

ORAL PRESENTATIONS

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SLEDAI-2K Responder Index 50 (SRI-50)

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Objective:

A number of outcome measures to assess disease activity in SLE patients have been developed. SLEDAI-2K (Systemic Lupus Erythematosus Activity Index-2K) is a reliable valid, simple, one-page activity index recording features of active lupus as present or not present. Thus its utility in clinical trials is limited as it cannot reflect partial improvement in a disease manifestation. The objective of this study is to develop a SLEDAI-2K responder measure which could document a minimum 50% improvement in disease manifestations among lupus patients.

Methods:

Derivation of SRI-50 (SLEDAI-2K Responder Index-50) from SLEDAI-2K: A new definition for each of the original descriptors of SLEDAI-2K was created to reflect a minimum improvement of 50%. The definitions of descriptors of SRI-50 were constructed based on a literature review for each specific organ system. The new assigned scores for the descriptors of SRI-50 were derived by dividing the score of SLEDAI-2K by 2. Assessing the content validity of the draft instruments: SRI-50 form was assessed by expert rheumatologists reviewing the instruments and providing critical feedback.

Results:

Testing of SRI-50: One hundred patients who had experienced lupus flares or had persistently active disease were assessed initially and then reassessed after treatment was initiated. SLEDAI-2K was determined on the first visit and again at the second visit along with SRI-50. Results: SRI-50 and the data retrieval form to accurately document the clinical and laboratory findings of each descriptor were developed. Seventy two patients didn't change their SRI-50 because their manifestations resolved or didn't meet the definition of SRI-50 Twenty eight patients with varying levels of disease activity at the first visit (3 had SLEDAI-2K 2, 3 had 4; 6 had 6; 6 had 8; 3 had 10; 2 had 12; 1 had 16, 1 had 18; 2 had 20; 1 had 21) were further studied with SRI-50. SRI-50 was able to demonstrate incomplete (but $\geq 50\%$) improvement which would not have been discerned using SLEDAI-2K. Such incomplete improvement was demonstrated in 13 of the 24 SLEDAI-2K descriptors and in 6 of the 9 organ systems that were present in these patients.

Conclusion:

Conclusion: SLEDAI-2K Responder Index-50 is a promising instrument that can describe partial improvement in disease activity between visits in lupus patients.

Ankylosing Spondylitis Patients with the ERAP1 K528 Variant have Significantly Faster Radiological Progression

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Objective:

The pathogenesis of ankylosing spondylitis (AS) is not well understood. Recently, polymorphisms in the endoplasmic reticulum aminopeptidase 1 (ERAP1) and ERAP2 genes were found to be associated with AS. It is not known how they influence the clinical variability in AS. We studied the effect of the ERAP1 and ERAP2 polymorphisms on radiological progression in AS.

Methods:

Caucasian AS patients (modified New York criteria) were followed prospectively in the spondylitis clinic. At baseline, the BASDAI, BASFI and BASMI were noted and x-rays taken. The radiographs were repeated every 2 years while the clinical data was updated annually. DNA was isolated from peripheral blood and genotyped for the rs30187, rs27044 and rs10050860 SNP of ERAP1 and rs2549782 of ERAP2 by allelic discrimination assay. Independently, two blinded readers calculated the mSASSS scores. The rate of change in mSASSS scores were noted by dividing the difference between the first and last mSASSS scores by the duration between the x-rays. The rate of change in mSASSS scores were compared between the genotypic groups using the Kruskal-Wallis test.

Results:

Seventy patients (10 females) had at least 2 x-rays at a mean \pm SD gap of 2.7 ± 0.9 years. The mean age and disease duration were 37.2 ± 13 years and 15.1 ± 10 years respectively. The mean baseline BASDAI, BASFI and BASMI scores were 4.9 ± 2.6 , 4.3 ± 2.9 and 2.5 ± 2.0 respectively. Forty-six patients were on anti-TNF medications for a mean duration of 15.7 ± 2.2 months. The mean baseline and follow up mSASSS scores were 17.2 ± 22.8 and 18.9 ± 23.2 respectively with a mean change of 1.7 ± 2.6 units and rate of change of 0.8 ± 1.5 units/year. The age, disease duration, baseline mSASSS scores and the mean duration of anti-TNF intake were comparable between the genotypic groups of ERAP1 and ERAP2. There was significant difference in the rate of change in mSASSS between the genotypic groups of the rs30187 SNP of ERAP1 ($H= 5.9$, $df=2$; $p=0.05$). Patients with C allele of rs30187 (K528 variant of ERAP1) progressed faster than the TT genotype with an OR of 9.3 (CI: 1.9-44.2; $p< 0.01$). There was no significant difference in the rate of change in mSASSS with the other polymorphisms.

Conclusion:

This is the first report to suggest that ERAP1 polymorphisms can affect the radiological severity in AS. Patients with the ERAP1 K528 variant have significantly faster radiological progression.

