PRECISION MEDICINE: MAXIMISING TREATMENT BENEFIT FOR RHEUMATOID ARTHRITIS PATIENTS

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Chairperson

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MEETING SUMMARY

This educational symposium was opened by Prof Ernest Choy, who introduced the concept of precision medicine and highlighted the importance of integrating current research with clinical experience to guide treatment decisions. He also highlighted the growing recognition of precision medicine within rheumatology. Prof Eric Ruderman then explored current medical views around the use of glucocorticoids (GCs) in rheumatoid arthritis (RA), revealing how uncertainty over the true risk/benefit ratio of these agents means that their impact as part of patient care must be further studied. Next, Prof Cem Gabay reviewed the evidence from clinical trials, registries, and real-world studies supporting biologic monotherapy as a treatment strategy in patients for whom methotrexate (MTX) is inappropriate. Prof Georg Schett then considered how current biomarker research might influence patient care in the future, especially with respect to assessing disease course and treatment responses in RA. Finally, Prof Choy presented a series of patient case studies, featuring practical issues faced by rheumatologists in the clinic, and drew upon the themes of the preceding presentations to highlight the value of a precision medicine approach to RA. Following closing remarks from Prof Choy, a lively discussion session enabled the audience to ask the expert panel about the wider clinical implications of their views.

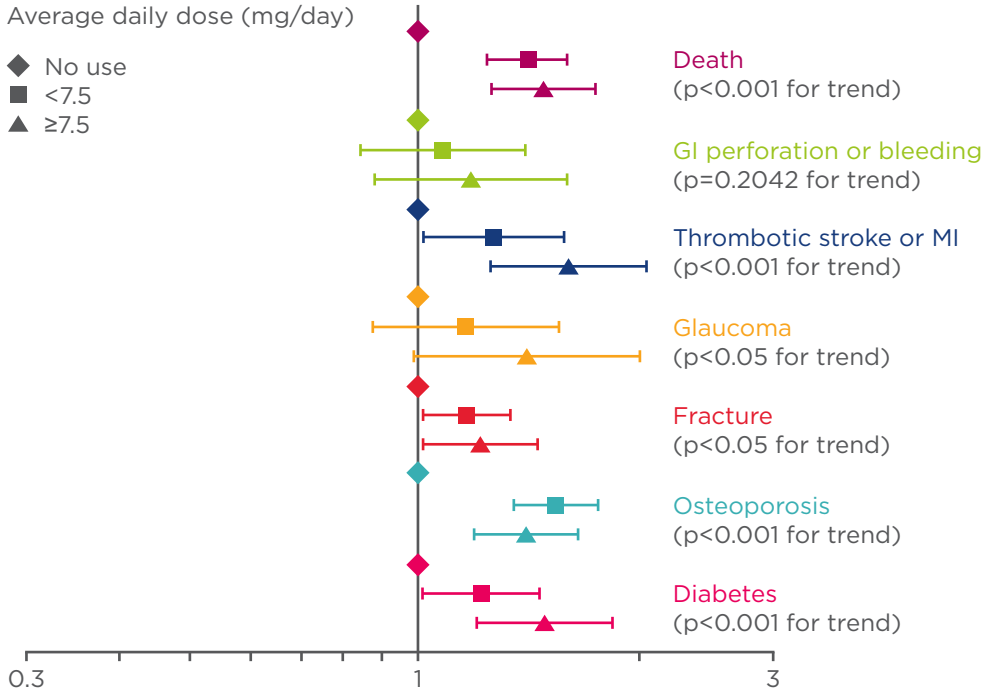

Figure 1: Increased risk of serious adverse effects associated with glucocorticoid use in UK population-based study.[11]

Forest plot displaying the adjusted odds ratio with 95% confidence intervals for the outcomes of interest with increasing average oral glucocorticoid use in patients with rheumatoid arthritis.

GI: gastrointestinal; MI: myocardial infarction.

Welcome and Introduction

Professor Ernest Choy

Precision medicine means providing the best available healthcare by identifying the needs and maximising the outcomes of individual patients. Recognition of precision medicine in the field of rheumatology is growing.[1,2] This approach not only integrates current research and clinical practice, but also requires close partnership and communication with the patient.

