

A novel treatment for **rheumatoid arthritis** **with renal insufficiency**

Dr. Shunsuke Mori



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Dr. Shunsuke Mori has been involved in developing novel treatments for rheumatoid arthritis. In this interview Dr. Mori elaborates on the current state-of-the-art in the field and recent contributions from the Mori laboratory.

To begin with, please explain how your current interest in rheumatoid arthritis was built upon your research background.

In the 1980s, a number of cytokines were identified as key mediators between the innate immune system and the adaptive immunity. My first achievement as a researcher was molecular cloning of a cDNA encoding rabbit interleukin-1 β (IL-1 β) and its receptor antagonist, a natural inhibitor of IL-1. I played a part in the IL-1 project during the early period of cytokine research in terms of the pathogenesis of inflammatory arthritis, which, in turn, aroused my interest in rheumatoid arthritis (RA) pathogenesis and treatment.

Where does your research fit in the larger context of current biomedical research?

A number of novel biological antirheumatic drugs have been approved for use in RA treatment. These drugs are targeted at specific molecules and pathways in the immune system, and their emergence has changed the course of RA and improved patient and social outcomes. My studies were carried out with the intention of providing information to rheumatologists who make therapeutic decisions.

Have you encountered any challenges in your research? How did you overcome them?

To draw definite conclusions, I planned multicentre studies with several cooperating institutions. A great deal of time and manpower were required to collect appropriate data regarding clinical variables and outcomes in target patient populations. I formulated research questions and conducted pilot studies, and then I coordinated the active participation and collaboration of candidate institutions.

Has your work led to any major discoveries to date, and if so, what could that mean for the patients and doctors alike?

My aim is to provide a safe, effective treatment option for individual RA patients who are suffering from complications and comorbidities. There are currently no reliable, evidence-based guidelines for deciding whether biological antirheumatic drugs can be safely introduced



and continued in RA patients who have RA-associated pulmonary diseases, chronic infectious diseases, renal insufficiency, etc. and for whom biological drugs are the first treatment option.

Tocilizumab (TCZ), a humanized monoclonal antibody against the IL-6 receptor, is effective and generally well-tolerated when used for RA patients. Although there was extra concern that TCZ may have an influence on protective antibody response to vaccinations, we showed that RA patients receiving TCZ can benefit from influenza and pneumococcal polysaccharide vaccinations. In fact, our findings are being used in the most recent European League Against Rheumatism (EULAR) recommendations for the management of RA.

Renal insufficiency is not uncommon in RA patients. It is recommended that most biological agents be used in combination with methotrexate (MTX), but MTX is contraindicated in patients with severe renal insufficiency. We showed that TCZ therapy has good efficacy parameters regardless of whether or not MTX is also used. In addition, TCZ effectively improved erythropoietin-resistant anaemia.

Do the pathways and proteins you are studying play any other roles in the organism?

Cytokines play a key role in communicating with the immune system and host tissue cells, possess pleiotropic functions across a broad range of tissues, and mediate a variety of normal physiologic and pathophysiological processes. They are also involved in growth, differentiation, drug resistance, and death of tumour cells. Inhibition of IL-1, IL-6, and tumor necrosis factor (TNF) through the use of

biological drugs is effective in the treatment of autoimmune, inflammatory diseases.

Do you envision any type of TCZ-based treatments and how they might be implemented?

While monotherapy with anti-TNF α inhibitors has considerable efficacy in the treatment of RA, a combined use with MTX is highly recommended for additional benefits and better outcomes. When that is not possible, TCZ can be a promising antirheumatic drug. I am now also planning a clinical study addressing the risks and benefits of TCZ therapy for polymyalgia rheumatica.

What long-term consequences might your studies have on future work and potentially on healthcare, society and policy?

I believe that our findings, namely the utility of TCZ therapy in RA patients with renal insufficiency and the availability of vaccinations in RA patients receiving TCZ therapy will provide important information for rheumatologists and may contribute to the development of guidelines and recommendations for biological antirheumatic therapies and vaccination policies.

Are you planning to expand your research interests? Where might you focus your attention and why?

I am planning to identify markers for predicting therapeutic responses to different types of biological antirheumatic drugs, which will be useful when selecting the most appropriate biological drugs for individual patients.

Towards developing new guidelines for treatment of rheumatoid arthritis

Rheumatoid arthritis, a commonly encountered autoimmune, inflammatory disease, has become prevalent amongst the elderly. Current research in the field, such as Dr. Shunsuke Mori's work focuses on treating rheumatoid arthritis when accompanied by complications such as pneumonia and renal insufficiency.

RHEUMATOID ARTHRITIS

The immune system comprises two major arms, namely innate and adaptive immunity. Inflammation forms a part of the innate immune system, namely a first-line defence of a living tissue to disease or infectious agents. Acute inflammatory responses are essential for the removal of external insults from the body and the repair of tissue. However, genetic defects in the regulatory mechanism of the immune system and a repeated or persistent environmental stress may produce chronic inflammation and autoimmunity as a result of defective self-tolerance, which can cause severe tissue damage and dysfunction.

I believe that our findings will provide important information for rheumatologists and may contribute to the development of guidelines and recommendations for biological antirheumatic therapies and vaccination policies.

Rheumatoid arthritis (RA) is one of the most common autoimmune, inflammatory diseases, in which abnormal systemic immune responses cause chronically inflammatory and persistently destructive processes in the synovium and other organs. It typically results in warm, swollen, and painful joints, which may result in low red blood cells, inflammation around the lungs, and inflammation around the heart. RA affects between 0.5 and 1 per cent of adults in the developed world with 5 to 50 per 100,000 people newly developing the condition each year. There is currently no cure for RA, but treatments can improve symptoms and slow the progress of the disease.



