Editor's Choice

Year in Review 2015-2016

Rheumatoid Arthritis

2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis (December 2015)

Singh et al.

ACR Annual Meeting; Nov. 7-11, 2015; San Francisco. Arthritis Care & Research Vol. 68, No. 1, January 2016, pp 1–25

New evidence-based guidelines for the pharmacologic treatment of rheumatoid arthritis (RA) have been issued by the American College of Rheumatology (ACR) to update and expand upon recommendations that were last revised in 2012[4]. The guideline addresses issues including the use of non biologic and biologic disease-modifying anti rheumatic drugs, tofacitinib, and glucocorticoids in early and established RA; approaches to treating-to-target and drug switching and tapering; treatment in high-risk patients; vaccinations; and screening for tuberculosis.

Discontinuation of biologic therapies

Discontinuation of adalimumab after achieving remission in patients with established rheumatoid arthritis: 1-year outcome of the HONOR study

- The HONOR study recruited patients treated with ADA+MTX who discontinued ADA after sustained remission for ≥ 6 months (DAS28<2.6) with stable MTX doses and no steroids. Were studied for 1 year.

Conclusions:

- The possibility of remaining ADA-free for 1 year was demonstrated in established patients with RA
- ADA can be discontinued without flaring in 79% patients with deep remission
- (DAS28-ESR ≤1.9), with similar rates in the ADA continuation group, and showed no functional or structural damage.
- ADA re administration to patients with flare during ADA discontinuation was effective.

Yoshiya Tanaka et al. *Ann Rheum Dis 2015;74:389-395*

Evaluating drug-free remission with abatacept in early rheumatoid arthritis (AVERT study)

- The AVERT study included patients with very early active RA who were randomised to subcutaneous ABT 125 mg plus MTX, ABT 125 mg monotherapy, or MTX.
- Patients with LDA at month 12 entered a second 12-month period of withdrawal of all RA therapies.
- A small but significant number of patients sustained drug-free remission in the ABT+MTX group compared with MTX alone at both 12 and 18 months (14.8% vs 7.8%, respectively; p=0.045).

Conclusion

- Abatacept plus MTX demonstrated robust efficacy compared with MTX alone in early RA, with a good safety profile.
- The achievement of sustained remission following withdrawal of all RA therapy suggests an effect of abatacept mechanism on autoimmune processes

Paul Emery et al. *Ann Rheum Dis* 2015;74:19-26

Psoriatic Arthritis

(EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update

Gossec L, et al.
Ann Rheum Dis 2016;75:499–510

1. Treatment should be aimed at reaching the target of remission or, alternatively, minimal/low disease.
2. In patients with PsA, NSAIDs may be used to relieve musculoskeletal signs and symptoms.
3. In patients with peripheral arthritis, particularly in those with many swollen joints, structural damage in the presence of inflammation, high ESR/CRP and/or clinically relevant extra-articular manifestations, csDMARDs should be considered at an early stage, with methotrexate preferred in those with relevant skin involvement.
4. Local injections of glucocorticoids should be considered as adjunctive therapy in PsAa; systemic glucocorticoids may be used with caution at the lowest effective dose.
5. In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD, usually a TNF inhibitor, should be commenced.
6. In patients with peripheral arthritis and an inadequate response to at least one csDMARD, in whom TNF inhibitors are not appropriate, bDMARDs targeting IL12/23 or IL17 pathways may be considered
7. In patients with peripheral arthritis and an inadequate response to at least one csDMARD, in whom bDMARDs are not appropriate; a targeted synthetic DMARD such as a PDE4-inhibitor may be considered.
8. In patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or local glucocorticoid injections, therapy with a bDMARD should be considered, which according to current practice is a TNF inhibitor
9. In patients with predominantly axial disease that is active and has insufficient response to NSAIDs, therapy with a bDMARD should be considered, which according to current practice is a TNF inhibitor.
10. In patients who fail to respond adequately to a bDMARD, switching to another bDMARD should be considered, including switching between TNF inhibitors.

New therapies for psoriatic arthritis

- **Ustekinumab (Stelara):** An interleukin-12/23 inhibitor monoclonal antibody : Approved for the treatment of active psoriatic arthritis in adults who have not responded adequately to previous treatment with csDMARDs. The drug was also approved for treatment of moderate to severe psoriatic plaques in adults.
- **Apremilast (Otezla) (an orally taken phosphodiesterase–4 inhibitor):** Approved for treatment of psoriasis and psoriatic arthritis (PsA). It is a phosphodiesterase-4 (PDE4) inhibitor, resulting in increased intracellular cAMP levels.
- **Secukinumab (Cosentyx):** An anti-IL17A antibody, (August 2015, Modified January 2016) approved for treatment of patients with moderate-to-severe plaque psoriasis and psoriatic arthritis (PsA). Secukinumab has shown extremely high skin responses in clinical trials and this is the first of several anti-IL-17 monoclonal antibodies in development.

