

August 1, 2016

Steven Pearson, MD, MSc
President, Institute for Clinical and Economic Review
Boston, MA 02109 USA

Re: Institute for Clinical and Economic Review (ICER) Review of Treatments for Rheumatoid Arthritis and Psoriatic Arthritis

Dear Dr. Pearson,

On behalf of the more than 50 million adults and 300,000 children in the United States with doctor-diagnosed arthritis, the Arthritis Foundation appreciates the opportunity to provide comments to ICER on the selected topic of rheumatoid arthritis (RA). RA is a complex chronic disease that can be difficult to treat, and people who suffer from the disease require regular, ongoing professional care. Further, a treatment that works well in one person might not work in another person with the seemingly identical disease characteristics, so patient access to the full range of treatment options is also critically important. The Arthritis Foundation also believes robust stakeholder engagement is a critical component of any evaluation that will have a direct impact on people with arthritis and the providers who treat them. We want our comments to inform ICER's process and help ensure that the final report reflects the complexity of the disease and the needs of the people who suffer from it.

Psoriatic Arthritis (PsA)

Psoriatic Arthritis (PsA) is an autoimmune disease in which a person's immune system mistakenly attacks healthy tissue, in this case the joints and skin. The faulty immune response causes inflammation that triggers joint pain, stiffness and swelling. The inflammation can affect the entire body and may lead to permanent joint and tissue damage if it is not treated early and aggressively. Most people with psoriatic arthritis have skin symptoms before joint symptoms. However, sometimes the joint pain and stiffness strikes first. In some cases, people get psoriatic arthritis without any skin changes. The disease may lay dormant in the body until triggered by some outside influence, such as a common throat infection. Another theory suggesting that bacteria on the skin triggers the immune response that leads to joint inflammation has yet to be proven. PsA and RA share some medical treatments, but are medically very different. The disease progression, treatments, and experiences of patients differ greatly between PsA and RA.

ICER proposes to couple RA and PsA together in their review, and the Arthritis Foundation strongly recommends the diseases be separated into two different reports. The patient community for PsA has very different experiences than the patient community for RA. Focusing on both diseases in one report will dilute the patient voice and not allow for a robust assessment of each disease. With that said, the Arthritis Foundation will focus their comments primarily on RA.

Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is an autoimmune disease in which the body's immune system – which normally protects its health by attacking foreign substances like bacteria and viruses – mistakenly attacks the joints. The cause of RA is not yet fully understood, although doctors do know that an abnormal response of the immune system plays a leading role in the inflammation and joint damage that occurs. Along with joint inflammation and pain, many people experience fatigue, loss of appetite and a low-grade fever. Because RA is a systemic disease, it may also affect organs and body systems. RA is a very complex disease that is hard to treat and patients often have to try and fail many medications before finding one that works. In fact, one estimate of rheumatoid arthritis patients taking one of the three first-generation biologics for at least 6 months showed that between 40-50% of them failed to meet the American College of Rheumatology 50% improvement criteria. Of patients who fail on a biologic, rheumatologists switch their patients to another biologic 90% of the time¹. To complicate the matter further, many drugs to treat arthritis are prescribed off-label. A one-size-fits all approach simply cannot work among this population. Innovative science is moving at a rapid speed, and any decision made today may need to be changed tomorrow; we are concerned about how revisions to any recommendations will be triggered in the future.

Further, we are also concerned that the title of the ICER report does not make it clear that this review will be conducted on the adult population only. There are over 300,000 children with arthritis and fewer than 350 pediatric rheumatologists across the country, meaning many of these children have to see an adult rheumatologist or a general pediatrician. Nationwide 75% of all medications for children are prescribed off label¹¹; therefore a report of this nature that includes the pediatric population would be premature, narrow in scope, and potentially detrimental.

Our final concern pertains to the timeline of ICER's review. The timeline of this review is very short from July 2016 to January 2017. Previous reviews conducted by ICER, like the Multiple Sclerosis drug review received an extended timeline, delaying the release of the final report to allow ample time to fully consider all aspects of the topic and to ensure that the report's findings are relevant and actionable for all stakeholders. We urge ICER to reevaluate the timeline of review for RA and PsA.

