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New data demonstrate the ability of MabThera to reduce the progression of joint damage when used as a first-line biologic treatment in rheumatoid arthritis

RA patients with enhanced response identified

New data show for the first time that a course of 2 infusions of MabThera 1000mg (rituximab, known as Rituxan within the United States) given every 24 weeks as the patient's first biologic can significantly slow down joint damage following 1 year of treatment, with virtually no progression of joint damage seen from six months¹.

The IMAGE study, presented at the European League Against Rheumatism (EULAR) annual congress, showed that methotrexate-naïve patients treated with 1000mg MabThera in combination with methotrexate (MTX), had three times less joint damage after 1 year (measured by Total Sharp Score) compared to those treated with methotrexate (MTX) alone.

In addition, 80% achieved a 20% improvement in their symptoms (ACR20) compared to MTX alone (80% vs 64%), while the percentage of these patients achieving a 70% improvement in symptoms compared to MTX alone was almost double (47% vs 25%). Patients taking MabThera also reported significantly improved physical function and quality of life, compared to those taking methotrexate alone².

“Clinically and functionally, these positive data clearly support the use of MabThera earlier in the rheumatoid arthritis treatment algorithm. These robust data add to the wealth of existing evidence for the use of MabThera across a broad range of RA patients, and give us a great new option to prevent joint damage in the early stages of the disease”, said the lead investigator, Professor Paul-Peter Tak, AMC/University of Amsterdam, Netherlands.

Joint damage in rheumatoid arthritis (RA) often begins early in the disease, so it is critical to treat patients as early as possible to reduce symptoms and stop irreversible damage before it occurs. This damage can lead to permanent disability affecting patients' ability to carry out normal everyday activities such as walking or dressing.

The study showed that when used as a first-line biologic only the approved 2 x 1000mg dose of MabThera plus MTX was shown to both significantly inhibit joint damage progression and improve clinical outcomes, compared to MTX alone.

Safety data from the IMAGE study are consistent with results from previous MabThera clinical trials and did not reveal any new or unexpected safety signals. Rates of serious adverse events and serious infections were similar between the two MabThera groups and the MTX-only group, further supporting the robust safety profile of this treatment.

Promising data which may predict enhanced response

Also presented today at EULAR, researchers have identified a group of rheumatoid arthritis patients who are two to three times more likely to achieve a significant improvement in their disease in MabThera studies³. Identifying which patients that are most likely to benefit from treatment with MabThera will assist physicians in finding the best therapy choice for patients sooner.

“Because we can’t predict which patients will benefit most from a particular treatment, many patients unfortunately cycle through several types of treatment before achieving the optimum individual response. If we can predict which patients are likely to have the best treatment outcome with MabThera, they can be offered this option early enough to gain maximum benefit in terms of symptom reduction and prevention of joint damage. Although further research is needed, these data could signal an exciting breakthrough in the future management of rheumatoid arthritis”, said lead investigator, Professor John Isaacs, Newcastle University, UK.

In trials of MabThera, a pooled analysis showed patients who were seropositive to either of two characteristic RA autoantibodies, rheumatoid factor (RF) or anti-cyclic citrullinated peptide (aCCP), were two to three time more likely to achieve a significant improvement in their disease following treatment with MabThera, compared to patients who did not have these autoantibodies. Autoantibody production is one of the potential mechanisms that is thought to contribute to disease activity and joint damage which occurs in RA with approximately 80% of the RA patient population being seropositive. The enhanced response observed in seropositive patients may be linked to one of MabThera’s modes of action, as it targets the B cells which produce autoantibodies⁴.

More information about the studies

IMAGE study

IMAGE was a Phase III, randomized, controlled, double-blind trial involving 748 patients to evaluate the safety and efficacy of MabThera in combination with MTX compared to MTX alone, in MTX-naïve patients with active RA. Patients in the MabThera arms were either treated with 2 x 1000mg or 2 x 500mg every 24 weeks. The primary endpoint was radiographic progression measured by total modified Sharp score at week 52.

In patients treated with 2 x 1000mg MabThera and MTX, the data show a significantly smaller change (0.359) in modified Total Sharp Score (mTSS) compared to patients on MTX alone (1.079; $p < 0.001$) - a lower progression of joint damage. Further, a significantly higher proportion of patients treated with MabThera and MTX had no progression in their joint damage over 1 year (64% vs 53% $p = 0.0309$). By week 52, 65% of these patients achieved a 50% improvement in symptoms (ACR50), while 47% had achieved a 70% improvement (ACR70), compared to 42% and 25% on MTX alone ($p < 0.0001$ for both ACR50 and ACR70 comparisons). Safety data from the study are consistent with results from previous MabThera clinical trials and further enhance the robust safety profile. Rates of serious adverse events and serious infections were similar between the two MabThera groups and the MTX only group.

