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Long-term efficacy and safety of biologic therapy in children with juvenile idiopathic arthritis or non-infectious uveitis

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Introduction: Juvenile idiopathic arthritis (JIA) and idiopathic uveitis are rare diseases associated with severe complications. Currently, in addition to the standard treatment strategies, biological agents result in a major step in the improvement of their management.
Objectives: The aim of this study is to assess long-term efficacy and safety of biologic therapy in children with JIA or non-infectious uveitis refractory to first-line immunosuppression treatment.
Methods: This is a retrospective study on children (16 years or younger) with JIA or non-infectious uveitis treated with biological agents between 2000 and 2015 in one pediatric hemato-oncology unit (Hôpital Universitaire Des Enfants Reine Fabiola, Brussels). Patients could receive more than one type of biologic agent during the follow-up.
JIA disease activity was evaluated (at baseline, after 6 months, 15 months, 2 years and then yearly) according to a modified pediatric ACR (Pedi ACR) core set criteria with 3 items (the level of C-reactive protein (CRP), the number of active joints and the number of limited joints) and by comparison of the duration of morning stiffness, the number of tender joints and the erythrocyte sedimentation rate (ESR). The improvement of intraocular inflammation was primarily assessed by anterior chamber cells (Tyndall grade) according to the definition of the Standardization of Uveitis Nomenclature (SUN) criteria but also according to the degree of inflammation in intermediate and posterior chamber and by the number of flares. Adverse events were classified according to the Common Terminology Criteria for Adverse Events.
Results: Of the 29 patients included, 24 had JIA (11 associated with uveitis), 4 had idiopathic uveitis and 1 had uveitis associated with Behçet's disease. Median age at diagnosis was 50 months (range: 29-96) and mean age at the start of biologic treatment was 100 months (SD: 50).
26 patients were treated with anti-TNF (Etanercept, Infliximab or Adalimumab), 2 with Abatacept, 2 with Canakimumab and 4 with Tocilizumab. All patients had been previously treated with methotrexate. The median duration of biological treatment was 45 months (range: 21-82).
The rate of patient's improvement was encouraging with 85/70/60/45%, 85/75/75/65%, 83/83/78/61%, 93/87/80/80%, 92/83/83/75% and 91/82/82/82% according to the modified Pedi ACR core set criteria 30/50/70/90 and 64, 62, 82, 63, 67 and 67% according to Tyndall at 6 months, 15 months, 2, 3, 4 and 5 years. Individual data regarding articular condition (duration of morning stiffness, number of active, tender and limited joints) decreased significantly ($p < 0.05$) at each evaluation until 4 years of treatment. The level of CRP and ESR decreased significantly ($p < 0.05$) at each evaluation, from 6 month to 7 years. The number of flares as well as the level of inflammation in anterior, intermediate and posterior chamber at 6 months, 15 months and 2 years of treatment decreased significantly ($p < 0.05$). The rate of patient achieving both articular and ophthalmic remission was 65%.
Severe adverse events occurred in 17% of the patients and were reversible for 80% of them.
Conclusion: In our studied population, biologic therapy is effective and safe. Their effects occur early and persist in long-term evaluation. American and European authorities approved these treatments in JIA but not yet in non-infectious uveitis. Additional data with longer follow-up and larger number of patients as well as randomized studies in uveitis are required.
Disclosure of Interest
None Declared.

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Kaposiform hemangioendothelioma arising in the leg mimicking juvenile idiopathic arthritis

