damage (in 36 joints or joint groups) and the JADI-E extraarticular damage (in 5 different organs/systems: ocular, musculoskeletal excluding joints, cutaneous, endocrine, any organ/system).

Results: A total of 953 patients (67.2% female, mean age 7.9 years (SD 4.8)) with JIA were included in ICON after a median disease duration of 6 months (IQR: 3.0–11.1). About half of the patients (46%) had oligoarthritis, followed by rheumatoid factor-negative polyarthritis (RF-PA) (26%) and enthesitis-related arthritis (11%). The mean disease activity score cJADAS10 was 9.8 (6.2) and the mean CHAQ was 0.57 (0.69) at enrolment. Any damage was reported for 58 patients (8.6%) at the 3-year-Follow-up (FU) (mean JADI-A 0.17, mean JADI-E 0.06, JADI-A >0: 6.1%, JADI-E >0: 3.1%). At the 4 year (mean JADI-A 0.17, mean JADI-E 0.07) and 6-year-FU (mean JADI-A 0.13, mean JADI-E 0.12), 8.6% and 10.7% of patients had any damage. The number of patients with articular damage did not change during FU (6-year-FU: 6.5%), whereas the proportion of patients with extra-articular damage slightly increased (6-year-FU: 5.0%). At the 6-year-FU, the most frequently scored joints were the knee joints, followed by the wrist. JADI-E was dominated by eye damage. Among the JIA categories, patients with RF+PA showed most frequently damage (16.7%), followed by patients with enthesitis-related arthritis (15.4%) and extended oligoarthritis (14.3%) at the 6 year FU. The JADI-A score significantly correlated (r=0.27, p<0.001) with the number of active joints and JADI-E with the cJADAS10 (r=0.14, p=0.041) However, there was no significant association between the JADI scores and quality of life (PedsQL), and functional limitations (CHAQ, all r<0.05).

Conclusions: About one in ten patients with JIA has developed any damage three, four and six years after disease onset. Thus, a relevant increase in damage over time does not occur under current therapeutic conditions. Articular and extra-articular damage is similarly frequent.

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THU0553 TNF-INHIBITOR AND LEFLUNOMIDE COMBINATION THERAPY IN POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS IN CLINICAL PRACTICE – LESSONS FROM THE GERMAN BIOLOGICS JIA REGISTRY (BIKER)

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Background: Leflunomide has been shown to be a safe and effective therapy for adult rheumatoid arthritis.

Objectives: Safety and efficacy of combination of TNF inhibitors with leflunomide versus methotrexate for treatment of polyarticular-course juvenile idiopathic arthritis (pcJIA) were assessed in the prospective BIKER registry 2000–2016.

Methods: 3 cohorts of pcJIA patients ageing 3–17 years were analysed: Patients receiving leflunomide starting a TNF inhibitor,[1] a TNF inhibitor starting leflunomide,[2] methotrexate starting a TNF inhibitor.[3] Efficacy was determined using the JADAS response criteria, JADAS-10 minimal disease activiy (MDA) and remission. Safety assessments were based on adverse events reports from the responsible physician.

Results: We identified 94 patients treated with Leflunomid-TNF-inhibitor in combination. 44 started a TNF-inhibitor on background Leflunomide, 50 started Leflunomide on background TNF inhibitor. 1361 patients starting a TNF-inhibitor on background Methotrexate served as control group. Differences in patients' chararteristics at baseline limit direct comparison. Patients of cohort 3 had higher CRP, patients of cohort 2, already treated with a biologic, had lower disease activity parameters such as mean active joint count, physician and patient global disease activity judgement and JADAS10. At month 6, upon MTX +TNFi 54.6%/41.7%/19.6% and upon LEF +TNFi 35.0%/36.2%/13.8% reached JADAS improvement/JADAs minimal disease activity/JADAS remission. Thus significantly more patients with MTX +TNFi reached JADAS improvement (OR 2.22 [1.44–3.44]; p<0.001) while there comparable rates of patients reached JADAS-MDA and JADAS-remission. In the LEF cohorts, there were 95 adverse events in 54 patients (58%) compared to 1845 events in 626 (46%) on MTX (OR 1.6 [1.0–12.4] p=0.031). No differences were noted for the number of infections, nausea or elevated transaminases.

