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Dysport® for the treatment of myofascial back pain: Results from an open-label, Phase II, randomized, multicenter, dose-ranging study

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ABSTRACT

Background and purpose: Botulinum toxin type A (BoNT-A) has antinociceptive and muscle-relaxant properties. The objectives of this study were to investigate the efficacy and safety of a single BoNT-A (Dysport®) treatment in myofascial back pain.
Methods: In this randomized, open-label, multicenter study, adults with myofascial lower back pain received Dysport® injections at four trigger points (60, 80 or 120 units per injection point). Patients were followed for 12 weeks. The *a priori* primary endpoint was a pooled evaluation, at Week 6, of seven measures of efficacy, including pain intensity (patient diary), modified Pain Disability Index (PDI) score, use of interfering concomitant analgesics, and patient-rated global efficacy. Optional assessments of pressure thresholds and tissue compliance were conducted. Safety was also assessed.
Results: A total of 202 patients were randomized to treatment and 189 patients received a low ($n = 57$), medium ($n = 57$), or high ($n = 75$) total dose of Dysport® at 34 centers in Germany between October 2002 and October 2003. All treated patients were included in the safety population; 8 patients were excluded from the intention-to-treat population. Patients had moderate to severe pain at baseline. At baseline, 120 patients were receiving concomitant analgesic therapy; 6.7%, 74.2% and 19.2% were considered to cause mild, moderate and severe interference with pain measurements, respectively. There was no difference between doses for the *a priori* combined primary endpoint. Patient-reported pain intensity scores at rest and on movement decreased significantly after treatment for all groups combined ($p < 0.0001$ at all visits). At Week 6, reductions in pain intensity at rest were 29%, 19% and 26% for the low-, medium- and high-dose groups, respectively; reductions in pain intensity on movement were 27%, 18% and 26%, respectively. Overall, patients who reported pain intensity reductions at Week 6 were evident within 3 weeks of treatment and were maintained for the 12 weeks of the study. In the total population, significant decreases in mean PDI sum scores from baseline were observed from Week 3 and were maintained through to the end of treatment (Week 12); no differences between the dose groups were observed. Pressure thresholds and tissue compliance also increased during the study. Adverse events were generally as expected for BoNT-A; the majority were mild or moderate in severity.
Conclusions: Dysport® treatment was associated with reductions in myofascial back pain and was well tolerated. No dose–response relationship was observed; treatment with Dysport® using a four-trigger-point injection protocol at 60 units per trigger point was associated with a clinically relevant and statistically significant improvement in pain and pain-related disability; there was no additional benefit from the higher doses.
Implications: Our findings are limited by the lack of a control group and further research is warranted to confirm the value of Dysport® for the treatment of myofascial back pain and confirm the optimum dosing in this indication.

1. Introduction

Myofascial pain syndrome is a chronic musculoskeletal disorder that is characterized by muscles in the shortened or contracted state with increased tone and stiffness [1–3]. These muscles contain tender, firm nodules called trigger points, which, on stimulation, transfer pain to surrounding areas [1–3]. The pathogenesis of myofascial pain syndrome is unproven but

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Abbreviations: ANOVA, analysis of variance; BoNT-A, botulinum toxin type A; ITT, intent-to-treat; LOCF, last observation carried forward; NSAIDs, non-steroidal anti-inflammatory drugs; PDI, Pain Disability Index; PP, per protocol; SD, standard deviation.
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several mechanisms have been proposed, such as muscle spindle hyperactivity or sustained depolarization of post-junctional muscle cells due to excessive acetylcholine release [3–5]. Various pharmacological and physical therapies are available for the treatment of myofascial pain syndrome, but the effects of these agents may only be short term (e.g. with therapeutic injections), their efficacies can be unreliable (e.g. non-steroidal anti-inflammatory drugs [NSAIDs], therapeutic injections) and many are limited by toxicities (e.g. NSAIDs, tricyclic antidepressants) [3,6–8].

Botulinum toxin type A (BoNT-A) is a neurotoxin complex that is currently used to treat various disorders involving muscle hyperactivity, including focal spasticity, blepharospasm, spasmodic torticollis, and hemifacial spasm. Importantly, BoNT-A also has antinociceptive and muscle-relaxant properties and has been used successfully to treat chronic pain [9–11]. Furthermore, evidence suggests that BoNT-A may modulate the activity of muscle spindles [12,13], which are thought to play a role in the pathogenesis of myofascial pain syndrome [3].

