ORIGINAL INVESTIGATIONS

Analysis of 5-year clinical and radiological outcomes in patients with psoriatic arthritis observed as part of the Treat to target strategy. Preliminary data

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Objective: *to analyze preliminary data on 5-year clinical and radiographic outcomes in patients with early psoriatic arthritis (PsA) observed as part of the Treat to target (T2T) strategy.*

Patients and methods. *We examined 37 patients (18 men and 19 women) with early PsA who met the CASPAR criteria (2006), who received treatment according to the principles of the T2T strategy for 24 months. The mean age of the patients was 43.3±11.7 years, the median (Me) of PsA duration was 72 [60; 90] months, psoriasis – 120 [88; 180] months, follow up – 62 [51; 81] months. After completion of participation in the T2T strategy, patients were followed up in a real clinical setting. Most of the patients used methotrexate, biologic disease modifying antirheumatic drugs and non-steroidal anti-inflammatory drugs. In the dynamics after 5 years, PsA activity was determined by the DAPSA index and the achievement of the minimum disease activity (MiDA). In 16 (43%) patients, a dynamic assessment of radiographic changes in the joints of the hands and feet was performed using the Sharp quantitative method modified for PsA (m-Sharp/vanderHeijde).*

Results and discussion. *By 24 months of therapy (the end of the T2T study), DAPSA remission was registered in 19 (52%) patients, in the same number of cases (16%) low (LDA), moderate (MDA) and high (HDA) disease activity was noted. Me DAPSA was 3.85 [0.67; 21.76], MiDA was detected in 22 (59.5%) patients. After 5 years of observation, Me DAPSA was 7.67 [2.2; 14.5]. Remissions according to DAPSA were achieved in 13 (35%) patients, LDA – also in 13 (35%), MDA – in 5 (14%), HDA remained in 6 (16%), MiDA – in 20 (54%). No significant differences were found when comparing disease activity at 24 months (at the end of the T2T study) and after 5 years of follow-up (p=0.41). In 11 (69%) out of 16 patients after 5 years, a negative trend was recorded in the assessment of radiological progression.*

Conclusion. *After 5 years of follow-up, 70% of patients with PsA treated at an early stage of the disease as part of the T2T strategy achieved remission or LDA, and 54% of patients remained in MiDA. In 69% of patients, despite the achievement of remission and MiDA, there was a negative radiological dynamic in the hands and feet.*

Key words: *psoriatic arthritis; early psoriatic arthritis; treatment; T2T strategy; clinical and radiological outcomes.*

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Analysis of 5-year Clinical and Radiological Outcomes in Patients with Psoriatic Arthritis Observed under the "Treat to Target" Strategy. Preliminary Data

Psoriatic arthritis (PsA) is a chronic immune-inflammatory disease of the joints, spine, and entheses that occurs in 30% of patients with psoriasis (PsO) [1]. PsA is classified as a group of peripheral spondyloarthritis (SpA) because the clinical picture is dominated by peripheral arthritis and/or dactylitis in the debut of the disease [2]. Early psoriatic arthritis (ePsA) is considered to be peripheral arthritis lasting up to 2 years [3].

In recent years, much attention has been paid to early diagnosis and timely initiation of PsA treatment, in connection with which the concept of Treat-to-Target (T2T) has been developed. The main principles of the T2T strategy in SpA, including PsA, were first presented in 2014, and then enshrined in the 2015 EULAR (European Alliance of Associations for Rheumatology) recommendations for PsA [4, 5]. The T2T strategy is based on the principle of regular assessment (every 3–6 months (mos) of treatment results, and treatment correction in the absence of effect. The proposed goal of PsA therapy is the achievement of remission, low (LDA) or minimal (MDA) disease activity. The realization of these goals helps to slow down structural changes in the joints and improve the functional status of patients [6].

The first randomized controlled trial, TICOPA, was devoted to comparing the effectiveness of the T2T strategy in ePsA with monthly control and the standard therapeutic approach. It was shown, that after 12 mos, a significantly higher number of patients in the intensive management group had achieved MDA compared to the standard follow-up group: 40% versus 28%, respectively [7]. The results of TICOPA were considered in the development of further international and Russian recommendations for treatment of PsA [5, 8].

