23	*P* value
Age at diagnosis, median (IQR)	12 (10.1–16.9)	12 (8.2–15.6)	0.28	13.4 (8.9–15.2)	11.7 (10.3–15.3)	0.70
Age at VDZ start, median (IQR)	15.8 (11.9–19.1)	16.4 (14.2–18.2)	0.83	16.5 (14.7–18.4)	15.1 (12.9–16.9)	0.19
Disease duration (years)	1.2 (0.1–3.5)	4.2 (1.3–7.7)	0.08	3.0 (1.0–5.5)	2.0 (0.4–3.7)	0.40
Female, No. (%)	3 (30)	14 (60)	0.10	15 (68)	6 (46)	0.20
CD behavior, No. (%)						
Nonstricturing, B1	9 (90)	20 (87)	1.0	–	–	
Stricturing, B2	1 (10)	2 (9)		–	–	
Penetrating, B3	0	1 (4)	0.12	–	–	
Perianal, *P*	1 (10)	9 (39)		–	–	
CD location, No. (%)						
Ileal, L1	5 (50)	0	0.001	–	–	
Colonic, L2	5 (50)	6 (26)		–	–	
Ileocolonic, L3	0	17 (74)	0.68	–	–	
Upper tract, L4	2 (20)	8 (35)		–	–	
UC extent, No. (%)						
Proctitis, E1	–	–		0	0	1.0
Left-sided, E2	–	–		3	1	
Extensive, E3	–	–		19	12	
wPCDAI, median (IQR)	26.2 (19.4–35.6)	35 (25.57.5)	0.14	–	–	
pMayo, median (IQR)	–	–		3.5 (2–5)	6 (3–6.5)	0.047
Number of prior anti-TNF agents						
1	–	9 (39)		–	11 (85)	
2	–	12 (52)		–	2 (5)	
3	–	2 (9)		–	0	
CRP at VDZ start, median (IQR)	4.2 (2–9.5)	3.0 (0.3–12.3)	0.51	1.2 (0.2–10.3)	4.9 (0.2–9.8)	0.84
Hemoglobin at VDZ start, median (IQR)	12.6 (11.5–15.2)	12.8 (11.5–13.7)	0.68	11.2 (10.3–12.9)	12.6 (10–13.2)	0.41
Albumin at VDZ start, median (IQR)	4.3 (3.8–4.6)	4.1 (3.3–4.3)	0.18	4.1 (3.6–4.3)	3.9 (3.4–4.2)	0.47

CD = Crohn disease; IQR = interquartile range; TNF = tumor necrosis factor α; UC = ulcerative colitis; VDZ = vedolizumab; wPCDAI = weighted pediatric Crohn disease activity index.

Vedolizumab Dosing

The majority of patients were treated with a VDZ dose of 300 mg each infusion. Six patients (9%) initiated treatment with VDZ at a dose below 300 mg and all had weights <30 kg (range 19–29 kg), and received doses between 6 and 10 mg/kg of VDZ. Half of these patients achieved a weight of at least 30 kg and were subsequently escalated to a dose of 300 mg before endoscopic assessment on VDZ. Dosing interval adjustment was performed in 36% of anti-TNF-exposed (11 patients to every 4 weeks, 1 patient to every 5 weeks, and 1 patient to every 6 weeks) and 12.5% of anti-TNF-naïve patients (2 patients to every 4 weeks and 2 patients to every 6 weeks) ($P = 0.03$). Reason for dose intensification was clinical nonresponse or persistent elevations in serum inflammatory markers on standard every 8-week dosing (16/17 patients). The 1 additional patient was initially under 30 kg with response to every 8-week dosing, but required dose intensification following significant weight gain.

Vedolizumab Outcomes

Endoscopic and Histologic Outcomes

Endoscopic assessment was assessed after a median duration of VDZ exposure of 49 (IQR 32–73) weeks. A total of 38% (25/66) of patients met the primary outcome of mucosal healing (composite of endoscopic remission [Mayo 0 or SES-CD ≤ 2] and histologic remission [Nancy Index score ≤1 or CD histologic activity score ≤1]). Significant differences in mucosal healing were not noted between CD and UC patients (42% and 34%, $P = 0.5$) or between anti-TNF-naïve and exposed patients (48% and 29%, $P = 0.1$). Baseline labs, including CRP, hemoglobin, ESR, and albumin, and disease activity indices were not associated with mucosal healing.

Endoscopic remission, independent of histology, was achieved by 51% of all patients (63% CD and 43% UC, $P = 0.1$). Significantly more anti-TNF-naïve patients achieved endoscopic remission when compared with those with prior anti-TNF exposure (66% vs 40%, $P = 0.03$). The separation remained significant in UC patients where the endoscopic remission rate was 59% in anti-TNF naïve and 15% in anti-TNF exposed patients ($P = 0.02$) (Fig. 1). A similar although not significant trend in endoscopic remission was also observed in CD (80% anti-TNF naïve v. 55% anti-TNF exposed, $P = 0.25$). Within the anti-TNF-exposed patients, CD patients had higher rates of endoscopic remission than UC patients (55% vs 15%, $P = 0.03$).

