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Recognizing the Value of Innovation in the Treatment of Rheumatoid Arthritis

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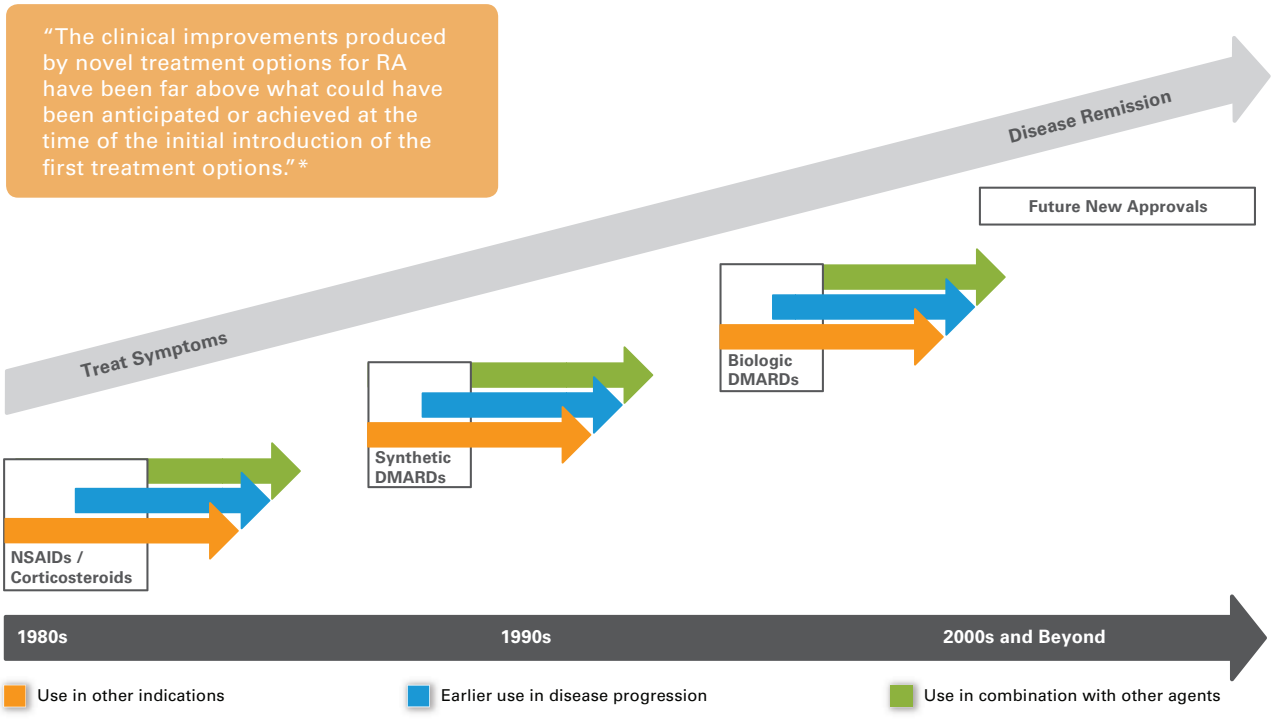
INTRODUCTION

In recent years, we have seen significant progress in our ability to diagnose and manage chronic diseases. Among autoimmune conditions such as rheumatoid arthritis (RA), lupus, and multiple sclerosis, treatment advances have played a major role in slowing disease progression, improving quality of life, and extending survival for many patients. One clear example of this is the gains that have been made over the past 20 years in the treatment of patients with RA. These gains have occurred through the careful collaboration between biopharmaceutical innovators and the Food and Drug Administration (FDA). This collaboration has resulted in the approval of multiple treatment options, and an evolution in our understanding of how best to apply these therapies to achieve optimal patient outcomes.

