POST HOC ANALYSIS

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

Howard Franklin[1]
Andrew C Barrett[1]
Ray Wolf[2]

[1]Department of Medical Affairs, Salix, a Division of Valeant Pharmaceuticals North America LLC, Bridgewater, NJ, USA; [2]Department of Medical Affairs, Valeant Pharmaceuticals North America LLC, Wilton Manors, FL, USA

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 ≥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, antidiarrheal 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 ~8.4% among noninstitutionalized adults, representing about 19 million people in the US,[1,2] and increases with age, with ~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

Correspondence: Ray Wolf
Department of Medical Affairs, Valeant Pharmaceuticals North America LLC, 2708 NE 10th Avenue, Wilton Manors, FL 33334, USA
Tel +1 954 541 5772
Email ray.wolf@valeant.com

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 ≥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 trial[25] 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 ≥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
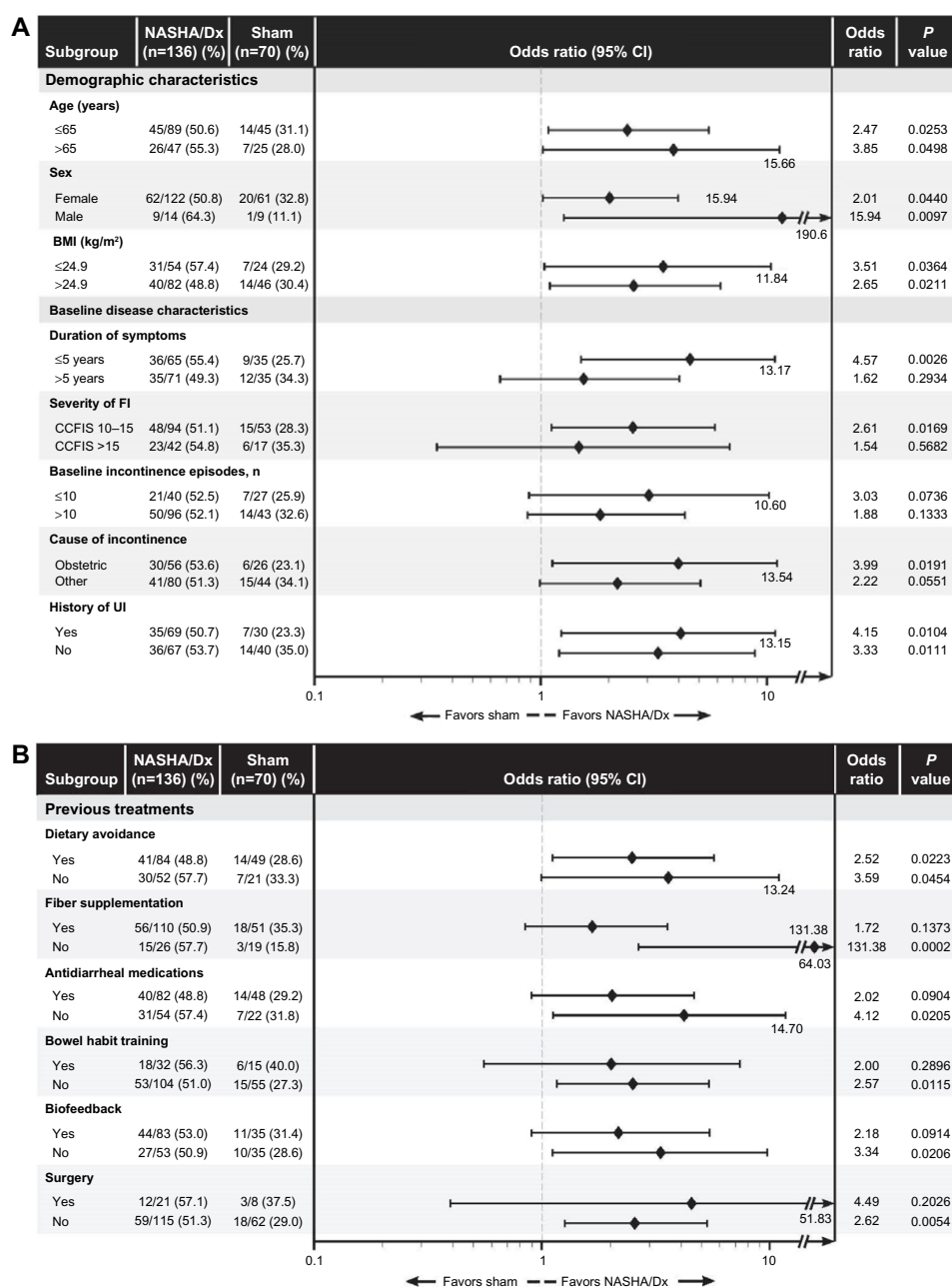
Figure 1 Patient response (ie, a decrease from baseline of ≥50% in the number of fecal incontinence episodes) to NASHA/Dx or sham treatment at 6 months.
Note: Patient response is based on (**A**) demographic and baseline characteristics and (**B**) previous treatment modalities.
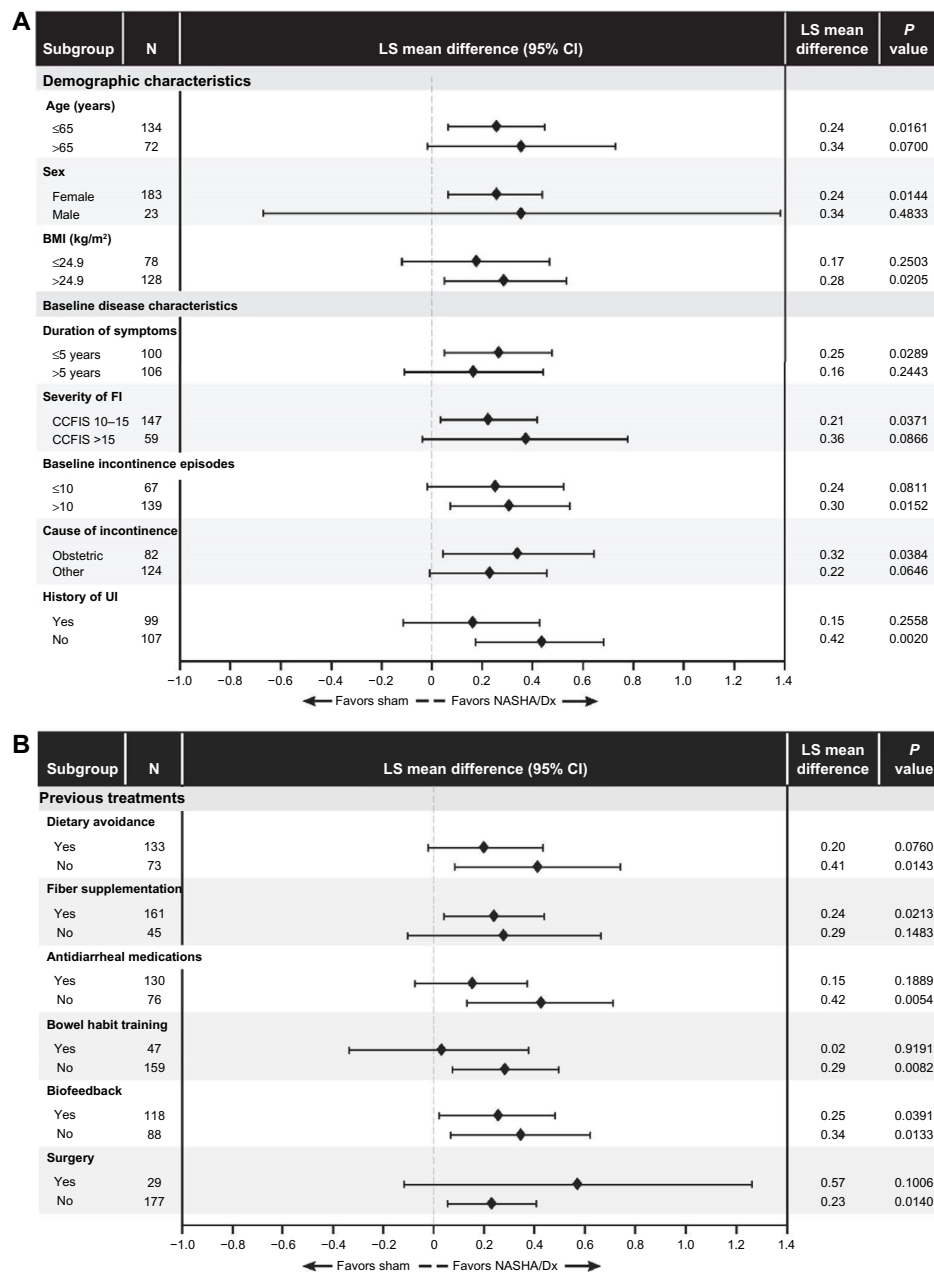**Abbreviations:** BMI, body mass index; CI, confidence interval; CCFIS, Cleveland Clinic Florida fecal incontinence score; FI, fecal incontinence; NASHA/Dx, non-animal stabilized hyaluronic acid/dextranomer; UI, urinary incontinence.

