Institution: University of Leeds

Unit of Assessment: 1

Title of case study: Improving drug-induced remission in rheumatoid arthritis, and safely stopping the long-term use of drugs without disease flare

Period when the underpinning research was undertaken: 2014-2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Paul Emery	Professor	1995-present
Philip Conaghan	Professor	1997-present
Frederique Ponchel	Associate Professor	1998-present
Richard Wakefield	Associate Professor	2001-present

Period when the claimed impact occurred: 2014-2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Immediate treatment is accepted as best practice in patients with rheumatoid arthritis (RA). The therapeutic goal has become remission as early as possible in the disease course to avoid lifelong disabilities. This has created new needs: optimising remission rate and managing remission.

Our researchers developed imaging scores and immunological biomarkers, which led to the design of risk models. These risk models are now used by clinicians to: (i) tailor treatment inducing remission; (ii) safely discontinue drugs once in remission. The immunological biomarker technology was transferred to the Leeds Teaching Hospitals NHS Trust (LTHT) in 2014 to develop a biomarker kit. Our research played a central role in developing the global technological gold standards needed for the reproducible evaluation of RA. Our research has directly shaped international guidelines, and has enabled a true precision medicine approach to RA.

2. Underpinning research (indicative maximum 500 words)

RA is a chronic systemic inflammatory joint disease, with substantial impact on the lives of millions of people, affecting ~430,000 people in the UK, and regarded as the largest cause of treatable disability in the Western world. RA represents a major economic burden (a 2020 international study calculated ~GBP3,650 per patient each year in Western countries), due to the high impact of RA in the working population. Within the first 12 months of illness 20% of patients stop work and experience a reduced quality of life.

The Leeds Institute of Rheumatic and Musculoskeletal Medicine (LIRMM) at the University of Leeds and Rheumatology Department at LTHT have been improving the treatment and care of RA - with public involvement - since the late 1990s. Based on our pioneering work, we established early arthritis clinical networks connecting primary and secondary care countrywide. This enabled the early referral of patients with inflammatory arthritis symptoms. Our work led to the revision of the RA international classification criteria (2010), resulting in more effective outcomes for RA, and demonstrating the importance of early aggressive therapy comparing synthetic and biological drugs.

The success of our work led to the development of an international committee organised by the European League Against Rheumatism (EULAR) chaired by **Emery** (2013), with the remit of customising an internationally recognised therapeutic strategy. The result was the Treat-to-Target (T2T) approach, placing remission as the target outcome. Following this, Leeds designed several

studies that demonstrated improved outcomes/remission rates in RA using this approach [**1**,**2**].

Guidelines and regular updates for the T2T approach (European/International recommendations) have resulted from our continued research and recommendations (**Emery**). The evaluation of T2T was extended to psoriatic arthritis in a UK multicentre, open-label, randomised, controlled trial - conceived and performed by Leeds in 2015. This constituted the sole study that used remission as outcome [**3**].

The positive outcome of the RCT resulted in funding from the MRC-ABPI (GBP3,500,000, **Emery/Ponchel,** Co-applicants from Leeds) for a UK-multicentre study (TACERA/RA-MAP), collecting samples for ongoing multi-omics approaches (analysis approaches of combined data sets from multiple platforms) to predict remission.

Leeds has been at the forefront of developing the role of ultrasound and MRI techniques for the management of patients with RA, and played a central role in establishing an international task force [**4**]. After undertaking a substantial validation phase of ultrasound and MRI techniques, new international guidelines were developed in 2017. Leeds was instrumental in highlighting the high prevalence of subclinical disease in patients considered to be in clinical remission over the past decade, who showed continued deterioration of bone/cartilage, suggesting persistent underlying low disease activity. This led to an increased recognition of the need to manage remission, while the definition of remission itself needed further research.

Following the discovery of dysregulation in circulating CD4 protein and T-cells subsets in RA, the quantification of T-cells anomalies [**5**,**6**] provided a novel stratification tool for managing RA. In order to translate this research into a clinical path, we transferred this technology to LTHT immunology services in 2014 for development using flow cytometry (a method used for the detection and quantification of particular cell components).

