CLINICAL OBSERVATIONS

The first results of a 6-year follow-up study of a patient with early psoriatic arthritis treated with a treat-to-target strategy

Tremaskina P.O., Loginova E.Yu., Korotaeva T.V., Sukhinina A.V.
V.A. Nasonova Research Institute of Rheumatology, Moscow, Russia
34A, Kashirskoe Shosse, Moscow 115522

The paper characterizes the basic principles of a treat-to-target (T2T) strategy for spondyloarthritis, including psoriatic arthritis (PsA). The data from observational cohort studies suggest that inadequate therapy for PsA increases the risk of structural progression. The results, obtained in the international randomized controlled Tight Control of Psoriatic Arthritis (TICOPA) trial and the Russian open-label observational REMARCA study, have justified the necessity of using the T2T strategy for early-stage PsA. The authors have analyzed their own results of a 6-year follow-up study of a patient with early PsA, in whom the T2T strategy was used.

Keywords: *spondyloarthritis; psoriatic arthritis; early stage; treat-to-target strategy.*
Contact: *Polina Olegovna Tremaskina;* ***polinatrem@yandex.ru***
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Psoriatic arthritis (PsA) is a chronic inflammatory joint disease with various clinical manifestations such as arthritis, dactylitis, enthesitis, spondylitis, which is usually observed in patients with psoriasis of the skin and nails [1]. Recently, the attention of researchers has been drawn to the early stage of the disease, especially to its timely diagnosis and pharmacotherapy. Recently, a new model of PsA development has been proposed, which helps to better understand the mechanisms underlying the transformation of psoriasis to PsA in patients at high risk of developing the disease. In accordance with this model, there are four phases of PsA development: preclinical, subclinical, prodromal and early [2, 3]. The pathogenetic mechanisms underlying each phase determine the need for more active treatment of patients with PsA already at the early stages of the disease [4]. It is assumed that such a strategy can change the course of the disease, as well as prevent the development of bone-destructive changes. Thus, according to the Danish register of PsA (n=11 960), the frequency of joint surgeries for this disease is higher in all age groups compared to that in the general population. In particular, in patients with PsA aged 18–40 years, this indicator is 15% higher than that in people over 60 years old in the general population. These data substantiate the need to raise awareness among doctors about a high risk of joint surgery in patients with PsA, which can be prevented by earlier active treatment, including the use of the «Treat to target» (T2T) strategy [5]. Until now, both in domestic and foreign literature, the long-term results of the T2T strategy have not been analyzed. This strategy is based on strict control over the results of treatment and timely changes in the tactics of therapy, depending on the achievement or failure of its main goals – remission or minimal disease activity (MDA) [6, 7]. In accordance with the main definitions of the T2T strategy, the state of remission in PsA is considered to be achieved when the DAPSA (Disease Activity Index for Psoriatic Arthritis) score is I4, and MDA – in the presence of 5 of the 7 following criteria: tender joint count I1; swollen joint count I1; PASI (Psoriasis Area and Severity Index) I1 or BSA (Body Surface Area) I3; patient pain visual analog scale (VAS) score I15 mm; patient global disease activity VAS score I20 mm, HAQ (Health assessment questionnaire) score I0.5, tender entheseal points I1 [8].

