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FRI0006

ASSOCIATION BETWEEN INTERLEUKIN-10 POLYMORPHISMS AND JUVENILE IDIOPATHIC ARTHRITIS: A META-ANALYSIS

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Background: Juvenile idiopathic arthritis (JIA) is the most common chronic arthritis in children. JIA is a heterogeneous group of complex diseases and the result of a combination of genetic and environmental factors. Multiple genes contribute to the risk of developing JIA. Interleukin-10 (IL-10) is an anti-inflammatory cytokine that is associated with inflammatory diseases. IL-10 is considered a candidate gene for JIA based on its chromosomal location and functional relevance.

Objectives: IL-10 genetic polymorphisms associated with JIA were previously identified, especially in haplotypes studies. However, results from different studies have been inconsistent. Thus, we investigated whether IL-10 polymorphisms were associated with susceptibility to JIA.

Methods: A meta-analysis was conducted of the associations between the IL-10–1082G/A, –819 C/T, and –592 C/A polymorphisms and JIA. A total of eight studies involving 1495 patients and 1670 controls were considered in the meta-analysis. This meta-analysis was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results: There was no association between the IL-10–1082G/A, –819 C/T, and –592 C/A polymorphisms and JIA in allele contrast and any of the genetic models (allele contrast: OR=0.90, 95% CI=0.79–1.02, p=0.09; OR=0.97, 95% CI=0.83–1.13, p=0.68; OR=0.92, 95% CI=0.81–1.06, p=0.24, respectively). Subgroup analyses revealed a significant association between the IL-10–1082 G allele and systemic JIA (OR=0.80, 95% CI=0.67–0.96, p=0.02). Meta-analysis of the IL-10 haplotype revealed no association between GCC, ACC, and ATA haplotypes and JIA.

Abstract FRI0006 – Figure 1. ORs and 95% CIs of the individual studies and pooled data for the associations between the IL-10 -1082 G allele and systemic JIA

Conclusions: This meta-analysis indicated lack of associations between IL-10 polymorphisms and susceptibility to JIA. However, there was a significant association between IL-10–1082 G allele and systemic JIA.

Abstract FRI0007 – Table 1

	N	Summary Random Effect Model		DOR Random Effect Model			Adjusted RDOR Random Effect Model		
		Sensitivity	Specificity	DOR	IC 95%	p	RDOR	IC 95%	p
Total	16	0.75	0.72	11.5	(6.5–20.1)	<0.001	1.15	(0.9–1.4)	0.117
Year before 2013	5	0.64	0.89	20.6	(4.5–94.4)	0.001	15.7	(4.8–51.8)	0.001
2013 and after	11	0.80	0.65	9.2	(5.2–16.2)	<0.001	1.0		
Countries in Asia	4	0.88	0.74	23.6	(8.8–63.5)	0.098	10.4	(3.2–33.7)	0.002
Countries in Europe	12	0.70	0.71	8.9	(4.7–17.5)	<0.001	1.0		
Joint included									
MCP	12	0.79	0.74	16.0	(8.1–31.9)	<0.001	11.3	(3.0–41.9)	0.003
MTP	4	0.78	0.67	9.6	(5.1–18.2)	<0.001	2.8	(1.2–6.3)	0.021
Wrist	11	0.82	0.73	18.6	(8.4–40.9)	<0.001	1.0		
Cutoff criteria									
GS≥1	6	0.86	0.57	16.5	(9.6–28.3)	0.503	6.0	(1.6–22.5)	0.009
GS≥2	5	0.66	0.69	5.6	(2.9–10.5)	0.025	2.4	(0.7–7.6)	0.139
GS≥3	3	0.74	0.79	12.9	(5.6–29.9)	0.314	3.1	(0.7–14.1)	0.132
PD≥1	9	0.67	0.72	7.9	(4.3–14.9)	0.003	3.9	(1.3–11.7)	0.018
PD≥2	7	0.73	0.77	9.6	(4.1–22.5)	<0.001	3.3	(0.9–11.8)	0.059
PD≥3	6	0.38	0.84	4.5	(5.2–9.4)	<0.001	2.0	(0.29–14.4)	0.462
Tenosynovitis	3	0.27	0.65	0.73	(0.01–82.8)	<0.001	1.0		
Erosions	6	0.40	0.84	3.3	(1.7–6.2)	0.242	1.0		

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FRIDAY, 15 JUNE 2018

Rheumatoid arthritis – prognosis, predictors and outcome

FRI0007

PERFORMANCE OF MUSCULOSKELETAL ULTRASONOGRAPHY (MSUS) AND OPTIMAL CUTOFF CRITERIA FOR PATIENTS AT RISK FOR RHEUMATOID ARTHRITIS: A META-ANALYSIS

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Background: The identification of patients with rheumatoid arthritis (RA) in the early stages of the disease leads to early treatment and improved outcomes. MSUS is a relatively easy, accessible and low cost method, which has been proven more sensitive in detecting findings suggestive of inflammatory arthritis than clinical or radiographic exams. Evidence shows that MSUS seems to bring additional knowledge when assessing the joints on patients with suspected RA, however, there is still controversy whether it can improve substantial discriminatory value for early arthritis.