Abstract THU0553 – Table 1. Baseline patients' and disease characteristics

	Cohort 1 (n=44) LEF+TNFi	Cohort 2 (n=50) TNFi+LEF	Cohort 3 (n=1361) MTX+TNFi
Female	28 (64%)	40 (80%)	937 (68.8%)
Age at disease onset, median (IQR)	6.9 (2.1;11.3)	6.2 (1.8;9.6)	7.4 (2.9;11.5)
Disease duration, median (IQR)	6.3 (3.0;8.5)	5.1 (2.0;7.2)	4.1 (1.3;6.0)
ANA positive, n (%)	19 (43%)	28 (56%)	647 (47.5%)
CRP, median (IQR)	14.8 (3;22)	9.5 (0.6;4,.5)	20.8 (1.4;23)
Active joint count, median (IQR)	6.2 (2;7.8)	3.5 (0;5.3)	7.3 (2;9)
Physician global, median (IQR)	5.3 (3.6;7.0)	2.6 (4.3;3.2)	5.4 (3.2;7,6)
Patient global, median (IQR)	4.4 (1.7;6.7)	2.9 (0.6;5.0)	4.4 (2.0;6.5)
CHAQ-DI, median (IQR)	0.59 (0;1))	0.5 (0;0.8)	0.7 (0.1:1.1)
JADAS10, median (IQR)	17 (13.1;19.2)	9.7 (12.5;3.5)	15.2 (11.5;22.5)

Abstract THU0553 – Table 2. Improvement at month 6 and tolerability

	Cohort 1 +2 LEF+TNFi	Cohort 3 MTX +TNFi	OR (Cohort 3 vs. 1+2)	P
JADAS improvement	35.1%	54.6%	2.2 [1.4–3.4]	<0.001
JADAS MDA (≤3.8)/ remission (≤1)	36.2%/ 13.8%	41.7%/19.6%		n.s.
AE (rate)	160 (57.4%)	1845 (46%)	0.63 [0.41–0.96)	0.031
Infections (rate)	37 (23.4%)	410 (22.2%)		n.s.
Nausea (rate)	9 (5.3%)	156 (8.5%)		n.s.
Elevated transaminases (rate)	8 (5.3%)	112 (6.1%)		n.s.

Conclusions: Combination with both leflunomide and methotrexate to treatment with TNF-inhibitors resulted in clinically meaningful improvements with a comparable rate of patients reaching JADAS-MDA and JADAS-remission at month 6 of treatment. Leflunomide turned out to be a well-tolerated alternative to methotrexate for polyarticular JIA.

Disclosure of Interest: None declared

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THU0554 RITUXIMAB (RTX) IN PAEDIATRIC DISEASES: DESCRIBING ITS PHARMACODYNAMICS WITH A FOCUS ON B-CELL DEPLETION AND REPOPULATION, INFECTIONS AND ANTI-DRUG ANTIBODIES

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Background: Rituximab (RTX) is increasingly used in rheumatologic,[1,2] hematologic[3] and renal diseases.[4] The induced B cell depletion can lead to hypogammaglobulinemia and thus an increased risk of infection.[5] B cell depletion is not always achieved, and this has a negative effect on therapeutic response.[6] Anaphylaxis is a frequent side effect of RTX and has been associated with the occurrence of anti-drug antibodies (ADA) against RTX.[7]

Objectives: To describe in different paediatric patient groups the pharmacodynamics of RTX in children by outcome variables, i.e. success of B-cell depletion and time of B cell repopulation, as well as the risk factors for severe infections and anaphylaxis.

Methods: Patient data of children who received RTX between 2008 and 2017 at our centre were retrospectively collected. Three patient subgroups were defined: autoimmune diseases (AID), immune dysregulation (ID) and renal diseases (RD). B cell repopulation was defined as a number above the cut-off value of B cell depletion (=0.050*10^6/l or <2% of the total amount of lymphocytes).

