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Novel pharmacotherapy of sarcoidosis

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ABSTRACT

Sarcoidosis is a multisystem granulomatous disease of unknown etiology that most commonly affects the lungs. Treatment of sarcoidosis can be challenging as it is often difficult to measure disease activity and distinguish active inflammation from fibrosis. Identifying the inflammatory mediators in sarcoidosis has led to the development and use of novel therapeutic agents. The goal of pharmacotherapy is to decrease granuloma accumulation, ameliorate symptoms and improve organ function. Systemic corticosteroids remain the first line treatment. Other immunosuppressive agents may be considered for the patients who respond poorly to corticosteroids or who experience significant adverse effects. An overview of pharmacotherapy of sarcoidosis is provided here.

Contents

1. Introduction

Sarcoidosis, a multisystem disorder of unknown etiology is characterized by variable clinical features and course (Hunninghake et al., 1999; Iannuzzi et al., 2007). Sarcoidosis can affect any organ system but the lungs are most commonly involved (90% of patients). Other commonly involved organs are eyes (40%) and skin (30%). Neurologic and cardiac involvement occurs in 5% to 25% of patients and signifies poor prognosis (Iannuzzi & Morgenthau, 2001). Sarcoidosis is most firmly diagnosed in the presence of consistent clinic-radiological features and non-necrotizing granulomas on biopsy of an affected organ and after excluding known causes of granulomatous disease. Pathogenesis involves the interplay of environmental and genetic factors. Because sarcoidosis often spontaneously resolves, asymptomatic patients may not require treatment. Corticosteroids have remained the first line drugs for those who require treatment. For patients who respond poorly to corticosteroids or who experience adverse effects, other immunosuppressive agents are available.

2. Immunopathogenesis of sarcoidosis (Fig. 1)

Sarcoidosis is thought to be caused by the interaction between environmental and genetic factors. Possible environmental antigens include infectious, organic, and inorganic agents. One possible explanation for the difficulty in identifying the sarcoidal antigen is that the causative agent is cleared but leaves behind an undegradable product that initiates a cross-reacting immune response to self-antigen. The disease likely begins with CD4+ T cells that interact with antigen presenting cells (APCs) to initiate granulomas formation and accumulation. APCs, in addition to producing high levels of tumor necrosis factor alpha (TNF-α), secrete interleukin-12, -15, and -18, macrophage inflammatory protein 1(MIP), monocyte chemotactic protein 1 (MCP-1), and granulocyte

Abbreviations: IL, Interleukin; PFT, Pulmonary function test; FVC, Forced vital capacity; DLCO, Diffusion capacity of carbon monoxide; CBC, Complete blood count; LFT, Liver function test; MTX, Methotrexate; AZA, Azathioprine; TPMT, Thiopurine S-methyltransferase; TNF-α, Tumor necrosis factor-alpha; NSAID, Non-steroidal anti-inflammatory drug; AICD, Automatic implantable cardiac defibrillator.

