Pro: The treatment of the granulomatous response is beneficial in acute sarcoidosis

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Introduction

Corticosteroids effectively suppress granulomatous inflammation in sarcoidosis. However, the role of corticosteroids remains unsettled nearly sixty years after the first report of their benefits. As in other contentious areas of medicine, we prioritize evidence from controlled clinical trials to guide decision-making. Despite the paucity of randomized, double-blind controlled evidence, the preponderance of data from the available trials is congruent: treatment of acute sarcoidosis is “on-balance” beneficial. To provide focus, I will limit my comments to recent-onset pulmonary sarcoidosis, defined as less than five years since diagnosis.

What are the benefits of treatment?

Targeted use of corticosteroids (CS) has been widely recommended in acute pulmonary sarcoidosis for patients with severe or progressive disease. This recommendation is based on decades of accumulated clinical experience, as well as several controlled trials that demonstrated clinically-important improvements of symptoms, chest radiographs and physiologic parameters. During long-term treatment, observational data confirmed that low-dose CS preserve lung function in both acute and chronic disease. Since fibrosis is thought to result from uncontrolled granulomatous inflammation, suppression of granulomas should prevent its development or progression. It is patently obvious that a placebo-controlled trial in patients with active disease and a fibrogenic phenotype would be unethical. On the other hand, most of the available data also suggest that treatment of patients with a high chance of good outcomes (e.g., Stage I CXR) does not confer substantial benefits.

In clinical practice the picture is not always so black-and-white. What should be done with patients who have disabling impairment of their quality of life from systemic symptoms, but without any at-risk organ? What about patients with modest physiologic impairment and mild to moderate symptoms? Some authors have suggested that these patients may also benefit from a short course of CS, under the rubric of a patient-led discussion about the pros and cons of therapy. If we took the viewpoint that treatment of non life-threatening disease somehow harms the patient, we might not favor any therapy for them. Should we be asking patients to delay relief of symptoms to allow more time for a spontaneous remission, a “natural deus ex machina”, to relieve us of making a decision?

Effect of treatment on the natural history

Controlled trials provide some information about whether more aggressive treatment influences the course of the disease. The first randomized, double-blind placebo-
controlled trial with long-term follow-up was conducted by Israel et al. in 90 African-Americans with recent-onset sarcoidosis and no immediate treatment indications. After a mean follow-up period of 5.3 years, the rate of serious relapse or progression was lower in patients randomized to three months of prednisone compared with placebo (24% vs. 38%). The final chest radiograph findings however, were not statistically different. When subsequent controlled studies of long-term outcomes failed to show a consistent durable benefit for corticosteroids, a general bias arose that corticosteroids do not influence the natural course of the disease. It is worth noting that none of these trials suggested a substantial long-term harm. Additionally, all the older studies suffer from multiple severe methodological flaws, including lack of placebo control, high rates of unaccounted drop-outs, fuzzy end-points, high proportions of patients with expected benign courses, and substantial under-powering. Indeed, data from similar idiopathic immune-mediated diseases, such as Crohn’s disease and rheumatoid arthritis, suggest that we may have been too un-aggressive with early therapy, rather than too aggressive, if the goal is to influence the natural history.

Two trials with more rigorous designs both suggest possible long-term benefits of early treatment. Pietinalho et al. randomized 189 newly-diagnosed Finnish patients to 3 months of prednisolone followed by inhaled budesonide for 15 months or to matching placebo. Over the subsequent 3½ year follow-up, treated patients with baseline Stages 2–3 CXR exhibited improvements in FVC and DLCO (net mean differences of −0.33L and −0.76 mmHg/kPa, respectively compared with placebo). In patients with more severe PFTs at baseline, the differences were greater and were apparent at the end of the three month systemic treatment period. During the follow-up period, 16/79 patients in the placebo group experienced a relapse, vs. 2/70 of the CS patients (p < 0.001). The results of this study are confounded by the sequential treatment with ICS, however, the bulk of therapeutic trials for ICS have been negative.

