Brilaroxazine Topical Liposomal-gel Formulation Displays Efficacy in the Imiquimod-induced Psoriatic Mouse Model

LB1745

Laxminarayan Bhat, Seema R Bhat, Arulprakash Ramakrishna, Muthukumar Amirthalingam*

Reviva Pharmaceuticals Holdings, Inc., Cupertino, California, USA (19925 Stevens Creek Blvd, Ste 100, Cupertino, CA 95014)

INTRODUCTION

Psoriasis is a systemic immune-mediated, chronic-residual dermal inflammatory disease with a global prevalence of ~125 million[1-4]. It presents as recurrent episodes of hyperkeratotic, erythematous plaques and silvery-coated scales on the skin[1-2]. Mental illness exists as a major comorbidity[3–7].

This condition's pathology involves an inflammatory skin response[2]. This process generates rapid keratinocyte multiplication, followed by cellular movement from the epidermal basal layer to the epidermis's upper layer, leading to thick dry patches or plaques (seen in 80% of cases)[8,9].

Serotonin (5-HT) and dopamine (D) play pathologic roles. 5-HT influences inflammation and immunity proliferation[10]. D stimulates the production of proinflammatory cytokines and the inciting of keratinocyte proliferation and differentiation[11–13].

Brilaroxazine (RP5063) displays a high affinity for $D_{2/3/4}$ and 5-$HT_{2A/2B/7}$ receptors and a moderate affinity for the serotonin transporter[14-18]. It brings an established efficacy, safety, and pharmacokinetic profile[14-18]. Preclinical work indicates that it influences pro-inflammatory and pro-fibrotic cytokines and chemokines[14,15,19]. A new liposomal-gel (lipogel) formulation offers a novel topical option for treating psoriasis.

OBJECTIVE AND METHODS

Objective:

This preclinical study assesses the efficacy of topical brilaroxazine in lipogel (Brilaroxazine Formulation) in a 5% imiquimod-induced psoriatic mouse model (BALB/c)[20].

Methods:

Animals and Groups: The study utilized three groups (n=6 per) of female BALB/c mice (8-10 weeks old, weight + 5 gm): 1) Sham, 2) Imiquimod, and 3) Imiquimod + Brilaroxazine.

Procedures: Psoriasis induction involved 5% imiquimod application to the animals' shaved backs (3 cm x 3 cm area) on the morning of Days 1-11. Brilaroxazine Formulation (1.5% w/w, topically daily) administration occurred 3 hours after induction.

Upon animal sacrifice on Day 12, investigators collected skin tissue from the test area, performed histology, and obtained blood for enzyme-linked immunosorbent assay to determine cytokine levels.

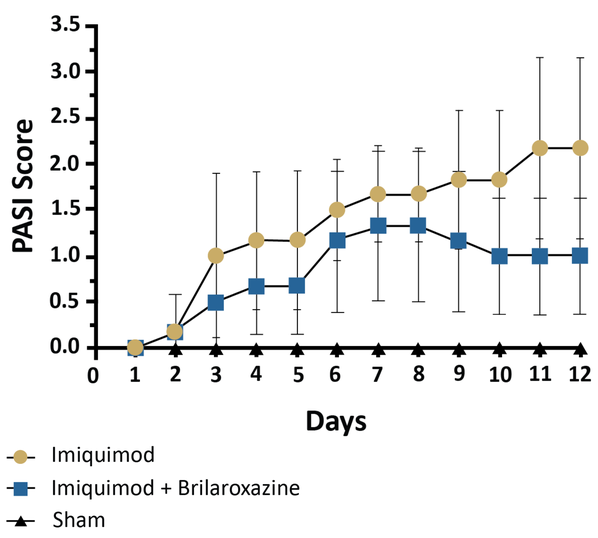
Assessments: 1) Psoriasis Area and Severity Index (PASI) scores (Days 1-12), 2) histology for Baker's score based on Hematoxylin and Eosin (H&E) stained tissue (Day 12), and 3) serum cytokine Tumor Necrosis Factor-alpha (TNF-α), Ki-67, and Transforming growth factor beta (TGF-β) (Day 12).

Analysis: One-way ANOVA followed by Dennett's multiple 't'-test, Post hoc (GraphPad Prism software), with a P value < 0.05 designating significance.

RESULTS

FIGURE 1

Comparative Effects on PASI Score from Days 1-12



Imiquimod+Brilaroxazine group PASI scores were consistently lower than those in the induced Psoriasis group Days 3-12 (P=0.03, Days 1-12), with maximum difference seen on Days 11-12.
PASI- Psoriasis Area and Severity Index.

