Targeted Immune Modulators for Rheumatoid Arthritis:
Effectiveness and Value

Revised Background and Scope
August 29, 2016

Stakeholder Input

This scoping document has been revised following useful input from patient and patient advocacy groups, relevant specialty societies, practicing rheumatologists, manufacturers, and payers. 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. While this document provides an overview on research methods, detailed protocols for both the evidence review and model will be posted to the ICER page on the Open Science website (https://osf.io/7awvd/) in the coming weeks. ICER looks forward to continued engagement with stakeholders throughout the entire project timeline, up to and including the public meeting in January. We have summarized many of the key inputs to the revised scoping document in the following paragraph.

Patients and advocacy organizations asked for further specifics on how patient-reported outcomes will be considered in the review, and suggested specific measures of interest. 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. Multiple stakeholders highlighted variability in disease course and trajectory, and suggested specific subgroups defined by patient characteristics, prognostic factors, and geography. Clinical groups and manufacturers urged consideration of real-world data for assessment of evidence on safety, durability of effect, and switching patterns given the widespread availability of such evidence for established therapies. These stakeholders also requested clarity on the definitions of the patient populations of interest as well as the definition of moderate-to-severe rheumatoid arthritis.

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. 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. Novel agents with anti-IL-6 and anti-JAK activity are also currently under regulatory review for an RA indication. Guidelines from the American College of Rheumatology recommend use of TIMs in patients with moderate-to-severe disease activity despite 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. There is therefore a need to seek evidence on patient subgroups, comorbidities, and other factors that can better inform treatment response and selection of appropriate medications.

Report Aim

This project will evaluate the health and economic outcomes of multiple TIMs for moderately-to-severely active rheumatoid arthritis, both as monotherapy and in combination with conventional DMARDs. The ICER value 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. We will conduct a systematic literature review using best practices for search strategy development and article retrieval. 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 4 for a detailed list of the agents of interest). We will also include studies with an active comparison to conventional DMARDs as well as placebo-controlled studies. We will consider combined use of direct and indirect evidence in network meta-analyses 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]

Analytic Framework

The general analytic framework for assessment of targeted immune modulators for moderately-to-severely active RA is depicted in Figure 1 on the following page. Note that this figure has been revised based on input from patient and clinical groups as well as manufacturers to clarify the patient population of interest as well as incorporate additional intermediate and long-term outcomes of interest.

Figure 1. Analytic Framework: Targeted Immune Modulators for Moderately-to-Severely Active Rheumatoid Arthritis

DMARDs: disease-modifying anti-rheumatic drugs
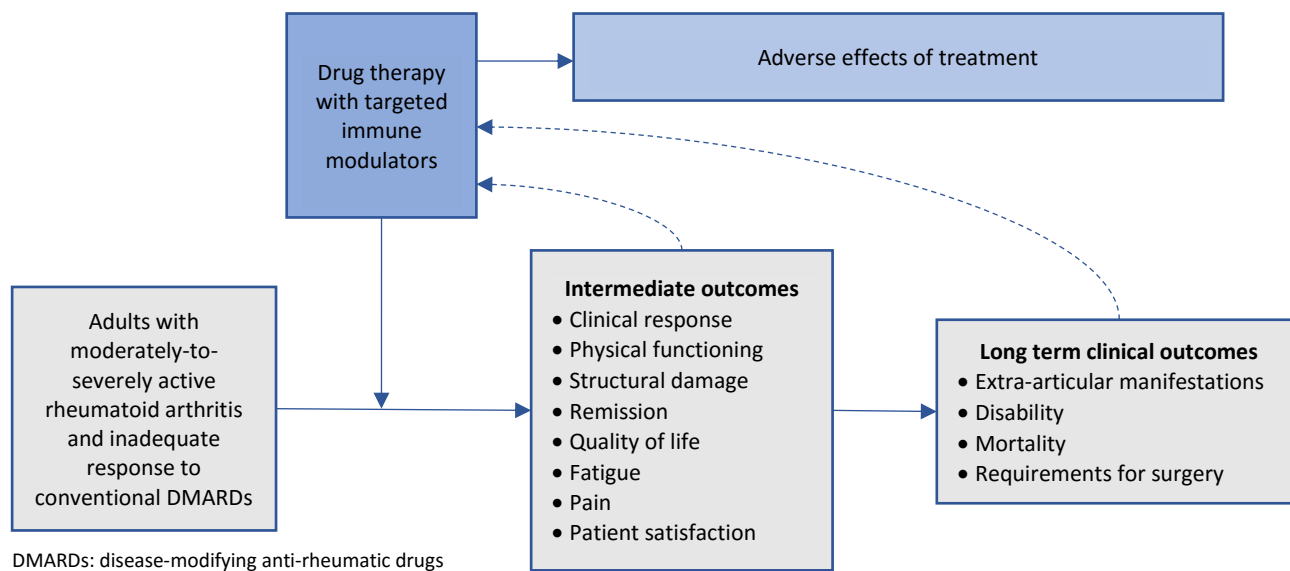
Populations

The population of focus for the review will be adults ages 18 and older with moderately-to-severely active rheumatoid arthritis 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.[10]

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 TIMs as monotherapy and in combination with conventional DMARDs; (c) route of administration (i.e., oral vs. self-injected vs. infused); and (d) setting of care (e.g., hospital-based vs. ambulatory infusion centers). Feedback received during the public comment period indicated additional subpopulations or stratifications of interest, including (e) presence of comorbidities (e.g., cardiovascular, psychiatric, malignancy); (f) both "early" (i.e., within 2 years of symptom onset) and established RA; (g) seropositivity for prognostic markers such as anti-cyclic citrullinated peptide (CCP) antibodies; (h) geography, in particular U.S.-based vs. non-U.S. settings; and (i) study funding (i.e., industry-sponsored vs. other funding sources).