The current European League Against Rheumatism (EULAR) recommendations outline that remission or low disease activity should be the goals of treatment in every patient.[3] Yet to achieve these aims, a greater understanding of the immune parameters for therapeutic intervention is needed. In particular, novel insights concerning cytokines involved in RA pathogenesis, such as interleukin (IL)-6, would help to guide appropriate therapeutic strategies.[4,5] The pivotal role of IL-6 in RA[5] was explored in a video at the beginning of the session, which highlighted the importance of further research in this area (available to view here).

Reviewing the Role of Glucocorticoids in Rheumatoid Arthritis Management

Professor Eric Ruderman

GCs are frequently prescribed by rheumatologists as they are known to be powerful, fast-acting anti-inflammatory drugs.[6] Yet, despite their long history in medicine, their introduction predated the establishment of regulatory requirements for safety and efficacy[6] and so there is a lack of certain data for GCs that would be considered as essential requirements for therapies approved in RA today. Chronic GC use has been associated with numerous side effects, some of which are potentially life-threatening, and the incidence of adverse events is influenced by GC dosage.[6,7] A better understanding of the true risk/benefit ratio of GCs is needed to determine how best to use these agents.[6-8]

Although controlled trials for GCs have been conducted, the published reports reveal important limitations such as short study duration and differing endpoints, thus observational data are needed to supplement the findings.[9] Data from a UK primary care database have highlighted that around half of patients with RA received a

prescription for a GC at some point in their follow-up, illustrating that these agents are still widely used.[10] The same UK source has also revealed the potential downside of using GCs. Increasing oral GC cumulative and average daily doses were clearly associated with greater risks of various serious adverse events, namely, diabetes, osteoporosis, fractures, glaucoma, hypertension, thrombotic stroke or myocardial infarction, gastrointestinal perforation or bleeding, and death (Figure 1).[11]

The risk of serious infections in patients on long-term GC therapy is a particular concern, with higher risks being observed with increasing age, cumulative dose, and longer duration of treatment.[12] This heightened serious infection risk is even observed in RA patients achieving Disease Activity Score 28 (DAS28) remission, a fact which suggests that the serious infection risk with GCs is not confounded by disease activity.[13] Furthermore, increased serious infection risk was also observed in anti-tumour necrosis factor (anti-TNF)-treated RA patients receiving low doses of GCs.[14] As with serious infections, the risk of myocardial infarction is also influenced not only by the total GC dose, but also by the cumulative dose over time.[11] Importantly, GC use has been associated with significantly increased mortality risk in patients with RA and may abrogate some of the cardiovascular benefits that have been described with MTX therapy.[7]

The current EULAR research agenda has identified several GC therapy-related knowledge gaps and the uncertainty over long-term safety of GC therapy has also been reflected in national guidelines and recommendations for the management of RA.[3,15,16] Although specific guidance is lacking, the general theme that emerges is that GCs should be used sparingly and that they should be tapered whenever possible.[3,15,16] Emerging observational data show the GC-sparing potential of biologics which illustrates a way forward to improving management. One French study showed that the GC-sparing effects of anti-TNFs were apparent within 3 months of initiation,[17] while another showed the decreased use of GCs in some biologic-experienced patients from Europe and Canada who were taking abatacept.[18] Similarly, two French observational studies have demonstrated the GC-sparing effect of tocilizumab accompanied by a decrease in disease activity.[19,20] Additional studies, such as the SEMIRA randomised controlled trial, which will assess whether it is possible to safely taper and discontinue GCs while maintaining disease activity control with tocilizumab, should contribute further valuable information on the GC-sparing potential of biologics and GC-tapering approaches.[21]

Overall, while the beneficial effects of GCs have been well documented, it is notable that significant adverse events associated with use of these agents have also been frequently described.[6-8] It is not only rheumatologists who are concerned about the risk/benefit ratio of GCs but also patients.[8] Therefore, the impact of GC treatment as part of care should be taken into account to maximise treatment outcomes as part of a precision approach.