For the first time in the world, the T2T strategy for early PsA was tested in the multicenter open controlled trial TICOPA. In 2014, the tactics of monitoring the results of therapy and changing the therapeutic plan, if necessary, every 3–6 months, which was used in this study, became the basis for the recommendations of the European League Against Rheumatism (EULAR) for the treatment of PsA. The aim of this randomized controlled trial was to compare the «tight» and standard approaches to the management of patients with PsA. In the first case, the patients' condition was monitored every 4 weeks with the possibility of modifying therapy, including the use of inhibitors of tumor necrosis factor α; in the second – every 12 weeks until the 52nd week of treatment. All patients were prescribed methotrexate (MT), mainly in the tablet form, up to a maximal dose of 25 mg/week, some in combination with leflunomide or sulfasalazine. In both groups, the achievement of MDA was assessed, as well as the response to therapy according to the criteria ACR20/50/70 and PsARC (Psoriatic Arthritis Response Criteria). The results obtained a year later showed the effectiveness of the T2T strategy: MDA was reached by 41% of patients. The ACR20/50/70 response in the «tight» control group was observed in 62, 51 and 38% of patients, respectively, which turned out to be significantly higher than in the group of the standard management. After a year, the analysis of the dynamics of X-ray changes revealed a slowdown in structural progression [9].

In Russia, the assessment of the effectiveness of the T2T strategy in early PsA was carried out as part of the REMARCA study. Throughout one year, every 3 months, the efficacy of subcutaneous MT therapy with a rapid dose escalation – from 5 to 25 mg/week was assessed in 44 patients. After 12 weeks of treatment, in the absence of low disease activity, remission, or MDA, the patients were prescribed a combination therapy with MT at a dose of 20–25 mg/week and adalimumab 40 mg once every 2 weeks. After 12 months, MDA was achieved in 65.9% of patients with early PsA (ePsA), remission according to DAS28 – in 56.8% of patients. The ACR20/50/70 response was observed more frequently than in the TICOPA study – in 88, 77 and 59% of cases. The authors associate this result with subcutaneous administration of MT, which increases its bioavailability [10]. Initially, 57% of patients with ePsA had joint erosion. One year after the start of treatment within the framework of the T2T strategy, 72.5% of patients with ePsA showed no radiographic progression, especially those who achieved MDA [11]. A similar association between achieving remission/MDA and fewer joint erosions, better functional and psychological status of patients was later confirmed by the results of large observational cohort studies and in subanalyses of randomized controlled trials [12]. It was also noted that at the early stage of PsA, patients more often achieve remission and MDA, which is demonstrated in the subanalysis of randomized controlled trials PRESTA and FUTURE 1–2 [13, 14].

The results of the above studies are based on a short-term assessment of the effectiveness of the T2T strategy in patients with ePsA. Previously, the analysis of long-term follow-up data with determination of the remission duration after completion of T2T treatment, and clinical and instrumental outcomes of ePSA was not carried out.

In the present work, an assessment of the progression of ePSA and the long-term results of using the T2T strategy in real practice has been undertaken; a 6-year observation is presented in which the T2T strategy was used in a patient with ePSA.

***Patient G.**, 28 years old, applied for the first time to the V.A. Nasonova Research Institute of Rheumatology in October 2013. Since 2011, he periodically noted discomfort and episodes of pain in the lumbar region, which were relieved by using non-steroidal anti-inflammatory drugs (NSAIDs) and physical exercises. In June 2013, psoriatic lesions first appeared on the scalp, elbows and knees; six months later, nail psoriasis developed. The patient's relatives have no psoriasis. At the same time, there was a sharp pain in the lower back, which worsened at rest, at night, when turning in bed. Treatment at the place of residence – NSAIDs (meloxicam) 15 mg/day, physiotherapy, massage, a single injection of diprospan 1.0 ml intramuscularly – did not give a noticeable effect. In August 2013, acute dactylitis of the third toe of the left foot developed, followed by arthritis of the left ankle joint. An outpatient examination based on magnetic resonance imaging (MRI) of the sacroiliac joints (SJ) revealed chronic bilateral sacroiliitis with signs of active inflammation in both SJs. The patient was prescribed nimesulide 200 mg/day for a month, with insufficient effect.*

