2022 EULAR Recommendations for RA management and tips for implementing guidelines into clinical practice

1 June 15:00–15:20 | Update of the EULAR recommendations on the management of rheumatoid arthritis | Prof. Josef S. Smolen
3 June 16:10–16:30 | Why is implementation of guidelines so difficult/important? | Prof. Loreto Carmona
3 June 16:30–16:50 | How should clinicians use guidelines best? | Dr. Estibaliz Loza

Update of the EULAR recommendations on the management of rheumatoid arthritis
| Prof. Josef S. Smolen, Medical University of Vienna, Austria

Why is the guideline updated?

- With the current rate of advances in clinical development, EULAR needs to update its management recommendations approximately every 3–4 years.
- Specifically, there are three aspects that need to be addressed:
  1. Recommendation on short-term use of glucocorticoids as part of the first treatment strategies—this was different from the ACR 2021 guidelines;
  2. Positioning of JAK inhibitors in patients who respond inadequately to methotrexate due to the safety issue raised by the ORAL Surveillance study of tofacitinib;
  3. Incorporation of new data on switching and tapering of biological disease-modifying antirheumatic drugs (bDMARDs).
### EULAR recommendations for the management of rheumatoid arthritis – 2022 update

Table 1. Updates in the 2022 EULAR recommendations on the management of rheumatoid arthritis

<table>
<thead>
<tr>
<th>Updated recommendations in 2022 (Numbering based on 2019 recommendations)</th>
<th>Evidence for the update</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6</strong></td>
<td>Short-term glucocorticoids should be considered when initiating or changing csDMARDs, in different dose regimens and routes of administration, but should be tapered and discontinued as rapidly as clinically feasible.</td>
</tr>
<tr>
<td></td>
<td>• Data from the 10-year follow-up CARRÉ cohort study and the 16-year CorEvitas registry showed no increased CV risk in patients whose cumulative glucocorticoid dose was limited to ≤1,000 mg.4,5</td>
</tr>
<tr>
<td></td>
<td>• The NORD-STAR study found combination use of methotrexate and glucocorticoids was non-inferior to methotrexate plus bDMARDs in terms of inducing clinical remission.3</td>
</tr>
<tr>
<td></td>
<td>• The 2019 EULAR recommendations on glucocorticoids differ from the 2021 updates to the ACR guidelines for RA management.1</td>
</tr>
<tr>
<td><strong>8</strong></td>
<td>If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a bDMARD should be added; JAK–inhibitors may be considered, but pertinent risk factors must be taken into account.</td>
</tr>
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<td></td>
<td>• The ORAL Surveillance study showed that tofacitinib was associated with increased risk of MACE and malignancy,2 prompting the recommendation to include risk assessment when prescribing JAK inhibitors.</td>
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<tr>
<td></td>
<td>• However, the Corona RA registry showed comparable risk for MACE and malignancy between tofacitinib and bDMARDs.4</td>
</tr>
<tr>
<td><strong>9</strong></td>
<td>bDMARDs and tsDMARDs should be combined with a csDMARD; in patients who cannot use csDMARDs as comedication, IL-6 inhibitors and tsDMARDs* may have some advantages compared with other bDMARDs.</td>
</tr>
<tr>
<td></td>
<td>• Clinical data show that patients continue to benefit after switching to a second IL-6 inhibitor.</td>
</tr>
<tr>
<td></td>
<td>• Risk assessment is recommended for those switching to a JAK inhibitor.</td>
</tr>
<tr>
<td><strong>10</strong></td>
<td>If a bDMARD or tsDMARD has failed, treatment with another bDMARD or a tsDMARD* should be considered, if one TNF–inhibitor or IL-6 receptor inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF-α/IL-6 receptor inhibitor.</td>
</tr>
<tr>
<td></td>
<td>• Clinical data show that patients continue to benefit after switching to a second IL-6 inhibitor.</td>
</tr>
<tr>
<td></td>
<td>• Risk assessment is recommended for those switching to a JAK inhibitor.</td>
</tr>
<tr>
<td><strong>11</strong></td>
<td>After glucocorticoids have been discontinued and a patient is in sustained remission, dose reduction of DMARDs (bDMARDs, tsDMARDs, and/or csDMARDs) may be considered.</td>
</tr>
<tr>
<td></td>
<td>Driven by cost considerations.</td>
</tr>
</tbody>
</table>

Updates versus the 2019 recommendations are in green.

*The following risk factors for CV events and malignancies must be considered when intending to prescribe a JAK–inhibitor: age over 65 years, current or ex-smoker, other CV risk factors, other risk factors for malignancy, risk factors for thromboembolic events. ACR, American College of Rheumatology; bDMARDs, biological disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic DMARDs; CV, cardiovascular; EULAR, European Alliance of Associations for Rheumatology; IL, interleukin; JAK, Janus kinase; MACE, major adverse cardiac event; RA, rheumatoid arthritis; TNF, tumor necrosis factor; tsDMARDs, targeted synthetic DMARDs.
1. 2010 ACR-EULAR classification criteria can support early diagnosis.