Monotherapy in the Rheumatoid Arthritis Treatment Landscape

Professor Cem Gabay

Biologic monotherapy is a treatment strategy in patients for whom MTX is inappropriate; real-world data from different national registries show that approximately a third of RA patients on biologics are on monotherapy.[22] The efficacy of MTX has been well characterised, and the current EULAR recommendations state that it should be part of the first treatment strategy in patients with active RA.[3] However, its use does present some patients with challenges, such as inadequate response and adverse events, as well as potential implications for their lifestyle.[23] This helps explain why some patients do not use MTX as prescribed, yet their rheumatologist may be under the impression they are fully adherent.[23] For example, Canadian healthcare claims data showed that 58% of patients prescribed biologic combination therapy with MTX did not collect their MTX prescription.[24] Such information highlights a disconnect between the rheumatologists' perceptions and the reality of patient MTX use.[23,24] Nevertheless, the reasons for this lack of adherence are multifactorial and need further exploration.[23,24]

The EULAR recommendations highlight that biologics should be combined with disease-modifying anti-rheumatic drugs (DMARDs), and that MTX is preferred.[3] If MTX treatment is inappropriate, tocilizumab monotherapy is recognised as a potential option;[3] this general approach for tocilizumab monotherapy is also recommended in a number of national guidelines.[15,16]

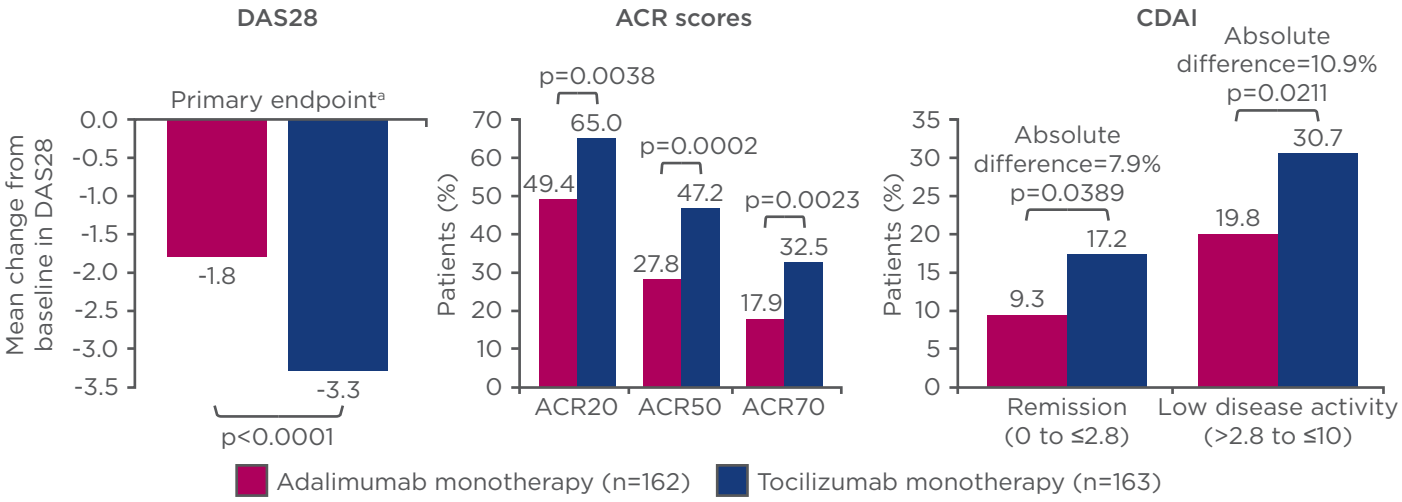

Figure 2: Superior efficacy of tocilizumab monotherapy versus adalimumab monotherapy in the ADACTA trial.[25]

[a]Adalimumab group: Baseline DAS28=6.8, Week 24 DAS28=5.0; Tocilizumab group: Baseline DAS28=6.7, Week 24 DAS28=3.4.

ADACTA head-to-head 24-week study of tocilizumab monotherapy vs. adalimumab monotherapy in patients who were intolerant to MTX or inappropriate for continued MTX.

DAS28: disease activity score 28; ACR: American College of Rheumatology; CDAI: clinical disease activity index; MTX: methotrexate.

