Author's response to reviews

Title: Efficacy of inhibition of IL-1beta in patients affected by rheumatoid arthritis and type 2 diabetes mellitus: cases report and discussion of literature

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Author's response to reviews:

Prof. Michael Kidd
Editor of Journal of Medical Case Reports

Sir,

enclosed please find a paper entitled “Efficacy of inhibition of IL-1# in patients affected by rheumatoid arthritis and type 2 diabetes mellitus: cases report and discussion of literature” which has been written by myself and co-workers. We would like to submit it for publication as a case report in Journal of Medical Case Reports. The manuscript has not been submitted or published elsewhere. All authors have approved the manuscript and agree with its submission to Journal of Medical Case Reports. All the Authors have disclosed no conflict of interest.

In this paper, we reported the positive effects of the inhibition of IL-1#, in 2 rheumatoid arthritis patients, affected by type 2 diabetes mellitus reaching both the therapeutic targets of the diseases, using a single biological agent, and tapering or discontinuing their antidiabetic therapies.

To our knowledge, this is the first report showing that targeting IL-1# might be considered a good therapeutic option in rheumatoid arthritis associated to type 2 diabetes mellitus patients.

We believe our findings would appeal to the readership of Your Journal because of, recently, it has been show that an expanding spectrum of diseases is responsive to IL-1# inhibition such as type 2 diabetes mellitus. In this context, the evidence that IL-1# was toxic for the insulin-producing #cell begins in 1985. This was a milestone report that advanced the field of “soluble factors” from mononuclear phagocytes playing a pivotal role in the pathogenesis of diabetes.
Soon thereafter, recombinant human IL-1# was shown to account for the death of the #-cell while sparing the #-cell. Hence, in 2007 the first clinical proof of a role for IL-1# in the pathogenesis of type 2 diabetes was reported by Larsen and co-workers which performed a randomized, placebo-controlled study of Anakinra, a human IL-1 receptor antagonist, for 13 weeks. In that study, improved insulin production and glycemic control was observed in Anakinra-treated patients. The fall in glycated hemoglobin was nearly 0.5% lower than that in placebo-treated patients. In addition to improved glycemic control, C-peptide levels increased and the ratio of proinsulin to insulin decreased, both indicators of improved #-cell function.

Furthermore, as far as the role of IL-1# in rheumatoid arthritis is concerned, IL-1# is expressed in abundance in the synovial membrane and it is well known that it in vitro is able to induce cytokines production by synovial mononuclear cells, and bone erosions by osteoclasts that are the typical hallmark of rheumatoid joint damage. On these bases, Anakinra has been found in a number of studies to significantly improve clinical signs of rheumatoid arthritis and was FDA approved in 2001 for moderately-severe rheumatoid arthritis with at least one failed DMARD therapy.

This paper points out that, Anakinra, prescribed for the treatment of relapsing rheumatoid arthritis, in 2 rheumatic patients with associated type 2 diabetes mellitus, controls not only the clinical pictures of rheumatoid arthritis, but also their metabolic status. In fact, in our patients, we observed that a single biological agent, administered to treat rheumatoid arthritis, showed the ability to control their metabolic disorder reaching both the therapeutic targets of the diseases, and tapering or discontinuing their antidiabetic therapies. These findings suggest that targeting IL-1# might be considered a good therapeutic option in these patients. In addition, an open, randomized, controlled, double-arms, multi-center study, whose primary endpoint is the efficacy of Anakinra in controlling signs and symptoms of type 2 diabetes mellitus, in rheumatoid arthritis patients affected by this metabolic disorder, is actually ongoing in our country (TRACK study, NCT02236481, www.clinicaltrial.gov).

On these bases, this paper might suggest the role of IL-1# in patients affected by rheumatoid arthritis associated to type 2 diabetes mellitus, and might suggest a possible target therapy in these patients. Furthermore, it may advance our understanding in management of patients affected by both rheumatic and metabolic diseases and it could be of interest in many areas of medicine such as rheumatology, diabetology and internal medicine.

Please let me know of your decision at your earliest convenience.

With my best regards,

Sincerely yours

Piero Ruscitti