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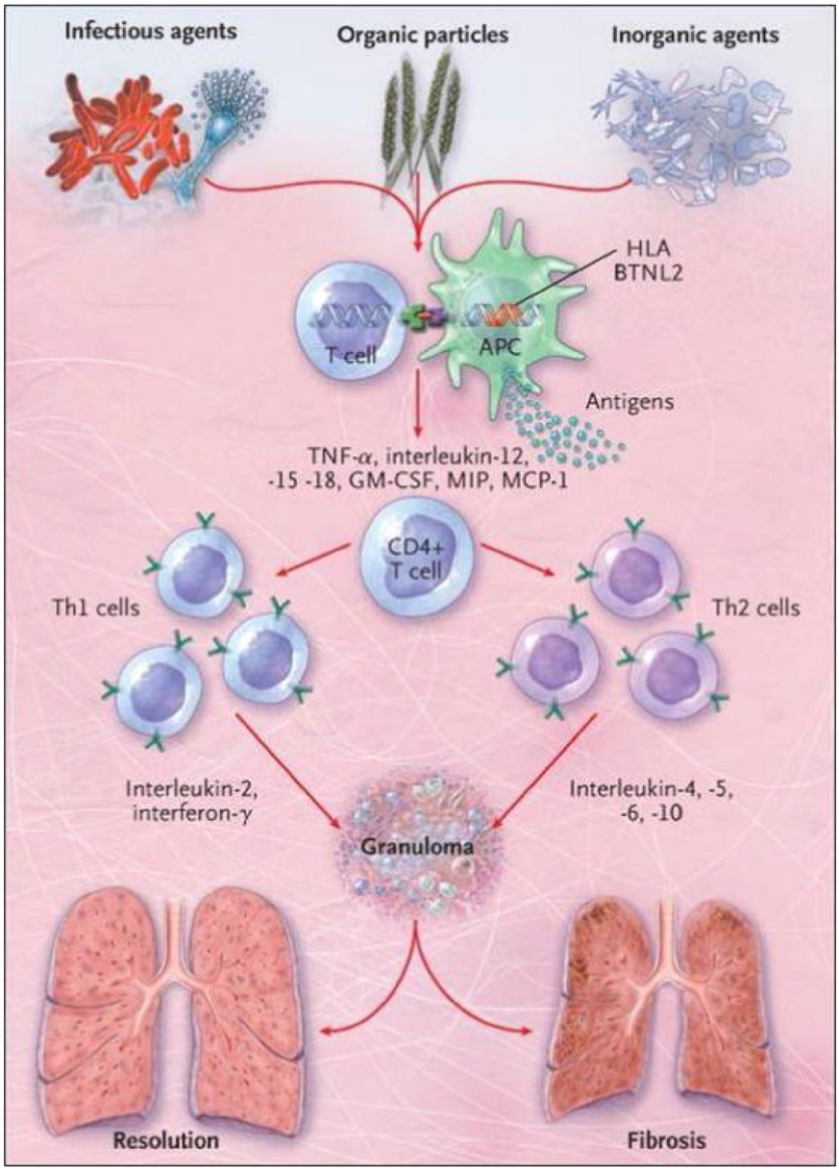

Fig. 1. Hypothetical model of the immunopathogenesis of sarcoidosis and immunologic rationale for treatment of the disease (Reproduced from Iannuzzi MC et al. N Engl J Med 2007; 357:2153–2165).

macrophage colony-stimulating factor (GM-CSF) (Agostini et al., 2000). Activated CD4+ cells secrete interleukin-2 and interferon-γ. Genetic factors likely control the efficiency of antigen processing and presentation and cytokine release. Evidence strongly supports a role for MHC class II and III genes in sarcoidosis susceptibility and phenotype (Rybicki et al., 2005; Valentonyte et al., 2005). Sarcoidal granulomas are organized, structured masses composed of a centralized collection of macrophages and their derivatives, epithelioid cells and giant cells, surrounded peripherally by T cells. Sarcoidal granulomas may persist, resolve, or lead to fibrosis. Alveolar macrophages activated in the context of a predominant type 2 helper (Th2) T-cell response appear to stimulate fibroblast proliferation and collagen production, leading to progressive fibrosis (Iannuzzi & Fontana, 2011).

3. Treatment of sarcoidosis

Spontaneous remission occurs in over 50% of patients. Patients with no or mild symptoms generally do not require treatment but should be monitored for signs of deterioration. Patients should be followed with pulmonary function tests (Spirometry), and markers of extrathoracic involvement (e.g. serum calcium and liver function tests, annual fundoscopic and slit lamp ophthalmologic evaluation).

Patients who require systemic treatment include those with

- Worsening symptoms,
- Limitation of activity,
- Markedly abnormal or deteriorating organ function,
- Neurologic or cardiac involvement,
- Posterior uveitis,
- Laryngeal involvement,
- Hypercalcemia and hypercalciuria,
- Disfiguring skin lesions

Identification of the inflammatory mediators in sarcoidosis has led to the use of pharmacotherapeutic agents (Table 1). Currently there is no clear evidence that indicates the efficacy of one agent over others. The goal of pharmacotherapy is to decrease granuloma accumulation, ameliorate symptoms and improve organ function. Oral corticosteroids are the mainstay of treatment. Although corticosteroids reduce symptoms and may slow disease progression, no evidence exists that they prevent fibrosis.