Welcome to this review of the 2014 American College of Rheumatology/Association of Rheumatology Health Professionals Annual Meeting, which was attended by Dr Daniel Ching, a Consultant Rheumatologist in Timaru, South Canterbury.

The ACR/ARHP Annual Meeting is the premier educational event for physicians, health professionals and scientists who treat those with or at risk for arthritis, rheumatic and musculoskeletal diseases. The annual meeting is a forum for physicians and health professionals to receive the most relevant and latest developments in rheumatology. Each year, the annual meeting draws thousands of abstracts submitted by rheumatologists and health professionals from around the world.

Abstracts may be downloaded in PDF format at [http://acrabstracts.org/advanced-search/](http://acrabstracts.org/advanced-search/). I hope you find the Conference Review stimulating and I look forward to your feedback.

Kind regards
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14-3-3η early RA biomarkers: Does seronegative RA exist?

Presenter: Dirkjan van Schaardenburg, Reade, Amsterdam, Netherlands

Summary: These researchers measured levels of the 14-3-3η serum protein and its corresponding anti-14-3-3η auto-antibodies in 409 patients with early rheumatoid arthritis (RA; satisfying the 2010 ACR/EULAR RA classification criteria). None of the patients had received prior disease modifying anti-rheumatic drug (DMARD) therapy and the median symptom duration was 4 months. The positive diagnostic cut-off for serum 14-3-3η protein levels was set at >0.19 ng/mL, for 14-3-3η auto-antibody level determination, a composite auto-antibody score (based on 6 peptides) of ≥380 U/mL was determined to be the best positive cut-off. A total of 275 (67%) patients were positive for the 14-3-3η protein (median 0.63 ng/mL) and 313 (77%) were positive for 14-3-3η auto-antibodies (median 527 U/mL). At baseline, 63% and 69% of patients tested positive for rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA), respectively. A total of 76% (n=310) of patients were positive for one or both of RF and ACPA, 93% (n=394) were positive for either of the 14-3-3η markers and 96% for any one of the 4 markers. Using 14-3-3η markers alone identified 23% more patients with early RA compared with use of RF/ACPA, an additional 27% of patients were identified when the 4 markers were combined.

Comment: First, we have RF; then ACPA and now 14-3-3η. This protein is hyper-expressed in chondrocytes and is similar to Toll-receptors and is found within the cells. There were several abstracts and an oral presentation on this. It is being developed in Canada. 14-3-3η markers identify 93% of early RA patients compared to RF/ACPA alone at 76%. Combining the 14-3-3η marker and its antibody, plus RF plus ACPA, captures 96% of early RA patients. If patients only have 14-3-3η auto-antibodies and a negative 14-3-3η protein test, they have significantly less severe RA disease and less joint damage. 14-3-3η Citr ratios are independent predictors, and a stronger predictor than ACPA in radiographic progression in RA. I look forward to this test being available commercially to help us with the diagnosis and to guide us in the treatment of rheumatoid patients.

If this is going to become commercially available, I hope they will come up with a more user-friendly name, such as CRB (Canadian Rheumatoid Biomarker).


Safety, tolerability, and functional activity of ABT-122, a dual TNF- and IL-17A–targeted DVD-Ig™, following single-dose administration in healthy subjects

Presenter: Heikki Mansikka, AbbVie, Inc, North Chicago, Illinois, USA

Summary: This single ascending dose placebo-controlled study assessed the safety, tolerability and dual functionality of ABT-122 administered intravenously (IV) or subcutaneously (SC) in 64 healthy volunteers. The selective binding domains in this novel Dual Variable Domain immunoglobulin protein (DVD-Ig™) target both tumour necrosis factor (TNF) and interleukin (IL)-17A. Groups 1 through 5 received ABT-122 at 0.1, 0.3, 1, 3, and 10 mg/kg IV, respectively, and Groups 6 through 8 received 0.3, 1, and 3 mg/kg SC, respectively. Each dose group comprised 8 subjects; 6 received active drug and 2 received placebo. Adverse event (AE) profiles did not differ by route of administration or by active drug versus placebo. No serious AEs or premature discontinuations due to AEs occurred. There were no infusion reactions, systemic hypersensitivity reactions or injection site reactions. No clinically relevant changes in laboratory parameters, vital signs, or ECG parameters occurred. All AEs were mild or moderate in intensity. The most frequently reported AEs were upper respiratory infection with both ABT-122 and placebo. In vitro analyses demonstrated dual binding and neutralising capacity for TNF and IL-17, which was time- and dose-dependent through 21 days, and up to 10 mg/kg, respectively.

