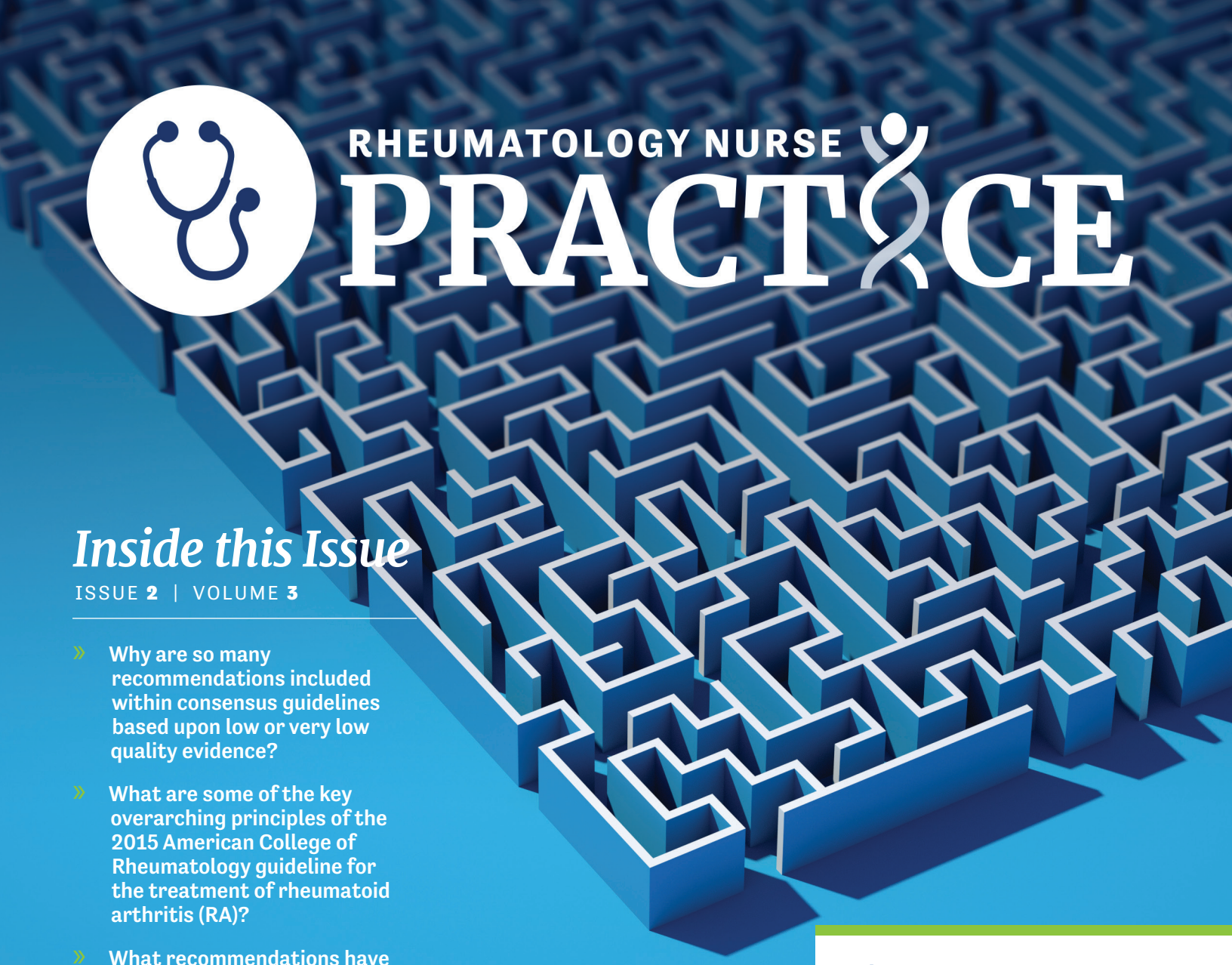

RHEUMATOLOGY NURSE PRACTICE

Inside this Issue

ISSUE 2 | VOLUME 3

- Why are so many recommendations included within consensus guidelines based upon low or very low quality evidence?
- What are some of the key overarching principles of the 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis (RA)?
- What recommendations have been made specific to patients with common comorbid conditions?
- How consistently do rheumatology practices adopt practices that are in alignment with consensus guidelines?

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Learning Objectives

1. *Discuss the clinical importance of strong vs. conditional recommendations included within the 2015 ACR guideline for the treatment of RA*
2. *List at least two overarching principles to guide RA care included within the 2015 ACR guideline*
3. *Assess the state of your current practice regarding tuberculosis screening and vaccinations in patients on conventional or biologic DMARD therapy, and identify any areas for improvement*
4. *Describe common barriers that influence adherence to RA treatment regimens*

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Making Sense of an Increasingly Complex Treatment Paradigm in RA

Rheumatology providers have never had more options for treating rheumatoid arthritis (RA) than they have today. The 2015 American College of Rheumatology (ACR) guideline for the treatment of RA addresses the use of more than a dozen medications: prednisone and other glucocorticoids; 4 traditional disease-modifying antirheumatic drugs (DMARDs); 8 biologic DMARDs; and tofacitinib, an oral small molecule tyrosine kinase inhibitor.[1] As treatment options expand, treatment algorithms are naturally becoming more complex. The 2015 ACR RA guideline includes 2 detailed algorithms for the treatment of patients with early and established RA, respectively, punctuated by 74 individual treatment recommendations.[1]

Clinical practice guidelines can serve multiple purposes, including aiding clinical decision-making in daily practice, reducing inappropriate care, minimizing geographic variations in practice, and streamlining the use of limited resources.[2, 3] However, guidelines are just that: guidance. Guidelines can promote beneficial outcomes, but only rheumatology providers can determine when to implement treatment choices based on the unique circumstances of each RA patient.[3]

ACTIVITY SUMMARY

In this issue of Rheumatology Nurse Practice, we will explore the main features of the 2015 ACR guideline for the treatment of RA, including how to interpret recommendations that carry different strengths and levels of evidence. Although clinical practice guidelines can feel overwhelming, this issue focuses on practical strategies for letting the treatment recommendations inform—rather than dictate—your approach to care of patients with RA.

STATUS OF ACR CLINICAL PRACTICE GUIDELINE PROJECTS

Figure 1

ACR Clinical Practice Guideline Development (status current as of March 1, 2017)[3]

GIOP, glucocorticoid-induced osteoporosis; JIA, juvenile idiopathic arthritis; OA, osteoarthritis; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis.

Treatment Guidelines: How Did We Get Here?

The ACR uses a 9-step process to develop, publish, and update clinical practice guidelines (Figure 1).[3] For the RA guideline, dozens of experts in guideline methodology were involved in the early phases of gathering, reviewing, and grading the latest RA clinical research. A Voting Panel that was comprised of 9 rheumatologists and 2 patient representatives then voted on which recommendations to include in the new guideline.[1] The latest RA treatment recommendations are in Phase 8, having been released at the 2015 ACR annual meeting and formally published in 2016. The ACR will continue to monitor new clinical trial results to determine the need for a guideline update (Phase 9). There is no present schedule for developing or reviewing guidelines; instead, this process is driven by the evolution of clinical evidence and standards of care.[3]

Two new ACR guidelines are currently in the peer-review stage (Phase 7): glucocorticoid-induced osteoporosis prevention and treatment, and the perioperative management of rheumatic disease medication in patients undergoing elective total hip or knee arthroplasty (developed in collaboration with the American Association of Hip and Knee Surgeons).[3-5] Both new clinical practice guidelines are slated for publication in 2017.[4, 5]

How to Interpret the Guidelines

To interpret which recommendations are appropriate for which RA patients, it is critical to understand both the strength of the recommendation and the quality of evidence supporting that recommendation.

Strength of Recommendation

Within the 2015 RA guideline, the ACR introduced 2 tiers of recommendations: strong and conditional. Strong recommendations are those whose benefits far outweigh the harms of the intervention in most cases. Therefore, strong recommendations apply to almost all patients with RA, with very few exceptions. In contrast, conditional recommendations involve some degree of uncertainly around the balance of harms and benefits. Although conditional recommendations are expected to apply to the majority of RA patients, many patients may prefer a different course of action.[1] Accordingly, conditional recommendations should be implemented in routine practice on a case-by-case basis, and only after an individual assessment of each patient's treatment needs and preferences. Of the 74 recommendations outlined in the 2015 RA guideline, 23% are strong and 77% are conditional.[1]

Quality of Evidence

The ACR panel judged the quality of evidence behind each recommendation using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria. The GRADE process assigns points to each study based on study design, consistency and generalizability of results, and other factors. Based on total scores, the quality of evidence is classified into 1 of 4 categories: high, moderate, low, or very low.

