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Prospective study to characterize adalimumab exposure in pediatric patients with rheumatic diseases

Tatjana Welzel[1,2,3,4*†], Klervi Golhen[1†], Andrew Atkinson[1,4,5], Verena Gotta[1], David Ternant[1,6], Jasmin B. Kuemmerle-Deschner[2], Christine Michler[2], Gilbert Koch[1], Johannes N. van den Anker[1], Marc Pfister[1†] and Andreas Woerner[3†]

Abstract

Background In pediatric rheumatic diseases (PRD), adalimumab is dosed using fixed weight-based bands irrespective of methotrexate co-treatment, disease activity (DA) or other factors that might influence adalimumab pharmacokinetics (PK). In rheumatoid arthritis (RA) adalimumab exposure between 2–8 mg/L is associated with clinical response. PRD data on adalimumab is scarce. Therefore, this study aimed to analyze adalimumab PK and its variability in PRD treated with/without methotrexate.

Methods A two-center prospective study in PRD patients aged 2–18 years treated with adalimumab and methotrexate (G_{A-M}) or adalimumab alone (G_A) for ≥ 12 weeks was performed. Adalimumab concentrations were collected 1–9 (maximum concentration; C_{max}), and 10–14 days (minimum concentration; C_{min}) during ≥ 12 weeks following adalimumab start. Concentrations were analyzed with enzyme-linked immunosorbent assay (lower limit of quantification: 0.5 mg/L). Log-normalized C_{min} were compared between G_{A-M} and G_A using a standard t-test.

Results Twenty-eight patients (14 per group), diagnosed with juvenile idiopathic arthritis (71.4%), non-infectious uveitis (25%) or chronic recurrent multifocal osteomyelitis (3.6%) completed the study. G_{A-M} included more females (71.4%; G_A 35.7%, $p = 0.13$). At first study visit, children in G_{A-M} had a slightly longer exposure to adalimumab (17.8 months [IQR 9.6, 21.6]) compared to G_A (15.8 months [IQR 8.5, 30.8], $p = 0.8$). Adalimumab dosing was similar between both groups (median dose 40 mg every 14 days) and observed DA was low. Children in G_{A-M} had a 27% higher median overall exposure compared to G_A, although median C_{min} adalimumab values were statistically not different ($p = 0.3$). C_{min} values ≥ 8 mg/L (upper limit RA) were more frequently observed in G_{A-M} versus G_A (79% versus 64%). Overall, a wide range of C_{min} values was observed in PRD (0.5 to 26 mg/L).

Conclusion This study revealed a high heterogeneity in adalimumab exposure in PRD. Adalimumab exposure tended to be higher with methotrexate co-treatment compared to adalimumab monotherapy although differences were not statistically significant. Most children showed adalimumab exposure exceeding those reported for RA

†Tatjana Welzel and Klervi Golhen contributed equally and should be considered as co-first authors.

†Marc Pfister and Andreas Woerner contributed equally and should be considered as co-last authors.

*Correspondence:
Tatjana Welzel
tatjana.welzel@ukbb.ch
Full list of author information is available at the end of the article

with clinical response, particularly with methotrexate co-treatment. This highlights the need of further investigations to establish model-based personalized treatment strategies in PRD to avoid under- and overexposure.

Trial registration NCT04042792, registered 02.08.2019.

Keywords Pharmacokinetics, Therapeutic drug monitoring, Pharmacodynamics, Target concentration, Drug exposure, Heterogeneity, bDMARDs

Background

Juvenile idiopathic arthritis (JIA) and non-infectious uveitis are common pediatric rheumatic diseases (PRD). Effective treatment of PRD is important to avoid chronic morbidity, diminished health-related quality of life, functional impairment, and long-term sequelae [1–4]. In recent years, treat-to-target (T2T) strategies, consensus treatment plans and treatment recommendations have been established to optimize the care and disease management of PRD patients [5–8]. These steps, together with the availability and approval of biological disease modifying antirheumatic drugs (bDMARDs) for use in pediatric patients, have improved PRD outcomes compared to historical cohorts [9, 10].

For two decades, tumor necrosis factor inhibitors (TNFi) are used in the treatment of PRD. The PRD treatment with TNFi aims to achieve inactive disease by elimination/neutralization of disease-mediating targets. Adalimumab (ADM) is an approved TNFi for the treatment of polyarticular JIA (PJIA), enthesitis associated arthritis (ERA) and non-infectious idiopathic uveitis. Oligoarticular JIA (OJIA) can be treated with ADM if there is inadequate response or intolerance to non-steroidal anti-inflammatory drugs (NSAIDs) and/or intra-articular steroids and at least one conventional disease modifying antirheumatic drugs (cDMARDs) [11]. In PRDs, ADM has been dosed per body surface area (BSA) in the past, and label recommendation recently switched to fixed weight-based dosing regimens with 20 mg subcutaneous (s.c) every other week (EOW) in infants and children weighing 10 to 30 kg, and 40 mg s.c. EOW in those ≥ 30 kg (like adults).

Disease activity (DA), co-treatment with methotrexate (MTX) and individual patients' characteristics are prone to influence drug exposure and treatment effectiveness. Growing evidence indicates a relationship between TNFi exposure and DA [12, 13]. High DA seems to be associated with lower drug exposure [14]. Low drug exposure can result in treatment ineffectiveness and risk of anti-drug antibody (ADA) development [15, 16]. However, higher exposure than needed for DA control can result in higher risk of adverse events and higher drug costs [17–19]. Furthermore, co-treatment with MTX may increase ADM concentrations [20]. As ADM is often combined with MTX in PRD patients, this might be an additional aspect to be considered during treatment and tapering. According to Krieckaert et al., population-based ADM concentration ranges associated with clinical response in adult patients with rheumatoid arthritis (RA), vary between 2 and 8 mg/L [21]. In adults with rheumatic diseases there is an increasing use of therapeutic drug monitoring (TDM) in clinical practice to provide more individualized drug dosing. However, TDM is difficult to use in PRD patients treated with ADM due to limited pharmacokinetic (PK) and pharmacodynamic (PD) knowledge, highlighting an urgent need of performing such investigations to optimize T2T strategies [22, 23]. The goal of this study was to investigate ADM concentrations in PRD patients treated with ADM, with and without MTX, to (i) better understand ADM exposure and its variability, (ii) analyze concentration changes over time, and (iii) increase current PK knowledge that will facilitate model-based personalized treatment in children with PRD.

