Research Review Speaker Series™

Psoriatic arthritis – early detection and advances in treatment

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About the speaker

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Professor McHugh graduated from Otago University Medical School New Zealand, completed physician training before specialising in the subspecialty of Rheumatology and has had research fellowships at the Walter Elisa Hall in Melbourne (1985), Yale University Medical School (1990-1991) and the National Heart and Lung Institute (2002-2004). He has been a Consultant Rheumatologist at the RNHRD since 1991, and Professor of Pharmacoepidemiology at the University of Bath since 2013.

Abbreviations used in this review

ACR = American College of Rheumatology
AS = ankylosing spondylitis
BMI = body mass index
CRP = C-reactive protein
DMARDs = disease-modifying antirheumatic drugs
HAQ = Health Assessment Questionnaire
HAQ-DI = Health Assessment Questionnaire disability index
IBD = inflammatory bowel disease
IL = interleukin
NSAIDs = non-steroidal anti-inflammatory drugs
PsA = psoriatic arthritis
RA = rheumatoid arthritis
TNF = tumour necrosis factor

This publication summarises two presentations by Professor Neil McHugh, Royal National Hospital for Rheumatic Diseases, University of Bath, UK, who addressed attendees of the 2016 New Zealand Rheumatology Association (NZRA) Annual Scientific Meeting, held in Napier in August.

PSORIATIC ARTHRITIS – IS EARLY DETECTION IMPORTANT?

Early in his career, Professor McHugh trained at the Wellington Regional Rheumatology Unit and it was there that he first became interested in psoriatic arthritis (PsA). A study undertaken by Professor McHugh and colleagues in 1987 involving 60 patients with PsA found an association between HLA-B27 and spondylitis and between HLA-DR4 and erosive disease.[1] The findings still hold true today in terms of some of the genetic associations identified in PsA and it is remarkable that these were evident with such a small study population. Genetic association studies in the current era require significantly larger study populations.

The spondyloarthropathies

PsA falls within the family of conditions termed the seronegative spondyloarthropathies (SpA) that share features in common such as spondylitis, sacroiliitis, uveitis, enthesitis, psoriasis, IBD, familial relationships and an association with HLA-B27.

In 1956, Verna Wright first described the entity of PsA in his study of 42 cases of psoriasis with arthritis and separated it from rheumatoid arthritis (RA).[2] He described an intriguing association between nail involvement and adjacent distal interphalangeal joint disease and demonstrated that PsA is progressive. At the time he described four patients with osteoarthritis and nail changes, and may have unwittingly described osteoproliferative PsA. Wright's proposal in 1961 that PsA was less severe than RA was contentious.[3] It is now well recognised that PsA can also be a severe and debilitating disease, with some patients not fully responding to modern treatments.

Epidemiology and burden of PsA

In the general population, the estimated incidence of PsA ranges widely from 6.4 to 41.3/100,000 cases per year.[4,5] Among those with pre-existing psoriasis, the estimated annual incidence rates also vary widely, from 310/100,000 cases in the Olmsted County population-based study to 2,700/100,000 cases in a Canadian prospective cohort study.[6,7] Professor McHugh explained that these incidence rates are approaching those of RA, although he does suspect that the higher figures seen in these studies may be due to their design and case selection.

Professor McHugh and colleagues are currently undertaking an analysis of UK Clinical Practice Research Datalink (CPRD) primary care records between 2000-2013 in order to describe the incidence and prevalence of important comorbidities in PsA including IBD, uveitis, diabetes, cerebrovascular disease, peripheral vascular disease and ischaemic heart disease. The CPRD holds primary care records for approximately 10% of the UK population. Professor McHugh and colleagues are particularly interested in determining if the incidence of osteoarthritis is increased in the population with psoriasis or PsA. While their findings have shown an incidence rate of osteoarthritis in the psoriasis population similar to that of controls, the incidence rate of osteoarthritis in the PsA population was found to be significantly higher than that in controls. Professor McHugh explained that it can be difficult to differentiate between the two diseases in clinical practice and that the rates to some extent may represent the misdiagnosis of osteoarthritis in PsA; the bony proliferation and burden of osteoarthritis in PsA is probably much greater than anticipated. Finzel et al. have demonstrated that the progression of osteophytes in PsA tends to continue despite treatment with methotrexate or TNF inhibitors.[8]

