Intrarectal injections of botulinum toxin versus placebo for the treatment of urge faecal incontinence in adults (FI-Toxin): a double-blind, multicentre, randomised, controlled phase 3 study

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Summary

Background Non-randomised studies assessing intrarectal botulinum toxin type A (BoNTA) injections for faecal incontinence are promising. We aimed to evaluate the efficacy of BoNTA for the treatment of faecal incontinence in a randomised study.

Methods In this randomised, double-blind, placebo-controlled study, we included adult patients who had at least one urgency or faecal incontinence episode per week for at least 3 months and who had experienced a failure of conservative or surgical treatment from eight French specialist hospital units with the skills to manage patients with faecal incontinence. Patients were randomly assigned (1:1) by a central web form to receive intrarectal submucosal injections of either 200 units of BoNTA (Botox; Allergan, Irvine, CA, USA; BoNTA group) or an equivalent volume of saline (placebo group), stratified by Cleveland Clinic Severity scores (CCS score; ≥12 or <12). Patients, investigators, study site staff, and sponsor personnel were masked to treatment allocation up to the 6-month visit. The primary endpoint was the number of episodes of faecal incontinence and urgency per day assessed using 21-day patient bowel diaries 3 months after the treatment. The primary analysis was performed using a modified intention-to-treat (mITT) approach (ie, in all the randomised patients who had received a treatment) with adjustment for baseline faecal incontinence and urgency episodes. After the final data collection at 6 months after injections, patients were unmasked and offered the BoNTA treatment if they were in the placebo group (rescue therapy) without masking, with an additional 6 months of safety follow-up. This trial is registered with ClinicalTrials.gov, number NCT02414425.

Findings Between Nov 25, 2015, and Nov 25, 2020, we randomly assigned 200 patients to receive either BoNTA (n=100) or placebo (n=100) injections. Due to withdrawals before the injections, 96 patients were included in the BoNTA group and 95 patients were included in the placebo group (mITT analysis). The mean number of faecal incontinence and urgency episodes per day in the BoNTA group decreased from 1·9 (SD 2·2) at baseline to 0·8 (1·8) at 3 months after the injections, and from 1·4 (1·1) to 1·0 (1·0) in the placebo group, with a baseline-adjusted mean group difference at 3 months estimated at −0·51 (95% CI −0·80 to −0·21, p=0·0008). No serious treatment-related adverse events were reported in the trial. The most frequently reported non-serious adverse event (treatment related or not) following the BoNTA or placebo injections was constipation (reported in 68 [40%] of 169 patients who received the BoNTA injections and 38 [40%] of 95 patients who received placebo injections).

Interpretation BoNTA injections are an efficacious treatment for urge faecal incontinence. Further research will define the optimum selection criteria, dose, site of injection, re-injection frequency, and long-term results.

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Introduction

Faecal incontinence, defined as the recurrent uncontrolled passage of faecal material,[1] is a common condition, with an estimated prevalence of 8·3% in the general adult population in the USA.[2] Faecal incontinence severely affects quality of life by causing psychological disability, stigmatisation, and social exclusion.[3] It also has a substantial economic impact on patients and health-care systems.[4]

Three recognised categories of faecal incontinence have been described. First, passive incontinence involves involuntary leakage without warning, suggesting anal hypotonia or hyposensitive rectum.[5] Second, urge incontinence is characterised by the inability to withstand an urge to defecate and is often attributed to anal hypocontractility or to a hypersensitive or hypercontractile rectum.[6] Third, mixed incontinence is a combination of passive and urge incontinence.[5] Treatment of faecal

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Research in context

Evidence before this study

We searched PubMed and the Cochrane library with the search terms "faecal/fecal incontinence" and "botulinum toxin" and identified only two series and one case report. The first series included six patients with faecal incontinence and hypercontractile rectum or reservoir. The second series was conducted by the same researchers and included the patients in the first series plus 20 new patients, nine of whom had a neo-reservoir following a proctectomy for rectal cancer. The case report concerned one patient who had faecal incontinence following an ileo-anal anastomosis. The two case series reported a short-term benefit from intrarectal botulinum toxin injections (500 units of Dysport; Ipsen, France) with less than 12 months of follow-up. They showed that rectal or reservoir injections of botulinum toxin for faecal incontinence are feasible, with minor and reversible adverse events. No previous study has shown that botulinum toxin injections are superior to placebo injections.

Added value of this study

To our knowledge, the present study is the first randomised controlled study of intrarectal botulinum toxin type A (BoNTA) injections in patients with urge faecal incontinence or urgency episodes, or both. Intrarectal injections of BoNTA (200 units of Botox; Allergan, Irvine, CA, USA) resulted in improvements in the primary endpoint, which was a decrease in faecal incontinence and urgency episodes per day compared with the placebo (saline), and they were well tolerated by the patients. Key secondary endpoints, including quality of life, delay to postpone defecation, and a positive general impression of the treatment, were better in patients treated with BoNTA injections than in patients treated with placebo injections.

Implications of all the available evidence

The results of the present study showed that intrarectal BoNTA injections as a therapeutic option are a promising approach for treating patients with urgency episodes and urge faecal incontinence refractory to first-line medical treatments. Further studies will be required to optimise the administration of the treatment (doses, injection sites), identify the best candidates, assess the duration of the effectiveness of the treatment, and continue to evaluate adverse effects.

incontinence depends on the presumed cause and severity of the problem.[7] Many patients can be managed using conservative treatments such as lifestyle changes, dietary improvement, anti-diarrhoeal medications, laxatives, colonic irrigation, or behavioural techniques such as biofeedback perineal training.[7] However, if symptoms persist, approved therapeutic options remain limited. They include sacral neuromodulation, perianal biomaterial injections to reinforce the anal barrier, or anal sphincter repair in patients with an external anal sphincter defect.[7] All these treatments have drawbacks, including a substantial risk of complications and re-interventions, unreliable availability in some countries, and a reduced response over time.[7] In the event of treatment failure, a colostomy might be the only alternative.[7] There is thus a need for safe and effective treatment options for faecal incontinence refractory to first-line medical treatments.

For many years, injections of intra-detrusor botulinum toxin type A (BoNTA) have been used to treat detrusor overactivity resulting in urge urinary incontinence, with good results and few side-effects.[8] BoNTA increases compliance and bladder capacity and delays the appearance of detrusor disinhibited contractions.[9] Based on the experience of urologists treating detrusor overactivity, we hypothesised that intrarectal BoNTA injections might inhibit spontaneous rectal contractions, increase rectal capacity and compliance, and, consequently, markedly relieve urge faecal incontinence in patients.[10,11] Two case series of BoNTA injections for the treatment of faecal incontinence resulted in improvements in severity symptoms and quality-of-life scores compared with baseline, with no serious adverse events.[10,11] However, to our knowledge, the outcome of intrarectal injections of BoNTA versus placebo has not been compared in a large, adequately powered, multicentre, randomised study.

The overall purpose of the present study was to evaluate the efficacy and safety of intrarectal BoNTA injections in adults with urge faecal incontinence in a randomised placebo-controlled study.

Methods

Study design and patients

We designed a randomised, double-blind, placebo-controlled, parallel group study and enrolled patients between Nov 25, 2015, and Nov 25, 2020, from eight French specialist hospital units with the skills to manage patients with faecal incontinence. A central approval for all centres was obtained from the local institutional review board (Haute-Normandie, Oct 17, 2014, number CPP 01/015/2014). The protocol was conducted in compliance with good clinical practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from all patients.