Interventions

Clinical experts and patient organizations advised us that it is not uncommon for patients to cycle through various therapies before finding a treatment option to which they both respond to and tolerate. We also received input that fail-first insurance policies often require patients to follow a specific sequence of TIM therapies, yet it is unclear whether established protocols are based on the most current clinical evidence. For these reasons we will consider a comprehensive list of TIMs with FDA indications for RA as well as two investigational therapies presently undergoing FDA review. However, we note that multiple stakeholders indicated that the IL-1 inhibitor anakinra is rarely used for adult RA in the U.S., so we have removed this agent from consideration. Interventions of interest are listed by class below.

- TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab)
- CD20-directed cytolytic antibody (rituximab)
- T-cell inhibitor (abatacept)
- IL-6 inhibitors (tocilizumab, sarilumab [investigational])
- JAK inhibitors (tofacitinib, baricitinib [investigational])

We will seek clinical evidence on all forms of the products listed above, including biosimilar and interchangeable biologic forms as data permit. 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.

Comparators

We expect that most available clinical trials of TIMs will have been conducted in patients without adequate response to initial therapy with conventional DMARDs, yet will involve comparisons to conventional agents nonetheless for purposes of regulatory approval. We will examine studies comparing TIMs 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 TIMs to evaluate for more contemporary comparisons. Comparisons of TIMs will be conducted among drugs with similar mechanisms of action (e.g., all TNF inhibitors) as well as between drugs with different mechanisms (e.g., IL-6 inhibitors vs. JAK inhibitors).

Finally, while studies with an active comparator arm are preferred, we will also include placebo-controlled trials as necessary to complete a planned network meta-analysis 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 the draft scoping 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 revised this list considerably based on stakeholder feedback to include additional patient-reported outcomes as well as important clinical and healthcare 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
- Key laboratory-based indices (e.g., erythrocyte sedimentation rate, C-reactive protein)
- Disease-specific and general health-related quality of life (e.g., HAQ-DI, SF-36)
- 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)
- Costs and cost-effectiveness of TIMs

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.

Stakeholders also recommended that we seek evidence describing the impact of dose levels, dose schedule, and dose changes on the outcomes of interest. Specifically, we will assess the impact of dose increases, dose decreases, and drug cessation during periods of sustained control or remission on long-term outcomes, as well as the effects of dose levels on the rates of serious adverse events. Where available, we will also seek information on the clinical rationale for dose adjustments.

Timing

Evidence on intervention effectiveness will be derived from studies of at least six months' duration, while information on potential harms will be obtained from studies of at least three months' follow-up.

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 U.S. setting; however, we recognize that studies conducted outside the U.S. will likely be required for a complete review of the evidence.

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.[11] As a complement to the evidence review, we will develop a cohort model to assess the cost-effectiveness of each of the TIMs listed earlier relative to conventional DMARDs as well as against alternative TIM agents. The model framework and inputs will be based on previous models that evaluated TIMs for RA management.[12-16] The target population will consist of adult patients with moderate-to-severely active RA who have an inadequate response to prior therapy. Alternative strategies will be evaluated, including (a) use of TIMs in TIM-naïve patients with an inadequate response to conventional DMARDs; and (b) use of a second TIM in patients with an inadequate response to initial TIM therapy. A lifetime time horizon will be used to reflect the chronic nature of RA. The economic evaluation will be from a health-system perspective, and will thus largely focus 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 TIM until death. After starting a TIM, the model will relate the American College of Rheumatology (ACR) response to the Health Assessment Questionnaire for Rheumatoid Arthritis Disability Index (HAQ-DI) after six months of therapy (consistent with other US peer-reviewed models).[12-16] Patients who withdraw from a TIM (due to lack of effectiveness and/or adverse events) may switch therapy up to three times. The first switch will be to an agent with a similar mechanism of action (e.g., TNF inhibitors, non-TNF biologic TIMs, JAK inhibitors); the second will be to a drug with a different mechanism of action; and the third will be to a palliative care state that involves conventional DMARD therapy. The model's sequential treatment pattern is consistent with the ACR 2015 Guidelines for the treatment of RA.[6] A cycle length of six months will be used to reflect the time needed to conclude a treatment's efficacy;[13] other treatment assessment durations (e.g., three months) will be considered in sensitivity analyses to reflect the timing of treatment decisions in typical rheumatology practice. The ACR response will be mapped with an increase in HAQ-DI score using statistical models previously developed. The HAQ-DI score will then be linked to utility and cost. The model will continue to simulate the long-term HAQ-DI score every six months until withdrawal from the treatment or death.

Key model inputs will include 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). ACR 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 will be estimated using evidence from published randomized controlled trials; data from long-term observational studies will be used to inform estimates of drug switching, durability of effect, and safety.

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 issues of treatment adherence, TIM price changes over time, and biosimilar introduction (e.g., interchangeability, transition costs, drug therapy costs, differences in drug delivery mechanisms, etc.).

In an additional analysis, we will also explore the potential health system budgetary impact of each treatment 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. These budgetary impact analyses will assume specific "uptake" rates for new products over a five-year period in the populations of interest, and will utilize available market share data for existing products to calculate current budget impact. This analysis will allow assessment of any need for managing the cost of such interventions.

More information on ICER's methods for estimating product uptake and calculating potential budget impacts can be found at: http://icer-review.org/wp-content/uploads/2016/02/Value-Assessment-Framework-slides-for-July-29-webinar-FINAL-corrected-8-22-1.pdf.

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