Long-term Safety and Efficacy of a New Botulinum Toxin Type A in Treating Glabellar Lines

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Objective: To evaluate the long-term safety of repeated administrations of a new botulinum toxin type A (Reloxin; Medicis Pharmaceutical Corp, Scottsdale, Arizona) in the treatment of moderate to severe glabellar lines.

Methods: Open-label assessment of 1200 patients receiving as many as 5 treatments of Reloxin over a 13-month period. The product was diluted in 2.5-mL sterile physiologic saline solution, 0.9%, without preservative to a concentration of 50 U of Reloxin per 0.25 mL of solution. Investigators injected 0.05 mL of the solution (10 U each) into each of 5 injection sites in the glabellar area on day 0 of each treatment cycle. There was a minimum 85-day gap between treatments. Postinjection clinical evaluation was performed on days 14 and 30 and monthly thereafter until retreatment, study completion, or early termination. The patients were telephoned on day 7 to check for adverse events (AEs) and concomitant medications, and patient diaries were used to document the onset of treatment effect.

Results: The majority (72%) of treatment-emergent AEs were considered unlikely or not related to study treatment. Probably or possibly related treatment-emergent AEs occurred in 36% of patients. The most frequently occurring related AEs were injection site disorders (18%), nervous system disorders (14% and 12% headache), and eye disorders (9%). Related AEs around the injection site or eyes were usually reported by day 7 and then resolved. Reported ptosis does not differentiate between brow ptosis and eyelid ptosis. A total of 45 patients had a total of 55 instances of ptosis across all cycles, with most episodes lasting less than 3 weeks. The rates of ptosis decreased during successive cycles from 2.4% in cycle 1 to 0.6% in cycle 5. The proportion of patients reporting an onset of response by day 7 ranged from 93% to 95%. By investigator assessment, the response rate (patients reporting none or mild glabellar line severity scale scores on day 30) ranged from 80% to 91% during cycles 1 to 5.

Conclusions: There was no evidence of cumulative AEs or tachyphylaxis with multiple Reloxin treatments over a period of 13 months. The treatments were well tolerated. The rates of ptosis decreased over successive cycles, and the proportion of responders by day 7 ranged from 93% to 95%.

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A GENERALLY ACCEPTED method for correcting the appearance of hyperkinetic lines of the face is the use of low doses of Clostridium botulinum toxin type A. One such product, Reloxin (Medicis Pharmaceutical Corp, Scottsdale, Arizona) (C botulinum type A toxin–hemagglutinin complex), has been in clinical use outside the United States for more than 15 years (marketed as botulinum neurotoxin [Dysport; Ipsen Biopharm Ltd, Wrexham, Wales]) for therapeutic indications such as dystonia and spasticity. It has been approved in more than 73 countries for various therapeutic indications and in 23 countries for the treatment of wrinkles (glabellar or hyperkinetic facial lines). In the United States, Reloxin has been under investigation for the treatment of glabellar lines since 2002. Many studies have been published in the peer-reviewed medical literature regarding the use of this biological agent.

Herein, we report data from a phase 3, open-label study of patients who received as many as 5 serial injections of Reloxin (50 U) for the treatment of glabellar lines. The primary objective of our study was to evaluate the long-term safety of repeated administrations of Reloxin for the treatment of glabellar lines. The secondary objectives were to assess the long-term clinical response to the use of Reloxin and to evaluate the duration of the effects (time to re-treatment).

METHODS

The study, which was a phase 3, open-label trial, was conducted at 21 centers in the United States. Patients were included if they had mod-
From MediciS Pharmaceutical Corp, Scottsdale, Arizona). New botulinum toxin type A (Reloxin), 10 U/0.05 mL diluted in physiologic saline at each injection point, was administered on day 0 of each treatment cycle at 5 injection points in the glabellar region (adapted with permission from Medicis Pharmaceutical Corp, Scottsdale, Arizona).

