Institution: University of Glasgow

Unit of Assessment: Unit 1; Clinical Medicine

Title of case study: Novel treatment for psoriatic arthritis receives regulatory approval

1. Summary of the impact

Psoriatic arthritis (PsA) is a chronic inflammatory disease of joints, skin and tendons that affects 0.5–0.8% of the population worldwide. PsA can cause substantial psychological and social problems and also causes increased risk of death from cardiovascular disease. Research conducted by Prof Iain McInnes at the University of Glasgow in partnership with leading pharmaceutical company, Janssen, has provided robust evidence of the clinical benefits and safety of the cytokine blocker ustekinumab, leading to its approval for use for PsA by the European Medicines Agency in July 2013. This was the first approval of a PsA drug with a new mode of action in a decade, providing a novel treatment for approximately 1.25 million PsA patients across Europe.

2. Underpinning research

Treatments for psoriatic arthritis (PsA)

It is generally accepted that drug development will most likely succeed when a putative target has been defined in the context of deeper understanding of the causes of disease ('pathogenesis'). The pathogenesis of PsA combines an exaggerated response to environmental triggers like infection or stress, operating on a predisposing inherited underlying genetic background. This leads to uncontrolled inflammation in affected tissues. First-line treatment of PsA involves symptom relief with painkillers and anti-inflammatory agents. Second-line treatment with conventional disease-modifying anti-rheumatic drugs (DMARDs) aims to dampen down the immune system, slowing disease progression and limiting joint damage. Conventional DMARDs are blunt instruments that interact with multiple, ill-defined immune-regulatory pathways. Their use may be associated with severe side effects, and drug resistance. Only 30% of patients are good responders, with the remainder exhibiting either partial or non-response – consequent long-term joint damage and hence disability occurs in up to 60% of individuals. By contrast, biologic DMARDs offer a more targeted approach. These antibody-based drugs are designed to modulate critical 'focal points' within the immune system that, when blocked, confer substantial beneficial impact on the signs, symptoms and progression of disease. Cytokines are small proteins that regulate immune function; they represent excellent focal points amenable to blockade by biologic medicines.

Pathogenesis-driven research facilitates targeted therapy of PsA with biologic DMARDs

The choice of the correct cytokine for targeting has now become a critical decision point in drug development. University of Glasgow rheumatologist Prof Iain McInnes has guided an internationally recognised research programme that aims to understand the cellular and molecular pathways behind the development of inflammatory joint diseases. McInnes' research group has not only helped to develop substantial understanding of the immunological processes that underlie the mechanism of action of biologic DMARDs, but has also been involved in clinical trials of these drugs in patients with PsA who did not respond to treatment with conventional DMARDs, and in the generation of international guidelines to govern their eventual clinical use. In particular, University of Glasgow advances in dissecting the roles of cytokines in the inflammatory process[1] have provided a platform for major pharmaceutical companies to develop pre-clinical findings into clinical trials of innovative therapies.

Tumour necrosis factor (TNF)

Drugs that specifically block the cytokine TNF were the first biologic DMARDs to be approved for use in patients with PsA. University of Glasgow research was the first to show that TNF blockers can reduce the risk of developing cardiovascular disease, a potential complication of PsA (2007).[2] In addition, McInnes was a member of the Steering Committee for GO-REVEAL, the first phase III study of a new TNF blocker, golimumab, that was conducted at 58 sites in North America and Europe. Treatment with this drug improved several symptoms of PsA, including pain; number of swollen joints/tendons; skin and nail symptoms; physical function; and quality of life (2009).[3]

Interleukin 17 (IL-17)
Although TNF blockers have expanded the therapeutic options for PsA, around half of all patients who receive these drugs either fail to respond or discontinue treatment because of severe side effects. Consequently, efforts are underway to identify and target other molecules implicated in this disease. Patients with PsA have increased levels of the cytokine IL-17A. McInnes, therefore, led a 24-week proof-of-concept trial of an IL-17A-blocking drug among 42 PsA patients recruited from 11 centres in Europe (2013).[4] Treatment with this drug improved measures of both disability and quality of life.