Patients and methods

Study design

This was an observational two-center prospective pilot-study in PRD patients treated with ADM. Children and adolescents aged 2 to 18 years were eligible if they had a confirmed diagnosis of JIA, non-infectious idiopathic uveitis or chronic recurrent multifocal osteomyelitis (CRMO), and if they were treated ≥ 12 weeks with ADM s.c. with or without MTX (s.c. or orally) between 08/2019 and 12/2021. Exclusion criteria were concomitant treatment with additional bDMARDs or cDMARDs, pregnancy, inability to comply with the study protocol and other concomitant chronic diseases, which could influence drug elimination. After informed consent (IC) process, study participants were subdivided into two study groups ($G_{A\text{-}M}$, G_A) based on their clinical treatment regimen. Study group $G_{A\text{-}M}$ consisted of patients treated with ADM and MTX; study group G_A consisted of children receiving ADM monotherapy. ADM s.c. was administered either by the parent, the patient or a nurse at home. Parents/patients were trained by health care professionals at treatment start. For each study participant, ADM maximum concentrations (C_{max}) were collected 1 to 9 days and minimum concentrations (C_{min}) 10 to 14 days'

post-administration during clinical visits. In addition, naïve children with clinical indication of ADM start were able to participate in a third study group (G_N) with ADM concentration measurements 3 to 7 days (C_{max}, Visit A) and 10 to 14 days (C_{min}, Visit B) after their first ADM administration. A detailed study schedule is presented in Supplementary material S1. Study data was captured in the web-based electronically secured database secuTrial®. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, the Human Research Act, and the Human Research Ordinance. The study was approved by the ethics committees of Nordwest- und Zentralschweiz (EKNZ, 2019–00916) and medical faculty and University Hospital Tuebingen (321/2019B01). The study was registered at ClinicalTrials.gov (NCT04042792).

Data collection

Baseline characteristics and treatment information (e.g. dose and administration frequency of ADM/MTX, concomitant treatment categorized as NSAIDs, systemic corticosteroids and intra-ocular steroids) were collected. Intra-articular steroid application was captured if administered between first and last study visit. Furthermore, DA scores and clinical and laboratory routine data were assessed at each study visit. Routinely measured laboratory parameters included C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR). In addition, clinical routine data available in patient health records were captured from ADM treatment start until study inclusion.

Disease Activity (DA) assessment

DA was captured by the physician global assessment (PGA) and patient's/parents' global assessment (PPGA). PGA and PPGA were recorded on a 10 cm visual analog scale (VAS) with 0 representing no DA and 10 representing maximum DA. In addition, DA was captured for patients with JIA by the Juvenile Arthritis Disease Activity Score (JADAS)-10. JADAS cut-off values for the DA status were based on Trincianti et al. [24] as follows: 1) OJIA: inactive DA $\leq$ 1.4; minimal DA 1.5–4; moderate DA 4.1–13; high DA > 13; 2) PJIA: inactive DA $\leq$ 2.7; minimal DA 2.8–6; moderate DA 6.1–17; high DA > 17. In ERA patients, cut-off values were based on active joint count (1–4 active joints: OJIA cut-off, $\geq$ 5 active joints: PJIA cut-off). Uveitis was defined by cells in the field of the anterior chamber in line with the standardization of the uveitis nomenclature (SUN) (grade 0: < 1 cell, grade 0.5+: 1–5 cells; grade 1+: 6–15 cells; grade 2+: 16–25 cells; grade 3+: 26–50 cells; grade 4+: > 50 cells) [25]. The SUN grades were translated to DA status as following: inactive: grade 0; minimal: grade 0.5+; mild: grade 1+; moderate: 2+ and severe: grade $\geq$ 3+ [26].

Adalimumab concentration measurement

Sample management was standardized (Supplemental material S2). Aliquots were transferred on dry ice by batches to the accredited collaborating laboratory (MVZ Dr Eberhard & Partner Dortmund, Dortmund, Germany). Analyses were performed with the same charge of an enzyme-linked accredited immunosorbent assay (EIA) using Dynex DSX automated ELISA system. Assay detection limit was 0.1 mg/L and lower and upper limits of quantification were 0.5 and 12 mg/L, respectively. Sera exceeding the upper limit of quantification were diluted 1:4, thus creating an upper limit of 48 mg/L.

Primary and secondary outcomes

The primary outcome was to compare ADM $C_{min} \geq 12$ weeks after first ADM administration in study participants with ($G_{A\text{-}M}$) and without MTX (G_A). Secondary outcomes included comparison of ADM concentrations and DA during treatment, dosing regimen, and the influence of body weight. Post hoc analysis included investigation of ADM C_{max} and C_{min} in treatment naïve patients (G_N) as well as PGA, PPGA and laboratory parameters since ADM start.

Hypothesis and sample size calculation

It was hypothesized that children in $G_{A\text{-}M}$ have higher ADM C_{min} compared to G_A. To determine if this difference was statistically significant, mean concentrations were estimated (following appropriate transformations to achieve normality) for each group (details in the protocol). With 90% power and a two-sided statistical significance level of 5%, recruitment was estimated at $2 \times 12 = 24$ patients (altogether) to detect a difference between the groups of 1.4 standard deviations or more. Furthermore, a 10% drop out in each group was assumed, resulting a recruitment target of $2 \times 14 = 28$ children for this study.

Statistical analysis

Patient characteristics were summarized using descriptive statistics; missing data addressing routine parameters are marked. Categorical values were represented as number (%) and continuous values as median (interquartile ranges; IQR). Comparative analyses between $G_{A\text{-}M}$ and G_A were conducted using the chi-square test for categorical variables and the Wilcoxon test for continuous variables. As stated above, the primary analysis compared log transformed mean C_{min} using a standard t-test. Linear regression models were fitted to determine associations

between the individual (log transformed) adalimumab concentrations and other factors (such as study group, visit age and gender) that may influence drug exposure as independent variables. Univariable and multivariable linear mixed effect models investigating relationship between adalimumab concentrations (log-transformed) and study group, age at visit were fitted with a random intercept slope for each participant. All analysis and graphs were performed utilizing R version 4.2.2.

