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PROSPECTIVE STUDY OF ADVERSE DRUG REACTIONS IN A BULGARIAN POPULATION OF PATIENTS WITH INFLAMMATORY JOINT DISEASES TREATED WITH BIOLOGICAL MEDICINAL PRODUCTS

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Abstract. To analyze Adverse Drug Reactions (ADRs) in a Bulgarian population of patients with inflammatory joint diseases who are eligible to receive treatment with biological medicinal products (BMP). A single-center, observational, open-label, prospective, non-interventional, pharmacoepidemiological study of clinical cases
of ADRs in a Bulgarian population of patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA), treated with BMP between March 2015 and October 2016. The study was conducted on a protocol basis and after signed informed consent. Patients were treated with: Etanercept, Adalimumab, Golimumab, Certolizumab pegol, Rituximab. It was a prerequisite not to have previous BMP treatment. The statistical analysis was made with SPSS version 16.0. 53 patients were screened, 5 did not meet the inclusion criteria; 47 enrolled, 5 withdrawn from the study, 42 analyzed. Disease distribution: RA – 40.5% (n = 17), PsA-19% (n = 8), AS-40.5% (n = 17). Women – 52% (n = 22), men – 48% (n = 20). 76% of the patients were treated with Adalimumab and Etanercept. In 17% of the patients (n = 7), biological treatment was discontinued due to serious ADRs. Three of them were grade 3 severity, 4 – grade 4 severity. The largest relative share was occupied by ADRs with grade 1 and 2 severity, whereas 63% of ADRs had grade 1 severity. The total number of reported and confirmed ADRs was 160. 3 ADRs meet the definition of SUSAR; 30 ADRs were unexpected; 127 ADRs were suspected. The overall incidence of ADR in the entire prospective study was 3.80 ADR/patient, the highest being AS – 4.35 ADR/patient. We have established a very high incidence of ADRs that is inappropriately higher than pre-authorization data for the analyzed BMP. The most common cause of discontinuation of biological therapy in patients with inflammatory joint diseases is the onset of ADR.

Key words: inflammatory joint diseases, adverse drug reactions, biological treatment, prospective study

Въведение

За първи път биологичен лекарствен продукт (БЛП) с терапевтични показания за приложение в областта на ревматологията е разрешен за употреба по Централизирана процедура на 02.06.1998 г. – Мабтера, с международно непатентно наименование (INN) ритуксимаб, с показания за лечение хронична лимфоцитна левкемия, неходжкинов лимфом и ревматоиден артрит [1]. От тогава досега разрешените за употреба БЛП, вкл. и подобни БЛП (биоподобни/biosimilar) с терапевтични показания за приложение в областта на ревматологията, са повече от 20 и масово навлизат в клиничната практика [2-6]. Предрегистрационните данни за безопасност и ефикасност са достатъчни за получаване на разрешение за употреба и пускане на пазара, въпреки че изследователската фаза е относително кратка по време и включва малък брой пациенти. В пострегистрационния период интерес за изследователите и клиницистите представят данните за терапевтичната ефективност, и то в сравнителен аспект, и най-вече данните за изявя на нежелани лекарствени реакции.

Цел

Първична цел е да проследим проспективно поява на нежелани лекарствени реакции (НЛР) и да направим обща оценка на лекарствената безопасност при българска популяция от пациенти с възпалителни ставни заболявания, които ще провеждат лечение с БЛП, чрез активно търсене по предварително зададени критерии. Вторични цели: НЛР да бъдат анализирани по вид, честота

INTRODUCTION

A biological medicinal product (BMP) with therapeutic indications for use in the area of rheumatology was authorized for the first time under a centralized procedure on 02.06.1998 – Mabthera, with international nonproprietary name (INN) Rituximab. It was authorized for the following indications – chronic lymphocytic leukemia, non-Hodgkin lymphoma, and rheumatoid arthritis [1]. Since then, there have been more than 20 authorized BMPs, including similar BMPs (biosimilars) with therapeutic indications for rheumatic diseases, and they are becoming more and more widespread in clinical practice [2-6]. Pre-authorization safety and efficacy data are sufficient to obtain marketing authorization and distribution authorization, although the research phase is relatively short in time and includes a small number of patients. In the post-authorization period, the therapeutic efficacy data are of interest to both investigators and clinicians, especially in terms of comparison, particularly the data of onset of adverse drug reactions.

