Institution: University College London

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Hereditary autoinflammatory disease programme: from endogenous pyrogen to the NHS cryopryin associated periodic syndrome (CAPS) Treatment Service at UCL, Royal Free Hospital.

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

The UCL Centre for Amyloidosis and Acute Phase Proteins has identified the cause and treatment for the prototypical cryopryin associated periodic syndrome (CAPS), and subsequently for a range of other hereditary and acquired autoinflammatory disorders. As a result of the research, canakinumab was licensed for this condition. In recognition, NHS Specialised Services commissioned the UK CAPS Treatment Service in 2010 to deliver life-changing IL-1 blocking therapy to the national caseload of CAPS patients at UCL.

2. Underpinning research (indicative maximum 500 words)

The notion of autoinflammatory diseases, i.e. chronic multisystem inflammatory disorders without evidence of cell-mediated or humoral autoimmunity, emerged with the molecular characterisation in the late 1990s of two monogenic inherited periodic fever syndromes, familial Mediterranean fever (FMF) and the TNF-associated periodic syndrome (TRAPS), both of which are frequently complicated by the development of reactive systemic (AA) amyloidosis, causing renal failure and early death.

Professor Philip Hawkins and Dr Helen Lachmann began to characterise the phenotype of patients referred to the NHS National Amyloidosis Centre with AA amyloidosis of undetermined inflammatory aetiology in the late 1990s. They identified patients in whom there was evidence of familial autoinflammatory disease, notably including those conforming to the description of Muckle-Wells syndrome, a rare disorder characterised by urticarial rash, aching limbs, hearing loss and amyloidosis. In collaboration with Dr Michael McDermott at Bart's and the London, they performed a genome wide genetic linkage study during 2000 in an Indian family with Muckle-Wells syndrome, and identified a defect in the NLRP3 (formerly NALP3) gene, which was reported simultaneously by a US group to be associated with familial cold urticaria, an apparently different, less severe hereditary inflammatory disease **[1]**. Hawkins and Lachmann undertook a collaborative study with Professor Jurg Tschopp in Lausanne through 2001-03, which demonstrated increased activity of mutated NLRP3 in the interleukin-1 (IL-1) processing inflammasome pathway in myelomonocytic cells, suggesting that excessive IL-1 production may contribute to the pathogenesis of the disease **[4]**. Hawkins' team firmly validated IL-1 as a therapeutic target in patients with NLRP3 mutations in 2003 through the reverse translational approach by demonstrating rapid and complete remission of Muckle-Wells syndrome complicated by advanced amyloidosis following treatment with recombinant IL-1 receptor antagonist **[2,3]**.

Further genetic and clinical phenotyping studies by Hawkins and Lachmann confirmed that Muckle-Wells syndrome, familial cold urticaria (now known as familial cold autoinflammatory syndrome) and the apparently sporadic very severe congenital disorder known as chronic infantile neurological, cutaneous and articular syndrome (CINCA) constituted a continuous spectrum of inflammatory disease caused by mutations in NLRP3 (now also known as cyropyrin). They subsequently collaborated with Novartis from 2004 to 2009, resulting in the development of a fully humanised monoclonal anti-IL-1β antibody, canakinumab, which they demonstrated produces near complete resolution of inflammatory disease activity in virtually all patients with CAPS, and which they have latterly shown also has high efficacy in other acquitted and hereditary autoinflammatory disorders including TRAPS. Proof of concept clinical studies **[5]**, followed by a pivotal randomised controlled trial of canakinumab in CAPS led by Hawkins, resulted in the approval of this new biologic agent for this orphan indication in the US and EU **[6]**, and Phase II/III studies are now

underway in patients with TRAPS.

Further translational studies have shown that inappropriate acute or chronic activation of the innate immune system, mediated substantially by IL-1, contributes to many other acquired chronic disorders, ranging from rare entities such as Schnitzler syndrome, to numerous very common conditions potentially including diabetes mellitus, atherosclerosis and asthma

This work was recognised by the NHS National Specialised Services, the national organisation responsible for the commissioning of highly specialised clinical services (formerly the National Commissioning Group), in supporting a national diagnostic and management advisory service for inherited 'fever' disorders as part of the NHS National Amyloidosis Centre in 1999, and subsequently the UK CAPS Treatment Service in 2010 to deliver highly effective IL-1 blocking therapy to the national caseload of CAPS patients.

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

[1] Aganna E, Martinon F, Hawkins PN, Ross JB, Swan DC, Booth DR, Lachmann HJ, Bybee A, Gaudet R, Woo P, Feighery C, Cotter FE, Thome M, Hitman GA, Tschopp J, McDermott MF. Association of mutations in the NALP3/CIAS1/PYPAF1 gene with a broad phenotype including recurrent fever, cold sensitivity, sensorineural deafness, and AA amyloidosis. Arthritis Rheum. 2002 Sep;46(9):2445-52. http://dx.doi.org/10.1002/art.10509

[2] Hawkins PN, Lachmann HJ, McDermott MF. Interleukin-1-receptor antagonist in the Muckle-Wells syndrome. N Engl J Med. 2003 Jun 19;348(25):2583-4. http://dx.doi.org/10.1056/NEJM200306193482523

[3] Hawkins PN, Lachmann HJ, Aganna E, McDermott MF. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. Arthritis Rheum. 2004 Feb;50(2):607-12. http://dx.doi.org/10.1002/art.20033

[4] Agostini L, Martinon F, Burns K, McDermott MF, Hawkins PN, Tschopp J. NALP3 forms an IL-1beta-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder. Immunity. 2004 Mar;20(3):319-25. http://dx.doi.org/10.1016/S1074-7613(04)00046-9