The natural history of PsA

Much of the information regarding the long-term outcome of PsA has come from observational studies. Many of these studies are hospital based and there is not a lot of perspective on what happens to PsA in the general population. Among 117 PsA patients assessed at the St Vincent's University Hospital Early Synovitis Clinic, 47% exhibited joint erosions in hands or feet within 2 years of disease diagnosis.[9] It is now well recognised that the burden of PsA, with regard to quality of life, is similar to that of RA.[10-12] There is also increasing awareness of important comorbidities in PsA such as obesity, cardiovascular disease and uveitis.[13] Furthermore, there is a high direct health cost associated with PsA and a high level of unemployment in this patient group.[14]

The majority of mortality studies in PsA show the disease to be associated with an increased risk of death, with estimated standardised mortality ratios as high as 1.62 compared with the general population.[15] However, a recent large study using The Health Improvement Network (THIN) data from the UK revealed no significant increased risk of mortality above that of the general population in individuals with PsA.[16]

Detecting early disease

Evidence suggests that up to 50% of PsA cases go undiagnosed in primary care and dermatology clinics.[17] The UK National Institute for Health and Excellence (NICE) guidelines recommend the annual screening of all psoriasis patients using the Psoriasis Epidemiology Screening Tool (PEST), see **Figure 1**.[18,19] It is well recognised that a delay in diagnosis is associated with poorer outcome.[20,21.] Other factors associated with poorer physical outcome (measured by HAQ) in PsA include smoking, age >50 years, symptom duration >1 year prior to diagnosis and female gender.[21] Symptom duration prior to diagnosis and smoking are two factors that can be changed and should receive attention for the prevention of long-term physical damage in this disease.

PEST screening questionnaire

Score 1 point for each question answered in the affirmative. A total score of 3 or more is indicative of psoriatic arthritis (sensitivity 0.92, specificity 0.78, positive predictive value 0.61, negative predictive value 0.95).

- Have you ever had a swollen joint (or joints)?
- Has a doctor ever told you that you have arthritis?
- Do your finger nails or toenails have holes or pits?
- Have you had pain in your heel?
- Have you had a finger or toe that was completely swollen and painful for no apparent reason?

In the drawing below, please tick the joints that have caused you discomfort (i.e. stiff, swollen or painful joints).

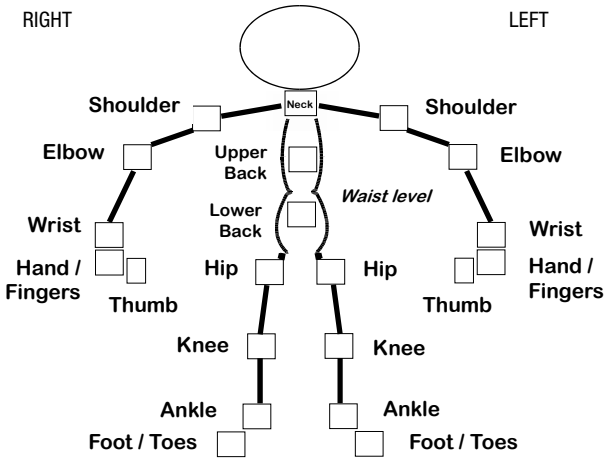

Figure 1: The Psoriasis Epidemiology Screening Tool (PEST).[19]

Other screening questionnaires developed for the early detection of PsA include the PAQ (Psoriatic Arthritis Questionnaire), PACE (Psoriatic Arthritis Screening and Evaluation) and ToPAS (Toronto Psoriatic Arthritis Screen). The PEST seems to be the most popular tool to use for its simplicity and feasibility. More recently an amalgamation of the PACE, PEST and ToPAS has been developed, incorporating the most discriminative questions from the existing instruments.[22]

Risk factors for PsA

Specific risk factors for PsA are outlined in **Table 1**. Factors depicted in bold have more evidence to support a strong association with PsA. A population-based study involving 75,395 individuals with psoriasis from The Health Improvement Network (THIN) revealed a strong correlation between the cumulative incidence of PsA and BMI, with higher BMI categories associated with an increased incidence of PsA (see **Figure 2**).[23]

Table 1. Risk factors for PsA

Lifestyle	**Obesity**[23], smoking[21]
Clinical	**Nail psoriasis**, uveitis, severity or pattern of psoriasis[6,7]
Imaging	Ultrasound evidence of enthesitis
Genetic biomarkers	**HLA-B27**, IL13, PTPN22
Other biomarkers	DC-STAMP, hsCRP, MMP-3, DKK-1, M-CSF, CPII:C2C

