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Combined therapy: rifaximin-α and arabinogalactan with lactoferrin combination effectively prevents recurrences of symptomatic uncomplicated diverticular disease (SUDD)

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

Background: Diverticulosis is the most common finding in the GI tract. Nearly half of the people with diverticula experience symptomatic uncomplicated diverticular disease (SUDD).

Aims: The primary endpoints of our study were to assess the effectiveness of combined therapy with rifaximin-α and arabinogalactan-lactoferrin in symptom reduction and normalization of bowel movements. The secondary endpoints were an assessment of efficacy in SUDD recurrence prevention and patients' compliance to the combined therapy.

Material and methods: A retrospective observational survey study was performed in 2019 among physicians experienced in diverticular disease (DD) treatment in Poland. Patients with previous episodes of recurrences treated with combined therapy (cyclic rifaximin-α at least 400 mg b.i.d/7 days/every month and continuous arabinogalactan-lactoferrin supplementation 1 sachet daily) were assessed after 3 and 6 months regarding symptoms' resolution in the three-point scale. The patients' SUDD history, diagnostic methods, treatment, and results, as well as patients' compliance were evaluated.

Results: 281 patients met inclusion criteria, and were further evaluated (67.6% women, median age 65 years). After 6 months of combined treatment, there was statistically significant reduction in the total severity score (sum from 8.5 [max 15 points] to 1.28; $p < 0.0001$); and improvement in each symptom score (median from 1.7 [max 3 points] to 0.26; $p < 0,001$). Stool frequency statistically normalized in every group. As many as 31.7% had complete symptom resolution. Patients' compliance with the therapy was very good and good in 92.9% of cases.

Conclusions and discussion: Combined therapy with cyclic rifaximin-α and continuous arabinogalactan combination with lactoferrin is effective in SUDD treatment in terms of symptom resolution, bowel movement normalization, prevention of recurrences with very good patient's compliance.

KEYWORDS: arabinogalactan, combined-treatment rifaximin-α, diverticulitis, eubiosis, lactoferrin, symptomatic uncomplicated diverticular disease (SUDD)

To the best of our knowledge, this is the first real-life, six-month study confirming the efficacy of combined therapy with rifaximin-α and arabinogalactan-lactoferrin in symptom resolution and bowel movement frequency normalization in symptomatic uncomplicated diverticular disease with excellent patients' compliance.

LIST OF ABBREVIATIONS

APC – immune cells
CRP – C-reactive protein
DD – diverticular disease
ESR – erythrocyte sedimentation rate
GALT – gut-associated lymphoid tissue
SCFA – Short Chain Fatty Acid
SUDD – symptomatic uncomplicated diverticular disease
WBC – white blood cells

INTRODUCTION

Diverticulosis is the most common abnormality of the large intestine. The spectrum of its manifestations varies from asymptomatic forms through mild symptoms to life-threatening complications such as perforation, hemorrhage, and an abscess requiring surgery. The most common form is a symptomatic uncomplicated diverticular disease (SUDD). It mainly involves the left colon. Mostly middle-aged and older people are affected (also diverticula formation increases with age), although younger age seems to be a factor for poor prognosis in case of the disease complications. It is estimated that in the last 20 years, recognition (and probably incidence) has significantly increased. The growing incidence translates into a higher percentage of hospitalizations due to severe forms of the disease every year. Due to the prevalence, the spectrum of symptoms and limited therapeutic options, diverticular disease is a challenge for patients, doctors, and the healthcare system. This is a phenomenon with significant treatment costs and a negative impact on the quality of life in developed countries [1–7].

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Several treatments are currently recommended for different forms of DD, but their effectiveness is still being discussed. Considering the etiology, a proposed drug used in treating this disease is the poorly absorbable eubiotic rifaximin-α (a positive modulator of the intestinal ecosystem that restores eubiosis via various mechanisms) [8]. It is also known for its direct and indirect anti-inflammatory mechanisms, which consist of transcription factors and cytokines inhibition through the pregnane X receptor as well as the reduction of bacterial virulence, adhesion, and translocation [8–11]. In 2019, the results of a long-term analysis were published by DiMario et al., which showed that even eight years of use of rifaximin-α brought year-by-year reduction of symptoms and risk of relapse. The best results in reducing the risk of relapse and the need for surgical intervention were achieved in the 3rd and 4th year of using rifaximin-α and sustained till the 8th year of rifaximin-α cyclic treatment [12].