Several studies have investigated the use of BoNT-A injections as a potential new treatment option for myofascial pain syndrome and most have shown a positive effect on treatment of pain [14–25]. However, the majority of these studies were case studies or small controlled clinical trials [15,18,20,22,24,25] and the two larger controlled clinical trials produced conflicting findings [16,17]. Göbel et al. conducted a large, double-blind, placebo-controlled study to evaluate the efficacy and tolerability of Dysport® in 145 patients with moderate-to-severe myofascial pain in cervical and/or shoulder muscles [17]. In this study, a significant improvement in pain levels was reported 4–6 weeks after injections of 400 units of Dysport® into the 10 most tender individual trigger points (40 units per trigger point). In contrast to the findings of Göbel et al., Ferrante et al. [16] conducted a large, double-blind, placebo-controlled study in 132 patients with myofascial pain and did not find a significant benefit with BoNT-A (Botox®) treatment. It has, however, been suggested that the low disease severity (patients with more than five active trigger points were excluded) of patients in this study may have influenced the findings [17].

Clostridium botulinum type A toxin–haemagglutinin complex (Dysport®, Ipsen Ltd, Slough, UK) is a highly purified and highly potent form of BoNT-A. Dysport® combines a well-established safety profile with excellent clinical efficacy in a wide range of neuromuscular disorders [26–33]. Although the efficacy of Dysport® for the treatment of myofascial pain has been documented in a prior placebo-controlled trial [17], the effective dose range of Dysport® for myofascial low back pain has not been established. Therefore, the aim of this pilot study was to investigate the efficacy and tolerability of a range of doses of Dysport® in a large number of patients with myofascial low back pain, in order to estimate the lowest effective dose. It should be noted that different BoNT-A products are available and that the units of these different preparations are not equivalent; in our study, dose specification of units refers exclusively to Dysport® and cannot be applied to other BoNT-A treatments.

2. Methods

2.1. Study design

This was an investigator-initiated, prospective, randomized, open-label, multicenter, Phase II study. The aims of the study were to investigate the efficacy and tolerability of a single Dysport® treatment in patients with myofascial back pain in the lower back, and to optimize the therapeutic dose of Dysport®. After a screening visit (Week −2), patients received treatment at Week 0 and were then assessed for 12 weeks, with visits scheduled at Weeks 3, 6 and 12 (±3 days). The study protocol was approved by the local ethics committee or institutional review board, and conducted according to the principles of good clinical practice and the Declaration of Helsinki. All patients gave informed consent prior to the study.

2.2. Patients

Adults aged at least 18 years were enrolled in the study if they had myofascial back pain affecting muscles of the lower back (pain in the region from the thoracic vertebra 7 downwards, including the gluteal muscles). Eligible patients were required to have experienced myofascial back pain for more than 3 weeks; have at least four trigger points (one-sided or two-sided, in at least two different muscles); a neuro-orthopedic basic diagnosis of spine involvement to rule out evidence of fractures, blocking of vertebral bodies, radicular irritation syndrome, or other noticeable problems. Patients were also required to have pain intensity at rest or on movement of at least 2 at baseline, rated using the 5-category Verbal Rating Scale (0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain; and 4 = very severe pain).

Patients were excluded from the study if they had specific back pain (e.g. tumours, radicular syndromes, spondylolistheses, nerve root irritations due to a discus prolapse, or due to inflammatory processes [hip arthrosis, spondyloptosis, osteomalacia, acute joint inflammations]); back pain in need of another causal therapy; or evidence of specific diseases of the musculoskeletal system (other than myofascial back pain) or diseases of neuromuscular transmission. Other major exclusion criteria included a history of surgery on the spine, fibromyalgia, pain as a primary expression of depression, or chronic respiratory ailments; prior treatment with BoNT-A; a known allergy or antibodies to BoNT-A; bleeding tendency at the time of injection (due to congenital hemorrhagic diathesis or due to drugs); pregnancy, lactation or the lack of a reliable contraceptive method in women of childbearing potential; any severe concomitant disease; alcohol, medication, or other drug abuse; and an inability to work for longer than 6 months.

2.3. Interventions

Patients were randomized to receive a total dose of 240, 320 or 480 units of Dysport® (500 units in 2.5 ml of 0.9% NaCl; Ipsen Pharma GmbH, Ettlingen, Germany). Randomization was carried out according to the random permuted block design, using a block size of 3 (RANCODE Professional Version, IDV, Gauting, Munich, Germany), independent of study center. Treatment was administered by injections at four trigger points (60, 80 or 120 units per injection point, respectively) using a 1-ml tuberculin syringe with a 27-gauge needle. Injections were administered with a safety margin of at least 3 cm lateral to the median line of the spine. The four most troublesome trigger points, in at least two different muscles on one or both sides of the body, were treated. The injection points were documented in a trigger-point scheme (sequential numbering from cranial to caudal in the case of several trigger points in one muscle).

2.4. Concomitant therapy

Concomitant physiotherapy during the study was permissible. However, procedures that could influence the trigger points were not permitted between Weeks −2 and 6. Physiotherapy and manual therapy for the treatment of vertebral blockage were allowed during the study.