[5] Lachmann HJ, Lowe P, Felix SD, Rordorf C, Leslie K, Madhoo S, Wittkowski H, Bek S, Hartmann N, Bosset S, Hawkins PN, Jung T. In vivo regulation of interleukin 1beta in patients with cryopyrin-associated periodic syndromes. J Exp Med. 2009 May 11;206(5):1029-36. http://dx.doi.org/10.1084/jem.20082481

[6] Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, Leslie KS, Hachulla E, Quartier P, Gitton X, Widmer A, Patel N, Hawkins PN; Canakinumab in CAPS Study Group. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med. 2009 Jun 4;360(23):2416-25. http://dx.doi.org/10.1056/NEJMoa0810787

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

Canakinumab was licensed for the treatment of CAPS, a new highly effective medicine for a rare orphan disease, in the EU **[a]** and the US in 2009 and in Japan in 2011 **[b]**. Data for licensing arose principally from the clinical trials led by Hawkins.

The NHS CAPS Treatment Service, established in 2010 as a result of Hawkins' research, and funded directly by the Department of Health, provides the national service for patients with autoinflammatory diseases, offering a clinical and genetic diagnostic service, and highly effective treatment with specific cytokine inhibitors **[c]**. Fifty patients with CAPS are currently receiving canakinumab treatment in the UK centre, at an annual cost of £3.6m, and nearly 300 patients are now being treated world-wide, 234 of whom have CAPS and the remainder having other autoinflammatory diseases **[d]**.

An international registry to document the safety and efficacy of canakinumab has been created **[e]**, to which Hawkins contributed design and serves as a member of the steering committee. Among the 241 CAPS patients enrolled on the registry, only two have discontinued treatment due to poor therapeutic response.

CAPS-causing mutations result in excessive production of interleukin 1β (IL-1β), which causes disabling multi-system inflammation from birth. Patients suffer severe fatigue, fever and muscle pains on a daily basis that mimic influenza, many symptoms of which are also caused by excessive IL-1β; clinical features include chronic anaemia and inflammation in the skin, eyes, joints and brain that presents as rashes, conjunctivitis, arthritis, chronic meningitis, blindness, deafness and in some cases cognitive impairment. About 25% of patients develop AA amyloidosis that results in kidney failure and death within 5-10 years. Growth and development are impaired, and puberty is delayed as a result of chronic severe inflammation. Patients with CINCA, the most severe CAPS phenotype, often die before adulthood.

Treatment of CAPS with the monoclonal IL-1β antibody, canakinumab, results in complete or near-complete remission of the disabling inflammation that affects the skin, eyes, joints and brain and causes the major flu-like symptoms and fevers. The overwhelming fatigue that impedes employment and social activities is abolished, corroborated in clinical studies through normalisation of the SF-36 quality of life and FACIT-F© fatigue scores. In the long term, there is every expectation that continued treatment with canakinumab will prevent the skeletal deformities, blindness, deafness and amyloidosis that commonly occur. Catch-up growth and age-appropriate sexual maturation have been observed in adolescents with CAPS who have been treated with canakinumab.

Feedback from patients treated with canakinumab **[f]** includes:

> *"I could not have imagined such a change in fortune due to this drug..."*
>
> *"My whole body ached, I had difficulty walking and had to be carried to bed. I missed a lot of school with severe headaches, and could not even have a bath due to the rash. I cannot believe the effect of this drug, my symptoms have completely disappeared."*
>
> *"My joints and whole body would swell right up, and I would itch until I would bleed, and had terrible migraines. I am now NORMAL!!!"*
>
> *"My joint inflammation and pains have completely disappeared"*
>
> *"My daughter had terrible headaches, conjunctivitis, and rashes, and was hardly able to get of bed. She was shunned at school, and put in a remedial class. It got so bad she took an overdose. After the drug all the symptoms vanished; she is happy and alive for the first time, and is now working and has her first boyfriend at 20 years old!"*
>
> *"Joints were excruciating, and now the symptoms have disappeared"*
>
> *"The effects have been absolutely life changing for me".*
>
> *"This is a wonder drug".*

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

[a] European Medicines Agency Evaluation of Medicines for Human Use, July 2009: CHMP assessment report for canakinumab. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001109/WC500031679.pdf

[b] Press releases on approval of canakinumab (tradename Ilaris)

- In US, 2009: http://www.drugs.com/newdrugs/new-biological-therapy-ilaris-approved-us-children-adults-caps-serious-long-auto-inflammatory-1472.html
- In Japan, 2011: http://www.novartis.com/newsroom/media-releases/en/2011/1550036.shtml

[c] National Specialised Commissioning Team Service Specification 2012/13: National treatment service for Cryopyrin Associated Periodic fever Syndromes (CAPS). http://www.specialisedservices.nhs.uk/library/36/Service_Specification_and_Standards___Cryopyrin_Associated_Periodic_fever_Syndromes_CAPS_2.pdf

[d] Patient numbers can be confirmed by Commissioning Support Manager, Royal Free Hospital. Contact details provided.

[e] International registry to document the safety and efficacy of canakinumab is at https://www.bconfidentregistry.com. β-Confident is a global, multicentre, prospective, observation registry study of patients diagnosed with CAPS and treated with canakinum A recent publication is: Tilson H, Primatesta P, Kim D, Rauer B, Hawkins PN, Hoffman HM, Kuemmerle-Deschner J, van der Poll T, Walker UA. Methodological challenges in monitoring new treatments for rare diseases: lessons from the cryopyrin-associated periodic syndrome registry. Orphanet J Rare Dis. 2013 Sep 10;8(1):139. http://dx.doi.org/10.1186/1750-1172-8-139

[f] Statements from patients with CAPS whose lives have been transformed by treatment with canakinumab. Copies available on request.