In most studies, the second proposed SUDD therapy component is soluble fiber, which is a subtract for butyrate, a crucial element in colonocyte nutrition. One recent study assessed the effectiveness of rifaximin-α with arabinogalactan (prebiotic, soluble fibre) and lactoferrin (multifunctional protein with anti-inflammatory potential) combination [13–16]. Arabinogalactan in cell and animal models is capable of enhancing natural killer cells and macrophages as well as the secretion of pro-inflammatory cytokines. In humans a clinical study demonstrated that larch arabinogalactan increased the body's potential to defend against common cold infection. Different hypotheses of this unique soluble fiber can be envisaged as larch arabinogalactan can possibly act indirectly through microbiota-dependent mechanisms and/or have a direct effect on the immune system via the gut-associated lymphoid tissue (GALT) [17]. This combination of arabinogalactan and lactoferrin, except for being an endogenous source of fatty acids (SCFAs), also acts as a prebiotic. It has been suggested that it can interact with the immune system either indirectly through the production of SCFAs that affect inflammatory responses via leukocyte function and cytokine production, or directly through the capacity of M-cells to transfer intact arabinogalactan through the intestinal barrier, delivering it to immune cells (APC). In the short-term evaluation of rifaximin-α and arabinogalactan-lactoferrin performed by Banasiewicz et al. results were promising, but long-term effectiveness still needs to be determined [18]. Also, due to the length of treatment, patient compliance may vary. Until now, there have been no studies assessing patients' acceptance of the proposed combined therapy with rifaximin-α and arabinogalactan-lactoferrin supplementation. Therefore, we conducted a retrospective observational survey study assessing the effectiveness of prolonged cyclic rifaximin-α treatment in combination with continuous arabinogalactan-lactoferrin combination supplementation in a group of patients with recurrent SUDD. We also assessed patients' compliance to the treatment.

MATERIALS AND METHODS (ACCORDING TO STROBE) [19]

It was a retrospective observational survey study conducted in outpatient clinics throughout Poland over a 6-month period in 2019. The aim of the study was to assess the effectiveness of cyclic (at least 400 mg b.i.d. for seven days per month) use of rifaximin-α (Xifaxan, Alfasigma S.p.A.) and arabinogalactan (5 g) lactoferrin (50 mg) combination (Fibraxine, Alfasigma S.p.A.) in symptom reduction and normalization of bowel movement frequency. The secondary endpoints were an assessment of combined treatment efficacy in SUDD recurrence prevention (remission maintenance) and patients' compliance to six months of combined therapy.

All patient data were anonymized, and the study was performed in accordance with the ethical standards of the institutional and national research committees.

Based on individual medical records, gastroenterologists, surgeons, and internal medicine specialists experienced in managing patients with DD completed enrolled patients' questionnaires concerning the main symptoms of SUDD, such as pain, abdominal tenderness, changes in bowel habits, and bloating, with the number of stools, during the observation period. All variables were evaluated on a 4-point scale at the beginning of and during the treatment. The effectiveness of the treatment was assessed every two months. The survey also included a detailed history of the patient's diverticular disease, the diagnostic methods used during the course of the disease, and overall results.

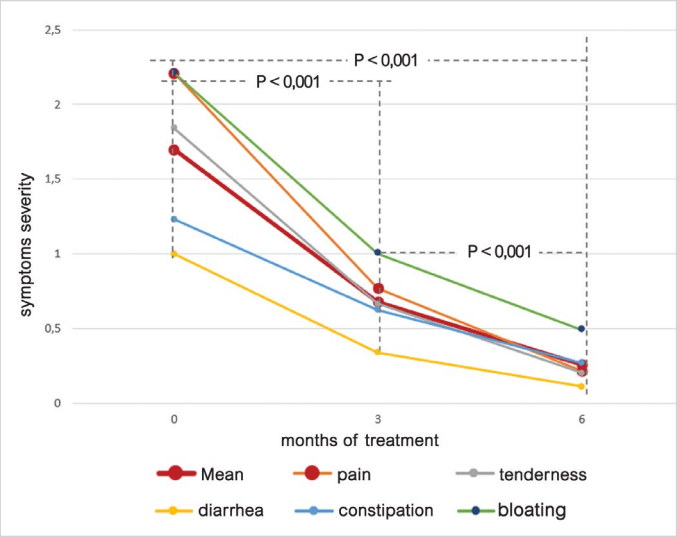
Hard copies of all the questionnaires, which were signed by the doctors and contained no patient data, were collected and stored at the research office. An electronic database was created after all the surveys had been obtained.

