Are we using too much Triamcinolone Acetonide for intralesional keloid therapy?

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Running Title

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BACKGROUND

Keloids are fibroproliferative skin lesions that develop during wound healing and are characterized by excessive dermal fibroblast proliferation and extracellular matrix deposition, leading to tissue growth far beyond the original wound boundaries. Intralesional corticosteroids remain the cornerstone of therapy for keloid disorder, yet dosing practices vary widely, and high concentrations of Triamcinolone Acetonide (TA) are frequently used without a clearly defined biological rationale, often resulting in significant adverse effects including localized skin atrophy, hypopigmentation, acneiform eruptions, telangiectasia and necrosis. We hypothesize that clinically used doses of TA exceed the dose required to achieve maximal biological effect on keloid fibroblasts.

METHODS

Primary normal human dermal fibroblasts (HDF-PA) and three patient derived keloid fibroblasts (K-PA, P9, P11 were treated for seven days with different concentrations (1-1000μM) of TA. Viable cells were quantified using a Coulter Counter, while the levels of fibrotic markers such as Type I collagen and alpha-Smooth Muscle Actin (α-SMA) were quantitated by immunofluorescence microscopy.

RESULTS

Increasing TA concentrations from 1μM to 50μM resulted in a dose-dependent decrease in viability of all samples (HDF-PA, K-PA, P9, and P11; $p < 0.0001$ for each comparison). However, the response reached a plateau at TA concentrations between 50-100μM. Similar results were observed in our immunofluorescence experiments where no further reductions in the levels of both Type I collagen and α-SMA were observed at TA concentrations beyond 100μM. No statistically significant differences were observed between successive higher concentrations (100–1000 μM), indicating that increasing TA beyond 100μM may not provide additional benefits.

To translate the in vitro findings into estimated in vivo exposure, a Quantitative In Vitro–In Vivo Extrapolation (QIVIVE) analysis was performed. We translated the effective in vitro concentrations of TA (50–100μM) into clinically relevant units. These correspond to approximately 0.022–0.043mg/cm3 of tissue, which are much lower than the intralesional TA doses used in the clinic, and are closer to 0.25-2mg/cm3 dose of TA used in rare studies where it was just as effective as higher doses for keloid therapy.

CONCLUSION

TA exhibits a dose-dependent inhibitory effect on fibroblast viability and the levels of fibrotic biomarkers that plateaus between 50–100μM in vitro. QIVIVE analysis indicates that the concentrations required for maximal biological effect (50–100μM) correspond to approximately 0.022–0.043 mg/cm3 of TA, which are between ~500-1000-fold lower than the intralesional doses (20–40mg) commonly used in the clinic currently. Our results suggest that standard high dose intralesional TA regimens for keloid therapy may far exceed the dose necessary for maximal therapeutic effect and may be primarily contributing to the commonly observed adverse effects. Based on our findings, we recommend testing TA doses of 0.1-1mg/cm3 in future clinical trials for keloid therapy