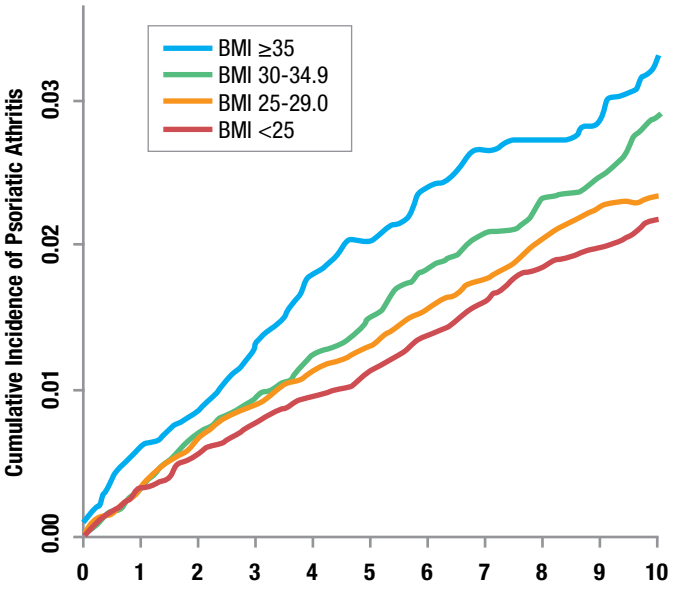

Figure 2. Time to PsA according to BMI category among patients with psoriasis.[23]

A study by Ash and colleagues has revealed a link between nail disease and subclinical enthesopathy, with patients with nail disease exhibiting a greater magnitude of underlying systemic subclinical enthesopathy than those with normal nails.[24] Ultrasound imaging studies have also shown a higher incidence of subclinical entheseal abnormalities in patients with psoriasis compared to a healthy population.[25] Ultrasound imaging may be useful for predicting which psoriasis patients may go on to develop PsA.[25]

Biomarkers are a useful tool for identifying psoriasis patients at risk of PsA and include cellular (circulating osteoclast precursors, DC-STAMP), soluble (hsCRP, OPG, MMP-3, DKK1, M-CSF, CPII:C2C) and genetic (HLA-B27, IL-13, PTPN22, IL-23R, TNFAIP3) biomarkers.[26] A study by Haroon et al., involving 282 PsA patients form Dublin, has shown certain class I HLA alleles and haplotypes implicated in susceptibility to play a role in determining specific features of the PsA phenotype.[27] For example, HLA-B27 is associated with a shorter interval between onset of psoriasis and onset of PsA, while the HLA*B27:05:02 haplotype is associated with enthesitis, dactylitis and symmetrical sacroiliitis, and the HLA*08:01:01 haplotype with synovial-based pathology including joint fusion and deformities, asymmetrical sacroiliitis and dactylitis.

Extending on the findings from the Dublin study, Professor McHugh and colleagues investigated the diversity of class I HLA associations in 219 PsA patients from Bath.[28] **Table 2** outlines the patterns of association of the different phenotypic features of PsA with certain HLA alleles. Professor McHugh highlighted the association between HLA-B27 and symmetric sacroiliitis, and the distinct haplotype in those with asymmetric sacroiliitis. From the combined Dublin and Bath cohorts, Professor McHugh and colleagues have identified 52 patients with arthritis mutilans and have found a distinct combined haplotype associated with this form of PsA.

Table 2. Patterns of association of the different phenotypic features of PsA with certain HLA alleles[28]

Characteristic	Positively associated alleles	Protective alleles
Family history of psoriasis	B*37:01:01; C*06:02:01	B*18:01:01
Psoriasis before age 18	B*55:01:01; C*06:02:01	B*27:05:02
Arthritis before psoriasis	B*27:05:02	B*55:01:01; C*06:02:01
Current PASI score	B*08:01:01	B*27:05:02
Any nail disease	B*08:01:01; B*18:01:01	B*39:01:01; C*06:02:01
Enthesitis	B*18:01:01; B*55:01:01; B*57:01:01	
Dactylitis	B*27:05:02	B*13:02:01; C*06:02:01
Symmetric sacroiliitis	B*27:05:02	C*06:02:01
Asymmetric sacroiliitis	B*08:01:01; B*38:01:01; B*55:01:01	

Potential gains of predicting PsA

The rewards of identifying PsA early benefit both the patient and the healthcare system. UK estimates suggest that mean total annual healthcare costs per patient as a function of disease severity in PsA range from £548 for the least severely affected (HAQ score <1.2) to £4832 for the most severely affected (HAQ score >2.6).[29]

Identifying patients with psoriasis who are at high risk of developing PsA will lead to the mitigation of disease damage and may ultimately drive down the healthcare costs associated with this disease.

