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TREATMENT OF RHEUMATOID ARTHRITIS: csDMARDS VERSUS bDMARDS. PROSPECTIVE STUDY TO EVALUATE DISEASE ACTIVITY

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Abstract. The assessment of disease activity is an essential component in the selection of therapeutic approach for the prevention of disability for patients with RA. The current study was conducted to evaluate the disease activity in patients on csDMARDs and bDMARDs after 6 months to 1-year of treatment and to determine whether the benefits of different therapies were sustained over time. For the purpose of the study were selected 220 patients with a mean age 55.05 ± 10.63 SD years, meeting the 1987 ACR classification criteria for RA. Patients were stratified according to treatment regimen into 2 age-matched treatment groups: 96 on csDMARDs and 124 on bDMARD therapy. Patient’s assessment of disease related pain, global health and physician assessment of global health was made by visual analogue scale (VAS) – 100 mm. Disease activity was the primary outcome domain. Independent joint assessor evaluated 28 joints on baseline, 6th and 12th month of the follow-up period. C-reactive protein (CRP) was used to measure the inflammation process. DAS28-CRP, CDAI and SDAI were calculated according to the standard formulas. Comparison was performed by analysis variance ANOVA. On baseline, patients on bDMARDs had a significantly higher mean time-averaged 28-joint disease activity score (5.03 ± 0.84 SD vs. 4.35 ± 1.20 SD, p < 0.001), CDAI (25.06 ± 7.32 SD vs. 20.83 ± 10.53 SD, p < 0.001) and SDAI (28.27 ± 8.74 SD vs. 23.19 ± 11.89 SD, p < 0.001) compared to those on csDMARDs. On the 6th month in both groups (bDMARDS and csDMARDs) we found significant decrease in mean DAS28 (p < 0.001, p < 0.001), although no significant difference in disease activity between the groups was measured by this indicator (3.75 ± 2.49 SD vs 3.90 ± 1.10 SD, p = 0.566). Patients on bDMARDs had significantly lower disease activity compared to those on csDMARDs after 6th and 12th month of treatment assessed by CDAI (13.43 ± 4.98 SD vs 16.81 ± 9.94 SD, p = 0.001; 8.65 ± 4.53 SD vs 15.86 ± 10.02 SD, p < 0.001), and SDAI (14.63 ± 5.42 SD vs 18.38 ± 10.49 SD, p < 0.001; 9.39 ± 4.92 SD vs 16.79 ± 10.5 SD, p < 0.001). Unlike results reported by DAS28-CRP which showed no change between the 6th and 12th month in patients receiving csDMARDs (3.90 ± 1.10 SD, 3.82 ± 1.12 SD, p = 0.156), we observed a statistically significant difference in all three time intervals (0, the 6th, 10th month) of the follow up period regarding to CDAI and SDAI. After a year prospective follow-up, therapy with biologic DMARDs results in sustained suppression – minimal disease activity assessed by DAS28-CRP, CDAI and SDAI, compared to patients receiving DMARDs who had moderate disease activity according to these tools. The therapy with bDMARDS was superior to csDMARDs therapy for suppressing disease activity (assessed by DAS28-CRP, CDAI and SDAI) of rheumatoid arthritis (RA) on the 6th and 12th month of the follow-up period.

Key words: treatment, rheumatoid arthritis, disease activity, biological therapy

Увод

Ревматоидния артрит (РА) е хронично, прогресиращо автоимунно заболяване, характеризиращо се със синоновиална пролиферация и деструкция на ставния хрущял и костите [1]. Естественият ход на болестта се характеризира както с периоди на висока възпалителна активност, с тенденция към хронифициране, така и с ниска болестна активност или ремисия. Усъвършенстването на методиките за измерване на болестната активност започва през 1950 г., когато е създаден първият инструмент за оценка [2]. Оттогава са направени много опити за подобряване и прецизираше на мониторинга на болестта по обективен начин, който обхваща не само клиничните показатели, но и резултати, докладвани от пациентите. Различните по-

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease characterized by synovial proliferation and destruction of articular cartilage and bone [1]. The natural course of the disease is characterized by both periods of high inflammatory activity, with a tendency to chronic, and with low morbidity or remission.

The improvement of the methodologies for measuring disease activity began in 1950 when the first evaluation tool was created [2]. Since then, many attempts have been made to improve and refinement of disease monitoring in an objective way that encompasses not only the clinical indicators but also the results reported by the patients. Vari-
Lечение на ревматоиден артрит...

Oulous disease activity indicators (DAS) include the following parameters: number of painful and swollen joints, patient self-assessment for global health and serum C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). The most commonly used methodology in rheumatology practice is disease activity score assessing 28 joints (DAS28), including either CRP or ESR [3].

At present, 63 tools for determining disease activity in RA patients are applicable. Following a detailed analysis of the methodologies in 2012, the ARC recommends six of them, which measure a single index and define the categories: low, moderate and high disease activity or clinical remission [4].

In daily rheumatology, DAS28, Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI) are the most widely used, which help rheumatologists to treat treatment to target and more effectively apply EULAR and ACR recommendations for the treatment of rheumatoid arthritis [5, 6].

The concept of disease activity is useful for assessing the current severity of disease and progression of the disease. Inflammatory activity should be differentiated from the severity of the disease, which is a concept that encompasses much broader aspects of the disease process and its consequences. The manifestations of the disease activity are reversible and represent the main goal of symptomatic treatment [7].

OBJECTIVE
To determine the disease activity (DAS28-CRP, CDAI, SDAI, global patient and physician evaluation of disease activity, inflammatory biomarkers) and follow-up response to therapy with csDMARDs and bDMARDs.

MATERIALS AND METHODS
For the purpose of this study, 252 patients, including 35 (14%) males and 217 (86%) females aged 18-85, were examined. Patients were selected according to pre-defined inclusion and exclusion criteria from the Rheumatology Clinic, University Hospital “St. Ivan Rilski” – Sofia. 32 patients (6 males and 26 females) were excluded from processing the study data due to a necessary change in therapy.
от Клиниката по ревматология, УМБАЛ “Св. Иван Рилски” – София. При обработката на данните от проучването бяха изключени 32 болни (6 мъже и 26 жени) поради наложителна промяна в терапията и неизпълнение на включващите критерии. Поради недостатъчния брой пациенти в терапевтичните групи с Leflunomide (5 болни), златни соли (4 болни) и Methotrexate + Chloroquine (4 болни) те са елиминирани от статистическата обработка.

За целта на изследването бяха селектирани 220 пациенти, от които 29 мъже (13%) и 191 жени (87%), покриващи класификационните критерии за РА на ACR от 1987 г. и на ACR/EULAR от 2010 г. Пациентите са проследени за период от 1 година – 0, 6-и и 12-и месец.

**Inclusion Criteria:**

1. Age over 18 years and voluntary consent to participate in the follow-up of RA treatment.
2. Confirmed diagnosis of RA according to the ACR criteria of 1987 and/or ACR/EULAR from 2010.
3. Different duration of disease.
4. Patients treated with different treatment regimens according to the standard of disease treatment: NSAIDs, stable csDMARDs in the last 3 months of treatment (Chloroquine 250 mg/daily, Sulfasalazine to 2.0 g/daily, Methotrexate 7.5 up to 25 mg/weekly.
5. Treatment with Methylprednisolone, Prednisolone or other equivalent Corticosteroid (CS) at a dose of up to 10 mg/daily and duration of therapy throughout the follow-up period.
6. Patients treated with bDMARDs at a stable dose of MTX or another with csDMARDs (6 months prior to bDMARDs) and/or CS therapy up to 10 mg/ daily and/or NSAIDs.
7. Patients in the individual treatment groups did not change the dose regimen and did not discontinue the csDMARDs or CS therapy during the entire follow-up period.

<table>
<thead>
<tr>
<th>Demographic characteristics / Demographic Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Възраст (год.) / Age (years)</td>
<td>18-85 г. / years</td>
</tr>
<tr>
<td>Пол (%) / Gender (%)</td>
<td>13% мъже / men; 87% жени / women</td>
</tr>
<tr>
<td>Продължителност на болестта (год.) / Duration of disease (years)</td>
<td>0.5-44 г.</td>
</tr>
<tr>
<td>RF (+) положителни / RF (+) positive</td>
<td>N = 198 (90%)</td>
</tr>
<tr>
<td>Анти-SSR (+) положителни / Anti-SSR (+)</td>
<td>N = 144 (65.5%)</td>
</tr>
<tr>
<td>Терапия / Therapy</td>
<td></td>
</tr>
<tr>
<td>Синтетични БПАРЛП (% / csDMARDs (%) and/or Corticosteroid</td>
<td>N = 96 (43.6%)</td>
</tr>
<tr>
<td>Биологични БПАРЛП (%) / bDMARDs (%)</td>
<td>N = 124 (56.4%)</td>
</tr>
</tbody>
</table>
Exclusion Criteria:
1. Patients with significant comorbidity, infectious diseases (HIV, tuberculosis), congestive heart failure (NYHA class III or IV), malignant hypertension, psychiatric disorders.
2. History of lymphoproliferative disease or neoplasia, manifested in the last 5 years.
4. Abuse of alcohol and narcotics.

96 patients treated with csDMARDs and/or CS were divided into 5 groups:
• Group 1 – Sulfasalazine therapy – 15 patients
• Group 2 – Methylprednisolone therapy – 15 patients
• Group 3 – Chloroquine therapy – 16 patients
• Group 4 – Methotrexate therapy – 20 patients
• Group 5 – Methotrexate + Methylprednisolone therapy – 30 patients

A total of 124 patients were treated with bDMARDs, divided into the following groups:
• Group 1 – Tocilizumab therapy – 30 patients
• Group 2 – Certolizumab pegol therapy – 16 patients
• Group 3 – Golimumab therapy – 22 patients
• Group 4 – Etanercept therapy – 20 patients
• Group 5 – Adalimumab therapy – 20 patients
• Group 6 – Therapy with Rituximab – 16 patients

A cross-sectional and longitudinal study of 220 patients followed at 0, the 6th and 12th month was performed. Data on demographics, indicators evaluating the patient’s disease activity, as well as results from disease-relevant laboratory tests, inflammatory biomarkers, ESR and CRP were collected. Physical examination of the musculoskeletal system was performed: 28 peripheral joints were evaluated, the physician and patient assessed the disease activity on a 100 mm visual-analogue scale. The activity of the disease was assessed by DAS28-CRP, CDAI, SDAI, calculated according to the standard formulas.

The statistical processing was done with SPSS 13.0. A descriptive analysis has been carried out with the help of groups of one or several indicators, summarizing indicators – relative share, average arithmetic, median, mode. An analysis of the difference in mean values was performed and the statistical significance of the differences was tested using the
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на средна разлика (ANOVA/t-test). Резултатите от тези модели са засичани с приложени непараметрични анализи, като целта е да се елиминира евентуално влияние от неспазване на изискванията на ANOVA моделите и в същото време да се използва максимално силен, параметричен статистически метод.

Резултати

При изследването на болестната активност за цялата кохорта от 220 пациенти, включени в крос-секционния и лонгитудиналния анализ, са използвани средните стойности (mean ± SD) на показателите DAS28, CDAI, SDAI на 0, 6-и и 12-и месец.

В началото на проследявания период пациентите, лекувани с ксБПАРЛП, са с по-ниски стойности на показателите за болестна активност (DAS28, CDAI, SDAI), отколкото болниите на лечение с 6БПАРЛП (фиг. 1, 2, 3).

При стратифициране на пациентите спрямо нивото на болестната активност, оценино чрез DAS28, установихме, че средните стойности при пациентите, лекувани с ксБПАРЛП, са 4.35 ± 1.2 SD в началото на проследявания период, отговарящ на умерена болестна активност. При групата болни, лекувани с 6БПАРЛП, се регистрира по-висока активност на болестта в сравнение с пациентите на терапия със синтетични БПАРЛП, или 5.03 ± 0.84 SD, която също се класифицира като умерена болестна активност (фиг. 1). Въпреки това се отчита статистически значима разлика между средните стойности на DAS28 за двете групи пациенти (p < 0.001). Разликата са обясними от гледна точка на критерийте за започване на биологично лечение, което е препоръчително при DAS28 > 5.2.

При двете терапевтични групи се наблюдава значимо намаление на средните стойности на DAS28 от изходното ниво до 12-и месец (p < 0.001), като то е пропорционално при пациентите на лечение с 6БПАРЛП (фиг. 1).

Значително клинично подобрение и статистически достоверно намаляване на болестната активност се установява при болни на лечение с ксБПАРЛП до 6-ия месец (p < 0.001). За период от 6-ия до 12-ия месец на проведеното проучване се наблюдава статистически значима разлика в нивото на болестната активност (p = 0.156).

Пациентите, които са се лекували с 6БПАРЛП, показват значимо подобрение по време на целия период на проследяване. При тях се наблюдава също значимо намаляване на болестната активност.

