Janus Kinase Inhibitors for Rheumatoid Arthritis: Effectiveness and Value

Background and Scope

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Background

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in adults, affecting between 1.3 and 1.8 million Americans.[1,2] RA is more common in women and may occur at any age, with peak incidence occurring at ages 50-60 years.[3] RA is typically characterized by morning stiffness and symmetrical joint swelling of the feet, hands, and knees, although any joint (and in some cases, internal organs and skin) may be involved.[3] RA is considered a clinical syndrome that encompasses several disease subsets, each of which involves a distinct inflammatory cascade that can lead to joint damage, deformity, and organ dysfunction.[4] The course of RA may be complicated by cardiac, hematologic, and other extra-articular manifestations.[3] Historically, RA was associated with both progressive disability and a shortened lifespan, although improvements in diagnosis as well as aggressive use of disease-modifying anti-rheumatic drugs (DMARDs) have greatly improved prognosis in the past 20 years.[5]

The chemotherapeutic agent methotrexate is the most widely used conventional DMARD; it is considered an "anchor drug" because of its effectiveness and tolerability as well as its potential to enhance the effectiveness of biologic and non-biologic drugs that are targeted at certain mediators of inflammation in RA, known collectively as targeted immune modulators (TIMs).[3] However, only about 50% of patients treated with methotrexate alone will receive sufficient reduction in disease activity or remission of symptoms.[3] Over the past 18 years, the introduction of TIMs has greatly improved prognosis for many RA patients. Agents with indications for RA include inhibitors or antagonists of multiple mediators of the inflammatory cascade, including tumor necrosis factor (TNF), the B-lymphocyte CD20 antigen, interleukin (IL) 1 and 6, Janus kinase (JAK), and T cells. Guidelines from the American College of Rheumatology (ACR) recommend the use of TIMs in patients with moderate-to-severe disease activity despite the use of conventional DMARDs.[6]

Uncertainty remains, however, regarding the relative effectiveness of the different types of TIMs as well as the appropriate sequence of initial and subsequent TIM therapy. In addition, there are long-term safety concerns with chronic use of TIMs in RA that may differ by dose and type of agent.[7] Feedback from patient groups also emphasized the highly individual experience with TIM therapy; some patients see immediate benefit from the first TIM they receive after failure of conventional

DMARDs, while others must make multiple attempts before finding an agent that works for them. Therefore, there is a need to seek evidence on patient subgroups, comorbidities, and other factors that can better inform treatment response and selection of appropriate medications.

Stakeholder Input

This scoping document has been developed following essential input from patients and patient advocacy groups, as well as practicing rheumatologists, specialty societies, insurers, and manufacturers. The input received has influenced our view of the patient populations and outcomes of interest as well as the optimal methods for our evidence review and simulation modeling efforts, which will be updated to reflect changes in knowledge and in disease management since the prior review. While this document provides an overview on research methods, detailed protocols for both the evidence review and model will be posted to the Institute for Clinical and Economic Review (ICER) page on the Open Science Framework website (https://osf.io/7awvd/). ICER looks forward to continued engagement with stakeholders throughout the entire project timeline, up to and including the public meeting in November 2019.

Patients and advocacy organizations emphasized the long-term nature of the disease and the importance of both the long-term perspective and the variability in disease course and treatment changes, including drug holidays. They highlighted the importance of patient-reported outcomes and offered to help integrate them into the report and model. Multiple stakeholders recommended the inclusion of real-world data for the assessment of evidence on safety, durability of effect, and switching patterns given the widespread availability of such evidence for established therapies. Both clinicians and patient groups emphasized that their treatment goals are to achieve minimal disease activity; a 50% improvement, e.g., ACR50, is not a successful outcome for a patient with 20 active joints. These groups also highlighted the impact and burden of RA on caregivers, and suggested that both caregiver measures and outreach to caregiver groups be part of the project process. Finally, stakeholders highlighted the important progress that has been made through the use of biologics: very few patients progress to disabling joint deformities with current treatments.

