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Longitudinal Studies of Botulinum Toxin in Cervical Dystonia: Why Do Patients Discontinue Therapy?

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Abstract

Background—Numerous studies have established botulinum toxin (BoNT) to be safe and effective for the treatment of cervical dystonia (CD). Despite its well-documented efficacy, there has been growing awareness that a significant proportion of CD patients discontinue therapy. The reasons for discontinuation are only partly understood.

Methods—This summary describes longitudinal studies that provided information regarding the proportions of patients discontinuing BoNT therapy, and the reasons for discontinuing therapy. The available data come predominantly from un-blinded long-term follow-up studies, registry studies, and patient-based surveys.

Results—All types of longitudinal studies provide strong evidence that BoNT is both safe and effective in the treatment of CD for many years. Overall, approximately one third of CD patients discontinue BoNT. The most common reason for discontinuing therapy is lack of benefit, often described as primary or secondary non-response. The apparent lack of response is only rarely related to true immune-mediated resistance to BoNT. Other reasons for discontinuing include side effects, inconvenience, cost, or other reasons.

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Discussion—Although BoNT is safe and effective in the treatment of the majority of patients with CD, approximately one third discontinue. The increasing awareness of a significant proportion of patients who discontinue should encourage further efforts to optimize administration of BoNT, to improve BoNT preparations to extend duration or reduce side effects, to develop add-on therapies that may mitigate swings in symptom severity, or develop entirely novel treatment approaches.

Keywords

Botulinum toxin; dystonia; cervical dystonia; torticollis; treatment

Introduction

Cervical dystonia (CD) is characterized by excessive contraction of neck muscles leading to abnormal movements and postures of the head (Dauer et al., 1998; Singer and Velickovic, 2008). The majority of patients also have neck pain (Charles et al., 2014; Patel et al., 2014); and many suffer from depression, anxiety and social withdrawal (Berman et al., 2017; Zurowski et al., 2013). Together these problems cause a substantial decrease in quality of life (Berman et al., 2005; Nastasi et al., 2016; Pekmezovic et al., 2009; Poewe et al., 1992; Slawek et al., 2007; Zetterberg et al., 2009).

Botulinum toxin (BoNT) was first introduced as a treatment for CD three decades ago. When it was introduced, it was described as a miracle drug. Over the years, numerous studies established BoNT to be remarkably effective in the treatment of CD (Albanese et al., 2015a; Hallett et al., 2013; Jankovic, 2017; Simpson et al., 2016). It is highly effective in reducing abnormal movements and pain, and improves quality of life. In experienced hands, side effects are infrequent or minor. As a result, BoNT is currently viewed as the treatment of first choice for CD.

Impressions regarding the efficacy of BoNT in CD come predominantly from studies focusing on short-term outcomes from expert centers. Fewer studies have addressed the long-term use of BoNT in CD in the broader community. However, longitudinal studies also uniformly conclude that BoNT is both safe and effective for many years (Ramirez-Castaneda and Jankovic, 2013). Despite the remarkable efficacy of BoNT as a treatment for CD, there has been increasing awareness that a significant proportion of patients discontinue treatment. The actual percentages of patients who discontinue, and the reasons for discontinuation are only partly understood. The purpose of this article is to review this evidence and provide recommendations for improving future treatments for CD.

Longitudinal studies of botulinum toxin in CD

Treatment follow-up studies

Several studies have addressed BoNT treatment outcomes for CD in follow-up studies that included specific durations of time or specific numbers of treatment cycles. The current review summarizes all available studies, focusing particularly on large longitudinal studies that included information regarding the percentage of patients who discontinued therapy

(Table 1), and/or insights into the reasons for discontinuation (Table 2). This review excludes studies focused on treatment outcomes but with little information regarding the portion of patients who discontinued or the reasons they discontinued (Dressler et al., 2013; Mejia et al., 2005; Mohammadi et al., 2009; Ramirez-Castaneda and Jankovic, 2013, 2014).

