Efficacy of Intralesional Botulinum Toxin A for Treatment of Painful Cutaneous Leiomyomas: A Randomized Clinical Trial

Haley B. Naik, MD, MHS; Seth M. Steinberg, PhD; Lindsay A. Middelton, RN, CGC; Stephen M. Hewitt, MD, PhD; Rena C. Zuo, BA; W. Marston Linehan, MD; Heidi H. Kong, MD, MHS; Edward W. Cowen, MD, MHS

IMPORTANCE Cutaneous leiomyomas can be associated with severe paroxysmal pain in which nerve conduction may have a key role. Medical management of painful cutaneous leiomyomas is generally unsatisfactory.

OBJECTIVE To assess the efficacy of intralesional botulinum toxin A in the management of pain associated with cutaneous leiomyomas.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, placebo-controlled pilot study conducted from January 5, 2009, to March 27, 2014. The setting was a single-center study at the National Institutes of Health among participants 18 years or older with cutaneous leiomyomas characterized by pain at least once weekly and pain of at least 4 on a pain scale ranging from 0 to 10.

INTERVENTIONS Eighteen participants were randomized to receive intralesional botulinum toxin A (5 U per 1 cm²) or equivalent volumes of intralesional saline placebo.

MAIN OUTCOMES AND MEASURES The primary outcomes were the differences in average lesional pain assessed by the Brief Pain Inventory and visual analog scale before and after ice provocation over a 4-week period.

RESULTS No significant difference in average lesional pain was observed between the study arms. Decreased pain was reported in the botulinum toxin vs placebo arms by visual analog scale scores before ice provocation (median, 0.00; range, −3.30 to 0.70 for botulinum toxin and median, 0.40; range, −1.30 to 1.50 for placebo; P = .06); however, this finding was nonsignificant. No significant difference was observed in change in pain after ice provocation. A significant difference was seen between the arms in skin-related quality of life by total Dermatology Life Quality Index (median, −4.00; range, −8.00 to 2.00 for botulinum toxin and median, 0.00; range, −1.00 to 4.00 for placebo; P = .007) and with the specific skin pain–related question on the Dermatology Life Quality Index (median, −2.00 to 1.00 for botulinum toxin and median, 0.00; range, −1.00 to 0.00 for placebo; P = .048). No significant difference was found in pain ascertained by Patient Global Impression of Change at week 4. No serious adverse events related to botulinum toxin use were observed.

CONCLUSIONS AND RELEVANCE The use of botulinum toxin to treat painful cutaneous leiomyomas was associated with improved quality of life and with a trend toward improved pain at rest.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00971620
Cutaneous leiomyomas are smooth muscle tumors, most often arising from the arrector pili muscle, that are associated with pain in 92% of affected individuals. Leiomomas may occur sporadically or in association with a dominantly inherited cancer genodermatosis, termed hereditary leiomyomatosis and renal cell cancer (HLRCC), in which multiple cutaneous lesions are common. The intense pain associated with cutaneous leiomyomas in this setting has led affected patients to contemplate suicide, and it often does not respond to systemic pain treatment. Local excision may be required for pain relief; however, not all lesions may be amenable to surgery given their location or number. For these patients, current management options are generally unsatisfactory.

The mechanism of pain associated with cutaneous leiomyomas is poorly understood but may be related to neuropeptide release, pressure on nerve fibers within the lesions, or contraction of the arrector pili muscle mediated via α-adrenergic receptors. Studies have demonstrated an increase in nerve density within and around leiomyomas compared with the surrounding dermis, with an associated increase in acetylcholinesterase (AchE) staining. Furthermore, murine nerve fibers in the arrector pili muscle are immunoreactive for calcitonin gene–related peptide (CGRP), a neuropeptide important in pain conduction. These data suggest that nerve conduction pathways could be targeted to treat pain associated with cutaneous leiomyomas.

Botulinum toxin has been used as an analgesic agent for the management of chronic pain syndromes, including chronic migraines and complex regional pain syndrome. By reducing muscle contraction, botulinum toxin decreases nociceptor sensitization by neuropeptides important in pain transmission, including substance P and CGRP. It has also been hypothesized that botulinum toxin may directly affect non-cholinergic neurons, thereby decreasing substance P, CGRP, and glutamate. In this study, we conducted a placebo-controlled trial to determine if pain associated with cutaneous leiomyomas could be reduced with botulinum toxin A.