Rationale for Update on Janus Kinase (JAK) Inhibitors for RA

Since the publication of the original ICER report in 2017, the Food and Drug Administration (FDA) approved baricitinib for moderate-to-severe RA. In addition, the FDA accepted the New Drug Application (NDA) of upadacitinib for Priority Review with expected approval in August 2019. Therefore, ICER decided to update the evidence for JAK inhibitors for adults with moderate-to-severe RA. We will search for newly published data on drugs included in the prior review as well as data on upadacitinib. We expect to integrate these new data in an updated network meta-analysis (NMA) as well as our evaluations of long-term cost-effectiveness and budgetary impact.

In addition, to better reflect clinical practice and guidelines using a treat to target approach, we will focus on measures of disease activity at three months. Patients not achieving remission or low disease activity after three months of therapy are typically switched to a different TIM. We are also updating our approach to modeling utilities ideally using direct measurement of the Health Assessment Questionnaire (HAQ) or the European League Against Rheumatism (EULAR) response criteria. Given the scope of these changes, we elected to focus on a limited set of therapies that are of particular clinical interest and will plan a full class update in the future that will incorporate the expected new ACR guidelines for RA and additional new therapies.

Report Aim

The objective of this review is to assess the comparative clinical effectiveness and value of JAK inhibitors for moderately-to-severely active RA, both as monotherapy and in combination with conventional DMARDs. Our prior NMAs will be updated with new trial data for JAK inhibitors considered in the last review and novel JAK inhibitors nearing likely FDA approval, such as upadacitinib. We will also review the clinical and economic evidence for infliximab-dyyb (Inflectra®, Pfizer). The ICER Value Assessment Framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms—including those not typically captured in the clinical evidence, such as innovation, public health effects, reduction in disparities, and unmet medical needs—are considered in the judgments about the clinical and economic value of the interventions.

Scope of the Assessment

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be collected from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

