Guideline Updates

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Each year at its annual meeting, the American College of Rheumatology (ACR) introduces new or updated evidenced-based clinical practice recommendations that reflect recent clinical trial results and/or incorporate newly approved treatments. These recommendations advise clinicians of important new data that can improve the quality, appropriateness, and cost-effectiveness of patient care. At this year's meeting, Jasvinder Singh, MD, MBBS, University of Alabama, Birmingham, Alabama, USA, presented updated recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs (DMARDS) for rheumatoid arthritis (RA). Bevra H. Hahn, MD, UCLA School of Medicine, Los Angeles, California, USA, presented new guidelines for the management of lupus nephritis.

Both sets of recommendations were developed using the RAND/UCLA Appropriateness Method, a formal group judgment method that contains elements of the Delphi technique and Nominal Group Process that uses clinically detailed 'scenarios' of diagnosis or treatment. Applying this method, the working group and core expert panel applied the results of a systematic review of the literature to create evidence reports and clinical scenarios, which were reviewed, rated, analyzed, and graded by members of the task force and eventually submitted to the ACR for finalization.

Updated Guidelines for Patients with Rheumatoid Arthritis

Among the important changes in the 2012 Updated Recommendations for the Treatment of RA are recommendations for the use of three newly approved drugs (tocilizumab, golimumab, and certolizumab), updated recommendations for switching therapies, indications for starting or resuming biologic or nonbiologic DMARDs, contraindications to the use of these agents, safety, and preventive immunizations. A key characteristic of these guidelines is that only "positive" recommendations are included, meaning that there are no statements on when NOT to start a therapy, based on efficacy considerations, and no statements when it is "permissible" to use an agent on the basis of safety considerations.

The ACR 2012 Task Force panel recommends that in both early RA (defined as disease duration <6 months) and established RA (defined as disease duration ≥6 months or meeting 1987 ACR classification criteria), the target for disease activity should be either remission (Disease Activity Score [DAS] <1.6) or low disease activity (DAS <2.4).

Patients with Established RA

Indications for DMARD Therapy and Switching Between DMARDs

- For patients with low disease activity after 3 to 6 months of DMARD monotherapy (hydroxychloroquine, methotrexate (MTX), minocycline, or sulfasalazine), add MTX or leflunomide
- For patients with at least moderate disease activity (DAS >2.4 but ≤ 3.7) after 3 months of MTX

  add another non-methotrexate DMARD to MTX **OR**

  switch to a different non-MTX DMARD

Independent Peer-Reviewed Highlights from the

American College of Rheumatology 75th Annual Scientific Meeting

When to Add a Biologic to DMARDs

- For patients with low disease activity and poor prognosis (eg, functional limitation, extraarticular disease, rheumatoid factorpositivity, and/or positive anti-CCP antibodies, and/or bony erosions by radiography) after 3 to 6 months of MTX monotherapy or DMARD combination, add or switch to an anti-TNF biologic
- For patients with at least moderate disease activity after 3 months of MTX monotherapy or DMARD combination therapy, regardless of prognosis:

  add or switch to an anti-TNF biologic **OR**

  add or switch to abatacept or rituximab in anti-TNF-naive patients **OR**

  add or switch to another DMARD

When to Switch Between Biologics

- Patients with at least moderate disease activity 3 months after failure of anti-TNF biologic should be switched to another anti-TNF biologic or a non-TNF biologic
- Patients with at least moderate disease activity 6 months after failing a non-TNF biologic (eg, abatacept, rituximab, or tocilizumab) should be switched to an anti-TNF biologic

Switching Between Biologics as a Result of an Adverse Event (FDA definition)

- Patients with at least moderate disease activity after failing an anti-TNF biologic because of a nonserious adverse event should be switched to another anti-TNF biologic or a non-TNF biologic
- Patients with at least moderate disease activity after failing a non-TNF biologic because of either a serious or nonserious adverse event should be switched to an anti-TNF biologic

Recommended Use of Biologics in RA Patients with Hepatitis is as Follows:

- Abatacept is recommended for patients with a past history of acute hepatitis B with positive hepatitis B core antibody
- Etanercept is recommended for patients with hepatitis C (whether treated or not)
- The use of biologics is not recommended for patients with untreated chronic hepatitis B or treated chronic hepatitis B with Child-Pugh Class B and higher

Approved Vaccinations

- Before starting a DMARD or a biologic, patients may receive:

  all killed vaccines (pneumococcal, influenza, and hepatitis B)

  recombinant vaccines (human papilloma virus vaccine)

  live attenuated vaccines (herpes zoster)
- Patients already taking a DMARD or a biologic can receive any of the above vaccinations, EXCEPT herpes zoster, which is recommended only during DMARD therapy and is contraindicated in biologic users

Other

Anti-TNF biologics are contraindicated in RA patients with New York Heart Association class III or IV congestive heart failure and an ejection fraction ≤50%.

