Janus Kinase Inhibitors and Biosimilars for Rheumatoid Arthritis: Final Policy Recommendations

January 9, 2020

Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the December 9, 2019 CTAF public meeting on the use of Janus kinase (JAK) inhibitors for rheumatoid arthritis (RA). At the meeting, ICER presented the findings of its revised report on these treatments and the CTAF voting panel deliberated on key questions related to their comparative clinical effectiveness, potential other benefits and contextual considerations, and long-term value for money at current prices. Following the votes, ICER convened a Policy Roundtable of two patients, two clinical experts, two payers, and two representatives from a pharmaceutical manufacturer to discuss how best to apply the evidence and votes to real-world practice and policy. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

A recording of the conversation can be accessed here, immediately followed the CTAF voting portion of the meeting. More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's report on these treatments, which includes the same policy recommendations, can be found here.

The roundtable discussion was facilitated by Dr. Steven D. Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Biosimilars

Biosimilars offer a tremendous unrealized opportunity to bring patients the benefits of the most effective treatments available while controlling costs for patients and the health care system. Looking at the evidence on one representative biosimilar, infliximab-dyyb, CTAF voted unanimously that the evidence was adequate to demonstrate that the biosimilar was clinically equivalent to its reference product, Remicade. Unfortunately, several significant barriers have limited the impact of biosimilars like infliximab-dyyb in the US health care system. At the CTAF meeting, two obstacles were highlighted: 1) a lack of trust among some clinicians and patients in the clinical equivalency of biosimilars, and 2) market barriers caused by current rebate structures that dominate autoimmune formulary placement decisions.

Related to these barriers, the Arthritis Foundation has highlighted three key principles for increasing uptake in biosimilars in a position statement, which garnered the support of many other organizations:

- Patient trust and physician confidence are crucial factors for broader uptake.

- Precise and consistent language is essential to prevent confusion and bias.
- Public policies that prohibit anticompetitive rebate structures, promote affordable out-of-pocket costs for patients, and enhance choice are critical.

Additional information regarding the Arthritis Foundation position on biosimilars may be found here. Position statements from the ACR and United Rheumatology may be found here and here, respectively.

Kaiser is an example of an organization where concerted efforts between the insurer and providers have dramatically increased the use of biosimilars in delivering high quality, guideline-concordant care to patients. Kaiser has focused not only on using lower cost biosimilars for patients beginning autoimmune treatment but has also worked to create a positive environment for switching patients over to biosimilars from reference products. To do this, Kaiser rheumatologists supported an overall process that created a leading role for clinical pharmacists, who were trained in how to present to patients the information about switching to a biosimilar from the reference product. Pharmacists reached out directly to patients, provided information about biosimilars, allayed fears about switching, and answered patients' questions. Kaiser also had their pharmacy outcomes group collect data following switching to biosimilars and demonstrated that patient satisfaction was excellent and that there were no worrisome changes in the DAS28 ESR or CRP levels. This kind of broad approach represents one best practice in efforts to build a system in which clinicians and patients feel enough trust to participate in large-scale switching of patients over to biosimilars.

Unfortunately, it is difficult to identify a "best practice" that can address the negative market incentives for biosimilars created by bundled rebates across indications that can cement preferred formulary status for leading autoimmune drugs like adalimumab (Humira). Indication-specific pricing and formulary development may have some potential to allow biosimilars to compete on a more even playing field, but short-term financial incentives for pharmacy benefit managers (PBMs) and plan sponsors to optimize rebates will continue to bedevil efforts to seek longer-term cost control through biosimilar competition unless major changes are made to the rebate system.

To address the trust and rebate barriers to biosimilar adoption, several policy recommendations are suggested:

1) **Clinical societies should educate their clinician members that the evidence behind biosimilars is sound and that whenever they are available at a lower cost than reference products, they should be the preferred option given the benefits of lower costs for patients and the health care system.**
2) **Patient groups should educate their members that biosimilars are as safe and effective as reference products and that starting on a biosimilar, or switching to one, is clinically responsible and may be financially beneficial.**
3) **Manufacturers should not use scare tactics to dissuade responsible switching to biosimilars.**

4) **Health plan sponsors, insurers, PBMs, and provider groups should work together to promote greater use of biosimilars by implementing switching programs that provide broad support to patients while assuring that patients who do not respond well to biosimilars are able to access reference products and/or obtain other targeted treatment options without delay.**
5) **Policymakers should continue work on alternatives to the current rebate system that will allow the market to reward the competitive advantages of lower priced, equally effective biosimilar treatment options. One helpful first step would be to ban the bundling of rebates across multiple indications.**

Plan Sponsors, Payers, and PBMs

1) **Reconsider the need for step therapy and any switching programs if pricing becomes better aligned with clinical value.**

There should be fair access for fair pricing. Current step therapy is not working to contain prices and is a result of a dysfunctional pricing system and the inability to use other mechanisms to lower costs for equally effective therapies. When developed using evidence-based standards and clinical expert input, step therapy can be a useful tool to steer patients to higher value therapies. The lack of evidence to support treatment sequencing makes evidenced-based step therapy impossible. For example, there is no evidence that the most commonly required first step therapy, an anti-TNF agent, is any more effective or safer than other therapies, such as the JAK inhibitors. At current prices, our analysis indicates that all of the TIMs under review exceed common cost-effectiveness thresholds but have comparable levels of effectiveness. Step therapy is not an unreasonable approach in this case, as the focus can be on the less expensive (or most heavily discounted) TIMs. However, if pricing were to become better aligned with clinical value for these therapies, payers should reconsider whether step therapy remains a necessary option.