IL-12 and IL-23
The cytokines IL-12 and IL-23 act in a common pathway of inflammation and genetic variants associated with this pathway are implicated in susceptibility to PsA. In 2009, McInnes' team was involved in a study using an experimental model of rheumatoid arthritis that demonstrated that these cytokines (along with IL-17A and cells of the immune system) were involved in the development of joint inflammation.[5] These findings establish the existence and role of these cytokines in a functional network involved in the pathogenesis of PsA.

University of Glasgow research sparks a collaborative partnership with Janssen

In March 2009, McInnes' world-leading research programme on the pathogenesis of arthritic disease presented an ideal environment for Janssen (a subsidiary of Johnson & Johnson previously known as Centocor) to directly seek out a collaborative partnership. This decision reflected McInnes' position within "*the rheumatologic scientific community as one of the key research minds working in the field today. His expertise, through his basic research in his laboratory at the University of Glasgow and clinical trials, is renowned.*" (Senior Director, Immunology R&D, Johnson & Johnson).[a]

The partnership focused on dual inhibition of IL-12 and IL-23 as a novel treatment for PsA. Janssen's drug portfolio included an IL-12 and IL-23 blocker (known as ustekinumab) that was already approved worldwide for the treatment of adult patients with the inflammatory skin condition psoriasis. The fact that PsA shares pathogenic features with psoriasis supported a novel use for this drug. McInnes subsequently led PSUMMIT 1, the first phase III clinical trial of ustekinumab as a therapeutic option for PsA (2013).[6] PSUMMIT 1 was initiated in October 2009 and McInnes was instrumental in the PSUMMIT 1 trial design, guiding the team to choose the most appropriate and clinically relevant end points; including not only established articular and skin scores, but also sub-analyses of treatment effects on dactylitis (swelling of the entire finger), enthesitis (inflammation at sites where tendons and ligaments attach to bone) and bone remodelling. A total of 615 adult patients were recruited at 104 sites in 14 countries in North America, Europe and Australasia. More than 49% of patients receiving ustekinumab experienced a 20% reduction in their arthritis symptoms by 24 weeks of treatment, while around 23% of patients receiving placebo achieved the same response. Notably, up to 38% and 28% of patients achieved a sustained 50% or 70% improvement when followed out to 1 year. Remarkable improvements were obtained in dactylitis (reduced by 100%) and enthesitis (reduced by approximately 80%) scores after 1 year. Ustekinumab also improved skin symptoms, measures of disability and quality of life. Favourable responses were maintained at 52 weeks and the safety profile was similar to that reported in psoriasis.

Key University of Glasgow researchers: Iain McInnes (Muirhead Chair of Medicine and Director of Institute of Infection, Immunity and Inflammation, 1993–present); Naveed Sattar (Professor of Metabolic Medicine, 1999–present); Foo Liew (Gardiner Chair of Infection, Immunity and Inflammation, 1991–2011).
Key research collaborators: Members of the PSUMMIT1 study group; see original article for details.[6]
Key researcher roles in PSUMMIT 1: All authors participated in the study design, analysis and manuscript writing.[6] As Lead Investigator, McInnes had full access to the study data and was ultimately responsible for the decision to publish.

3. References to the research

1. McInnes IB & Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. *Nat Rev Immunol* 2007; 7: 429–442 doi:10.1038/nri2094.
2. Sattar N *et al.* Effects of tumor necrosis factor blockade on cardiovascular risk factors in psoriatic arthritis: a double-blind, placebo-controlled study. *Arthritis Rheum* 2007; 56: 831–839 doi:10.1002/art.22447.
3. Kavanaugh A *et al.* Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009; 60: 976–986 doi:10.1002/art.24403.
4. McInnes IB *et al.* Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. *Ann Rheum Dis* 2013 (online ahead of print 29 January) doi:10.1136/annrheumdis-2012-202646.
5. Lemos HP *et al*. Prostaglandin mediates IL-23/IL-17-induced neutrophil migration in inflammation by inhibiting IL-12 and IFNγ production. *PNAS USA* 2009; 106: 5954–5959 doi:10.1073/pnas.0812782106.
6. McInnes IB *et al.*, on behalf of the PSUMMIT 1 Study Group. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* 2013; 382: 780–789 doi:10.1016/S0140-6736(13)60594-2

