Expert Forum

New Zealand Rheumatology Association with
New Zealand Health Professionals in Rheumatology
ANNUAL SCIENTIFIC MEETING 2015

Making Education Easy

3-6 September 2015, Millennium Hotel, Queenstown

In this review:

This publication is a summary of selected presentations delivered at the 2015 New Zealand Rheumatology Association (NZRA) Annual Scientific Meeting, held jointly with the New Zealand Health Professionals in Rheumatology (NZHPR), in Queenstown in early September. The Organising Committee, Dr Daniel Ching (Convenor), Dr Peter Chapman, Prof. Lisa Stamp, Dr John O'Donnell, Dr Rafi Raja, Jan Ipenburg, Jan Drake and Eddy van Til, organised an impressive line-up of international and local speakers, including keynote speakers Prof. Bhaskar Dasgupta and Prof. Peter Taylor from the UK, and local invited speakers Prof. Lutz Beckert, Helen Hills, Dr Alan Pithie, Prof. Ian Reid, Assoc Prof. Catherine Stedman and Dr Gareth Treharne.

This year's award recipients from the Free Paper session were Dr Rebecca Grainger, University of Otago, Wellington and Hutt Valley DHB, who was awarded the Tom Highton prize for her paper on an app for patient-led management of RA, and Dr Nick Kennedy, Dept. of Rheumatology and Immunology, Christchurch Hospital, who was awarded the Bob Grigor prize for his paper on native joint septic arthritis.

We hope you enjoy our selection of topics from the meeting and find them useful to you in your clinical practice.

KEYNOTE SPEAKERS

Professor Bhaskar Dasgupta, Southend University Hospital, UK.

Prof. Dasgupta is the Head of Rheumatology and Clinical Director of Research & Audit at Southend University Hospital, and holds an Honorary Professorship at Essex University and a Visiting Professorship at Anglia Ruskin University.

Professor Peter Taylor, University of Oxford, UK.

Prof. Taylor was appointed to the Norman Collison chair of musculoskeletal sciences at the University of Oxford in October 2011. He directs the clinical trials unit of the Kennedy Institute of Rheumatology and Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences based in the Nuffield Orthopaedic Centre, and is a Fellow of St. Peter's College, Oxford.

Abbreviations used in this review

ACPA = anti-citrullinated protein antibody
ACR = American College of Rheumatology
ALT = alanine aminotransferase
APR = acute phase reactants
AS = ankylosing spondylitis
BMD = bone mineral density
BMI = body mass index
CDAI = Clinical Disease Activity Index
CRP = C-reactive protein
CT = computed tomography
CVD = cardiovascular disease
DAS28 = Disease Activity Score of 28 joints
DMARD = disease-modifying antirheumatic drug
EPO = erythropoietin
ESR = erythrocyte sedimentation rate
EULAR = European League Against Rheumatism
FBC = full blood count
GCA = giant cell arteritis
GM-CSF = granulocyte-macrophage colony-stimulating factor
HBsAg = hepatitis B virus surface antigen
HBV = hepatitis B virus
HRCT = high-resolution computed tomography
IBD = inflammatory bowel disease
IFN = interferon
IL = interleukin
IPF = Idiopathic pulmonary fibrosis
JAK = Janus kinase
MAP = mitogen-activated protein
MRI = magnetic resonance imaging
NSAID = non-steroidal anti-inflammatory drug
NSIP = non-specific interstitial pneumonia
OA = osteoarthritis
PDGF = platelet-derived growth factor
PET = positron emission tomography
PMR = polymyalgia rheumatica
PROs = patient-reported outcomes
PsA = psoriatic arthritis
QALYs = quality-adjusted life years
RA = rheumatoid arthritis
RAPID = Routine Assessment of Patient Data
RF = rheumatoid factor
SDAI = Simplified Disease Activity Index
SLE = systemic lupus erythematosus
STAT = Signal Transducer and Activator of Transcription
SYK = spleen tyrosine kinase
TAB = temporal artery biopsy
VEGF = vascular endothelial growth factor
WHO = World Health Organisation

NEW THERAPIES IN INFLAMMATORY ARTHRITIS: WHAT ARE THE IMPLICATIONS FOR PATIENT MANAGEMENT?

– Professor Peter Taylor, University of Oxford, UK

Biologics such as adalimumab, infliximab and golimumab are protein-based drugs with specific extracellular targets (cytokine receptors or cell-associated receptors). Access to innovative biologic treatments in rheumatoid arthritis (RA), as in other diseases, is significantly limited by cost, as these agents are expensive to manufacuture.[1] Biosimilars may be the solution to this problem; however, due to the manufacturing process and molecular complexity of biologics, it is extremely difficult to make an exact copy, especially of a monoclonal antibody, and it must be recognised that biosimilars are not identical to the innovator drug.[2-4]

Biological product complexity

During manufacture, variations may arise in the primary amino acid sequence of a monoclonal antibody via a number of mechanisms and there is a potential for as many as 100 million variations to the original molecule.[5] A small change can make a big difference, with the presence or absence of one sugar residue affecting the biological activity of the agent.[6] Such changes in immune effector function may influence potency, but may also affect the safety of the drug. Stringent regulations are in place regarding how similar biosimilars must be to their innovator drug and analytical technologies for comparing biosimilars with their reference product are rapidly advancing. [2,4,7]

Prof. Taylor explained that biosimilars are now available in the UK and that biologics will now become more affordable. He cautions that if clinicians do not fully understand the biology behind biologic biosimilars, it may be the pharmacists who dictate which agents patients receive. Furthermore, the safety of biosimilars may be difficult to ascertain in the short term, as relatively small numbers of patients are tested prior to approval of such agents and a safe comparison of rare events cannot be made with certainty. Post-marketing surveillance will therefore be extremely important.

Novel therapies

New therapies in inflammatory arthritis are advancing quickly. Prof. Taylor stressed the importance of understanding the basics of the biology behind these new therapies in order to make appropriate management decisions for patients. Extracellular targets investigated have included the cytokines IL-6, GM-CSF, IL-20 and IL-17, while intracellular targets include p38 MAP kinase, spleen tyrosine kinase (SYK) and Janus kinase (JAK1, 2 and 3).[8] Cytokines act as chemical messengers which engage a response in a responder cell by binding to the receptor on the cell surface. When a particular pathway is implicated in the pathogenesis of a disease, therapies can be designed to target that pathway at different stages by targeting the ligand (cytokine), the receptor or the intracellular signaling. **Figure 1** shows an example of inhibiting the action of IL-6 by using agents designed to block its action at these sites.

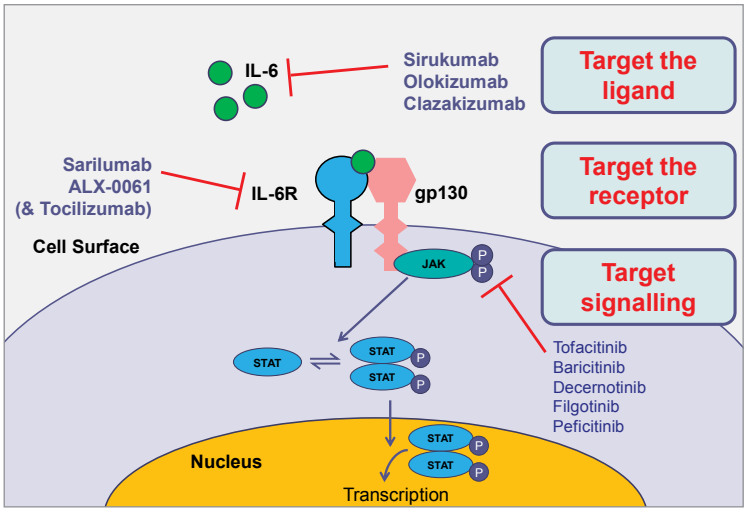

Figure 1. Targeting inflammatory pathways: IL-6 as an example.

A phase II study has shown sirukumab, a human monoclonal antibody, which targets IL-6 to be effective in RA.[9] Clazakizumab has also shown efficacy in RA, but development of the agent has been halted due to concerns about its commercial viability.[10] Sarilumab, which targets the IL-6 receptor has shown efficacy in RA in combination with methotrexate.[11] Prof. Taylor pointed out that the anti-IL-6 agents show similar ACR20, 50 and 70 responses in RA patients to anti-TNFs, and that while having increasing numbers of such agents on the market will drive prices down, they will not necessarily improve individual outcomes. Agents inhibiting the cytokine GM-CSF pathway include MOR103 (targeting the ligand) and mavrilimumab (targeting the receptor), and both agents have shown promising results in Phase II trials in RA.[12,13]

Agents targeting intracellular signalling target the JAK-STAT pathway (see **Figure 1**); JAK is a family of intracellular tyrosine kinases that transduce cytokine-mediated signals via this pathway, which leads to the binding of STATs to DNA and the regulation of transcription. A wide range of different cytokines (IL-2/4/6/7/12/15/21/23, GM-CSF, IFN and EPO) exert their effect via the JAK family.[14] It will be important to consider the implications of blocking a number of pathways with a single agent (i.e. it may be efficacious for a single agent to block IL-6 and GM-CSF, but deleterious for it to block IFN and EPO) and clinical trial data should be carefully investigated. Trials of the JAK inhibitors including tofacitinib (Phase III), perficitinib (Phase IIb) and baricitinib (Phase IIb) in RA patients have shown good results.[15-17] Prof. Taylor pointed out that the efficacy of these agents also seems to be similar to that of biologics in RA. Furthermore, JAK inhibitors are administered orally and some patients may prefer this mode of administration over parenterally administered biologics. JAKs are also relatively cheap to manufacture.