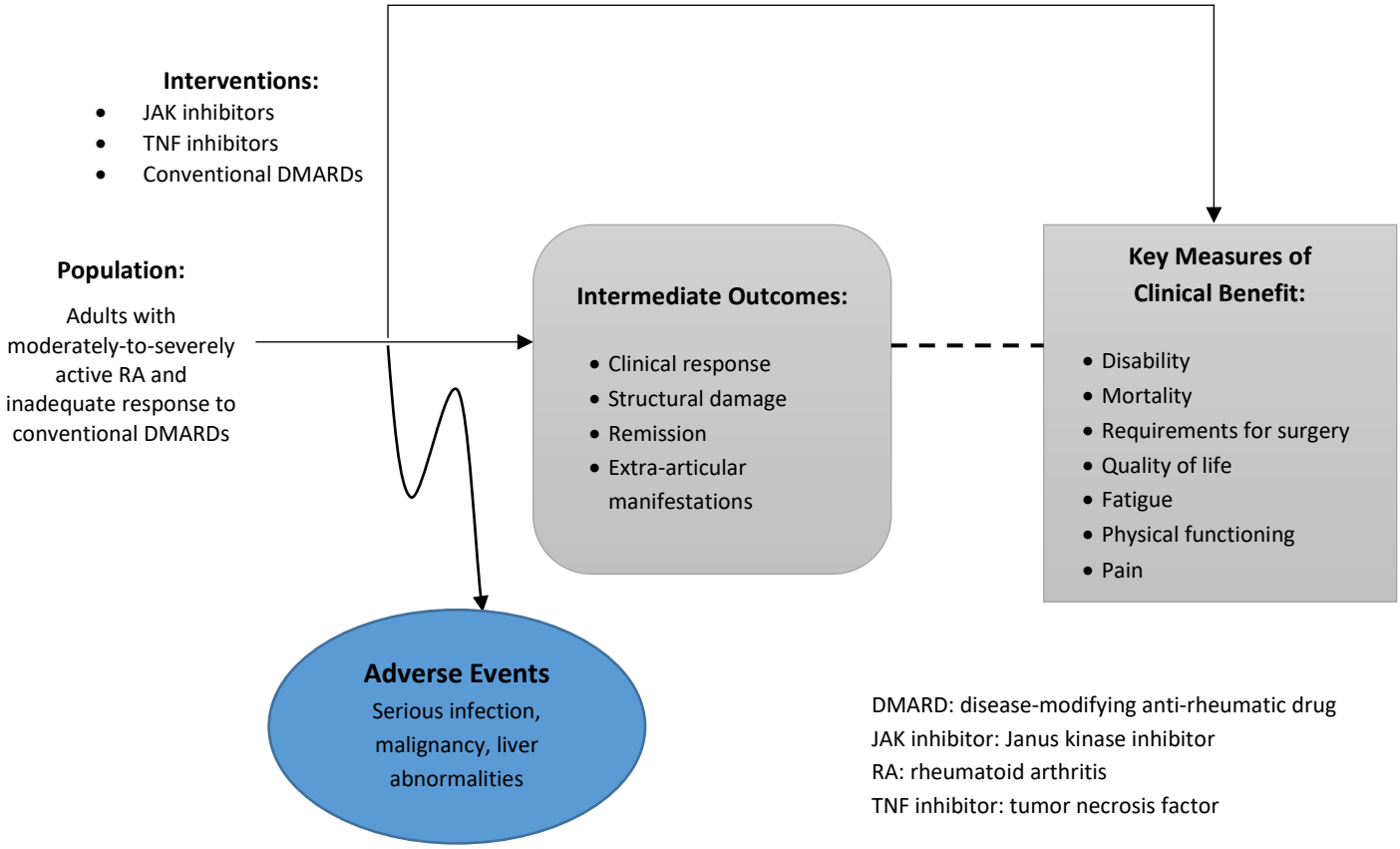
Wherever possible, we will seek out head-to-head studies of these interventions (see page 5 for a detailed list of the agents of interest). We will also include studies with an active comparison to conventional DMARDs or TNF inhibitors with or without conventional DMARDs. We will use direct and indirect evidence in NMAs of selected outcomes. Data permitting, we will account for differences in trial populations using established techniques, such as regression-based analysis of control arm response rates or analyses of risk differences.[8,9] Full details regarding the literature

search, screening strategy, data extraction, and evidence synthesis will be provided in a research protocol published on the Open Science Framework website.

Analytic Framework

The general analytic framework for assessment of JAK inhibitors for moderately-to-severely active RA is depicted in Figure 1 below.

Figure 1. Analytic Framework: JAK Inhibitors for Moderately-to-Severely Active RA



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded grey boxes; those within the rounded boxes are intermediate outcomes (e.g., clinical response), and those within the squared-off boxes are key measures of benefit (e.g., disability). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.[10]

Populations

The population of focus for the review will be adults ages 18 and older with moderately-to-severely active RA and inadequate response to or intolerance of conventional DMARDs. Level of disease activity will be defined according to validated and frequently used scales in RA (i.e., Disease Activity Score [DAS28], Clinical Disease Activity Index [CDAI], Simplified Disease Activity Index [SDAI]). Note that this focus will not include children, adolescents, or adults with juvenile forms of RA or other inflammatory arthritis, now collectively known as juvenile idiopathic arthritis (JIA). Feedback from patient groups and clinicians suggested that the clinical presentation and disease trajectory of these patients differs substantially from those with the adult form of RA.[11]

We will also seek evidence on key subpopulations and/or data stratifications of interest. Among those suggested by stakeholders during the open input period were a) evaluation of both TIM-naïve patients *and* those with inadequate response to or intolerance of initial TIM therapy; b) use of JAK inhibitors as monotherapy and in combination with conventional DMARDs. Feedback received for the prior report indicated additional subpopulations or stratifications of interest, including a) presence of comorbidities (e.g., cardiovascular, interstitial lung disease, psychiatric, malignancy); b) both "early" (i.e., within two years of symptom onset) and established RA; c) seropositivity for prognostic markers such as anti-cyclic citrullinated peptide (CCP) antibodies; d) geography, in particular US-based versus non-US settings; and e) study funding (i.e., industry-sponsored vs. other funding sources).