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ANOVA/ t-test models. The results of these models are detected with applied nonparametric analogs, the aim being to eliminate the potential impact of non-compliance with the ANOVA requirements and at the same time to use a maximally strong, parametric statistical method.

Results

In the study of the disease activity, the mean values (mean ± SD) of the DAS28, CDAI, SDAI at 0, 6 and 12 months were used for the entire cohort of 220 patients included in the cross-sectional and longitudinal analysis.

At the beginning of the follow-up period, patients treated with csBDMARDs had lower disease activity score (DAS28, CDAI, SDAI) than patients treated with bDMARDs (Figures 1, 2, 3).

Patients stratification according to the disease activity level as assessed by DAS28, showed that the mean values in patients treated with csDMARDs were 4.35 ± 1.2 SD at the beginning of the follow-up period corresponding to moderate disease activity. Higher disease activity was recorded in the group of patients treated with bDMARDs (5.03 ± 0.84 SD), than in patients with synthetic csDMARDs, which is also classified as moderate disease activity (Figure 1). However, there was a statistically significant difference between the mean DAS28 values for the two groups of patients (p <0.001). The differences are explicable from the point of view of the criteria for starting biological treatment, which is recommended for DAS28 > 5.2.

In both treatment groups, there was a significant reduction in baseline DAS28 values from baseline to 12 months (p < 0.001), more pronounced in patients treated with bDMARDs (Figure 1).

Significant clinical improvement and a statistically significant reduction in disease activity were observed in patients treated with csDMARDs until 6 month (p < 0.001). No statistically significant difference in the level of disease activity (p = 0.156) was found for a period from the 6th to 12th month of the follow-up period.

Patients treated with bDMARDs showed significant improvement over the entire follow-up period. They showed a significant reduction in disease activ-
Treatment of rheumatoid arthritis

At the 6th month in both treatment groups, we found a significant decrease in the mean DAS28 values from baseline, with no statistically significant difference in disease activity measured by this score between csDMARDs and bDMARDs ($p = 0.566$). When compared to the 12th month of follow-up we found that patients with bDMARDs had low/minimal disease activity – mean DAS28 2.92 ± 0.73 SD. In patients treated with conventional synthetic DMARDs, mean DAS28 values of 3.82 ± 1.12 SD were defined as moderate disease activity (Figure 1).

We recorded a statistically significant difference between the DAS28 values for the comparator groups ($p < 0.001$). It is noteworthy that in the group treated with csDMARDs, the disease activity decreased to the 6th month and the achieved effect of therapy remained at the 12th month. Unlike the first group, the patients of biological treatment show a sustained decrease in DAS28 throughout the observation period. At baseline similar DAS28 mean values in both genders were recorded. A significantly lower disease activity is measured by this parameter in females at 12th month, compared with males ($p = 0.027$).

In order to achieve a more comprehensive and in-depth analysis of the change in disease activity...
вследствие на проведено лечение, използване CDAI. Промените в средните стойности на CDAI са аналогични с результатите за DAS28.

Обяснимо, при пациентите на биологична терапия има по-високи изходни стойности за CDAI – 25.06 ± 7.32 SD, отразяващи по-висока болестна активност. При пациентите, лекувани със сБПАРЛП, изходната средна стойност на CDAI е 20.82 ± 10.53 SD и отговаря на умерена болестна активност (фиг. 2). Установихме статистически значима разлика между двете терапевтични групи (p = 0.001).

Както и при оценката, извършена чрез DAS28, така и анализът на данните, илюстриран чрез CDAI, показа трайно намаляване на болестната активност на 6-ия месец от проследявания период и за двете групи пациенти. Болните, лекувани с ксБПАРЛП, продължават да са с умерена болестна активност – CDAI 16.81 ± 9.94 SD, въпреки намаляването на средната стойност на показателя. При изследваните лица на биологична терапия се установи CDAI 13.43 ± 4.98 SD, дефиниран като умерена болестна активност. Отчете се значително подобряние по отношение на болестната активност при лечението с бБПАРЛП. За групата пациенти на терапия с бБПАРЛП при изходни средни стойности, съответстващи на висока болестна активност, на 6-ия месец наблюдавахме сигнificantната разлика в средните стойности за CDAI на 0, 6-и и 12-и месец за групата на лечение с ксБПАРЛП, нивото на болестната активност остана в категорията на умерено активно заболяване.

За разлика от отчетените резултати чрез DAS28, които не показват промяна между 6-и и 12-и месец, при пациентите на лечение с бБПАРЛП наблюдавахме статистически значима разлика в между 6-ия и 12-ия месец по отношение на CDAI (p = 0.049), фиг. 2.

По отношение на половите различия, не се установи статистически значима разлика между болестната активност при мъжете и жените, въпреки че и при трите измервания мъжете са с по-високи средни стойности за CDAI.

Извършихме оценка на болестната активност на нашата кохорта болни и чрез показателя SDAI. Получените резултати са аналогоични на измерените чрез CDAI (фиг. 3).

Пациентите на терапия с бБПАРЛП имат изходно по-високи средни стойности за SDAI – 28.27 ± as a result of the treatment we used CDAI. Changes in mean values of CDAI are similar to those for DAS28.

Clearly, patients with biological therapy have higher CDAI baseline values – 25.06 ± 7.32 SD, reflecting higher disease activity. In patients treated with bDMARDS, the baseline mean CDAI was 20.82 ± 10.53 SD and responded to moderate disease activity (Figure 2). We found a statistically significant difference between the two treatment groups (p = 0.001).

As with the DAS28 evaluation, and the data analysis illustrated by CDAI shows a sustained reduction in disease activity at the 6th month of the follow-up period for both patient groups. Patients treated with csDMARDs continue to have moderate disease activity – CDAI 16.81 ± 9.94 SD, despite the decrease in the mean of the indicator. Patients on biological therapy had CDAI 13.43 ± 4.98 SD, defined as moderate disease activity. Significant improvement in disease activity was reported for bDMARDs group. For the group of patients on biological therapy at baseline was observed mean values for high disease activity, at the 6th month a significant decrease to a level compatible with moderate disease activity and at 12th month the improvement reached minimal disease activity (p < 0.001), (Fig. 2).

Despite the significant difference in the mean CDAI at 0, the 6th and 12th month for the csDMARDs treatment group, the level of disease activity remained in the moderate active disease category. In contrast to the reported results with DAS28, which did not show a change between the 6th and 12th month, we observed a statistically significant difference in the three time-points of the observed CDAI (p = 0.049) in the patients with csDMARDs (Fig. 2).

In terms of gender differences, there was no statistically significant difference between male and female disease activity, although for all three measurements men had higher mean CDAI scores.

We evaluated the disease activity in our cohort with the SDAI indicator. The results obtained are similar to those measured by CDAI (Figure 3).
8.74 SD, отколкото групата с ксБПАРЛП, за която SDAI е 23.17 ± 11.89 SD. Подобно на получените резултати за CDAI, болниите на биологична терапия имат изходно висока болестна активност, която на 6-и месец е намаляла до средни стойности 14.63 ± 5.42 SD, дефинирани като умерена болестна активност, а на 12-и месец се регистрира минимална болестна активност (SDAI = 9.39 ± 4.92 SD). При болните, лекувани с ксБПАРЛП, се установяват аналогични резултати по отношение на болестната активност, оценена чрез CDAI. В трите временни интервала се наблюдава статистически снимки на разлика за средните стойности на SDAI (фиг. 3), the group with csDMARDs for which the SDAI was 23.17 ± 11.89 SD. Similar to the results obtained for CDAI, the patients on biological therapy had baseline high disease activity, which at 6th month decreased to mean values of 14.63 ± 5.42 SD, defined as moderate disease activity, and at the 12th month a minimum disease activity (SDAI = 9.39 ± 4.92 SD). Patients treated with csDMARDs showed similar results with respect to the disease activity assessed by CDAI. In the three time intervals, a statistically significant difference was observed for mean values of SDAI (Figure 3).

Фиг. 2. Динамика в средните стойности на CDAI през 12-месечния период на лечение

Fig. 2. Dynamics in mean CDAI values over the 12-month treatment period

Фиг. 3. Промяна в средните стойности на SDAI през 12-месечния период на лечение

Fig. 3. Change in the mean values of SDAI during the 12-month treatment period
Nonetheless, the disease activity remained in the moderate active disease category in the csDMARDs treatment group.

In a parallel comparison of SDAI mean values between the two groups of patients, we found a statistically significant difference in the three time intervals (0 month – $p < 0.001$, the 6th month – $p = 0.001$, the 12th month – $p < 0.001$).

Similar to the CDAI results, gender differences did not reveal a statistically significant difference between male and female disease activity, although for all three measurements men had higher mean SDAI scores.

**Discussion**

Taking into account the EULAR’s guiding principles for RA treatment, we evaluated the effect of therapy through the change in disease activity in our cohort of 220 patients treated with csDMARDs and bDMARDs after one-year prospective follow-up. The results obtained gave us reason to assume that treatment with biological products is reasonably practiced in patients with higher disease activity.

At the start of the follow-up period, the significantly lower values of the DAS28, CDAI, SDAI in the csDMARDs group were recorded compared to patients on bDMARDs. At the 6th month, we observed a significant reduction in disease activity as assessed by the 3 parameters in patients with conventional synthetic drug therapy compared to baseline, which showed a significant effect after initiation of therapy with them.

However, we did not see any significant improvement in the follow-up from 6 months to 12 months in this group of patients. Patients with bDMARDs retain the effect of treatment, and 12.5% of those treated are categorized as remission (assessed by DAS28) at the 12th month. In contrast, in patients who underwent biological treatment, a sustained decrease in disease activity (DAS28, CDAI, SDAI) was observed in both time intervals, and at the end of the follow-up period, 29.8% achieved clinical remission (assessed by DAS28).

However, there was no significant difference in DAS28 values between patients at bDMARDs and csDMARDs at the 6th month. A significantly higher number of patients treated with bDMARDs (33.1%)
evaluated by DAS28 were stratified in the minimal disease activity group, compared to patients on csDMARDs (22.9%). Most patients in conventional synthetic therapy (50%) achieved moderate disease activity at the end of the follow-up period.

When assessing the disease activity with CDAI, we found that the group of biological therapy had significantly lower values for this indicator than the csDMARDs group at all three time intervals. In contrast to the reported results with DAS28, which did not show a change between the 6th and 12th month, we observed a statistically significant difference in the three time intervals from the follow-up period with respect to CDAI in patients treated with bDMARDs.

Similar results were obtained from the SDAI assessment, which gave us reason to assume that bDMARDs treatment is more effective than conventional synthetic therapy. Regardless of the minimal differences we observed, from the results obtained for DAS28, CDAI, SDAI, we have assumed that all three methodologies accurately assess the activity of the disease and are sensitive to changes in the categories: low, moderate and severe disease activity.

The data we have received confirm the results reported by the Norway DMARD Registry for the treatment of RA [8]. Analysis of registry data indicates that the morbidity and response to Methotrexate, Sulfasalazine and TNF-α inhibitors is similar, but according to the published results of randomized clinical trials, treatment with TNF-α inhibitors is more effective. Several randomized clinical trials reported results for lower disease activity in patients treated with TNF-α inhibitors compared to methotrexate [9-16]. Convincing results for delaying the radiographic progression of the disease are found in patients on biological therapy [10].

The results obtained confirm the data reported in the foreign literature by Choi et al. For a better therapeutic response to bDMARDs treatment as assessed by the DAS28, CDAI, SDAI, and the ACR 20/50/70/90 response criteria [16]. Clearly, we are seeing a tendency for an increase in the number of patients starting biological treatment worldwide, as well as in the Republic of Bulgaria.

According to Hockley and Pease data for patients with diagnosed RA, between 7 and 16% are...
В. Бояджиева, Н. Стоилов, М. Иванова и др.

При нарастващия брой болни, лекувани с bDMARDs, се следват световните тенденции за терапия на RA. Приложението им за лечение на възпалителните ставни заболявания е изключително важен подход, който е намалил инвалидизацията на пациентите през последните години. Подобряването на качеството на живот и намаляването на болестната активност са основната цел по време на терапията на пациентите. Подобряването на тези два показателя води до намаляване на разходите за лечение на заболяването, като същевременно позволява ресоциализацията на болниите.

Библиография / Reference

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9. Lipsky PE, Van Der Heijde DM, ST Clair EW et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. treated with biological products [17,18]. However, access to this type of treatment varies considerably between countries. According to the EFPIA report, about 5% of patients in Austria are treated with bDMARDs, while in Norway this share reaches 30% in 2008 [19].

The increasing number of patients treated with bDMARDs followed the global treatment trends for RA. Their use in the treatment of inflammatory joint diseases is an extremely important approach that has reduced the disability of patients in recent years. Improving quality of life and reducing disease activity are the main goal during the therapy of patients. Improving these two indicators leads to a reduction in the cost of treatment of the disease, while allowing for their re-socialization in society.