Histologic remission was achieved by 42% of patients (44% CD and 40% UC, $P = 0.76$). There was a nonsignificant trend towards improved histologic remission rates in anti-TNF naïve patients (52% vs 33%, $P = 0.13$) (Fig. 1).

Endoscopic remission was documented in 41% (7/17) of those who underwent dose interval shortening and 56% (28/50) of those who remained on every 8-week dosing ($P = 0.29$). Similarly, histologic remission was found in 24% (4/17) of those with

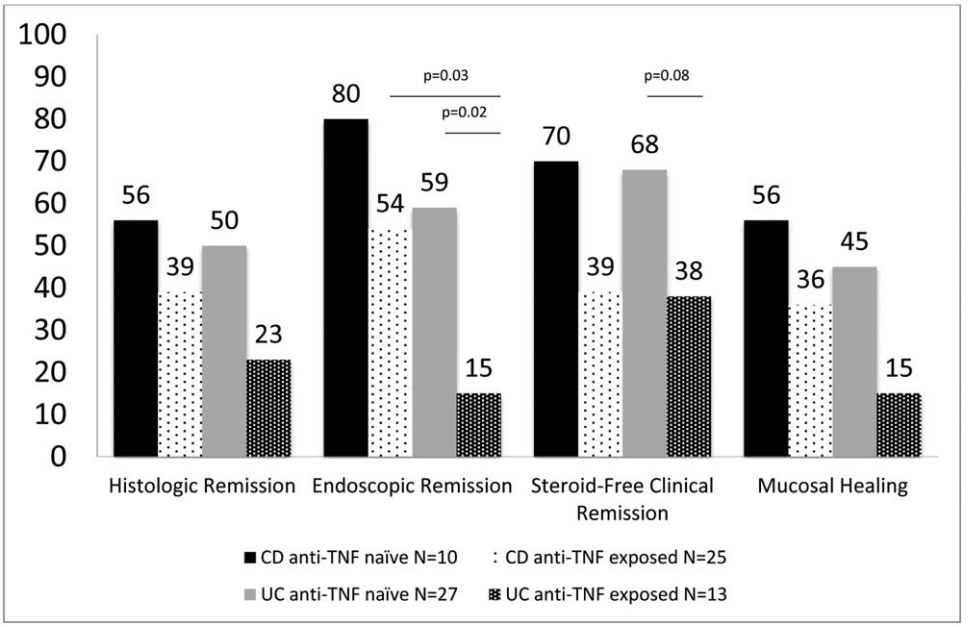

FIGURE 1. Remission rates in CD and UC: anti-TNF naive versus exposed. CD = Crohn disease; TNF = tumor necrosis factor; UC = ulcerative colitis.

shortened interval and 28% (14/50) who received VDZ at the standard 8-week interval ($P = 0.72$).

Clinical Outcomes

Assessment of steroid-free clinical remission rates was performed at the time of endoscopic assessment on VDZ. At the time of VDZ initiation, 65% of patients were on an oral corticosteroid and this decreased by 66% at the time of endoscopic assessment. Steroid-free clinical remission rates were 57% for UC and 48% for CD ($P = 0.5$). On univariate analysis, anti-TNF exposure significantly impacted steroid free clinical remission rates (69% and 39% in anti-TNF naïve and exposed patients, respectively, $P = 0.01$) (Fig. 1). CD patients had a median decrease in wPCDAI of 20 (IQR 7.5–27.5) and UC patients had a median decrease of 3 (IQR 1–4) in pMayo score. Anti-TNF naïve and exposed patients had similar degrees of improvement in their clinical severity scores. At last clinic follow-up after a median of 32.5 (IQR 26.2–38.8) months, 66% of pediatric patients remained on VDZ. A greater number of these patients were anti-TNF naïve (75% vs 58%, $P = 0.15$). All CD patients who remained on VDZ at time of the most recent follow-up were in remission or had mild disease according to wPCDAI score (median 0 [IQR 0–16.3]). Twenty of 23 UC patients (87%) had a pMayo score of 0 at the time of last follow-up. The remaining 3 patients had scores of 1, 2, and 3 in a single patient each.

Biomarker Outcomes

Median fecal calprotectin levels at baseline were available for 28% of patients and were slightly more elevated in UC compared with CD (508 [IQR 329–1673] vs 373 [IQR 212–891] μg/g, $P = 0.53$). Baseline values of fecal calprotectin were numerically but not statistically lower in those who achieved mucosal healing (217 [IQR 69–819] vs 626 [308–1089] μg/g, $P = 0.18$). Fecal calprotectin levels within 4 weeks of the endoscopic endpoint were available for 32% of patients (42% CD and 23% UC). Median calprotectin was 242 ug/g (IQR 54–478) for those without histological healing and 55 ug/g (IQR 17–272) for those with histological healing, $P = 0.2$.