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Introduction: Kaposiform hemangioendothelioma (KHE) is a rare vascular neoplasia that usually arises in children as a superficial or deep soft tissue mass of the extremities with variable clinical presentation. KHE typically presents as an ill-defined, red to purple, indurated plaque and is often complicated by the Kasabach–Merritt phenomenon (KMP), a condition of severe thrombocytopenia and consumptive coagulopathy.
Objectives: Herein we describe a pediatric patient with atypical KHE sent to rheumatological evaluation for suspected Juvenile Idiopathic Arthritis (JIA).
Methods: A 6 year old girl was referred to our Rheumatology Center for a chronic painful swelling of the right ankle. No history of trauma was reported, remote anamnesis was silent. Ankle swelling had appeared 2 years before but in the last months the patient had mild knee swelling as well.
At physical examination there were no signs of arthritis except for an ankle perimalleolar swelling, nodular subcutaneous lesions were palpable at right foot medial side, skin was normal. Knee and ankle range of motion were normal.
Laboratory exams were all within the normal range, without signs of phlogosis or thrombocytopenia. Ultrasound revealed the presence of three hypoechoic and vascularized nodules, identified as synovial cysts or ganglia. MRI showed a T1 hypointense, T2 hyperintense tissue with multiple confluent nodules and strong enhancement. The tissue was perischeletric and subfascial and stretched from the ankle to the peri-meniscal tissue of the knee.
Results: A biopsy was performed and KHE was diagnosed.
Conclusion: Differential diagnosis in JIA is often difficult as heterogeneous lesions may present with peritendineal or joint swelling.
Even if soft tissue tumors are rare in children, their presence should always be excluded when physical examination and imaging are atypical for JIA.
In this case the presence of palpable subcutaneaus noduli hypoechoic and vascularized at ultrasound could be firstly considered as "synovial cysts": MRI revealed no signs of concomitant articular synovisits, so this hypothesis was rejected.
In case of atypical arthritis, MRI should always be performed for his help in diagnosing other condition mimicking JIA such as atypical KHE or other neoplastic lesions.
When tumor is suspected biopsy remains the diagnostic gold standard.
Disclosure of Interest
None Declared.

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Hypocomplementemia in children with juvenile idiopatic arthritis treated with tocilizumab: personal records

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Introduction: The relieve of a reduction in complement levels was recently reported in adults with Rheumatoid Arthritis treated with tocilizumab (TCZ). However, there are no data in children with Juvenile Idiopathic Arthritis (JIA) treated with TCZ.

Objectives: We evaluated complement levels in JIA children treated with TCZ for a systemic or a polyarticular form, and correlated them to clinical, biochemical parameters and to the response to the treatment.
Methods: 11 patients with active JIA (5 with polyarticular JIA; 6 with systemic JIA; 4 M/7 F); mean age 14 ± 7SDS) were treated with TCZ (7 after anti-TNF failure and 4 naives). All the patients were followed for the evaluation of clinical therapy response and of laboratory parameters. Laboratory parameters (leucocytes and thrombocytes count, liver enzymes, C3 and C4 levels) episodes of infections, allergic reactions, and autoimmune diseases were evaluated. 7/11 received DMARDs associated with TCZ.
Results: All the patients had normal complement levels pre-TCZ treatment: C3:90-180 mg/dl; C4: 10-40 mg/dl. 7/11 patients showed an early (within 3 months of treatment) hypocomplementemia. The reduction of C3 and C4 were coupled, even if in 3/7 children C3 was less reduced than C4. The complement depletion did not increase at the 6th month, while persisted during the ongoing therapy.
1/11 patients did not respond adequately to TCZ and 2/11 showed a flare of the disease during TCZ treatment. In these patients, C3 and C4 were in the normal range with a significant direct correlation with CRP, ESR, SAA. In 3 patients the treatment was stopped (2 for adverse reactions, 1 for the poor response to the treatment) with normalization of C3/C4 factors in the follow-up. In all patients no signs for the development of infection were observed; one patient showed leukopenia.
Conclusion: In our patients C3 and C4 decrease has a significant correlation with clinical response, while we did not observe hypocomplementemia in children and in the periods of lack in response to TCZ. The levels of C3 and C4 were more related to the efficacy than PCR or ESR values, which in 1 patient decreased in presence of clear clinical worsening. It can be hypothesized that complement factors are consumed during the clearance of immune complexes (anti-IL6Ab-IL6); however the reduction in complement levels is believed to be linked to the inhibition by TCZ of IL6 stimulation of hepatocyte acute phase protein synthesis and of complement upregulation. The number of children studied is too small to reach conclusions, but the authors hypothesize that the dosage of the C3 and C4 can be a rapid and sensitive marker of the response to anti-IL6 treatment, could be included in the follow-up of these patients and must be correlate to clinical outcome.
Disclosure of Interest
None Declared.

