patients (75%), presented by polyarthrites in 7/9 (77.8%), and oligoarthrites in 2/9 (22.2%). Two patients (16.7%) had cataract, one (8.3%) had bilateral uveitis, and one (8.3%) had optic atrophy. Sensorineural hearing loss was observed only in 3/12 (25%). Hydrocephalus was detected in 3/12 (25%). Delayed mental and psycho-speech development was observed in 6/12 (50%) patients. In 3/12 (25%), the development of MAS was recorded.

All patients had nucleotide variants in NLRP3 gene. According to NGS results and clinical characteristics, 8/12 (66.7%) patients were diagnosed with MWS and 4/12 (33.3%) had CINCA/NOMID syndrome. In children with MWS, heterozygous variant c.2173C>A in NLRP3 gene was the most common (5/8 (62.5%) patients). One of 8 (12.5%) patients with novel heterozygous variant c.2861C>T was detected; also one child (12.5%) have heterozygous variant c.5980G>A and one (12.5%) – heterozygous variant c.9434A>G. Four patients with CINCA/NOMID syndrome also had heterozygous variants in NLRP3 gene: c.5980G>A, c.2173C>A, c.1991T>C and c.796C>T.

Prior to genetic testing, 12/12 (100%) patients received NSAIDs; 6/12 (50%) were c.796C>T and 4/12 (33.3%) had CINCA/NOMID syndrome. In children with MWS, heterozygous variants were individual. In patients with CINCA/NOMID syndrome all nucleotide variants were individual. NLRP3 was estimated in 91.6% of patients. The most frequent variant of the NLRP3 gene in MWS was c.2173C>A. In patients with CINCA/NOMID syndrome all nucleotide variants were individual.

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TOFACITINIB POPULATION PHARMACOKINETICS IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS: A POOLED ANALYSIS OF DATA FROM THREE CLINICAL STUDIES

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Background: Tofacitinib is an oral JAK inhibitor that is being investigated for juvenile idiopathic arthritis (JIA).

Objectives: To describe tofacitinib pharmacokinetics (PK) in patients with JIA, identify potential covariates accounting for variability in exposure, assess the formulation effect of oral solution vs tablet and propose a simplified dosing regimen.

Methods: This was a pooled analysis of data from 3 tofacitinib clinical studies in patients with JIA aged 2−<18 years: a Phase 1, open-label (OL), non-randomised study (NCT01513902); a Phase 3, randomised, double-blind, placebo-controlled, withdrawal study (NCT02592434); and an OL long-term extension study (NCT01500551). Tofacitinib was dosed at 5 mg twice daily (BID) in patients ≥40 kg or at body weight (BW)-based doses BID in patients ≤40 kg, to achieve average trough concentrations (C0) comparable with those in patients receiving 5 mg BID. A sparse PK sampling scheme was applied, and the plasma samples were assayed using a validated, sensitive and specific high-performance liquid chromatography tandem mass spectrometric method (lower limit of quantification = 0.100 ng/mL). A nonlinear mixed-effects modelling approach was used for the population PK model, and population parameter variability was assumed to be log-normal. Covariates related to patient demographics, disease characteristics, concomitant medications and formulation (oral solution vs tablet) were selected using a stepwise covariate modelling approach, and parameter-covariate relationships were evaluated using stepwise forward-inclusion (p<0.05) backward-deletion (p>0.001) procedures. The effect of time-varying BW on oral clearance (CL/F) and apparent volume of distribution (V/F) was characterised using an allometric model. Final model quality was assessed by Visual Predictive Check (VPCs).

Results: Of 246 patients in the analysis, 74.0% were female; 87.8% were white, 2% black, 10.2% were ‘other’ races and no patients were Asian. Median (range) BW was 46.3 (11.1−121.8) kg. Initially, 100 patients received oral solution and 146 patients received tablets; 11 patients switched formulations during the studies. A one compartment disposition model with first-order absorption and a lag time sufficiently described the data. Final estimates for CL/F and the first-order absorption rate constant (k) for tablets were 26.1 L/hr, 89.2 L and 2.78 hr−1, respectively. The only statistically significant covariate was a formulation effect on k. All parameters were estimated adequately. Estimated allometric exponents were 0.310 for CL/F and 0.537 for V/F. Absorption was described with an estimated lag time of 0.16 hr, and the oral solution had a 1.64-fold faster absorption rate vs the tablet. VPCs sufficiently described the observed data over time, across BWs and ages.

