BOTOX® (Botulinum toxin type A, BoNTA, Allergan) in the management of chronic migraine

Dr Manjit S. Matharu

Migraine is a neurovascular disorder characterised by headaches that are usually unilateral, throbbing, and accompanied by nausea and sensitivity to light, sound or movement.1 Migraine can be classified based on the frequency of headache attacks.2,3 Episodic migraine is diagnosed when patients have up to 14 headache days per month,2 while more frequent, chronic migraine is characterised by at least 15 headache days per month for at least 3 months, where at least 8 of those days are with migraine.3

Patients with chronic migraine form a significant part of general neurology and subspecialty headache practice, and often pose an ongoing therapeutic challenge. The first step towards effective management of chronic migraine is identification of factors which can contribute to headache chronicity, including medication overuse, co-administration of medications (such as nitrates) which may exacerbate migraine, and consideration of other medical factors (obstructive sleep apnoea, intracranial hyper- or hypotension or other causes of secondary headache) that may coexist.4,5

Treatment of chronic migraine involves a combination of effective, abortive strategies in addition to a prophylactic agent.6 Options for abortive therapy include simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), triptans and ergots while opioids should be avoided.6 However, overuse of abortive treatments exists in a significant proportion of chronic migraine patients, and therefore the focus of management is often on limiting their intake.7

The issue of how to optimally treat medication overuse in chronic migraine is one where received wisdom prevails without a strong evidence base. The traditional approach has been firstly to discontinue the overused medication where possible, or at least limit it to the recommended maximum frequencies outlined by the ICHD-II criteria.3 This approach has been justified on the basis that medication overuse can in itself cause headache, as well as making the features of the underlying pain harder to characterise, and may interfere with the efficacy of prophylactic treatment.8 This final point in particular is open to dispute, as it lacks well-controlled supportive data. Strategies for efficient management of medication overuse must centre on patient education: it is vital to discuss the treatment plan, explain what symptoms can be expected, that an increase in headache severity may occur initially and should be transient, and that a ‘wash-out’ period will enable subsequent treatment to be directed at the patient’s true underlying headache rather than a secondary, drug-induced one.6

The use of prophylaxis in the management of chronic migraine has been recommended to reduce headache frequency, severity and duration in addition to improving the disability associated with the disease.4 However, whilst many currently available prophylactic migraine treatments have been shown to be beneficial in the treatment of episodic migraine, few studies have been conducted in the chronic migraine population. The current evidence base of preventive drugs in chronic migraine is limited to randomised controlled trials (RCT) of topiramate8,10 besides a small RCT and a comparator trial of valproate.11,12

Introduction to BOTOX® (botulinum toxin type A, BoNTA, Allergan)

Botulinum toxin is produced by Clostridium botulinum, a Gram-positive anaerobic bacterium.13 Clostridium botulinum toxin type A, the active constituent of BOTOX® (Allergan), has recently been specifically licensed for headache prophylaxis in adults with chronic migraine (headaches on ≥15 days per month of which at least 8 days are with migraine).13 In addition to chronic migraine, BOTOX® is licensed in the UK for blepharospasm, hemifacial spasm, idiopathic cervical dystonia including spasmodic torticollis, severe hyperhidrosis of the axillae and focal spasticity.12

Examining the evidence for BOTOX® in chronic migraine

The safety and efficacy of BOTOX® as a prophylactic treatment option for patients with chronic migraine have been assessed in the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) programme, the largest comprehensive clinical trial programme in chronic migraine to date.14 The PREEMPT clinical trial programme consisted of two Phase III studies of chronic migraine patients, involving a total of 1384 adults from sites across Europe and North America.14 The studies comprised a 24-week randomised, double-blind, placebo-controlled phase followed by a 32-week open-label phase.14 The individual PREEMPT studies were conducted simultaneously with essentially identical designs, allowing the results to be pooled to determine the precision of and variability around the results for the primary and all secondary endpoints.14

In the PREEMPT studies, eligible patients were randomised to receive BOTOX® (155–195 units) or placebo administered at 31–39 sites across seven specific muscle groups of the head, neck and shoulders every 12 weeks (Figure 1).14 Patients recorded headache symptoms and medications via a daily telephone diary.14 Two-thirds of patients overused acute pain medications during the 28-day baseline period.14

