Int. J. Radiation Oncology Biol. Phys., Vol. 80, No. 5, pp. 1505–1511, 2011

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.04.017

THE VALUE OF BOTOX-A IN ACUTE RADIATION PROCTITIS: RESULTS FROM A PHASE I/II STUDY USING A THREE-DIMENSIONAL SCORING SYSTEM

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Purpose: Acute radiation proctitis (ARP) is a common side effect of pelvic radiotherapy, and its management is challenging in daily practice. The present phase I/II study evaluates the safety and efficacy of the botulinum toxin A (BTX-A) in ARP treatment for rectal cancer patients undergoing neoadjuvant high-dose-rate endorectal brachytherapy (HDREBT).

Methods and Materials: Fifteen patients, treated with neoadjuvant HDREBT, 26-Gy in 4 fractions, received the study treatment that consisted of a single injection of BTX-A into the rectal wall. The injection was performed post-HDREBT and prior to the development of ARP. The control group, 20 such patients, did not receive the BTX-A injection. Both groups had access to standard treatment with hydrocortisone rectal aerosol foam (Cortifoam) and anti-inflammatory and narcotic medication. The ARP was clinically evaluated by self-administered daily questionnaires using visual analog scores to document frequency and urgency of bowel movements, rectal burning/tenesmus, and pain symptoms before and after HDREBT.

Results: At the time of this analysis, there was no observed systemic toxicity. Patient compliance with the self-administered questionnaire was 100% from week 1 to 4, 70% during week 5, and 40% during week 6. The maximum tolerated dose was established at the 100-U dose level, and noticeable mean differences were observed in bowel frequency ($p = 0.016$), urgency ($p = 0.007$), and pain ($p = 0.078$).

Conclusions: This study confirms the feasibility and efficacy of BTX-A intervention at 100-U dose level for study patients compared to control patients. A phase III study with this dose level is planned to validate these results.

Acute radiation proctitis, Botox, Endorectal brachytherapy, Rectal cancer.

INTRODUCTION

Acute radiation proctitis (ARP) (1-4) refers to radiation-induced injury of the rectum, which usually occurs during or within 3 months after radiotherapy. Symptoms include urgency (tenesmus), frequent mucus discharges, pressure causing burning sensations, pain, and occasional bleeding (3, 5, 6). ARP is also observed after curative treatment with radiation therapy for gynecological (7) and prostate cancer (8, 9), as well as in patients receiving adjuvant/neoadjuvant radiation for endometrial carcinoma (10) and rectal cancer (11). The prevalence of ARP is difficult to ascertain in the literature but has been reported to vary from 2% to 30% for prostate carcinoma. The medical treatment of ARP is often unsatisfactory (12, 13) and remains a constant concern for the radiation oncologist. In some instances, topical steroids (14), sucralfate enemas (15), and aminosalicylic acid derivatives (16) have been reported to provide partial relief, but in many other cases, patients will require intervention using narcotics. In small pilot studies, amifostine (Ethyol), an organic thiophosphate compound, presumably acting as a free radical scavenger, has been shown to decrease ARP symptoms when administered intrarectally before radiation treatment (9, 17–20). Vernia *et al*. (21) reported a small study with 20 patients with ARP after external beam pelvic radiation for cervix or prostate cancer randomized to receive 80 mM topical sodium butyrate by enema or sodium chloride (placebo) once a day for 3 weeks. Patients who received sodium butyrate showed improvement or became symptom-free within the duration of the treatment. However, the product is not available on the market.

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Conflict of interest: none.

Received Nov 16, 2009, and in revised form March 30, 2010. Accepted for publication April 2, 2010.

Preoperative high-dose rate endorectal brachytherapy (HDREBT) was introduced about 10 years ago. This new radiation treatment modality has been shown to be very effective in downstaging and downsizing rectal cancer in our routine practice (22-25). Virtually all patients undergoing this treatment modality experience, to various degrees, ARP symptoms. After HDREBT, the symptoms usually start 7 to 10 days after treatment completion (Fig.1) and continue to the time of surgery with resection of the irradiated tissues, 5 to 8 weeks after completion of treatment. These side effects impact the patient's quality of life.

