

Achievement of minimal disease activity in psoriatic arthritis according to the time of administration of synthetic disease-modifying antirheumatic drugs, a comparative analysis of the efficacy of oral and subcutaneous methotrexate.

Data from the All-Russian Psoriatic Arthritis Registry

Korotaeva T.V.¹, Loginova E.Yu.¹, Gubar E.E.¹, Korsakova Yu.L.¹, Sedunova M.V.²,
Pristavsky I.N.², Kushnir I.N.³, Umnova I.F.⁴, Kudishina S.S.⁵

¹V.A. Nasonova Research Institute of Rheumatology, Moscow; ²Clinical Rheumatology Hospital Twenty-Five, Saint Petersburg; ³S.V. Belyaev Kemerovo Regional Clinical Hospital, Kemerovo; ⁴Regional Clinical Hospital, Omsk; ⁵Vladivostok Clinical Hospital Two, Vladivostok
¹34A, Kashirskoe Shosse, Moscow 115522, Russia; ²30, Bolshaya Pod'yacheskaya St., Saint Petersburg 190068, Russia; ³22, Oktyabrsky Prospekt, Kemerovo 650000, Russia; ⁴3, Berezovaya St., Omsk 644111, Russia; ⁵57, Russkaya St., Vladivostok 690105, Russia

The goal of psoriatic arthritis (PsA) therapy is to achieve remission or minimal disease activity (MDA). According to the EULAR guidelines, synthetic disease-modifying antirheumatic drugs (sDMARDs), methotrexate (MTX) in particular, are first-line therapy for PsA.

Objective: to study the rate of MDA achievement after initiation of sDMARD therapy in patients with early- and late-stage PsA and the efficacy of oral and parenteral MTX.

Patients and methods. The investigation enrolled 253 patients (93 men and 160 women) diagnosed with PsA who met the appropriate 2006 CASPAR (Classification criteria for Psoriatic ARthritis) criteria and were recorded in the All-Russian PsA Registry. The median (Me) age was 47 (Min 20 – Max 82) years. All the patients took sDMARDs: MTX (n=211) that was received orally (as tablets) (n=102) and parenterally (n=109); leflunomide (n=7); sulfasalazine (n=24); apremilast (n=10); and tofacitinib (n=1). According to the disease duration at sDMARD treatment initiation, the patients were divided into two groups. Group 1 included 165 patients with an early PsA duration of less than 2 years and Group 2 consisted of 88 patients with a disease duration of >2 years. The efficiency of oral and parenteral MTX was evaluated in 182 patients (68 men and 114 women). Every 6 months, the patients underwent a standard rheumatology examination that included PsA activity assessment. The efficiency of MTX therapy was evaluated from MDA achievement (5 out of the 7 criteria) in the patients.

Results and discussion. After sDMARD prescription, MDA was achieved in 39 (24%) of the 165 patients with early PsA and in 4 (5%) of the 88 long-term patients. The patients who started sDMARD at an early stage of the disease were significantly more likely to achieve MDA than those with late-stage PsA (odds ratio (OR) 6.5; 95% confidence interval (CI) 2.2–18.9). At 11 years after sDMARD therapy initiation, the cumulative MDA achievement rate in the patients with late-stage disease was 5% (p<0.05). MDA was achieved by 16.5% of the 182 patients receiving oral or subcutaneous MTX. MDA was observed in 25 (31%) patients who received parenteral MTX and in only 5 (5%) patients who took oral MTX. The patients who received parenteral MTX were significantly more likely to achieve MDA than those who took oral MTX as tablets (OR 8.8; 95% CI 3.2–24.3). Following 27-month parenteral MTX therapy, the cumulative rate of MDA achievement was 48%, whereas after oral MTX treatment, that was 7% (p<0.05). In the patients who achieved MDA, the mean dose of parenteral MTX was 17 mg/week, and in those who failed, that was 15 mg/week. The mean dose of oral MTX was 15 mg/week, regardless of MDA achievement.

Conclusion. The administration of sDMARD at an early stage of PsA lasting less than 2 years allows MDA to be achieved significantly more often and faster than at later stages of the disease. Among sDMARDs, preference is mostly given to the use of MTX in real clinical practice; the treatment with the latter enables 16.5% of patients to achieve MDA. Parenteral MTX significantly enhances the efficiency of therapy and can achieve MDA in almost one third (31%) of patients.

Keywords: psoriatic arthritis; minimal disease activity; synthetic disease-modifying antirheumatic drugs; methotrexate.