Why would guideline committees bother making recommendations based on very low quality evidence? In many cases, very low quality evidence is all that is available. Guideline committees make their best attempt at translating this evidence, while noting its poor quality. Most recommendations in the 2015 ACR RA guideline are based on low or very low quality evidence.[1] Rheumatology providers should take this into account when considering the applicability of specific recommendations to individual patients with RA.

Trends in ACR Guideline Quality

One recent analysis examined 8 current ACR clinical practice guidelines involving 403 treatment recommendations for patients with RA, osteoarthritis (OA), gout, and other rheumatic diseases. Of these recommendations, only 10% were both strongly recommended (indicating a high benefit-to-harm ratio for most patients) and supported by high-quality evidence. Most strong recommendations involved OA.[6] The 2015 ACR RA guideline includes only 2 recommendations that are ***both*** strong and supported by high-quality evidence:[1]

1. Add 1-2 DMARDs when disease activity remains high despite anti-TNF monotherapy, and
2. Continue biologic DMARDs or tofacitinib in patients who achieve low disease activity, rather than discontinuing or tapering these medications

If these trends seem discouraging, don't fret: the overall quality of ACR guidelines actually appears to be improving. Another recent analysis evaluated 14 ACR guidelines published in 3 time periods: 1999 to 2004; 2005 to 2014; and 2015 to 2016. Researchers graded each guideline on 6 criteria: scope, stakeholder involvement, methodology, clarity, applicability, and editorial independence. The average total scores for each period show a clear trend upward, from <50% of the total possible score for guidelines published before 2004 to >90% for those published since 2015. Total scores improved from 71% for the 2008 RA guideline to 96% for the 2015 RA guideline.[7]

Critics of the 2015 ACR RA guidelines argue that it missed the mark by failing to address some of the most pressing questions in modern RA care.[8] These questions are now priorities for future guideline updates, including the following:

- The role of combination regimens and biologic agents as initial RA treatment
- The relative strengths and limitations of novel therapies
- Optimal dosing of biologic DMARDs
- Use of imaging and biomarkers to guide treatment choices

2015 ACR RA Guideline: A Roadmap for Individualized Therapy

The ACR RA recommendations include several overarching principles to guide RA care.

First, all treatment decisions should be made based on shared decision-making between the patient and the rheumatology provider. Second, all treatment decisions should be made in accordance with the following Treat to Target (T2T) principles:

- **Determine a treatment target.** Most patients should aim to achieve clinical remission, but low disease activity is an acceptable alternative for patients with advanced disease.
- **Select a composite measure of disease activity** such as the Clinical Disease Activity Index (CDAI) or the Disease Activity Score with 28 Joint Counts (DAS28) to quantify a patient's disease activity.
- **Measure disease activity** every 1 to 3 months after starting a new treatment regimen.
- **Adjust treatment** every 3 months until the goal of clinical remission (or low disease activity) is reached.
- **Maintain clinical remission** (or low disease activity) to prevent further joint damage, control symptoms, and preserve physical functioning. Consider controlled tapering in select patients in remission.
- **Readjust treatment** if disease activity ever increases beyond the threshold of remission (or low disease activity).

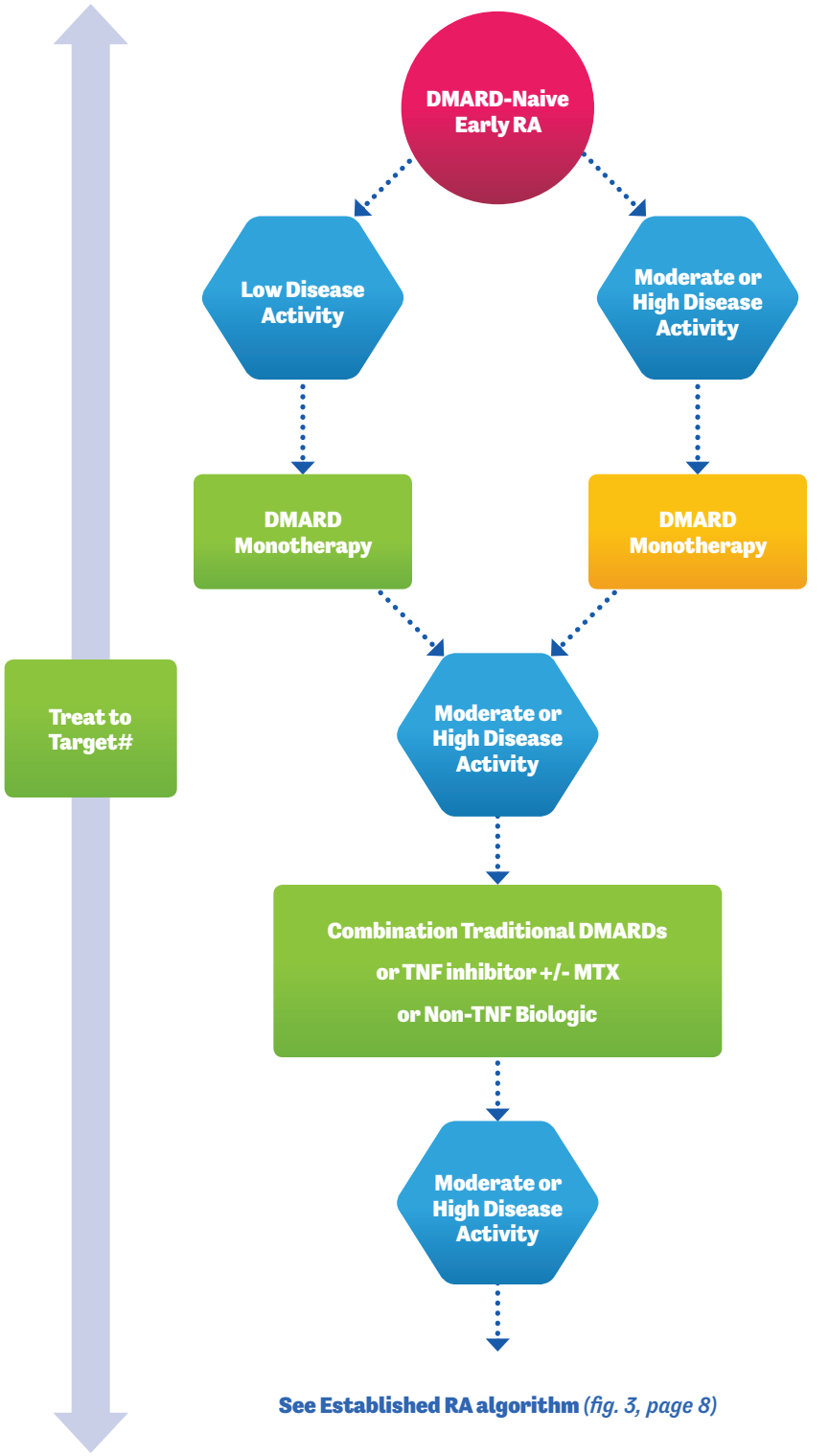


Figure 2. *Treatment Recommendations for Early RA*[1]

The optimal choice of RA therapy depends on several key disease features, beginning with its duration. Patients with early RA (<6 months duration) may be started on one treatment path (Figure 2), while those with established RA (>6 months duration) follow a slightly different course (Figure 3). Additional treatment decisions depend on the severity of RA disease activity, response to treatment, and treatment history.[1] Therefore, while all RA patients should share the common target of clinical remission (or low disease activity), the ACR guideline provides enough flexibility to enable patients to take the journey best suited to their individual needs.

Although the presence of poor prognostic factors such as rheumatoid factor (RF) positivity and extraarticular disease influenced treatment selection in previous ACR guidelines,[9] prognostic features are not included in the 2015 algorithms.[1] Of note, the 2016 EULAR guidelines continue to incorporate poor prognostic features to influence RA treatment decisions (see Sidebar).[10]

Patients with High-Risk Comorbidities

Treatment selection for patients with RA is often driven by the presence of comorbidities. The 2015 ACR guideline outlines several treatment preferences for patients with current comorbidities and/or a history of treated or untreated conditions. In many cases, these are conditional recommendations based on very low evidence. However, in the absence of more robust evidence, guidance from the ACR may be helpful in choosing a treatment path.