For new medicines used to treat RA, initial FDA approval, which is based on rigorous, prospective clinical trials, represents an important initial step. However, initial FDA approval is often just the starting point. Recognizing the full value of new treatments for RA has occurred over time through a complex process of incremental gains in knowledge and research. This process involves the accumulation of treatment improvements and an expanding body of evidence on clinical value over time; in other words, a "step-wise transformation" may take place over time within a given disease area. For patients with RA, this evolution in our understanding of the disease biology and how certain novel therapies are optimally applied to patient care has been demonstrated through discovery, clinical development, and post-approval, real-world clinical practice, which has led to substantial clinical gains, improving patients' quality of life and reducing the impact of the disease.

Because medical progress with individual compounds may be realized incrementally over time, the optimal role and full value of a therapy typically cannot be known at the time of initial FDA approval or market launch. While rigorous clinical research of new medicines must be conducted to secure FDA regulatory approval, these studies are designed for controlled evaluation of the safety and efficacy of a new product, usually in a narrowly specified population and under carefully outlined conditions. Therefore, phase III pivotal trials have limitations in their ability to capture the broader and longer-term clinical and quality of life benefits that may be associated with a specific therapy when physicians accumulate evidence using the new agents in real-world settings.

Rheumatoid Arthritis: The Evolution of Clinical Value for Patients



* K.S. Upchurch and J. Kay, "Evolution of treatment for rheumatoid arthritis," *Rheumatology (Oxford)* 51, suppl. 6 (2012); vi28-vi36.

Rheumatoid Arthritis: Symptoms and Treatment

The Centers for Disease Control and Prevention (CDC) estimated in their most recent data that 1.5 million Americans suffered from RA in 2005.[1] RA is a progressive and painful condition in which the body's immune system attacks its own tissues, specifically a thin membrane that lines the joints called the synovium. Until the late 1990s, clinicians treated RA with synthetic disease modifying anti-rheumatic drugs (DMARDs) (primarily methotrexate [MTX]), nonsteroidal anti-inflammatory drugs (NSAIDs), and low-dose corticosteroids. The advent of biologic DMARDs, combined with the growing ability to objectively evaluate and define outcomes in the treatment of RA, has dramatically altered the course of this disease and the way it is managed. Treatment of RA has transformed from managing symptoms to aiming for disease remission by inhibiting specifically targeted biochemical pathways of inflammation.

This white paper is one in a series of reports focused on recognizing value in biopharmaceutical innovation. The first white paper, *Recognizing Value in Oncology Innovation* (June 2012), demonstrated how the full clinical value of a cancer therapy typically evolves significantly after FDA approval. Similarly, a white paper released in December 2012, *Recognizing the Value of Innovation in HIV/AIDS Therapy*, examined the step-wise evolution in HIV/AIDS therapy, which transformed what was once considered a uniformly fatal disease into a manageable, chronic condition for patients who have access to medicines. In this white paper, we will explore the various ways in which additional clinical value — including improved outcomes and quality of life — is realized over time for RA patients. In each of these disease areas, for many therapies, this evolution over time reveals a much greater clinical value based on real-world experience than was able to be demonstrated at launch, particularly for first-in-class therapies. At times, of course, real-world experience can prove a medicine to be less valuable than initially expected, or higher value in some subgroups and lower value in others, which also reflects the evolution in understanding and optimal patient care.

The pathways identified in this white paper illustrate some of the ways the value of therapeutics for RA change over time, including a few that are shared in common with cancer and HIV/AIDS treatments. These include:

- Use in combination with other agents
- Use earlier in treatment line and earlier in disease state
- Use in different disease indications†

As noted in our previous papers, initial FDA approval often marks the "starting point" for a number of additional evaluations of a novel therapy. 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. As physicians test and assess the impact of new treatment options in real-world clinical practice, they attain incremental clinical breakthroughs. Understanding how this progress is achieved — as well as how the evidence supporting it evolves — is important to sustaining an environment for future advances.

In the case of RA, biologic DMARDs have proven to be effective in a broader cohort of patients than were represented in the clinical trial data submitted for initial FDA approval. Individual and combination therapies have expanded opportunities for improved disease control and remission, particularly when used in patients with earlier disease stages who were not tested as part of pre-approval trials.

