THINK RHEUMATOID ARTHRITIS: CAUSES, CONSEQUENCES, AND MANAGEMENT

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MEETING SUMMARY

Prof Josef Smolen opened the symposium and briefly described the aims of the meeting. Co-host Prof Constantino Pitzalis first discussed the pathophysiology of rheumatoid arthritis (RA), identifying the pro-inflammatory cytokines involved and explaining why specific drugs only work in certain conditions. Prof Simon Jones followed with a discussion on comorbidities and adverse events associated with interleukin (IL)-6 intervention in rheumatic disease. Dr Frank McKenna presented on the psychological impact of RA, including mood changes and development of depressive disorders, and Prof Smolen described the upcoming therapeutic approaches for the condition while also comparing and contrasting existing treatment options. The symposium concluded with a question and answer session.

Pathophysiology of Rheumatoid Arthritis

Professor Costantino Pitzalis

RA is a chronic inflammatory condition characterised by proliferative synovitis, which normally involves angiogenesis, infiltration of lympho-monocyte cells, and production of pro-inflammatory cytokines, and leads to chronic destruction of the joint. Because the disease is heterogeneous, it is important to understand what accelerates destruction of the joints in some patients and not others to ensure that appropriate treatment can be directed at those patients.
The disease can be divided into pre-clinical and clinical phases. In the pre-clinical phase, the development of RA involves a complex interplay between genotype, environmental triggers, and chance. Genetic predisposition to RA and encounters with some environmental insults, such as an infection, can lead to immunological dysfunction and initiate the production of auto-antibodies, such as anti-cyclic citrullinated peptide (anti-CCP) or rheumatoid factor antibodies. Auto-antibodies can be silent for up to 15 years, thus, patients may have systemic autoimmunity but show no symptoms. Some patients may then progress to an aggressive form of the disease, while others may have a mild form of RA.

At present, there is no cure for RA, which is why identifying immune-dominant initiating factors, understanding what leads to the diverse disease evolution in some patients and not others, and why some patients respond to particular treatment while others do not, could be crucial to effectively stopping joint damage with first-line treatment.

Genome-wide analyses identify risk alleles associated with immune signalling involved in RA. These include nuclear factor-κB-dependent signalling and T cell stimulation, activation, and functional differentiation alleles. Environmental factors that may trigger the disease include infection (Epstein-Barr virus, parvovirus, cytomegalovirus, Escherichia coli, or Proteus bacterial species), trauma, smoking, and gastrointestinal microbiome. Another trigger is altered post-transcriptional regulation: all patients with RA have dysregulated citrullination of peptides which means proteins are no longer recognised as ‘self’ as they are secreted, leading to auto-antibody production/autoimmunity. Although all these triggers are known, it is unclear which one(s) drive the disease. Loss of tolerance to certain proteins leads to aberrant immune response to ‘self’ proteins in the regional lymph nodes and secondary lymphoid organs: antigen-presenting dendritic cells present ‘self’ antigens to specific major histocompatibility complex II molecules, driving the production of pro-inflammatory cytokines, activating T cells which in turn activate B cells to produce auto-antibodies, a characteristic feature of RA.
Auto-antibodies can form larger immune complexes that can further stimulate the production of pro-inflammatory cytokines, including tumour necrosis factor (TNF-α), through complement and Fc-receptor activation. The production of anti-CCP antibodies is a key event in RA and it has been shown that the titre of the anti-CCP antibody rises dramatically before the development of clinically apparent disease. Low titres of these antibodies may be present in patients with RA and then suddenly rise rapidly and trigger RA. Auto-antibodies most likely bind citrullinated antigens within the joint itself, forming new complexes that initiate an inflammatory escalation. A non-specific infection or trauma, for example, may lead to the arrival of dendritic cells or neutrophils into the joint presenting citrullinated auto-antigens. Since the patient has systemic autoimmunity, the auto-antibodies bind these antigens locally. Further immunological response then progresses to pro-inflammatory cytokine production via T cell and macrophage activation, as well as differentiation of some T helper cells that induce B cells to produce more auto-antibodies locally.

In the acute phase response, IL-6 has the greatest effect on acute-phase protein levels leading to synthesis of proteins such as fibrinogen, C-reactive protein (CRP), hepcidin, and serum amyloid A. The response further leads to the activation of endothelial cells and subsequently angiogenesis. Moreover, activation of osteoclasts results in bone erosion, while inhibition of chondrocyte metabolism causes cartilage damage (Figure 1).

Various drugs target different cytokines (e.g. TNF-α and IL-6 blockers), yet the response pattern is the same for the treated patients: around 60% of patients achieve a 20% improvement in symptoms, 40% of patients experience a 50% improvement, and 20% of patients show 70% improvement in symptoms after treatment. This may indicate that the population of patients treated is very resistant and requires new medication, or that alternative mechanisms are at work. Adherence to treatment may be an issue, as well as formation of anti-drug antibodies.

