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Comparison of an "On-Demand" Canakinumab regimen with fixed-frequency Canakinumab in treating colchicine-resistant familial Mediterranean fever in children: a multicenter study

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Introduction: Canakinumab, an inhibitor of interleukin-1 (IL-1b), has shown to be safe and effective in preventing attacks of familial Mediterranean fever (FMF) in individuals with colchicine-resistant (crFMF). The manufacturer recommends monthly subcutaneous injections as the standard prescription. Nevertheless, a specific group of our patients receives treatment through an "on-demand canakinumab" (COD) strategy, which involves longer intervals between drug administrations.
Objectives: This multicenter study aimed to compare the disease activity and drug safety between an "on-demand canakinumab" (COD) strategy and a "fixed-frequency canakinumab" (CFF) strategy for the treatment of children with colchicine-resistant familial Mediterranean fever (crFMF).
Methods: A retrospective analysis was conducted using data collected from three Israeli pediatric rheumatology centers. The study included children under 18 years of age with crFMF who received canakinumab treatment. Demographic parameters, clinical characteristics, cumulative drug dosages, and adverse events were compared between children treated with COD and CFF strategies.
Results: Out of the 51 children included in the study, 25 (49%) were treated with the COD strategy, while 26 received the CFF strategy. The demographic parameters and most disease features did not significantly differ between the two groups. Both strategies demonstrated a significant reduction in FMF attacks after the introduction of canakinumab. The median number of attacks per month did not significantly differ between the COD and CFF groups (0.33 (0.08, 0.58) vs. 0.13 (0, 0.5), respectively, P=0.485). However, the mean monthly dose was lower in the COD group compared to the CFF group (1.13±1.13 vs. 3.16±1.46 mg/kg, $p < 0.001$). Adverse events were similar between the two groups.
Conclusion: The COD strategy for individuals with crFMF achieved comparable efficacy and safety to the CFF strategy, while requiring a lower accumulated dose of canakinumab. This suggests that the COD regimen may be a less immunosuppressive and more cost-effective approach for treating children with colchicine-resistant familial Mediterranean fever.

Patient Consent
Not applicable (there are no patient data)

Disclosure of Interest
None declared

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Haploinsufficiency A20: a novel mutation with unusual presentation

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Introduction: A20 is a protein encoded by the tumor necrosis factor alpha-induced protein-3 gene (TNFAIP3), that plays a key role in the inhibition of pro-inflammatory moleculeS. Loss of function mutations in this gene, causing A20 haploinsufficiency, lead to Behçet-like phenotypes, although disease manifestations may vary widely.
Results: A 15-year-old female with history of "PFAPA-like" episodes from 3 to 5 years of age, presented with a 12-month history of recurrent mensal episodes of fever, asthenia, anorexia, odynophagia, cervical lymphadenopathies and abdominal pain, lasting up to 3 days. She also reported genital aphthous lesions in 2 events. Additionally, she mentioned a 2-month history of right omalgia, with periods of ipsilateral intermittent clavicular tumefaction. Familiar history was irrelevant. Complementary investigation revealed a moderate increase in inflammatory markers (maximum CRP 121mg/L and serum amyloid A 8 mg/dL), with normalization between episodes. Bone MRI and scintigraphy showed signs of sternoclavicular inflammatory arthropathy. Arthrocentesis was performed, showing negative cultural exams and no neoplastic cells on anatomopathological evaluation. Considering the possibility of non-bacterial chronic osteomyelitis (CNO), treatment with naproxen was started.
In the following months, although partial improvement in sternoclavicular arthritis, recurrent fever persisted with reported oral ulcers in one episode. Immunogenetic study revealed HLA-B15 positivity. Considering a possible overlap of CNO with Behçet's disease, colchicine was initiated.
As episodes kept occurring monthly, the patient underwent treatment with azathioprine, up to a maximum dose of 100 mg/day (~2 mg/kg/day). After 6 months of disease improvement (less intense and frequent attacks), crisis reemerged with the prior periodicity, with sternoclavicular arthritis worsening in episodes. Next generation sequencing panel for autoinflammatory diseases revealed a novel heterozygotic variant c.1632T>C in the TNFAIP3 gene. Parents genetic testing is currently pending. Treatment with adalimumab was initiated with complete resolution of inflammatory episodes and sternoclavicular arthritis - currently with 4 months follow-up.
Conclusion: A20 haploinsufficiency is a diagnosis with growing recognition as an important monogenic mimic of Behçet's disease. Genetic evaluation should therefore be considered in atypical cases. Although we report a novel mutation, and while sternoclavicular arthritis is not a described feature of this disease, we believe it may be connected with the inflammatory bursts. Parents genetic evaluation will bring us new insight regarding this matter.

