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Incorporating the Treat-to-Target Concept in Rheumatoid Arthritis

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Stanley Ferrell, RPh, MBA; Tamar Sapir, PhD; and Davecia R. Cameron, MS

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Incorporating the Treat-to-Target Concept in Rheumatoid Arthritis

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Target Audiences
This activity is designed to meet the educational needs of physicians, pharmacists, and nurses in managed care.

Overall Goal
The overall goal of the supplement is to provide health care professionals with information on the recent advances in rheumatoid arthritis (RA) management, how to optimize the use of disease-modifying antirheumatic drugs (DMARDs), and how to incorporate the treat-to-target paradigm in contemporary clinical practice to improve outcomes for patients.

Learning Objectives
After completing this activity, the participant should be better able to:

1. Evaluate the evidence that supports recently published consensus recommendations for treating to target in RA
2. Assess the potential utility of conventional DMARDs, U.S. Food and Drug Administration (FDA)-approved biologic agents, and emerging therapies for RA in treat-to-target paradigms
3. Apply treat-to-target recommendations that offer the greatest promise for improving patient outcomes in RA

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The listed authors received compensation from PRIME Education, Inc., for participating in the live continuing education activity and for writing the supplement.

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The authors of these articles reported no mention of off-label use of the drugs described in this supplement.

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ABSTRACT

BACKGROUND: Recent publications have proposed revisions to disease classification criteria, new definitions of remission, and guidelines for implementing treat-to-target strategies for the management of patients with rheumatoid arthritis (RA). Despite developments leading to this practice-changing approach, the concept of treat to target has not yet been widely accepted or implemented in managed care. At the 24th Annual Meeting & Expo of the Academy of Managed Care Pharmacy (AMCP), held in San Francisco on April 18, 2012, a 4-hour activity titled *Incorporating New Treat-to-Target Guidance and Strategies in RA: What Managed Care Needs to Know* was conducted in association with AMCP's Continuing Professional Education Partner Program. The practicum featured didactic presentations, a roundtable session, and an expert panel discussion detailing research evidence, ideas, and discussion topics central to the treat-to-target concept in RA and its applications to managed care.

OBJECTIVES: To (a) discuss recent advances in RA management, (b) evaluate strategies to optimize the use of disease-modifying antirheumatic drugs (DMARDs), and (c) explain how to incorporate the treat-to-target paradigm in contemporary clinical practice and clinical care models in order to improve outcomes for patients.

SUMMARY: The past decade has seen a tremendous amount of change in the field of rheumatology. The early and aggressive treatment of RA, including the use of novel biologic agents, has been shown to have favorable patient outcomes in reducing synovial inflammation, delaying joint damage, and maintaining functional status, leading to the recently published revisions in classification criteria and updated recommendations for the utilization of conventional DMARDs and biologic agents in the treatment of RA. The revised classification criteria can be used to diagnose RA patients at an earlier point in the disease course by placing greater emphasis on clinical features that manifest early in the disease process. The concept of achieving tight control of RA and treating to target has been well established and utilizes early diagnosis, aggressive treatment, and regular monitoring, leading to positive outcomes in a significant number of patients with RA who achieve current treatment goals of low levels of disease activity or clinical remission.

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Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with significant functional limitations and disability. It is a systemic autoimmune inflammatory disorder characterized by synovial inflammation leading to joint tenderness, swelling, and stiffness, eventually causing cartilage damage, bone erosions, and joint destruction.[1-5] About 1.5 million adults in the United States were diagnosed with RA in 2007 and are at increased risk of cardiovascular disease and thus increased mortality. While reported incidence and prevalence varies from study to study, the prevalence rate is approximately 0.5% to 1% of the U.S. population, increasing with age, and showing to be the highest in women over the age of 65 years.[6-8] The decreased quality of life experienced by patients with RA contributes to reduced employment rates and increased direct and indirect costs.[6] In 2010, it was estimated that the total annual cost of RA in the United States, excluding intangible costs, reached $19.3 billion (in 2005 dollars), representing approximately $14,900 per patient with RA.[9]

Genetic factors contribute up to 50% of the risk of developing RA. Two antibody markers are associated with RA: rheumatoid factor (RF), a classic autoantibody directed against the Fc fragment of Immunoglobulin G (IgG), and anti-cyclic citrullinated peptide (anti-CCP). In patients with RA, 50% to 80% are positive to either one or both antibody markers.[10] Smoking is one of the main environmental risk factors associated with anti-CCP-positive RA, and the disease is 3 times more common in women than in men.[8] Synovial inflammation resulting in joint damage and physical disability are the hallmarks of RA.

Treatment advances in minimizing inflammation, delaying joint damage, and improving patient outcomes have been seen with the use of conventional disease-modifying antirheumatic drugs (DMARDs) and biologic agents. Currently, treatment goals have evolved from simply treating inflammation to inhibiting progressive joint destruction and attaining low disease activity (LDA) and then to the more lofty goal of accomplishing clinical remission in some patients by utilizing treat-to-target approaches.[11] With the use of DMARDs and biologic agents soon after diagnosis, clinicians can now more effectively decrease pain, swelling, and progressive joint damage in order to improve function and quality of life and to preserve the patients' roles in society.[12]

The use of treatment targets to improve outcomes has been implemented in clinical practice for the management of patients with various conditions such as hypertension, diabetes, and hyperlipidemia. For the care of these patients, clinicians monitor blood pressure and use laboratory tests for blood glucose, hemoglobin A1c, cholesterol, and triglycerides and modify treatment accordingly; patients are informed of these clinical tests and their treatment targets, respectively.[13-15] Similarly, the recent American College of Rheumatology (ACR) consensus on RA disease activity measures allows physicians to implement standardized treatment targets in managing patients with RA.[16]

RA Classification Criteria and Diagnosis

Diagnosing RA begins with a thorough medical history of the patient, focusing on the presence, location, and duration of joint pain, stiffness, and swelling as well as a physical exam assessment of synovitis (e.g., pain, swelling, tenderness <6 weeks or ≥6 weeks).[17] Laboratory tests are performed to support a diagnosis of RA. Tests include radiographs of the hands, wrists, and feet, testing for RF, anti-CCP, erythrocyte sedimentation rate (ESR), and serum C-reactive protein (CRP)

TABLE 1 2010 Rheumatoid Arthritis Classification Criteria

Criteria	Score
Joint Involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints excluded)	2
4-10 small joints (large joints excluded)	3
>10 joints (at least 1 small joint)	5
Serology	
Negative RF and negative anti-CCP	0
Low-positive RF or low-positive ACPA (≤3 times the upper limit of normal)	2
High-positive RF or high-positive ACPA (>3 times the upper limit of normal)	3
Symptom Duration	
<6 weeks	0
≥6 weeks	1
Acute Phase Reactants	
Normal CRP and ESR	0
Abnormal CRP or ESR	1

Source: Aletaha D, Neogi T, Silman AJ, et al. Arthritis Rheum. 2010;62(9):2569-81.[17]

When adding up the score of each of the 4 categories, a total score of ≥6/10 is needed for classification of a patient as having definite RA.