Novel therapies not effective in RA

IL-17 is important in inflammatory diseases, particularly in psoriasis, and the inhibition of this cytokine with agents such as ixekizumab, secukinumab and brodalumab in RA has been investigated.[18] While brodalumab has demonstrated efficacy in psoriasis, it has not been effective in RA.[19] A Phase IIa trial of IL-20 inhibition in RA showed promising findings, especially in seropositive patients, however this was not supported by the phase IIb trial.[20] p38 MAP kinase is activated in the RA synovium and p38 drives the production of TNF. It was therefore thought that targeting p38 might have beneficial effects in RA; however, studies have not supported this theory.[21] A phase II trial undertaken by Prof. Taylor and colleagues investigating the SYK inhibitor fostamatinib in RA, revealed the agent to be no more effective than adalimumab as a monotherapy; for this reason and for concerns about toxicity, including hypertension, diarrhoea and neutropenia, the agent was withdrawn.[22] Another approach has been to inhibit phosphodiesterase 4 with apremilast, which has shown efficacy in psoriatic arthritis, however this has shown to be not effective in RA.[23]

The "ceiling effect" of biologic efficacy in RA

Prof Taylor pointed out that the ACR50 response rates at week 24/30 across a number of trials investigating a range of biologics in RA do not usually exceed 40%, indicating that there is most likely more than one inflammatory pathway involved in the pathogenesis of the rheumatoid syndrome.[24-32] We therefore need to aim to simultaneously target a number of pathways in this disease.

TAKE-HOME MESSAGES:

- Current biologic therapies target extracellular cytokines, receptors or cell-surface targets
- There are many new monoclonal antibody biologics in development
- Synthetic small molecules can be made with selectivity for intracellular targets/enzymes
- Targets not taken forward into the clinic include p38 MAP kinase and SYK
- JAK pathways modulate the incoming signal of an important subset of pro-inflammatory cytokines.

POLYMYALGIA RHEUMATICA

– Professor Bhaskar Dasgupta, Southend University Hospital, UK

Ploymyalgia rheumatica (PMR) carries a significant healthcare burden and estimates in the UK suggest an incidence rate of 8.4 per 10,000 person-years.[33] In the US, the prevalence of PMR in individuals aged >50 years is estimated to be 739 per 100,000 person-years, with a higher prevalence in females.[34] An analysis from the US suggests that PMR is associated with a significant incremental cost of US$2233 at the 10th percentile of costs and US$27,712 at the 90th percentile.[35] These costs are mainly related to comorbid cardiovascular conditions, hospital stays and imaging. Individuals with PMR are more likely to have a history of myocardial infarction, peripheral vascular and cerebrovascular diseases; ORs 1.78 (95% CI 1.13-2.82), 2.21 (95% CI 1.37-3.60) and 1.60 (95% CI 1.08-2.39), respectively.[35]

The diagnostic challenge in PMR

Of all the rheumatologic conditions, PMR carries the greatest diagnostic challenge. The differential diagnosis between PMR and elderly-onset RA can be difficult as these diseases have a similar clinical presentation.[36] In fact, a study of 116 patients with PMR-like symptoms (shoulder pain and raised ESR) revealed that 35% had an eventual diagnosis of RA and approximately one-quarter of PMR patients have peripheral synovitis.[36,37] Furthermore, late-onset spondyloarthropathy may mimic PMR.[38]

Guidelines for managing PMR

The British Society of Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) 2010 guidelines developed by Prof. Dasgupta and colleagues aim to enable a safe and specific diagnostic process for PMR, using continued assessment and discouragement of hasty initial treatment.[39] The guidelines state that the diagnosis of PMR should start with evaluation of core inclusion and exclusion criteria (see **Figure 2**).

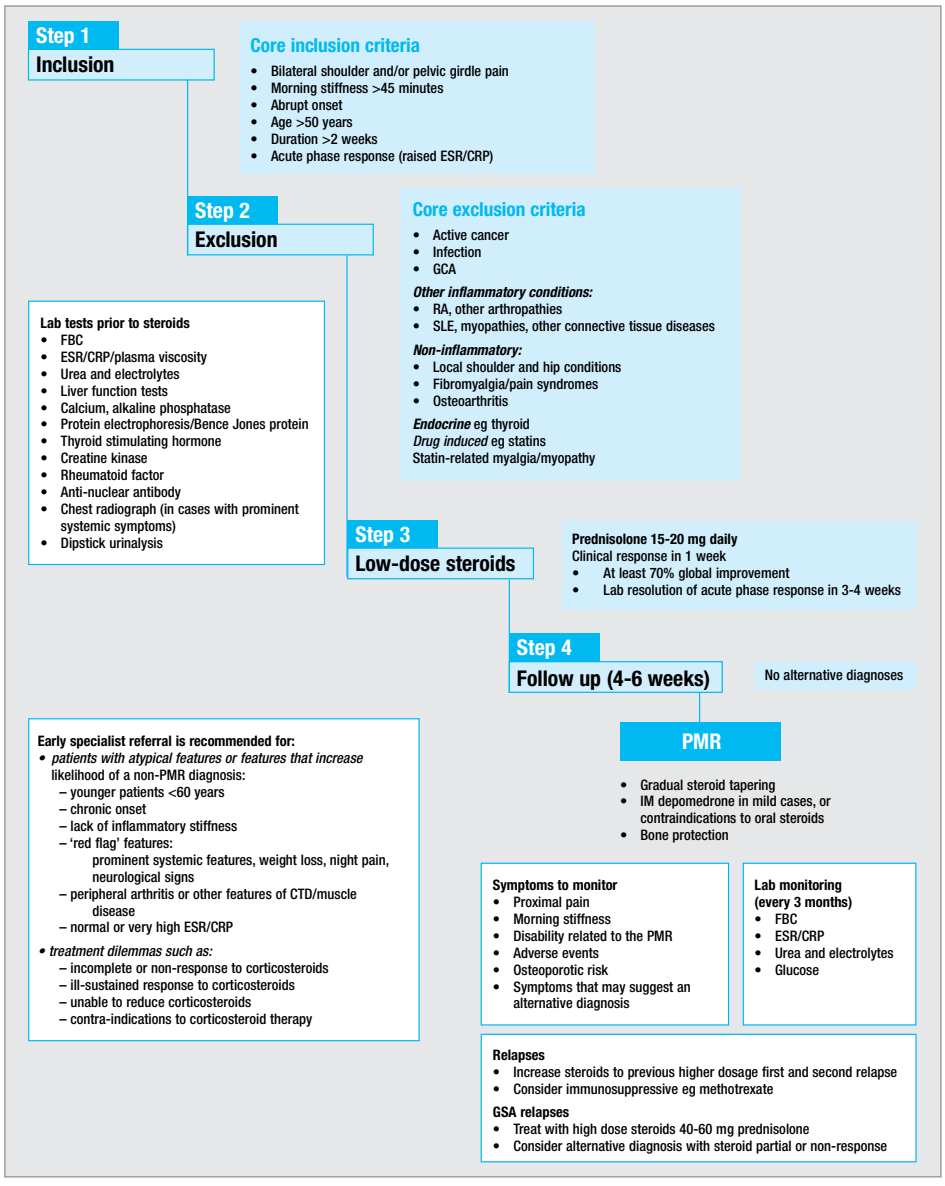

Figure 2. BSR/BHPR recommended approach to the diagnosis and management of polymyalgia.[39]

Non-PMR clues include: younger age; chronic onset of symptoms; lack of shoulder involvement; peripheral arthritis; spinal involvement; male gender; severe constitutional symptoms; very high CRP/ESR; normal CRP/APR; and a poor response to low dose steroids.

The 2012 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for PMR also developed by Prof. Dasgupta and colleagues uses a scoring alogorithm.[40] The patient must first meet the following three criteria: age ≥50 years; bilateral shoulder aching; abnormal CRP/ESR. The patient may then be scored as follows: morning stiffness > 45 minutes = 2 points; hip pain or limited range of motion = 1 point; normal RF or ACPA = 2 points; absence of other joint pain = 1 point. A score of ≥4 is categorised as PMR; at a score of 4 there is 72% sensitivity and 65% specificity for discriminating all comparison subjects from PMR. Adding ultrasound assessment for which an extra 2 points may be scored for specific criteria, a score ≥5 increases the sensitivity to 92%.[41]

The need for imaging in PMR

Imaging in patients with PMR is important for a number of reasons, including the fact that inflammatory markers may be discordant with disease activity. Ultrasound, MRI and PET are important in disease diagnosis, monitoring and for assessing large artery involvement. Prof. Dasgupta believes that all new patients with PMR should undergo ultrasound of the shoulder and hip, and other involved structures. There should also be a clinically driven search for non-PMR clues and appropriate imaging for suspected infection, cancer, GCA, spondyloarthropathy and large vessel vasculitis (ideally an ordinary contrast CT scan of the chest, abdomen and pelvis).