2. “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 although more adverse events without added benefit are to be expected, especially if MTX is combined with glucocorticoids.

3. The treatment target is clinical remission according to ACR-EULAR definitions 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 insufficient improvement (less than 50% of disease activity) is seen after 3 months.

4. Sustained remission ≥ 6 months ACR/EULAR index based or Boolean remission.

5. Consider contraindications and risk, TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6R inhibitors, or rituximab (under certain conditions); in patients who cannot use csDMARDs as comedication IL6-inhibitors and tsDMARDs have some advantages.

6. The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAK-inhibitor. Age over 65 years, history of current or past smoking, other cardiovascular risk factors, other risk factors for malignancy, risk factors for thromboembolic events.

7. The most frequency used combination comprises methotrexate, sulfasalazine and hydroxychloroquine.

8. Dose reduction or interval increase can be safely done with bDMARDs and tsDMARDs with little risk of flares, stopping is associated with high flare rates, most but not all patients can recapture their good state upon re-institution of the same bDMARD/tsDMARD, but before all this glucocorticoids must have been discontinued.

9. From a different or the same class.
Why is implementation of guidelines so difficult/important?

| Prof. Loreto Carmona, Rheumatologist and clinical epidemiologist. Scientific director of Inmusc, Spain

- Implementation of guidelines refers to the use of guidelines in clinical practice. But the adherence is low, leading to suboptimal patient outcomes.
  - A population-based longitudinal study revealed that higher adherence to guidelines resulted in lower hospitalization in patients with early RA.\(^7\)
  - While dissemination of evidence-based recommendations is necessary, it is insufficient to influence clinical practices and behaviour.\(^8\)-\(^11\)
  - There is currently limited knowledge in implementation science; more understanding on including factors influencing framework provision and implementation is needed.

How should clinicians use guidelines best?

| Dr. Estíbaliz Loza, Instituto de Salud Musculoesquelética, Madrid, Spain

Implementation science offers an approach to understanding why guidelines are suboptimally applied and may provide insights to help improve guideline adherence in clinical practice.

Suggestions for effective implementation of guidelines

- Check the guideline quality
- Understand the scope
- Make adaptations
- Prioritize those elements that are most important locally
- Use available resources to increase uptake (e.g. leaflets, checklists, courses, clinical sessions)
- Design strategies to help increase uptake in your own environment
- Measure before and after to further refine the implementation
References

10. Portier E, et al. Disease activity outcome measures are only available in half of the electronic medical files of patients with axial spondyloarthritis followed in an outpatient clinic: the results of an audit of a tertiary-care rheumatology department. Rheumatol Int. 2022;42(5):825-829.
Difficult-to-treat rheumatoid arthritis

Difficult-to-treat rheumatoid arthritis
| Prof. Jacob M. van Laar, UMC Utrecht, The Netherlands

- Difficult-to-treat rheumatoid arthritis (D2T RA), according to EULAR, is defined as:

1. Failure of ≥2 b/tsDMARDs with different mechanisms of action, after progression on csDMARD therapy

   AND

2. Presence of signs suggestive of active or progressive disease, defined as displaying ≥1 of:
   
   A. At least moderate disease activity (according to validated composite measures that include joint counts, such as DAS28-ESR>3.2 or CDAI>10)
   
   B. Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other)
   
   C. Inability to taper glucocorticoid treatment (e.g. unable to reduce prednisone dose to <7.5 mg/day or equivalent)
   
   D. Rapid radiographic progression (with or without signs of active disease)*
   
   E. Presence of RA symptoms that reduce quality of life (despite disease being well controlled according to A–D)

   AND

3. Management of symptoms is perceived as problematic by rheumatologist and/or patient

* Rapid radiographic progression: change in van der Heijde-modified Sharp score ≥5 points at 1 year.

bDMARDs, biological DMARDs; CDAI, Clinical Disease Activity Index; csDMARDs, conventional systemic DMARDs; DAS28-ESR, Disease Activity Score-28 for Rheumatoid Arthritis with ESR; DMARDs, disease-modifying antirheumatic drugs; RA, rheumatoid arthritis; tsDMARDs, targeted synthetic DMARDs.