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DMARD withdrawal in juvenile idiopathic arthritis patients in clinical remission. A single center observational study

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Introduction: Treatment with biologic and non-biologic DMARDs leads into clinical remission most juvenile idiopathic arthritis (JIA) patients. The potential of adverse effects from prolonged treatment must be balanced with the risk of disease flare after withdrawal of DMARDs.
Objectives: To estimate the likelihood of maintaining clinical remission (CR) after discontinuation of treatment with DMARDs in patients with JIA.
Methods: A retrospective chart review was conducted in a cohort of 272 patients with non-systemic JIA treated with MTX +/– anti-TNFα. In 29 patients; age at last follow up 8,7 (3,6-16,5) years, (24 girls; 22 oligo-, 6 polyarthritis, 1 ERA; 20/29 ANA + ve) with longstanding CR, defined according to Wallace criteria, treatment was withdrawn; initially by increasing dose intervals and by treatment discontinuation after 3 months. MTX was the first drug to withdraw. The median duration of patient observation was 63 (30-70) months. Disease activity was measured by JADAS. Data, expressed as median value and range, were analyzed by GraphPad prism 7, Mann Whitney non-parametric t-test for continuous variables.
Results: Nine out of 29 patients were treated with MTX and anti-TNFα (6 polyarthritis, 2 oligo + uveitis). All patients flared after MTX withdrawal. Combined treatment was re-initiated. Among the remaining patients, treated with MTX alone, 14/20 (70%) flared within 9,5 (1-25) months after treatment withdrawal. In 4/14, disease flare was more severe than that manifested before treatment cessation. The median duration of remission on treatment did not differ between patients with sustained remission; 24,5 (20–48) months; time to follow-up 15 (3-26)months;and those who flared; 28,5 (22-84) months ($p = 0,25$). Total duration of treatment with DMARDs prior to discontinuation was 35 (20-91) months for those who flared and 31,5 (20-55) months for those who remained into remission ($p = 0,5$). The median duration from the time of diagnosis of JIA to the initiation of MTX was similar between the 2 groups 13,3 (2,5-23) months in those who sustained remission 14,8 (1,2-86) in those who flared ($p = 0,9$). The category of JIA, sex, and age at diagnosis were not associated with the risk of relapse.
Conclusion: The majority of JIA patients relapsed after treatment discontinuation, despite longstanding remission on-medication. Withdrawal of both drugs was impossible; all patients relapsed after MTX discontinuation. Our data support the notion that clinical remission does not indicate biological inactivity. Parameters evaluated in everyday clinical care cannot predict the outcome of treatment withdrawal
Disclosure of Interest
None Declared.

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Discontinuation of biologic therapy in jia patients in croatia, two centre- 8 year experience

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Introduction: The introduction of biologic agents has revolutionized the treatment of juvenile idiopathic arthritis (JIA) due to their efficacy, speed of onset and tolerability. A numerous clinical practice guidelines and consensus statements on the criteria for biologic therapy (BT) introduction have been developed, however, the consensus on cessation of biologic agents has not been harmonized.
Objectives: Presentation of our experience on discontinuation of biologic therapy in JIA patients.
Methods: We conducted a retrospective two centre analysis of patients with JIA diagnosis according to ILAR criteria, treated with BT from January 2008 to May 2016. Demographic information, duration of the treatment, number of biologic agents used and discontinuation rate were extracted using medical charts. Successful discontinuation was defined as cessation of the drug due to disease control according to Wallace criteria and musculoskeletal ultrasound inactive disease.
Results: Total of 92 patients (87% female, 13% male) with different JIA subtypes, non-responders or intolerant to syntetic DMARDs, were treated with one or more biologicals. Median disease duration, from onset to the introduction of first BT, was 3.4 years (0.4-13 years). Patients were diagnosed with poli JIA in 68.5%, oligo JIA in 18.5%, ERA in 6.4%, systemic JIA in 3.3% and psoriatic JIA in 3.3%. In 88 patients first biologic drug was anti-TNF agent (etanercept in 54 pts, adalimumab in 18 pts, infliximab in 16 pts) and 3 pts were initially treated with tocilizumab and one patient with anakinra.
By the May 2016, 4 patients were lost from the follow up, 9 patients were transferred to adult rheumatology department while on BT, and 52 patient were still on BT. In 27 patients (29.3%) BT was successfully