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Background: Juvenile idiopathic arthritis (JIA) is a well-known chronic rheumatic disease of childhood characterised by progressive joint destruction and severe systemic complications.
Immune cells are known to trigger the pathophysiological cascade in JIA, but there is little information regarding the contribution made by Mesenchymal stem cells (MSCs). These cells are able to modulate the immune response and decrease the level of pro-inflammatory cytokines. With addition of regenerative property it makes MSCs potential candidates for clinical application as immunosuppressants in treatment of autoimmune diseases.
Objectives: To investigate MSCs proliferation, viability and immunomodulatory function in JIA and healthy children.
Methods: MSCs were separated from peripheral blood (PB) and synovial fluid (SF) of JIA patients and healthy controls. Cell proliferation rate was counted by Population doublings per day (PDD) during 9 days, in the last of which alamarBlue™ assays were performed to assess cell viability. Due to measure senescence MSCs were stained with SA-β-galactosidase. Immunofluorescence was used to examine the expression of p16, p21, p53. Oxidative stress was measured with DCFH-DA. Cell cycle analysis was evaluated with Propidium Iodide and analysed by Accuri® C6 Flow Cytometer.
Commercially-available bone marrow mesenchymal stem cells (BM-MSCs) were treated with graded concentrations of pro-inflammatory cytokines (0.1-100 ng/ml) with following examination of cell viability. Mixed lymphocyte reactions (MLR) were performed to measure MSC immunomodulatory ability *in vitro*.
Results: The growth kinetics of JIA-MSCs were different from healthy controls. JIA-MSCs divided slowly and appeared disorganised with large cytoplasm and loads of outgrowth. They demonstrated a decrease in cell proliferation (negative PDD) and metabolic activity. Difference in growth kinetics and metabolic activity were found inside the JIA PB group with some evidence of response following biological treatment. Thus, PB-MSCs from patients treated with TNFi and anti-IL6 medications had notably higher cell proliferation and metabolic activity against JIA patients received other therapy. Considering this difference, it was hypothesised that cytokines obtained in a high amount in PB and SF of JIA patients may influence MSCs viability. To prove this BM-MSCs were treated with cytokines and demonstrated a dose-dependent decrease in metabolic activity significantly after TNFα and IL1, no significantly after treatment with IL6. Both BM-MSCs treated with cytokines and JIA-MSCs displayed high level of reactive oxygen species.
Cell cycle analysis revealed that JIA-MSCs were arrested in G0/G1 phase with low number of mitotic cells. In addition, the number of senescence-associated SA-β-gal-positive cells was notably higher in JIA-MSCs. Furthermore, JIA-MSCs expressed high level of immunofluorescence for p16, p21 and p53 which played an important role in regulating the senescence progress of MSCs.
Results of MLR showed the ability of BM-MSCs to decrease the percentage of activated T-helpers, T-suppressors, B-cells and natural killers proliferation, while JIA-MSCs lost this property.
Conclusion: Taken together current research has demonstrated that under the influence of proinflammatory cytokines JIA-MSCs suffered from oxidative stress and disruption of metabolic activity acquire senescent morphology, shorten of telomere length, arrest in G0 phase of cell cycle and finally loss of immune regulation. We are continuing our research to determine the mechanisms that are responsible for the impaired phenotype with the aim of identifying new therapeutic strategies for the treatment of JIA.
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THU0496 APPLICATION OF SYSTEMS BIOLOGY-BASED IN SILICO TOOLS TO OPTIMIZE TREATMENT STRATEGY IN STILL'S DISEASE

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Background: Systemic Juvenile Idiopathic Arthritis (sJIA) and Adult Onset Still's Disease (AOSD) are manifestations of an autoinflammatory disorder with complex pathophysiology and significant morbidity, together also termed Still's disease.
Objectives: To investigate the optimal treat-to-target strategy for Still's disease by in silico models based on systems biology.
Methods: Molecular characteristics of Still's disease and data on biological inhibitors of interleukin (IL)-1 (anakinra, canakinumab), IL-6 (tocilizumab, sarilumab), glucocorticoids as well as conventional disease-modifying anti-rheumatic drugs (DMARDs, methotrexate) were used to construct in silico mechanisms of action (MoA) models by means of Therapeutic Performance Mapping System technology (TPMS). TPMS combines artificial neuronal networks (ANN), sampling-based methods and artificial intelligence. The models were validated with publicly available expression data from sJIA patients (Fig.1).