Patient Consent
Yes, I received consent

Disclosure of Interest
None declared

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Familial Behçet-like autoinflammatory disease-3 (AIFBL3), caused by heterozygous mutation in the rela gene: a case report

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Introduction: The autoinflammatory features of Behçet's disease (BD) and the role of innate immunity dysregulation have been highlighted

and BD can be considered as the crossroad of autoinflammatory and autoimmune diseases.
Objectives: We describe the case of a 9-year-old caucasic male, who presented at age 6 y with recurrent episodes of fever, oral ulcers and pain at the limbs, hands, wrists. At the physical examination the child showed functional limitation of flexion and extension movements of the wrists (left > right) and a bilateral mild joint stiffness of the shoulders. He showed a mild delay in the stages of psychomotor development, and a mild hypotrophy of the muscles of the lower limbs.
Methods: The metabolic disease expert excluded metabolic diseases, based on the metabolic diagnostic investigations. Ultrasound documented knees joint effusion in the lateral supra-patellar seat with synovial membrane's thickening and evident right knee synovial phlogosis, minimal on the left. A Whole body MRI, reported intra joint fluid effusion in external lateral seat and in sub patellar seat of the left knee. Intraspongious edema of the cuboid of the right foot. The eye examination with slit lamp was normal; HLA-B27, Anti-streptolysin O titer, pharyngeal swab and specific serologies for infectious diseases were negative. Fecal calprotectin was normal. Antinuclear antibodies (ANA) were positive 1:320 with a granular pattern.
Results:
The genetic study in NGS for autoinflammatory diseases revealed a heterozygous mutation, defined as VUS, of the RELA gene: c.1537C>G (p.Pro513Ala). Mutations of the RELA gene are associated with a familiar autoinflammatory disease Behçet's disease (BD)-like type 3, with an autosomal dominant transmission. The Familial Behçet-like autoinflammatory disease-3 (AIFBL3), caused by heterozygous mutation in the RELA gene on chromosome 11q13, is characterized predominantly by chronic mucocutaneous ulceration.
Conclusion: The patient did not yet fulfil the paediatric BD (PEDBD) nor ICBD criteria for the diagnosis of paediatric BD, however it is well described that BD is an evolutionary disease, and clinical manifestations may appear over the years (1-3).
Monogenic BD-like conditions are increasingly recognized and to date have been found to predominantly involve loss-of-function variants in TNFAIP3. This case describes a child carrying the RELA gene mutation, with clinical symptoms evoking BD. The RELA gene mutations are conditions related to dysregulated NF-κB activation and need a strict follow-up and a prompt start of treatment, also in patients who do not fulfil the diagnostic criteria for BD.

Patient Consent
Yes, I received consent

Disclosure of Interest
None declared

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BD-like disease associated with TNFAIP3 gene mutation: a case report
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Introduction: Behçet's disease (BD) is a chronic, multifactorial systemic vasculitis with a strict link with autoinflammatory and autoimmune diseases. It can affect various organs and tissues, with recurrent oral and genital ulcers, skin lesions, joint pain and swelling (1), eye inflammation, gastrointestinal disease (2-3). Monogenic BD is a rare subtype of the disease, shows an earlier age of onset and a more severe disease course. One gene associated with monogenic BD is TNFAIP3, encoding A20, a protein regulating inflammation and immune response. Loss-of-function mutation in TNFAIP3 triggers a new autoinflammatory disease: HA20, characterized by a wide range of clinical pictures, caused by chronic inflammation, as BD.
Objectives: We describe the case of a 11-year-old boy firstly diagnosed at the age of 9 years, with hypertension, secondary to renal arteries stenosis, ascending aortic ectasia, celiac trunk ectasia, superior mesenteric artery stenosis, documented by ecocolordoppler, angio-MRI and angio-TC. The first suspected diagnosis was Takayasu arteritis. The mother received the diagnosis of SLE, the maternal grandmother had Moschowitz disease.
Methods: For the start of limbs pain, periodic attacks of fever, oral aphthae he was referred to the Pediatric Rheumatology unit. He did not present swelling of knees, ankles, wrists, fingers, conformed by echography.
Results: MRI documented bilateral sacroiliitis, confirmed the preexisting vascular lesions, showed slightly thickened walls of sigma, with signs of inflammation. The eye examination with slit lamp was normal. He showed positive ENA, anti-C1q, anti-cardiolipin, anti-thyroglobulin, anti-thyroid peroxidase antibodies. SAA 22 (nv<6). HLA-B51 is absent.
The genetic molecular analysis of autoinflammatory diseases, showed a heterozygous variant of TNFAIP3 classified as VUS (p.Ala545Val) with maternal segregation. Pathogenetic variants of TNFAIP3 gene are related to a dominant inherited familial autoinflammatory syndrome BD-like.
However, despite the severity of the clinical picture, the patient did not yet meet neither ICBD, nor ISG, nor PEDBD diagnostic criteria. However, the genetic background, the family history and the severe vasculitis guide the diagnosis in this challenging case.
Conclusion: The correlation between TNFAIP3 and Takayasu or SLE was recently proposed, however, our patient developed clinical signs, as bowel inflammation and sacroiliitis, supporting to the diagnosis of BD. Genetic counseling may be recommended for patients with monogenic BD. The diagnosis of monogenic BD should be made by a qualified healthcare team, based on a comprehensive evaluation of the patient's symptoms, medical history, physical examination, and genetic testing.
Trial registration identifying number:

Patient Consent
Yes, I received consent

Disclosure of Interest
None declared

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The thousand faces of mevalonate kinase deficiency: a challenging case
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Introduction: Mevalonate Kinase Deficiency is a rare inborn error of metabolism with an autosomal recessive inheritance due to mutations in the *MVK* gene. Residual enzymatic activity between 1 and 10% is associated to hyperimmunoglobulinemia D syndrome (HIDS)