The patient was hospitalized to the V.A. Nasonova Research Institute of Rheumatology in November 2013. On examination, the condition was satisfactory. Height – 176 cm, body weight - 85 kg, body mass index - 27.44 kg/m^2. Psoriatic plaques in the scalp, elbow and knee joints (BSA 1%), psoriatic onychodystrophy of the hands and feet (marginal onycholysis). Acute dactylitis of the II and III toes of the left foot (Fig. 1, a), arthritis of the left ankle joint, the 2nd, 3rd and 4th metatarsophalangeal joints of the left foot, pain and limitation of movement in the left hip joint. Pain with inflammatory rhythm and limitation of movement in the lumbar spine. Vertebral indices: Schober's symptom – 4 cm, lateral slopes in the lumbar spine – 21 cm in both directions, chest excursion – 6 cm (Fig. 2, a). Tender joint count (TJC) from 68/28–8/0, swollen joint count (SJC) from 66/28–7/0, Ritchie index – 15, patient pain visual analog scale (VAS) score – 96 mm, patient global disease activity VAS score – 72 mm, physician's disease assessment – 65 mm, DAS – 3.83 , DAS28 – 4.31, DAPSA – 29.19, BASDAI (Bath Ankilosing Spondylitis Disease Activity Index) – 4.2 (high activity), HAQ – 0.875.

Laboratory examination: ESR (according to Westergren) – 24 mm/h, CRP – 43.9 mg/l, HLA-B27 – positive, rheumatoid factor (RF) <9.5 IU/ml, antibodies to cyclic citrullinated peptide – 0,1 unit/ml. Blood biochemical parameters are within the normal limits.

Radiography of the hands and feet: erosion of the 3rd metatarsophalangeal joint of the left foot, multiple cystic lucencies in the heads of the metatarsal bones on the left (Fig. 3, a). X-ray examination of the pelvic bones diagnosed bilateral sacroiliitis stage II (Fig. 4, a). Ultrasound investigation of the joints revealed signs of active synovitis of the 2nd, 3rd and 4th metatarsophalangeal joints of the left foot. Ultrasound of the entheses in the area of the elbow and knee joints revealed signs of inflammation: areas of increased echo density at the point of attachment of the triceps muscle tendon on both sides, as well as a decrease in echo density and thickening in the area of attachment of the medial collateral ligament to the femur on the left.

The patient met the PsA classification criteria – CASPAR (ClASsification criteria for Psoriatic Arthritis, 2006), as he had signs of inflammatory joint disease (arthritis, spondylitis, enthesitis) and scored 5 points out of 6: skin psoriasis (2 points), psoriatic nail dystrophy, dactylitis, negative RF (1 point each). A clinical diagnosis was established: PsA, early stage, erosive polyarthritis IIb stage of the joints of the left foot, acute dactylitis of II and III toes of the left foot, spondylitis, bilateral sacroiliitis stage II, MRI-active, HLA-B27 (+), inflammatory back pain, high activity (DAS 3.83, BASDAI 4.2), functional impairment II. Vulgar psoriasis, limited form, progressive stationary stage. Psoriatic nail dystrophy.

In November 2013, the patient was included in the REMARCA study. At the moment of inclusion, the duration of PsA was 3 months. The patient was prescribed MT at a dose of 10 mg/week with an increase in the dose by 5 mg every 2 weeks to 20–25 mg/week; the therapy with nimesulide 200 mg/day was continued, intra-articular glucocorticoids were administered (1.0 ml). After discharge, the patient was followed up on an outpatient basis, visiting a doctor once every 3 months. After six months of treatment, according to the T2T strategy, remission and MDA were achieved. There were no clinical signs of dactylitis, arthritis, enthesitis, and inflammatory back pain (see Fig. 1, b). Limitations of movements in the spine were not detected during the examination (see Fig. 2, b). TJC from 68/28–0/0, SJC from 66/28–1/0, patient pain visual analog scale (VAS) score/patient global disease activity VAS score/physician's disease assessment – 0/0/0, ESR – 6 mm/h, CRP – 2.5 mg/l, BSA – 0%, DAS – 0.66, DAS28 – 0, DAPSA – 1.25, BASDAI – 0.2. After achieving remission, the patient's condition was assessed every 3 months, the MT dose was reduced to 15 mg/week.