Aim

Our primary aim is to follow the onset of adverse drug reactions (ADRs) prospectively and make a general assessment of drug safety in a Bulgarian population of patients with inflammatory joint diseases, who will be treated with BMPs, through active search according to preset criteria. Secondary aims: analyze ADRs by type, incidence, and degree of severity; assess
Prospective study of adverse drug reactions...  

Materials and methods

Study design: a single-center, observational, open-label, prospective, non-interventional, pharmacoepidemiological study of clinical cases of ADRs in a Bulgarian population of patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis, treated with biological medicinal products. The study was conducted from March 2015 to October 2016, according to a predefined protocol. All participants signed an informed consent form. The protocol and the informed consent were prepared according to the provisions of LMPHM and the Health Law, in compliance with the ethical principles set in the Declaration of Helsinki and Good Clinical Practice Guideline [7-11]. The study also complies with the research practices described in the Good Pharmacoepidemiological Practice of the International Society for Pharmacoepidemiology (ISPE) [12].

Patients included in the study must have one of the following diseases: rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA), and be assessed as eligible for treatment with one of the medicinal products with the following International Nonproprietary Names (INN): Etanercept, Adalimumab, Golimumab, Certolizumab pegol, Rituximab, including with or without Methotrexate.

Inclusion criteria: Patients included in the study must meet all of the following criteria: 1. Men and women aged ≥ 18 years; 2. Men and women with a definite diagnosis: Rheumatoid arthritis – the presence of 4 or more criteria according to the standards established by the American College of Rheumatology (ACR) [13-16], or Ankylosing spondylitis – the presence of radiographic data of sacroiliitis and at least one clinical criteria according to the modified ACR criteria [17], or Psoriatic arthritis – the presence of inflammatory joint disease and three or more points, according to the psoriatic arthritis classification criteria (Classification for Psoriatic Arthritis criteria – CASPAR) [18]; 3. No prior treatment with BMPs – Etanercept, Adalimumab, Golimumab, Certolizumab pegol, Rituximab. An exception to this requirement is acceptable for patients, who will
адалимумаб, гольimumаб, цертолизумаб пегол, ритуксимаб. Извън изключение от това изискване е допуснато за пациенти, които ще провеждат лечение с ритуксимаб. Те обаче нямат показанието за прилагане на TNF-α инхибитори на TNF-α, но са имали незадоволителен терапевтичен отговор и при тях се назначава биологична терапия от втора линия: 4. Да не са провеждали лечение с биологични лекарствени продукти; 5. Да отговарят на критерийте на НЗОК за лечение с БЛП [19]; 6. Подписано и датирано информирано съгласие, че пациентите са запознати с всички аспекти на проучването.

Изключващи критерии: 1. Отказ от подписване на информирано съгласие; 2. Възраст под 18 години; 3. Пациенти с RA, AS или PsA, провеждали предхождащо лечение с БЛП; 4. Пациенти с RA, AS или PsA, провеждали предхождащо лечение с биологични лекарствени продукти; 5. Несъответствие с критерийте на НЗОК за лечение с БЛП. 6. Оттегляне на вече подписано информирано съгласие.

Скриниращата визита се провежда след подписване на информирано съгласие и до 4 седмици от започване на биологичното лечение. Всеки пациент получава анкетна карта за регистриране на НЛР и инструкции за нейното попълване. Проучването включва 2 проследяващи визити през 6 месеца. За целите на проспективното проучване са разработени Клинични карти за пациента, в зависимост от това на какъв вид лечение ще бъде всеки един от тях. Клиничните (анкетни) карти са изработени в съответствие с КХП на съответния лекарствен продукт и съдържат данни за подозирани НЛР, както са установени в предрегистрационния период.

Оценката на безопасността е направена чрез анализ на събраната информация, получена от анкетните карти на пациентите. Безопасността на биологичното лечение при всеки пациент бе проследявана през 6 месеца до 12-ия месец включително. Определяхме големината на популацията, анализирахме получените данни за НЛР по брой пациенти, лица, демографски показатели и др. Провеждахме анализ на епидемиологични данни и съотношения. Личните данни на пациентите, включени в това фармакоепидемиологично проучване, са защитени. Всеки пациент можеше да оттегли съгласието си за участие в проучването по собствено желание или да отпадне по преценка на изследователя.