Prevalence of Femoroacetabular Impingement in Individuals Undergoing Total Hip Replacement for Osteoarthritis – A Retrospective Radiographic Review

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Objective:

Recently, femoroacetabular impingement (FAI) has been suggested as the major cause of primary hip osteoarthritis. We assessed the prevalence of FAI detected radiographically in a comparatively young cohort that underwent total hip replacement (THR) for primary hip osteoarthritis.

Methods:

The Vancouver Coastal Health Authority Total Joint Replacement Service database was used to identify subjects aged < 55 years with pre-operative radiographs acquired prior to a THR procedure for primary hip osteoarthritis during 2007-2008. Exclusion criteria based on diagnostic codes included hip fracture, rheumatoid arthritis, hip infection, osteonecrosis, congenital and other hip dysplasia, and other secondary causes of osteoarthritis. Eighty-two subjects were included in the study by random selection. Two radiologists reviewed together the classic radiographic FAI signs to form consensus for definitions, then independently assessed the retrospective pre-operative radiographs (AP pelvis and lateral views) for each subject. Using a standardized scoring tool, subjects were categorized as: definite FAI, no FAI, and not possible to exclude FAI due to advanced osteoarthritis. In the event of disagreement between the radiologists for a given subject, consensus was achieved by discussion.

Results:

Of 470 THR cases identified, 82 were randomly selected. Seven of the 82 subjects were subsequently excluded due to lack of pre-operative radiographs (N=3), readmission of subject already selected (N=3), and radiograph of inadequate diagnostic quality (N=1). Of 75 subjects, 49 (65%) were male. Mean age was 49.5 ± 4.7 . Definite FAI was present in 27 subjects (36%) and no FAI in 25 subjects (33%). In 23 subjects (31%), FAI could not be excluded due to advanced osteoarthritis. Thus, of those that could be adjudicated clearly, 27 of 52 (52%) had FAI. Of the 27 subjects with FAI, 5 cam-type, 13 pincer-type, and 9 mixed-type cases were identified. Consistent with previous studies, there was a male predominance in cam-type features (70% of males vs. 0% of females) and a female predominance in pincer-type malformations (100% of females vs. 75% of males). Interrater reliability was assessed for each radiographic measurement ($k = 0.72$ for presence of FAI; $k = 0.88$ for pistol grip deformity.)

Conclusion:

FAI is common in young subjects undergoing total hip replacement for primary osteoarthritis. Since other work proposes that it is FAI combined with specific physical activities that result in osteoarthritis, the findings suggest a potential for prevention of hip osteoarthritis in the future.

Outcomes in Patients with Systemic Lupus Erythematosus (SLE) with and without a Prolonged Serologically Active Clinically Quiescent (SACQ) Period

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Objective:

SACQ SLE patients discordance presents a clinical dilemma: does active serology alone warrant treatment? We explore outcomes in patients with and without a prolonged SACQ period by comparing the rate of damage accrual, as measured by the SLICC/ACR Damage Index (SDI), and incidences of renal damage and of coronary artery disease (CAD) over 5-10 years.

Methods:

SLE patients followed from 1970-2008 with visits ≤ 18 months apart were identified. SACQ was defined as a ≥ 2 -year sustained period without clinical activity, with persistent serologic activity (increased anti-dsDNA and/or hypocomplementemia), during which antimalarials were permissible, but not steroids/immunosuppressives. SACQ patients were matched for age, sex, disease duration, decade of clinic entry, and SDI at the beginning of the SACQ period, with SLE controls. Groups were compared on the bases of change in SDI, and incidences of CAD and renal damage. Descriptive statistics were used; comparisons made using paired t- and McNemar tests.

Results:

55 SACQ patients and 110 controls were identified. The median SACQ period was 158 weeks. Fewer SACQ patients used antimalarials (60% vs 77.3%) ($p=0.004$), steroids (18.2% vs 76.4%) or immunosuppressives (5.5% vs 43.6%) ($p<0.0001$ for both) over the 5 year period. SDI at 3 years from the start of the SACQ period was 0.70 ± 1.27 vs. 1.13 ± 1.54 in controls ($p<0.0001$), at 5 years was 0.89 ± 1.37 vs 1.36 ± 1.66 ($p<0.0001$), at 7 years was 0.94 ± 1.28 vs 1.71 ± 1.86 ($p=0.0001$), and at 10 years was 1.26 ± 1.68 vs 2.26 ± 2.23 ($p=0.001$); intergroup difference in damage significantly increased over 10 years. SDI difference was mainly independent of corticosteroid effects. Two (3.6%) SACQ patients had CAD prior to study start vs. 7 (6.4%) controls ($p=0.32$), with 1 (1.8%) new case in SACQ patients vs 8 (7.3%) in controls over 10 years ($p=0.06$). Baseline serum creatinine did not differ between groups ($p=0.90$). By definition, SACQ patients had no baseline proteinuria, versus 13 (12.3%) controls ($p<0.0001$). One (1.8%) SACQ patient and 17 (15.5%) controls had renal damage at 5 years ($p=0.0006$), and two (3.6%) SACQ patients, vs 26 (23.6%) controls had renal damage at 10 years ($p<0.0001$).