Congestive Heart Failure

> *Recommendation: Use combination DMARDs or non-TNF biologics or tofacitinib over anti-TNF biologics.*[1] *(Conditional recommendation; moderate to very low quality evidence)*

Heart failure (HF) currently affects approximately 6.5 million adults in the United States. The prevalence is expected to exceed 8 million adults by 2030.[12] Given the burden of systemic inflammation, patients with RA have twice the risk of developing HF when compared with adults without RA.[13]

Unfortunately, rheumatology providers have limited evidence to guide RA treatment in patients with HF. The ACR conditionally recommends conventional DMARDs, non-TNF biologics, and tofacitinib over anti-TNF biologics, but also acknowledges that this recommendation is based on "very low quality" evidence.[1] Other studies suggest that anti-TNF agents do not worsen outcomes for RA patients who develop HF.[14, 15]

When weighing the potential risks and benefits of specific therapies, it is important to consider the role of anti-TNF therapy in improving cardiovascular outcomes for patients with RA. In a recent British registry study of 14,258 RA patients with no history of cardiovascular events followed for more than 3 years, anti-TNF therapy (adalimumab, etanercept, or infliximab) was associated with a significant 39% reduction in the risk of myocardial infarction compared with conventional DMARD therapy.[16] Non-TNF biologic DMARDs also improve cardiovascular risk profiles in patients with RA, in part due to their dampening effects on systemic inflammation.[17]

Hepatitis B

> ***Recommendation:*** *Manage patients with hepatitis B the same as patients without this condition.[1] (Strong recommendation; very low quality evidence)*

The risk of hepatitis B virus (HBV) reactivation during biologic DMARD therapy among patients with a history of HBV infection is low. One study followed 96 patients with RA and resolved HBV who started treatment with abatacept (18%), golimumab (17%), tocilizumab (17%), infliximab (11%), adalimumab (7%), and certolizumab pegol (5%). After starting biologic DMARD therapy, patients underwent repeated HBV DNA testing every 1 to 3 months. In total, 6.3% developed HBV reactivation during the median follow-up period of 19 months.[18] Concomitant use of glucocorticoids may increase the risk of HBV reactivation in patients taking nonbiologic or biologic DMARDs.[19]

Hepatitis C

> *Recommendation: Manage patients with hepatitis C who have received effective antiviral therapy the same as patients without this condition; use DMARDs over anti-TNF biologics in patients with hepatitis C who have not successfully undergone antiviral treatment.[1] (Conditional recommendation; very low quality evidence)*

The risk of liver toxicity is low among RA patients with HCV who are taking nonbiologic or biologic DMARDs.[20] In an analysis of 38,433

How do the ACR and EULAR RA Guidelines Compare?

In March 2017, EULAR published its updated recommendations for the management of RA with synthetic and biologic DMARDs.[10] The EULAR recommendations share many common principles with the ACR guidelines, including a focus on achieving early disease control and involving patients in decisions about their care. Despite some differences (Table 1), it was noted during a presentation at the 2016 EULAR conference that the ACR 2015 and EULAR 2016 guidelines have come much closer together than the ACR 2008/EULAR 2010 and ACR 2012/EULAR 2013 iterations.[11]

Table 1
Differences Between the ACR and EULAR RA Guidelines[1, 10]

	ACR Guideline	EULAR Guideline
Glucocorticoid therapy	Weaker support for short-term use to manage RA flares	Stronger support for short-term use
Biologic DMARD monotherapy	Included as an option in select patients	Biologics recommended in combination with MTX or other csDMARDs
Disease duration	Classified as early (<6 months) or established (>6 months) RA	Not used to differentiate subgroups of RA patients
RA treatment phases	Not used to differentiate subgroups of RA patients	Classified as csDMARD-naïve, csDMARD-experienced, or bDMARD-experienced
Poor prognostic factors	No longer used for stratification	Used for stratification: RF/ACPA positivity, very high disease activity, early joint damage
Biosimilars	Not included in treatment algorithms	Approved anti-TNF biosimilars included as alternatives to 'originator' anti-TNF agents

csDMARD, conventional synthetic DMARD (e.g., methotrexate, sulfasalazine, leflunomide).

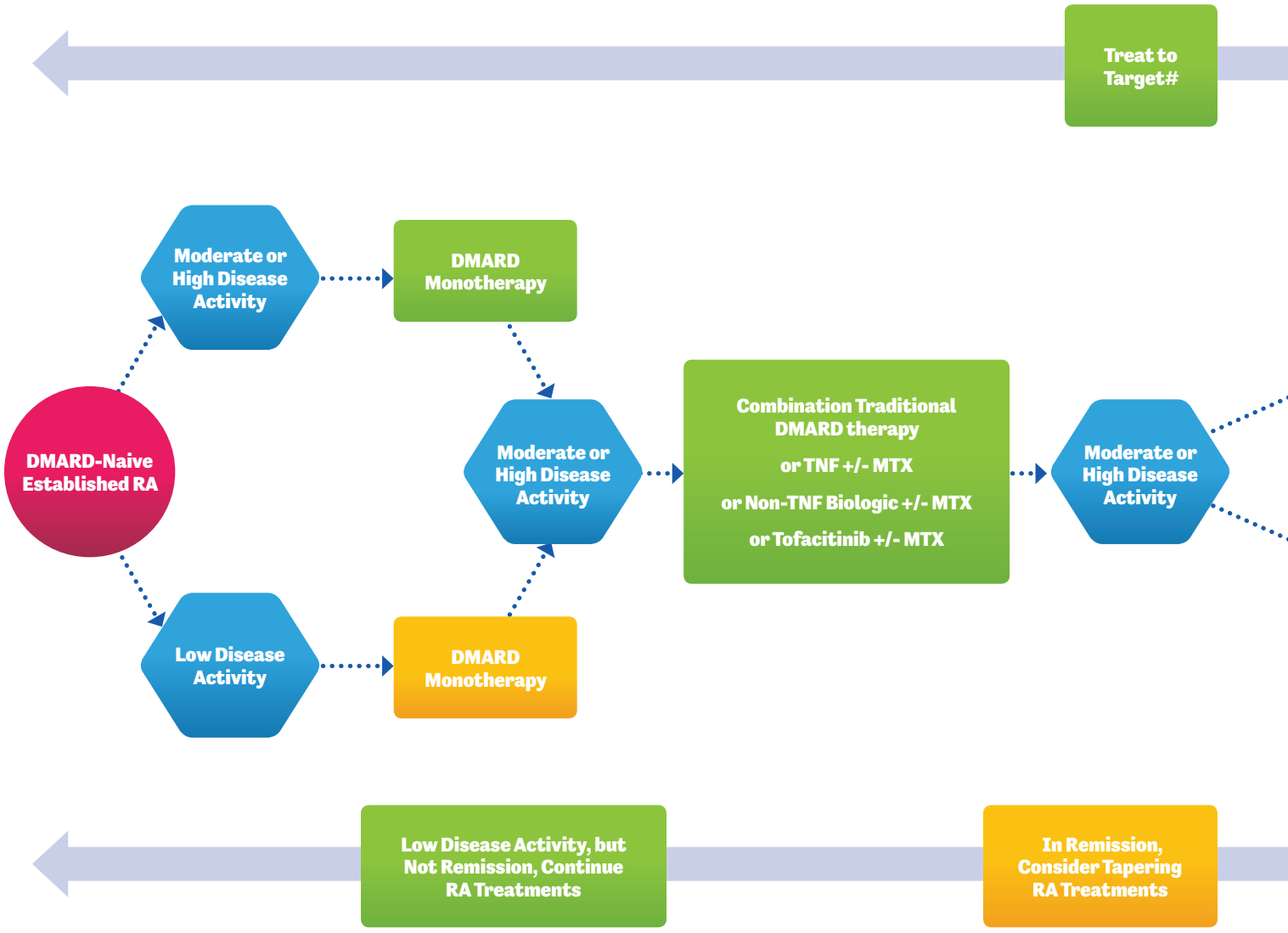


Figure 3
Treatment Recommendations for Established RA[1]

