Significant progress has been made in recent years in our ability to diagnose and treat rheumatoid arthritis (RA), a devastating autoimmune disease that causes progressive joint deterioration and pain in millions of Americans. Therapeutic advances have transformed the RA treatment paradigm over the last twenty years, from focusing on symptom management to now aiming for slowed disease progression and even disease remission.

The remarkable progress made against RA has not come through a single large therapeutic breakthrough, but rather through a complex process of ongoing introductions of new treatment options and incremental gains in our knowledge and understanding of the underlying disease and how RA best responds to various therapies. This dynamic, “step-wise” transformation of progress is seen across many other disease states as well, such as HIV/AIDS and many forms of cancer. While the initial Food and Drug Administration (FDA) approval of a new treatment is a critical first step, the full value and utility of a therapy continues to evolve as research progresses and physicians accumulate evidence in real-world clinical settings.

This step-wise process by which our understanding evolves over time often reveals therapeutic benefits that were unknown or unanticipated at the time of initial FDA approval, including use in combination with other therapies, use earlier in the treatment line or disease state, and use in additional disease indications.

**COMBINATION THERAPY**

Since the first approval of biologic disease modifying anti-rheumatic drugs (DMARDs) in the late 1990s, research has revealed a synergistic effect when these medicines are used in combination with synthetic DMARDs. Studies have shown that a synthetic DMARD used in combination with a biologic DMARD demonstrated greater efficacy than either treatment used alone.

---

**Rheumatoid Arthritis: The Evolution of Clinical Value for Patients**

“The clinical improvements produced by novel treatment options for RA have been far above what could have been anticipated or achieved at the time of the initial introduction of the first treatment options.”


† This may include both new indications approved by the FDA and off-label uses supported by research and deemed clinically appropriate by physicians. The evidence in this paper focuses on new FDA-approved indications.

†† It should be noted that biologics are combined with non-biologics but not with other biologics in the treatment of RA.
A systematic review from 2007 pooled data from thirteen individual clinical trials that examined four biologic DMARDs (etanercept [Enbrel®], adalimumab [Humira®], infliximab [Remicade®], and anakinra [Kinere®]) concluded that the use of methotrexate (a commonly used synthetic DMARD) in combination with any of these biologic agents increased the efficacy of each treatment further than when used alone.⁴

**EARLIER USE OF THERAPEUTICS**

There is a growing body of evidence that earlier initiation of therapy in the course of disease can be highly beneficial for RA patients.⁵

In fact, a 2012 update to the American College of Rheumatology (ACR) guidelines for the treatment of RA, specifically recommends more aggressive earlier treatment.⁶ These guidelines recognize that earlier initiation of treatment can offer patients the best chance of disease remission and better long-term outcomes, in addition to preventing irreversible joint damage.

Long-term follow-up revealed that 46 percent of patients who received treatment earlier in disease achieved remission, compared to only 31 percent of patients treated at an advanced stage.⁷

**USE IN ADDITIONAL DISEASE INDICATIONS**

As physicians and researchers gain an understanding of the underlying mechanism of inflammatory diseases, therapeutics initially developed for use in RA have shown efficacy in other disease indications. In particular, many medications have proven to be beneficial across a spectrum of other autoimmune conditions that share similar molecular pathways, including Crohn’s disease, ankylosing spondylitis, ulcerative colitis, and juvenile idiopathic arthritis, among others.

Additional uses of these therapies across disease areas may not have been fully anticipated at the time of initial approval but were recognized through real-world use and research that built over time.

**CONCLUSION**

Over the past two decades, our understanding of the optimal clinical role and value of new treatments has evolved, both alone and in combination with other therapies, yielding dramatic patient benefits. Additionally, critical knowledge regarding the timing of treatment has revealed that utilization of therapy at earlier stages in the disease cycle offers the best opportunity for disease control and remission. Many therapies have also been shown to provide incremental and previously unrecognized benefit in entirely new indications.

Because of the incremental and evolving nature of clinical research, it is important to recognize that the full value of a treatment is not completely understood at the time of initial market approval. This necessarily requires that patients, and the clinicians who treat them, have full access to a range of treatment options. Policy approaches that seek to assess the definitive value of a therapy at the time of introduction to the market will fail to capture its full value over time and will act as a disincentive to long-term research and innovation. On the other hand, policies that are sensitive to the way value emerges over time will help incentivize future innovation.

“Current therapy for RA is such that progression from symptom onset to significant disability is now no longer inevitable, and RA patients can anticipate comfortable and productive lives on medical therapy... Patients with RA can now expect to experience a quality of life that previously was unavailable to patients during the 20th century.”⁸

— Dr. Katherine Upchurch and Dr. Jonathan Kay, Rheumatology (Oxford)

---