Medications for RA

There are many medications for RA. The goals of RA treatment are to stop inflammation, relieve symptoms, prevent joint and organ damage, improve physical function and overall well-being, and to reduce long-term complications. Treatments for RA vary from medications that primarily ease the symptoms to medications that slow or stop the course of the disease. Nonsteroidal anti-inflammatory drugs (NSAIDs) are available over-the-counter and by prescription. They are used to help ease arthritis pain and inflammation. NSAIDs include such drugs as ibuprofen, ketoprofen and naproxen sodium, among others. Corticosteroids are also used to slow disease activity. Corticosteroid medications, including prednisone, prednisolone and methyprednisolone,

are potent and quick-acting anti-inflammatory medications. They may be used in RA to get potentially damaging inflammation under control, while waiting for NSAIDs and DMARDs to take effect. Because of the risk of side effects with these drugs, doctors prefer to use them for as short a time as possible and in doses as low as possible. Disease-modifying antirheumatic drugs (DMARDs) are drugs that work to modify the course of the disease. Traditional DMARDs include methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, cyclophosphamide and azathioprine. These medicines can be taken by mouth, be self-injected or given as an infusion. Biologics are a subset of DMARDs and may work more quickly than traditional DMARDs. Biologics target specific steps in the inflammatory process and do not diminish the immune response, as is the case with some other RA treatments. In many people with RA, a biologic can slow, modify or stop the disease – even when other treatments have not adequately helped. Finally, JAK inhibitors, another subcategory of DMARDs known as “JAK inhibitors” block the Janus kinase, or JAK, pathways, which are involved in the body’s immune response. Tofacitinib belongs to this class.

Further, biosimilars will be entering the marketplace in the near future. Specifically, the FDA approved the biosimilar of Remicade in the spring and the FDA Arthritis Advisory Committee has recommended approval of the biosimilars of Humira and Enbrel. These complex, genetically engineered products offer new and hopefully more affordable treatment opportunities for people with inflammatory, autoimmune forms of arthritis. The economic impact of biosimilars on the market is largely unknown and the physiological impact of switching between a biologic and biosimilar is also unknown. Anecdotal evidence suggests that if a patient is switched to a biosimilar and it does not prove effective they may have trouble switching back to a biologic. We encourage a longer look back period in order to effectively evaluate the value of biosimilars to the patient and marketplace. There have been major strides in innovative treatments for people with RA and this is a very uncertain time for the market place. Therefore, making decisions about the value of a drug without robust supporting data is questionable. ICER should carefully consider the process used to evaluate and make decisions regarding biosimilar medications once they are on the market, so the patient experience can be fully evaluated. Further as new treatments and more robust information about these treatments become available, how will these decisions be revised in the future?

Patient Community

Forty-one per 100,000 people were diagnosed with RA annually from 1995-2007. The incidence of RA rises with age and is typically two to three times higher in women than men. The onset of RA, in both women and men, is highest among those in their sixtiesⁱⁱⁱ. In 2007, RA accounted for 22% of all deaths due to arthritis and other rheumatic conditions in the United States. Many patients with RA also suffer comorbidities such as cardiovascular disease, mental health conditions, infections, and malignancies^{iv}. Of adults diagnosed with arthritis 47% also have at least one of the previously listed conditions. Many deaths in individuals with RA are attributable to cardiovascular causes, including ischemic heart disease and stroke. RA also has a disproportionate effect on military veterans. Data from the Veterans Affairs Rheumatoid

Arthritis registry confirms that the mortality rate among veterans with RA is more than double the rate among those without RA, yet the reasons are unknown.

People with RA also experience reduced quality of life and diminished work capacity, and are twice as likely to have activity limitations. During an RA flare it can be hard to even get out of bed in the morning, or to perform the most basic tasks like opening a jar. A recent study by Andrade et al. (2016) found that among people with RA decreased handgrip strength and hand ROM most frequently resulted in activity limitations, followed by decreased dexterity and impaired vitality. The researchers suggest activity limitations are very complex and multifactorial, further emphasizing the fact that one-size fits all approaches do not work among this population^v.

Because of the nuanced nature of arthritis treatment, we are particularly concerned about the implications of this ICER report limiting treatment options for RA patients. As stated previously, medications that have proven to be clinically effective in treating RA may not work for a particular person, whereas a drug that is not clinically indicated to treat that form of RA may be the only drug that works for that person. Patient experience has shown that while a particular drug may work for a period of time it may not be efficacious for the duration of the patient experience. Again, RA is a complex disease in which treatment is very patient-specific. The majority of current value frameworks aims to help payers with formulary decision-making and may leave out the patient perspective when determining value. Therefore, all of the aforementioned considerations should be taken into account when making decisions about RA medications.

