Institution: University College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Tocilizumab – a new treatment for Rheumatoid Arthritis in adults and Juvenile Idiopathic Arthritis in children

1. Summary of the impact

Research at UCL into the use of tocilizumab has led to a new treatment and improved care for patients with juvenile idiopathic arthritis (JIA) and rheumatoid arthritis (RA) in adults. The drug is now approved around the world and recommended by NICE guidelines and is the standard of care in children with systemic onset JIA. It has been prescribed in every rheumatology centre in the UK for patients with severe RA. The impact of the drug on patients is to prevent disability, halt joint damage, improve function and increase quality of life.

2. Underpinning research

Context: Juvenile idiopathic arthritis (JIA) is the most common rheumatological inflammatory disease of children, affecting ~15,000 children in the UK. The most severe form of JIA is systemic onset (sJIA) accounting for around 10% of all JIA patients. This sub-type can cause joint pain, damage, blindness, disability and even death, as well as long term sequelae (poor growth, low bone density). sJIA is associated with potentially fatal complications such as macrophage activation syndrome. Some problems such as growth delay and osteoporosis also arise from steroids, which may be necessary to treat life-threatening aspects of sJIA or very severe arthritis. The level of disability which progresses into adulthood often results in long-term dependence. Rheumatoid arthritis in adults is a separate condition but shares many features with JIA, notably joint pain, destructive joint inflammation with consequent disability and systemic complications which if left untreated can be serious or rarely life-threatening; similarly, treatment can be limited due to adverse effects or loss of effectiveness.

Early translational work: Interleukin (IL)-6 is a powerful driver of inflammation and is produced in response to infection. The UCL group led by Professor Woo were the first in 1998 to demonstrate that specific genetic variations in the genes that control production of IL6 were present in patients with sJIA and that these variations were associated with elevated levels of IL6 in the blood of these patients **[1]**. A further study in 2003 Woo's group defined these genetic abnormalities of IL6 genes in more detail in different families **[2]**. These robust scientific studies underpinned the rationale for subsequent clinical studies targeting IL6 as a treatment for sJIA.

Early Clinical Studies: Tocilizumab is a monoclonal antibody targeted toward the IL6-receptor. In 1999, UCL was one of two UK centres running a study into the use of tocilizumab in adult patients, and the first outside of Japan to treat adult patients with RA with this drug **[3]**. This work was published in 2002 and showed the range of doses of toculizumab that had beneficial effects to reduce joint inflammation. In 2005, Woo led the first clinical, early (phase II) study outside of Japan that investigated escalating doses of the drug in sJIA **[4]**. This proof-of-principle study was run by UCL as lead centre with additional centres recruiting in Birmingham (UK) and France. The escalating protocol was based on the adult trial described above. Of the 18 children who participated in the study, 11 were recruited by the UCL lead site.

Late-Phase Clinical Study: The early phase dose escalation study (ref [3]) informed a phase III, multi-centre, international study investigating the safety and efficacy of tocilizumab in sJIA. This represents the largest randomised, placebo-controlled study ever in this relatively rare disease group and in total 112 children participated. This study was conducted over five years in 43 participating centres around Europe. In total UK contributed eight patients of whom five were from UCL/ICH. This study unequivocally demonstrated clear efficacy of tocilizumab in sJIA **[5]**.

3. References to the research

[1] Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, Woo P. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest. 1998 Oct 1;102(7):1369-76. http://dx.doi.org/10.1172/JCI2629.

[2] Ogilvie EM, Fife MS, Thompson SD, Twine N, Tsoras M, Moroldo M, Fisher SA, Lewis CM, Prieur AM, Glass DN, Woo P. The -174G allele of the interleukin-6 gene confers susceptibility to systemic arthritis in children: a multicenter study using simplex and multiplex juvenile idiopathic arthritis families. Arthritis Rheum. 2003 Nov;48(11):3202-6. http://dx.doi.org/10.1002/art.11300

[3] Choy EH, Isenberg DA, Garrood T, Farrow S, Ioannou Y, Bird H, Cheung N, Williams B, Hazleman B, Price R, Yoshizaki K, Nishimoto N, Kishimoto T, Panayi GS. Therapeutic benefit of blocking interleukin-6 activity with an anti-interleukin-6 receptor monoclonal antibody in rheumatoid arthritis: a randomized, double-blind, placebo-controlled, dose-escalation trial. Arthritis Rheum. 2002 Dec;46(12):3143-50. http://dx.doi.org/10.1002/art.10623