Guidelines for the ethical design of step therapy exist in the literature.[104] The key elements include:

- Ensure that short-term cost savings are weighed against long-term outcome and costs.
- Ensure that first step drugs are clinically appropriate.
- There should be high likelihood that the patient will attain treatment goals with step therapy.
- First step therapy should not cause long-term harm.
- Moving from the first step based on clinical groups should be quick and easy.
- Failure of first step therapy should be clearly defined.
- Relevant new evidence should be rapidly reviewed leading to appropriate modifications.
- Rationale and rules should be explicit and transparent.

2) **If pricing does not fairly align with patient benefit, plan sponsors may consider the option of benefit designs requiring patients to switch from their current therapy to a lower cost, equally effective option. In all such efforts, the clinical effectiveness of the required therapy and the cost overall should be closely monitored.**

Traditionally, payers have authorized coverage of continuation of existing therapies when a patient switches to their plan. However, the high cost of TIMs has led some plans to drop this "grandfathering" of prior therapy even when it is not included on their formulary. It is incumbent upon payers to monitor the impact of such policies on patients to ensure that they are not harmed and that the goal of cost containment for the plan is actually met.

3) **Requiring switching for patients who have achieved adequate treatment response on a particular drug raises the risk of irremediable harm should the new treatment not prove equally effective. Therefore, these programs must meet an extremely high bar of evidence and must have ample, efficient means by which clinicians can request exceptions on clinical grounds.**

Patients should never be required to switch back to a prior therapy that they have been failed by. They should stay within the same drug class with the availability of an immediate path back to their initial therapy.

4) **Increase transparency around the role of discounting and rebate practice in formulary design.**

Patients and providers expressed concerns around a lack of transparency regarding the connection between discounting/rebate practice and formulary design, as the terms are typically confidential and current designs do not always lead to cost-effective choices. For example, many of the TIMs in our prior review were more effective than adalimumab in head-to-head studies and less expensive, but are disadvantaged in most formulary designs. Transparency is an important first step in educating the general public on the role of rebates in formulary design as well as how the savings are shared among patients, PBMs, and health plans.

5) **Design innovative risk-sharing payment agreements, including outcome-based contracts with manufacturers and shared risk agreements with accountable care organizations.**

The Policy Roundtable discussion mentioned other efforts that might yield cost savings beyond price reductions and rebate negotiations. Pay-for-performance agreements have increased in popularity; as a relevant example, payers might receive an additional rebate for patients who do not achieve clinical remission during TIM therapy. Payers could also develop contracts with accountable care organizations that share both financial risk and savings for optimized use and sequencing of TIM therapies. Finally, if TIMs with multiple indications beyond RA (e.g., Crohn's disease, psoriasis) show markedly different clinical performance and costs, indication-specific formularies should be developed to recognize these differences.

Clinical Societies and Manufacturers

1) **Establish standardized assessments to allow for rigorous direct and indirect comparisons of evidence across studies and therapeutic alternatives.**

The field of rheumatology should be applauded for its work in developing core sets of clinical and patient-reported outcomes measures with strong internal and external validity in RA clinical studies. However, these measures have proliferated, with variations on the same theme (e.g., multiple disease activity and radiographic progression measures) making cross-study comparisons problematic. Clinical societies and manufacturers should collaborate to develop a standardized *and* limited "must have" list of clinical outcome measures at specific time-points for clinical trials and post-marketing studies.

Public Policy Decision Makers

1) **In a dysfunctional market system, in order to protect patients today and improve their future access to innovative therapies, policy makers may need to consider some form of regulatory intervention to ensure that drug prices and price increases do not continue their current upward trajectory, driving prices further from reasonable alignment with the added benefits for patients.**

The discussion highlighted that the current "marketplace" for RA drugs is not working to align prices with value in a way that would reward new innovative drugs while also reaping the benefits of competition to keep drugs affordable. One result is that patients and clinicians face heavy access restrictions from insurers who lack other effective methods to control unsustainable cost increases. In addition, innovative companies cannot compete on price for RA-specific products in the face of rebate-driven agreements that cover multiple indications beyond RA. If some or all of the measures described above cannot be implemented or are not effective, policymakers should consider some form of regulatory intervention to address rebate structures and price increases in order to increase true competition and better protect patients.

