Rheumatoid Arthritis Treatment and Monitoring of Outcomes—Where Are We in 2007? Controversies and Opportunities

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Abstract

Rheumatoid arthritis (RA) treatment has witnessed major advances over the last 10 to 20 years. Methotrexate has emerged as the cornerstone of treatment with new biologic agents being used in addition in severe and resistant patients. New drugs being developed with novel modes of action are promising to expand treatment options and help provide better disease control for RA patients. In addition to medications, equally important is aggressive disease activity monitoring using one of the composite scores available in order to match treatments to disease activity. Disease activity score (DAS), DAS28 (with a 28 joint count), clinical disease activity index (CDAI), simplified disease activity index (SDAI), and routine assessment of patient index data (RAPID) are valuable tools and should be used in routine care to achieve disease control.

The treatment of rheumatoid arthritis (RA) has seen important changes over the last 10 to 20 years. Methotrexate (MTX) emerged as the drug of choice in the mid-1980s; however, a large number of patients in those years were also treated with some combination of parenteral gold and other modestly effective drugs, such as penicillamine, sulfasalazine, or hydroxychloroquine. Combination treatment, which is now considered the standard treatment option when patients fail their first disease modifying antirheumatic drug (DMARD), was rarely used. The usual practice was to stop the ineffective DMARD and start a new one and repeat as needed.

Over the last decade, these practices began to change, with the result that the number of options available to clinicians has increased and our approach to treatment has evolved as well. This has also led to improved outcomes with the older DMARDs, in most cases, MTX.

Initially, DMARDs were reserved for patients who showed evidence of advanced disease or erosions or of failing nonsteroidal antiinflammatory drugs (NSAIDs). When one DMARD failed, patients were switched to another DMARD, rather than having the new medication added on top of the current treatment. Aggressive treatment programs evolved with the introduction of MTX, the use of which was initially hampered by concerns related to toxicities, but these have since been shown to be milder than previously thought. Relative to the use of DMARDs early on, sulfasalazine, not MTX, was prescribed as the first agent in the majority of patients, and until recently remained the most commonly prescribed DMARD in Europe.

During the early to mid-1990s, a new and different paradigm evolved; rather than the “go-low, go-slow” admonitions from the gold and penicillamine era, modern treatment evolved to a more aggressive “go steady, be ready” approach: the dose was increased until a good therapeutic response was achieved and the patient was closely followed for disease activity. Put succinctly, the objective became to match the aggressiveness of the treatment to the aggressiveness of the disease. The TICORA (Tight Control of Rheumatoid Arthritis) study demonstrated that with strict control of disease activity, by using standardized disease assessment instruments and adjusting treatment according to preset goals, it is possible to achieve high degrees of remission with traditional DMARDs.
Three important factors have led to this more aggressive approach in the modern treatment of RA:

1. The disease is now recognized to be associated with significant mortality, morbidity, diminished quality of life, and disability.
2. Aggressive treatment has been shown to more effectively improve both symptoms and quality of life measures.
3. DMARD treatments have been shown to effectively retard radiographic progression of disease.

MTX was, and is today, the cornerstone of DMARD regimens. MTX appears also to be the cornerstone of treatment for the foreseeable future. It is the DMARD most used by rheumatologists, the one with the highest continuation rates at 5 years (only recently matched by biologic agents), and it has only a few clinically important adverse events. Recent years also have taught us much about MTX, including the value and utility of pharmacogenetic analysis, and also about as many as a dozen poli-dependent enzymes that could be affected by MTX, which could predict both response and toxicity. The recent anti-tumor necrosis factor (TNF) inhibitor trials have also provided very valuable information about MTX and its efficacy in RA treatment. In one recent study, when trials of TNF versus MTX naive patients were examined, MTX was as effective as TNF inhibitors in controlling both disease activity and radiographic progression.

The introduction of TNF inhibitors in 1998 provided new therapies and options in RA treatment. Remission has become more of a possibility for more patients, especially when these drugs are used in combination with MTX, as shown elegantly in the PREMIER study; the study demonstrated a combination of adalimumab with MTX was more effective in controlling both radiologic progression and symptoms than either MTX or adalimumab alone. One important point to keep in mind when translating results from RCTs (randomized controlled trials), of not just TNF inhibitors but all new and forthcoming treatments, is that patients enrolled in an RCT rarely are similar to patients seen in routine care, which is the clinical setting of the majority of our RA patients.