At baseline, all patients had moderate to severe glabellar lines, were aged 18 years or older, and had a negative pregnancy test result if they were women of childbearing years. Patients were excluded if (1) they had undergone previous treatment with Reloxin or other botulinum toxin within 85 days of study entry; (2) if they received treatment to areas other than the glabellar area during the study; (3) if their dermatologist was unable to substantially reduce their glabellar lines by manually spreading them apart; (4) or if they had undergone facial plastic surgery or aesthetic procedures such as tissue augmentation or brow-lifts, dermal resurfacing, or any procedure or concurrent therapy considered by the investigator to interfere with the evaluation of the study medication. Patients were also excluded because of pregnancy, active infection in the glabellar area, chronic drug or alcohol abuse, clinically diagnosed anxiety or depression, current facial palsy or neuromuscular junction disorders, or any other condition or circumstance that might either pose a risk to the patient or interfere with the investigator’s ability to acquire satisfactory clinical data. The study included 1200 patients, all of whom provided informed consent, and the study protocol was approved by the appropriate institutional review boards and the US Food and Drug Administration. The patients received as many as 5 treatment cycles of Reloxin for moderate to severe glabellar lines with at least 85 days between treatments. The product was diluted in 2.5-mL sterile physiologic saline solution, 0.9%, without preservative to a concentration of 50 U of Reloxin per 0.25 mL of solution. Using a 30-gauge needle, 0.05 mL of the solution (10 U) was injected into each of 5 injection sites in the glabellar area on day 0 of each cycle (Figure 1). A treatment cycle lasted a minimum of 85 days from Reloxin injection until the return of moderate glabellar lines, at which point the patient was eligible for another cycle of treatment.

Glabellar Line Severity Score

At baseline, all patients had moderate to severe glabellar lines, according to a glabellar line severity scale (GLSS) score of 2 or 3 at maximum frown, by investigator assessment and (independently) patient assessment. (The GLSS is a validated 4-point scale with glabellar lines graded as 0 [none], 1 [mild], 2 [moderate], or 3 [severe].) The patients used a similar instrument for their self-assessment.

**Efficacy Assessments: Onset and Duration**

In evaluating clinical effect, a responder was defined as having a 1- to 2-point reduction in GLSS score (eg, reduced to 0 or 1 at maximum frown from 2 or 3 at the time of treatment). The patients were assessed for response at each visit. The secondary efficacy end points were time to onset of effect and duration of effect. The patients completed a diary card on days 1 to 7 of each treatment cycle to record the onset of effect, identified as the first day a patient responded yes to the question, “Since being injected have you noticed any effect on the appearance of your glabellar lines?”

Patients who exhibited moderate (2) or severe (3) glabellar lines at maximum frown after Reloxin treatment by both investigator-determined GLSS score and patient self-assessment score could be re-treated after a minimum of 85 days. If both scores were not in agreement, the patients were not eligible for re-treatment at that visit and were reassessed at the next scheduled monthly visit. Because the study was designed with a fixed maximum duration of 13 months, many patients had truncated duration assessment in cycles 4 and 5. For this reason, the duration was analyzed only for cycles 1, 2, and 3.

**Safety Assessment**

The primary end point, the safety of Reloxin treatment, was assessed throughout the study by monitoring adverse events (AEs) and vital signs. Also, serum samples were tested for the presence of anti–Reloxin antibodies.

Adverse events and concomitant medications were reviewed by a phone call on postinjection day 7 of each treatment cycle and updated at every clinic visit. Investigator and patient assessments took place at screening (day 0), on days 14 and 30, and then monthly until re-treatment, study completion, or early termination. The final study visit occurred at month 12 of the study or 30 days after the patient’s final study treatment, whichever was later.

**Results**

Twelve hundred patients were enrolled in this study, and each patient was treated with at least 1 cycle of 50 U of Reloxin. Most patients (95%) were 65 years or younger, with a median age of 48 years, and a large majority were female (90%) and white (94%). Demographic information is presented in Table 1, and patient disposition is shown in Figure 2. A total of 1052 patients (88%) completed the 13-month study, and 148 patients discontinued the study. Most of the patients who discontinued the study did so because of a subjective decision or because they were unavailable for follow-up. Only 1 patient dropped out because of a lack of efficacy, and 8 patients (<1%) who discontinued the study owing to AEs, only 1 patient did so for an event that was probably related to study treatment.

**Safety**

The majority of treatment-emergent AEs (TEAEs) were considered unlikely or not related to study treatment.
Probably or possibly related AEs (RAEs) occurred in 36\% of patients. Of the 2838 TEAEs that were experienced by 880 patients (73\%) (Table 2), 804 (28\%) were considered RAEs (Table 3). The incidence of TEAEs was highest during the first treatment cycle and decreased with each treatment cycle (Table 3). Only 8 patients over all cycles experienced TEAEs that were severe and possibly, or probably, related to treatment: 4 patients in cycle 1; 3 patients in cycle 2; and 1 patient in cycle 3. The severe RAEs included 1 incident of eyelid ptosis, 1 incident of streptococcal pharyngitis, 3 events of headache, and 138 of the headache events (11\%) contributed to treatment: 178 of 1200 patients (15\%) received headache, and 1 event of sinus headache, 1 event of dizziness, and 1 event of injection site irritation.