Strongly recommended treatment option/strategy

Conditionally recommended treatment option/strategy

Disease activity

Algorithm pathway for most patients

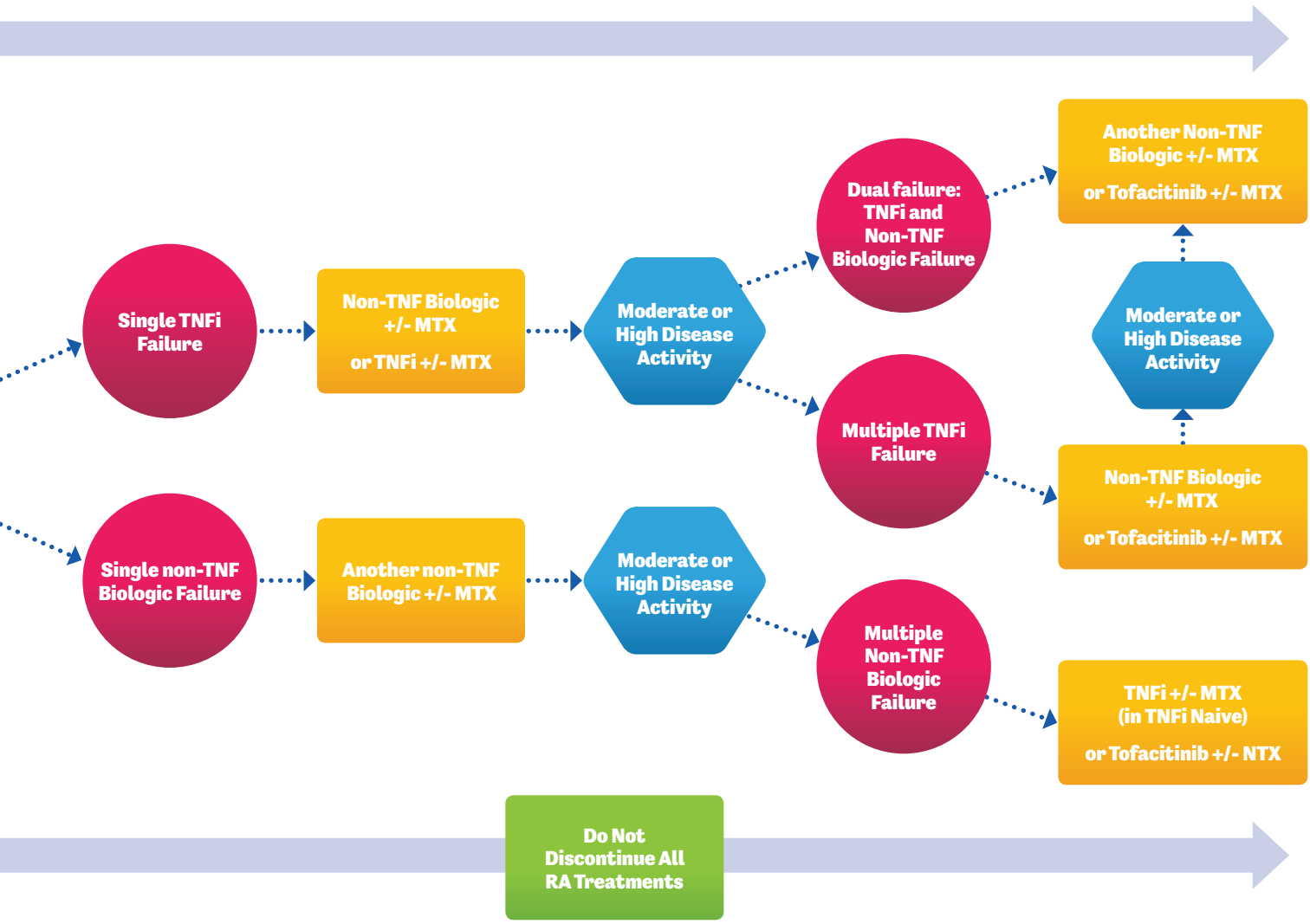
Disease state or prior treatment state

RA patients who were treated within the Veterans Administration (VA), 748 patients had chronic HCV with detectable HCV RNA levels. Within the first year of treatment with nonbiologic and/or biologic DMARDs, only 3.4% of patients with HCV experienced any hepatotoxic events. Liver toxicity was defined as alanine transaminase (ALT) levels ≥100 IU/L or a 1-log increase in HCV RNA levels. Although the overall rates were low, hepatotoxicity was significantly more likely in patients who were treated with biologic DMARDs than in those treated with nonbiologics (4.8% vs 2.3%). Regardless of the type of RA treatment, most episodes of liver toxicity (78%) occurred within the first 6 months of treatment.[20]

History of malignancy

Recommendations:

1. *Skin cancer: use DMARDs over biologics and over tofacitinib in patients with treated or untreated melanoma or non-melanoma skin cancer.*[1] *(Conditional recommendation; very low quality evidence)*
2. *Lymphoma or other lymphoproliferative disorder: use rituximab over anti-TNF therapy (Strong recommendation; very low quality evidence); use combination DMARD therapy, abatacept, or tocilizumab over anti-TNF therapy.*[1] *(Conditional recommendation; very low quality evidence)*



3. *Solid organ cancer: manage patients with previously treated solid organ cancer the same as patients who were never diagnosed with cancer.*[1] *(Conditional recommendation; very low quality evidence)*

Skin cancer

Understanding the relationship between RA treatment and cancer risk can be challenging, particularly for low-incidence cancers that require very large numbers of patients to detect a statistically significant and causal relationship. One meta-analysis representing 15,418 patients with RA found no association between anti-TNF therapy and any form of cancer, apart from non-melanoma skin cancer (NMSC). In that analysis, treatment with adalimumab, etanercept, or infliximab doubled the risk of NMSC compared with non-biologic RA therapy.[21]

Another study examined the interaction between anti-TNF therapy and the subtypes of NMSC, including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), in more than 51,000 RA patients in Sweden.[22] Over 15 years of follow-up, patients with RA had a 22% increased risk of BCC compared with the general population of Swedish adults without RA. Anti-TNF therapy (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab) did not further exacerbate the risk of BCC relative to non-biologic therapy. In contrast, patients with RA had an 88% increased risk of SCC compared with the general population, and anti-TNF therapy further increased the risk of SCC by 30%. These risks are relative, however, and the overall incidence of skin cancers was low. The level of risk translates to 1 additional case of SCC for every 1,600 years of anti-TNF treatment.[22]

In another Swedish registry study, anti-TNF therapy increased the risk of melanoma by 50% over 10 years compared with non-biologic therapy. In this analysis, treatment with adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab would result in 1 additional case of melanoma per 5,000 years of anti-TNF therapy.[23] In contrast, a recent multinational registry study found no correlation between anti-TNF therapy and melanoma risk among 1.3 million RA patients from 11 European countries. In this study, conducted in collaboration with EULAR, there was also no

link between melanoma and non-TNF biologics, including rituximab, abatacept, and tocilizumab.[24]

Lymphoma

Patients with alerted immune function are susceptible to Epstein-Barr virus (EBV), a lymphotropic herpes virus that infects B cells and increases the risk of lymphoma and other lymphoproliferative disorders (LPDs).[25] In patients with RA, blood tests indicate a B-cell EBV load that is 10 times higher than that among adults in the general population.[26] The ACR recommends rituximab, a B-cell targeted therapy, as the preferred choice for RA treatment in patients with a history of lymphoma or other LPDs.[1] The safety of abatacept and tocilizumab has also been demonstrated, with no increase in B-cell EBV load or EBV-associated lymphoma after up to 3 years of treatment.[27]

Solid tumors

Patients with a history of solid tumors can be reassured that biologic DMARD therapy does not increase the risk of developing another malignancy.[1] Indeed, some evidence suggests that anti-TNF and non-TNF biologics have a protective effect. One recent observational study evaluated the risk of new malignancies among 425 patients with a history of cancer who started RA treatment with conventional DMARDs, anti-TNF therapy, or rituximab. After 5 years, the calculated rate of new cancer diagnoses per 1,000 person-years was 59.1 in the conventional DMARD group, 26.8 in the anti-TNF group, and 24.7 in the rituximab group.[28] Another study focusing specifically on breast cancer recurrence in RA found no differences between women who started anti-TNF therapy (n = 120) and women treated with nonbiologic therapy (n = 120). Women entered the study after a median of 9.4 years from their initial breast cancer diagnosis. After a median follow-up of 4.9 years on RA treatment, the risk of recurrent breast cancer was 15 cases per 1,000 person years in the anti-TNF group, and 16 cases per 1,000 person years in the nonbiologic treatment group.[29]