ACPA = anti-citrullinated protein antibody; CCP = cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RF = rheumatoid factor.

levels.[18-20] Although up to 50% of patients can be negative to both RF and anti-CCP testing, ESR and CRP levels are often elevated in patients with RA.[21] Yet, a positive result for either RF or anti-CCP can increase the overall diagnostic sensitivity, and a positive result for both tests can increase the diagnostic specificity.[21]

A joint working group from the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) developed updated classification criteria in 2010 to assist in earlier diagnosis (Table 1).[17] While previous classification criteria identified the disease by features associated with the later stages of RA, the newly revised classification system concentrates on factors associated with the inflammatory disease present at the onset of RA. The new criteria set allows for earlier diagnosis and may set the stage for the use of effective therapy early on, which can then be used to more effectively prevent the accrual of long-term joint damage and disability.[17] Four major factors are considered in the new classification criteria: the number and types of joints involved, the presence or absence of RF and/or CCP autoantibodies, laboratory markers of inflammation (ESR and/or CRP), and the duration of symptoms of synovitis at time of assessment. Synovitis must be confirmed in at least 1 joint, and other causes for synovitis such as psoriatic arthritis or gout must be ruled out. Patients who achieve a score of 6 or more (of a possible 10) from the individual scores in the 4 domains described above are considered to have a definitive diagnosis of RA.[17]

The Use of DMARDs and Biologic Agents in the Treatment of RA

The pharmacologic approach to treating RA has traditionally been a mixture of nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen, analgesics, glucocorticoids, and DMARDs. Conventional DMARDs include hydroxychloroquine (HCQ), leflunomide (LEF), methotrexate (MTX), or sulfasalazine (SSZ). MTX remains the most widely used standard DMARD for the treatment of RA due to its low cost, long-term effectiveness, and acceptable safety profile. Yet, clinicians need to undertake measures to monitor MTX-associated adverse effects (e.g. elevations in hepatic enzymes, alopecia, oral ulcer, cytopenia, interstitial pneumonitis).[22] Glucocorticoids, such as prednisolone and methylprednisolone, interact with steroid-specific receptors to inhibit inflammatory cells and suppress inflammation, reducing swelling and pain.[23] Glucocorticoids at low doses are commonly used in patients who are being switched from one DMARD therapy to another, controlling pain and inflammation while waiting for the next therapy to start working.[23] Conventional DMARDs are slow acting and work by dampening the inflammatory process, inhibiting joint damage, and preserving joint structure and function.[24] SSZ and HCQ historically were used in patients with mild disease but today are not widely used alone, at least not as primary therapy. LEF may be used as an alternative treatment in patients who have had toxicity or tolerability issues with MTX.[25]

Understanding the pathophysiology of RA is a key step in the development of more effective treatments. Over the past 20 years, an improved understanding of the pathogenesis of RA has led to the development of biologic DMARDs. While the exact etiology of the disease is not yet fully known, research has identified several important factors, including T cells, B cells, and cytokines. Several cytokines that play an especially critical role are tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6). Novel biologic therapies that build on these premises include agents that work by selectively inhibiting mechanisms required in the inflammatory and immune response. An example of selective inhibition are the TNF inhibitors or monoclonal antibodies that bind specifically to TNF and/or TNF receptors.[26] Currently, U.S. Food and Drug Administration (FDA)-approved biologic DMARDs for the treatment of RA include adalimumab, etanercept, infliximab, golimumab, certolizumab pegol, abatacept, anakinra, rituximab, tocilizumab, and the recently approved oral tofacitinib. Rituximab and tocilizumab are currently approved in the United States only for patients who have failed a TNF-inhibitor.[27] Table 2 lists the drug, drug classification, mode of action, and dose/route of administration of the agents used in the treatment of RA.

TABLE 2 Overview of Traditional Therapies and Biologic Agents Used in the Treatment of Rheumatoid Arthritis

Drug Generic Name (Trade Name)	Type of Agent	Mode of Action	Dose (Route of Administration)
methylprednisolone[109] (Medrol, Depo-Medrol, Solu-Medrol) prednisone[110] (Deltasone, Sterapred, LiquiPred) prednisolone[111] (Orapred, Pediapred, Prelone, Delta-Cortef, Econopred)	Glucocorticoids	Anti-inflammatory and immunosuppressive	Varies
hydroxychloroquine[112] (Plaquenil)	Antimalarial	Blocks the activation of toll-like receptors on plasmacytoid dendritic cells	200-400 mg daily (oral)
leflunomide[113] (Arava)	Pyrimidine synthesis inhibitor	Inhibits mitochondrial enzymes and prevents expansion of activated autoimmune lymphocytes	10-20 mg daily (oral)
methotrexate[112] (Trexall, Folex, Rheumatrex)	Anti-metabolite, purine synthesis inhibitor	Inhibits enzymes involved in purine metabolism, inhibits T-cell activation and expression	10-25 mg weekly (oral or SC)
sulfasalazine[112] (Azulfidine, EN-tabs, Sulfazine)	Sulfa drug	Anti-inflammatory	1,000-1,500 mg twice daily (oral)
etanercept[114] (Enbrel)	sTNFR fusion protein, TNFα inhibitor	Inhibits soluble TNFα thus reducing the inflammatory response	50 mg weekly (SC)
infliximab[80] (Remicade)	TNFα inhibitor	Deactivates biological activity of soluble and transmembrane TNFα and inhibits the effective binding of TNFα with its receptors, thus reducing the inflammatory response	3-10 mg/kg every 4-8 weeks (IV)
adalimumab[81] (Humira)			40 mg every other week or weekly (SC)
certolizumab pegol[82] (Cimzia)			400 mg at weeks 0, 2, 4; then 200 mg every other week. Maintenance dose of 400 mg every 4 weeks can be considered (SC).
golimumab[84] (Simponi)			50 mg every 4 weeks (SC)
anakinra[115] (Kineret)	IL-1 receptor antagonist	Blocks activity of interleukin, a protein in the body that causes joint damage	100 mg daily (SC)
abatacept[116] (Orencia)	sCTLA-4-Ig recombinant fusion protein	Inhibits T-cell activation	500-1,000 mg based on body weight every 2 weeks for 3 doses (IV), then every 4 weeks or 125 mg weekly (SC)
rituximab[75] (Rituxan)	Anti-CD20 monoclonal antibody	Binds to CD20 expressed on B-cells; B-cells contribute to the immune process that leads to inflammation and joint damage	2 × 1,000 mg infusions 2 weeks apart (IV) with steroids pre-medication (IV)
tocilizumab[85] (Actemra, RoActemra)	Humanized monoclonal antibody targeting the IL-6 receptor	Binds soluble and membrane bound IL-6 receptor thus suppressing its pro-inflammatory effects	4 mg/kg every 4 weeks, followed by an increase to 8 mg/kg based on clinical response (IV)
tofacitinib[72] (Xeljanz)	Small molecule Janus kinase (JAK) inhibitor	Inhibits intracellular signaling mediated by the JAK-STAT pathway	5 mg bid as monotherapy or in combination with methotrexate or other nonbiologic DMARDs (oral)

DMARDS = disease-modifying antirheumatic drugs; SC = subcutaneous; sTNFR = soluble tumor necrosis factor receptor; TNF = tumor necrosis factor; IV = intravenous; mg = milligrams; kg = kilograms; IL = interleukin; sCTLA4-Ig = soluble cytotoxic T-lymphocyte-associated antigen 4 immunoglobulin; CD20 = cluster of differentiation 20.