Methods

We conducted a single-center, 12-week, randomized, double-blind, placebo-controlled pilot study from January 5, 2009, to March 27, 2014. The study protocol can be found in Supplement 1. This study was approved by the National Cancer Institute Institutional Review Board. Written informed consent was obtained from participants at the time of enrollment.

Eligible participants were adults 18 years or older with histopathologic confirmation of cutaneous leiomyoma, at least 1 symptomatic leiomyoma with pain of at least 4 on a pain scale ranging from 0 to 10, and pain occurring at least once weekly. Exclusion criteria included the following: metastatic disease; known allergy to botulinum toxin; botulinum toxin therapy in the previous 6 months; neuromuscular junction disorder or peripheral motor neuropathic disorder; pain from other diseases requiring narcotics or causing severe acute debilitating pain; use of pain medications, neuropeptide release, pressure on nerve fibers within the lesions, or contraction of the arrector pili muscle mediated via α-adrenergic receptors. Studies have demonstrated an increase in nerve density within and around leiomyomas compared with the surrounding dermis, with an associated increase in acetylcholinesterase (AchE) staining. Furthermore, murine nerve fibers in the arrector pili muscle are immunoreactive for calcitonin gene–related peptide (CGRP), a neuropeptide important in pain conduction. These data suggest that nerve conduction pathways could be targeted to treat pain associated with cutaneous leiomyomas.

Botulinum toxin has been used as an analgesic agent for the management of chronic pain syndromes, including chronic migraines and complex regional pain syndrome. By reducing muscle contraction, botulinum toxin decreases nociceptor sensitization by neuropeptides important in pain transmission, including substance P and CGRP. It has also been hypothesized that botulinum toxin may directly affect non-cholinergic neurons, thereby decreasing substance P, CGRP, and glutamate. In this study, we conducted a placebo-controlled trial to determine if pain associated with cutaneous leiomyomas could be reduced with botulinum toxin A.

Methods

We conducted a single-center, 12-week, randomized, double-blind, placebo-controlled pilot study from January 5, 2009, to March 27, 2014. The study protocol can be found in Supplement 1. This study was approved by the National Cancer Institute Institutional Review Board. Written informed consent was obtained from participants at the time of enrollment.

Eligible participants were adults 18 years or older with histopathologic confirmation of cutaneous leiomyoma, at least 1 symptomatic leiomyoma with pain of at least 4 on a pain scale ranging from 0 to 10, and pain occurring at least once weekly. Exclusion criteria included the following: metastatic disease; known allergy to botulinum toxin; botulinum toxin therapy in the previous 6 months; neuromuscular junction disorder or peripheral motor neuropathic disorder; pain from other diseases requiring narcotics or causing severe acute debilitating pain; use of pain medications, neuropeptide release, pressure on nerve fibers within the lesions, or contraction of the arrector pili muscle mediated via α-adrenergic receptors. Studies have demonstrated an increase in nerve density within and around leiomyomas compared with the surrounding dermis, with an associated increase in acetylcholinesterase (AchE) staining. Furthermore, murine nerve fibers in the arrector pili muscle are immunoreactive for calcitonin gene–related peptide (CGRP), a neuropeptide important in pain conduction. These data suggest that nerve conduction pathways could be targeted to treat pain associated with cutaneous leiomyomas.

Botulinum toxin has been used as an analgesic agent for the management of chronic pain syndromes, including chronic migraines and complex regional pain syndrome. By reducing muscle contraction, botulinum toxin decreases nociceptor sensitization by neuropeptides important in pain transmission, including substance P and CGRP. It has also been hypothesized that botulinum toxin may directly affect non-cholinergic neurons, thereby decreasing substance P, CGRP, and glutamate. In this study, we conducted a placebo-controlled trial to determine if pain associated with cutaneous leiomyomas could be reduced with botulinum toxin A.
before and after ice provocation between the 2 study arms from weeks 0 to 4.