Taking a biopsy of the diseased tissue would provide a molecular and histological

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**Figure 2: Identification of tissue pathotypes (digital pathology).**

H&E: haemotoxylin and eosin stain.
characterisation that could identify the pathway driving the disease in specific patients. To date, three different synovial pathotypes have been identified: a lymphoid pathotype in which there are many B cells, which form large aggregates in disease tissue of patients never treated with disease-modifying anti-rheumatic drugs (DMARDs); a myeloid pathotype characterised by high inflammation and virtually no B cells; and a fibroid pathotype that involves very little inflammatory infiltrate (Figure 2), driven by cell types other than immunological cells.

Biopsy is a complex and invasive procedure for the patient, so it is important to also evaluate peripheral blood for biomarkers. A study in the USA has shown that the defining circulating biomarkers are soluble intercellular adhesion molecule 1 (ICAM1) and chemokine (C-X-C motif) ligand 13 (CXCL13); these are expressed at highest levels in the myeloid and lymphoid phenotypes, respectively. In a head-to-head comparison of adalimumab versus tocilizumab, nearly 70% of patients with high levels of CXCL13 and low levels of ICAM1 treated with tocilizumab achieved a 50% improvement in the condition.

Comorbidities and Adverse Events Associated with Interleukin-6 Intervention in Rheumatic Disease

Professor Simon Jones

Of the number of drugs that target inflammatory cytokines, either directly or through their signalling receptors, each has a unique mode of action and individual pharmacodynamic properties that impact the way the drug works within a clinical setting. These drugs are very effective at targeting inflammation, thus also possibly affecting host defence, behaviour, and wellbeing.

In inflammatory arthritis, IL-6 is a primary driver of inflammation. Early studies have shown that mice deficient in IL-6 and challenged to become arthritic, were actually resistant to the pathology. Other evidence from when the anti-IL-6R receptor blocking monoclonal antibody tocilizumab was introduced has shown that IL-6 is a major component both in the regulation of inflammatory outcomes (acute phase response) and the immune activation processes. IL-6 is fundamentally linked with the control of cell survival and apoptotic mechanisms. It is also heavily associated with the differentiation of T cells, and has the ability to promote proliferation of certain cell types such as B cells.

Currently, there are a number of different drugs targeting IL-6, although only tocilizumab is approved for the treatment of RA. These include very specific anti-IL-6 blockers and anti-IL-6R blockers, and less selective Janus kinase (JAK) inhibitors, soluble IL-6 receptor (sIL-6R) blockers, and signal transducer and activator of transcription (STAT) 3 blockers. These drugs affect downstream events such as transcription factors and signalling pathways, which are regulated as a consequence of engagement of IL-6 with its receptor complex.

While IL-6 is a primary driver of RA outcomes, it is a wider acting cytokine that plays a role in adaptive and innate immunity. Under normal homeostasis, IL-6 is also involved in physiological responses. It is controlled partly by circadian rhythms, regulating glucose metabolism, lipid and iron transport, bone turnover, appetite, neuropsychological behaviour, and other mechanisms. Therefore, targeting IL-6 pathways not only targets its ability to control inflammation, but also much more systemic processes in the body. For example, intervention with tocilizumab shows interference with normal homeostasis observed through serum lipid changes. In patients with active RA, systemic CRP levels are elevated as part of the acute response, while there is a decrease in levels of triglycerides and cholesterol. When this decrease is controlled by biologic intervention (such as tocilizumab), CRP and serum amyloid A levels normalise, but an increase in circulating lipids is observed.

There are two modes of IL-6 signalling that are activated in the body as part of the immune response: classical IL-6 receptor signalling and IL-6 trans-signalling. In classical signalling, released IL-6 binds to a membrane receptor which consists of an α-chain IL-6 receptor (non-signalling by nature). It couples with a second β-subunit, glycoprotein 130 (gp130), which elicits the signal. The IL-6 receptor is confined to subsets of leukocytes, hepatocytes, and epithelial cells. However, the gp130 molecule is more highly expressed and is found on every cell type in the body. It is also known that IL-6 receptor (α-chain) is released into circulation at about 25–35 ng/mL and has the capacity to bind IL-6. This heterodimeric complex can then activate cell types that express gp130 on their cell surface.
broadening the repertoire of cells that become responsive to IL-6. In terms of RA, structural cells within the joint primarily express gp130 but lack the IL-6R (found on inflammatory cells arriving at the site of inflammation) on their cell surface. sIL-6R/IL-6 complexes can then activate gp130 (trans-signalling). There is also a form of soluble gp130 (200–400 ng/mL) which can only bind sIL-6R/IL-6 complexes, thus acting as a natural antagonist in this particular system. In murine models of RA, when soluble gp130 is added to wild-type mice, disease activity is inhibited.

