Botulinum Toxin A: New and Future Applications

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Off Label Discussion

• Off Label uses of products will be discussed
• Non-FDA approved products will be discussed
• Non-peer reviewed data may be discussed

From Sausage to Liquid Gold

• Discovered in 1820 by Dr. Justinus Kerner – “Fatty toxin” from injected sausage
• 1980 Dr. Alan Scott published its use for Strabismus
• 1992 Drs. Jean and Alistair Carruthers published its use for glabellar lines
• World market is projected to reach 4.9 Billion by 2018

Botulinum Toxin A (BTA) – What is it good for….?

• Approved indications:
  – Rhytides
  – Hyperhidrosis
  – Chronic Migraines
  – Strabismus
  – Blepharospasm
  – Cervical Dystonia
  – Limb spasticity
  – Urinary incontinence

Unapproved Dermatology uses

• Flushing / Erythema
• Raynauds
• Hailey-Hailey
• Psoriasis
• Dyshidrotic eczema
• Entropion
• Hydrocystomas
• Pruritus

Conflict of Interest

• Investigator:
  – Revance Therapeutics
  – Valeant Therapeutics
  – Galderma
  – Anterios (now Allergan)
What else?

- TMJ
- Trigeminal Neuralgia
- Vocal disorders
- Oropharyngeal dysphagia
- Cerebral palsy
- Parkinsons symptoms
- Plantar Fasciitis
- Myofascial pain?
- Obstructive sleep apnea
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What’s New?

Available BTA: What’s the big deal

- OnabotulinumtoxinA (Botox®)
  - Only one with Crow’s feet indication
- AbobotulinumtoxinA (Dysport®)
  - More diffusion?
  - Conversion 2.5-3:1 with Botox units
- IncobotulinumA (Xeomin®)
  - No complexing proteins
  - Store at room temp before dilution
  - Equivalent dosages to Botox?

Prevention is key

Consistent


Erratic

Forehead

- Superficial and Deep injections have similar efficacy
- Superficial are less painful

Sneath et al. Injecting Botulinum Toxin at Different Depths is Not Effective for the Correction of Eyebrow Asymmetry. Dermatologic Surgery. 2016 Jan 162-167

Lower face

- Lower facial shaping
- Masseter hypertrophy
- Parotid enlargement (HIV)

Decreased pain of injection

- Mix with lido for hyperhidrosis
  - Decreased pain vs NS
  - No change in efficacy
- pH elevation with Ringer’s acetate?
  - Decreased injection site pain (47%)
  - No decreased efficacy in blepharospasm


Combination is all the rage

- Combination treatments are safe
  - Consensus statement by ASDS
- Combination treatments are synergistic
  - Lips
  - Lower face
  - Upper face
  - Neck


Potential combinations

- BTA + Filler
- BTA + Kybella
- BTA + Tightening
- BTA + Laser

Dermatologic Surgery May supplement 2016

Coming soon:
New Injectables

- DaxibotulinumtoxinA (RT002)
- Evosyal® (DWP-450)
- MT10109L
- AI-09

DaxibotulinumtoxinA

- Bound to TransMPS® peptide
- Less diffusion to adjacent muscles?
- Higher dosages without side-effects?
- Longer lasting?


**DaxiA glabellar lines – Belmont Study**

- 268 patients - Five arms:
  - Three different doses of DaxibotulinumtoxinA for Injection (20U, 40U, 60U)
  - BOTOX® Cosmetic (onabotulinumtoxinA) (20U - comparator)
  - Placebo

- Efficacy evaluations versus baseline:
  - Every 4 weeks for up to 36

- Assessments:
  - Primary: 1 point improvement IGA-FWS at Week 4. Duration of response

**BELMONT Phase 2 Study:**

- All five groups exhibited excellent overall safety profile
- No serious adverse events
- Adverse events were predominantly localized, transient and mild in severity and typically injection related (erythema and pain)

