

# The Dermatologist

## Dermal Scarring Challenges

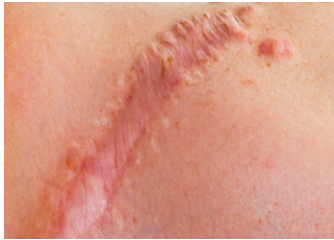
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When our patients with hypertrophic scarring ask us for help, we dermatologists face a set of challenges. The first 2 challenges are physical: we want to do everything we can to make the scars less visible while at the same time helping to alleviate the pain—including the itching and tingling—that is often associated with hypertrophic scarring and keloids.

These scars can require intermittent intralesional injections with triamcinolone acetonide to decrease their size. And if the scars are located over joints, patients can experience further trouble—there can be severe limitations in movement as the scars contract over time, including the fine finger movements that are vital to perform certain tasks. These physical challenges may contribute to a patient facing economic hardships linked to the inability to work.

At the same time, there is also a third challenge: we want to help our patients overcome their invisible scars—the negative social and emotional consequences that almost always go hand-in-hand with their physical scarring. Only if we are aware of all of these challenges—and how they work together to impact our patients' quality of life—can we give them the effective care they need and deserve.

We need to remember that the social and emotional toll triggered by scarring, while less immediately obvious to the eye than the physical toll, is just as “real” to our patients. Abnormal scars can be aesthetically distressing, disfiguring, and psychosocially disabling.<sup>1</sup> The deformity our patients experience can lower their self-confidence and self-esteem. This, in turn, can trigger or exacerbate their social isolation, and be the source of anxiety and depression. In certain cases, they may experience sleep disturbances and even posttraumatic stress disorder. Overall, the social stigma resulting from scarring, in tandem with its physical effects and severe pain, can contribute to a decreased quality of life for them.

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*Figure. RXI-109 was administered by intradermal injection over 3 months. Current cohorts are being treated over 6 months with additional doses to determine the best treatment regimen.*

However, in spite of these serious physical, psychological, and social challenges, this is an area of high unmet medical need, with no universal standard of care and no FDA-approved drugs for the prophylactic prevention of scarring in the patient population with a predisposition to develop these disfiguring scars.<sup>1,2</sup> Given the large number of surgical procedures and the negative effect of hypertrophic scarring on our patients' physical and emotional health and quality of life, there is a significant market for a scar prevention therapeutic.

One potential therapy to reduce the formation of hypertrophic scars focuses on connective tissue growth factor (CTGF), an extracellular matrix protein that plays a key role in tissue regeneration and repair. During wound healing, CTGF modulates signals from a wide range of factors in the cells and in this way controls critical cellular pathways including scar deposition and remodeling. CTGF is involved in the differentiation of fibroblasts to contractile myofibroblasts, which are the main cells responsible for the deposition of collagen. Elevated levels of CTGF-dependent signaling can prolong the tissue repair process and lead to increased collagen deposition and scarring.<sup>1,3</sup>

## **The RNAi Mechanism**

How can we reduce the expression of CTGF—and by doing so, reduce our patients' hypertrophic scarring? One potential approach involves RNAi-based therapy.<sup>1-6</sup> RNAi—short for RNA interference—is a naturally occurring phenomenon by which short double-stranded RNA molecules interfere with the expression of targeted genes.<sup>1,2,7,8</sup> The development of therapeutics based on RNAi technology takes advantage of this phenomenon and potentially allows us to reduce the expression of particular genes within living cells. For example, RNAi targeting of CTGF can reduce the overexpression of the CTGF protein that stimulates collagen production and scar formation. The theory is, “reduced scar proteins, reduced scar tissue.”

Scientists at RXi Pharmaceuticals have developed a proprietary RNAi compound that targets CTGF. Drug-like properties—such as high potency, target specificity, serum stability, reduced immune response activation, and efficient cellular uptake—were built into the RNAi compound. This platform of novel compounds are termed “self-delivering” RNAi compounds, or sd-rxRNA, in part because they are very efficiently taken up by the cells.

## **Clinical Studies to Date**

A clinical candidate, RXI-109, is in development at RXi Pharmaceuticals. It is an sd-rxRNA that targets CTGF to reduce dermal and ocular scarring. Single- and multiple-dose, dose-escalation studies were initiated in 2012 in healthy volunteers for the treatment with RXI-109 to reduce the recurrence of hypertrophic scarring following planned surgeries. These 2 studies demonstrated the safety and tolerability of the compound and also provided the first evidence of clinical activity in a surgical setting.

In the first phase 2 study (initiated in November 2013), the participants with a long hypertrophic scar in the lower abdominal region received scar revision surgery and treatment with the compound over the first month after surgery. The participants received the compound or placebo on a blinded basis at the distal ends of their revised scar, leaving a central untreated section of the scar. Each participants' revised scar provides the opportunity to compare the appearance of the revised areas after treatment with the compound or placebo or when left untreated, allowing for the within-participant comparison of the 3 revised scar segments.

Preliminary data from the first phase 2 hypertrophic scar studies were used to help design a follow-on phase 2 study that is being conducted in the participants in which 1 long or 2 shorter hypertrophic scars are surgically revised.<sup>9</sup> Treatment of the revised areas with RXI-109 is being compared directly to revised areas that are left untreated on the same participant. Preliminary data from the initial 2 cohorts of the study indicated that scars were less visible after treatment for 3 months (Figure). Based, in part, on this new information, 2 more cohorts were added to this study in November 2015

to evaluate extended dosing regimens out to 6 months to determine if clinical results are improved if dosing is continued further into the extended proliferation phase of wound healing that leads to hypertrophic scarring.

Lastly, the compound is also being evaluated in a phase 1/2 study for its safety, tolerability, and clinical activity in the eye. This is a dose-escalation study in which the participants with late-stage, wet age-related macular degeneration (AMD) with the risk of subretinal fibrosis will be treated with the compound; as in dermal scarring, CTGF is known to play a role in retinal scarring. Reduction of CTGF in the eye may reduce the formation of retinal fibrosis that often accompanies late-stage AMD and contributes to vision loss.

Work involving RNAi-based therapy could one day translate into effective treatments for our patients with hypertrophic scarring—and other types of scarring—who have had little luck with existing treatment options. At the same time, it might also help us assist our patients with some of the important social and emotional challenges that they often face—giving them the potential for improved healing not only on their skin but in their mind as well.

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