Patients were eligible for inclusion if they were aged 18 years or older, had at least one urgency or faecal incontinence episode per week on average for at least 3 months, and had experienced a failure of conservative (ie, biofeedback, diet modification, laxatives, or anti-diarrhoeal drugs) or surgical (ie, sacral neuromodulation, sphincter repair) treatment. For pragmatic reasons, patients were allowed to continue treatments that could influence digestive motility (ie, laxatives, anti-diarrhoeal

drugs, morphine, anticholinergics, etc) provided the treatment was stable during the study. The exclusion criteria included passive faecal incontinence as the main symptom, anorectal malformation or tumour, colorectal resection sequelae, pelvic radiotherapy, inflammatory bowel disease, rectal prolapse, faecal impaction, external anal sphincter defects that can be repaired, a rapidly progressive neurological disease (in less than 6 months), pregnancy (urinary test needed to be negative for women of childbearing age), ongoing anticoagulant or anti-aggregating treatment, a contraindication for rectoscopy or BoNTA injections, and exposure to BoNTA in the past 3 months. The full list of eligibility criteria is given in the appendix (pp 1–2). Demographic data, including sex assigned at birth (with options female and male), were collected at screening as reported by the patients.

Randomisation and masking

Just after the assessment of inclusion criteria and the signing of the informed consent form at visit M–1 (21–60 days before injections), the patients were randomly assigned (1:1) to receive intrarectal injections of either BoNTA (BoNTA group) or saline (placebo group). The block-permuted (block size 8) centralised randomisation schedules were generated by the statistician before study initiation and were distributed to the web form in the electronic case report form (e-CRF). The randomisation was stratified by Cleveland Clinic Severity scores (CCS score; ≥12 or <12).[12] This cutoff was chosen arbitrarily to provide enough patients with a CCS score above and below 12. We stratified the randomisation based on the CCS score rather than on the primary outcome (ie, faecal incontinence and urgency episodes) because randomisation based on the bowel diaries would have required an additional visit. It would also have added a risk of missing data for randomisation if the patient did not complete the diary. Up to the 6-month visit, the patients, investigators, study site staff, and sponsor personnel were all masked to treatment allocation, with the exception of the clinical supply staff and the designated safety staff, who were not involved in study outcome assessments. Numbered syringes were prepared by the study pharmacists. The syringes for the two groups were identical in appearance. In the event of an emergency, the investigator could unblind the allocation by contacting the medical monitor. Unblinding was performed for all willing participants at the 6-month visit to allow the patients in the placebo group to receive BoNTA rescue therapy (open-label extension phase). This unblinding was performed individually for each patient at each centre by the clinician investigator via the e-CRF. Since the randomisation was centralised, it was not possible for the investigator to predict the randomisation group of another patient. After the 6-month visit (M6), the patients, investigators, study site staff, biostatisticians, and sponsor personnel were no longer masked to the treatment allocation.

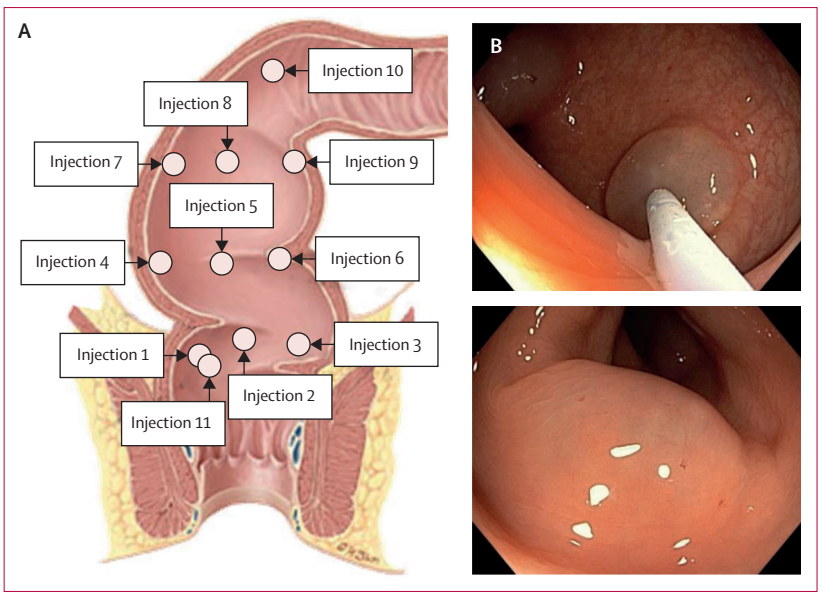

Figure 1: **Endoscopic image of the 11 sites of the submucosal intrarectal injections of botulinum toxin (A) and the mucous membrane elevation (B)**

Figure modified with markings after adaptation of "Colon" from Servier Medical Art by Servier, licensed under a Creative Commons Attribution 3.0 Unported License.

Procedures

See **Online** for appendix

Visits, procedures, and assessments are described in the appendix (pp 3–4). The injections were performed at visit M0, 21–60 days after inclusion and randomisation. Before undergoing the procedure, patients were given a standard bowel preparation consisting of four sachets of polyethylene glycol 4000 diluted in 4 L of water to be taken the day before the injections. The injections were performed as previously described.[10,11] The BoNTA (200 units of Botox; Allergan, Irvine, CA, USA) was diluted in 10 mL of a 0·9% NaCl (saline) solution. The placebo consisted of 10 mL of saline solution. Both preparations were colourless. Ten injections of 1 mL of BoNTA (20 units each) or placebo were administered using a 0·5 mm sclerotherapy needle during flexible sigmoidoscopy in unsedated patients. Three injections were given in a semi-circumferential manner in the wall of the rectum starting 5 cm above the dentate line (point 1 on figure 1) and ending 10 cm and 15 cm proximally (figure 1). The submucosal injections produced a mucous membrane elevation, such as the elevation seen before mucosal resections (figure 1). After the tenth injection, a final injection was performed at level 1 (point 11 in figure 1) to flush the remaining BoNTA or placebo from the syringe. The injection procedure was chosen empirically[10] on the basis of two objectives: (1) administer the BoNTA along the entire length of the rectum and (2) in a hemi-circumferential way to avoid severe constipation. All physicians who performed the procedure were trained using a video.

Patient demographics, clinical characteristics, and eligibility were assessed before randomisation. Before the treatment and at the 1-month (M1), 3-month (M3),

and 6-month (M6) post-injection visits, we collected bowel diaries (appendix p 5) completed at home for 21 consecutive days before the visit, CCS scores,[12] a completed French validated version of the American Society of Colon and Rectal Surgeons Quality-of-Life questionnaire for faecal incontinence (FIQL),[13] delay to postpone defecation (ie, the time patients estimated they were able to delay their defecation; ≤1, 1–5, 5–15, ≥15 min), and adverse events. The baseline subjective questionnaires were completed by the patients after randomisation between M–1 and M0 visits.