Abstract. The aim of the study is to establish the frequency and sustained remission and low disease activity in patients with RA in the course of long-term treatment with synthetic and biological means (DMARDs) in real conditions. In the conditions of retrospective data analysis of real clinical practice, there were included 209 patients suffering from RA. Activity indexes of RA in all patients were analyzed in the last year of treatment with bDMARDs. The average age of the patients is 59.01 years old. The dominants sex is female (84.6%). The beginning of treatment with biological therapy is delayed with an average of 8.21 year. In all activity indexes of RA, which were monitored in the beginning of the 6th and the 12th months, there was established a significant difference in their variation for the periods surveyed. There is a general trend towards lowering the values of our indicators. In the beginning of the monitored period, the patients going into remission (DAS28 CRP) are approximately 3 times less – 11% (n = 23) in comparison with those in the end of the study – 32.99% (n = 64) (p < 0.001). In 10% of the cases a sustained remission is observed by both combined indexes (DAS28 ESR and DAS28 CRP) (p < 0.001). Today the accurate way is the “treat to target” strategy. The purpose is lowering the activity of the disease to very low levels (or remission) and achieving a long-term remission which is now real and achievable.

Key words: rheumatoid arthritis, biological therapy, remission, low disease activity
The rheumatoid arthritis (RA) is characterized by inflammation of the joints, leading to their destruction. This leads to lowering their functional capacity, ability to work and decreased quality of life in patients with RA [15]. A progress in understanding the pathogenesis of RA helped in developing new therapeutic purposes and new treatment guidelines, targeting remission [13]. However, there is more than one criterion to determine remission [4]. There are used at least three definitions for remission: (DAS28) < 2.6 and 2.3, simplified activity index (SDAI) ≤ 3.3 and clinical activity index (CDAI) ≤ 2.8 [9, 12]. Recently ACR/EULAR suggested new criteria for remission in patients with RA [6, 7]. Relatively little is known about the duration of remission in everyday clinical practice. Since remission is a stated goal of RA, it would be important to compare the remission criteria and to examine the duration of remission in RA patients [10].

The aim of the study was to determine the frequency and duration of remission and low disease activity in RA patients during long-term synthetic and biological treatment (DMARDs) in real-world conditions.

**MATERIALS AND METHODS**

In the conditions of retrospective data analysis of real clinical practice, there were included 209 patients suffering from RA. The diagnosis of RA was based on the ACR Criteria 1987 [2]. Conditions for inclusion in the study were: bDMARDs, available medical documentation (dossier of the patients conducting treatment with bDMARDs in St. Marina University Hospital – Varna) duration of treatment without interruption at least 6 months before the beginning of the study.

All available documentation of the patients in the database of “St. Marina” and ambulatory procedure No. 42 were analyzed. In addition, laboratory test were demanded outside “St. Marina” available in the dossiers of patients at their GPs. The indicators of all patients were analyzed in the last year of treatment with sDMARDs (Table 1).
The results were statistically processed using comparative analysis ($\chi^2$, ANOVA), correlation analysis (Spearman – $\rho$), dispersion analysis (mean ± SD), variation and regression analysis. For a statistically significant level we assumed $p < 0.05$. The results are calculated with the statistical software SPSS v. 23.0 for Windows.

**Results**

1. **Profile of the patients with RA**

The characteristics of the patients included in the study are presented in table 2. The average age of the patients is 59.01 years. There is a female prevalence (85.2%).

The duration of the treatment with biological agents in the study group is 3.24 times less than that of the disease. The onset of treatment with biological agents is delayed by an average of 8.21 years.

2. **Clinical and laboratory indicators of activity of RA in the last one year of treatment with biological agents**

The dynamics of clinical, laboratory and disease indices over the last year of treatment with bDMARDs is presented in Table 3.

All the RA activity indicators that were followed up at the beginning, at the 6th month and at the
Таблица 2. Характеристика на болните / Table 2. Characteristics of the patients

<table>
<thead>
<tr>
<th>Показател / Indicator</th>
<th>Брой (%) / Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Пол / Sex</td>
<td></td>
</tr>
<tr>
<td>мъже / male</td>
<td>31 (14,80%)</td>
</tr>
<tr>
<td>жени / female</td>
<td>178 (85,20%)</td>
</tr>
<tr>
<td>Възраст / Age</td>
<td>mean ± SD (range)</td>
</tr>
<tr>
<td>PA (ACR 1987)</td>
<td>209 (100,0%)</td>
</tr>
<tr>
<td>Ревматоиден фактор / Rheumatoid factor</td>
<td>209 (100,0%)</td>
</tr>
<tr>
<td>Давност на артрита / Duration of the arthritis</td>
<td>mean ± SD (range)</td>
</tr>
<tr>
<td>X-ray stage</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>71 (34,0%)</td>
</tr>
<tr>
<td>III</td>
<td>63 (30,10%)</td>
</tr>
<tr>
<td>IV</td>
<td>75 (35,90%)</td>
</tr>
<tr>
<td>II</td>
<td>114 (54,50%)</td>
</tr>
<tr>
<td>III</td>
<td>95 (45,50%)</td>
</tr>
<tr>
<td>Лечение на PA / Treatment of RA</td>
<td></td>
</tr>
<tr>
<td>Симптоматично: / Symptomatically:</td>
<td></td>
</tr>
<tr>
<td>НСПВС</td>
<td>90 (43,10%)</td>
</tr>
<tr>
<td>Methylprednisolon</td>
<td>119 (56,94%)</td>
</tr>
<tr>
<td>Methylprednisolon – доза</td>
<td>5,55 mg ± 2,33 mg (2-12)</td>
</tr>
<tr>
<td>sDMARDs:</td>
<td></td>
</tr>
<tr>
<td>Methotrexat</td>
<td>133 (64,0%)</td>
</tr>
<tr>
<td>Methotrexat – доза</td>
<td>11,86 mg ± 3,83 mg (2,5-25,0)</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>9 (4,31%)</td>
</tr>
<tr>
<td>Leflunomide – доза</td>
<td>20 mg</td>
</tr>
<tr>
<td>Без sDMARDs</td>
<td>67 (32,10%)</td>
</tr>
<tr>
<td>bDMARDs:</td>
<td></td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>93 (44,50%)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>77 (36,80%)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>5 (2,40%)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>13 (6,20%)</td>
</tr>
<tr>
<td>Certolizimab pegol</td>
<td>2 (1,0%)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>6 (2,9%)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>13 (6,20%)</td>
</tr>
</tbody>
</table>

Периоди от лечението на болни от PA (год.)

Periods of treatment of RA patients

![Graph](image.png)

Фиг. 1. Периоди от лечението на болни от PA / Fig. 1. Periods of treatment of RA patients
и на 12-ия месец, беше установена съществена разлика в изменението им за изследваните периоди (табл. 3). Наблюдава се обща тенденция към понижаване на стойностите на разглежданите от нас показатели.

Болните в ремисия (DAS28 СУЕ) в началото на изследването периода са значително по-малко 5.7% (n = 12) в сравнение с тези в ремисия в края (12 м.) – 11.86% (n = 23) (р < 0.001). Подобна тенденция се установява и при болни в ремисия според DAS28 CRP. В началото на изследването период болните в ремисия са приблизително три пъти по-малко – 11% (n = 23), в сравнение с тези в края – 32.99% (n = 64) (р < 0.001).

Има статистически значимо увеличение на честотата на болни в ремисия, измерена както с DAS28 СУЕ, така и с DAS28 CRP, в началото и в края на изследвания период (р < 0.001).

3. Продължителна ремисия в хода на дълготрайно лечение с биологични средства

Анализът на болни в ремисия и по двата комбинирани индекса в началото на проследяването (DAS28 СУЕ и DAS28 CRP) показва, че всички болни, които са били в ремисия, остават в ремисия една година по-късно и постигат продължителна ремисия за период от 12 месеца (р < 0.001).

Table 3. Comparative analysis of changes in activity indicators of RA at baseline, at 6 months and at the end (12 months)

<table>
<thead>
<tr>
<th>Показател / Indicator</th>
<th>Mean ± SD (0 мес. / month)</th>
<th>Mean ± SD (6 мес. / month)</th>
<th>Mean ± SD (12 мес. / month)</th>
<th>0-6 мес. / month</th>
<th>0-12 мес. / month</th>
<th>6-12 мес. / month</th>
</tr>
</thead>
<tbody>
<tr>
<td>СУЕ / ESR</td>
<td>23.92 ± 17.20</td>
<td>22.32 ± 17.19</td>
<td>21.57 ± 16.38</td>
<td>9.27 (р &lt; 0.001)</td>
<td>7.15 (р &lt; 0.001)</td>
<td>12.60 (р &lt; 0.001)</td>
</tr>
<tr>
<td>CRP</td>
<td>6.37 ± 7.09</td>
<td>5.49 ± 8.92</td>
<td>5.12 ± 7.91</td>
<td>7.67 (р &lt; 0.001)</td>
<td>9.48 (р &lt; 0.001)</td>
<td>29.37 (р &lt; 0.001)</td>
</tr>
<tr>
<td>ББС / NTJ</td>
<td>4.24 ± 2.71</td>
<td>3.20 ± 1.83</td>
<td>2.84 ± 1.63</td>
<td>8.28 (р &lt; 0.001)</td>
<td>5.63 (р &lt; 0.001)</td>
<td>20.42 (р &lt; 0.001)</td>
</tr>
<tr>
<td>БОС / NSJ</td>
<td>1.22 ± 2.19</td>
<td>0.66 ± 1.28</td>
<td>0.52 ± 1.08</td>
<td>24.40 (р &lt; 0.001)</td>
<td>22.55 (р &lt; 0.001)</td>
<td>86.11 (р &lt; 0.001)</td>
</tr>
<tr>
<td>VAS – GP</td>
<td>36.56 ± 11.34</td>
<td>34.02 ± 9.11</td>
<td>31.56 ± 8.22</td>
<td>20.57 (р &lt; 0.001)</td>
<td>11.73 (р &lt; 0.001)</td>
<td>20.04 (р &lt; 0.001)</td>
</tr>
<tr>
<td>DAS28 СУЕ / ESR</td>
<td>3.85 ± 0.83</td>
<td>3.55 ± 0.76</td>
<td>3.42 ± 0.74</td>
<td>3.17 (р = 0.011)</td>
<td>1.94 (р = 0.027)</td>
<td>14.05 (р &lt; 0.001)</td>
</tr>
<tr>
<td>DAS28 СУЕ-П / ESR-П</td>
<td>0.43 ± 0.08</td>
<td>0.41 ± 0.09</td>
<td>0.39 ± 0.09</td>
<td>0.856 (р = 0.694)</td>
<td>3.12 (р &lt; 0.001)</td>
<td>4.93 (р &lt; 0.001)</td>
</tr>
<tr>
<td>DAS28 CRP</td>
<td>3.37 ± 0.71</td>
<td>3.01 ± 0.72</td>
<td>2.88 ± 0.63</td>
<td>1.58 (р = 0.231)</td>
<td>3.04 (р = 0.079)</td>
<td>21.51 (р &lt; 0.001)</td>
</tr>
</tbody>
</table>
The analysis of patients, who only had DAS28 ESR-remission at the beginning of the study, showed that after 12 months they achieved also a DAS28 CRP-remission ($p < 0.001$). There were only 3 patients who retained the result of DAS28 ESR < 2.6 without reaching DAS28 CRP-remission.

We found a four-fold increase in the patients who achieved remission on both combined activity indices at the end of the study (12th month), as in 10% it is a sustained remission on both combined indices (DAS28 ESR and DAS28 CRP) ($p < 0.001$).

The change in RA's disease activity in patients with an initial remission at the baseline, measured by DAS28 ESR and DAS28 CRP, showed that at the end of the study 63.6% maintained a remission state (achieving a sustained remission), another 36.4% progressed to low disease activity (DAS28 ESR and DAS28 CRP 2.6 ÷ 3.2). Of the patients with an initial low disease activity, 23.10% achieved remission on both combined activity indices at the end of the study (12th month), as in 10% it is a sustained remission on both combined indices (DAS28 ESR and DAS28 CRP) ($p < 0.001$).
с тези, които не го приемат (р < 0.001) (ρ = 0,550, p < 0.001). Намалението на активността на RA при болни с умерена висока активност в началото на наблюдавания период в 25% от случаите се дължи на приема на Methotrexate.

Установява се съществена разлика в промяната на активността на RA през наблюдавания период в зависимост от рентгеновия стадий на RA, като зависимостта между рентгеновия стадий и активността варира от умерена до сила. При болни във втори рентгенов стадий се установява намаление на активността при 49% от болниците, прогресиране при 6% от болниците (р < 0.001) (ρ = 0,494, p < 0.001). При 60% от болниците в трети рентгенов стадий се установява намаление на активността, прогресиране при 3% от болниците (ρ = 0.001) (ρ = 0,371, p = 0.004). При 45% от болниците в четвърти рентгенов стадий се установява намаление на активността, а прогресиране – при 7% от болниците (ρ = 0.001) (ρ = 0,521, p < 0.001).