Comment: We all know that previous trials combining two biologics did not improve the efficacy and in fact, they increased the risk of adverse effects. Although TNF inhibitors have been the cornerstone of biologic RA treatment, new treatment options are required. Apparently, IL-17 and TNF pathways synergise, which means there is a number of companies developing candidates that simultaneously target both TNF and IL-17. ABT-122 is a Dual Variable Domain immunoglobulin that targets both TNF and IL-17A, showing improved efficacy over TNF inhibitor or IL-17 blockade alone in vitro. This compound has now gone into a phase 2 study, with a couple of sites in New Zealand participating, and it will be very interesting to see how efficacious and safe it will be. AbbVie obviously has confidence in this mode of action because they have developed a back-up compound (ABBV-257), which is another Dual Variable Domain immunoglobulin targeting both TNF and IL-17, as a back-up to ABT-122.

Prediction of remission by patients and physicians: Does the doctor know best?

Presenter: WG Bensen, St. Josephs Hospital and McMaster University, Hamilton, Ontario, Canada

Summary: This study sought to determine which global measure – physician (MDGA) or patient (PtGA) assessment – of RA disease activity is a more valid predictor of disease remission based on 28 Joint Disease Activity Score (DAS28), Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) criteria. Data were obtained from 657 RA patients (mean age 56.2 years and disease duration of 10.1 years) treated with infliximab between 2002 and 2012 with available information on disease remission at 6, 12, or 18 months. Significant (p<0.001) associations were observed between both PtGA and MDGA and achievement of remission at the corresponding assessments regardless of remission type. PtGA proved to be a better predictor than physician assessments at predicting DAS28 remission at all 3 time points, whereas in regard to SDAI and CDAI criteria, physicians were generally better than patients at predicting remission (the superiority was not consistent over time). Outcomes were similar for the prediction of low disease activity (LDA).

Comment: See below.


Improvements in the proportion of patients achieving DAS, CDAI, and SDAI remission by omitting the patient global assessment (PtGA): an analysis from a prospective, observational registry

Presenter: Philip Baer, Private Practice, Scarborough, Ontario, Canada

Summary: This real-world, routine clinical care setting in Canada involved 1019 RA patients treated with infliximab from 2002–2014 or with golimumab from 2010–2014. The researchers explored the extent to which PtGA may reflect symptoms related to fibromyalgia, low back pain, osteoarthritis, depression or other conditions besides RA disease activity. They constructed modified versions of DAS28 (mDAS28), CDAI (mCDAI), and SDAI (mSDAI) by omitting PtGA from the formulas. The standard definitions were considered to be the gold standard and ROC curve analysis was used to identify new thresholds for the modified versions. Strong correlations were observed between the standard and modified versions of DAS28 (r=0.98; p<0.001), CDAI (r=0.99; p<0.001) and SDAI (r=0.99; p<0.001). ROC analysis yielded new thresholds for remission and LDA of mDAS28 (remission=2.6, LDA=3.1), mCDAI (remission=2.9, LDA=10.9), mSDAI (remission=3.3, LDA=10.9). Cross-tabulation of the standard and modified thresholds showed that an additional 10.1%, 10.6% and 17.8% of non-remission cases for DAS28, CDAI and SDAI respectively, would be classified as remitters with the modified definitions. Similarly, an additional 11.5%, 21.2% and 20.6% of non-LDA cases for DAS28, CDAI and SDAI respectively, would be classified as LDA.