Over the last 2 decades, botulinum toxin A (BTX-A) therapy has been used in the treatment of patients with both acute and chronic inflammatory pain and those with several other conditions of chronic striated muscle spasticity (26–30). Its efficacy has also been demonstrated in cases of focal smooth muscle contractions such as achalasia (31–33), chronic anal fissure (34, 35), and more recently, in overactive neurogenic bladder (36) and in the treatment of detrusor-sphincter dyssynergia, urinary retention, and chronic prostatic pain (37, 38). Accordingly, based on the mechanisms of action and therapeutic efficacy of BTX-A under conditions of muscle spasticity, the present phase I/II study was conducted to evaluate the safety and efficacy of Botox-A in radiation-induced proctitis.

METHODS AND MATERIALS

Study design

This was a single-institution dose escalation study of BTX-A for patients undergoing neoadjuvant HDREBT. The institutional review board approved this study, and a written informed consent was obtained from each of the participants.

Patients

Fifteen consecutive resectable rectal cancer patients treated with neoadjuvant HDREBT were recruited in this study. The control group consisted of 20 consecutive such patients treated with neoadjuvant HDREBT. Patients with myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other disorder that might interfere with neuromuscular function were ineligible for the study.

Treatment

Radiotherapy. HDREBT treatment consisted of a standard dose of 26 Gy in four fractions delivered to the intramesorectal deposits, as documented by magnetic resonance imaging. The technical aspects of this treatment and long-term benefits have previously been described (22–25).

BTX-A. The BTX-A injection was given immediately after the last session of HDREBT. BTX-A treatment consisted of the administration of one injection divided equally among four quadrants (at 12, 3, 6, and 9 o'clock), in the rectal walls close to the site of treatment but at least 5 cm above the radiated volume, marked by the upper endorectal clips placed for tumor targeting at the end of HDREBT treatment, prior to the development of proctitis. This measure is used to avoid injecting tissue that is expected to become inflammatory. This timing was selected to minimize patient discomfort. All patients were allowed access to standard treatment with hydrocortisone rectal aerosol foam (Cortifoam) and anti-inflammatory and narcotic medications at the time of symptom development.

The objectives of this study were to define a dose level that achieved at least 50% symptom relief and possible drug-related toxicity. We studied a minimum of 3 patients at each dose level. The first 3 patients received the 25-U injection. If no side effects were observed, the subsequent 3 patients received the next dose level, 50-U injection. If one of these 3 patients had any side effects from the BTX-A, an additional 3 patients were enrolled at the same dose. If none of these 3 patients developed any toxicity, then dose escalation continued. If 2 of 3 patients developed any grade 3 side effects, the present dose level was defined as the maximum tolerated dose (MTD). Similarly, at any dose level where 1 to 2 of 3 patients achieved 50% symptom relief and no grade 3 side effects were observed, an additional 3 patients received the same dose level; or the dose escalation continued until a nearly symptom-free level or MTD was achieved, whichever comes first.

Treatment outcome measurements. The patients in the control group were evaluated prior to study initiation, using a self-administered calendar with visual analog scoring to rate and record the following parameters: adverse events, frequency of bowel movements, night bowel movements, rectal burning/tenesmus, and pain; the self-report also documented the impact of symptoms on normal life activities on a weekly basis (8), from completion of HDREBT to surgery.

Similarly, patients recruited to the BTX-A study received the same self-administered calendar immediately after the BTX-A injection, on the last HDREBT treatment day. Both groups were evaluated in clinics to monitor any potential adverse events every 2 weeks until surgery.

For both bowel urgency and frequency, patients were instructed to take note of daily frequency, the number of toilet rushes that resulted in no bowel movement (N_{false}/day) and the number of actual bowel movements per day (N_{bm}/day). Daily frequencies were further sorted into five bins: 0/day, 1 to 4/day, 5 to 10/day, 11 to 20/day, and 21 and more per day. For anal pain symptoms, patients were instructed to score the intensity on a scale from 0 (no pain) to 10 (extremely painful) during every bowel movement. Patients were also asked to record their symptoms for a 6-week period post-brachytherapy and BTX-A injection treatments.