- Approximately 5–20% of the RA population fulfil the EULAR criteria for D2T RA.
- Furthermore, patients with D2T RA often present with comorbidities and extra-articular manifestations, which can lead to inappropriate treatment decisions.
D2T RA versus non-D2T RA

- A prospective, cross-sectional study compared the clinical features between individuals with D2T RA and those with non-D2T RA\(^1\) (table 1):

**Table 1. Clinical features of D2T RA versus non-D2T RA**

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Features of D2T RA vs non-D2T RA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease onset</strong></td>
<td>Early-onset disease more likely</td>
</tr>
</tbody>
</table>
| **Comorbidities**              | Likely to have more comorbidities, including recurrent infections, osteoporosis and gastrointestinal disease  
|                                | More likely to have fibromyalgia and depression                                                  |
| **DMARDs**                     | More failure of DMARDs                                                                           |
|                                | Higher risk of treatment-related adverse events                                                  |
| **Outcomes**                   | Worse physical function, more pain and fatigue, and lower quality of life                         |
| **Predictors of D2T status**   | Low socioeconomic status or education level                                                      |
| **Socioeconomic consequences of D2T status** | Higher economic cost, driven by reduced work productivity and increased need for carers    |

D2T, difficult-to-treat; DMARDs, disease-modifying antirheumatic drugs; RA, rheumatoid arthritis.

Treatment-related adverse events are one of the main causes for treatment non-adherence among patients with D2T RA, and good rapport between patients and healthcare professionals is therefore of critical importance.\(^3\)

**Table 2. To manage D2T RA, a holistic approach is necessary, and the points to consider according to 2022 EULAR guidelines are as follows:**

| 1. If a patient has a presumed D2T RA, the possibility of misdiagnosis and/or the presence of a coexistent mimicking disease should be considered as a first step | 3. Composite indices and clinical evaluation should be interpreted with caution in the presence of comorbidities, in particular obesity and fibromyalgia, as these may directly heighten inflammatory activity and/or overestimate disease activity |
| 2. Where there is doubt on the presence of inflammatory activity based on clinical assessment and composite indices, ultrasonography may be considered for this evaluation | 4. Treatment adherence should be discussed and optimized within the process of shared decision-making |
| 5 | After failure of a second or subsequent b/tsDMARD and particularly after two TNF inhibitor failures, treatment with a b/tsDMARD with a different target should be considered | 8 | In patients with concomitant HBV/HCV infection, b/tsDMARDs can be used and concomitant antiviral prophylaxis or treatment should be considered in close collaboration with the hepatologist |
| 6 | If a third or subsequent b/tsDMARD is being considered, the maximum dose, as found effective and safe in appropriate testing, should be used | 9 | In addition to pharmacological treatment, non-pharmacological interventions (i.e., exercise, psychological, educational and self-management interventions) should be considered to optimize management of functional disability, pain and fatigue |
| 7 | Comorbidities that impact quality of life either independently or by limiting RA treatment options, should be carefully considered and managed | 10 | Appropriate education and support should be offered to patients to directly inform their choices of treatment goals and management |
| 11 | Consider offering self-management programs, relevant education and psychological interventions to optimize the patient's ability to manage their disease confidently |

bDMARDs, biologic DMARDs; D2T, difficult-to-treat; DMARDs, disease-modifying antirheumatic drugs; EULAR, European Alliance of Associations for Rheumatology; HBV, hepatitis B virus; HCV, hepatitis C virus; TNF, tumor necrosis factor; tsDMARDs, targeted synthetic DMARDs; RA, rheumatoid arthritis.

The 2022 EULAR points to consider for the management of D2T RA:

- Determine the presence of persistent signs and symptoms despite the treatment of RA.
- Determine if the patient fulfills the EULAR definition of D2T RA. If the definition is not fulfilled, take the next step following RA treatment recommendations.
- If the case meets the definition of D2T RA, assess the possibility of a misdiagnosis. If there is a possibility, re-diagnose and treat adequately. If there is no misdiagnosis, assess for comorbidities that mimic arthritis signs and symptoms, and/or interfere with arthritis assessment.
- Determine the presence arthritis activity. If the findings are inconclusive, use ultrasonography. If arthritis activity is absent, do not escalate disease-modifying antirheumatic drug (DMARD) treatment and instead increase focus on nonpharmacological treatments.
- If arthritis activity is confirmed, assess treatment adherence. If the patient is adherent to treatment, intensify or switch to another DMARD. Manage comorbidities that limit RA-treatment options. If the adherence is suboptimal, discuss with patient to optimize treatment adherence.
Neuroinflammation and neuropathic pain mechanisms in rheumatoid arthritis

| Prof. Camilla Svensson, Karolinska Universitetssjukhuset, Stockholm, Sweden |

- There is a misalignment between joint inflammation and pain.
  - Joint pain frequently persists in patients with RA despite low or no disease activity.
- The collagen antibody-induced arthritis (CAIA) model\(^5\) shows that there is a shift in the mechanism of pain from the initial inflammatory phase to a neuropathic-like phase where osteoclasts are involved, changing the structure and function of nociceptors. (Table 1)
  - This can be explained by the varying changes of osteoclast activity and innervation during the inflammatory and late phases, and how different interventions influence hypersensitivity.