The study population consisted of male and female patients who were diagnosed with SUDD at least six months before the baseline visit.

SUDD was defined typically as recurrent or persistent symptoms such as abdominal pain located mainly in the left lower quadrant, abdominal tenderness, bloating, constipation, diarrhoea in patients with previous endoscopically or radiologically diagnosed diverticula. Patients with ongoing diverticulitis, with inflammatory bowel disease (including microscopic colitis) or who were treated with a systemic antibiotic (for reasons other than SUDD), were excluded from the study. Slight elevations of white blood cell count (WBC), ESR, CRP, or calprotectin in the absence of systemic symptoms such as fever did not exclude from the study.

Cyclic rifaximin-α treatment was defined as at least 800 mg daily (two 200-mg tablets twice a day) administered seven days a month for six months. Arabinogalactan-lactoferrin combination supplementation was defined as continuous (daily) administration of at least 1 sachet containing 5 g and 50 mg of ingredients, respectively.

The physicians selected all consecutive patients fulfilling the inclusion criteria during the study period based on their medical records. In the end, only those patients who were treated with combined therapy, who were available for medical evaluation (visit to a doctor's office) after 3 and 6 months of the beginning of the treatment and for whom detailed documentation was available, were evaluated. Symptoms: abdominal pain, tenderness, diarrhoea, constipation, and bloating were assessed on a 4-point scale (0 – no symptoms, 1 – mild, 2 – moderate, 3 – severe). The number of stools was declared by the patients. All data were collected at each visit (at baseline and after 3 and 6 months). The total symptom score was calculated by summing up the individual symptoms at each time point (maximal value: 15) and determining the median symptom severity (maximal value: 3). If laboratory tests we performed, the patients' WBC, ESR, CRP, and calprotectin values were obtained. Age, gender, duration of the disease, number of flares, severity of symptoms at the beginning of treatment and changes in



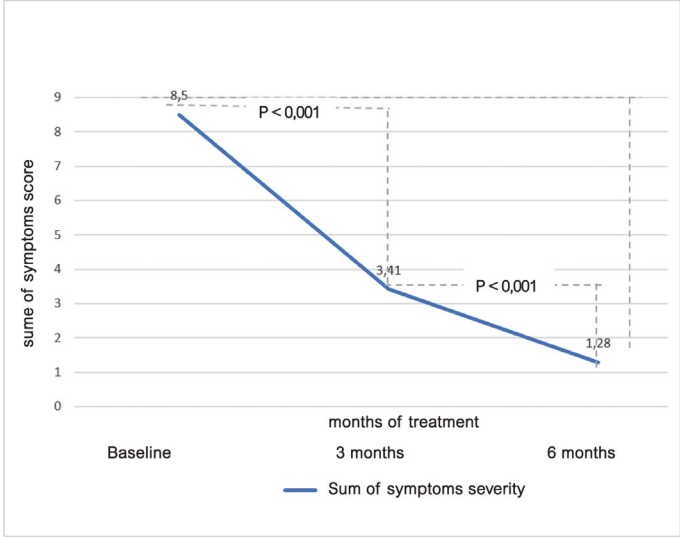


Fig. 1a. i 1b. Detailed analysis of symptom reduction with statistical assessment. The P-value was calculated for each variable for each analysis in every visit. (a) Mean symptom severity (0–3-point scale); (b) Mean symptom severity (sum of symptoms 0–15-point scale).

Tab. I. Patient demographics.