Results

Study population

In total, 14 patients in $G_{A\text{-}M}$ and G_A completed the study between September 26, 2019 and June 28, 2021 (Fig. 1). $G_{A\text{-}M}$ included more females (71.4%) and children tended to be diagnosed at an earlier median age (6.3 years [IQR 2.4, 9.0]) compared to G_A (35.7% females, 8.8 years [IQR 5.7, 10.1], $p=0.2$). At first study visit, median age was similar in $G_{A\text{-}M}$ and G_A. Most children ($n=20$, 71.4%) were diagnosed with JIA; a history/active JIA-associated uveitis (JIA-uveitis) was documented in six of 12 children with JIA in $G_{A\text{-}M}$, and in three out of eight in G_A (Table 1, Supplementary material S3). Seven (25%) children were diagnosed as non-infectious idiopathic uveitis with five being included in G_A. One patient in G_A was diagnosed with CRMO. At time of study inclusion, children in $G_{A\text{-}M}$ were treated slightly longer with ADM (17.8 months [IQR 9.6, 21.6]) compared to those in G_A (15.8 months [IQR 8.5, 30.8], $p=0.8$). Median ADM dose and administration frequency were similar between both groups. Children in $G_{A\text{-}M}$ received weekly MTX (median dose per BSA 9.0 [6.6, 9.8] mg/m^2). Concomitant PRD treatment included systemic corticosteroids, NSAIDs and ocular steroids (Table 1, Supplementary material S4). Median follow-up time between first and last study visit was 4.4 months [IQR 3.5, 6.2] and 2.9 months [IQR 2.6, 3.4] for $G_{A\text{-}M}$ and G_A, respectively (Table 1).

Primary outcome

Median ADM C_{min} was 10.6 mg/L [IQR 8.9, 20.3] in $G_{A\text{-}M}$ compared to 11.1 mg/L [IQR 6.6, 15.3] in G_A, but this difference was not statistically significant at the 5% level (t-test of log transformed C_{min} measurements; $p=0.3$, Table 2, Fig. 2).

Secondary outcomes

Most children with JIA had inactive or minimal DA classified by JADAS-10 at first study visit ($G_{A\text{-}M}$ 66.7%; G_A 87.5%) with stable DA or slight DA improvement observed at last study visit ($G_{A\text{-}M}$ 75%; G_A 87.5%). DA of uveitis in children with JIA or idiopathic uveitis was captured as absent, minimal, or mild at first and last study visit with only small changes between both visits. Median CRP and median ESR were normal in $G_{A\text{-}M}$ and G_A at both study visits (Table 3, Supplementary material figure S1A and S1B). In addition, median PGA and median PPGA were overall low (Table 3, Supplementary material S5). Uni- and multivariable linear mixed effect models revealed no statistically significant relationship between ADM concentrations (log-transformed) and study group and age at visit (Supplementary material S6).

Most children treated ≥ 12 weeks showed higher ADM C_{max} compared to C_{min} values (Fig. 3). Furthermore, a high inter-individual variability in C_{min} was

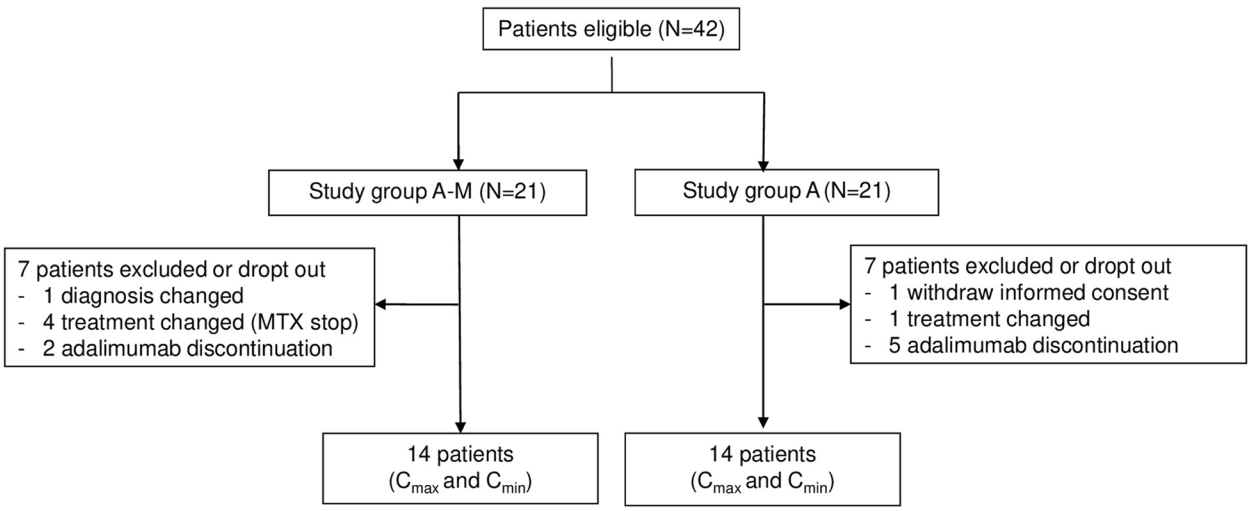

Fig. 1 Study Flow chart. Abbreviation: *Study group A-M* adalimumab and methotrexate co-treatment, *Study group A* adalimumab alone, C_{max} maximum adalimumab concentration collected 1 to 9 days after adalimumab administration, C_{min} minimum adalimumab concentration collected 10 to 14 days after adalimumab administration, *MTX* methotrexate

Table 1 Characteristics of children with PRD treated with adalimumab ≥ 12 weeks with or without methotrexate