Comment: Although we are encouraged to perform a disease composite score at every visit and to treat target, most of us are making a judgement every day as to how much weight to put on the patients’ global assessment, especially as other co-morbidities may affect the patients’ global assessments of their inflammatory arthritis. We still need to listen to patients and have the clinical acumen to deal with patients with a high global assessment but not much pain, little or no swollen joints and normal inflammatory indices by dealing with whatever it is in the patients’ life that is causing the high global assessment, which might be fatigue or fibromyalgia or social stress, and not increase their anti-rheumatic therapy. The patients’ global assessment could account for up to 10.1% of patients not being in remission and 11.5% of patients not being classified as having LDA using DAS28, which is the most commonly used composite instrument. On the other side of the picture, we also need clinical acumen to encourage the patient to increase their anti-rheumatic therapy if their global assessment and/or pain is unusually low compared to swollen and tender joints, or their raised inflammatory indices.

Session: Rheumatoid Arthritis - Clinical Aspects II. Abstract 943.

Economic evaluation of sequencing strategies in the treatment of psoriatic arthritis in the United States

Presenter: Thomas Tencer, Celgene Corporation, New Jersey, USA

Summary: This economic analysis used a lifetime Markov state transition cohort model to compare the treatment sequences of apremilast followed by adalimumab followed by etanercept against adalimumab followed by etanercept in the treatment of psoriatic arthritis (PsA), in order to assess the impact of placing apremilast before biologics in PsA patients who had failed conventional DMARD therapy, from a US payer perspective. The apremilast arm provided an additional 2.53 years with a Psoriatic Arthritis Response Criteria (PsARC) response and an additional 0.78 quality-adjusted life-years (QALYs). Total time spent on the biologics was reduced by 0.34 years and time spent in best supportive care was reduced by 2.85 years. Under base-case assumptions, placing apremilast before biologics was found to be the dominant strategy (costs reduced by $US28,794). Sensitivity analyses indicated that several parameters (e.g., cost of best supportive care and baseline utility) influence the incremental cost-effectiveness ratio. Similar results were obtained with different biologic drugs in the sequence.

Comment: Apremilast (Otezla®), a PDE4 inhibitor, was approved by the FDA in March 2014 for the treatment of PsA and in September 2014 for psoriasis. It is currently being registered in Australia and will be in New Zealand. It apparently costs at least 30% less than the biologics in the US at approximately $US20–21,000 per year, which was the cost of biologics in the US when they first became available in 1999, but apparently the cost of biologics in the US can rise each year with inflation, etc, unlike the cost of drugs in Australasia. The CHMP has also recommended the approval of apremilast for the treatment of psoriasis and PsA. The question is when do we use this, if and when it becomes available. Although it does not have as much data as the TNF inhibitors, it is a very safe medication that does not appear to need regular laboratory monitoring. Its most common adverse effect is diarrhoea. My impression is that apremilast might not be as effective as the TNF inhibitors but there are no head-to-head trials. It will be a welcomed addition to the treatment of psoriasis and PsA if it is funded by PHARMAC because of its lower cost.

Session: Spondyloarthropathies and Psoriatic Arthritis - Clinical Aspects and Treatment II. Abstract 1595.
Choosing not so wisely: The tale of antinuclear antibody testing

Presenter: Tejas Sheth, Albert Einstein College of Medicine / Yeshiva University, New York, USA

Summary: This retrospective analysis examined the demographics, indication of testing and outcomes of 851 patients who underwent antinuclear antibody (ANA) testing at a single US hospital laboratory. In 91% of cases, ANA testing was performed despite a history of systemic lupus erythematosus (SLE). In 223 cases, ANA subserologies (ANAS) were ordered along with initial ANA; of the 15 that were positive, all had positive ANA results. A positive ANA result was more likely in female patients (OR 2.92; 95% CI, 1.86 to 4.58) and those with a history of autoimmune disease (AI) (OR 6.76; 95% CI, 4.37 to 10.44), while positive ANAS were more likely in patients with a history of AID (OR 7.87; 95% CI, 1.72 to 35.95) and those with a positive ANA result (p<0.001). ANA results were not associated with patient age or location. Results of ANA testing were more likely to be negative when ordered in family medicine, paediatrics and gastroenterology (ORs 2.61, 2.3 and 5.04 respectively) as compared to rheumatology. Follow-up data from 567 visits showed that on 12 occasions (2.07%) a positive ANA result resulted in a change in management.

