Although Peyronie’s disease (PD) was recorded in the medical history more than 200 years ago, its primary management modality has been always surgery without any evidence based alternative until now. Despite the numerous medical treatment options offered to patients in the active phase of the disease (vitamin E, colchicine, pentoxifylline, PABA, NSAID), no oral medical treatment proved useful in meaningful penile curvature improvement in the active phase (1).

Despite the lack of FDA approval, various intraleral injection (ILI) treatments had been tried and proven useful in different degrees. AUA guidelines allowed off label usage of IFN-2b and channel blockers whereas they were suggested with an evidence level of B and C respectively in ISSM 2016 PD guidelines (1,2). About 54% of the patients who received IFN-2b treatment ILI had meaningful (>20%) curvature improvement with a mean curvature change of 9° in comparison with placebo (3). The literature is contradicted in the efficacy of calcium channel blocker, verapamil and its efficacy showed significance in only some of the studies (4).

Collagenase clostridium histolyticum (CCH; Xiaflex; Auxilium Pharmaceuticals, Inc., Chesterbrook, PA, USA) is the most recently introduced ILI for PD and the first FDA-approved medical treatment modality for the disease and suggested by AUA/EAU guidelines with a grade B recommendation (2,5). CCH’s efficacy in penile curvature and patient’s symptom improvement was assessed initially in IMPRESS I and II trials which were important milestones in FDA approval of CCH. In these trials patients received up to 8 injections of 0.58 mg CCH which was two injections per cycle separated by 1–3 days and the second injection of each was followed 1–3 days later by penile plaque modeling. The patients with PD were stratified by baseline penile curvature (30°–60° vs. 61°–90°) and randomized into either placebo or treatment groups. In the post hoc meta-analysis of IMPRESS trials, men who were treated with CCH had a mean 17.0°±14.8° change per subject (34% curvature improvement), compared with a mean 9.3°±13.6° change in the placebo group (P<0.0001). In addition the mean change in PD symptom bother score was significantly improved in treatment group vs. placebo group (2.8±3.8 vs. −1.8±3.5, P<0.0037) (6). In a following open label phase 3 study which included CCH naive or placebo injected patients (n=347), 34.5% improvement in curvature degree (33° to 35°) and 3.3 increase in PD symptom bother domain score were achieved, similar to previous studies (7).

Curvature degree and PD symptom-bother reduction effect of CCH were assessed further in subsequent studies investigating subgroups. These subgroups were stratified by penile curvature deformity (30°–60°, 60°–90°), PD recommendation.
onset duration (1–2, 2–4, >4 yr), penile calcification level (no calcification, noncontiguous stippling, and contiguous calcification), and erectile function [EF; International Index of Erectile Function–Erectile Function domain (IIEF-EF) scores: 1–5, 6–16, ≥17; no sexual activity, low and high EF, respectively]. While therapy arm was significantly better than placebo arm in both in curvature and PD symptom-bother improvement for all subgroups. The significance of curvature improvement was valid for both 30°–60° and 60°–90° groups, but difference in change in symptom bother score did not reach significance in the 60°–90° group (P=0.071). The discrepancy between curvature and patient satisfaction in patients with greater curvature degrees (>60°) may indicate possible unsatisfactory results for greater curvatures (8,9). In our opinion the key part of the matter actually lies in the remaining curvature degrees. In the 30°–60° group, mean initial and post treatment curvature degrees were 44° and 29° since CCH provided 15° improvement in this group. The final curvature was below 30° which is the usually accepted threshold of sexual disability. On the other hand mean initial and post treatment curvature angulations were reported as 72° and 47° respectively as CCH provided 25° curvature change in 60°–90° subgroup. The remaining 47° curvature was above both the usual limit of 30° and 45° defined by Hellstrom et al. While positive response to global assessment of PD (GAPD, ≥1 point improvement) was observed in patients with residual penile curvature ≤45, this assessment is also impede by the fact that negative GAPD ratings were calculated as zero in the statistical analysis (10).

