

## *Meeting Report*

### European Masterclass on Rheumatology

Thursday and Friday, 8–9 May 2008  
Royal College of Physicians of Ireland  
No. 6 Kildare St, Dublin 2



## Introduction

Dr John Donohoe, *President, RCPI*



This series of Masterclass educational workshops currently being organized by the Royal College of Physicians of Ireland is aimed at highlighting advances in those areas of medicine which are most significant and the most rapidly evolving.

When the Officers of the College were approached by Bristol-Myers Squibb with an offer to provide an unrestricted educational grant to support a European Masterclass on Rheumatology the opportunity was enthusiastically accepted.

Rheumatological conditions represent a substantial health burden facing society in this country. They are of increasing importance to the health of both the individual and the community and carry significant financial and social implications. Efforts directed towards an understanding of basic and novel aspects of these conditions are particularly appropriate.

A Faculty of College Fellows was convened and nominations were made for topics and speakers. It was gratifying to see that those invited, leaders in the world of rheumatology, immediately accepted. As a result, a strong programme, delivered in a focused manner by internationally recognised speakers, was put in place, and designed as an intense day-long session.

Each presentation was tight, concise and of the highest scientific standard.

The College was pleased that many specialists and trainees were represented in the large attendance. This booklet contains summaries from those presentations and will serve as a useful review of novel insights into the topics covered, for trainee and specialist alike.

I would like to thank Prof Michael Molloy, Vice President of the College, for providing the welcome address on my behalf and I must also thank the enthusiastic support of all of the presenters. The contribution of the Fellows of the Faculty, Prof Michael Molloy, Prof Barry Bresnihan, Prof Douglas Veale and Dr Paul O'Connell, ensured the delivery of an outstanding programme which achieved just the right balance.

Finally, I wish to thank Bristol-Myers Squibb for their continued support of superior quality educational programmes.

Thank you and congratulations.

Yours sincerely,

Dr John Donohoe  
President, RCPI

## Opening Address

Prof Michael Molloy, *Vice President, RCPI*



"It is my great privilege and pleasure as Vice-President of the Royal College of Physicians of Ireland to welcome you to our European Masterclass on Rheumatology. It is a particular pleasure to welcome our international speakers," said Prof Molloy as he opened the meeting for the 110 delegates attending from thirteen participating countries.

The Masterclass concept has evolved over the past year in the College, and brings together experts in emerging or controversial topics, providing a forum for in depth review and discussion. This is our second Masterclass which has been made possible by an unrestricted educational grant from Bristol-Myers Squibb, and we are extremely grateful for it. Without this support, this kind of meeting would likely be impossible.

I'd like to thank the chairs of the meeting today for their time and involvement, Dr Gaye Cunnane Consultant Rheumatologist, St James' Hospital Dublin; Dr Alexander Fraser, Consultant Rheumatologist, Mid-Western Regional Hospital, Limerick, Ireland; Prof Geraldine McCarthy, Consultant Rheumatologist, Mater Misericordiae University Hospital, Dublin; Prof Douglas Veale, Consultant Rheumatologist, St Vincent's University

Hospital, Dublin, and Dr Paul O'Connell, Consultant Rheumatologist, Beaumont Hospital, Dublin.

A special thanks to the speakers for travelling so far and for making this such a challenging programme. I also hope that you enjoy the College," stated Prof Molloy as he reflected on the many great physicians who had passed through the College doors. "During the Golden Age of Irish medicine, we had some of the biggest names in medicine practicing here at the Royal College of Physicians of Ireland - Graves, Stokes, Chain, and Corrigan - names emblazoned in history forever. Hopefully the next generation of experts are here at the moment," he concluded.

# 1

*European Masterclass on Rheumatology*

## **Evolving Concepts in Therapeutics of Systemic Lupus Erythematosus**

**Prof Mary K Crow**, *Prof of Medicine and Immunology, Weill Medical College of Cornell University, New York, USA*



*Peggy Crow is Professor of Medicine at Weill Medical College of Cornell University and Benjamin M. Rosen Chair in Autoimmunity and Inflammation Research, Senior Scientist, and Director of Rheumatology Research at Hospital for Special Surgery in New York City. She is also Co-Director of the Mary Kirkland Center for Lupus Research and was previously the Director of the Immunology Graduate Program at Weill Graduate School of Medical Sciences. Prof Crow received her M.D. at Cornell, Internal Medicine and Rheumatology subspecialty training at New York Hospital, and post-doctoral research training at Rockefeller University.*

*Prof Crow's first research contribution was the observation that T lymphocytes can be activated by autologous antigen presenting cells and generate immunosuppressive T cell activity. While at Rockefeller University, in the laboratory of Dr Henry Kunkel, she was among the first to characterize and study the functional properties of human dendritic cells. At Hospital for Special Surgery, Prof Crow has studied the effects of superantigens on T cell-dependent immune responses; characterized the oligoclonal T cells that comprise the cellular infiltrate in the rheumatoid synovium; studied the functional consequences for B lymphocytes of cognate help from T cells;*

*and demonstrated the altered regulation of CD40 ligand in lupus T cells. Prof Crow's most recent work has defined the role of interferon-alpha in systemic lupus erythematosus. She continues to investigate the underlying triggers and mediators of autoimmunity in the prototype rheumatic diseases, SLE and rheumatoid arthritis, and the cellular and cytokine mediators of uncontrolled immune system activation in those disorders.*

*Prof Crow has been active in leadership roles in professional organizations and foundations. She was President of the American College of Rheumatology from 2005-2006 and is President of the Henry Kunkel Society.*

In September, 1948 Philip S. Hench, Charles H. Slocumb and Howard F. Polley, administered 'compound E' to a patient with rheumatoid arthritis and later to patients with Systemic Lupus Erythematosus (SLE), rheumatic fever and ankylosing spondylitis. "This 'Compound E', or cortisone as it became known, showed a remarkable response in patients with rheumatoid arthritis, and shortly after they began treating other arthritic and inflammatory diseases. Very quickly it was recognised that cortisone was a potent therapeutic," explained Prof Mary Crow as she opened her Masterclass presentation. This was a discovery which resulted in very quick approval at the level of the FDA in the United States, and the awarding of the Nobel Prize to Kendall and colleagues for their discovery the following year (1950). Subsequently, therapeutic use of cortisone was followed by antimalarials and nitrogen mustard, cyclophosphamide and azathioprine in the 1950s, advised Prof Crow commenting, "It is really frustrating and discouraging to recognise that these remain the core drugs we use to this day for the treatment of Lupus. So, it is my goal today to review for you some of the

## Evolving Concepts in Therapeutics of Systemic Lupus Erythematosus (Cont.)

recent genetic observations and how they inform our current understanding of the immunopathogenesis of Lupus, which I think is taking us quite a long way towards understanding how we might better target Lupus therapeutically.”

Lupus is a prototype systemic autoimmune disease, characterised by an immune response broadly directed against self. It is a genetic disease, with increased monozygotic twin concordance for disease susceptibility over dizygotic twins by about ten fold. Furthermore, there is a strong familial aggregation among patients with SLE and those with related diseases and a high sibling occurrence rate compared to unrelated individuals. Except in the rare cases of complement deficiency, the inheritance pattern of SLE does not follow simple Mendelian rules, which suggests that genetic risk in most lupus patients arises from the combination of a number of relatively common variations in several different genes. The functional effects of these gene variants result in immune system activation and inflammation that targets the vasculature, a common theme in the pathogenesis of SLE. Livedo reticularis is an example of this: a vascular condition characterised by a purplish mottled discoloration of the skin, usually on the legs. This discoloration is described as ‘lacy’ or ‘net-like’ in appearance, and is often associated with SLE. “Onionskinning of the splenic arterioles and damage to the blood vessels of the glomerular capillary are characteristic of Lupus pathology.”

Noting the conclusion of an Editorial published in *Nature Genetics* in 2007,<sup>1</sup> Prof Crow highlighted that research into the genetics of human disease is proceeding at an unprecedented pace. “The number of gene variants associated with common human disease identified by genome-wide association studies in 2007, exceeds those identified in the entire preceding decade.” As these

genetic studies bear fruit, scientists and clinicians are provided with new ideas as to how these diseases can be targeted therapeutically, but the new genetic data also confirms what immunologists have understood for decades, that virtually all components of the immune system are involved in Lupus and other rheumatic diseases. “The completion of the human genome sequence and advances in how we analyse gene variation have really accelerated progress. Importantly, the cost of sequencing human genomes, or certainly completing single nucleotide polymorphism analysis, has become so much more manageable,” explained Prof Crow.