Conclusion: Tofacitinib population PK in patients with JIA were adequately described by a one compartment model parameterised in terms of CL/F, V/F and first-order absorption with a lag time. Drug absorption from the oral solution was faster than from the tablet. Tofacitinib does not require dose modification or restrictions for any covariates, except BW, to account for differences in C0. Based on the results of this analysis, a simplified BW-based dosing regimen was proposed.

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Background: Biological treatment (BT) has changed perspectives for JIA patients. Increasing data from real life experience have been reported.

Objectives: To compare drug survival, safety and efficacy of BT in patients with JIA idiopathic Arthritis (JIA).

Methods: A retrospective observational study was conducted on JIA patients followed in a referral hospital and who had received at least one BT between 1999 and 2019.

Results: 218 BT in 130 JIA patients were analyzed. 67.7% were women with a median age at diagnosis of 8 years old IQR (3-13) and a median age at the beginning of the BT of 15 years old IQR(7.8-21). 21.5% of the patients had uveitis during follow-up. BT were indicated due to: arthritis(73.9%), uveitis(10.1%), arthritis and uveitis(2.7%), systemic activity(6.3%) and macrophage activation syndrome (1.8%). There were 130 BT started in 1st line, 55 in 2nd line, 20 in 3rd line, 10 in 4th line and 2 in 5th line.

The 1st line BT most frequently indicated was Etanercept (ETN) up to 40%, followed by 30% Adalimumab (ADA) and 16.2% Infliximab (INF). The median duration of the 1st line was 51 months (IQR (14-109.3). However, 53.8% of the 1st line BT were switched: 28.3% due to adverse events, 25.7% due to 1st failure and 25.7% due to 2nd failure. The BT that were discontinued were: INF (76.2%) and Anakinra (ANAK) (75%) due to adverse events and ETN (59.6%) due to 1st and 2nd failure. 55 patients started a 2nd BT: 43.6% received ADA and 20% Tocilizumab (TCZ) with a median duration of 43 months IQR (12-90). 22 of 55 BT required a change: 75% of ETN and 59% of INF prescribed in 2nd line were discontinued. The causes were: 40% 1st failure, 28% 2nd failure and 12% remission. In 1st line 87.6% of patients received TNF inhibitors, 74% maintained the target in 2nd line. In 3rd line TCZ was the most frequent BT. 71.5% of patients continue on BT. BT was withdrawn in 20 of 130 patients due to remission (40%), adverse events (30%), and pregnancy (10%).

In the analysis by decades, 80 BT (36.7%) were started from 1999 to 2008 and 138 BT (63.3%) from 2009 to 2019. In the 1st decade ETN and INF were the most frequently prescribed and in the 2nd decade, ADA and TCZ (p <0.0001). The 1st BT in the 2nd decade were indicated sooner compared to the 1st decade: mean 119.5 months SD(109.2); 2nd decade: mean 53.9 months SD(99.7); p <0.0001). In 1st BT line, the BT prescribed in the 2nd decade had a shorter duration than those in the 1st decade (1st decade: mean 84.1 months SD(71.8); 2nd decade: mean 51.7 months SD(5); p <0.0001).

In the survival analysis, TCZ and ADA were the BT with the highest survival (p=0.001). Of the 31 patients that started TCZ, 61.3% continue on TCZ, with a median duration of 46 months IQR(25-59) and 36/68(52.9%) still on ADA with a median duration of 61.5 months IQR(30.5-98).

Conclusion: 42.3% of patients required more than one BT. Since the onset of the BT there has been a change in prescription, probably related to the emergence of new targets and the evidence provided by clinical trials and guidelines. TCZ and ADA were the BT with the highest survival rate. On the other hand, INF and ANAK were the ones with the lowest survival rate. The most common causes of BT change in 1st line were adverse events in relation to INF and ANAK. In 2nd line there was a high rate of change in those patients who maintained TNFi, related to 1st failure.

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