Rationale Based Repurposing of FDA-Approvedagents for Keloid Management: Anin Vitro Study

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BACKGROUND

Effective management of keloid disorder remains elusive, as it often resists monotherapy and demonstrates a high rate of recurrence. Several FDA–approved drugs developed for treating both fibrotic and unrelated conditions have the potential to target key pathways involved in keloid pathogenesis, and some of these have been used for treating keloids with limited efficacy. However, the effects of combinations of these drugs have not been studied systematically. Given the multifactorial nature of keloid formation, we hypothesized that rationally designed drug combinations could produce additive/synergistic anti–fibrotic effects on keloids when administered locally at lower doses, thereby reducing side effects and the development of resistance to treatment.

METHODS

Primary keloid fibroblasts cultured from surgically removed keloids were expanded and used at low passage. All procedures involving human–derived tissues were approved by the Florida State University Institutional Review Board (IRB STUDY00001981, Approval Date: 05/08/2021) following informed consent from all donors. Cells were seeded in triplicate and either left untreated, or treated for seven days with single, double, triple, and quadruple combinations of the following FDA–approved drugs:

Triamcinolone Acetonide (TA), Nintedanib (Nin), Pirfenidone (Pir), Sulindac (Sul), Minoxidil (Mino), Vorinostat (Vor), Verteporfin (Vtf), and Verapamil (Vera) — administered with or without low–dose (1 Gy) ionizing radiation (IR). Relative cell viability was measured by counting cells on a Coulter Counter. Synergistic interactions among drug combinations were assessed using Bliss Independence analysis. Levels of type I collagen and alpha –Smooth Muscle Actin (α–SMA) were measured by indirect immunofluorescence and Western blotting.

RESULTS

At the concentrations employed, single–agent treatments yielded modest reductions in keloid fibroblast viability (~84.5%). In contrast, triple and quadruple combinations significantly decreased viability to 42.6% and 26.8%, respectively. Radiation increased the impact of most drugs. A dramatic reduction in type I collagen levels was observed with triple–drug combinations, particularly after 7 days of treatment, indicating a time–dependent anti–fibrotic effect.

CONCLUSION

This study demonstrates that rationale–based combinations of FDA–approved drugs can synergistically suppress keloid fibroblast viability, proliferation, and fibrotic markers *in vitro*. By targeting multiple fibrotic pathways at once, these drug combinations make it harder for keloid fibroblasts to develop resistance, a potential problem with single–drug treatments. Additionally, due to their additive/synergistic effects when used in combinations, lower doses of individual drugs are required, which would reduce the potential for adverse effects. These findings highlight the therapeutic promise of low–dose, multi–agent, locally administered therapies as a more effective approach for managing keloid disorder. *Combinations of these FDA approved agents can now be tested by clinicians for safety and efficacy in keloid patients following intralesional or topical administration, with or without superficial radiation.*

Disclosure Declaration

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