The secondary outcomes included (1) persistence of pain control at week 12 based on the BPI and VAS scores, (2) change in quality of life as measured by total DLQI, (3) change in participant pain based on the PGIC, (4) change in magnitude and frequency of painful episodes based on the daily pain diary, and (5) change in immunohistochemical staining of nerve fibers and neuropeptides from weeks 0 to 12. Pain severity and pain interference were also assessed by the BPI. Pain severity was defined by the mean of the worst, least, average, and current pain scores, and pain interference was defined as the mean of the 7 BPI interference items based on consensus recommendations for BPI use in chronic pain clinical trials.13

Lesional skin samples were collected at weeks 0 and 12 in both study arms and submitted for routine diagnostic evaluation in the Laboratory of Pathology, Center for Cancer Research, National Cancer Institute. At the completion of the trial, immunohistochemical evaluation for c-fos (a marker of neuronal activation after pain stimulation) and AchE was performed using formalin-fixed, paraffin-embedded tissue. Four-micrometer sections were deparaffinized in xylene and graded alcohols and were subjected to antigen retrieval in citrate buffer (pH 9) for 20 minutes in a pressure cooker. Anti–c-fos (ab27436, rabbit polyclonal at 1:4 dilution; Abcam) and anti-AchE (ab2802, mouse monoclonal clone ZR3 at 1:100 dilution; Abcam) primary antibodies were applied to tissues for 60 minutes at room temperature. Antigen-antibody complexes were visualized using a 3,3′-diaminobenzidine chromogen (Dako North America). Slides were counterstained with hematoxylin. Positive and negative controls were used to ensure the specificity of the immunohistochemical reactions. Immunohistochemistry was reviewed and scored by an observer (S.M.H.) blinded with respect to timepoint and treatment. The c-fos staining was scored as 0 (none), (1) (scattered), 2 (<66% of tumor cells), or 3 (≥66% of tumor cells). The AchE staining was scored as 0 (none), 1 (rare), 2 (scattered), or 3 (focal or greater).

The sample size for this pilot study was determined to provide an adequate number of patients to identify a difference between the 2 study arms using a 1-sided, 2-sample $t$ test with $\alpha = .10$. A planned accrual of 18 participants (9 patients per study arm) permitted the trial to have 78% power to assess a difference in the primary end points equal to 1 SD of the difference between time points. Given the small sample size, the differences in the primary and secondary end points were compared between the study arms using the Wilcoxon rank sum test, and $P < .05$ was considered statistically significant for the primary end points. For the set of exploratory analyses performed, $P < .01$ was considered statistically significant. The difference in the medians between the study arms for the primary end points was determined using a Hodges-Lehmann estimator. Daily pain diary VAS scores were evaluated by averaging the values for each sequential 7-day period for the first 12 weeks and assessing for the differences in the values between the 2 study arms with an exact 2-tailed Wilcoxon rank sum test.

Analyses of immunohistochemical studies were performed by comparing the difference in staining scores between the study arms from weeks 0 to 12 using the exact Wilcoxon rank sum test. Spearman rank correlation analyses were performed to determine the correlation between changes in pain score from baseline to week 4 and changes in immunohistochemical score, focusing on results obtained separately by study arm. For these correlations, $|r|$ exceeding 0.70 would be considered a strong correlation, while $|r|$ between 0.50 and 0.70 would be considered a moderately strong correlation.

Results

Twenty-four patients with cutaneous leiomyomas were screened for participation. Eighteen participants were randomized and equally distributed into 2 study arms, with 9 participants in each arm (Figure 1).

A female predominance was present in both study arms (8 of 9 for botulinum toxin and 6 of 9 for placebo). Because of the small number of patients, we observed variation in location and distribution of lesions between the study arms. All participants who underwent HLRCC genetic testing were found to have a fumarate hydratase mutation. One participant elected not to undergo testing. The volume of injected study drug did not differ significantly between the 2 study arms (mean [SD], 2.41 [0.70] mL for botulinum toxin and mean [SD], 1.12 [0.38] mL for placebo; $P = .17$) (Table 2 in Supplement 2). Most participants characterized their pain as sharp (83% [15 of 18]), tender (81% [13 of 16]), stabbing (75% [12 of 16]), shooting (72% [13 of 18]), penetrating (71% [12 of 17]), or miserable (71% [12 of 17]).

