

Identifying factors associated with clinical success in patients treated with NASHA[®]/Dx injection for fecal incontinence

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Purpose: Injection with the bulking agent consisting of non-animal stabilized hyaluronic acid/dextranomer (NASHA[®]/Dx) is well tolerated and efficacious for the treatment of fecal incontinence (FI); however, the patient population that may derive maximum benefit has not been established. This post hoc responder analysis assessed demographic and baseline characteristics predictive of responsiveness to NASHA/Dx treatment.

Methods: Adults with a Cleveland Clinic Florida fecal incontinence score (CCFIS) ≥ 10 were randomized to receive NASHA/Dx or sham treatment. The primary end point was response to treatment (ie, decrease from baseline of $\geq 50\%$ in number of FI episodes) at 6 months; a prespecified secondary end point was change in fecal incontinence quality of life (FIQL) score at 6 months. Post hoc subgroup analyses were performed for baseline and demographic characteristics and prior FI treatments.

Results: Overall, response to treatment was significantly greater with NASHA/Dx versus sham injection (52.7% vs 32.1%; $P=0.0089$). All subgroups analyzed demonstrated evidence of improvement, favoring NASHA/Dx versus sham treatment for both response to treatment and change in the FIQL coping/behavior subscale score. For the primary end point, a significantly greater percentage of patients with CCFIS ≤ 15 , FI symptoms ≤ 5 years' duration, or obstetric causes of FI responded to NASHA/Dx treatment versus patients receiving sham treatment (51.1% vs 28.3%, $P=0.0169$; 55.4% vs 25.7%, $P=0.0026$; and 53.6% vs 23.1%, $P=0.0191$, respectively). The mean change in the FIQL coping/behavior score significantly favored NASHA/Dx versus sham treatment for patients with CCFIS ≤ 15 ($P=0.0371$), FI symptoms ≤ 5 years' duration ($P=0.0289$), or obstetric causes of FI ($P=0.0384$). Patients without a history of specific FI treatments (eg, antiarrheal medications, biofeedback, surgery) were more likely to respond to NASHA/Dx versus sham treatment for both end points.

Conclusion: Although all subgroups analyzed showed evidence of quantitative and qualitative benefit from NASHA/Dx therapy, patients with characteristics indicative of mild-to-moderate FI may exhibit the greatest benefit.

Keywords: responder analysis, quality of life, coping/behavior, Solesta

Introduction

The prevalence of fecal incontinence (FI) is $\sim 8.4\%$ among noninstitutionalized adults, representing about 19 million people in the US,^{1,2} and increases with age, with $\sim 17\%$ of adults ≥ 65 years and as many as 50% of nursing home residents affected.³⁻⁶ FI is often a multifactorial disorder with a diverse etiology.⁷ For example, a grade 3 or 4 episiotomy was an obstetric risk factor for pelvic floor injury, even decades after childbirth, in a population-based study comparing women with and without FI.⁸ However, anal

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sphincter damage or injury unrelated to childbirth and neuromuscular and muscular diseases are also potential causes of FI.⁷ The clinical symptoms of FI are compounded by negative psychosocial effects (eg, diminished self-esteem, social withdrawal, and anxiety), and total costs associated with FI (ie, direct medical and nonmedical costs, indirect costs) average \$4,110 annually per patient in the US, with substantially higher costs in certain cases.^{3,9}

Treatment options for patients with FI include pharmacologic and surgical approaches as well as dietary modification and alternative therapies (eg, biofeedback).^{10,11} The choice of treatment modality depends on multiple factors, including the cause(s) of incontinence; degree of impairment and impact on functional status; the setting (eg, community or nursing home); comorbidities; and, ultimately, patient preference.¹⁰ Dietary modification, often coupled with fiber supplementation and bowel habit training, is recommended as a first-line treatment for patients with FI, and patients with diarrhea or loose stools may gain benefit from antidiarrheal medication as an early treatment measure.¹² Biofeedback is a potentially efficacious option in patients with mild-to-moderate FI but is largely dependent on proper training and patient adherence.¹¹ For some identifiable anal sphincter defects, surgical repair may be considered early in the treatment algorithm.^{11,13} The most common surgical intervention for patients with FI resulting from an injury to the external anal sphincter is sphincteroplasty;¹⁴ however, studies have failed to demonstrate long-term durability of this treatment.^{15–17} It is interesting to note that current trends suggest that surgery is being reserved for patients who have more severe FI and/or those whose FI has been refractory to other treatments,¹¹ but it is unclear whether surgical intervention in general, which may be associated with increased morbidity and length of hospitalization, is more efficacious in the long term than nonsurgical (eg, minimally invasive) FI treatment approaches.¹⁸

