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Case Report
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Low Back and Buttock Pain in a NOMID/CINCA Syndrome Patient Under Canakinumab Therapy - Time for Another Biologic?

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Abstract

Introduction: NOMID/CINCA Syndrome (Neonatal Onset Multisystem Inflammatory Disease/ Chronic Infantile Neurologic Cutaneous and Articular Syndrome) is a rare inflammatory periodic fever syndrome responding to treatment with IL-1 antagonists. Axial Spondyloarthritides (axSpA) are a group of diseases responding to TNF (Tumor Necrosis Factor alpha) or IL-17 antagonists. Overlap syndromes of these two entities have, so far, not been described. Of importance, NOMID/ CINCA syndrome does not respond to treatment with TNF antagonists and only a small subgroup of axial spondyloarthritides may respond to IL-1 antagonists.

Combination therapy of anakinra, an IL-1 antagonist, and the TNF antagonist etanercept, was associated with an increased rate of infections in RA patients.

Case Report: A 25-year-old woman with NOMID/CINCA-syndrome successfully treated with canakinumab developed inflammatory back pain and was, subsequently, diagnosed with axial spondylarthritis. After an ineffective therapeutic approach with both initial intra-articular spinal glucocorticoids injections and, subsequently, sulfasalazine, etanercept was initiated. Under this combined etanercept and canakinumab treatment both diseases, NOMID/CINCA-syndrome and axial spondylarthritis, were controlled and no severe infection developed.

Conclusion: In summary, this case demonstrates a favorable response to treatment with canakinumab and etanercept in combination in a patient with an overlap syndrome of NOMID/ CINCA-syndrome and axial spondylarthritis with an acceptable safety profile. Such a combination therapy should be given with care and after other therapeutic alternatives failed.

Keywords: Canakinumab; Etanercept; NOMID/CINCA syndrome; Axial spondylarthritis

Introduction

NOMID/CINCA syndrome (Neonatal Onset Multisystem Inflammatory Disease/Chronic Infantile Neurologic Cutaneous and Articular Syndrome) is a rare inflammatory periodic fever syndrome, formerly also known as Prieur-Griscelli syndrome [1]. It presents with arthritis, skin rashes, non-infectious meningitis, hearing loss, papilledema, increased intracranial pressure with headache, nausea and vomiting, and mental retardation/lack of intellectual development among other signs and symptoms. Caused by a mutation in the CIAS1 gene, which leads to an uncontrolled activation of caspase-1 and cleavage of pro-IL-1 to active IL-1 [2], its onset is in the newborn. CIAS1 mutations are associated with a group of diseases, Cryopyrin-Associated Periodic Syndromes (CAPS), which have manifestations of different severity, from the least severe kerato-endotheliitis fugax hereditaria to Familial Cold Auto-Inflammatory Syndrome (FCAS), Muckle-Wells Syndrome (MWS), and the most severe form, NOMID/CINCA-syndrome. All of these can be treated successfully with IL-1 antagonists [3] [4]. Data on effective treatment of NOMID/CINCA-syndrome with TNF antagonists are sparse.

Axial Spondyloarthritides (axSpA) are HLA B27 associated diseases comprising ankylosing spondylitis, psoriatic arthritis, reactive arthritis and enteropathic spondyloarthritis. All of these may present with arthritis, enthesitis, dactylitis, sacroiliitis, uveitis, psoriasis, and inflammatory bowel disease. First-line treatment of spondyloarthritis is with NSAIDs [5]. If unsuccessful, conventional synthetic Disease Modifying Drugs (csDMARDs) are used for peripheral joint involvement. For axial skeletal symptoms, second-line therapy is with biologics such as TNF (Tumor Necrosis

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Factor Alpha) or IL-17 antagonists. The use of IL-1 antagonists was successful in a small subgroup of axSpA patients [6]. However, IL-1 antagonists have never been used systematically in axSpA patients.

Overlap syndromes in rheumatology frequently involve connective tissue diseases, e.g. SLE, myositis, or scleroderma, or arthritis for example RA. Overlap syndromes are two different entities that may develop from a similar pathway, e.g. different connective tissue diseases. However, an overlap syndrome or a potential co-existence of an axSpA and an auto-inflammatory syndrome has, so far, not been described to our knowledge.