Conclusion:

SLE patients with a prolonged SACQ period have significantly less damage accrual over 5-10 years compared to matched controls, supporting the practice of active surveillance without treatment (with steroids/immunosuppressives) during the SACQ period.

Novel Gene – Gene Interaction of Susceptibility Loci in Ankylosing Spondylitis

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Objective:

With the exception of HLA-B27, the genetics of ankylosing spondylitis (AS) involves multiple genes with small effect sizes scattered across the genome. To date gene-gene interactions have not been determined in AS as most haplotype association methods are restricted in length and consist of alleles from contiguous SNPs. These approaches have limited capacity to detect epistasis from multiple genes. We hypothesize that interactions between different chromosomes may play a role in AS susceptibility.

Methods:

We have developed a cooperative coevolutionary algorithm (CCA) to detect gene-gene interactions from case-control haplotype data; moreover, this algorithm can tolerate up to 15% missing/ambiguous positions in haplotype data arising during haplotype phasing from genotypes. Further, the algorithm can compute epistatic associations from genes spanning multiple chromosomes. The algorithm was tested on data from the Wellcome Trust (WTCCC) AS cohort.

Results:

When coevolutionary algorithm was applied to the WTCCC-AS dataset of non-synonymous, we captured 1145 haplotypes and the most significant haplotypes consisted of major alleles from the nsSNPs rs7530511, rs11209026, rs17482078, rs10050860, rs2287987, rs3130977, rs3819300, rs2523608, rs1131896, rs2256028, rs12216124, rs3132468 located in chromosome 1, 2, 5 and 6. All the captured haplotypes consist of suffixes from MHC genes. Strong interactions were observed within the non-MHC genes IL23R, ERAP1 and MHC genes PSORS1C1, HLA-B, MICA, MICB. The most significant haplotype with the highest frequency difference in case and control was observed in the MHC nsSNPs, TCAGG ($p < 1.0 \times 10^{-4}$, HRR = 10.27(95% CI 8.78-12.02)). Among the non-MHC genes, IL23R and ERAP1 show strong interaction with MHC genes (5×10^{-4}). These results show long range interactions between non-MHC and MHC genes which has been hypothesized, but not previously reported.

Conclusion:

The result of analysis for real datasets using our novel co-evolutionary algorithm demonstrates the advantages of detecting long-range haplotypes from multiple genes. This is the first ankylosing spondylitis study to demonstrate gene - gene interaction within and outside the MHC region.

Care Gap in Patients with Rheumatoid Arthritis who are Eligible for Biologics Based on Provincial Access Criteria

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Objective:

Biologic therapy has been shown to be effective for the treatment of rheumatoid arthritis (RA). In each province many Canadian patients must access public funds to pay for these medications, and must meet specific clinical criteria in order to gain access to them. These frequently include having an inadequate response to trials of methotrexate (MTX) at doses of at least 20 mg per week and usually at least 1-2 other disease modifying anti rheumatic drugs (DMARDs) most often in combination. In 7/10 provinces an adequate trial of Leflunomide (LEF) is also required. The objective of the study was to determine if patients with active early rheumatoid arthritis (ERA) who are eligible for biologic therapies based on Ontario access criteria are actually receiving therapy after 12 months of follow up.

Methods:

Patients with ERA were studied in the Canadian Early Arthritis Cohort (CATCH), a prospective cohort where data are collected according to a standardized protocol. All Ontario patients in CATCH with moderate to severe RA followed for at least 12 months were analyzed. Eligibility for biologics was determined by Ontario access criteria which included all of: (1) at least five swollen joints (2) evidence of erosions or RF or anti-CCP (3) an adequate trial of MTX at doses of ≥ 20 mg, a trial of LEF + combination of DMARDs.

Results:

226 were patients followed to 12 months. Of those, 41 patients (18.1 %) met Ontario access criteria for the use of biologics. 14.6% (33) of patients at 12 months met Ontario criteria for access to biologic therapies and could have access to these medications. The actual percentage of patients on a biologic at 12 months was 6.6% (15 patients). The average DAS level of patients who could have access to biologic therapies but were not yet receiving them by 12 months was 4.53 (s.d. 1.25). 27 of these 33 patients (81.8%) had a DAS28 of > 3.1 , and of these 12 patients had a DAS28 of > 5.1 .

Conclusion:

A number of patients who could have access to biologic therapies by a public funding structure are not receiving these therapies after 12 months of follow up, despite having moderate to high disease activity. The reasons for this gap in care needs to be further explored.