THE ANTI-INFLAMMATORY PROPERTIES OF IVERMECTIN AND BRIMONIDINE IN THE TREATMENT OF PAPULOPUSTULAR ROSacea

INTRODUCTION

- Rosacea is often characterized by persistent central facial erythema and recurrent inflammatory papules/pustules.
- The pathophysiology of papulopustular rosacea (PPR) is not fully understood.
- Multiple immune, inflammatory, and vascular processes are likely involved.
- Ivermectin 1% (IVM) cream has anti-inflammatory properties and has been shown to be effective against papules/pustules of rosacea.
- Ivermectin treatment reduces pro-inflammatory cytokines and chemokines, inhibits leukocytes, and modulates the cathelicidin pathway.
- Brimonidine 0.2% (BR) gel has been shown to be effective against persistent facial erythema.
- Brimonidine is an alpha 2 adrenergic agonist responsible for vasoconstriction of superficial blood vessels.
- Two recent studies investigate IVM and BR when used in combination for the treatment of PPR.

METHODS

Study 1

- A 12-week intradermal phospholipid-12-acetate (TPA) induced inflammation model was designed to investigate the anti-inflammatory effect of IVM in BALB/c ByJ R mice.
- Ear edema was induced in the right ear of female mice by topical application of TPA (0.01%). Followed by treatment with:
  - Topical vehicle
  - IVM (0.1% to 1%)
  - BR (0.2%)
  - IVM + BR
- An anti-inflammatory control (Betamethasone valerate 0.01% or indomethacin 5%) was measured using a micrometer pre- and 6 hours after TPA application.

Study 2

- This was a multicenter, randomized, double-blind, vehicle-controlled, and parallel group comparison study that included subjects with moderate to severe rosacea (Investigator Global Assessment [IGA] ≥3, scale 0-4), characterized by persistent diffuse moderate to severe erythema (Clinical Erythema Assessment [CEA] ≥3, scale 0-4) and inflammatory lesions (ILI) ≥15 papules/pustules.
- Treatments:
  - Randomized 1:1:2, 2 active and 1 vehicle group, respectively:
    - IVM (0.9%) + BR (0.33%) active treatment groups:
      - IVM + BR: 12 week subgroup (n = 49): Once daily IVM + BR for 12 weeks
      - IVM + BR: 4 week subgroup (n = 46): Once daily IVM + BR vehicle for 4 weeks; followed by IVM + BR for the remaining 8 weeks
    - Vehicle group:
      - Once daily IVM vehicle and BR vehicle for 12 weeks (vehicle group, n = 95)
- A daily skin care regimen of gentle cleanser, moisturizing lotion, and facial moisturizer SPF 15 sunscreen.
- Efficacy and safety endpoints:
  - IGA success (IGA 0-1; ‘clear’ or ‘almost clear’), 5-point scale, week 12; hours after BR application IGA at each visit.
  - CEA, 100% reduction in IL count, and subject global improvement of rosacea.
  - AEs were monitored throughout the study.

RESULTS

Study 1

- Anti-inflammatory synergy was observed between IVM and BR in the mouse model.
- IVM + BR had a similar effect on ear edema at 6 hours when compared with a potent corticosteroid or NSAID (Figure 1 and 2).

Study 2

- Subjects who began IVM + BR treatment at baseline had an improved rate of IGA success when compared with both vehicle and subjects who began BR treatment at week 8 (Figure 3).
- Subjects who began IVM + BR treatment at baseline had improved CEA assessments at week 12 when compared with both vehicle and subjects who began BR treatment at week 8 (Figure 4).
- Subjects who began IVM + BR treatment at baseline were more likely to achieve a 100% reduction in lesions at week 12 when compared with both vehicle and subjects who began BR treatment at week 6 (Figure 5).

Safety

- Only 3 treatment-related AEs in 6 subjects (2.2%) were reported; none were serious or severe.
- One related AE leading to discontinuation (allergic dermatitis on the chest) was reported in the IVM + BR/SW group.
- Related worsening of rosacea was observed in similar frequency with I (2.2%) AE in the active IVM + BR groups vs. 3 (2.1%) AEs in the vehicle group.

SUMMARY

- Rosacea therapy requires a global and patient-specific approach that targets its varied symptoms and mechanisms, including both the inflammatory pathways and vascular components of the disease.
- In the mouse model:
  - IVM significantly reduced our skin swelling.
  - BR acted synergistically with IVM to enhance anti-inflammatory activity.
- In the clinical study:
  - Simultaneous administration of IVM 1% cream with BR 0.33% gel demonstrated superior efficacy compared to their respective vehicles for the treatment of moderate to severe rosacea.
  - The IVM + BR association was well tolerated, with less than 5% related AEs.
- The regimen of IVM + BR is safe and effective option for the comprehensive management of this complex disease.
- These studies support that initiating rosacea therapy with IVM + BR, along with a complete daily skin care regimen, may improve and accelerate the efficacy of IVM treatment, without requiring increased therapy.
- Treating with IVM + BR from the start was more effective than an initial period of IVM treatment alone followed by IVM + BR.

REFERENCES