A new treatment approach to fibrodysplasia ossificans progressiva patients - the canakinumab experience

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INTRODUCTION

Fibrodysplasia ossificans progressiva (FOP), is the most catastrophic form of heterotopic ossification (HO), due to an ongoing intracellular signaling through the bone morphogenic protein pathway. Painful swellings usually appear by the age of 3-4 years (Fig. 1), but the typical bilateral greater toes deformity can be noted at birth (Fig. 2). Unfortunately, there is no effective prophylactic treatment to change the course of this disease. The recurrent paroxysmal appearance of inflammatory "lumps", and the fact that macrophages derived from FOP patients are in a pro-inflammatory state, as reported before, hint that FOP "behaves" as an auto-inflammatory disease.
Moreover, interleukin 1 (IL1) has been linked to the mineralization of human and mice bone marrow mesenchymal cells.

OBJECTIVES

To lower the rate of FOP flares, and limit the symptoms and residual lesions, by using the anti- IL1β agent canakinumab (CKB).

METHOD

Patients' data were analyzed, to characterize the efficacy of CKB in ameliorating the progression of FOP

RESULTS

Three FOP patients are currently treated with CKB 4mg/kg/month, with a total experience of over 4 patient yrs. Markedly lowered rate of HO flares was documented: once monthly (vs. 3-4/month) in the male patient and almost none (vs. once monthly) in both female patients. In general, **no** new HO sites were documented, but existing HO sites may kept growing under CKB, although growth rate was much lower, & response to corticosteroids was better (less doses were needed). Some of the cartilaginous lumps were diminished under CKB alone. While unmeasurable levels of IL-1β were found in the 3 plasma samples obtained from the 1st patient during treatment, high levels of IL-1b (~90-fold higher compared to average levels of healthy controls) were found during a flare, after CKB treatment was withheld for 7.5 weeks (Fig. 3).

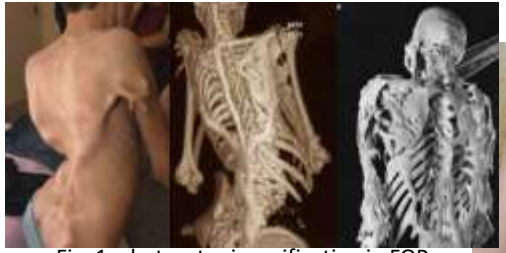

Fig. 1 – heterotopic ossification in FOP

Fig. 2 – greater toes deformity

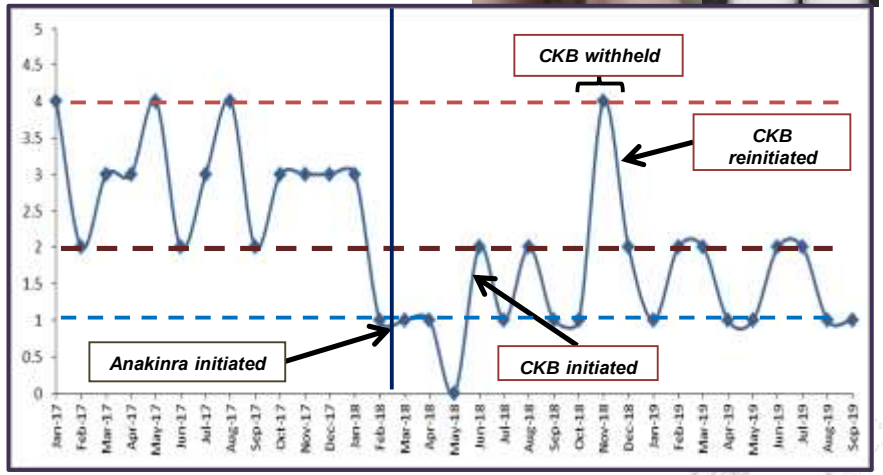

Fig. 3 – Number of FOP heterotopic ossification flare-ups per month in patient #1

CONCLUSIONS

Our data may suggest that FOP flares are mediated by IL-1β, & that anti-IL-1 agents may have a role in ameliorating the natural FOP progression. FOP itself may be included under the umbrella of auto-inflammatory syndromes in the future, but further international exploration with other patients is needed.