Results: B cell measurements were performed in 53/55 patients. B cell depletion was not achieved in 9 patients. In the 35 patients with B cell repopulation, median time until repopulation was 155 days (IQR 105–222): in the AID group (n=12) 129 days (IQR 77.5–243, p=0.363), in the ID group (n=5) 172 days (IQR 154–181, p=0.574) and in the RD group (n=18) 163 days (IQR 121–229, p=0.847). After RTX treatment, in 36 patients IgG levels were measured of which 14 (39%) had low IgG levels on at least one occasion (median 7 g/L [range 0.6–38.1 g/L]). Severe infections leading to hospitalisation occurred in 15 (27%) cases. An allergic reaction during or directly after RTX infusion was observed in 27 patients (49%). Anaphylaxis, defined as a systemic allergic reaction, characterised by impairment of airway, breathing, circulation or consciousness, occurred in 10 of these patients (18% of total cohort). Seven patients were tested for anti-RTX antibodies of whom 6 tested positive: 5 patients in the AID-group and one patient with renal disease. Allergic reactions occurred in all 6 while RTX failed to induce B cell depletion in 4 of these.

Conclusions: Time-to-B-cell-repopulation after RTX did not significantly differ between different paediatric patients groups. Severe infections were common (27%) in the cohorts studied. It is unclear from our data whether this is merely related to RTX treatment. Presence of ADA against RTX seems to predict failure of B-cell depletion and/or anaphylaxis after RTX treatment.

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THU0555 GUIDELINES FOR JUVENILE IDIOPATHIC ARTHRITIS MANAGEMENT: IS THERE A ROOM FOR COMBINED METHOTREXATE AND LEFLUNOMIDE THERAPY IN THE TREATMENT RECOMMENDATIONS