New Treatment Options

In 2006 two new treatments for RA, abatacept and rituximab, became available. Several other new options are also proving promising and may be available in the near future.

Abatacept

Abatacept became available for RA treatment in early 2006 and has a novel mechanism of action; it blocks the second signal transduction between the antigen presenting cell and the T cell and leads to a decrease of the downstream signal transduction. Abatacept is infused intravenously (IV) over 30 minutes at baseline, at 2 weeks and 4 weeks after baseline as the loading doses, and every 4 weeks, thereafter.

Abatacept has been studied separately in patients who have had an inadequate response to MTX and TNF inhibitors. In the AIM (Abatacept in Inadequate responders to Methotrexate) trial, patients who had had an inadequate response to MTX, as determined by their physicians, were randomized to placebo or abatacept while they continued taking their MTX. At 1 year, ACR 20, 50, and 70 responses were 73.1%, 48.3%, and 28.8% for abatacept and 39.7%, 18.2%, and 6 greater than 1% for placebo. Also, at 1 year, abatacept-treated patients showed statistically significant slowing of structural damage progression compared to placebo, with a 50% reduction in change from baseline in Genant-modified Sharp scores. Recently presented 2-year data of the AIM trial shows that the clinical response achieved at 1 year is maintained through the second year. In this trial, there was no difference between the overall incidence of adverse events in abatacept and placebo treated patients; however, the incidence of important adverse events increased with abatacept treatment, with serious infections being the most common. Discontinuation due to serious adverse events was similar between the two groups. No difference was noted in the incidence of neoplasm (benign or malignant).

As an accompanying editorial pointed out, this study, as most of the clinical trials of biologics are, was limited by a very select cohort of patients with very active disease who had failed MTX. These patients represented only a small group of patients seen in the real world. Abatacept is a good addition to our therapeutic arsenal, but its true place in RA treatment will be determined as more patients are exposed.

Abatacept has also been studied in patients who have had inadequate response to TNF inhibitors in the ATTAIN (Abatacept Trial in Treatment of Anti-TNF Inadequate Responders) trial. Patients who had failed another DMARD in addition to a TNF inhibitor were washed out of their TNF inhibitors, maintained on their other DMARDS, and randomized to either abatacept or placebo; 391 patients were treated. At 6 months, ACR 20, 50, and 70 scores were 50.4%, 20.3%, and 10.2% for abatacept and 19.5%, 3.8%, and 1.5% for placebo. No differences for serious adverse events were noted for the groups. This cohort had close to 12 years of disease duration and failed multiple DMARDS, in addition to a TNF inhibitor; some had failed two TNF inhibitors before being enrolled. In the long-term extension of the ATTAIN trial, where the patients were followed as open-label subjects, these responses were sustained.

Rituximab

Rituximab was approved in early 2006 for use in RA; however, it had been used for the treatment of B-cell lymphoma since 1997. Rituximab affects the B-cell lineage; it is an antibody directed at CD20. Rituximab is delivered by IV infusion, specifically by two separate infusions, each lasting around 4 to 5 hours, two weeks apart. The timing of the following infusion is determined by the response of each
Table 1 Newly Approved and Soon to Come DMARDs

<table>
<thead>
<tr>
<th>Name</th>
<th>Mode of action</th>
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<tbody>
<tr>
<td>Abatacept</td>
<td>T cell secondary signal modulator</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Selective (CD20+) B cell depletion</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Anti-IL-6 receptor monoclonal antibody</td>
</tr>
<tr>
<td>HuMax</td>
<td>Selective (CD20+) B cell depletion</td>
</tr>
<tr>
<td>Belimumab</td>
<td>Inhibits B lymphocyte stimulator (BLyS)</td>
</tr>
<tr>
<td>Atacicept</td>
<td>Inhibits B lymphocyte stimulator (BLyS)</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>PEGylated anti-TNF monoclonal antibody</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Anti-TNF monoclonal antibody</td>
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Individual patient to this initial treatment course.