Ice provocation testing resulted in increased lesional pain at baseline (mean [SD], 1.13 [0.40] before provocation and mean [SD], 5.64 [0.67] after provocation; $P < .001$). No significant difference in change in average pain was observed between the 2 study arms from weeks 0 to 4 (median; range, −6.00 to 2.00 for botulinum toxin and median, 0.00; range, −5.00 to 3.00 for placebo; $P = .70$) (Hodges-Lehmann estimator of the median difference, 0.00; 95% CI, −2.00 to 4.00) (Figure 2A). However, 44% (4 of 9) of participants in the botulinum toxin arm reported greater than 50% reduction in average pain compared with 22% (2 of 9) of participants in the placebo arm (eTable 2 in Supplement 2). Reduced pre–ice pain provocation from weeks 0 to 4 was observed in the botulinum toxin arm compared with the placebo arm (median, 0.00; range, −3.30 to 0.70 for botulinum toxin and median, 0.40; range, −1.30 to 1.50 for placebo; $P = .06$) (Hodges-Lehmann estimator of the median difference, −0.70; 95% CI, −1.90 to 0.00); however, this finding was statistically nonsignificant (Figure 2B). We observed that 56% (5 of 9) of participants who received botulinum toxin demonstrated reduced pre–ice pain provocation VAS scores compared with 11% (1 of 9) of participants who received placebo. Five participants who received placebo compared with 1 participant who received botulinum toxin reported increased pre–ice pain provocation from weeks 0 to 4 (eTable 2 in Supplement 2). No significant difference was seen in change in perceived pain after ice provocation between the study arms from weeks 0 to 4 (median, −1.60; range, −6.40 to 0.70 for botulinum toxin and median, −1.00; range, −6.30 to 5.70 for placebo; $P = .67$) (Hodges-Lehmann estimator of the median difference, −0.60; 95% CI, −3.80 to 1.90) (Figure 2C).
Although reduced pain severity was reported in all participants who received botulinum toxin from weeks 0 to 4, the difference between the study arms did not reach statistical significance (median, −2.25; range, −5.00 to −0.25 for botulinum toxin and median, −0.75; range, −3.75 to 0.50 for placebo; \( P = .10 \)) (Figure 2D). No significant difference in interference of pain in daily activities was noted from weeks 0 to 4 between the study arms.

Skin-related quality of life significantly improved in patients who received botulinum toxin compared with patients who received placebo (median, −4.00; range, −8.00 to 2.00 for botulinum toxin and median, 0.00; range, −1.00 to 0.00 for placebo; \( P = .007 \)) (Figure 2E). We further observed significantly reduced skin pain in the botulinum toxin arm from weeks 0 to 4 as ascertained by question 1 on the DLQI (“Over the last week, how itchy, sore, painful or stinging has your skin been?”) (median, −1.00; range, −2.00 to 1.00 for botulinum toxin and median, 0.00; range, −1.00 to 0.00 for placebo; \( P = .048 \)) (Figure 2F).

All participants randomized to placebo elected to receive open-label botulinum toxin at week 12 and demonstrated superior improvement in post–ice pain provocation VAS scores (median, 4.10; range, −2.50 to 5.90 for botulinum toxin and median, −0.30; range, −8.50 to 1.10 for placebo; \( P = .004 \)) compared with participants from weeks 12 to 24 treated with botulinum toxin at week 0 (Figure 3A). Average pain scores from weeks 12 to 24 were also decreased in the botulinum toxin arm vs the placebo arm; however, this difference did not reach statistical significance (median, 1.00; range, −4.00 to 4.00 for botulinum toxin and median, −1.50; range, −4.00 to 2.00 for placebo; \( P = .07 \)) (Figure 3B).

No significant differences in pre–ice pain provocation, post–ice pain provocation, average pain, pain severity, pain interference, or skin-related quality of life were seen between the study arms from weeks 0 to 12. In addition, no significant difference in the median change in PGIC scores was observed between the study arms from weeks 4 to 12. Pain diary scores at time points throughout the 12-week clinical trial did not differ significantly between the study arms. The use of rescue pain medications was infrequent in both study arms. Eight study participants recorded the use of over-the-counter rescue pain medications; of these, 6 of 8 reported 5 or fewer instances of pain medication use for cutaneous leiomyomas.