PMR treatment guidelines

The recently published 2015 EULAR/ACR recommendations for the treatment of PMR developed by Prof. Dasgupta and colleagues include the following: establish a diagnosis; assess severity; list co-morbidities; make an individualised choice of steroid dose; provide education; provide advice on a range of motion exercises; provide ready access to treatment of flares and adverse events; review co-medication; assess risk factors; and establish a minimum clinical and laboratory dataset before treatment (consider chest x-ray and other imaging).[42]

It is strongly recommended that NSAIDs be avoided in PMR. Glucocorticoid therapy should be individualised to a minimum effective dose, with a recommended initial dose of 12.5-25 mg prednisone or equivalent. The aim is to reduce the glucocorticoid dose to 10 mg by 4-8 weeks and taper thereafter by 1 mg every 4 weeks; relapse may be treated by reverting to the original dose.

At lower doses, the benefits of glucocorticoid therapy tend to outweigh the risks in the majority of patients with PMR. Intramuscular steroids should be considered as an alternative to oral prednisone in patients with milder disease and for minimalising the glucocorticoid effects in those with co-morbidities such as hypertension.[43]

Steroids or bust?

Prof. Dasgupta explained that while long-term steroids are the mainstay of treatment for PMR, a significant number of patients relapse during treatment. A study of 129 newly diagnosed PMR patients following a tapered steroid schedule of oral prednisolone starting at 15 mg/day revealed one and two year relapse-free survival rates of 68.8% (95% CI 58.8%-75.3%) and 42.4% (95% CI 33.1%-51.4%), respectively.[44] It is recommended that patients with a poorly sustained response to steroids and a high risk of relapse be treated with methotrexate early in their disease course.[42] Methotrexate is also recommended in cases where the initial assessment shows severe disease, and in patients who exhibit risk factors for glucocorticoid side effects. There is currently no role for other DMARDs in PMR, except for leflunomide, which has shown efficacy in PMR in a case-series study by Prof. Dasgupta and colleagues.[45] With regard to biologics, there is no evidence for the efficacy of infliximab or etanercept in PMR, but Prof. Dasgupta has found tocilizumab effective in patients with refractory PMR and large vessel vasculitis.

In conclusion, Prof. Dasgupta explained that he is increasingly convinced that PMR and GCA are part of the same disease and they are difficult to differentiate, as there are many overlapping symptoms. PMR is an under-researched condition and many issues around treatment need to be addressed. Studies are underway to improve the understanding of the pathogenesis of PMR.

UPDATE ON MANAGEMENT OF OSTEOPOROSIS: MONITORING AND TREATMENT

– Professor Ian Reid, University of Auckland

Prof. Reid explained the cellular mechanisms by which bone remodeling occurs and that during menopause the activity of osteoclasts is ramped up with increased numbers of remodelling sites in trabecular bone. This causes the destruction of the microanatomy of such bone leading to an increased risk of osteoporosis and subsequent increased fracture risk. In fact, approximately 50% of Caucasian women will experience a fracture after menopause.[46] Prevention of such destruction is paramount; however, it is never too late to intervene in osteoporosis, as the destructive activity of osteoclasts can be successfully stopped with the use of oral bisphosphonates, preserving what integrity remains of the bony skeleton.

Prof. Reid pointed out that osteoporosis is not a disease, but rather a natural part of ageing. Bone loss to some degree occurs in all individuals after middle age and with the progressive loss of bone density over time, we see an increased risk of fracture in general.[46] Of note, the risk of vertebral and hip fracture in older men is almost as high as it is in older women.[46]

Assessing fracture risk

A US study assessing potential risk factors for hip fracture in 9516 white women aged ≥65 years, revealed a 27.3-fold higher annual hip fracture risk in those with multiple risk factors and low bone density.[47] The FRAX® WHO Fracture Risk Assessment Tool is a useful online assessment for fracture risk (https://www.shef.ac.uk/FRAX/tool.jsp) with different calculation tools available for different ethnic groups. Prof. Reid believes that the UK calculation tool gives the best calibration for fractures for the NZ white population, rather than the FRAX® NZ calculation tool. The FRAX® tool breaks down fracture risk into risk of hip fracture and risk of major osteoporotic fracture (hip fracture, clinically relevant vertebral fracture, proximal humerus fracture and distal forearm fracture). However, Prof. Reid pointed out that these are only half of the types fractures seen in postmenopausal women and that the risk calculated by the tool may in fact represent half the actual risk.[48] Also, while the FRAX® tool accounts for glucocorticoid use, it is simply a yes or no answer and does not adjust for dose used. Kanis et al. suggest increasing the FRAX® calculated risk by 15% if the prednisolone (or equivalent) dose is >7.5 mg/day and reducing the risk by 20% if the dose is <2.5 mg/day.[49] The contribution of lumbar spine BMD to fracture risk has also been assessed and it is estimated that for each T-score unit that spine T-score is lower than femoral neck T-score, total fracture risk increases by 30%.[50]

The Garvan fracture risk calculator is also a useful tool (http://www.garvan.org.au/promotions/bone-fracture-risk/calculator/) and factors in how many previous fractures an individual has had. This can have a significant impact on an individuals future fracture risk; the FRAX® risk tool does not take this factor into account. Prof. Reid tends to use both the Garvan and FRAX® tools in his practice. This can help determine which patients may need assessment of their falls risk and interventions to manage this.

Pharmacotherapy of bone

Cells involved in bone remodelling and agents that impact on them are depicted in **Figure 3**. Osteocytes, regulators of bone homeostasis and remodeling, work through two signaling proteins, RANKL, the principal regulator of osteoclastogenesis and sclerositn, an inhibitor of bone formation.[51,52] Parathyroid hormone, one of the principal regulators of bone turnover, responds to serum calcium. Serum calcium also regulates calcitonin production in the thyroid; calcitonin receptors are present on osteoclasts. Parathyroid hormone stimulates both osteoblasts and osteocytes. Bisphosphonates, the principal agents for the treatment of osteoporosis, act directly on the osteoclasts on the surface of the bone.

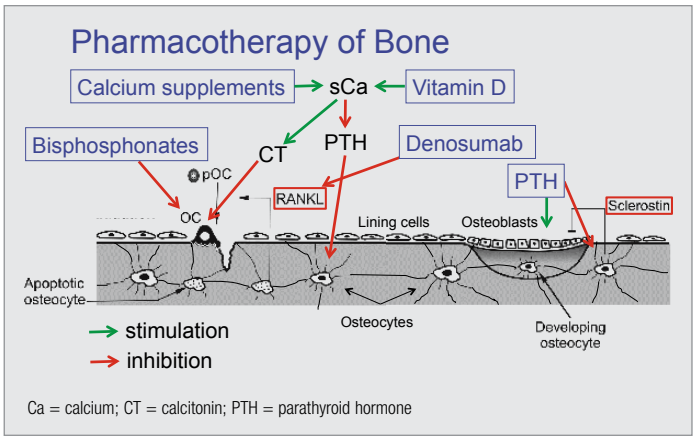

Figure 3. Cells and agents involved in the remodelling of bone.

High doses of calcium inhibit bone turnover. A study in men undertaken by Prof. Reid and colleagues revealed that calcium 1200 mg/day has effects on bone mineral density in men similar to that in postmenopausal women, but that a dose of 600 mg/day is ineffective.[53] A meta-analysis by Bolland and colleagues has shown a 1.4% increase in hip BMD compared with placebo after 1 year of calcium supplementation, a 1.3% increase at 2 years and a 1.2% increase after ≥3 years.[54] It is clear that calcium does not exhibit a cumulative effect and is not particularly effective at reducing fracture rates.[55,56] Furthermore, there is an increased risk of kidney stones, gastrointestinal adverse events, myocardial infarction and stroke with calcium supplementation.[56-58] It is preferable to optimise dietary calcium intake to 500-1500 mg/day rather than use supplemental calcium.[59] Likewise, the use of vitamin D supplementation for osteoporosis prevention in those without specific risk for vitamin D deficiency is inappropriate and should be reserved for those individuals at risk of osteomalacia.[60]

Bisphosphonates, including alendronate, risedronate and zoledronate have demonstrated efficacy in the prevention of hip, vertebral and non-vertebral fractures.[61] Patients should be reassessed after 5 years of treatment on such agents as there is an increased of sub-trochanteric fracture with long-term use; this increased risk decreases by 70% in the first year after discontinuation of the agent.[62]

TAKE-HOME MESSAGES:

- Calcium from diet rather than supplementation
- Vitamin D supplementation in frail elderly (and others at risk of 25D <40 nmol/L)
- Bisphosphonates are effective drugs with a high ratio of benefit to risk
  - Use when fracture risk justifies
  - Consider drug-free holidays or lower doses for long-term use.