VARIABLE	
Age (years)	64.8 (24–92)
Male gender, n (%)	90 (32)
Duration of DD (years)	4.6 (1–19)
Number (%) of patients with recurrences	236 (84)
Diagnostic test revealing DD (%)	100
Colonoscopy, n (%)	264 (94)
Computed tomography, n (%)	137 (48.7)
Patients treated initially with other drugs	252 (85%)
Mean number of stools per week (diarrhea/constipation)	20/3.12
If performed, baseline laboratory test elevated	
· WBC, n (%)	191 (84.9)
· CRP, n (%)	89 (44.2)
Number of patients assessed	267

Continuous variables are shown as the mean. DD – diverticular disease, WBC – white blood cell count, CRP – C-reactive protein.

Tab. II. Patients' baseline characteristics.

SYMPTOM SCORE (0–3 POINTS)	MEDIAN	SD
Pain	2.21	0.73
Tenderness	1.84	0.94
Diarrhea	1.0	1.21
Constipation	1.23	1.25
Bloating	2.21	0.92
All symptoms combined	1.7	0.53
Sum of symptom score (maximum 15 points)	8.5	2.66
Number of stools per week:		
· diarrhea predominant,	20	8.5
· constipation predominant,	3.1	1.9
· mixed.	10.7	8.1

the severity of the symptoms were assessed as potential predictors of the disease course and responses to treatment.

STATISTICAL METHODS

The baseline analysis of the endpoint and other efficacy assessments were based on the per-protocol (PP) population, which included all patients treated with appropriate doses of rifaximin-α. We used the T-test, the Chi-squared test, Fisher's exact test, or the Wilcoxon-Mann-Whitney test for statistical evaluation. With regard to differences in treatment, 95% confidence intervals (CIs) were applied. All statistical tests were conducted at the bilateral nominal level of an error rate of 0.05.

RESULTS

A total of 296 patients were assessed for eligibility. Among them, 281 patients were treated with an appropriate dose of rifaximin-α and arabinogalactan-lactoferrin, and then they were included in further evaluation. The detailed characteristics of the participants are presented in Tab. I. The median age of the population was 64.8 years. The population was predominantly female. The mean and median duration of DD was 4.6 years. Colonoscopy was the most common diagnostic method revealing diverticulosis. A total of 59.8% of patients had more than one examination confirming DD diagnosis. As much as 84% (68.2% women) had at least one episode of symptom recurrence. At baseline, most of the patients in whom laboratory tests were performed (225 patients) had at least one parameter (WBC, CRP) elevated.

Before starting rifaximin-α therapy, 85% of patients received other drugs (5-aminosalicylates [5-ASA], antibiotics, spasmolytics, prokinetics, probiotics, laxatives, and analgesics) although the efficacy of those therapies in DD remains unproven. Of them, 51% were discontinued after the introduction of combined treatment with rifaximin-α and arabinogalactan-lactoferrin.

The total symptom sum score at baseline was 8.5 (max. 15). The most severe symptoms were pain and bloating equally. The mean number of stools per week was 20 for diarrhea and 3.1 for constipation-predominant cohorts, respectively. Detailed characteristic is presented in Tab. II.

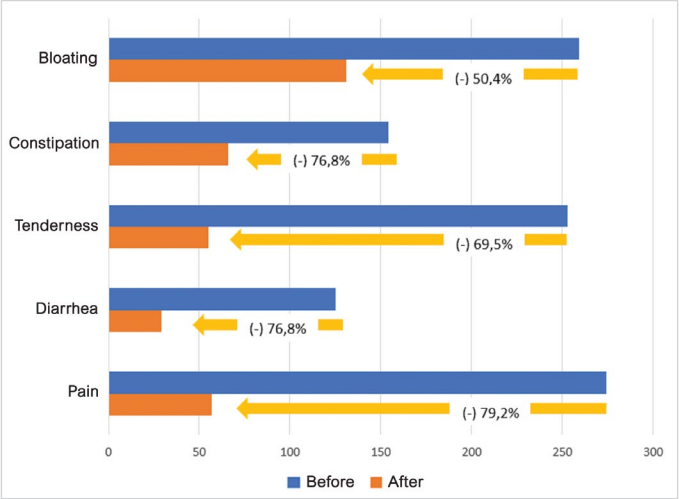


Fig. 2. Number of patients with complete symptom resolution after 6 months as compared with the start of the treatment. Arrows show the percentage of patients in whom symptoms resolved totally.