Contact: Tatiana Viktorovna Korotaeva; tatianakorotaeva@gmail.com

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Psoriatic arthritis (PsA) is a chronic inflammatory disease of the joints, spine, and entesis, which is usually observed in psoriasis patients. Due to the progressive lesion of the musculoskeletal system and skin, PsA has a negative impact on the patient's working ability, quality of life, and social adaptation. [1] A PsA therapy aims at achieving remission, low or minimal disease activity (MDA). According to modern concepts, the early start of a medication in active PsA is associated with better clinical and radiological outcomes and has a significant positive effect on the prognosis of the disease. [2–4] The 2019 EULAR (European League Against Rheumatism) guidelines propose methotrexate (MTX) as the first synthetic basic disease-modifying anti-rheumatic drugs to be used in patients with polyarthritis and skin lesions. [5] Data on the use of MTX in real clinical practice are discordant. Only single randomized controlled trials (RCTs) prove its efficacy in PsA. However, the widespread use of MTX is associated with its supposed efficacy shown in psoriasis and rheumatoid arthritis, wide availability, and affordability.

The **purpose** of our research was to study the frequency of achieving MDA after the start of a sDMARDs therapy in patients with early and advanced PsA included in the All-Russian PsA Registry, as well as to evaluate the oral and parenteral MTX efficacy.

Patients and methods. 253 (93 male and 160 female) PsA patients were enrolled in the study, whose diagnosis meets the 2006 CASPAR (Classification criteria for Psoriatic Arthritis) criteria, and who have been registered in the All-Russian PsA Registry. The median patients' (Me) age was 47 (range 20–82) years old. All patients received sDMARDs: 211 (83,4%) patients took MTX, 102 of them orally and 109 parenterally (29 IM, 80 SC); 7 took leflunomide, 24 took sulfasalazine, 10 took apremilast, and 1 patient took tofacitinib. Patients were categorized into two groups depending on the duration of their disease at the time of sDMARDs initiation. Group 1 included 165 patients with early PsA lasting for ≤ 2 years, and group 2 included 88 patients with the disease lasting >2 years.

Oral and parenteral MTX efficacy was additionally evaluated in 182 patients (68 male and 114 female). Of these, 102 (56%) had MTX as tablets, the remaining 80 (44%) had it parenterally.

The proportion of tender joints (TJC, tender joint count) out of 78 was counted at the baseline and then once every 6 months, as well as swollen joints (SJC, swollen joint count) out of 76, the Ritchie index, the severity of joint pain and the patient and the doctor's overall assessment of the disease activity in accordance with the Visual Analog Scale (VAS), the number of inflamed entesis was calculated using the LEI (Leeds Enthesitis Index), the HAQ functional index (The Health Assessment Questionnaire), the level of CRP, mg/L, in blood serum and ESR (mm/h, according to Westergren).

The proportion of psoriatic skin lesions was estimated under BSA (Body Surface Area, from 0 to 100%). If BSA was $>3\%$, the PASI (Psoriasis Area and Severity Index) was calculated scoring from 0 to 72.

To assess PsA activity, the MDA criteria were used: TJC ≤ 1 , SJC ≤ 1 , PASI ≤ 1 or BSA ≤ 3 , patient pain score ≤ 15 mm, overall assessment of the disease activity ≤ 20 mm, HAQ ≤ 0.5 , number of inflamed entesis ≤ 1 . [10, 11] The number of patients who achieved MDA (in 5 criteria out of 7) or remission under DAPSA (Disease Activity Psoriatic Arthritis score) ≤ 4 was determined once during the follow-up during the MTX therapy.

Data statistical processing was performed using the program Statistica 10. At that, the average values of the parameters (M) and the standard deviation (SD) were calculated. When the distribution differed from the normal one, the median (Me [25th; 75th percentiles]), 95% CI, and Min-Max were calculated. The cumulative Kaplan–Meyer analysis, the Breslow, Tarone–Ware, and Log Rank tests were performed. The differences were considered statistically significant at $p < 0.05$.

Results. 43(17%) out of 253 PsA patients achieved MDA during sDMARD treatment. Comparative analysis showed that MDA was achieved significantly more frequently in group 1 where it was observed in 24% of (39 out of 165) patients than in group 2 where it was observed in 5% of (4 out of 88) patients; OR 6.5; 95% CI 2.2–18.9. The cumulative frequency of achieving MDA was 42% in early PsAs, 21 months into the sDMARD therapy, while it was 5% in advanced PsAs, 11 years into the sDMARD therapy, which was significantly less frequent compared to patients with early PsA ($p < 0.05$, Breslow, Tarone–Ware tests; Fig. 1).