While it may appear that trans-signalling plays a greater role in inflammation and classical signalling controls homeostatic mechanisms, the roles may be reversed as well (e.g., acute response in classical mode, and sleep and haematoxylenes control via the trans-signalling pathway). One example of this dual nature is the role of IL-6, acting through its receptor, in controlling activities in the liver, such as glycogen consumption and regeneration. Under the control of IL-6 or IL-R blockade, there is an effect on iron transport linking the blockade to anaemia. Liver enzymes (aspartate aminotransferase/alanine transaminase) are also elevated in some patients, indicating liver damage; adding IL-6 to some experimental liver models shows that animals can actually be protected from liver damage with this wide-acting cytokine.

Studies of gastric tumours showed that any impact that distorts the control of IL-6 signalling is likely to influence homeostatic control of the regenerative process within the gut and lead to a loss of mucosal integrity (diverticulitis), gastric perforation, and other complications currently linked with tocilizumab and IL-6 intervention. Studies show that IL-6 plays an important role in controlling barrier maintenance (similarly to controlling infections). Recurrent episodes of infection are important for driving the IL-6 involvement in steering the adaptive immunity, promoting or enhancing antimicrobial defence. At the same time, the effect may be detrimental and drive tissue injury and damage.

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The Psychological Impact of Rheumatic Disease

Doctor Frank McKenna

The most commonly observed comorbidity in RA patients is depression. A study of almost 4,000 patients across Europe has shown a 15% prevalence in this psychological condition. A meta-analysis by Matcham et al. demonstrated that in a group of patients with a score of >11 in the Hospital Anxiety and Depression Scale (HADS), 15% of patients with RA were also depressed. However, with the group of patients that scored HADS >8, about one-third had some psychological aspect to their illness.

Depression appears to be a similar risk factor for mortality as respiratory disease and only slightly less than cardiovascular disease or malignancy. A study from India showed a positive correlation of about 0.45 between the Disease Activity Score 28 (DAS28) in patients with RA and severity of depression, indicating a moderate linear relationship between the two conditions. The relationship was also shown through disability indices such as the Health Assessment Questionnaire (HAQ). Interestingly, sleep disturbances in RA patients appear to reduce the pain threshold. A study of nine healthy volunteers deprived of sleep over a 6-day period showed changes in their pain threshold, particularly when limiting their slow wave (deep) sleep. In just over 100 patients with moderate or active RA, all on methotrexate (MTX), there was a close correlation between the visual analogue scale of pain and the Pittsburgh Sleep Quality Index (r=0.65). A similar correlation was also shown between sleep deprivation or disturbance and fatigue in RA (r=0.63). A study by Nicassio et al. demonstrated how pain, depression, and also income contribute to sleep disturbance in RA. Given that many people with RA lose their work due to the disease, lower or no income further exacerbates the psychological condition of these patients.

In patients with fibromyalgia, there was a likely correlation between arthritic pain, depression and anxiety, and sleep quality. Patients with fibromyalgia have many more psychological problems. They often sleep poorly and feel sleepy when awake, which also relates to patients with RA who wake with pain. In RA patients who already have depression and anxiety, their sleep quality relates to them having disturbed sleep, which is not the case for patients with fibromyalgia. The latter perceive sleep quality and sleepiness differently, and sleepiness is associated with other factors, some of which relate to their mood, particularly due to reduction in the slow-wave and rapid eye movement sleep stages. Patients with fibromyalgia do not stay in the stable sleep stage, may have a high DAS28 even though they may have no...
inflammatory disease, and have no tenderness in their joints, like in RA, but are tender everywhere. 

About 15% of RA patients, however, have secondary fibromyalgia or fibromyalgic RA (FRA). Compared with patients with RA only, patients with FRA experience more insomnia, mood disturbance, diffuse pain, and more tender joints, and thus show higher DAS scores. Patients with FRA are often treated with more biologics and show less erosion and rheumatoid factor. In the USA, a multi-biomarker disease activity (MBDA) score has been developed that contains 12 different factors. MBDA score correlates strongly with levels of CRP and swollen joints. Patients with FRA score higher MBDA and receive more treatment. Ultrasound data for these patients account not for the inflammatory markers, but for the amount of disease activity, which is greater in FRA. Another study by Pollard et al. showed that FRA affects 12–17% of RA outpatients and results in worse functional outcomes, but DAS28 scores over-interpret active disease in FRA.