Adapted from Gabay C et al.[25]

These conclusions for tocilizumab were reinforced by the results of the head-to-head ADACTA trial, where tocilizumab as monotherapy was shown to be statistically superior to adalimumab monotherapy in terms of DAS28 response, American College of Rheumatology (ACR) responses, and Clinical Disease Activity Index (CDAI) response (Figure 2).[25] The ACT-RAY study has also extended understanding of tocilizumab monotherapy;[26,27] the 24- and 52-week data compared an add-on strategy (tocilizumab in combination with MTX) with a switch strategy (tocilizumab with placebo) in patients with an inadequate response to MTX.[26,27] ACT-RAY demonstrated that for patients who cannot be treated with MTX, a switch to tocilizumab monotherapy is an option that may provide a robust level of disease control and radiographic benefits but does not result in any additional safety concerns.[26,27]

With anti-TNFs the comparative clinical results between combination and monotherapy are different from those reported for tocilizumab. Data from the PREMIER trial showed that adalimumab and MTX combination therapy was superior to both MTX and adalimumab monotherapy in all outcomes measured.[28] Similarly, the results of the TEMPO trial showed that etanercept and MTX combination therapy resulted in significantly greater improvement in DAS and in more patients achieving disease remission than either MTX or etanercept monotherapy.[29]

Other analyses suggest distinct characteristics of tocilizumab as monotherapy compared with other biologics. A network meta-analysis of trial findings found that the Health Assessment Questionnaire Disability Index (HAQ-DI) improvements with anti-TNFs, abatacept, and tocilizumab in combination with MTX were comparable.[30] However, while the HAQ-DI improvements with tocilizumab as monotherapy were similar to that of tocilizumab in combination with MTX, anti-TNFs as monotherapy appeared to be less efficacious than anti-TNFs in combination with MTX.[30]

The monotherapy findings for tocilizumab have also been investigated in broader populations than in clinical trials. ACT-SURE, an open-label safety and effectiveness study conducted in 25 countries, found that tocilizumab had a comparable safety profile, and was similarly effective, when used as monotherapy or in combination with DMARDs.[31] Data from the Pan-European registry TOCERRA also support the

effectiveness of tocilizumab monotherapy.[32] CDAI decreased rapidly after the start of tocilizumab, regardless of whether it was used as monotherapy or in combination with DMARDs.[32] For CDAI remission, there was no significant difference between the various tocilizumab treatment groups (with or without concomitant DMARDs) at any of the time points.[32] Importantly, the ACT-UP study, a multinational, observational study, found that tocilizumab was well tolerated as monotherapy in routine clinical practice, with comparable safety results to tocilizumab in combination with MTX.[33] The impact of tocilizumab monotherapy on patient-reported outcomes is also emerging from patient registry data analysis. The US CORRONA registry data showed improvements at 1 year with tocilizumab monotherapy for all reported measures, regardless of prior anti-TNF history.[34]

There remains a gap in our understanding of how to predict patient response to different biologics, particularly when given as monotherapy. Studies have been undertaken to explore biomarkers, but validation of the results is essential. For example, variable findings have been reported for CD11c with anti-TNF monotherapy and so larger biologic monotherapy biomarker studies are required.[35]

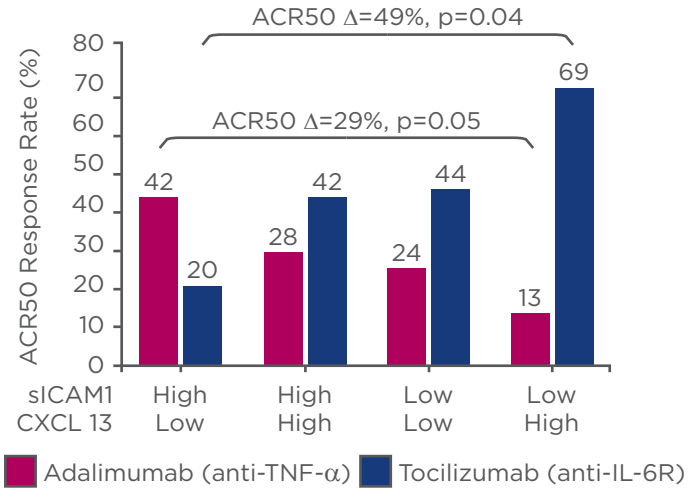

Figure 3: Lymphoid (CXCL13) and myeloid (sICAM1) serum biomarkers define rheumatoid arthritis patient subgroups with differential clinical response to adalimumab compared with tocilizumab in the ADACTA trial.[36]

ACR: American College of Rheumatology; CXC13: C-X-C motif chemokine 13; sICAM1: soluble intercellular adhesion molecule 1; anti-TNF-α: anti-tumour necrosis factor alpha; anti-IL-6R: anti-interleukin 6 receptor; RA: rheumatoid arthritis.

