LEUKOTRIENE RECEPTOR ANTAGONISTS (LTRA) AND SILICONE IMPLANT CAPSULAR CONTRACTURE

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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, and ultimately wound contracture. (1,2,3) Wound contracture is a complication of wound healing that can cause functional limitations, aesthetic derangements, and deformity, and is dreaded by both patients and surgeons.

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, CSF, and more 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)

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). (9,10,11,16)

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. 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. (10,11)

MEDICINE 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 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. (3,4,5,9,10,11,12,13,16,17,19)

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. 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. (3,14,15,16,17,18)

The current recommendations for treatment of breast implant capsular contracture include massage, compression, oral vitamin E, and finally surgery. As noted, the fibrous capsule formed during the foreign body response is living tissue and is capable of regrowth and regeneration following damage and even surgical resection. Breast implant capsular contracture recurrence after surgery has been documented in up to 54% of patients. Moreover, capsule surgery involves further risks of hematoma, infection, rupture, asymmetry, and further revision. (10,11,20)

CONCLUSIONS >

Capsular contracture is a common problem after silicone implant surgery (i.e., breast, testicle). This fibrotic tissue can cause hardening, distortion, compression, and deformation of tissue leading to compromised aesthetics, pain, deformity, and subsequent surgery. (14,15)

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. The better-known Baker Classification and lesser-known Anton Paar Mammacompliance systems are used for measuring breast implant hardness and capsular contracture. Based on these measurements, LTRA have been shown to prevent, treat, and reverse capsular contracture. Severe cases may still benefit with evidence showing up to a 22% increase in compliance. The effects of LTRA appear to only last as long as the drug is administered. Upon discontinuation after one year, it can be expected that in many patients mammary compliance will decrease and may return to pre-treatment levels. (16,21,22)

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. LTRA use in this setting is off-label and the risks, benefits, and alternatives should always be discussed between physician and patient. Despite this, evidence over the last twenty years has continued to show LTRA are effective in many patients for reducing pain, breast capsule distortion, and improving aesthetics who are either not surgical candidates or who do not wish to undergo surgery.

FUTURE DIRECTION >

The better-known Baker Classification and lesser-known Anton Paar Mammacompliance systems are used for measuring breast implant hardness and capsular contracture. While sufficient, the authors believe both may be somewhat subjective with weak intraobserver and interobserver reproducibility. A more objective method is needed to evaluate, diagnose, and classify capsular contracture.

Investigate further the initiating biochemical cascade and the multifactorial causes of capsular contracture.

Compare LTRA with other immunosuppressant and antiinflammatory drugs (mTOR inhibitors, glucocorticoids, NSAIDs, taxanes, etc.) while measuring inflammatory cell inhibition, collagen deposition, and capsule formation.

It has been mentioned that silicone implants and severe capsule formation may contribute to the formation of auto-immune diseases. If true, could LTRA decrease the incidence?

When can patients discontinue LTRA when treating capsular contracture? How long does the anti-inflammatory effect last? Does the risk of capsular contracture peak?

The incorporation of biological components of allogeneic or xenogeneic origin such as dermal matrices, potentially using stem cells, into tissue-engineered or regenerative approaches should be explored for preventing implant-associated capsular contracture.

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