Isorhamnetin inhibited the production of NO and PGE₂, and the expression of iNOS and COX-2. The production of COMP and CTX-II were also inhibited in MIA-induced OA rats.

Conclusion: Isorhamnetin may modulate the inflammatory progression of OA in MIA-induced OA rats. The prevention of cartilage damage was found in OA after adequate isorhamnetin treatment. Isorhamnetin may serve as a potential agent for the management of OA.

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FRI0532

SONIC HEDGEHOG PROMOTES PROLIFERATION, MIGRATION AND INVASION OF FIBROBLAST-LIKE SYNOVIOCYTES IN RHEUMATOID ARTHRITIS VIA P38-MAPK SIGNALING

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Background: Abnormal activation of Sonic hedgehog (Shh) signaling has been found in synovium from patients with rheumatoid arthritis and inhibition of Shh signaling pathway suppresses the proliferation and migration of fibroblast-like synoviocytes in rheumatoid arthritis (RA-FLS). However, the mechanism how Shh signaling promotes tumor-like behavior of RA-FLS is not well elucidated.

Objectives: In this study, we aimed to investigate the effect of Shh on p38 MAPK kinase signaling and hypothesized that Shh promotes proliferation, migration and invasion of RA-FLS via p38-MAPK signaling.

Methods: Cultured RA-FLSs were treated with Smoothed agonist (SAG) or IL-1 β combined with Smoothed antagonist (Cyclopamine). The levels of phosphorylation of p38, its upstream kinases including TGF β activated kinase 1 (TAK1), MKK3, MKK6 and downstream target MAPKAPK2 (MK-2) were determined by western blot. The functional state of p38 was determined using in vitro kinase assay. Cell proliferation was evaluated by Cell Counting Kit -8 assay. Cell migration and invasion were performed by Transwell assay. The expression of matrix metalloproteinase proteins (MMPs), IL-6 and IL-8 was examined by real-time PCR.

Results: SAG rapidly increased phosphorylation of p38, TAK1, MKK3, MKK6 and MK2 in RA-FLS and combination of SAG and p38 inhibitor significantly decreased the phosphorylation of these kinases ($P < 0.01$). Inhibition of Shh significantly decreased the levels of phosphorylation of p38, TAK1, MKK3, MKK6 and MK2 in IL-1 β stimulated RA-FLS ($P < 0.05$). In vitro kinase assay showed that stimulation of SAG significantly increased the kinase activity, and the kinase activity was inhibited by p38 inhibitor. Furthermore, SAG increased cell proliferation, migration, invasion and production of MMP1, MMP3, MMP13, IL-6 and IL-8. However, these enhanced activities of RA-FLS were inhibited in the presence of p38 inhibitor.

Conclusion: The study indicates that Shh is associated with activation of p38 MAPK signaling in RA-FLS and Shh may promote the tumor-like behavior of RA-FLS via p38 signaling.

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Paediatric rheumatology

FRI0533

ETHNICITY AND NEONATAL LUPUS RISK IN A LARGE MULTI-ETHNIC COHORT

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Background: Neonatal Lupus (NL) is an acquired autoimmune disorder of newborns secondary to the transplacental passage of maternal anti-Ro

and/or anti-La. Approximately 2% of children exposed to these antibodies develop NL. Prior studies have suggested that babies of non-European ancestry have a higher proportion of cardiac NL when compared to babies of European ancestry. This finding has not been consistently replicated.

Objectives: To examine the association between ethnicity and clinical manifestations of NL in our multi-ethnic population.

Methods: We conducted a cohort study of our large, multi-ethnic NL clinic population. The Neonatal Lupus clinic at the Hospital for Sick Children, Toronto, Canada was established in 1986. Children born to anti-Ro and/or anti-La antibody positive mothers are referred to the NL clinic. Antenatal testing is completed due to maternal rheumatologic diagnosis, a prior child born with NL and/or a history of symptoms that prompted physician testing for these antibodies. Beginning in 2011, families routinely reported ethnicity (Canadian census categories). We divided our NL patient cohort in European and non-European groups; the non-European group includes patients of African, Latin American, East Asian, South Asian and Mixed non-European ancestry (i.e. combination of two or more of non-European ethnicities). We included children assessed in the NL clinic ≤ 1 year of age between January 2011 to April 2018. There were 59 children censored for this analysis (7 missing ethnicity and 52 Mixed European-Non European ancestry). We analyzed prospectively collected data from our NL database, on specific NL manifestations: cardiac (heart block, myocarditis, endocardial fibroelastosis), dermatologic (typical rash of NL), hematologic (cytopenias), hepatic (transaminitis) and neurologic (macrocephaly). The frequency of NL clinical manifestations was compared among ethnicity groups (Fisher's exact test). We tested the association between ethnicity and NL clinical manifestations in logistic models.

Results: Our study included 301 children, 149 (50%) female and 164 (55%) with NL (Table 1). The median follow-up period was 12.2 months (IQR: 4.8, 28.8 months). Ethnicity data was available for 294 (98%) of the children. The non-European group (40%) was comprised of East Asian (14%), South Asian (13%), African (10%), Latin American (2%) and Mixed Non-European ancestry (17%). We did not observe a difference between European and Non-European babies in the proportion with NL, nor any difference in the frequency of specific NL manifestations (p-values > 0.3).