The differences in immunohistochemical staining of AchE (median, 1.00; range, 0.00 to 2.00 [\( n = 5 \)] for botulinum toxin and median, 0.00; range, −1.00 to 0.00 [\( n = 3 \)] for placebo; \( P = .07 \)) and c-fos (median, −1.00; range, −1.00 to 0.00 [\( n = 5 \)] for botulinum toxin and median, 0.00; range, 0.00 to 1.00 [\( n = 3 \)] for placebo; \( P = .07 \)) between the 2 study arms from weeks 0 to 12 did not reach statistical significance but suggested increased spread of AchE and decreased neuronal activation, respectively, in participants treated with botulinum toxin. Although based on limited data, these findings were further supported by a negative correlation between AchE staining from weeks 0 to 12 (Figure 4) and changes in pre–ice pain.

RCC indicates renal cell carcinoma.
provocation (Spearman $r = -0.92$, $P = .03$ [n = 5]) and post–ice pain provocation (Spearman $r = -0.72$, $P = .17$ [n = 5]) from weeks 0 to 4 in participants treated with botulinum toxin.

No significant adverse events were observed during this study. However, participants reported pain associated with intralesional injection of both botulinum toxin and placebo.

In A through F, vertical lines ending in small horizontal line segments represent the 25th to 75th percentiles; the medians are shown as a plus sign when the data are adequately spread to distinguish these from the first or third quartiles. BPI indicates brief pain inventory; DLQI, Dermatology Life Quality Index; VAS, visual analog scale.

All images are original magnification $\times$320. Comparing A and C, increased acetylcholinesterase expression in nerve fibers is observed after botulinum toxin administration, consistent with increased spread of acetylcholinesterase. Comparing B and D, decreased c-fos expression in the leiomyoma tumor cells is observed after botulinum toxin administration, consistent with decreased neuronal activation.
Discussion

In this study, we demonstrated that the use of intraleSIONal botULInum toxin is associated with improvement in skin-related quality of life. We also showed that intraleSIONal botULInum toxin is associated with improved pain at rest and reduced pain severity associated with cutaneous leiomyomas; however, these findings were not statistically significant.

The use of botULInum toxin has demonstrated efficacy for the management of other chronic pain conditions, including chronic migraines, complex regional pain syndrome, and neuropathic pain.\textsuperscript{7,8} Improvement following botULInum toxin injection has also been described for cutaneous leiomyoma pain in 2 case reports.\textsuperscript{2,13} To our knowledge, our study is the first controlled trial that systematically examines the efficacy of botULInum toxin for chronic pain associated with a skin condition.

The inherent subjectivity associated with pain perception presents unique challenges for the study of pain. What may be considered moderate pain by one individual might be perceived as intense pain by another. As a result, the differences in pain perception make it difficult to compare absolute pain scores from one individual or study arm with those of another. Therefore, to standardize pain assessment in this study, we chose to compare the differences in individual pain scores between time points in both study arms.

Cutaneous leiomyomas may be associated with pain at rest that may wax and wane over several minutes to hours. Using pain VAS scores to assess pain at rest, we observed a trend toward reduced pain in participants who received botULInum toxin compared with those who received placebo; however, this change did not reach statistical significance, possibly because of the limited sample size.

Based on the BPI, we observed reduced pain severity in patients treated with botULInum toxin, although this result did not reach statistical significance. Nevertheless, these data suggest that botULInum toxin may reduce the intensity of pain associated with these lesions. We also found a marked improvement in skin-related quality of life and skin pain in the botULInum toxin arm compared with the placebo arm. These findings indicate that amelioration of chronic skin pain may improve quality of life by reducing skin pain and improving social, emotional, and functional status.

The exact mechanism of pain reduction by botULInum toxin is not well understood. However, our immunohistochemical data suggest 2 possible mechanisms. First, botULInum toxin may reduce cutaneous leiomyoma pain through blockade of cholinergic pathways, which may lead to reduction in arrector pili muscle contraction as demonstrated by increased spread of AchE\textsuperscript{14} from weeks 0 to 12. Second, botULInum toxin may reduce neuronal activation as demonstrated by decreased c-fos staining from weeks 0 to 12. In various settings, c-fos is known to be a marker of neuronal activation.

