RA Current Treatment Update

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Disclosures

Abbvie: Speaker
Pfizer:  Speaker, Consultant
Horizon Pharma: Consultant, Speaker
Mallinckrodt: Consultant, Speaker
Medac Pharma: Consultant
Agenda

- Review most recent changes in the rheumatoid arthritis treatment guidelines.
- Discuss the optimal dosing of methotrexate.
- Consider treatment tapering strategies.
Gems from the 2015 ACR RA treatment guidelines
2015 RA Guidelines

• Similarities with previous guidelines:
  – Frequent disease activity assessments, treatment escalation or switching, targeting the most optimal outcome for the patients

• New aspects of the 2015 guidelines:
  – Uses GRADE Methodology vs Rand UCLA Appropriateness Method
  – Includes new types of therapies
  – Discusses care for certain high-risk patient populations
  – Provides guidance on tapering and discontinuation to meet patient-desired goals
  – Makes recommendations based on patients' disease activity level only (vs both disease activity and prognosis)

GRADE Method: Defining Recommendations

Strong

- The panel is very confident that the benefits of the recommendations outweigh the harms (or vice versa)

Conditional

- The panel is uncertain about the balance of the benefits and harms as a result of low evidence quality
  - Preference sensitive
  - Warrants a shared decision-making approach

Instruments to measure RA disease activity/define remission

- Patient Activity Score (PAS)
- Routine Assessment of Patient Index Data 3 (RAPID 3)
- Clinical Disease Activity Index (CDAI)
- Disease Activity Score (DAS)
- Simplified Disease Activity Score (SDAI)

These 6 measures were endorsed by the American College of Rheumatology in 2012. Other measures are now available to clinicians, but they were not included in this guideline because it was beyond the scope of this review. Adapted from ref. 16.
RA treatments reviewed for 2015 that were different from 2012 Guidelines

- Corticosteroids
- Tofacitinib
- No anakinra (“Anakinra was considered but not included in these guidelines due to its infrequent use in RA and lack of new data since 2012”)
- Azathioprine, cyclosporine, minocycline and gold were considered but not included in these guidelines due to their infrequent use in RA and/or lack of new data since 2012
ACR statements that may help with payors

• If a patient has low RA disease activity or is in clinical remission, switching from one therapy to another should be considered only at the discretion of the treating physician in consultation with the patient.
• Arbitrary switching between RA therapies based only on a payer/insurance company policy is not recommended.
Recommendations in RA patients with high-risk comorbidities

- Congestive heart failure
- Hepatitis B
- Hepatitis C
- Malignancy
- Previous serious infections
Recommendations for High-Risk Patients

• Previous serious infection*
  – Use combination DMARDs over TNFi
  – Use abatacept over TNFi

• Previously treated or untreated skin cancer*
  – Melanoma or non-melanoma
    ▪ Use DMARDs over biologic
    ▪ Use DMARDs over tofacitinib

*Conditional recommendations supported by low-level evidence are largely based upon expert opinion and clinical experience.

Recommendations for High-Risk Patients (cont)

- Previously treated lymphoproliferative disorder*
  - Use rituximab over TNFi (*strong recommendation*)
  - Use combination DMARDs or abatacept or tocilizumab over TNFi

- Previously treated solid organ malignancy*
  - Same therapy as in patients without this condition

*Conditional recommendations supported by low-level evidence are largely based upon expert opinion and clinical experience.
Recommendations for High-Risk Patients (cont)

• Active hepatitis B infection and receiving effective antiviral treatment*
  – Same therapy as a patient without this condition

• Hepatitis C infection and receiving effective antiviral treatment†
  – Same therapy as a patient without this condition

*Strong recommendations were largely based upon the recent American Association for the Study of Liver Diseases cases series and clinical experience.
†Conditional recommendations for hepatitis C were largely supported by very low-level evidence based upon case series and clinical experience.
Recommendations for High-Risk Patients (cont)

- Established RA and CHF*
  - Combination DMARDs or non-TNF biologic or tofacitinib over TNFi

- Established RA and CHF worsening on current TNFi therapy*
  - Combination DMARDs or non-TNF biologic or tofacitinib over another TNFi

*Conditional recommendations supported by clinical experience and FDA safety warning with TNFi.

2015 ACR RA Guidelines: Possible Controversies

- There may be recommendations in the guidelines that a clinician may not agree with.