The most frequently occurring RAEs (reported by >3\% of patients) were injection site events (18\%), nervous system disorders (14\% and 12\% headache), and ocular events (9\% and 4\% ptosis). Only 1 patient discontinued the study owing to RAEs (dermatochalasia of the left upper eyelid and an injection site reaction). Injection site reactions were primarily reported on day 0 (127 patients [11\%]) and day 7 (113 patients [9\%]), and reports steeply declined thereafter to 1\% or less. Often, headache was attributed to treatment: 178 of 1200 patients (15\%) reported headache, and 138 of the headache events (11\%) were considered treatment related.

**OCULAR AES**

The majority of AEs around the eyes were reported during the day 7 telephone contact (102 patients [9\%]) and resolved within 3 weeks. The incidence decreased over successive cycles. All reports of ptosis were collected without differentiation between brow ptosis and eyelid ptosis. A total of 45 patients had a total of 55 events of ptosis during the study after 4214 treatments with Reloxin (1.3\%) (Figure 2). Ptosis occurred in fewer than 2\% of patients in any single cycle, and if it did occur, it was generally within the first 14 days (94\%). There were 3 reports of ptosis starting at day 30 or 60 (Table 4).

![Figure 2. Patient disposition and exposure to a new botulinum toxin type A (Reloxin; Medicis Pharmaceutical Corp, Scottsdale, Arizona).](image_url)

**EFFICACY: ONSET OF RESPONSE**

Based on patient diary cards, the onset of the effect of Reloxin treatment was seen within 1 day in some cases, and the median time to onset was 3 days for all cycles (Figure 3). The cumulative proportion of patients responding to treatment reached by day 7 (the end of the diary period) in all cycles ranged from 93\% to 95\%. The overall median duration of effect at maximum frown (for the first 3 cycles) was approximately 88 days by investigator assessment and 84 days by patient assessment (Figure 4). A small proportion of patients (2\% in cycle 1 and 7\% in cycle 2) had a response that persisted up to 336 days based on investigator assessment. A higher percentage of patients (32\%) in cycle 3 did not exhibit moderate or severe glabellar lines because their investigator-assessed response continued past the end of the fixed study duration.

**RESPONSE AT 30 DAYS**

The proportion of responders in each cycle at day 30 was calculated and compared using 2 approaches to imputing missing values. First, missing values were imputed using the average of all nonmissing values; second, missing values were replaced by the patient’s baseline value,
conservatively assuming nonresponse. The results are presented in Table 5. At day 30 of each successive cycle, the proportion of responders increased by investigator’s assessment at maximum frown, using the average value of imputation for the missing values (Figure 5).

The primary objective of the present study was to evaluate the long-term safety of repeated administrations of Reloxin. However, given the need for benefit assessments, secondary objectives included the demonstration of the clinical effect of Reloxin in the treatment of glabellar lines. By every measure—investigators’ and patients’ assessments of glabellar lines at maximum frown, the onset of effect, and the duration of effect—Reloxin demonstrated an efficacy that did not diminish with repeated treatments. The onset of effect was seen as soon as 24 hours and at a median of 3 days during all cycles. By self-assessment, 93% to 95% of the patients re-
sponded to treatment by day 7, the end of the diary period, allaying concerns about potential tachyphylaxis. Between 80% and 91% of the patients had a response at day 30 of each cycle, based on investigator assessment. Investigator assessment of the patients at maximum frown at 30 days indicated very little variation during the 5 cycles.

Table 4. Patients Reporting Ptosis by Visit and Treatment Cycle

<table>
<thead>
<tr>
<th>Day of Visit</th>
<th>Cycle 1 (N=1200)</th>
<th>Cycle 2 (n=1145)</th>
<th>Cycle 3 (n=1031)</th>
<th>Cycle 4 (n=661)</th>
<th>Cycle 5 (n=177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>7</td>
<td>21 (1.8)</td>
<td>10 (&lt;1)</td>
<td>5 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>14</td>
<td>6 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>30</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>60</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Figure 3. The median time to onset of a new botulinum toxin type A (Reloxin; Medicis Pharmaceutical Corp, Scottsdale, Arizona) effect was 3 days for all cycles, and the cumulative proportion of responders in all cycles ranged from 93% to 95% by 7 days.

Figure 4. Kaplan-Meier estimates for the duration of response to treatment with a new botulinum toxin type A (Reloxin; Medicis Pharmaceutical Corp, Scottsdale, Arizona) measured by investigator’s assessment of glabellar lines at maximum frown: intent-to-treat population.
values were replaced by the mean of all nonmissing values. Excluded from efficacy duration analyses because fewer than half the patients entering those cycles reached relapse by the scheduled end of follow-up. Missing baseline (day 0 of the cycle). The denominator for proportions is the number of patients in the treatment cycle. Based on defined conventions, cycles 4 and 5 were frown.