Given the rarity of HLRCC and sporadic skin leiomyomas, our study was limited by a small sample size, which may have impaired our ability to detect small differences between the study arms. Furthermore, the inherent subjectivity in how pain is experienced between patients may have biased our results toward accepting the null hypothesis. Although ice provocation has been used to assess provoked pain in the setting of cutaneous leiomyoma previously, this measure is not validated as yet, and the degree of pain provoked by ice can vary among patients. To date, no reliable objective measure of pain has been devised to quantify the degree of provoked pain. Given these limitations, we used several validated measures of pain to corroborate our primary outcome assessments. Unfortunately, repeated provoked measurements at each time point were not possible because of escalation in pain following multiple provocations, as well as ethical considerations regarding repeated pain induction. Nevertheless, the double-blind nature of the study and the use of validated pain scales provide preliminary evidence that botULInum toxin has potential usefulness for sensory pain associated with skin disease, including skin leiomyomas.

All but one patient in this study underwent fumarate hydratase testing, confirming a diagnosis of HLRCC. Therefore, based on our cohort, we cannot draw conclusions about the differences in pain mechanism or severity in sporadically occurring cutaneous leiomyomas. IntraleSIONal administration of botULInum toxin and placebo led to temporary worsening of pain symptoms. Nonetheless, all participants who received intraleSIONal placebo at week 0 chose to enroll in the extension arm and receive open-label botULInum toxin, suggesting that pain associated with intraleSIONal drug administration is tolerable. The development of a topical formulation of botULInum toxin may circumvent this practical limitation.\textsuperscript{15,17}

Conclusions

In conclusion, we demonstrated in this study that botULInum toxin is associated with improvement in skin-related quality of life in individuals with cutaneous leiomyomas. We further showed that botULInum toxin may reduce pain at rest associated with cutaneous leiomyomas by specifically reducing pain intensity. BotULInum toxin may reduce pain associated with cutaneous leiomyomas through cholinergic mechanisms or through reduction in neuronal activation. To our knowledge, this is the first systematic study to demonstrate the benefit of botULInum toxin for pain amelioration associated with cutaneous leiomyomas. Given the rarity of cutaneous leiomyomas, a multicenter trial would likely be required to obtain a sample size sufficient to further determine the efficacy of skin pain reduction by botULInum toxin. Ideally, future studies would use a topical formulation of botULInum toxin to improve tolerability and adherence to therapy.
As Smooth as Honey—The Historical Use of Honey as Topical Medication

Raheel Zubair, MS, Nasir Aziz, MD

A supersaturated solution of glucose and fructose—while that may not sound like the description of a wonder drug, honey has been revered as a medication with powerful healing properties across a diverse group of cultures. Take this passage from the Quran in the chapter entitled “The Bee” (Surat a-Nahl): “And your Lord taught the honey bee to build its cells in hills, on trees, and in (men’s) habitations; Then eat to all of the produce of the earth, and find with skill the spacious paths of its Lord: there issues from within their bodies a drink of varying colors, wherein is healing for men.”

The use of honey in the topical treatment of wounds and other cutaneous disorders has endured the rise and fall of civilizations. The first recorded use of honey as a wound-healing agent dates back to 2600-2200 BCE, where it is mentioned in an ancient Egyptian trauma manual currently referred to as the Edwin Smith Papyrus.1 Hippocrates, the father of medicine and author of the eponymous oath every physician swears, recommended honey for wounds of the head, ears, and lips.2

Famed Roman poet and orator Ovid espoused the cosmetic use of honey in his poem Medicamina Faciei Femineae (Cosmetics for the Female Face). He provided a recipe that uses honey to even out skin pigmentation.

The eons have not extinguished the role of honey in dermatology. A recent systematic review1 of 26 clinical trials found there is moderate-to-high quality evidence that honey-impregnated dressings may help heal partial-thickness burns and infected postoperative wounds faster than conventional dressings. Another randomized clinical trial supported the use of honey for the treatment of painful, recurrent aphthous ulcers.3

In a rapidly changing world, it is reassuring to see that certain natural remedies have withstood the test of time. If history is any indication, the use of honey in dermatology will continue to evolve and will likely be used to treat a wide array of conditions. How sweet it is!

Author Affiliations: Georgetown University School of Medicine, Washington, DC (Zubair); Department of Dermatology, Howard University College of Medicine, Washington, DC (Aziz).

Corresponding Author: Raheel Zubair, MS, 1932 38th St NW, Washington, DC 20007 (rz23@georgetown.edu).

REFERENCES