Only 16.5% of the 182 patients treated with oral or parenteral MTX achieved MDA. 25 (31%) of the 80 patients who were administered MTX parenterally achieved MDA, while the remaining 55 (69%) did not. Only 5 (5%) of the 102 patients treated with oral MTX achieved MDA. MDA was observed significantly more frequently during parenteral MTX than during oral MTX (OR 8.8; 95% CI 3.2–24.3). The cumulative frequency of achieving MDA was 48% during 27 months of parenteral MTX therapy, and 7% during oral administration of MTX ($p < 0.05$). (Fig. 2) The median subcutaneous MTX dose in patients who achieved MDA was 17 mg/week (range 10–25), in those who did not achieve MDA it was 15 mg/week (range 10–20). The dose of oral MTX was 15 mg/week (range 10–20) irrespective of achievement of MDA.

Discussion. In clinical guidelines, the goal of a PsA therapy is defined as achieving remission or MDA. [1, 5] Data from PsA registries indicate a low level of achievement of PsA therapy goals in real clinical practice. For example, only 23% of 148 patients in the American CORRONA registry [6] achieved MDA during the follow-up period of 15.7 months. In the all-Russian RU-PsART registry, MDA was observed in 22% of patients (60 out of 274) during 11 months of follow-up on average. [7] In our opinion, low incidence of MDA in real clinical practice can be explained by infrequent prescription of active therapy in early disease, when there is a window of opportunity to change the course of the disease.

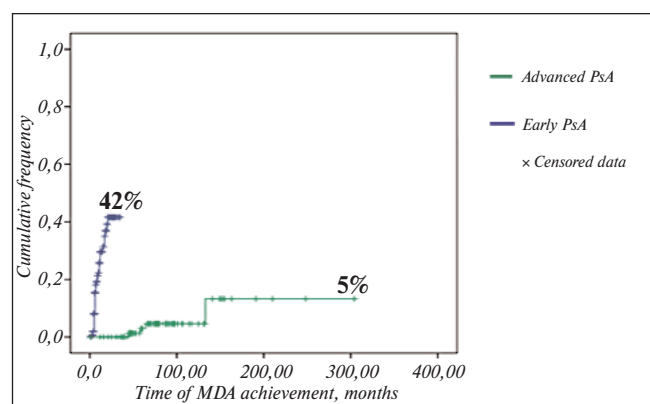


Fig. 1. The cumulative rate and time of MDA achievement after starting sDMARD therapy in early and late PsA

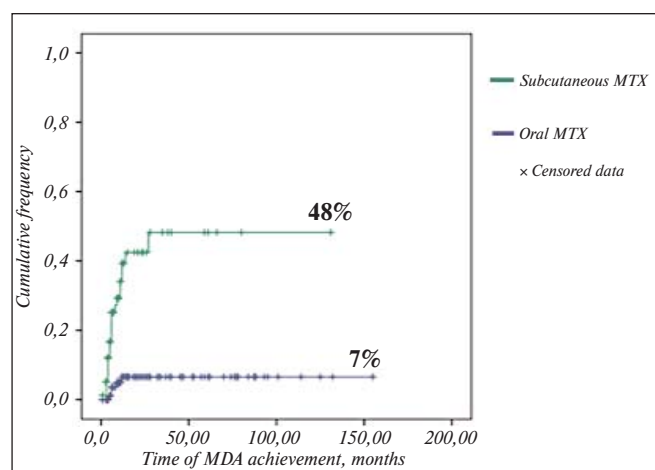


Fig. 2. The cumulative rate and time of MDA achievement in patients with PsA after starting therapy with oral and subcutaneous MTX

The results of this study showed that the prescription of sDMARD allows achieving MDA only in 17% of PsA patients in real clinical practice. Meanwhile, patients with early PsAs are significantly more likely and faster to achieve MDA during treatment with sDMARD than chronic ones.

Among the sDMARDs recommended as a PsA treatment, MTX is the first-line product, despite the lack of evidence and conflicting data on its efficacy in PsA. An analysis of treatments PsA patients receive in real clinical practice in Russia showed that 77.5% of them take sDMARDs, mainly MTX (83%). [8]

In the report of B.J. Sheane et al., [9] only 29 (17.4%) out of 167 PsA patients achieved MDA by 6 months of MTX therapy, 97 (58.1%) achieved SJC ≤ 1 , and 138 (82.6%) achieved PASI ≤ 1 . Only 22 (13.2%) patients assessed the overall disease activity ≤ 20 mm on VAS. Inflammatory pain in the lower back and dactylitis were associated with a low rate of achieving MDA.

