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A PROPOSED ADJUNCT TREATMENT OF ARTHROFIBROSIS IN TOTAL KNEE ARTHROPLASTY

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WOUNDS AND HEALING >

CONTRACTION VS. CONTRACTURE

Wound contraction is part of the normal physiologic healing response of a tissue, varying in intensity, and functioning to reduce the size of the defect and the amount of repair. Contraction involves myofibroblasts (from fibroblasts under the influence of TGB-β) which function to pull collagen into the damaged tissue. Proteins within the myofibroblast interact with the newly formed collagen to make the extracellular matrix and ultimately the base for wound contraction. (1,2)

Leukotrienes are one of several molecules involved in the inflammatory phase of wound healing and contraction. These pro-inflammatory substances are associated with granulocytes and the chemotaxis of inflammatory cells. (3,4,5)

Too often, wound contraction accelerates into a pathophysiologic response. Accelerated contraction (involving leukotrienes, collagen, myofibroblasts, granulocytes) and scar formation can lead to hypertrophy, disorganized collagen formation and deposition, adhesions, and wound contracture. (1,2,3)

FOREIGN BODY RESPONSE

The human body naturally elicits a response to foreign objects. Upon implantation of a foreign body, an inflammatory cascade begins. This process involves cells (granulocytes, lymphocytes, monocytes, macrophages) and inflammatory molecules (TGF-β, PDGF, interleukins, leukotrienes). Once macrophages are recruited, the process is again accelerated via TNF-α and interleukins. (6,7,8)

Wound contracture occurs spontaneously and cannot be predicted with current methods. The inflammatory response to implanted foreign bodies also cannot be predicted. The foreign body response while typically classified as allergic or non-allergic, can lead to capsule formation around the foreign body. This capsule can then further undergo contracture, noted as capsular contracture, similar to accelerated, inflammatory wound contracture. (3,8,9)

BREAST IMPLANTS >

CAPSULAR CONTRACTURE

Capsular contracture is a common problem after silicone implant surgery (i.e., breast, testicle, calf). This inflammatory reaction of fibrotic tissue can cause hardening, distortion, compression, and deformation of tissue leading to compromised aesthetics, pain, deformity, and subsequent surgery. (4,13)

Fibrous capsule formation is an inflammatory host reaction following the implantation of biomaterials. Capsule formation involves many processes including but not limited to the foreign body reaction, inflammation cascades, coagulation cascades, granulation tissue formation, complement cascade, and protein adsorption and deposition. TGF-β in particular is a potent fibrotic, angiogenic, and inflammatory mediator involved. Cell layers form (monocytes, macrophages, foreign body giant cells), separating the granulation tissue from the implant or biomaterial. Again, capsule formation involves several cell lineages and inflammatory molecules (TGF-β, TNF-α, leukotrienes, PDGF). (6, 9,10,14)

The fibrous capsule can interfere with the implant or biomaterial function and ultimately its medical or prosthesis indication. The degree of fibrosis, if severe, may impede or inhibit function and aesthetics. The capsule does not grow indefinitely but eventually reaches a steady state, remaining a living tissue. The time needed to reach this state varies greatly but ultimately can interfere with medical device functioning (i.e., electrical signal transduction in neuroprosthetics and pacemakers, aesthetics of silicone implants). It is important to note the capsule is also capable of regrowth if damaged and/or removed. (6,10)

BREAKTHROUGHS >

LEUKOTRIENE RECEPTOR ANTAGONISTS (LTRA)

Leukotrienes are synthesized by many inflammatory cellsLeukotrienes are potent mediators of inflammation leading to increased vascular permeability, inflammatory cell chemotaxis (eosinophils in particular), mucous hypersecretion, and neuronal stimulation. Leukotrienes are involved in myofibroblast differentiation and also specifically regulate TGF-β and collagen production. Eosinophils are further associated with angiogenesis, coagulation, and TGF-β. It is reasonable to imply leukotrienes play a role in wound contracture, capsule formation, and therefore capsular contracture. (3,4,5,6,9,10,11,12,14,15,17)