TREATMENT AND COMPLICATIONS

While the cause of RA is not clear, it is believed to involve an approximately equal contribution of genetic and environmental factors. The underlying mechanism involves the body's immune system attacking the joints. The goals of treatment are to minimize symptoms such as pain and swelling, to prevent bone deformity, and to maintain day-to-day functioning. This can often be achieved using two main classes of medications: analgesics and disease-modifying antirheumatic drugs (DMARDs).

Antirheumatic drugs act by altering the underlying process that causes RA, and using these drugs has changed how RA is managed, while improving patient outcomes. There are two main classes of antirheumatic drugs. Biological antirheumatic drugs were designed to target specific molecules and pathways in the immune system. Synthetic antirheumatic drugs include methotrexate (MTX), which is the most important and useful DMARD. MTX is used as the first-line antirheumatic drug, but in most cases, combinations of synthetic antirheumatic drugs with biological drugs are required to achieve low disease activity or remission.

Dr. Shunsuke Mori's research efforts attempt to bridge a gap in the knowledge regarding the best use of currently available antirheumatic

drugs for optimal care. RA patients often have complications or comorbidities. While guidelines and recommendations regarding biological therapy for RA patients have been developed worldwide by the scientific societies and healthcare authorities, doctors worldwide are not provided with reliable guidelines for deciding whether biological antirheumatic drugs can be used as treatment for RA patients who have RA-associated pulmonary diseases, chronic infectious diseases, renal insufficiency, etc. and for whom biological is the first treatment option. As an example, renal insufficiency is not uncommon in RA patients. It is recommended that most biological agents be used in combination with MTX, which is, however, contraindicated in patients with severe renal insufficiency.

TOCILIZUMAB: A STEP FORWARD

Vaccinations for influenza and pneumococcal pneumonia are strongly recommended for RA patients, because these patients are at an increased risk of contracting infectious diseases. Tocilizumab (TCZ), a humanized monoclonal antibody against the interleukin-6 (IL-6) receptor, is effective and well tolerated by RA patients. IL-6 was considered an essential factor for antibody production, and therefore there was special concern that TCZ may have an influence on the protective antibody response to vaccinations. Dr. Mori's work showed that TCZ did not impair immunogenicity of either of these vaccines in RA patients and that no severe adverse effects were observed. Thus RA patients receiving TCZ can benefit from influenza and pneumococcal polysaccharide vaccinations. Dr. Mori's findings are currently being used in the most recent European League Against Rheumatism (EULAR) recommendations for management of RA.

Cytokines, a class of small proteins involved in cell signalling, are known to mediate communicating between the innate immune system and the adaptive immunity. Cytokines, particularly IL-6, IL-1, and tumour necrosis factor (TNF), are essential in driving healthy inflammatory processes. Dr. Mori's team performed a multicentre study which indicated that TCZ therapy is efficient in RA patients with renal insufficiency whether or not MTX is also used. In addition, TCZ effectively improved erythropoietin-resistant anaemia in this patient population. Anaemia associated with chronic inflammatory disease is common and typically mild in patients with normal functioning kidneys. In patients with renal insufficiency, however, there is primary deficiency in erythropoietin production, which leads to more severe anaemia. Dr. Mori's findings showed that blocking of the IL-6 activity by TCZ is

beneficial to RA patients with renal insufficiency and anaemia, and TCZ may be a first-choice biological agent for such patients.

While monotherapy with anti-TNF α inhibitors has considerable efficacy in the treatment of RA, a combined use with MTX is highly recommended for improved outcomes. In the cases where MTX is contraindicated or not tolerated, such as in patients with renal insufficiency or in those with hypersensitivity to MTX, anti-TNF α inhibitors have to be used without MTX, often with no disease remission. Dr. Mori found that in contrast, TCZ, even in a single use, can be a promising antirheumatic drug for these patient groups. Therefore, Dr. Mori is currently evaluating the long-term safety and efficacy of TCZ monotherapy for RA patients with severe and end-stage renal insufficiency.

HEALTHCARE APPLICATIONS

The drugs used to treat RA have individual advantages and disadvantages. Some patients fail antirheumatic treatment with a particular biological drug (primary lack of efficacy), but may show a satisfactory response to another drug. In some cases, patients respond well to a biological drug at its first use, but its efficacy can disappear during the treatment (secondary loss of efficacy). Nevertheless, no guidelines have been established that outline how to use these drugs for optimal patient care. Although it is currently difficult to maintain clinical remission without continued biological antirheumatic therapy, a window of opportunity may exist in some RA patients for inducing long-term remission. Dr. Mori's future research aims are to identify clinical and genetic markers for predicting therapeutic responses to different types of biological drugs, which will prove useful when considering tailor-made therapies suitable for each individual patient.

The utility of TCZ therapy in RA patients with renal insufficiency and the availability of vaccinations in those receiving TCZ, will, in Dr. Mori's opinion, provide a treatment option for rheumatologists in real-life medical practice and will also contribute to the development of vaccination policies. Since 2014, Dr. Mori has participated in a project aimed at producing a set of guidelines for management of polymyalgia rheumatica (PMR), a different type of inflammatory rheumatic disease that affects elderly individuals, and the results of this project have been published, with the title "2015 recommendations for management of PMR: a EULAR and American College of Rheumatology collaborative initiative." Dr. Mori is additionally planning a clinical study addressing the risks and benefits of TCZ therapy for PMR.

Researcher Profile



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Dr. Shunsuke Mori is the Director of Clinical Research at the Department of Rheumatology, Clinical Research Center for Rheumatic Diseases, NHO Kumamoto Saishunsou National Hospital. Currently Dr. Mori is interested in studying rheumatoid arthritis and has made significant advances in the treatment of rheumatoid arthritis with renal insufficiency.

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