RECIPIENT OF THE BOB GRIGOR PRIZE

NATIVE JOINT SEPTIC ARTHRITIS: EPIDEMIOLOGY, DEMOGRAPHICS AND MICROBIOLOGICAL CAUSES IN A NEW ZEALAND POPULATION

– Dr Nick Kennedy, Christchurch Hospital

Septic arthritis is an uncommon but important cause of the acute swollen painful joint. Prompt recognition is essential to limit joint damage. Even with effective treatment this condition has an associated mortality of around 11%, increasing to 16% in the elderly.[63,64] The incidence of this condition is increasing in western countries, and this is likely due to the increasing age of populations, increasing medical comorbidities, increased bacterial resistance, increased skin and soft tissue infections, orthopaedic procedures and underlying rheumatic disease and its treatment.[65,66]

Dr Kennedy and colleagues investigated the epidemiology, demographics and microbiology of adult native joint septic arthritis in their study undertaken in Canterbury over a 5-year period in individuals with and without an underlying rheumatic disorder. A total of 248 eligible adults (aged ≥16 years; median age 60 years; 166 male) meeting Newman's criteria for native joint septic arthritis and resident in the Christchurch District Health Board region were included in the study.[65] Among the cases, 162(65%) were classified as Newman's A (organism Identified from joint aspirate), 43 (17%) were classified as Newman's B (organism identified from other source [i.e. blood]) and 43 (17%) were classified Newman's C (clinical features of septic arthritis with radiological evidence of septic arthritis or turbid synovial fluid aspirate from joint).

The overall incidence rate of septic arthritis in the study was 12/100,000 per year, which was higher than all previous studies of Western populations where the rate has been 4-10/100,000, including prosthetic joints.[66,67] The incidence rate for each of the 5 years studied did not differ significantly. The rate of septic arthritis was found to dramatically increase with increasing age. There was a single joint involved in 92.3% of cases, and multiple joints in 7.7% of cases. The shoulder was the most commonly affected joint (21.4% of cases), followed by the knee (21%), hand (14.9%), hip (10.5%) and ankle (7.3%); the sacroiliac joint was the least affected joint (3.2%).

The most common causative organism was *Staphylococcus aureus* (46.3% of cases) with Beta haemolytic Streptococci the second most common (14.9%). Of interest, 10 cases (4%) were caused by *Propionibacterium acnes* and nine of those cases involved the shoulder post rotator cuff repair. Coexisting inflammatory rheumatic disease was present in 67 (27%) cases, 11 patients were taking prednisone, 10 were receiving methotrexate, three were taking hydroxychloroquine and one patient was on a biologic (adalimumab). The cause of septic arthritis was iatrogenic in 16.9% of cases; 12.5% had a recent joint procedure while 4.4% had had a joint injection within the preceding weeks. The rate of iatrogenic infection compares favourably to other studies.[66] Crystal arthropathy was evident in 33 (13.4%) cases, highlighting that the presence of crystals does not exclude the diagnosis of septic arthritis. Overall, the 30-day mortality rate was 2%, while the 90-day mortality rate was 6%; 52% of those deceased at 90 days had positive blood cultures.

TAKE-HOME MESSAGES:

- There is a high incidence of septic arthritis in the Canterbury population
- The mortality rate of septic arthritis was low
- Septic arthritis commonly coexists with inflammatory arthritis especially crystal arthropathies
- Finding crystals on aspirate doesn't exclude infection
- Immunosuppression including biological therapy is less of a factor than anticipated as a cause septic arthritis
- A considerable number of cases (11) were preceded by joint injection.

RECIPIENT OF THE TOM HIGHTON PRIZE

"NOT FLYING UNDER THE RADAR": A QUALITATIVE STUDY EXPLORING USEFULNESS AND IMPACT OF AN APP FOR PATIENT-LED MANAGEMENT OF RHEUMATOID ARTHRITIS

– Dr Rebecca Grainger, University of Otago, Wellington and Hutt Valley DHB

Dr Grainger pointed out that Treat-to-Target goals are not always achieved in clinical practice in RA. Partly this is due to resources and workforce issues. She also explained that individuals with RA live with this condition every day, but clinic visits may occur only two to three times per year. People with RA report that in normal daily life their RA is constantly in the background and requires continued micromanagement. When their RA symptoms start to move into the foreground, they employ self-management strategies, and generally it is only when their symptoms become unmanageable that they seek medical help.[68]

To aid patients in the ongoing management of their RA, Dr Grainger and colleagues proposed the development of a smartphone app. Patients could record their disease activity metrics with the app, with the data communicated to the RA team. The team could then suggest an action if the metrics deteriorated or the patient requested it. The app could hold data about the patient's medications, and record patient-reported outcomes (PROs) and self-reported tender and swollen joint counts. Composite measures such as the DAS28 could be included. The app could have a communication facility for patient concerns.

Dr Grainger and colleagues sought feedback from potential stakeholders (9 RA patients, 4 rheumatologists, 3 rheumatology nurses, 2 arthritis educators and 2 GPs) regarding the app and its content, functionality and processes, via a qualitative interview process. Four themes emerged: readiness to use an app, app usability and communication, pros and cons of PROs and issues around resource allocation and patient engagement with the rheumatology service. While some patients were enthusiastic about the concept of the app, others thought it would not work for them. Healthcare professionals recognised that in the future patients would expect such mobile health options, but were apprehensive of its impacts, especially with regard to privacy, security of data and impact on health professionals' workflow. Both groups felt that the app needed to be intuitive and easy to use, and that training should be provided. Patients valued the potential opportunity to record the impact of RA on their lives, but believed that PROs fail to capture all aspects of their disease experience. All patients were unaware of the DAS28. Both parties believed it might be empowering to record and track PROs over time, but expressed that individuals could become too focused on measuring disease activity, leading to anxiety.

With regard to resource allocation and engagement, patients stated that care should be rationed according to need and highly valued the face-to-face appointments, but commented that reduced frequency of appointments would be acceptable if urgent appointments were available when needed. They also felt that the app would increase engagement with the rheumatology service and give reassurance between visits. Healthcare professionals were concerned that the app could lead to inequitable access, increase workloads and increase patient anxiety. Further feedback was that the app could avoid the booking of unnecessary appointments and ensure that patients are not falling under the radar when their disease is active.

Dr Grainger has approached the Hutt Valley Hospital IT department, who have agreed to integrate the app data coming from patients own smartphones into the hospital medical record (Concerto). A prototype app is currently being developed and will be tested in the near future.

TAKE-HOME MESSAGES:

- Patients and healthcare professionals are keen to have an app for RA patients
- Healthcare professionals are apprehensive about the impact of an app on workloads and flow.

ARE MUSCULOSKELETAL CLINICAL TRIAL OUTCOME MEASURES WHAT PATIENTS AND THEIR DOCTORS REALLY NEED TO KNOW ABOUT BEST CARE? – *Professor Peter Taylor, University of Oxford, UK*

Clinical assessment tools in RA, such as the ACR score, DAS28, CDAI and RAPID3 have limitations.[69-72] Prof. Taylor pointed out that in most trials the clinical outcome measure will be the ACR20, but in practice, patients don't really care about the ACR20, which represents only a ≥20% improvement from baseline. The goal of treatment in RA is to maximise long-term quality of life; this is achieved by controlling symptoms and preventing structural damage (Treat to Target holds the hypothesis that this is achievable by optimally controlling inflammation over time). Achieving this leads to the normalisation of function and improved social participation. However, most patients will not achieve this aspirational target of sustained remission.

A Scandinavian study comparing clinical and patient-reported outcomes in patients with RA treated in two time periods, 1998-99 and 2011-12, revealed better RA-related clinical outcomes in the latter period, as would be expected with more active anti-rheumatic therapy available.[73] However, in the latter period, patients reported worse general health and higher comorbidity rates. This may be due to higher expectations of RA treatments in the current era and a lower acceptance of high disease activity. Pain, functional disability and fatigue are important health domains to RA patients.[74] With this in mind, we must aim to treat the totality of the disease, not just aim for specific clinical targets. Multidisciplinary teams are required to help manage all aspects of disease with a patient centric approach. Prof. Taylor explained that we must be aware that patient's perspectives may differ from the physician's with regard to their disease and the impact of its symptoms, and that there is a discordance between patient and physician assessments of disease activity.[75,76]

Pain in RA

Generally, pain is the symptom that causes the most difficulty for RA patients.[77] Prof. Taylor explained that the anatomical origin of arthritis pain is complex and that recording a global impression of pain (as is often undertaken in clinical trials) is not very informative. Pain is a complex set of neural, humoral and emotional events. It includes release of noxious mediators, inflammation, peripheral and central sensitisation, and remodeling of synaptic contacts.