LTRA (montelukast, zafirlukast) are FDA approved for the treatment and management of allergic rhinitis and asthma. Interestingly, LTRA were noted in 1996 to improve pigmented, hypertrophied cutaneous scarring. In 2002 zafirlukast was also noted to improve capsular contracture of silicone breast implants, softening the fibrous capsule and avoiding the need for surgical correction. Because wound contracture occurs spontaneously, LTRA may not play a preventive role. However, in capsular contracture in the setting of a foreign body, there may be a significant and progressive inhibitory effect. (4)

Montelukast in particular was shown to inhibit collagen maturation in accelerated excisional wound contraction. Zafirlukast was shown to reduce the occurrence of factors directly and indirectly connected with capsular contracture including decreased angiogenesis and vessel formation, thinner capsules, lower capsule collagen density, decreased leukotriene-producing mastocytes, and decreased eosinophil counts. It has been described that increased vascularization occurs surrounding implants, contributing to capsule formation. LTRA decreases vascularization, zafirlukast in particular inhibits the eosinophilic influx and contractile activity thereby inhibiting the formation of a severe capsule and preventing capsular contracture. (3,4,13,14,15,16)

TOTAL KNEE ARTHROPLASTY POSTOPERATIVE ARTHROFIBROSIS

Arthrofibrosis, or joint stiffness, is a complication following TKA reported in up to 19.8% of TKA surgeries. This complication presents clinically as restricted knee range of motion, knee stiffness, edema, warmth, and tenderness. It may lead to significant functional deficits and an inability to perform activities of daily living. In severe cases, patients are permanently left with limited mobility and decreased quality of life. (19,22)

Contributing postoperative factors include patient compliance and pain, but arthrofibrosis is thought to be due to an exaggerated local inflammatory response leading to hypertrophic, noncompliant fibrosis and scar formation. Mechanisms of pathogenesis of postoperative fibrosis include inflammatory and immune cell activation and recruitment, as well as cytokine and inflammatory mediator cascades including TGF-β, IL6, and leukotrienes, and finally the differentiation of myofibroblasts and collagen production. (22,23,24)

Patients with a history of hypertrophic scars and keloid formation are at an increased risk of arthrofibrosis, evidence supporting excessive fibrosis, scarring, and collagen deposition as a major etiology of arthrofibrosis. These etiologies have also been associated with TGF-β. (19,20,21,22)

CONSIDERATIONS >

DUE TO SIMILARITIES IN THE ETIOLOGIES AND PATHOPHYSIOLOGIES OF ARTHROFIBROSIS AND CAPSULAR CONTRACTURE, THE AUTHORS PROPOSE LTRA BE FURTHER EVALUATED IN TKA ARTHROFIBROSIS. EVIDENCE SUPPORTING LTRA USE IN CAPSULAR CONTRACTURE HINTS AT THE POSSIBILITY FOR USE IN TREATMENT OF, AND PREVENTING PROGRESSION OF JOINT STIFFNESS AND TKA POSTOPERATIVE ARTHROFIBROSIS.

LTRA SHOULD ALSO BE COMPARED WITH OTHER IMMUNOSUPPRESSANT AND ANTIINFLAMMATORY DRUGS (MTOR INHIBITORS, GLUCOCORTICOIDS, NSAIDS, TAXANES) IN BOTH CAPSULAR CONTRACTURE AND ARTHROFIBROSIS WHILE MEASURING INFLAMMATORY CELL INHIBITION, COLLAGEN DEPOSITION, CAPSULE FORMATION, RANGE OF MOTION, AND JOINT STIFFNESS.

CONCLUSION >

LTRA are inexpensive (montelukast $0.25/day; zafirlukast $1/day), oral medications with low adverse reaction risk that have been shown to be effective in preventing and treating breast implant capsular contracture in several studies and in a meta-analysis of 1710 patients. (18)

The authors postulate the involvement of leukotrienes, granulocytes (i.e., eosinophils), protein and coagulation cascades, macrophages, and collagen in capsule formation and capsule contracture is what underlies the mechanism by which LTRA help prevent, treat, and resolve capsular contracture of silicone implants. Stemming from a common pathophysiology, LTRA may also be beneficial in reducing fibrosis, scarring, and joint stiffness in TKA patients experiencing decreased range of motion, pain, and limited mobility. LTRA use in this setting is off-label and the risks, benefits, and alternatives should always be discussed between physician and patient.

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