Anorectal manometry was performed with the technique available at each centre (ie, conventional or 3D high-resolution manometry [3D-HRM]) to record anal pressures, rectal contractility, and rectal sensation to balloon distension at M–1 and M0 visits just after the injections and at the M1 visit. The interpretation of the anorectal manometry findings was based on the London classification.[14] The normal values were defined according to local criteria at each centre (ie, based on conventional or 3D-HRM results). Rectal barostat measurements were added at the M0 visit just before the injections and at the M1 visit at the three centres equipped with a barostat (ancillary study).[15]

At the M6 visit, the patients were asked about their general impression of the treatment and their desire to receive intrarectal injections in case of recurrence. The questions asked were: "Did you find that the injection was beneficial/useful?", "Did the injection improve your quality of life?", and "Would you ask for a new injection next time?". After the final data collection at M6, the patients were unmasked and those in the placebo group were offered the BoNTA treatment (rescue therapy) without masking, with 6 additional months of safety follow-up.

Outcomes

The primary efficacy endpoint was the number of faecal incontinence and urgency episodes per day at 3 months after injection (M3 visit), according to the 21-day bowel diaries. An urgency episode was defined as a sudden need to rush to the bathroom to empty one's bowels. An evaluation at 3 months for the main criterion was chosen because a previous study[11] reported that the median duration of effectiveness of the injections was 4·5 months, and we did not want to miss the maximum effect of the BoNTA with a too long an evaluation time (ie, at 6 months). The rationale for using both urgency episodes and incontinence was because patients restrict their activities according to the accessibility of the toilets, which artificially reduces the risk of stool leakage. Secondary efficacy endpoints were the number of faecal incontinence and urgency episodes per day at M1 and M6 visits, the percentage of patients who had a 50% or greater reduction in the number of faecal incontinence and urgency episodes per day compared with baseline at M1, M3, and M6 (post-hoc criteria), CCS scores, FIQL scores, mean number of bowel movements per day (according to the bowel diaries), self-reported delay to postpone defecation, anorectal and barostat measurements, and general impression of the patients regarding the efficacy of the treatment and improvement in quality of life. Safety outcomes included self-reported solicited adverse events by the patients (constipation, abdominal pain, faintness, haemorrhage, asthenia) and adverse events reported by the physicians. The severities of the adverse events and the relation between adverse events and treatment were declared by the physicians and recorded according to Common Terminology Criteria for Adverse Events (version 5.0). The investigating physician at each site who included, treated, and followed up the patient decided whether an adverse event was treatment-related or not. The study endpoints are detailed in the appendix (p 6), and the protocol is available in the appendix (pp 7–52).

Statistical analysis

The primary analysis was performed using a modified intention-to-treat (mITT) approach, in which all randomised patients who had received a treatment (placebo or BoNTA) were included and were analysed according to their randomisation group. At the M0, M1, M3, and M6 visits, the number of faecal incontinence and urgency episodes in the 21-day diaries completed before the visits were summed to compute the number of faecal incontinence and urgency episodes. This number was averaged for non-missing days to compute the average number of faecal incontinence and urgency episodes per day (primary outcome). Missing data (empty diaries or patients who withdrew from the study after the injections) were imputed by the median of the two groups pooled together if the data were missing at baseline, and by the last observation carried forward (LOCF) method if the data were missing for other visits. The average number of faecal incontinence and urgency episodes per day at the M3 visit was compared between randomisation groups using an analysis of covariance (ANCOVA) adjusted by the average number of faecal incontinence and urgency episodes per day (linear effect) at M0 (baseline) for the primary analysis, with a two-sided type I error rate set at 5%.

Subjective secondary endpoints (faecal incontinence and urgency episodes at M1 and M6, CCS scores, FIQL scores, number of bowel movements per day, delay in postponing defecation) were analysed using the mITT approach, with a baseline imputation using the median and the LOCF imputation, except for the delay in postponing defecation, where imputation by the modal class of pooled groups was used at baseline. Analyses of secondary outcomes were not adjusted to baseline values except for faecal incontinence and urgency episodes at M1 and M6 to ensure consistency with the primary analysis (post-hoc decision). Patients who had a