In addition, successful competitive collaborations for rheumatoid arthritis studies such as the Wellcome Trust Case Control Consortium (WTC) and the North American Rheumatoid Arthritis Consortium (NARAC) have contributed to recent breakthroughs in this field. “For Lupus it took just a few months longer for the research to hit,” explained Prof Crow while presenting work by the group SLEGEN<sup>2</sup> published in February this year which identified genetic variants associated with a diagnosis of SLE in women and a further study published in the *NEJM*<sup>3</sup> which demonstrated significant concordance with the SLEGEN paper in terms of the genes identified. “I think the message that we gain from studying the products of these consortia, is that virtually all elements of the immune system are expressing gene variants which are associated with Lupus.”

The new genetic data and our current understanding of SLE pathogenesis point to involvement of innate immune system activation, adaptive immune system activation, immune effectors mechanisms and targeting damage to the vasculature. However, the exact patho-aetiology of SLE remains elusive. An extremely complicated

Figure 1

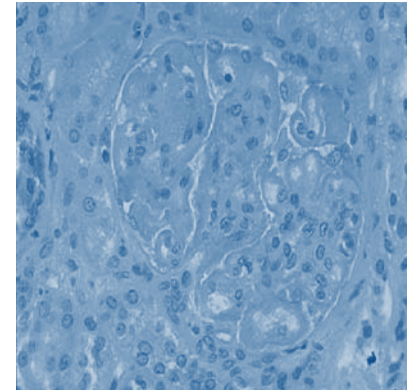


Figure 2



and multifactorial interaction among various genetic and environmental factors is involved, as demonstrated by the above studies. “There has been an increasing understanding of the important role of the innate immune response, mediated by cells which are readily available and which express Toll-like receptors (TLRs). The discovery of the TLR family has really been critical to gaining an understanding of *all* of the autoimmune and inflammatory diseases,” Crow said. “In Lupus particularly, there is growing evidence for the role of RNA as a trigger, possibly at the initiation of the disease, but at least as an amplifying factor, in activating the innate immune response through the Toll-like receptors. Interferon-alpha is now recognised as an important mediator, particularly in Lupus, and interferon-alpha production is a consequence of activation of these cells by RNA.”<sup>4</sup>

Recent studies by Graham *et al.*<sup>5</sup> and Sigurdsson *et al.*<sup>6</sup> have identified a haplotype of Interferon Regulatory Factor 5 (IRF5) that is significantly associated with SLE, as well as inflammatory bowel disease, multiple sclerosis, and possibly RA. The variant of this transcription factor-encoding gene that may be most important is defined by four copies of an insertion-deletion polymorphic sequence, CGGGG, located in the gene promoter. “In our lab we investigated IRF5 to demonstrate if it actually does have a functional relationship to the activation of the interferon pathway in SLE,” said Prof Crow who presented data which showed that the IRF5 SLE-risk haplotype is associated with increased serum IFN-alpha activity and is ‘down-stream’ of several of the Toll-like receptors. IRF5 is a transcription factor activated by TLR-dependent signaling, it is constitutively expressed by many immune system cells, is regulated by type 1 interferon and may modulate the expression of type 1 interferon and inflammatory cytokines.

## Evolving Concepts in Therapeutics of Systemic Lupus Erythematosus (Cont.)

“Moving to the adaptive immune system, we can consider some of these new gene variants, and where they are likely to be active in the immune system,” stated Prof Crow. “There is a very interesting molecule called STAT4 which has come out quite strongly in studies of both RA and Lupus.<sup>8</sup> It has probably been best studied in the context of modulation of the production of cytokines by T-Cells and natural killer cells and in research which has shown that it might be involved in antigen presenting cells which are stimulated by interferon-alpha. One of the potential sites of activation of STAT4 is related to its involvement in IL-12 and IL-23 receptor signaling in the T cell,” said Prof Crow, who also presented data on Lupus-associated genetic variants of BLK, which is a kinase involved in B cell activation, and BANK1, an adaptor protein involved in B cell activation.

Discussing Lupus-associated genetic variants implicated in immune effector mechanisms, Prof Crow commented, “We’ve known about the role of complement as a genetic factor for many decades, with complement deficiencies predisposing to developing Lupus, and Fc receptors were confirmed in some of these recent studies. What was particularly interesting was the identification of a gene called ITGAM, which has many other names (CD11b, MAC-1 or CR3). Its gene product mediates adhesion between leukocytes and endothelial cells. Increased expression of ITGAM’s gene product was previously shown to be associated with increased disease activity in Lupus,” she said. “Now the new genetic data further support ITGAM as highly associated with SLE. So this raises the question of whether one of the genetic factors that contribute to Lupus is being played out at the level of leukocyte-endothelial cell interaction, mediated by cell surface adhesion molecules encoded by ITGAM?”

“That brings me back to my earlier discussion of the different vascular abnormalities you see in Lupus, such as glomerular capillary lesions, splenic vasculopathy and livedo reticularis, which were really emphasised in the early text books on Lupus. I think perhaps we have become so enthralled with all of the immunologic alterations in Lupus, that we haven’t sufficiently studied the effector interactions that are stimulated by immune system activation, but that play out at the level of the vasculature.”

In conclusion, Prof Crow commented that the application of genetic insights to human Lupus may lead to the prediction of disease, the identification of biomarkers that define disease activity or disease subsets, and finally that Lupus-associated genes and related molecular pathways may suggest new targets for therapy.

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## T-Cell Targeted Therapies and Therapeutic Tolerance

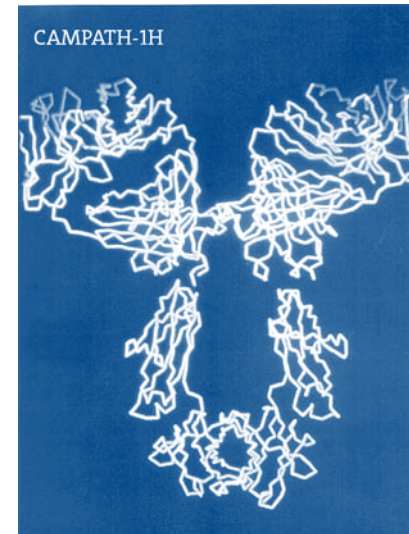
Prof John Isaacs, Newcastle University



John Isaacs is Professor of Rheumatology at Newcastle University, where he also directs the Wilson Horne Immunotherapy Centre. He runs a translational research group with a focus on novel T-cell targeted immunotherapies and therapeutic tolerance. His involvement with biological therapies extends back over 20 years: his PhD focused on antiglobulin responses and monoclonal antibody effector function, following which he co-ordinated some of the first biologics studies in rheumatoid arthritis. He is a member of the Department of Health's Expert Advisory Group on Clinical Trials and also chairs the Arthritis Research Campaign's Clinical Study Group for Inflammatory Arthritis.

"The concept of therapeutic tolerance goes back many years and considers that, in autoimmune disease, if somehow we can regain control of T-cells (which are largely seen as the Generals of the immune system), everything else should fall back in place, producing a default response of cell tolerance," advised Prof John Isaacs. It has long been recognized that therapies which deplete lymphocytes often improve symptoms in patients with refractory autoimmune disease, however with the consequent risk of lymphopenia. Initial attempts in man resulted in CAMPATH-1H, the first humanised therapeutic antibody. "CAMPATH-1H recognises the antigen CD52 on human lymphocytes and is very good at killing cells by a number of mechanisms - targeting B-cells, T-cells and NK-cells," stated Prof Isaacs. Presenting results from his own study which assessed the impact of prolonged lymphopenia on morbidity and mortality, Isaacs *et al*,<sup>1</sup> studied fifty-three patients who had previously received CAMPATH-1H therapy for rheumatoid arthritis between 1991 and 1994 in the United Kingdom. A retrospective, matched-cohort study of mortality was also performed with 102 control subjects selected from the European League Against Rheumatism database, which comprises patients with rheumatic disorders who have received immunosuppressive drugs. The research team concluded that despite the occurrence of profound and long-lasting lymphopenia following treatment with CAMPATH-1H, the therapy was not associated with a detectable excess of mortality nor with an unusual spectrum of infections, at least during a medium-term period of followup. In fact, the causes of death and the spectrum of infections documented were similar to those expected in a hospital-based RA cohort. With the authors commenting that these data were also relevant to patients receiving CAMPATH-1H therapy

Figure 3



for other indications, and to patients receiving other lymphodepleting therapies such as autologous stem cell transplantation. Recent data on this cohort,<sup>3</sup> has demonstrated that despite continued lymphopenia 11.8 years after therapy, the patient cohort did not exhibit any excess mortality or unusual infection-related morbidity, and surgery was well tolerated, commenting, 'this should be reassuring for patients and clinicians who are considering lymphocytotoxic or other immunomodulatory therapy for RA'.