Comment: See below.

Session: Quality Measures and Quality of Care. Abstract 1457.

Improper use of antinuclear antibody (ANA) test can result in misdiagnosis, increased patient anxiety, and wasted health care resources

Presenter: Sahar Eivaz Mohammadi, Jersey City Medical Center-Barnabas Health, New Jersey, USA

Summary: This study retrospectively analysed the charts of patients who underwent ANA testing was performed at a US community hospital over a 1-year period. The researchers compared the justification for ordering ANA testing against clinical and laboratory parameters for SLE classification as set out by the 2012 Systemic Lupus International Collaborating Clinics (SLICC). During the study period, ANA was ordered for 465 patients, 58 (12.47%) of whom had prior history of connective tissue disorders (CTDs) and 4 (0.98%) had prior ANA positivity. Of the remaining 403 patients, ANA was positive (titres >1:80) in 28 patients (8.4%) and negative (titre <1:40) in 375 (93.05%). Out of all 465 cases, only one new case of antiphospholipid antibody syndrome was identified. A total of US$39,297 was spent on ANA and US$57,165 on additional testing ordered alongside or after a positive ANA. A high number of cases involved ordering ANA sub-serologies without knowing the ANA.

Comment: I am delighted to see these 2 abstracts and there were other similar abstracts such as 1340, and I share the frustration of these authors. The general population have positive ANAs varying between 15–30%, depending on the quoted studies, and I often quote a figure of 27%. Like many rheumatologists, I spend a lot of time reassuring patients, GPs and physicians of false negative test results. I actively discourage testing for ANA and its sub-serologies unless there is a good clinical indication in patients of whom we are suspicious of ARA (autoantibody-associated rheumatic disease, ref-Rheumatology 2014;417(1):120-2). I applaud the “Choosing Wisely” campaign in America, which is endorsed by ACR, and many of you are probably familiar with its publications to encourage doctors to avoid doing unnecessary investigations and giving unnecessary treatment.


Reducing therapy in rheumatoid arthritis patients in ongoing remission

Presenter: Judith Haschka, University of Erlangen-Nuremberg, Erlangen, Germany

Summary: The RETRO study evaluated tapering and discontinuation of DMARD therapy in RA patients in stable long-lasting remission (DAS28-erythrocyte sedimentation rate [ESR] <2.6) and assessed predictors of disease recurrence. Patients on ≥1 conventional and/or biological DMARDs were randomised into 3 trial arms: (1) Arm 1 (control group), continue full-dose conventional and/or biological DMARD treatment for 12 months; (2) Arm 2, reduce the dose of all conventional and/or biological DMARD treatment by 50% for 12 months; (3) Arm 3, reduce the dose of all conventional and/or biological DMARD treatment by 50% for 6 months before discontinuing DMARD therapy. Patients with disease recurrence (DAS ≥2.6) restarted the original therapy. Of the 101 patients evaluable at 1 year (38 patients in Arm 1, 36 patients in Arm 2 and 27 in Arm 3), 66.3% remained in remission. The flare rate was significantly lower in the control group (15.8%) than in trial Arms 2 (38.9%: p=0.036) and 3 (51.9%; p=0.003); the between-group difference was not significant for the reduction arms. In multivariate logistic regression analysis, ACpA positivity and treatment reduction were identified as predictors of subsequent flares.

Comment: See below.

Session: Rheumatoid Arthritis - Clinical Aspects II: Remission and De-escalation of Therapy. Abstract 940.