Data from the Russian observational study REMARCA (Russian invEstigation of MethotrexAte and biologicals for eaRly aCtive Arthritis) also confirmed the effectiveness of the T2T strategy in ePsA patients who received methotrexate (MTX) monotherapy or MTX in combination with the tumor necrosis factor-α (TNF-α) inhibitor adalimumab (ADA) for one year [9].

However, to date, the long-term outcomes of the strategy for ePSA have not been studied.

The aim of the study was to analyze 5-year clinical and radiological outcomes of the T2T strategy in ePsA.

Patients and methods. Thirty seven (M/F–18/19) PsA patients fulfilling CASPAR criteria (2006) were included in the study [10]. The mean age of the patients was 43.3±11.7 years, median (Me) duration of PsA was 72 [60; 90] mos; PsO – 120 [88; 180] mos, and the follow-up was 62 [51; 81] mos.

Patients with ePsA were included in the open observational study REMARCA, conducted at V.A. Nasonova Research Institute of Rheumatology from April 2012 to October 2017. Initially, all patients were treated with MTX at a dose of 10 mg/week with subsequent dose escalation to 20–25 mg/week; if remission and/or MDA were not achieved after 3–6 mos, ADA 40 mg once every 2 weeks was added to the treatment.

During the 2-year follow-up, 20 (54%) of 37 patients were on MTX monotherapy, the remaining 17 (46%) were on MTX + ADA combination therapy. After 2 years, the number of patients receiving MTX monotherapy and MTX + ADA combination therapy decreased to 16 (43%) and 8 (22%), respectively. After completion of the follow-up under the T2T strategy, some patients were switched to other disease-modifying antirheumatic drugs (DMARDs) and synthetic DMARDs, such as leflunomide (LEF), sulfasalazine (SULF), tofacitinib (TOFA), and apremilast.

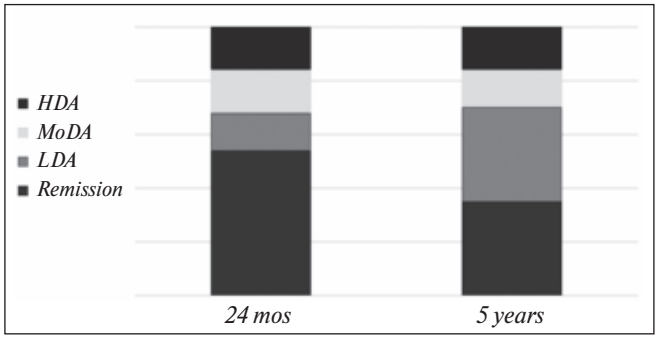
At baseline, and then every 3 mos during the 2-year and 5-year follow-up, all patients underwent standard rheumatologic examination with assessment of tender joint count (TJC) out of 68, swollen joint count (SJC) out of 66, patient-reported pain intensity and global disease activity on the visual analogue score (VAS), physician-reported disease activity (VAS, 0–100 mm), the HAQ (Health Assessment Questionnaire) functional index, and CRP (mg/L). Entheses tenderness was determined using the LEI (Leeds Enthesitis Index), and PsA activity was determined using the DAPSA (Disease Activity In Psoriatic Arthritis) index. Gradation of the disease activity according to the DAPSA: remission, 0–4; LDA, 5–14; moderate activity (MoDA), 15–28; high activity (HDA), >28 [11]. We assessed the proportion of patients (%) who achieved MDA: TJC ≤1, SJC ≤1, PASI ≤1 or BSA (Body Surface Area) ≤3, patient-reported pain intensity on VAS ≤15 mm, patient-reported global disease activity on VAS ≤20 mm, HAQ ≤0.5, number of inflamed entheses ≤1. MDA was considered to be achieved when a patient had 5 of 7 criteria [12]. The area of psoriatic skin lesions was assessed by the BSA index (%).