Previous serious infection

> *Recommendation: Use combination DMARD therapy or abatacept over anti-TNF therapy.[1] (Conditional recommendation; very low quality evidence)*

Serious infections in patients with RA are generally described as infections that require hospitalization and/or parenteral antibiotics to manage. The risk of serious infection for patients taking MTX or other conventional DMARDs is approximately 2%, or about 20 serious infections per 1,000 patients per year.[30] Biologics further increase the risk of serious infection by suppressing mediators of normal immune system function.[30] Among the biologic DMARDs, abatacept is associated with the lowest risk of serious infection.[31] However, the ACR notes that the recommendation for conventional DMARDs and abatacept over anti-TNF therapy is conditional and based on "very low quality" data.[1]

A recent meta-analysis representing 42,330 patients with RA showed that the dose of biologic DMARD, as well as the use of biologic-based combination therapy, influences infection risk.[30] These findings may be helpful for educating patients about the balance of benefit and harm associated with biologic treatment.[32] Relative to conventional DMARDs, rheumatology providers using biologic DMARDs can expect to see the following numbers of serious infections per 1,000 patients per year:[30]

- Low-dose biologics: no additional infections, or 20 total infections
- Standard-dose biologics: 6 additional infections, or 26 total infections
- High-dose biologics: 17 additional infections, or 37 total infections
- Combination biologics: 55 additional infections, or 75 total infections

Other Management Considerations

Clinical practice guidelines address other aspects of RA care intended to keep patients safe and healthy over the long term. In general, the 2015 guideline endorses the same recommendations for laboratory monitoring and tuberculosis (TB) screening described in the 2012 and 2008 publications. There is one exception: the recommendations are now expanded to include patients who are treated with tofacitinib.[1]

Laboratory Monitoring

Table 2 outlines recommendations for laboratory monitoring during treatment with conventional DMARDs. For patients treated with biologic DMARDs and small molecule therapy, laboratory monitoring recommendations differ by agent. Refer to the prescribing information for individual anti-TNF therapies, non-TNF biologics, and JAK inhibitors for monitoring recommendations.

Tuberculosis Screening: Keep Up the Good Work

Thanks to current protocols for TB screening—and treatment when indicated—the risk of TB among patients taking biologics is very low.[33] One study examined 133 patients with RA who were treated with anti-TNF agents within the VA system for an average of 5.4 years, during which the patients had an average of 3.6 TB screening tests. The

	Duration of DMARD Therapy		
	<3 months	3-6 months	>6 months
Methotrexate	2 to 4 weeks	8 to 12 weeks	12 weeks
Leflunomide	2 to 4 weeks	8 to 12 weeks	12 weeks
Sulfasalazine	2 to 4 weeks	8 to 12 weeks	12 weeks
Hydroxychloroquine	None	None	None

Table 2
Laboratory Monitoring for Patients Taking Conventional DMARDs*[1]

**Monitoring includes complete blood count, liver transaminase levels, and serum creatine levels. Frequency of monitoring may increase for patients with comorbidities, those with abnormal laboratory results, and/or those taking multiple medications*

screening protocol included baseline screening with Tuberculin skin test (TST) or Quantiferon TB Gold Test (QFT) before starting biologic therapy, and repeat screening for latent TB infection. Only 1 patient converted from a negative to a positive TST after more than 6 years of treatment with infliximab and MTX. In this study, the risk of converting to a positive TB test was 0.14 cases per 100 patient years.[33] In another study set in a low-endemic area, 4.0% of 547 patients with RA who were starting biologic therapy had a positive QFT result indicating latent TB infection. Of these patients with a positive QFT, all were treated with isoniazid therapy before starting a biologic DMARD. After a mean follow-up of 20 months on biologic therapy, no patients had a reactivation of their latent TB infection.[34]

Vaccinations: Room for Improvement

The 2015 ACR vaccine recommendations are largely similar to those published in 2012 and 2008, except for the added nuance of 'strong' versus 'conditional' recommendations (Table 3). The recommendations related to herpes zoster (shingles) vaccination are conditional, and rheumatology providers are asked to apply the Centers for Disease Control and Prevention adult immunization guidelines to inform treatment decisions.[35] As a live vaccine, however, the herpes zoster vaccine is currently not recommended once patients have started anti-TNF or non-TNF biologics.[1] By comparison, the ACR now strongly recommends the use of killed vaccines against pneumococcal disease, influenza, and HBV for patients already taking biologic therapy.[1] Vaccine recommendations in future ACR guidelines may change with the availability of new safety and efficacy data. The ongoing phase 2 Varicella Zoster Vaccine (VERVE) trial is evaluating the safety of a live zoster vaccine in patients on anti-TNF therapy; preliminary findings are expected later in 2017.[36]

Several recent studies provide insight regarding the risk of shingles in patients undergoing treatment for RA. As a class, biologic DMARDs appear to have similar effects on herpes zoster infection risk. In a study of 25,274 Medicare recipients who were taking biologic therapy for RA, 336 patients (1.3%) experienced herpes zoster infections during treatment. The risk of infection was similar across all biologics, including those with anti-TNF and non-TNF mechanisms of action. The study also examined the risk of recurrent infections. Among 1,037 patients with a history of herpes zoster infection at baseline, 14 had a recurrent herpes zoster infection. Therefore, the risk of a recurrent herpes zoster infection during biologic DMARD therapy was 2.1 infections per 100 person years.[37] Compared with biologic DMARDs, tofacitinib is associated with a 2-fold higher risk of herpes zoster infections, resulting in approximately 3.9 infections per 100 patient years.[38]

Corticosteroid use may increase the risk of herpes zoster infection during biologic therapy. In a study of 3,483 patients taking non-biologic or biologic DMARDs, 25 (0.72%) developed a herpes zoster infection after an average of 10.5 months on therapy. Compared with patients treated with MTX alone, the risk of herpes zoster infection was 2.5-fold higher for patients taking biologics, and 3-fold higher for those taking biologics with concomitant corticosteroids.[39]

While these findings underscore the importance of immunization before starting RA treatment, real-world vaccination rates remain low. In one academic rheumatology practice, only 37% of RA patients had a documented discussion about herpes zoster immunization and/or received the vaccine in 2015.[40]

	Killed Vaccines			Recombinant Vaccine	Live Attenuated Vaccine
	Pneumococcal	Influenza (intramuscular)	Hepatitis B	Human papilloma virus	Herpes zoster
Before Starting Therapy					
DMARD monotherapy	Yes	Yes	Yes	Yes	Yes
DMARD combinations	Yes	Yes	Yes	Yes	Yes
Anti-TNF biologics	Yes	Yes	Yes	Yes	Yes
Non-TNF biologics	Yes	Yes	Yes	Yes	Yes
When Already Taking Therapy					
DMARD monotherapy	Yes	Yes	Yes	Yes	Yes
DMARD combinations	Yes	Yes	Yes	Yes	Yes
Anti-TNF biologics	Yes	Yes	Yes	Yes	No
Non-TNF biologics	Yes	Yes	Yes	Yes	No

Strong recommendations Conditional recommendations

Table 3
Vaccine Recommendations for Patients Starting or Receiving RA Treatment[1]

Guidelines in Clinical Practice: Challenges and Opportunities

Despite their limitations, RA treatment guidelines can make a clinically meaningful difference in patients' lives. In one study, patients were significantly more likely to achieve clinical remission within 2 months of starting RA therapy, and more likely to remain in remission at 2 years, when their physicians were more adherent to T2T strategies (ie, switching DMARD treatment if remission was not attained).[41] Better physician adherence to T2T also significantly improved physical functioning after 3 years.[42] Another study showed that close adherence to ACR DMARD safety recommendations, including routine laboratory monitoring and patient education around medication risk, enhances treatment safety. Among 250 RA patients treated with 518 medications who were treated according to the ACR safety recommendations, the risk of serious adverse events was low (1.8%), all adverse events were resolved according to guideline recommendations, and no patients experienced irreversible side effects.[43]

Implementing new RA treatment recommendations can be challenging for many rheumatology practices. One study examined treatment patterns among 3,157 RA patients both before and after publication of the 2008 ACR guidelines. Prior to the guideline update, adherence to DMARD recommendations ranged from 24% to 47% for RA patients with moderate to high disease activity and/or poor prognostic features. By late 2009, prescribing patterns had not significantly changed for these patients.[44] In a Dutch study of 994 office visits with 137 RA patients, guideline adherence varied widely. Only 23% of patients received DMARDs consistent with the recommended sequence, while 67% of visits involving moderate to high disease activity resulted in a therapy change.[2]

To successfully implement the ACR treatment guidelines, rheumatology clinics may need to adopt practices that may be new to patients and providers. These include the use of composite disease measures, frequent disease monitoring, and frequent treatment adjustments. The T2T algorithm is time-sensitive, yet long waits for laboratory results and delayed approvals for switching medications can slow progress. Additional issues such as the complexity of the drug regimen, patients' beliefs about treatment, and out-of-pocket costs can also erode adherence to treatment recommendations (Figure 4).[45]

Insurance Coverage and Cost Barriers

In a recent position statement, the ACR outlined several priorities for ensuring access to RA

care.[46] According to the ACR, "administrative burdens associated with the delivery of high-cost treatments, including but not limited to prior authorizations, should be minimized, streamlined, and made more uniform."[46] Unfortunately, prior authorizations and high out-of-pocket (OOP) costs remain common challenges for patients with RA.