Figure 1. Injection protocol for BOTOX® in chronic migraine.13

<table>
<thead>
<tr>
<th>Site</th>
<th>Muscle</th>
<th>Number of units*</th>
<th>Additional units*, if necessary</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Procerus</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>B</td>
<td>Frontalis</td>
<td>F (15 each side)</td>
<td>–</td>
</tr>
<tr>
<td>C</td>
<td>Frontalis</td>
<td>20 (15 each side)</td>
<td>10 (up to 2 sites)</td>
</tr>
<tr>
<td>D</td>
<td>Temporalis</td>
<td>40 (20 each side)</td>
<td>10 (up to 2 sites)</td>
</tr>
<tr>
<td>E</td>
<td>Occipitalis</td>
<td>30 (15 each side)</td>
<td>–</td>
</tr>
<tr>
<td>F</td>
<td>Cervical paraspinal</td>
<td>20 (15 each side)</td>
<td>–</td>
</tr>
<tr>
<td>G</td>
<td>Trapezius</td>
<td>30 (15 each side)</td>
<td>10 (up to 6 sites)</td>
</tr>
</tbody>
</table>

*The ‘load’ by which the potency of preparations of BOTOX® is measured should be used to calculate dosages of BOTOX® only and is not transferable to other preparations of botulinum toxin.

Efficacy of BOTOX® in chronic migraine

Results from the PREEMPT study demonstrated statistically significant reductions across multiple headache symptom measures. Patients treated with BOTOX® had an average of 8.4 fewer headache days at week 24 compared with baseline, versus 6.6 for placebo (p<0.001). In addition, a greater percentage of BOTOX®-treated than placebo-treated patients had a decrease of at least 50% from baseline in the frequency of headache days at all time points from week 4 to 24 (47% vs 35% at week 24; p<0.001).14 Patients in the BOTOX® group also experienced a significantly greater reduction in the frequency of migraine days, moderate/severe headache days and cumulative total headache hours on headache days (all p<0.001), as well as in the frequency of headache episodes (p=0.009) and migraine episodes (p<0.001).14

The reduction from baseline in headache days achieved in the 24-week double-blind phase was maintained in the open-label phase, with a continued fall in the frequency of headache days up to
56 weeks. In the open-label phase, patients receiving BOTOX® throughout achieved significantly greater reductions from baseline in headache days compared with patients initially treated with placebo (p<0.05).

Patients treated with BOTOX® experienced an improvement in health-related quality of life.

Safety of BOTOX® in chronic migraine

In the PREEMPT studies, treatment-related adverse events were consistent with the known tolerability profile of botulinum toxin type A when injected into the head and neck muscles, and no newly emerged safety findings were observed. Additionally, during the 24-week double-blind phase, the nature and frequency of adverse events were similar in the two arms.

In the double-blind phase of the PREEMPT study, the only adverse events reported with an incidence of more than 5% were neck pain (8.7%) and muscular weakness (5.5%) in the BOTOX® group, and upper respiratory tract infection (5.3%) in the placebo group. Most events were mild or moderate in severity and resolved without sequelae. Serious adverse events occurred in 4.8% of BOTOX® patients and 2.3% of placebo patients. In the open-label phase, during which all patients were exposed to BOTOX®, the adverse events occurring at a rate more than 5% were neck pain (5.8%) and sinusitis (5.1%), while serious adverse events occurred in 3.8% of patients. There was one treatment-related serious adverse event in the group receiving BOTOX® that resulted in hospitalization due to migraine.

Summary

BOTOX® is currently the only pharmacotherapy specifically licensed for the prophylactic treatment of headache in adults with chronic migraine (headaches on ≥15 days per month of which at least 8 days are with migraine) in the UK. Results from the PREEMPT clinical trial programme have demonstrated that BOTOX® is effective and generally well tolerated in the prophylactic treatment of chronic migraine when it is administered as described in the PREEMPT injection protocol.

While introducing BOTOX® into clinical practice may pose a service challenge for provision, with the requirement for three-monthly injections by a trained injector, the required investment in the infrastructure of headache services is likely to be rewarding as this novel therapeutic approach in the management of chronic migraine holds the potential to significantly improve the quality of life of this patient group.

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Address for correspondence: Headache Group, Institute of Neurology, Queen Square, London WC1N 3BG

Email: m.matharu@ion.ucl.ac.uk; Fax: +44 7092 120797

Further information is available from: Allergan Limited, Marlwood International, The Parkway, Marlwood, Bucks SL7 1YL. UK. Legal Category: POM.

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References