In 16 (43%) of 37 patients, X-ray changes in the joints of the hands and feet were studied using the Sharp–van der Heijde method, modified for PsA (m-Sharp/van der Heijde), before therapy and after 5 years. We counted erosions (ER) in the hands and feet (maximum score 320), joint space narrowing (JSN) in the hands and feet (maximum score 208) according to a common methodology, as well as the total Sharpe score (TSS), which implies summing ER and JSN in the hands/feet (maximum score 528) [13]. The number of patients with ER in the hands and feet before therapy and after 5 years was determined. An increase in TSS after 5 years of follow-up was considered a negative dynamic of X-ray progression.

During statistical processing of the data, we calculated the mean values of the indices (M) and standard deviation (SD). Me and interquartile range [25th percentile; 75th percentile] were calculated if the distribution differed from normal. Comparison of the quantitative data in dynamics was performed using Mann–Whitney test, analysis of dynamics of quantitative data using Wilcoxon criterion. Differences were considered statistically significant at $p<0.05$. The data were analyzed using Statistica 10 software.

The study was approved by the local ethical committee of V.A. Nasonova Research Institute. Informed consent was obtained from all study participants.

Results. *Characteristics of PsA activity, achievement of remission and MDA.* After 24 months of follow-up Me DAPSA was 3.85 [0.67; 21.76]. DAPSA remission was observed in 19 (52%) patients (Fig. 1), LDA, MoDA and HDA – in the same number of cases (16%). After 5 years Me DAPSA reached 7.67 [2.2; 14.5], there were no significant differences with the data after 24 mos (p=0.4). By this time, remission according to DAPSA was observed in 13 (35%) patients, no significant differences were found in comparison with the indicators after 24 months (p=0.1), while LDA was registered in a significantly larger number of patients – 35% (p=0 .03). At the same time, the number of patients with MoDA and HDA did not change statistically significantly: 5 (14%) and 6 (16%), respectively. Of the 19 patients who were in remission at 24 mos of follow-up, only 7 (35%) remained in stable remission after 5 years of follow-up, while the remaining 13 (65%) showed negative dynamics.



Dynamics of PsA activity according to DAPSA at 24 months and 5 years of follow-up

By the 24th month of the study, MDA was detected in 22 (59.5%) patients, and after 5 years, in 20 (54%) patients. About half of the patients (45%) lost their MDA status after completion of T2T follow-up.

Characteristics of peripheral arthritis activity and body mass index (BMI). The dynamics of all assessed indicators by the 24th month of observation and after 5 years is presented in Table. 1.

By the 24th month, the Me parameters of PsA activity were: TJC – 3.27 [0; 6], SJC – 0 [0; 5], patient-reported global disease activity VAS – 10 [0; 46], patient-reported pain intensity VAS – 15 [0; 50], CRP – 2.7 [1.1; 14.6], HAQ – 0 [0; 0.5], and after 5 years – TJC – 2 [0; 5], SJC – 1 [0; 4], patient-reported global disease activity VAS – 20 [5; 40], patient-reported pain intensity VAS – 20 [2; 40], CRP – 3.4 [1.2; 6.25], HAQ – 0.375 [0; 0.75], there were no significant differences between the indicators in dynamics (p>0.05 for all cases).

By 5 years of follow-up, there was a statistically significant increase in BMI: from 26.8±4.5 to 27.8±5.2 kg/m2, respectively (p=0.004).

Characteristics of psoriatic lesions of the skin and nails. At 24 mos and 5 years of follow-up, there was a significant increase in the area and severity of PsO according to BSA (see Table 1): from

Table 1. Dynamics of clinical and laboratory parameters, Me [25th; 75th percentile]

Index	After 24 mos follow-up	After 5 years follow-up
TJC	3.27 [0; 6]	2 [0; 5]
SJC	0 [0; 5]	1 [0; 4]
Patient-reported global disease activity (VAS)	10 [0; 46]	20 [5; 40]
Patient-reported pain intensity (VAS)	15 [0; 50]	20 [2; 40]
CRP	2.7 [1.1; 14.6]	3.4 [1.2; 6.25]
BSA	0.5 [0; 2]	1 [0.1; 2.5]*
HAQ	0 [0; 0.5]	0.375 [0; 0.75]
DAPSA	3.85 [0.67; 21.76]	7.67 [2.2; 14.5]
IBM	27.4 [23.3; 30]	27.5 [23.7; 31.8]*

*p<0,05 when comparing parameters after 24 mos and 5 years (Wilcoxon test).