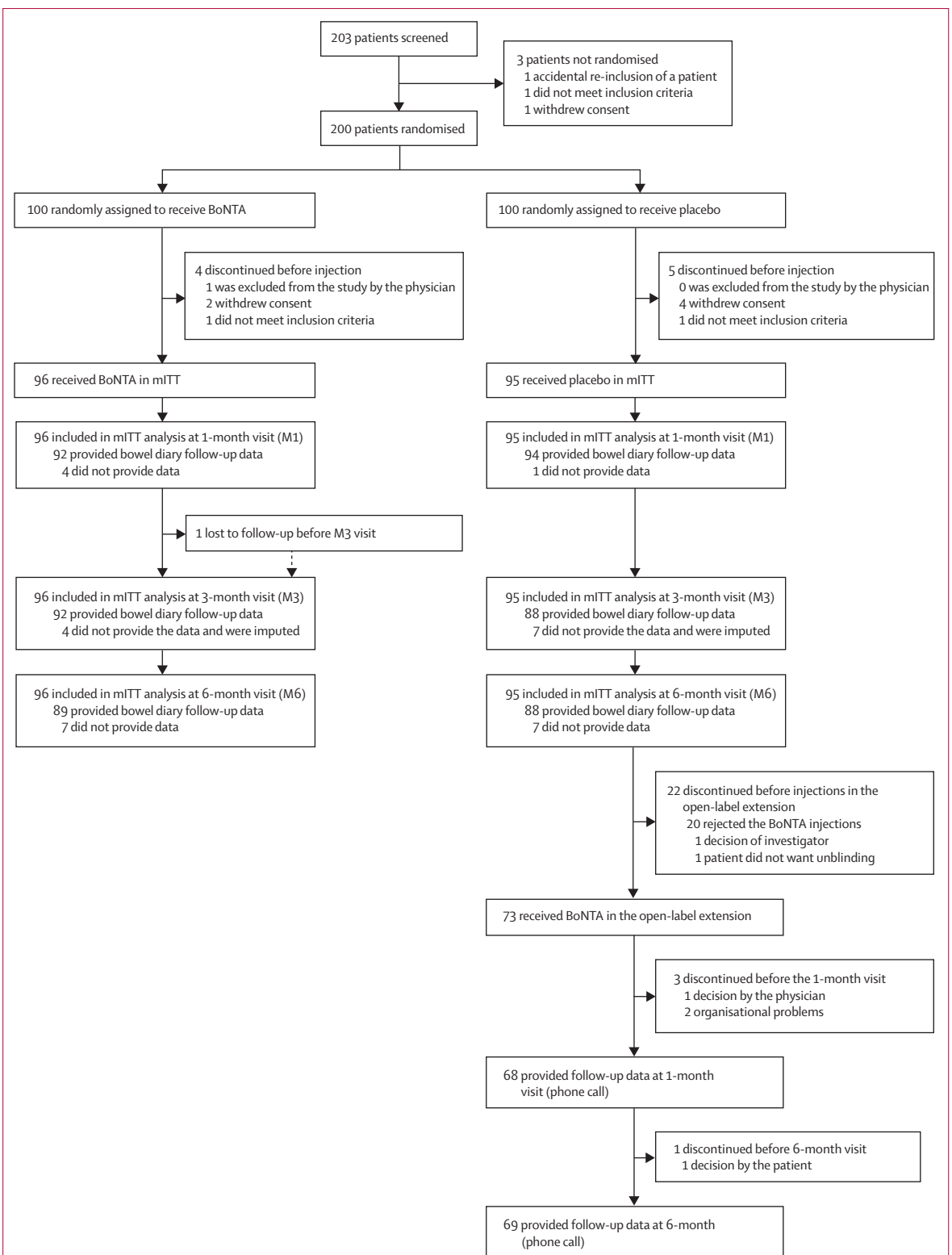

***Figure 2*: Trial profile**

	BoNTA group (n=96)	Placebo group (n=95)
Sex		
Female	88 (92%)	87 (92%)
Male	8 (8%)	8 (8%)
Mean age (years)	61·4 (10·9)	62·1 (10·5)
Mean BMI (kg/m²)	25·7 (4·8)	26·3 (5·0)
Mean duration of symptoms (months)	94·8 (68·6)	91·8 (86·9)
Type of faecal incontinence		
Urge	53 (55%)	55/94 (59%)
Mixed (with urge faecal incontinence predominant)	43 (45%)	39/94 (41%)
Causes of faecal incontinence*		
Idiopathic†	42 (44%)	40 (42%)
Neurological disease	36 (38%)	28 (29%)
Pudendal neuropathy	26 (27%)	19 (20%)
Peripheral neurological disease (diabetic neuropathy, cauda equine syndrome, sacral plexus injury)	4 (4%)	6 (6%)
Central neurological disease (multiple sclerosis)	6 (6%)	3 (3%)
Sphincter injury	19 (20%)	27 (28%)
Obstetric injury	16 (17%)	18 (19%)
Other injury	3 (3%)	9 (9%)
Sphincter atrophy	8 (8%)	11 (12%)
Other	8 (8%)	14 (15%)
Previous treatments for faecal incontinence*		
Anti-diarrhoeal medications	65 (68%)	57 (60%)
Laxatives, suppositories, irrigations	37 (39%)	36 (38%)
Biofeedback, pelvic floor exercises	74 (77%)	77 (81%)
Anal sphincter repair	7 (7%)	9 (9%)
Sacral neuromodulation	25 (26%)	14 (15%)
Other anal surgery	1 (1%)	1 (1%)
Other	32 (33%)	29 (31%)
Relevant medical history*		
Rectopexy	11 (11%)	7 (7%)
Rectocele repair	10 (10%)	3 (3%)
Sigmoidectomy for diverticulitis	0	4 (4%)
Hysterectomy	8 (8%)	11 (12%)
Anal surgery (excluding faecal incontinence therapy)	8 (8%)	14 (15%)
Pelvic surgery	12 (12%)	21 (22%)

Data are n (%) and mean (SD). BoNTA=botulinum toxin A. *One patient could have more than one cause of faecal incontinence and previous treatments or medical histories. †Idiopathic faecal incontinence was defined by any faecal incontinence with or without sphincter weakness, the cause of which could not be determined (no anatomical or neuropathic injury or atrophy).[16]

Table 1: **Baseline characteristics of the modified intention-to-treat population**

50% reduction from baseline in the number of faecal incontinence and urgency episodes per day at the M1, M3, and M6 visits were compared between the two groups using a post-hoc mITT analysis with an adjustment to baseline using an ANCOVA to explain the chance of a reduction of 50% or more (binary variable) by randomisation group (binary variable) and the baseline number of faecal incontinence and urgency episodes per day (quantitative variable). For the manometric and barostat data, we used a per-protocol analysis that excluded all patients with missing data for the outcome (pairwise complete observation analysis). We compared randomisation groups using a two-sided Student's *t*-test without a multiple testing procedure. We did post-hoc subgroup mITT analyses to evaluate the possible effects of modifications to the subgroups based on clinical characteristics that were more likely to predict the efficacy of BoNTA injections: age, type of faecal incontinence (ie, urge or mixed with predominantly urge faecal incontinence), pre-study use of anti-diarrhoeal medications or laxatives, duration of faecal incontinence, maximal rectal tolerable volume, and main causes of faecal incontinence. The ratio of the M6 baseline-adjusted treatment effect (BoNTA *vs* placebo) to the M3 baseline-adjusted treatment effect for the number of faecal incontinence and urgency episodes was estimated by percentile bootstrap to determine whether the treatment effect (BoNTA *vs* placebo) was reduced at the M6 visit (post-hoc analysis).

Adverse events were recorded for 6 months in the mITT sample and for an additional 6 months in the open-label extension of the study. Adverse events occurring after the rescue therapy were attributed to the BoNTA treatment while adverse events before the rescue therapy were attributed to the randomisation group. We did the comparison of the frequency of constipation of patients who received the BoNTA or placebo injections by percentile bootstrap taking into consideration the fact that some patients had received both injections.

A statistical power at 80% (with a 5% one-sided error rate) was originally computed for 200 randomised patients, assuming that the mean weekly number of faecal incontinence and urgencies was 5 (SD 5) at baseline[10] and would be reduced at the M3 visit to 3·75 (5) in the placebo group (25% relative reduction) and 2 (5) in the BoNTA treatment group (60% relative reduction), with an intra-participant Pearson's correlation coefficient of 0·50. This calculation was based on the asymptotic normal approximation formula (ie, infinite degrees of freedom) with rounding down of the sample size in each group (100·94 patients rounded to 100 patients). When the protocol was amended on March 18, 2021, the type I error rate was changed to 5% two-sided with a dilution of 10% due to patients lost at follow-up. The power was reduced to 73% for the 200 study patients, which was deemed acceptable. All analyses were done using R statistical software (version 4.2.1, R Foundation for Statistical Computing, Austria). This trial is registered with ClinicalTrials.gov, number NCT02414425.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing the report.

Results

Between Nov 25, 2015, and Nov 25, 2020, of the 203 patients who consented to participate and were

screened, 200 were randomly assigned to receive either intrarectal BoNTA (n=100) or placebo injections (n=100; figure 2). Nine patients withdrew from the trial before the injections, four in the BoNTA group and five in the placebo group (mainly because of consent withdrawal). 191 patients (96 in the BoNTA group and 95 in the placebo group) received the injections and were included in the mITT group for the primary analysis. These 191 patients were included by eight centres, with a median number of inclusions per centre of 21·5 patients (IQR 11·25–33·50, range 6–49) and a constant inclusion rate of 4·8 patients per centre per year (appendix p 53), which was close to that initially set (ie, six patients per year per centre, which corresponds to the usual recruitment rate of patients with faecal incontinence in France). 180 patients (92 in the BoNTA group and 88 in the placebo group) had bowel diary data at 3 months (M3 visit) and 11 (four in the BoNTA group, seven in the placebo group) had their M3 data imputed by LOCF (figure 2). The balance of baseline demographic and clinical data between the mITT randomisation groups was compatible with randomisation (table 1). Table 2 shows baseline and follow-up data for primary and secondary outcomes.

The mean number of faecal incontinence and urgency episodes per day decreased from 1·9 (SD 2·2) at baseline to 0·8 (1·8) at the M3 visit in the mITT BoNTA group and from 1·4 (1·1) at baseline to 1·0 (1·0) at the M3 visit in the mITT placebo group. For the mITT baseline-adjusted analyses, the difference of the means of the number of faecal incontinence and urgency episodes per day in the BoNTA group versus the placebo group was estimated at –0·37 (95% CI –0·69 to –0·06; p=0·02, post-hoc analysis) at the M1 visit, –0·51 (–0·80 to –0·21; p=0·0008, primary analysis) at the M3 visit, and –0·38 (–0·71 to –0·04; p=0·03, post-hoc analysis) at the M6 visit (table 2; figure 3). The ratio between the M6 difference and the M3 difference was 0·75 (95% CI 0·25 to 1·24, p=0·26, post-hoc analysis). At the M3 visit, a 50% or greater reduction in the number of faecal incontinence and urgency episodes per day was noted in 69 (72%) patients in the BoNTA group and in 44 (46%) patients in the placebo group (adjusted difference 27·1%, 95% CI 13·3 to 40·8, p=0·0001, post-hoc analysis).