Case Presentation

We present a 26-year-old female patient with NOMID/CINCA-syndrome, whose symptoms began early after birth. She suffered from recurrent urticaria, peripheral arthritis, hearing loss, chronic systemic inflammation, papilledema, and growth retardation during the first years of her life. At the age of 15 years, genetic testing of CIAS1 showed the T348M mutation, so that NOMID/CINCA-syndrome was diagnosed. Specific therapy with the IL-1 receptor antagonist anakinra 100 mg daily s.c. was established, which resolved all signs and symptoms of NOMID/CINCA-syndrome, except for hearing loss. Growth retardation was subsequently caught up. As the patient suffered aversion to the daily anakinra injections, it was replaced with canakinumab 150 mg s.c. every two months.

At 26 years of age our patient developed inflammatory low back and buttock pain at rest and during the night. Magnetic Resonance Imaging (MRI) of the lumbar spine showed facet joint inflammation, for which intra-articular injections with local anesthetics and glucocorticoids were ineffective. On evaluation of the MRI images, active sacroiliitis on the right side was detected in the TIRM sequences (Figure 1), which fulfilled the ASAS criteria [7]. HLA-B27 tested positive on PCR analysis, establishing the diagnosis of axSpA. When symptoms did not respond to sulfasalazine, this drug was discontinued and etanercept started in addition to canakinumab. The inflammatory back pain symptoms improved rapidly, but recurred when etanercept was temporarily discontinued due to pharyngitis caused by a conventional coronavirus. No other infections were noted during a total of 12 months of combination therapy with canakinumab and etanercept until today.

Discussion

To our best knowledge, this is the first description of a patient with NOMID/CINCA-syndrome and concomitant axial SpA that improved after the addition of etanercept to ongoing treatment with canakinumab. This combination was effective and appeared to be safe in our patient.

Overlap syndromes of different autoimmune diseases are a rare but well-known phenomenon [8]. In this case it is, however, interesting that two diseases, namely, NOMID/CINCA and axSpA, developed subsequently. Both have completely different central cytokines in their pathogenesis: IL-1 and TNF. Whether this is rather an overlap syndrome or co-existence of two immunological or inflammatory diseases, respectively, remains open. This discussion, however, is not relevant to the treatment decision in this case.

A therapeutic approach to treat two different diseases, responding to IL-1 (NOMID/CINCA) or TNF antagonists (axSpA), but not *vice versa*, is a difficult task. Therefore and because of fearing potential adverse events, this combination therapy was initially not introduced.

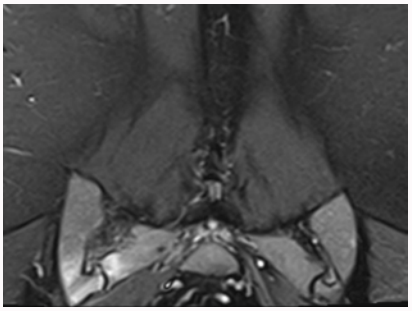

Figure 1: Short Tau Inversion Recovery (STIR) sequences in a transversal MRI of the lumbar spine and the sacroiliac joint. Bone marrow edema (hypersensitivity) can be detected on 4 subsequent slides of the right sacroiliac joint.

Only after failure of sulfasalazine and injections into the facet joints, the clinical need required escalation of the therapeutic strategy with a TNF antagonist. The good efficacy of the canakinumab - etanercept combination therapy proved that this decision was correct in this case.

Genovese et al showed that combination therapy of anakinra with the TNF antagonist etanercept [9] provided no additional benefit in RA patients. However, combination therapy of anakinra and etanercept was associated with an increased risk of adverse events as compared to etanercept monotherapy treatment in the studied RA patients. The severe infection rate of 7.4% in the combined anakinra and etanercept of RA patients [9] was increased compared to none in the etanercept monotherapy group for infections requiring antibiotic therapy in the Genovese study with a follow up of 6 months. On the other hand, this means that 92.6% of the patients did not suffer from such severe infection. Still, as this rate is increased the decision of an anakinra and etanercept combination therapy should be taken with circumspect and reasoning. Therefore, we initially hesitated to combine canakinumab and etanercept, introducing the latter only after the unsuccessful use of sulfasalazine. The treatment, however, was safe until today in our patient.

As an alternative, tofacitinib could be considered, as it successfully antagonizes IL-1 and has been shown to be effective for axSpA [10]. However, these data had not been published at the time we took the decision for the canakinumab - etanercept combination therapy.

Conclusion

This patient's favorable response to the treatment with canakinumab - etanercept combination therapy shows that, in rare situations, such a combination therapy can be given with reasonable safety. However, this decision has to be taken with care and after trying potential alternatives.

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