**Institution: University of Leeds**

**Unit of Assessment: UOA1 Clinical Medicine**

**Title of case study:**
Case Study 7. Changing the treatment paradigm of rheumatoid arthritis: early diagnosis and aggressive treatment to attain remission leads to sustained improvements in health and quality of life.

## 1. Summary of the impact

Research in Leeds led by **Professor Paul Emery** pioneered early diagnosis and treatment for patients with rheumatoid arthritis (RA), with the aim of disease remission rather than reduction of symptoms. This approach has transformed management of RA and is now standard practice for patients worldwide. It has led to greatly improved disease control, increased quality of life and reduced disability as well as direct productivity gains of an estimated £4 million per year to the UK economy.

## 2. Underpinning research

Treatment for rheumatoid arthritis (RA) had traditionally been conservative, using a step-wise approach to manage the symptoms of the disease as they progressed. **Paul Emery** (Professor of Rheumatology, Leeds, 1995- ) was the first to turn this model on its head, proposing an ambitious protocol driven by early diagnosis and aggressive treatment with the aim of achieving disease remission defined by complete suppression of synovial and systemic inflammation. In 1995, Emery moved to Leeds to lead a multi-disciplinary research group, who designed and delivered a series of seminal studies to provide the evidence and establish the validity of this proposed treatment model.

With **Philip Conaghan** (Senior Lecturer then Professor of Musculoskeletal Medicine 1997- ), **Joe Devlin** and **Andrew Gough** (both Research Fellows 1996-99), **Emery** showed that early RA patients with a sustained acute phase response suffer irreversible joint damage, resulting in pain and long term functional disability (1). Further work demonstrated the substantial long-term consequences of incomplete suppression of inflammation in early RA, where persistent synovial inflammation led to increased functional disability, osteoporosis and structural joint damage (2).

The group then carried out research looking at the effectiveness of early diagnosis and aggressive treatment. Their work established that the greatest predictor of persistence of disease was symptom duration of greater than 12 weeks, a key step in establishing the importance of early treatment. In collaboration with national (Maini, Imperial College London) and international partners (Smolen, Vienna and Breedveld, Lieden), the first international trials of anti-TNF therapy were conducted in patients with RA . The Leeds group were the first to use biologic therapy for remission induction in patients with very early disease and demonstrated significant long benefits at eight years (3). In a subsequent study (4) for the first time remission was used as an endpoint and the effectiveness and lack of side effects demonstrated the feasibility of biologic therapy first line. Consequently, remission has been accepted as the outcome of choice in early therapy.

In addition, the Leeds group established the importance of using validated outcome measures, which are both disease specific and reflect what is important to patients. Alongside **Richard Wakefield** (Senior Lecturer, Leeds 1996- ), they identified that clinical measures of response to treatment are inadequate as subclinical synovitis exists in patients who have satisfied clinical remission criteria, resulting in “silent”, irreversible joint damage (5). Importantly, the group identified that this sub-clinical inflammation can be detected only through imaging with MRI and ultrasound, questioning the importance of clinically driven criteria as the sole foundation for treatment decisions.

With **Alan Tennant** (Professor of Rehabilitation Studies, 1999- ), the Leeds team developed the RA-WIS, a work instability scale, which was the first instrument designed and validated for the unique needs of patients with RA. This tool is now widely used internationally to assess the impact

of RA on individuals' work. The RA-WIS was the primary outcome for a novel randomised controlled trial led by Leeds of early treatment of patients still in work with biologic agent adalimumab (6).

Work at Leeds established that the early diagnosis of RA results in suppression of inflammation and leads to higher rates of remission. Following on from this, the group designed a number of novel trials whose primary endpoint was remission. The results of these studies established that importantly, this remission could be sustained without the use of expensive biologics (4). Long-term follow-up at eight years has confirmed the success of this approach and the Leeds group have found that very early treatment to remission results in the ability to cease therapy, and have shown the immunological basis for this, proving the need to treat for remission and not just symptom reduction.