In 2012, the ACR published an update to the 2008 ACR recommendations for the utilization of conventional DMARDs and biologic agents in the treatment of RA.[27] This update focused on the indications for DMARDs and biologic agents, switching (or combining) between using conventional DMARDs and biologics, the use of biologics in high-risk patients, and vaccinations for patients who currently receive DMARDs or biologics. Table 3 shows the ACR recommendations update for the treatment of early (disease duration of < 6 months) and established (disease duration of ≥ 6 months) RA.[27]

Measuring Outcomes and Assessing Disease Activity

There are 3 clinical factors that can aid clinicians in decision making: RA disease activity assessment, disease duration, and prognostic factors of poor outcomes. A change in the patient's disease activity can be assessed using the ACR response criteria. The hybrid measure ACR20/50/70 response criteria of a treatment incorporates a patient-specific definition of continuous improvement, based on whether the patient has at least 20%/50%/70% improvement in swollen and tender joint counts, along with comparable improvement in at least 3 of the

TABLE 3 American College of Rheumatology (ACR) Recommendations Update for the Treatment of Early (<6 months) and Established (≥6 months) Rheumatoid Arthritis

Disease Activity (Disease Duration)	Recommended Drug Therapy
Low (<6 months) without features of poor prognosis[a]	DMARD monotherapy
Moderate (<6 months) without features of poor prognosis[a]	DMARD monotherapy
Moderate (<6 months) with features of poor prognosis[a]	Combination DMARD therapy (double and triple therapy)[b]
High (<6 months) without features of poor prognosis[a]	DMARD monotherapy Or HCQ and MTX
High (<6 months) with features of poor prognosis	TNF inhibitor with or without MTX Or Combination DMARD therapy (double and triple therapy)[b]
Low (≥6 months) without features of poor prognosis[a]	DMARD monotherapy ↓ *Reassess*[c] ↓ Add MTX, HCQ or LEF (as appropriate) ↓ *Reassess*[c] ↓ **B.** Add or switch to TNF inhibitor biologic[d] ↓ *Reassess*[c] *or if nonserious adverse event*[e] ↓ **C.** Switch to TNF inhibitor biologic or non-TNF inhibitor biologic (if there is a serious evente switch to non-TNF biologic only) ↓ *Reassess*[c] ↓ **D.** Switch to another type or category of TNF inhibitor or non-TNF inhibitor biologic
Low disease activity (≥6 months) with features of poor prognosis[a] OR Moderate/high disease activity (≥6 months)	MTX monotherapy or combination DMARD therapy (including double or triple therapy)[b] ↓ *Reassess*[c] ↓ Add or switch to another DMARD → *Reassess*[c] → Follow points B to D above Or Add or switch to abatacept or rituximab ↓ *Reassess*[f] *or if any adverse event*[g] ↓ Switch to TNF inhibitor biologic or non-TNF inhibitor biologic ↓ *Reassess*[c] ↓ Switch to another type or category of TNF inhibitor or non-TNF inhibitor biologic

Modified from: Singh JA, Furst DE, Bharat A, et al. Arthritis Care Res. 2012;64(5):625-39.[27]

[a]*Patients were categorized based on the presence or absence of 1 or more of the following poor prognostic features: functional limitation (e.g., Health Assessment Questionnaire score or similar valid tools), extra-articular disease (e.g., presence of rheumatoid nodules, RA vasculitis, Felty's syndrome), positive rheumatoid factor or anti-cyclic citrullinated peptide antibodies, and bony erosions by radiograph.*

[b]*Combination DMARD therapy with 2 DMARDs, which is most commonly MTX-based with some exceptions (e.g., MTX + HCQ, MTX + SSZ, SSZ + HCQ) and triple therapy (MTX + HCQ + SSZ).*

[c]*Reassess after 3 months and proceed with escalating therapy if moderate or high disease activity in all instances except after treatment with a non-TNF inhibitor biologic, where reassessment is recommended at 6 months due to a longer anticipated time for peak effect.*

[d]*If after 3 months of intensified DMARD combination therapy or after a second DMARD has failed, the option is to add or switch to an TNF inhibitor biologic.*

[e]*Serious adverse events were defined per the U.S. Food and Drug Administration (FDA); all other adverse events were considered nonserious adverse events.*

[f]*Reassessment after treatment with a non-TNF inhibitor biologic is recommended at 6 months due to anticipation that a longer time to peak effect is needed for non-TNF inhibitor compared with TNF inhibitor biologics.*

[g]*Any adverse event was defined as per the FDA as any undesirable experience associated with the use of a medical product in a patient. The FDA definition of serious adverse event includes death, life-threatening event, initial or prolonged hospitalization, disability, congenital anomaly, or an adverse event requiring intervention to prevent permanent impairment or damage.*

RA = rheumatoid arthritis; DMARD = disease-modifying antirheumatic drug (includes hydroxychloroquine [HCQ], leflunomide [LEF], methotrexate [MTX], minocycline [MIN], sulfasalazine [SSZ]); TNF = tumor necrosis factor.

following 5 measures:[28]

- Patient's Global Assessment using a 10-cm visual analog scale (VAS 0-10)
- Physician's Global Assessment (VAS 0-10)
- Patient's Assessment of Pain (VAS 0-10)
- Acute-phase reactant (measures of CRP and ESR)
- Functional disability as assessed by the Health Assessment Questionnaire Disability Index (HAQ-DI)

RA disease activity can also be assessed as high, medium, or low based on several validated instruments that quantify absolute rather than relative RA disease activity at any given point in time (Table 4).[27] These measures include disease activity score in 28 joints (DAS28), simplified disease activity index (SDAI), clinical disease activity index (CDAI), or routine assessment of patient index data (RAPID3). The prognostic factors utilized in making optimal treatment decisions include functional limitation as determined by the HAQ-DI, extra-articular disease, high titer seropositivity for RF or anti-CCP, and/or bony erosions by plain film radiography.[27]

TABLE 4 *Measuring Rheumatoid Arthritis Disease Activity to Define Remission*

Instrument	Thresholds of Disease Activity Levels
Routine Assessment of Patient Index Data 3 – RAPID3 (range 0 to 30)	Remission: <3 Low activity: ≥3 to 6 Moderate: ≥6 to 12 High: ≥12
Clinical Disease Activity Index – CDAI (range 0 to 76.0)	Remission: ≤2.8 Low activity: >2.8 to 10.0 Moderate: >10 to 22.0 High: >22.0
Disease Activity Score in 28 Joints – DAS28 (range 0 to 9.4)	Remission: <2.6 Low activity: ≥2.6 to <3.2 Moderate: ≥3.2 to ≤5.1 High: >5.1
Simplified Disease Activity Index – SDAI (range 0 to 86.0)	Remission: ≤3.3 Low activity: >3.3 to ≤11.0 Moderate: >11.0 to ≤26.0 High: >26.0

Source: Singh JA, Furst DE, Bharat A, et al. Arthritis Care Res. 2012;64(5):625-39.[27]

Disease Activity Score (DAS28)

In contrast to the ACR criteria that are based on change in status, the DAS28 is based on absolute status. The DAS28 relies on the clinician's assessment of the patient's joints, the patient's overall self-assessment of disease activity, and laboratory markers of inflammation (CRP or ESR).[29] During the examination, a physician determines the number of swollen and tender joints in 28 joints, including the knees, shoulders, elbows, wrists, and the small joints (metacarpophalangeal [MCPs] and proximal interphalangeal [PIPs]) in the hands. A formula ($0.56 \times \sqrt{}$ [tender joints] $+ 0.28 \times \sqrt{}$ [swollen joints] $+ 0.70 \times \ln$ [ESR/CRP] $+ 0.014 \times$ general health VAS) is used to determine the score.[30] Scores using this measure can be used to quantify disease activity on a patient's first visit to the clinic and be used in subsequent visits for comparison. The scoring system has been validated for use in clinical trials as well as routine patient care.[31,32] There are several online tools that can easily be accessed to aid in the calculations.[33,34] A drawback of the DAS28 is the need to have the ESR or CRP values on the day of the examination; these are not always immediately available to the clinician during the patient's visit.[31,32]