For every BTX-A dose group, we performed linearly weighted averaging for bowel urgency and bowel frequency for every week, using the following expressions:

$$\text{Bowel Urgency} - BU_{Dose}^{Week} = \sum_{j=1}^{5} \omega_j \cdot \left[\frac{1}{N_{Pat,Does}} \sum_{i=1}^{N_{pat,Does}} \left(N_{false}/day\right)^i \right]_j$$

$$\text{Bowel Frequency} - BF_{Dose}^{Week} = \sum_{j=1}^{5} \omega_j \cdot \left[\frac{1}{N_{Pat,Does}} \sum_{i=1}^{N_{pat,Does}} \left(N_{bm}/day\right)^i \right]_j$$

In the above expression, index, i, counts the number of patients in the particular dose group in which $N_{\text{Pat,Dose}}$ is the total number of patients in the same dose group. Index j runs over the five frequency bins, whereas the weighting factors (ω_j) represent linear averages of the corresponding daily frequencies: ω_j = {0, 2.5 (for the 1–4/day bin), 7.5 (for the 5–10/day bin), 15 (for the 11–20/day bin), and 21 (for the 21+/day bin)}.

For the anal pain symptom, the recorded values were also averaged for every patient on a weekly basis and then further averaged for the particular dose group having $N_{\text{Pat,Dose}}$ patients in total.

Finally, averaged bowel urgency, bowel frequency, and anal pain values were plotted as a function of the elapsed time after HDREBT,

and BTX-A injection treatments were stratified by the amount of BTX-A injected.

A repeated measures analysis of variance was performed to assess the effect of the dose. The following parameters were including in the model: the dose (control, 25 U, 50 U, 100 U, and 150 U), the time (week 1–6) and the dose∗time interaction. All contrasts were tested. No adjustment was made for multiple comparisons.

RESULTS

In the treatment group, 8 patients had lower-third tumors, and 7 patients had middle- third tumors. In the control group, 11 patients had tumors located in the lower third, and 9 patients had tumors in the middle third. Tumor location is an important factor in ARP manifestation, with a trend toward more pronounced expression in patients with lower-third tumors. No systemic toxicity associated with the use of BTX-A was observed in this series, which is consistent with observations in the literature (26-38). Patient compliance with the self-administered questionnaire was 100% from week 1 to 4, 70% during week 5, and 40% during week 6, due to scheduled surgery. Figure 1 shows the evolution of ARP after treatment in the control group. Three patients received 25 U, and three received 50 U of BTX-A. At the 100-U dose level a noticeable difference (50% of symptom response in all three ARP components, frequency, urgency, and pain) was documented in 2 of 3 patients; therefore, an additional 3 patients received the same dose level. At the 150-U dose level, patients 2 and 3 developed severe constipation, urgency, and pain requiring admission to the emergency room. They were documented as having fecal impaction requiring enemas and were discharged 48 hours later with an oral laxative regimen. As these were major adverse events, the MTD was declared at the 100-U level. There is a significant mean difference between pain level in the group receiving 100 U (less pain) compared with that of all other groups (Table 1). There are significant mean differences in bowel frequency (p = 0.016), urgency (p = 0.007), and pain (p = 0.078) in the 100-U group (less frequencies) compared with those of all other groups. The 150-U group experienced significantly higher bowel frequencies than the control group (Table 2). Patients in the 150-U group had a significantly different mean score in bowel urgency than patients in the 50-U and 25-U groups and the control groups (higher score in 150-U group) (Table 3). No other contrast level was found significant. Time and the dose∗time interaction were found to be not significant in any models. Figure 2 is a three-dimensional (3D) representation using radar diagrams of the anal pain, bowel frequency, and bowel urgency at different doses of BTX-A tested. In the diagrams, the control group score has been arbitrarily set at 1. Averaged values from different dose/patient populations have been normalized to the corresponding values of the control group. Values less than 1 indicate improvement of the patients' symptoms compared to the control, while values over 1 correlate with worsening of the patients' symptoms. From Fig. 2, it can be inferred that 100 U of BTX-A represents the optimal dose, since the associated anal symptoms, pain, bowel frequency, and urgency, all scored below 1 during the entire course of the post-treatment survey. This dose compares favorably to the other doses used in the study. All the axes have been set to the same value of 2 in order to follow the relative discomfort of the patient in time compared to the control group.

