A phase III study comparing secondary long-term prophylaxis versus on-demand treatment with vWF/FVIII concentrates in severe inherited von Willebrand disease

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Background. There is a lack of prospective clinical trials specifically designed to evaluate the benefits of prophylaxis with vWF/FVIII concentrates in patients with inherited von Willebrand disease (vWD). The aim of the study was to compare efficacy of secondary long-term prophylaxis (PRO) with vWF/FVIII in the prevention of bleeding episodes in severe vWD patients to standard of care (on-demand treatment; ODT).

Materials and methods. In this 12-month, phase III, open-label study (PRO.WILL), vWD patients (aged ≥6 years) were randomised to PRO (n=9; 5 completed) or ODT (n=10; 7 completed) treatment with Fanhdi®/Alphanate® (Grifols) according to current licensing status for use in vWD. We assessed the proportion of patients who did not present any spontaneous bleeding episode, adverse events (AEs) or thrombotic events.

Results. All patients on ODT had vWD type 2 or 3 vs 70% of patients on PRO. All ODT patients experienced bleeds vs 60% on PRO. PRO patients showed fewer bleeds (n=32 vs n=172 [112 in the same patient, mostly mucosal]; p<0.0001) and lower risk of bleeding (relative attributable risk estimate: −0.667; 95% CI: −2.374, −0.107; p<0.001). Most frequent bleeds in ODT and PRO groups were, respectively, epistaxis (n=52 vs n=15) and gastrointestinal (n=13 [9 in the same patient] vs n=1). While most bleeds lasted one day under ODT (31/32), only epistaxis did so in PRO group (14/15). No AEs due to study medication were observed.

Discussion. Despite the small sample size and the heterogeneity of the study population, patients on vWF/FVIII prophylaxis showed a reduction in bleeding risk and rate compared to on-demand treatment.

Keywords: secondary long-term prophylaxis, on-demand treatment, von Willebrand disease, von Willebrand factor, factor VIII.

Introduction

von Willebrand disease (vWD) is caused by reduced or dysfunctional von Willebrand factor (vWF), a complex multimeric glycoprotein that plays a key role in haemostasis1. vWD patients show excessive and frequent mucocutaneous bleeding episodes (e.g. epistaxis, menorrhagia and gastrointestinal bleeds)2, and in severe cases, especially in vWD type 3, spontaneous bleeds into joints, soft tissues and other sites may occur3-5.
vWD is categorised into three major types. Type 1 vWD is the most common (65-70% of all cases), and is characterised by a quantitative deficiency of vWF. A qualitative defect in the vWF molecule is the cause of type 2 vWD (25-30% of all cases), which is in turn classified into types: 2A and 2B, 2M, and 2N, depending on their functional defects. Total or near total absence of vWF characterises type 3 vWD, the most severe and rare type affecting about 1 in 500,000 people\(^1\).

The main treatment options for vWD patients are desmopressin (DDAVP)\(^6\), plasma-derived vWF-containing FVIII concentrate (vWF/FVIII) or pure vWF (plasma-derived or recombinant)\(^7\). DDAVP induces the transient increase of vWF, FVIII and tissue plasminogen activator (t-PA), although its cellular mechanism of action has not been fully elucidated\(^8\). Importantly, severe/moderate vWD forms, particularly vWD type 2A and 2M, are unresponsive to DDAVP due to a lack of vWF in storage compartments or to the release of an abnormal vWF\(^9\).

Substitutive therapy with vWF/FVIII or pure vWF is the treatment of choice for type 3 and type 2B vWD, and also for patients responsive to DDAVP who are undergoing surgery or a procedure with high bleeding risk\(^7\). The relative content of FVIII and vWF in commercially available vWF/FVIII products varies, with products with a vWF:FVIII ratio ≥1 being preferred for vWD treatment\(^7\). On-demand treatment (ODT) is the standard of care for bleeding, primarily through the administration of DDAVP and/or vWF/FVIII concentrates. Conversely, prophylaxis with vWF/FVIII concentrates is a preventive treatment option in patients with vWD, and its efficacy and safety have been suggested\(^1\). Although secondary long-term prophylaxis (PRO) is currently an option for an increasing number of vWD patients\(^7\), there is a lack of prospective clinical trials specifically designed to evaluate the benefits of such a PRO vs ODT using vWF/FVIII concentrates in severe vWD\(^10,11\).