However, the compound failed to establish itself successfully in rheumatoid arthritis, although it continues to be developed for multiple sclerosis, advised Prof Isaacs "but it may yet be revisited in other autoimmune diseases," he said. Subsequent research<sup>2</sup> focused on anti-CD4 showed limited evidence for efficacy, producing side effects such as long-term lymphopenia, rashes at high dose, mild-to-moderate first-dose reactions and limitations in predicting biological activity due to a lack of tolerance

biomarkers. "However, I *don't* think these early drugs really were ineffective. I just don't think we were very good at understanding them," said Prof Isaacs. "I'd go as far as to say that if it wasn't for anti-TNF, the biologics revolution really wouldn't have taken off in rheumatoid arthritis, as the early experiences were very disappointing."

Looking to the future and novel therapeutic strategies, Prof Isaacs reflected on the first therapeutic antibody that was used widely, OKT3, "In the early 1980s it was used to reverse acute renal failure, very effectively, however patients got very sick and some died. So a potent, but tricky drug, and again this was a first-dose reaction we were seeing and was the reason that OKT3 was never developed for autoimmune indications. It was felt to be too toxic for what was considered to be non-fatal and non-organ threatening diseases. This may be questioned now." In the last ten-years, significant research has been undertaken to make these types of antibodies safer. "The key here are Fc *gamma* receptors (FcγR)," stated Prof Isaacs. Recently, a large body of evidence has demonstrated that FcγR plays a critical role in mediating some of the adverse effects of antibodies, "Fc *gamma* receptors on the effector cells do the cross linking. So, if you can somehow interrupt this interaction, you may have antibodies which can target T-cells, or CD3, which don't cause such side effects," said Prof Isaacs, presenting data from an NEJM paper<sup>4</sup> published in 2005 which investigated the effects of an aglycosylated human IgG1 antibody directed against CD3 (ChAglyCD3) for recent onset Type 1 diabetes patients to determine their insulin needs at 18-months. "Patients receiving placebo treatment in this study progressed as you would expect of a patient with diabetes and exhibited pretty significant insulin needs at 18-months. However the patients

## T-Cell Targeted Therapies and Therapeutic Tolerance (Cont.)

who had received the anti-CD3 had very minimal insulin requirements. So I think the diabetes world is becoming quite excited by these and other results which show perhaps, not the switching off of the disease, but certainly a delay in onset.”

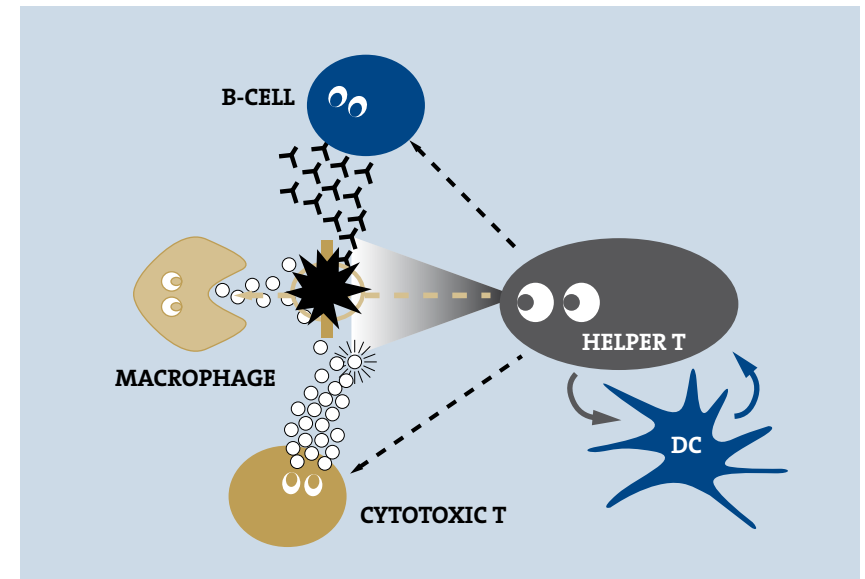
Further anti-CD3 research, this time in Ulcerative Colitis (UC),<sup>5</sup> showed 44% endoscopic remission at day 30, with 45% of patients requiring no further therapy by 12-months. “Cytokine release was observed,” advised Prof Isaacs, commenting, “This was previously, really difficult to treat UC, so it seems that across the inflammatory diseases, this could potentially be an important target.” The challenge for researchers is the development of tolerance-inducing biologicals for illnesses such as RA.<sup>6</sup> “We know in RA that chronic inflammation drives immunity. The key concept is that in the many animal models of tolerance induction, it may take many weeks, even longer, for tolerance to develop – it is not an instantaneous effect. If your tolerogenic drug isn’t also anti-inflammatory, then you have a window where the patient doesn’t seem to be getting better and you don’t know why. In addition, there is some evidence in the literature that anti-inflammatory drugs, such as COX-2 inhibitors, may hinder tolerance induction. Some immunosuppressive drugs have similar limitations,” stated Prof Isaacs. Without relevant biomarkers to assess the effectiveness of a tolerogenic drug, clinicians are limited in measuring its effect.

“This is a really difficult situation to be in,” advised Prof Isaacs, presenting data from the ATTAIN trial<sup>7</sup> which investigated abatacept (CTLA4-Ig), a new agent designed to block a key costimulatory signal required for T-cell activation. “With the ATTAIN study, looking at the percentage of patients achieving low disease activity and remission, it really is a creeping effect with time, perhaps

suggesting that it is gradually switching off the disease process. It may take three months for patients to get better with abatacept and then you begin to see more and more patients responding to it. However, it’s difficult as we have no markers to tell us in the interim whether we are actually affecting their autoreactivity. So, we desperately need tolerance biomarkers. They would help to choose a dose of therapy, duration of therapy and should really be independent of inflammation.” The challenge is where to look for the biomarkers, advised Prof Isaacs. “My bias is that we should probably be looking in the synovium, and we are looking at transcriptional profiles. In addition, we should also look at assays of autoreactivity, after all, that is the root of autoimmunity.”

In conclusion, Prof Isaacs discussed cellular therapy and the role of dendritic cells, in particular their role in modulating T cells and as a result the potential to target dendritic cells. “We are looking at developing what we are calling a Tolerogenic Dendritic Cell vaccine,” said Prof Isaacs. “Drug modulated dendritic cells have a stable anti-inflammatory cytokine profile, they induce hyporesponsiveness in memory T cells and they deviate naïve T cells to produce IL-10 rather than gamma interferon. This is a very consistent profile,” commented Isaacs. “We have shown we can also do this with RA patient blood, generating tolerogenic dendritic cells which can process and present candidate RA auto-antigen, and we can now generate them using GMP media and supplements.” As a result cellular therapies provide a potential alternative for immune modulation and may assist in overcoming some limitations of the more conventional agents. “While they are expensive to produce and the protocols are likely to be complex, they may provide an important proof of concept – plus information on biomarkers,” stated Prof Isaacs.