	Total (*N* = 28)	**Study group A-M ($G_{A\text{-}M}$, *n* = 14)**	**Study group A (G_A, *n* = 14)**	***p*-value**
General information study cohort				
Female sex, n (%)	15 (53.6)	10 (71.4)	5 (35.7)	0.13
Median age at diagnosis, years [IQR]	7.1 [4.4, 10.1]	6.3 [2.4, 9.00]	8.8 [5.7, 10.1]	0.19
Median age at first visit, years [IQR]	11.3 [8.9, 13.2]	11.3 [8.9, 13.5]	11.5 [9.3, 12.8]	0.82
Median body weight, kg [IQR]	38.7 [31.9, 54.1]	35.7 [31.7, 52.7]	43.7 [33.0, 54.9]	0.59
Comorbidities, n (%)	3 (10.7)	0	3 (21.4%)[a]	0.22
Diagnosis, n (%)				
JIA	20 (71.4)	12 (85.7)	8 (57.1)	0.21
Idiopathic Uveitis	7 (25.0)	2 (14.3)	5 (35.7)	
CRMO	1 (3.6)	0	1 (7.1)	
Disease activity				
Median CRP, mg/L [IQR] (ref < 10) *Missing, n (%)*	0.3 [0.1, 1.1] *1 (3.6)*	0.1 [0.1, 0.3]	0.6 [0.3, 1.3] *1 (7.1)*	0.01
Median ESR, mm/h [IQR] (ref < 15) *Missing, n (%)*	5.5 [4.0, 6.3] *4 (14.3)*	6.0 [5.0, 7.0] *1 (7.1)*	4.00 [4.0, 6.0] *3 (21.4)*	0.28
Median PGA, cm [IQR]	0 [0, 1.0]	0.50 [0, 1.8]	0 [0, 1.0]	0.53
Median PPGA, cm [IQR]	0 [0, 1.0]	1.00 [0, 1.8]	0 [0, 0]	0.05
Adalimumab treatment				
Median time since start, months [IQR]	17.6 [8.4, 25.1]	17.8 [9.6, 21.6]	15.8 [8.5, 30.8]	0.78
Absolute median dose, mg [IQR]	40.0 [28.8, 40.0]	40.0 [25.0, 40.0]	40.0 [30.0, 40.0]	0.77
Median dose per BSA, mg/m^2 [IQR]	25.3 [22.9, 28.3]	25.1 [21.3, 32.0]	25.4 [23.6, 27.2]	0.93
Median frequency, days [IQR]	14.0 [14.0, 14.0]	14.0 [14.0, 14.0]	14.0 [14.0, 14.0]	0.35
Methotrexate treatment				
Median time since start, months [IQR]	n.a	23.4 [19.7, 59.2]	n.a	n.a
Absolute median dose, mg [IQR]		11.0 [10.0, 15.0]		
Median dose per BSA, mg/m^2 [IQR]		9.0 [6.6, 9.8]		
Median frequency, days [IQR]		7.0 [7.0, 7.0]		
Concomitant treatment at inclusion, n (%)				
Corticosteroids, systemic[b]	2 (7.1)[b]	2 (14.3)[b]	0	0.09
NSAIDs, on demand	4 (14.3)	2 (14.3)	2 (14.3)	
NSAIDs, fix administration	3 (10.7)	1 (7.1)	2 (14.3)	
Ocular steroids[b]	4 (14.3)	4 (28.6)	0	

Abbreviation: *BSA* Body surface area, *CRMO* chronic recurrent multifocal osteomyelitis, IQR Inter-quartile ranges, *i.v.* intravenous, *JIA* juvenile idiopathic arthritis, *kg* kilogram, *mg* milligram, *n.a.* not available, *NSAIDs* non-steroidal anti-inflammatory drugs, *p.o* per os, GA-M study group adalimumab and methotrexate, GA study group adalimumab, p—values: chi-square test for categorical variables; Wilcoxon test for continuous variables

[a] Comorbidities: patella luxation left (*n* = 1), autism spectrum disorder (*n* = 1), muscular tension (*n* = 1)

[b] dosing regimen is shown in the Supplementary material S4

detected (0.5 to 26 mg/L) with C_{min} ranges between 2.5 to 26 mg/L and 0.5 to 19.6 mg/L in $G_{A\text{-}M}$ and G_A, respectively. In this study, C_{min} of 78.6% (*n* = 11) of children in the $G_{A\text{-}M}$ and 64.3% (*n* = 9) of children in the G_A group were ≥ 8 mg/L (Table 2, Fig. 3). In $G_{A\text{-}M}$, all children were treated with a fixed ADM dosing regimen (*n* = 4 with 20 mg, *n* = 10 with 40 mg) and in G_A ten children (*n* = 2 with 20 mg, *n* = 8 with 40 mg). Four children in G_A received BSA-adjusted dosing (24 mg/m^2) resulting in 25 mg ADM injection in one and 30 mg in three (Fig. 4). The median ADM overall exposure (C_{min} and C_{max}) was 15.6 mg/L [IQR 10.1, 22.3] in $G_{A\text{-}M}$ and 12.3 mg/L [IQR 7.4, 16.6] in G_A. The distribution of ADM concentrations for the dosing regimen are shown in Fig. 4, showing that concentrations are well scattered around IQR, independent of dosing and dosing approach (fixed dosing versus BSA-based dosing). When analyzing all 56 measured ADM concentrations, the median overall concentration was 13.8 mg/L [IQR 8.4, 18.5]. Of five children weighting < 30 kg, four

Table 2 Adalimumab concentration and treatment information in children with PRD

	Study group A-M ($G_{A\text{-}M}$, $n=14$)		Study group A (G_A, $n=14$)		Total ($n=28$)	
	C_{max}	C_{min}	C_{max}	C_{min}	C_{max}	C_{min}
Adalimumab concentration, mg/L						
Median [IQR]	16.6 [11.9, 25.0]	10.6 [8.9, 20.3]	16.0 [8.2, 18.7]	11.1 [6.6, 15.3]	16.0 [10.6, 22.3]	10.9 [7.6, 16.1]
Median overall [IQR]	15.6 [10.1, 22.3]		12.3 [7.4, 16.6]		13.8 [8.4, 18.5]	
Mean (SD)	17.5 (7.5)	13.5 (7.8)	14.2 (7.2)	10.4 (6.0)	15.8 (7.4)	12.0 (7.0)
Range (min, max)	5.2, 28.4	2.5, 26.0	4.2, 25.2	0.5, 19.6	4.2, 28.4	0.5, 26.0
≥ 8 mg/L, patients (%)	12 (85.7)	11 (78.6)	10 (71.4)	9 (64.3)	22 (78.6)	20 (71.4)
Time after last adalimumab administration, days						
Median [IQR]	3.5 [2.0, 6.8]	12.0 [10.3, 13.0]	5.0 [4.3, 6.8]	12.0 [11.0, 13.0]	5.0 [2.0, 7.0]	12.0 [11.0, 13.0]
Range (min, max)	1.0, 7.0	10.0, 14.0	2.0, 8.0	10.0, 14.0	1.0, 8.0	10.0, 14.0
Time to adalimumab sample collection after adalimumab start, months						
Median [IQR]	11.2 [7.50, 17.4]	18.2 [9.5, 22.0]	11.8 [7.4, 27.8]	16.2 [8.3, 31.1]	11.8 [7.3, 22.3]	17.9 [8.2, 25.6]
Range (min, max)	3.5, 62.3	4.8, 66.7	3.6, 44.4	3.7, 41.5	3.5, 62.3	3.7, 66.7
Adalimumab dose administered						
Absolute median dose, mg [IQR]	40.0 [25.0, 40.0]		40.0 [30.0, 40.0]		40.0 [28.8, 40.0]	
Median dose per BSA, mg/m^2 [IQR]	25.1 [21.3, 31.2]	24.5 [21.0, 32.0]	25.1 [23.6, 26.8]	25.4 [23.8, 27.0]	25.1 [22.9, 27.6]	25.1 [22.8, 28.6]