Health Assessment Questionnaire-Disability Index (HAQ-DI)

The HAQ is one of the first self-report functional status (disability) measures, developed originally in 1978 as a comprehensive measure of health outcome based on 5 patient-centered dimensions (death, disability, discomfort, drug toxicity, and dollar costs). The HAQ-DI assesses the extent of the patient's ability to perform activities of daily living over the past week.[35,36] Twenty items in 8 categories are measured: dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and common daily activities. The HAQ-DI gives the practitioner information about the patient's functional status that may or may not be obvious through the routine patient encounter without specific questioning.[35,36] For each item, there is a 4-level difficulty scale that is scored from 0 (no difficulty) to 3 (unable to perform activity), and the score for each category is determined by the highest component score in each category, unless aids or devices are required.[35] The HAQ-DI has been widely used for research purposes in both experimental and observational studies as well as in clinical settings. It has also been shown to be more predictive of RA disease progression than some other clinical measures. Interestingly, an increase of 1 unit in the HAQ-DI score over the first 2 years of disease is reflective of a risk of 90% greater disability and 87% greater costs over the next few years.[35,36] The HAQ-DI may be a good predictor of future cost of treatment, functional status, work disability, risk of death, and the need for joint replacement surgery.[37-40] Although HAQ-DI is sensitive to change, clinicians need to be aware that this tool uses an ordinal scale rather than a linear scale, which may result in similar changes in scores among patients irrespective of their baseline measurement.[41]

Defining Clinical Remission

Clinical remission in RA was originally defined in 1981 as the absence of signs and symptoms of significant inflammatory disease activity and is a realistic goal for many patients.[42] In 2011, the ACR/EULAR collaborative group revised the definition of remission.[43] To be considered as having disease that is in remission, a patient must satisfy all of the following factors:

- Tender joint count ≤ 1
- Swollen joint count ≤ 1
- CRP ≤ 1 mg/dL

TABLE 5 *Treat-To-Target Consensus Guidelines for Rheumatoid Arthritis*

1. The primary target for treatment of rheumatoid arthritis should be a state of clinical remission.
2. Clinical remission is defined as the absence of signs and symptoms of significant inflammatory disease activity.
3. While remission should be a clear target, based on available evidence, low disease activity may be an acceptable alternative therapeutic goal, particularly in established long-standing disease.
4. Until the desired treatment target is reached, drug therapy should be adjusted at least every 3 months.
5. Measures of disease activity must be obtained and documented regularly, as frequently as monthly for patients with high/moderate disease activity or less frequently (such as every 3–6 months) for patients in sustained low disease activity or remission.
6. The use of validated composite measures of disease activity, which include joint assessments, is needed in routine clinical practice to guide treatment decisions.
7. Structural changes and functional impairment should be considered when making clinical decisions, in addition to assessing composite measures of disease activity.
8. The desired treatment target should be maintained throughout the remaining course of the disease.
9. The choice of the (composite) measure of disease activity and the level of the target value may be influenced by consideration of comorbidities, patient factors, and drug-related risks.
10. The patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist.

Source: Smolen JS, Aletaha D, Bijlsma JW, et al. Ann Rheum Dis. 2010;69:631-37.[11]

- Patient global assessment ≤ 1 (on a 0-10 scale)
- Alternatively, an SDAI score of ≤ 3.3 can be used to determine remission.[43] See Table 4 for levels of remission for other measures.

Aletaha and colleagues performed a secondary analysis of data from 6 clinical trials of RA (2,763 patients) to examine functional limitation and identify reversible and irreversible components of disease in RA using the disability index of the HAQ as a measure of function.[44] In patients achieving clinical remission (n = 295, HAQ < 2.6), average HAQ scores, despite being in clinical remission, increased gradually with the duration of RA from 0.19 (< 2 years of RA) to 0.36 (2 to < 5 years) to 0.38 (5 to < 10 years) to 0.55 (≥ 10 years). The researchers concluded that irreversible functional limitation begins to develop within 2 years. If a patient delays treatment, irreparable damage will occur, even if treatment successfully reduces disease activity.[44]

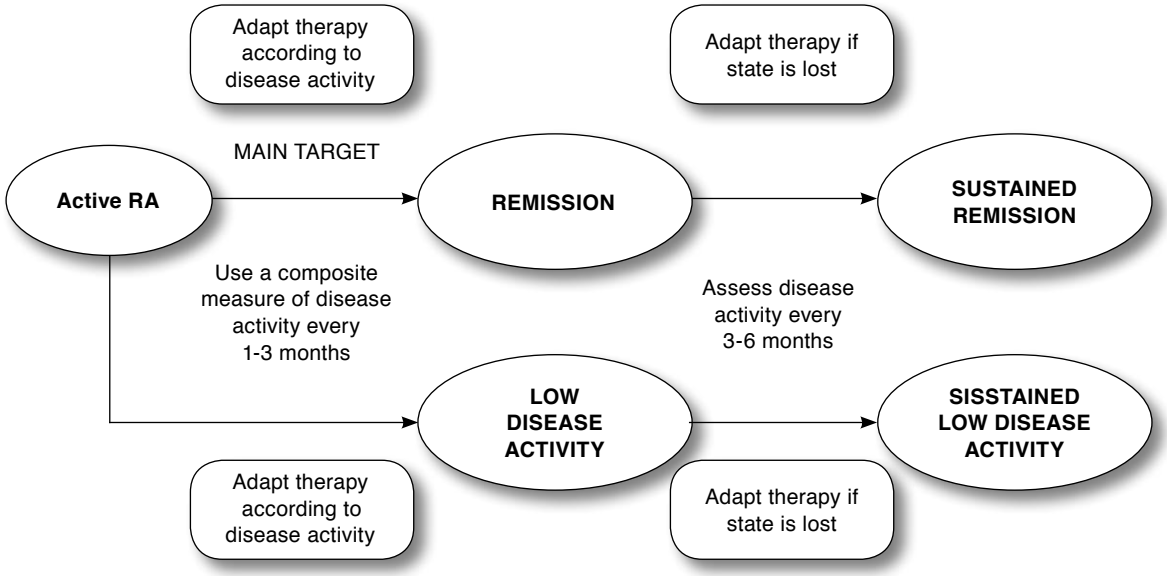
While remission remains the goal for patients with RA, it is not going to be achieved by all patients.[8,11,43] LDA may be a more reasonable target for patients with long-standing disease, prior treatment failures, and/or significant comorbidities.[8,11] Many patients with active RA may choose LDA as a desired target compared with trying for clinical remission at any and all costs.[8,11] LDA, according to the new recommendations, should be the minimal aspired goal, and with this group of patients, it is important to maintain a sustainable LDA as with patients in remission.[11]

Treating to Target in RA Management

Paradigmatic changes in RA management over the past 2 decades are mainly attributed to several factors: (1) early initiation of DMARDs has been shown to lessen joint damage and improve physical activity when compared with delayed treatment initiation, (2) disease activity can be assessed reliably due to definition of core set variables and development of composite measures, (3) novel DMARDs and biological agents have been shown to improve outcomes, (4) structured patient-shared treatment decisions for a treatment target leads to better outcomes than traditional means of follow-up, and (5) rapid attainment of remission can halt joint damage irrespective of the type of treatment.[11] Yet, these insights were not clearly formulated or adapted until 2010, when a set of guidelines, *Treating rheumatoid arthritis to target: recommendations of an international task force*, was published, which addressed the timely evidence and the principles of treating to target in RA.[11] A task force of more than 60 international RA experts formed to discuss and propose a set of recommendations based on evidence from systematic literature reviews and expert opinions with the aim to improve the management of RA in clinical practice.[11,45] This resulted in 10 recommendations (Table 5), which are the cornerstones of current RA management. These include earlier diagnosis, early and aggressive treatment of RA, regular assessments, and modification of therapy if needed.[11] In addition to these recommendations, the task force proposed 4 overarching principles that form the basis of the treat-to-target paradigm:

- The treatment of RA must be based on a shared decision between patient and rheumatologist.
- The primary goal of treating the patient with RA is to maximize long-term health-related quality of life through control of symptoms, prevention of structural damage, normalization of function, and social participation.
- Abrogation of inflammation is the most important way to achieve these goals.
- Treatment to target by measuring disease activity and adjusting therapy accordingly optimizes outcomes in RA.