Perianal injection of bulking agents has been advanced as a minimally invasive treatment option for patients with FI, and studies evaluating a number of different bulking materials have been reviewed recently.¹⁹ The bulking agent consisting of non-animal stabilized hyaluronic acid/dextranomer (NASHA[®]/Dx) is a relatively newer option that has been characterized as being efficacious in several uncontrolled studies^{20–23} and randomized, controlled studies.^{24,25} In one randomized, double-blind, sham-controlled clinical study of NASHA/Dx in 206 patients with FI, 52.7% of patients in the NASHA/Dx group had a decrease from baseline of $\geq 50\%$ in the number of FI episodes compared with 32.1% of patients in the sham treatment group at 6 months post-injection.²⁵

Although almost all patients who received therapy derived at least some benefit from injection, it is unclear whether certain demographics, baseline characteristics, and/or previous FI treatments may be predictive of response to treatment with bulking agents such as NASHA/Dx.¹⁹ Studies of other treatments for FI have suggested that baseline and demographic characteristics, such as age, severity of disease, and type of FI, may be predictive of response.^{20,26–29} Accordingly, we conducted a post hoc responder analysis of data from the randomized, double-blind, sham-controlled trial²⁵ to examine demographic and baseline characteristics, including previous treatments, that might predict optimal responsiveness to NASHA/Dx treatment.

Methods

Patients and study design

Details of the patient population, inclusion and exclusion criteria, and study design have been described previously.²⁵ Briefly, patients 18 to 75 years of age with FI (Cleveland Clinic Florida fecal incontinence score [CCFIS] ≥ 10) and ≥ 4 episodes of FI during a 2-week time frame from the US and Europe were randomized (2:1) to receive transanal injections of NASHA/Dx or sham treatment. Immediately before receiving treatment, patients received a cleansing enema. Using an anoscope, four 1 mL injections were administered (1 mL in each quadrant [posterior, left lateral, anterior, and right lateral] of the submucosa of the anal canal), ~ 5 mm above the dentate line, without the use of anesthesia. The procedure for patients receiving sham treatment was similar, except that no substance was injected. At 1 month, patients with no persistent adverse events but persistent FI (CCFIS ≥ 10) were offered one retreatment procedure. Patients and study investigators were blinded to treatment administered during the first 6 months post-injection. During this 6-month period, patients underwent a clinical anorectal assessment and proctoscopy at 3 and 6 months.²⁵ The study was approved by the ethics committees and institutional review boards of all participating centers. All patients provided signed, informed consent.

Assessments

The primary efficacy end point was response to treatment, defined as a decrease from baseline of $\geq 50\%$ in the number of FI episodes at 6 months.²⁵ A secondary end point was assessment of the fecal incontinence quality of life (FIQL) scores, which include four subscales (ie, lifestyle, coping/behavior, depression/self-perception, and embarrassment)³⁰ at 6 months. The primary end point and

the FIQL coping/behavior subscale, chosen based on the significant improvement reported during the pivotal study,²⁵ were further analyzed by subgroups, which comprised baseline and demographic characteristics (ie, sex, age, body mass index, severity of FI, duration of FI, history of urinary incontinence, number of FI episodes, and cause of FI) and use of prior FI treatment modalities (ie, dietary avoidance, fiber supplementation, antidiarrheal medications, bowel habit training, biofeedback, and surgery).

Statistical analyses

For analysis of the primary end point, efficacy was evaluated in the intention-to-treat (ITT) population for each of the subgroups. As prespecified in the study protocol, odds ratios and corresponding 95% confidence intervals were generated for each comparison between NASHA/Dx and sham treatment using the logistic model, with baseline number of FI episodes, sex, and treatment center as covariates. For the primary end point, missing data were handled with the primary imputation method. In this prespecified scheme, baseline diary data were carried forward to 6 months for patients who were withdrawn from the study for any reason before or at the 6-month visit and did not have valid 6-month diary data. If a patient had not withdrawn from the study before the 6-month visit but had no valid diary data at 6 months, the most recent data were carried forward for them. For analysis of the FIQL coping/behavior subscale, change from baseline to 6 months was calculated in the ITT population for each subgroup using the prespecified imputation method of last observation carried forward. Least-squares (LS) means were estimated for NASHA/Dx and sham treatments in a given subgroup using the analysis of covariance model with baseline FIQL subscale score, sex, and treatment center as covariates. Differences in LS means, corresponding 95% confidence intervals, and *P*-values were generated from the same analysis model.