While patients in the 30°–60° curvature group may be saved from undergoing surgery, 47° is still above the surgical threshold (>30°) and the patients may still need to be operated. In a recent clinic non-controlled trial (n=69), negated need for surgery and penetration restoration were reported by 57% and 52% of the patients respectively after 23° curvature improvement (38%, P<0.0001) (11). Yang et al. reported similar results for penile penetration restoration (45.5%) in study investigating 49 PD patients (12). In conclusion we suggest recommending CCH ILI injection to only patients with 30°–60° curvature as potential treatment. Admittedly, Nesbit/plication surgery may be used instead of grafting after CCH injection for patients with 60°–90° curvature.

The safety of CCH administration is one the most important aspects and has been recently investigated in a study pooling safety analysis data of patients who received at least one dose of CCH in any of six clinical studies. In these six studies including three randomized, double-blind, placebo-controlled studies and three open-label safety and efficacy studies, adverse effects (AE) were investigated using categories including treatment-emergent AEs, treatment-related AEs, and serious AEs (SAEs). In addition possible immunogenicity-related AEs were assessed using increased anti-AUX-I and anti-AUX-II antibody levels. Out of 1,044 pooled patients, at least one treatment related AE (TRAЕ) was reported 85.8% of the patients. The most frequent AEs (≥25% of the patients) were penile hematoma, pain and swelling. While most of the patients (75%) had mild or moderate TRAEs, severe TRAEs were reported in 111 patients out of 1,044 (10.6%). Severe penile hematoma was observed in 39 patients (3.7%) whereas serious TRAEs were reported in 9 patients (0.9%). Out of the nine patients, five had penile hematoma and four had corporal ruptures which were managed either conservatively (n=1) or surgically (n=3). If we include the nine patients with typical popping sound, sudden penile detumescence and hematoma combination, corporal rupture incidence increase to 13 patients (1.3%). Although ≥95% of the patients anti-AUX I and II after two injection cycles, no association could be found between incidence, duration and severity of AEs and antibodies escalation (13).

Current article aims to expand the knowledge about adverse effects by surveying members of Sexual Medicine Society of North America (SMSNA). All 693 members of SMSNA were reached via survey monkey using their valid email addresses. This anonymous survey included 33 questions in total but if question 10 (whether corporal rupture happened: yes/no) was answered negatively, the remainder of the survey was terminated. The survey questioned both the general experience of the members using CCH and their approach to hematomas/corporal ruptures occurring during CCH treatment.

The survey was completed by 14.4% of 693 SMSNA members (n=100) and 36%, 23%, and 41% of responding members had performed <10, 11 to 20, and >20 CCH injections respectively. Discontinuation of anti-platelets and anti-coagulants were recommended by 54% of members to prevent hematoma. While more than one-third of them (37%) did not recommend dressing, removal of the dressing at day 1 was suggested by 50% of them. In accordance with IMPRESS trials, 89% of the responders recommend manual modelling to the patients at injection intervals. Surprisingly more than one-third of the physicians (39%) extrapolated their experience with verapamil and interferon alfa to CCH ILI and recommended traction therapy during
CCH therapy despite the lack of evidence based studies or prospectus suggestions.

Encountering severe hematoma in more than >10% of the patients were reported by 27% of the responder. Since 3.7% severe hematoma and 80% total hematoma were reported in Carson et al. (13) study, the hematoma rates may be investigated further in post marketing studies. Subjective categorization of penile bleeding (“injection site hematoma (mostly reported as injection site bruising), penile hematoma (mostly reported as penile bruising), contusion, ecchymosis, penile haemorrhage (mostly reported as penile ecchymosis), and injection site haemorrhage (mostly reported as injection site ecchymosis)”) might lead to different hematoma incidence reports. Hematoma drainage was performed by 9% of responders in case of penile hematoma. In case of hematoma, 83% of the responder preferred conservative management and 84% of them delayed the next CCH injection. An interesting detail was that no increase of hematoma incidence was detected in anti-coagulant/platelet using patients and patients whom penile dressing was not applied.