Table 2. Characteristics of patients depending on the treatment regimen

Index	mono-MTX (n=20)	MTX + ADA (n=17)
Age, years: M±SD Me [25th; 75th percentile]	 42.9±11.8 38 [33; 50]	 43.8±11.7 40 [34; 53]
PsA duration, mos, Me [25th; 75th percentile]	66 [57; 83]	75 [71; 95]
PsO duration, mos, Me [25th; 75th percentile]	107 [83; 156]	144 [89; 228]
Follow-up duration, mos, Me [25th; 75th percentile]	61 [48; 69]	72 [51; 84]
HLA B-27-associated PsA, n (%)	6 (31.5)	8 (47)

0.5 [0; 2] to 1 [0.1; 2.5] respectively (p=0.01). The number of patients with PsO nails also increased: from 12 (32.4%) to 18 (48.6%), respectively.

Characteristics of enthesitis and dactylitis. At the 24th month, enthesitis was detected in 13.5% of patients. After 5 years, the number of patients with enthesitis doubled. In the same period, dactylitis was recorded in a larger number of patients: in 18.9% and 32.4%, respectively.

Characteristics of pharmacotherapy. After 24 months of follow-up under the T2T strategy, 16 (43%) patients continued MTX monotherapy, 8 (22%) continued MTX + ADA combination therapy, 4 (11%) received SULF, 3 (8%) received TOFA, and 5% of patients received apremilast, another 5% – LEF. The need for NSAIDs persisted in 29 (78%) patients. Intra-articular injections of glucocorticoids were administered to 6 (16%) patients. Current observation (5 years or more) shows a decrease in the number of patients using drug therapy: MTX is used by 12 (32%) patients, ADA – 11 (30%), MTX + ADA – 3 (8%).

Depending on the treatment regimen, patients were divided into two groups: group 1 (n=20) received MTX monotherapy (mono-MTX) for 24 months of the study as part of the T2T strategy, group 2 (n=17) received combined therapy with MTX + ADA. The duration of MTX intake was 20 [13, 46.5] months. For various reasons, MTX was canceled in 32 (86%) patients, of whom 24 (75%) had an exacerbation of the disease against this background.

Comparative analysis of patient groups at 24 mos and 5 years of follow-up is presented in Table. 2. In the mono-MTX group, the mean age was 42.9±11.8 years, Me duration of PsA and PsO was 66 [57; 83] and 107 [83; 156] mos, respectively, Me follow-up – 61 [48; 69] mos. In the MTX + ADA group, the mean age was 43.8±11.7 years, Me duration of PsA and PsO was 75 [71; 95] and 144 [89; 228] mos, Me follow-up – 72 [51; 84] mos. The DAPSA index at the beginning of treatment was higher in the MTX + ADA group – 34 [24; 61] than in the mono-MTX group – 27 [17.5; 49]. HLA-B27 positivity was detected in 6 (31.5%) and 8 (47%) patients of the 1st and 2nd groups, respectively.

The dynamics of clinical and laboratory parameters, BSA, HAQ, DAPSA index, as well as enthesitis and dactylitis are presented in Table. 3. It is noteworthy that in the mono-MTX group, after the end of the follow-up, there was a decrease in laboratory activity: at the 24th month, Me CRP was 2.4 [0.9; 6.7], after 5 years – 2.1 [0.9; 5.5]. Assessment of PsA activity by DAPSA did not reveal significant differences between the two groups (p>0.05).

Dynamics of X-ray progression. X-ray examination of the hands and feet in dynamics was performed in 16 patients. Radiographic progression was assessed by two independent radiologists using a modified Sharp/van der Heijde method: TSS = ER + JSN.