[4] Woo, P, Wilkinson, N, Prieur, AM, Southwood, T, Leone, V, Livermore, P, Wythe, H, Thomson, D, and Kishimoto, T. Open label phase II trial of single, ascending doses of MRA in Caucasian children with severe systemic juvenile idiopathic arthritis: proof of principle of the efficacy of IL-6 receptor blockade in this type of arthritis and demonstration of prolonged clinical improvement. Arthritis Res Ther, 2005. 7(6): R1281-8. http://dx.doi.org/10.1186/ar1826

[5] De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, Cuttica R, Ravelli A, Schneider R, Woo P, Wouters C, Xavier R, Zemel L, Baildam E, Burgos-Vargas R, Dolezalova P, Garay SM, Merino R, Joos R, Grom A, Wulffraat N, Zuber Z, Zulian F, Lovell D, Martini A; PRINTO; PRCSG. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012 Dec 20;367(25):2385-95. http://dx.doi.org/10.1056/NEJMoa1112802.

4. Details of the impact

The research described above underpins the routine use in clinical practice of tocilizumab for patients with sJIA and RA. Widespread use of the drug is reflected by the high levels of sales reported by manufacturers Roche, who report 496m CHF (£335m) in sales of the drug in just the first half of 2013 (up 33% on the previous year, due to increasing demand) **[a]**.

Rheumatoid Arthritis (RA): Our 2002 paper was the first randomised controlled trial showing that inhibition of IL-6 significantly improved the signs and symptoms of RA and normalised the acute-phase reactants. The first phase III study (CHARISMA **[b]**) built on our work, citing ref [3] as the proof-of-concept, randomised, controlled, dose escalation study upon which its design was based. This trial is in turn cited by all of the later phase clinical studies that ultimately led to tocilizumab being approved by the EMA in January 2009 **[c]** and by the FDA in January 2010 **[d]** for use in RA. NICE approved its use within the UK in August 2010 **[e]**.

Since this date tocilizumab has been prescribed in every rheumatology centre in the UK for patients with severe RA. There is evidence that tocilizumab halts joint damage, improves function and increases quality of life **[f]** and hence allows engagement with employment. This is articulated well by one patient with RA treated with tocilizumab, highlighted in a case study from the National Rheumatoid Arthritis Society, who was able to return to work as a result **[g]**.

Around 690,000 people (~1% population) in the UK have RA. At University College London Hospital (UCLH) around 25% of patients with RA are treated with a biologic drug, of whom around 10-15% receive tocilizumab (amounting to around 50 patients) where other biologic treatments have failed. Extrapolating more widely, this suggests that between 15,000 and 20,000 patients with RA may be being treated with tocilizumab within the UK, and hundreds of thousands worldwide.

sJIA: The initial basic science work of Prof Woo and the first early-phase clinical study led by UCL underpinned the large phase III study by De Benedetti el al published in the NEJM in 2012, to which UCL was the largest UK contributor. This seminal phase III study (also known as the TENDER trial) has ultimately led to tocilizumab being licensed for use in sJIA by the FDA in May 2013 **[h]** and by the EMA in June 2013 **[i]**. It is adopted as treatment for sJIA around the world.

The National Institute for Health and Clinical Excellence (NICE) recommended use of tocilizumab for sJIA in a technology appraisal in December 2011 **[j]**. This was based on data presented in abstract form by De Benedetti et al. prior to the NEJM publication of the full article in 2012. This reflects how compelling the data were and the potential severity of the condition thus warranting guidelines to be issued prior to publication of the full article.

The use of tocilizumab for sJIA has also been endorsed by the British Society of Paediatric and Adolescent Rheumatology (BSAPR) and incorporated into their national standards of care **[k]**. Hence this is now in routine use within clinical practice for sJIA and offers patients with this severe condition another option in case they do not respond to standard treatment with methotrexate.

Impact on patients with sJIA treated with tocilizumab: Data from the national registry of patients being treated with tocilizumab have not been published yet, but based on the prevalence of JIA and the proportion of those with sJIA refractory to methotrexate it is likely to run into the many hundreds. At Great Ormond Street Hospital and UCLH there are currently 21 children and adolescent patients being treated with tocilizumab who would otherwise have had active disease with its potential problems and most likely would have been on high dose steroids and suffering the complications of this also.

