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LETTER

Revisiting the Chondrotoxicity of Intra-Articular Triamcinolone Acetonide in Osteoarthritis: Dose Dependence and Experimental Model Heterogeneity [Letter]

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Dear editor

We have read with great interest the comprehensive review by Wan et al[1] on the efficacy and safety of intra-articular triamcinolone acetonide (TA) for osteoarthritis (OA). The authors systematically summarized its pharmacology, efficacy, and safety, providing valuable guidance for clinical practice. We commend their balanced discussion on TA-related chondrotoxicity.

However, the controversy over TA's chondrotoxicity has not been fully explained by heterogeneity in existing evidence. As rehabilitation physicians routinely performing intra-articular injections, we wish to clarify this issue. Conflicting findings on TA's chondrotoxicity are primarily attributable to two key factors: heterogeneity of experimental model systems and dose-dependent effects. A more granular analysis of these factors could help bridge the gap between preclinical findings and clinical practice.

A major source of divergent findings lies in differences between in vitro systems. Most studies reporting significant chondrotoxicity have adopted monolayer chondrocyte cultures, in which cells are deprived of their native three-dimensional extracellular matrix (ECM) environment.[2,3] In contrast, when chondrocytes are maintained within intact cartilage explants—preserving the physiological ECM architecture and cellular heterogeneity—TA exerts substantially less detrimental effects. Porter et al[2] demonstrated that at physiologically relevant doses, TA had minimal negative impact on chondrocyte viability, proliferation, and ECM synthesis in full-thickness cartilage explants, even under inflammatory challenge with interleukin-1β. Notably, TA not only failed to inhibit matrix synthesis but also mitigated glycosaminoglycan loss in inflamed cartilage, suggesting an anti-catabolic rather than chondrotoxic profile. Sherman et al[3] similarly reported that full-thickness cartilage explants exhibited reduced loss of cell viability compared to monolayer cultures when exposed to corticosteroids, attributing this difference to the protective effects of intact ECM and cellular heterogeneity. These consistent findings confirm that the intact ECM not only maintains chondrocyte physiology but also actively modulates their response to TA, explaining the divergent results between monolayer and explant models. The lack of physiological ECM in monolayer cultures artificially increases chondrocyte susceptibility to corticosteroids, leading to overestimation of chondrotoxic risk. Therefore, monolayer culture data should be interpreted cautiously, and explant or 3D models are preferred for preclinical safety assessment of TA.

A second critical variable is the administered dose. As systematically reviewed in a landmark systematic review by Wernecke et al,[4] glucocorticoids exert time- and dose-dependent effects on articular cartilage, with beneficial anti-inflammatory outcomes at lower doses or shorter durations and potential detrimental effects at higher doses or prolonged exposure. The dose-dependent effect of TA is likely related to its dual role: low doses suppress pro-inflammatory cytokines and catabolic activity, while high or repeated doses may disrupt chondrocyte metabolism and ECM synthesis. A 2023 non-inferiority randomized controlled trial by Utamawatin et al[5] demonstrated that 10 mg of TA was non-inferior to 40 mg in

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improving pain in symptomatic knee OA at 12 weeks, with both doses significantly improving pain and quality of life. While some studies suggest that 40 mg may offer superior efficacy in severe inflammatory OA, the non-inferiority of lower doses in pain relief provides a rationale for dose optimization. Importantly, higher doses offer no significant additional clinical benefit but may increase cumulative cartilage exposure and systemic adverse effects such as transient hyperglycemia or hypothalamic-pituitary-adrenal axis suppression. This dose-response relationship has profound clinical implications, suggesting that the traditional 40 mg starting dose may not be necessary for all patients and that lower doses could achieve comparable symptomatic relief with a potentially better safety margin.

These considerations have several practical implications for clinicians. First, preclinical evidence from monolayer cultures should not be overinterpreted as directly applicable to clinical scenarios. Given that intact ECM in vivo likely mitigates TA's chondrotoxic potential, the concern that a single intra-articular TA injection inevitably damages cartilage may be overstated, particularly when doses are moderate and injection frequency is limited. Second, dose selection should be individualized. For patients with mild-to-moderate OA without marked inflammation, a lower dose (10–20 mg per injection) is recommended to balance efficacy and safety, based on the non-inferiority evidence.[5] For severe inflammatory OA or acute flares, 40 mg may be considered temporarily, but repeated high-dose administration (eg., more than 3 times annually) should be avoided to minimize cumulative risk. The same principle applies to different joint sites, although the knee has been the most studied; extrapolation to other joints (eg., hip, shoulder, hand) should be made with caution until joint-specific data emerge. Third, clinicians should consider combining TA with other OA treatments (eg., physical therapy, weight management, chondroprotective agents such as hyaluronic acid) to achieve comprehensive management and potentially reduce the need for repeated corticosteroid injections.[1]

Future research should focus on three areas: (1) standardizing preclinical models by requiring explant-based or 3D culture systems for chondrotoxicity assessment; (2) conducting long-term prospective studies to evaluate cartilage outcomes (eg., via MRI or biomarker changes) after repeated low-dose versus high-dose TA injections; and (3) exploring whether the dose-response relationship varies by OA stage (early vs. advanced) or joint type. Such efforts will help establish evidence-based dosing guidelines that maximize therapeutic efficacy while minimizing potential harm to articular cartilage.

In conclusion, conflicting chondrotoxicity data of TA are mainly caused by model heterogeneity and dose dependency. Monolayer cultures may overestimate risk, while clinically relevant doses show a favorable safety profile in explant models. Rational evidence interpretation, individualized dosing (10–20 mg for most patients, 40 mg reserved for severe flares), and appropriate monitoring are critical for safety. We appreciate the valuable work by Wan et al[1] and hope that our perspectives support better clinical practice.

Disclosure

The authors declare no conflicts of interest in relation to this communication.

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