More promising biomarker results have been generated in a sub-study of the ADACTA head-to-head biologic monotherapy trial, where lymphoid (CXC motif chemokine 13 [CXC13]) and myeloid (soluble intercellular adhesion molecule 1 [sICAM1]) serum biomarkers defined RA patient subgroups with differential clinical response to adalimumab and tocilizumab monotherapy (Figure 3).[36] A higher ratio in favour of CXCL13 was associated with an increased likelihood of response to tocilizumab monotherapy. In contrast, a higher ratio favouring ICAM-1 was associated with an increased likelihood of response to adalimumab monotherapy.[36] These represent the first biomarker findings indicating differential clinical response to anti-TNF and anti-IL-6 receptor agents used as monotherapy.[36] Validation of these initial biomarker findings will help predict the response to biologic monotherapy and so enable the selection of the right drug for the right patient.

Can Biomarkers Help Guide Biologic Treatment Approaches?

Professor Georg Schett

Although advances are being made in the field of RA, biomarker research has lagged behind in areas such as oncology, a fact which necessitates more efforts in research to drive progress for the future.[37,38]

A biomarker is an objectively measured indicator of normal biological or pathogenic processes or of response to treatment.[38] Biomarkers are identified by preclinical studies and clinical assays are then developed, which must be validated retrospectively and prospectively before they are accepted in the clinic.[38] A biomarker is fundamentally different to an outcome. A biomarker is a process-centred instrument and has no meaning to the patient. In contrast, an outcome is a patient-centred instrument and has immediate meaning to the patient.[37] The biomarker C-reactive protein (CRP) will not have relevance for the patient, but the outcome of RA will be evident to the patient.

Prognostic biomarkers predict the course of a disease irrespective of treatment, whereas predictive biomarkers predict treatment response.[38] Elevated CRP is an example of prognostication of relevance to rheumatologists as it is independently linked to risk of vascular and non-vascular deaths.[39] Hard endpoints require a long period of follow-up

before they become apparent; therefore, surrogate outcomes are useful in clinical practice. Surrogate outcomes or effects on surrogate outcomes should correlate with clinical outcomes or effects on clinical outcomes, respectively.[38]

In RA, structural damage is a surrogate outcome for death and several prognostic biomarkers for structural damage have been identified. Anti-citrullinated protein antibodies (ACPA), rheumatoid factor (RF), CRP, calprotectin, matrix metalloproteinase-3, 14-3-3η, receptor activator of nuclear factor kappa B ligand (RANKL) and osteoprotegerin, C-terminal cross linking of Type-I and Type-II, have all been identified as prognostic biomarkers for poor structural outcomes in RA.[40-43]

It is now possible not only to predict a surrogate outcome, but also to predict a clinical outcome such as the onset of RA. This will be important for the future of precision medicine as it will help define patients early. A promising approach is combined analysis of prognosticators, such as autoantibodies which are known to precede the onset of RA. It has been shown that more patients with a combination of RF, ACPA, and 14-3-3η autoantibodies progress than those with only one of these biomarkers.[40,41]

A more difficult field is the prediction of treatment response. Analogous to the field of oncology, there is now an appreciation that RA is a heterogeneous disease, varying between patients and driven by different immunopathological processes and that subgroups of patients can be identified so that they can be stratified to individual treatments.[44] For example, RF and anti-cyclic citrullinated peptide (anti-CCP) seropositivity are predictive of better treatment responses to rituximab and to abatacept in biologic-naïve RA patients at 6 months.[45-47] Yet, a similar association between anti-CCP seropositivity and treatment response has not been observed for anti-TNF therapies, and may be indicative that autoantibody development is not intimately linked to the production of TNF.[48]