Figure 4



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**Prof Rene Westhovens,***Department of Musculoskeletal Sciences, Catholic University of Leuven, Belgium*

*René Westhovens obtained his M.D. degree from the Katholieke Universiteit Leuven, Belgium, in 1979 and was trained in Internal Medicine and Rheumatology in Leuven from 1979 to 1984.*

*In 1993, Prof Westhovens joined the Department of Rheumatology in the University of Leuven, where he is now head of the clinic. His main interests are in the treatment of Rheumatoid Arthritis with special focus on the multidisciplinary approach. His PhD degree was obtained in 1999 with the thesis "Prognostic factors and outcome in rheumatoid arthritis".*

*He took part in several international collaborative studies as the Cobra Project on Intensive Combination Therapy in Early RA and in ECRAF on a genome screen for RA susceptibility loci. Prof Westhovens was also involved in a number of multicenter clinical trials in phase 1, 2 and 3 of various pharmacological agents for the treatment of RA.*

*Currently he is Professor at the Medical Faculty and the Faculty of Kinesiology and Rehabilitation Sciences of the Catholic University of Leuven.*

"It is important as we discuss the future therapeutic strategies for refractory rheumatoid arthritis that we consider the term 'refractory,'" advised Prof Westhovens as he commenced his presentation in the Masterclass programme. "What is refractory RA? Is this late RA? Is it poor prognosis RA? Is it inappropriately treated RA? Is it methotrexate or anti-TNF refractory RA and how do we define 'refractory'?" he asked. Then considering which strategies to utilise for this condition, Prof Westhovens asked how many anti-TNF agents should be tried before allowing for a treatment with a different mechanism of action. "Which mode of action do we then consider?" he asked. "Are there data to consider new biologics with a different mechanism of action before anti-TNF agents? Can anti-TNF therapy be effectively and safely used after B-cell depleting therapy or co-stimulation blockade? And what about co-stimulation blockade after rituximab or vice versa?" he asked.

Before answering any of these questions, however, Prof Westhovens emphasised the importance of treating RA early and appropriately. "I think therapy strategies in early RA may partly define the status of future refractory RA, or the amount of patients that will be refractory," he said, presenting two studies from his own laboratory;<sup>1,2</sup> the first demonstrating that in a more intensively followed and treated group of RA patients, 80% achieved low disease activity or remission at 2-years, compared with only 60% in those treated with standard clinical care. "This shows how important it is to do in daily practice what randomised controlled trials do. This is one of the first reports to show that you can really achieve major improvements in patients." In the second study, which investigated daily practice effectiveness of a step-down treatment, in comparison with a tight step-up for early rheumatoid

arthritis, Westhovens and colleagues studied patients with severe RA and no contra-indications who were treated with step-down therapy (n=19), the others step-up (n=52). Step-down patients received a modified combination therapy in early RA (COBRA) of sulphasalazine (SPS), 2 g daily, and methotrexate (MTX), 15 mg weekly, combined with step-down oral prednisolone (start 60 mg daily, fast tapering to 7.5 mg over 6 weeks, discontinuation from week 28). At week 40, patients were randomised to maintenance therapy with either SPS or MTX if disease activity score-28 (DAS28) was acceptably low. The step-up group started DMARD monotherapy.

Results showed that in the step-down group, more patients completed the first year without unplanned DMARD changes and without dosage adjustment and fewer had DMARD changes due to side effects or inefficacy compared with step-up group, with the number of adverse events comparable. MTX proved to be the most effective maintenance therapy after step-down. The DAS response, proportion of patients in remission, HAQ response and proportion of patients without disability at 4 months was higher in the step-down group. "In daily practice, a step-down treatment strategy for early RA is more effective than a step-up approach," advised Prof Westhovens. "I think we can in the future improve significantly the prognosis with early RA treatment, resulting in perhaps less refractory patients. However, Prof Westhovens acknowledged the problem of defining MTX refractory status, as discussed by Boers in his paper<sup>3</sup> which queried the dosage of MTX in clinical trials as being too low, stating, "I think we should perform true placebo trials of three months' duration to prove that the drug is intrinsically active and then move to active comparator trials. Clinicians will thank us. So will patients."

"What is TNF failure?," asked Westhovens. "How many anti-TNF agents does a patient have to fail before considering another mechanism of action (MOA)? And which MOA?" Research published by Vander Cruyssen<sup>4</sup> *et al* in 2006 considered that although there is strong evidence supporting the short-term efficacy and safety of anti-tumour necrosis factor- $\alpha$  agents, few studies had examined the long-term effects. The authors commenting at the time, that in most countries, anti-TNF- $\alpha$  therapy is reserved for patients who are refractory to classical DMARD therapy. These patients may require TNF- $\alpha$  blockade for an extended time, investigating infliximab 3 mg/kg in combination with MTX specifically in their study. "Interestingly, 60% at four-years survived on the drug, and this in a group of very severe patients who had a mean baseline failure of 3.9 DMARDs, and a mean disease duration of 10 years at baseline." One hundred eighty-four (38.4%) patients were withdrawn from treatment for the following reasons: 81 (16.9%) due to safety issues (including 28 infections, 18 immune-allergic reactions, and 9 malignancies), 65 (13.6%) due to inefficacy, and 38 (7.9%) for 'elective' reasons. However, the main elective reason to stop infliximab treatment was the decision by the physician or the patient to switch to a new subcutaneous TNF- $\alpha$  blocker which became available during the trial. "Apparently, rheumatologists switch from one effective drug to another effective drug – which does not make sense," advised Prof Westhovens. "If we continue like this, spoiling effective drugs, we do a bad job."

Looking at efficacy reasons to switch from an anti-TNF agent, Prof Westhovens suggested this could take place where there is no ACR 20/EULAR response at 6 weeks to 4 months, where there is a 'primary insufficient response', i.e. the patient never gains an ACR 50/EULAR

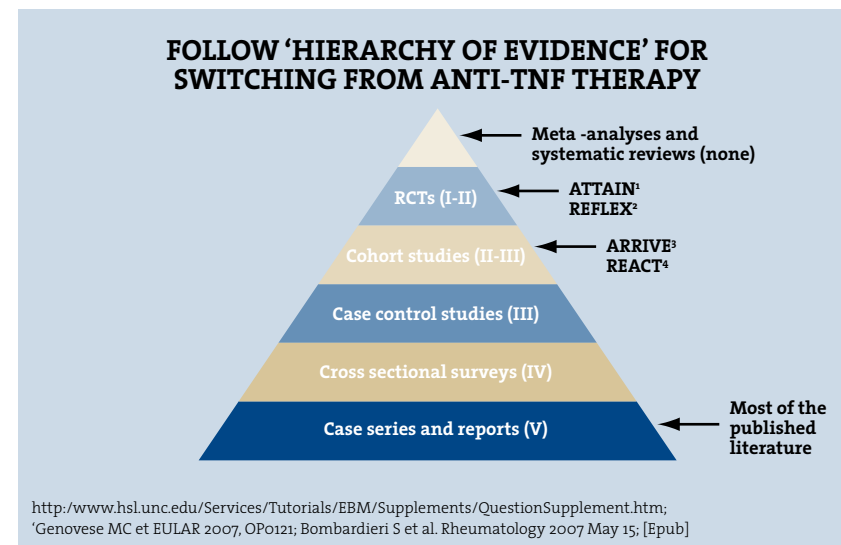
GOOD/DAS 28  $\leq$  3.2 by 6 months or where there is a secondary non-response - when the initial adequate response is lost. "There are a lot of safety reasons which could lead us to switch from TNF blockade such as serious infections, specifically septic arthritis, tuberculosis or opportunistic infections, positive ANA with symptoms, systemic manifestations such as nodulosis, vasculitis or rheumatoid lung disease. There are issues with congestive heart failure class III or IV and neurologic symptoms, but these occur in a minority if patients,"<sup>5</sup> he added. In addition there are many reasons to stop TNF antagonists in clinical practice advised Prof Westhovens, citing lack of efficacy<sup>6,7</sup>, safety issues,<sup>8</sup> or both of these issues, cautioning the audience against stopping effective therapy simply due to 'elective reasons'. "The definition of a non-responder is not easy and I think there is a difference between clinical judgement and formal scoring.<sup>9</sup> Was the therapy optimal anti-TNF therapy?"<sup>10,11</sup> In addition we need to be aware of the complaints patients have, as they do not always relate to insufficient disease control. We must manage the changing expectations of patients and physicians," he said.

Small studies have shown an improvement in disease activity in patients with RA who have switched between anti-TNF therapies for reasons of inefficacy. However, it was not clear whether switching improves longer term outcomes, such as disability. Presenting data published in 2007<sup>12</sup> from an anti-TNF to anti-TNF Switch as part of a UK National cohort (n=856) study, Prof Westhovens commented, "First anti-TNF discontinuation due to inefficacy is associated with an increased rate of second anti-TNF discontinuation due to inefficacy (HR = 2.7; 95% CI [2.1-3.4]). Similarly, the probability of discontinuing second anti-TNF for intolerance is higher for patients who have discontinued first

anti-TNF for intolerance, but not inefficacy (HR = 2.3; 95% CI [1.9-2.9])," said Prof Westhovens, advising clinicians to follow the 'hierarchy of evidence' for switching from anti-TNF therapy and asking the audience to consider the data for the current biologic alternatives to anti-TNF agents such as abatacept and rituximab.