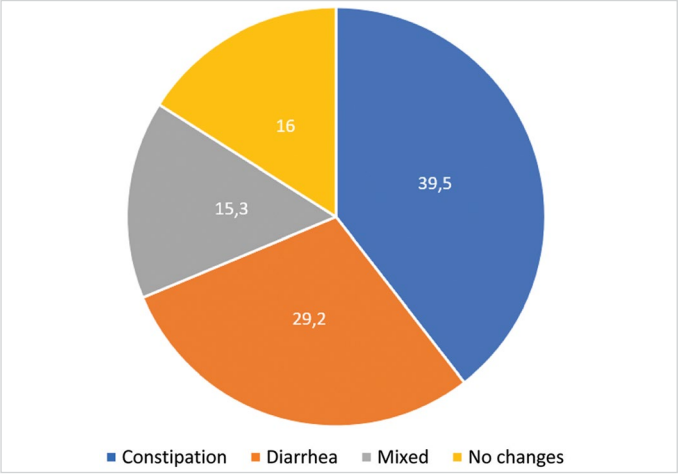


Fig. 3. Baseline bowel movement habits (per week).

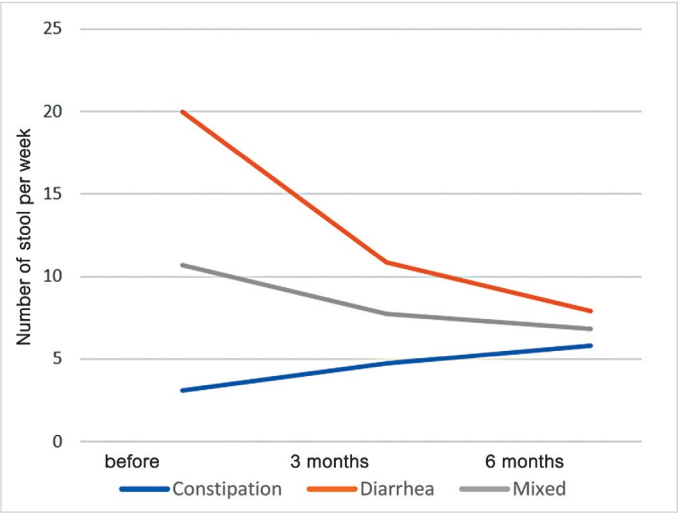


Fig. 4. Number of stools change during the treatment in therms of starting point.

After 6 months of combined treatment with rifaximin-α and arabinogalactan-lactoferrin combination, there was a statistically significant reduction in all symptom severity scores, regarding both the total symptom score and each symptom assessed. All combined symptoms decreased after three and six month to 0.68 and 0.26 respectively ($P < 0.001$) and the total symptom score to 3.41 and 1.28 ($P < 0.0001$) respectively. Abdominal pain decreased from 2.21 to 0.21 points; tenderness from 1.84 to 0.20; diarrhoea from 1.0 to 0.11; constipation from 1.23 to 0.27; and bloating from 2.21 to 0.49 (detailed assessment – Fig. 1a.). As per sum of symptoms assessed, we also noticed statistically significant improvement after three and six months (Fig. 1b.). A total of 31.7% of patients were asymptomatic (resolution of all symptoms with 0 points indicated on the scale) after six months (P for all values <0.001). The greatest symptom improvement after six treatment cycles was observed in pain and diarrhea (79.2 and 76.8%, of patients respectively). A significant improvement was observed for each symptom ($P < 0.001$) (Fig. 2.). Reduction of all symptoms by a minimum of 70% was experienced by 85.4% of patients.

We found significant normalization of all analysed laboratory tests, leucocytosis, ESR, CRP, and calprotectin. There was no statistically significant correlation between the severity of symptoms at baseline and the reduction in laboratory abnormalities. In the multivariate analysis, we did not find any differences between genders regarding the duration of the disease, number of flares, severity of symptoms at baseline, and after treatment. We also examined whether other potential cofounders constitute risk factors, but we observed that the duration of the disease, severity of symptoms, and the number of flares were not risk factors that influenced treatment effectiveness in our cohort.