Our research produced imaging and immunological tools able to define the depth of remission that needs to be achieved before drugs can be discontinued safely while maintaining a patient's quality of life [**5**,**6**]. This led to the creation and establishment of the Leeds prospective joint research/NHS remission clinic (2016), which subsequently developed imaging and T-cell biomarkers defining the depth of remission [**4**,**5**,**6**]. Importantly, the identification of biomarkers indicating the depth of remission (including patient reported outcome measures), provided a logical approach for tapering drugs safely and stratifying the risk of flare [**6**].

3. References to the research (indicative maximum of six references)

1. **Emery P**, Hammoudeh M, FitzGerald O, Combe B, Martin-Mola E, Buch MH, Krogulec M, Williams T, Gaylord S, Pedersen R, Bukowski J, Vlahos. Sustained remission with etanercept tapering in early rheumatoid arthritis (PRIZE). N Engl J Med 2014; 371:1781-1792. DOI: 10.1056/NEJMoa1316133
2. Smolen JS, **Emery P**, Fleischmann R, van Vollenhoven RF, Pavelka K, Durez P, Guérette B, Kupper H, Redden L, Arora V, Kavanaugh A. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial. Lancet 2014; 383(9914):321-332. DOI: 10.1016/S0140-6736(13)61751-1
3. Coates LC, Moverley AR, McParland L, Brown S, Navarro-Coy N, O'Dwyer JL, Meads DM, **Emery P**, **Conaghan PG**, Helliwell PS. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised, controlled trial. Lancet 2015; 386(10012): 2489-2498. DOI: 10.1016/S0140-6736(15)00347-5
4. D'Agostino MA, Terslev L, Aegerter P, Backhaus M, Balint P, Bruyn GA, Filippucci E, Grassi W, Iagnocco A, Jousse-Joulin S, Kane D, Naredo E, Schmidt W, Szkudlarek M, **Conaghan PG**, **Wakefield RJ**. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce- *Part 1:* definition and development of a standardised, consensus-based scoring system. *Part 2*: reliability and application to

multiple joints of a standardised consensus-based scoring system. RMD Open 2017; 3(1). DOI: 10.1136/rmdopen-2016-000428 and 10.1136/rmdopen-2016-000427

5. **Ponchel F,** Burska AN, Hunt L, Gul H, Rabin T, Parmar R, Buch MH, **Conaghan PG, Emery P**. T-cell subset abnormalities predict progression along the Inflammatory Arthritis disease continuum: implications for management. Sci Rep 2020; 10: 3669. DOI: 10.1038/s41598-020-60314-w
6. Gul HL, Eugenio G, Rabin T, Burska A, Parmar R, Wu J, **Ponchel F**, **Emery P**. Defining remission in rheumatoid arthritis: A comparison of multi-dimensional remission criteria and patient reported outcomes. Rheumatology 2019; 59(3): 613-621. DOI: 10.1093/rheumatology/kez330

4. Details of the impact (indicative maximum 750 words)

The burden of RA is of great economic significance. Treating RA costs the NHS an estimated GBP560M per year. The estimated costs are as high as GBP3.8 billion per year with the inclusion of nursing costs and private expenditure, while the costs associated with sick leave (up to 30 days per patient) and work-related disability are GBP1.8 billion per year. It is estimated that 90% of the overall rheumatology health budget is spent on biologics drugs for just 10% of patients. New patients using biologics increase yearly, hence the urgent need to establish new tools to stratify patients in order to: (a) use less expensive therapies to induce remission as early as possible; (b) limit costs of drugs when no longer necessary (once remission is achieved) while maintaining patients' quality-of-life.

The translational research delivered by Leeds has transformed the current management of RA from diagnostic/prognostic uncertainties (prescribing drugs with a "trial-and-error" approach) towards true precision medicine.