A British Thoracic Society (BTS) trial focused on acute sarcoidosis with persistent infiltrates and no immediate treatment indications. Of 183 patients with Stages 2–3 chest radiographs, 58 patients neither deteriorated nor improved during an initial six month observation period after diagnosis. The utility of the six-month time point has been confirmed in the ACCESS cohort, where the requirement for CS at six months was the strongest predictor of clinically bothersome disease at two years. These 58 subjects were alternately assigned to treatment with prednisolone (30 mg daily tapered to a goal maintenance dose of 10 mg daily, n = 27) or for 18 months or treatment only if there was definite deterioration (n = 31). The dose was adjusted to maintain the maximum radiographic improvement without intolerable side-effects. The number of patients requiring CS at the end of the trial was 5/27 in the treated group vs. 4/31 in the observation group. Dyspnea was less in the treatment group at 5 years, despite the absence of baseline differences in dyspnea. Fibrosis score increased in the observation group but decreased in the treatment group. FVC and Tlco both improved only in the treatment group. These two larger well-designed trials both point in one direction and accord with the early work by Israel et al.: long-term course is favorably affected by early use of CS but proof requires well-designed trials, rigorous follow-up, and adequate numbers of participants.

Are corticosteroids harmful?

Corticosteroids can cause toxicity and hypothetically may adversely affect the prospects for spontaneous resolution. Since the major toxicities of CS are dose-dependent, it follows that treatment strategies that minimize the cumulative dose will lead to a more favorable risk-benefit ratio. In a series of 181 patients followed longitudinally at Johns Hopkins, 91% were successfully maintained with <15 mg/d and 65% <10 mg/d of prednisone. Other authors also have suggested that pulmonary sarcoidosis should rarely require average prednisone doses >20 mg/d, and that tapering can start within one month. These observations suggest that many of the purported toxicities of corticosteroids may be a function of overly aggressive dosing regimens. Despite this fact, the data from most of the controlled trials do not support a major toxicity risk. When side-effects develop they are typically minor and reversible. For example, the median excess weight gain due to corticosteroids in controlled trials ranges from 3.6 to 5 kg, and there were no persistent differences between treated and untreated groups at 5 years in the BTS study. I agree with DeRemee that the toxicities of properly managed corticosteroid regimens are substantially over-stated. In addition, the advent of a range of effective steroid-sparing agents allows successful mitigation of many of the purported therapy-limiting toxicities.

Do corticosteroids prevent resolution of sarcoidosis? In a single-center retrospective series, relapse rates were 74% if corticosteroids were used to induce “remission,” whereas patients who had experienced spontaneous remissions relapsed only 8% of the time. Swedish Löfgren’s patients with HLA DRB1*03 relapsed more frequently if they were treated with CS. However, the implication that CS prevent remissions is not really borne out by the data available from the controlled trials. If treatment did prevent resolution of sarcoidosis, one would expect that subjects in the treatment arm of the CS trials would demonstrate worse outcomes, but they do not.

Conclusion

Having sarcoidosis approximately doubles the mortality rate; sarcoidosis mortality and morbidity in the U.S. and Europe are mainly related to progressive lung disease. For example, the effects of pulmonary sarcoidosis on quality of life are similar to those reported in survivors of ARDS, AIDS, end stage renal disease and moderate to severe COPD. Although there are trials that show no long-term benefits of early CS treatment, the most rigorous studies suggest lower rates of relapse, better lung function, fewer symptoms and less fibrosis. Importantly, there is no strong signal in the available studies to suggest a worse long-term outcome in the treated patients. While not advocating that every patient with recent-onset sarcoidosis should be treated, is the use of CS, on balance, beneficial? Some clinical
situations are clear-cut, but the reason this issue generates controversy is the existence of a large gray area. It is our opinion that the risks to the patient of progressive pulmonary disease are far weightier than the risks of steroid toxicity. In conclusion, the best data available now all suggest that the judicious and titrated use of CS is more likely to be beneficial than to be harmful. As the evidence suggests that the judicious and titrated use of CS is more likely to be beneficial than to be harmful. As the evidence suggests that the judicious and titrated use of CS is more likely to be beneficial than to be harmful. As the evidence suggests that the judicious and titrated use of CS is more likely to be beneficial than to be harmful. As the evidence suggests that the judicious and titrated use of CS is more likely to be beneficial than to be harmful. As the evidence

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