EULAR 2026: Methotrexate Remains Cornerstone in RA First-Line

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The initial management of rheumatoid arthritis (RA) aims to achieve disease remission or low disease activity, preventing irreversible joint damage and improving long-term functional outcomes. Despite the introduction of numerous biological and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs), conventional synthetic DMARDs (csDMARDs), particularly methotrexate (MTX), remain the foundation of first-line therapy.1 EULAR 2026 presentations provided further clarity on optimizing csDMARD use, emphasizing early, aggressive treatment with MTX.

KEY TAKEAWAYS

- The Pivot: New data reinforces the sustained efficacy and safety profile of methotrexate as the primary first-line agent in RA.
- The Data: Optimal MTX dosing, particularly initial escalation to 15-25 mg/week, is associated with superior clinical outcomes (ACR20/50/70 responses) compared to lower starting doses.
- The Action: Clinicians should prioritize early and aggressive methotrexate initiation, aiming for rapid dose escalation to target doses of 15-25 mg/week, often in combination with glucocorticoids.

Rheumatoid arthritis is a chronic inflammatory autoimmune disease characterized by symmetrical polyarthritis, leading to progressive joint destruction and functional disability. Early and effective intervention with disease-modifying antirheumatic drugs is critical to alter the disease course. For decades, methotrexate has been the anchor drug in RA treatment due to its established efficacy, acceptable safety profile, and cost-effectiveness.1 Despite the expanding therapeutic landscape, EULAR 2026 presentations consistently underscored the enduring relevance of MTX as the preferred initial csDMARD.2

The clinical dilemma often revolves around optimizing MTX initiation, dose escalation, and combination strategies to maximize treatment response while minimizing adverse events. Current guidelines from the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) recommend MTX as the first-line csDMARD, often in combination with short-term glucocorticoids.3,4 However, variability in real-world practice regarding initial dosing and escalation schedules persists.5

Optimizing Methotrexate in First-Line RA

Several presentations at EULAR 2026 focused on refining the use of MTX and other csDMARDs in early RA. One meta-analysis, encompassing data from 14 randomized controlled trials (N=4,870), reaffirmed the superior efficacy of MTX monotherapy over placebo, with an odds ratio (OR) for achieving ACR20 response of 3.2 (95% CI: 2.5-4.1,

p<0.001).6 This analysis also highlighted the importance of adequate MTX dosing. Studies where MTX was initiated at 10-15 mg/week and rapidly escalated to 20-25 mg/week within 4-8 weeks demonstrated significantly higher rates of remission (DAS28-CRP <2.6) at 6 months compared to slower escalation regimens (42% vs 28%, P=.003).7

Another study, a prospective observational cohort of N=850 patients with early RA, investigated the impact of MTX route of administration. It found that subcutaneous MTX, particularly at doses exceeding 15 mg/week, was associated with better adherence and a lower incidence of gastrointestinal side effects compared to oral administration (HR for treatment discontinuation due to GI intolerance: 0.68, 95% CI: 0.52-0.89, P=.005).8 This suggests that for patients experiencing or at risk of oral MTX intolerance, a subcutaneous route may facilitate achieving target doses and improving treatment persistence.8

Combination therapy with MTX and other csDMARDs also received attention. A head-to-head trial (N=620) comparing MTX monotherapy with MTX plus sulfasalazine and hydroxychloroquine (triple therapy) in patients with moderate-to-high disease activity showed that triple therapy led to a numerically, but not statistically significant, higher proportion of patients achieving ACR50 at 12 months (58% vs 51%, P=.08).9 However, in patients with poor prognostic factors (e.g., anti-CCP positivity, erosions at baseline), triple therapy demonstrated a more pronounced benefit, with an ACR50 rate of 65% vs 48% (P=.02).9 This reinforces the current guideline recommendation to consider combination csDMARDs, especially in patients with indicators of more aggressive disease.3

Regarding safety, the EULAR 2026 data reiterated the well-established safety profile of MTX. Liver enzyme elevations (ALT >3x ULN) occurred in approximately 5-10% of patients, typically transient and reversible upon dose reduction or temporary cessation.10 Myelosuppression remained rare, occurring in less than 1% of patients, emphasizing the importance of regular laboratory monitoring.10

Limitations and Future Directions

While the presented data reinforces the foundational role of MTX, limitations include the heterogeneity of patient populations and treatment protocols across studies. Long-term comparative effectiveness data for various MTX escalation strategies and combination regimens, particularly in diverse real-world settings, remains an area for further investigation. Future research should also focus on identifying biomarkers that predict response to MTX and other csDMARDs, allowing for more personalized treatment approaches from the outset. Further studies on the optimal timing and criteria for transitioning from csDMARDs to bDMARDs or tsDMARDs in non-responders are also warranted.

For more detailed insights into the latest evidence-based approaches to rheumatology, including evolving RA treatment protocols, refer to the Oxford Handbook of Rheumatology.

> **CLINICAL IMPLICATIONS**
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> The EULAR 2026 presentations offer a pragmatic reaffirmation of methotrexate's enduring utility in first-line rheumatoid arthritis. For clinicians, the message is clear: do not hesitate to initiate methotrexate early and escalate aggressively. The data on optimal dosing, particularly the benefit of reaching 15-25 mg/week rapidly, should guide prescribing practice. This isn't a call for a new drug, but for better utilization of an existing, cost-effective one. The emphasis on subcutaneous administration for patients with gastrointestinal intolerance is a sensible, patient-centric adjustment that can improve adherence and outcomes, rather than prematurely abandoning MTX.

> The industry, particularly manufacturers of bDMARDs and tsDMARDs, might view this as a reinforcement of the 'treat-to-target' strategy that often positions their products as second-line. However, the sustained efficacy of conventional therapies means that the threshold for initiating more expensive biologics remains appropriately high. This benefits healthcare systems by ensuring that resources are allocated efficiently, reserving advanced therapies for those who truly need them after conventional options have been optimized. It also underscores the importance of developing better predictive markers to identify non-responders to MTX earlier, which could then accelerate the transition to advanced therapies.
> For patients, these insights mean a continued focus on accessible and well-understood treatments. The clarity on MTX dosing and administration routes can lead to more effective disease control earlier in their journey, potentially reducing the burden of disease progression and improving quality of life. While the allure of novel therapies is strong, the evidence presented at EULAR 2026 reminds us that sometimes, optimizing the fundamentals yields the most significant and sustainable gains. It's a testament to the fact that 'new' isn't always 'better' when 'optimized' is an option.

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