Superior Antiproliferative and Combinatorial Synergistic Effects of a Rock Inhibitor in Multiple Models for Keloid Disease

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Abstract:

Keloid disease (KD) is a common fibroproliferative disorder with ill-defined treatment strategy and frequent recurrence. The urgent unmet need for effective drugs is hampered by the lack of suitable study models. AMA0825, a novel Rock inhibitor, has shown antifibrotic and antipro-liferative effects in other fibrotic conditions. Hence, we evaluated the role of AMA0825 utiliz-ing an in vitro, ex vivo and innovative spheroid model, demonstrating a promising methodol-ogy for evaluating KD treatments. Cell proliferation assay and real-time cell analysis evalua-tion of AMA0825 exhibited a significantly more potent antiproliferative effect with an IC50 of 28.19 ± 1.6 nM, compared to dexamethasone (IC50 = 35.35 ± 2.6 µM) and triamcinolone (IC50 =37.84 ± 3 µM). This effect was corroborated by immunocytochemistry (decreased Ki67 ex-pression) and flow cytometry which showed AMA0825 effectively arrested keloid fibroblasts in the G1 phase of the cell cycle. In the spheroid model, AMA0825 reduced cell proliferation at logarithmic concentrations (50-50000 nM), outperforming dexamethasone (80 µM). How-ever, at low concentrations, AMA0825 showed no antifibrotic effect in spheroid and ex vivo model. Statistically significant synergistic effects were observed when combining AMA0825 with dexamethasone. Overall, our study highlights the potential of Rock inhibitors, particularly AMA0825, as an effective antiproliferative agent for targeting KD.

Keywords:

keloid disease, Rock inhibitor, cytotoxicity, 3D spheroid.