FIGURE 1 *Treat-to-Target Model for Rheumatoid Arthritis*



Source: Smolen JS, Aletaha D, Bijlsma JW, et al. Ann Rheum Dis. 2010;69:631-37.[11]

The recommendations and overarching principles guide the model (Figure 1) for treating to target, which begins with a diagnosis of active RA. Patients should be assessed using a composite measure of disease activity as frequently as every 1 to 3 months to monitor target achievement (remission or, at the minimum, LDA), and therapy should be adjusted along the way according to disease activity until the target is reached. Once the target has been attained, patients should be evaluated every 3 to 6 months to ensure that remission (or LDA) are maintained.[11,27]

There have been several studies published that show that tight control results in greater improvement and a higher percentage of patients achieving the preset goal of LDA or remission when compared with the control intervention.[45-49]

In the Tight Control of Rheumatoid Arthritis (TICORA) study, 65% of patients in the tight control group versus 16% of the contrast group achieved remission based on DAS < 1.6 ($P < 0.0001$).[46] In the Finnish Rheumatoid Arthritis Combination Therapy Trial (FIN-RACo) trial, subanalysis of patients completing the study resulted in 68% of patients achieving remission in the tight control group (DAS28 < 2.6, corrected) versus 41% in the control group.[47] In the Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA) study, 50% of patients in the tight control group, using a computer decision model, achieved remission versus 37% in the control group ($P = 0.029$).[48] In the BehandelStrategieën (BeSt) study, remission was achieved in 38% to 46% of patients in tightly controlled groups, based on DAS < 1.6.[49]

How Various RA Therapies Fit Into the Treat-to-Target Paradigm

Early and aggressive treatment of RA has been successful in decreasing short-term disability by reducing inflammation, pain, and swelling and preventing long-term disability by minimizing the progression of RA in patients with established disease. Such outcomes can be achieved with the use of conventional DMARDs and biologics, which have shown to be effective in treating joint inflammation and in slowing progression.[11,27] Several investigational drugs with different biologic targets are in development at various clinical trial phases for the treatment of RA (Table 6).

Efficacy of Biologics for Early RA

With the available evidence showing that early institution of DMARDs can improve long-term outcomes in patients with RA, attention is focused on how to identify patients at an even earlier stage in their journey.[11] The time duration for early RA varies widely, with durations ranging between a few weeks (often called "very early RA") and up to 2 to 3 years.[50,51]

Several trials support the argument for initiating early treatment to target for RA and stress the importance of early diagnosis to avoid long-term, irreversible damage to joints.[52-57] The Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis (COMET) trial compared MTX monotherapy with combination therapy of MTX and etanercept in MTX-naïve patients with RA (N = 542) who had early moderate-to-severe disease (3-24 months duration).[52] Results of the study

TABLE 6 Emerging Therapies for Rheumatoid Arthritis

Agent	Administration Route	Clinical Trial Phase
Target: IL-6 or IL-6 receptor		
ALD518 (BMS-945429)	IV	II
Olokizumab	SC	II
ALX-0061	IV	I/II
SAR153191/REGN88	SC	II/III
Target: IL-17		
Secukinumab (AIN457)	SC	II/III
AMG827	SC	II
LY2439821	SC	I/II
Action: B-Cell Depletors or Modulators		
LY2127399	IV	II/III
Ofatumumab	IV	II/III
PF-05280586 (similar to rituximab, a monoclonal antibody anti-CD20)	IV	I/II
Action: Kinase Inhibitors		
BMS-582949 (MAPK)	Oral	I/II
Fostamatinib (SYK)	Oral	II/III
Ly3009104 (JAK)	Oral	II
GLPG0634 (JAK1)	Oral	II
Miscellaneous Action/Targets		
Umbilical Cord-Derived Mesenchymal Stem Cells (UC-MSCs)	IV	I/II

IL = interleukin; IV = intravenous; SC = subcutaneous; MAPK = p38 mitogen-activated protein kinase; SYK = spleen tyrosine kinase; JAK = Janus kinase.

showed that, after 1 year, approximately 50% of the patients in the combination therapy group achieved remission, compared with 28% of patients in the MTX monotherapy group (effect difference 22.05%, 95% CI = 13.96-30.15%; $P < 0.0001$).[52] A post hoc analysis of this study demonstrated that treatment of very early RA (≤ 4 months) achieved greater LDA (79% vs. 62%; $P < 0.05$) and DAS28 remission (70% vs. 48%; $P < 0.05$) than treatment of early RA (> 4 months and < 2 years) when treated with etanercept + MTX.[53] The PREMIER trial randomized patients with < 3 years of disease duration (N = 497) to MTX monotherapy, adalimumab monotherapy, or a combination of MTX and adalimumab.[54] Similar to the previous study, a higher proportion of patients (35%) achieved remission in the MTX plus adalimumab group followed by open-label adalimumab compared with 13% in the adalimumab monotherapy group and 14% in the MTX monotherapy group, over 5 years of treatment.[54] Both the ASPIRE and GO-BEFORE trials also showed that for patients with active RA in its early stages, combination therapy with MTX and a biologic may provide greater clinical, radiographic, and functional benefits than treatment with MTX alone. In the ASPIRE study, at week 54, MTX-naïve patients had a higher percentage of ACR improvement with combinations of infliximab (3 mg/kg) and MTX (38.9%; $P = 0.028$) compared with patients in the MTX plus placebo arm (26.4%).[55] The GO-BEFORE trial looked at the safety and efficacy of golimumab with MTX versus MTX alone in MTX-naïve patients who had active RA for at least 3 months. This study showed that patients in the combination arm of golimumab plus MTX had a significantly better response compared with patients who received MTX plus placebo only (ACR50 response at week 24 was 38.4% vs. 29.4%; $P = 0.053$, respectively).[56] In the Early Erosive Rheumatoid Arthritis (AGREE) study, a greater proportion of patients who achieved remission (43.2% vs. 22.7%; $P < 0.001$) or LDA (57.4% vs 40.6%; $P = 0.008$) was seen with abatacept plus MTX versus MTX alone, respectively, after 1 year of therapy.[57]

In all of these studies, even though there was a benefit in combination therapy over monotherapy, there were patients who responded well to monotherapy. The Swedish Farmacotherapy (SWEFOT) trial (N = 487) evaluated patients with RA duration of < 1 year who were started on MTX monotherapy for 3 to 4 months. Patients refractory to MTX (i.e., those who had not achieved LDA but who could tolerate MTX) were randomized to treatment with infliximab plus MTX or to conventional treatment (additional SSZ and HCQ). Interestingly, it was shown that the frequency of EULAR-defined good/moderate/no response prior to the randomization was 34%/41%/25%, respectively, meaning that about a third of the patients achieved the target response with early treatment with MTX alone and did not need additional treatment.[58] In the PREMIER study, the use of TNF inhibitors in early RA produced results similar for MTX-naïve patients who were treated with MTX alone or TNF inhibitor therapy alone.[54] It is only when MTX is combined with a biologic that there is an improvement in response. This, along with the likelihood that a meaningful proportion of patients will respond to MTX alone, is one of the reasons that the consensus is to initially treat with MTX.[27]