Collectively, these data showed that non-neuronal cells such as osteoclasts may contribute to pain by generating a more “neuropathic pain”-like state in stages of low-grade inflammation in RA.

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### Table 1. Changes to bone and joint conditions and impact of various interventions in the collagen antibody-induced arthritis (CAIA) model

<table>
<thead>
<tr>
<th>Phase (Day # after mechanical stimulation)</th>
<th>Inflammatory phase (Day 12)</th>
<th>Post-inflammation (neuropathic-like) phase (Day 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHANGES AFTER INDUCTION OF JOINT INFLAMMATION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synovitis</td>
<td>O</td>
<td>X</td>
</tr>
<tr>
<td>BMD, bone volume, trabecular bone mass(^4)</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Osteoclast activity</td>
<td>Increased</td>
<td>No change</td>
</tr>
<tr>
<td>Nerve fibres in periosteum</td>
<td>Increased</td>
<td>Increase during inflammatory phase persisted</td>
</tr>
<tr>
<td>Netrin-1 (an axonal guidance factor) expression</td>
<td>–</td>
<td>Increased vs inflammatory phase</td>
</tr>
<tr>
<td><strong>RESPONSE TO INTERVENTIONS APPLIED AFTER JOINT INFLAMMATION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoclast inhibition</td>
<td>· Does not reverse hypersensitivity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>· No influence on innervation of the periosteum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>· Reverses hypersensitivity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>· Prevents outgrowth of nerves in the periosteum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>· Inhibits netrin-1 mRNA</td>
<td></td>
</tr>
<tr>
<td>Macrophage depletion</td>
<td>–</td>
<td>Does not reverse hypersensitivity</td>
</tr>
<tr>
<td>Netrin-1 neutralization</td>
<td>No effect</td>
<td>· Reverses mechanical hypersensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>· Prevents increase in innervation of periosteum</td>
</tr>
<tr>
<td>Anti-inflammatory agent(^1,2) (e.g. COX inhibitors, TNF inhibitors, HMG81 neutralizing antibodies)</td>
<td>Reverses hypersensitivity</td>
<td>Does not reverse hypersensitivity</td>
</tr>
<tr>
<td>Treatment for neuropathic or neuroplastic pain</td>
<td>Reverses hypersensitivity</td>
<td>Reverses hypersensitivity</td>
</tr>
</tbody>
</table>

CAIA, collagen antibody-induced arthritis; COX, cyclooxygenase; mRNA, messenger RNA; TNF, tumor necrosis factor.
References

Optimizing management in older patients with rheumatic disease

Impact of ageing in rheumatic disease
| Dr. Andrea Giusti, Medical Specialties ASL3 Genova, Italy

2 June 13:35‒13:55 | Treating the elderly: caveats from a geriatricians perspective | Prof. Michael Drey
2 June 13:55‒14:15 | Safety and efficacy of DMARDs in older patients? | Prof. Rik Lories
2 June 14:15‒14:35 | Active ageing: what is it and what we can do for our patient? | Prof. Ivan Bautmans

Treatment goals may differ between older patients with rheumatic disease versus younger patients

<table>
<thead>
<tr>
<th>Elderly patients</th>
<th>Younger patients</th>
</tr>
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<tbody>
<tr>
<td>Treatment focus</td>
<td>Treatment focus</td>
</tr>
<tr>
<td>• Reducing disability</td>
<td>• Lowering disease activity</td>
</tr>
<tr>
<td>• Improving quality of life</td>
<td>• Maintaining or improving work productivity</td>
</tr>
<tr>
<td>• Reducing risk of death</td>
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</tbody>
</table>

• Older patients may also have a different disease course than younger patients, with a tendency for:
  - More severe disease at baseline and at 12 months
  - Lower likelihood of clinical remission
  - Higher likelihood of treatment with conventional synthetic disease modifying antirheumatic drugs (csDMARDs) and steroids instead of biological DMARDs

• Results from clinical trials may not always apply to elderly patients.2–4
• Pharmacodynamics differ in younger versus older patients.4
• Rheumatologists should focus on functional ability and psychosocial health in addition to disease control when treating older adults with rheumatic diseases.

Ageing affects both innate and adaptive immunity

• Ageing increases basal interleukin (IL)-1 and IL-6, with associated increased inflammation and impaired tumour suppression and response to infection.5–7
• Ageing is associated with an increased production of self-reactive T cells and an imbalance of regulatory T cells.6
Treating the elderly: caveats from a geriatrician’s perspective
| Prof. Michael Drey, Clinic of the University of Munich, Germany

Multimorbidity and polypharmacy are the main drivers of outcomes in older patients with rheumatic disease

- Multimorbidity often increases with age, and tends to lead to polypharmacy (the concurrent use of >5 pharmacotherapies).
- The more drugs taken, the lower the response rate, the higher the hospitalization rate and drug-related issues (Figure 1).