Here we report the results of the PRO.WILL study, which aimed to assess the efficacy of PRO with vWF/FVIII concentrates in the prevention of bleeding episodes in severe vWD patients unresponsive to DDAVP, compared to ODT.

**Materials and methods**

**Study design and objectives**

This was a 12-month, international, multicentre, phase III, randomised, open-label, parallel-group study conducted at 13 centres in Italy, Germany and Spain (EUDRACT n: 2006-001383-23). The study was conducted in accordance with the ethical principles set out in the Declaration of Helsinki and was approved by the ethics committees of the participating centres. Written informed consent was obtained from the patients or, in the case of children, from their legal guardian.

The primary objective was to evaluate if PRO with a vWF/FVIII concentrate was effective in preventing spontaneous bleedings in patients with severe vWD unresponsive to DDAVP when compared with ODT.

**Patients and randomisation**

Patients who met the following criteria were included in the study: ≥6 years of age with severe inherited vWD as previously defined\(^3\), with frequent bleeding episodes (defined as ≥5 bleeding episodes in the last 12 months, or ≥3 episodes of haemarthrosis at the same joint or ≥2 episodes of gastrointestinal haemorrhage either unexplained or in association with underlying gastrointestinal angiodysplasia with requirement of vWF/FVIII therapy), and with lack of DDAVP responsiveness (defined as a relative increase in plasma Factor VIII procoagulant activity [FVIII:C] and ristocetin co-factor activity [vWF:RCo] levels of at least 3-fold over baseline and absolute increase to 30 IU/dL or more for both measures) or contraindication or intolerance to DDAVP.

Key exclusion criteria included the presence of alloantibodies against vWF or FVIII, acquired von Willebrand syndrome (AvWS), advanced liver cirrhosis, pregnancy or breastfeeding, planned invasive procedures within three months, conditions predisposing to gastrointestinal bleeding (unrelated to vWD), concomitant autoimmune anaemia and thrombocytopenia.

The randomisation list was generated by SAS software (SAS Institute Inc., Cary, NC, USA). The random codes for treatment assignment and to track recruitment were provided by a centralised computerised system. Randomisation was stratified according to the type of bleeding (gastrointestinal, haemarthrosis and epistaxis/other bleeding).

**Investigational vWF/FVIII product**

Fanrdi® (Instituto Grifols S.A., Barcelona, Spain) and Alphanate® (Grifols Biologicals Inc., Los Angeles, CA, USA) used in this study are highly purified, doubly virus-inactivated vWF/FVIII concentrates with standardised vWF:FVIII concentrations that share the manufacturing process. Retrospective studies have demonstrated the clinical efficacy and safety of the study product in vWD patients, not only in the management of bleeding episodes and surgery\(^14,15\), but also in secondary prophylaxis of severe vWD\(^3\). In addition, a prospective, multicentre study showed the product to effectively stop active bleeding episodes and provide adequate haemostasis for surgical or invasive procedures\(^36\).
**vWF/FVIII treatment procedures**

Before entering the study, a wash out of ten days from the last vWF/FVIII infusion was mandatory. For both PRO and ODT, vWF/FVIII was used according to current licensing status for use in vWD in each participating country.

Prophylaxis patients with previous recurrent haematomas or haemarthrosis received 60 IU vWF:RCo per kg of body weight every third day (rounded up to available pack sizes). Patients with previous mucosal bleedings received the same dose every second day.

On-demand treatment patients received 40-60 IU vWF:RCo per kg of body weight (rounded up to available pack sizes) at the onset of each bleeding episode. Infusions could be repeated every 12 hours at the discretion of the investigator responsible.