One third of the responders (34%) encountered at least one corporal rupture which happened 5 (median)/ 10 (mean) days (range, 0.5–30 days) after CCH injection in general. Corporal rupture incidence was not associated with user experience (≤30 vs. >30 and ≤50 vs. >50 treated patients). Corporal fracture incidences were reported as 0.3% in IMPRESS trials whereas a higher rate of 1.3% was reported by Carson et al. (13) in their pooled data of six studies when suspected cases were also included. Total number of ruptures reported by the authors was 41 in total (1, 2 and 3 ruptures reported by 26, 6 and 1 physicians). While exact percentage cannot be calculated due to lack of total patient number, a rough estimation of total patient number may be done. If we accept a median case number for each patient number interval reported by the members (5 for 1–10, 15 for 11–20 etc.), number of patients included in the study may be approximated as 1,200 and thus an incidence of 3.3% will be reached. Both of these prevalence numbers indicate a higher rate of corporal fracture complications than reported in IMPRESS trials. This variance between studies may be due to under-reporting of the prescribers, subjective differential diagnosis of corporal rupture, severe penile hematoma and subcutaneous haemorrhage. In the two post marketing clinic trials, corporal rupture incidence was reported as 0% (11) and 2% (12). These suspicions may only be confirmed with the help of additional longitudinal prospective trials.

Two predominant causes of rupture were reported as vigorous intercourse (38%) and nocturnal erections (31%). While 2 weeks sexual intercourse prohibition following CCH injection was suggested in prescribing pamphlet, 14 out of 32 (44%) respondents reported longer rupture time than the recommended 2 weeks window. Therefore we agree with the suggested minimum intercourse prohibition time of 4 weeks.

Diagnosis method was history/physical exam or additional imaging in 49% and 51% of patients respectively. Penile plaque was the source of rupture in 84% of cases and 67% of the responders managed it via surgery intervention. Similar to rupture incidence, surgical intervention rate was also not related to experience with ILI CCH. Surgeons operated the cases after a median time of 10.5 hours (range, 3–36 hours) in accordance with penile fracture management principles. Distal circumcision and degloving technique was used in 76% of the cases and 62% of the responder assessed the tissue quality worse than the one encountered in normal penile fracture cases (14). Levine et al. reported seven men who underwent either plicaton or grafting surgery following unsatisfactory CCH injection after a mean time of 182 days. Penile curvature <20° and normal penile rigidity were achieved in all of the patients and no intraoperative difficulty were observed by the surgeons different from standard PD surgery (15). The difficulty difference reported by the two studies may be due to that Levine et al. operated a non-fractured, non-hemorrhagic penis after 6 months whereas penile fracture surgery was performed in a hematoma medium only after 10.5 hours (range, 10–36 hours) by SMSNA members.

No significant difference was reported by SMSNA members in EF, ability to have intercourse, change in penile curvature, and abscess development, patient and physician satisfaction after surveillance and surgery. Only reported difference was in mean time to resumption of sexual intercourse (4.8 vs. 7.2 weeks). However follow-up time was rather short for both groups (120 and 83 days) and curvature may be encountered in the long-term follow-up. There is a drastic difference between two options for penile fracture cases (surgery success 92% vs. 59%). In our opinion this experience from past fracture cases should be used when dealing with post CCH ruptures and surgery should be performed if needed in the first 24–72 hours after rupture time onset.

Despite its limitations (subjective reporting of the physicians, low response rate), this article reflects the clinical practices of roughly 12.5% of CCH users. Higher rupture and severe hematoma incidences than expected is
the most interesting point of the article and forces us to vigorously search for AEs while using CCH. Increasing sexual prohibition to 30 days is the most concrete data of the study.

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None.

**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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