One of the first longitudinal studies included data from 616 CD patients treated with abobotulinumtoxinA over a 7 year period from 1988–1995 in Germany (Kessler et al., 1999). This study focused on a subgroup of 303 patients (49%) who had at least 6 treatment sessions. This subpopulation was followed for an average duration of 3.2 years, and the results indicated sustained benefits with only minor and transient side effects. Of course, these conclusions are likely to be influenced by inclusion criteria that required at least 6 treatment sessions. The obvious question that arises is what happened to the 51% of cases who did not meet these inclusion criteria? Telephone interviews were conducted for a subgroup of 155 patients who discontinued therapy, and multiple reasons were ascertained. The most common reasons were changes in treatment center, lack of efficacy, and adverse events (Tables 1–2).

Another early study attempted to gain insight from the patient perspective via a survey of 155 CD patients treated with onabotulinum toxinA over a 6 year period from 1991–1997 in the USA (Brashear et al., 2000). Although the majority of patients reported success with treatments, 22% discontinued. The most common reasons for discontinuation were lack of efficacy, expense, and adverse events. Another 14% of patients did not return the survey, so the actual percentage of patients who discontinued may be higher (Tables 1–2).

A third study described treatment of 235 patients with various movement disorders with onabotulinumtoxinA over a 10-year period from 1990–1999 in Canada (Hsiung et al., 2002). The duration of follow-up ranged from 2–10 years. Among 106 patients with CD, sustained benefits were found for 68% at 2 years and 63% at 5 years. This result implies that 32–37% did not have sustained benefits. During the entire study period, 46% of patients discontinued treatment. The most common reasons for discontinuation were primary or secondary non-response (Tables 1–2).

Another study from Germany addressed 100 consecutive CD patients first treated with abobotulinumtoxinA between 1989–1992 and followed for an average of 5 years (Haussermann et al., 2004). Only 6 patients were lost to follow-up and 4 died. Of the remaining 90 patients, most had sustained benefits, but 37% discontinued. The most common reasons were adverse events or spontaneous improvement in dystonia no longer requiring therapy (Tables 1–2), although examinations to verify spontaneous improvement were not conducted.

A study from Norway described 94 patients with CD treated with onabotulinumtoxinA for a minimum of 1.5 years and followed for an average of 5.5 years (Skogseid and Kerty, 2005). The majority retained good responses with few side effects. The impressions of the neurologists were compared with the impressions of the patients using a clinical global impression (CGI) scale. The neurologists reported significantly more positive outcomes than the patients. After combining results from patients and neurologists, 33% were considered to

have an outcome that was not satisfactory. Fourteen patients (18%) did not return for follow up treatments. The most common reason was remission of disease (Tables 1–2), although examinations to confirm remission were not conducted.

Another study summarized results from 70 patients with CD treated with onabotulinumtoxinA or rimabotulinumtoxinB from 1997–2006 in the USA (Gill et al., 2013). The majority of patients had sustained benefits, but 30% discontinued. The most common reasons for discontinuation included secondary non-responsiveness or cost (Tables 1–2).

Overall, these longitudinal studies uniformly paint a very positive picture of long-term use of BoNT in CD, with sustained benefits and minimal side effects. However, this picture may not provide an accurate depiction of the real-world experience of BoNT since the majority of these studies focused mostly on the subgroup of patients who continued therapy. Presumably, the majority of patients who return have had positive outcome. A large percentage of patients did not meet strict inclusion criteria or discontinued therapy, and less information is available on these groups. Additionally, all available studies were reported by tertiary care centers with a high degree of experience with BoNT and CD. Outcomes in these centers are likely to be better than the broader community of providers, who have less experience. From the limited available evidence (Table 1), the overall weighted average of patients who discontinue therapy appears to be approximately 30% (Tables 1–2), even at expert centers.