- There are some recommendations (ie, for high-risk patient populations) that are based on little or no evidence.

- The guidelines provide direction on common clinical scenarios, but recognize that patients need an individualized approach to management and treatment.

2015 ACR RA Guidelines: Summary

- Current 2015 guidelines are different in several ways from earlier guidelines
  - GRADE methodology was used
  - Guidelines were based on disease activity level rather than both disease activity and prognosis
- 77% of the recommendations were conditional; 23% were strong
- Not all aspects of RA management are covered

Optimization of methotrexate in RA
Methotrexate in RA

- Methotrexate (MTX) remains the cornerstone therapy for patients with rheumatoid arthritis (RA), with well-established safety and efficacy profiles and support in international guidelines.
- Clinical and radiologic results indicate benefits of MTX monotherapy and combination with other agents, yet patients may not receive optimal dosing, duration, or route of administration to maximize their MTX response.
The vast majority of RA patients in the United States initiate treatment with oral MTX

Results for 39,440 RA patients starting MTX treatment in the United States:

- Oral MTX: 90.4%
- SC MTX: 9.6%
Objective: This study examines MTX prescribing practices in the US from 2009 to 2014.

Methods: Symphony Health Solutions which covers 274 million patients in the US was used to identify patients diagnosed with RA who were naïve to MTX in 2009 and 2012. Data was collected including medication use and doses, demographics, and medical co-morbidities.
In patients who had five year follow up data available oral (PO) MTX was started in 35,640 in 2009 and 44% remained on this during the follow-up.

Of the 20,041 patients who changed therapy during the study period 87% had the addition of or switch to a biologic, while 13% were changed from PO to subcutaneous (SC) MTX.

The mean PO dose prior to the start of a biologic was 15.3 mg/week +/- 5 mg.

Comparison of 2009 to 2012 showed a modest increase in the mean dose of PO MTX from 15.3 mg to 15.9 mg/week and a small but statistically significant (p < 0.0001) increase in the use of SC MTX after failure of PO MTX from 13% to 16% of patients.

Conclusion

- MTX is underutilized in the treatment of RA with suboptimal dosing, inadequate duration of therapy, and failure to use subcutaneous administration.
- Comparison of MTX use between the 2009 and the 2012 cohorts demonstrate only a marginal increase in the dose of PO MTX and the use of SC MTX.
SC Administration Improves MTX Bioavailability

Single center, open-label, randomized, 2-period, 2-sequence, single-dose, crossover study in 4 dose groups (7.5 mg, 15 mg, 22.5 mg, and 30 mg) with 54 healthy adults

Significant Improvement in Disease Control Following Switch From Oral to SC MTX

Retrospective analysis of 103 RA patients switched from oral to SC MTX:

• 40 switched due to inadequate efficacy of oral MTX
• 63 patients switched due to gastrointestinal side effects of oral MTX

SC, subcutaneous; DAS, disease activity score.
Significantly Better Disease Control With SC vs Oral MTX

**ACR Responses†**

<table>
<thead>
<tr>
<th></th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>70</td>
</tr>
<tr>
<td>ACR50</td>
<td>59</td>
</tr>
<tr>
<td>ACR70</td>
<td>33</td>
</tr>
</tbody>
</table>

**EULAR Remission†**

<table>
<thead>
<tr>
<th></th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral MTX 15 mg (n=187)</td>
<td>24</td>
</tr>
<tr>
<td>SC MTX 15 mg (n=188)</td>
<td>34</td>
</tr>
</tbody>
</table>

† Week 16 results were carried forward for patients who switched from oral to SC MTX or had their SC MTX doses increased from 15 to 20 mg/wk.

Prospective Comparison of SC and Oral MTX

Prospective 6-month study to assess the efficacy, safety, and compliance of SC vs oral MTX in 92 patients with active RA according to ACR criteria

<table>
<thead>
<tr>
<th></th>
<th>SC MTX (n=46)</th>
<th>Oral MTX (n=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years, mean ± SD</td>
<td>45.54 ± 12.42</td>
<td>44.63 ± 13.99</td>
</tr>
<tr>
<td>Male (%)</td>
<td>5 (11)</td>
<td>12 (26)</td>
</tr>
<tr>
<td>Disease duration months, mean</td>
<td>49.74</td>
<td>49.0</td>
</tr>
</tbody>
</table>

ACR, American College of Rheumatology; MTX, methotrexate; RA, rheumatoid arthritis; SC, subcutaneous; SD, standard deviation