It is also well recognised that work disability is a major burden in patients with PsA, with a study of 400 UK PsA patients by Prof McHugh and colleagues reporting absenteeism and presenteeism rates of 14% and 29%, respectively, productivity loss of 46% and unemployment of 25%.[30] The study revealed increased disease activity and worse physical function to be associated with greater levels of presenteeism and productivity loss.

Professor McHugh explained that early detection of PsA presents a potential `window of opportunity' to prevent the progression of this disease. He pointed out that most of the data so far are limited to retrospective studies and that prospective studies are required to demonstrate the true benefit of early intervention in this condition. He has recently received a National Institute of Health Research grant to investigate the outcomes of early detection of PsA.

ADVANCES IN THE TREATMENT OF PSORIATIC ARTHRITIS

There has been an amazing escalation in available treatments for PsA since it was first described as a clinical entity in the 1960s. The earliest treatments for PsA were restricted to NSAIDs and corticosteroids and then the DMARDs methotrexate and sulfasalazine that were modestly effective. The major breakthrough came with the development of the anti-TNF inhibitors, of which five are licensed for use in PsA (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol). Even more agents are now becoming available and there are more in the pipeline.

Anti-TNF therapy

All the currently approved anti-TNF agents including adalimumab, infliximab and etanercept have demonstrated clinical efficacy with an ACR20 response in up to 60% of recipients.[31] While up to 40% of PsA patients may not respond to biologic therapy, these agents are certainly effective treatments for all domains of disease including slowing of radiological damage.[31] But another question we must ask is do we have the correct outcome measure for demonstrating efficacy in PsA? Most of our current measures have been cribbed from RA, but are there better outcome measures for PsA patients that include giving voice to the patient's experience? The latest set of OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) core domains now include measures such as fatigue, emotional wellbeing and participation, although the instruments have yet to be fully defined.

In a prospective observational UK study by Professor McHugh and colleagues examining factors influencing work disability in PsA, preliminary results after 6 months show that in working participants, absenteeism, presenteeism, productivity loss and activity loss were all improved to a far greater extent by the use of anti-TNF agents (n = 65) than with DMARDs (n = 164) and this was also true for secondary endpoints such as fatigue, peripheral joint scores and quality of life measures (in press).[30]

Switching anti-TNFs

The effectiveness of switching to a second or third TNF inhibitor in patients with PsA was investigated in a Swedish cohort study, which found that ACR20 response rates at 12 weeks fell from 47% for first time switches and to 22% for second time switches.[32] The study also revealed a median drug survival time of 64 months for first time switches and 14 months for second time switches. In the study, higher HAQ scores predicted premature drug withdrawal. These findings suggest that other therapeutic options should be considered after a second course of anti-TNF. Positive predictors of response to anti-TNF therapy include male gender, high CRP, younger age and possibly concomitant methotrexate. Negative predictors of response to anti-TNF therapy include smoking, obesity and high HAQ-DI.

Dose optimisation of anti-TNFs

A real-world TNF inhibitor dose reduction study in PsA has shown that 60% of individuals with severe PsA who achieve low disease activity on therapy can successfully have their anti-TNF dose reduced by one-third for a mean of 1 year and maintain efficacy.[33]

New therapies

Newer agents for the treatment of PsA include the anti-TNFs apremilast (which targets the PDE4 pathway), secukinumab (IL-17 pathway) and ustekinumab (IL-12/IL-23 pathway).