Results

Patient population

A total of 206 patients (NASHA/Dx, *n*=136; sham, *n*=70) were included in the ITT population. Demographic and baseline characteristics of the overall population were similar between the two treatment groups and have been previously reported.²⁵ Patients in the NASHA/Dx and sham treatment groups were mostly female (90% vs 87%, respectively) and of similar age (mean 61.8 vs 60.1 years, respectively), and had a similar body mass index (mean 25.8 vs 26.4, respectively). Baseline CCFIS (mean 14.0 vs 13.0, respectively)

and number of FI episodes (15.0 vs 12.5, respectively) were comparable between groups. At least half of patients receiving NASHA/Dx or sham treatment had previously undergone dietary modification (62% vs 70%, respectively), fiber supplementation (81% vs 73%, respectively), use of antidiarrheal drugs (60% vs 69%, respectively), or biofeedback (60% vs 50%, respectively) as treatment for FI. Only 15% and 11% of patients receiving NASHA/Dx or sham treatment, respectively, had undergone prior surgical intervention for FI.

Efficacy

The data for each subgroup analyzed generally favored NASHA/Dx versus sham treatment for the primary end point (Figure 1A and B). A significantly greater percentage of patients with a CCFIS of 10–15, indicative of less severe disease,²⁸ responded to treatment with NASHA/Dx compared with patients receiving sham treatment (51.1% vs 28.3%, respectively; *P*=0.0169); a greater percentage of patients with CCFIS >15, or more severe FI, responded to treatment with NASHA/Dx compared with sham treatment, but this finding was not significant (54.8% vs 35.3%, respectively; *P*=0.5682). Patients with FI symptoms of ≤5 years' duration had a significantly higher response rate with NASHA/Dx compared with sham treatment (55.4% vs 25.7%, respectively; *P*=0.0026). A greater percentage of patients with obstetric causes of FI responded to treatment with NASHA/Dx compared with sham treatment (53.6% vs 23.1%, respectively; *P*=0.0191).

While all patients were required to fail at least some form of previous therapy, in general, patients who had not received prior FI treatment via antidiarrheal medications, bowel habit training, biofeedback, or surgery were significantly more likely to respond to NASHA/Dx versus sham treatment (Figure 1B). With the exception of dietary avoidance, no significant differences were observed in patients with a medical history positive for other individual FI treatment.

Overall, subgroup analyses of the change from baseline to 6 months in the FIQL coping/behavior subscale favored treatment with NASHA/Dx versus sham treatment (Figure 2A and B). For patients with a CCFIS of 10 to 15 and duration of disease ≤5 years, indicators of mild-to-moderate disease, treatment with NASHA/Dx was significantly favored compared with treatment with sham (LS means difference in FIQL subscale score, 0.21 [*P*=0.0371] and 0.25 [*P*=0.0289], respectively). Patients with an obstetric etiology of FI had a greater change in the FIQL coping/behavior subscale following treatment with NASHA/Dx compared with sham

