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Editorial

Endpoints in sarcoidosis: More like IPF or asthma?

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Sarcoidosis remains an enigmatic disease. Its cause is unknown, the indications for treatment are often unclear, and its natural history is variable. An additional important enigmatic issue that has hampered clinical sarcoidosis research is the failure to develop reliable and universally accepted clinical endpoints.

As pulmonary sarcoidosis is thought to be an interstitial lung disease, the traditional primary endpoint that has been selected for clinical trials is the forced vital capacity (FVC) [1,2], mirroring a common endpoint in clinical trials of idiopathic pulmonary fibrosis (IPF). Indeed, in a survey of sarcoidosis experts [3], the FVC was the consensus recommendation as the premiere clinical endpoint for pulmonary sarcoidosis trials.

There is strong clinical evidence supporting the FVC as a reliable clinical endpoint in IPF. Several studies of mixed groups of patients with IPF and fibrotic non-specific interstitial pneumonitis (NSIP) found that a serial decline in FVC over 6–12 months was associated with an increased mortality [4–7].

However, there are many important differences between IPF and pulmonary sarcoidosis that may not justify extrapolating the FVC endpoint from the former disease to the latter. First, IPF is a relentlessly progressive restrictive disease with a high mortality. In IPF, the FVC almost uniformly declines over time. Pulmonary sarcoidosis, other the other hand, is not necessarily progressive. In fact, in terms of spirometry, there is a tendency for it to improve, if not normalize over time in the majority of patients [8,9]. Second, pulmonary sarcoidosis is rarely fatal. The estimated age adjusted sarcoidosis-related mortality rate in the United States has been estimated between 3 and 6 per 1,000,000 [10]. Certainly, the FVC cannot be used as a surrogate biomarker for death in sarcoidosis. Third, although sarcoidosis is often classified as an interstitial lung disease, the disease may predominantly affect the airways and cause significant airflow obstruction [11,12]. Therefore, in a significant percentage of pulmonary sarcoidosis patients, the predominant symptoms and quality of life impairment are better reflected by physiologic measurements of airflow obstruction than by measurements of lung restriction such as the FVC. Fourth, unlike IPF which is an isolated pulmonary disease, sarcoidosis often has pulmonary and extrapulmonary manifestations. Therefore, the treatment of a pulmonary sarcoidosis patient is often directed at improving quality of life issues caused by associated a) extrathoracic sarcoidosis; b) parasarcoidosis syndromes [13] such as fatigue [14] and small fiber neuropathy [15]; and c) anti-sarcoidosis therapy, specifically corticosteroids [16,17] that are not recommended for the treatment of IPF [18]. The FVC does not accurately reflect these extrapulmonary manifestations of the disease.

To summarize, the prototypical patient enrolled in an IPF trial is an individual with significant dyspnea and functional impairment with a restrictive lung disease that is expected to worsen clinically and physiologically with a significant chance of death within the following 5 years. The prototypical pulmonary sarcoidosis patient enrolled in a clinical trial is an individual with pulmonary restriction and/or obstruction who has active granulomatous inflammation in the lung that responds to corticosteroids and other anti-granulomatous therapy. The pulmonary sarcoidosis patient's pulmonary function waxes and wanes over time, depending upon the dosing of corticosteroids [19] and other anti-sarcoidosis therapy. The pulmonary function of some of these patients will decline if their granulomatous inflammation is undertreated, and they may develop permanent reductions in pulmonary function from worsening lung fibrosis. However, this fibrosis is usually not imminently life-threatening and rarely causes rapid declines in physiology, as evidenced by the fact that the placebo group in several recent sarcoidosis trials (the majority of whom were receiving a maintenance dose of corticosteroids) did not demonstrate a significant decrement in FVC over the trial period [1,2].

This description of a pulmonary sarcoidosis trial participant displays many similarities to a patient with chronic asthma. Like sarcoidosis, chronic asthma is rarely fatal, with a mortality rate of less than 3/100,000 [20]. Although chronic asthma may result in acute exacerbations that dramatically reduce lung function, permanent lung damage usually does not develop acutely. Rather, progressive and permanent fixed airflow obstruction may develop over time in chronic asthma patients if the disease is undertreated (remodeled asthma). Although corticosteroids are very effective in asthma

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and are commonly used to treat acute asthma exacerbations, the side effects of corticosteroids make them unattractive for long-term use. Like the chronic sarcoidosis patient, the concerns in the chronic asthma patient are not primarily focused on the prevention of death but rather on quality of life impairment, the severity of symptoms, rate of exacerbations and the need for additional therapy. Because of these clinical asthma features, the forced expiratory volume in 1 s (FEV1) is not an ideal endpoint in asthma trials. More useful endpoints are the frequency of exacerbations, the need for rescue inhalers, corticosteroid dependence and dose, quality of life and asthma-related symptoms.

We would encourage consideration of similar endpoints in pulmonary sarcoidosis trials as in asthma trials that we believe more closely reflect important health issues of pulmonary sarcoidosis patients than those that can be extrapolated from the FVC. Potential endpoints that come to mind include quality of life measures, symptoms of cough, dyspnea, and wheeze, the frequency of exacerbations of sarcoidosis (requiring corticosteroid bursts or additional anti-sarcoidosis therapy), and corticosteroid-sparing effects of interventions.

Summary of conflict of interest of the authors

MAJ is a consultant for Biogen. No other author has a conflict of interest to disclose.

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Marc A. Judson
Division of Pulmonary and Critical Care Medicine, MC-91, Albany Medical College, Albany, NY 12208, USA
E-mail address: judsonm@mail.amc.edu