The relationship between the mechanism of action of a biologic drug and biomarkers is clearly complex, and prior assumptions of an interaction may prove to be invalid. With tocilizumab for example, baseline CRP and IL-6 levels are not predictive of clinical outcomes following treatment.[49] Multi-biomarker disease activity scores, which are based on the serum levels of 12 different proteins, are also not predictive of response to tocilizumab treatment.[50] In the future it will be important to appreciate that there are different biomarkers showing immune activation; biomarkers such as CRP, fibrinogen, and serum amyloid A have been well described with respect to the acute phase response, but other processes are being investigated. For example, as shown in the biomarker sub-study of the ADACTA trial, CXCL13 appears important in innate/adaptive immune activation.[36]

A challenging but central goal is to find predictors for treatment response in order to tailor treatment for individual subsets of RA. The ongoing Phase III STRAP (Stratification of Biologic Therapies for RA by Pathobiology) study, conducted by the MATURA industry–academia consortium, is expected to generate important data in this regard.[51] The three biologics that will be studied in the STRAP study are rituximab, etanercept, and tocilizumab.[51] Through the use of biopsies the investigators aim to subtype patients to better understand the underlying disease pathways.[51] The outcomes of STRAP are eagerly awaited. If predictors of response to drugs can be reliably identified, then patients with RA would be able to receive the drug that they are most likely to respond to earlier than is possible at present.

Innovating Future Treatment Approaches in Rheumatoid Arthritis Through Previous Clinical Experiences

Professor Ernest Choy

The insights from clinical practice are essential for the effective delivery of precision medicine.

In case study 1, a 58-year-old female patient initiated treatment with MTX in 2012, which improved her condition. She was given adalimumab with MTX in 2014 after displaying signs of worsening disease activity but she still experienced disease progression. The general view of the audience was that a switch to an alternative biologic agent would be an appropriate future clinical approach for such a patient. The discussion highlighted the importance of considering adherence and working in partnership with the patient. This theme was then further explored by looking at observational data which confirmed that patient adherence to medication is suboptimal, but that

the reasons behind the phenomenon are complex and multifaceted.[52,53]

In case study 2, a 52-year-old male patient initiated treatment with MTX in 2011 but this had limited effect. In 2013, he was switched to etanercept plus MTX and his symptoms improved. In 2016, prednisone was added to his treatment regimen but he complained of fatigue, mood changes, insomnia, and weight gain despite disease activity being moderately controlled. The subsequent discussion with the audience centred on the uncertainty regarding the risk/benefit profile of GCs, and how this needed to be factored into clinical decision-making to ensure that the patient received the optimal treatment approach. From a practical perspective, this necessitates consideration of the patient's age, intended GC treatment duration and dose, as well as comorbidities and co-medications.[8-12]

In case study 3, a 60-year-old female patient initiated treatment with MTX, hydroxychloroquine, and intramuscular GC injection in June 2015. She was switched to subcutaneous MTX following a dose increase that resulted in nausea and loss of appetite. After failing to attend several appointments, she experienced a flare of her RA and, when brought to the clinic by her sister, admitted to her physician that she had stopped all treatment due to hair thinning. The audience recognised this case as highlighting the need for better dialogue with patients[3] and the fact that partnership was essential for the delivery of precision medicine. Patients may have different viewpoints on healthcare from those of physicians and so a shared approach may lead to improvements in health outcomes, coping behaviour, adherence, and satisfaction with care.[54,55]

SUMMARY

An increasing focus on precision medicine in RA will drive better patient outcomes. As part of this, the impact of GCs, which are commonly used agents, must be further studied due to the uncertainty surrounding the true risk/benefit profile of these drugs. Biologic monotherapy is a valuable treatment strategy in patients with RA for whom MTX treatment is inappropriate and data from registry and real-world data corroborates what has been seen in clinical trials. Looking to the future of precision medicine in RA, continuing research into predictive biomarkers for treatment response will enable better care to be delivered to patients earlier in the disease process. Precision medicine relies on the close integration of current research and clinical practice to better guide decision-making and ultimately ensure treatment benefits for RA patients are maximised.

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