MTX-Inadequate Responders

For the patient whose disease progresses (determined as having active RA) while on MTX monotherapy (MTX-inadequate responders), switching to a combination of MTX plus a biologic may offer additional improvement and greater clinical, radiographic, and functional benefits. Indeed, multiple studies, including those described above, have confirmed the benefit of adding a TNF inhibitor to patients with an inadequate response to MTX alone. Abatacept, rituximab, and tocilizumab have also been demonstrated to be effective in this population, although only abatacept is currently FDA-approved for use as a first-line biologic after MTX in the United States.[59-61]

The question of whether patients who have not responded to MTX therapy will benefit more from the addition of multiple nonbiologic DMARDs or of a biologic DMARD is of additional interest. The SWEFOT study showed that the addition of infliximab for patients who had not achieved LDA

with MTX monotherapy resulted in better clinical outcomes (EULAR and ACR response criteria) at 1 year compared with patients receiving triple therapy consisting of SSZ, HCQ, and MTX.[58] The Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) study, however, showed that the triple therapy (MTX + SSZ + HCQ) and the addition of etanercept to MTX were equally efficacious at 2 years; follow-up data suggested that the addition of etanercept provided significant radiographic benefit compared with the triple therapy (0.64 vs. 1.69; $P = 0.047$).[61-63]

Which Drugs Follow TNF Inhibitors?

TNF inhibitors share the same target molecule, yet structural differences among them may lead to different clinical activity in inflammatory conditions other than RA (e.g., Crohn's disease).[64] The clinical importance of these differences remains largely unknown, and there are likely other factors that play a role in the variability of clinical responses, such as genetic differences in the treated patients (e.g., shared epitope genotype, TNF, and TNF-receptor polymorphisms, antibody-mediated clearance of TNF inhibitors, and different pharmacokinetic profiles).[64] Because of the differing characteristics of TNF inhibitors, switching RA patients from one TNF inhibitor to another may be advantageous in case of treatment failure (or adverse effects) with the TNF inhibitor that was originally prescribed. Additionally, there are several new biological non-TNF drugs that are now available with different mechanisms of action (abatacept, rituximab, tocilizumab, and tofacitinib) that may provide additional benefit for the RA patient who has failed a TNF inhibitor.[65]

Patients who have no response to a first TNF inhibitor are considered primary TNF failures. They appear to have less response to switching to a second or a third TNF inhibitor, presumably because their disease is not as driven by TNF pathways.[65-68] Patients who do respond for a time on TNF inhibitors and then have disease progression are considered secondary failures and generally appear to respond more effectively when switching to another TNF inhibitor than patients with primary failure.[65-68] Both types of patients may respond to a biologic agent with a different mechanism of action. A prospective cohort study nested within the Swiss Clinical Quality Management RA cohort included patients who had an inadequate response to at least 1 TNF inhibitor and subsequently received either 1 cycle of rituximab or an alternative TNF inhibitor.[69] Fifty patients received 1 cycle of rituximab and 66 patients were treated with a second or a third alternative TNF inhibitor. DAS28 scores were found to be more favorable in the group receiving rituximab compared with the group that received alternative TNF inhibitors ($P = 0.01$). At the 6-month follow-up, the mean decrease in the DAS28 was -1.61 (95% CI -1.97, -1.25) among patients receiving rituximab and -0.98 (95% CI -1.33, -0.62) among those receiving subsequent TNF inhibitor therapy. Bias was encountered in this study, though due to purposeful selection of a second agent.[69]

Both rituximab and abatacept have been shown to be effective in patients who have failed to respond adequately to a TNF inhibitor. The efficacy and safety of rituximab in this situation was assessed in the REFLEX trial, where rituximab plus MTX was evaluated in patients with active RA who had an inadequate response to TNF inhibitors. At 24 weeks, a single course of rituximab plus MTX resulted in clinically significant improvements in disease activity ($P < 0.0001$), with ACR20 (51% vs. 18%), ACR50 (27% vs. 5%), and ACR70 (12% vs. 1%) responses and moderate-to-good EULAR responses (65% vs. 22%) when compared with placebo.[60] Similar results were seen in the ATTAIN trial, where patients with active RA and an inadequate response to TNF inhibitor therapy were randomly assigned to receive abatacept or placebo along with background MTX. The ACR20/50/70 responses for patients receiving abatacept after 6 months were 50.4%/20.3%/10.2% and 19.5%/3.8%/1.5% in the placebo group ($P < 0.001$)[70] and were maintained over 5 years of treatment.[71]

The IL-6 cytokine is an alternative mechanistic target for RA treatment that has provided a recently approved biologic therapy for RA—tocilizumab.[59] Joint inflammation in RA leads to the production of IL-6 and its receptor, IL-6R, which is expressed on effector cells that cause and prolong inflammation. Tocilizumab is a humanized anti-IL-6R monoclonal antibody that inhibits the binding of IL-6 to its receptor.[59] In the phase III RADIATE trial, 499 patients with active RA who were refractory to TNF inhibitor therapy were randomized to either 8 mg/kg or 4 mg/kg IV tocilizumab arms or placebo every 4 weeks with stable MTX weekly for all participants for 24 weeks. At week 24, ACR20 was achieved by 50%, 30.4%, and 10.1% of patients in the 8 mg/kg, 4 mg/kg, and placebo groups, respectively ($P < 0.001$ for both tocilizumab groups vs. control). DAS28 remission (DAS28 < 2.6) rates at week 24 were 30.1%, 7.6%, and 1.6% of 8 mg/kg, 4 mg/kg, and control groups ($P < 0.001$ for 8 mg/kg and $P = 0.053$ for 4 mg/kg vs. control).[59]

Tofacitinib is a novel, oral janus kinase (JAK) inhibitor that has recently received approval by the FDA for use in patients with moderately to severely active RA who have had inadequate responses or intolerance to MTX. Tofacitinib may be used as monotherapy or in combination with MTX or other nonbiologic DMARDs and should not be used in combination with biologic DMARDs or with potent immunosuppressives, such as azathioprine and cyclosporine. A 6-month, double-blind, placebo-controlled study with 399 RA patients with inadequate response to one or more TNF inhibitors and on background treatment with MTX were randomized to receive tofacitinib at 2 different doses (5 mg or 10 mg twice daily) or placebo. At 3 months, the ACR20/50/70 response rates for tofacitinib were 41.7%/26.5%/13.6% ($P < 0.05$) for the 5 mg dose and

48.1%/27.8%/10.5% ($P < 0.0001$) for the 10 mg dose, compared with 24.4%/8.4%/1.5% in the placebo group. The number of patients in remission (DAS28 ≤2.6) was significantly higher for tofacitinib compared with patients in the placebo arm at 3 months (6.7% for 5 mg, 11.2% for 10 mg, and 1.7% for placebo; $P < 0.05$), and this proportion increased even more at 6 months (10.7% for 5 mg, and 15.8% for 10 mg; $P < 0.05$).[72]