TABLE 1

Histological Observations

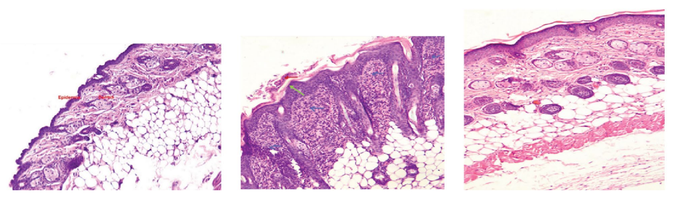
100x Magnification	
Group	**Observations**
Sham	Normal epidermis (1-3 layers), no inflammatory infiltration
Imiquimod	Increased epithelial layers 3-7 layers (green), increased keratinization, Munro's abscess (red arrow), severe inflammatory (blue) infiltration
Imiquimod + Brilaroxazine	Reduced epithelial thickness (3-4 layers), reduced inflammatory infiltration, absence of parakeratinization, absence of Munro's abscess
400x Magnification	
Group	**Observations**
Sham	Epithelium 1-3 layers, no inflammatory infiltration, very little keratin in stratum corneum
Imiquimod	Severe acute and chronic inflammatory infiltration, Kogoj pustule
Imiquimod + Brilaroxazine	Reduced epithelial thickness, reduced inflammatory infiltration

FIGURE 2

H&E Staining of Skin Histology

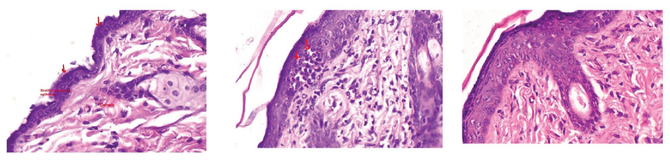
100x Magnification

A. Sham B. Imiquimod C. Imiquimod + Brilaroxazine



400x Magnification

A. Sham B. Imiquimod C. Imiquimod + Brilaroxazine

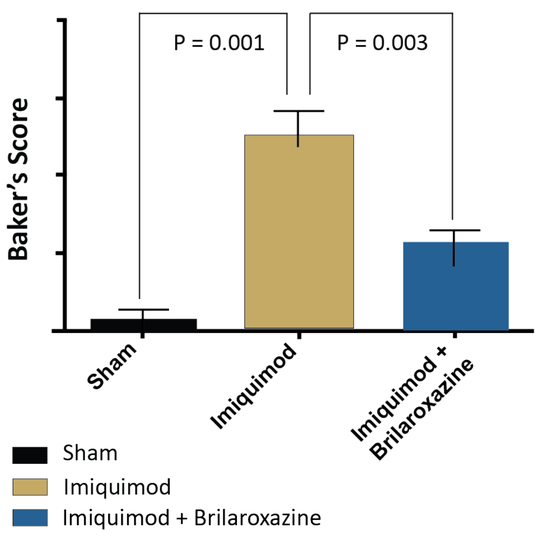


Differences in histology and H&E staining appear between Sham with the Imiquimod and Imiquimod+Brilaroxazine groups and between the latter two groups.

H&E: Hematoxylin and Eosin

FIGURE 3

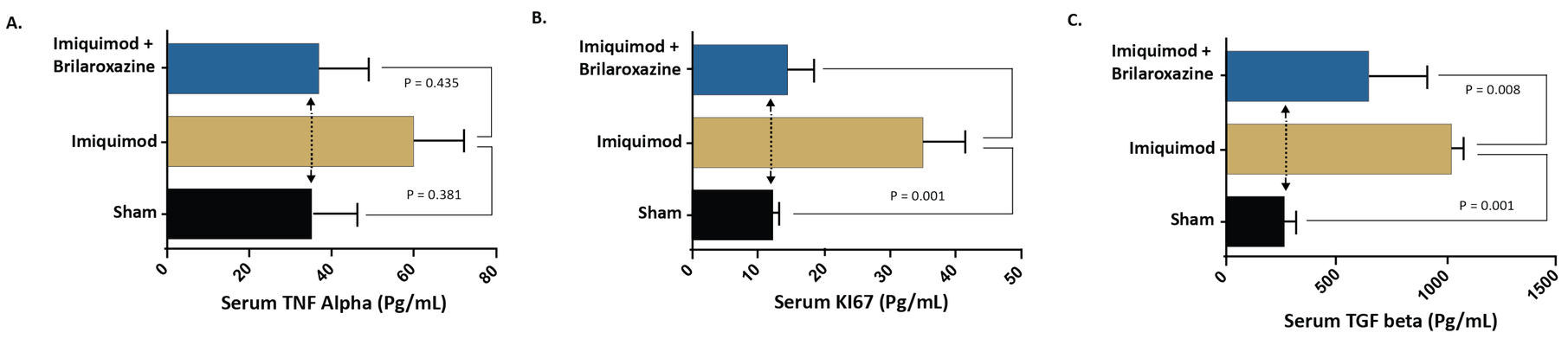
Baker's Scores



Baker's score comparisons were significant for the Sham (P=0.001, Imiquimod) and the Imiquimod+Brilaroxazine (P=0.003, Imiquimod) groups.

FIGURE 4

Serum Pro-inflammatory Cytokine Levels



The Imiquimod+Brilaroxazine group displayed lower serum Ki67 (P=0.001, Imiquimod) and TGF-β, P=0.008, Imiquimod) and similar serum TNF-α levels to the Sham group(Figure 4a,b,c).