Impact on technologies

Imaging technology is one of the flagships of UK musculoskeletal research, while imaging biomarker research has been a strength in Leeds for over two decades. Since 2010, Leeds has provided leadership and professional representation in international organisations - notably within the European League Against Rheumatism (EULAR) with presidency and chairing of executive committees and taskforces (**Emery**), and within the international Outcome Measures in Rheumatology Clinical Trials group (**Emery/Conaghan/Wakefield**). Leeds was instrumental in establishing the technological gold standards needed for reproducible evaluation of RA worldwide [**4**].

Immunological biomarkers: Following the discovery of dysregulation of certain circulating CD4 and T-cells subsets in early RA (**Ponchel/Emery/Conaghan**), a novel stratification tool for managing RA was developed using flow cytometry technology [**5**,**6**]. We transferred this technology to the LTHT immunology service (2014), which has demonstrated the feasibility and value of all blood tests being performed in NHS routine settings [**5**]. These data leveraged the design of two studies: (i) an industry sponsored trial randomising patients for standard-of-care versus biological therapy based on a low/high T-cell risk; (ii) a protocol integrating patients into the decision for tapering of therapy based on good prognostic using imaging and T-cell biomarkers. [Both studies were delayed due to Covid-19 although both have now restarted.]

Impact on health and welfare

Our research led to the development of effective treatment pathways for RA, improving patients' quality of life. Leeds demonstrated the need for and impact of early aggressive strategies (the T2T model) in RA (2007-2014). The T2T model was universally adopted in Europe (2016) and in the UK (2018), generating novel National Institute for Health and Care Excellence (NICE) guidelines for standard-of-care [**A**,**D**].

According to Emeritus Professor and Emeritus Chairman, Department of Medicine, Medical University of Vienna, and former EULAR President:

*"The dissemination of this approach has dramatically transformed the way RA is treated in the UK and internationally. It allowed rheumatologists to understand the importance of having the right treatment target (i.e. remission)...The ways in which RA is managed and treated today, undoubtedly would not be the same if it were not for Paul Emery's commitment to RA patients and his leadership in the T2T Steering Committee [**A**]."*

The T2T model has transformed the care of RA patients across the globe. We ensured the work had maximum impact by creating an international clinical fellowship programme in Leeds, hosting over 20 delegates (including professors and clinical fellows) from many countries. Visitors who attended the programme provided positive feedback, stating how the learning acquired in Leeds has changed rheumatology clinical practice in their countries of origin [**E**]:

- One delegate from Japan testified that the training was later applied to clinical practice in Japan. They stated that clinical practice in Japan was advanced as a result of integrating imaging techniques into the implementation of T2T strategies with anti-rheumatic drugs including biological agents [**Ei**].
- A delegate from France stated that during their time at Leeds, they were trained in a medical technique that could not be learnt in France: arthroscopic synovial biopsy for patients with chronic inflammatory rheumatism. They also testified that the advancement of their career (i.e. professorship) was directly related to the experience they gained in Leeds and multiple continued collaborations since then [**Eii**].
- Another visiting professor from France stated that they could directly apply the standardised approach to RA care learnt in Leeds, integrating imaging research into the clinical pathway for patients in France. As a result, they were able to initiate several research programmes focused on ultrasound in RA, Scleroderma and Psoriatic Arthritis. Furthermore, this experience directly contributed to their career progression and appointment as head of a rheumatology institute in Rome (August 2020) [**Eiii**].

The most evident beneficiaries of this research are patients with early RA (about 25,000 new cases per year). Nevertheless, ~40% of patients do not achieve the T2T goal with NICE approved drugs. Our immunological biomarker research has produced a new tool to identify these patients [**5**], enabling tailoring of standard-of-care (i.e. current T2T) versus a more aggressive therapy for poor prognosis patients (ongoing TEEMS trial, delayed by Covid-19 pandemic). The creation of remission clinics has allowed such patients to become part of the decision to taper their treatment. The Leeds prospective joint research/NHS remission clinic (2016) has ~60 patients in remission per month, is run by two clinical nurse specialists (CNS) (one research, one NHS), and is overseen by a dedicated research fellow and a consultant (**Emery**) [**F**].