When analyzing X-ray changes, a statistically significant negative trend in TSS was revealed, Me which amounted to 51 by 24 months [25; 69], and after 5 years – 56 [35; 105] (p=0.002); Me ER was initially equal to 0.5 [0; 4.75], while after 5 years it in-

creased to 2 [0; 8.75] (p=0.012); Me JSN at the onset of PsA was at the level of 44.5 [24; 66], after 5 years it significantly increased – to 52.5 [31.5; 96.5] (p=0.002).

Negative radiological dynamics was found in 11 (69%) patients, and only 5 (31%) had no changes. In 9 (56%) patients, an increase in the number of erosions was observed, while initially in 3 of them there were no erosions. An increase in JSN was detected in 11 (69%) patients.

By 5 years of follow-up in patients with negative X-ray dynamics, DAPSA Me was 13 [5.5; 21] points, in patients with no negative dynamics – 10 [2; 49] points, which corresponded to low inflammatory activity. The majority of patients (81.8%) who had negative dynamics according to radiography were from the mono-MTX group.

Table 3. Dynamics of indicators depending on the treatment regimen after 24 mos and 5 years of follow-up, Me [25th; 75th percentile]

Index	mono-MTX (n=20)		MTX + ADA (n=17)	
	24 mos	5 yrs	24 mos	5 yrs
TJC	0 [0; 6]	1 [0; 5]	0 [0; 4]	2 [0; 4]
SJC	0 [0; 5]	0 [0; 4]	0 [0; 4]	2 [0; 4]
Patient-reported global disease activity VAS	7 [0; 28]	18 [2; 32]	15 [0; 49]	20 [5; 50]
Patient-reported pain intensity VAS	7 [0; 45]	17 [0; 40]	15 [0; 50]	20 [2; 40]
CRP	2.4 [0.9; 6.7]	2.1 [0.9; 5.5]	4 [1.2; 17.7]	4.9 [1.7; 7.9]
BSA	0.1 [0; 1]	0.5 [0; 1]	0.5 [0; 2.5]	2.5 [0.1; 8]
HAQ	0 [0; 0.375]	0.125 [0; 0.625]	0.375 [0; 0.5]	0.375 [0; 0.875]
DAPSA	2.17 [0.3; 21.7]	6.23 [0.9; 13.8]	4.55 [2.6; 18.6]	7.67 [2.2; 18.8]
Enthesitis, n (%)	3 (15)	4 (20)	2 (11.7)	6 (35)
Dactylitis, n (%)	4 (20)	5 (25)	3 (17)	7 (41)

Discussion. The TICOPA trial has proven the effectiveness of the T2T strategy for 1 year compared with standard patient follow-up [7]. These data are in full agreement with the results of the observational REMARKA study [9]. We present for the first time the results of a 2-year follow-up of patients treated in accordance with the basic principles of this strategy. It was shown that by the end of the T2T study (24 months), more than a half (52%) of the patients achieved remission, MDA was detected in almost 60% of cases.

Recently, 5-year clinical outcome results from the TICOPA study in the intensive management and standard observation groups have been published. It was noted that PsA activity was similar in both groups, while LDA (TJC and SJC, dactylitis and enthesitis, active psoriasis) was observed in 69% and 76% of patients, respectively, in the group of intensive management and standard observation. In contrast to the TICOPA, our study assessed long-term results in achieving MDA and remission/LDA according to DAPSA, but despite this, similar results were obtained: PsA activity at the end of T2T therapy and after 5 years did not differ. Interestingly, the use of MTX in the TICOPA study decreased in both groups, while the use of genetically engineered biological drugs (bDMARDs) increased [14]. In contrast, in our cohort of patients, after the end of follow-up with the T2T strategy, the use of both MTX and bDMARDs decreased by more than 50%. Thus, in patients who previously received active treatment, adherence to therapy decreased after the cessation of strict regular monitoring.

X-ray progression was not assessed in the TICOPA study due to the insufficient number of participants who had radiographs of the distal feet and hands over time. In our study, in 43.2% of patients, such radiographs were available for analysis.