In March 2015 (15 months of T2T therapy) due to a long-term remission (no clinical manifestations, TJC/SJC 0, DAPSA 0.9, BASDAI 0), MT was canceled after a consultation with the attending physician. The patient continued to be followed up within the T2T strategy for the next 18 months, while drug-free remission persisted for 12 months.

In March 2016, pain and swelling appeared in the joints of the feet, TJC from 68/28–3/0, SJC from 66/28–2/0, DAPSA – 13.78, which corresponded to low PsA activity. X-ray examination of the hands in November 2016 showed no erosion; narrowing of the joint space of the 4th, 5th distal and 4th proximal interphalangeal joints of the right hand; the 4th, 5th distal, 3–5th proximal interphalangeal joints, the 1st metacarpophalangeal joint of the left hand was noted (Fig. 5, a). No erosions were found in the feet; narrowing of the 1st interphalangeal and 3rd, 4th and 1st metacarpophalangeal joints of the left foot was detected. The dynamics of radiological changes was assessed by an independent radiologist using the Sharp quantitative method, modified for PsA (m-Sharp/van der Heijde). The total score (TS) m-Sharp/van der Heijde is the sum of the erosion count and the joint space narrowing count [11]. Each joint is rated as 1 – normal (with possible soft tissue edema), 2 – superficial erosion, 3 – erosion and narrowing of the joint space, and 4 – disorganization (including ankylosis, complete destruction of the joint) or need for surgery. Sharp/van der Heijde TS – 26 points. In connection with the exacerbation of the disease from March 2016, the patient independently resumed treatment with MT 10 mg/week, followed by an increase in the dose to 20 mg/week and taking NSAIDs. At the next visit in November 2016: TJC from 68/28–3/0, SJC from 66/28–2/0, patient pain visual analog scale (VAS) score – 30 mm, patient global disease activity VAS score – 52 mm, physician's disease assessment – 27 mm, HAQ – 0.25, ESR – 10 mm/h, CRP – 7.8 mg/l, BSA – 0.3%, damage to the nails of the hands and feet, DAS – 1.91, DAS28 – 2.43, DAPSA – 12, BASDAI – 3.7. It was recommended to continue the treatment with subcutaneous MT at a dose of 20 mg/week. Against the background of the resumption of therapy in January 2017, remission was achieved, but in a more distant period – after 10 months, while previously remission was achieved after 6 months. The patient continued treatment with MT at a dose of 15 mg/week.

In the next 2 years, the patient was not observed, because, according to his own words, there was a drug remission. At this stage of the course of the disease, it was not possible to achieve a drug-free remission; after the patient independently decreased the dose of MT to 10 mg/week, and then to 10 mg every 2 weeks, in January 2019 an exacerbation occurred, arthritis of the 3rd distal interphalangeal joint of the right hand and 5th distal interphalangeal joint of the left hand. Disease status at the time of exacerbation: low activity (DAPSA 11.2). He discontinued MT therapy in July 2019 on his own due to poor tolerance in the form of nausea.

The examination findings on the last visit in September 2019 (2 months without basic anti-inflammatory therapy): acute dactylitis of the fourth toe of the left foot, pain in the thoracic and lumbar spine. TJC from 68/28–4/0, SJC from 66/28–4/0, patient pain visual analog scale (VAS) score – 60 mm, patient global disease activity VAS score – 60 mm, physician's disease assessment – 50 mm, BSA – 1%, DAPSA – 20.2, BASDAI – 4, 6, total onychodystrophy of the hands and feet. Blood test: ESR – 12 mm/h, CRP – 12.3 mg/l. Disease status: moderate activity. On the radiograph of the hands from April 2019, there was a slight negative dynamics in comparison with 2016, an increase in the number of narrowed joint spaces, ero-