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Objectives: To set recommendations for the management of children and adolescents living with JIA and assess whether there is a room for combined methotrexate and leflunomide therapy, adopting treat to target approach.
Methods: the treatment guidelines were developed based on systematic review, local studies, formal consensus and feedback. Initiation of methotrexate or leflunomide was recommended for polyarticular JIA children who, after 3 month of treatment, did not respond to methotrexate or leflunomide monotherapy, or those whose DMARD dose could not be optimised; a new management step was introduced where a combination of both medications was administered. This was a multicentre study including 76 JIA patients who had been treated with the combination of methotrexate plus leflunomide. All patients were classified according to the International League of Associations for Rheumatology (ILAR) criteria. Recorded data included: demographics, JIA subtype, reason for starting combined treatment, treatment duration, withdrawals, causes of discontinuation, efficacy and safety. Patients were classified as "responders" or "non-responders". Responders were those patients with articular improvement ≥ACR-Paediatric 30 and/or ocular improvement according to the Standardisation of Uveitis Nomenclature Working Group (SUN) definitions. Efficacy was assessed at 3, 6- and 12 month and outcomes were compared to methotrexate monotherapy.
Results: Out of the 76 children there were, oligoarthritis (34%), polyarthritis (31%), systemic JIA with synovitis (>4 joints) (20%), and psoriatic arthritis (15%). Mean age at initiation of combined therapy 10.2±3.4 years, mean disease duration is 9.4±4.8 months. The combined therapy was superior to methotrexate alone and did not significantly increase the rate of adverse events. ACR-Ped 30 was achieved in 64% at 3 months, 75% at 6 months. This was superior to methotrexate alone (37.3% and 53.8%; p<0.01 at 3- and 6 months respectively). At 1 year, 81% reached Ped 30, 74.5% reached ACR-Ped 50, 64% achieved ACR-Ped 70 whereas 51% met ACR-Ped 90 criteria. There were no serious adverse events. One of the two DMARDs was stopped in 51% of the children; of them: 25% were due to adverse events, clinical remission in 25% whereas 21% were switched to anti-TNF therapy according to guidelines due to inefficacy or loss of efficacy. All patients who had had uveitis responded well and achieved clinical remission.
Conclusions: For the children with polyarticular JIA who did not respond to monotherapy with methotrexate, combination of methotrexate and leflunomide treatment appeared to be efficacious and maintain a durable response. The current recommendation would be to use combined methotrexate and leflunomide in children with polyarticular JIA who are either intolerant to higher methotrexate doses or who did not have a satisfactory response to methotrexate. The combination should be considered prior to the use of a biologic agent.
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THU0556 IMPACT OF METHOTREXATE ON GROWTH IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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Background: Juvenile idiopathic arthritis (JIA) is a heterogeneous group of chronic inflammatory disease which could be responsible for functional impairment and severe growth disturbance. Conventional disease-modifying antirheumatic drugs, such as methotrexate (MTX), may improve growth velocity especially by regulating systemic inflammation.
Objectives: The objective of this study was to evaluate the effect of MTX on growth parameters in pre-pubertal children with JIA and to determine the factors affecting the growth velocity.
Methods: We assessed height and changes in the height standard deviation score (SDS) at disease onset, at the onset of MTX and at the last follow-up visit in a cross-sectional study of JIA children. All patients were pre-pubertal when MTX began and were followed for at least 6 months afterward. We compared growth parameters (height, growth rate, weight and body mass index (BMI)) in responders and non-responders to MTX. The growth rate was defined as the number of millimetres of height acquired during 1 year. Associations between changes in the height SDS and discrete variables were evaluated using chi-square or Fisher's exact tests. The significance level was set at 0.05.
Results: We enrolled 36 pre-pubertal children with JIA (24 boys and 12 girls) who had been treated with MTX orally. Median patient age was 6.2 years[4–13] at the onset of MTX and 8.4 years [6.1–14.9] at the latest follow-up. The median disease duration was 2.7 years [2.5–5.3]. Twenty-one patients (58.3%) had oligoarticular JIA, 2 patients (5.5%) had systemic JIA, 10 (27.7%) had polyarticular JIA and 3 (8.3%) had enthesitis-related arthritis. Nineteen children (52.7%) had received corticosteroids during an average period of 1.7 years [0.6–3] with a mean of 10 mg/day of prednisone or equivalent. The median duration of MTX at the latest follow-up was 3.1 years [0.62–5.5] with a mean MTX dose of 10 mg/m2/week.[10–15] Twenty-eight patients responded to MTX treatment and 8 did not. There were no significant differences between the responders and non-responders for age at treatment initiation, disease duration and mean MTX dose. At MTX onset, no significant differences between the two groups in terms of height (p=0.52), growth rate (p=0.08), weight (p=0.74) and BMI (p=0.9) were found. One year after MTX therapy, mean height (0.2 versus −1.1; p=0.03), mean growth rate (0.5 versus −2.9 SDS; p=0.01), mean weight (0.4 versus −2.3 SDS; p=0.01) and mean BMI (0.6 versus −1.9; p=0.04) were significantly higher in the responder group than in non responders, respectively. At the latest follow-up, this increase was significantly maintained for growth rate (p=0.001) and height (p=0.002) in the responder group. In the multivariate analysis, patients who required more than 10mg/m^2/week of MTX, systemic JIA and patients with reliance on steroids had a significantly lower growth velocity after the onset of MTX (p<001, p=0.02, p=0.02 respectively).
Conclusions: In our study, the increase in growth parameters in pre-pubertal children with JIA was associated with a better control of the disease activity under MTX therapy.
Disclosure of Interest: None declared
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THU0557 THERAPEUTIC DRUG MONITORING OF BIOLOGICALS IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS (JIA): AN OVERVIEW OF CURRENT PRACTICE IN ANTI-TNF THERAPY

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Background: Juvenile idiopathic arthritis (JIA) is the most prevalent paediatric rheumatic disease.[1] Long term complications include physical disability and a decreased quality of life.[2,3] Since the introduction of anti-TNF drugs for JIA, its prognosis has improved significantly.[1] Personalised medicine is the next step to improve treatment in JIA. Anti-TNF trough levels and demonstration of the presence of anti-drug antibodies (ADA) could help individualise treatment decisions in JIA patients, but evidence supporting this is missing.

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