When assessing radiographic progression, it was found that after 5 years of follow-up, almost two-thirds of patients had negative X-ray dynamics in the hands and feet. This is consistent with the analysis of data from a cohort of PsA patients from Toronto, in whom joint erosions appeared on average after 6.8 ± 6.1 years [15]. We also found that half of the patients had an increase in the number of erosions of the hands and feet compared with the initial data, which coincides with the results of D. Wu et al. [16], who, using high-resolution computed tomography, showed that in PsA patients hand joint damage in the form of erosions and enthesophytes significantly increases within 5 years, despite the use of TNFα inhibitors. Simultaneously with an increase in the number of erosions in the joints, our study revealed an increase in the number of patients with enthesitis, dactylitis, and psoriatic lesions of the nails, i.e., factors of an unfavorable PsA prognosis associated with joint erosion and functional disorders [17].

Probably, the negative X-ray dynamics is a consequence of the termination of observation within T2T. Patients switched to treatment "on demand", which was expressed in irregular visits, self-adjustment of the dose of drugs. Moreover, in some cases, patients did not visit a rheumatologist in the last 5 years. In addition to administrative reasons, the negative radiological dynamics and formation of erosions are affected by PsA activity, which was demonstrated earlier in the work of E.Yu. Loginova et al. [18], in which, after a year of observation and treatment under the T2T strategy, the number of patients with erosions and JSN increased. Possibly, delayed diagnosis also leads to worse radiographic findings in PsA. Thus, a delay in starting therapy for more than 6 mos after the onset of the disease may be associated with

worsening of clinical and X-ray outcomes of PsA [19]. This is consistent with the modern concept of the subclinical course of PsA, according to which, long before any clinical manifestations, patients with PsO can show inflammatory changes in the joints and entheses detected by highly sensitive methods of radiological diagnostics [20]. Given the presence of a subclinical stage of PsA, it can be assumed that with a disease duration of less than 2 years, there may already be changes characteristic of its advanced stage, which is indirectly confirmed by our data.

A subanalysis of a number of studies in patients who achieved MDA revealed a lower rate of X-ray progression in the joints of the hands and feet [21]. However, in the present study, based on the observation of patients with PsA in real clinical practice, despite the achievement of MAD in most patients (54%), almost two thirds of them (62.5%) had negative radiographic changes. These results are consistent with those of R. Landewe et al. [22], who also found no association between PsA activity and its radiographic progression in patients treated with ADA.

Thus, it is important not only to clarify the concept of "PsA remission", taking into account clinical, immunological and instrumental data, but also to assess the relationship between the achievement of this status and the progression of the disease. So far, various activity indices, including DAPSA, are used in clinical practice to assess remission [23]. It is possible that in the future the concept of "PsA remission" will be determined by an integral index that takes into account both clinical and instrumental data, as well as outcomes reported by patients.

Further studies are needed on a larger cohort of patients, including the analysis of pharmacotherapy, for an in-depth assessment of long-term clinical and radiological outcomes.

Conclusion. Evaluation of the long-term results of the T2T strategy confirms its effectiveness in reducing PsA activity according to the DAPSA index. During the 5 years of follow-up, there was no significant deterioration in the course of the disease when assessing TJC, SJC, patient-reported global disease activity on VAS, patient-reported pain intensity on VAS, CRP and functional status according to HAQ. Most patients (70%) were in remission or had low PsA activity.

Despite the achievement of remission and low PsA activity, the number of patients with enthesitis, dactylitis, skin lesions, as well as negative X-ray dynamics is increasing.

These preliminary findings raise questions about the maintenance of clinical remission in PsA, as well as the association between achieving remission and radiological progression. Further studies of long-term outcomes of PsA in a larger cohort of patients are planned.

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Conflict of Interest Statement

The investigation has been conducted within scientific topic №1021051503111-9 "Improving the diagnosis and pharmacotherapy of spondyloarthritis based on comparative results of studying prognostic (including molecular biological, molecular genetic, clinical imaging) factors of disease progression and the level of patient's quality of life".

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