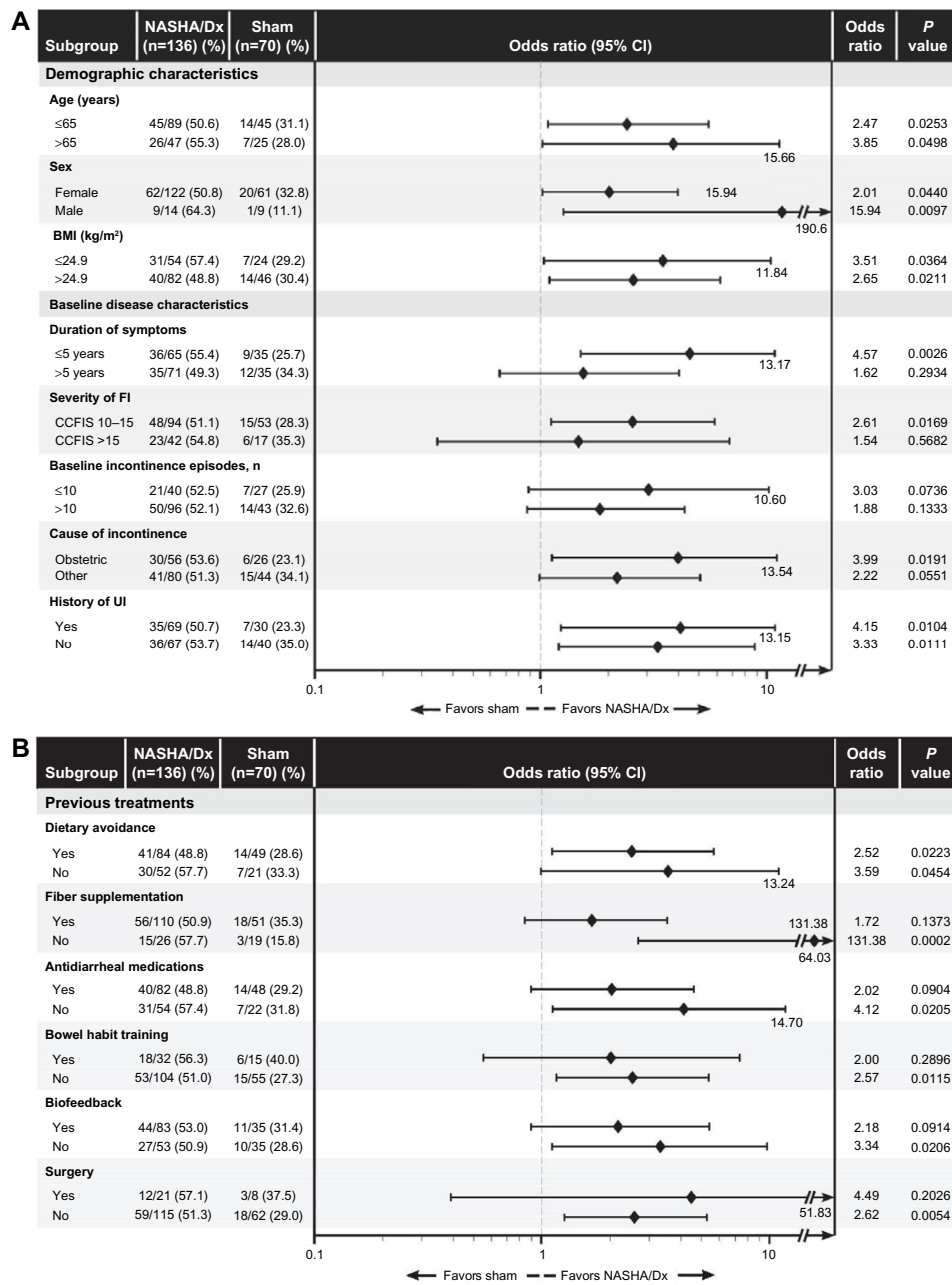


Figure 1 Patient response (ie, a decrease from baseline of ≥50% in the number of fecal incontinence episodes) to NASHA/Dx or sham treatment at 6 months.

Note: Patient response is based on (A) demographic and baseline characteristics and (B) previous treatment modalities.

Abbreviations: BMI, body mass index; CI, confidence interval; CCFIS, Cleveland Clinic Florida fecal incontinence score; FI, fecal incontinence; NASHA/Dx, non-animal stabilized hyaluronic acid/dextranomer; UI, urinary incontinence.

treatment (LS means difference, 0.32; $P=0.0384$). Patients without a history of treatment consisting of any one or more of antidiarrheal medications, bowel habit training, biofeedback, or surgery were also significantly more likely to respond to NASHA/Dx versus sham treatment (Figure 2B).

Discussion

Results of a randomized, double-blind, sham-controlled clinical trial in patients with FI showed that injection with

NASHA/Dx decreased the number of FI episodes by at least 50% in 52.7% of patients at 6 months compared with 32.1% of patients receiving sham treatment.²⁵ Previous studies have suggested that treatment response in patients with FI may be affected by demographic and baseline disease characteristics, including age, severity of disease, and type of FI.^{20,26} Because clinical trials may be designed to select for a homogeneous population of patients with FI, rather than for specific baseline or demographic characteristics,³¹ post hoc analyses