Targeting IL-12/IL-23

The PSUMMIT-1 (n = 615) and PSUMMIT-2 (n = 312) phase III RCTs investigated the use of ustekinumab (45 or 90 mg at weeks 0, 4 and 12) in PsA patients who had experienced an inadequate response to methotrexate and/or biologic therapy.[34-36] PSUMMIT-1 revealed ACR20 response rates at week 24 of 42.4% and 49.5% in 45 and 90 mg ustekinumab recipients, compared to an ACR20 rate in placebo recipients of 22.8% ($p < 0.0001$ for both comparisons).[34] In PSUMMIT-2, more ustekinumab (45 and 90 mg) recipients (43.8%) than placebo-treated (20.2%) patients achieved ACR20 at week 24 ($p < 0.001$).[35] Significant treatment differences were observed for week 24 HAQ-DI improvement ($p < 0.001$), ACR50 ($p \leq 0.05$) and PASI75 ($p < 0.001$), with all benefits sustained through week 52.[35] In PSUMMIT-2, approximately 50% of patients had previously received a TNF inhibitor. Pooled radiographic results from both studies demonstrated inhibition of structural damage.[36] Analysis of PSUMMIT-2 results showed no impact of methotrexate use on differential ACR20 response, but a slightly lower response in those who had previously received a biologic agent.[35]

Professor McHugh has limited experience with the use of ustekinumab in his patients; however, he does report favourable results. Ustekinumab is recommended by NICE as a possible treatment, alone or with methotrexate, for adults with active PsA, if TNF inhibitors are contraindicated or the patient has failed one or more anti-TNF agents.[37] They recommend that the agent be stopped after 24 weeks if it is not working.

Targeting IL-17

The Future 1 phase 3 study evaluated the efficacy and safety of secukinumab in 606 patients with PsA receiving either IV secukinumab 10 mg/kg at weeks 0, 2 and 4 followed by SC secukinumab at a dose of either 150 or 75 mg every 4 weeks, or placebo for 16-20 weeks then either 150 or 75 mg every 4 weeks.[38] The ACR20 response rates at week 24 were 50%, 50.5% and 17.3% for the 150, 75 mg and placebo groups, respectively ($p < 0.001$ for both comparisons with placebo). Secondary endpoints including resolution of dactylitis and enthesitis were significantly better in the secukinumab groups than in the placebo group. Furthermore, radiographic progression was inhibited through week 52 in both erosion and joint space narrowing in secukinumab recipients when compared with controls.[39]

Other agents currently under investigation for treating PsA targeting the IL-17A pathway include Ixekizumab (IL-17A), bimekizumab (IL-17A + IL-17F), COVA322 (IL-17A + TNF-α), ABT-122 (IL-17A + TNF-α) and guselkumab (IL-23p19).

Targeting PDE4

The Psoriatic Arthritis Long-term Assessment of Clinical Efficacy 1 (PALACE 1) study compared apremilast with placebo in patients (n = 504) with active PsA despite prior DMARD and/or biologic therapy and found significantly ($p < 0.001$) higher rates of ACR20 response at week 16 in apremilast 20 mg twice-daily (31%) and 30 mg twice-daily (40%) recipients compared with placebo (19%) recipients.[40] Similar findings were seen in the subsequent PALACE 2 and 3 trials, with the agent showing clinically meaningful improvements in signs and symptoms of PsA, physical function and psoriasis through week 52.[41,42] Pooled safety data from the PALACE 1, 2 and 3 trials revealed gastrointestinal adverse events to be the most common, generally occurring early in treatment.

Other potential therapies

A number of other agents have been investigated for the treatment of PsA including abatacept (T-cell inhibitor), which is currently being investigated in a phase 3 study, tocilizumab (IL-6 receptor blocker), which has shown mixed results, clazakizumab (IL-6 inhibitor) and tofacitinib (Jak1/3 inhibitor).

A treat-to-target strategy for PsA

The TICOPA RCT involving 206 early PsA patients receiving any DMARD revealed that tight control of PsA disease activity through a treat-to-target approach as opposed to standard care significantly improves joint outcomes for newly diagnosed patients.[43] The finding of the study prompted both GRAPPA and EULAR to recommend a treat-to-target approach in their revised guidelines.[44,45]

The target in treating PsA, is minimal disease activity (MDA) and this is achieved if five of the following criteria are met:[46]

- Tender joint count (0-68): ≤1
- Swollen joint count (0-66): ≤1
- Patient global activity VAS (0-100): ≤20
- Patient pain VAS (0-100): ≤15
- HAQ-DI (0-3): ≤0.5
- Tender entheseal points (0-13): ≤1
- PASI (0-72): ≤1 or BSA (0-100): ≤3%

Professor McHugh pointed out that some of these criteria are largely patient perception dependent and he believes that the MDA remaining a target for treatment in the future is debatable.

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