One recent study of biologic DMARD coverage evaluated 2,737 formularies participating in the Medicare Advantage and Medicare Part D plans across all 50 states. Although all plans covered at least 1 biologic DMARD for patients with RA, most (97%) required prior authorization. In addition, rather than a fixed-dollar copayment, most plans (81% to 100%) required that patients pay a percentage of the drug costs (i.e., percentage coinsurance). The average coinsurance for biologics was 29.6%, resulting in mean out-of-pocket (OOP) costs of $2,712 to $2,774 before before patients reached the 'catastrophic' phase of coverage, when they transitioned to paying 5% of drug costs. For reference, nearly all plans covered 6 of the most common non-biologic DMARDs at fixed copayments of $5 to $10 per month, without the need for prior authorizations.[47]

The financial burden of cost-sharing creates a major barrier to maintaining effective RA treatment over time. One recent study examined the phenomenon of "prescription abandonment" among RA patients who were prescribed biologic DMARDs.[48] Prescription abandonment occurs when patients take a prescription to the pharmacy, but leave without their medication because of an unresolved insurance claim denial (e.g., prior authorization or step-therapy requirement), the co-pay price, fear of side effects, or other issues. In the study of Medicare recipients with RA, 18.2% abandoned their prescription for a biologic DMARD during the 6-month follow-up period. The total OOP cost for 6 months of drug refills was the

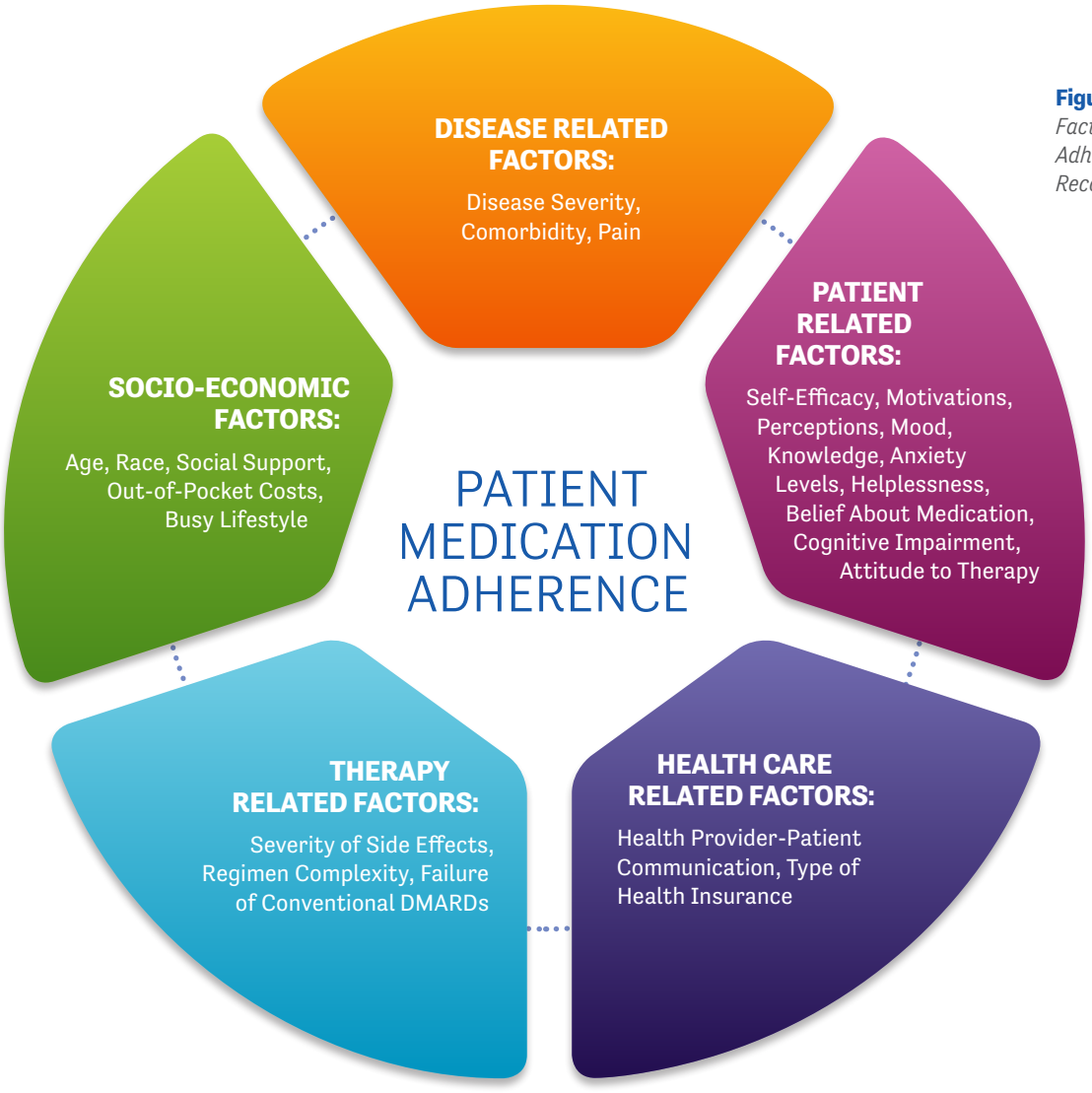


Figure 4
Factors Influencing Adherence to RA Treatment Recommendations[45]

strongest predictor of abandoning a prescription. Only 1.3% of patients with the lowest OOP costs (≤$250) abandoned their biologic, compared with 32.7% of those with the highest OOP costs (>$550).[48]

Multiple studies demonstrate the cost effectiveness of achieving tight RA disease control with biologics, especially in patients who have failed non-biologic DMARDs.[49, 50] However, the ACR has not incorporated cost-effectiveness studies into the RA guidelines, and these studies have not been used to inform Medicare's coverage policies for biologic DMARDs.[47] Until coverage policies enable better access to biologic DMARDs, rheumatology nurses can lessen the burden of OOP costs for patients by facilitating prior authorizations and addressing other potential barriers.

Summary

The 2015 ACR RA treatment guideline addresses common questions in rheumatology practice, including the optimal use of conventional DMARDs, biologic agents, and tofacitinib. Within its flexible framework, clinicians can provide individualized treatment based on patient preferences, responses to prior RA therapy, and the presence of high-risk comorbidities. Additional recommendations on TB screening, vaccinations, and laboratory monitoring protect the long-term well-being of patients with RA. By implementing the ACR guideline recommendations in appropriate patients, rheumatology nurses can be instrumental in helping patients to achieve the T2T goals of clinical remission or low disease activity.

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Learning to Meet Our Patients Where They Are

by Iris Zink, MSN, NP, RN-BC

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As a rheumatology nurse practitioner with 16 years of experience, I have seen a lot of patients with rapidly progressing disease. Unquestionably, after nearly 2 decades of experience with biologic therapies, the use of early, aggressive therapy is best for most of our patients with RA. Recent recommendations from the American College of Rheumatology (ACR) support rapid escalation of treatment in patients who do not respond to initial and subsequent therapeutic regimens.[1]

However, we should recognize that there are always outliers to early and aggressive treatment plans. One such patient of mine is Deb, a 59-year-old woman who presented to her primary care physician in 2011 with pain in multiple joints, especially in her hands, which was affecting her activities of daily living. Lab tests showed that Deb had a positive rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP), which prompted a referral to a local rheumatologist. Based upon an erythrocyte sedimentation rate (ESR) of 50 mm/hr and a C-reactive protein (CRP) of 2.6 mg/L, she was started on methotrexate (MTX), which I am sure most of us would concur was the most logical starting point.