Вероятността за намаление на активността на RA в зависимост от рентгеновия стадий варира от 13,70% до 27,10% при различните рентгенови стадии.

**Discussion**

The goal of treatment of RA patients today is to achieve clinical and laboratory remission. "Treat to target" strategy and "tight control" in recent years have proved to be a successful step towards achieving a greater success in mastering RA activity. According to some authors, even the strategy itself leads to some percent of decrease in the RA activity, regardless of the therapy applied [5, 14]. Our results from the last one year, when a „tight control“ was applied to patients undergoing a biological treatment, show an increase in the frequency of remission and a significant decrease in RA activity. The evaluation of the activity in both combined indices (DAS28 ESR and DAS28CRP) and the presence of remission and low disease activity in both combined indices, found that there is a moderate dependence between them. Our results show that the frequency of remission and low disease activity with DAS28 CRP is higher than the DAS28 ESR. Similar results are also found by other authors [11]. The sustained remission (12 months) found by us in 10% of patients undergoing treatment in real clinical conditions due to the
Изследване на активността на РА при болни с умерен и тежък РА се потвърждават и от други автори [3].

Изводи
Изследването на болестната активност на РА при болни, провеждащи лечение с биологични средства, показа, че днес правилният подход е стратегията treat to target. Целта е намаляване на активността на заболяването до много ниски нива (или ремисия) и постигане на продължителна ремисия и сега тя е реална и достижима.

Библиография / Reference

Our results on the effect of Methotrexate on disease activity in patients with moderate and severe RA confirm these reported by other authors.

Conclusions
The study of RA disease activity in patients undergoing biological treatment has shown that the right approach today is "treat to target" strategy. The goal is to decrease the activity of the disease to very low levels (or remission) and achieve sustained remission and this is now real and achievable.


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NEWLY DEVELOPED DYNAMIC SPLINT VS. DYNAMIC OUTRIGGER SPLINT FOR POSTOPERATIVE TREATMENT OF EXTENSOR TENDON RUPTURE IN PATIENTS WITH RHEUMATOID WRISTS: A PRELIMINARY STUDY

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Abstract. Aim and object of the study: Extensor tendon rupture in patients with rheumatoid wrists causes dysfunction of the hand and necessitates tendon reconstruction and surgical treatment of the wrist joint. Dynamic outrigger splints using rubber bands have been used for early postoperative mobilization of the fingers. However, these splints are bulky and cause discomfort. We developed a new dynamic splint, which is compact and uses torsion springs instead of the rubber bands used in conventional outrigger splints. The splint extends the metacarpophalangeal joints using a volar finger bar. The objective of this study was to compare the clinical outcomes and subjective assessments between patients treated with the two types of splint. Methodology: Fourteen wrists (14 patients) were included. Clinical outcomes (range of active motion of the metacarpophalangeal joint) and subjective assessments were investigated in patients treated with either an outrigger splint or our new dynamic splint. Results: There were no differences in clinical outcomes between patients treated with the two kinds of splint. The new splint performed better in terms of the subjective assessment of changing clothes and bulkiness. Conclusions: The new splint yielded equivalent clinical outcomes and better subjective assessments compared to conventional outrigger splints due to its reduced size.

Key words: newly developed dynamic splint, dynamic outrigger splint, extensor tendon rupture, treatment

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by progressive systemic inflammation. RA primarily affects the lining of the synovial joints and destroys both articular cartilage and subchondral bone, leading to functional limitations and disability [1].

Spontaneous extensor tendon rupture in patients with a rheumatoid wrist is a complication of RA. Tendon rupture often affects the ulnar fingers, especially the little finger, leading to immediate dysfunction of the hand and the need for tendon reconstruction and treatment for distal radioulnar joint (DRUJ) in most patients [2, 3].

After surgery for extensor tendon injuries, the fingers are immobilized for a few weeks, after which exercise is allowed [4-6]. Before 2000, some authors reported that early finger motion exercises could result in earlier recovery, a shorter period of rehabilitation, and lower costs than immobilization therapy [7-9]. Early movement programs are also beneficial to the repaired tendon, both biomechanically and biochemically [9]. Postoperative therapy tends to involve a dynamic outrigger splint with rubber bands to allow active flexion and passive extension of the fingers [7-9]. However, based on our experience, outrigger splints are large and patients complain about the discomfort, possible trauma, poor appearance, and presence of a large outrigger bar on the dorsal side of the splint making it difficult to change clothes. With these complaints in mind, we developed a new dynamic splint with the aim of improving patient subjective assessments. The purpose of this study was to compare the clinical outcomes and subjective assessments between patients treated with either our new dynamic splint or a traditional outrigger splint.

MATERIALS AND METHODS

We retrospectively reviewed the clinical data of patients who were diagnosed with RA and under-
went surgery for extensor tendon reconstruction and treatment of the distal radioulnar joint for extensor tendon ruptures at the wrist. We performed verbal or written analysis of patients’ subjective assessments during splint use. We could not make contact with 11 patients because of relocation or death. This study included the remaining 14 patients (14 wrists). Written informed consent for publication was obtained from all patients, and the study was approved by the institutional review board of our institution.

Surgical procedures

Surgical procedures were performed under general or local anesthesia using air tourniquet control. A dorsal incision over the wrist was made. The extensor retinaculum was incised using a step-cut method through the 5th compartment to the 4th compartment. The extensor tendons were exposed and the synovium around the healthy and free ends of the tendons was removed. The excursion of the proximal end of the ruptured tendons was assessed by pulling distally. When the excursion was 15-20 mm, the condition of the proximal stump was judged as the available amplitude of the muscle, a tendon graft was selected as a reconstruction method, and the palmaris longus was harvested. When the excursion was poor, different reconstruction methods, i.e. tendon transfer and end-to-side suture technique (the distal end of the ruptured tendon was sutured to the adjacent extensor tendon) were selected. Thereafter, procedures for the wrist joint and DRUJ were performed based on the preoperative radiograph and instability of the wrist, namely the Sauvé-Kapandji procedure, Darrach procedure, and total wrist fusion [10, 11]. Tendon reconstruction was then performed using an interfacing suture for all tendons. The dorsal capsule was repaired. The extensor retinaculum was repaired by lengthening and placed over the tendons to prevent bowstringing. The wrist and fingers were covered by bulky dressing and the wrist and MCP joints were immobilized in the neutral position and at 0° of extension, respectively.

Postoperative therapy and dynamic splints

At 2 days after surgery, the splint was applied and passive extension by dynamic assistance and active flexion of the fingers were started under instruction by a hand therapist during hospitalization. Two kinds of splint were used. A conventional-type dynamic outrigger splint was used in eight patients (group O), whereas a newly developed dynamic splint assisted by torsion springs was used in six patients (group T). The former splint had been used until February 2006, whereas the latter had been used since March 2006. The former splint was forearm-based and included an outrigger with rubber bands (Fig. 1A). Four rubber bands were attached to the index to little fingers. The tension of each band could be adjusted by the length and thickness of the rubber band for each finger independently (Fig. 1B, C). The latter splint was forearm-based and included a bar and torsion springs (Fig. 2A). This was custom-made splint made by orthotist. The torsion springs were made of piano wire and the thickness and winding number of the springs were adjusted depending on the strength of grip and finger extension of the patient before surgery. The finger bar was located volar to the proximal phalanx of the fingers and the springs acted to bring the fingers into the extended position at the MCP joint (Fig. 2B, C). The bar was on a uniform plane and its strength was adjusted by the springs. As such, the tension could not be adjusted for each finger independently. Except for sleeping, the patients put on the splint. At night, the wrist and fingers were immobilized in neutral and extended.

Fig. 1. Conventional dynamic outrigger splint

(A) Appearance of the splint. The splint is forearm-based and consists of the outrigger bar with rubber bands. (B) Dorsal view of the splint. Rubber bands attached to the proximal fingers extend the metacarpophalangeal joints of the fingers. (C) Volar view of the splint. Rubber bands attached to the proximal fingers.
positions, respectively, using another static splint. Massage was started at 2 weeks after surgery to reduce edema. Once self-training was possible, rehabilitation was performed at an out-patient clinic. The splint was removed and active motion of the MCP joint and wrist joint was started at 6 weeks after surgery. Free use of the hand was allowed at 3 months after surgery.

Objective and subjective assessments
Objective outcomes for tendon reconstruction were assessed by the active range of motion of the MCP joint at the final follow-up. They were evaluated using a standard goniometer and classified by Geldmacher’s criteria, as modified by Sakuma et al. [12, 13]. The criteria were categorized into three groups: good = an active flexion arc ≥ 45° and an extension lag < 20°, fair = an active flexion arc ≥ 45° and an extension lag 20-40° or an active flexion arc < 45° and an extension lag < 20°, or poor = an active flexion arc < 45° and an extension lag 20-40° or an extension lag ≥ 40°.

We performed subjective assessments of patients treated with the two types of splint. The items assessed were as follows: general performance of rehabilitation (difficult/moderate/easy), changing clothes (difficult/moderate/easy), eating meals (difficult/moderate/easy), finger flexion exercise (difficult/moderate/easy), finger extension exercise (difficult/moderate/easy), and bulkiness of the splint (large/moderate/good). Each item was classified into three stages and scored. Poor assessments were given scores of 0 and good assessments scores of 2. We showed both splints to the patients and asked them which they would select for future therapy. Patient satisfaction with splint therapy was scored by the patients themselves using a visual analog scale: i.e. no satisfaction (0) to full satisfaction (100).

Statistical analysis
Statistical analysis was performed as follows. To analyze the objective outcomes and subjective assessments, each finger and patient was included, respectively. To analyze objective outcomes, we combined the fair and poor groups. To analyze subjective outcomes, the responses with scores 1 and 2 were combined. Differences between the groups were assessed by the chi-square test or Mann-Whitney U-test. Fisher’s exact test was also used where appropriate. Statistical significance was set at $p < 0.05$.

RESULTS
Demographic data of the patients (table 1)
There were 13 women in the final cohort. The average age of the patients at surgery was 53 (range: 30-79) years. The average duration after diagnosis with RA was 8.7 (range: 1-21) years. The average Larsen grade of the affected wrist was 4.0 (range: 2-5), whereas that of the affected metacarpophalangeal (MCP) joint was 1.6 (range: 0-4) [14]. The right side was involved in 11 patients and the left in 3 patients. The average number of fingers with ruptured extensor tendons was 1.9 (range: 1-3). The average duration from symptoms of tendon rupture to surgery was 8.8 (range: 1-84) months. Surgical procedures for DRUJ were the Sauvé-Kapandji procedure in 8 patients, Darrach procedure in 3 patients, and total wrist fusion in 3 patients. Tendon reconstructions were end-to-side suturing in 19 fingers, tendon transfer in 1 finger, and tendon graft in 7 fingers.
Clinical characteristics of the patients

For objective outcomes, nine fingers had good, five had fair, and one had poor results in group O. Nine fingers had good and three had fair results in group T (p = 0.70, Table 2). All fingers with fair and poor results in group O and two of three fingers with fair results in group T had multiple affected fingers (rate of "good": single; 6/7, multiple; 12/20, p = 0.36). The average extension range of the MCP joint of the little finger was -4.4° (range: 30 to -30) in group O and -8.7° (range: 0 to -20) in group T, whereas the average range of flexion was 76.9° (range: 40 to 90) in group O and 64° (range: 35 to 85) in group T (p = 0.85, 0.21, respectively). The average extension range of the MCP joint of the ring finger was -11.7° (range: 0 to -30) in group O and -3.3° (range: 0 to -20) in group T, whereas the average range of flexion was 75.8° (range: 30 to 90) in group O and 71.7° (range: 60 to 85) in group T (p = 0.18, 0.20, respectively). The extension range of the MCP joint of the middle finger was -30° in group O and -20° in group T, whereas the range of flexion was 70° in group O and 80° in group T (one finger in each group).

Table 2. Objective outcomes after treatment

<table>
<thead>
<tr>
<th>Objective outcomes</th>
<th>Outrigger splint (group O)</th>
<th>New dynamic splint (group T)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 fingers</td>
<td>Good</td>
<td>Fair</td>
<td>Poor</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>
For subjective assessments, there were statistically significant differences in changing clothes and bulkiness of the splint between the two types of splint, with the new splint receiving fewer “difficult or large” responses (Table 3). There was no significant difference in the selection of the different splints for future therapy and satisfaction with splint therapy between patients treated with the two types of splint.

