Key Questions with Ratings

For each voting question, the following scale was used to identify the level of confidence - with a score of 1 being low or no confidence and 5 representing high confidence. A score of ≥2.5 is considered intermediate confidence that there is robust clinical literature to support the question.

1 — 2 — 3 — 4 — 5
Low Confidence *Intermediate* *High Confidence*

1. Please describe the level of certainty in the evidence supporting the selection of first-line and alternate medical therapies for rheumatoid arthritis (RA), as outlined in the American College of Rheumatology (ACR) guidelines.

Final Rating: 4

There was consensus among the subject matter experts (SMEs) that treatment based upon ACR criteria is well-validated and has been confirmed in clinical practice.

2. Specifically, how robust is the evidence supporting TNF-inhibitors (TNFis) as a first line therapy (for patients who have failed therapy with Disease-modifying anti-rheumatic drugs (DMARds)) in RA (please provide)? What is the rationale for this practice, given that only about one-third of patients will adequately respond to this class of treatments?

Final Rating: 3.5

Two of the three SMEs replied that this rationale for therapy is mostly based on current usage and the fact that the TNFis were among the first biologics available. However, true head-to-head data in RA is lacking.

The third SME replied that level of response to TNF blockers is much greater than 1/3. Adequate response, if defined by ACR 20, would be 60-70%. The same percentage would hold if one is using a Clinical Disease Activity Index (CDAI) score of mild to moderate. Moreover, 20%-30% of patients on TNF blockers reach remission as defined by CDAI or Disease Activity Score (DAS), which was unheard of with DMARD therapy prior to the introduction of TNF blockers as a treatment option.

3. Are you aware of any payor-imposed mandates regarding prescribing TNFis as first-line therapy (for patients who have failed therapy with DMARds) in RA? If so, please comment.

Final Rating: 4

There was consensus that numerous insurance companies require failure of at least 1 and sometimes 2 TNFis before approving the use of other biologics for the treatment of RA.

One SME stated that the requirement to have failed multiple TNF blockers prior to trying another biologic is unreasonable, since RA is driven by different cytokines from patient to patient. If a patient is well-controlled on one TNF blocker, and then starts to fail therapy, it is certainly reasonable to introduce another TNF blocker. However, if the patient has very little response to a TNF blocker, it is true that they may respond better to a different TNF blocker, or maybe a different mode of delivery, but a limited response to a TNF blocker should allow the provider to consider therapies with different mechanisms of action.

4. What does the literature define as 'clinical response' in RA? Is there variability in the definitions of clinical response used by practicing rheumatologists, in the literature, or in practice guidelines (ie ACR-20 vs ACR-50)?

Final Rating: 4.5

There was consensus that there are multiple clinical response measures and that the ACR responses (ACR 20, 50, and 70), being measures of disease improvement, are primarily used for studies ('treat-to-target') and medication approvals, but are not otherwise practical for clinical use.

There was also consensus that other measures, such as the Routine Assessment of Patient Index Data 3 (Rapid3), Simplified Disease Activity Index (SDAI), CDAI, and DAS (defined above), are better measures of actual disease activity and are more clinically practical. The RAPID works well in patients with only RA, but faulters when patients have more than one diagnosis. The VECTRA DA has been proposed as a more objective measure of disease activity, but also is inaccurate when patients are taking Interleukin-6 (IL-6) blockers or have other inflammatory (or potentially inflammatory) conditions.

5. Please discuss the validity of using blood vs synovium as the more appropriate indicator of RA activity and treatment response. According to the literature, does disease activity in the blood correlate to what is happening in the synovium? Could differences be a possible reason for nonresponse to therapy?

Final Rating: 3.5

It was agreed that though synovium may be a better source to test, it is much more difficult to obtain, especially if serial measurements are needed. Certainly, differences between blood and synovium could be present, but synovial sampling or biopsy is not practical.

6. What does the literature support as the primary clinical and laboratory indicators to consider when choosing a drug to treat RA - at a given time, or in a given sequence?

Final Rating: 3

Two SMEs replied that there are no good clinical or laboratory indicators to help guide physicians toward one specific treatment for RA.

One SME further explained that ACR guidelines offer the best treatment pathway. There are certain clinical situations where TNF blockers or other DMARDS or biologic treatments are either indicated, or contraindicated, but for the most part, there are no clinical or lab indicators to help guide physicians towards one specific treatment for RA. If patients are positive for Cyclic Citrullinated Peptide (CCP) antibodies, have erosions on x-ray, and have significantly elevated inflammatory markers, they are most likely going to need biologic treatment based upon the literature. However, there is no proven indicator to guide decision making between biologic therapies.

Another SME replied that the PRISM test has been proposed as a way to predict nonresponse to TNF-inhibitors but he was not very familiar with the methodology and performance of the test. He also noted that there has been one post-hoc analysis with dual positive RA patients (+ Rheumatoid Factor (RF) and CCP antibodies) responding better to abatacept (a T-cell modulator).

7. What is the level of certainty in the literature regarding anti-TNFi antibody testing in RA? Should it be performed and, if so, when?

Final Rating: 2

One SME replied that testing may occasionally be useful, if there is an unexpected loss of response to a TNFi.

Two SMEs agreed that, even though a significant percentage of patients on TNF blockers may have antibodies to TNF blockers, these antibodies are not clinically meaningful and do not correlate with response to treatment. One SME further clarified that this was more of an issue in the early 2000s when there were limited options to treat RA and Crohn's disease. As more agents come to market, it is easier to simply switch agents if patients develop issues that are felt to be possibly related to anti-drug antibodies.

8. What biomarkers are currently available for predictive testing to guide targeted therapy selection in RA and what is the evidence for their use?

Final Rating: 1.5

One SME replied that there is some evidence in the literature that CCP-positive patients may respond better to either abatacept or rituximab, but plenty of CCP-positive patients respond to TNF blockers as well, so currently available predictive testing is very limited.

Two SMEs replied that there is no specific biomarker about which they are aware.

9. What is the certainty of evidence in the literature to support the use of new technologies in predictive testing for the treatment of RA? Are such tests being offered clinically and, if so, how?

Final Rating: 2.5

One SME commented that precision medicine using new predictive tests has been the goal of RA treatment for years, given the importance of getting patients on appropriate therapy quickly (preferably in the first 6-12 months of disease). Because it typically takes at least 3 months to assess the response rate to medication, it is critical that we have testing available to help guide this process. Certainly, if a patient has failed a DMARD therapy, that would be the right time to consider predictive testing for treatment.

Two SMEs replied that such tests are not offered clinically (and that any tests that are offered are investigational). One SME commented that he is not aware of any level 1 CPT codes that have been approved.

10. Regarding the new technologies and biomarkers discussed in the previous questions, does the literature support their use in only limited clinical situations and/or populations? Do you have concerns regarding their use or limitations? What are potential barriers to their implementation in practice (if any)?

Final Rating: 3

One SME replied that he has concerns about their use and that he does not think they need to be used repeatedly, but as more knowledge accumulates about the details of such testing and how it may change during therapy, he may reconsider his response.

Another SME replied that potential barriers or limited usage are only related to limited data at this point. If there are new technologies and markers to predict response to different treatment regimens, this would greatly benefit the majority of rheumatoid patients, especially those who fail DMARD therapy, as the goal is to start appropriate biologic therapy as soon as possible, to limit long-term sequela of chronic active rheumatoid arthritis.

The third SME agreed that having a test that could predict response (or non-response) to a TNFi would help shorten the 'trial and error' phase to finding an effective biologic therapy.