Registry studies

Several recent studies have attempted to obtain a more realistic picture of BoNT treatment outcomes using multicenter designs. CD-PROBE is a registry study that addressed 3 treatment cycles with onabotulinum toxinA (Jankovic et al., 2015). In this study, 88 sites in the USA enrolled 1046 CD patients, but 52% withdrew prior to completing the study (Table 3) (Jankovic et al., 2015). The most common reasons for withdrawing were “lost to follow-up” and “withdrawal of consent” (Table 3). Adverse events or actual worsening did not appear to be common (3%). Lack of benefit led to withdrawal for only small proportion (8%). Even among patients who continued in the study, minimal or no benefit was reported by 52% after their first treatment, 44% after their second treatment, and 36% after their final treatment. Similar to the prior study from Norway (Skogseid and Kerty, 2005), physician-estimated benefits were greater than patient-estimated benefits across all treatment sessions.

ANCHOR-CD is a registry study that addressed 4 treatment cycles with abobotulinumtoxinA. In this study, 41 sites in the USA enrolled 350 CD patients; but 37% withdrew prior to completing the study (Trosch et al., 2017). The most common reasons for withdrawing included “patient decision”, “investigator decision”, and “lost to follow-up” (Table 4). Among those who continued, adverse events appeared to be uncommon (1%). However, minimal or no benefit was reported by 56% after their first treatment, 57% after their second treatment, 51% after their third treatment, and 47% following their final treatment. Physician-estimated benefits were again higher than patient-estimated benefits.

CD-PROBE and ANCHOR-CD were designed to provide a more accurate “real world” picture of BoNT treatment of CD in the community. These studies may provide a more realistic picture than single-site studies from expert centers, but not one that is truly “real world” for several reasons. First, the majority of patients were recruited by centers with high patient volumes, so they were more likely to receive treatments from very experienced physicians. Second, strict exclusion criteria favored the recruitment of patients who were more likely to have good responses. Finally, the true reasons patients withdrew from these studies cannot be accurately determined because of the use of categories such as “withdrawal of consent”, “lost to follow-up”, and patient or investigator “decision”. Because the true reasons for withdrawal for the majority remain unknown, the percentages of patients withdrawing because of poor responses or adverse events in a community sample cannot be determined from these studies.

The Dystonia Coalition is an international multi-center study aimed at better understanding the clinical evolution of all isolated dystonia syndromes (www.dystoniacoalition.org). Although it was not designed as a longitudinal study for BoNT treatment, some data are collected regarding BoNT use. A recent cross-sectional report included 2026 subjects enrolled at 37 sites, including 930 subjects with CD (Pirio Richardson et al., 2017). Overall, a surprisingly large proportion of the CD subjects (35.6%) were not using any type of BoNT, although the reasons were not determined. This low rate of BoNT use may reflect a referral bias involving selective recruitment of newly evaluated patients who had not yet been offered therapy, selective recruitment of the most challenging cases who failed prior therapy, incomplete data entry, or other factors. However, the vast majority of patients in the Dystonia Coalition study are recruited from BoNT clinics, where patients are regularly returning for therapy. Therefore, it is also possible that the proportion of CD patients receiving BoNT is positively biased in this study, because patients not receiving therapy would be less likely to be returning on a regular basis to be recruited. Although we cannot determine why so many patients were not using any type of BoNT in the Dystonia Coalition cohort, the overall percentages are consistent with the high drop-out rates from CD-PROBE and ANCHOR-CD.

In another registry study (INTEREST IN CD), 38 centers in Europe and Australia enrolled 404 subjects with CD and followed responses to any of the type A BoNTs over one treatment cycle (Misra et al., 2012). Although this study was not designed to provide longitudinal data regarding BoNT outcomes, the results are interesting because four different criteria were used to measure outcomes, and all four criteria had to be met to achieve the diagnosis of “responder”. Overall, 98% of treated patients met the criterion of >25% improvement on the TWSTRS, 74% met criterion of absence of significant adverse events, 70% met the criterion for improvement on CGI provided by both patient and clinician, and 49% met the criterion of benefit >12 weeks. Only 29% were viewed as “responders” because they met all four criteria. This study highlights the different conclusions that arise from arbitrarily-defined outcome measures. Further studies are needed to determine how these outcome measures might relate to patient-reported outcomes and changes in quality of life.