**Upcoming Therapeutic Approaches in Rheumatoid Arthritis**

**Professor Josef Smolen**

Currently, the American College of Rheumatology 70% improvement criteria (ACR70) rates are similar between different biologics treating RA. For all agents (including MTX, abatacept, golimumab, tocilizumab, and rituximab), with increasing drug experience there is a decreased response. ACR70 rates were achieved in 30–45% of MTX-naive patients, in 20% of MTX-experienced, and finally in 10% of anti-TNF-experienced patients. After treatment with MTX and three biological agents, about 50% of patients still showed insufficient response. Patients who did not respond to anti-TNFs displayed 10-12% response to all other biological agents.

While there are only two drugs, abatacept and rituximab, for T cell and B cell directed mode of action, respectively, there are five compounds (infliximab, etanercept, adalimumab, certolizumab, and golimumab) and three European Medicines Agency (EMA)-approved biosimilar TNF inhibitors (including infliximab [CT-P13]) for the treatment of RA. For IL-6 inhibition, there is only one drug available on the market, tocilizumab. There is also one IL-1 inhibitor, anakinra, which does not appear to be efficacious.

A new human monoclonal antibody to IL-6, sirukumab, has been investigated in a multicentre, randomised, double-blind, placebo-controlled, parallel-group study that will last 104 weeks with a 16-week follow-up. More than 1,600 patients with active RA (of at least 8 years duration) despite DMARD therapy, have been randomised (1:1:1) to sirukumab 100 mg once every 2 weeks (q2w), 50 mg once every 4 weeks (q4w), and placebo.

**Figure 3: Radiographic data.**

*p<0.001 versus placebo based on Van Der Waerden analysis of variance. Based on imputed values by EE rules and then missing data rules. VdH-S: Van der Heide/Sharp; mITT: modified intention-to-treat; q4w: once every 4 weeks; q2w: once every 2 weeks; EE: early escape; PBO: placebo; SIR: sirukumab.
At baseline, patients had high CRP levels, more than 80% were auto-antibody positive with a HAQ score of 1.5–1.6, and DAS28-CRP scores of around 5.9. This was a population of patients with severe torn joint damage and a high propensity to develop progression of joint damage. A dramatic and fast reduction in radiographic progression was observed after 6 months and sustained through 1 year of treatment. Around an 88% reduction was observed in the 100 mg q2w group at Week 52 (Figure 3).

In comparison, in the LITHE study of tocilizumab (this is not a head-to-head comparison and scores are also different), 70–74% inhibition of progression of joint damage was observed over 1 year. In the sirukumab study, almost 60% of patients achieved American College of Rheumatology 20% improvement criteria at Week 16 and maintained the response over a year. American College of Rheumatology 50% improvement criteria results were similar to those in the LITHE study, with 30–33% of patients achieving the response (versus 12% on placebo).

In terms of remission rates (measured by the Clinical Disease Activity Index [CDAI]), a significant difference was observed between sirukumab and placebo: 3-times as many patients on the study drug achieved remission. The same pattern was observed for CDAI in low disease activity. Changes in HAQ scores were also significant compared with placebo (p≤0.001), while the mean change in physical and mental components of the short-form 36 questionnaire was more than twice as much in the treatment group as in the placebo arm. Fatigue was also significantly improved in treated patients compared with those on placebo (p<0.001). IL-6 affects fatigue and mood in RA by influencing the hypothalamic pituitary adrenal axis, explaining why when a patient is infected and/or experiencing inflammation, they feel more tired.

In terms of safety, 3.1% of patients on placebo, and 2.9% (50 mg) and 4.7% (100 mg) of patients treated with sirukumab experienced more than one serious adverse event at 18 weeks. The rates of serious infections were 2.6% (placebo), 4.6% (50 mg), and 3.8% (100 mg) per 100 patient-years. The rate of cardiovascular events was higher in the 50 mg arm but similar between the placebo and 100 mg groups at 52 weeks. It is unclear whether the different results for the two sirukumab doses were due to therapy or a chance occurrence.

Overall, in DMARD-inadequate responders, sirukumab 50 mg q4w and 100 mg q2w reduced signs and symptoms of RA, inhibited radiographic progression, and improved health-related quality of life. Both co-primary endpoints and all major secondary endpoints were met, with both sirukumab doses showing statistically significant improvements compared with placebo.

In summary, RA is a heterogeneous disease that would benefit from stratifying patients based on pathotype and blood biomarkers allowing for more targeted and efficacious treatment. The mode of action of a particular drug has its benefits and side effects, and it is important to understand why a drug displays many specific characteristics in various processes, which are sometimes considered comorbidities or adverse events. There is increased morbidity and mortality in patients with RA who have psychological symptoms related to sleep, depression, fatigue, and pain, complicating disease assessment further. A new anti-IL-6 monoclonal antibody drug, sirukumab, showed promising efficacy and safety profiles, consistent with the known profile of existing anti-IL-6 treatment for RA.

REFERENCES