The DANCER (Dose-ranging Assessment International Clinical Evaluation of Rituximab in RA) trial studied rituximab in patients who have failed MTX. At week 24, 54%, 34%, and 20% ACR 20, 50, and 70 responses, respectively, were seen with rituximab, compared to 28%, 13%, and 5% in the placebo group. This study also examined the use of oral glucocorticoids for a two-week period versus IV glucocorticoids only at baseline and 15 days, given with rituximab, versus no glucocorticoids. Results showed that the oral steroids seemed to have no clinical effect on ACR 20, 50, or 70 responses. This has led to the recommendation that only IV steroids are needed before infusing rituximab for the purposes of avoiding infusion related reactions.

In the REFLEX (Randomized Evaluation of Long-term Efficacy of rituximab in RA) trial, patients who had an inadequate response to TNF antagonists and who were on weekly MTX with mean disease duration of 12 years, were studied. Subjects were randomized to receive either placebo or rituximab. Just as in the abatacept TNF failure trials, the ACR 20, 50, and 70 responses were 51%, 27%, and 12%, respectively, with rituximab treatment.

In both trials, infusions reactions were rare. The steroid infusions seem to help minimize the risks. In addition, there were no statistically significant differences in serious adverse events between rituximab and placebo treated patients, except for infections where placebo patients had 3.7 events for 100 patient-years, and rituximab patients had 5.2 for 100 patient-years of treatment.

Both abatacept and rituximab are promising additions to our arsenal. Their true place in the treatment of RA will be more apparent once more patients have been treated with them and there are long-term outcome data from prospective longitudinal databases.

Other new agents are on the horizon, with promising preliminary results from phase 2 and 3 trials. Table 1 lists some of the drugs that may be in use for RA treatment within the next 3 to 5 years.

Tocilizumab

Another new target in RA treatment is interleukin-6 (IL-6). IL-6 is a proinflammatory cytokine expressed in RA synovium and detected in circulation and synovial fluid in active patients. It has been shown to increase proliferation of synovial fibroblasts. IL-6 also appears to be involved in damage to the cartilage. Tocilizumab is a humanized anti-IL-6 receptor monoclonal antibody, formerly known as MRA. It has been studied in RA patients with active RA despite MTX treatment. The CHARISMA (Chugai Humanized Anti-human Recombinant Interleukin Six Monoclonal Antibody) trial randomized RA patients with inadequate response to MTX. Patients were randomized to seven arms, three with different doses of tocilizumab, either as monotherapy or in combination with MTX, or MTX with placebo, with monthly infusions.

The primary efficacy outcome was an ACR 20 response at 16 weeks. A total of 359 patients were randomized. Most patients had less than 12 months of RA duration. An ACR 20 response was achieved in 61% and 63% of tocilizumab patients, at 4 mg/kg and 8 mg/kg, respectively, as monotherapy, and in 63% and 74% of patients receiving tocilizumab with MTX in similar doses. The MTX and placebo groups had 41% ACR 20 responses. A similar result also was seen with DAS28 values.

In general, tocilizumab was well tolerated. Two cases of sepsis were seen in the 8 mg/kg tocilizumab with MTX group. A sawtooth pattern of liver function test elevations was seen in the tocilizumab groups; all results returned to normal 8 weeks after the last infusion. There were also moderate but reversible increases in nonfasting total cholesterol and triglyceride levels and reversible reductions in the high-density lipoprotein cholesterol; mean atherogenic index was unchanged. Reversible decreases in neutrophil levels were seen. Tocilizumab is viewed as a promising agent that is currently undergoing large scale phase III studies and may be a useful addition to our arsenal.

HuMax CD 20

HuMax CD20 is another CD 20 (+) B-cell targeting antibody, similar to rituximab, but it is fully humanized. In a small number of patients with active RA who have failed one or more DMARDs, including TNF inhibitors, initial data suggest 50% ACR 20 responses. It is infused as two infusions that are 2 weeks apart.