**Table 3. Subjective assessments after treatment**

<table>
<thead>
<tr>
<th>Subjective assessments</th>
<th>Outrigger splint (group O)</th>
<th>New dynamic splint (group T)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>easy</td>
<td>moderate</td>
<td>difficult</td>
</tr>
<tr>
<td>General performance of rehabilitation</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Changing clothes</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Eating meals</td>
<td>0</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Finger flexion exercise</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Finger extension exercise</td>
<td>2</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Bulkiness of the splint</td>
<td>good</td>
<td>moderate</td>
<td>large</td>
</tr>
<tr>
<td>Splint selection for future therapy</td>
<td>O: 2</td>
<td>T: 6</td>
<td></td>
</tr>
<tr>
<td>(O vs. T)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Satisfaction (VAS)</td>
<td>57.4 (12–96)</td>
<td>63.8 (46–83)</td>
<td></td>
</tr>
</tbody>
</table>

The values are expressed as the average (range). O: conventional dynamic outrigger splint, T: dynamic splint assisted by torsion springs. VAS: visual analog scale.

**DISCUSSION**

In this study, we investigated the efficacy of a newly developed dynamic splint assisted by torsion springs for the postoperative treatment of extensor tendon ruptures in patients with RA. This new system is different from the conventional outrigger splint in that the bar is replaced with a volar finger bar, reducing the bulkiness on the dorsal side and making the new splint more compact. This retrospective continuous study revealed that this new splint did not reduce finger motion and yielded better results for the subjective items changing clothes and bulkiness of the splint when compared to a traditional outrigger splint.

There were concerns regarding extension contracture (especially with respect to the ulnar fingers when treated with our new splint) because it was not possible to adjust each finger individually. However, there was no difference in the movement of the little finger between the two splints. A previous study showed that tendon excursion to minimize adhesion at the repaired site was 5 mm [15]. For 5 mm of tendon gliding, approximately 40° of MCP joint motion of the little finger is necessary, depending on the moment arm [16]. Careful attention and instruction for finger motion were provided to patients to prevent extension contracture and adhesion of the extensors. With these considerations in place, the new splint achieved both compact size and acceptable finger motion.

There were no significant differences in terms of which splint patients selected for future therapy and satisfaction with splint therapy between patients treated with the two kinds of splint, although only two of eight patients in group O selected outrigger splint. From these results, it appears that the patients were not completely satisfied by the new splint. The items that patients were unsatisfied with (defined based on half of patients giving a score of 0 or 1) were “general performance of rehabilitation”, “changing clothes”, “eating meals”, “bulkiness of the splint”, and “finger flexion exercise”. Generally, patients with RA have very poor grip strength due to joint destruction, disability in other joints, and illness. With the above in mind, further improvement of our new splint is desirable in the future through the following: weight reduction by using different materials or altering the strength of the spring postoperatively.

In this study, 60% of patients with multiple tendon injuries experienced fair and poor objective outcomes in both splint groups. A previous study also...
showed similar results: postoperative finger motions were worse in patients with multiple extensor ruptures than in those with a single rupture [4, 5, 13]. Sakuma et al. reported that the number of ruptured extensor tendons was significantly correlated with the results of tendon reconstruction and significantly associated with preoperative surgical delays [13]. We agreed with their recommendation that early surgical intervention in the treatment of extensor tendon ruptures with RA wrists is important to improve outcomes.

This study has several limitations that should be mentioned. First, the number of patients was small. Second, the follow-up rate was 44%. Third, the backgrounds of the patients were different, including surgical procedures. This might have been affected by the period in which surgery was performed. Moreover, group O included patients with total wrist fusion. Because the effect of tenodesis at the wrist joint is ameliorated by fusion, the range of motion at the MCP joint might have decreased.

In conclusion, we developed a new dynamic splint assisted by torsion springs for the postoperative treatment of extensor rupture in RA wrists by removing the dorsal outrigger from an outrigger splint and instead using a torsion spring to make the system more compact. Our new splint provided equal active range of motion of the MCP joint compared to conventional dynamic outrigger splints. Subjective assessments revealed that the new splint was superior to conventional outrigger splints in terms of changing cloths and bulkiness, which are two of the main complaints of patients treated using these splints. This new splint could lead to improved patient quality of life during treatment.

This study has not been published before.

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Conflicts of Interest: None

No parts of the article, including ideas, texts, and graphics are copied from elsewhere.

References

REVIEWS

CARDIOVASCULAR DISEASE IN PATIENTS WITH PSORIATIC ARTHRITIS: CORRELATION OR CAUSATION?

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Abstract. Psoriatic arthritis (PsA) is a pleiotropic inflammatory disease from the spectrum of spondyloarthritis which can potentially affect many organ systems. The chronic nature of the inflammatory milieu presented in rheumatic diseases, is similar to that of atherosclerosis, suggesting a common pathogenic basis. Effector cells of innate and adaptive immunity along with pro-inflammatory cytokines and other immune mediators may work together to potentiate endothelial damage and accelerate cardiovascular diseases (CVD). Thus, the risk of CVD and associated complications in PsA might be elevated, especially in patients with severe psoriasis, long-standing disease, and multiple comorbidities. This narrative review focuses on the prevalence of CVD in PsA patients, the overlapping molecular features in the pathogenesis of both conditions, and summarizes the benefits of the current treatments on impairments resolution.

Key words: cardiovascular disease, psoriatic arthritis, treatment

ВЪВЕДЕНИЕ

Psoriatic arthritis (PsA) is a chronic systemic inflammatory disorder characterized by enthesal and joint inflammation, affecting about 0.05% to
засяга около 0.05-0.25% от общата популация и от 6 до 41% от болни с псориазис [1]. Той е хетерогенно заболяване, принадлежащо към спектъра на спондилоартритите, което може да за- сегне много органи и системи. Многобройни са доказателствата, подкрепящи връзката на ПсА с редица съпътстващи заболявания (ССЗ), мозъчносъдови, периферносъдови, гастроинтестинални, бъбречни заболявания, злоачествени заболявания, инфекции и разстройства на настроението [2, 3].

Отдавна е известно, че хроничното системно възпаление, характерно за ревматичните забо- лявания, наподобява процесите на атеросклероза. Ето защо теоретично двете състояния биха могли да споделят общо патогенетична база: в атеросклеротичните лезии се откриват ефекторни клетки на вродения и адаптивния имунитет, в комбинация с провъзпалителни цитокини и други имунни медиатори, където играят важна роля в индуцирането, прогресията и рутурата на плаките [4, 5, 6]. Проблемът със сърдечно-съдовия риск при хроничните артропатии е от съществено значение за ежедневната клинична практика. Посочените ревматични заболявания се считат за нефатални, но техният хроничен характер и тяхната прогресия често водят до по-висока заболяемост и смъртност в резултат на ССЗ. Установено е, че ССЗ и метаболитният синдром се срещат по-често при болни с ПсА, в сравнение с здравите индивиди. В атеросклеротичните плаки на болни от ПсА се откриват възпалителни медиатори. Това внушава, че хроничното възпаление действа независимо и/или синергично с традиционните рискови фактори в патогенезата на атеросклерозата [7].

В обзора е разгледан подробно рискът от ССЗ при болни с ПсА, като се акцентира върху общите патогенетични механизми и патоморфологични характеристики.

За целта е осъществен систематичен преглед на литературата, публикувана в научната база данни Medline (PubMed) и Cochrane. В PubMed се срещат, както MeSH термини, така и съответните термини в свободен текст. Бяха използвани следните ключови думи за търсене (синоними и комбинации): „псориатичен артрит” И „ риск”, И „сърдечно-съдови заболявания”, ИЛИ „ затлъстяване”, ИЛИ „ метаболитен синдром”, ИЛИ „ хипертония”, ИЛИ „ диабет”, или „инсулинова резистентност”, ИЛИ „ противовъзпалително лечение”, ИЛИ „ ендотел”. търсенето обхваща период до януари 0.25% of the general population and 6% to 41% of the psoriasis patients overall [1]. It is considered a heterogeneous disease, belonging to the spectrum of spondyloarthritides, which can potentially affect many organ systems. Increasing evidence support the association between PsA and multiple comorbidities, including obesity, metabolic syndrome, cardiovascular disease (CVD), cerebrovascular, peripheral vascular, gastrointestinal, kidney diseases, malignancy, infection, and mood disorders [2, 3].

It has long been theorized that the chronic systemic inflammatory milieu presented in rheumatic diseases resembles the process of atherosclerosis, suggesting a common pathogenic basis. Effector cells of innate and adaptive immunity along with pro-inflammatory cytokines and other immune mediators are found in atherosclerotic lesions, where they play an important role in induction, progression and rupture of plaques [4, 5, 6]. The issue of cardiovascular risk in chronic arthropathies and the significance of said risk on clinical implications in daily practice are of considerable importance. While most rheumatic diseases are regarded as nonfatal, their chronic nature and subtle progression often lead to an accelerated death by CVD. In particular, CVD and metabolic syndrome appear more common in patients with PsA than in controls. Inflammatory mediators have been found in atherosclerotic plaques of PsA patients. This finding suggests that chronic inflammation acts independently and/or synergistically with the traditional risk factors in the pathogenesis of atherosclerosis [7].

In this review, we have focused on CVD risk and the underlying mechanisms associated with the PsA in order to get a clear and concise picture of both interrelated pathological processes.

We carried out a literature search using the scientific literature databases Medline (PubMed) and Cochrane library. In PubMed, both MeSH terms and relevant free-text terms were used. The following search terms (synonyms and combinations) were applied: "psoriatic arthritis" AND "risk" AND "cardiovascular diseases", OR "obesity", OR "metabolic syndrome", OR "hypertension", OR "diabetes", OR "insulin resistance" OR "anti-inflammatory treatment" OR "endo-
PsA is related to a cluster of comorbidities, which are frequent and need to be assessed and treated. The association between psoriasis and metabolic co-morbidities is well established, although not although still not fully understood. The prevalence and magnitude of the classic risk factors for CVD like diabetes, hyperlipidaemia, hyperuricemia, arterial hypertension, as well as myocardial infarction (MI), cardiovascular mortality and morbidity are noteworthy in PsA patients [8, 9]. Nonconventional risk factors such as raised levels of homocysteine, excessive alcohol consumption, depression and anxiety, kidney disease, malignancy, and infection are also often seen in this patient population [10, 11]. A positive correlation between increased risk of adverse cardiovascular events and earlier-onset disease, psoriasis area, and severity index scores have been observed [12, 13]. In several studies of PsA cohorts the prevalence of hypertension amounted to 19.9-47.3%; for diabetes mellitus – 7.8-20.2%; for dyslipidemia – 11.6-47.5%; for obesity – 6.0%; for chronic liver disease/cirrhosis/hepatitis –18.1%; multi-comorbidity is seen in 9.9% and metabolic syndrome in 19.9% [14, 15]. A prospective follow up by Gladman et al. evaluated the risk of several outcomes attributable to CVD among PsA patients in comparison to data from the general population. The authors found that the occurrence of MI is 2.5-fold higher (Standardized prevalence ratios [SPRs] 2.57; 95% CI 1.73 to 3.80) and the prevalence of angina (SPRs 1.97; 95% CI 1.73 to 3.80) and hypertension (SPR 1.90 95% CI 1.59 to 2.27) in PsA patients is twice that in the population-based controls. The data for congestive heart failure (SPRs 1.19; 95% CI 0.50 to 2.86) and cerebrovascular accident (SPRs 0.91; 95% CI 0.34 to 2.43) did not show any magnitude of difference [12]. Moreover, a study by Gulati et al indicates that the CV risk factors in PsA were present before the diagnosis was established. Compared to controls patients who developed PsA had higher BMI, lower HDL-c and more were smokers [16].
Сърдечно-съдови заболявания при пациенти със страдащи от възпалителни ставни заболявания показва, че относителният и абсолютният риск от ССЗ според систематичното измерване на коронарния риск (SCORE), оцениващо 10-годишния риск от фатално атеросклеротично СС събитие, е сходен при ревматоиден артрит (РА), аксиален спондилоартрит и ПсА, въпреки че при ПсА хипертонията и затълстването са по-чести [17]. При проследяването средното време за развитие на първия сърдечно-съдов рисков фактор е 20.5 месеца за РА, 18.1 месеца за псориазис, а най-кратко – 17.4 месеца – за ПсА [18]. При пациентите с ПсА е налице значително по-висок риск от затълстване, високи гликемии на гладно и повишен общ холестерол и холестерол с ниска плътност (LDL холестерол), в сравнение с тези с РА [19]. В голяма австралийска кохорта е установено, че честотата на депресията, хипертонията, диабета, исхемичната болест на сърцето и други съпътстващи заболявания е по-голяма при ПсА в сравнение с РА [20]. Метаанализ от Horreau и съавтори [21] доказва, че рискът от ранно коронарно заболяване и MI е по-висок при болни с тежък псориазис и ранно начало на болестта. В противоположност, анализ на Egeberg и съавтори [22] не показва връзка между ПсА и риска от MI; рискът е увеличен само при болни на възраст < 50 години и предимно при липса на ПсА.