Въвеждането на данните, тяхната първоначална обработка, графичното представяне и статистическите изчисления са направени със SPSS, версия 16.0. Използвахме следните статистически методи на empirical data processing: Descrip-
тистически методи за обработване на емпирични данни: дескриптивен анализ – средна аритметична, мода, медиана като мярка на централната тенденция; стандартно отклонение; доверителен интервал; вариационен анализ на количествени променливи; Т-критерий на Student за сравняване на средни величини при нормално разпределение; метод на Clopper-Pearson.

**Резултати**

В проучването бяха скринирани общо 53 пациенти, допуснати за лечение с БЛП в периода 14 април 2015 г. – 28 май 2015 г. От общия брой скринирани, 5 пациенти получиха отказ за започване на лечение; 1 пациент почина преди получаване на разрешение за провеждане на биологично лечение. Общо 47 пациенти бяха включени в клиничното наблюдение след започнато лечение с БЛП. В хода на проучването 5 от скринираните пациенти и започнали биологично лечение бяха свалени от активно проследяване преди изтичане на едногодишния период на проспективното проучване поради следните причини: 1 пациент е с предшестващо биологично лечение с анти-TNF – не отговаря на заложените включващи критерии да не е провеждал лечение с БЛП; 1 пациент в хода на проучването оттегли информираното съгласие и 3 пациенти не продължиха лечението след 6-ия месец поради причина, различна от изява на НЛР. Едногодишното наблюдение обхвана общо 42 пациенти, от които 20 мъже и 22 жени. Разпределението на пациентите по видове заболявания е представено на фиг. 1. Средна възраст на мъжете е 47,6 г., а на жените – 54,6 г.

В 17% от случаите (n = 7) биологичното лечение е спряно в хода на проспективното наблюдение поради изява на сериозни НЛР – фиг. 2.

**Results**

In this study, a total of 53 patients were screened and admitted to BMP treatment from 14 April 2015 to 28 May 2015. Out of the total number of the screened patients, 5 patients have been denied treatment; 1 patient died prior to the receipt of the authorization of the administration of biological treatment. A total of 47 patients were included in the clinical observation after the beginning of BMP treatment. In the course of the study, 5 of the patients, who were screened and started biological treatment, withdrew from the active follow-up prior to the expiry of the 1-year period of the prospective study for the following reasons: 1 patient had prior biological treatment with anti-TNF – he did not meet the preset inclusion criteria of absence of prior BMP treatment; 1 patient withdrew his Informed Consent Form in the course of the study, and 3 patients did not continue their treatment after the 6th month for any other reason, different from the onset of ADRs. The one-year observation included 42 patients – 20 men and 22 women. The distribution of the patients by type of disease is presented in Fig. 1. Men's average age is 47.6, and women’s average age is 54.6.

In 17% of the cases (n = 7), biological treatment was discontinued in the course of the prospective observation due to the onset of serious ADRs – Fig. 2.
The results show the relative share of the cases, in which the biological treatment was discontinued – 25.5% (out of 47 patients, 7 withdrew due to severe ADRs, 5 withdrew for other reasons).

The severity of the identified serious ADRs was assessed according to the common terminology criteria for ADRs (Common Terminology Criteria for Adverse Events by National Cancer Institute – CTCAE version 4.03, June 14, 2010) [20]. Three ADRs were assessed with grade 3 severity, and the rest four ADRs had grade 4 severity.

Analysis of results in patients with AS. Patient data were assessed by basic demographic parameters – age, sex, age groups, type of biological treatment by medicinal product, the average age of the followed-up patients. The AS group included 18 patients – 15 were observed and followed up for a full 1-year period, of them ten men and five women. All patients had a 12-month treatment cycle with the respective BMP, except for one patient, who was treated for only 6 months. In two patients, the treatment was discontinued due to the onset of serious ADRs. The analysis of the demographic parameters shows that men are 2 times more than women, and this is observed in all age groups. The average age of the men and women in the AS group was equalized – men’s average age is 45.8, and women’s average age was 45.6. No patients with AS were included in the age group over 65 (Table 1).

The patients in the AS group received treatment with three types of BMP – Etanercept, Adalimumab, and Golimumab. The group of the patients treated with Adalimumab had the largest share, whereas there was only one observed patient treated with Golimumab.