Significant differences between the BoNTA group and the placebo group were observed for delay to postpone defecation but not for bowel movements per day or CCS scores (table 2).

At the M6 visit, just before unblinding, 72 (76%) of the 95 patients in the BoNTA group reported finding the injection beneficial or useful compared with 40 (43%) of 94 in the placebo group (p<0·0001, Fisher's exact test), 71 (76%) of the 94 patients in the BoNTA group reported that the injection improved their quality of life compared with 35 (37%) of 94 in the placebo group (p<0·0001), and 82 (86%) of 95 patients in the BoNTA group said they would ask for a new injection next time compared with 70 (75%) of 93 in the placebo group (p=0·06, Fisher's exact test).

At the M1, M3, and M6 visits, the FIQL scores for coping and behaviour were significantly higher in the BoNTA group than in the placebo group (table 2). This

	BoNTA group (n=96)	Placebo group (n=95)	Mean difference (95% CI)	p value
Mean number of faecal incontinence and urgency episodes per day (baseline-adjusted mITT)				
Baseline	1·9 (2·2)	1·4 (1·1)	..	..
M1	0·9 (1·9)	1·0 (1·0)	–0·37 (–0·69 to –0·06)*	0·02
M3	0·8 (1·8)	1·0 (1·0)	–0·51 (–0·80 to –0·21)†	0·0008
M6	1·0 (2·0)	1·0 (1·1)	–0·38 (–0·71 to –0·04)*	0·03
Number of patients with a reduction of ≥50% in the number of faecal incontinence and urgency episodes per day (baseline-adjusted mITT)				
M1	70 (73%)	40 (42%)	31·8% (18·2 to 45·4%)*	<0·0001
M3	69 (72%)	44 (46%)	27·1% (13·3 to 40·8%)*	0·0001
M6	66 (69%)	44 (46%)	24·5% (10·6 to 38·4%)*	0·0006
Mean number of bowel movements per day (unadjusted mITT)				
Baseline	2·2 (1·6)	2·0 (1·0)	..	..
M1	1·6 (1·3)	1·8 (0·9)	–0·24 (–0·57 to 0·08)‡	0·14
M3	1·5 (1·4)	1·8 (0·9)	–0·23 (–0·55 to 0·10)‡	0·17
M6	1·5 (1·2)	1·7 (1·0)	–0·24 (–0·55 to 0·08)‡	0·14
Delay to postpone defecation (unadjusted mITT)				
Baseline				
≤1 min (score 1)	40 (42%)	39 (41%)	..	..
1–5 min (score 2)	48 (50%)	50 (53%)	..	..
5–15 min (score 3)	6 (6%)	4 (4%)	..	..
≥15 min (score 4)	2 (2%)	2 (2%)	..	..
Mean score	1·7 (0·7)	1·7 (0·7)	..	..
M1				
≤1 min (score 1)	14 (15%)	22 (23%)	..	..
1–5 min (score 2)	40 (42%)	50 (53%)	..	..
5–15 min (score 3)	23 (24%)	17 (18%)	..	..
≥15 min (score 4)	19 (20%)	6 (6%)	..	..
Mean score	2·5 (1·0)	2·1 (0·8)	0·42 (0·16 to 0·67)‡	0·002
M3				
≤1 min (score 1)	15 (16%)	18 (19%)	..	..
1–5 min (score 2)	39 (41%)	50 (53%)	..	..
5–15 min (score 3)	24 (25%)	21 (22%)	..	..
≥15 min (score 4)	18 (19%)	6 (6%)	..	..
Mean score	2·5 (1·0)	2·2 (0·8)	0·31 (0·06 to 0·57)‡	0·02
M6				
≤1 min (score 1)	18 (19%)	26 (27%)	..	..
1–5 min (score 2)	38 (40%)	46 (48%)	..	..
5–15 min (score 3)	25 (26%)	20 (21%)	..	..
≥15 min (score 4)	15 (16%)	3 (3%)	..	..
Mean score	2·4 (1·0)	2·0 (0·8)	0·39 (0·13 to 0·64)‡	0·003
Mean Cleveland Clinic Score (unadjusted mITT)				
Baseline	12·2 (3·7)	12·1 (3·7)	..	..
M1	8·6 (5·0)	9·8 (4·3)	–1·26 (–2·58 to 0·06)‡	0·06
M3	8·2 (4·8)	9·3 (4·2)	–1·13 (–2·42 to 0·16)‡	0·09
M6, mean (SD)	8·7 (5·0)	10·0 (4·7)	–1·25 (–2·64 to 0·14)‡	0·08

(Table 2 continues on next page)

	BoNTA group (n=96)	Placebo group (n=95)	Mean difference (95% CI)	p value
(Continued from previous page)				
Mean faecal incontinence quality-of-life score (unadjusted mITT)				
Baseline, mean (SD)				
Lifestyle	2·3 (0·9)	2·2 (0·8)	..	..
Coping and behaviour	1·6 (0·5)	1·6 (0·5)	..	..
Depression and self-perception	2·4 (0·8)	2·5 (0·8)	..	..
Embarrassment	1·8 (0·7)	1·9 (0·6)	..	..
M1, mean (SD)				
Lifestyle	2·7 (1·0)	2·5 (0·9)	0·17 (−0·10 to 0·45)‡	0·21
Coping and behaviour	2·2 (0·9)	1·9 (0·7)	0·30 (0·07 to 0·53)‡	0·01
Depression and self-perception	2·9 (0·9)	2·8 (0·9)	0·09 (−0·17 to 0·35)‡	0·49
Embarrassment	2·4 (0·9)	2·3 (0·8)	0·10 (−0·14 to 0·35)‡	0·40
M3, mean (SD)				
Lifestyle	2·9 (1·0)	2·6 (0·9)	0·28 (0·01 to 0·55)‡	0·04
Coping and behaviour	2·4 (0·9)	2·0 (0·8)	0·39 (0·15 to 0·64)‡	0·002
Depression and self-perception	3·0 (0·9)	2·9 (0·9)	0·08 (−0·18 to 0·35)‡	0·55
Embarrassment	2·5 (0·9)	2·3 (0·8)	0·19 (−0·05 to 0·43)‡	0·13
M6, mean (SD)				
Lifestyle	2·8 (1·0)	2·6 (0·9)	0·23 (−0·05 to 0·51)‡	0·11
Coping and behaviour	2·3 (0·9)	1·9 (0·7)	0·34 (0·10 to 0·58)‡	0·005
Depression and self-perception	2·9 (1·0)	2·8 (0·9)	0·16 (−0·11 to 0·43)‡	0·25
Embarrassment	2·4 (0·9)	2·2 (0·8)	0·18 (−0·07 to 0·42)‡	0·16

Data are mean (SD) or n (%), unless otherwise specified. The means and percentages described in each group are unadjusted. BoNTA=botulinum toxin A. mITT=modified intention to treat. *Post-hoc analysis. †Primary analysis. ‡Secondary analysis.