**3. References to the research**

1) **Devlin J, Gough A,** Huissoon A, et al. The acute phase and function in early rheumatoid arthritis. C-reactive protein levels correlate with functional outcome. Journal of Rheumatology 1997; 24: 9-13.
*This paper provided the rationale for the suppression of inflammation in the treatment of patients with RA showing the first good data that CRP as a surrogate marker correlated with function which was seen as the gold standard measure.*

2) **Conaghan PG,** O'Connor P, **McGonagle D,** et al. Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. Arthritis & Rheumatism 2003; 48: 64-71.
*This landmark study simultaneously imaging of synovitis and bone damage in the same patients over 12 months provided the conclusive data that inflammation and joint damage are strongly related and that in the absence of inflammation there was little joint damage.*

3) Quinn MA, **Conaghan PG,** O'Connor PJ, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis & Rheumatism 2005; 52: 27-35.
*This was the first remission induction study with a TNF inhibitor which showed that patients rapidly reached remission and maintained that state when the biologic was withdrawn.*

4) **Emery P,** Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008; 372: 375-82.
*This international collaboration showed that therapy with combination of a TNF inhibitor and methotrexate was effective but also that serious adverse events were not increased by therapy. It also was the first study to use the now standard outcome of remission as an end point.*

5) Brown AK, **Conaghan PG,** et al. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 2008; 58: 2958-67.
*A year-long study of patients in remission at baseline showing for the first time that sensitive imaging with ultrasound and MRI could detect sub-clinical synovitis in patients treated with DMARDs in remission and that sub-clinical disease correlated with significant radiological progression in that individual joints. This formed the basis of current use of high resolution ultrasound.*

6) Bejarano V, Quinn M, **Conaghan PG,** et al. Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. Arthritis & Rheumatism 2008; 59: 1467-74.
*A long-term follow up of (4) showing that one year's treatment with biologics produced significant benefits eight years later in a small number of patients. It was the first study to find that early,*

*biologic therapy combined with methotrexate reduced job loss and improved productivity.*

**4. Details of the impact**

RA is a chronic, systemic, inflammatory joint disease, affecting 600,000 people in the UK and is the largest cause of treatable disability in the Western world. Given its high prevalence in the working population, RA represents a major economic burden through both direct costs of care and through loss of employment, with one in five employed RA patients having to stop work within the first 12 months of illness. Treating RA costs the NHS an estimated £560 million each year, with wider annual costs associated with sick leave and work related disability of £1.8 billion. With inclusion of nursing home costs and private expenditure, the estimated costs are as high as £3.8 billion a year. The research undertaken by the Emery group at Leeds has had a major impact on how the disease is viewed, diagnosed and treated, leading to substantial improvements in the health and quality of life of patients with RA and reduced financial costs, both within the UK and internationally.

**Impact on health and welfare**
Research at Leeds has shown the need and impact of early, aggressive care, a model that has been universally adopted in the UK.

The National Audit Office's guidelines on the management of RA – a pivotal document commissioned by the House of Lords to review the NHS standards of treatment for patients – cites Leeds work prominently [A]. Our work (4) provided the basis for a recommendation that: "It is important that treatment is started early to minimise damage to joints, and there is increasing evidence that aggressive treatment very soon after the onset of symptoms can lead to remission." In the same report, the Rheumatology Service at Leeds is used as an example of excellence in early treatment and multidisciplinary care.

Guidelines from the National Institute for Clinical and Health Excellence (NICE) recommended urgent treatment for RA [B]. The full guideline document quotes two Leeds papers which established the superiority of imaging to detect synovitis and the need to identify this early and a further five papers establishing the importance of aggressive treatments particularly in early disease and where the prognosis is poor. Underlining the importance of early diagnosis, the British Society of Rheumatology has recommended banded tariffs to see patients within three weeks of referral [C].