Belimumab

Belimumab, also known as LymphoStat-B, is an inhibitor of B-lymphocyte stimulator (BLyS), which is involved in the growth and survival of B cells. BLyS has been shown to be correlated with elevated rheumatoid factor (RF) and also has been found in blood and the synovial fluid of RA patients. Phase 2 trials using BlyS have been conducted in RA patients who have failed one or more DMARD, including TNF inhibitors. Treatment consisted of an infusion every 2 weeks for the first 3 doses and every 4 weeks thereafter. At 24 weeks, there was significant improvement in ACR 20 scores in 35% of patients, compared with 16% of those in the placebo group achieving this level. It is helpful to keep in mind that this cohort had an average of 11 years of disease,
with around 40% having failed a TNF inhibitor.

**Atacicept**

Another potential inhibitor of BLyS is atacicept, a recombinant fusion protein containing the extracellular, ligand-binding portion of the receptor TACI and the Fc portion of human IgG. It has been recently studied in a double blind, placebo controlled, dose escalation study in RA patients. Twenty three patients treated have had no serious adverse events, most being mild or moderate. Preliminary analysis show that atacicept penetrated synovial fluid and also led to 40% to 45% reductions in IgM-RF, IgA-RF, and IgG-RF. Early results from this study show improved ACR 20 and DAS28 responses after 6 months. Final results of the trial are pending and it is premature to pass judgment on this product.

**Certolizumab**

A new method of delivering anti-TNF agents is also being studied that involves PEGylation, the site specific addition of polyethylene glycol, which can enhance the pharmacokinetic properties of a molecule, decreasing its volume of distribution and clearance and increasing its half-life. Certolizumab is a PEGylated Fab fragment of a humanized anti-TNF monoclonal antibody. RA trials with this agent are underway as of this writing.

**Golimumab**

Golimumab is a new human monoclonal antibody to TNF-alpha that can be administered subcutaneously or intravenously; phase II studies have been performed. One hundred seventy-two RA patients with active disease, despite DMARD therapy, were randomized to placebo or golimumab and treated for 16 weeks. At 16 weeks, 62% of golimumab versus 37% of placebo treated patients achieved an ACR 20 response; 27% of golimumab treated patients were in remission as defined by DAS28.

**Disease Activity Monitoring**

RA treatment is a fast changing and advancing area. Not only are we getting better at using the drugs we already have, new medications are available to us and more are being developed. Our main challenge is, and will be, to identify which patients are responding to our treatments and to objectively quantify their response or nonresponse. Without using the proper tools for this aim, we will fall short of providing the best opportunity for disease control in our patients.

The TICORA\(^4\) and the Dutch BeSt\(^5\) (Behandel Strategieen) studies have demonstrated the importance of close monitoring of RA patients. However, this is in contrast to what happens in the real world. Rheumatologists generally apply few quantitative measures in making clinical decisions. In the United States, fewer than 10% of rheumatologists use questionnaires in routine clinical care, and fewer than 15% perform a formal joint count at each visit.\(^6\)

Evidence-based medicine has become the holy grail of modern medical practice; however, practicing clinicians often depend primarily upon their own impressions or the impressions of trusted colleagues concerning what has worked in the past, sometimes taking into account widely publicized RCTs. Substantial evidence shows that the majority of the patients seen in routine care would not qualify to participate in contemporary RA clinical trials because of their restrictive inclusion and exclusion criteria.\(^7\) Furthermore, the trials are usually of short duration, typically less than a year, and do not provide substantial information about important long-term outcomes, such as work disability, joint replacement surgery, and mortality.

The Health Assessment Questionnaire (HAQ) and its derivatives have been shown to be the best predictors of functional and work disability, costs, joint replacement surgery, and mortality. They are at least as good as joint counts, radiographs, and laboratory tests in predicting these outcomes.\(^8\) In addition, patient questionnaires can be used in all rheumatic diseases, including osteoarthritis, systemic lupus erythematosus, fibromyalgia, scleroderma, and ankylosing spondylitis.\(^9\)

Composite scores are usually required in rheumatology but especially in RA, because there is no one measure that can be used in all patients. Hence, various different outcome measures are used in RCT and are recommended for use in clinical care. The ACR Core Data set was developed to provide a consistent set of outcome measures for RA. ACR 20, 50, and 70 responses have been used and are good tools, with some differing opinions as to which one is more clinically relevant; however, as a group, they are cumbersome to use in real world clinical care. This has led to alternatives being developed for both RCT and clinical care (Table 2).