TNF: Tumor Necrosis Factor; TGF: Transforming Growth Factor

DISCUSSION

This preclinical study represents an initial proof-of-concept (PoC) for the Brilaroxazine Formulation's activity via multiple positive signals- PASI, histology, and cytokine. It also supports D and 5-HT receptors as viable psoriasis targets and offers an initial glimpse at changes indicating anti-inflammatory and anti-fibrotic effects.

5-HT and D receptor actions underlie these effects. 5-HT regulates inflammation and immunity, particularly 5-$HT_{2B/7}$ receptors[10]. Receptor expression appears significantly altered in psoriatic skin at multiple dermal layers, and systemic proinflammatory cytokines contribute to this condition's pathogenesis[21-24]. $D_{2/3/4}$ receptors regulate keratinocyte proliferation and differentiation, modulate the immune system, and stimulate IL-6 and IL-8, leading to multiple pathological effects [11,13, 25,26].

Brilaroxazine mediates psoriasis through $D_{2/3/4}$ and 5 $HT_{1A/2A/2B/7}$ receptors, plus SERT[14,15,18]. Notable is its mitigation of pro-inflammatory cytokine levels in pulmonary arterial hypertension and idiopathic pulmonary fibrosis (IPF)[14, 15,19]. and anti-fibrotic effects as evidenced by its reduction of collagen levels in the later condition[15,19]. The lipogel formulation, a topical, semisolid delivery system, provides targeted, direct contact with the plaque target area, aiding in attaining adequate dermal levels. It leads to direct drug penetration, mediates 5-HT's actions on multiple dermal layers to control the disease process, and reduces systemic exposure and side effects[27].

The brilaroxazine formulation with the lipogel delivery system offers a potential option for psoriasis, which has links to mental illness (as high as 36%) and can impair psychosocial function[3–7]. Brilaroxazine's clinical development program involves phase 2 and 3 studies for its oral formulation in schizophrenia and plans for other psychiatric indications[28-29].

CONCLUSION

This evaluation of brilaroxazine lipogel formulation activity using an imiquimod-induced psoriatic mouse model (BALB/c) provides an initial PoC via its effects on PASI, H&E staining, Baker's scores, and proinflammatory cytokines.

This approach offers a new target and novel delivery system for further investigation.

REFERENCES

1. Aleem D, Tohid H. Rev Colomb Psiquiatr. 2018..
2. Kamiya K, et al. Int J Mol Sci. 2019.
3. Liu L, et al. Psychiatry Res. 2023.
4. Wu JJ, et al. Journal of the European Academy of Dermatology and Venereology. 2017.
5. Hedemann TL, et al. Gen Hosp Psychiatry. 2022
6. Biljan D, et al. Collegium antropologicum. 2009.
7. Sampogna F, et al. British Journal of Dermatology. 2006.
8. Armstrong AW, Read C. JAMA. 2020.
9. Raharja A, et al. Clinical Medicine. 2021.
10. Roumier A,. Chapter 10 - Serotonin and the Immune System. In: Pilowsky PM, ed. Serotonin. Academic Press; 2019.
11. Parrado AC, et al. Neuroimmunomodulation. 2012.
12. Pani L, et al. Mol Psychiatry. 2000.
13. Wardhana M, et al. Maced J Med Sci. 2019.
14. Bhat L, et al. Eur J Pharmacol. 2017.
15. Bhat L, et al. Eur J Pharmacol. 2017.
16. Cantillon M, et al. Eur J Drug Metab Pharmacokinet. 2018.
17. Cantillon M, et al. Clin Transl Sci. 2018.
18. Cantillon M, et al. Clin Transl Sci. 2018.
19. Bhat L. ESMED. 2023.
20. Van Der Fits L, et al. The Journal of Immunology. 2009.
21. Nordlind K, et al. Arch Dermatol Res. 2006.
22. Morita T, et al. Neuron. 2015.
23. Lundeberg L. Arch Dermatol Res. 2002.
24. Thorslund K. Karolinska Institutet (Sweden). 2012.
25. Fuziwara S, et al. Journal of Investigative Dermatology. 2005.
26. Besser MJ, et al. J Neuroimmunol. 2005;169(1-2):161-171
27. Aggarwal G. Asian Journal of Pharmaceutics. 2018.
28. Safety and Efficacy of Brilaroxazine (RP5063) in Schizophrenia (RECOVER). NCT05184335. ClinicalTrials.gov.
29. RP5063 in Subjects with Schizophrenia or Schizoaffective Disorder. NCT01490086. ClinicalTrials.gov.

DISCLOSURES AND ACKNOWLEDGEMENTS

Funding Source: Grant supporting the study was awarded to Aaray Health Solutions Pvt Ltd, India from Reviva Pharmaceuticals Holdings, Inc.

Acknowledgments: John M. York, PharmD, MBA, Akita Biomedical, Inc. provided editorial support, and Reviva Pharmaceuticals Holdings, Inc. funded this effort.