**Efficacy and safety assessments**

Patients were evaluated at the baseline randomisation visit and at monthly follow-up visits. The primary efficacy end point was the proportion of patients who did not present any spontaneous bleeding episode (defined as occurring in the absence of concomitant trauma, local injury, invasive diagnostic or surgical procedures) during the study period.

Secondary efficacy end points included: the incidence rate of spontaneous bleedings (episodes per patient-time), the interval between randomisation and the first bleeding episode after randomisation, the mean duration of spontaneous bleeding episodes, the mean number of infusions per spontaneous bleeding episode, and the mean dose of vWF/FVIII concentrate administered per spontaneous bleeding episode (only for bleeding episodes requiring treatment with FVIII/vWF concentrates).

Safety end points included monitoring adverse events (AEs) and thrombotic events, together with blood analysis parameters. AEs were classified according to severity (serious [SAE], non-serious), maximum intensity (mild, moderate, severe), and causality to the study treatments (unrelated, unlikely, possibly, probably).

**Statistical analysis**

The sample size estimation was based on the preliminary data presented by Federici et al., where in a cohort of 11 patients enrolled in a programme of secondary long-term prophylaxis and observed for a period of 3-15 months, a proportion of 64% reached the end point "complete prevention of spontaneous bleeding". It was also expected that approximately 10% of ODT patients would not show any recurrence of bleeding, given the brief observation period and the unpredictability of these events. Assuming a one-sided significance level of 0.05, 24 patients (12 per treatment group) would have provided a power of 90% to prove an absolute difference between the two groups in preventing spontaneous bleeding of around 60% and a power of 80% to prove an absolute difference of around 50% (NQuery Advisor, 6.0 [Statsols, Cork, Ireland]).

Data are presented as mean±standard deviation (SD), median and range, or median and first and third quartiles (Q1, Q3), whenever appropriate. For primary efficacy analysis, a χ² test was performed. For secondary efficacy analysis, Student's t-test or non-parametric Wilcoxon test, in case of non-normality, were performed. Attributable risk (AR) and its 95% confidence interval (CI) were estimated to evaluate the absolute difference of incidence between treatment groups. p<0.05 was considered statistically significant. Log rank test was performed to compare the difference between treatments in time (days) elapsed between randomisation visit and the first bleeding episode (time free from event). All statistical analyses were produced using SAS® release 9.4 or later (SAS Institute Inc).

**Results**

A total of 22 patients were screened between October 2006 and August 2016, and 19 were randomised: 9 to the ODT group and 10 to the PRO group. Twelve patients (7 ODT and 5 PRO) completed the full set of study visits, 3 of whom presented major protocol deviations (all in the ODT group). A flowchart showing patients’ details during the study and reasons for discontinuation is available in Figure 1.

**Patients’ characteristics**

Most patients were male (7 ODT, 7 PRO). The median age at study inclusion was 54 years (Q1, Q3: 45-64) in the ODT group and 28 years (Q1, Q3: 15-48) in the PRO group. Following randomisation at enrolment, vWD type 3 was the most common disease type in the ODT group while vWD types 1, 2A and 3 were equally common in PRO group (Table I). The detailed clinical characteristics of patients at baseline are shown in Table II. Due to the different distribution of vWD types in ODT vs PRO, the levels of vWF/FVIII activities were higher in PRO but the clinical severity of the two groups assessed by bleeding score was similar (Table II).

**Efficacy outcomes**

All 9 patients (100%) in the ODT group and 6 out of 10 patients (60%) in the PRO group experienced bleeding during the study. Four PRO patients discontinued the study despite not having any bleeding episodes (2 patients withdrew their consent and 2 patients were lost to follow up). Considering those patients who dropped out, the actual statistical power was 69.2%.

The mean number of bleeding episodes per patient
was higher in the ODT group (medians: 8.0 [Q1, Q3: 2.0, 13.0] vs 5.5 [Q1, Q3: 2.0, 9.0] in the PRO group; \( p<0.0001 \)), resulting in an incidence rate of 1.41 per patient-month in the ODT group (172 episodes, although it should be noted that 112 of them occurred in a single patient) and 0.34 in the PRO group (32 episodes).