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

A

Subgroup	N	LS mean difference (95% CI)	LS mean difference	P value
Demographic characteristics				
Age (years)				
≤65	134		0.24	0.0161
>65	72		0.34	0.0700
Sex				
Female	183		0.24	0.0144
Male	23		0.34	0.4833
BMI (kg/m²)				
≤24.9	78		0.17	0.2503
>24.9	128		0.28	0.0205
Baseline disease characteristics				
Duration of symptoms				
≤5 years	100		0.25	0.0289
>5 years	106		0.16	0.2443
Severity of FI				
CCFIS 10–15	147		0.21	0.0371
CCFIS >15	59		0.36	0.0866
Baseline incontinence episodes				
≤10	67		0.24	0.0811
>10	139		0.30	0.0152
Cause of incontinence				
Obstetric	82		0.32	0.0384
Other	124		0.22	0.0646
History of UI				
Yes	99		0.15	0.2558
No	107		0.42	0.0020

−1.0 −0.8 −0.6 −0.4 −0.2 0 0.2 0.4 0.6 0.8 1.0 1.2 1.4
← Favors sham — Favors NASHA/Dx →

B

Subgroup	N	LS mean difference (95% CI)	LS mean difference	P value
Previous treatments				
Dietary avoidance				
Yes	133		0.20	0.0760
No	73		0.41	0.0143
Fiber supplementation				
Yes	161		0.24	0.0213
No	45		0.29	0.1483
Antidiarrheal medications				
Yes	130		0.15	0.1889
No	76		0.42	0.0054
Bowel habit training				
Yes	47		0.02	0.9191
No	159		0.29	0.0082
Biofeedback				
Yes	118		0.25	0.0391
No	88		0.34	0.0133
Surgery				
Yes	29		0.57	0.1006
No	177		0.23	0.0140

−1.0 −0.8 −0.6 −0.4 −0.2 0 0.2 0.4 0.6 0.8 1.0 1.2 1.4
← Favors sham — Favors NASHA/Dx →

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 FI[25] 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.

Acknowledgments

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.