Randomised controlled non-inferiority study of dose reduction and withdrawal of adalimumab and etanercept in rheumatoid arthritis

Presenter: Noortje van Herwaarden, Sint Maastrichts Kliniek, Nijmegen, Netherlands

Summary: 180 patients with RA and LDA while using adalimumab or etanercept were randomised to a dose reduction strategy or usual care in daily clinical practice. The TNF inhibitor dose reduction strategy consisted of stepwise increases in the interval between injections every 3 months until flare (i.e., DAS28-C-reactive protein [CRP] increase >1.2 or DAS28-CRP increase >0.6 and current DAS28-CRP ≥3.2, compared to baseline DAS28-CRP) or discontinuation. In case of flare, the TNF inhibitor was restarted or escalated. At 18 months’ follow-up, the cumulative incidence of persistent DAS28-CRP flare (i.e., lasting ≥12 weeks) was not significantly higher in the dose reduction group compared to the usual care group (10% vs 12%). Mean DAS28-CRP remained low, with only a small albeit significant between-group difference observed at 9 months’ follow-up. Health Assessment Questionnaire (HAQ) scores and quality of life (QoL) remained stable in both groups. In the dose reduction group, the TNF inhibitor was successfully stopped at 18 months in 20% of patients, the interval successfully increased in 43% and no dose reduction was possible in 37% of patients. Incidence and types of serious AEs were similar between groups. Costs were significantly lower in the dose reduction group (mean difference per patient €9k).

Comment: Since the advent of adalimumab, the first biologic funded by PHARMAC on 01.01.2006, we have enjoyed the satisfaction of seeing more RA patients achieving remission or LDA. I am sure we all have such patients whose disease has been well controlled on biologics for several years. We have also had patients who have had to stop their biologics for months, and sometimes over a year, because of other co-morbidities such as surgery, infection, malignancy, and these patients have not flared. Sooner or later, we need to incorporate reduction of therapy into our practice. This should be done gradually as per the above studies, such as increasing the dose interval of the biologic. Some of our patients have longer intervals because they forget, and I have a couple of patients who simply increased the interval of their biologic therapy because they know it is expensive and they want “to do their bit”. I would still not reduce therapy in patients with poor prognostic factors such as patients with rheumatoid nodules and those who are ACpA-positive. During question time, a member of the audience asked Dr van Herwaarden if it was difficult to recruit patients for his study, and he reported that it was a study that was easy to recruit for because many patients are keen to reduce or stop their treatment. We need to be cognisant of our patients’ opinion on this and need to learn how to select those patients whose treatment we can gradually reduce.


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Safety of zoster vaccination administration in rheumatic patients on current biologic therapy

Presenter: Stephen Lindsay, Ochsner Clinic Baton Rouge, Los Angeles, USA

Summary: The safety of the herpes zoster (HZ) vaccine was evaluated in patients with RA, PsA or ankylosing spondylitis (AS) currently using biologics (by IV infusion in 160 patients; SC in 142) at a single infusion centre. A total of 110 infusion patients (68%) were vaccinated; over 60% had been on biologic >5 years and 5% for <1 year. No cases of disseminated HZ developed. One patient had significant swelling and tenderness at the injection site. Most common reasons not to vaccinate included recent HZ (n=11), age <50 years (n=14), disease activity issues (n=7), and no history of previous HZ (n=10). No cases of disseminated HZ were observed. Most common reasons not to vaccinate included recent HZ (n=11), age <50 years (n=14), and disease activity issues (n=5). None in the SC cohort. Prior to 2012, only 7% and 8% of the cohorts developed HZ at 16 and 20 months and none in the SC cohort. Prior to 2012, only 7% and 8% of the cohorts had received HZ vaccine.

Comment: Herpes zoster vaccination (HZV) is being advertised in NZ, and it is a live vaccine. The recommendation from various guidelines is that no live vaccine should be given to a patient who is immunocompromised in case it spreads and becomes disseminated, causing great harm to patients. However, there is an increased risk of shingles in patients on immunosuppressives, possibly more so in patients who are on tocilizumab. Following reports of inadvertent HZV of people who are currently taking biologic therapy with no adverse effects (JAMA. 2012;308(1):43-9), Stephen Lindsay’s group created a protocol for HZV vaccination in their patients. Patients have to meet certain exclusion criteria such as pregnancy, no infection or malignancy, have to be older than 50 years and have stable disease, meaning low or moderate disease activity on two successive visits. HZV was timed according to the next scheduled biologic and/or methotrexate dose, which were both withheld. HZV vaccination was given, and both methotrexate and the biologic would be resumed at the next scheduled dose. There were no cases of HZV infection within 6 weeks post-vaccination, nor flares of their rheumatic diseases. Apparently, NIH is now going to fund a much larger randomised controlled study using this protocol to compare HZV vaccine against placebo.