The frequency and incidence rate of bleeding episodes during the study is shown in Table III. The most frequent site of "other" bleeding events in ODT was gums. In the PRO group, 9 of the 13 gastrointestinal bleeding episodes occurred in one single patient.

Table II - Clinical characteristics of patients at baseline according to treatment groups. Data are presented as mean±standard deviation or number (%).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>On-demand (N=9)</th>
<th>Prophylaxis (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVIII:C (IU/dL)</td>
<td>31.0±27.5</td>
<td>43.4±36.5*</td>
</tr>
<tr>
<td>vWF:RCo (IU/dL)</td>
<td>6.0±0.0</td>
<td>10.3±11.3*</td>
</tr>
<tr>
<td>vWF:Ag (IU/dL)</td>
<td>32.9±45.4</td>
<td>67.9±93.6*</td>
</tr>
<tr>
<td>Bleeding time (minutes)</td>
<td>35.7±1.15</td>
<td>18.2±6.6*</td>
</tr>
<tr>
<td>Prothrombin time ratio</td>
<td>1.1±0.1</td>
<td>1.1±0.1</td>
</tr>
<tr>
<td>Partial thromboplastin time ratio</td>
<td>1.5±0.4</td>
<td>1.8±0.5</td>
</tr>
<tr>
<td>Bleeding score</td>
<td>15.0±8.5</td>
<td>14.7±6.7</td>
</tr>
<tr>
<td>Number of bleeding episodes needing vWF/FVIII treatment†</td>
<td>11.8±8.9</td>
<td>12.8±14.2</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>8.2±9.5</td>
<td>9.0±14.9</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0.2±0.7</td>
<td>1.1±1.5</td>
</tr>
<tr>
<td>Haemarthrosis</td>
<td>1.3±2.7</td>
<td>2.0±6.3</td>
</tr>
<tr>
<td>Muscular haematoma</td>
<td>1.8±5.0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0.2±0.4</td>
<td>0.7±2.2</td>
</tr>
<tr>
<td>Number of patients who:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>had a family history of bleeding episodes</td>
<td>6 (67)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>received on-demand treatment with vWF/FVIII†</td>
<td>8 (89)</td>
<td>9 (90)</td>
</tr>
<tr>
<td>received other drugs or transfusions related to vWD†</td>
<td>1 (11)</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>

*p<0.05. †In the 12 months before baseline. ‡Including anaemia, splenomegaly, hypertension, coronary bypass, ventricular arrhythmia, hepatomegaly, chronic viral infection, diabetes mellitus, hyperlipidaemia, vertigo. N: number; FVIII: factor VIII; vWD: von Willebrand disease; vWF:RCo: ristocetin co-factor activity; vWF:Ag: vWF antigen.

Overall, the risk of bleeds was lower in the PRO vs the ODT group with a relative AR estimate of −0.667 (95% CI: −2.374, −0.107; \( p<0.001 \)).

The mean time from baseline to the first bleeding episode was 66.0±33.7 days vs 34.6±10.5 days in the ODT group. The median event-free interval was 23 days in both groups. According to a Kaplan-Meier analysis, the difference was not significantly different (\( p=0.2795 \)) (Figure 2).

The duration (days) of bleeding episodes per patient was shorter in the ODT group for each type of haemorrhage (Table IV). Most episodes lasted one day (151/172; 88%) or two days (19/172; 11%) in the ODT group, with a single muscle haematoma lasting.
Prophylaxis treatment in von Willebrand disease

Table III - Number and incidence rate of bleeding episodes during the study according to treatment groups.