Therefore, it is important to understand that the full clinical value and potential of a therapy may only be identified and realized over time.

As a result of this "step-wise" innovation, the treatment paradigm for RA patients has shifted from addressing relief of symptoms to targeting therapy to achieve disease remission.

† 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.

USE IN COMBINATION WITH OTHER AGENTS

The treatment paradigm for RA has evolved to include more routine use of combination therapies. Combination treatments for RA have now been shown to provide the best opportunity for clinical response and disease remission, even beyond the level of outcomes captured in clinical trials at the time of FDA approval.

Since the approval of biological DMARDs in the late 1990s, researchers and clinicians have expanded the evidence of a synergistic effect when these biologics are combined with MTX, revealing more benefits for patients in combination with each other than either treatment used alone.†† There has been an increasing volume of recently published data documenting this effect in the management of RA.[2]

A systematic review from 2007 used meta-analytical techniques to pool data from 13 individual clinical trials.[3] Analysis included studies of four biologic DMARDs (etanercept [Enbrel®], adalimumab [Humira®], infliximab [Remicade®], and anakinra [Kineret®]), and concluded that the use of MTX in combination with any of these biologic agents increased the efficacy of each treatment further, as measured by the American College of Rheumatology (ACR) ACR20 criteria.

The evolution of combination therapies can be traced back through the development of etanercept, the first biologic approved to treat RA. The controlled trials that led to FDA approval of etanercept demonstrated that etanercept monotherapy yielded superior symptom improvement compared to both placebo and to MTX, the traditional synthetic DMARD frequently used to treat RA.[5] While combination therapy did show a slightly improved response over monotherapy, it was not emphasized in the initial prescribing information for etanercept based on these early studies.

Since the FDA approval of etanercept, additional clinical studies have proven the benefits of combining newer biologic agents, such as etanercept, with MTX to improve patient outcomes, in some cases beyond the levels observed with monotherapy of either type of agent. The older generation of therapies has found renewed utility in combination with the new generation. Physicians and patients have observed better clinical response rates, functional capacity, and quality of life from treatment with these combinations than from monotherapy.[6]

Disease Measurements

ACR20

The ACR20 is a standard criterion used to measure the effectiveness of treatments in clinical trials for RA. This measurement was developed in 1995 when the American College of Rheumatology (ACR) formed a new composite scoring mechanism, defining treatment efficacy for patients in clinical trials as a greater than 20 percent improvement in tender and swollen joint counts and in at least three out of five other core measures, including: 1) Physician assessment of disease activity, 2) Patient assessment of disease activity, 3) Patient assessment of pain, 4) Patient assessment of physical function, and 5) A measure of inflammation using blood markers.[4]

When infliximab was approved for the treatment of RA in 1999, it was specifically indicated to be dosed in combination with a stable regimen of MTX. The pivotal, multinational phase III trial illustrated the benefit of a regimen of infliximab plus MTX in comparison to MTX-only treatment. The first published results showed the control of signs and symptoms of RA at 30 weeks and also showed the inhibition of structural bone damage at 54 weeks.[7,8] An additional year of follow-up revealed a significant clinical response in patients receiving combination therapy as evidenced by measured ACR20 criteria. Patients receiving MTX plus placebo had an ACR20 response of 16 percent while patients receiving a combination of infliximab and MTX had significantly higher ACR20 responses between 40 and 48 percent ($P<0.0001$ for all groups). Additionally, there was a marked improvement in physical functioning and quality of life as measured by the Medical Outcomes Study Short Form 36 health survey (SF-36). Finally, radiographic evaluation of joint damage and structural weakening showed that there was significantly less progression in patients receiving

†† It should be noted that biologics are combined with non-biologics but not with other biologics in the treatment of RA.

combination therapy, with no evidence of dose response.[9] These data were not available at the time the FDA granted initial approval of infliximab for the treatment of rheumatoid arthritis.