4. Details of the impact

Biologic DMARDs have revolutionised treatment of patients with PsA. Even so, partial responses occur in approximately 60% of patients and over 5 years up to 60% of patients will withdraw from treatment owing to drug intolerance or loss of effect. Consequently, there remains a considerable unmet need for these patients. Ustekinumab is unique among the biologic DMARDs that have been approved to treat PsA, as it targets a novel pathway. The clinical findings of PSUMMIT1 underpinned Janssen's application to EMA to extend the European marketing licence for ustekinumab to include patients with PsA. This application was approved in July 2013. University of Glasgow research has, therefore, exerted considerable influence by facilitating EU licensing authorisation for a new use of an existing drug. Furthermore, the University of Glasgow has a unique claim to this impact as no other UK institutions were represented on the PSUMMIT1 steering committee.

PSUMMIT1 provides the evidence base for ustekinumab as a novel treatment for PsA

Janssen is a subsidiary of Johnson & Johnson, the 2012 market leader in pharmaceuticals, with sales of approximately $67 billion and a research and development spend of almost $8 billion. In July 2009, Janssen invited McInnes to be Lead Investigator on the PSUMMIT1 trial of ustekinumab (ClinicalTrials.gov identifier NCT01009086).[b] As the sole UK researcher, McInnes was joined on the Steering Committee by three North American rheumatologists and two dermatologists (from Spain and the USA). The preliminary results of PSUMMIT1 were presented by McInnes at the European League Against Rheumatism (EULAR) annual congress in June 2012; this meeting was held in Berlin and attracted more than 15,000 delegates from over 115 countries. The data caught the attention of online news outlets, including Medscape.[c] Speaking to Medscape, the chair of the committee of EULAR for abstract selection explained the novelty of PSUMMIT 1: "*This is a first-in-kind [study].... They can get two for the price of one here, because if you can help the skin and the joints, that's a good outcome.*"

McInnes remains a key consultant for Janssen in directing their clinical trials of ustekinumab, including evaluating effects on PsA-related structural damage to the joints (PSUMMIT 1 and PSUMMIT2). This aspect is particularly important as damage to the joints predicts loss of function and possible disability.

EMA approves ustekinumab as a novel therapy for PsA

On 6 December 2012, Janssen filed ustekinumab for EMA regulatory approval as a treatment for adults with PsA, citing the results of PSUMMIT1 in support of this application. The EMA Committee for Medicinal Products for Human Use (CHMP) granted Janssen's bid to extend the use of ustekinumab on 25 July 2013.[d,e,f] Media coverage of the EMA ruling included FirstWord Pharma.[g] Janssen summed up the impact of the CHMP ruling: "*It was with the exceptional guidance of Prof McInnes that this study medication was brought to phase III and CHMP approval for treatment of PsA … More importantly for the medical community, it represents the first new mechanism of action to achieve clinical and radiographic efficacy for this condition since the approval of anti-TNF agents approximately one decade ago.*"[a] Ustekinumab for treatment of PsA was approved by the Federal Drug Administration in September 2013.

Conservative estimates suggest that at least 0.5% of the EU population, approximately 2.5 million people, are likely to have PsA. Assuming half of these individuals will require treatment with a biologic DMARD, the potential uptake of ustekinumab for this novel indication could exceed 1.25 million patients across the 28 member states. Consequently, EMA approval of ustekinumab represents a breakthrough for individuals who might otherwise be left without treatment options for this devastating disease.

5. Sources to corroborate the impact

a. Statement from Senior Director, Immunology R&D, Johnson & Johnson (available on request)
b. Detailed description of PSUMMIT1 in the ClinicalTrials.gov database, NCT01009086
c. Coverage of PSUMMIT 1 at EULAR 2012 by Medscape (registration required – PDF available on request)
d. EMA assessment report, 2013 (PDF available on request)
e. CHMP meeting report, 2013
f. EMA summary of opinion, 2013
g. Coverage of EMA approval by FirstWord Pharma