Ankylosing spondylitis

Baeten D, Sieper J, Braun J, et al.
Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. N Engl J Med 2015; 373:2534

- Secukinumab, an anti-interleukin (IL)-17A monoclonal antibody, has been approved for use in the United States and other countries for ankylosing spondylitis (AS).
- It was beneficial for patients with active AS in two phase 3 multicenter trials involving a total of nearly 600 patients with active disease despite optimal nonsteroidal anti-inflammatory drug therapy, some of whom had

also responded inadequately to disease-modifying antirheumatic drugs, including tumor necrosis factor (TNF) inhibitors.

- Patients who received the higher dose of secukinumab were significantly more likely, compared with those receiving placebo, to achieve an ASAS20 response at week 16 (approximately 60 versus 29 percent). Responses were sustained at week 52.
- Infections, including candidiasis, were more common in patients receiving secukinumab.
- Secukinumab may provide a treatment option for patients with AS who have an inadequate response to TNF inhibitor therapy

Systemic lupus erythematosus

Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis

D'Cruz D, Sangle S, et al.
Ann Rheum Dis 2016; 75:526–531.

Objective: To report the 10-year follow-up of the *MAINTAIN* Nephritis Trial comparing azathioprine (AZA) and mycophenolate mofetil (MMF) as maintenance therapy of proliferative lupus nephritis, and to test different definitions of early response as predictors of long-term renal outcome. **Methods:** In 2014, data on survival, kidney function, 24 h proteinuria, renal flares and other outcomes were collected for the 105 patients randomised between 2002 and 2006, except in 13 lost to follow-up. **Results:** Death (2 and 3 in the AZA and MMF groups, respectively) and end-stage renal disease (1 and 3, respectively) were rare events. Time to renal flare (22 and 19 flares in AZA and MMF groups, respectively) did not differ between AZA and MMF patients. Patients with good long-term renal outcome had a much more stringent early decrease of 24 h proteinuria compared with patients with poor outcome. The positive predictive value of a 24 h proteinuria <0.5 g/day at 3 months, 6 months and 12 months for a good long-term renal outcome was excellent (between 89% and 92%). Inclusion of renal function and urinalysis in the early response criteria did not impact the value of early proteinuria decrease as long-term prognostic marker. **Conclusions:** The long-term follow-up data of the *MAINTAIN* Nephritis Trial do not indicate that MMF is superior to AZA as maintenance therapy in a Caucasian population suffering from proliferative lupus nephritis. Moreover, we confirm the excellent positive predictive value of an early proteinuria decrease for long-term renal outcome

REMISSION IN SLE: CONSENSUS FINDINGS FROM A LARGE INTERNATIONAL PANEL ON DEFINITIONS OF REMISSION IN SLE (DORIS)

Van Vollenhoven RF, Aranow C, Bertias G, et al.
EULAR** 2015, Rome. **Abstract OP0092

Background: Treat-to-target recommendations identified "remission" as a target in SLE but recognize that there is no generally accepted definition for remission in this disease.
Objectives: To achieve consensus, in a large multi-party international panel, on potential definitions for remission in SLE.
Methods: An international expert panel of sixty rheumatologists, nephrologists, dermatologists, clinical immunologists, and patient representatives participated in preparatory exercises, a full-day face-to-face meeting, and follow-up exercises and electronic voting rounds.
Results: Eight key statements regarding remission in SLE achieved >90% agreement (table). There were different viewpoints on the required duration of remission. In addition, the panel expressed strong support (>90%) for the following *principles* which will guide the further development of remission definitions:

I. *A definition of remission in SLE will be worded as follows:* Remission in SLE is a durable state characterized by [a definition of: absence of symptoms, signs, abnormal labs, (serology)]
   Ia. *Remission-off-therapy* requires the patient to be on no other treatment for SLE than maintenance antimalarials.
   Ib. *Remission-on-therapy* allows patients to be treated with maintenance antimalarials, stable, low-dose steroids (prednisone ≤5 mg/d), maintenance immunosuppressives and/or stable (maintenance) biologics.

II. Assessment of clinical symptoms and signs should be based on a validated index, e.g., clinical-SLEDAI =0, BILAG D/E only, clinical ECLAM =0; supplemented with PhysGA <0.5 (0-3), and with labs included.

III. For testing the construct validity of each potential remission definition the most appropriate outcomes (dependent variables) are: Death, Damage, Flares, and HR-QOL measures.

	Statement	% in favor
1	Remission is a desirable outcome for the patient with SLE	100%
2	Remission in SLE includes, at the very least, the absence of major symptoms and signs of SLE.	100%
3	Remission in SLE is not the same as a cure.	100%
4	Remission in SLE is not the same as low disease activity.	93%
5	Remission is a state that, if sustained, is associated with a low likelihood of adverse outcome	100%
6	"Serological activity" in SLE generally refers to the presence of anti-DNA antibodies and/or hypocomplementemia.	100%
7	Treatment with antimalarials does not preclude the patient from being considered to be in remission.	98%
8	Treatment with moderate- or high-dose steroids does preclude the patient from being considered in remission.	98%

Conclusions: The work of this international consensus panel provides a framework for testing individual definitions of remission against longer-term outcomes.