ADRs are systematized according to MedDRA System Organ Class, version 12.0 [21].
тяхното честотно разпределение е представено на фиг. 3, а тяхното типизиране – на фиг. 4. Общият брой на съобщените и потвърдени НЛР е 74. От тях сериозни НЛР (довели до отпадане от проучването) са 2, от които 1 НЛР отговаря на дефиницията за SUSAR, а втората попада в групата на подозираните; неочакваните са 9; а подозираните – 64.

Table 1. Demographic data of patients with AS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18-45 years</td>
<td>4 (26.66 %)</td>
<td>2 (13.33%)</td>
<td>6 (40.0%)</td>
</tr>
<tr>
<td>Age 46-65 years</td>
<td>6 (40.0%)</td>
<td>3 (20.0%)</td>
<td>9 (60.0%)</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Number</td>
<td>10 (66.66%)</td>
<td>5 (33.33%)</td>
<td>15 (100.0%)</td>
</tr>
<tr>
<td>Average</td>
<td>45.8</td>
<td>45.6</td>
<td>45.7</td>
</tr>
<tr>
<td>Median</td>
<td>53.0</td>
<td>53.0</td>
<td>53.0</td>
</tr>
<tr>
<td>Mode</td>
<td>53.0</td>
<td>53.0</td>
<td>35.0</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>14.9</td>
<td>15.0</td>
<td>15.0</td>
</tr>
</tbody>
</table>

Fig. 3. ADRs systematized according to MedDRA System Organ Class, version 12.0
We assessed the relation of ADRs with the treatment received, as follows: Certain (casual connection) – 5; Probable/Likely relation – the drug is associated with the onset of ADR, but there is no reproducibility of laboratory data – 51; Possible relation – there is a temporary relation between the drug and ADR – 18; Unlikely – ADR occurs during the administration of the drug, but the reason is different – 0; Unassessable/Unclassifiable relation – the onset of ADR is not associated with the drug – 0. We found ADRs in 13 out of a total of 15 patients in the AS group, including registered deviations in the laboratory tests. Only two patients in the AS group did not report any ADRs. They had no deviations in the laboratory tests, which could be considered ADRs.

Analysis of results in patients with RA. Demographic data were analyzed in the same way (Table 2). The RA group included 20 patients – 14 patients, of them 2 men and 12 women were observed and followed up for a full 1-year period. Two patients had treatment for only 6 months: the first patient required a switch to another biological medicine after the 6th month due to unsatisfactory therapeutic response, and the treatment of the second patient was discontinued due to his continuous absence from the country. In three patients, the treatment was discontinued due to the onset of a serious ADR. One patient had exclusion criteria and was not followed up. The analysis of the demographic parameters shows that women are 6 times more than men, and this is observed in both age groups. In the 18-45 age group, there was only 1 man and 1 woman. The average age of the men with RA, who completed the study, was 49.5, whereas the average age of the women with RA, who completed the study, was 10 years more – 59.4.

Фиг. 4. Видове НЛР

Fig. 4. Types of ADRs
The patients in the RA group received treatment with 5 medicinal products – Etanercept, Adalimumab, Golimumab, Certolizumab pegol, and Rituximab. The Adalimumab group had the largest share, and the smallest share was seen in the observed patients receiving Certolizumab pegol and Rituximab. ADRs under MedDRA and their incidence distribution are presented in Fig. 5.

The total number of reported and confirmed ADRs were 67 (Fig. 6). There were 3 serious ADRs, of which 1 ADR met the definition of SUSAR, and the other 2 fell into the group of suspected ADRs; there were 15 unexpected ADRs and 51 suspected ADRs.

Table 2. Demographic data of patients with RA

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Men n-2</th>
<th>Women n-12</th>
<th>Total n-14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18-45 years</td>
<td>1 (7.1%)</td>
<td>1 (7.1%)</td>
<td>2 (14.2%)</td>
</tr>
<tr>
<td>Age 46-65 years</td>
<td>1 (7.1%)</td>
<td>6 (42.9%)</td>
<td>7 (50.0%)</td>
</tr>
<tr>
<td>Age &gt; 65 years</td>
<td>–</td>
<td>5 (35.8%)</td>
<td>5 (35.8%)</td>
</tr>
<tr>
<td>Number</td>
<td>2 (14.2%)</td>
<td>12 (85.8%)</td>
<td>14 (100.0%)</td>
</tr>
<tr>
<td>Average</td>
<td>49.5</td>
<td>59.4</td>
<td>58.0</td>
</tr>
<tr>
<td>Median</td>
<td>–</td>
<td>64.0</td>
<td>62.0</td>
</tr>
<tr>
<td>Mode</td>
<td>–</td>
<td>63.0</td>
<td>60.0</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>11.4</td>
<td>11.6</td>
<td>12.3</td>
</tr>
</tbody>
</table>