Safety Issues with Biologic Therapies

Although biologic agents are an important addition to the therapeutic armamentarium for RA, caution must be used due to potential adverse effects that may occur.[73] The most common immediate adverse effects for intravenous biologic agents are infusion reactions that range from minor to life-threatening and injection-site reactions for agents that are administered subcutaneously.[73] Treatment limiting infusion reactions can be managed by coadministration of corticosteroids or antihistamines, or by slowing the infusion rate.[73,74] Fatal infusion reactions have been associated with rituximab (boxed warning on prescribing information), where 80% of the fatal reactions reported occurred on the first infusion.[75]

Infections are also a cause for concern when biologic agents are used. A patient's history regarding infections is important to note when these agents are prescribed and, given the risk of infections by all of these agents, it is not recommended that patients be treated with simultaneous combinations of biologic agents.[76] Increased susceptibility to tuberculosis (TB) or reactivation of latent TB has been linked to the use of TNF inhibitors. Patients should be tested for TB and evaluated for the risk of latent TB. A complete history should be taken and include history of prior exposure to TB, prior drug use/drug addictions, HIV infections, birth or extended living in a region of high TB prevalence and a history of working or living in high-risk areas for TB (e.g., jails, homeless shelters, drug rehabilitation centers).[77,78] TNF inhibitors should not be started or should be held when serious infections and/or opportunistic infections occur. Infections noted include systemic fungal infections, listeriosis, acute abscess, septic arthritis, osteomyelitis and sepsis.[78] Many TNF inhibitor and other biologic agent prescribing labels contain boxed warnings about infections, including adalimumab, etanercept, infliximab, golimumab, certolizumab, tocilizumab, and tofacitinib.[79-85] Additionally, in patients on biologics, live vaccinations should be avoided in patients and household contacts.[76]

The risk of lymphoma is increased 2 to 5 times in patients with RA compared with the general population.[76] There is a similar risk of lymphoma and other malignancies seen in patients with RA who are taking TNF inhibitors although the data on this is conflicting. The approved TNF inhibitors, adalimumab, etanercept, infliximab, golimumab, and certolizumab, all have warnings of lymphoma and other malignancies that may be fatal, having been reported in children and adolescent patients treated with TNF inhibitors.[79-82,84] Rituximab is associated with tumor lysis syndrome, severe mucocutaneous reactions (some with fatal outcomes), and progressive multifocal leukoencephalopathy.[75] Neutropenia, liver function abnormalities, thrombocytopenia and elevated lipids have been observed in clinical trials for patients treated with tocilizumab.[85-87] Worsening congestive heart failure and subsequent increased mortality has also been linked to the TNF inhibitors, as well as hematologic abnormalities, demyelination disorders, hepatotoxicity, and hepatitis B reactivation.[76,79-85] Safety concerns were demonstrated as well with the recently approved drug tofacitinib, where serious infections were developed in 6 patients who were receiving tofacitinib, and common adverse events were headache and upper respiratory tract infection. Tofacitinib treatment was associated with elevations in low-density lipoprotein cholesterol levels and reductions in neutrophil counts. Cases of lymphoma and other cancers also were reported, and the drug's labeling carries a boxed warning about the risks.[72]

Implementing Treat to Target in Practice and Strategies to Overcome Barriers

Despite the clear advantages of using the treat-to-target strategy to manage patients with RA (e.g. early diagnosis, prompt and intensive medical care, frequent patient assessment, tight control), there are several challenging barriers to the implementation and achievement of the concept and its goals in practice.[88-92] Some of these barriers include lack of access to both biologic and nonbiologic DMARDs in some groups of patients (e.g., low income, low health literacy) and perceived lack of efficacy of the medications. Often, perceived lack of efficacy is because patients are not receiving the appropriate medications or being treated fully according to the goals of the treat-to-target concept.[88,92] A study conducted by Schmajuk and colleagues found that the receipt of available DMARDs among patients in Medicare managed care plans with a diagnosis of RA remained low (30%-52%) between 2005 and 2008. Receipt of DMARDs varied significantly across enrollees in different health care plans, and DMARD use was low for older patients, men, and low socioeconomic groups.[88] Additional barriers to incorporate treat to target in practice may be due to concerns of the health care management team that this approach may be too time-consuming, involves complicated data recording, and/or involves reimbursement issues.[89-92]

Because RA is a complex disease associated with multiple comorbidities, managed care professionals must pay special attention to the possibility of challenging and unsafe changes to a patient's overall care, lack of communication among the patient's health care team, and underutilized or unproductive resources in the RA population. A unified approach to measuring RA treatment targets and patient quality of life from a population management perspective may be of significant benefit

to improve outcomes. Such standards are not typically provider driven and perhaps can be a standard set within public payers such as the Centers for Medicare & Medicaid Services (CMS).

There are also issues regarding the cost-effectiveness of RA treatment. When RA is diagnosed early, there is the risk of expensive medications being prescribed to patients where there is the possibility of spontaneous remission, which may be seen in 13% to 55% of individuals presenting with undifferentiated arthritis.[89] Additionally, there is the potential of time lost from work because of treatment or drug-related toxicities and/or, in some cases, patients can die because of treatment.[90] Treatment costs also increase with early therapy, with biologics costing up to 10 times more than conventional nonbiologic DMARDs.[89,91] Yet, benefit from early therapy, with the potential for patients to experience fewer disability days, less productivity loss, fewer days in the hospital, and fewer subsequent joint replacements, may offset the increased medication monetary cost.[89,91] Thus, the total (direct and indirect) long-term costs related to various therapeutic strategies is an important aspect for the health care team to consider.[89]

An interprofessional coordinated care model that is made up of the patient, pharmacist, and a case manager can aid with the difficulties in transition of care of patients and address some of the issues that patients may have with access to treatment.[93,94] More importantly, the improved communication between this team and the prescribing physician can help overcome many barriers to the implementation of the treat-to-target concept in RA practice. The main benefits of a collaborative approach are that it serves patients in transition who have complicated discharge needs, multiple providers, and several medications prescribed by various providers. Also addressed by this model are the needs of patients experiencing gaps in care, elderly patients with several chronic conditions, frequent users of health care, and at-risk populations that include patients with special needs and disabilities.[93,94]

Pharmacists play an integral role in managing patients' RA therapy regimen and should be incorporated into the case management of patients with RA since they can offer access to real-time pharmacy deployment data for the appropriate case management staff.[94] When potential medication therapy issues are raised by the case management staff, the pharmacist can report them to appropriate pharmacy staff and provide medication therapy management services.[95] Pharmacists are on the front line of dispensing and monitoring RA medications, offering patients much-needed information about drug adverse events and possible drug-drug interactions and adherence advice. Similar to the role of the case manager, the pharmacist manages a patient's therapy regimen and works with the patient's physician and insurance companies to provide the best treatment for the patient.[95] The role of the case manager is to bring the recommendations of the pharmacist into the management of the current case program and to bring full circle the evaluation and management of patients with RA. This collaboration between the case manager, patient, and pharmacist may offer some improvement to clinical, economic, and quality-of-care outcomes and, most importantly, can help improve patients' adherence to prescribed medications.[96] Studies show that patients benefit from multidisciplinary team care compared with nonteam care.[97] Often, the office of the primary care physician and the rheumatologist make the arrangements for managing the RA patient, but more and more, this responsibility is assigned to a case manager.[96] The case manager utilizes several skills to organize the total care experience needed to manage patients with RA, including those required to build relationships with both the patient and their families.[96] Additionally, the case manager is called on to understand the patient's overall condition and home situation and organize care among providers, agencies, and individuals. Their responsibilities also include providing the physician with information on patient compliance, response to treatment, and general functioning.[96]

