

SARCOIDOSIS REQUIRING SYSTEMIC TREATMENT: WHY NOT A STEROID-SPARING REGIMEN UP-FRONT?

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“Long-term use of prednisone, especially at high doses, can cause serious side effects (1).” We believe that this sentence, taken from the webpage on sarcoidosis on the NIH/NHLBI website, is probably an understatement. On the one hand, a majority of sarcoidosis patients respond favorably to oral prednisone at doses starting at 40 mg a day or less, with recommendation for steady reduction in dosage to 5-10 mg a day, before tapering off completely (2, 3). On the other hand, there is an unfortunate minority of patients whose condition does not respond, who remain on larger than desirable corticosteroid doses too long, and later on present with more advanced disease and more steroid complications. The negative impact of corticosteroid-related side effects in some patients with sarcoidosis is legendary among physicians who see a substantial number of subjects with this disease. This situation has probably arisen because many sarcoidosis patients are being treated by pulmonologists, or other healthcare providers, who have not had experience with, and feel comfortable in prescribing alternate anti-inflammatory regimens, such as are widely used in immunologically-mediated diseases, and in transplantation medicine.

The recent rheumatology and gastroenterology literature has had discussion about “step-up” and “step-down” regimens of drug combinations for rheumatoid arthritis, Crohn’s disease, and other chronic inflammatory diseases. “Step-up” refers to starting with a medication thought to be “gentler”, for want of a better term, then “stepping-up” with a more potent one if necessary. “Step-up” does not refer to starting with a lower dose of a medicine, then increasing it. “Step-down” or “top-down” means

starting with a more potent, steroid-sparing regimen at first, with the plan to later “step-down” the regimen when the patient’s inflammatory disease is improved (4-7). While the step-down approach has proven effective medically, as well as cost-beneficial in patients with other chronic inflammatory diseases, such an approach has not been well-studied, or studied at all, as far as we can determine, in patients with sarcoidosis. We hypothesize that the step-down approach, using a corticosteroid-sparing regimen upfront, will prove more effective than starting with corticosteroid alone, waiting until corticosteroid side-effects have occurred, and then to “step-up” to another regimen, either by adding another drug, or by making a complete change. At the least, we think that this is a question that should be properly studied.

An excellent review of drug treatment of sarcoidosis was published in the fall of 2008, with a thoughtful algorithm about drugs to be used in patients with severe single-organ or multi-organ disease who had failed topical therapy, or, in patients with extensive skin disease, who had failed to respond to hydroxychloroquine. It was proposed that such a patient be started on prednisone 20-40 mg daily as a single agent (8). Our thought is: “the sarcoidosis community” should organize therapeutic trials to address the step-down approach in the treatment approach in the type of patient referred to above.

Parallel studies can be designed comparing upfront treatment with (1) corticosteroids and methotrexate, corticosteroids and mycophenolate mofetil, and perhaps also “arms” using steroids and

azathioprine or leflunomide, versus corticosteroids alone. We propose using already established, although non-FDA approved treatment regimens.

Although for various reasons probably harder to carry out, an interesting and perhaps quite important arm would be a regimen of minocycline and an angiotensin II receptor blocker without corticosteroids, and compare it with the prednisone alone arm of the above trial, as well as the combination regimens. Both minocycline and angiotensin II receptor blockers have documented anti-inflammatory properties (9, 10), and minocycline already has been recommended for skin sarcoidosis.

Angiotensin II receptors are increased in patients with active sarcoidosis (11) and there is an unconfirmed suggestion that this type of drug may modulate symptoms of sarcoidosis (12). The hypothesis here would be that, for chronic sarcoidosis patients needing treatment, the combination of minocycline and an angiotensin II receptor blocker would be more effective, and have fewer and less severe side effects, than corticosteroid alone.

Our proposed approach has limitations. Because of the multiorgan nature of the disease, and the variability of the indications for therapy, it will surely take several hundred patients and a multicenter approach. The rheumatology community has been successful in the past in designing trials which allow physicians to work together in a multifaceted approach to investigate the pathogenesis and therapy of rheumatoid arthritis, scleroderma, and other entities.

This could be a model for what needs to be done in sarcoidosis. Our patients deserve the highest

standards of ethical, efficient, and rational research. Our key message is a call to arms to the sarcoidosis community to work together to provide the best for our patients.

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