The percentage of patients who achieved improvements in their symptoms on the lower dose of MabThera 2 x 500mg was also statistically significant compared to MTX alone (77%;60%;43% at ACR20/50/70) however this lower dose did not produce a statistically significant inhibition of joint damage, confirming that the currently licensed dose (2 x 1000mg) is the most optimal dose of MabThera.

MabThera also improved the physical function of patients, which was assessed at regular intervals during the study using a number of standard health-related quality of life tools, such as HAQ-DI, FACIT, and SF-36. Patients also reported significantly lower levels of fatigue, one of the most commonly reported debilitating symptoms experienced by people with rheumatoid arthritis.

Biomarkers study

A post-hoc analysis looked at a pooled cohort from 2 Phase III studies, which included patients where MabThera was added to existing methotrexate (MTX), the current standard RA therapy. MabThera was given by IV infusion on days 1 and 15. A total of 670 patients were included in the pooled analysis. The analysis determined the serological status of patients by analysing the presence of specific autoantibodies (rheumatoid

factor, RF and anti-cyclic citrullinated peptide, a-CCP), and compared the clinical outcomes at weeks 24 and 48 of those who were seropositive (those who tested positive for RF and/or aCCP) to those who were seronegative. The measures included ACR and EULAR responses, as well as DAS28 scores.

At week 24, seropositive patients were more than twice as likely to achieve an ACR response (ACR20 or ACR50) than those who were seronegative. At week 48 seropositive patients were more than three times more likely to achieve a 70% improvement in symptoms (ACR70) compared to seronegative patients (6.9 vs 20.9%). Seropositive patients also had significantly greater falls in Disease Activity scores, and were more likely to achieve a low disease status by week 48.

About Roche's diagnostic assays for RA

The diagnosis of rheumatoid arthritis relies on clinical symptoms and laboratory tests, such as rheumatoid factor, C-reactive protein and Anti-CCP. All assays are offered by Roche Diagnostics.

Rheumatoid factor (RF) is a term used to describe a group of autoantibodies known as rheumatoid factors.

The RF test is considered the basic screen and hallmark for the autoimmune disorder rheumatoid arthritis (RA). It is considered an early marker since its presence is associated with an increased risk of developing RA in people with mild arthritic symptoms. C-reactive protein (CRP) is one of several markers of inflammation that are at elevated levels in patients with rheumatoid arthritis (RA). Both assays are available on Roche's cobas 6000 (c501 module), cobas Integra und Modular ANALYTICS.

The identification of citrulline as target of a whole set of autoantibodies detected in the sera of RA patients has led to the development of anti-CCP assays that possess a high specificity for RA. Roche's Elecsys Anti-CCP plays an important role in the early diagnosis and treatment of rheumatoid arthritis and provides an excellent tool for primary care physicians and rheumatologists. It is designed for use on the Elecsys / cobas e electrochemiluminescence immunoassay systems.

About rheumatoid arthritis and MabThera

Rheumatoid arthritis (RA) is an autoimmune disease characterised by inflammation that leads to stiff, swollen and painful joints. This ultimately results in irreversible joint damage and disability. MabThera selectively targets B cells and represents a highly effective therapeutic approach for RA in addition to existing treatments such as disease-modifying anti-rheumatic drugs (DMARDs) and tumour necrosis factor (TNF) inhibitors.

Roche Personalised Healthcare

Personalised Healthcare (PHC) is an approach to fit the treatment to the patient. The concept takes into

account the information about a patient's genotype, gene expression profile, or other biomarkers, such as serum proteins, to further tailor medical care to the patient's needs. PHC is a key enabler helping to bring more clinically differentiated treatments to the market and to identify individuals at risk for common diseases such as cancer, heart disease, and diabetes, and provide appropriate preventative measures. Similar information can be used to identify subsets of patients who are more likely to respond well to a targeted therapy, making healthcare more effective. Roche has developed a number of personalised healthcare solutions within the oncology and virology fields, and is now pursuing a similar approach with autoimmune diseases.

About Roche

Headquartered in Basel, Switzerland, Roche is a leader in research-focused healthcare with combined strengths in pharmaceuticals and diagnostics. Roche is the world's largest biotech company with truly differentiated medicines in oncology, virology, inflammation, metabolism and CNS. Roche is also the world leader in in-vitro diagnostics, tissue-based cancer diagnostics and a pioneer in diabetes management. Roche's personalised healthcare strategy aims at providing medicines and diagnostic tools that enable tangible improvements in the health, quality of life and survival of patients. In 2008, Roche had over 80'000 employees worldwide and invested almost 9 billion Swiss francs in R&D. The Group posted sales of 45.6 billion Swiss francs. Genentech, United States, is a wholly owned member of the Roche Group. Roche has a majority stake in Chugai Pharmaceutical, Japan. For more information: www.roche.com.

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