The TGF-β Neutralizing Antibody 1D11 Reduces Knee Stiffness In Vivo

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INTRODUCTION: A devastating complication of primary total knee arthroplasty (TKA) is arthrofibrosis, where scar tissue deposition in and around the joint decreases knee range of motion, typically leading to significant patient morbidity. After TKA, about 5% of patients develop arthrofibrosis. TGF-β signaling is believed to contribute to scar tissue formation, including downstream SMAD proteins that translocate to the nucleus and upregulate expression of profibrotic genes. There are three isoforms of TGF-β: TGF-β1, TGF-β2, and TGF-β3. All three isoforms have been implicated in pro-fibrotic processes across organ systems. The TGF-β isoforms could be crucial therapeutic targets in the prevention of arthrofibrosis after TKA. The TGF-β neutralizing antibody 1D11 blocks all three isoforms of TGF-β and therefore could represent a potential prophylactic intervention for arthrofibrosis by preventing the excessive or dysregulated signaling of these profibrotic cytokines.

METHODS: Following approval from our Institutional Animal Care and Use Committee (IACUC), 40 Sprague-Dawley rats were randomly assigned to four experimental groups (n = 10 per group). All rats underwent index immobilization surgery, during which a lateral parapatellar arthrotomy was performed to access the knee joint. The cruciate ligaments were transected, and the knee was hyperextended to disrupt the posterior capsule. Small cortical defects were created on the medial and lateral femur to simulate bone cuts, and a 2-0 stainless steel suture was passed from the midshaft of the tibia around the femur and tied to lock the knee in flexion. After 8 weeks of immobilization, all rats underwent a second surgery to remove the suture and were allowed free cage activity for 4 weeks. Throughout the study, rats received intraperitoneal injections of either a TGF-β–neutralizing antibody (1D11) or an isotype control. Injections were administered on day –3 (pre-treatment), day 0 (day of index surgery), and every other day for two weeks following index surgery (**Figure 1**). The same injection regimen was repeated at the time of remobilization surgery. At the end of the 4-week remobilization period, rats were euthanized, and hind limbs were harvested for stiffness testing using a custom load-cell–based device that simultaneously measured torque and joint angle. All limbs were tested within a torque range of 1–10 N·cm. Kruskal-Wallis with Dunn's multiple comparison test was used to evaluate significant differences in knee stiffness between the groups.

RESULTS SECTION: Throughout the torque range of 1–10 N·cm, rats that received 1D11 at index and remobilization surgeries (1D11-1D11 group) and rats that received isotype control at index and 1D11 at remobilization (Control-1D11 group) were significantly less stiff compared to rats that received isotype control at index and remobilization surgeries (Control-Control). The 1D11-1D11 and Control-1D11 groups were not significantly different from each other or from the 1D11-Control group. Compared to the Control-Control group, the 1D11-1D11 and Control-1D11 groups had greater range of motion by a mean of 18±4.1° and 19±3.4°, respectively.

DISCUSSION: These findings support the role of TGF-β signaling in the development of arthrofibrosis following knee surgery and suggest that TGF-β neutralization may be a viable approach to mitigate postoperative joint stiffness. Notably, treatment with 1D11 at the time of remobilization, either alone or in combination with early treatment, significantly reduced stiffness compared to controls. This indicates that TGF-β–driven fibrosis remains an active and targetable process even after the initial injury phase. The lack of additional benefit in the dual-treatment group suggests that timing of intervention may be as important as duration. Overall, these results highlight 1D11 as a promising therapeutic candidate for reducing arthrofibrosis risk after TKA.

SIGNIFIGANCE/CLINICAL RELEVANCE: Arthrofibrosis remains a challenging complication following total knee arthroplasty, with limited effective treatments. This study demonstrated that targeting TGF-β signaling with the neutralizing antibody 1D11 significantly reduced postoperative joint stiffness in a preclinical animal model. These findings suggest that the inhibition of the TGF-β signaling pathway during and around the surgical period may offer a novel therapeutic approach to prevent arthrofibrosis and improve functional outcomes after TKA.

IMAGES AND TABLES:

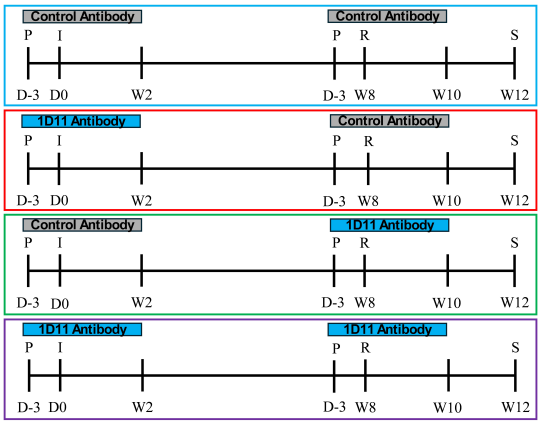

Figure 1. Experimental design showing timeline and antibody treatment. P = pre-treatment, I = index surgery, R = remobilization surgery, S = sacrifice, D = day, W = week.

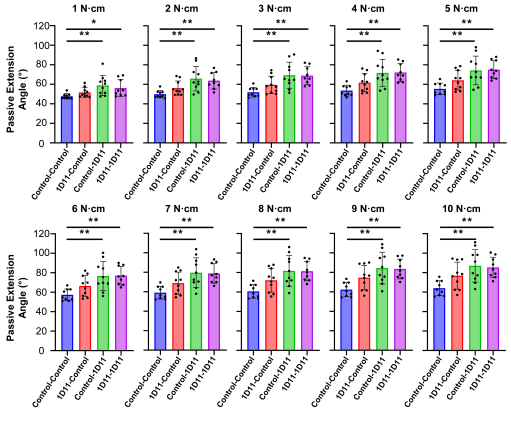

Figure 2. Biomechanical analysis showing angles across a torque range of 1-10 N·cm. p* = 0.03 and p** = 0.002-0.008.