A subsequent study of infliximab showed similar benefits of combination therapy with MTX. This trial examined the treatment benefits among patients with an RA diagnosis of less than three years duration. Clinical response rates were significantly higher in the infliximab and MTX combination groups compared with the patient group receiving solely MTX.[10]

Disease Measurements

ACR50 and ACR70

As RA treatment strategies improved from the late 1990s to the early 2000s, some physicians began to view the ACR20 threshold for measuring symptom improvement as a less sensitive measure of treatment differences. The magnitude of symptom improvement for patients on biologics largely surpassed the 20 percent improvement threshold represented by the ACR20 measurement. Thus, in 2007, the ACR proposed a revision of the ACR20, creating an updated hybrid outcome measure that includes 50 percent and 70 percent improvements (ACR50 and ACR70). The ACR acknowledged then that the prior threshold for response (ACR20) had "been criticized as less sensitive to change" and was "thought to be low."[11] This shift reflected the gains made in RA treatment due in no small part to new, better therapeutic agents and their use in effective combinations.

The availability of long-term longitudinal data has confirmed the significant clinical success that can be achieved by treating with biologics and synthetic DMARDs in combination. For instance, one of the clinical trials referenced in the original FDA approval of adalimumab ("Study III") demonstrated that adalimumab plus MTX yielded ACR20 responses of 63 percent and 59 percent at Month 6 and Month 12, respectively, but ACR70 responses of only 21 percent and 23 percent[12] (See Table 1). While these data revealed the benefit of combination therapy over monotherapy, more robust information was necessary to confirm the results.

It was not until the publication of a later two-year study, PREMIER, that long-term outcomes confirmed that a substantial proportion of patients could achieve ACR70 and clinical remission. Patients with early, aggressive RA were randomized to three treatment arms: combination of adalimumab plus MTX, adalimumab monotherapy, and MTX monotherapy.[13] At the end of year two, combination treatment with adalimumab plus MTX led to significantly better clinical response, physical functioning, and radiographic imaging of joint spacing than either drug alone.

A 2010 report presented data from an extension of the PREMIER study that followed patients for an additional three years. In the extension study, all patients were placed on adalimumab monotherapy and evaluated based on their initial treatment designation from the original PREMIER study. As this was an open-label study, both the researchers and trial participants knew which treatment was being administered and if necessary, could modify treatment. During the extension period (years three to five), patients originally in the combination therapy arm had a notably better clinical response as measured by ACR70 and

Table 1: Disease Response at Six and Twelve Months

Study III: Methotrexate Combination (Six and Twelve Months)

Response		Placebo + MTX N=200	adalimumab + MTX N=207
ACR20	Month 6	30%	63%
	Month 12	24%	59%
ACR50	Month 6	10%	39%
	Month 12	10%	42%
ACR70	Month 6	3%	21%
	Month 12	5%	23%

Source: FDA Humira® (adalimumab) full prescribing information, http://www.accessdata.fda.gov/drugsatfda_docs/label/2002/adalabb123102LB.htm#clin, 2002.

Disease Measurements

DAS28

The DAS28 score is calculated by a complex mathematical formula, which includes the number of tender and swollen joints (out of a total of 28), the erythrocyte sedimentation rate (ESR, a blood marker of inflammation), and the patient's global assessment of health. A DAS28 score greater than 5.1 indicates active disease, less than 3.2 indicates well controlled disease, and less than 2.6 indicates disease remission.[14]