In the ATTAIN trial<sup>13,14</sup> the authors commented that a substantial number of patients with rheumatoid arthritis have an inadequate or unsustained response to TNF inhibitors. As a result, they conducted a randomised, double-blind, phase III trial to evaluate the efficacy and safety of abatacept, a selective costimulation modulator, in patients with active rheumatoid arthritis and an inadequate response to at least three months of anti-TNF therapy. Patients were randomly assigned in a 2:1 ratio to receive abatacept or placebo on days 1, 15, and 29 and every 28 days thereafter for 6 months, in addition to at least one disease-modifying anti-rheumatic drug. Patients discontinued anti-TNF therapy before randomisation. "At six months, the rates of ACR 20 responses were 50.4% in the abatacept group and 19.5% in the placebo group (p<0.001); ACR 50 responses were 20.3% in the abatacept treated group and 3.8% in placebo and ACR 70 responses were also significantly higher in the abatacept group than in the placebo group (10.2% vs. 1.5%, p=0.003)," stated Prof Westhovens. At six months, significantly more patients in the abatacept group than in the placebo group had a clinically meaningful improvement in physical function, as reflected by an improvement from baseline of at least 0.3 in the HAQ disability index (47.3% vs. 23.3%, p<0.001). The incidence of adverse events and peri-infusional adverse events was 79.5% and 5.0%, respectively, in the abatacept group and 71.4% and 3.0%, respectively, in the placebo group. The incidence of

FIGURE 5



serious infections was 2.3 % in each group. "Looking at the 3-year data<sup>15</sup> an increasing proportion of abatacept plus DMARD(s) treated patients achieved ACR responses. This is consistent with what I see in daily practice. So the pattern of response with abatacept is certainly different to the patterns of response of TNF blockers."

"In addition, it is always interesting to see low disease activity and remission as it means so much for the patient", commented Prof Westhovens, discussing data from the AIM trial<sup>15</sup> which showed an increasing proportion of abatacept-treated patients achieved low disease activity scores (53.2%) and remission (37.5%) through 3 years. Comparing abatacept or infliximab to placebo,<sup>16</sup> the change in DAS 28 score at 6 months demonstrates that both abatacept and infliximab are superior to placebo. "Looking at the data at 1-year you see that the DAS score is even more improved in the abatacept group compared to infliximab. And one of the

things that came out of this study is that there were more events with infliximab which were *not* known in other trials. There were numerically increased serious infections with infliximab vs abatacept (8.5% vs 1.9%), including tuberculosis with infliximab, which was not seen in the abatacept arm. So clearly, there seems to be a difference in serious infections and this needs to be further investigated in clinical trials," stated Prof Westhovens.

"One of the few studies that addresses the speed of how rapidly you can switch from one biological to another is the ARRIVE trial<sup>17</sup> with abatacept," commented Westhovens. In the earlier ATTAIN study of abatacept in TNF inadequate responders, patients with RA were washed out of their TNF antagonists before beginning therapy with abatacept. In clinical settings, a prolonged washout period may not be feasible due to ongoing disease activity of patients and a need to initiate a new therapy. However, there are concerns that the TNF antagonist may exhibit a 'carry

over' effect, especially in terms of safety, with prior studies as discussed above evaluating the combination of abatacept with other biological DMARDs showing an increase in infections in patients compared to abatacept in combination with non-biological DMARDs. The ARRIVE trial was designed to assess the clinical safety and tolerability of abatacept with a shorter TNF antagonist washout period. Authors Schiff *et al*, have demonstrated that abatacept was generally safe and well tolerated in this subset of US patients (n=842) with active RA and an inadequate response to anti-TNF therapy, regardless of whether or not patients had a washout period. "At least from this trial, it seems to be quite safe to switch from a TNF blocker to abatacept," said Prof Westhovens.

With regards to rituximab, Prof Westhovens considered the many unanswered questions relating to this therapy, despite the significant ACR response demonstrated with rituximab plus MTX at week 24 as shown in the REFLEX trial and his own positive clinical experiences.<sup>18</sup> "One of the problems with rituximab is when should you retreat? What is the optimal dose? What is the optimal strategy for combination with other drugs (other than MTX)? What is the long-term efficacy of repeat dosing? What can I do after rituximab failure (ACR 50=25%)? Should I treat RF/CCP negative patients? What is the safety profile with respect to immunoglobulin reduction *vis a vis* infection and response to vaccination? What are the safety issues with long-term B cell depletion?" he asked.<sup>19,20</sup>

In closing Prof Westhovens postulated on some open questions relating to abatacept; "What is the efficacy of abatacept in early arthritis, early undifferentiated arthritis, and other rheumatic diseases? How and when does one start abatacept after rituximab is stopped? Can abatacept be used in

patients who cannot be treated with TNF blocking agents because of CHF, demyelinating diseases or tuberculosis? What is the safety of restarting anti-TNF after abatacept or starting rituximab after abatacept?"<sup>19</sup> Registry data for rituximab and abatacept are awaited, advised Westhovens, commenting that there is a need for strategy trials and consideration about combining different targeted therapies. In addition, he asked the audience of international rheumatologists to consider seriously patient preferences in future therapy decisions, commenting that drugs with different mode of actions are still needed, but it will be a real challenge to evaluate them!

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## Measuring Joint Deterioration and Disease Progression

**Prof Harry K Genant**, Emeritus Professor of Radiology, Medicine, Epidemiology and Orthopaedic Surgery, University of California School of Medicine, San Francisco, and Synarc Inc., San Francisco, CA, USA



Harry K Genant received his medical degree from Northwestern University in Chicago, Illinois and completed his internship on the Osler Service at Johns Hopkins University in Baltimore, Maryland. He received residency training in Medicine and in Radiology at the University of Chicago. He assumed a faculty position at the University of California, San Francisco, achieving the rank of Professor of Radiology, Medicine, Epidemiology and Orthopaedic Surgery. He founded the Osteoporosis and Arthritis Research Group (OARG) in the Department of Radiology, UCSF, and served as its Executive Director. This group, once numbering over 130 physicians, scientists and research associates, was recognized as a leading source of research on the development and assessment of noninvasive and quantitative imaging methods for osteoporosis, arthritis and orthopaedics. In 1998 he co-founded Synarc, Inc, a global, contract research organization (CRO) specializing in management of quantitative imaging and biomarkers in large, multicenter, multinational, pharmaceutical drug trials. He serves as a Member of the Board for Synarc.

Prof Genant has been editor or co-editor of more than 30 books and author or co-author of more than 170 chapters or invited

articles, over 500 articles in peer-reviewed scientific and medical journals, and over 1500 abstracts presented at national and international scientific and professional gatherings. He is on the editorial boards of Osteoporosis International and the Journal of Clinical Densitometry, and he is an Associate Editor of Bone.

He has served as President of the Association of University Radiologists, Scientific Chair or President of the First through Sixth International Congresses on Osteoporosis in China, President of the International Skeletal Society, Chair of the WHO Task Force on Osteoporosis, and member of the Board of Directors of the International Osteoporosis Foundation and Co-Director of its Global Initiatives on Vertebral Fracture Assessment and on Measures of Bone Quality.

Numerous methods for reading abnormalities of rheumatoid arthritis in hand and wrist radiographs have been proposed over the past several decades. In 1971, Sharp *et al* outlined a scoring method for the hands and wrists; which proposed twenty nine areas in each hand and wrist for erosions, and 27 for joint space narrowing (JSN). Subsequently, a modification that included assessment of the feet and other refinements was proposed by Genant in 1983.<sup>2</sup> Further modifications were addressed in 1985<sup>3,4</sup> and in 1986 another modification was devised by Fries *et al* (with the participation of Sharp and Genant)<sup>5</sup> followed in 1989, by van der Heijde who modified the method described by Sharp in 1985.<sup>6-8</sup> There were many commonalities and modest differences among these methods, one of which is the variation in the number of joints that are scored. "In the 1980s there were a series of important workshops, conducted principally under the direction of John T. Sharp and a number of other prominent

rheumatologists and radiologists who were involved in trying to optimise the approach to imaging, looking specifically at how many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis," advised Prof Genant as he presented on imaging joint destruction in RA and the experience with newer biologics in his presentation. "One of the several workshops that I participated in was the Beaver Creek Conference on Radiologic Assessment of RA which looked at the ability to reduce many of the joints, and eliminate those in the evaluation without losing critical information with regards to either diagnostic, or more importantly, to monitoring disease effects. And it was in part related to these series of conferences, that the various modified-Sharp, the Genant-modified-Sharp and the van der Heijde-modified-Sharp evolved, recognising that it was possible to reduce the numbers of joints without sacrificing sensitivity and/or specificity," said Prof Genant.

