EULAR RECOMMENDATIONS FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS – 2016 UPDATE

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DISCLOSURES

Grant support and/or honoraria from Abbvie, Astra-Zeneca, BMS, Boehringer-Ingelheim, Celgene, Celtrion, GSK, ILTOO, Janssen, Lilly, MSD, Novartis-Sandoz, Pfizer, Roche-Chugai, Samsung, UCB

Co-Editor of Textbook “Rheumatology“ (Elsevier)

Contributor to UpToDate
Of Note

• Wordings of recommendations have been decided and voted on in April 2016 – these are set
  • Level of Agreement was voted on in May 2016
• The comments reflect the discussions and decisions for reflection in the text
  • Wording of comments subject to change upon finalization of the manuscript
• Figure reflects wording of recommendations
  • Subject to subtle changes
Methodology

• The Task Force followed the 2014 updated EULAR SOP\(^1\)
• The evidence was based on 3 SLRs
• The level of evidence was judged according to the grading by the Oxford Centre for Evidence-based-Medicine\(^2\)

\(^1\) van der Heijde et al, Ann Rheum Dis 2015;74:8–13
## Steering Committee

### Rheumatologists
- Hans Bijlsma
- Gerd Burmester
- Maxime Dougados
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- Robert Landewé (Epi)
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- Katerini Chatzidionysiou

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- Peter Nash
- Tsutomu Takeuchi

### North America
- Vivian Bykerk
- Kenneth Saag

### Latin America
- Mario Cardiel
- Edoardo Mysler
“... we will carefully follow the developments in the field and anticipate that yet another update may be needed in 2–3 years.”
### Types of Treatments for RA: Nomenclature

<table>
<thead>
<tr>
<th>Synthetic DMARDs (sDMARDs)</th>
<th>Biological DMARDs (bDMARDs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional synthetic (csDMARDs)</td>
<td>Biological originator (boDMARDs)</td>
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<tr>
<td>MTX, SSZ, LEF</td>
<td>Biosimilar (bsDMARDs)</td>
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<tr>
<td>Targeted synthetic (tsDMARDs)</td>
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Tofacitinib

### Overarching principles 2013

| A. | Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist. |
| B. | Rheumatologists are the specialists who should primarily care for RA patients. |
| C. | RA incurs high individual, societal and medical costs, all of which should be considered in its management by the treating rheumatologist. |

**New B = previous recommendation 14; now considered an overarching principle**

### Overarching principles 2016

| A. | Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist. |
| B. | |
| C. | Rheumatologists are the specialists who should primarily care for RA patients. |
| D. | RA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist. |

98-100% of votes, LoA: 9.7 – 9.9
**Recommendations 1-5**

<table>
<thead>
<tr>
<th>Final set of 14 recommendations on the management of RA - 2013</th>
<th>Final set of 14 recommendations on the management of RA – 2016 (SoR; LoA)</th>
</tr>
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<tbody>
<tr>
<td><strong>1.</strong> Therapy with <strong>DMARDs</strong> should be started as soon as the <strong>diagnosis</strong> of RA is made.</td>
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<td><strong>2.</strong> Treatment should be aimed at reaching a target of remission or low disease activity in every patient.</td>
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<td><strong>3.</strong> Monitoring should be frequent in active disease (every 1-3 months); if there is <strong>no improvement</strong> by at most <strong>3 months</strong> after treatment start or the target has not been reached by 6 months, therapy should be adjusted.</td>
<td><strong>3.</strong> Monitoring should be frequent in active disease (every 1-3 months); if there is <strong>no improvement</strong> by at most <strong>3 months</strong> after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted. <em>(B; 9.5)</em></td>
</tr>
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<td><strong>4.</strong> MTX should be part of the <strong>first</strong> treatment strategy in patients with active RA.</td>
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</tr>
<tr>
<td><strong>5.</strong> In <strong>case</strong> of MTX contraindications (or early intolerance), <strong>sulfasalazine or leflunomide</strong> should be considered as part of the (first) treatment strategy.</td>
<td><strong>5.</strong> In <strong>patients</strong> with a contraindication to MTX (or early intolerance), <strong>leflunomide or sulfasalazine</strong> should be considered as part of the (first) treatment strategy. <em>(A; 9.0)</em></td>
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<tr>
<td>Recommendation 6</td>
<td></td>
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<td>In DMARD naïve patients, irrespective of the addition of glucocorticoids, <strong>conventional synthetic DMARD monotherapy or combination therapy</strong> of conventional synthetic DMARDs should be used.</td>
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<th>Recommendation 7</th>
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<td><strong>Recommendation 4 states that MTX should be part of the first treatment strategy</strong> – the term “strategy” inherently does not exclude combinations of csDMARDs; however, it does not primarily recommend it.</td>
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<th>Recommendation 8</th>
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<tr>
<td>Several recent trials (tREACH, Care-RA) revealed that MTX monotherapy in combination with glucocorticoids is not less efficacious than combination of csDMARDs plus glucocorticoids, but has less safety issues.</td>
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</tbody>
</table>
And ACR? 2015 ACR guideline for the treatment of early RA

* Monotherapy with csDMARD is strongly recommended over triple therapy. MTX is preferred initial csDMARD

### Recommendations 6-8

6. In DMARD naïve patients, irrespective of the addition of glucocorticoids, **conventional synthetic DMARD monotherapy or combination therapy** of conventional synthetic DMARDs should be used.