Current Literature

Early and aggressive medical research and treatment is needed to reduce the incidence of and relieve disabling symptoms of RA. Unfortunately, there are vast gaps in the literature surrounding RA medications and clinical trials. It is very concerning that there are limited long-term studies regarding the natural occurrence of RA or innovative RA medications, indicating potential underreporting of outcomes, adverse events and safety concerns^{vi}. RA patients may be switched between medications frequently, but these changes are only reported administratively, and therefore the reasons for prescribing patterns are largely unknown. In order to ascertain clinical intent for changes in treatment, more robust data sources are needed^{vii}. Many of the clinical trials conducted for RA are not random populations and tend to be homogenous in nature; therefore many populations of people may be under-represented. For example, patients with early or mild RA who are otherwise healthy and have infrequent visits to their doctor are under-sampled^{viii}. It is extremely important to understand the early onset of RA, because the first two years is a critical time when the patient is most susceptible to irreversible structural damage.

Furthermore there is a large imbalance among industry-funded studies and academic institutions. Paul and Ranganathan (2011) found that industry-funded studies far outnumber those conducted by the government or academic institutions, with 73.2% of studies funded by industry and only 18.9% funded by academic/government institutions. Even more concerning is the length of

study: industry funded studies only lasted on average 12 months, whereas academic studies lasted for more than 24 months^{ix}. Short trial durations may not capture the full range of benefits or adverse events of a medication. We hope that ICER will take the current body of literature and research gaps into account when developing the scoping draft document.

Overall, the Arthritis Foundation wants to ensure people with arthritis have access to the medications they need to function in daily life. We are concerned that this clinical effectiveness and economic review of RA drugs could lead to patients losing access to the drugs and treatments they depend on to maintain a functional quality of life. Some people spend years cycling through different treatments before they find one that works for them. If a person stops treatment, it could lead to joint degeneration, organ damage, and even joint death. The Arthritis Foundation cannot support any recommendations that could result in a patient on a stable drug no longer having access to that drug. To that end, we urge ICER to consider the critical need for adherence to drug regimens, and the perspective of patients and stakeholders to ensure that the scoping document and subsequent final report has the broadest possible relevancy.

Again, thank you for the opportunity to participate in the public comment period on the ICER selected topic of Rheumatoid Arthritis. Please contact Sandie Preiss, Arthritis Foundation National Vice President of Advocacy and Access, at 202-887-2910 or spreiss@arthritis.org with questions or for more information.

Sincerely,



Sandie Preiss
Vice President, Advocacy and Access
Arthritis Foundation

ⁱ Renda-Baum, Regina; Wallenstein, Gene; Koncz, Tamas; Kosinski, Mark; Yang, Min; Bradley, John; Zwillich, Samuel. "Evaluating the Efficacy of Sequential Biologic Therapies for Rheumatoid Arthritis Patients With an Inadeq

ⁱⁱ Yoon, E. Y., Dombkowski, K. J., Rocchini, A., Lin, J.-J., & Davis, M. M. (2007). Off-label Utilization of Antihypertensive Medications in Children. *Ambulatory Pediatrics: The Official Journal of the Ambulatory Pediatric Association*, 7(4), 299-303. <http://doi.org/10.1016/j.ambp.2007.04.005>

ⁱⁱⁱ Centers for disease control and prevention. (2016). In *Rheumatoid Arthritis*. from <http://www.cdc.gov/arthritis/basics/rheumatoid.htm>

^{iv} Centers for disease control and prevention. *Comorbidities*. CDC, 2015. Web. 1 Aug. 2016. http://www.cdc.gov/arthritis/data_statistics/comorbidities.htm.

^v Andrade, J., Brandão, M.,B., Pinto, M. R. C., & Lanna, C. C. D. (2016). Factors associated with activity limitations in people with rheumatoid arthritis. *The American Journal of Occupational Therapy*, 70(4), 1-7. doi:<http://dx.doi.org/10.5014/ajot.2016.017467>

^{vi} Ryan, C., Korman, N. J., Gelfand, J. M., Lim, H. W., Elmets, C. A., Feldman, S. R., ... & Van Voorhees, A. S. (2014). Research gaps in psoriasis: opportunities for future studies. *Journal of the American Academy of Dermatology*, 70(1), 146-167.

^{vii} Yazici, Y., Shi, N., & John, A. (2008). Utilization of biologic agents in rheumatoid arthritis in the United States: analysis of prescribing patterns in 16,752 newly diagnosed patients and patients new to biologic therapy. *Bulletin of the NYU hospital for joint diseases*, 66(2), 77-77.

^{viii} Yazici, Y., Shi, N., & John, A. (2008). Utilization of biologic agents in rheumatoid arthritis in the United States: analysis of prescribing patterns in 16,752 newly diagnosed patients and patients new to biologic therapy. *Bulletin of the NYU hospital for joint diseases*, 66(2), 77-77.

^{ix} Paul, J. R., & Ranganathan, P. (2012). Clinical trials in rheumatoid arthritis: a status report from the ClinicalTrials.gov website. *Rheumatology international*, 32(6), 1831-1835.