Assessing therapeutic response

Prof. Taylor pointed out the importance of accurately determining clinical response with robust measures in RA clinical trials. Continuous measures of change in inflammatory joint activity, such as the DAS28, CDAI and the SDAI comprise binary components (the joint is either swollen or it is not!) In contrast, ultrasonography provides a continuous accurate measure of inflammation and can differentiate disease severity in RA, correlating closely with DAS28.[78] Furthermore, 2D and 3D power Doppler ultrasound have proven to be extremely useful tools for measuring joint vascularity as a pharmacodynamic measure of therapeutic response in RA.[79-82] Ultrasound may reveal structural damage in joints that appear normal on x-ray and Doppler may be helpful in predicting erosions in early RA. Such imaging might have utility in predicting which patients will derive benefit from the early use of biologic therapy.[83]

While there are a number of issues around the use of MRI in RA, studies show that it is superior to x-ray for assessing synovitis, osteitis, bone erosion, joint-space narrowing and cartilage loss, and may be useful in dose ranging studies.[84] A study undertaken by Prof. Taylor and colleagues using MRI to examine dose dependency of baracitinib on joint changes in patients with erosive RA revealed dose-dependent suppression of synovitis, osteitis and total inflammation at 12 and 24 weeks with baricitinib 4 mg and 8 mg.[85] MRI in RA may be optimised using dynamic contrast enhancement and this has great potential to provide quantitative measures of inflammatory activity.[86] A study undertaken by Prof. Taylor and colleagues using automated dynamic contrast enhanced MRI of the wrist in healthy volunteers revealed robust measures over time with little longitudinal change, suggesting the suitability of this modality in monitoring change in RA patients.[86]

Subjective measures

Prof. Taylor explained that while it is important to understand the pathological mechanisms behind RA and to use technology to quantify inflammation and pain, we need to include subjective measures of disease activity that are important to patients, such as measures of fatigue and quality of life. It is then that measurable, achievable individual treatment targets can be set. To this end, Prof. Taylor and colleagues have developed a multi-dimensional ipad tool to measure patient wellbeing. The tool gives information about the impact of RA on the patient's life at the current time and allows for psychometric profiling. The tool, which provides a means by which to measure what is important to the patient, has been successfully trialed in five countries and is now being tested in clinical trials.

TAKE-HOME MESSAGES:

- Sensitive imaging modalities, particularly ultrasound and MRI have the potential to detect subclinical synovitis
- Imaging can be used to quantify local inflammation with greater accuracy than binarised clinical joint assessments; however, it is NOT a substitute for a thorough clinical examination!
- Research points to the use of imaging biomarkers as having prognostic value and use for patient stratification
- Quantitative imagining technologies have value in early phase clinical trials in determining a robust signal of efficacy
- Personalised measures of wellbeing allow assessment of subjective response to therapy in domains important to the patient.

INFECTIOUS COMPLICATIONS IN PATIENTS WITH RHEUMATOLOGICAL DISORDERS

– Dr Alan Pithie, Christchurch

Individuals with rheumatological conditions have a 1.5- to 2-fold increased risk of infection.[87,88] A study of 113 patients with Wegener's Granulomatosis at a single centre in France revealed 53 major infections (pneumonia 19, herpes zoster 9, cellulitis 4, discitis and septic arthritis 3, and bacteraemia 2) among 35 patients.[89] In the study, cyclophosphamide and corticosteroids were found to be associated with a higher risk of infection. The risk of serious infection with TNF inhibitor use has been widely reported in Registry data. A Japanese RA registry reported that among 1144 patients observed for one year, the incidence of serious infection was 6.42/100 person-years for biological DMARDs compared with 2.64/100 person-years for non-biological DMARDs.[90] Biologic use was found to be a significant independent risk factor for serious infection; RR 2.37 (95% CI 1.11-5.05). Data from the British Society for Rheumatology Biologics Registry (BSRBR) show that the risk of serious infection is greatest in the first 6 months of treatment, with an adjusted HR of 1.8 (95% CI 1.3-2.6).[91] A large US retrospective cohort study (Safety assessment of Biological Therapy [SABER]) of four large automated databases found the serious infection (requiring hospitalisation) rate among 10,484 RA patients to be 8.16/100 person-years for biologic therapy and 7.78/100 person-years for non-biologic therapy.[92] In the study, the non-viral opportunistic infection rate with anti-TNF agent therapy was found to be 2.7/100 person-years compared with a rate of 1.7/100 person-years for those receiving non-biological DMARDs (adjusted HR 1.6; 95% CI 1.0-2.6).[93] The rates of serious skin and soft tissue infection in the BSRBR were found to be 1.6/100 person-years with anti-TNF therapy and 0.7/100 person-years with non-biological DMARDs (adjusted HR 1.4; 95% CI 0.9-2.4).[94] The rates for shingles were 1.6/100 person-years vs 0.8/100 person-years (adjusted HR 1.8; 95% CI 1.2-2.8).

Vaccine preventable infections

EULAR have formulated 13 recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases, including the recommendations to assess vaccination status at initial work up, to vaccinate during stable disease, to avoid live attenuated vaccines in immunosuppressed patients, to encourage influenza and pneumococcal vaccines, to consider herpes zoster vaccination, and for travellers to receive standard recommended vaccines, except live vaccines such as yellow fever.[95] In NZ the two available pneumococcal vaccines are the 23-valent polysaccharide vaccine (PPSV23) and the 13-valent conjugate vaccine (PCV13; this replaced the 7- and 10-valent vaccines). The optimal use for maximal antibody response appears to be PCV13 followed by PPSV23.[96]

The risk of herpes zoster infection is increased 1.5-2-fold in those with RA and other autoimmune conditions.[97] Live attenuated zoster vaccine has been shown to reduce the risk of herpes zoster by 70% in immunocompetent individuals 50-59 years and by 51% in those over 60 years of age.[97] Among 18,683 zoster vaccinated patients with immune mediated disease, there was a 40% reduction in herpes zoster, and no cases of herpes zoster among 633 patients receiving biological therapy. Furthermore, in a single site study of 152 rheumatic patients receiving biologic therapy, zoster immunisation was not associated with any cases of disseminated herpes zoster or significant local reaction.[98]

RA patients receiving biologic therapy also have an increased risk of tuberculosis.[99] Tuberculosis incidence rates for those on infliximab have ranged between 144-2162/100,000 person-years compared with incidence rates between 5.2-85/100,000 person-years in the general population.[99]

DMARDS/BIOLOGICS AND VIRAL HEPATITIS

– Associate Professor Catherine Stedman, Christchurch Hospital and University of Otago, Christchurch

Hepatitis B virus (HBV) is a global problem with an estimated 350 million long-term carriers worldwide.[100] Approximately 75% of long-term carriers live in the Asia Pacific region and it estimated that there are over 90,000 HBsAg-positive individuals living in NZ (the majority are of Māori, Pacific or Asian ethnicity).[101] The NZ Hepatitis B Screening Programme revealed high prevalence rates in the following ethnic groups: Māori 5.8%; Cook Island 7.4%; Niuean 9.1%; South East Asian 9.3%; Chinese 9.4%; and Tongan 13.3%.[102]

Testing for HBV

There are two types of HBV carriers, life-long carriers and those who have had acute HBV and have resolved their infection. Initial investigations for HBV status prior to starting immunosuppressants should include HBV Serology (HBsAg, anti-HBs and anti-HBc), HBV DNA (viral load) if HBsAg or anti-HBc positive, and liver function tests. Anti-HBs is a marker of immunity while anti-HBc is a marker of resolved or current infection. If an individual is HBsAg-positive they are considered to have chronic HBV but may either be active or inactive carriers.[103] Active carriers have a lot of virus with high HBV DNA levels and raised ALT levels. These individuals require antiviral therapy (usually lifelong) and should not be started on immunosuppressants until antiviral treatment is initiated. Inactive carriers have reasonably good immune control over the virus, normal liver function tests and low or undetectable HBV DNA levels. These individuals are not normally treated; however, they are at a high risk of reactivation if immunosuppressed. Also at risk of reactivation of HBV are those individuals who have previously had acute HBV and resolved their infection. These individuals may test HBsAg-negative but have a positive core antibody.

HBV status and immunosuppression

A review of 23 studies involving a total of 620 patients with markers of HBV who had received anti-TNF-α for rheumatic diseases revealed 13 reactivations among 416 with `past' HBV infection and 46 reactivations among 204 HBsAg positive individuals.[104] A 12% HBV reactivation rate was found in a review of nine studies involving 122 HBsAg positive patients receiving anti-TNFs or DMARDs; all cases resolved.[105] A review of six studies involving 144 patients with rheumatic diseases receiving steroids showed 30 HBV reactivations after 5-9 months of treatment.[104] These findings suggest that antiviral prophylaxis be considered in HBsAg positive patients starting steroids. In another study, among 211 patients (23 HBsAg positive and 188 HBsAg negative/anti-HBc positive) who received DMARDs without antiviral prophylaxis, four patients developed HBV reactivation.[106] Reactivation rates among 468 patients with resolved HBV infection (HBsAg negative, anti-HBc positive) receiving anti-TNF therapy for rheumatic diseases revealed an HBV reactivation rate of 1.7%; all were treated, with good outcomes.[107]

Prior to immunosuppression all individuals should be tested for HBV status and depending on results, the following should be undertaken:

1. **All HBV serology negative:** Recommend vaccination; proceed with immunosuppression
2. **HBV anti-HBs positive and anti-HBc negative:** These individuals have HBV immunity from vaccination. Proceed with immunosuppression.
3. **HBsAg positive:** These individuals have a risk of HBV reactivation with immunosuppression. This risk is related to the level of immunosuppression (greatest risk with chemotherapy/rituximab, followed by anti-TNFs/rituximab, then steroids/DMARDs). Those who have active HBV should receive entecavir, while inactive carriers should receive lamivudine prophylaxis. Antiviral therapy should be continued for 12 months after cessation of immunosuppression. Due to the lower risk of reactivation with DMARDs, antiviral prophylaxis is not funded in NZ and the alternative is to monitor HBV viral load and liver function every 3 months and intervene if necessary. With steroids there is a moderate risk of reactivation and antiviral prophylaxis is funded. Individuals receiving combination immunosuppression are at higher risk of HBV reactivation and should receive lamivudine prophylaxis.
4. **Resolved HBV (HBsAg negative, anti-HBc positive):** There is no clear indication for prophylactic antiviral therapy during anti-TNF therapy in these patients, but their HBV DNA and liver function should be monitored at least every 3 months, long-term. If their viral load increases, antiviral therapy should be initiated. In those receiving rituximab, consider prophylaxis especially if on steroids. There are no clear guidelines for those receiving DMARDs, but they should be monitored long-term with appropriate therapy if reactivation occurs.

