Author's response to reviews

Title: Systemic autoimmune disease in asbestosis rapidly responding to anti-interleukin-1beta antibody canakinumab

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Dear Editor
BMC Musculoskeletal Disorders

Re: MS: 1150558630149144
Title: Systemic autoimmune disease in asbestosis rapidly responding to anti-interleukin-1beta antibody canakinumab.
Laura Niccoli, Emanuele Cassarà, Olga Kaloudi, Carlotta Nannini, Micaela Romagnoli and Fabrizio Cantini

Dear Editor:
thank you for your kind message of February 24, 2015.
I agree with your suggestions and have modified the manuscript accordingly.
All changes in the revised manuscript have been highlighted in bold.
Each modification has been approved by all authors.
I trust the paper can now be accepted for the publication in BMC Musculoskeletal Disorders.
I look forward to receiving a reply as soon as possible.

Yours sincerely,

Fabrizio Cantini MD

Reviewer 1: Charles Dinarello.

1. Reviewer’s concern: “Why we did not measure IL-1#”. Circulating IL-1# measurement is not available in our laboratory. However, due to its intracellular or cell membrane location, we believe that serum levels of IL-1# measurement is not a reliable expression of tissue inflammation.

2. According to the reviewer’s suggestions we modified the text (line 146 to 163) as follows: “Over the last decades, experimental studies have shown the crucial role exerted by IL-1 in pulmonary homeostasis and pathology 16,17. The IL-1 family is composed by IL-1alpha and IL-1beta, two major agonistic molecules, and IL-1R antagonist (IL-1Ra) that bind to the same IL-1 receptor 18. IL-1alpha precursor, which is present intracellularly in healthy tissues and during hypoxic death (but not in apoptosis), is released from cells undergoing necrosis and is biologically active, while IL-1beta precursor is produced by monocytes and macrophages, and it is activated after cleavage by caspase 1 which in turn is activated by NALP3 inflammasome 18. Regarding the lung, experimental studies have shown that in absence of inflammatory stimuli, alveolar type II cells enhance the production of prostaglandin E2 which in turn inhibits fibroblast proliferation through an IL-1 alpha mediated pathway 19. Under inflammatory stimuli such as silica or asbestos inhalation, IL-1 beta seems to play a pivotal role in the pathogenesis of fibrosis and mesothelioma 10. Indeed, inhaled silica or asbestos are captured by macrophages with activation of NALP3 inflammasome which induces the conversion of procaspase 1 in an active form to cleave the IL-1 beta precursor in active IL-1beta with consequent fibrotic nodules formation 10,20. IL-1beta is also involved in T-lymphocyte activation with subsequent dysregulated autoimmunity and autoantibody production 21. An increased release of IL-1beta by alveolar macrophages in patients with asbestosis was reported around 20 years ago 16, and increased serum levels have been found in coal workers with pneumoconiosis and in cement mason apprentices 22,23.” We added references 17,18,19,20,22,23.

3. Reviewer’s concern: “Recent papers on anti-IL1 alpha and why we did not use anakinra”. According to these suggestions we changed the text as follows (line 164 to 174): “Based on the consistent body of evidence of the pathogenic role of inflammasome-dependent release of IL-1beta in patients with asbestosis and related systemic autoimmune disease, we decided to treat our patient with canakinumab, a specifically targeted anti-IL-1beta antibody, which has been licensed for the treatment of inflammasome-mediated autoinflammatory syndromes 24. The dramatic improvement of clinical features and acute phase reactants over 1 week encouraged us to continue the treatment, and, at the 4-month visit, the patient achieved clinical remission. Similar favorable results have been recently reported in a patient with silicosis treated with anakinra, an IL-1 receptor antagonist acting on both IL1 alpha and IL-1 beta 25. Differently from this report, given the central pathogenic role of IL-1 beta, we decided to
employ canakinumab due to its selective action directed against this cytokine, and, according to patient’s preference, for its lower frequency of administration.” Reference 25 was added.

Reviewer 2: Takemi Otsuki.

1. Reviewer’s concern: diagnosis of asbestosis. We agree with the reviewer that pleural plaques in our patient indicate past asbestos exposure and that the diagnosis of pulmonary asbestosis should satisfy the ILO radiological criteria. We believe that our patient had a mild form of asbestosis with slight impairment of respiratory function and prominent asbestos-induced systemic autoimmune features. According to the reviewer we modified the text as follows (line 106) “a diagnosis of mild asbestosis with prominent asbestos-induced systemic autoimmune disease features was made”.

2. Line 57-63. Reviewer’s concern: Silicosis as most frequent cause of autoimmune disorders. We agree with the reviewer’s suggestion and we modified the text as follows: “Among pneumoconioses, silicosis represents the most frequent condition inducing systemic autoimmune disorders 3. However, also asbestosis is known to be associated with serum antinuclear antibody (ANA), rheumatoid factor (RF) positivity 4, and may be complicated by autoimmune diseases such as systemic lupus erythematosus (SLE), systemic sclerosis and rheumatoid arthritis (RA) are 5-7. We added also the reference 3 “Otsuki T, Maeda M, Murakami S, Hayashi H, Miura Y, Kusaka M, et al. Immunological effects of silica and asbestos. Cell Mol Immunol. 2007;4:261-268.”