Conclusion: In our multiethnic NL cohort of children born to mothers with positive anti-Ro and/or anti-La antibodies, there was no association between ethnicity and NL, nor specific NL manifestations. Future analyses will examine the effect of maternal ethnicity and rheumatic disease status on the risk of NL and specific NL manifestations.

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Table 1. Neonatal Lupus Clinical Manifestations in European and non-European children.

	European n = 99 (%)	Non-European n = 143 (%)	p-value
Female	45 (45%)	72 (50%)	0.51
NL	48 (48)	80 (56)	0.29
Cardiac	10 (21)	11 (14)	0.32
Dermatologic	11 (23)	19 (24)	1.00
Hematologic	18 (38)	33 (41)	0.71
Hepatic	26 (54)	42 (53)	1.00
Neurologic	6 (13)	4 (5)	0.17

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FRI0534

ORAL GLUCOCORTICOID AND NEWLY TREATED DIABETES MELLITUS, HYPERTENSION, AND THROMBOSIS IN CHILDREN WITH CHRONIC DISEASES

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Background: Systemic glucocorticoid use is associated with a well-known spectrum of toxicities. Nonetheless, the risks of cardiometabolic complications in children are poorly understood.

Objectives: We sought to quantify rates of newly treated diabetes mellitus, hypertension, and venous thromboembolism (VTE) associated with oral glucocorticoid exposure in children. We hypothesized that oral glucocorticoids were associated with each complication in a dose-dependent manner, most strongly with current or recent glucocorticoid exposure.

Methods: Using Medicaid claims data (2000-2010), we identified children ages 1-18 diagnosed with immune-mediated diseases (inflammatory bowel disease, juvenile idiopathic arthritis, or psoriasis) or a non-immune comparator condition (attention-deficit/hyperactivity disorder) based on diagnostic codes $\pm$ pharmacy claims. We studied time-varying oral glucocorticoid exposures using pharmacy claims after a ≥ 6 -month glucocorticoid-free baseline period, categorizing dose as low (<0.25 mg/kg/day), medium (0.25-0.99 mg/kg/day), or high (≥ 1 mg/kg/day) based on prescribed prednisone-equivalent dosage and age-/sex-imputed weights. Primary outcomes were incident treatment of diabetes (type 1 or 2), hypertension, and VTE. We used Cox regression and weighted cumulative exposure models¹ to estimate adjusted hazard ratios (aHRs) and number needed to harm (NNH) for varying patterns of glucocorticoid exposure.

Results: We followed 932,517 children (21.3% glucocorticoid-exposed) for 1.6 million person-years. Glucocorticoid usage varied by disease (Table). After adjusting for age, sex, race/ethnicity, calendar year, inclusion diagnosis, comorbidities, other medications, and healthcare usage, we found strong dose- and time-dependent relationships between glucocorticoid exposure and rates of newly treated diabetes, hypertension, and VTE (Figure 1). These effects increased with longer durations of exposure and declined within 6 months after stopping (Figure 2). Sustained low-dose exposures (e.g., 0.1 mg/kg/day) appeared relatively safe (aHR <1.2), but risks increased even with brief high-dose exposures (2 mg/kg/day $\times$ 7 days) (aHR 1.7-2.2). Risk differences were highest for hypertension (number needed to harm [NNH]: 2 mg/kg/day $\times$ 7 days, 6,206-17,894; 2 mg/kg/day $\times$ 30 days, 233-671) and lowest for VTE (NNH: 2 mg/kg/day $\times$ 7 days, 54,886-612,350; 2 mg/kg/day $\times$ 30 days, 1,977-22,045). Absolute risks were higher for children with immune-mediated diseases (e.g., diabetes, 2 mg/kg/day $\times$ 30 days, NNH: 424-691) than for those with ADHD (NNH: 959).

Table. Distribution of dose and duration of oral glucocorticoids by disease cohort.

Cohort	Aspect	25th %	50th %	75th %
ADHD	Duration	5	5	7
ADHD	Dose	0.41	0.74	1.24
IBD	Duration	5	27	47
IBD	Dose	0.29	0.59	0.92
JIA	Duration	5	9	30
JIA	Dose	0.16	0.33	0.88
PSO	Duration	5	6	10
PSO	Dose	0.3	0.63	1.14

Units: duration, days; dose, mg/kg/day.

Figure 1. Associations of glucocorticoid timing and dose with newly treated outcomes based on Cox regression models.

aHR, adjusted hazard ratio; CI, confidence interval

Figure 2. Associations of glucocorticoid timing and dose with newly treated outcomes based on weighted cumulative exposure models.

Line plots show associations of daily glucocorticoid dose, duration, and recency with outcomes.

Conclusion: In children with various chronic conditions, current oral glucocorticoid use is strongly associated with newly treated diabetes, hypertension, and VTE in a dose- and duration-dependent fashion. Hypertension is a more common glucocorticoid-related complication than diabetes or VTE, but in absolute terms, all of these complications are uncommon in children.

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FRI0535 COMPARISON OF SERUM BIOMARKERS FOR THE DIAGNOSIS OF MACROPHAGE ACTIVATION SYNDROME COMPLICATING SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS: CLINICAL SIGNIFICANCE OF SERUM NEOPTERIN LEVELS

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Background: Macrophage activation syndrome (MAS) is a severe life-threatening condition that complicates systemic juvenile idiopathic arthritis (s-JIA). Differentiating MAS from these conditions is essential for selecting appropriate therapeutic interventions in a timely manner. However, there is no definite biomarkers that can effectively diagnose MAS.