Two months after starting MTX, Deb did not feel any better and went back to her rheumatologist to ask what else could be done. She explained that her joint pain was as bad as ever. Since current Treat to Target guidelines recommend switching therapy frequently ("at least every 3 months") in patients who do not reach their treatment target,[2] Deb's rheumatologist decided that the most appropriate step would be to initiate a conversation about adding adalimumab to her MTX regimen.

This, however, is where the story diverges from the expected path. Deb was not comfortable with the discussion around the addition of a biologic. She did not feel that her rheumatologist listened to her or answered her questions appropriately. As a college-educated woman, she wanted

answers that made sense, and she didn't feel as if she had gotten them. Consequently, Deb went to another rheumatologist for a second opinion.

At this visit, X-rays were taken, and no structural damage was seen. While her ESR and CRP levels were still elevated, Deb's new provider listened when she told her that her morning stiffness lasted for only 1 hour, about 30 minutes less than a few months ago before she started MTX. Consequently, instead of escalating her to a biologic, she was taken off the MTX and started on a new NSAID.

Two months later, on her initial return visit, I met Deb. She was doing about the same as before—no worse but no better. We talked about her immune system and specifically focused on ways that lifestyle changes could improve her quality of life. Deb was clearly a scared patient—scared by being diagnosed with a chronic, lifelong disease, and scared that her initial treatment forays had not resulted in noticeable improvements in her symptoms. She wanted to take better control of her disease, so she agreed to start exercising more and initiated a weight loss program.

After a few cycles of "yo-yo dieting," she came back to me for a re-check of her RA. My initial step was to order a multibiomarker disease activity score (MBDA) test to assess her current disease activity. Her score came back as a 30, showing low-to-moderate disease activity. Upon questioning, Deb reported that her morning stiffness still generally lasted about an hour or so, but that her joint pain had improved with regular exercise and use of the NSAID. At this point, I felt reassured that we were on the right path since her MBDA score was in the low-to-moderate range, and we continued with conservative therapy.

On her next return visit 3 months later, Deb looked discouraged, and I immediately knew that something was wrong. Her weight issues remained a problem, as evidenced by her high leptin levels (which can be fueled in part by being overweight).[3] Deb explained to me that she had tried and failed 3 different weight loss programs in the past few months.

Sensing her frustration, we decided to try a weight-loss medication—lorcaserin HCl—to see if that might help. Six months later, Deb had lost 20 pounds and had significantly reduced pain and increased energy. She requested that her NSAID dosage be reduced, and she seemed highly motivated to lose 15 more pounds to get her closer to her goal weight.

I spoke to Deb about an anti-inflammatory diet called the Whole30 Programs that encourages people to eliminate foods thought to be related to inflammation such as sugar, grains, dairy, and legumes for 30 days.[4] While remaining on lorcaserin, Deb decided to give this program a shot. After 30 days, she had dropped 10 more pounds. As her weight went down, her joint pain improved. Being curious, I retested her RF and anti-CCP; both tests were now negative. Her most recent MBDA score is <20.

Quick admission: In my 16 years of experience, I have only seen 3 cases of RA that seemed to go away and stayed in remission on NSAIDs alone. Deb is not, therefore, a typical patient. I do believe, however, that in our patients with RA whose immune system is turned on, lifestyle changes can have a profound effect on reducing inflammation. Deb is one of those patients with a positive attitude, and she was willing to try anything to get her disease in remission with the fewest medications possible.

While we should always heed the recommendations of expert consensus groups such as those coordinated by the ACR regarding the treatment of disease, we should also remember that not every patient will respond to treatment regimens the way we expect. There is often only a narrow window of opportunity to listen to a new patient and help them respond to the changes of their immune system. Treatment needs to be tailored to the individual and not to the numbers on a page. By listening to and hearing our patients, we may sometimes be led in atypical directions that nonetheless help our patients solve their most significant problems.

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When Patient Care Can't Wait for Guidelines

by Elizabeth Kirchner, CNP, RN-BC

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Raise your hand if you've heard of "checkpoint inhibitors." OK, maybe don't really raise your hand since you are probably sitting alone somewhere. Or maybe you're riding the bus or train, and you don't want people staring at you with the "Check out the crazy lady raising her hand like a loon" look. Perhaps you just want to think about raising your hand, OK?

All set? Great. Because you should ALL be (thinking about) raising your hands—whether you are aware of it or not, I'm guessing that all of you have heard of checkpoint inhibitors. Some people call them "cancer immunotherapy," some people (namely the companies that sell them) call them Keytruda (pembrolizumab), Opdivo (nivolumab), Tecentriq (atezolizumab), or Yervoy (ipilimumab). You may have seen an ad for 1 or more of these on TV, once… or twice… or 762 times a day.

Remember back in August 2015 when former President Jimmy Carter announced he had metastatic melanoma and then, 4 months later, he was back in the news announcing his scans showed no signs of cancer? He got pembrolizumab. So these drugs are clearly out there benefitting lots of patients, and that's awesome.

What is less awesome is the side effects that come with these medications. Since they "take the brakes off the immune system," that means they tend to cause a lot of problems in terms of immune activation. The list of side effects related to checkpoint inhibitors is long and touches on just about every organ system and body part that exists—including joints.

Since I work in a large tertiary care center with a very large oncology department, it was inevitable that these patients would find their way to us over in rheumatology, asking for help with their joint pain. They

Without question, guidelines are helpful... But so much of what we do falls outside the norm, and our patients would be in real trouble if we all waited around for guidelines to provide us with a roadmap for every condition that passes through our clinic doors.

were very clearly frustrated, having beaten "The Big C" but unable to enjoy life because of debilitating arthritis. Almost all of these patients were still on their checkpoint inhibitors, either as part of a clinical trial or as off-study medication.

We had lots of questions when these patients started showing up in our clinic in greater and greater numbers. What should we do? How should we treat them? What drug-drug interactions should we worry about? Would it be OK to use immunosuppressants when the whole point of their oncology treatment was to get their immune system to fight cancer? If we did use immunosuppressants, would patients be more likely to develop infections? If they were on a clinical trial, would we jeopardize their ability to stay in the trial if we treated their arthritis?

Because these drugs are so new and testing is ongoing for many of them, there were no guidelines to help us. Actually, there was basically nothing to help us. Those of us in the Immune Related Adverse Event Clinic (2 docs, a fellow, and me) had to decide: Do we treat these patients aggressively now or do nothing and wait for guidelines and the medical literature to catch up?

This is an extreme example of what all of us face in the clinic almost every day. In rheumatology, sometimes it seems as if the exception to the rule IS the rule. Without question, guidelines are helpful. I am grateful to all of the clinicians who dedicate their time and expertise to craft them, and I absolutely consider them to be a valuable clinical tool. But so much of what we do falls outside the norm, and our patients would be in real trouble if we all waited around for guidelines to provide us with a roadmap for every condition that passes through our clinic doors.

So getting back to our story—yes, we currently treat patients on checkpoint inhibitors who develop joint pain. We have made some mistakes along the way and learned from them (hot tip: always check with a protocol nurse before initiating prednisone on a patient who is receiving drug through a clinical trial. Turns out there are dosing restrictions. Strict ones.). We have also seen patients improve to varying degrees, and one class of drug in particular seems to be standing out as especially effective (I would love to tell you which one, but since there are no randomized controlled trials, that would be über-irresponsible of me). We would never have known that if we hadn't been willing to take a chance and treat patients with a brand-new clinical presentation.

I encourage all of you to use guidelines when they are available, but don't be afraid to do research, collaborate with your colleagues in other departments, and reach out to other rheumatology providers when you see a patient who needs help but there are no "rules" to follow. Our patients need help now, and they can't afford to wait around for the guidelines to catch up!

P.S. You can think about putting your hands down now.

Going Beyond Numbers on the Page

by Jacqueline Fritz, RN, MSN, CNS, RN-BC

"How are my numbers?"

It's a question that I get daily from my patients, often on several occasions. Patients will call and ask for a copy of their lab report or, if they are enrolled in our online portal program, after they check their values on their computer. "Oh my God, what does RDW stand for?" or "Why is my sodium so high?" Sometimes, it's due to nothing more than not drinking enough water!