Поради нисък брой на мъжете параметри не са изчислени

Due to the low number of men, median and mode are not calculated.
Връзката на НЛР с провежданото лечение е следната: сигурна връзка – 4; вероятна връзка – 32; възможна връзка – 30; съвпадение – 1; негативна връзка – 0. В групата с RA при всички пациенти установихме НЛР, в т.ч. и отклонения в проведените лабораторни изследвания, които приемаме също за НЛР.

Анализ на резултатите при пациенти с ПсА. Демографските показатели са представени в таблица 3.

Пациентите в групата с ПсА са провеждали лечение с 2 продукта – 3 с etanercept и 3 с adalimumab. НЛР са систематизирани по системо-органи класове и честотно им разпределение е показано на фиг. 7.

Общият брой на съобщените и потвърдени НЛР е 19 (фиг. 8). От тях: сериозни НЛР (довели до отпадане от проучването) – 2, от които 1 НЛР отговаря на дефиницията за SUSAR, а другата попада в групата на подозирани; неочаквани – 6; подозирани – 12. Само при един пациент в групата с ПсА не установихме НЛР.

The relation of ADRs with the treatment received is as follows: Certain (casual connection) – 4; Probable relation – 32; Possible relation – 30; Unlikely – 1; Unassessable/Unclassifiable relation – 0. We found ADRs in all patients in the RA group, including registered deviations in the laboratory tests, which we also considered ADRs.

Analysis of results in patients with PsA. Demographic data are presented in Table 3.

The patients in the PsA group received treatment with 2 products – 3 patients were treated with Etanercept, and 3 patients were treated Adalimumab. ADRs are systematized according to system-organ classes, and their incidence distribution is presented in Fig. 7.

The total number of reported and confirmed ADRs is 19 (Fig. 8). There were 2 serious ADRs (leading to withdrawal from the study), of which 1 ADR met the definition of SUSAR, and the rest fell into the group of suspected ADRs; Unexpected ADRs – 6; Suspected ADRs – 12. We did not find any ADRs only in one patient in the PsA group.

Таблица 3. Демографически данни на пациенти с ПсА – пол и възраст

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Men n – 4</th>
<th>Women n – 2</th>
<th>Total n – 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18-45 years</td>
<td>1(16.66%)</td>
<td>0 (0.0%)</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>Age 46-65 years</td>
<td>2(33.33%)</td>
<td>2(33.33%)</td>
<td>4 (66.67%)</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>1(16.66%)</td>
<td>0 (0.0%)</td>
<td>1 (16.66%)</td>
</tr>
<tr>
<td>Number</td>
<td>4(66.67%)</td>
<td>2(33.33%)</td>
<td>6(100.0%)</td>
</tr>
<tr>
<td>Average</td>
<td>51.5</td>
<td>50.0</td>
<td>51.0</td>
</tr>
<tr>
<td>Median1</td>
<td>61.0</td>
<td>–</td>
<td>59.0</td>
</tr>
<tr>
<td>Mode1</td>
<td>56.0</td>
<td>–</td>
<td>56.0</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>15.5</td>
<td>15.0</td>
<td>15.25</td>
</tr>
</tbody>
</table>

Поради нисък брой на жените, median и mode не са изчислени

Due to the low number of women, median and mode are not calculated.
Summary of the prospective study. Adalimumab and Etanercept are the most prescribed BMPs in Bulgaria and have a share of 77% of the total prescription of BMPs; the share of the rest of the products is 23%.

ADRs systematized under MedDRA are presented in Fig. 10 with their relative shares. The first 5 most frequent ADRs were 1. Blood and lymphatic system disorders – 35 cases; 2. Infections and infestations – 24 cases; 3. Investigations – 19 cases; 4. Hepatobiliary disorders – 18 cases, and 5. General disorders and administration site conditions – 11 cases.