Scleroderma

Finally New Hope for Scleroderma: Three major advances in SSc research were seen this year.

1) The FASSCINATE Actemra study a double-blind, placebo-controlled, phase 2 study included 87 PSS patients and showed improved skin scores and significantly better FVC measures in those treated with tocilizumab. Another phase III trial is being planned.
   The FASSCINATE study presented at EULAR 2015 was instrumental as Actemra (tocilizumab) (TCZ) Gets "Breakthrough" Status from the FDA for Scleroderma
   Khanna D, et al. *OP0054. Eular Congress of Rheumatology; June 10-13, 2015; Rome*

2) A novel report of fresolimumab, an anti-TGF-β monoclonal antibody, being tested in a trial of 15 SSc patients (with mean disease duration of 8 months). The results of this open-label study showed nearly all patients had significant decreases in skin scores, which correlated with skin biopsy scores.
Lisa M. Rice et al. *J Clin Invest. 2015;125(7):2795-2807*

3) The results of a head-to-head trial in scleroderma lung study II showed the benefits (and less toxicity of mycophenolate compared to cyclophosphamide.
Tashkin D, et al. *Results of Scleroderma Lung Study II" Chest 2015;*

The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation

Götestam Skorpen C, et al.
Ann Rheum Dis 2016;0:1–16

Points to consider for use of antirheumatic drugs in pregnancy

1. csDMARDs proven compatible with pregnancy are hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus and colchicine. They should be continued in pregnancy for maintenance of remission or treatment of a disease flare.
2. csDMARDs methotrexate, mycophenolate mofetil and cyclophosphamide are teratogenic and should be withdrawn before pregnancy.
3. Non-selective COX inhibitors (non-steroidal anti-inflammatory drugs, NSAIDs) and prednisone should be considered for use in pregnancy if needed to control active disease symptoms. NSAIDs should be restricted to the first and second trimesters.
4. In severe, refractory maternal disease during pregnancy methylprednisolone pulses, intravenous immunoglobulin or even second or third trimester use of cyclophosphamide should be considered.
5. csDMARDs, tsDMARDs and anti-inflammatory drugs with insufficient documentation concerning use in pregnancy should be avoided until further evidence is available. This applies to leflunomide, mepacrine, tofacitinib and selective COX II inhibitors.
6. Among bDMARDs continuation of tumour necrosis factor (TNF) inhibitors during the first part of pregnancy should be considered. Etanercept and certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage.
7. bDMARDs rituximab, anakinra, tocilizumab, abatacept, belimumab and ustekinumab have limited documentation on safe use in pregnancy and should be replaced before conception by other medication. They should be used during pregnancy only when no other pregnancy-compatible drug can effectively control maternal disease.

Points to consider for use of antirheumatic drugs during lactation

1. csDMARDs and anti-inflammatory drugs compatible with breast feeding should be considered for continuation during lactation provided the child does not have conditions that contraindicate it. This applies to hydoxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus, colchicine, prednisone, immunoglobulin, non-selective COX inhibitors and celecoxib.
2. csDMARDs, tsDMARDs and anti-inflammatory drugs with no or limited data on breast feeding should be avoided in lactating women. This applies to methotrexate, mycophenolate mofetil, cyclophosphamide, leflunomide, tofacitinib and cyclooxygenase II inhibitors other than celecoxib.
3. Low transfer to breast milk has been shown for infliximab, adalimumab, etanercept and certolizumab. Continuation of TNF inhibitors should be considered compatible with breast feeding.
4. bDMARDs with no data on breast feeding such as rituximab, anakinra, belimumab, ustekinumab, tocilizumab and abatacept should be avoided during lactation if other therapy is available to control the disease. Based on pharmacological properties of bDMARDs, lactation should not be discouraged when using these agents, if no other options are available.

FDA Warning About Januvia Joint Pain

www.fda.gov/Drugs/DrugSafety In August 2015

- Januvia has been widely advertised and is one of the best-selling diabetes drugs.
- The U.S. Food and Drug Administration (FDA) warning that the type 2 diabetes medicines sitagliptin (Januvia) (sitagliptin + metformin) (Janumet) and other (DPP-4) inhibitors may cause joint pain that can be severe and disabling.
- Symptoms can start within a day of beginning one of these drugs or come on gradually, after years of use without symptoms.
- After the patients discontinued the DPP-4 inhibitor medicine, their symptoms were relieved, usually in less than a month. Some patients developed severe joint pain again when they restarted the same medicine or another DPP-4 inhibitor.
- Health care professionals should consider DPP-4 inhibitors as a possible cause of severe joint pain and discontinue the drug if appropriate.