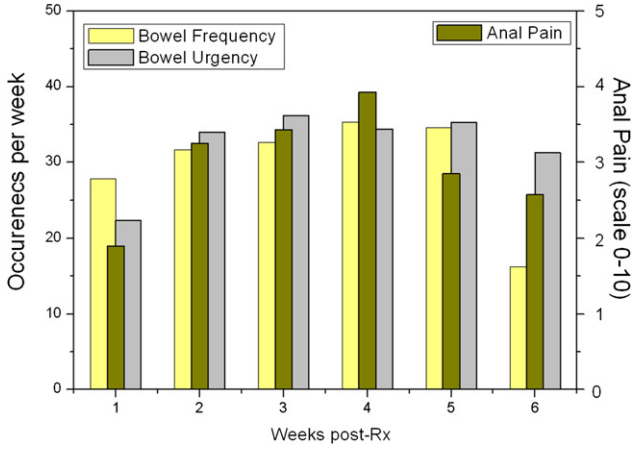

Fig. 1. Evolution of proctitis symptoms after treatment in the control group. Incidences of bowel frequency and bowel urgency are given in units of occurrences per week (left, y-axis), whereas the anal pain is given in relative units spanning from 0 to 10 (right, y-axis).

DISCUSSION

ARP is a clinical syndrome characterized by frequency, urgency, and occasionally pain and bleeding. It differs from chronic proctitis, a condition in which bleeding and mucus frequency dominate. Patients were carefully monitored from treatment completion to the time of surgery at 6 to 8 weeks later. ARP is characterized by periods of normal life activity alternating with sudden onset of rectal spasm with frequent mucus discharge and degrees of pain. Bleeding was infrequently documented, if not improved, after brachytherapy treatment.

ARP is frequently triggered by food intake. The existence of normal activity periods suggests that spasm, not inflammation, is the dominant component associated with patient symptomatology.

The main effects of BTX-A have been observed at the signal transmission level of neuromuscular junctions. The incorporation of BTX-A in the preterminal cholinergic nerve

Table 1. Anal pain score

Dose level (U)	Adjusted mean (SE)	Contrast
150	3.94 (0.67)	
100	1.26 (0.54)	<150 U (p = 0.002)
		<50 U (p = 0.016)
		<25 U (p = 0.014)
		<Control (p = 0.078)
50	3.35 (0.62)	
25	3.28 (0.62)	
Control	2.88 (0.26)	

Abbreviation: SE = standard error.

Table 2. Bowel frequency

Dose level (U)	Adjusted Mean (STD)	Contrast
150	42.5 (4.7)	> Control ($p = 0.034$)
100	18.3 (3.4)	< 150 U ($p < 0.001$) < 50 U ($p = 0.006$) < 25 U ($p = 0.022$) < Control ($p = 0.016$)
50	34.9 (3.9)	
25	31.9 (3.9)	
Control	29.7 (2.3)	

Abbreviation: STD = Standard Deviation.

endings blocks the release of acetylcholine in the synaptic cleft by interfering with the synaptic vesicle fusion to the presynaptic membrane and causes a partial blockage of neuromuscular junctions (39, 40). Remarkably, it does not induce motor neuron death or degeneration (41).

Due to the success encountered with BTX-A as a therapeutic option, new applications are continually sought. In the pelvic region, chronic anal fissure associated with internal sphincter spasm has been traditionally treated with sphincterotomy (surgery). Although glyceryl trinitrate (GTN) paste has also been established as a treatment option, it has significant shortcomings such as headaches, relapse, and tachyphylaxis. As a single well-tolerated approach, BTX-A is now the preferred treatment for this condition. Brisinda *et al*. (34) reported a phase III study comparing BTX-A to GTN, where a 96% response rate in the BTX-A arm vs. 60% in the GTN arm ($p = 0.005$) was noted. No patient in either group had fecal incontinence, but in the GTN group, moderate to severe headaches were observed in 20% of patients. That study concluded that BTX-A was the more effective nonsurgical treatment for chronic anal fissure.