Abbreviation *BSA* Body surface area, *IQR* Interquartile ranges, *SD* standard deviation, *mg* milligram, mL milliliter, *min* minimum, *max* maximum, *m* meter, $G_{A\text{-}M}$ study group adalimumab and methotrexate, G_A study group adalimumab

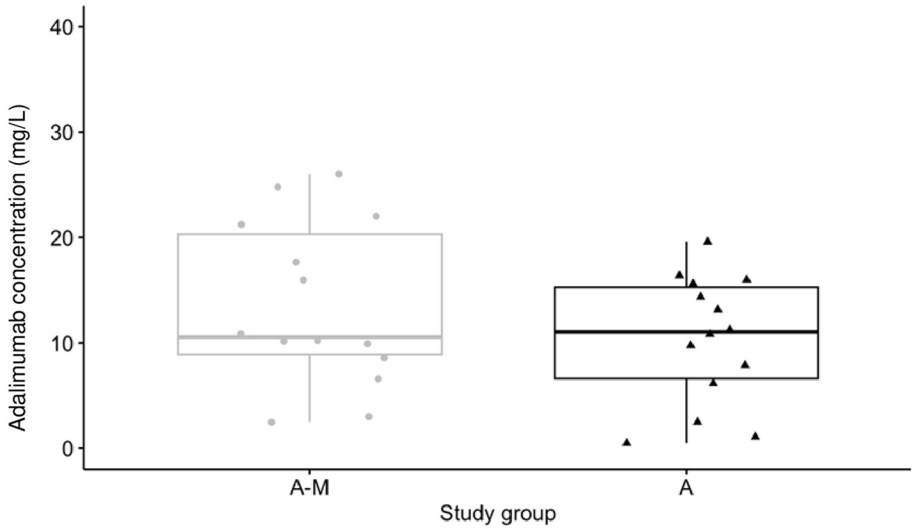

Fig. 2 Boxplot of adalimumab minimal concentrations (C_{min}) in children with PRD with and without methotrexate co-treatment. Legend: Adalimumab C_{min} concentrations collected 10–14 days after adalimumab administration in pediatric patients with rheumatic diseases in study group A-M (adalimumab and methotrexate treatment) and study group A (adalimumab alone); t-test of log transformed C_{min} $p=0.3$. The box of the boxplot limits the interquartile ranges (IQR)

had a fixed dosing regimen. The 23 children weighting > 30 kg received either a fixed ADM dosing regimen or a BSA-adjusted regimen; no child in the G_A group had adalimumab $C_{min} > 18.5$ mg/L (Fig. 4). No influence of systemic corticosteroids or ocular steroids on ADM concentrations could be shown (Supplementary material figure S3). During clinical routine

Table 3 Disease activity at first and last study visit in children with PRD

	Study group A-M (G_{A-M})		Study group A (G_A)	
	First study visit	**Last study visit**	**First study visit**	**Last study visit**
Disease activity parameters, median [IQR]				
CRP, mg/L (ref < 10) *Missing, n (%)*	0.1 [0.1, 0.3]	0.300 [0.1, 2.1]	0.6 [0.3, 1.3] *1 (7.1)*	0.5 [0.3 1.0] *1 (7.1)*
ESR, mm/h (ref < 15) *Missing, n (%)*	6.0 [5.0, 7.0] *1 (7.1)*	5.0 [5.0, 7.0] *1 (7.1)*	4.0 [4.0, 6.0] *3 (21.4)*	7.0 [5.0, 8.0] *3 (21.4)*
PGA, cm	0.5 [0, 1.8]	1.0 [0, 1.8]	0 [0, 1.0]	0 [0, 0]
PPGA, cm	1.0 [0, 1.8]	0.5 [0, 2.0]	0 [0, 0]	0 [0, 0]
Disease activity in children with JIA (based on the JADAS-10), n (%)				
	n = 12		*n* = 8	
Inactive	4 (33.3)	4 (33.3)	6 (75.0)	7 (87.5)
Minimal	4 (33.3)	5 (41.7)	1 (12.5)	0
Moderate	2 (16.7)	3 (25.0)	1 (12.5)	1 (12.5)
High	1 (8.3)	0	0	0
Missing	1 (8.3)	0	0	0
Disease activity in children with uveitis (based on cells in field by SUN), n (%)				
	n = 8 *(n = 2 idiopathic uveitis, n = 6 JIA-uveitis)*		*n* = 8 *(n = 5 idiopathic uveitis, n = 3 JIA-uveitis)*	
Absent	8 (100)	5 (62.5)	5 (62.5)	7 (87.5)
Minimal	0	2 (25.0)	2 (25.0)	0
Mild	0	0	1 (12.5)	1 (12.5)
Missing	0	1 (12.5)	0	0

Abbreviation *CRP* c-reactive protein, *cm* centimetre, *ESR* erythrocyte sedimentation rate, *JIA* Juvenile idiopathic arthritis, *JADAS* Juvenile Arthritis Disease Activity Score, *IQR* Inter-quartile ranges, *L* litre, *mg* milligram, *PGA* physician global assessment, *PPGA* patient's /parents global assessment, *ref.* reference values, *SUN* standardization of the uveitis nomenclature, G_{A-M} study group adalimumab and methotrexate, G_A study group adalimumab

monitoring, ADA assessment was performed in 10 children of the whole cohort. No ADA were detected.

Additional post hoc exploratory analyses

The eight ADM naïve patients (G_N) consisted of six females and two males with a median age of 12.8 years [IQR 11.0, 15.6] at study visit. They were diagnosed with JIA (62.5%) and idiopathic uveitis (37.5%). All children received 40 mg ADM, five had MTX co-treatment. After first ADM injection, the median ADM C_{min} was 5.8 mg/L [IQR 3.8, 7.3] (Supplementary material S7). Assessed DA over the treatment since ADM start showed a decrease of PPGA and PGA particularly in the first year in both study groups. In G_{A-M}, the PGA and PPGA tended to plateau at a 1 cm, whereas a secondary increase was detected in G_A until first study visit (Supplementary material figure S2A and B).