References

1. Bharucha AE, Wald A, Enck P, Rao S. Functional anorectal disorders. *Gastroenterology*. 2006;130(5):1510–1518.
2. Ditah I, Devaki P, Luma HN, et al. Prevalence, trends, and risk factors for fecal incontinence in United States adults, 2005–2010. *Clin Gastroenterol Hepatol*. 2014;12(4):636–643.
3. Bharucha AE. Fecal incontinence. *Gastroenterology*. 2003;124(6):1672–1685.
4. Nelson R, Furner S, Jesudason V. Fecal incontinence in Wisconsin nursing homes: prevalence and associations. *Dis Colon Rectum*. 1998;41(10):1226–1229.
5. Markland AD, Goode PS, Burgio KL, et al. Incidence and risk factors for fecal incontinence in black and white older adults: a population-based study. *J Am Geriatr Soc*. 2010;58(7):1341–1346.

6. Leung FW, Schnelle JF. Urinary and fecal incontinence in nursing home residents. *Gastroenterol Clin North Am*. 2008;37(3):697–707.

7. Tan JJ, Chan M, Tjandra JJ. Evolving therapy for fecal incontinence. *Dis Colon Rectum*. 2007;50(11):1950–1967.

8. Bharucha AE, Fletcher JG, Melton LJ III, Zinsmeister AR. Obstetric trauma, pelvic floor injury and fecal incontinence: a population-based case-control study. *Am J Gastroenterol*. 2012;107(6):902–911.

9. Xu X, Menees SB, Zochowski MK, Fenner DE. Economic cost of fecal incontinence. *Dis Colon Rectum*. 2012;55(5):586–598.

10. Shah BJ, Chokhavatia S, Rose S. Fecal incontinence in the elderly: FAQ. *Am J Gastroenterol*. 2012;107(11):1635–1646.

11. Van Koughnett JA, Wexner SD. Current management of fecal incontinence: choosing amongst treatment options to optimize outcomes. *World J Gastroenterol*. 2013;19(48):9216–9230.

12. Madoff RD, Parker SC, Varma MG, Lowry AC. Faecal incontinence in adults. *Lancet*. 2004;364(9434):621–632.

13. Altomare DF, De FM, Giuliani RT, Catalano G, Cuccia F. Sphincteroplasty for fecal incontinence in the era of sacral nerve modulation. *World J Gastroenterol*. 2010;16(42):5267–5271.

14. Galandiuk S, Roth LA, Greene QJ. Anal incontinence-sphincter ani repair: indications, techniques, outcome. *Langenbecks Arch Surg*. 2009;394(3):425–433.

15. Lehto K, Hyoty M, Collin P, Huhtala H, Aitola P. Seven-year follow-up after anterior sphincter reconstruction for faecal incontinence. *Int J Colorectal Dis*. 2013;28(5):653–658.

16. Zutshi M, Tracey TH, Bast J, Halverson A, Na J. Ten-year outcome after anal sphincter repair for fecal incontinence. *Dis Colon Rectum*. 2009;52(6):1089–1094.

17. Glasgow SC, Lowry AC. Long-term outcomes of anal sphincter repair for fecal incontinence: a systematic review. *Dis Colon Rectum*. 2012;55(4):482–490.

18. Brown SR, Wadhawan H, Nelson RL. Surgery for faecal incontinence in adults. *Cochrane Database Syst Rev*. 2013;7:CD001757.

19. Maeda Y, Laurberg S, Norton C. Perianal injectable bulking agents as treatment for faecal incontinence in adults. *Cochrane Database Syst Rev*. 2013;2:CD007959.

20. Danielson J, Karlbom U, Sonesson AC, Wester T, Graf W. Submucosal injection of stabilized nonanimal hyaluronic acid with dextranomer: a new treatment option for fecal incontinence. *Dis Colon Rectum*. 2009;52(6):1101–1106.

21. Dodi G, Jongen J, de la Portilla F, Raval M, Altomare DF, Lehur PA. An open-label, noncomparative, multicenter study to evaluate efficacy and safety of NASHA/Dx gel as a bulking agent for the treatment of fecal incontinence. *Gastroenterol Res Pract*. 2010;2010:467136.

22. Schwandner O, Brunner M, Dietl O. Quality of life and functional results of submucosal injection therapy using dextranomer hyaluronic acid for fecal incontinence. *Surg Innov*. 2011;18(2):130–135.