<table>
<thead>
<tr>
<th>Type of bleeding episode</th>
<th>On-demand (N= 9)</th>
<th>Prophylaxis (N= 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Rate</td>
</tr>
<tr>
<td>Any type</td>
<td>172</td>
<td>1.41</td>
</tr>
<tr>
<td>Mucosal bleeding</td>
<td>164</td>
<td>1.34</td>
</tr>
<tr>
<td>epistaxis</td>
<td>52</td>
<td>0.42</td>
</tr>
<tr>
<td>other bleedings</td>
<td>112†</td>
<td>0.92</td>
</tr>
<tr>
<td>Joint and muscle bleeding</td>
<td>7</td>
<td>0.05</td>
</tr>
<tr>
<td>haemarthrosis</td>
<td>3</td>
<td>0.02</td>
</tr>
<tr>
<td>muscle haematoma</td>
<td>4</td>
<td>0.03</td>
</tr>
<tr>
<td>Gastrointestinal haemorrhage</td>
<td>1</td>
<td>0.01</td>
</tr>
</tbody>
</table>

†All in one single patient (106/112 bleeding gums). ‡Nine in one single patient. N: number.

Figure 2 - Probability of remaining free of a first spontaneous bleeding episode during the study. ODT: on-demand treatment; PRO: prophylaxis treatment; n: number.

Table IV - Duration of bleeding episodes during the study and number of patients who experienced them, according to treatment groups.

<table>
<thead>
<tr>
<th>Type of bleeding episode</th>
<th>Patients (N)</th>
<th>On-demand</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (N)</td>
<td>1 2 3 4</td>
<td>Patients (N)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>6</td>
<td>36 16</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Haemarthrosis</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Muscle haematoma</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>110 1</td>
<td>2</td>
</tr>
</tbody>
</table>

N: number.

three days and a single episode of other bleedings lasting ≥4 days. In the PRO group, a 1-2-day duration was observed for 14/32 episodes of epistaxis (44%) and one episode of other bleedings (3%), while other episodes lasted longer: 3 days for one (3%) epistaxis and one (3%) haemarthrosis; ≥3 days for 13/32 (41%) gastrointestinal bleeds; ≥4 days for one (3%) episode of other bleedings; and 6 days for one (3%) muscle haematoma.

vWF/FVIII treatment during the study

The median study duration was 12.1 months (Q1, Q3: 11.7-12.9) in the ODT group and 10.5 (Q1, Q3: 2.3-11.9) in
the PRO group. In the PRO group, vWF/FVIII concentrate doses were infused either every third day (n=2) or every second day (n=3).

The mean dose of FVIII recorded at the randomisation visit for 8 PRO patients was 38.6±16.0 IU/kg. On subsequent visits, the mean doses of FVIII remained consistent with that at randomisation (range: 36.3±9.25 IU/kg to 42.0±3.5 IU/kg).

In the ODT group, most bleeding episodes required the use of vWF/FVIII concentrates (162/172; 94.2%) compared to 14/32 (43.7%) in the PRO group. The mean dose of FVIII was higher in the ODT group for epistaxis (ODT 47.9 IU/kg vs PRO 17.9 IU/kg) and muscular haematoma episodes (ODT 81.5 IU/kg/PRO 47.2 IU/kg); the reverse was observed for gastrointestinal bleeding (ODT 160.0 IU/kg / PRO 272.5 IU/kg) and haemarthrosis (ODT 49.1 IU/kg / PRO 92.2 IU/kg).

Safety outcomes

All 19 patients were evaluable for AEs. None of the clinical AEs observed were considered to be due to study medication. Seven patients prematurely discontinued the study (2 ODT; 5 PRO) (Figure 1). No patient discontinued the study due to an AE. One patient in the PRO group had an intestinal perforation, (reported as severe) that resolved with a combination of concomitant medication and hospitalisation. This event was not considered to be related to the study medication. No patient died during the study.

Three patients (33.3%) in the ODT group and 6 patients in the PRO group (60.0%) experienced AEs. AEs consisted mostly of blood and lymphatic system disorders (anaemia and lymphadenopathy). Only one SAE, an intestinal perforation (reported as severe and resolved during the study) was observed in the PRO group. Severe hypertension was reported in one ODT patient. No thromboembolic events were observed. A summary of patients with AEs is shown in Table V.

Haematologic abnormalities at the end of study were observed in 8 ODT patients and 4 PRO patients. Low haemoglobin levels (5/8 ODT patients and 2/4 PRO patients) and low erythrocyte counts (5/8 ODT patients and 3/4 PRO patients) were the most frequent.