Early, aggressive treatment improves patients' quality of life by reducing pain and increasing functional ability and participation in valued activities, including work. Access to early referral is now expected by patients and is part of the Arthritis and Musculoskeletal Alliance "Standards of Care for Rheumatoid Arthritis" [D]. This defines appropriate support to enable those with RA to lead independent lives and reach their full health potential. Standard 4 says: "All people with suspected inflammatory arthritis should be seen by a specialist in rheumatology within 12 weeks of referral from their GP, to confirm diagnosis and enable prompt and effective treatment" citing Leeds research.

Based on the Leeds model, the care of patients with RA has been transformed across the globe [E,F]. Early, aggressive treatment is part of the joint European and American Guidelines [G], which directly influences the care of more than 11.4 million people with RA. Treating to remission is now a target recommended by several international bodies, which cite Leeds research in the evidence, including that of an international taskforce which refers to 17 Leeds papers [G,H]. Through Leeds' highly successful International Fellowship programme, we have hosted over 25 clinical fellows from 15 countries, which has directly led to the setting up of arthritis networks in Argentina and Brazil and the Gulf states, in addition to Sweden, Netherlands and Germany.

**Impact on the economy**
The National Audit Office estimates that the financial impact to the NHS of adopting the early treatment model is substantial [A]. Figures suggest 26,000 newly diagnosed patients in the UK

each year, half of whom seek early referral. While earlier, more rapid treatment increases the initial costs, modelling has suggested that these costs would be more than offset by decreases in lost productivity and improved quality of life. It is estimated that by treating those who are seen early is associated with an additional annual cost of £2.2 million but productivity gains of £6.2 million.

**Impact on public policy and services**

**Emery** was instrumental in launching the Fit for Work Europe Initiative (www.fitforworkeurope.eu/), an organisation showing that improvements in early intervention, treatment and return to work practices could help people of working age stay in work [I]. This report, launched at the Houses of Parliament in 2009, gained the attention of policymakers and the media, informed Government thinking on early intervention, prompted a debate in the UK parliament and contributed to the initiation of a Government review of the costs and benefits of treatment and care for rheumatoid arthritis patients in the UK. As a result, in September 2010, the Fit for Work Europe Coalition was launched in Brussels to highlight to policymakers and relevant stakeholders the importance of early detection, prevention and management of musculoskeletal disease [I]. The European League Against Rheumatism estimates that this has led to many millions of additional funding allocated to musculoskeletal disease [F].

**5. Sources to corroborate the impact**

[A] National Audit Office. Services for people with rheumatoid arthritis (2009). http://www.nao.org.uk/wp-content/uploads/2009/07/0809823.pdf (see pg 11, 28).

[B] National Collaborating Centre for Chronic Conditions. Rheumatoid arthritis: national clinical guideline for management and treatment in adults (2009). http://www.ncbi.nlm.nih.gov/books/NBK51812/pdf/TOC.pdf (see pg 25, ref 20 (1); pg 32 ref 64 (4) and pg 44 ref 69 (2).

[C] British Society of Rheumatology. Best Practice Tariff: Early Inflammatory Arthritis. http://publications.nice.org.uk/support-for-commissioning-for-rheumatoid-arthritis-cmg51/the-commissioning-and-budgeting-tool

[D] The Arthritis and Musculoskeletal Alliance Standards of Care for people with Inflammatory Arthritis (2004). (see pg 21 which cites two Leeds studies). http://www.nras.org.uk/includes/documents/cm_docs/2012/a/arma_standards_of_care_for_ia.pdf

[E] Corroborative Letter from British Society of Rheumatology President, Professor Chris Deighton. Available on request.

[F] Corroborative Letter from EULAR President, Professor Maurizio Cutolo. Available on request.

[G] Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Annals of the Rheumatic Diseases 69: 1580-88. (see page 1583).

[H] Smolen JS, Aletaha D, Bijlsma JW, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Annals of the Rheumatic Diseases 69: 631-37.

[I] Corroborative Letter from President of WorkFit, Steve Bevan. Available on request.