Leeds Biomedical Research Centre (BRC) is an international centre of excellence in musculoskeletal disease research that provides infrastructure supporting research based on NIHR grant income (partnership between LIRMM, University of Leeds, and LTHT). Since its inception it has received GBP20 million in funding. Patients within the Leeds BRC set-up are in direct proximity to our research facility. We run PPI groups and organise events to allow the public to contribute to basic science research [**G**]. During our PPI events, patients visit our laboratory facilities while our staff/students demonstrate the use and value of several techniques and pieces of equipment. This set-up has improved our patient-researcher relationship, allowing us to include PPI groups in refining clinical objectives.

Impact on public policy and services

Leeds research was instrumental in informing the creation of national (NICE guidelines) and international guidelines (EULAR guidelines) around the early management of RA [**B**,**D**] and once remission is achieved (American College of Rheumatology guidelines) [**H**].

Emery was a key member of the International T2T Steering Committee (sole UK representative), which has developed 10 recommendations aimed at informing patients and rheumatologists about the T2T model to reach optimal outcomes early in the RA disease course (2010-2013). The committee met regularly over the REF2021 assessment period and amended the

recommendations considering new research, and directly involving patients' contributions, which emphasised the importance of a shared decision-making process. The Steering Committee was instrumental in changing national/international guidelines. For example, their recommendations were incorporated into EULAR international guidelines in 2016 and UK NICE guidelines in 2018 [**A**,**B**,**C**,**D**]. The NICE guideline additionally provides recommendations around monitoring RA after achieving the T2T (i.e. remission).

For patients in remission, the previous practice was to continue drugs but some drugs have significant side effects and high costs. **Emery** contributed to the establishment of an international agreement on the clinical rational for discontinuing drugs. In 2013, an international EULAR imaging taskforce was initiated (**Conaghan**, leader and UK representative) and this provided guidance for the management of RA (2016-2017) [**4**]. Our work on defining the depth of remission with imaging and T-cell biomarkers [**4**,**5**,**6**] led to the discontinuation of the use of drugs which were no longer necessary but had potential side effects (notably biologics). Our work also incorporated imaging of the joints in the clinical pathway (2017, **Wakefield**). The EULAR guidelines were revisited by the taskforce, and updates released in 2017 [**4**].

In 2015, following consultation with **Emery**, the American College of Rheumatology released recommendations for the treatment of RA patients in remission where the tapering of drugs (notably biologics) was outlined [**H**].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[**A**] Testimonial from Emeritus Professor and Emeritus Chairman, Department of Medicine, Medical University of Vienna describing Emery's work in the Treat-to-Target approach committee, leading to the 2016 EULAR guidelines and 2018 NICE guidelines stating the importance of shared decision making.

[**B**] 2016 update of the EULAR recommendations for the management of early arthritis. Ann Rheum Dis, 2017; DOI: 10.1136/annrheumdis-2016-210602

[**C**] EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis, 2017; DOI: 10.1136/annrheumdis-2016-210715

[**D**] The model of early aggressive treatment strategies in RA was universally adopted in the UK generating novel NICE guidelines for standard-of-care; Rheumatoid arthritis in adults: management; https://www.nice.org.uk/guidance/ng100

[**E**] Testimonials from international visitors who attended the International Clinical Fellowship Programme:

I. Senior Lecturer, Department of Allergy and Clinical Immunology, Chiba University Hospital, Japan
II. Head of Department of Rheumatology, Amiens-Picardie University Hospital, France
III. Director of the Rheumatology Department, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy

[**F**] University of Leeds webpage for the Leeds prospective remission research clinic (2016). (https://medicinehealth.leeds.ac.uk/medicine/doc/leeds-prospective-remission-clinic).

[**G**] NIHR Leeds Biomedical Research Centre welcome guide for patients and the public who want to be involved in advising on research. https://leedsbrc.nihr.ac.uk/wp-content/uploads/sites/70/2020/03/Welcome-Pack-1.pdf

[**H**] 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. American College of Rheumatology, 2015; DOI: 10.1002/acr.22783