TAKE-HOME MESSAGES:

- Hepatitis B screening is essential prior to commencing immuno-suppression, especially monoclonal antibodies
- HBsAg positive patients have the highest risk of reactivation
- Anti-HBc positive, HBsAg negative patients remain at low risk of reactivation, but require long-term monitoring
- Combination immunosuppression including steroids or monoclonal anti-bodies confer higher risk of HBV reactivation than traditional DMARDs.

ABOUT RESEARCH REVIEW
Research Review is an independent medical publishing organisation producing electronic publications in a wide variety of specialist areas. Research Review publications are intended for New Zealand medical professionals.

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Expert Forum publications are designed to encapsulate the essence of a local meeting of health professionals who have a keen interest in a condition or disease state. These meetings are typically a day in duration, and will include presentations of local research and discussion of guidelines and management strategies. Even for local events it is not always possible for everyone with a similar therapeutic interest to attend. Expert Forum publications capture what was said and allows it to be made available to a wider audience through the Research Review membership or through physical distribution.

INTERSTITIAL LUNG DISEASE

– Professor Lutz Beckert, University of Otago, Christchurch

Idiopathic pulmonary fibrosis

In 2002, the American Thoracic and the European Respiratory Societies released a useful classification for idiopathic interstitial pneumonias.[108] Idiopathic pulmonary fibrosis (IPF) constitutes approximately 50% of all interstitial lung diseases seen in respiratory clinics, has a mean age of onset of 70 years, a prevalence in individuals over 70 years of age of approximately 200/100,000, an average survival or 2.4 to 3 years and a 5-year survival rate of 20%.[109] IPF can be diagnosed from HRCT scanning and predominantly involves the lower half of the chest, with a honeycomb appearance.

It is thought to result from aberrant wound healing in response to repetitive lung injury. The initial insult is to the alveolar epithelial cells, which causes vascular damage and inflammation followed by macrophage invasion of the alveoli, fibroblast recruitment, proliferation and activation and finally, extracellular matrix synthesis and cross linking.[110]

Many agents have been tried unsuccessfully, including the combination of prednisone, azathioprine, and N-acetylcysteine, which was found to increase the risks of death (8 vs 1; $p = 0.01$) and hospitalisation (23 vs. 7; $p < 0.001$) in comparison to placebo.[111]

However, two agents have now been identified that slow the progression of the disease, pirfenidone and nintedanib. These agents are not available in NZ at present, however, they are expected to be funded soon; in the meantime some patients may be eligible for clinical trials.

Non-specific interstitial pneumonia

Non-specific interstitial pneumonia (NSIP) is a clearly defined illness most commonly seen in females with an onset around the age of 50 years. It is characterised by increased lung density with preserved lung architecture, slight subpleural sparing and mild traction bronchiectasis.[109] On CT it shows more ground glass changes with little or no honeycombing and some translucency. Biopsy tissue from throughout the lung has the same pathology, with both temporally and spatially homogenous fine interstitial fibrosis, not inflammation, a mixed cellular and fibrotic pattern, relative preservation of the background alveolar walls, and minimal fusion into thicker structures.

The survival time for IPF and NSIP is very different; at 120 months the percentage of patients still alive is about 39%.[112] In a study of patients with NSIP, 88% of them also fulfilled the criteria of a connective tissue disease or undifferentiated connective tissue disease; including conditions such as RA, Raynaud's, arthralgia, or signs and symptoms such as dry mouth or autoantibodies.[113] So it appears that NSIP is the principle lung illness associated with established connective tissue disease. When a patient with RA presents with lung abnormalities consider NSIP, although you should keep in mind that it may be an infection or a drug reaction, for example TNF-α inhibitors or IL-6 agents may cause fibrosis.

Connective tissue disease may initially present as interstitial lung disease, for example in 10-30% of patients it is the initial presentation of a myopathy.[114] These patients are often seen first by a respiratory physician, as the interstitial lung disease may precede the systemic symptoms associated with the underlying connective tissues disease, which may be missed because of the acuteness of presentation and the extrathoracic manifestations may be overlooked because they are subtle.[114] A third disease type has been termed Interstitial lung disease with features of autoimmunity. This is an undifferentiated connective tissue disease, the 'formes fruste' of connective tissue disease.[114]

Survival in patients with NSIP is significantly affected by the underlying cause of the disease, NSIP with an associated connective tissue disorder or with an unspecified connective tissue disorder has a relatively good prognosis (≈70% at 120 months) in comparison with patients with idiopathic NSIP (≈35% at 120 months).[115] Unlike IPF, patients with NSIP may respond to prednisone/azathioprine/cyclophosphamide, but the evidence is limited.

Drug related interstitial lung diseases

Nitrofurantoin is the most common cause of drug-induced pulmonary disease.[116] It is serious, can be fatal and is entirely preventable. The use of nitrofurantoin should be limited to 6 months, it should be withdrawn at first sign of pulmonary damage and should be avoided in patients with poor respiratory reserve. Another drug that causes lung disease is amiodarone that may present as pneumonia – cessation of the drug results in recovery. Methotrexate pneumonitis is a rare and unpredictable complication of methotrexate use.[117] A prospective audit on 233 patients followed for 2 years found two patients developed methotrexate pneumonitis, 1 case/192 patient-years, or an incidence >1%.[118] A review from the Mayo clinic has shown that methotrexate lung disease can have interstitial inflammation (71%), interstitial fibrosis (59%), hyaline membranes (8%), granuloma formation (35%), giant cells (26%), and bronchiolitis obliterans (8%).[117]

MANAGING CO-MORBIDITIES IN RHEUMATIC DISEASE: CVD RISK AND RA PATIENT EDUCATION

– Dr Gareth Treharne

It is well established that the risk of CVD in RA is elevated compared with the general population and comparable with the magnitude of risk in type 2 diabetes mellitus.[119] As increased atherosclerosis probably begins prior to or around the onset of RA, it is important for patients and health professionals to be aware of RA-specific CVD risk at the time of RA diagnosis, but a recent investigation revealed that half of RA patients and US primary care doctors had no knowledge about this risk.[120,121] Another recent study reports that only 3% of Dutch RA patients with a high 10-year CVD risk (≥20%) realised their risk.[122] The QRISK2 lifetime CVD risk calculator is one of the first that can be used in the general population and recognises RA as a risk factor for CVD to the same extent as diabetes, smoking, and other factors.[123]

A recent publication from the Consortium of Rheumatology Researchers of North America (CORRONA) cohort included 23,605 RA patients with 437 CVD events over a median 2.2 years of follow-up.[124] CV risk was predicted by: being male, diabetes, hyperlipidaemia, hypertension, smoking, age >50 (linear), disease duration ≥10 years, disability (modified Health Assessment Questionnaire [HAQ] disability index >0.5), disease activity (CDAI >10), and daily prednisone use. Dr Treharne noted that this analysis did not consider historic NSAID use, which might have increased CV risk in the past.

EULAR has developed evidence-based recommendations for CV risk management in patients with RA.[125] They advise that scores derived from CVD risk calculators other than the QRISK2 (which includes RA as a CV risk factor) should be multiplied by 1.5. They also recommend undertaking regular CV risk assessments and after changes to antirheumatic treatment. Known CVD risk should be treated with statins and antihypertensives and disease activity should be controlled. They recommend using NSAIDs and steroids with caution.

The lack of clinical trials means that the ideal CVD prevention (CVP) in RA remains unknown.[126] Based on limited current evidence and extrapolation of data from studies in other patient populations, the CVP in RA should include: control of inflammation, encourage adjusted physical activity, healthy diet and weight control, as well as smoking cessation. Two psychologically-informed interventions are described that aimed to help RA patients reduce their CVD risk through broad changes to lifestyle factors associated with CVD or smoking cessation specifically.

Project 1: CVD risk reduction

This patient education initiative, led by Holly John, considered all of these behavioural risk factors as a means of reducing CVD risk in RA patients.[127] An initial rigorous planning process developed two parallel versions of the Heart Disease Fact Questionnaire (HDFQ-RA): testing revealed that RA patients score a median of 9/13 and the hardest questions to answer were those asking about cholesterol and RA-specific CVD risks. A RA patient leaflet about CVD risk was developed. Qualitative consultation was undertaken with RA patients and health professionals (including consultants, nurses, GPs, cardiologists, etc.) about timing, format and approach for patient education around CVD risk reduction. The project

also reviewed psychological theories around ways to encourage people to change their behaviour. This initiative included an intervention group, which enrolled 52 RA patients who met as a group once a week for 8 weeks. They received CVD education, a CVD assessment, selected one CVD-related goal to focus on, and they undertook self-monitoring. The control group included 58 RA patients (well matched with the intervention cohort, except for TNF inhibitors), who received no group-based intervention but were given the CVD leaflet and routine care. The 8-week group intervention led to a greater increase in CVD knowledge, reduction of blood pressure, and greater intentions to exercise and eat a low fat diet. There was no effect on smoking cessation. Moreover, there was no difference between the groups on actual exercise and dietary behaviours.