Table 2: **Comparison of clinical outcomes between the BoNTA and placebo groups at 1, 3, and 6 months after injection**

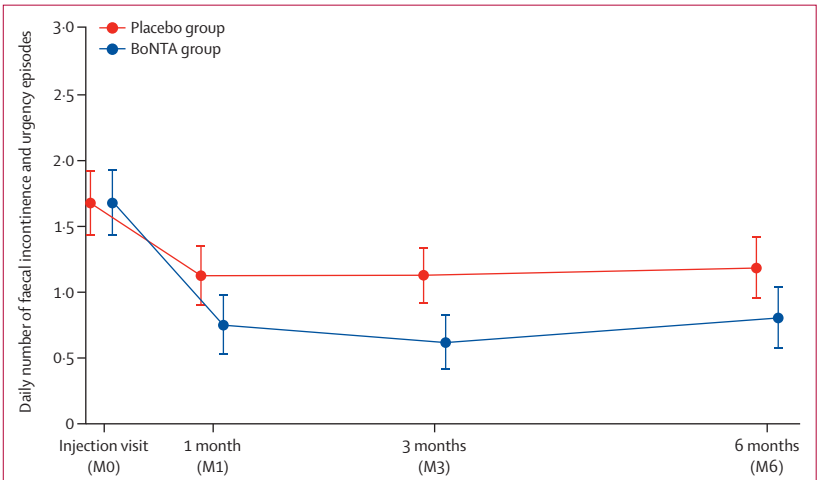

Figure 3: **Baseline-adjusted means of the number of faecal incontinence or urgency episodes per day, by treatment group and, based on the adjusted linear model, by visit**
Values in the graph include means and 95% CIs. The results are derived from a mITT baseline-adjusted analysis. mITT=modified intention to treat.

was also the case for the lifestyle score, but only at the M3 visit (table 2). Scores did not differ significantly for the other two categories (depression and self-perception, and embarrassment; table 2).

According to the London classification, disorders of anal tone, contractility, and rectal sensation did not differ significantly between the BoNTA group and the placebo group (appendix p 54). The significant difference in the percentage of patients with rectal hyposensitivity between the two groups observed at the M1 visit was not conclusive, probably due to chance, given the large number of tests performed (appendix p 54). The number of spontaneous rectal contractions recorded during the manometry was too small for statistical analysis (appendix p 54). Rectal barostat measurements at M1 post-injection were planned for all the patients at the three centres equipped with barostats. However, only 55 (25 in the BoNTA group, 30 in the placebo group) of the 78 patients (34 in the BoNTA group, 44 in the placebo group) at these three centres underwent the barostat assessment. No significant differences were found in volume, pressure, or rectal compliance (appendix p 55).

The subgroup post-hoc analysis showed that the BoNTA treatment was significantly better in patients aged 70 years or older (p=0·04 for the interaction test; appendix 56). No other interaction test was significant.

At least one adverse event was reported in 94 (56%) of the 169 patients who received the BoNTA injections. These 169 patients included 96 patients in the BoNTA group and 73 patients in the placebo group following the rescue therapy. At least one adverse event was reported for 61 (64%) of the 95 patients who received the placebo injections before the rescue.

The proportion of patients who had adverse events categorised as serious was low in both groups (three [2%] of the 169 patients treated with BoNTA versus one [1%] of the 95 patients in the placebo group; table 3). These serious adverse events were all considered unrelated to the study and none of them led to unmasking of treatment allocation.

The most frequently reported adverse event (related or not to treatment) after the BoNTA or placebo injections was constipation (table 3). Constipation was reported in 68 (40%) of the 169 patients who received the BoNTA injections and 38 (40%) of the 95 patients who received the placebo injections. The difference in the proportion of patients with constipation between patients who received BoNTA injections and those who received placebo was estimated at 0·2% (95% CI −9·4 to 9·8; p=0·96) according to the percentile bootstrap.

Following a quality control assessment of the randomisation, we identified ten deviations from the unblinding procedure due to premature unblinding between the M3 and M6 visits in two centres. Three post-hoc sensitivity analyses were performed to assess the effect of these deviations on the results of the primary analysis. First, excluding these ten patients from the primary mITT analysis changed the baseline-adjusted BoNTA effect on the number of faecal incontinence and

	BoNTA exposure (n=169 [96 BoNTA + 73 rescue])			Placebo exposure (n=95 [before rescue therapy])		
	Overall	Related	Unrelated	Overall	Related	Unrelated
Serious adverse events						
Pneumopathy	1/1 (1%)	0	1/1 (1%)	0	0	0
Urinary tract infection*	1/1 (1%)	0	1/1 (1%)	0	0	0
Thyroid nodule	1/1 (1%)	0	1/1 (1%)	0	0	0
Phlebitis	0	0	0	1/1 (1%)	0	1/1 (1%)
Non-serious adverse events						
Constipation	115/68 (40%)	98/58 (34%)	17/17 (10%)	47/38 (40%)	42/34 (36%)	5/5 (5%)
Abdominal pain	42/31 (18%)	24/18 (11%)	18/17 (10%)	40/25 (26%)	30/22 (23%)	10/7 (7%)
Asthenia	10/6 (4%)	5/2 (1%)	5/5 (3%)	11/9 (9%)	9/8 (8%)	2/2 (2%)
Diarrhoea	10/9 (5%)	2/1 (1%)	8/8 (5%)	7/5 (5%)	5/4 (4%)	2/2 (2%)
Bloating	6/4 (2%)	4/2 (1%)	2/2 (1%)	11/6 (6%)	10/5 (5%)	1/1 (1%)
Anal, rectal, or perineal pain	3/2 (1%)	2/1 (1%)	1/1 (1%)	8/4 (4%)	7/3 (3%)	1/1 (1%)
Bleeding	6/4 (2%)	3/3 (2%)	3/3 (2%)	5/4 (4%)	5/4 (4%)	0
Urinary tract infection	4/3 (2%)	0	4/3 (2%)	3/3 (3%)	0	3/3 (3%)
Nausea or vomiting	5/5 (3%)	0	5/5 (3%)	1/1 (1%)	0	1/1 (1%)
Dizziness	2/2 (1%)	0	2/2 (1%)	2/2 (2%)	2/2 (2%)	0
Faecal incontinence	4/3 (2%)	3/2 (1%)	1/1 (1%)	0	0	0
Cephalalgia	3/3 (2%)	0/0	3/3 (2%)	0	0	0
Haemorrhoids	2/1 (1%)	2/1 (1%)	0	1/1 (1%)	1/1 (1%)	0
Respiratory tract infection	0	0	0	2/1 (1%)	0	2/1 (1%)
Zona	2/2 (1%)	0	2/2 (1%)	0	0	0
Aphthous stomatitis	0	0	0	1/1 (1%)	0	1/1 (1%)
Shoulder surgery	0	0	0	1/1 (1%)	0	1/1 (1%)
Nephritic colic	0	0	0	1/1 (1%)	0	1/1 (1%)
Depression	1/1 (1%)	0	1/1 (1%)	0	0	0
Diabetes	1/1 (1%)	0	1/1 (1%)	0	0	0
Bone fracture	0	0	0	1/1 (1%)	0	1/1 (1%)
Erratic defecation hours	1/1 (1%)	1/1 (1%)	0	0	0	0
Phlebitis	1/1 (1%)	0	1/1 (1%)	0	0	0
Colonic polyp	0	0	0	1/1 (1%)	0	1/1 (1%)
Coronary stenting	0	0	0	1/1 (1%)	0	1/1 (1%)
Hypertensive crisis	1/1 (1%)	0	1/1 (1%)	0	0	0
Vaginal pruritus	1/1 (1%)	0	1/1 (1%)	0	0	0
Scleroderma	0	0	0	1/1 (1%)	0	1/1 (1%)
Trauma	1/1 (1%)	0	1/1 (1%)	0	0	0
Vertigo	0	0	0	1/1 (1%)	0	1/1 (1%)

Data are number of adverse events/number of patients (%). The adverse events reported in this table were from the 191 patients who received injections (modified intention-to-treat sample). This includes 96 patients treated by BoNTA during the blinded period, 95 patients treated by placebo during the blinded period, and 73 patients from the placebo group who received BoNTA injections as rescue therapy in the open-label period. Adverse events were attributed to the last treatment received or to the randomisation arm for events that occurred between the randomisation and the injections. *This serious adverse event was assigned to the BoNTA group for conservative reasons because the patient received rescue therapy. But, as the date of the urinary tract infection is unknown, we do not know whether the event occurred before or after the BoNTA injection.