Напредъкът в молекулярните и имунологичните изследвания доведе до разбирането, че мастната тъкан има секреторни свойства, тъй като тя произвежда голямо разнообразие от разтворими медиатори – адипокини. Повечето от тях имат провъзпалителна активност и участват в регулирането на имунния отговор. По този начин затълстването поддържа нискостепенна системна възпалителна среда, която може да задейства или да усили други възпалителни заболявания, включително имуномедираните състояния. През последните години съществуват съществени доказателства, че повечето от тези молекули са възможни потенциални мишени за лечение на ПсА и PsA. Нещо повече, това оказва връзка между ПсА и риска от MI; рискът е увеличен само при болни на възраст < 50 години и предимно при липса на ПсА [22].

Натрупват се доказателства, че повишава риска за окуларни и метаболитни заболявания [23, 24]. Въпреки повишаването на артериалната хипертония при болни с псориазис, патофизиологичният механизъм за развитието ѝ не е на

Comparison of the CVD risk profiles in patients with inflammatory joint diseases revealed that the relative and absolute risk of CVD according to Systematic Coronary Risk Evaluation (SCORE), estimating the 10-year risk of a fatal atherosclerotic CV event, is comparable across the patients with rheumatoid arthritis (RA), axial spondylarthropathy (axSpA) and psoriatic arthritis (PsA), although patients with PsA were more often hypertensive and obese [17]. The mean time to development of the first CV risk factor during follow-up was 20.5 months for RA, 18.1 months for psoriasis, and the shortest – 17.4 months for PsA [18]. PsA patients had a significantly higher risk for obesity, high fasting glucose, and total and LDL-cholesterol levels, compared to those with RA [19]. The prevalence of depression, hyperlipidaemia, diabetes, history of ischaemic heart disease and other comorbidities have been estimated higher in PsA than RA participants in a large Australian cohort [20]. A meta-analysis by Horreau et al. [21] found the risk of early coronary artery disease and MI was more pronounced for patients having severe psoriasis and for those with psoriasis of early onset. In analyses restricted to patients with PsA, age-specific strata did not show any association between psoriatic arthritis and MI risk, the risk was increased only among patients < 50 years of age, and predominantly present in patients without PsA [22].

Advances in molecular and immunological research, has led to the understanding that adipose tissue has secretory properties, since it produces a wide range of soluble mediators – adipokines. Most of them carry a pro-inflammatory activity and are involved in the regulation of the immune response. Thus, obesity sustains a systemic low-grade inflammatory environment that can trigger or amplify other inflammatory disorders, including immune-mediated conditions. In recent years, there is strong evidence suggesting a pathogenic role of obesity on both the occurrence and the severity of psoriasis and PsA. Moreover, it aggravates the evolution of both diseases and increases the risk of cardiovascular and metabolic comorbidities [23, 24].
пълно изяснен. Все пак се счита, че съвместната
изява на двата патологични процеса може да се
cъврже с повишения на аниотензин-кон-
вертиращия ензим (ACE), ендотелин-1 (ET-1) и
ренин при псориазис [25, 26]. Друго възможно
обяснение е, че мастната тъкан при псориазис
каза като основен източник на ангиотензиноген,
който по-късно се превръща в мощните вазослас-
tик ангиотензин II, така че намаляването на те-
лесното тегло води до понижаване на кръвното
налягане [27].

Хиперурикемията, която е рисков фактор за
ССЗ, често се наблюдава при ПсА, особено при
затлъстяване и по-голяма продължителност на
заболяването [28, 29]. Едно от обясненията за
появата й е ускореният търновър на епидерми-
sа при псориазис, което води до увеличаване на
синтеза и разрушене на пуринитите като след-
ствие – до свръхпроизводство на пикочна кисе-
лина [30]. Пикочната киселина е не само маркер
за метаболитния синдром и свързаните с него
сърдечно-съдови рискови фактори, но също така
и агент, провокиращ системно възпаление и вро-
dени имунни отговори [31]. Интересна концеп-
ция за връзката между ПсА и хиперурикемията е
представена от Tsuruta и съавтори. Те предпола-
gат, че ПсА може да бъде повлян от провъзпали-
tелната природа на уратните кристали, които са
силен стимулатор на вродения имунитет. Автори-
tе установяват, че хиперурикемията е независим
рисков фактор за ПсА и посочват, че кристализа-
cцията около ставите може да индуцира ПсА при
лица с псориазис [32]. От друга страна, повише-
nата пикочна киселина има способността да ин-
dуцира васкуларната дисфункция и увредирането
на ендотела чрез редукция на азотния оксид (NO)
и експресията на възпалителни цитокини чрез
нуклеарния фактор-κВ (NF-κβ) [33].

АТЕРОСКЛЕРОЗА И ЕНДОТЕЛНА
ДИСФУНКЦИЯ

Атеросклерозата като основен компонент на
ССЗ споделя общи патогенетични механизми с
хроничното възпаление при ПсА. Струпването на
макрофаги, ендотелната дисфункция, изчерпва-
нето на ендотелните прогениторни клетки, пови-
шените нива на С-реактивен протеин (CRP) и ин-
трацелуларната адхезионна молекула 1 (ICAM-1),
oxидативният стрес, toll-like рецепторното сигна-
лизиране, образуването на нуклеотид-свързващ
олигомеризиращ домейн-подобен рецепторен
протеин 3 (NLRP-3) инфламасома и продуциране
determined. However, it is considered that the co-
existence of both conditions can be related with
an increased level of the angiotensin-converting
enzyme, endothelin-1 (ET-1), and renin in the pa-
tient with psoriasis [25, 26]. One of the possibilities
is that adipose tissue in those affected by psoria-
sis serves as the main source of angiotensinogen,
which is later turned into angiotensin II, that is why
a decrease in body weight leads to lower blood
pressure [27].

Hyperuricemia which is a risk factor for CVD
is often seen in PsA, especially in patients with
obesity and longer disease duration [28, 29]. One
plausible explanation for its appearance is the ac-
celerated epidermal turnover rates in psoriasis,
leading to increase in purine synthesis and break-
down, and as a consequence, overproduction of
uric acid [30]. Uric acid is not only a marker of the
metabolic syndrome and associated cardiovascular
risk factors but also an agent provocateur
of systemic inflammation and the innate immune
responses [31]. An interesting insight into the as-
sociation between PsA and hyperuricemia is pre-
sented by Tsuruta et al. They have suggested that
PsA might be influenced by the pro-inflammatory
nature of urate crystals, which are a strong stimu-
lator of innate immunity. The authors found that
hyperuricemia is an independent risk factor for
PsA and point out that crystallization in and around
joints may induce PsA in psoriatic subjects [32].
On the other hand, elevated uric acid has an abil-
y to induce the endothelium injury and vascular
dysfunction to development of CVD by a reduction
of nitric oxide (NO) and expression of inflamma-
tory cytokines through the NF-κB [33].
на провъзпалителни цитокини, като тумор-некрозис фактор-алфа (TNF-α), интерлеукин (IL)-1β, IL-6, IL-17, TNF-подобен цитокин 1A, са някои от механизмите, участващи в атерогения процес [34, 35, 36]. Съществуват данни, че при болни с ПсА е ускорено образуването на коронарни пла- ки в сравнение със здравите лица, независимо от наличието или липсата на метаболитно заболява- не (патиентите с метаболитен синдром и тези без метаболитен синдром имат сходни по вид пла- ки). Активността на задължението, нивото на CRP и плазмената глюкоза, продължителността на задължението са независими предиктори за по-голяма тежест на пла- ките [37, 38].

Ендотелната функция е наруена при ПсА дори при липса на конвенционални рискови фак- тори [39]. Най-често използваната неинвазив- на методика за оценка на ендотелната съдова функция – процентът на медираната от кръвния ток дилатация (FMD), е значително по-малък при болни с ПсА и RA, отколкото при здрави лица. Средната дебелина на каротидната интима-медия (IMT) също е по-голяма при задължението при възпалителни ар- тропатии, което казва връзката между възпа- лението и атеросклерозата и подчерта тяхния, но активен системен процес, засягащ сърдечно- съдовата система [40]. По данни от проучвания IMT при ПсА е независим фактор, свързан с бо- лестната активност, гръбначно-засягане и не и с периферния артрит и конвенционалните рискови фактори за атеросклероза [41]. Пациен- тите с ПсА могат да имат повишена ригидност на камерната и артериалната стена, водеща до диастолна дисфункция, дори без левокамерно ремоделиране [42].

ПОТЕНЦИРАНО УВРЕЖДАНЕ НА СЪДОВЕТЕ

Метаболизъм на глюкозата

Метаболитен синдром се наблюдава при до 50% от пациентите с ПсА, което го прави едно от най-честите съпътстващи заболявания [43]. Доказателствата, свързващи консумацията на бога- ти на въглехидрати храни (особено подсладени със захар, рафиниран въглехидрати) със ССЗ, непрекъснато се увеличават [44]. Този прием на преработени въглехидрати има неблагоприятен ефект върху захарния и липидния профил, съд- даващи предпоставка за метаболитен синдром, диабет и коронарна болест на сърцето [45]. По- ради това диетата трябва да бъде правилно из- градена и променена, тъй като може да влоши метаболитния профил.

flammatoty cytokine production, such as tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, IL-6, IL-17, TNF-like cytokine 1A, are some of the mechanisms implicated in the atherogenic process [34, 35, 36]. Data exist that PsA patients have accelerated coronary plaque formation compared to controls independent of metabolic disease. Patients with metabolic syndrome and those without metabolic syndrome had similar plaque burdens and types. Disease activity, C-reactive protein level, disease duration, and plasma glucose level were independent predictors of higher plaque burden [37, 38].

Endothelial function is impaired in PsA even in the absence of conventional risk [39]. The most commonly utilized non-invasive assessment of vascular endothelial function – the Flow-mediated dilatation (FMD) percentage was found to be significantly smaller in both PsA and RA patients than in the healthy controls. Also, the median carotid intima-media thickness (IMT) an accessible and reliable method to assess subclinical atherosclerosis was found greater in inflammatory arthritides, which demonstrated the relationship between inflammation and atherosclerosis and highlights the silent but active systemic process affecting the cardiovascular system [40]. IMT in PsA has been shown to be independently associated with parameters of disease activity, spinal involvement but not with peripheral arthritis, and conventional risk factors of atherosclerosis [41]. Patients with PsA may have increased ventricular and arterial stiff ness as a cause of myocardial diastolic dysfunction, even without evidence of left ventricular (LV) remodelling [42].

Potentiated damage of vasculature

Glucose metabolism

Metabolic syndrome can be seen in up to 50% of the patients, making it one of the most common comorbidities in PsA [43]. The evidence linking carbohydrate-rich foods (especially sugar-sweetened, refined carbohydrates) with CVD has been steadily increasing [44]. This intake of highly processed carbohydrates has an unfavorable effect on the glucose and lipid profile, which may have implications for metabolic syndrome, diabetes, and coronary heart disease [45]. Because of that, diet should be properly assessed and modified as it can worsen the metabolic profile.
Endothelial damage

The endothelial glycocalyx is a pericellular matrix that consists of a network of membrane-bound proteoglycans and glycoproteins that cover the endothelium luminally [46]. Damage to the glycocalyx during hyperglycaemic states or from inflammatory molecules like CRP and TNF-alpha seems to be an initial and critical step in provoking endothelial dysfunction [47, 48, 49]. As it mediates transduction of shear stress–induced NO release, modulates vascular permeability, and harbours a wide array of anticoagulant proteins, the glycocalyx is a critical signalling platform for determining the fate of endothelial cells and atherosclerosis [50, 51]. The model for the role of the glycocalyx as a barrier to leukocyte-endothelium adhesion, during the inflammatory process in which the shedding of the endothelial glycocalyx exposes adhesion molecules on the endothelium surface and promotes adhesion of immune cells, has interesting applications [52]. The overreaction of the immune system in the pathogenesis of trauma-induced PsA and the proposed “deep Koebner’s phenomenon” can influence the expression of psoriatic disease [53]. Can these mechanisms act in a parallel manner potentiating damage to the vessel wall? (Figure 1)

Fig. 1. Mechanism of potentiated vascular damage in psoriasis/psoriatic arthritis. Destruction of endothelial glycocalyx from the inflammatory environment and/or metabolites exposes adhesion molecules on the cell surface. This allows an upregulated immune response that promotes endothelial damage and increases vascular permeability to cells, mediators and lipoproteins.
Molecular and immune cell regulation

Pro-inflammatory and anti-angiogenic CD4+Foxp3+ Tregs play an essential pathogenetic role in chronic ischemic heart failure to promote immune activation and pathological LV remodelling. Diffuse expansion and proliferation of dysfunctional Tregs with pro-inflammatory features, deficient immunosuppressive capacity, and heightened anti-angiogenic effects play a role in the pathological processes of hypertrophy, fibrosis, and tissue neovascularization. Neovascularisation is mediated both by TNF receptor 1 – dependent effects on endothelium and Treg mediated regulation of circulating angiogenic cells mobilization and recruitment [54]. Dysregulated angiogenesis is implicated in the formation of immature vessels psoriatic arthritis joints results [55].

