

EDITORIAL

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As Thomas Jefferson once wrote, “the art of life is the art of avoiding pain.” Many disease processes produce pain, and, today, avoidance of pain relies primarily on therapeutic interventions. Despite extensive research into pain pathogenesis, and development and testing of experimental therapeutics, millions suffer with unremitting chronic pain that does not respond to available therapeutic choices. One major hurdle in developing new therapeutics is that clinical trial outcomes are subjective, relying on self-reported symptoms. These nonobjective measures can confound trial outcomes, in part because of placebo effects and reporter variability. In this volume of *Molecular Medicine*, Dahan and colleagues show a way forward in developing therapeutic agents for neuropathic disease that focuses on true disease modification rather than relying on patient-reported symptoms alone (1).

Over the last decade, it has become clear that diverse diseases are associated with the onset of small nerve fiber loss and damage (SNFLD), a neuropathy of the sensory and autonomic nervous systems. Afflicted patients develop not only severe pain, but also autonomic symptoms that are highly variable depending on the specific organ affected. Clinicians frequently miss this form of neuropathy because of the nonspecific signs and

symptoms and because typical neurological testing cannot directly assess the function of these small nerve fibers. SNFLD is most often seen in patients with diabetes and prediabetes, but it also occurs in many other diseases or can be idiopathic.

Patients with the orphan disease sarcoidosis often have SNFLD, and like many conditions, the current treatments of sarcoidosis do not effectively treat its symptoms. *Molecular Medicine* published the first phase 2 double-blind, placebo-controlled trial evaluating the novel tissue-protective and repair-activating compound ARA 290 against placebo in the SNFLD of sarcoidosis by using patient-reported outcomes (2). The results showed a significant improvement in the active treatment arm. On the basis of data obtained from preclinical models of nerve injury that show that ARA 290 reduces inflammation and accelerates axon regrowth, a second trial of ARA 290 in the SNFLD of sarcoidosis was designed to focus on the objective endpoints of change in nerve fiber density of the cornea and in skin biopsies, as well as semiobjective endpoints of change in functional exercise capacity and quantitative sensory testing. In addition to highlighting the therapeutic potential of this targeted molecular approach to treating pain, this article provides a frame-

work for objective clinical trial design that incorporates evidence of neuronal growth linked to improvements in clinical function.

REFERENCES

1. Dahan A, *et al.* (2013) ARA 290 improves symptoms in patients with sarcoidosis-associated small nerve fiber loss and increases corneal nerve fiber density. *Mol. Med.* 19:334–45.
2. Heij L, *et al.* (2012) Safety and efficacy of ARA 290 in sarcoidosis patients with symptoms of small fiber neuropathy: a randomized, double-blind pilot study. *Mol. Med.* 18:1430–6.

DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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