Interstitial cystitis (IC) is a disorder characterized by the sensory urinary symptoms of pain, frequency, and urgency, all very similar to those of proctitis (42, 43). Traditional treatment options are oral and intravesical agents, neurostimulation, vaginal massage, and surgery; but none of these regimens is very effective (44–46). Neurogenic inflammation has been identified as an important component of this medical condition (47). Recently, Smith *et al*. (48) conducted a pilot study of 13 patients with refractory IC treated with a single application of BTX-A. More than 69% (9/13 patients) of the patients noted improvements.

Table 3. Bowel urgency

Dose level (U)	Adjusted Mean (STD)	Contrast
150	45.1 (6.7)	>100 U ($p = 0.007$) >50 U ($p = 0.004$) >25 U ($p = 0.005$)
100	20.6 (5.8)	
50	18.2 (6.3)	
25	18.5 (6.3)	
Control	32.2 (3.8)	

Abbreviation: STD = Standard Deviation.

A significant difference was observed in the IC symptom index ($p < 0.05$) as well as in frequency, nocturia, and pain by visual analog scale ($p < 0.01$). These parameters were correlated with the urodynamic capacity evaluation ($p < 0.01$). These preliminary results are quite encouraging in view of the similarity of these patients' symptoms to those of our patients with radiation proctitis. Last, the use of BTX-A has been documented in a case report (49) of a patient with severe radiation-induced proctitis resistant to conventional narcotics. Twenty-four hours after a single injection of BTX-A, the pain decreased dramatically, and the analgesic drug delivery system was removed after 48 hours.

The single-injection approach and minimal side effects eliminate noncompliance issues, thus making BTX-A an appealing therapeutic tool. It is very convenient and safe compared to oral, enema, or intravenous administration.

Unlike the case of patients treated with external beam radiation therapy, treatment with preoperative HDREBT for selected patients offers the advantage of allowing for a small sample size, as the incidence of ARP is universal and predictable, and is the treatment's only side effect. Using a patient self-administered symptom visual analog scale allowed better symptom discrimination than having the treating physician or clinical research assistant scoring patient response to BTX-A based on the common toxicity criteria. This evaluation tool, self-administered on a daily basis, allowed quantitative assessment and expression as mean value over a time period that the latter method does not allow. Thus, ARP is captured more globally as a function of time as shown in Fig 1. The symptom index to control patients receiving conventional treatment during this BTX-A dose escalation study provided a better assessment of the intervention, and finally, a pyramidal presentation of the ARP symptoms, as shown in Fig 2, offered the advantages of providing a 3D visual overview of BTX-A effect on ARP expression. The results of our phase I/II study suggest a clinical response at 100 U and a MTD of 100 U, while severe fecal impaction in 2 of 3 patients, likely due to localized ''rectal paralysis'' induced by BTX-A, and reactive bowel hyper motility proximal to the fecal impaction was noted at 150 U. Consequently, this led to accentuation of bowel urgency, frequency and pain.

As suggested in Fig. 2, the benefits are observed at all three levels of symptoms, urgency, frequency, and pain. Our results support the concept that BTX-A acts via a combination of mechanisms to alleviate ARP symptoms. As discussed by Hallett (39), BTX-A has been shown to block neuromuscular transmission by inhibiting acetylcholine release and weakening muscles, resulting in less involuntary contraction. Hallett (39) argues that a more complex mechanism of action is likely at work, involving an effect not only on the neuromuscular junction but also on sensory input and that the secondary changes associated with it. Cui *et al*. (50), using the rat formalin inflammatory pain model, described a direct antinociceptive effect of BTX-A, and this was supported by Aoki's (51) literature review showing that BTX-A also blocks peripheral sensitization and, indirectly, reduces central sensitization. Finally, we acknowledge that these results are from