Figure 1. Relationship between polypharmacy and adverse event or response rates.

<table>
<thead>
<tr>
<th>Polypharmacy stratified into 3 categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic cohort 83% DMARD comparator arm 17%</td>
</tr>
<tr>
<td>≤5</td>
</tr>
<tr>
<td>6–9</td>
</tr>
<tr>
<td>≥10</td>
</tr>
<tr>
<td>Additional risk per drug</td>
</tr>
<tr>
<td>SAE per 100 years</td>
</tr>
<tr>
<td>17.9</td>
</tr>
<tr>
<td>31.5</td>
</tr>
<tr>
<td>46.2</td>
</tr>
<tr>
<td>HR 1.13</td>
</tr>
<tr>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>EULAR “Good Response” rate, %</td>
</tr>
<tr>
<td>34</td>
</tr>
<tr>
<td>25</td>
</tr>
<tr>
<td>23</td>
</tr>
<tr>
<td>OR 0.92</td>
</tr>
<tr>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

SAE, serious adverse event; EULAR, European Alliance of Associations for Rheumatology.

Inappropriate medication for geriatric patients should be reduced

- FORTA (Fit FOR The Aged) is a tool recommended to improve drug prescription in older patients.
- Functional status along with frailty, gait speed and other pre-existing comorbidities should be considered during prescription.

Safety and efficacy of DMARDs in older patients
| Prof. Rik Lories, Department of Development and Regeneration KU Leuven, University Hospitals Leuven, Belgium

Points to consider in managing older patients with rheumatic disease

- Consider risks of infection, vaccination status, frailty and comorbidities.
- Therapeutic goal and the choice of therapy should be tailored according to the patient’s biological age or presence of particular risk factors for infection (Table 1). Lower dose methotrexate should be considered for elderly patients given that they generally have poor renal function.
Active ageing: what is it and what we can do for our patient?

| Prof. Ivan Bautmans, Vrije Universiteit Brussel (VUB), Belgium |

Two of the most important aims when managing older patients with RMDs are:

- To preserve locomotor capacity i.e. balance, muscle and joint function. 21
- To maintain vitality that incorporates energy and metabolism, neuromuscular strength and the immune/inflammation/stress response. 22

Sarcopenia underpins frailty among the elderly and contributes significantly to loss of locomotor function and vitality. 23

Inflammageing is the concept of the inflammation of ageing, which contributes to loss of muscle mass and increased adiposity. 24

Exercise (mainly resistance training) can reduce inflammageing, resulting in reductions in IL-6 and C-reactive protein and a shift from a pro-inflammatory to an anti-inflammatory profile in older adults. 25

Regular exercise is important to maintain these benefits, with measurable changes seen within 6 to 12 weeks of intervention. 26, 27

CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; CV, cardiovascular; IL, interleukin; MACE, major adverse cardiac events; TNF, tumour necrosis factor.

### Table 1. Key considerations when using advanced therapies for rheumatoid arthritis. 16-20

<table>
<thead>
<tr>
<th>Class of therapy</th>
<th>Key considerations</th>
</tr>
</thead>
</table>
| **TNF inhibitors**<sup>16,17</sup> | - Associated with mild risk of infection (potentially to a lesser extent than csDMARDs or steroids)  
- Contraindicated in severe heart failure |
| **IL-6 inhibitors**<sup>24,25</sup> | - Affect lipid levels in blood (impact on CV risk unknown)  
- Interact with corticosteroids  
- Affect CRP as marker of infections  
- Diverticulitis and skin infections |
| **Abatacept**<sup>23</sup> | - More side effects vs. other DMARDs (a numerical increase in the risk of psoriasis and overall malignancy) and should not be considered in patients >75 years |
| **JAK inhibitors**<sup>20</sup> | - Increased risk of varicella zoster infection and other infections  
- Increased risk of thrombo-embolic events  
- Increased risk of MACE and cancer (among >65 years) reported in the ORAL Surveillance study of tofacitinib |
| **IL-17 or IL-23 inhibitors** | - No known issues so far but more data are needed |

*See references 16-27 for detailed information.*
References

After the emergence of biological disease-modifying antirheumatic drugs (bDMARDs), came Janus kinase (JAK) inhibitors. With them came the expectation that they:

- Had strong efficacy overall and as monotherapy
- Had a fast onset of action
- Helped patients achieve clinical remission
- Inhibited disease progression

**Promise 1: Efficacy**

[Fulfilled] In rheumatoid arthritis (RA), JAK inhibitors are associated with favourable efficacy among insufficient responders (IRs), compared to methotrexate (MTX) or tumor necrosis factor (TNF) inhibitors, and long-term response is possible.