Survey studies of patient perspectives

Most clinical trials focus on physician-rated scales of motor improvements or clinical global impressions of the treating physician. However, the Norwegian study described above revealed that patients with CD tended to rate their outcomes less enthusiastically than their physicians (Skogseid and Kerty, 2005). The same phenomenon was observed in both the CD-PROBE (Jankovic et al., 2015) and ANCHOR-CD (Trosch et al., 2017) registry studies. The reasons for these discrepancies between patients and their doctors are not clear. When trying to understand the frequency and reasons for discontinuing therapy or withdrawing from a study, surveying the patient perspective is critical.

An internet-based survey was used to collect information about treatment from 1071 anonymous respondents with self-identified CD from 38 different countries (Comella and Bhatia, 2015). Among the 907 patients who had received at least one treatment with BoNT, 56% of patients reported that they were fairly or completely satisfied with their treatments. Another 24% reported they were fairly or completely dissatisfied, and the remaining 20% were neutral. Among those who were not satisfied, 40% reported that BoNT treatment did not work, 33% reported adverse events, 16% were unhappy with the long treatment intervals, and 9% raised concerns for expense.

Another survey addressing satisfaction of CD patients with BoNT treatments was conducted by structured interviews with 136 patients who had been treated for an average of 45 months in Canada, France, Germany and USA (Sethi et al., 2012). At peak therapeutic effects, 72% reported they were very satisfied and 16% were somewhat satisfied. Just prior to injections when therapeutic effects were waning, only 14% were very satisfied, 47% were somewhat satisfied, and 39% were not satisfied at all. These results show that satisfaction with BoNT treatment in CD varies significantly according to the stage of the injection cycle, most likely because of the waxing and waning effect of BoNT over time. Some patients have dubbed this the “yo-yo” effect.

Survey studies are valuable because they address the patient perspective, which occasionally does not parallel assessments provided by their treating physicians. However, survey studies suffer some known limitations including biases associated with how questions are asked and which subjects decide to complete the survey. On one hand, methodical surveys conducted by treating physicians avoid selection bias, but are subject to known psychological influences regarding the interview process. For example, a patient who experiences a poor outcome from BoNT treatment from a highly-respected physician may give a polite response rather than an accurate one to avoid causing any offense. In this situation, surveys conducted by treating physicians or their staff are subject to a positive bias. On the other hand, anonymous surveys are thought to be conducive to more honest responses. However, negative experiences may provide a more powerful motivator to subjects to complete these surveys, creating a bias towards negative responders. Despite these limitations, well-designed survey studies are essential, and the available results are strikingly consistent in identifying a large percentage of CD patients who are not satisfied with BoNT treatment.

Another reason for discrepancies between patient and physician impressions is that the measures we rely on to estimate efficacy may not be the ones that matter most to patients.

For example, many studies of BoNT in CD use a minimum of 25% improvement in the TWSTRS as the criterion for successful treatment. Is 25% reduction in TWSTRS sufficient improvement for a patient to want to continue therapy? Even when patients are queried about their impressions, their answers are subject to arbitrary criteria for interpreting success. For example, many of the studies summarized above asked patients what percentage overall improvement they experienced following treatment. However, the investigators then defined a minimum of 50% improvement as an arbitrary criterion for success. Is 50% improvement sufficient for a patient to want to continue therapy? If the bar is set to unambitious criteria such as 25% improvement in TWSTRS or 50% improvement in patient CGI, outcomes may be highly statistically significant from clinical trials, yet unsatisfactory from the patient perspective.

Other relevant studies

A common theme for many of the follow-up and registry studies was patient-reported lack of efficacy, despite the typically remarkable efficacy of BoNT reported from clinical trials of CD. Only a few studies have addressed the fate of CD patients who claim unsatisfactory responses due to lack of efficacy. A study of 20 patients in the UK who were referred to an expert center for apparent secondary non-response revealed that 45% had good responses after adjustments to the dose and pattern of injections (Cordivari et al., 2006). Another study of 43 patients in the Netherlands seeking a second opinion from an expert center due to primary or secondary non-response revealed that satisfactory responses could be achieved in 60% by altering the treatment dose and muscles patterns injected with the aid of electromyography true resistance to be uncommon (Nijmeijer et al., 2013). A third study of 35 consecutive CD patients seeking a second opinion from an expert center in the USA due to primary or secondary non-response revealed that satisfactory responses could be achieved in 71% by altering the dose and pattern, although electromyography was not required (Jinnah et al., 2016).