2) **Public policy decision makers should ban the bundling of rebates across indications.**

We understand that rebates are a major impediment to the alignment of overall pricing with outcomes. Bundling and rebates present almost insurmountable obstacles to value-based pricing and represent a wall against innovation for new products trying to enter the market with only a single indication. In addition, bundling leads to step therapy that does not always match the FDA indications for the drugs nor their evidence base or clinical guidelines. Finally, patients' copays are linked to the WAC, so their out-of-pocket costs remain high, even though rebates reduce the cost for payers and PBMs. Eliminating rebates is the first step towards improving value for therapies for RA.

Research Community

1) **Researchers and research funding agencies should prioritize studies that identify biomarkers predicting response to currently available therapies or classes of therapies (personalized medicine).**

The current treatment paradigm is based on trial and error and the majority of patients fail to respond adequately to their first TIM. Clinicians urgently need tools that can help them identify the therapy that will work best for each individual patient that they treat.

2) **Researchers should separate outcomes that measure inflammation from those that measure pain.**

Research should not try to capture all aspects of RA in one measure. There should be several essential outcomes and patient-reported outcomes should complement the more objective outcomes. Therapies that target inflammation, such as TIMs, are best assessed by measures like ESR, CRP, swollen joint, and the prevention of joint destruction. Other therapies, such as those addressing central pain mediators, are best assessed through patient-reported outcomes such as joint pain, joint stiffness, and fatigue.

3) **Randomized trials and observational studies should include outcomes that are both patient-centered and patient-driven.**

Patient-centered outcomes are answered by patients, while patient-driven outcomes are those that are coproduced by patients during the design phase of the studies and reflect values that are meaningful to patients. Both are essential in order to capture the value of treatments to patients.

4) **The FDA should require that randomized trials include patients reflecting the average RA patient population.**

Patients, specialists, and their respective society representatives reported that 80% to 90% of the patients they treat with TIMs would not have been eligible to participate in the pivotal randomized trials, primarily due to lower numbers of inflamed joints and lower levels of inflammatory markers (CRP, ESR). Specialists have concerns about using the estimates of benefits and harms from the clinical trials when counseling their patients about the relative benefits and harms of the therapeutic options and patients do not feel adequately represented in the trials.

5) **The FDA should require that randomized trials of new therapies always include an active comparator.**

It is unethical to randomize patients to a placebo added to a therapy that they have already been failed by (i.e., placebo + conventional DMARD in a patient population with moderately-to-severely active disease on conventional DMARD therapy) given that multiple TIMs have been demonstrated to be clinically superior to conventional DMARD therapy alone in this population. If the FDA feels that a placebo control is essential to demonstrate clinical efficacy, then the trial should still include a third arm with an active comparator. Head-to-head randomized trial data is essential to support comparative clinical effectiveness analyses, NMAs, and economic analyses with low uncertainty.

References

1. Nayak RK, Pearson SD. The ethics of 'fail first': guidelines and practical scenarios for step therapy coverage policies. *Health affairs (Project Hope).* 2014;33(10):1779-1785.

Appendix

Appendix Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the December 9, 2019 CTAF Public Meeting.

Appendix Table 1. ICER Staff and Consultants and COI Disclosures

Name	Organization	Disclosures
Pamela Bradt, MD, MPH	Institute for Clinical and Economic Review	*
Rick Chapman, PhD, MS	Institute for Clinical and Economic Review	*
Laura Cianciolo	Institute for Clinical and Economic Review	*
Monica Frederick	Institute for Clinical and Economic Review	*
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Judith Walsh, MD, MPH	University of California, San Francisco	*

*No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

Appendix Table 2. CTAF Panel Member Participants and COI Disclosures

Name	Organization	Disclosures
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*No relevant conflicts of interest to disclose, defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.

†Richard Seiden did not participate in voting due to his prior treatment with one of the agents under review.

Appendix Table 3. Policy Roundtable Participants and COI Disclosures

Name	Organization	Disclosures
Happy Chan, DO, FACR	Blue Shield of California	Employee of Blue Shield of California.
Andrew L. Concoff, MD, FACR, CAQSM	United Rheumatology	Served as a consultant and/or speaker to Flexion Pharmaceuticals, Exagen, Inc., and UCB.
Peggy Ehling	Arthritis Foundation Local Leadership Board Los Angeles	No conflicts of interest to disclose.
Julie Eller	Arthritis Foundation	The Arthritis Foundation receives more than 25% of its funding from health care companies.
Kirstin Griffing MD, MS, FACR	Eli Lilly and Company	Employee of Eli Lilly and Company.
Marc Jensen, PharmD	Pfizer	Employee of Pfizer.
Christopher Phillips, MD	American College of Rheumatology; Paducah Rheumatology	Served as a PI on several upadacitinib trials conducted through an independent multi-specialty clinical research center.
John S. Yao, MD, MPH, MBA, MPP, CPC, FACP	Anthem Blue Cross	Employee of Anthem Blue Cross.