Disease activity score (DAS) and its derivatives, DAS28 (with a 28-joint count), DAS-CRP (using CRP in place of ESR) are widely used in RCT. The advantage of providing a

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<th>Table 2</th>
<th>Comparison of Composite Scores Commonly Used in RA</th>
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<tr>
<td></td>
<td>DAS28</td>
</tr>
<tr>
<td>Swollen joint</td>
<td>+</td>
</tr>
<tr>
<td>Tender joint</td>
<td>+</td>
</tr>
<tr>
<td>Physician global</td>
<td>+</td>
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<tr>
<td>ESR/CRP</td>
<td>+</td>
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<tr>
<td>Patient global</td>
<td>+</td>
</tr>
<tr>
<td>Functional score</td>
<td>+</td>
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<td>Pain</td>
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score for current disease activity, rather than a change score, as in ACR 20, 50, and 70, makes this a more “true” reflection of disease activity. However, it requires a calculator to compute the score using a complicated formula. A website also provides a scoring tool; however, this and the fact that at least a 28-joint count is required for the score, has led to it being used rarely in clinical practice.

The simplified disease activity index (SDAI) and its simpler version (no acute phase reactant needed) the clinical disease activity index (CDAI) has been proposed recently. Both are strongly correlated with DAS, but since they share most of the components of DAS, this is to be expected. CDAI has the advantage of performing a calculation right at the time of a patient visit since it does not require a laboratory test.

The global arthritis score (GAS) is the sum of three measures, patient pain, raw mHAQ, and tender joint count, and is also closely correlated with both SDAI and DAS.

Routine assessment of patient index data (RAPID) was developed with the aim of solving an important problem in the monitoring of patients in clinical care: the reality that the instrument needs to be easy to use for both the patients and rheumatologists while performing as well if not better than the other available scores. This index of only three patient reported outcome measures from the core data set—physical function, pain, and global estimate—distinguishes active from control treatments in clinical trials as effectively as ACR or DAS criteria. The calculation of the score requires no gadgets, no blood test results, nor a joint count. It takes less time than a 28-joint count, DAS28 or HAQ scoring, and is highly correlated in the routine care setting with SDAI and CDAI.

The need to use a tool to assess our patients is obvious, and all of the measures discussed above perform within the same range of response and are robust. The most user friendly measure has a better chance of succeeding and improving both patient care and rheumatologists’ efficient use of time. We currently use the RAPID in our clinics and some of the private practices, and teach our fellows to do the same. With more hands on experience most rheumatologists, we feel, would find this a useful and acceptable tool.

**Conclusions**

For now, our best strategy for treating RA patients arguably is to start with MTX, with or without low dose steroids, and treat aggressively. We need to monitor patient response with one of the available tools, the DAS28, SDAI, CDAI, GAS, RAPID, or the like, and adjust treatment according to these scores. Patients with inadequate responses after 3 to 6 months should have one of the biologic agents added to MTX to optimize treatment. Current data suggests that, in MTX, failures using a combination of MTX and a TNF inhibitor do better than those using a TNF inhibitor alone. So, rather than change to another drug, the right action would seem to be to add a new DMARD.

Despite very good results with MTX and TNF inhibitor combinations, around 10% to 15% of patients still do not have an adequate response. The new medications on the market and those in development, like new cytokine inhibitors with a different mode of action, will be the next treatment options for these patients.

After some time, when all of these agents have been in use long enough, the main determinant as to which agent to use will be based on patient preference, adverse event profiles, ease of use, and most likely a pharmacogenomic profile of each patient. Today our treatments work for a large number of our patients. The future of RA treatment also looks promising for the remainder of patients with RA, those whose symptoms and disease course continue to challenge our clinical and research endeavors.

**Disclosure Statement**

Yusuf Yazici, M.D. is a member of the Speakers’ Bureaus of Pfizer, Amgen, Boehringer Ingelheim, Genentech, and BMS; a Consultant for Roche, Celgene, BMS, and Schering Plough; an Advisory Board member of Centocor, BMS, Genentech, and Roche; and a recipient of Educational Grants from Abbott, Centocor, and Genentech. Steven B. Abramson, M.D., has received Consulting fees from Pfizer and Novartis.

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