### Summary

**Efficacy**

- Duration: Median duration 23.6 weeks for Daxibot 40U dose vs. 18.8 weeks for Onabot 20U (p=0.020), as measured by a 3 point improvement in IGA-FWS
- Daxibot resulted in higher response rates vs. Onabot at 24 Weeks:
  - DaxibotulinumtoxinA 40U and 60U doses continued to deliver clinically meaningful higher response rates vs. onabotulinumtoxinA as assessed by None or Mild wrinkle severity
  - Combined treatment arm efficacy results indicate 31% of subjects maintain None or Mild wrinkle severity vs. onabotulinumtoxinA at 24W

**Safety:**

- Appears to be safe and well tolerated, with no serious adverse events
- Dose response observed – Daxibot 40U dose selected for Phase 3 Program

**BELMONT Phase 2 Study with DaxibotulinumtoxinA:**

**Is it dose or product?**

**Phase 3 Program:**

- Design of Pivotal Trials: two randomized, double-blind, placebo-controlled studies (n=300 each) to evaluate the safety and efficacy of a single treatment of Daxibot 40U for the treatment of moderate to severe glabellar lines at sites in US & Canada

  - Primary efficacy endpoint: composite of the proportion of subjects who achieve a score of 0 or 1 (none or mild) and a two-point improvement from baseline in glabellar line severity on the IGA-FWS and PFWs scales, at maximum contraction (frown), at Week 4

- Open-label Safety Study: designed to evaluate long-term safety of RT002 for the treatment of moderate to severe glabellar lines following single and repeat treatment administration.

  - The study is expected to enroll approximately 1,500 patients at multiple sites in the US. Depending on the number of treatments and duration of follow-up

  - Topline results expected in Q4 2017

**Evosyal®**

- Nabota in Korea
- Acquired for licensing Evolus -> Alphaeon
- Equivalent to onabotA?
- Completed Phase III trials

MT10109L

- Allergan
- Prediluted BotA
- Equivalent to onabotA?
- Better response at week 16 than onabotA


AI-09

- Eirion Therapeutics (spun off Anterios)
- Pre-diluted BotA
- NDS formulation
- Stable longer in solution?
- TBD

Topical BTA?

- Compared injectable BotA v topically applied
- Topically applied abobotA has no effect on static or dynamic wrinkles
- Cannot penetrate skin


Topical BTA by laser delivery

- Split faced study of combination of CO2 resurfacing & BTA topical
- vs CO2
- Blinded assessment 3.4 : 2.7
- Significant?


NAFL + BTA vs BTA

- 15 units of topical BTA (onabot) on left side vs NS
- Greater wrinkle reduction and patient satisfaction on BTA treated side
- Non-physician blinded


Not just overseas

- With topical BTA (100 units / 0.1 ml)
- With topical NS

Is There a Future for Topical BTA?

- ANT-1207 (Allergan, formerly Anterios)
- RT-001 (Revance)

ANT-1207

- NDS platform for transcutaneous absorption
- Topical BTA applied in office
- Completed phase 2 trials for hyperhidrosis, acne, periocular rhytids
- Acquired by Allergan in 2016

Ant-1207 Hyperhidrosis

- Single application vs placebo
- Forehead
- Followed for 12 weeks
- Significant?

ANT-1207 acne

- Improvement to mild or better
- Lesion Counts

Ant-1207 lateral canthal lines

- Single application
- Occlusion
- Mixed results
- Formulation issues

12 week, 2 point improvement in rating

RT-001 (daxibotulinumtoxinA)

- TransMTS® Peptide
  - + Lysine chain with transduction domains at either end
  - Allows penetration through epidermis
- Applied in office (occlusion?)
- Completed phase 2 trials for hyperhidrosis and lateral canthal lines
- Phase 3 for lateral canthal lines...
RT-001 – Lateral Canthal lines

• IGA > 2 pt improvement: 52.4:14.3
• PSA > 2pt: 38.1:19.0
• Applied under occlusion
• Formulation issues
• Retested
• Phase 3 (no occlusion)
• Failed to meet end points


Conclusions

• New applications in multiple fields
• Combination is key
• New injectable forms soon
• Topical efficacy TBD