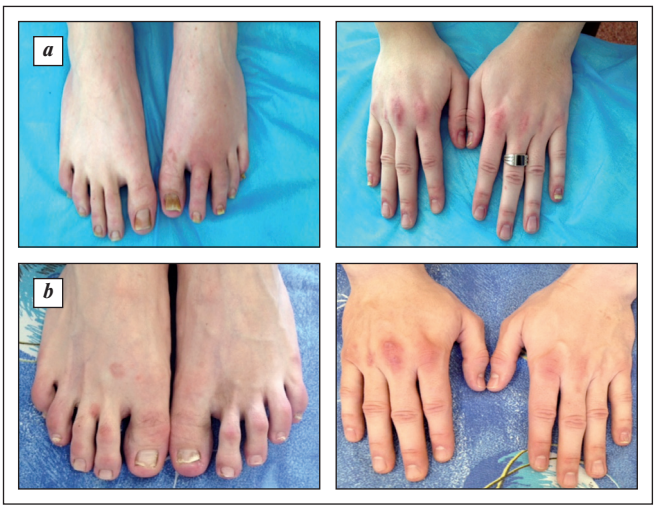

Fig. 1. *Start of T2T – acute dactylitis of the II and III toes of the left foot, onychodystrophy of the nails of the hands and feet (a); after 6 months of T2T use – remission, absence of painful and swollen joints, nail damage persists (b)*

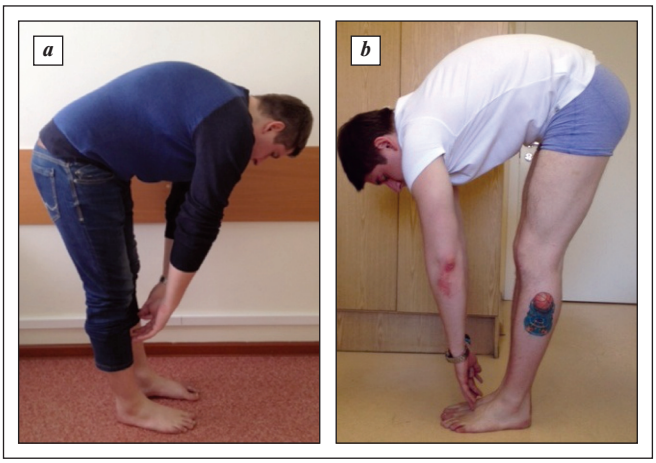

Fig. 2. *Improvement of vertebral indices: before the start of therapy (a) and at the 6th month of T2T treatment (b)*

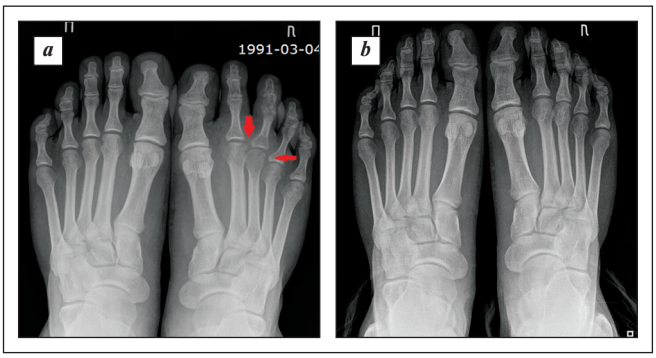

Fig. 3. *Radiographs of the feet, performed in 2013 (a) and 2019 (b). Arrows indicate erosion of the 3rd metatarsophalagus joint of the left foot. There is a negative dynamic*

sion of the third distal interphalangeal joint (see Fig. 5, b). In the feet – no negative dynamics compared with November 2016.