The second assessed outcome was bowel movement normalization in patients with altered bowel habits: diarrhea, constipation, or mixed pattern (patients' symptom distribution, Fig. 3.). We found that after three and six months of combined therapy with rifaximin-α and arabinogalactan-lactoferrin in patients with constipation, the number of stool per week statistically significantly ($P < 0.001$) increased(from 3.1 to 5.8), i.e. normalized. Conversely, in patients with diarrhea and mixed bowel habits we observed normalisation as well. Patients started to have fewer bowel movements (from 20 to 7.9 per week for diarrhea and from 10.7 to 6.8 for mixed pattern), which also reached statistical significance (Fig. 4.).

To assess the effectiveness of prolonged treatment, the most important is patients' compliance with the prescribed therapy. In our cohort, 31% of patients followed doctors' recommendations strictly and 92.9% strictly and very good. Evaluation of compliance using a designed questionnaire was performed by both the doctors and the patients during each visit.

Additionally, we compared a small subset of patients (27 individuals) treated with a higher dose of rifaximin-α (1200 mg per day). We found that patients who were prescribed 1200 mg of rifaximin-α per day had a more complicated disease with longer-lasting symptoms and, more often they had a diarrheal form of the disease. There was no difference in symptom severity. After three and six months of treatment, pain improved statistically (almost twice) in 1200 mg group as compared to the 800 mg group. Although after 3 months the overall symptoms resolved more often, after 6 months there was no difference between both groups in the severity of the symptoms.

DISCUSSION

The goal of SUDD treatment is complex and comprises of symptom control, dysbiosis treatment (to restore and maintain eubiosis),

recurrence prevention, and reduction of the complication rate [20–22]. To date, four large-scale studies by Papi et al., Latella et al. and Collechia et al. which were later confirmed by Bianchi's et al. metanalysis have established the efficacy of rifaximin-α with fiber in SUDD treatment [23–27]. Also recently, DiMario et al. showed that even 8 years of use of rifaximin-α (but without specified fibre supplements) brought year-by-year reduction of symptoms and risk of relapse [12]. Thus, it is proven that cyclic rifaximin, probably with some kind of fibre supplementation is effective in SUDD treatment. However, currently no studies are investigating the impact of prolonged therapy with rifaximin-α combined with arabinogalactan-lactoferrin on the course of SUDD. A recent work of Banasiewicz et al. has compared the treatment with rifaximin-α alone and the one combined with arabinogalactan-lactoferrin in a three-month period. They found that both therapies were effective in symptom resolution, but additionally, the combined therapy significantly improved (normalized) stool quality (assessed with Bristol scale) and stool frequency in patients with altered bowel habits and also improved SUDD patients' quality of life [18].

To the best of our knowledge, our study is the first longitudinal real-life study evaluating the use of rifaximin-α with arabinogalactan-lactoferrin combination showing a gradual improvement in symptoms, regardless of other treatments, or even a reduction in the use of other therapies in favor of the studied therapy. Our assessment of the arabinogalactan-lactoferrin positive impact on the normalization of bowel movement is consistent with previous studies evaluating a high-fiber diet on bowel habits [28, 29]. In a large EPIC population study (47033 respondents) assessing the frequency of hospitalizations for diverticulitis, it was found that people on a high-fiber diet (over 25.5 g/d) had a lower risk of hospitalization than those on a low-fiber diet which was dependent on the regular bowel habits [30]. So far, there are no studies assessing patients' compliance which is crucial in case of long--term treatment. We found that patients accept the necessity and costs of the therapy for the price of treatment effectiveness. Thus patients' hesitation should be no longer a concern. Future studies are needed to confirm our primary analysis showing that the dose of 1200 mg per day may be better than 800 mg in terms of pain treatment and deep remission of SUDD.

Our study has some limitations. Due to its retrospective nature, we were unable to adequately assess the accuracy of the population included, but it is worth noting that the doctors chose the patients to include. We are therefore concerned that, despite restrictive inclusion criteria, the doctors selected only those who responded exceptionally well to the treatment.

CONCLUSION

In this first real-life, six-month study we confirmed the efficacy of combined therapy with rifaximin-α and arabinogalactan--lactoferrin in symptom resolution and bowel movement frequency normalization in symptomatic uncomplicated diverticular disease (SUDD) with excellent patients' compliance.

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