Prospective Comparison of SC and Oral MTX: ACR Responses

- **ACR20**:
  - **SC MTX (n=46)**: 93%
  - **Oral MTX (n=46)**: 80%
  - *P* = 0.02

- **ACR50**: 89% vs. 72%
  - *P* = 0.03

- **ACR70**: 11% vs. 9%
  - *P* = 0.72

ACR, American College of Rheumatology; MTX, methotrexate; SC, subcutaneous; SD, standard deviation

Prospective Comparison of SC and Oral MTX: Adverse Events

MTX, methotrexate; SC, subcutaneous; SD
Multicenter prospective study of patients with early RA (symptoms ≤1 year) initiating MTX therapy

Comparison of the effectiveness of starting with SC or oral MTX over the first year

Longitudinal multivariable models, adjusted for potential baseline and time-varying confounders, were used to compare treatment changes due to inefficacy or toxicity and treatment efficacy

Initiation of Treatment With SC or Oral MTX: Real-world Results From the Canadian Early Arthritis Cohort (CATCH)

MTX, methotrexate; RA, rheumatoid arthritis; SC, subcutaneous

## CATCH Cohort: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Oral MTX (n=417)</th>
<th>SC MTX (n=249)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (SD)</td>
<td>54 (14)</td>
<td>51 (15)</td>
<td>0.068</td>
</tr>
<tr>
<td>Female, %</td>
<td>75.1</td>
<td>73.1</td>
<td>0.57</td>
</tr>
<tr>
<td>Number of comorbidities, mean (SD)</td>
<td>2.2 (1.8)</td>
<td>2.5 (1.9)</td>
<td>0.041</td>
</tr>
<tr>
<td>Symptom duration, mean months (SD)</td>
<td>5.2 (2.7)</td>
<td>5.2 (2.8)</td>
<td>0.61</td>
</tr>
<tr>
<td>Seropositive (RF or ACPA), %</td>
<td>78.8</td>
<td>82.0</td>
<td>0.35</td>
</tr>
<tr>
<td>Erosions present on hand or foot x-rays (%)</td>
<td>24.4</td>
<td>31.1</td>
<td>0.08</td>
</tr>
<tr>
<td>HAQ-DI (0-3)</td>
<td>1.1 (0.69)</td>
<td>1.1 (0.69)</td>
<td>0.52</td>
</tr>
<tr>
<td>DAS28, mean (SD)</td>
<td>5.5 (1.4)</td>
<td>5.5 (1.4)</td>
<td>0.86</td>
</tr>
<tr>
<td>Starting dose of MTX, mean mg (SD)</td>
<td>17.2 (3.8)</td>
<td>22.3 (3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;20, %</td>
<td>5.0</td>
<td>45.2</td>
<td></td>
</tr>
<tr>
<td>15-20, %</td>
<td>56.8</td>
<td>27.8</td>
<td></td>
</tr>
<tr>
<td>&lt;15, %</td>
<td>38.1</td>
<td>27.0</td>
<td></td>
</tr>
<tr>
<td>Concurrent use of systemic glucocorticoids, %</td>
<td>48.0</td>
<td>51.8</td>
<td>0.34</td>
</tr>
<tr>
<td>Oral, %</td>
<td>24.2</td>
<td>13.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Intramuscular or intra-articular, %</td>
<td>27.8</td>
<td>41.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concurrent use of other DMARDs, %</td>
<td>53.0</td>
<td>42.6</td>
<td>0.009</td>
</tr>
<tr>
<td>Concurrent use of biological therapy, %</td>
<td>2.2</td>
<td>0.4</td>
<td>0.071</td>
</tr>
</tbody>
</table>

ACPA, anti-citrullinated protein antibodies; DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; RF, rheumatoid factor; SC, subcutaneous; SD, standard deviation

Better Persistence Is Achieved With SC vs Oral MTX: CATCH Cohort

MTX, methotrexate; SC, subcutaneous; PO, oral
## Reasons for Treatment Failure: SC vs Oral MTX

<table>
<thead>
<tr>
<th>Reason for Treatment Failure</th>
<th>SC MTX (n=249) %</th>
<th>Oral MTX (n=417) %</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total treatment failures</td>
<td>49%</td>
<td>77%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inadequate efficacy only</td>
<td>28%</td>
<td>59%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Toxicity only</td>
<td>3%</td>
<td>2%</td>
<td>0.63</td>
</tr>
<tr>
<td>Both inadequate efficacy and toxicity</td>
<td>18%</td>
<td>16%</td>
<td>0.57</td>
</tr>
</tbody>
</table>