Discussion

This prospective pilot-study increases understanding of ADM PK and its variability in children with PRD with and without MTX co-treatment. Children with MTX co-treatment (G_{A-M}) had a 27% higher median overall exposure compared to ADM monotherapy (G_A), although median ADM C_{min} were not statistically different between both groups. C_{min} values ≥ 8 mg/L were more frequent observed in G_{A-M} versus G_A (78.6% versus 64.3%). A high variability in ADM concentrations were detected in both study groups. In this study cohort the overall DA was low in both groups, PGA and PPGA of patients in the G_{A-M} group tended to plateau. These findings indicate and strengthen the need for personalized dosing strategies to optimize treatment in children with PRD.

In this study, children with PRD showed high inter-individual variability in ADM exposure, which tended to be increased by MTX co-treatment. The ADM concentrations in most children in this study exceeded concentration ranges reported in adults with RA and other inflammatory rheumatic diseases. In adult patients with RA treated with ADM 40 mg EOW ≥ 12 to 28 weeks, trough concentrations (C_{trough}) ranging from 4.4 to 8 mg/L have been reported to be sufficient to reach adequate clinical response [12, 27]. In addition, C_{trough} cut-off values of 1.3 mg/L at 6 months and of 1.0 mg/L at 12 months of treatment were associated with a good DA control in RA patients [28]. ADM concentrations > 8 mg/L were shown to have no additional

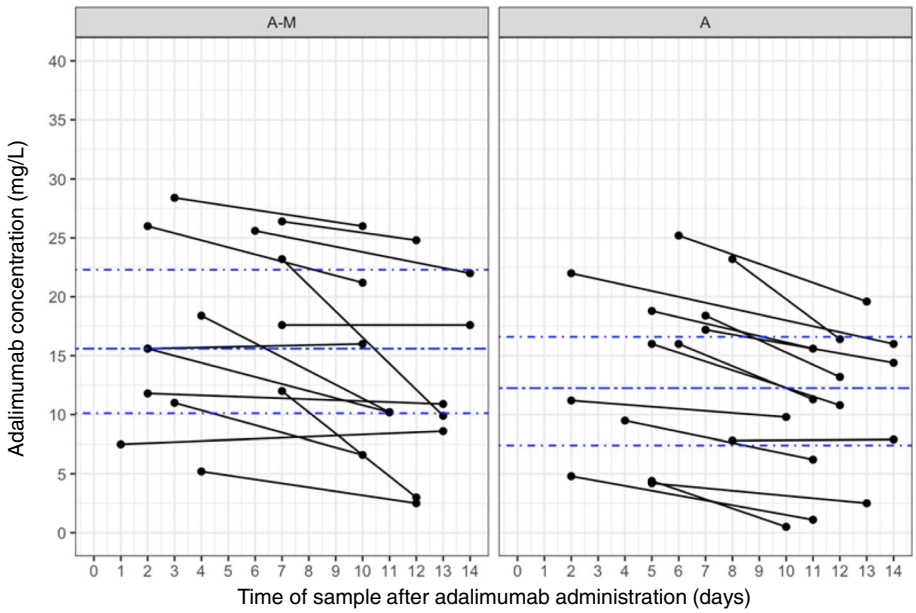

Fig. 3 Adalimumab exposure in children with PRD with and without methotrexate co-treatment depending on sample time. Legend: Adalimumab exposure in children with PRD treated with adalimumab and methotrexate (A-M) and adalimumab alone (A) after ≥ 12 weeks. Maximal adalimumab concentrations were collected after 1 to 9 days (C_{max}) and minimal concentrations (C_{min}) after 10 to 14 days. The *dash blue lines* represent the interquartile ranges [IQR] and the median concentrations per study group (A-M: 15.6 mg/L [IQR 10.1, 22.3]; A: 12.3 mg/L [IQR 7.4, 16.6])

beneficial effect on DA in RA [12]. Chen et al. suggested ADM dose reduction in remitted RA patients with $C_{trough} > 6.4$ mg/L [29]. Population-based ADM concentration ranges associated with clinical response have been described for RA to vary between 2 to 8 mg/L [21]. Further data for spondylarthritis and psoriatic arthritis as well as for other inflammatory diseases, e.g. inflammatory bowel disease or psoriasis indicate ADM target concentrations during maintenance therapy between 1 to 10 mg/L [21, 30–34]. Due to the quite consistent results in different inflammatory conditions, it seems reasonable to extrapolate these target ranges for PRD. In this study, 78.6% of children treated with ADM and MTX and 64.3% of children with ADM monotherapy had $C_{min} \geq 8$ mg/L. The observation towards higher ADM exposure in children compared to adults with RA or other inflammatory diseases is in line with existing studies and raises the question if children with PRD and remission might have higher ADM exposure as needed for DA control. Children with PJIA aged 4 to 17 years treated with ADM 40 mg EOW and MTX had mean C_{trough} of 10.4 mg/L ($n = 14$) at week 16 and 14.4 mg/L at week 60 [35]. PJIA children ($n = 6$) treated with 20 mg ADM EOW and MTX had a mean C_{trough} of 6.73 mg/L after 16 weeks with increase to 14.3 mg/L at week 60 [35]. Doeleman et al. reported median C_{trough} of 14.9 mg/L [IQR 10.3, 16.2] in children with JIA, who had adequate response to ADM 24 mg/m^2 (maximum 40 mg) EOW [13]. Rashid et al. detected median ADM C_{trough} of 10.2 mg/L in children with JIA [22]. In children with ERA treated with ADM 24 mg/m^2 (maximum 40 mg) EOW, mean C_{trough} were 7.5 to 11.8 mg/L between weeks 12 and 52 [20]. Mean ADM C_{trough} in children with PJIA aged 2 to 4 years or age ≥ 4 years weighing < 15 kg treated with ADM 24 mg/m^2 (maximum 20 mg) EOW were comparable to those measured in children aged 4 to 17 years [35, 36]. In this study, we assessed C_{min} and C_{max} ADM concentrations, whether other studies used C_{trough}. To date, it is unclear whether sampling at C_{trough} compared to other time points (e.g. C_{max}) is important [21]. In RA patients, one study observed correlations between time of ADM administration, sampling time, and concentration, while another study did not show any influence of sample timing, with the exception of C_{trough} predicting successful dose reduction [37, 38]. In our study, higher C_{max} compared to C_{min} concentrations strengthen the importance of sampling time, even in long-term treatment. The high inter-individual variability, the ADM exposure exceeding those of other inflammatory conditions, and the possible importance of sampling time highlight the need of better PK understanding in PRD patients to optimize dosing regimen.