Patient education is an important aspect of ensuring that the treat-to-target paradigm is successful due to the technical nature of medical language. This may be a barrier for patients to understand the value of their treatment.[98-100] One of the recommendations of the treat-to-target guidelines (Table 5) states that "the patient has to be appropriately informed about the treatment target and the strategy planned to reach this target under the supervision of the rheumatologist" and thus stresses the need for shared decision making between the physician and the patient.[11,100] It is imperative that patients be appropriately informed about the potential benefits and risks of RA therapies. They should be educated about their treatment goals and regimens to increase understanding and adherence. Medical and medication information that is understandable and written in lay language may help patients make informed decisions about their treatment and understand the risks and benefits.[100,101] Patient self-reported surveys of 1,193 patients with RA or ankylosing spondylitis have shown that easily understood information and involvement in medical decisions are strongly associated with increases in satisfaction and improvement in adherence to their treatment among the majority of the patients.[101] Another study looked at a different approach to improving patients' adherence to injectable RA medications, maximizing therapeutic outcomes, and enhancing physical functioning and health-related quality of life by empowering patients (through shared treatment decision making) and improving their knowledge of their disease.[102] A national pharmacy benefits manager (PBM) implemented an RA disease therapy management (DTM) program as an enhanced offering to patients receiving specialty pharmacy services. This innovative program utilized a patient-centered model to give coordinated health care interventions and communicate with patients about substantial self-care efforts. The

DTM program supplied patients with education and support to develop skills in the self-management of their symptoms and medication regimen, all while supporting the relationship between the physician and the patient. Results from the study showed that patients enrolled in the RA DTM program had higher adherence to their injectable RA medications compared with patients at community pharmacies who were not enrolled in a comparable program. Patients who completed the RA DTM program showed improvements in patient-reported outcomes (short form-12 physical component and HAQ-DI scores), but there was no improvement in the short form-12 mental scores or work productivity.[102] Additionally, the Medication Therapy Management (MTMP) programs required by CMS as part of Medicare Part D benefits has RA as a target population for outreach, counseling, and provision of CMR (Comprehensive Medication Reviews) that will improve member engagement and outcomes through pharmacists' review.[103]

Conclusions

Key breakthroughs have been made in the management of RA: today, clinicians are able to diagnose RA in a more effective manner, and there are several new and emerging therapeutic agents that are available for patients. Updated guidelines and clear goals for the treatment and management of RA are published. The available biologic therapies, coupled with achievable targets for remission and LDA, are effective in treating inflammation, slowing joint damage, and improving the quality of life for RA patients. While the cost-benefit ratio of many of these biologic agents may be a challenge to defend, the advantages to initiating therapy early, with patients experiencing fewer disability days, less productivity loss, fewer days in the hospital, and fewer subsequent joint replacements, may offset the initial medication monetary cost.

Additionally, payers are demanding a focus on quality of RA care to patients and programs such as MTMPs that may improve member engagement and outcomes through pharmacist review. Therefore, the collaborative efforts of managed care with physicians, pharmacists, and case managers as well as the empowerment and education of patients are of utmost importance to the implementation and success of the treat-to-target concept in clinical RA practice.

Commentary: Managed Care Perspective on Treat to Target in RA

Managed care pharmacists apply various population management principles for government and employer-sponsored benefits.[95] Systematic oversight of health plan members being treated for RA can ensure the provision of quality, cost-effective prescription drug benefits. Some such oversight of drug therapy is already mandated by payers, especially Medicare- and Medicaid-sponsored plans. MTMPs are required for certain Medicare Part D patients with chronic diseases, including RA.[103] The management programs designed and overseen by pharmacists in the managed care setting ensure not only that patients reach treat-to-target goals but also do so in the most cost-effective manner.[95] This is particularly important in the treat-to-target approach for RA where more than one provider is involved in the integrated RA care.[94]

With more decision makers involved in the general treatment of RA, overall patient drug therapies are more complex and may result in possible errors in prescribing or even gaps in care. Additionally, many of the newer RA medication therapies are considered specialty pharmaceuticals, which are often considered as high-cost, biotechnology-based molecules that frequently require parenteral administration.[104] Specialty drug management demands unique practices for patients, health plans, and employers, and the services needed to manage these include medication management, patient management, cost management, and distribution.[105]

Prior authorization (PA), step therapy, and drug utilization review (DUR) are key medication management tools that encourage the provision of quality and cost-effective prescription drug therapies for RA patients. The fundamental goal of PA is to promote the appropriate use of medications.[106] Pharmacists assist by supporting the RA treat-to-target goals while simultaneously managing the drug benefit by avoiding inappropriate medication use and promoting the use of evidence-based medication therapy. As mentioned earlier, many biologic DMARDs require proactive monitoring due to FDA boxed warnings regarding increased risk of serious infections leading to hospitalization or death. The PA, prior to dispensing any medications, will systematically confirm additional clinical patient information to ensure appropriate use and even drug coverage that is not always available via the prescription claims system or electronic records. Other helpful information such as lab data or HAQ scores garnered from PA may promote treatment to target by ensuring that disease activity measurement data is regularly obtained and communicated across the care team and adjusting therapy based on the physician, case manager, and pharmacist team approach, which optimizes clinical outcomes in RA.

Step therapy requires the use of a clinically recognized first-line drug before approval of a more complex and often more expensive medication, for which the safety, effectiveness, and value may not be as well established.[107] In the treat-to-target paradigm, therapeutic adjustments (addition/change in medication) are based on RA disease activity assessment, disease duration, and prognostic factors of poor outcomes. Step therapy may be employed to confirm that ACR guidelines for treating to these targeted outcomes are being measured and to ensure that an evidence-based approach is employed. For example, step therapy may be utilized by a health plan to confirm a history of TNF inhibitor use by the patient before approving the use of the biologic agent such as rituximab. This

can be an automated process using claims utilization management systems in conjunction with the point-of-sales systems by the PBM. The systematic process attempts to prevent the inappropriate use of less established safety profile medications and ensures that the more costly treatments are used for patients needing them who have not reached RA target treatment goals.

DUR promotes patient safety through utilization management systems that may help to identify potential patient-level health and safety issues. DUR is a 2-part process conducted by managed care pharmacists within the point-of-sale claims system linked to the pharmacies and/or retrospectively identifying interventions with physicians.[108] In the first part, known as CDUR (concurrent DUR), the health plan or PBM's electronic monitoring system screens prescription drug claims to identify problems such as therapeutic duplication, drug-disease contraindications, incorrect dosage or duration of treatment, drug allergy, and clinical misuse or abuse. When used for patients with RA, this system may find potentially harmful drug interactions or problems where duplicate biologic therapy is not appropriate.[108] The second part is retrospective DUR (RDUR) and involves periodic claims data review to identify patterns of abuse, fraud, gross overuse, gaps in care, or medically unnecessary care and implements corrective action when needed.[108] For example, RA patients' prescribers may be identified and sent an intervention letter that shows their patients who are at risk for drug-drug interactions with concurrent use of LEF and MTX (at high doses), which may result in increased risk of hepatotoxicity and bone marrow toxicity.[108]

In summary, managed care tools and principles have the ability to incorporate treat-to-target guidelines as an evidence-based approach. Many health plans and PBMs have initiated some elements of RA management using the model within their PA, step therapy, and DUR programs to ensure optimal clinical outcomes with limited resources. Expanding the use of managed care pharmacy management principles will likely be seen as interprofessional coordinated-care models evolve to merge medical and pharmacy protocols.

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