Objectives: To assess the diagnostic value of MSUS and optimal cutoff criteria for the diagnosis of RA in patients with arthralgia and non-classified arthritis.

Methods: We conducted a meta-analysis for original studies evaluating ultrasound on patients with arthralgias and non-classified arthritis, published in Pubmed, EMBASE and Cochrane databases until December 2017. Statistical analysis included i) the calculation of sensitivity and specificity for ultrasound ii) summary receiver operating characteristic (SROC) curves for a linear regression model iii) I squared test for heterogeneity.

Results: Sixteen studies were included in the review. The overall sensitivity and specificity were 0.75 (95% CI 0.62, 0.88) and 0.72 (95% CI 0.60, 0.83) respectively. The overall diagnostic odds ratio (DOR) was 11.45 (95% CI 6.52, 20.11). The relative DOR for studies performed in Asia (10.43, p=0.002), published before 2013 (15.71, p=0.001) and involving MCP (11.27, p=0.003) and MTP (2.78,

p=0.021) exhibited higher diagnostic performance. Meta-regression after adjusting for country, year, and type of joint involved, showed that Grey Scale (GS) ≥ 1 RDOR 6.0 (95% CI 1.6, 22.5; p=0.009) and Power Doppler (PD) ≥ 1 RDOR 3.9 (95% CI 1.3, 11.7, p=0.018) had greater diagnostic accuracy when compared to higher cutoff values.

Conclusions: MSUS is a valuable diagnostic tool when used in patients with arthralgia and at risk for RA. GS ≥ 1 and PD ≥ 1 combined have better discriminative ability for diagnosing RA due to the overall specificity is greater than for either alone.

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FRI0008

TISSUES ARE DIFFERENTLY MODULATED BY TOCILIZUMAB AND METHOTREXATE; ASSESSMENT OF CONNECTIVE TISSUE METABOLITES IN THE AMBITION STUDY

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Background: Response to any treatment in rheumatoid arthritis (RA) is assessed by symptomatic changes, such as swollen joint count. Such assessments does not provide information regarding the effect of the treatment at tissue level. Chronic inflammation has a detrimental effect resulting in elevated levels of tissue remodelling and the release of extracellular matrix (ECM) metabolites into the circulation. The tissues consist mainly of interstitial matrix, basement membrane and cells, which are all affected by auto-immune disorders. Tissue metabolites can be measured in serum as biomarkers of tissue remodelling.

Objectives: The purpose was to investigate if tissue remodelling is differently modulated by tocilizumab (TCZ) and methotrexate (MTX).

Methods: The AMBITION study, a phase III RCT with tocilizumab vs. Methotrexate in which TCZ monotherapy (8 mg/kg every 4 weeks) was compared to methotrexate monotherapy over 24 weeks in patients with moderate-severe RA (AMBITION, NCT00109408). TCZ is a compound that inhibits the IL-6 receptor. Tissue metabolites were measured in baseline and 8 weeks sera (n=319) by ECM specific ELISAs: Connective tissue remodelling was measured by C3M (type III collagen degradation), basement membrane remodelling by C4M (type IV collagen), inflammation by C-reactive protein (CRP) and its metabolite CRPM. Comparison between groups were done by ANCOVA adjusting for age, gender, BMI and disease duration.

Results: Tissue remodelling was increased by 10% in the placebo group and significantly (p<0.001) inhibited by both MTX and TCZ compared to placebo. Inhibition with TCZ was 14% greater than that of MTX (p=0.0005). Basement membrane remodelling was likewise inhibited by both MTX and TCZ; the effect of TCZ was 20% greater than MTX (p<0.0001). MTX had limited effect on CRP and its metabolite CRPM compared to placebo or baseline. TCZ reduced the level to 27% and 73% of baseline, respectively. Although the effect of TCZ was much greater when assessing CRP, this was the least significant response marker, due to the huge placebo modulation, as well as the general high variation in response. Only changes in CRP was correlated to 8 week changes in DAS (rho=0.27, p=0.001) in the TCZ group. In the MTX group all changes in markers were correlated to change in DAS (rho=0.28 to 0.41, p<0.001). Only changes in C4M and CRP in the TCZ treatment arms were significantly correlated with DAS changes (rho=0.31, p<0.05).

