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

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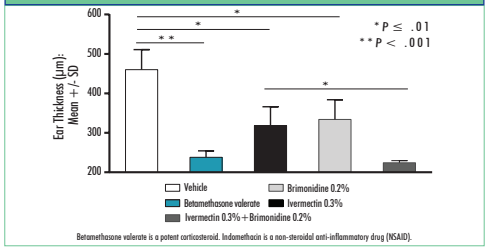
INTRODUCTION

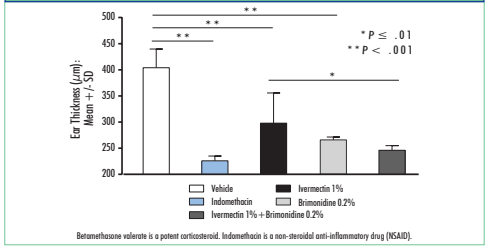
- Rosacea is often characterized by persistent centrofacial erythema and recurrent inflammatory papules/pustules
  - The pathophysiology of papulopustular rosacea (PPR) is not fully understood
  - Multiple immune, inflammatory, and vascular processes are likely involved
- Ivermectin 1% (IVM) cream has anti-inflammatory properties and has been shown to be effective against papules/pustules of erythema[1,2,3]
  - Ivermectin treatment reduces pro-inflammatory cytokines and chemokines, inhibits leukocytes, and modulates the cathelicidin pathway
- Brimonidine 0.33% (BR) gel has been shown to be effective against persistent facial erythema[2]
  - 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

Figure 1. Ear Edema Measured 6 Hours Post-treatment



Betamethasone valerate is a potent corticosteroid. Indomethacin is a non-steroidal anti-inflammatory drug (NSAID).

Figure 2. Ear Edema Measured 1 Hour Post-treatment



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METHODS

Study 1

- A 12 O tetradecanoylphorbol-13-acetate (TPA)-induced inflammation model was designed to investigate the anti-inflammatory effect of IVM in BALB/c ByJ Rj 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%)
- Right ear thickness (μm) was measured using a micrometer pre- and 6 hours after TPA application

Figure 3. IGA Success

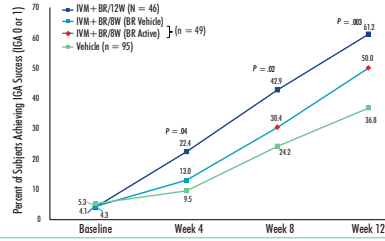
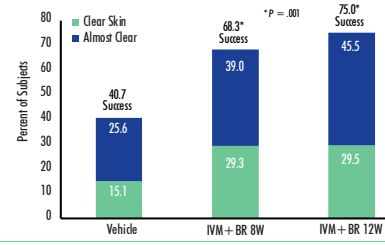


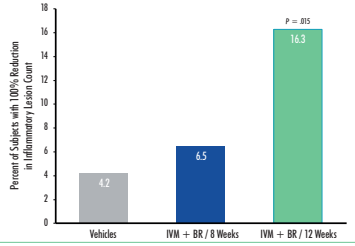
Figure 4. CEA at Week 12, Hour 3



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] $\geq$3, scale 0-4), characterized by persistent diffuse moderate to severe erythema (Clinician Erythema Assessment [CEA] $\geq$3, scale 0-4) and inflammatory lesions ([IL] 15-70 papules/pustules).
- Treatments
  - Randomized 1:1:2, 2 active and 1 vehicle group, respectively
  - IVM (1%) + BR (0.33%) active treatment groups:
    - IVM+BR/12W subgroup (n = 49): Once daily IVM + BR for 12 weeks
    - IVM+BR/8W 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 (0/1 [clear/almost clear], 5-point scale, week 12, 3 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

Figure 5. Percent of Subjects Achieving 100% IL Reduction



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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 8 (Figure 5)

Safety

- Only 8 treatment-related AEs in 6 subjects (3.2%) were reported; none were serious or severe.
- One related AE leading to discontinuation (allergic dermatitis on the chest) was reported in the IVM+BR/8W group.
- Related worsening of rosacea was observed in similar frequency with 1 (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 ear 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 a safe and effective option for the comprehensive management of this complex disease
- These studies suggest 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 impairing tolerability
- Treating with IVM+BR from the start was more effective than an initial period of IVM treatment alone followed by IVM+BR

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