In all three studies focusing on treatment failures, true immunologically-mediated resistance was uncommon. Instead, all of these studies seemed to imply that “lack of efficacy” in many cases was more related to the dose and muscle selection. This result is consistent with many reports indicating that immunologically-mediated resistance to BoNT is rare, particularly with currently used preparations (Brin et al., 2008; Coleman et al., 2012; Fabbri et al., 2015; Ferreira et al., 2015; Lange et al., 2009; Mejia et al., 2005).

These studies also pointed to certain characteristics of CD that predicted poor responses. Other studies have focused on characteristics that predict good responses in CD (Misra et al., 2012), or characteristics that predict secondary non-responsiveness (Ferreira et al., 2015). From all of these studies combined, characteristics associated with poor outcomes included patients with anterocollis as the predominant manifestation, tremor-dominant CD, anterior/posterior shift of the head in the sagittal plane, previous surgery for CD, use of neuroleptics, and overall severity or requirement for high doses. CD patients with these characteristics are often excluded from clinical trials of BoNT, to maximize detection of benefits. However, these patients are not refused treatment when they present for treatment unrelated to clinical

trials. There are no good statistics on the relative prevalence of these difficult-to-treat cases, or their disposition when BoNT fails.

Summary and future prospects

The goal of this article is not to suggest that BoNT is a bad treatment for CD. In fact, BoNT remains the treatment of first choice because it is the most effective and the safest treatment currently available. However, the published studies paint a picture of outcomes that is skewed by patient selection criteria, treatment by elite centers, how dropouts are handled, and terminology that obfuscates understanding why so many patients discontinue. BoNT is a very good treatment for CD, but a significant percentage of patients seem to saying it is not good enough. This review focused only on longitudinal studies of BoNT treatment of CD, so it is not clear if there are high discontinuation rates for other disorders that are treated with BoNT such as blepharospasm or laryngeal dystonia. Further scrutiny of these other populations would be useful to determine if high discontinuation rates are specific to CD, or a more general phenomenon for BoNT therapy.

The goal of this review is to provide a new perspective based on existing data to encourage the development of better treatments for CD. Identifying why so many patients discontinue therapy is the first step that is required to improve therapy. The reasons that patients discontinue therapy appear to be varied, although they have not been methodically studied. The most common reasons include lack of efficacy, side effects, unrealistic expectations, high cost and inconvenience. Means to address some of these problems are within reach already. For example, the apparent lack of efficacy is often due to suboptimal dose patterns (Cordivari et al., 2006; Jinnah et al., 2016; Nijmeijer et al., 2013). This problem points to the need for better education regarding optimal doses and muscle selection, or identification of subtypes of patients with complex patterns of dystonia that are known to be more challenging to treat. Some patients discontinue for lack of efficacy after only a single treatment session. This problem points to the need for better counseling of patients regarding dose titration, or more aggressive titration schedules. In other cases, patients discontinue because of unexpected or intolerable side effects. Since side effects are typically minimal or transient in experienced hands, this problem seems to point again to the need for better education of injectors and patients. Several studies have pointed to unrealistic patient expectations as a reason for discontinuing therapy. This problem can be addressed by better counseling of patients regarding expected benefits, potential side effects, and the need for customization of doses and muscle patterns.

Other reasons that patients discontinue therapy are more challenging to address, such as inconvenience due to the need for repeated dosing. In the future, improvements in therapy may involve modifications of BoNT preparations to extend duration or reduce side effects, the development of adjunctive therapies that may mitigate swings in symptom severity associated with treatment cycles, or entirely novel treatment approaches. Fortunately, efforts are underway in all of these areas to improve treatment (Albanese et al., 2015b; Jankovic, 2017).