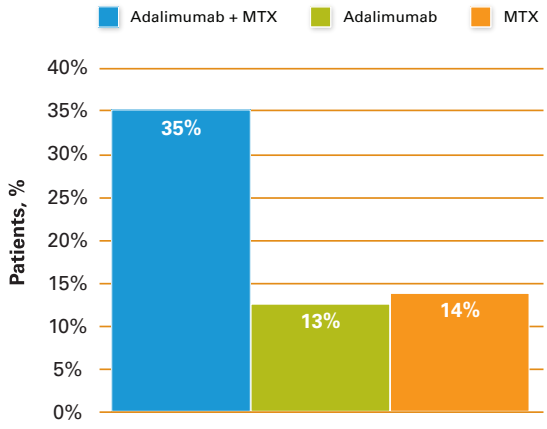
the DAS28 score, another common measure of disease activity in RA. In fact, at the end of five total years of treatment, 35 percent of patients who originated on the combination arm exhibited comprehensive disease remission compared to thirteen percent and fourteen percent of patients on the adalimumab and MTX monotherapy arms, respectively (See Figure 1).[15]

Echoing the PREMIER study, the COMET (COmbination of Methotrexate and ETanercept) trial results showed that 50 percent of patients with early RA treated with a combination of etanercept and MTX achieved clinical remission after one year, compared with only 28 percent of patients on MTX alone.[16] In addition, 80 percent of the combination group achieved radiographic non-progression compared with 59 percent on MTX alone.

USE EARLIER IN TREATMENT LINE OR DISEASE STATE

In addition to an improved understanding of the value of treatments used in combination, research has also demonstrated the benefits of initiating treatment earlier to better control disease progression and improve long-term outcomes among RA patients. Real-world clinical practice and clinical studies have given physicians and researchers a better understanding of the impact of initiating therapies at various points in the disease cycle; patients achieve superior treatment response and duration of remission when biologic therapy is initiated as early as possible, rather than at the point when a patient fails to respond after a series of treatments with several different synthetic DMARD agents.

Figure 1: Comprehensive Disease Remission* at Year Five

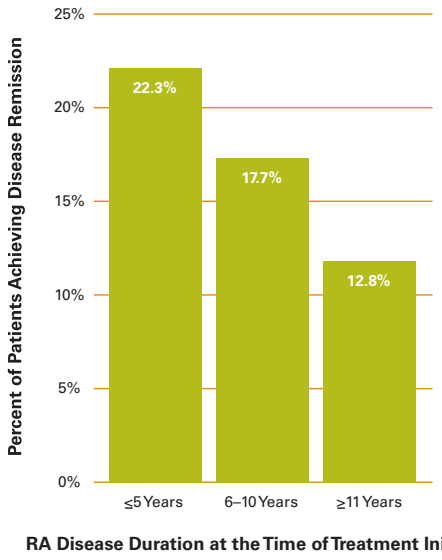


***The triple criteria for disease remission include clinical remission (DAS28 score less than 2.6); no radiographic progression (ΔmTSS ≤0.5); and normal function (HAQ ≤ 0.5).**
Source: D. Van der Heijde, F.C. Breedveld, A. Kavanaugh, et al., "Disease activity, physical function, and radiographic progression after longterm therapy with adalimumab plus methotrexate: 5-year results of PREMIER," *Journal of Rheumatology* 37, no. 11 (2010): 2237–2246.

Prior to the approval of biologic options, many patients with RA would begin treatment with only NSAIDs and low-dose corticosteroids. Treatment with a synthetic DMARD was typically delayed until joint damage was documented.

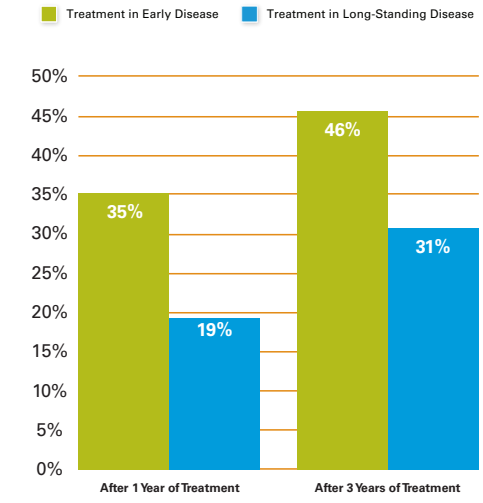
Over the last decade, as biologics and new combination regimens have become available, the utility and role of biologic therapies in the treatment of RA has expanded, with increasing data to support much earlier initiation of treatment.[17] The 2012 update to the ACR treatment recommendations for RA specifically recommends, "more aggressive treatment in patients with early RA," which is a change from the 2008 ACR recommendations.[18] The rationale for this shift was attributed to several considerations: "1) the expectation that the earlier the treatment the better the outcome, 2) the thought that joint damage is largely irreversible so prevention of damage is an important goal, and 3) the data that early intensive therapy may provide the best opportunity to preserve physical function and health-related quality of life and reduce work-related disability." This growing evidence documenting that early