Although a trend to highest exposure under MTX co-treatment was observed, no statistical difference in ADM C_{min} for ADM monotherapy or MTX co-treatment was documented. Existing data suggest an influence of

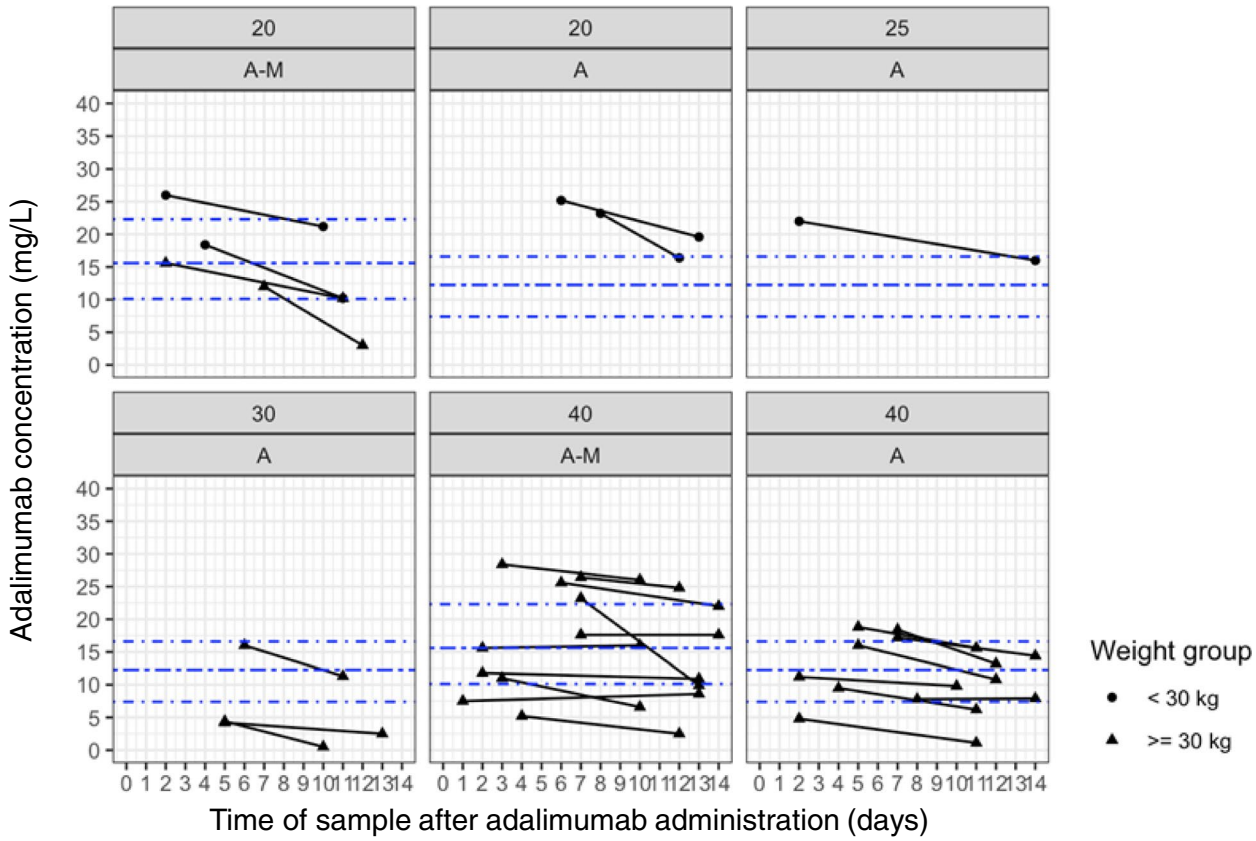

Fig. 4 Adalimumab exposure in children with PRD with and without methotrexate co-treatment depending on dosing. Legend: Adalimumab exposure in children with PRD treated with adalimumab and methotrexate (A-M) or adalimumab alone (A) ≥ 12 weeks with adalimumab absolute doses of 20, 25, 30 or 40 mg. Maximum adalimumab concentrations were collected after 1 to 9 days (C_{max}) and minimum concentrations after 10 to 14 days (C_{min}). The *dash blue lines* represent the interquartile ranges [IQR] and the median concentrations per study group (A-M: 15.6 mg/L [IQR 10.1, 22.3]; A: 12.3 mg/L [IQR 7.4, 16.6]). *Triangle*: body weight ≥ 30 kg, *dot*: body weight < 30 kg

treatment response on ADM exposure. ADM concentrations have been described to be lower in patients with high DA or treatment failure compared to those in remission or with low DA [13, 39–42]. This could be explained by the lower amount of TNF targets in inactive disease resulting in higher ADM exposure with standard dosing than needed for TNF target neutralization [43]. Most children had inactive or minimal DA and have been treated long-term. The overall good DA control might be a possible explanation for the relatively high exposure in this study, raising the question whether the exposure was higher than needed to control DA. This would, strengthen a taper approach after stable remission is achieved. Particularly, as higher ADM exposure in remitted patients is not associated with additional beneficial effects on DA but increased risk of adverse events and higher drug costs [12, 17–19, 27]. However, low exposure may increase the risk for ADA, associated with loss of treatment response [16, 44–46]. The risk of ADA seems to increase over time, whereas MTX co-treatment might reduce the risk [44, 47, 48]. In this study, no standardized ADA assessment was performed. However, in the ten assessed children no ADA were detected. This contrasts with other studies, although comparisons are difficult due to differences in assays [23]. Up to date, no consistent observation that ADA formation is associated with secondary ADA treatment failure has been shown [23] and, there is evidence that ADM with and without MTX co-treatment is effective in long-term-treatment with comparable treatment responses [49, 50]. This highlights the importance of defining concentration target ranges, PK driven personalized treatment approaches and taper strategies in PRD with sustained remission to avoid ADM over- and underexposure.