When we consider the treatment and development of novel therapies for epilepsy, the usual stated goal is 100% relief of seizures to permit patients to return to a normal life. Despite the availability of multiple effective anticonvulsants, this goal has been a strong motivator driving the development of new and better anticonvulsants. In view of these goals typically used for epilepsy, we should re-evaluate typical criteria used as outcome measures for CD, such as 25% improvement in the TWSTRS or 50% improvement in patient global assessments. Similar to other disorders, more attention should be directed to patient-reported outcomes, or quality of life measures. If we want to improve patient satisfaction, we need to address what matters most to patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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M Hallett serves as Chair of the Medical Advisory Board for and may receive honoraria and funding for travel from the Neurotoxin Institute. He may accrue revenue on US Patent #6,780,413 B2 (Issued: August 24, 2004): Immunotoxin (MAB-Ricin) for the treatment of focal movement disorders, and US Patent #7,407,478 (Issued: August 5, 2008): Coil for Magnetic Stimulation and methods for using the same (H-coil); in relation to the latter, he has received license fee payments from the NIH (from Brainsway) for licensing of this patent. He is on the Editorial Board of approximately 20 journals, and received royalties and/or honoraria from publishing from Cambridge University Press, Oxford University Press, and Elsevier. Dr. Hallett's research at the NIH is largely supported by the NIH Intramural Program. Supplemental research funds have been granted by UniQure for a clinical trial of AAV2-

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Highlights

- Longitudinal studies uniformly reveal botulinum toxin to be safe and effective in the treatment of cervical dystonia
- Despite the record of safety and efficacy, approximately one third of patients discontinue therapy over time
- The reasons for discontinuing therapy are only partly understood, because of the paucity of information regarding patients who discontinue
- Further studies exploring these reasons are needed to guide improvements in the treatment of this population

Table 1

Longitudinal studies of BoNT treatment in CD

| Study | Total cases | Total CD cases studied | Follow up treatment cycles | Average follow up years (range) | Percent discontinuing |
|--------------------------|-------------|------------------------|----------------------------|---------------------------------|-----------------------|
| Kessler et al., 1999 | 616 | 303 | at least 6 | 3.2 (1.3–5) | 26.3 ¹ |
| Brashear et al., 2000 | 155 | 133 | NR | NR | 21.9 ² |
| Hsiung et al., 2002 | 235 | 106 | average: 11.9 | NR (2–10) | 46 |
| Haussermann et al., 2004 | 100 | 90 | at least 1 | 5.0 (0.25–12) | 33 |
| Skogseid and Kerty, 2005 | 94 | 78 | average, 18.5; range 7–31 | 5.5 (1.5–10) | 17.9 |
| Gill et al., 2013 | 70 | 70 | average, 11.5; range 0–39 | NR | 30 |

¹The actual rate of patients discontinuing was not given, but 162/616 patients (26.3%) did not return for follow-up.

²Survey not returned by 22 subjects, so this estimate may be too low. NR=not reported. The overall weighted average for all patients discontinuing across these studies was 30%.

Table 2

Reasons for discontinuation of BoNT treatment in CD

| Reason | Kessler et al., 1999 | Brashear et al., 2000 | Hsiung et al., 2002 | Haussermann et al., 2004 | Skogseid and Kerty, 2005 | Gill et al., 2013 | TOTAL |
|------------------------|----------------------|-----------------------|---------------------|--------------------------|--------------------------|-------------------|------------|
| Total Cases | 155 | 51 | 49 | 33 | 14 | 21 | 272 |
| Primary non-response | 19.3% (33) | 21.6% (11) | 22.4% (11) | 3.0% (1) | 14.3% (2) | 14.3% (3) | 18.4% (50) |
| Secondary non-response | 9.9% (17) | 3.9% (2) | 18.4% (9) | 9.1% (3) | NR | 38.1% (8) | 13.6% (37) |
| Adverse events | 15.8% (27) | 27.4% (14) | 6.1% (3) | 33.3% (11) | NR | 9.5% (2) | 15.8% (43) |
| Improved/remitted | 15.2% (26) | NR | 8.2% (4) | 18.2% (6) | 35.7% (5) | 4.8% (1) | 15.4% (42) |
| Moved | 21.1% (36) | 2.0% (1) | 6.1% (3) | NR | NR | NR | 14.3% (39) |
| Inconvenience | NR | 13.7% (7) | 6.1% (3) | 36.4% (12) | NR | 9.5% (2) | 6.2% (17) |
| Cost | NR | 13.7% (7) | 4.1% (2) | NR | NR | 23.8% (5) | 2.5% (7) |
| Other | 17.4% (27) | 31.4% (16) | 2.0% (1) | NR | 35.7% (5) | 4.8% (1) | 11.8% (32) |
| Lost to follow up | 4.1% (7) | 43.1% (22) | 26.5% (13) | NR | 14.3% (2) | NR | 8.1% (22) |