[Partially fulfilled] JAK inhibitors induce remission and delay radiographic progression in some but not all patients.

- Before the introduction of JAK inhibitors, efficacy (in terms of American College of Rheumatology [ACR] response criteria) was comparable across bDMARDs in RA.²
- Studies so far have shown that JAK inhibitors have at least similar efficacy to bDMARDs in patients with RA who had insufficient response to MTX or TNF inhibitors.³,⁴
  - In the MTX-IRs population:
    - Fast onset: one study showed that over 90% of patients with RA achieved ACR20 within 4 weeks of treatment with a JAK inhibitor⁶
    - Strong efficacy as monotherapy: another study showed that with JAK inhibitor monotherapy, approximately 60% of patients achieved ACR20 within 3 months³
    - Studies found JAK inhibitors to be associated with numerically⁷ or statistically⁸ higher ACR response rates than adalimumab; response to JAK inhibitors was maintained from 12 to 52 weeks⁸
  - A further study showed treatment with a JAK inhibitor induced Disease Activity Score-28 (DAS28) remission at Month 3 in TNF-IRs.⁴
- Consequently, the 2019 European League Against Rheumatism (EULAR) recommendations for RA management added JAK inhibitors as an alternative to bDMARDs; this recommendation remains in the 2022 update.⁷
- Clinical remission (by Simple Disease Activity Index, Clinical Disease Activity Index, or DAS28) with JAK inhibitors among MTX-IRs ranged from 5 to 15% and disease progression was observed in some patients.¹⁴ Radiographic progression was also slowed down with JAK inhibitors in most patients, although progression was still observed in 10–15% of patients.
Promise 2: Adherence
[Fulfilled] Longer adherence of JAK inhibitors than TNF inhibitors.

- Only 50% of patients had sustained therapy with TNF inhibitors in 2 years, largely because of loss of efficacy.\(^9\)
- In contrast, with JAK inhibitors, the “half-life” of adherence was approximately 5 years, irrespective of whether they were used alone or in combination with MTX.\(^9\)
  - This may be related to the fact that JAK inhibitors are small molecules and not immunogenic.

Promise 3: Safety
[Fulfilled] With the exception of herpes zoster reactivation, JAK inhibitors have a generally benign safety profile compared with bDMARDs.
[Need more data] In at-risk populations however, JAK inhibitors may be associated with increased risk of infections, deep vein thrombosis, malignancies and major adverse cardiac events (MACE).

- Combined data showed that JAK inhibitors were not associated with an increased risk of malignancies, serious infections, or MACE when compared with bDMARDs.\(^{10-14}\)
  - An increased risk of reactivation of herpes zoster was observed.
- Meta-analyses found no increased risk of MACE or malignancies with JAK inhibitors over bDMARDs.\(^{13,15,16}\)
- The German RABBIT registry found no increased risk of MACE with JAK inhibitors over TNF inhibitors in a real-world setting, even among those with high cardiovascular (CV) risk.\(^{18}\)
- However, in the ORAL Surveillance and the STAR-RA study, tofacitinib was associated with an increased risk of CV events and malignancies among patients with RA with CV risk factor.\(^{17,18}\)
  More surveillance and real-world data are needed.

Promise 4: Simple mechanism of action
[Partially fulfilled] JAK inhibitors are competitive inhibitors of adenosine triphosphate (ATP) but are not 100% specific and selective.\(^{19,20}\) Selectivity reduces with higher doses.

- JAKs are the second largest class of proteins in human mammals, modulating signals of inflammatory cytokines (JAK1), growth signalling in blood cells (JAK2) and T cell cytokines (JAK3).
- JAKs exist as dimers/trimers in cells; however, no JAK1 dimer exists in cells – JAK1 only combines with other JAK isoforms.
References


7. Smolen JS. Update of the EULAR recommendations on the management of rheumatoid arthritis. Presented at: European Alliance of Associations for Rheumatology (EULAR) 2022; 1-4 June 2022; Copenhagen, Denmark.