Table 3: **Adverse events reported by patients or physicians or both**

urgency episodes per day at the M3 visit from –0·51 (95% CI –0·8 to –0·21) to –0·50 (–0·79 to –0·21). Second, excluding the two centres with these protocol deviations, which involved 49 and 31 patients, respectively, changed the effect to –0·54 (95% CI –0·85 to –0·24). Finally, the baseline-adjusted BoNTA effect at the M3 visit was estimated at –0·29 (95% CI –1·52 to 0·95) in these ten patients (five in the placebo group, five in the BoNTA group).

Discussion

In the present randomised study, a single series of intrarectal injections of 200 units of BoNTA provided a significant improvement in incontinence symptoms compared with placebo at the M3 visit (primary outcome) as well as at the M1 and M6 visits (secondary outcomes). These results were consistent with the two preliminary case series that studied the use of BoNTA to treat faecal incontinence.[10,11]

As there is no consensual endpoint for evaluating the treatment efficacy of faecal incontinence, the choice of a primary endpoint in studies remains challenging.[16] We opted for a composite main criterion that summed faecal incontinence and urgency episodes for three main reasons. First, this composite endpoint increased the statistical power without multiplying the tests. Second, urgency per se was one of our main therapeutic targets. Finally, urge faecal incontinence episodes were not likely to reflect urgency perfectly. Indeed, the inability to postpone defecation frequently results in restrictions on patients leaving home, with strict planning of access to toilet facilities, as some patients have no or only a few faecal incontinence episodes.[7] However, unlike the results from previous studies that used BoNTA to treat faecal incontinence and that reported improvements in the faecal incontinence severity score (ie, CCS score) when comparing patients with themselves (before *vs* after injection),[10,11] no significant differences in CCS scores between the BoNTA and placebo groups were found. This disparity is probably due to differences in study design and chance (the differences almost reached the pre-specified p value threshold for significance). The inclusion of a placebo group helps take into account the well recognised positive evolution of functional digestive symptoms after any therapeutic intervention, even simulated.[17] This placebo effect probably explains why all the patients in the present study (whether treated with BoNTA or not) asked for an injection of the previously used product. In addition, the CCS score is not the best tool to assess the efficacy of BoNTA treatments for urge faecal incontinence because it assesses the nature and frequency of faecal incontinence episodes but not of urgency episodes, which was one of our main therapeutic targets. In addition, two other criteria used to calculate the CCS score (ie, gas incontinence and wearing protection) were unlikely to be improved by the BoNTA injections. Gas incontinence is rarely improved by faecal incontinence treatments.[18] Wearing protection often requires more than 6 months to observe changes because it takes time for the patient to gain confidence.[19]

Although the intrarectal BoNTA injections resulted in a significant reduction in the mean number of faecal incontinence and urgency episodes per day, the clinical benefit of these findings can be questioned, as a reduction of 0·5 episodes per day while still having 0·8 (SD 1·8) episodes per day may or may not be helpful. However, it resulted in a positive effect on patient perception of BoNTA efficacy and on improvements in quality of life for at least 6 months after the treatment. Interestingly, we found a significant effect on the lifestyle and coping or behaviour subscales of the FIQL. Previous studies have shown that the inability to postpone defecation is likely to cause hypervigilance of rectal sensation and anxiety, which alters the behaviour of patients to anticipate faecal leakages.[20] The improvement in the coping or behaviour subscale could be a consequence of the improvement in the delay to postpone defecation observed in the present study. Altogether, these data indicate that the improvement in incontinence symptoms following the BoNTA treatment translated into beneficial effects on the lives of the patients.

Our key secondary endpoints included the determination of the mechanisms of action of BoNTA on anorectal function. In urology, BoNTA treatments were first introduced on the basis of the theory that BoNTA temporarily blocks the presynaptic release of acetylcholine from the parasympathetic innervation and produces a paralysis of the detrusor smooth muscle.[9] Indeed, BoNTA injections have been shown to increase bladder capacity and volume at the first reflex detrusor contraction and to decrease detrusor pressure during bladder filling and voiding.[9] These urodynamic changes underlie the significant symptomatic improvement in the frequency of urge urinary incontinence episodes reported by patients.[21] Additionally, the improvement in the sensation of urinary urgency suggests that BoNTA has an effect on bladder afferent pathways.[9] Although we found a comparable improvement in bowel urgency, we did not observe any significant changes in rectal sensory thresholds, maximal capacity, or compliance by anorectal manometry or barostat evaluations. We also failed to demonstrate any alteration in spontaneous rectal contractions recorded during anorectal manometry. Several reasons may explain these results: the small number of patients explored by barostat, the best-validated method to measure visceral sensitivity,[22] the absence of prolonged colorectal manometry, which is the most useful and widely used technique to investigate colonic motility,[23] and the 1-month assessment time after the intrarectal injections established from previous urodynamic studies may not be adequate. Given that the present study was not designed to answer this specific objective, it is difficult to draw any firm conclusions from our results.

In the present study, submucosal injections of BoNTA using the endoscopic approach had few risks. Most side-effects were not severe and were as common in the placebo group as in the BoNTA group, which may suggest that adverse effects (constipation, abdominal pain, bleeding, bloating, diarrhoea, anal pain) might be more related to the technique used (colonic purge, colonic air insufflation, submucosal injections) and to the patient's faecal incontinence than to the injected product. That was particularly the case for the most frequent adverse event (ie, constipation). Potential systemic side-effects of BoNTA, such as asthenia, have rarely been reported and, once again, were found in both groups, making it impossible to attribute them to the intrarectal BoNTA injections.

The results of the present study should be interpreted in the context of some limitations. The bowel diary was unclear about whether faecal incontinence following an urge would count both as one urgency and one faecal incontinence episode or whether it would only count as

one faecal incontinence episode given that some patients might have interpreted it one way or the other. This might lead to a non-differential measurement bias in the total number of faecal incontinence and urgency episodes. However, the mode of calculating faecal incontinence and urgency episodes chosen by the patients themselves may be less likely to fluctuate during the study because it is the simplest and most intuitive way for the patients to declare faecal incontinence and urgency episodes. There were ten premature uses of the M6 unblinding procedure. However, systematic data monitoring guaranteed that the paper-based patient bowel diary (primary outcome) collected at the M3 visit had been correctly recorded in the electronic case report form. Sensitivity analyses were reassuring and showed that unmasked patients had no better outcomes than masked patients, and that the two centres that had deviated from the unblinding protocol had no better results than the other centres. The present study was not powered to allow precise assessments of differential treatment efficacies between subgroups of patients. A significant interaction between treatment and age was found, but the poor power and multiple testing make this finding doubtful. The present study had a 6-month follow-up, which we considered a good compromise between evaluating the short-term efficacy of intrarectal BoNTA injections and its well known limited duration of efficacy.[21] However, the large uncertainty of the 6-month versus the 3-month efficacy ratio did not allow us to identify a loss in treatment efficacy over this period. Our cohort of patients continues to be followed up for longer-term efficacy and safety.