Interventions

The interventions of interest for this review are listed below.

- Tofacitinib (Xeljanz®; Pfizer)
- Baricitinib (Olumiant®; Eli Lilly)
- Upadacitinib ([investigational]; AbbVie)
- Biosimilar exemplar: Inflectra® (infliximab-dyyb)

We will seek clinical evidence on all the products listed above. We note, however, that biosimilar data will be presented separately, given differences in study design and intent (i.e., non-inferiority vs. superiority) relative to clinical studies of the originator products. We hope to use these data and the economic analyses to encourage a more general discussion on the role of biosimilars and interchangeability status in RA.

Comparators

We will examine studies comparing JAK inhibitors to conventional DMARD monotherapy or combination therapy (including triple therapy with the conventional DMARDs methotrexate,

sulfasalazine, and hydroxychloroquine) to assess performance versus historical standard treatments, but will also seek head-to-head studies between the JAK inhibitors and TNF inhibitors to evaluate for more contemporary comparisons.

Finally, while studies with an active comparator arm are preferred, we will also include placebo-controlled trials as necessary to complete a planned NMA of the effects of treatment on key measures of effectiveness that will combine direct and indirect evidence.

Outcomes

This review will examine key clinical outcomes associated with RA. In conversations held to develop this document, patient organizations advised us that clinical trials are often lacking robust information on patient-reported outcomes, and suggested a focus on recently-developed measures such as those described in the federally-funded PROMIS toolkit (http://www.healthmeasures.net/explore-measurement-systems/promis). We have adjusted this list considerably based on stakeholder feedback to include additional patient-reported outcomes as well as important clinical and health care utilization measures.

- Mortality
- Treatment response (e.g., ACR20, ACR50, and ACR70, area-under-the-curve analysis)
- Measures of disease activity, remission, and remission loss (e.g., DAS28, CDAI, SDAI)
- Radiographic evidence of structural damage
- Disease-specific and general health-related quality of life (e.g., Health Assessment Questionnaire for Rheumatoid Arthritis Disability Index [HAQ-DI], SF-36 [Short Form Survey])
- Pain (e.g., visual analog scales)
- Other patient-reported outcomes (e.g., patient satisfaction, measures of fatigue, morning joint stiffness)
- Productivity loss and caregiver burden
- Requirements for joint replacement or other surgical intervention
- Utilization of key healthcare resources (e.g., hospitalization, rehabilitation, assisted living)
- Cardiovascular events
- Treatment-related adverse events (e.g., serious infection, malignancy, liver abnormalities)

While we will seek to assess these outcomes quantitatively, some measures may not be widely reported and will necessitate descriptive analysis only. Where possible we will report the absolute risk reduction and number needed to treat in addition to the relative risk reduction for the treatment comparisons.

Timing

Studies of three and six months' duration will be prioritized for response to therapy, however long-term evidence is preferred for harms.

Settings

All relevant settings will be considered, including outpatient as well as ambulatory and hospital-based infusion centers. Several stakeholders commented on the importance of geography for our review given differences in treatment guidelines and practice patterns. We will focus attention on studies pertinent to the US setting; however, we recognize that studies conducted outside the US will likely be required for a complete review of the evidence.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These elements are listed in Table 1 below.