The total number of the reported and confirmed ADRs were 160 (Fig. 11). 3 ADRs meet the definition of SUSAR; Unexpected ADRs – 30; Suspected ADRs – 127.
Fig. 9. Distribution of patients by type of BMP used for treatment

Fig. 10. Relative share of ADRs by System-Organ Class

Fig. 11. Types of ADRs
The summarized data of the number of ADRs of the three diseases and their distribution by a degree of severity under CTCAE (version 4.03, June 14, 2010) are presented in Fig. 12 ADRs with grade 1 and 2 severity had the greatest relative share, and grade 1 severity had 63%.

The relation between ADR and the treatment received (Fig. 13) was as follows: Certain (casual connection) – 10; Probable relation – 92; Possible relation – 56; Unlikely – 2; Unassessable/Unclassifiable – 0.

Table 4 and Fig. 14 present the summarized data of the absolute number and relative shares of ADRs in the patients in the three groups of analyzed diseases (AS, RA and PsA) followed up in the prospective study.

Obviously, the incidence of ADRs was found to be very high and disproportionately higher than the pre-authorization data. The highest incidence was found in the AS group – 4.35 ADR/patient. The total ADR incidence in the entire prospective study was measured at ~ 4 (four) ADRs/patient.
Демографската характеристика на включениите в проспективното проучване пациенти отговаря на епидемиологичните данни за България, типична е за българската популация и съответства на данните за европеидната раса.

Adalimumab и etanercept са най-предписваните БЛП в България и заемат дял от 77% от общото предписание на биологични продукти, а останалите продукти заемат дял от 23%.

Делът на пациентите с РА, провеждали монотерапия, е 29.4% (5 от 17 пациенти), а при пациентите с ПсА – 75% (6 от 8 пациенти), или 44% от всички болни са провеждали монотерапия.

Установихме много висок относителен дял – 17.0%, на изява на сериозни НЛР, довели до прекратяване на лечението. Проспективно установената честота на НЛР е 3,80/пациент. Този резултат изявява честотата на изявените НЛР като много чести по системо-органната класификация по MedDRA.

**Таблица 4. Установени НЛР в трите групи анализирани заболявания**

Table 4. ADRs identified in the three groups of analyzed diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of patients</th>
<th>ADRs</th>
<th>Relative share</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>17</td>
<td>74</td>
<td>4.35 ADRs/patient</td>
</tr>
<tr>
<td>RA</td>
<td>17</td>
<td>67</td>
<td>3.94 ADRs/patient</td>
</tr>
<tr>
<td>PsA</td>
<td>8</td>
<td>19</td>
<td>2.38 ADRs/patient</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>160</td>
<td>3.80 ADRs/patient</td>
</tr>
</tbody>
</table>

**Фиг. 14. Обобщени данни за установените НЛР в трите групи анализирани заболявания**

Fig. 14. Summarized data of ADRs identified in the three groups of analyzed diseases

### Обсъждане

Демографската характеристика на включениите в проспективното проучване пациенти отговаря на епидемиологичните данни за България, типична е за българската популация и съответства на данните за европеидната раса.

Adalimumab и etanercept са най-предписваните БЛП в България и заемат дял от 77% от общото предписание на биологични продукти, а останалите продукти заемат дял от 23%.

Делът на пациентите с РА, провеждали монотерапия, е 29.4% (5 от 17 пациенти), а при пациентите с ПсА – 75% (6 от 8 пациенти), или 44% от всички болни са провеждали монотерапия.

Установихме много висок относителен дял – 17.0%, на изява на сериозни НЛР, довели до прекратяване на лечението. Проспективно установената честота на НЛР е 3,80/пациент. Този резултат изявява честотата на изявените НЛР като много чести по системо-органната класификация по MedDRA.

### Discussion

The demographic characteristics of the patients included in the prospective study correspond to the epidemiological data for Bulgaria. They are typical of the Bulgarian population and consistent with the data of the Caucasian race.

Adalimumab and Etanercept are the most prescribed BMPs in Bulgaria and have a share of 77% of the total prescription of BMPs; the share of the rest of the products is 23%.

The share of the patients with RA, who had monotherapy, was 29.4% (5 of 17 patients), and the share of the patients with PsA was 75% (6 of 8 patients), or 44% of all patients, who had monotherapy.