FIGURE 2: Remission of Disease as Impacted by the Timing of Biologic Treatment Initiation



Source: 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.

FIGURE 3: Proportion of Patients Achieving Disease Remission in Early vs. Long-Standing Disease*



***Early disease is defined as disease duration less than or equal to two years while long-standing disease is defined as disease duration greater than or equal to ten years.** Source: Y. Yazici, D. Moniz Reed, C. Klem, et al., "Greater remission rates in patients with early versus long-standing disease in biologic-naïve rheumatoid arthritis patients treated with abatacept: a post hoc analysis of randomized clinical trial data," *Clinical and Experimental Rheumatology* 29, no. 3 (2011): 494-499.

initiation of a biologic, combined with a synthetic DMARD like MTX, leads to better long-term outcomes, has led to a shift in the goals of RA treatment — from managing disease progression and pain to aiming for lowered disease activity or remission. These biologics were approved for disease management, but researchers have learned over time that they can also lead to disease remission, making this an increasingly realistic goal.

Results from the 2005 BeSt study showed that patients who initiated early combination therapy (either of MTX + prednisone or MTX + infliximab) experienced more rapid functional improvement, less progression of radiographic joint damage, and fewer side effects than patients who received MTX alone or step-up combination therapy (where, beginning with MTX, additional therapies were added if the measured response to treatment was still insufficient).[19] In fact, in the first year of follow up, there was no progression of joint damage in 93 percent of the patients who received combination MTX and infliximab therapy early in the disease course, compared with 87 percent of patients who received combination MTX and prednisone, 73 percent of patients who were on step-up combination therapy, and 67 percent of patients who were receiving monotherapy treatment.

A large 2011 study drawing from the Consortium of Rheumatology Researchers of North America (CORRONA) registry examined the impact of starting treatment earlier in the course of disease. The study identified patients newly initiated on a biologic treatment and compared the likelihood of remission for patients at different stages of disease. Of patients initiated on a biologic at fewer than five years disease duration, 22.3 percent achieved remission, as compared to only 17.7 percent of patients who initiated therapy with six to ten years of disease duration and 12.8 percent among patients who initiated treatment after more than eleven years of disease duration (P<0.001).[20] (**See Figure 2**)

A post hoc analysis of data from a randomized clinical trial studying abatacept (Orencia®) revealed greater remission rates and disease response in RA patients with early disease (duration less than two years) compared with patients who had long-standing disease (greater than ten years). (**See Figure 3**) These results support the use of abatacept earlier in disease course.[21]

Some of the studies mentioned earlier in this report, which demonstrated the value of combination therapy in the treatment of RA, also illustrated the benefit of initiating treatment earlier in disease state. The COMET trial enrolled only patients who had had moderate-to-severe RA for only three to 24 months and had never received treatment before; over half of patients receiving combination therapy in this study achieved improved physical functioning.[16] The researchers concluded that, "These data build on the results in patients with more longstanding disease than those included in this study, further supporting the value of early intervention."

Likewise, the researchers in the PREMIER study, which also examined combination therapy in a patient population with early, aggressive disease, noted that, "Early intervention that prevents irreversible damage would appear to offer the best opportunities for achievement of favourable outcomes in patients with early, aggressive RA. In early intervention studies…this therapeutic window can be as short as months."[13]

These clinical studies point to the growing body of evidence supporting the benefits of earlier use of combination synthetic DMARDs and biologic therapy to treat RA. The sooner patients diagnosed with RA are treated, the more likely they are to achieve and sustain remission before the onset of irreversible joint damage.