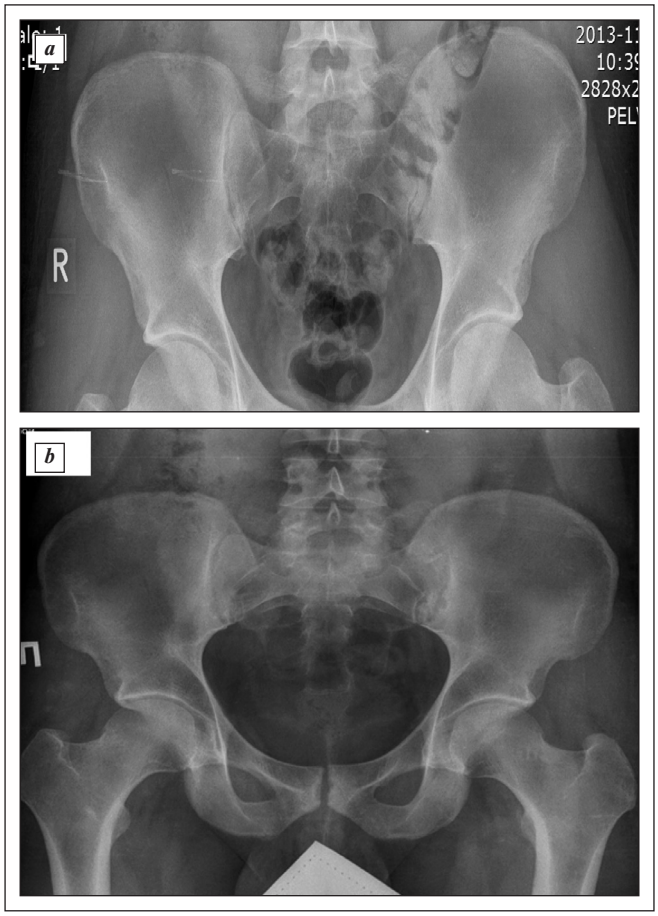

Fig. 4. *Radiographs of the pelvis. Progression of sacroiliitis. At the onset of the disease – bilateral sacroiliitis stage II (a); after 6 years of T2T use – bilateral sacroiliitis stage III (b)*

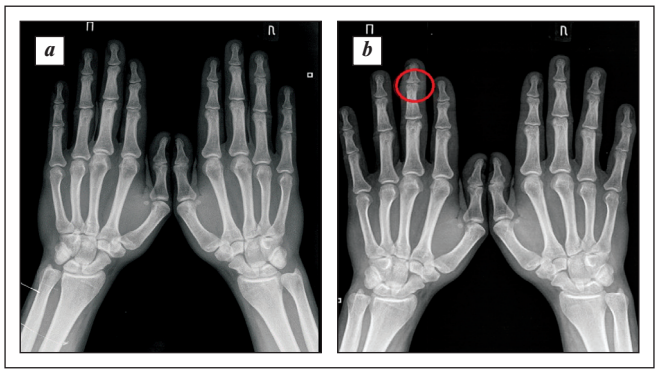

Fig. 5. *Radiographs of the hands, performed in 2016 (a) and 2019 (b). Increased number of narrowed fissures, erosion of the 3rd distal interphalangeal joint, increased Sharp count*

TS Sharp/van der Heijde – 31 points, deterioration by 5 points (see Fig. 3, b). Bilateral progression of sacroiliitis, stage III (see Fig. 4, b). MRI of the sacroiliac joint from 2019: active bilateral sacroiliitis.

Taking into account the impossibility of resuming MT intake, moderate activity of peripheral arthritis and active spondylitis, since the end of September 2019, a targeted synthetic DMARD inhibitor of Janus kinases, tofacitinib, 5 mg 2 times a day, was prescribed, the tolerance of the therapy was satisfactory.