As rheumatology nurses, we are trained to always evaluate a patient's lab results and often withhold refills or infusions if the patient does not comply with having labs checked in a timely manner. We care for the *whole patient*—not just numbers or joint counts, but the entire body. Inflammatory diseases—and especially rheumatoid arthritis (RA)—can affect arteries, lungs, blood vessels, and many other systems. Our common treatments have potential side effects such as infection, liver toxicity, and neutropenia, just to name a few, that we also need to be mindful of.

Education of our patients is key to successful management of their disease. Patients may know they have RA, but they rarely remember all the ramifications of the disease. When we weigh a patient and a scent of cigarette smoke is obvious, it's a good time to remind patients that RA can and does affect the lungs. The usual response I get is something like, "Oh, I thought it *just* affected my bones."

So when patients ask me, "How are my labs?" I take that as an opportunity to do more than simply review their numerical

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values with them. My typical answer to that question, therefore, is "Well, how are you?" I often need to explain to patients that we do not treat pieces of paper, but that we treat people. It's often safe to assume that a patient wants to avoid coming in for an office visit when they call and ask about "their numbers."

Numbers, unfortunately, don't often tell the full story with our patients. Without a clinical correlation, without us seeing and touching our patients, numbers offer an incomplete window into overall well-being.

Lab values can, of course, be incredibly useful. For instance, they can show whether a medication is causing liver toxicity, which leads to a phone call asking the patient to adjust their dose of methotrexate or reduce the frequency in which they take a "harmless over-the-counter" medication such as ibuprofen. Even during these calls, I reinforce the need for the patient to come in for their next office visit to talk about their overall well-being.

Let me relay a brief anecdote that demonstrates the value of looking past the numbers.

Jan is a 35-year-old female who came to our office 18 months ago with typical symptoms of joint pain and morning stiffness. She had a positive family history of RA through her maternal grandmother. Upon her initial presentation, we ran the usual battery of laboratory tests. Her C-reactive protein was sky high, at 30.8 (normal is between 0 and 5.0). Her rheumatoid factor (RF) was also significantly elevated – RF IgM of 302 (normal range: 0-25), RF IgG of 65 (normal range: 0-20), and RF IgA of 205 (normal range: 0-35)

She was diagnosed with RA and started on a regimen of weekly methotrexate (15 mg) and daily leflunomide (10 mg). Based upon Treat to Target guidelines, we set remission as our treatment goal.[1]

Eighteen months later, we appear to be on the right track. Jan's C-reactive protein levels have normalized. She claims to have no morning stiffness or joint swelling. Her most recent Health Assessment Questionnaire score is 0.0. Even her x-rays appear normal with no evidence of erosive disease. Obviously, I was thrilled with her improvement and congratulated her on her success and adherence to our treatment regimen.

But alas the "performance" is never over! Jan's RF immunoglobulins show that her RA remains quite active in her blood, so although her disease appears to be in remission from a qualitative perspective, we need to remain vigilant to keep her disease activity under control. Additionally, Jan has an upcoming wedding, so we have begun discussions of potential adjustments to her medication regimen if she hopes to become pregnant in the near future.

I have consistently ensured Jan that we are a team, and that as long she remains in adherence to future scheduled visits, medications, and lab tests, we can hopefully continue to keep her days as symptom-free as possible.

As medicine has become increasingly compartmentalized, it is challenging for those of us in rheumatology to manage a patient's entire body system and remain alert for key changes that may signal likely changes in a patient's overall health and quality of life. With a growing arsenal of medications at our disposal, being aware of and monitoring for likely side effects is a constant vigil. Talking to and asking questions of our patients, and making sure that they come in to talk to us face-to-face and not just on the phone, remains paramount to optimizing outcomes.

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Taking a Stand for the Rheumatology Nurse

by Sheree C. Carter, PhD, RN, RN-BC

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Recently, my Google Alert set for "rheumatology nursing" notified me of a curious short article out of Ireland. As we know, tragic, sensational, and even "fake news" often tops the priority list of newsfeeds instead of heartwarming, positive, and inspiring news stories and events that perhaps make us feel a little bit better about ourselves and our chosen line of work. This little story that popped up was one of those that may otherwise have gotten lost were it not for my targeted alert setting. I'm glad I didn't miss it.

The article began by replaying events from prior years, starting in 2013, when Dr. Muhammad Haroon was appointed as a rheumatologist at University Hospital Kerry (UHK), a facility located in an underserved geographic area of Ireland.[1] According to a tweet from one of Dr. Haroon's patients, it took a year on a waiting list before she was able to have her first visit in the rheumatology clinic at UHK with Dr. Haroon.[2]

By all accounts, Dr. Haroon is a skilled and well-liked physician who is highly valued within the community. However, Dr. Haroon had been literally a one-man show throughout the initial years of his tenure at UHK as his rheumatology clinic consisted of just himself with no nursing support.

The crux of the article I read then skipped forward a few years to 2016, when Dr. Haroon asked for the addition and appointment of a Rheumatology Advanced Nurse Practitioner (ANP) to help the backlog of patients trying to get an appointment at UHK. He even had an experienced rheumatology ANP candidate in mind for that position, who he recommended.[1] However, the candidate was told that the Health Service Executive—the agency responsible for public funds going to health and social services in Ireland that is headed by the Irish Minister of Health[3]—had determined that this candidate would be required to accept a reduced grade position from her current assignment as an ANP, as well as a cut in pay. Understandably, she turned down the offer.[4]

While the story could have ended there. Dr. Haroon took the bold step of petitioning on behalf of the ANP candidate, going so far as to apparently tender his resignation due to the lack of support for rheumatology services at UHK.[1,4] According to one news article, the Rheumatology Unit at UHK was the only one in all of Ireland not staffed with an ANP or any other medical assistant.[1]

After news of Dr. Haroon's resignation was brought to light, Arthritis Ireland joined him in his petition to support the appropriate title and pay for an ANP.[5] Earlier this year, Dr. Haroon and Arthritis Ireland saw some positive movement when UHK was able to bring on a clinic nurse manager, approve the ANP position, and retain Dr. Haroon as the rheumatologist.[4] Kudos to Dr. Haroon, Arthritis Ireland, and the ANP in question for standing their ground on this professional and community service issue.

This story, however, is not one that was neatly wrapped in a bow. Due to the amount of time it took to resolve the issues, the experienced ANP who initially was ready to accept the post at UHK took another position in another part of Ireland. UHK did indeed hire a clinic nurse manager to help Dr. Haroon, but this individual was

inexperienced in rheumatology and will need to acquire the training necessary to be accredited as a clinic nurse specialist. As we all know, this takes time and experience. We certainly are empathetic to the new experiences she will be faced with as she learns about the complex diseases and treatment options we all encounter every day. Hopefully, this new experience will enrich and assist her career as a rheumatology nurse.

Nurses are among the unsung heroes in healthcare. We are always adapting to a myriad of changes, often seemingly without effort. Nurses are flexible and adaptable and can quite literally fix just about anything with a pair of hemostats and bandage tape (right?). Our ability to adjust and adapt is a career trait that is always assumed but not clearly identified as essential.

This short news blurb from Ireland in the international news superhighway has great significance for rheumatology nurses, providing evidence for the value of the nurse in practice. Here was a rheumatologist willing to resign his post not only because he wasn't able to bring on a rheumatology nurse in his practice, but because the candidate he thought best was not going to be recognized for the grade and pay equivalent to her education and experience.

The rheumatology nurse is an essential team member in rheumatology care not only from a pharmacologic perspective (eg, delivery of infusion treatments, monitoring for side effects, obtaining blood samples for treatment monitoring) but also from a non-pharmacologic care perspective. In a systematic review, Ndosi and colleagues noted significant positive effects of nurse-led care on quality of life and other outcomes in patient self-management, knowledge, and satisfaction.[6] Furthermore, Kuninkaammiemi and colleagues reported individual counselling/education sessions for as little as 15 minutes over 2-3 routine follow-up visits can show measured changes in patients' nutritional indices, activity levels, and mobility scales, as well as numerous satisfaction/quality of life improvements.[7]

Today's nurses are responsible for much more than just acute care protocols and fundamental tasks. Nurses identify risk factors and apply preventive measures. That is why you are advancing your knowledge by reading this publication. We are all key to a successful patient-centered collaborative care model. Fundamental improvements in patient outcomes can be attained when you build your educational portfolio and become more empowered as a true nursing professional. Just look at the literature for the evidence... and ask for Dr. Haroon's opinion if you ever meet him.

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