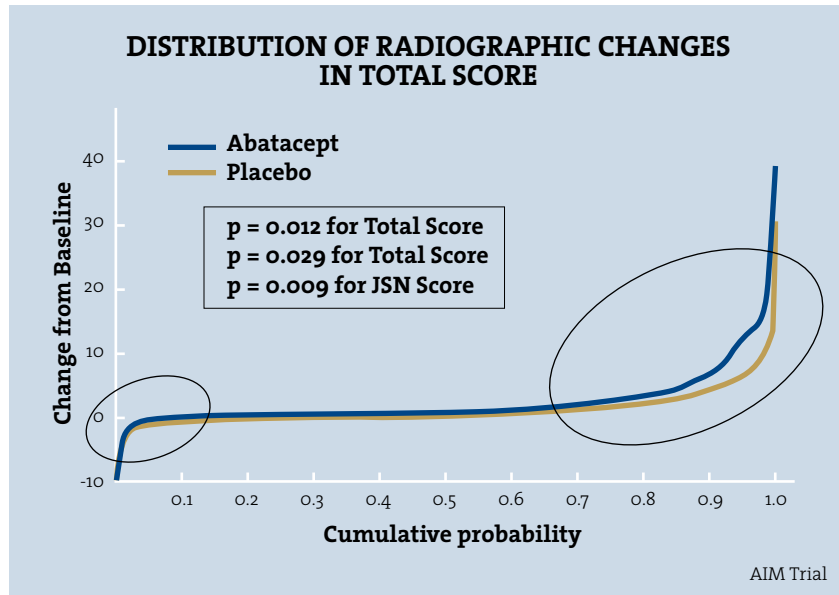
"Some of the early work, interestingly, utilised combinations of scoring methods and the Etodolac Study<sup>9</sup> conducted over a period of almost a decade, looked at the progression of radiographic joints changes. In this particular study, John Sharp used his technique, while Barbara Weissman and I used our Genant-modified scoring, and these scores were actually merged, despite the slightly varying joints and scaling of the two systems. Part of the reason that combining was possible was because the two methodologies correlated very well with each other," said Prof Genant. Subsequent research included the assessment of rheumatoid arthritis using the Genant-modified Sharp scoring method on digitised and original radiographs.<sup>10</sup> "This provided considerable advantages, to

the extent that the digital information was comparable to the conventional radiographs, and allowed one to have multiple readers working on different workstations simultaneously, to also manipulate the images in ways to make it somewhat more precise and accurate to evaluate, in accordance with certain regulatory requirements and providing an audit trail," explained Prof Genant.

"With the introduction of effective biologics, an issue which became of importance and which was addressed by the OMERACT committee," was the issue of whether there is repair of erosions in RA," advised Prof Genant. In this study, we performed two exercises: The first asked the committee members, as a panel of experts, to express agreement or disagreement with the presence of improvement in features of bone erosion in images submitted by members as examples of healing in RA. The second exercise presented panel members with 28 pairs of serial images, 14 chosen to illustrate progression and 14 chosen to illustrate repair. Agreement was tested on 8 items. This study provides evidence that repair of bone damage in RA does occur, resulting in some degree of improvement, which was recognised by a majority of a panel of experts.

"In the late 1990s and into 2000 and beyond, magnetic resonance imaging was beginning to make a major play in the evaluation of various arthritides,<sup>12</sup> with many investigators including Oostergaard and Peterfy, being leaders in this field," said Prof Genant. Further developments have led to a novel multispectral (MS) MRI analysis method to quantify changes in bone lesion volume in the hands of RA patients.<sup>13</sup> "In all MRI trials in RA today the images are read using some variation of the RAMRIS scoring that was developed over 6 years by our OMERACT MRI Working Group."

Figure 6



Looking to the application of these techniques in clinical trials, Prof Genant explained, “With regards to the Sharp vs Larsen score methods used in clinical trials, the Sharp method differs by separating erosion and joint space narrowing (JSN), providing somewhat greater linearity and sensitivity to change and to a large extent it has supplanted the Larsen approach in most of the clinical trials currently conducted. Then there have been modifications by Sharp, Genant and van der Heijde, with slightly different erosion scales, JSN scales and locations are very similar, with some sites eliminated with one of the scoring systems or the other, however there is about a 90% overlap of evaluation of the same sites in the hands and feet.” The Genant-modified and van der Heijde-modified Sharp Scoring Systems are the method used in

the majority of the ongoing and currently planned clinical trials.

The Genant-modified Sharp Scoring System evaluates 14 sites for erosion, using an 8-point scale, 0.0 to 3.5, in 0.5 increments. 0 for negative, 1 for mild, 2 for moderate 3 for severe and +0.5 for worse, with a maximum score of 49 per hand, normalised typically to 50. With regards to joint-space narrowing 13 sites are evaluated using a 9-point scale from 0.0 to 4.0 with a maximum score of 52 per hand and normalised to 50. “The 4 here is for ankylosis,” he said “This normalization equally weights erosion and joint space narrowing,” advised Prof Genant. Within the feet all of the methods use typically 6 sites (1<sup>st</sup> IP and 1<sup>st</sup>-5<sup>th</sup> MTP joints), which are also utilised by Genant, with the 8-point erosion scale, a maximum score of 42 per foot, normalised to 45. For joint

space narrowing in the foot, the same 6 sites are evaluated with the 9-point scale 0 to 4. The maximal total score, combining erosions and joint space narrowing is 290 for the Genant-, 448 for the van der Heijde- and 392 for the Sharp-Modified Sharp Scoring systems. The absolute differences relate to the different scaling and exact joints evaluated. Nevertheless, all the scoring systems inter-correlate well.

Presenting radiographic data from the AIM trial,<sup>14</sup> which showed abatacept blocks progression of joint damage in RA patients failing methotrexate (MTX), with abatacept users demonstrating a 50% reduction in joint space narrowing scores, erosion scores, and total scores, compared with participants taking MTX plus placebo. Prof Genant commented, “If one looks at this in terms of the median changes, from a visual perspective these typically are not very helpful, so increasingly researchers are using the cumulative probability display, which shows the distribution of radiographic changes in total score. Drug responsiveness or lack thereof is shown where the two ends of the curves separate, with the efficacy shown in the abatacept group.” (Refer Figure 6).

These researchers looked at erosion at 14 sites in the hand and wrist, and joint space narrowing at 13 sites and measured progression via the Genant-modified Sharp scoring system. In a follow-up study,<sup>15</sup> investigators looked at the reproducibility of the radiographic results found in the AIM trial, and determined that “Interclass correlations (ICC) were very high for both the changes at baseline, and for follow-up or change,” advised Prof Genant. Looking at results for 2-years, Genant *et al.*<sup>16</sup> found an increasing effectiveness of both erosion, JSN and total score relative to the first year. A total of 467/536 (87%) patients treated in the open-label period were included

in the primary analysis at Year 2. Data shows that 2 years of abatacept treatment slowed progression of structural damage in RA patients with an inadequate response to methotrexate, with the effect seen at year 2 significantly better than that in year 1. “These data indicate that abatacept inhibited structural damage progression and that radiographic progression was further inhibited during Year 2 of abatacept treatment compared with Year 1. Through 2 years of abatacept treatment, 50% of patients had no progression of structural damage. Among abatacept-treated patients who did not progress at Year 1, 79% did not progress at Year 2. These data support the durability of response and increasing effect of abatacept over time,” explained Prof Genant.