Discussion. PsA is a chronic, disabling disease associated with an increased risk of joint destruction. Treatment of the patient with early PsA according to the T2T principles contributed to the rapid achievement of the goal of therapy 6 months after its start. After the termination of MT therapy, drug-free remission of PsA was observed for 12 months. The first exacerbation of the disease was recorded 12 months after the completion of T2T therapy. There was no return to the previous status observed at the onset of the disease; at the moment of exacerbation, low PsA activity was demonstrated. Resumption of MT treatment at a dose of 20 mg/week contributed to the achievement of remission again, but it took a longer period (10 months of MT therapy). A decrease in the MT dose to 10 mg/week made it possible to maintain the state of remission, while a decrease in the MT dose to 10 mg every 2 weeks led to an exacerbation of the disease. Drug-free remission at this stage was not achieved. Despite the remission of peripheral arthritis, which was observed twice within 6 years, there was an X-ray progression of sacroiliitis, the appearance of erosions in the joints of the hands. Also, skin and nail psoriasis persisted throughout the period of observation.

Thus, the described clinical case demonstrates the effectiveness of the T2T strategy in real practice. To form the final judgments about the possibility of introducing the T2T strategy into routine clinical practice, further analysis of the long-term results (more than 5 years) of its use in ePSA is required, including an assessment of the dynamics of clinical manifestations, disease activity, structural and inflammatory changes in the joints and spine. At present, our work continues. According to the preliminary data, 14 (63.6%) out of 22 patients followed up for 5 years within the framework of this strategy, achieved remission of the disease.

The T2T strategy demonstrates high efficiency, and its implementation in clinical practice has been actively discussed recently. Recent surveys show that doctors are ready to follow the principles of T2T, but some of them are not prepared to use the methods of assessing the disease activity. Currently, the DAPSA activity index and the MDA criterion, the achievement of which is a predictor of a slowdown in clinical and radiological progression, are considered the most accessible for use in routine practice [15].

Further studies of the long-term results of the T2T strategy in larger cohorts of patients are required, including the widest possible use of questionnaires, assessment of the activity and radiological progression of the disease.

REFERENCES

1. Коротаева ТВ. Псориатический артрит: классификация, клиническая картина, диагностика, лечение. Научно-практическая ревматология. 2014;52(6):650-9. [Korotaeva TV. Psoriatic arthritis: classification, clinical presentation, diagnosis, treatment. *Nauchno-prakticheskaya revmatologiya = Rheumatology Science and Practice*. 2014;52(6):650-9. (In Russ.)]. doi: 10.14412/1995-4484-2014-650-659

2. Насонов ЕЛ, Коротаева ТВ, Лила АМ, Кубанов АА. Можно ли предотвратить развитие псориатического артрита у пациентов с псориазом? Научно-практическая ревматология. 2019;57(3):250-4. [Nasonov EL, Korotaeva TV, Lila AM, Kubanov AA. Can the development of psoriatic arthritis be prevented in patients with psoriasis? *Nauchno-prakticheskaya revmatologiya = Rheumatology Science and Practice*. 2019;57(3):250-4. (In Russ.)]. doi: 10.14412/1995-4484-2019-250-254

3. Scher JU, Ogdie A, Merola JF, et al. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. *Nat Rev Rheumatol.* 2019 Mar;15(3):153-66. doi: 10.1038/s41584-019-0175-0.

4. Van Mens LJJ, de Jong HM, Fluri I, et al. Achieving remission in psoriatic arthritis by early initiation of TNF inhibition: a double-blind, randomised, placebo-controlled trial of golimumab plus methotrexate versus placebo plus methotrexate. *Ann Rheum Dis.* 2019 May;78(5):610-16. doi: 10.1136/annrheumdis-2018-214746. Epub 2019 Feb 26.

5. Guldberg-M?ller J, Cordtz RL, Kristensen LE, et al. Incidence and time trends of joint surgery in patients with psoriatic arthritis: a register-based time series and cohort study from Denmark. *Ann Rheum Dis.* 2019 Nov;78(11):1517-23. doi: 10.1136/annrheumdis-2019-215313. Epub 2019 Jul 12.