Experts in the field have stressed the importance of this "treatment window of opportunity" in patients with recently-diagnosed disease.[22-25] Early intervention is now recognized by physicians and many disease groups as the best method for preventing extensive joint damage and halting the progress of the disease.

Aggressive intervention earlier in the disease course, made possible by more effective utilization of synthetic and biologic DMARDs, and the emergence of more precise and objective measures of efficacy, has had a significant impact on RA treatment approaches. Remission and lowered disease activity have become the goals in RA treatment.[26] In 2011, the ACR released a joint publication with the European League Against Rheumatism (EULAR) redefining RA remission and recommending that this new definition be uniformly applied and widely used in RA clinical trials.[27]

Never before has remission been required as a specific endpoint in clinical trials, but as the full benefit of newer RA treatment options has been demonstrated in clinical practice and research, it has prompted clinical experts to change the standard of treatment success.

USE IN ADDITIONAL DISEASE INDICATIONS

Improved understanding of RA disease pathology has had a direct impact on the development of biologic therapies to treat not only RA but a host of other inflammatory conditions over the past two decades. With better comprehension of how these conditions evolve and progress, many therapies have become more targeted and have proven to be beneficial for a series of other related disease indications.

Many immunologically-mediated inflammatory conditions share specific signal transduction pathways with known roles in the pathogenesis of inflammation and joint and tissue destruction. Because certain inflammatory diseases share these common molecular underpinnings, biologic agents designed to target a specific component of one signal pathway have proven to be effective treatments for multiple other disease types as well. For instance, biologic DMARDs such as etanercept and adalimumab were initially approved by the FDA in 1998 and 2002, respectively, for the treatment of RA based on their blocking effect on TNF-α action. TNF-α is an inflammatory cytokine that participates in a variety of inflammatory disorders. Additional clinical studies of both etanercept and adalimumab — among other biologics — have shown that these medicines are effective not only in the management of RA, but also multiple other clinical indications associated with inflammation that is mechanistically related to TNF-α, such as Crohn's disease, juvenile idiopathic arthritis, and plaque psoriasis (**See Table 2**).

Another striking example of this expansion to additional indications is infliximab, which was originally indicated for Crohn's disease in 1998 and quickly gained FDA approval for RA in 1999. In subsequent years, infliximab received supplemental approval for a number of other

Table 2: FDA-Approved Biologic Agents for Forms of Rheumatoid Arthritis by Indication and Year of Indication Approval

Indication	Crohn's Disease	RA	Refractory RA	Refractory Crohn's	Juvenile Idiopathic Arthritis	Psoriatic Arthritis	Ankylosing Spondylitis	Plaque Psoriasis	Ulcerative Colitis	Pediatric Crohn's
infliximab (Remicade®; anti-TNF-α)	1998	1999				2005	2004	2006	2005	2006
etanercept (Enbrel®; anti- TNF-α)		1998			1999	2002	2003	2004		
anakinra (Kineret®; IL-1 receptor antagonist)			2001							
adalimumab (Humira®; anti-TNF-α)	2007	2002			2008	2005	2006	2008	2012	
abatacept (Orencia®; T-cell modulator)		2005			2008					
rituximab (Rituxan®; B-cell inhibitor)			2006							
certolizumab (Cimzia®; anti-TNF-α)		2009		2008						
golimumab (Simponi®; anti-TNF-α)		2009				2009	2009			
tocilizumab (Actemra®; IL-6 receptor antibody)		2010			2011					

1st Approved Indication
2nd Approved Indication
3rd Approved Indication
4th Approved Indication
5th Approved Indication
6th Approved Indication
7th Approved Indication

Source: U.S. FDA, Drugs@FDA: FDA Approved Drug Products, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ (data current as of 01 January 2013).

indications, including ankylosing spondylitis, ulcerative colitis, psoriatic arthritis, pediatric Crohn's disease, and plaque psoriasis.[28] FDA approval for each expanded indication was based upon clinical and radiographic data from pivotal clinical studies, which showed that these biologics were safe and effective beyond their initial therapeutic uses.