Baseline CRP was not a significant predictor of mucosal healing [healing: 2 mg/L (IQR 0.3–5.9); no healing: 5.35 mg/L (IQR 0.3–13), $P = 0.16$). Additionally, no differences in CRP were noted at the time of endoscopic assessment between those achieving mucosal healing [1.6 mg/L (IQR 0.4–3.5)] and those who did not [2.1 mg/L (IQR 0.4–13), $P = 0.23$].

DISCUSSION

Objective endpoints, such as endoscopic remission have gained acceptance as a treatment target in Crohn disease and ulcerative colitis because of association with improved outcomes, such as decreased risk of dysplasia, colectomy, and hospitalizations (23–26). Additionally, clinical symptoms do not correlate well with endoscopic outcomes. This was particularly evident in CD patients in the SONIC trial (27). This change towards utilizing objective endpoints like endoscopic healing is now being reflected in the FDA guidance for future IBD targets. There is also movement towards including histologic outcomes as a secondary endpoint in clinical trials. New definitions of mucosal healing will include a composite of both endoscopic (macroscopic) and histologic indices. It does, however, remain unclear as to whether a patient's outcome is improved if both are achieved as compared with one or the other. To date, there have been limited real world data on this composite endpoint and how our current therapies perform with this outcome.

Our data demonstrates that mucosal healing was achieved in 38% of pediatric patients treated with VDZ; this was similar between CD and UC. The clinical endpoints similarly did not differ between CD and UC. However, what did separate out VDZ outcomes in our cohort was a history of anti-TNF exposure. This is in keeping with our previously published pediatric experience that focused on clinical endpoints only (15). Whenever evaluating objective endpoints in this new cohort, we found higher rates of endoscopic and histologic remission in our anti-TNF-naïve patients, although this only met statistical significance for endoscopic

remission. The most notable differences observed between anti-TNF-naïve and exposed were in ulcerative colitis patients (59% vs 15% endoscopic remission); however, these anti-TNF-naïve patients had slightly less severe disease at baseline compared with the anti-TNF-exposed patients.

Of particular interest in our study was that the highest rates of mucosal healing were observed in the anti-TNF-naïve CD patients (56%). These patients had mostly uncomplicated inflammatory CD. The VERSIFY mucosal healing study similarly showed a marked difference in endoscopic outcomes in the face of anti-TNF exposure in CD patients (5). Although anti-TNF agents are considered most effective for stricturing and penetrating phenotypes, the favorable outcomes in inflammatory CD naïve to anti-TNF, suggest that VDZ should be more strongly considered as a potential first-line therapy for uncomplicated CD.

We did not identify any significant associations of clinical or demographic characteristics with mucosal healing. Serologic markers of disease activity including CRP, albumin, and hemoglobin were all comparable both at baseline and at the time of follow-up, and thus, were not a significant predictor of response. Our cohort, however, had mostly normal baseline values for these serum markers limiting their use in monitoring disease response.

Vedolizumab dose-finding studies are underway for the pediatric population. Patients in our study were treated with a range of 6–10 mg/kg with a maximum dose of 300 mg. Twenty-three percentage of patients in our cohort underwent dose interval shortening. Although the randomized clinical trials did not show a difference between every 8-week and every 4-week dosing, subsequent reports have documented incremental gain in response in patients who underwent interval shortening (2,3,7,14). Our data did not find higher rates of endoscopic or histologic remission in those who underwent dose interval shortening compared with those who remained at standard dosing, however, 41% of patients undergoing dose intensification for nonresponse were found to have endoscopic remission on follow-up biopsy. This suggests a role for a trial of interval shortening in pediatric nonresponders on standard dosing.

Limitations of this study include the retrospective nature of the chart review and relatively small sample size. However, this is the largest cohort study published to date on the composite endpoint of mucosal healing in pediatric patients exposed to VDZ. Additionally, reasons for dose adjustments and collection of drug concentrations and anti-VDZ antibody data was neiyher protocolized nor available in all patients. This limited a more robust assessment as to whether dose-escalation needs and outcomes were driven by pharmacokinetics as is seen with anti-TNF.

CONCLUSIONS

A growing arsenal of therapies is becoming available for the treatment of IBD. As this occurs, an understanding of the impact of drug sequence on medication effectiveness and disease outcomes is becoming increasingly important. In our small but well-characterized pediatric cohort, we confirmed that anti-TNF exposure does indeed influence endoscopic outcomes. Larger studies are needed to determine if observed differences are because of true biologic effect of anti-TNF exposure versus a reflection of disease severity and duration in patients who are started on VDZ. Dose-finding studies in children are ongoing and should provide some additional clarification in a larger cohort of patients with a prospective randomized design.

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