In conclusion, submucosal intrarectal BoNTA injections were well tolerated and were efficacious in treating urge faecal incontinence and urgency episodes. Further studies will be required to optimise the administration of the treatment, identify the best candidates to receive therapy, assess its duration of efficacy, and continue the evaluation of adverse effects. Nevertheless, BoNTA could become a valuable tool for the treatment of urge faecal incontinence, subject to confirmatory phase 3 trial(s) required for market approval.

Contributors

A-ML planned the study and wrote the protocol with VB, GG, EL, and AG. A-ML, MQ, FZ, LS, VV, GA, IE, FM, VB, JP, CB, HD, and GG helped recruit the patients and collect and interpret the data. A-ML, EL, and AG obtained and analysed the data. A-ML, EL, and AG drafted the manuscript. GG and AG verified the data reported in manuscript. A-ML, MQ, FZ, LS, VV, GA, IE, FM, VB, JP, CB, HD, and GG participated in drafting the manuscript and editing it critically for important intellectual content. A-ML and GG gave final approval of the version to be submitted and of any edited versions. GB helped proofread the manuscript.

Declaration of interests

A-ML is a consultant for Medtronic. FZ is a consultant for Coloplast. LS has received grants from Takeda, Janssen, and AbbVie, is a consultant for Takeda, and has received grants for educational support from Takeda, Janssen, and AbbVie. GA receives support for learning sessions from Wellspect, honoraria for presentations from Laborie, Coloplast, and Convatec, and support for meetings with Coloplast and IPSEN, and sits on the advisory boards of Coloplast, Convatec, and IBSA. FM lectures for Laborie, Medtronic, and Dr Falk; his spouse is employed by MSD. IE lectures for Takeda, MSD, and Viva Healthcare. AG gives paid statistical courses to Gleamer (medical imaging enterprise). GG is a consultant for Kyowa Kirin, Enterra Medical, and Naturex; gives lectures for Lilly, Medtronic, Laborie, Kyowa Kirin, Enterra Medical, and Coloplast; and has a contract from Dr Falk. MQ, VV, HD, VB, JP, CB, and EL declare no competing interests.

Data sharing

Data collected for the study, including individual participant data and a data dictionary defining each field in the set, will not be made available to others. The study protocol can be found in the appendix (pp 7–52). No other data are available.

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References

1 Rao SS, Bharucha AE, Chiarioni G, et al. Anorectal disorders. *Gastroenterology* 2016; **150:** 1430–42.
2 Whitehead WE, Borrud L, Goode PS, et al. Fecal incontinence in US adults: epidemiology and risk factors. *Gastroenterology* 2009; **137:** 512–17.
3 Nelson R, Norton N, Cautley E, Furner S. Community-based prevalence of anal incontinence. *JAMA* 1995; **274:** 559–61.
4 Miner PB. Economic and personal impact of fecal and urinary incontinence. *Gastroenterology* 2004; **126:** S8–S13.
5 Bharucha AE, Fletcher JG, Harper CM, et al. Relationship between symptoms and disordered continence mechanisms in women with idiopathic faecal incontinence. *Gut* 2005; **54:** 546–55.
6 Chan CLH, Lunniss PJ, Wang D, Williams NS, Scott SM. Rectal sensorimotor dysfunction in patients with urge faecal incontinence: evidence from prolonged manometric studies. *Gut* 2005; **54:** 1263–72.
7 Bharucha AE, Knowles CH, Mack I, et al. Faecal incontinence in adults. *Nat Rev Dis Primers* 2022; **8:** 53.
8 NICE. Urinary incontinence and pelvic organ prolapse in women: management [NICE Guideline No.123] National Institute for Health and Care Excellence, 2019.
9 Apostolidis A, Dasgupta P, Fowler CJ. Proposed mechanism for the efficacy of injected botulinum in the treatment of human detrusor overactivity. *Eur Urol* 2006; **49:** 644–50.
10 Bridoux V, Gourcerol G, Kianifard B, et al. Botulinum A toxin as a treatment for overactive rectum with associated faecal incontinence. *Colorectal Dis* 2012; **14:** 342–48.
11 Gourcerol G, Bénard C, Melchior C, et al. Botulinum toxin: an endoscopic approach for treating fecal incontinence. *Endoscopy* 2016; **48:** 484–88.
12 Jorge JM, Wexner SD. Etiology and management of fecal incontinence. *Dis Colon Rectum* 1993; **36:** 77–97.
13 Rullier E, Zerbib F, Marel A, Amouretti M, Lehur PA. Validation of the French version of the Fecal Incontinence Quality of Life scale (FIQL). *Gastroenterol Clin Biol* 2004; **28:** 562–68.
14 Carrington EV, Heinrich H, Knowles CH, et al. The international anorectal physiology working group (IAPWG) recommendations: standardized testing protocol and the London classification or disorders of anorectal function. *Neurogastroenterol Motil* 2020; **32:** e13679.
15 Melchior C, Gourcerol G, Chastan N, et al. Effect of transcranial magnetic stimulation on rectal sensitivity in irritable bowel syndrome: a randomized, placebo-controlled pilot study. *Colorectal Dis* 2014; **16:** O104–O111.
16 Vaizey CJ. Faecal incontinence: standardizing outcome measures. *Colorectal Dis* 2014; **16:** 156–58.
17 Musial F, Klosterhalfen S, Enck P. Placebo responses in patients with gastrointestinal disorders. *World J Gastroenterol* 2007; **13:** 3425–29.
18 Melchior C, Gourcerol G, Bridoux V, Ducrotte P, Menard JF, Leroi AM. Efficacy of antibiotherapy for treating flatus incontinence associated with small intestinal bacterial overgrowth: a pilot randomised trial. *PLoS One* 2017; **12:** e0180835.

19 Leroi AM, Parc Y, Lehur PA, et al. Efficacy of sacral nerve stimulation for fecal incontinence: results of a multicenter double-blind crossover study. *Ann Surg* 2005; **242:** 662–69.
20 Pahwa AK, Khanijow KD, Harvie HS, Arya LA, Andy UU. Comparison of patient impact and clinical characteristics between urgency and passive fecal incontinence phenotypes. *Female Pelvic Med Reconstr Surg* 2020; **26:** 570–74.
21 Yokoyama T, Chancellor MB, Oguma K, et al. Botulinum toxin type A for the treatment of lower urinary tract disorders. *Int J Urol* 2012; **19:** 202–15.
22 Whitehead WE, Delvaux M. Standardization of barostat procedures for testing smooth muscle tone and sensory thresholds in the gastrointestinal tract. The Working Team of Glaxo-Wellcome Research, UK. *Dig Dis Sci* 1997; **42:** 223–41.
23 Camilleri M, Bharucha AE, di Lorenzo C, et al. American Neurogastroenterology and Motility Society consensus statement on intraluminal measurement of gastrointestinal and colonic motility in clinical practice. *Neurogastroenterol Mot* 2008; **20:** 1269–82.