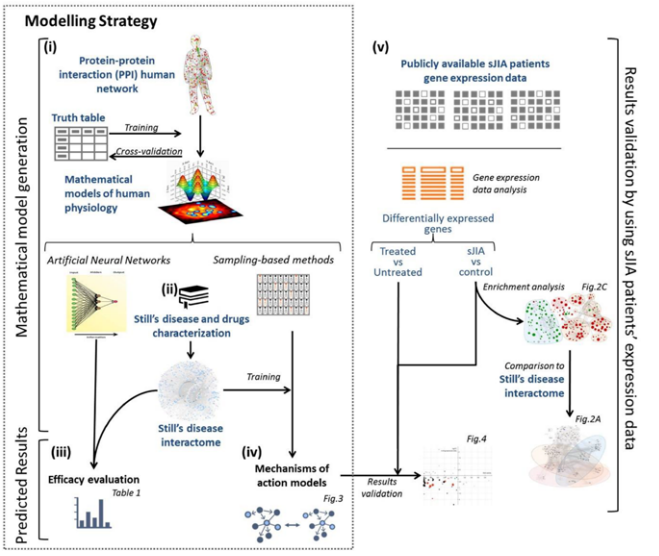

Figure 1. Schematic TPMS approach used to evaluate the Still's disease treatments efficacy and their MoA

Results: Biologicals demonstrated more pathophysiology-directed efficiency than non-biological drugs. IL-1 blockade mainly acts on the innate immune system, while IL-6 signaling blockade has a weaker activity on the innate immunity and rather affects the adaptive immunity (Table 1). The MoA models showed that the IL-1β inhibitor canakinumab is more efficient than the IL-6 receptor inhibiting antibody tocilizumab in the autoinflammatory/systemic phases of Still's disease. MoA models reproduced 67% of the information obtained from expression data (Fig.2).

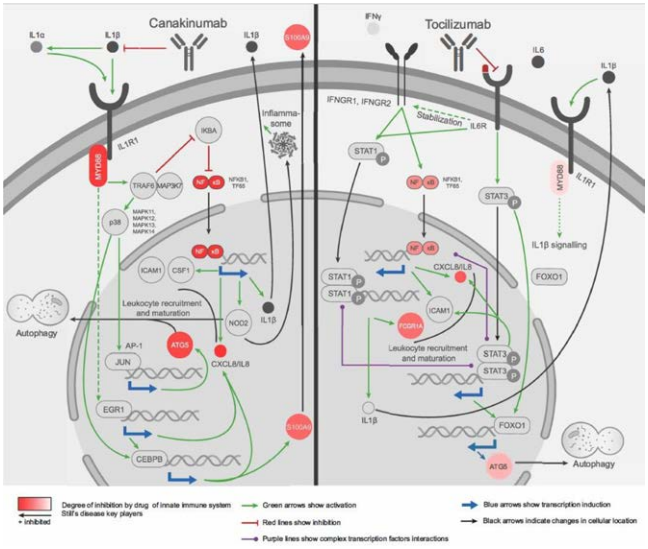

Figure 2. Systems biology-based MoA models of canakinumab and tocilizumab focused on innate immune system modulation. Canakinumab preferably modulates NF-κB, IL-8 (CXCL8), MyD88, S100A9 and ATG5, which are involved in processes of general innate immune inflammation, neutrophil recruitment, activation and autophagy, whereas tocilizumab preferably modulates FCGR1, which is involved in neutrophil activation

Conclusion: Systems biology-based modelling supported the preferred use of biologics as immunomodulatory treatment strategy for Still's disease. This further encourages early IL-1β blockade in initial autoinflammatory/systemic phases of Still's Disease to prevent the development of disease or drug-related complications. Further studies are needed to determine the optimal timeframe of the window of opportunity for canakinumab treatment.