Th17 and IL-17 have important roles in the clearance of extracellular bacterial and fungal infections. However, strong evidence also implicates the Th17 lineage in autoimmune and inflammatory disorders [56]. IL-17 exerts both pro-atherogenic and anti-atherogenic effects depending on the context [57]. Treg dysregulation and conversion into IL-17-producing Tregs potentially perpetuate the inflammatory process that characterizes the disease. This conversion that is mediated by IL-22 is an important concept in psoriasis pathophysiology – a process which can be reversed by anti-TNF therapy [58, 59].

Signalling pathways induced by the pro-inflammatory cytokine TNF-α play a key role in the cellular responses to inflammation and injury. Persistent activation of TNF-α signal transduction pathways has deleterious effects on tissues by inducing a chronic inflammatory response and may contribute to vascular dysfunction, hypertension, development and progression of atherosclerosis, and adverse cardiac remodelling [60].

IL-1 is the prototypical pro-inflammatory cytokine. It has an important role in atherosclerosis, acute MI, and heart failure. IL-1 promotes the formation of the atherosclerotic plaque and facilitates its progression and complication. A considerable body of evidence implicates IL-1 in the pathophysiology of CVD and an IL-1 blockade seems to reduce re-
IL-1 decreases the frequency of cardiovascular events induced by atherosclerosis in patients with prior MI and elevated CRP [61].

Chronic overproduction of IL-6 plays a causal role in CVD. A mechanism of the innate immune system independent of IL-6 seems to contribute to PsA, which may explain why anti-IL-6 therapy with Tocilizumab is ineffective [62].

CRP is an acute phase protein synthesized by hepatocytes in response to pro-inflammatory cytokines, which plays an important role in the complement pathway, apoptosis, phagocytosis, NO release, and cytokine production, particularly IL-6 and TNF-α [63]. Levels higher than 10 mg/L are associated with an over 4% risk of developing a fatal CVD in 10 years [64].

The NLRP3 inflammasome plays a key role in the initiation of innate immune response that after both priming and activation can induce the secretion of pro-inflammatory cytokines (i.e., IL-1β, IL-18) or cause pyroptosis, through caspase-1 activation. The contribution of the NLRP3 inflammasome to the pathological process of atherosclerosis, cardiac ischemia/reperfusion injury, and other nonischemic cardiac diseases is worthy of attention [65]. The expression of NLRP3 in psoriatic biopsy samples is significantly upregulated and is associated with accumulation of IL-1β and caspase-1 [66].

Serum levels of vascular endothelial growth factor (VEGF) and matrix metalloproteinases 3 (MMP 3) are elevated in PsA [67]. VEGF may aggravate atherosclerosis by enhancing vessel permeability to LDL [68]. Metalloproteases play key roles in adverse cardiovascular remodelling, atherosclerotic plaque formation and plaque instability, vascular smooth muscle cell migration, and restenosis that lead to coronary artery disease [69].

YKL-40, a chitinase-like glycoprotein associated with inflammation and tissue remodelling, is elevated in a significant percentage of patients with psoriatic arthritis, but not in patients with psoriasis [70]. YKL-40 is emerging as a biomarker for CVD playing a role in the differentiation of monocytes to activated macrophages. Elevated levels are seen in endothelial dysfunction, cell reorganization and tissue remodelling during atherogenesis, coronary artery disease and MI [71].
**Effect on therapy**

The hypothesis that an interaction between cardiovascular disease status and disease-modifying antirheumatic drug (DMARD) use is supported by multiple studies. A population-based longitudinal cohort study by Ogdie et al. including patients with PsA (N = 8706), psoriasis (N = 138 424) and unexposed controls (N = 81 573) aimed to quantify the risk of major adverse cardiovascular events (MACE) and found the risk of MACE was higher in patients with PsA not prescribed a DMARD (HR 1.24, 95% CI 1.03 to 1.49), patients with psoriasis not prescribed a DMARD (HR 1.08, 95% CI 1.02 to 1.15) and patients with severe psoriasis (DMARD users: HR 1.42, 95% CI 1.17 to 1.73) [72]. In studies of patients with severe psoriasis, systemic anti-inflammatory treatment with methotrexate or biological agents was associated with lower CV event rates compared to patients treated with other antipsoriatic therapies [34, 73]. Current biologic use was associated with a reduction in major cardiovascular events, but no reduction in risk was seen in those who had ceased biologic therapy [74]. Anti-psoriatic biologic therapies seem to confer a cardiovascular benefit but the exact mechanism must be further elucidated [75]. Anti-TNF therapy's favourable effects on CVD risk is partially explained by modulation of lipids, however, these changes were only small and require further study [76]. Garshick et al., however, found no suggestive evidence for elevating statin use [77].

IL-17 can have both protective and exacerbating effect on atherosclerosis, but early data from anti-IL-17 therapy suggests no increased CVD risk compared to placebo or other classes of biologics but results should be interpreted with caution [57].

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**Prevention and Screening**

Disease activity should be controlled optimally in order to lower CVD risk [79]. Targeted screening for CVD should be held on a regular basis. Physicians who treat individuals with psoriasis and PsA should address modifiable risk factors. These include sedentary lifestyle, alcohol, and refined carbohydrate consumption, smoking, obesity, hypertension, hyperlipidaemia and diabetes [80]. Identifying risks can assist in incentivising patients to adopt simple but sustainable lifestyle changes [81].

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a prohormone that is an independent predictor for cardiac events like asymptomatic or symptomatic left ventricular dysfunction, coronary artery disease and myocardial ischemia [82]. Analysis may provide clinicians with a simple method to detect high risk PsA patients. NTproBNP ≥ 200 pg/mL or SCORE ≥ 3% resulted in an approximately four-fold increase in risk of all-cause death and of cardiovascular events in the overall rheumatic disease patient population [83].

**Conclusion**

The ever-growing body of evidence confirms that increased CVD risk in PsA is present, especially in patients with severe psoriasis, longer disease duration, and multiple comorbidities. The prolonged inflammatory burden may be an important cause of early cardiovascular disease. It is difficult to conclude if the risk factors are caused by psoriasis and PsA or share a common pathogenesis, as risk factors are usually present even before diagnosis. Intricate overlapping features and mechanisms may work together to potentiate endothelial damage and progression of atherosclerosis. In all cases, risk factors should be identified and properly treated.


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A CLINICAL CASE OF A PATIENT WITH SCLERODERMA-LIKE SYNDROME IN CHRONIC GRAFT-VERSUS HOST DISEASE

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Abstract. Chronic graft versus host disease is observed within the first 100 days following allogeneic hematopoietic stem cell transplantation and can affect all tissues and organs (in 80% of the cases, it affects the skin). There are some clinical correspondences between chronic graft versus host disease and certain autoimmune diseases, such as systemic scleroderma, Sjogren's syndrome, autoimmune hepatitis. We present a case of a 54-year-old man with manifested disease resistant to corticosteroids, and Methotrexate 25 mg/weekly every other month was prescribed.
with no significant clinical improvement. In terms of the differential diagnosis, the question remains whether or not this is a case of paraneoplastic systemic scleroderma – autoimmune phenomena accompanying malignancy and often preceding it for months.

Key words: chronic graft-versus host disease, allogenic haematopoietic stem cell transplantation, scleroderma-like syndrome

INTRODUCTION

Chronic graft-versus host disease (GVHD) is the most significant complication in patients with allogenic haematopoietic stem cell transplantation (HSCT) [1]. The most common manifestations of chronic GVHD include cutaneous, hepatic, oral, and ocular changes and infections. Skin changes may be in the form of lichen planus or scleroderma-like round and hard lesions, which initially appear on the lower limbs [2-3]. However, generalized skin involvement resembling systemic scleroderma (SSc) with diffuse cutaneous sclerosis is also possible [4].

After HSCT, various autoantibodies are observed: anti-nuclear (ANA), anti-mitochondrial (AMA), anti-smooth muscle (ASMA), anti-cardiolipin (ACLA), anti-liver-kidney microsomal (LKM), anti-DNA, anti-neutrophil cytoplasmatic (ANCA), anti-thyroid antibodies. The pathogenetic mechanism of the onset of these autoantibodies is still poorly understood, since the T-cell and B-cell immune response has been suppressed for a long time [5].

SSc is a chronic systemic disease characterized by autoantibody synthesis, inflammation, functional and structural changes in the small vessels, and progressive cutaneous and visceral sclerosis [6].

CASE REPORT

A 54-year-old man was hospitalized in a rheumatology clinic for the third time due to muscle weakness, difficult movements, thickening of the skin of the extremities and the body, trophic ulcers in the lower legs. As concurrent diseases he reported arterial hypertension and latent hepatitis B infection, for which he had been receiving Lamivudine 100 mg/d for 3 years. The patient was allergic to Penicillin.

In December 2011, when he was for the first time in the clinic, he had severe knee, back and shoulder pain, fever up to 38.7°C, edema first on the left and then on the right knee and ankles, morning stiffness...
for about 30 minutes. The clinical examination found flexion contracture of the right elbow, muscle hypotrophy of the lower limbs, reduced mobility in the hips and in all parts of the spine. The tests showed borderline anti Chlamidia trachomatis IgA, ESR 20 mm/h, CRP 277 mg/l, Hemoglobin 80 g/l, serum iron 6.2 mcmol/l, total iron-binding capacity 40 mcmol/l. Bone scintigraphy found increased mineral metabolism in hip and sacroiliac joints, C7-Th10 vertebrae, knee, ankle and metatarsal bones. It was assumed that this was a case of reactive arthritis. Sulfasalazin 2.0 g/daily and NSAIDs treatment was proposed but it had no therapeutic effect.

The patient was referred to a hematology clinic, where chronic myelomonocytic leucosis type 2 with transformation into acute myeloblast leucosis was diagnosed. Treatment with Hydroxyurea, consolidation treatment with Cyclophosphamide and radiation of the whole body were administered. In May 2012, allogeneic bone marrow transplantation from an unrelated donor with a bright period of a year and a half was carried out. Immunosuppressive treatment with Ciclosporin and Methotrexate was given.

Due to the persistent high levels of the liver enzymes, liver biopsy was performed in July 2013. Histological data gave reason to seek a recurrent, probably viral infection. It was assumed that the diffuse liver fibrosis may be due to toxic changes as a result of the cytostatic and immunosuppressive therapy. As HBV DNA was 14 IU/ml, latent hepatitis B virus (HBV) infection was accepted and treatment with Lamivudine started. In December 2012, Epstein-Barr virus infection (EBV) was also found – EBV DNA values were 233,500 copies/ml.

An ophthalmic examination in April 2014 established conjunctival hyperemia, severely reduced tear secretion and presence of foamy secretion. In October 2014, the skin biopsy concluded that the changes observed were morphologically similar to those in chronic GVHD.
IgM(+), VZV IgG(+). От декември 2013 г. е регистрирана поликлонална хипергамаглобулинемия с високи свободни вериги kappa и lambda.

През 2014 г. пациентът е лекуван за втори път в Клиниката по ревматология, където ултразвуково изследване на раменни стави показа хронична двустранна тендинопатия на ротаторния маншон и студени ерозии в ентезата на сухожилието на m. супраспинатус вляво.

От физикалния преглед при последната госпитализация установихме: бледорозова, суха, лющащо се, уплътнена кожа по крайниците, гърдите, корема и гърба, с еритемомакулозни и хиперпигментни лезии в областта на тялото, язви по подбедриците – една в областта на дясната и две по-малки с крусти в областта на лявата, ливедо по долните крайници.

Установихме: намалена респираторна подвижност на грудния кош; хепатомегалия – черният дроб се палпираше на 2 см под ребрената дъга; наличие на флексионни контрактури на лакътните и коленните стави; мекотъкани отоци по глезените с ограничени движения в тибооталарните стави.

Лабораторните изследвания показаха: СУЕ 55 mm/h, тромбоцити 437x10^9/l, MCV 103 fl, пикочна киселина 429 micromol/l, общ белтък 106.7 g/l, ASAT 49 U/l, ALAT 61 U/l, C-реактивен протеин – 16.7 mg/l, урея 8.2 mmol/l, креатининов клирънс – 93 ml/min, Serratia

However, polyclonal hypergammaglobulinaemia with high free kappa and lambda chains has been found since December 2013.