We found a very high relative share of 17.0% of onset of serious ADRs, which led to discontinuation of treatment. The incidence of the prospectively identified ADRs was 3.80/patient. This result demonstrates the very high incidence of the identified ADRs, according to MedDRA System Organ Class.
If we complete the number of the cases of treatment discontinuation due to ADR with the number of cases of treatment discontinuation for any other reason, the relative share of the cases of discontinuation of the biological treatment in the prospective study is 25.5%, which share constitutes 1/4 of the total number of patients and is relatively higher compared to the pre-authorization data.

The highest incidence was seen in the hepatobiliary disorders, blood and lymphatic system disorders, infections and infestations, and deviations in the tests.

Conclusions

Proactive search, monitoring, and analysis of ADRs, through doctors’ active participation in pharmacovigilance and the informed choice and cooperation of the patients, at the same time, is an essential approach in the administration of biological treatment and ensures its success.

Administration of monotherapy with BMPs, considering their combined use with Methotrexate, is a significant deviation from the established EULAR standards of treatment of inflammatory joint diseases with biological medicines [21-29].

The most common reason for discontinuation of the biological therapy in patients with inflammatory joint diseases is the onset of ADRs.

Patients with inflammatory joint diseases treated with BMPs must be monitored for the following ADRs regularly: hepatobiliary disorders, blood, and lymphatic system disorders, and infections and infestations.

Biological therapy in the patients we followed up did not increase the risk of neoplasms, compared to the results of some European studies in this area [30].

Patients with inflammatory joint diseases eligible for biological therapy must be provided with information on the nature of the disease, BMP mechanism of action, and the necessity of active monitoring for deviations from the preset criteria. Thus, they will take an active part in the process of treatment, assessment of therapeutic effectiveness, and ADR reporting [31].
Библиография / References


7. Закон за лекарствените продукти в хуманната медицина (в сила от 01.01.2007 г.) [Cited 2015 June 30]. Lex.bg.


ACPA IN SALIVA AND THEIR ASSOCIATION WITH PERIODONTITIS AND RHEUMATOID ARTHRITIS

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Резюме. Антициркулинираните протеинови антигени (ACPA) се формират под действие на възникналите в организма антигени и са част от етиологията на ревматоидния артрит (РА). Те са чувствителен и високоспецифичен показател за RA. В изследването участват 105 пациента на възраст от 32 до 85 години (средна възраст 50,6 ± 13,07), разпределени в четири групи: I група – с пародонтит (П) и без RA (с диагностицирана остеоартроза) – 26 човека; II група – с П и с RA – 28 човека; III група – без П и с RA – 26 човека; IV група – без П и без RA – 25 човека. При всички пациенти са извършени клинични и лабораторни изследвания за диагностика на RA и остеоартроза, клинично пародонтално изследване и събрана нестимулирана цялостна слюнка. Установихме, че при пациентите с RA нивата на ACPA в слюнка са значително по-високи спрямо здравите лица (p < 0,0001). Установихме, че пациентите с П имат значително по-високи нива на ACPA в слюнка спрямо здравите лица (p < 0,0001). При пациентите с П установихме значима корелация между концентрацията на ACPA в слюнка и показателите: PISA, PD, BOP, съответно (p < 0,001, p = 0,003, p = 0,007). При пациентите с RA резултатите ни показват значима корелация между концентрацията на ACPA в слюнка и показателите: ACPA в серум (p < 0,0001); концентрация на RF в серум (p < 0,0001); DAS 28 (CRP) (p = 0,009). На основата на установените зависимости между ACPA в слюнка и показателите на RA може да се предположи високата концентрация на ACPA в слюнка като леснодостъпен показател за RA, но са необходими допълнителни изследвания, за да се потвърди като съответен маркер. Установената връзка между показателите на П и ACPA в слюнка потвърждава възможността на пародонталното възпаление върху този показател и обяснява леченето на П като начин за превенция и контрол на RA.