23. La Torre F, de la Portilla F. Long-term efficacy of dextranomer in stabilized hyaluronic acid (NASHA/Dx) for treatment of faecal incontinence. *Colorectal Dis*. 2013;15(5):569–574.

24. Dehli T, Stordahl A, Vatten LJ, et al. Sphincter training or anal injections of dextranomer for treatment of anal incontinence: a randomized trial. *Scand J Gastroenterol*. 2013;48(3):302–310.

25. Graf W, Mellgren A, Matzel KE, Hull T, Johansson C, Bernstein M. Efficacy of dextranomer in stabilised hyaluronic acid for treatment of faecal incontinence: a randomised, sham-controlled trial. *Lancet*. 2011;377(9770):997–1003.

26. Tan E, Ngo NT, Darzi A, Shenouda M, Tekkis PP. Meta-analysis: sacral nerve stimulation versus conservative therapy in the treatment of faecal incontinence. *Int J Colorectal Dis*. 2011;26(3):275–294.

27. Fernández-Fraga X, Azpiroz F, Aparici A, Casaus M, Malagelada JR. Predictors of response to biofeedback treatment in anal incontinence. *Dis Colon Rectum*. 2003;46(9):1218–1225.

28. Stojkovic SG, Lim M, Burke D, Finan PJ, Sagar PM. Intra-anal collagen injection for the treatment of faecal incontinence. *Br J Surg*. 2006; 93(12):1514–1518.

29. Feretis M, Chapman M. The role of anorectal investigations in predicting the outcome of biofeedback in the treatment of faecal incontinence. *Scand J Gastroenterol*. 2013;48(11):1265–1271.

30. Rockwood TH, Church JM, Fleshman JW, et al. Fecal Incontinence Quality of Life Scale: quality of life instrument for patients with fecal incontinence. *Dis Colon Rectum*. 2000;43(1):9–16.

31. Umscheid CA, Margolis DJ, Grossman CE. Key concepts of clinical trials: a narrative review. *Postgrad Med*. 2011;123(5):194–204.

32. Andromanakos N, Filippou D, Skandalakis P, Papadopoulos V, Rizos S, Simopoulos K. Anorectal incontinence: pathogenesis and choice of treatment. *J Gastrointestin Liver Dis*. 2006;15(1):41–49.

33. Wynne JM, Myles JL, Jones I, et al. Disturbed anal sphincter function following vaginal delivery. *Gut*. 1996;39(1):120–124.

34. Sultan AH, Kamm MA, Hudson CN, Thomas JM, Bartram CI. Anal-sphincter disruption during vaginal delivery. *N Engl J Med*. 1993;329(26):1905–1911.

35. Handa VL, Blomquist JL, Knoepp LR, Hoskey KA, McDermott KC, Munoz A. Pelvic floor disorders 5–10 years after vaginal or cesarean childbirth. *Obstet Gynecol*. 2011;118(4):777–784.

36. Stenberg A, Läckgren G. A new bioimplant for the endoscopic treatment of vesicoureteral reflux: experimental and short-term clinical results. *J Urol*. 1995;154(2 Pt 2):800–803.

37. Watson NF, Koshy A, Sagar PM. Anal bulking agents for faecal incontinence. *Colorectal Dis*. 2012;14 Suppl 3:29–33.

38. Solesta® [package insert]. Edison, NJ: Oceana Therapeutics, Inc.; 2011.

39. Bohle B, Belvis F, Vial M, et al. Menopause and obstetric history as risk factors for fecal incontinence in women. *Dis Colon Rectum*. 2011;54(8): 975–981.

40. Mellgren A, Pollack J, Matzel K, Hull T, Bernstein M, Graf W. Long-term efficacy of NASHA/Dx injection therapy (Solesta) for treatment of fecal incontinence. *Dis Colon Rectum*. 2012;55(5):35.