(Reloxin; Medicis Pharmaceutical Corp, Scottsdale, Arizona) at maximum

The tolerability and lack of cumulative AEs of repeated doses of Reloxin were demonstrated over the 13-month period of this study. The majority of TEAEs were considered unrelated to treatment, with only 36% of patients experiencing RAEs. Most were of mild or moderate severity; there were only 8 severe RAEs reported over all treatment cycles, and only 1 resulted in study discontinuation. The RAEs mostly fell into 3 categories: injection site events, events around the eyes, or nervous system disorders (including headaches). The incidence of ptosis was highest in cycle 1, decreasing over successive cycles of therapy, from 29 of 1200 (2.4%) in cycle 1 to 1 of 177 (0.6%) in cycle 5. Only 55 ptosis events occurred in 45 patients after a total of 4214 Reloxin treatments (1.3%).

Most AEs around injection sites or around the eyes were reported by day 7 in all cycles and usually resolved within 3 weeks. Headache, which was often attributed to treatment, occurred in 178 of 1200 patients (15%). No clinically significant mean changes from baseline were observed in vital signs, and no evidence of antibody formation to Reloxin was seen after repeated cycles of treatment.

In conclusion, multiple cycles of treatment with 50 U of Reloxin were well tolerated and maintained a clinical effect over 13 months. The incidence of TEAEs decreased over time, showing no evidence of cumulative safety issues after more than 4000 treatments with Reloxin. No tachyphylaxis was seen, as 80% to 91% of patients responded to repeated treatments at day 30 of each cycle (based on investigator assessment), and the cumulative proportion of patients reporting onset of response by day 7 in all cycles ranged from 93% to 95%. The median onset of effect was 3 days after injection, and treatment response persisted in some patients for 336 days.

Table 5. Proportion of Responders at Day 30 Using Investigator’s Assessment and Patient’s Self-Assessment of Glabellar Lines at Maximum Frown

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cycle 1 (N=1200)</th>
<th>Cycle 2 (n=1145)</th>
<th>Cycle 3 (n=1031)</th>
<th>Cycle 4 (n=681)</th>
<th>Cycle 5 (n=177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator’s assessment at maximum frown</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of responders</td>
<td>1004</td>
<td>1027</td>
<td>941</td>
<td>580</td>
<td>142</td>
</tr>
<tr>
<td>Proportion</td>
<td>0.837</td>
<td>0.897</td>
<td>0.913</td>
<td>0.877</td>
<td>0.802</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.82-0.86</td>
<td>0.88-0.91</td>
<td>0.90-0.93</td>
<td>0.85-0.90</td>
<td>0.74-0.86</td>
</tr>
<tr>
<td>Patient’s assessment at maximum frown</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of responders</td>
<td>897</td>
<td>945</td>
<td>895</td>
<td>535</td>
<td>130</td>
</tr>
<tr>
<td>Proportion</td>
<td>0.748</td>
<td>0.825</td>
<td>0.868</td>
<td>0.809</td>
<td>0.734</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.72-0.77)</td>
<td>(0.80-0.85)</td>
<td>(0.85-0.89)</td>
<td>(0.78-0.84)</td>
<td>(0.67-0.80)</td>
</tr>
</tbody>
</table>

A responder is defined as a patient who had no wrinkles or mild wrinkles at maximum frown at the specified visit and moderate wrinkles or severe wrinkles at baseline (day 0 of the cycle). The denominator for proportions is the number of patients in the treatment cycle. Based on defined conventions, cycles 4 and 5 were necessarily being truncated for more than 50% of patients who had those cycles. A small proportion (2% in cycle 1 and 7% in cycle 2) had a response that persisted in some patients for 336 days. This study was designed to Reloxin was seen after repeated cycles of treatment.

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Administrative, technical, and material support: Moy, Maas, Monheit, and Huber.

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REFERENCES


Call for Papers

The Archives of Facial Plastic Surgery will publish a theme issue on Asian facial plastic and reconstructive surgery. These manuscripts should be focused on the unique characteristics of procedures performed on Asian patients and should be of broad interest. Joseph K. H. Wong, MD, will be the guest editor for this theme issue, which will be published in the November/December 2009 issue of the Archives of Facial Plastic Surgery. We are interested in receiving articles on either cosmetic or reconstructive topics from surgeons in Asia or those in other geographical areas who have significant experience with these procedures. Manuscripts received by June 1, 2009, will have the best chance for acceptance.