6. Coates LC, Moverley AR, McParland L, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomized controlled trial. *CJEM*. 2017 Mar;19(2):156-8. doi: 10.1017/cem.2015.105. Epub 2015 Nov 20.

7. Smolen JS, SchЖ ls M, Braun J, et al Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann Rheum Dis.* 2018 Jan;77(1):3-17. doi: 10.1136/annrheumdis-2017-211734. Epub 2017 Jul 6.

8. Wervers K, Luime JJ, Tchetverikov I, et al. Comparison of disease activity measures in early psoriatic arthritis in usual care. *Rheumatology (Oxford)*. 2019 Dec 1;58(12):2251-59. doi: 10.1093/rheumatology/kez215.

9. Coates LC, Cook R, Lee KA, et al. Frequency, predictors, and prognosis of sustained minimal disease activity in an observational psoriatic arthritis cohort. *Arthritis Care Res (Hoboken)*. 2010 Jul;62(7):970-6. doi: 10.1002/acr.20162.

10. Коротаева ТВ, Логинова ЕЮ, Каратеев ДЕ и др. Стратегия «Лечение до достижения целик при раннем псориатическом артрите (предварительные результаты исследования РЕМАРКА). Научно-практическая ревматология. 2014;52(4):376Р80. [Korotaeva TV, Loginova EYu, Karateev DE, et al. Treat-to-target strategy for early psoriatic arthritis (preliminary results of the REMARCA study). *Nauchno-prakticheskaya revmatologiya = Rheumatology Science and Practice*. 2014;52(4):376-80. (In Russ.)]. «doi: 10.14412/1995-4484-2014-376-380

11. Логинова ЕЮ, Коротаева ТВ, Смирнов АВ и др. Особенности поражения осевого скелета при раннем псориатическом артрите (исследование РЕМАРКА). Научно-практическая ревматология. 2016;54(Прил 1):15-9. [Loginova EYu, Korotaeva TV, Smirnov AV, et al. Specific features of axial skeleton involvement in early psoriatic arthritis (the REMARCA trial). *Nauchno-prakticheskaya revmatologiya = Rheumatology Science and Practice*. 2016;54(1S):15-9. (In Russ.)]. doi: 10.14412/1995-4484-2016-1S-15-19

12. Wervers K, Luime JJ, Tchetverikov I, et al. Time to minimal disease activity in relation to quality of life, productivity, and radiographic damage 1 year after diagnosis in psoriatic arthritis. *Arthritis Res Ther.* 2019 Jan 16;21(1):25. doi: 10.1186/s13075-019-1811-4.

13. Kirkham B, de Vlam K, Li W, et al. Early treatment of psoriatic arthritis is associated with improved patient-reported outcomes: findings from the etanercept PRESTA trial. *Clin Exp Rheumatol.* Jan-Feb 2015;33(1):11-9. Epub 2014 Dec 22.

14. Strand V, Mease P, Gossec L, et al. FUTURE 1 study group. Secukinumab improves patient-reported outcomes in subjects with active psoriatic arthritis: results from a randomised phase III trial (FUTURE 1). *Ann Rheum Dis.* 2017 Jan;76(1):203-7. doi: 10.1136/annrheumdis-2015-209055. Epub 2016 May 11.

15. Coates LC, Helliwell PS. Treating to target in psoriatic arthritis: how to implement in clinical practice. *Ann Rheum Dis.* 2016 Apr;75(4):640-3. doi: 10.1136/annrheumdis-2015-208617. Epub 2015 Dec 15.

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Tremaskina P.O. *https://orcid.org/0000-0003-4005-1745*
Loginova E.Yu. *https://orcid.org/0000-0001-6875-4552*
Korotaeva T. V. *https://orcid.org/0000-0003-0579-1131*
Suhinina A.V. *https://orcid.org/0000-0003-1505-7563*