Sarcopenia in the clinical expression of rheumatic diseases and its treatment

2 June 15:50‒16:10 | Primary sarcopenia in rheumatoid arthritis and osteoarthritis patients | Prof. Alfonso Jose Cruz-Jentoft
2 June 16:10‒16:30 | Molecular and cellular mechanisms regulating muscle regeneration | Prof. James White
2 June 16:30‒16:50 | JAK-STAT pathway inhibition in rheumatoid arthritis: the creatine kinase paradox | Dr. Aranzazu Mediero

Primary sarcopenia in rheumatoid arthritis and osteoarthritis patients
| Prof. Alfonso Jose Cruz-Jentoft, Hospital Universitario Ramón y Cajal (IRICYS), Madrid, Spain

Definition of sarcopenia
- In 2010, the concept of sarcopenia changed from only ‘low muscle mass’ to ‘low muscle mass and low muscle function’. An operational definition of sarcopenia by the European Working Group on Sarcopenia in Older People (EWGSOP2) is as follows:

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Low muscle strength + Low muscle quantity/quality + Low physical performance
Probable sarcopenia
Definite sarcopenia
Severe sarcopenia
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Link between sarcopenia, rheumatoid arthritis (RA) and osteoarthritis (OA)
- A meta-analysis showed that up to 25.4% of patients with RA had sarcopenia. Cytokine pathways are associated with sarcopenia development in patients with RA.
- Patients with RA with sarcopenia are at a higher risk of falls, fractures, low bone mineral density, cardiometabolic risk and endothelial dysfunction than those with RA only.
- Knee OA may increase the risk of sarcopenia due to pain, immobility, preinflammatory cytokines, and myostatin.

How to manage sarcopenia
- Resistance-based exercise prevents sarcopenia by improving lean mass, strength, and physical function.
- Recommendations suggest increasing protein intake to:
  - 1.0‒1.2 g/kg/day among adults >65 years
  - 1.2‒1.5 g/kg/day among those with acute or chronic diseases
  - up to 2 g/kg/day for those with severe illness or injury or marked malnutrition
- Specifically for patients with RA, general recommendations for the prevention and treatment of sarcopenia in elderly patients should apply.
- For patients with OA, exercise alone or in combination with dietary intervention, may have a positive effect in preventing sarcopenia, especially among those patients with comorbid obesity.

Link between sarcopenia, RA and OA:
- Patients with RA are at risk of sarcopenia.
- Knee OA may increase the risk of sarcopenia due to pain, immobility, preinflammatory cytokines, and myostatin.
Molecular and cellular mechanisms regulating muscle regeneration

| Prof. James White, Duke University School of Medicine, United States of America |

- Skeletal muscle has a remarkable regenerative capacity and satellite cells play a critical role in muscle regeneration.
- The immune system is involved in the regeneration process; following a micro-tear, immune cells enter a proinflammatory (clear-up) phase, then a regenerative (repair) phase before resolution.
- In a mechanistic view of a mouse model with sarcopenia and RA, muscle enters a proinflammatory state, with increased interleukin (IL)-6 levels, reduced expression of the MyoD and Myogenin genes, and increased expression of the Atrogin-1 gene (promoting muscle degradation).14
  - The opposite pattern was seen during an endurance-based exercise.
- Research shows that satellite cells from patients with RA generally appear normal, and muscle in patients with RA is inherently healthy.25

JAK-STAT pathway inhibition in rheumatoid arthritis: The creatine kinase paradox

| Dr. Aranzazu Mediero, FIIS-Fundación Jiménez Díaz, Madrid, Spain |

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway has antagonistic effects on skeletal muscle (Figure 1).16,17
- Maintaining the balance of the two pathways is important for healthy skeletal muscle homeostasis.
- JAK1/STAT1 is activated during satellite cells, proliferation state, while JAK2/STAT3 promotes satellite cell differentiation.

Creatine kinase (CK) is involved in the myofiber formation process18 and could be a biomarker of cumulative muscle mass loss in chronic inflammation
- CK levels are associated with lean muscle mass, and decreased CK levels have been observed in frail patients.

Increased CK levels after treatment with JAK inhibitors may be associated with an increase in muscle mass
- Increased CK levels after treatment with JAK inhibitors has been observed in patients with inflammatory conditions including RA.
- Tofacitinib increases muscle mass in an antigen-induced arthritis model of sarcopenia.
  - Tofacitinib attenuated JAK/STAT activation, decreased atrogene expression, and restored muscle cell differentiation markers to baseline.
  - The increase in muscle mass was accompanied by an increase in CK presence, supporting the role of CK as a valuable marker of muscle gain following treatment with JAK inhibitors.
References

Can we induce drug-free remission in inflammatory arthritis?