Concluding with some data from the REFLEX study,<sup>17</sup> Prof Genant commented, “Rituximab significantly inhibits radiographic progression in RA patients with an inadequate response or intolerance to one or more TNF inhibitors. This study provided the first indication that a B cell-targeted therapy can inhibit radiographic progression. These REFLEX findings also provide the first evidence of inhibition of radiographic progression in patients with an inadequate response or intolerance to 1 or more TNF inhibitors.”

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*She was appointed to St James's Hospital in 2003 where she is in clinical practice as Consultant Rheumatologist. She has published 14 original papers in peer-reviewed journals, in addition to editorials and review articles.*

“With targeted biologic therapies we have seen a revolution in the management of rheumatic disease and we now have new treatment goals, where we can actually prevent structural damage and prevent functional decline in patients with inflammatory arthritis. We can now realistically achieve low disease activity states or remission,” commented Dr Doran as she introduced her presentation on the safety issues surrounding TNF blocking agents and the newer biologics for the treatment of RA.

“What are the risks for patients on biologic therapies and what should patients be warned about? What needs to be checked prior to starting a biologic therapy? And which patients should not receive biologic therapies?” Initially, RCTs provide some data as to safety in biologics, however the limitations of RCTs in finding unexpected adverse events are well known, advised Dr Doran, particularly as a highly selective group of patients are enrolled in clinical trials, they are generally rather short term and the numbers are relatively small.

“With regards to TNF blocking agents, we now have a significant amount of data available from disease and drug-based registries; practice and population-based registries and health care utilisation databases.”

Antitumour necrosis factor (TNF) therapy has revolutionised the treatment of inflammatory arthritis. However, cytokine manipulation also has potentially deleterious consequences, because TNF- $\alpha$  has physiological and pathological roles. Currently, three TNF- $\alpha$  antagonists are available: two monoclonal antibodies (infliximab and adalimumab) and one soluble TNF- $\alpha$  receptor (etanercept). “TNF $\alpha$  is involved in host defence and tumour surveillance, so the major concerns when these agents became available were whether these patients were going to have a higher risk of developing infections,

malignancies or other potential side effects,” said Dr Doran, presenting data from a retrospective longitudinal cohort study<sup>1</sup> of 609 RA patients and 609 non-RA study subjects (mean age 58.0 years; 73.1% female) followed up for a mean of 12.7 years and 15.0 years, respectively, with results reflecting higher mortality among the group with RA and demonstrating a two times risk of serious infections in the RA group (infections requiring hospitalization, and any documented infection in patients) compared to the control group. The authors postulated that this may be due to the immunomodulatory effects of RA, or to agents with immunosuppressive effects used in its treatment. “We did not find that methotrexate increased infection risk, but certainly steroids at a dose greater than 5mg per day did increase infection risk. Use of some of the other disease modifying agents such as azathioprine and cyclophosphamide did increase infection risk,” said Dr Doran. “So this has made it a little more difficult to interpret some of the findings from the studies.”

But, does anti-TNF therapy increase infection risk in RA? “Data shows a definite increased risk for tuberculosis (TB) in RA patients treated with anti-TNF therapy. Recommendations vary between countries for TB screening because of different underlying incidence rates, vaccination prevalences that influence the risk of latent TB, and the interpretation of screening test results. However, there are notable recurrent themes in the recommendations:<sup>2-4</sup>

All patients should be screened for latent TB in accordance with national guidelines prior to starting anti-TNF therapy. Chest x-rays are universally recommended;

Many guidelines recommend skin testing, whilst others suggest that immunosuppressives decrease the value of this. More sophisticated and reliable

tests for latent TB are becoming available, and may be incorporated into future guidelines;

Patients with latent TB or at high risk of TB should receive prophylactic anti-TB treatment prior to commencing anti-TNF therapy.

“All patients on anti-TNF therapy should be closely monitored for TB and should be screened for latent disease prior to commencing therapy,” advised Dr Doran.

Other opportunistic infections include fungal infections such as Histoplasmosis, Cryptococcus, and cases of Pnuemocystis carinii usually in patients on high dose steroids in addition to anti-TNF therapies. “There have been a number of viral infections that have been reactivated, including Hepatitis B, with all three TNF blocking agents being indicated in increased viral load in patients with pre-existing disease. However, to date, there is no evidence that Hepatitis C is affected adversely in patients on these drugs. Varicella has been shown to cause very severe infections in patients on TNF blocking agents, and patients who are non-immune to Varicella can develop a very severe disseminated primary infection, which can be fatal.”

The question of bacterial infection with anti-TNF agents has caused significantly more controversy with a number of recent studies showing conflicting results,<sup>5,7</sup> likely due to methodologic issues, particularly with regards to the definition of exposure period and choice of control group. “It is very likely, although not fully proven yet, that there is an increased risk and patients do need to be counseled about this,” stated Dr Doran. The types of bacterial infections seen in RA patients on TNF blocking agents are mostly common bacterial infections, with the areas affected being the skin, joint infections and respiratory tract.

“There have been some unusual bacterial infections and some very serious cases of Listeriosis, some of which have been fatal, so precautions regarding food-borne infections should also be provided to patients prior to starting therapy.”

TNF- $\alpha$  plays an important role in surveillance of malignancy<sup>8</sup> and hence there is a theoretical risk of increased tumor formation with anti-TNF- $\alpha$  agents. “RA patients have increased risk of developing certain malignancies,” advised Dr Doran. “Particularly, they seem to have increased risk of lymphoma, cancer of the haematopoietic system, skin cancers and lung cancers. But the question again is does anti-TNF therapy further increase the risk of malignancy? The results in general are quite conflicting. There certainly doesn’t seem to be enough evidence to say definitively that anti-TNF therapy increases the risk, but some studies did find an increased risk of lymphoma above that seen at baseline in RA. The concomitant use of Methotrexate and other DMARDs has made this more difficult as these therapies in themselves might increase the risk,” said Dr Doran. “It is certainly possible from the data at the moment that TNF inhibitors may confer a small increase in risk. With regards to solid malignancy, combination with cyclophosphamide significantly increases risk and is not recommended.”

A recent US observational study by Wolfe *et al.*,<sup>9</sup> concluded that biologic use in RA was not associated with increased overall risk of malignancy. However, when examined separately, the risks for both non-melanotic skin cancer and melanoma were increased with biologic therapy (OR: 1.5; 95% CI: 1.2-1.8; OR: 2.3; 95% CI 0.9-5.4, respectively). For patients with a history of malignancy, what is the risk of future malignancy? “There is very little data regarding this,” explained Dr Doran, probably due to a reluctance on behalf

of treating physicians to date to use TNF blocking agents in this patient population, and she cautioned that extreme vigilance would be required if used in this situation.

Auto-immune disorders, with development of a positive ANA and rare cases of lupus-like syndrome, have been reported and treatment should be stopped if these occur. “When TNF blocking agents are stopped in these instances symptoms do tend to resolve. There have been some reports of new-onset Psoriasis which is somewhat surprising as these medications have been used to treat this condition and also exacerbations of existing psoriatic skin lesions have been shown.”

Demyelinating disease is another important issue and again there have been a number of case reports with optic neuritis and multiple sclerosis reported. It has been suggested that TNF inhibitors may unmask latent disease, so in patients with any history of neurological symptoms or who develop new neurological symptoms, these drugs should be stopped. “Once the therapy is stopped these symptoms tend to resolve,” advised Dr Doran. New heart failure has been reported with infliximab in particular and also exacerbation of existing heart failure, explained Dr Doran.

“The issue of pregnancy and lactation is another area where there is a paucity of research, however there is no known teratogenicity from these agents and there have been at this stage quite a large number of women who have been exposed during pregnancy to all of the TNF blocking agents without any definite adverse effects as far as I am aware,” said Dr Doran, advising however that females should not become pregnant while on treatment and that contraception should be utilised for a period after discontinuing anti-TNF therapy.

With regards to vaccines, it seems the effect of inactivated vaccines may be diminished while on therapy, and vaccinations should be brought up to date prior to therapy, particularly influenza and pneumococcal vaccines. “Live vaccines should be avoided while on biologic therapy,” added Dr Doran.

With regards to the new biological agents, Dr Doran suggested that the potential risks of biologic therapies must be interpreted in context of their benefits. Prior to commencing any biologic therapy, the individual risk-benefit profile should always be considered and discussed with the patient. Tuberculosis screening should be performed and immunisation undertaken. While patients are on biologic therapy and after stopping therapy a high degree of vigilance is needed particularly with regard to routine and opportunistic infections and malignancy.