Discussion

While there have been a number of retrospective and prospective clinical studies using vWF/FVIII to assess secondary long-term prophylaxis in clinically severe vWD\(^1\)\(^{-}\)\(^{27}\), the PRO.WILL is the first randomised clinical trial to compare the efficacy in the prevention of bleeds of PRO treatment with vWF/FVIII in severe DDAVP-unresponsive vWD patients.

In most of the previous studies, the targeted vWD patient profile was a challenging one\(^27\)\(^{-}\)\(^{29}\). The same

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**Table V** - Summary and numbers of patients with adverse events according to treatment groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>On-demand (N=9)</th>
<th>Prophylaxis (N=10)</th>
<th>Total (N=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of AEs reported</td>
<td>12</td>
<td>25</td>
<td>37</td>
</tr>
<tr>
<td>Number of distinct AEs by preferred term</td>
<td>9</td>
<td>21</td>
<td>30</td>
</tr>
<tr>
<td>Number of patients with AEs, N (%)</td>
<td>Any AE</td>
<td>3 (33.3)</td>
<td>6 (60.0)</td>
</tr>
<tr>
<td></td>
<td>Serious AEs</td>
<td>0</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td></td>
<td>Severe AEs</td>
<td>1 (11.1)</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td></td>
<td>Concomitant medication for AEs</td>
<td>3 (33.3)</td>
<td>4 (40.0)</td>
</tr>
<tr>
<td>Treatment dosage adjusted/temporarily interrupted due to AEs</td>
<td>0</td>
<td>1 (10.0)</td>
<td>1 (5.3)</td>
</tr>
</tbody>
</table>

N: number; AEs: adverse events.
incidence rate and the overall risk of bleeds were in the expected ranges and lower in the PRO group, with the exception of gastrointestinal haemorrhage. The reasons why gastrointestinal bleeds seemed to respond poorly to PRO treatment remains unclear, although that could be partially ascribed to the propensity for this bleeding type, including a possible underlying gastrointestinal angiodyplasia, of the single outlier patient who experienced most (80%) of the episodes.

While there was no significant difference in the time to the first bleeding episode between groups, the duration of bleeds was longer in the PRO group for all bleeding types except epistaxis. This could be explained by the fact that almost all bleeds in the ODT group required treatment with vWF/FVIII concentrate, whereas less than half of the bleeding episodes in the PRO group required additional treatment.

Regarding safety, the infusion of vWF/FVIII was well tolerated in this patient population and no clinical AEs related to the study medication were reported. Importantly, there were no thromboembolic events, which constitute a theoretical risk associated with repeated infusions of vWF/FVIII usually due to high circulating levels of FVIII. The most common hematologic laboratory abnormalities were consistent with the underlying vWD.

Conclusions
Overall, the prophylactic use of vWF/FVIII concentrates appeared to be associated with a lower risk and frequency of bleeding episodes in severe vWD patients unresponsive to DDAVP, although more data are needed for gastrointestinal bleeding. Despite the small sample size of clinically severe vWD and its associated heterogeneity in the baseline characteristics of the participating patients, the PRO.WILL study supports for the first time in a randomised manner the efficacy of secondary long-term prophylaxis in reducing the bleeding risk and rate in severe vWD. Further prospective clinical trials should address the obstacles to the use of prophylaxis in vWD and enrolment issues identified in this trial. Finally, larger cohorts of patients are required to allow a concrete assessment of the value of the prophylactic use of vWF/FVIII in high-risk vWD patients to be made.

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Authorship contributions
FP and ABF were the lead investigators. ABF contributed to the study design. FP and ABF analysed the data and interpreted the results. EP, GC, PG, RDC, PS, AB, MM, GG, GB, VJ-Y, CK and AI recruited the patients and collected the data. GC, PG, RDC, PS, ABF, MM, GG, GB, VJ-Y, CK, and AI interpreted the results and contributed intellectual content. FP and ABF helped write the manuscript. All Authors read and approved the final version for publication.

Disclosure of conflicts of interest
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