Project 2: RA-specific smoking cessation support

This ongoing intervention is being led by Lisa Stamp and conducted by Pip Aimer.[128] The first phase consisted of collaboration with Arthritis New Zealand funded by HRC Partnerships for New Zealand Health Delivery about delivering the 3-month individualised smoking cessation intervention. A subsequent consultation phase with RA patients included focus groups and interviews about barriers to smoking cessation as well as ex-smokers' successes. A comprehensive review of the literature on smoking cessation was undertaken. Patients in the intervention group were provided with 1-on-1 contact with Arthritis Educators (4 timepoints), weekly emails for 12 weeks and a support website as well as printed materials addressing education, pain, exercise opportunities, coping and support. The control group was given routine care: ABC (Ask, give Brief advice, Cessation support) plus nicotine replacement therapy, and encouraged to use their own strategies.

At the 6-month follow-up, 5/19 (26%) patients in the intervention group had quit smoking (most had done so immediately), while 4/21 (21%) controls had also quit. Similar moderate rates of smoking cessation were seen in both groups: 53% of patients in the intervention group achieved a ≥50% reduction in number of cigarettes per day versus 42% of controls. The findings from these interventions suggest that routine smoking cessation efforts are effective and also possibly suggest that the study participants were motivated participants compared to those who declined to be involved.

Future research – Depression and CVD

RA patients with diagnosed CVD are more likely to be depressed.[129] Depression predicts coronary artery calcium in RA (controlling for CRP, BMI and smoking).[130] Lower happiness is associated with fatigue and physical inactivity in RA and OA.[131] The question arises as to whether psychological interventions help improve mood, energy and exercise levels in RA and have an impact on CVD?

TAKE-HOME MESSAGES:

- For CVD risk assessment with RA patients, either:
  - Use the QRISK2 lifetime CVD risk calculator[123]
  - Multiply other calculators by 1.5 (to avoid underestimation of risk)[125]
- Group CVD education for RA patients can improve knowledge and good intentions
- Continue to offer ABC/nicotine replacement therapy for RA patients who smoke.

GIANT CELL ARTERITIS

– Professor Bhaskar Dasgupta, Southend University Hospital, UK

The earliest description of what may be temporal arteritis was recorded in the Tadhkirat of All ibn Isa of Baghdad (c. 940–1010 AD), which became the standard resource for the anatomy of the eye, external and internal diseases of the eye and their treatment (including conjunctivitis, cataracts, and trachoma), and numerous remedies and their effect on the eye.[132] Histological aspects of clinical cases of giant cell arteritis (GCA) were described by Horton and colleagues in 1932,[133] and the characteristic symptoms of GCA were defined by the ACR 1990 criteria.[134]

Now, these criteria are considered to be very limited as to our understanding of GCA. They were primarily intended to distinguish one form of vasculitis from another; they fail to distinguish patients with other causes of headache from GCA. For example, the criteria do not mention jaw or tongue claudication, visual symptoms, or large vessel vasculitis. Prof. Dasgupta suggests that the criteria can be expanded to ensure that they are fit for purpose, with reference to the clinical cases described by Horton and colleagues in 1932.[133] He suggests the additions of headache of 1 week's duration, polymyalgia and constitutional symptoms. Other artery abnormalities need to be added to temporal artery abnormality, while CRP could probably be added to ESR (the level is yet to be determined). Abnormal imaging is also important.

Prof. Dasgupta and colleagues developed guidelines in 2010 for the management of GCA.[135] The therapeutic armamentarium has expanded since then, offering options beyond steroid therapy. Now, we have a better understanding about the pathophysiology of GCA disease initiation and progression. The disease is initiated in response to an unknown antigen, with dendritic cells within the vessel adventitia consequently activating CD4 helper T cells. Currently, it is thought that TH1 and TH17 cells are mediated by different cytokines, leading to the secretion of IL-17 and activation of macrophages secreting PDGF and VEGF, giving rise to the neoangiogenesis as well as the hyperplasia that causes complications. These macrophages also secrete their own cytokines (IL-1β, IL-6, TNF-α), resulting in disease amplification. PDGF contributes to vascular smooth cell activation and migration into the intimal layer. Giant cells and granulomata form within the medial layer along the now fractured internal elastic lamina, and further destruction occurs. In larger vessels, particularly the aorta, damage to the vessel wall eventually leads to aneurysm formation. Recent research indicates potential involvement of neutrophils in GCA disease progression, with evidence of an escaped proinflammatory phenotype when corticosteroid therapy is tapered at 6 months, suggesting that this may signal a subclinical disease re-emergence.[136]

The BSR guidance on temporal artery biopsy (TAB) is considered to be the diagnostic gold standard, providing prognostic information on intimal hyperplasia on biopsy.[135] The guidance advises early TAB in all cases, preferably within a week of starting steroids. The degree of intimal hyperplasia on TAB histology appears to be closely related to neuro-ophthalmic complications of GCA.[137] Importantly, such information may not be available from temporal artery ultrasound. The multinational TABUL study has been designed to compare the diagnostic accuracy of temporal artery ultrasound with that of biopsy and to evaluate the cost-effectiveness of ultrasound with TAB in GCA. It intends to recruit 402 patients; 100 have been enrolled from Southend University Hospital. Prof. Dasgupta has retrospectively analysed Halo score data from 90 patients with GCA according to ACR criteria, to determine the usefulness of a semi-quantitative Halo score, whereby the 'halo' sign at each branch was scored according to grade and a total Halo Score (HS) was formed by the sum of grades from all the sites. A ROC curve analysis compared the HS with positive TAB and yielded an AUC of 0.81 (95% CI 0.68 to 0.93), with different cut-offs for the HS depending on whether the aim is to determine sensitivity or specificity (e.g. cut-off of 4 = 90.5% sensitivity and specificity of 71.0%; cut-off of 7 = 90.3% specificity and sensitivity of 42.9%). This concept needs further exploration. However, ultrasound has limitations. It requires expertise and a learning curve, depends on variability in equipment and settings, standardisation of image acquisition, and the results depend on pre-test probability of GCA.

Prof. Dasgupta and colleagues consider CT scans very useful for the diagnosis of large-vessel vasculitis (LVV). They also find FDG-PET-CT very useful, particularly in monitoring treatment. The PET scan detects axillary arteries, the hallmark of GCA.

A fast track GCA pathway

Southend Hospital has made a case for a Fast Track GCA pathway, enabling urgent recognition and prompt corticosteroid therapy (see **Figure 4**).[138] GCA is associated with a high incidence of irreversible ischaemic complications, which may partly result from diagnostic and treatment delay. Obstacles to early recognition of GCA include a delayed presentation (predominantly elderly patients), delayed referral (failure to recognise symptoms/urgency) and delayed therapy (multiplicity of referral notes).

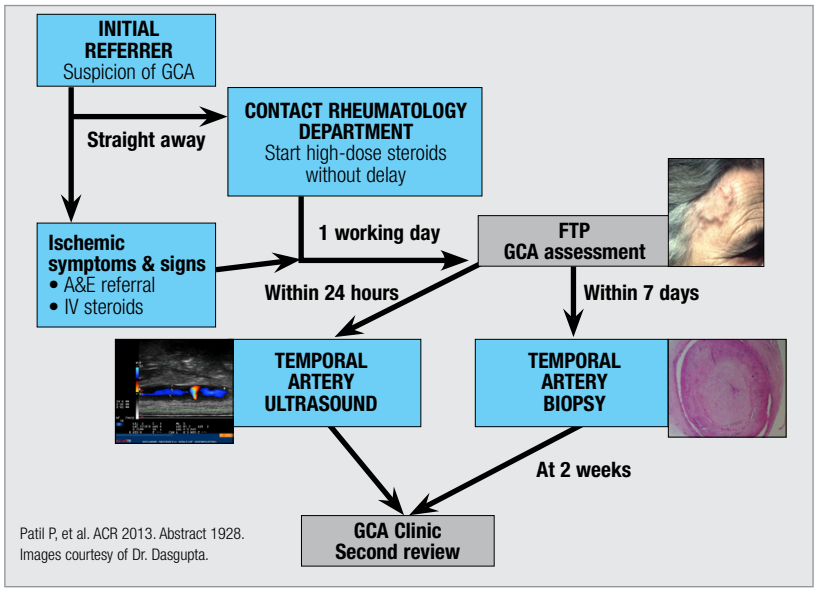

Figure 4: Southend Fast Track Referral Pathway.[139]

A retrospective audit of the fast track referral pathway (FTP) introduced into Southend Hospital in 2012 reduced the percentage of patients with GCA presenting with vision loss (i.e. 9% vs 23–29% of patients presenting with vision loss between 2003–2011) and decreased the "symptom to steroid time" from 46.5 days in 2008 to 30.25 days in 2012.[139] The average cost of diagnosing and treating a patient with suspected GCA is £2600 with the conventional pathway and £2200 with the FTP. Moreover, analyses of FTP results estimate a gain in QALYs of 2.6 among patients who retain sight, while the incremental cost-effectiveness ratio of implementing the FTP is –£840 per QALY. Notably, this analysis did not account for the enormous social costs of blindness.[140]

From the perspective of the FTP, suspect GCA in a patient with unexplained constitutional symptoms plus limb claudication, headaches, jaw pain, transient ischaemic attack, stroke, eye symptoms, and back pain. Atypical presentations include GCA without headaches; jaw and tongue pain, dysphagia; constitutional symptoms, anaemia; low acute phase markers of GCA; occipital GCA; and polymyalgic GCA. Prof. Dasgupta emphasised that GCA can occur without headache.