# CATCH Cohort: Changes in Treatment

<table>
<thead>
<tr>
<th>Change in Treatment</th>
<th>SC MTX</th>
<th>Oral MTX</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changed route of MTX</td>
<td>3</td>
<td>20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Increased dose of MTX after 3 months</td>
<td>24</td>
<td>58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Added/switched a non-biological DMARD</td>
<td>22</td>
<td>33</td>
<td>0.004</td>
</tr>
<tr>
<td>Added a biologic</td>
<td>10</td>
<td>12</td>
<td>0.41</td>
</tr>
<tr>
<td>Decreased dose of MTX after 3 months*</td>
<td>10</td>
<td>4</td>
<td>0.006</td>
</tr>
<tr>
<td>Stopped a non-biological DMARD*</td>
<td>7</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

Patients may have had more than one change.

* Must have had another treatment change, side effect or increased DAS28 to be considered a treatment failure.
Lower DAS28 Scores Are Achieved With SC vs Oral MTX: CATCH Cohort

$P<0.05$ for SC vs oral SC MTX at 3, 6, and 9 months

MTX, methotrexate; SC, subcutaneous.
## CATCH Cohort: DAS28 Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Estimate for SC MTX (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS28, mean difference</td>
<td>-0.38 (-0.64 to -0.10)</td>
<td>0.04</td>
</tr>
<tr>
<td>DAS28 remission, OR</td>
<td>1.15 (1.05 to 1.25)</td>
<td>0.002</td>
</tr>
<tr>
<td>DAS28 sustained remission*, OR</td>
<td>1.02 (0.96 to 1.06)</td>
<td>0.43</td>
</tr>
<tr>
<td>HAQ-DI, mean difference</td>
<td>-0.02 (-0.13 to 0.10)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* Defined as DAS28 <2.6 on 2 consecutive visits

CI, confidence interval; DAS, Disease Activity Score; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; OR, odds ratio; SC, subcutaneous

CATCH Cohort Sites: Relation Between SC MTX Use and Patient Outcomes

DAS, Disease Activity Score; MTX, methotrexate; SC, subcutaneous
CATCH: Conclusions

SC MTX is an attractive alternative to oral drug delivery for the treatment of RA

Initial treatment with SC vs oral MTX has been associated with:

- Greater efficacy
- Better disease control
- Lower rates of treatment changes
- Decreased frequency of gastrointestinal adverse events

MTX, methotrexate; RA, rheumatoid arthritis; SC, subcutaneous
Switching or Adding: Is There a Difference?

It does not appear to matter for tocilizumab

ABT, abatacept; ACR20/50/70, 20%/50%/70% improvement in American College of Rheumatology criteria; ANA, anakinra; aTNF, anti-tumor necrosis factor; CrI, credible interval; MTX, methotrexate; TCZ, tocilizumab; TOF, tofacitinib

MTX Optimization Summary

- Patients for whom MTX treatment fails because of intolerability or inadequate efficacy may be “rescued” by switching to subcutaneous MTX.
- Consideration should also be given to starting with subcutaneous MTX given its favorable bioavailability and pharmacodynamic profile.
- Starting patients on subcutaneous MTX or switching from oral to subcutaneous delivery is likely to improve treatment persistence.
• If a patient is switched from oral to subcutaneous MTX, a concomitant dosage increase should be avoided. After the change in delivery route, the dose may be titrated as needed.

• If a patient has tolerated MTX monotherapy but has not responded adequately, the patient also may be prescribed another agent. In such cases, the MTX dosage and route of administration used before treatment augmentation should be maintained, with titration as needed.
Tapering Treatment in RA
• In the 1990s, Duke trained all fellows to inform new RA patients that their condition was life long and that they would be disabled within 5 years.
• But today, disease-modifying anti-rheumatic drugs (DMARDs), both synthetic and biologic, can send the disease into remission.
• We also have many ways to define “remission.”
Defining Remission in RA

http://dx.doi.org/10.1136/annrheumdis-2016-209201
Defining Remission in RA

Clinical remission
Absence or very low-level symptoms related to arthritis assessed by standardised scores and cut-offs (DAS28 < 2.6, DAS44 < 1.6, SDAI < 3.3, CDAI < 2.8, ACR/EULAR remission)