Secukinumab, a monoclonal antibody to interleukin-17A, significantly improves signs and symptoms of active ankylosing spondylitis: results of a 52-week phase 3 randomized placebo-controlled trial with intravenous loading and subcutaneous maintenance dosing

Presenter: Dominique L. Baeten, Academic Medical Centre/University of Amsterdam, Netherlands

Summary: This phase 3 study recruited 371 patients with active AS fulfilling modified New York Criteria and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) >4 despite current or previous therapy with NSAIDs, DMARDs and/or TNF inhibitors and randomised them to receive IV secukinumab 10 mg/kg (Week 0, 2, 4) followed by SC secukinumab 75 mg every 4 weeks (10 IV → 75 SC), or SC secukinumab 150 mg every 4 weeks (10 IV → 150 SC); placebo was given on the same IV and SC schedules. At week 16, ASAS20 response rates were significantly higher with secukinumab than with placebo (p<0.01 for each dose); in addition, improvements with both doses of secukinumab versus placebo were observed for all pre-specified secondary endpoints and responses were sustained through week 52. Secukinumab showed rapid onset of action, with significant improvements in ASAS20, ASAS40, high-sensitivity CRP, ASAS5/6 and BASDAI recorded at week 1. Secukinumab was generally well tolerated and there were no unexpected safety findings.

Comment: See below.


Secukinumab, a human anti–interleukin-17A monoclonal antibody, improves active psoriatic arthritis and inhibits radiographic progression: efficacy and safety data from a phase 3 randomized, multicenter, double-blind, placebo-controlled study

Presenter: Philip J. Mease, Swedish Medical Center and University of Washington, USA

Summary: In this phase 3 study, 606 adults with active, moderate-to-severe PsA were randomised to secukinumab or placebo. Secukinumab was given as a 10 mg/kg IV loading dose at weeks 0, 2 and 4, then as either 75 mg SC (10 IV→75 SC) or 150 mg SC (10 IV→150 SC) every 4 weeks from week 8. Placebo was given on the same schedules. At week 24, ACR20 response rates were significantly higher with both secukinumab dose groups compared with placebo (~50.0% for both secukinumab dose groups vs 17.3% for placebo; p<0.0001). All pre-specified secondary endpoints, including dactylitis, enthesis, SF36 physical summary scores, HAD-Disability Index, DAS28-CRP, ACR50, 75% and 90% improvements in the Psoriasis Area and Severity Index, and modified total Sharp score were achieved by week 24 and reached statistical significance; active dose separated from PBO as early as week 1 for ACR20, DAS28-CRP, and HAD-DI. Improvements in all primary and secondary endpoints were sustained through week 52. Secukinumab significantly inhibited radiographic joint structural damage at week 24 compared with placebo. Secukinumab was well tolerated throughout the study.

Comment: This is the first of three IL-17A inhibitors coming to the market. This mode of action seems effective with acceptable AEs. It is good to have another agent to treat patients with PsA and AS who have failed TNF inhibitors. In fact, the CHMP has now recommended approval of secukinumab for both psoriasis and PsA, and therefore the indication for these conditions might well be approved by the EMA within the next three months.


Secukinumab improves active ankylosing spondylitis: clinical and radiographic outcomes in a randomised placebo-controlled trial

Author: Stephen Lindsey's group created a protocol for HZV vaccination in their patients. Patients have to meet certain exclusion criteria such as pregnancy, no infection or malignancy, have to be older than 50 years and have stable disease, meaning low or moderate disease activity on two successive visits. HZV was timed according to the next scheduled biologic and/or methotrexate dose, which were both withheld. HZV vaccination was given, and both methotrexate and the biologic would be resumed at the next scheduled dose. There were no cases of HZV infection within 6 weeks post-vaccination, nor flares of their rheumatic diseases. Apparently, NIH is now going to fund a much larger randomised controlled study using this protocol to compare HZV vaccine against placebo.


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