Why is better treatment needed?

Long-term corticosteroids are the mainstay of treatment in GCA but are associated with side effects, as well as increased risks of diabetes and hip fracture. Steroid-sparing therapies include methotrexate, azathioprine, cyclophosphamide and ciclosporin, which are either associated with high levels of toxicity or are ineffective in GCA.[141-147] Prof. Dasgupta and colleagues have found leflunomide effective in GCA.[148,149] Studies of TNF inhibitors in GCA have been disappointing,[150,151] as have case reports of rituximab[152] and adalimumab.[153] An ongoing study in the US is investigating abatacept in GCA. The front-runner is IL-6 in GCA. First described in 1990, the rationale of IL-6 blockade is that IL-6 is upregulated in inflamed arteries of patients with GCA and in the peripheral circulation.[154,155] This is supported by data from Southend Hospital showing that 8 patients with refractory FDG-PET-positive LVV treated with tocilizumab were classified as responders in terms of clinical- and patient-reported assessments, PMR/GCA symptoms and inflammatory markers. However, tocilizumab only suppresses GCA; as soon as tocilizumab was discontinued, the patients relapsed. Tocilizumab was associated with few side effects (transient neutropenia n = 1; hypercholesterolaemia n = 1; recurrent infections n = 2).

The efficacy and safety of IL-6 blockade is being investigated in the GiACTA study, in which patients with GCA will receive tocilizumab for 52 weeks followed by a 2-year open-label extension. Another study is investigating IL-1 blockade in GCA with gevokizumab. Prof. Dasgupta and colleagues are about to start recruiting for a study examining the efficacy and safety of sirukumab in patients with GCA. Expressions of interest are being sought from New Zealand investigators.

The Polymyalgia Rheumatica & Giant Cell Arteritis UK (PMRGCAuk) is a registered charity established to meet the needs of people with these debilitating conditions, their friends, families and helping professionals. Oganisations such as the PMRGCAuk offer support, raise awareness and promote research. An international symposium and imaging workshop on GCA, PMR and LVV will be hosted by Southend Hospital from 10-12 March 2016. Prof. Dasgupta invites anyone interested in attending to contact him.

NEW ZEALAND RHEUMATOLOGY AUDIT NETWORK: RESULTS OF EARLY DATA COLLECTION IN RHEUMATOID ARTHRITIS

– Associate Professor Will Taylor, University of Otago, Wellington

Regular audit is necessary for practice quality improvement and is mandatory for registration with the NZ Medical Council. Routine, prospective collection of clinical data makes regular audit much more feasible and more about actual practice rather than an audit of documentation. Embedding clinical data recording into the daily workflow of clinical practice is useful to facilitate completeness of data collection.

An audit using the Audit4 software from S4S has been undertaken in NZ in a number of participating rheumatology practices. The Audit4 software is a complete practice management tool (apart from billing and appointments) that integrates patient details, laboratory results, imaging results, clinical notes, disease-specific instruments and prescribing. It provides templates for pathology requests, prescriptions and letters. Australian rheumatology practices have adopted this software leading to a clinical research consortium (OPAL) and a number of publications.[156-158]

Data was extracted from participating rheumatology practices on 626 RA patients (65% female; mean age 62 years; mean disease duration approx. 10 years) entered into the Audit4 database between 10 July 2013 and 1 May 2015. DAS28 scores were available from 285 patients (46%). Approx. 60% of patients had low disease activity scores or were in remission. There was no correlation seen between DAS28 score and disease duration. Biologics were used by 179 patients (see **Figure 5** for details). Regarding time to biologic discontinuation, the first biologic used tended to be used for longer (median of 73 months) than the second (median of 22 months). The overall median time from disease diagnosis to starting biologics was 11.5 years.

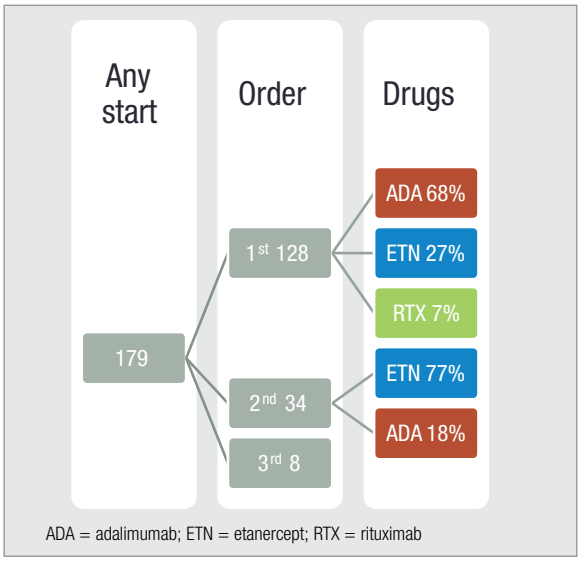

Figure 5: Biologics use in the New Zealand Rheumatology Audit Network

TAKE-HOME MESSAGES:

- It is feasible for auditable registry data to be collected in the context of ordinary clinical care and for different practices to pool results
- DAS28 is not yet being recorded consistently
- 40% of patients are in moderate or high disease activity
- Adalimumab is the most common first choice of biologic (68%); etanercept is the most common second choice of biologic (77%)
- First biologic continues for a median of 73 months, whereas second biologic continues for a median of 22 months
- Biologics are commenced after a median of 11.5 years.

A REVIEW OF 311 HLA B27 PATIENTS SEEN OVER 27 YEARS BY A SINGLE RHEUMATOLOGIST

– Dr Ant Gear, MidCentral Health

Dr Gear believes there are issues with the current classification system for spondyloarthropathies. He believes that it is the B27-associated diseases that should define the spondyloarthritis (SpA) group of diseases; this would include some psoriatic arthritis (PsA) and some inflammatory bowel disease (IBD), but not all. He explained that most PsA is different clinically, on imaging and genetically to the rest of the SpA group and therefore these patients don't belong in the group.

Dr Gear undertook an audit of HLA B27 patients seen in his practice over a 27-year period. The purpose of the audit was to assess the spectrum of HLA B27 disease in a typical rheumatology clinic, to review the progression from one manifestation of disease to another, to assess the long-term outlook of these patients and to provide information about who might benefit from early biologics and other treatments. 311 HLA B27-positive patients were identified. This comprised 22% of the patients tested for HLA B27. He only tissue typed PsA patients if they had other features suggestive of SpA. Of the 311 patients, 189 (61%) were male. The average age at presentation was 37 years (range 4-72 years). Among 267 patients for whom complete clinical records were available, 53.2% were classified as having peripheral SpA, 44.9% were classified as having axial SpA, about half of whom had proven AS. 16% of the total had reactive arthritis which was included in the peripheral SpA group. Non HLA B27 associated conditions accounted for 10.1% of patients. Some patients had both axial and peripheral SpA. Associated conditions were: psoriasis 13.7% and IBD 4.6%.

Long-term follow-up (11-27 years) data on 65 patients (58% male) were analysed. These patients averaged 30.8 years of age at disease onset and were an average of 51.8 years of age at last review. In this group of patients, disease progressed as follows: 5/13 (39%) patients with non-radiographic axial SpA developed AS; 8/49 (16%) patients with peripheral SpA developed AS; and 3/49 (6%) of patients with peripheral SpA developed non-radiographic axial SpA. TNF inhibitors were prescribed for 31 patients as follows: 18 AS (1 also had ulcerative colitis); 3 AS + peripheral SpA; 6 peripheral SpA (1 also had Crohn's disease); 2 PsA; 3 IBD; and 1 RA.

Dr Gear suggests that SpA is induced by antigens, especially those associated with the microbiome, interacting with the immune system in patients with a genetic susceptibility particularly HLA B27. The microbiome is affected by various exogenous and endogenous factors, leading downstream to axial SpA, AS, peripheral SpA and uveitis. He believes that psoriasis and IBD are upstream from the genetic susceptibility to arthritis and should be taken out of any classification criteria of SpA. He also suggests that possibly TNF inhibition will not be required for most HLA B27 SpA patients.

TAKE-HOME MESSAGES:

- Peripheral SpA is more common than axial SpA
- Peripheral and non-radiographic axial SpA can progress to AS, but in less than half of patients
- Less than 15% of HLA B27-positive patients have psoriasis
- Psoriasis, IBD and infections (such as gastroenteritis and sexually-transmitted diseases) occur upstream of HLA B27
- Uveitis, peripheral and axial SpA occur downstream
- Not all psoriatic or IBD arthritis should be under the SpA umbrella.

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