Rheumatoid arthritis treatments continue to demonstrate increased value through additional research.

New data reveals broader benefits than anticipated at the time of FDA approval.

CONCLUSIONS

- Conventional, point-in-time assessments of RA therapies risk significantly under-valuing innovative treatments, because they do not capture gains in sustained disease remission and benefits of targeted treatment that are demonstrated over time.
- Rapid scientific advances in recent years have uncovered additional evidence regarding the full value and best use of innovative RA treatments, which was not fully understood at the time of their initial FDA approval:
    1. Individual patient characteristics can be important predictors of treatment response.
    2. Receiving treatment earlier in the progression of the disease can result in sustained disease remission.
    3. Advances in treatment have proved so successful in improving outcomes that they have raised the bar for the very definition of treatment success. Levels of improvement that a few decades ago would have seemed unattainable are now the standard for successful treatment.
- As a result of the complexity of the disease and the evolving body of evidence on treatment options, patients and their physicians must have the autonomy to make the treatment decisions that best accommodate individual needs and preferences.

FINDINGS

1 | Individual patient characteristics can be important predictors of treatment response.

A growing body of evidence is enabling clinicians to identify genetic predictors of treatment response to biologic disease-modifying anti-rheumatic drugs (DMARDs), a mainstay of RA treatment for many patients.

Evolving understanding of these important linkages between specific characteristics and response to treatment holds promise in enabling more targeted therapy, resulting in better outcomes for patients.

- GENE INDICATORS: Emerging blood-based gene expression tests can identify as much as 60% of patients who will not respond to TNF-inhibitor therapy, a main class of biologic DMARDs. This allows selection of alternative biologic therapies and helps avoid the use of ineffective medicines. This could reduce non-response to TNF-inhibitor therapy by up to 50% in the population as a whole and significantly reduce the costs and complications of unsuccessful TNF-inhibitor therapy.[1]

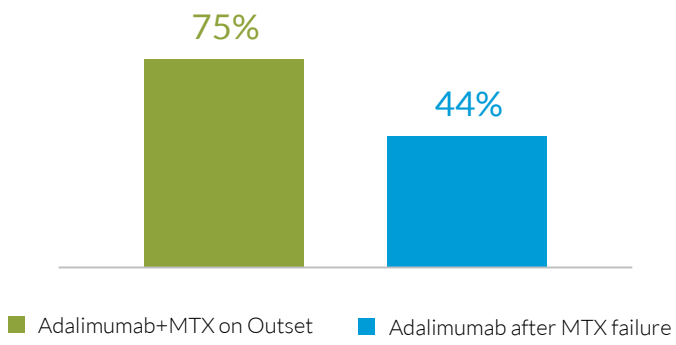
- PROTEIN INDICATORS: Specific proteins that circulate in the blood have been shown to predict patient response to biologic DMARDs, improving population response rates to biologic therapies by 10%.[2]
- ULTRASOUND ASSESSMENTS: The review of ultrasound assessments of joint deterioration alongside standard clinical assessments of disease activity can help identify which patients are suitable for reduced dosing of treatments. In fact, a quarter of patients in a recent study were determined to be able to sustain rheumatoid arthritis remission without continuing biologic therapy.[3]

2 | Receiving treatment earlier in the progression of the disease can result in sustained disease remission.

In the years since biologic therapy approval for RA treatment, a substantial body of evidence has demonstrated that patients achieve and sustain remission at higher rates when biologic therapy is initiated earlier in both the progression of disease and the treatment sequence.

- Biologics were initially approved for disease management and used later in disease progression, after a patient failed to respond treatment with synthetic DMARDs. Evidence developed subsequently has demonstrated that initiating biologic therapy earlier in the progression of RA improved remission rates. For example, in 2011, results from a study of a registry of North American RA patients found that patients initiated on a biologic at fewer than five years disease duration, 22.3% achieved remission, as compared to only 17.7% of patients who initiated therapy with six to ten years of disease duration and 12.8% among patients who initiated treatment after more than eleven years of disease duration.[4]
- More recently, studies have shown that biologic therapy earlier in the treatment sequence substantially improves rates of remission and the durability of remission once achieved. In 2014, results published from the OPTIMA trial showed that 75% of treatment naïve patients receiving MTX+adalimumab in combination at the outset sustained remission at 18 months as compared with 44% of patients who received MTX alone first and added adalimumab after 6 months.[5]
- In 2016, a systematic review of 15 RCTs conducted since 2004 indicated that 50% of early RA patients treated with a TNF inhibitors + MTX could expect to sustain clinical remission for 1 year after discontinuation of the biologic therapy as compared with 13% of established RA patients.[6] This study indicates that earlier use of biologic therapy increases the likelihood of biologic-free sustained remission. These results are supported by findings from the OPTIMA trial, discussed above, which showed that 65% of patients who began treatment with a combination biologic and MTX therapy and achieved remission at 6 months sustained remission for a subsequent 12 months after discontinuing adalimumab.[5]