Abstract FRI0008 – Table 1

Table	Mean change baseline (%)	8-week from	Lower 95%-CI	Upper 95%-CI	8 week change difference	P value
Connective tissue metabolite (C3M)						
PLACEBO	111		101	120	TCZ vs. PLACEBO	<0.0001
MTX	88		83	94	MTX vs. PLACEBO	0.0001
TCZ	74		69	79	TCZ vs. MTX	0.0005
Basement membrane remodeling metabolite (C4M)						
PLACEBO	107		98	116	TCZ vs. PLACEBO	<0.0001
MTX	87		82	93	MTX vs. PLACEBO	0.0007
TCZ	67		62	72	TCZ vs. MTX	<0.0001
C-reactive protein metabolite (CRPM)						
PLACEBO	112		91	133	TCZ vs. PLACEBO	0.005
MTX	99		87	111	MTX vs. PLACEBO	ns
TCZ	73		61	85	TCZ vs. MTX	0.0091
C-reactive protein (CRP)						
PLACEBO	450		214	686	TCZ vs. PLACEBO	0.007
MTX	102		-36	240	MTX vs. PLACEBO	0.034
TCZ	27		-110	164	TCZ vs. MTX	ns

Conclusions: Chronic inflammation results in an increased amount of tissue remodelling. There was a significant difference in the magnitude of effect MTX and TCZ on tissue remodelling. In addition there was a disconnect between tissue remodelling and change in disease activity, which was treatment dependent.

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FRI0009

A COMPARISON OF THE JOINT SYNOVITIS AND TENOSYNOVITIS USING ULTRASONOGRAPHY AND HISTOPATHOLOGICAL FINDINGS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: In the treatment of rheumatoid arthritis (RA), the early diagnosis and early medical treatment via tight control have become increasingly important with the advent of biological therapy. In addition, the existence of inflammation without bone destruction on magnetic resonance imaging has been found to be significantly associated with symptoms in the patient standpoint type inspection of early RA patients.

Objectives: This study was conducted to clarify the differences between the joint synovium and tendon sheath synovium, local disease activity using ultrasonography (US) and the findings on a synovial histopathological evaluation.

Methods: Between March 2011 and November 2017, 663 synovectomies were surgically treated, and synovial biopsies were performed at the time of surgery. Among them, 75 tendon sheath synovia and 588 joint synovia were investigated. A total of 81 men and 582 women were examined, with an average age of 64 years old. We examined the finger in 312 cases (39 tendons, 273 joints), wrist in 323 cases (33 tendons, 290 joints) and ankle in 28 cases (3 tendons, 25 joints). There were no cases with both tendon sheath synovium and joint synovium. Just before surgery, the US probe was placed on the dorsal and palmar/plantar aspect of the joint or the tendon sheath to evaluate the activity of local synovitis. The maximum grade of power Doppler (PD) signal was determined, ranging from 0 to 3. The serum C reactive protein (CRP), matrix metalloproteinase-3 (MMP-3) and DAS28 values were also examined just before surgery. A histopathological examination of the gathered synovium at the surgical site was performed using the Rooney score (RS).

Results: For the tendon sheath synovium, PD0, 14 cases; PD1, 32 cases; PD2, 19 cases and PD3, 10 cases were observed, with an average score of 1.33. For the joint synovium, PD0, 114 cases; PD1, 179 cases; PD2, 209 cases and PD3, 86 cases were observed, with an average score of 1.45. Regarding the DAS28, for the tendon sheath synovium, the average score was 3.59, and for the joint synovium, the average score was 3.61. Regarding the CRP, for the tendon sheath synovium, the average score was 0.64, and for the joint synovium, the average score was 0.66. Regarding the MMP-3, for the tendon sheath synovium, the average score was 113, and for the joint synovium, the average score was 123. There were no marked differences in the grade of PD, DAS28, CRP or MMP-3 between the synovia. The rate of synoviocytes hyperplasia did not differ between the synovia, but the rates of fibrosis and proliferating blood vessels were significantly high in the tendon sheath synovium, perivascular infiltrates of lymphocytes, focal aggregates of lymphocytes, diffuse infiltrates of lymphocytes was significantly high in joint synovium.