In 2014, the patient was hospitalized in the rheumatology clinic for the second time, where chronic bilateral rotator cuff tendinopathy and cold erosions in the tendon enthesis of left supraspinatus muscle were found. The physical examination during the latest hospitalization revealed: pale pink, dry, peeling and thickened skin of the limbs, chest, abdomen and back with macular erythema and hyperpigmented lesions on the thorax, ulcers on the legs – one on the right leg and two smaller ulcers with crusts on the left leg, livedo reticularis on the lower limbs.

We found reduced respiratory mobility of the chest; hepatomegaly – the liver was palpated at 2 cm below the costal margin; there were also flexion contractions of the elbow and knee joints; soft-tissue edemas on the ankles with limited movements in the distal tibiotalar joints.

Laboratory test results: elevated erythrocyte sedimentation rate (ESR) – 55 mm/h, Thrombocytes – 437 x 10^9/l, MCV – 103 fl, uric acid – 429 mcmol/l, total protein – 106.7 g/l, ASAT – 49 U/l, ALAT – 61 U/l, CRP – 16.7 mg/l, borderline urea – 8.2 mmol/l, lower creatinine clearance – 93 ml/min, Serratia

Снимка 1. Гръб – макуларен еритем и хиперпигментирани лезии

Image 1. Back – macular erythema and hyperpigmented lesions

Снимка 2. Гърди и корем – макуларен еритем и хиперпигментирани лезии

Image 2. Macular erythema and hyperpigmented lesions on the chest and abdomen
93 ml/min, при микробиологично изследване на урина се изолира Serratia marcescens 104 – 105, протеинурия 0.82 g/24 h.

При имуноелектрофореза на серумни имуноглобулини се установиха: kappa free light chains (FLC) 129.5 mg/l (3.3-19.4), lambda FLC 35.19 mg/l (5.7-26.3), ratio 3.68 (0.26-4.65); kappa FLC в урината 228. 85 mg/l (0.012-32.7), lambda FLC 6.79 mg/l (< 4.99). Серумното ниво на β2 микроглобулин бе 5.1 mg/l (1.0-2.4).

Имунологични изследвания: с оглед мнофакторната клинична картина при пациента с преобладаване на мускулна слабост и кожни симптоми бяха направени следните изследвания – Antinuclear antibodies (ANA) by Indirect immunofluorescence (IIF), Anti-neutrophilic cytoplasm antibodies (ANCA) by IIF, immunoblot analysis for detection of human autoantibodies of the IgG class to nuclear and systemic sclerosis antigens: nRNP/Sm, Sm, ssA, ssB, Ro-52, Scl-70, PM-Scl, PM-Scl 100, PM-Scl 75, RP 11, RP 155, Ku, PDGFR, Jo-1, Cenp-A, Cenp-B, Fibrillarin, NOR 90, Th/To, PCNA, dsDNA, Nucleosomes, Histones, Rib-P, DFS-70, AMA-M2. По повод основната диагноза и данните за съпътстваща инфекция изследвахме криоглобулини, C3 и С4 фракции на комплемента и имуноблот анализ за откриване на човешки антитела, свързани с паранеопластични неврологични синдроми. Автоантителата от клас IgG са от 12 различни антигена: Amphiphysin, CV2, Ma2/Ta, Ri, Yo, Hu, Rec, SOX1, Titin, Znc4, GAD65, Tr.

Резултатите показаха висок титър на антиинулеарните антитела > 1:1280 (< 1:160), като marcescens 104 – 105 isolated in microbiology urine test, proteinuria 0.82 g/24 h.

Immune electrophoresis of serum immunoglobulins found: kappa free light chains (FLC) 129.5 mg/l (3.3-19.4), lambda FLC 35.19 mg/l (5.7-26.3), ratio 3.68 (0.26-4.65); kappa FLC in urine 228. 85 mg/l (0.012-32.7), lambda FLC 6.79 mg/l (< 4.99). The serum β-2 microglobulin level was 5.1 mg/l (1.0-2.4).

In view of the multifactorial clinical condition of the patient, with predominance of muscle weakness and skin symptoms, the following immunological test were conducted: – Antinuclear antibodies (ANA) by Indirect immunofluorescence (IIF), Anti-neutrophilic cytoplasm antibodies (ANCA) by IIF, immunoblot analysis for detection of human autoantibodies of the IgG class to nuclear and systemic sclerosis antigens: nRNP/Sm, Sm, ssA, ssB, Ro-52, Scl-70, PM-Scl, PM-Scl 100, PM-Scl 75, RP 11, RP 155, Ku, PDGFR, Jo-1, Cenp-A, Cenp-B, Fibrillarin, NOR 90, Th/To, PCNA, dsDNA, Nucleosomes, Histones, Rib-P, DFS-70, AMA-M2. We also tested cryoglobulins, C3 and C4 fractions of the complement and immunoblot analysis for detection of human autoantibodies of the IgG class to nuclear and systemic sclerosis antigens: nRNP/Sm, Sm, ssA, ssB, Ro-52, Scl-70, PM-Scl, PM-Scl 100, PM-Scl 75, RP 11, RP 155, Ku, PDGFR, Jo-1, Cenp-A, Cenp-B, Fibrillarin, NOR 90, Th/To, PCNA, dsDNA, Nucleosomes, Histones, Rib-P, DFS-70, AMA-M2. We also tested cryoglobulins, C3 and C4 fractions of the complement and immunoblot analysis for detection of human autoantibodies associated with paraneoplastic neurological syndromes. These autoantibodies of the IgG class are against 12 different antigens: Amphiphysin, CV2, Ma2/Ta, Ri, Yo, Hu, Rec, SOX1, Titin, Znc4, GAD65, Tr.

The results showed high-titer antinuclear antibodies > 1:1280 (< 1:160), with a mixed type of
Клиничен случай на склеродерма-подобен... A clinical case of a patient with scleroderma-like...

При разреждане на серума в титър 1:80 (фиг. 1) се виждат ясно разграничими, дифузно оцветени ядърни структури в интерфазните ядра на HEP-2 клетките, характерен образ за AC-8 хомогенно нуклеоларно светене (anti-PM/Scl-100). Едновременно с това се откриват ярки, фини точки в интерфазните ядра и дележните форми на клетките, насочващи към AC-3 (центромерен) тип светене. Цитоплазмата на интерфазните клетки е с мрежовидно флуоресцентно светене, образ, типичен за AC-21 (антимитохондриални антитела – AMA-M2). При този нисък титър на разреждане на серума не може добре да се разпознае плетоморфния характер на AC-14 (CENP-F), като за наличието му подсказват единствено слабовидими нишки на делителното вретено.

При разреждане на серума в титър 1:320 (фиг. 2) се избистряха характерната картина на плетоморфното светене на anti-CENP-F. Наблюдават се различни по интензивност на светене групи от клетки, в зависимост от фазата на клетъчен цикъл. Клетките в метафаза показват характерен за AC-14 (anti-CENP-F) изглед. Миксоплазмата на митотичните клетки е дифузно оцветена.

immunofluorescence image, according to the International Consensus on ANA Pattern (ICAP), including: AC-3, AC-8, AC-14, AC-21. Serum dilution in titre of 1:80 (Fig. 1) revealed clearly visible and diffusely stained nuclear structures in the interphase nuclei of the HEP-2 cells, which is a typical image of AC-8 homogeneous nucleolar illumination (anti-PM/Scl-100). At the same time, there were bright, fine dots in the interphase nuclei and dividing cell forms, which suggested AC-3 (centromere) type of illumination. The cytoplasm of the interphase cells had network-fluorescent illumination, which is an image typical of AC-21 (Anti-mitochondrial antibodies – AMA-M2). With this low titre of serum dilution, the pleomorphic nature of AC-14 (CENP-F) cannot be well recognized, and its presence is suggested only by the slightly visible fibers of the cell division spindle.

Serum dilution in titre of 1:320 (Fig. 2) demonstrated pleomorphic illumination of anti-CENP-F. Groups of cells of different illumination intensity were observed, depending on the cell cycle phase. The cells in metaphase had an image typical of AC-14 (anti-CENP-F). The mitotic cell myxoplasm was diffusely stained.

Фиг. 1. IIF на Hep-2 клетки, 40х увеличение. Разреждане на серума 1:80

Fig. 1. IIF of Hep-2 cells, 40x magnification. Serum dilution 1:80

От язва на дясната подбедрица се изолира Serratia marcescens, като в подкрепа за наличието на възпалителен процес е и повишената С3 фракция на комплемента.

При рентгенография на бели дробове и сърцето се установиха финоивицести фиброзни сенки перихилерно вляво, сусpekция за пръстеновидна фиброзна сянка ретрокардиално от същата страна и данни за инкапсулат в десния kostodiaphragmalен синус. Изследвахме също: DLCO – 40%, VC 48%, FEV 1 49%, a FEV1/ FVC бе 102%.


При ултразвуковото изследване на стави се установи малък хидропс в тибиоталарната и талонавикуларната става без Power doppler PD (+) сигнал вдясно, леко изразен мекотъканен оток, а вляво – умерен излив в тибиоталарната и малък в талонавикуларната става без PD (+) сигнал.

The immunoblot method proved the following specific autoantibodies against: CENP A–37 SI (< 5), CENP B–60 SI (< 5), PM/Scl-100–9 SI (< 5), NOR90–6 SI (< 5), AMA-M2–82 SI (< 5). All the other immunological markers were negative.

*Serratia marcescens* was isolated from the ulcer on the left lower leg. The inflammation process was also evidenced by the elevated C3 fraction of the complement.

The X-ray of lungs and heart showed finely-striped fibrous shadows around the hilus of the left lung, suspected ring-shaped fibrous shadow retrocardially on the same side and encapsulation in the right costodiaphragmatic sinus. We also tested: DLCO – 40%, VC 48%, FEV 1 49%. FEV1/ FVC was 102%.


Joint ultrasonography showed small hydrops in the distal tibiotalar and talonaviculal joints with no Power Doppler PD (+) signal on the right, slightly pronounced soft-tissue edema and moderate effusion in the tibiotalar joint and a small one in the talonaviculal joint with no PD (+) signal on the left.
Echocardiography demonstrated II+ degree insufficiency, and ECG revealed ventricular extrasystolic arrhythmia.

Computer axial tomography (CT) of lungs and heart presented pronounced fibrous changes in the right base of the lung, and diffuse parenchymal process of the kidneys.

US examination of thyroid gland showed a well vascularized hypoechogetic node of 7.7/6.7 mm in the right lobe of the gland.

**DISCUSSION**

We present a clinical case of chronic GVHD following HSCT from unrelated donor with scleroderma-like skin changes due to fibrosis and partial dermal hyalnosis without affecting the face, advanced hepatic fibrosis, pulmonary fibrosis, frequent viral infections, eye symptoms, myofascial involvement with contractures of elbow and knee joints.

The combination of antibodies against CENP A and CENP B is a highly specific sign of patients with SSc [6]. These antibodies also occur in 10-30% of the patients with primary biliary cirrhosis, and this type of patients are presented with simultaneous manifestation of SSc or Raynaud’s phenomenon. Anti-CENP-F are very rarely identified.

The high titer in patients indicates a hyperproliferative process. It was established that 61% of the patients have a tumor process (breast or lung carcinoma), and the rest have a chronic inflammatory disease of the liver or gastrointestinal system, undifferentiated connective tissue disease, as well as chronic GVHD. PM/Scl-100 antibodies are typical of an overlapping syndrome between Polymyositis/ SSc, Raynaud’s phenomenon, as well as interstitial pulmonary diseases without an autoimmune component.

Borderline anti NOR90 suggests possible development of systemic connective tissue disease and/ or malignant process. High anti AMA-M2 is a sure sign of the onset of an autoimmune process in the liver, which is also evidenced by the slightly elevated ASAT and ALAT aminotransferases. AMA-M2 are sure and predictive sign of primary biliary cirrhosis. They are also reported in chronic GVHD and are usually associated with high ANA, including nucleo-
nuclear type illumination. They are also observed in patients with extensive chronic GVHD [7].

It remains unclear if this is a case of systemic scleroderma as a late-onset paraneoplastic syndrome with capillaroscopic changes typical of Raynaud's phenomenon, pronounced diffuse skin thickening, non-response to photopheresis, Ciclosporin, Tacrolimus, Mycophenolate mofetil, corticosteroids, Imatinib, multiple changes in the immunological parameters with the presence of antibodies specific of paraneoplastic scleroderma. It is possible that both diseases have a parallel course.

Chronic GVHD is a serious consequence and concerns the long-term survival of the graft in allogeneic HSCT. Its clinical manifestation resembles many systemic autoimmune diseases, such as SSc, SLE, Sjogren syndrome, with the presence of multiple autoantibodies. Their clinical relevance and predictive value in acute or chronic GVHD are being discussed [8]. Administration of anti-CD20 monoclonal antibody in chronic GVHD has successful clinical and immunological result [9].

The patient prognosis is unfavorable, as the elevated light free chains in the serum and urine and high β2 microglobulin will exacerbate the renal failure with the need of chronic dialysis.

**References:**