The panel has also developed recommendations for the use of biologics in RA patients with previously treated malignancy (Table 1).

Table 1. The Use of Biologics in RA Patients with Previously Treated Malignancy.

Treated Malignancy	Recommended Biologic
Solid malignancy or nonmelanoma skin cancer >5 years ago	Any
Solid malignancy or nonmelanoma skin cancer <5 years ago	Rituximab
Melanoma >5 years ago	Rituximab
Lymphoproliferative malignancy (ever)	Rituximab

Updated Guidelines for Patients with Lupus Nephritis

The new Guidelines for the Management of Lupus Nephritis contain recommendations for screening, treatment, and patient management. Since treatment is dependent on biopsy results, the guidelines include treatment algorithms and recommendations for inducing improvements in various histological types of lupus nephritis, with a section on how to maintain improvements in patients who respond.

The panel has assigned a Level of Evidence (LOE), based on the strength of the supporting data, to each recommendation. A: Evidence derived from multiple randomized controlled trials (RCTs) or a meta-analysis;

B: Evidence based on a single RCT or nonrandomized study; C: Recommendation based on consensus, expert opinion, or case series.

Renal Biopsy (All LOE: C)

- Every patient with clinical evidence of active lupus nephritis, previously untreated, should undergo renal biopsy unless strongly contraindicated
- Biopsy results should be classified by the current International Society of Nephrology/Renal Pathology Society classification [www.theisn.org]
- The recommended therapeutic strategies are based on knowing the classification of nephritis on renal biopsy

All patients with lupus nephritis should receive the following adjunctive therapies:

- Hydroxychloroquine (LOE: C)
- Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for proteinuria ≥0.5 g/24 hrs or equivalent protein/creatinine ratio (LOE: A)
- Maintain blood pressure ≤130/80 mm Hg (LOE: A)
- Statins for low-density lipoprotein cholesterol level (LDL) >100 mg/dL (LOE: C)
- Pregnancy counseling for fertile women (LOE: C)

Treatment algorithms have been developed for patients with ISN/RPS Class III/IV proliferative disease with and without crescents, which include recommendations for induction therapy, maintenance therapy for responders, and treatment approaches for nonresponders. For patients with Class V, purely membranous disease with nephrotic-range proteinuria (≥3 g/24 hours), the recommendation is to begin with mycophenolate mofetil (MMF) 2 to 3 g+prednisone 0.5 mg/kg daily for 6 months. Patients who improve can be moved to a maintenance regimen of MMF 1 to 2 g/day or azothioprine 2 mg/kg/day. Patients who do not improve should be treated with cyclophosphamide 500 to 1000 mg/twice per month for 6 months + a steroid pulse that is followed by daily prednisone (0.5 to 1.0 mg/kg/day). New recommendations have also been issued for lupus nephritis in pregnancy.

Monthly monitoring is recommended for all patients with lupus nephritis (Table 2).

Despite progress, a significant unmet need remains for patients with lupus nephritis. Approximately 20% to 35% of patients do not respond to treatment, and for many patients, response is slow (8 to 52 weeks). In addition, many responders can not completely discontinue therapies.

Dr. Hahn noted that the recent approval of belimumab for adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) has led to a number of inquiries from SLE patients with lupus nephritis. She stressed that belimumab has not been studied in SLE patients with active nephritis. Although a post hoc analysis [Petri MA. *Lancet* 2011] of the published trial [Navarra SV et al. *Lancet* 2011] showed a significant ($p<0.03$) reduction in renal flares in the belimumab group, this was in patients with a history of nephritis, not currently active nephritis.

Table 2. Minimal Suggested Monthly Intervals for Monitoring of Lupus Nephritis.

	Blood Pressure	Urinalysis	Protein/ Creatinine Ratio	Serum Creatinine	C3/C4 Levels	Anti-DNA
Active nephritis at onset of treatment	1	1	1	1	2	3
Previous active nephritis – non currently	3	3	3	3	3	6
Pregnant with active GN at treatment onset	1	1	1	1	1	1
Pregnant with previous nephritis – non currently	1	1	3	3	3	3
No prior or current nephritis	3	6	6	6	6	6

GN=glomerular nephritis.

Both guidelines will be published in *Arthritis Care & Research*.