Imaging/Serological Remission
Clinical remission PLUS
- No signs of ultrasound synovitis
- No signs of MRI synovitis or osteitis
- No serologic signs of inflammation

Immunological Remission
Clinical and imagingserological remission PLUS
- Rheumatoid factor and ACPA negative
- Rheumatoid factor and ACPA seroconversion is documented

http://dx.doi.org/10.1136/annrheumdis-2016-209201
Optimizing therapy in inflammatory arthritis: prediction of relapse after tapering or stopping treatment for rheumatoid arthritis patients achieving clinical and radiological remission

- This study aims to assess clinical, lab/immunological or imaging (joint ultrasonography) markers able to predict disease relapse in RA patients in sustained remission when tapering or stopping their treatment.
- One hundred fifty-seven RA patients in clinical remission (DAS-28 <2.6 for >6 months), receiving treatment with sDMARDs and bDMARD therapy, were randomly allocated into any of five groups.
Optimizing therapy in inflammatory arthritis: prediction of relapse after tapering or stopping treatment for rheumatoid arthritis patients achieving clinical and radiological remission

<table>
<thead>
<tr>
<th>Group</th>
<th>DMARD</th>
<th>Biologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>full</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>50%</td>
<td>off</td>
</tr>
<tr>
<td>4</td>
<td>off</td>
<td>off</td>
</tr>
<tr>
<td>5</td>
<td>full</td>
<td>full</td>
</tr>
</tbody>
</table>
Optimizing therapy in inflammatory arthritis: prediction of relapse after tapering or stopping treatment for rheumatoid arthritis patients achieving clinical and radiological remission

• Forty joints were assessed ultrasonographically (DAS-28 joints + ankles + metatarsophalangeal joints) and prospectively monitored for 12 months.
• The primary endpoint was sustained remission for 12 months.
• Patients were considered as having a relapse when the DAS-28 score was >3.2 and anti-rheumatic treatment was escalated.

Optimizing therapy in inflammatory arthritis: prediction of relapse after tapering or stopping treatment for rheumatoid arthritis patients achieving clinical and radiological remission

- Relapse rates were significantly higher in patients whose ultrasound scores raised within 3 months of stopping their medications (P < 0.001 for both GS and PD scores)
- Cox regression identified ACPA positivity (at baseline) and progression of functional disability (at 2 months) as predictors for relapse.
- Joint ultrasonographic assessment, ACPA positivity and worsening functional disability predicted relapse within a short term after discontinuation of the treatment.
- RA patients whose DAS-28 score was <2 were more likely to remain in remission.

<table>
<thead>
<tr>
<th>Group</th>
<th>Relapse Frequency</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>41.9%</td>
</tr>
<tr>
<td>2</td>
<td>59.3%</td>
</tr>
<tr>
<td>3</td>
<td>67.7%</td>
</tr>
<tr>
<td>4</td>
<td>77.4%</td>
</tr>
<tr>
<td>5</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

Defining Patients Eligible for DMARD Tapering

- DMARD tapering should be considered in patients who meet the criteria for remission:
  - DAS28 score of 2.6 units, or DAS44 < 1.6 units
  - Not all patients in remission have an absence of symptoms, but instead show some disease activity.
- SDAI < 3.3
- CDAI < 2.8
- ACR/EULAR recommend a sustained remission of at least six months.
- And once tapering has begun, use stable DMARD treatment with respect to type and dose of DMARDs over the last 6 months.
- Do not use glucocorticoids to maintain remission state (Exception: stable doses of low-dose glucocorticoids (≤5 mg prednisolone per day).
Predicting Risk for Relapse

• Anti-citrullinated autoantibody negativity and the presence of deep remission, such as absence of ultrasound synovitis or normal serum markers of inflammation, are associated with higher chances to achieve drug-free remission.

• Disease relapses occur more often in patients starting TNF inhibitors late in their disease course.
Monitoring and Relapse Management

- Monitoring should be planned and conducted regularly to detect relapses as early as possible.
- Patient education is essential — specifically about the risks of relapse and how to manage a relapse.
- Most studies show that reintroducing the patient’s former DMARD regimen will recapture remission.

Agenda

• Review most recent changes in the rheumatoid arthritis treatment guidelines.
• Discuss the optimal dosing of methotrexate.
• Consider treatment tapering strategies.
Questions