Efficacy of MTX as part of the treatment strategy to achieve the goal (T2T) was analyzed in 206 patients with early peripheral PsA in TICOPA, an open multicenter RCT. [10] 188 (91.2%) patients received the MTX monotherapy during the first 12 weeks, including 104 patients who were administered a dose of >15 mg/week, of which only 5 were administered it subcutaneously. 40.8% of patients achieved ACR20, 18.8% achieved ACR50 and 8.6% achieved ACR70 by 12 weeks of therapy; 22.4% achieved MDA, 27.2% achieved improvement in skin score and PASI75. The proportion of patients who achieved ACR20, ACR50 and PASI75 tended to increase among those receiving MTX at a dose of >15 mg/week.

In our study, MDA was observed in 16.5% of patients treated with MTX, which is congruent with the results of the Toronto PsA cohort. [9] However, a comparative analysis of MTX administrations showed benefits of prescribing parenteral MTX, in which MDA was achieved in 31% of cases compared to 5% in oral administration.

Parenteral MTX increases its bioavailability leading to rapid and complete absorption of the product, higher levels in serum, and less diverse adverse effects compared to oral administration. [11, 12] Clinical experience confirms that subcutaneous MTX is more efficient than oral one and can have a significant advantage when there is an insufficient response to oral MTX. For instance, the advantage of subcutaneous MTX compared to its oral administration was shown in a cohort of patients with early RA whose disease lasted no longer than 1 year, in terms of both duration and efficacy of the treatment which was evaluated according to DAS28. [13] Subcutaneous MTX compared to oral administration is associated with a better safety profile and a lower incidence of gastrointestinal adverse events.

Pre-filled syringes of Methotrexate-Ebeve (CJSC "Sandoz") with an automatic needle protection system are optimal for subcutaneous injections. The technique of assembling the syringe and injecting is extremely simple ensuring patient adherence to treatment and its continuity. The Luer lock system prevents the product from leaking out when opened, and a well-graded scale allows the patient to control the amount of product administered, which is important if the therapeutic dose is to be adjusted.

The REMARCA trial, [4] which aimed at studying the efficacy of the T2T strategy in early peripheral PsA, involved 44 patients with the disease lasting for >2 years. All patients were initially prescribed the subcutaneous MTX therapy at a dose of 10 mg/week which increased by 5 mg every 2 weeks up to 20–25 mg/week. 55% of patients achieved MDA or DAPSA remission within 3 months, which was maintained for 12 months of follow-up with the MTX maintenance dose of 15 mg/week. It is obvious that the effect achieved during the MTX treatment in more than half of the cases is associated with subcutaneous administration of the medicine in early PsA at a dose of 20–25 mg/week for at least 12 weeks.

R.J. Mease et al. [14] compared the efficacy of the MTX and etanercept (ETC) monotherapies and that of the combination MTX and ETC therapy in PsA patients. Significantly more patients receiving the ETC monotherapy and combination therapy achieved MDA and ACR20 by week 24 compared to the MTX monotherapy. This double-blind RCT confirmed efficacy of oral MTX monotherapy at a dose of 20 mg/week in PsA patients: 50.7% of them achieved ACR20, 22.9% achieved MDA.

Conclusion. sDMARDs prescribed in early PsA lasting less than 2 years allows achieving a recommended therapy goal, i.e. MDA, significantly faster and more frequently than in advanced disease. The majority of PsA patients would be prescribed MTX above all other sDMARDs in clinical practice; at that, 16.5% of them would achieve MDA. Subcutaneous MTX significantly increases the efficacy of the treatment and leads to the achievement of MDA in almost a third (31%) of patients, which makes such administration more feasible in PsA.

Thus, the early administration of sDMARDs, parenteral MTX in particular, will allow to optimize the therapy of PsA patients in real clinical practice.

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Conflict of Interest Statement

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Korotaeva T.V. <https://orcid.org/0000-0003-0579-1131>
Loginova E.Yu. <https://orcid.org/0000-0001-6875-4552>
Gubar E.E. <https://orcid.org/0000-0001-5015-7143>
Korsakova Yu.L. <https://orcid.org/0000-0001-5968-2403>
Sedunova M.V. <https://orcid.org/0000-0002-3355-2093>
Pristavsky I.N. <https://orcid.org/0000-0002-2189-3085>
Kushnir I.N. <https://orcid.org/0000-0003-2405-2342>
Umnova I.F. <https://orcid.org/0000-0002-2168-8954>
Kudishina S.S. <https://orcid.org/0000-0002-1443-9079>