Values show percent of total patients and actual number in parentheses discontinuing treatment at their study center. Percentages may add up to more than 100 if patients gave more than one reason. The “other” category includes pregnancy, death, other illness, preference for other treatments, unknown, or discontinuation by physician for unspecified reasons. NR=not reported.

Table 3

Reasons for withdrawal in CD-PROBE

| Reason | Pre-treatment visit | Treatment visit 1 | Treatment visit 2 | Treatment visit 3 | Total (N) | Total (%) |
|----------------------|---------------------|-------------------|-------------------|-------------------|------------|-------------|
| Lost to follow up | 1 | 72 | 60 | 110 | 243 | 23.2 |
| Withdrew consent | 2 | 52 | 34 | 7 | 95 | 9.1 |
| Lack of response | 0 | 49 | 34 | 2 | 85 | 8.1 |
| Adverse event | 0 | 26 | 6 | 0 | 32 | 3.1 |
| Physician discretion | 0 | 12 | 8 | 1 | 21 | 2.0 |
| Financial | 0 | 5 | 5 | 1 | 11 | 1.0 |
| Moved | 0 | 2 | 6 | 2 | 10 | 1.0 |
| Other | 2 | 5 | 2 | 1 | 10 | 1.0 |
| Non-study injector | 0 | 2 | 5 | 0 | 7 | 0.7 |
| Travel burden | 0 | 1 | 1 | 5 | 7 | 0.7 |
| Recovered/remission | 0 | 2 | 4 | 0 | 6 | 0.6 |
| Other health issues | 0 | 5 | 0 | 0 | 5 | 0.5 |
| Time burden | 0 | 1 | 1 | 3 | 5 | 0.5 |
| Death | 0 | 2 | 1 | 1 | 4 | 0.4 |
| Pregnancy | 0 | 1 | 1 | 1 | 3 | 0.3 |
| TOTAL | 5 | 237 | 168 | 134 | 544 | 52.3 |

Data for this table were taken from Figure 2 of the CD-PROBE study (Jankovic et al., 2015). The percentages are calculated according to the total 1046 subjects recruited.

Table 4

Reasons for Withdrawal in ANCHOR-CD

| Reason | Treatment visit 1 | Treatment visit 2 | Treatment visit 3 | Treatment visit 4 | Total (N) | Total (%) |
|-----------------------|-------------------|-------------------|-------------------|-------------------|-----------|-----------|
| Patient decision | 40 | 15 | 8 | 4 | 67 | 19.1 |
| Investigator decision | 6 | 3 | 0 | 0 | 9 | 2.6 |
| Sponsor decision | 2 | 1 | 1 | 1 | 5 | 1.4 |
| Lost to follow-up | 11 | 4 | 4 | 9 | 28 | 8.0 |
| Adverse event | 2 | 0 | 1 | 0 | 3 | 0.9 |
| Cost | 3 | 1 | 1 | 0 | 5 | 1.4 |
| Other | 4 | 2 | 3 | 1 | 10 | 2.9 |
| TOTALS | 68 | 26 | 18 | 15 | 127 | 36.3 |

Data for this table were taken from Figure 1 in the ANCHOR-CD study (Trosch et al., 2017). The percentages are calculated according to the total 350 subjects recruited.