Table 1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Potential Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to "the comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

Simulation Models Focusing on Comparative Value

TIMs for moderate-to-severe RA are expensive, and there is evidence that both their prices and the proportion of those costs paid by patients have increased substantially in recent years.[12] As a complement to the evidence review, we will develop a cohort model to assess the cost-effectiveness of each of the JAK inhibitors listed earlier relative to conventional DMARDs as well as against alternative JAK inhibitors and TNF inhibitors. The model framework and inputs will borrow from ICER's previously built RA model as well as other models that have evaluated TIMs for RA management.[13-17,18,19] The target population will consist of adult patients with moderate-to-severely active RA who have an inadequate response to prior therapy with conventional DMARDs. A lifetime time horizon will be used to reflect the chronic nature of RA. The economic evaluation will be from a health care sector perspective, and will thus focus largely on direct medical and pharmacy costs.

The sequential treatment cohort model will simulate a hypothetical homogenous cohort of patients, with baseline characteristics similar to the populations of the randomized controlled trials identified in the evidence review, from the initiation of a JAK inhibitor until death. After starting a JAK inhibitor, the model will relate the ACR response to the HAQ-DI directly or by mapping to an appropriate disease activity index after three months of therapy aligning with a treat-to-target approach, consistent with other previously published models.[18,19] In the prior model, patients who withdrew from a TIM (due to lack of effectiveness and/or adverse events) could switch therapy up to three times. The first switch was to an agent with a similar mechanism of action (e.g., TNF inhibitors, non-TNF biologic TIMs, JAK inhibitors); the second was to a drug with a different mechanism of action; and the third was to a palliative care state that involves conventional DMARD therapy. The model's sequential treatment pattern was consistent with the ACR 2015 Guidelines for the treatment of RA, but this will be updated to reflect current practice and the anticipated update to the ACR guidelines for RA this calendar year.[6] The updated model will likely include more lines of therapy, with each line after the first representing a market-basket of TIMs of a specific class (with no repetition of class) and the last line representing a market-basket of TIMs across all classes. This change from the previous ICER RA model attempts at aligning with current clinical practice in RA. A cycle length of three months will be used to reflect the time needed to review a treatment's efficacy prior to deciding treatment switch, again attempting to align with current clinical practice in RA. Depending on data availability, the HAQ-DI estimates for the interventions assessed as well as those for subsequent lines of therapy will be informed directly by trial data. The HAQ-DI score will then be linked to utility and cost. In the absence of the required HAQ-DI data, we will map EULAR responses to HAQ or ACR to EULAR responses which will then be mapped to HAQ. The model will continue to simulate the long-term HAQ-DI score every three months until withdrawal from the treatment or death.

Key model inputs will include the detailed HAQ-DI observations, EULAR responses or the distribution of ACR response (e.g., percent of patients achieving a less than 20% improvement, a 20-49% improvement, a 50% or greater improvement, etc.), quality of life values, and costs associated with drug therapy (i.e., dose level and frequency, administration, vial wastage), physician visits, hospitalizations, and other key measures of resource use (e.g., surgical intervention, assistive devices, rehabilitation, or assisted living). Disease activity response probabilities will differ between interventions to reflect the differences in effectiveness. Based on stakeholder feedback, however, health care costs associated with non-response are greater than those among responders, so these differences will be reflected as well. Treatment effectiveness, treatment persistence, safety, and cost data will be estimated from relevant trials or real-world evidence, as applicable and available.

The health outcome of each intervention will be evaluated in terms of responses achieved, life-years, and quality-adjusted life years (QALYs). Relevant pairwise comparisons will be made between treatment pathways, and results will be expressed in terms of the marginal cost per QALY gained, cost per life-year gained, and cost per response or remission achieved. We will conduct a separate analysis to attempt to extend the perspective to a societal one in order to include the indirect costs due to productivity losses and caregiver burden. Given available evidence, further scenario analyses will address i) conducting the analysis in a TIM-experienced population, and ii) results over a shorter time-horizon.

In an additional analysis, we will also explore the potential health system budgetary impact of upadacitinib over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the simulation model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2018/05/ICER-value-framework-v1-21-18.pdf.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These are services that would not be directly affected by TIMs (e.g., need for joint replacement) as these services will be captured in the economic model. Rather, we are seeking services used in the current management of RA beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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