7. **Many glucocorticoid treatment strategies exist**, such as application of oral low- or intermediate-dose, of a single intramuscular injection or a single intravenous application, the latter two approaches usually having lower cumulative doses.

8. In contrast to the data available for the 2013 update, the tofacitinib database has been enlarged by long-term extension studies which did not reveal new safety issues. Also another Jak-inhibitor, baricitinib, has completed phase 3 trials and revealed significant efficacy (also compared with a TNF-inhibitor) without new safety issues.
9. In patients responding insufficiently to MTX and/or other conventional synthetic DMARD strategies, with or without glucocorticoids, biological DMARDs (TNF inhibitors, abatacept or tocilizumab, and under certain circumstances rituximab) should be commenced with MTX.

10. Patients who have failed a first biological DMARD should be treated with another biological DMARD; patients who have failed a first TNF-inhibitor therapy, may receive another TNF-inhibitor or a biologic with another mode of action.

11. Tofacitinib may be considered after biological treatment has failed.

12. If a patient is in persistent remission, after having tapered glucocorticoids, one can consider tapering biological DMARDs, especially if this treatment is combined with a conventional synthetic DMARD.

There is compelling evidence that all bMARDs, including tocilizumab, convey better clinical, functional and structural outcomes in combination with csDMARDs, especially MTX. This may not be the case for Jak-inhibitors, although baricitinib in combination with MTX had better structural, though not better clinical and functional outcomes than as a monotherapy.
In patients responding insufficiently to MTX and/or other conventional synthetic DMARD strategies, with or without glucocorticoids, **biological DMARDs** (TNF-inhibitors, abatacept or tocilizumab, and under certain circumstances rituximab) should be **commenced with MTX**.

Patients who have failed a first biological DMARD should be treated with another **biological DMARD**; patients who have **failed a first TNF-inhibitor** therapy, may receive another TNF-inhibitor or a biologic with another mode of action.

In cases of **sustained long-term remission**, **cautious reduction** of conventional synthetic DMARD dose could be considered, as a **shared decision between patient and physician**.

If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD. **(B; 9.0)**

This recommendation was regarded an overarching principle and now constitutes principle B.
Level of Evidence, Strength of Recommendation and Level of Agreement

• Most recommendations (n=8) have a high level of evidence and strength of recommendation according to the Oxford Evidence Based Medicine categorization (A)

• Most recommendations have attained a very high level of agreement among the many task force members, ranging from 9 to 10 on a 0 to 10 scale.

• Three items have achieved a somewhat lower level of agreement, namely in the order of 8.5 to 8.7 on a 0 to 10 scale
  • Glucocorticoid use (#6)
  • Use of another csDMARD strategy in the absence of poor prognostic factors (#7)
  • Tapering of csDMARDs in persistent remission (#12)
Phase I

No contraindication for methotrexate

Clinical diagnosis of rheumatoid Arthritis

Contraindication for methotrexate

Start methotrexate

Combine with short-term glucocorticoids

Start leflunomide or sulfasalazine

Failure phase I: go to phase II

No achieve target within 6 months

Achieve target within 6 months

Yes Continue

1 2010 ACR-EULAR classification criteria can support early diagnosis. 2 The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. 3 Methotrexate should be part of the first treatment strategy; while combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs. 4 TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab or respective well studied and EMA/FDA approved biosimilars), abatacept, IL-6-inhibitors, or rituximab (under certain conditions); in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDs have some advantages. 5 Current practice would be to start with a bDMARD (in combination with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (Jak-inhibitors). 6 The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine. 7 Efficacy and safety of bDMARDs after Jak-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. 8 Efficacy and safety of a Jak-inhibitor after insufficient response to a previous Jak-inhibitor is unknown.
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Summary: EULAR 2016 Recommendations Update

• Elaborated by rheumatologists from all over the world, patients, health professionals
• Developed for a large target audience
  • Rheumatologists, patients, physicians and other health professionals involved in care for RA patients, rheumatology societies, hospital managers, health insurance representatives, politicians
• Based on 3 systematic literature reviews and expert opinion
• Comprises of 4 overarching principles, 12 recommendations
  • Defines treatment targets and treatment-to-target
  • Develops a hierarchy of therapeutic approach
    • Stratification by risk once the initial csDMARD plus glucocorticoid treatment failed the target
    • All DMARD types: csDMARDs, bDMARDs, tsDMARD and bsDMARD addressed
• High level of evidence - large majority vote for individual items and high level of agreement: 8x >9/10, 4x 8-9/10
• Research agenda
EULAR 2016 Recommendations Update in Perspective

Compared to ACR 2015 update\(^1\), 2016 EULAR recommendations

- Are somewhat clearer about glucocorticoid use
- Recommend to use bDMARDs in combination with csMARDs (MTX) rather than as monotherapy
- Do not distinguish RA patients by disease duration (early vs established) but by treatment phases (csDMARD-naive, csDMARD-experienced, bDMARD-experienced)
- Use prognostic factors for stratification
- But the two sets have come much closer together than the 2008/2010 and 2012/2013 versions and thus closer than ever before

\(^1\)Singh et al, Arthritis Care Res 2016
Acknowledgement

• Epidemiologist: Robert Landewé
• Fellows: Katerini Chatzidionysiou, Jackie Nam, Sofia Ramiro
• Steering Committee and Task Force with particular thanks to Dèsirée van der Heijde