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## Evolving and Novel Options for the Treatment of Osteoporosis

**Prof Laurence Rubin**, Professor of Medicine, University of Toronto, Head, Division of Rheumatology, St Michael's Hospital, Toronto, Canada.



Laurence A. Rubin graduated Magna Cum Laude from the University of Ottawa (1977), completed speciality training in Internal Medicine (1982) and Rheumatology (1983) at the University of Toronto. From 1983-1986, he was awarded an Arthritis Society Research Fellowship to pursue further postgraduate studies at the National Cancer Institute/NIH in Bethesda, Maryland, USA. In 1986 he returned to Canada as Assistant Professor, Departments of Medicine and Immunology, University of Toronto and staff member, Division of Rheumatology, Sunnybrook Health Science Centre. In 1992, he was promoted to Associate Professor, moved to Women's College Hospital to become Division Head of Rheumatology, and Founding Director, Multidisciplinary Osteoporosis Program. In July 1994, he was appointed Associate Physician-in-Chief at Women's College, and in 1997-98 served as Acting Physician-in-Chief at that site.

In 2000, Prof Rubin assumed his current position of Head, Division of Rheumatology and Staff Member, Metabolic Bone Clinic at St Michael's Hospital. In 2003, he was promoted to Professor, Medicine, University of Toronto.

He held a Clinical Associateship from The Canadian Arthritis Society from 1986-1992

and in 1992 received the Sanofi Winthrop Canadian Rheumatism Association Young Investigator's Award. He has been the recipient of peer reviewed grant support from the Arthritis Society, the Medical Research Council, Heart and Stroke Foundation, the Leukaemia Research Fund, the Physicians' Services Incorporated Foundation, Dairy Farmers and the Natural Science and Engineering Research Council (NSERC) and has published over 60 peer reviewed papers. Dr Rubin's main research interests have focused on hereditary factors that contribute to autoimmune inflammatory disorders, metabolic bone disease and osteoporosis.

In the final lecture of the Masterclass programme, Dr Rubin outlined a challenging list of objectives for his presentation including a review of the bone remodelling cycle and implications for treatment; consideration of anti-resorptives and anabolics – current and 'near term' options and a review of novel anabolic modalities and the potential for their application.

The bone remodeling cycle involves a complex series of sequential steps that are highly regulated. "The process is one of use and repair. So the concept is that we have a variety of events and these events occur in a cyclical fashion with several key cell types critical to the process; the osteoclast which clearly has a relevance in rheumatology, the osteoblast, which is the reparative part of the process and involved in bone formation, and the osteocyte which represents the structural component of bone directing many of the important physical functions and some of the key anabolic events," advised Prof Rubin.

"The efforts at treatment to date have been directed at reducing bone resorption by down regulating osteoclast function, and this has been quite successful – this is

the basis of action for the Bisphosphonates. The current and future interest lies in those treatments that can improve bone formation directly. The risk here is that we do so in a manner that does not maintain a normal, or coupled, process," he said.

"Throughout our lives we are repairing about 10% of our skeleton every year and it occurs in a coordinated fashion," said Prof Rubin. Describing in detail the elements involved in bone remodelling Dr Rubin discussed systemic factors and hormones such as PTH, vitamin D, interleukins (ILs), growth hormone (GH), and oestrogen which activate osteoblasts. Osteoblasts lay down bone matrix. A large component of this is Type 1 collagen. P1CP and PINP, two markers of bone turnover which reflect bone formation by osteoblasts. Bone specific alkaline phosphatase (BSAP) and osteocalcin are other products of osteoblastic activity which are measured in the serum as an assessment of bone formation. Other products produced by the osteoblast include M-CSF, IL-1, -6, -11, TNF (tumour necrosis factor), and TGF-beta (transforming growth factor). These compounds also can stimulate osteoclast differentiation and activity, and increase bone resorption. In addition, the osteoblast produces a ligand called RANKL. When this ligand comes in contact with its receptor RANK (which is on the surface of the osteoclast), in the presence of M-CSF, the osteoclast will be activated.

"There are a host of other factors that play a role here. The key to remember is that these things are occurring in a coordinated fashion, and maintained as such until in women for example there is a loss of estrogen at menopause, or in cases due to the introduction of drugs that disrupt the process and lead to damage.

There are three current major resorption inhibitors: Bisphosphonates, Estrogen and selective estrogen-receptor modulators

(SERMs). The effect of these agents are to reduce resorption sites and improve bone microarchitecture by decreasing the number of cavities. They also produce shallower resorption sites, improving bone balance, slowing bone turnover rate, allowing for increased bone mass and improved bone strength and quality. Observations to date show that fracture reduction is out of proportion to the increase in bone mass, so it is not necessary to demonstrate an improvement in BMD to demonstrate a reduction in fracture rate," explained Prof Rubin.

Among newer therapies, Zoledronic acid, a 1-hydroxy-2-imidazole-1-yl-phosphonoethyl bisphosphonic acid monohydrate has demonstrated efficacy in primary fracture reduction.<sup>1</sup> In the paper by Black et al, during a 3-year period, an annual infusion of 5 mg of zoledronic acid significantly reduced the risk of fracture at all key osteoporotic fracture sites, including the two primary end points, vertebral and hip fractures. The 70% reduction in the vertebral-fracture rate was greater than the 3-year reduction previously observed for oral bisphosphonates (40 to 50%)<sup>2-7</sup> and the reductions in fracture rates associated with other antiresorptive agents.<sup>8-10</sup> All other prospectively defined categories of fracture, including non-vertebral fractures and clinical vertebral fractures, were also significantly reduced ( $p < 0.001$  for all comparisons).

In a randomised, double-blind, placebo-controlled trial published in the NEJM,<sup>11</sup> 1065 patients were assigned to receive yearly intravenous zoledronic acid (at a dose of 5 mg), and 1062 patients were assigned to receive placebo. The infusions were first administered within 90 days after surgical repair of a hip fracture. All patients (mean age, 74.5 years) received supplemental vitamin D and calcium and the median follow-up was 1.9

## Evolving and Novel Options for the Treatment of Osteoporosis (Cont.)

years. At study conclusion, investigators determined that an annual infusion of zoledronic acid within 90 days after repair of a low-trauma hip fracture was associated with a reduction in the rate of new clinical fractures and with improved survival. "In terms of newer agents on the anti-resorptive side, this is by far, the newest and most interesting of the new agents, an extremely potent bisphosphonate," said Prof Rubin. "What is also very interesting about this drug is that it continues to work even in patients who have had the most severe hip fracture. Zoledronate is given as a once a year medication. There are a few adverse events, the most notable and as yet unexplained is the onset of atrial fibrillation (late onset >30days PI) which was seen in only one of the three major trials," commented Prof Rubin. Zoledronate has also been associated with two 'potential' cases of osteonecrosis of the jaw (ONJ) in all the OP studies to date.

The objective of anti-resorptive therapy should be to inhibit resorption without decoupling formation, he advised, outlining that current anti-resorptive therapies have limits to their effectiveness, with investigators looking to potential combination with anabolic therapy.

Results from several clinical trials show that a further new therapy, denosumab, may be an effective treatment for osteoporosis. The human monoclonal antibody binds to the receptor activator of nuclear factor  $\kappa$ -B ligand (RANKL), which is responsible for osteoclast differentiation, activation and survival, inhibiting RANKL action.<sup>12</sup> The efficacy and safety of subcutaneously administered denosumab were evaluated over a period of 12 months in 412 postmenopausal women with low bone mineral density<sup>13</sup>. Denosumab treatment resulted in an increase in bone mineral density at the lumbar spine of 3.0 to 6.7 percent (as compared with an


increase of 4.6 percent with alendronate and a loss of 0.8 percent with placebo), at the total hip of 1.9 to 3.6 percent (as compared with an increase of 2.1 percent with alendronate and a loss of 0.6 percent with placebo), and at the distal third of the radius of 0.4 to 1.3 percent (as compared with decreases of 0.5 percent with alendronate and 2.0 percent with placebo).

Prof Rubin went on to describe several other possible therapies for the treatment of osteoporosis including teriparatide, cathepsin k inhibition and strontium ranelate, concluding that anabolic agents have sophisticated mechanisms of action with the potential for significant increase in bone mass and quality.

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