There is now evidence to demonstrate that tocilizumab halts radiological structural damage of the joints in patients with sJIA **[l]**. There is a direct relationship between prevention of joint damage and preservation of function. There is also evidence that tocilizumab restores normal growth velocity, which is typically impaired in active sJIA **[m]**. The preservation of joints and hence function coupled with the restoration of normal growth in children with sJIA being treated with tocilizumab all point towards less disability in these patients and hence less dependence on healthcare and social services as they progress into adulthood. Hence biologic treatment has transformed the long-term outcome of these patients as in the pre-biologic era, sJIA was associated with the worst disabilities and outcomes in adults **[n]**. This prevention of disability is more likely to lead to patients being able to engage in active employment. This extrapolation is supported by long-term outcome data showing that adults with childhood onset arthritis are more likely to be employed if they have good function, which occurs if arthritis is better controlled during childhood due to prevention of damage to joints **[o]**.

5. Sources to corroborate the impact

[a] Roche Half-Year Report 2013: http://www.roche.com/hy13e.pdf

[b] Maini RN, Taylor PC, Szechinski J, Pavelka K, Bröll J, Balint G, Emery P, Raemen F, Petersen J, Smolen J, Thomson D, Kishimoto T; CHARISMA Study Group. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum. 2006 Sep;54(9):2817-29. http://dx.doi.org/10.1002/art.22033

[c] EMA approval for toculizumab for adults

[d] Roche announce FDA approval for toculizumab for adults with RA: http://www.roche.com/media/media_releases/med-cor-2010-01-11.htm

[e] NICE Technology Assessment 198. Tocilizumab for rheumatoid arthritis. http://guidance.nice.org.uk/TA198

[f] Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland AM, Vernon E, Ambs P,

Fleischmann R. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum. 2011 Mar;63(3):609-21. http://dx.doi.org/10.1002/art.30158.

[g] National Rheumatoid Arthritis Society http://www.nras.org.uk/about_rheumatoid_arthritis/living_with_rheumatoid_arthritis/case_studies/female/my_experiences_on_tocilizumab.aspx

[h] Roche press release about the approval of tocilizumab for JIA, stating that "*This approval was based on positive data from a Phase III study known as TENDER*." http://www.roche.com/media/media_releases/med-cor-2011-04-18.htm

[i] http://www.arthritisresearchuk.org/news/general-news/2013/june/tocilizumab-approved-in-europe-to-treat-rare-childhood-arthritis.aspx

[j] NICE TA238. Tocilizumab for rheumatoid arthritis. Aug 2010 http://www.nice.org.uk/ta198 http://www.nice.org.uk/nicemedia/live/13627/57489/57489.pdf.

[k] British Society for Paediatric and Adolescent Rheumatology Standards of care in JIA http://bspar.org.uk/downloads/clinical_guidelines/Standards_of_Care.pdf

[l] Inaba Y, Ozawa R, Imagawa T, Mori M, Hara Y, Miyamae T, Aoki C, Saito T, Yokota S. Radiographic improvement of damaged large joints in children with systemic juvenile idiopathic arthritis following tocilizumab treatment. Ann Rheum Dis. 2011 Sep;70(9):1693-5. http://dx.doi.org/10.1136/ard.2010.145359

[m] Yokota S, Imagawa T, Mori M, Miyamae T, Takei S, Iwata N, Umebayashi H, Murata T, Miyoshi M, Tomiita M, Nishimoto N, Kishimoto T. Long-term treatment of systemic juvenile idiopathic arthritis with tocilizumab: results of an open-label extension study in Japan. Ann Rheum Dis. 2013 Apr;72(4):627-8. http://dx.doi.org/10.1136/annrheumdis-2012-202310.

[n] Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. Rheumatology (Oxford). 2002 Dec;41(12):1428-35.

[o] Malviya A, Rushton SP, Foster HE, Ferris CM, Hanson H, Muthumayandi K, Deehan DJ. The relationships between adult juvenile idiopathic arthritis and employment. Arthritis Rheum. 2012 Sep;64(9):3016-24. http://dx.doi.org/10.1002/art.34499.