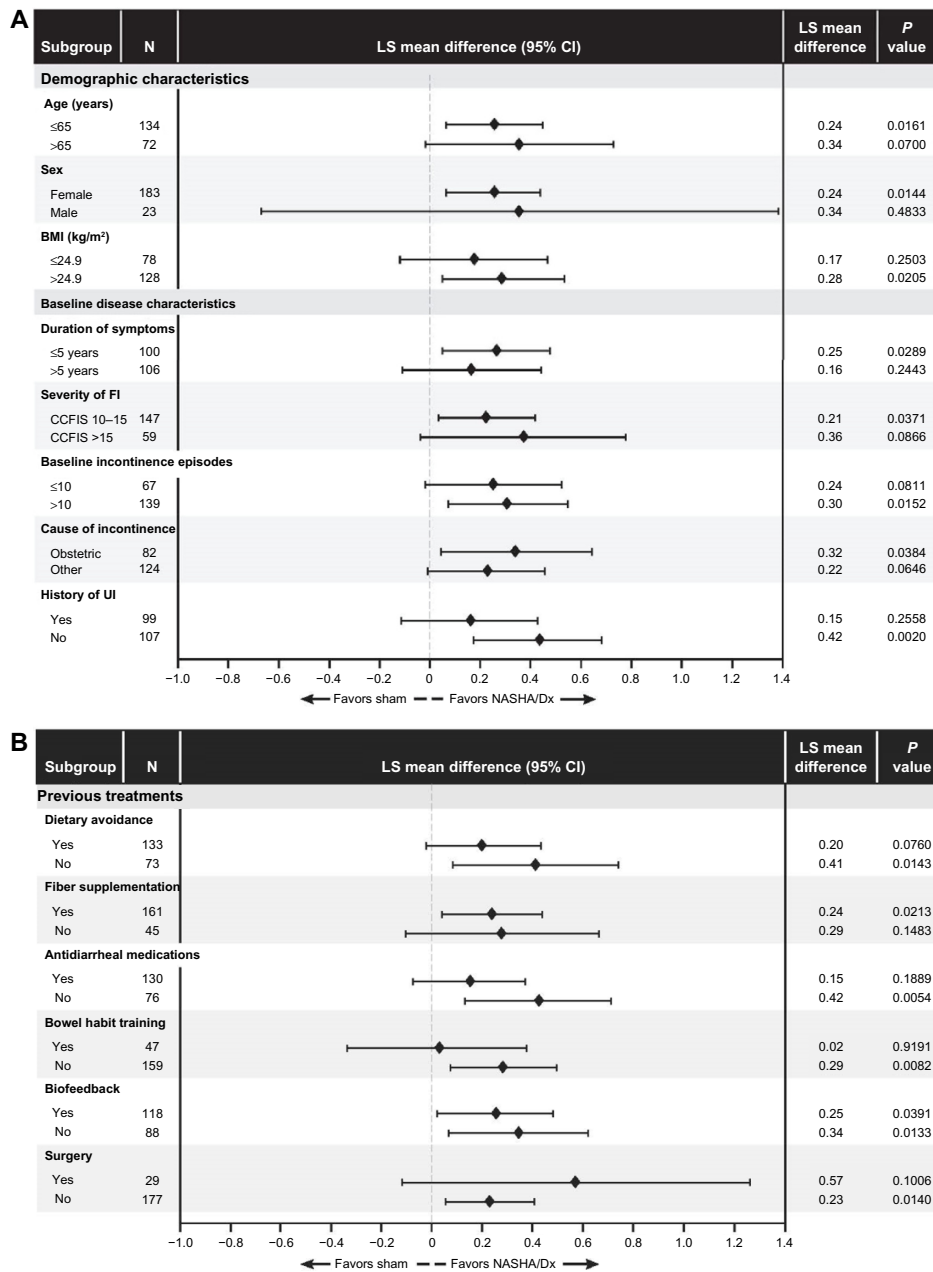


Figure 2 Change in FIQL coping/behavior subscale score from baseline to 6 months in patients receiving NASHA/Dx or sham treatment. **Note:** Change in FIQL coping/behavior subscale score based on **(A)** demographic and baseline characteristics and **(B)** previous treatment modalities. **Abbreviations:** BMI, body mass index; CCFIS, Cleveland Clinic Florida fecal incontinence score; CI, confidence interval; FI, fecal incontinence; FIQL, fecal incontinence quality of life; LS, least-squares; NASHA/Dx, non-animal stabilized hyaluronic acid/dextranomer; UI, urinary incontinence.

may provide insight into the profile of patients who may derive the maximum benefit from a specific treatment. This post hoc responder analysis of data from the randomized, double-blind, sham-controlled clinical study of NASHA/Dx in patients with FI²⁵ was conducted to examine demographic and baseline disease characteristics, including previous FI treatments, that might be predictive of treatment success.