This study has several limitations. First, the C_{min} difference between $G_{A\text{-}M}$ and G_A was smaller than expected and the inter-individual variability relatively large, and hence the sample size of 28 patients may have been too small to demonstrate significant C_{min} differences. However, PK studies in pediatrics can be designed with six to

12 subjects [51], and we could gain valuable insights in ADM exposure and ADM PK in children with PRD. Second, based on study design, children with stable remission and therefore clinical indication of MTX/ADM discontinuation were replaced, which might be associated with a certain selection bias. As non-adherence or unsteady administration can be a potential confounder by studying drug exposure [42], this study design ensured high quality data of compliant patients. Third, in this pilot-study we focused on ADM exposure in children with PRD and long-term treatment and data was mainly originated from school age children and adolescents. Low ADM concentrations were observed infrequently, what might be explained as no infants participated, C_{min} instead of C_{trough} concentrations were collected and participants had long-term treatment with overall good DA control. As children with lower age and weight might tend to lower bDMARD exposure, their ADM concentrations might be lower [23]. Further research in early disease stages, infants and high disease activity is needed. Fourth, a heterogeneous PRD population (JIA, idiopathic uveitis, CRMO) was included although, most children were JIA patients.

Conclusion

This prospective pilot-study in children with PRD and long-term ADM treatment with and without MTX co-treatment aimed to analyze ADM PK and its variability to better understand ADM exposure in children with PRD. Children with MTX co-treatment ($G_{A\text{-}M}$) had a 27% higher median overall exposure compared to ADM monotherapy (G_A), although C_{min} were not statistically significant different between both groups. A high overall variability in C_{min} was observed in both groups, and most children with PRD had ADM C_{min} exceeding upper target ranges reported for RA (≥ 8 mg/L) and other inflammatory diseases, particularly those with MTX co-treatment (78.6% versus 64.3%). These findings, together with target ADM concentration ranges based on exposure-clinical response relationships, highlights the need of further pharmacological investigation to establish model-based personalized treatment approaches to avoid particularly drug overexposure in children with PRD.

Abbreviations

ADA	Anti-drug antibodies
ADM	Adalimumab
bDMARD	Biological diseases modifying antirheumatic drugs
BSA	Body surface area
cDMARD	Conventional diseases modifying antirheumatic drugs
C_{min}	Minimal concentration (collected 10 to 14 days after last adalimumab administration)
C_{max}	Maximal concentration (collected 1 to 9 days after last adalimumab administration)
CRP	C-reactive protein
CRMO	Chronic recurrent multifocal osteomyelitis
DA	Disease activity
EIA	Enzyme-linked immunosorbent assay
EOW	Every other week
ERA	Enthesitis-associated juvenile idiopathic arthritis
ESR	Erythrocyte sedimentation rate
G	Group
IQR	Interquartile ranges
JADAS	Juvenile Arthritis Disease Activity Score
JIA	Juvenile idiopathic arthritis
mg	Milligram
mL	Milliliter
MTX	Methotrexate
NSAIDs	Non-steroidal anti-inflammatory drugs
OJIA	Oligoarticular juvenile idiopathic arthritis
PD	Pharmacodynamics
PK	Pharmacokinetics
PGA	Physician global assessment
PJIA	Polyarticular juvenile idiopathic arthritis
PPGA	Patients/parents global assessment
PRD	Pediatric rheumatic diseases
RA	Rheumatoid Arthritis
S.C.	Subcutaneous
SD	Standard deviation
SUN	Standardization of the uveitis nomenclature
TDM	Therapeutic drug monitoring
T2T	Treat-to-target
TNF	Tumor necrosis factor
TNFi	Tumor necrosis factor inhibitor
VAS	Visual analog scale
µg	Microgram

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12969-023-00930-8.

Additional file 1: Table S1. Study schedule. **Table S2.** Sample management. **Table S3.** JIA subgroups by study group. **Table S4** Corticosteroids treatment details at inclusion. **Table S5.** Grading by cells in the field of the chamber (SUN) and JADAS-10 scores in PRD patients with juvenile idiopathic arthritis and uveitis. **Table S6.** Univariable and multivariable linear mixed effect models investigating relationship between adalimumab concentrations (log-transformed) and study group, visit age and gender. **Table S7.** Characteristics adalimumab naïve children receiving the first adalimumab dose. **Figure S1.** Adalimumab concentrations and inflammatory marker. **Figure S2.** Adalimumab concentrations and disease activity captured by PGA and PPGA. **Figure S3.** Adalimumab exposure in children with PRD with adalimumab by study group with and without concomitant corticosteroid treatment.

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Authors' contributions

TW, KG, AA, VG, DT, JKD, CM, JvA, GK, MP, AW have contributed to the study design and conceptualization. TW, AW, JKD, CM have performed the data

gathering. Statistical analysis was performed by KG, supervised by AA and VG. The original draft was prepared by TW and KG, supervised by AA, VG, JvA, MP, AW. The manuscript was critically reviewed and edited by all authors. All authors have approved this version to be submitted for publication.

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Availability of data and materials
The data analyzed during the current study are not publicly available due to ethical considerations (no informed consent for further use). In case of reasonable requests, the corresponding author can be contacted, and ethics committee approval might be obtained for further use.

Declarations

Ethics approval and consent to participate
Appropriate ethic approvals from the local responsible competent ethics committees were obtained (Ethic committee Northwest Switzerland (EKNZ) 2019–00916, Ethics Committee of the medical faculty and the University Tuebingen 321/2019B01).

Consent for publication
Not applicable.

Competing interests
All authors declare that they have no COI for this study.

Author details
[1]Pediatric Pharmacology and Pharmacometrics, University Children's Hospital Basel, University of Basel, Basel, Switzerland. [2]Division of Pediatric Rheumatology, Department of Pediatrics and Autoinflammation Reference Centre Tuebingen (arcT), University Hospital Tuebingen, Tuebingen, Germany. [3]Pediatric Rheumatology, University Children's Hospital Basel, University of Basel, Basel, Switzerland. [4]Pediatric Research Center, University Children's Hospital Basel, University of Basel, Basel, Switzerland. [5]Division of Infectious Diseases, Washington University School of Medicine in St. Louis, St. Louis, MO, USA. [6]Université de Tours, service de pharmacologie médicale, Tours France, Université de Tours, EA 4245 T2I, Tours, France.

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