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Paediatric rheumatology

THU0497

MAINTENANCE OF MINIMAL DISEASE ACTIVITY OR INACTIVE DISEASE STATUS AND PATIENT-REPORTED OUTCOMES IN INDIVIDUAL PAEDIATRIC PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS TREATED WITH SUBCUTANEOUS ABATACEPT

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Background: Maintenance of clinical response over time has been shown in individual patients (pts) with polyarticular-course juvenile idiopathic arthritis (pJIA) treated with SC abatacept (ABA).[1] It is unknown whether each individual pt with sustained efficacy also consistently maintains the previously reported shorter-term benefits on patient-reported outcomes (PROs)[2,3] over time.
Objectives: Investigate whether combined efficacy and stringent, optimal PRO responses to ABA treatment are maintained by individual pts with pJIA over time.
Methods: In this analysis of the intent-to-treat population, pts in two age cohorts (2–5 and 6–17 yrs) who achieved clinical response to weekly SC ABA (10–<25 kg [50 mg], 25–<50 kg [87.5 mg], ≥50 kg [125 mg]) at Mo 4 (time point of primary pharmacokinetic endpoint[4]) were followed for 2 yrs. Stringent efficacy outcomes (Juvenile Arthritis Disease Activity Score 27 [JADAS27] minimal disease activity [MDA; ≤3.8] and inactive disease [ID; ≤1] status) were combined with optimal PRO endpoints (childhood [C]HAQ-DI=0, Parental Global Assessment [PaGA] ≤1 and Pain visual analogue scale [VAS] <35). Combined efficacy and PRO responses were analysed at Mos 4, 13 and 21.
Results: 219 pts entered the study (46 [21.0%] 2–5 yrs; 173 [79.0%] 6–17 yrs); a subgroup of these pts achieved a clinical response at Mo 4 (Table 1). Many pts who achieved JADAS27 MDA or JADAS27 ID combined with optimal PROs at Mo 4 sustained their response at Mo 13, and at both Mo 13 and Mo 21 in the 2–5-yr and 6–17-yr cohorts (Table 1). Across the cohorts, 33–88% of pts maintained a combined JADAS27 MDA with optimal PRO responses through Mo 21. Where estimable, median times to combined efficacy and specific optimal PRO responses were consistent across the cohorts (Table 2; Figs 1, 2).

Table 1. Proportion of pts with combined efficacy and optimal PRO responses at Mos 4, 13 and 21

Endpoint	Responders at Mo 4		Responders at Mos 4 and 13*		Responders at Mos 4, 13 and 21*	
	2–5 yrs (n=46)	6–17 yrs (n=173)	2–5 yrs	6–17 yrs	2–5 yrs	6–17 yrs
JADAS27 MDA and CHAQ-DI=0	9 (20)	34 (20)	5/9 (56)	25/34 (74)	3/9 (33)	16/34 (47)
JADAS27 MDA and PaGA ≤1	8 (17)	14 (8)	8/8 (100)	7/14 (50)	7/8 (88)	5/14 (36)
JADAS27 MDA and Pain VAS <35 mm	28 (61)	70 (41)	25/28 (89)	58/70 (83)	21/28 (75)	43/70 (61)
JADAS27 ID and CHAQ-DI=0	7 (15)	20 (12)	2/7 (29)	13/20 (65)	1/7 (14)	9/20 (45)
JADAS27 ID and PaGA ≤1	6 (13)	10 (6)	4/6 (67)	4/10 (40)	4/6 (67)	4/10 (40)
JADAS27 ID and Pain VAS <35 mm	17 (37)	31 (18)	10/17 (59)	22/31 (71)	8/17 (47)	17/31 (55)

Data are n (%) or n/N (%). *% based on n of pts who achieved response at Mo 4 (denominator)

Table 2. Kaplan–Meier estimates for median (95% CI) times (mos) to achieving combined efficacy and optimal PRO responses

Endpoint	2–5 yrs	6–17 yrs
JADAS27 MDA and CHAQ-DI=0	21.5 (6.8, NE)	21.5 (13.1, 24.4)
JADAS27 MDA and PaGA ≤1	NE (15.9, NE)	24.6 (24.3, NE)
JADAS27 MDA and Pain VAS <35 mm	2.8 (1.9, 2.9)	3.8 (3.7, 6.6)
JADAS27 ID and CHAQ-DI=0	NE (18.4, NE)	24.4 (18.7, NE)
JADAS27 ID and PaGA ≤1	NE (21.3, NE)	24.6 (24.3, NE)
JADAS27 ID and Pain VAS <35 mm	3.8 (3.8, 10.3)	13.2 (10.3, 15.9)

NE=not estimable

Conclusion: Many individuals with pJIA who achieved stringent efficacy and PRO measures with weekly SC abatacept by Mo 4 sustained them over 2 years. Time to achieve combined efficacy and Pain VAS <35 response was shorter than that for PaGA ≤1 and CHAQ-DI=0.

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