Regardless of subgroup analyzed, there was a general trend in favor of NASHA/Dx versus sham for the treatment

of FI. Interestingly, patients who had symptoms consistent with mild-to-moderate FI at baseline (ie, CCFIS ≤15,²⁸ duration of FI ≤5 years, exposure to few prior FI treatment modalities), and those in whom the primary cause of FI was obstetric-related were more likely to benefit from treatment with NASHA/Dx compared with sham treatment. A similar profile of subgroup responsiveness was observed for the FIQL coping/behavior subscale, where patients with mild-to-moderate FI at baseline (CCFIS ≤15, duration of FI ≤5 years,

exposure to few prior FI treatment modalities) and an obstetric etiology of FI had a significant change in the FIQL coping/behavior subscale score at 6 months. These data suggest that the optimal patient population for treatment with NASHA/Dx may be patients with mild-to-moderate FI, and that reductions in FI episodes may translate into meaningful enhancements in some FI-related quality of life measures. It should be noted that there were no changes in other FIQL subscales (ie, lifestyle, depression, and self-perception) at 6 months in the overall population,²⁵ although significant improvements were observed at 12 months in all of these domains.

The potential treatment benefit observed with NASHA/Dx in patients who had an obstetric FI etiology is interesting and may be related to the nature of the trauma incurred during childbirth. As a neurologic etiology of FI following childbirth (eg, pudendal neuropathy) is different than a sphincter tear during childbirth, it would be valuable to further understand potential treatment benefits for this obstetric-related FI population when subgrouped by etiology. However in the current study, additional data on the etiology of obstetric trauma were unavailable for further analysis of potential differences. Maintenance of anal pressure in the anal canal is important for continence,³² as anal pressure has been shown to decrease in many patients following vaginal delivery for at least 6 to 10 weeks compared with anal pressure before childbirth.³³ Further, mechanical or neurologic damage to the anal sphincter following vaginal delivery (eg, forceps delivery, tears) is not uncommon and has been shown to affect 35% of patients with no previous pregnancies in one study;^{32,34} instrumentation-assisted vaginal delivery has been significantly associated with FI 5 to 10 years after childbirth.³⁵ These data are not entirely surprising, given that normal anorectal function relies on the neuromuscular integrity of the anal canal and surrounding sphincter muscle.³² The benefit observed in patients with obstetric damage may be related, at least in part, to the mechanism of action of NASHA/Dx. The dextranomer microspheres establish a scaffold for fibroblasts, smooth muscle cells, and collagen to grow around, stabilizing the tissue near the injection sites, and sealing the anal canal to an extent,^{20,21,36–38} thus restoring anal pressure.^{32,37} Obstetric trauma and injury is a risk factor for FI,³⁹ and these findings suggest that this patient population may be likely to benefit from treatment with NASHA/Dx.

The inclusion of a sham control arm in this study was a strength that allowed for control of selection and response biases by investigators and patients. The assessment of subgroup responsiveness under such randomized, controlled conditions was, therefore, clinically meaningful. Nevertheless,

this analysis has limitations. Due to the post hoc nature of the assessments, one limitation is that the study was not specifically powered to test for efficacy in various subgroups. Further, some of the subgroups had a small number of patients, thus limiting ability to interpret the results. Another limitation is that durability of response with NASHA/Dx has been shown for up to 3 years,⁴⁰ but data for sham treatment beyond 6 months are lacking in the current study because patients in the sham treatment arm were offered open-label treatment with NASHA/Dx after the short (6-month) blinding period and were excluded from further analysis.²⁵ Finally, given that post hoc analyses are hypothesis-generating endeavors, the results described herein warrant a well-powered, prospective, controlled study in patients with mild-to-moderate FI.

Conclusion

Injection with NASHA/Dx is an efficacious treatment for patients with FI, and data suggest that patients with mild-to-moderate FI may represent the population that would be most likely to respond to treatment. Future prospective studies are warranted to support these findings and help identify the factors that determine responsiveness to injectable bulking agents.

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Disclosure

Howard Franklin and Andrew C Barrett are former employees of Salix. Ray Wolf is an employee of Valeant Pharmaceuticals. The authors report no other conflicts of interest in this work.

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