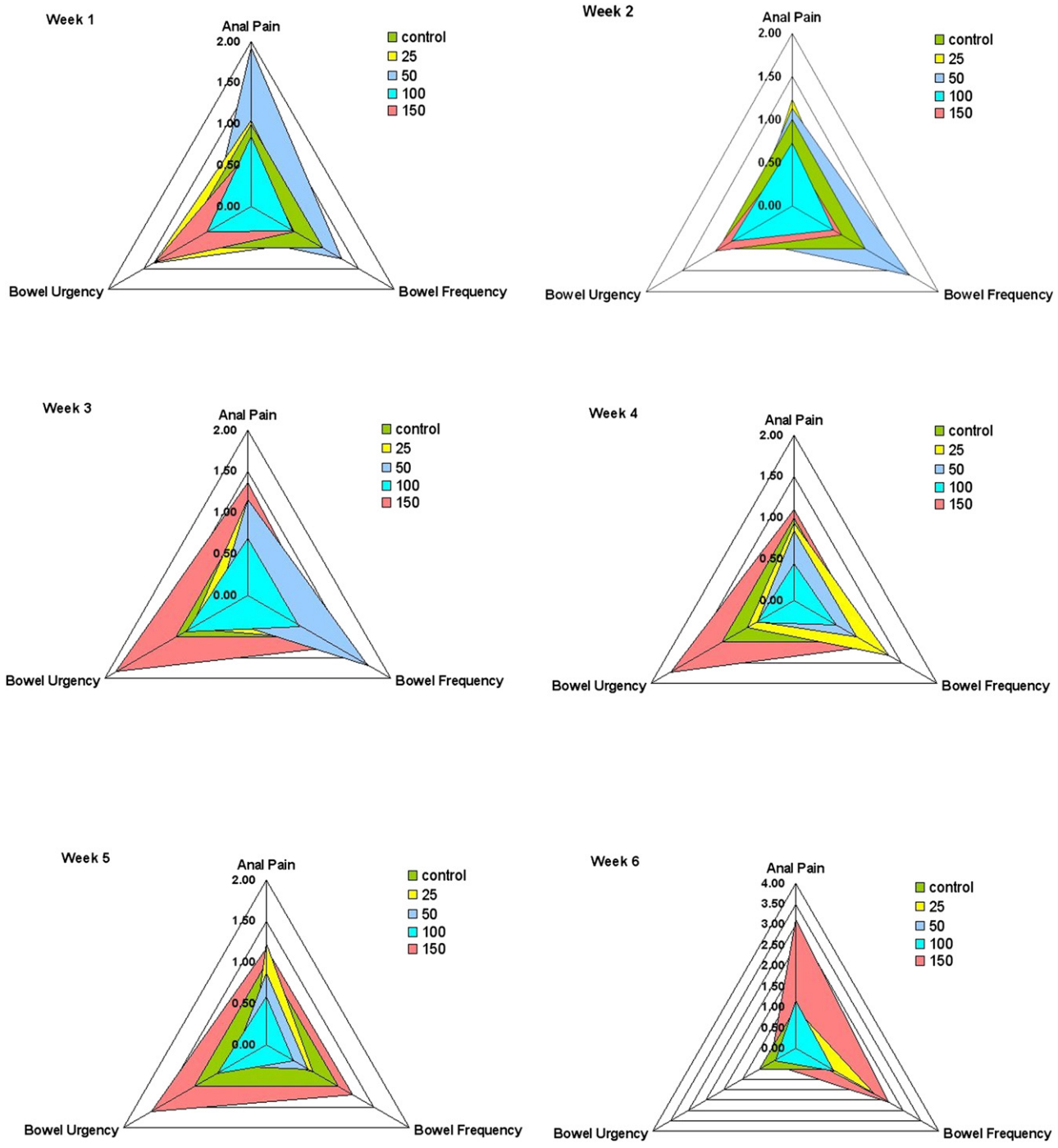

Fig. 2. 3D expression of symptom response using radar diagrams of the anal pain, bowel frequency, and bowel urgency, with various tested doses of BTX-A during the study and as a function of time. Averaged values from different dose/patient populations have been normalized to the corresponding values of the control group. Values less than 1 indicate improvement of the patients' symptoms compared to those of the control, while values over 1 correlate with worsening of the patients' symptoms.

a small phase I/II study conducted on BTX-A-treated patients, and results expressed are for uncontrolled but consecutive patients.

CONCLUSIONS

In summary, the results of this phase I/II study show a highly favorable reduction of all three ARP symptoms when analyzed as a symptom response index and are in keeping with the above mechanisms of action of BTX-A, as suggested in the literature. Nevertheless, we acknowledge that our study sample with 15 patients is small and that our results definitively deserve validation in the future with a phase III randomized study using 100 U of BTX-A as the MTD prior to definitive acceptance as an effective treatment.

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