Remission Rates at 18 Months for Biologic Combination Therapy Initiated Earlier and Later in Disease



3 | Advances in treatment have proved so successful in improving outcomes that they have raised the bar for the very definition of treatment success. Levels of improvement that a few decades ago would have seemed unattainable are now the standard for successful treatment.

Defining a successful clinical outcome for the treatment of a disease reflects a growing understanding of both the disease and the probable response to treatment. In RA therapy, rapid advances in the treatment paradigm have led to substantive changes over time to evidence-based practice guidelines that reflect ever-higher targets for disease remission. These guideline changes demonstrate the value that continues to emerge as our understanding of medicines, and how best to use them, evolves.

- BEYOND ACR20: ACR20, a measurement developed in 1995, defines the treatment efficacy of a therapy as a greater than 20% improvement in tender and swollen joint counts. In 2008, the American College of Rheumatology (ACR) updated the outcome measure to include 50% and 70% improvements, reflecting the additional value revealed by ongoing research demonstrating that the use of biologic therapies in combination with synthetic DMARDs and earlier in patients' progression can deliver clinical benefits well beyond ACR 20. [7]
- TARGETING REMISSION: In 2015 the ACR again revised its treatment guidelines to include a recommendation that all RA patients should be treated to a target of remission or low disease activity.[8] Previously, halting the progression of the disease was the outcome that most accurately demonstrated the impact of a medicine. However, ongoing accumulation of evidence has demonstrated that patients can now achieve disease remission as a result of a growing understanding of how to best use the medicines.[9]

REFERENCES

1. Thomson, Ty M. *et. al*., Blood-based Identification Of Non-responders To Anti-tnf Therapy In Rheumatoid Arthritis, BMC Medical Genomics (2015) 8:26, 1-12.
2. Nair, S.C. *et. al*., A Personalized Approach to Biological Therapy Using Prediction of Clinical Response Based on MRP8/14 Serum Complex Levels in Rheumatoid Arthritis Patients, PLoS One (2016) 11:3, 1-12.
3. Marks, JL *et. al*., Does Combined Clinical And Ultrasound Assessment Allow Selection Of Individuals With Rheumatoid Arthritis For Sustained Reduction Of Anti-tumor Necrosis Factor Therapy?, Arthritis Care Research (2015) 67:6, 746-53.
4. D.E. Furst, A.L. Pangan, L.R. Harrold, *et. al*., "Greater likelihood of remission in rheumatoid arthritis patients treated earlier in disease course: Results from the CORRONA registry," Arthritis Care and Research (Hoboken) 63, no. 6 (2011): 856-64.
5. Smolen JS, *et. al*. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: the randomised controlled OPTIMA trial, Lancet (2014) 383(9914):321-32.
6. Tanaka, Y. Stopping Tumour Necrosis Factor-targeted Biological DMARDs in Rheumatoid Arthritis. Rheumatology (2016) 55(suppl 2):ii15-ii22.
7. Saag, Kenneth *et. al*., American College of Rheumatology 2008 Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis, Arthritis & Rheumatism (2008) 59:6, 762-84.
8. Singh, Jasvinder *et. al*., 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis, Arthritis Care & Research (2015) Special Article, 1-25.
9. Singh, Jasvinder *et. al*., Biologics Or Tofacitinib For Rheumatoid Arthritis In Incomplete Responders To Methotrexate Or Other Traditional Disease-modifying Anti-rheumatic Drugs: A Systematic Review and Network Meta-analysis, Cochrane Database of Systematic Reviews (May, 2016).