There has been substantial momentum in biologic use over the past decade. Many FDA-approved biologics have been approved for up to six additional indications beyond their initial indication. A nuanced understanding of the pathophysiology of disease and the role that these targets play, is critical in order for physicians and researchers to unlock the broader potential of biologics. Because certain molecular targets occupy similar signal pathways in other organ systems of the body, there has been a natural expansion of indications within the class of biologic treatments. Biologic agents that target specific components of the immune response have proven to have a much broader range of efficacy than was initially anticipated. For instance, adalimumab, certolizumab pegol (Cimzia®), and others have been shown to interfere with the body's inflammatory response in inflammatory bowel disease (IBD), including many forms of Crohn's Disease, by targeting specific cytokines. Understanding how to target these types of molecular pathways has revealed more biologic treatment options for patients suffering from a wide range of conditions, such as IBD, psoriasis, and ankylosing spondylitis, in addition to those patients suffering from RA.

CONCLUSION

Substantial clinical gains have been made in the treatment of RA over the past two decades. Advances in treatment and the clinical endpoints or metrics used to evaluate treatment success have fundamentally shifted the paradigm for doctors and patients, redefining what is considered a successful clinical outcome. The standard definition of remission as put forth by the ACR and EULAR is a higher goal than what was thought possible decades ago. This new standard is now widely disseminated and recommended for use in RA clinical trials, indicating that remission is an achievable and realistic treatment objective. The likelihood of achieving this objective has been significantly enhanced by the step-wise transformation we have seen in treatments, with increased availability of innovative biologic therapies and varied mechanisms of action. Through an ongoing evolution of treatment options and research guiding the standard of care, we have achieved a revolution in patient outcomes.

> *"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."*
>
> – Dr. Katherine Upchurch and Dr. Jonathan Kay, *Rheumatology (Oxford)*[29]

These gains have been made slowly but steadily through a complex series of incremental improvements in treatment over time. The introduction of new medicines is clearly a vital step in advancing treatment options and improving outcomes for patients. However, the full value of new medicines often emerges over time through continued research and changes in practice, revealing broader benefits that may not have been proven or even anticipated at the time of initial FDA approval.

Over the past two decades, a greater understanding of the optimal clinical role and value of new treatments has evolved, both alone and in combination with other therapies. Additionally, critical knowledge regarding the timing of treatment has revealed that utilization of combination treatments at earlier stages in the disease cycle offer the best opportunity for disease control and remission. Many therapies have been shown to provide incremental and previously unrecognized benefit in entirely new indications. Many drugs for RA have received expanded FDA approval to include multiple other serious autoimmune disorders.

By examining RA treatment as a case study, this paper illustrates the extent to which the initial assessment of a therapy based solely on available evidence at the time of market launch often substantially underestimates the full clinical value of the treatment to patients. The analysis builds on prior work which has identified similar dynamics in other areas, such as HIV/AIDS and cancer treatment. It is important to recognize that over time, through real-world practical experience and clinical research, a growing body of published data documenting this experience has revealed unforeseen elements of value for individual therapies that were not known at the time of initial FDA approval. This necessarily requires that patients, and the clinicians who care for them, have access to a full range of therapeutic options so that they can adapt their treatment plans as researchers learn more about the role and utility of each medicine.

These findings hold important implications for policy makers as well as patients and physicians. 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 ensure that new treatments are available to patients, properly valued, and assessed over time. Such policies, which are in line with the scientific process, will also promote future advances by properly incentivizing innovation. Continued innovation and evolution with both existing and as-yet undiscovered therapies provides hope for future clinical advances that will benefit individual patients and society as a whole.

ENDNOTES

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