Inflammatory arthritis end-game: remission, lasting remission, and cure

| Prof. Ronald van Vollenhoven, Chair of the Department of Rheumatology and Clinical Immunology at the Amsterdam University Medical Centers (UMC), The Netherlands

- Treatment-free remission or cure in rheumatoid arthritis (RA) does occur but is rare.
  - The BeSt trial, in which patients with recent-onset active RA were followed up for 4 years, demonstrated drug-free remission in 8–18% of patients regardless of treatment strategy.  
- Guidelines provide recommendations on initiating, selecting, and stepping up therapy during active disease, but when and how to step down treatment after achieving remission is less well defined.
- The likelihood of treatment-free remission may increase with first-line use of biological disease-modifying antirheumatic drugs (bDMARDs) but definitive evidence is lacking.
  - The PRIZE study showed that after stopping treatment for 6 months, the remission rate in those who had received induction therapy with etanercept plus methotrexate (MTX) was substantially higher than those who had received MTX only or no treatment at all.  
  - A meta-analysis suggested that a tumor necrosis factor inhibitor plus MTX may be associated with a higher likelihood of achieving treatment-free remission than MTX only, but statistical significance was not achieved.  
  - The NORD-STAR study confirmed that bDMARDs were associated with improved efficacy versus conventional therapy, but it is unknown if the benefit is maintained upon cessation.  

How successful are tapering strategies in real life?

| Prof. Robert B.M. Landewé, Amsterdam University Medical Center, The Netherlands

- The 2022 European Alliance of Associations for Rheumatology (EULAR) recommendations for RA management included specific guidance on tapering:
  - Recommendation 11: After glucocorticoids have been discontinued and a patient is in sustained remission, dose reduction of DMARDs (bDMARDs, targeted synthetic DMARDs [tsDMARDs] and/or conventional synthetic DMARDs [csDMARDs]) may be considered.
  - Treatment tapering has been assessed in multiple studies (Table 1).  

Highlights from debate about drug-free remission in inflammatory arthritis

- While studies provided insights on potential outcomes with varying tapering strategies, they do not provide concrete solutions on how to taper individual patients – more real-world experience is needed.

**Table 1. Outcomes of different tapering trials in rheumatoid arthritis.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Endpoint</th>
<th>Radiographic progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEAM-RA</strong></td>
<td>ETN + MTX</td>
<td>SDAI remission during 48 weeks</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>ETN withdrawal + MTX</td>
<td></td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>ETN + MTX withdrawal</td>
<td></td>
<td>53%</td>
</tr>
<tr>
<td></td>
<td>No withdrawal</td>
<td></td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>· 50% of patients with RA who received ETN plus MTX and subsequently discontinued MTX were in sustained SDAI remission over 48 weeks.</td>
<td></td>
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<tr>
<td></td>
<td>· 70–80% and 92–100% of patients regained SDAI remission and low disease activity, respectively, after retreatment.</td>
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<tr>
<td><strong>TARA</strong></td>
<td>TNFi + csDMARDs</td>
<td>Flare-free during 104 weeks</td>
<td>67% (yr 1) 39% (yr 2)</td>
</tr>
<tr>
<td></td>
<td>csDMARD tapering (yr 1) then TNFi tapering (yr 2)</td>
<td></td>
<td>50% (yr 1) 53% (yr 2)</td>
</tr>
<tr>
<td></td>
<td>TNFi tapering (yr 1) then csDMARD tapering (yr 2)</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>· Over a 2-year tapering period, the sequence in which drugs are tapered may not matter.</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>· Less than 1 in 3 patients achieved drug-free remission.</td>
<td></td>
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<tr>
<td><strong>ARCTIC REWIND</strong></td>
<td>TNFi + csDMARDs</td>
<td>DAS44 &gt;1.6-based cumulative flare rate at 12 months</td>
<td>Tapering: 26% Continuation: 6%</td>
</tr>
<tr>
<td></td>
<td>csDMARD: 50% tapering vs. continuation</td>
<td></td>
<td>More progression with tapering</td>
</tr>
<tr>
<td></td>
<td>TNFi: 50% tapering then stop vs. continuation</td>
<td></td>
<td>Tapering: 63% Continuation: 5%</td>
</tr>
<tr>
<td></td>
<td>· Compared with csDMARD tapering, tapering TNFi may be associated with more flares.</td>
<td></td>
<td>Similar</td>
</tr>
<tr>
<td></td>
<td>· csDMARDs remain an important anchor therapy, as tapering csDMARDs may be associated with radiographic progression.</td>
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</tbody>
</table>

csDMARDs, conventional disease-modifying antirheumatic drugs; DAS, Disease Activity Score; ETN, etanercept; MTX, methotrexate; RA, rheumatoid arthritis; SDAI, Simple Disease Activity Index; TNFi, tumor necrosis factor inhibitor; yr, year.

- Biomarkers (e.g., regulatory T cells) or imaging technologies may help identify patients who are more likely to achieve drug-free remission, but clinical and patient-reported outcomes should be considered.
- Early treatment, however, is associated with improved outcomes.
- Smoking cessation programs should be offered to patients with rheumatic diseases, as smoking, unequivocally, affects RA disease progression and reduces chance of remission.
- Drug-free remission is possible even though therapies against RA largely work by suppressing rather than eradicating inflammation.
References