Ключови думи: ACPA, пародонтит, ревматоиден артрит

Abstract. Anti-cyclic citrullinated peptide antibodies (ACPA) are formed by the action of host-generated antigens and are part of the etiology of rheumatoid arthritis (RA). They are a sensitive and highly specific indicator of RA. In the study were involved 105 subjects aged 32 to 85 years (Mean age 50,6 ± 13,07), divided into four groups: Group I – with periodontitis (P) and without RA, with diagnosed osteoarthritis – 26 patients; Group II – with P and RA – 28 patients; Group III – without P and with RA – 26 patients; Group IV – without P and RA – 25 individuals. All patients underwent clinical and laboratory tests for the diagnosis of RA and osteoarthritis, a clinical periodontal examination, and unstimulated whole saliva was collected. We found significantly higher salivary ACPA levels in RA patients compared to healthy subjects (p < 0.0001). In P patients, we found significantly higher levels of ACPA in saliva than in healthy subjects (p < 0.0001). Among P patients, we found a significant correlation between ACPA concentration in saliva and the following indicators: PISA, PD, BOP respectively (p < 0.001, p = 0.003, p = 0.007). Among RA patients, our results showed a significant correlation of ACPA concentration in saliva with the following indicators: serum ACPA concentration (p < 0.0001); serum RF concentration (p < 0.0001); DAS 28 (CRP) (p = 0.009). Based on the established
correlation between salivary ACPA levels and RA indicators, a high concentration of ACPA in saliva may be suggested as an easily accessible indicator of RA, but further studies are needed to ascertain this possibility. The established association between periodontal parameters and salivary ACPA levels confirms the effect of periodontal inflammation on salivary ACPA concentration and justifies the treatment of P as a way of preventing and controlling RA.

Key words: ACPA, periodontitis, rheumatoid arthritis

INTRODUCTION

In the last two decades, anti-cyclic citrullinated peptide antibody (ACPA) has been known as antibodies formed by the action of antigens originated in the body, and ACPA are part of the etiology of rheumatoid arthritis (RA). ACPA are a sensitive indicator of RA, but significantly more specific than the Rheumatoid factor (RF) for diagnosing RA, and can be found in RF-negative patients with RA. [1, 2]. Their presence in blood serum is associated with more severe clinical signs, greater bone destruction, and a greater risk of an aggressive course of the disease [3]. The role of the extraarticular citrullination in the pathogenesis of RA remains to be elucidated. There is evidence that in the case of periodontitis (P), the enzyme peptidylarginine deaminase (PPAD) of periodontal pathogen Porphyromonas gingivalis and human PAD-4 are major factors in peptide citrullination in inflamed periodontal tissues, which stimulates ACPA production. Saliva collection, on the other hand, is easy, fast, inexpensive, and non-invasive, making it a convenient biological fluid for the diagnosis and monitoring of RA if disease markers are identified in it.

OBJECTIVE

To determine ACPA concentration in saliva in patients with P, with RA, with both diseases, and in healthy subjects. Comparison of salivary and serum ACPA levels. Comparison of ACPA concentration in saliva with clinical periodontal parameters and with RA indicators.

MATERIAL AND METHODS

The study involved a total of 105 patients, aged 32 to 85 years (Mean age 50.6 ± 13.07), 71 women and 34 men, divided into four groups: Group I – patients with P and without RA (diagnosed osteoarthri-
RA (diagnosed osteoarthritis) – 26 patients; Group II – patients with P and RA – 28 patients; Group III – patients without P (with periodontal health) and with RA – 26 patients; Group IV – patients without P (periodontal health) and RA – 25 individuals.

Patients included in the study are over 18 years of age, have at least nine teeth, have not received antibiotic treatment in the last three months, have not undergone periodontal treatment in the last six months, do not need antibiotic prophylaxis during oral procedures, including periodontal probing. Patients who have diabetes or other disease affecting their immune status were excluded. Pregnant and lactating women were excluded.

The research was ethically conducted according to the Helsinki Declaration of the World Medical Association. The Institutional Council on Medical Science of Medical University – Sofia approved the study protocols, including the recording of clinical measurements and the collection of saliva samples. All subjects signed informed consent prior to entry into the project and after reading the notification letter.

All patients underwent clinical examination and laboratory tests for the diagnosis of RA and osteoarthritis – history, physical examination, complete blood count, inflammatory biomarkers – erythrocyte sedimentation rate, C-reactive protein; immunological parameters – serum concentration of rheumatoid factor class IgM (RF-IgM) and serum concentration of ACPA. Peripheral blood from the cubital vein on an empty stomach was obtained from all the patients and was tested in the clinical laboratory and clinical immunology. An X-ray examination of palms and fingers of both hands was performed regarding the diagnosis of joint disease. The Disease Activity Score – CRP (DAS-28 (CRP), which is a composite index, including clinical and laboratory data, have been determined.

All participants received a clinical periodontal examination, which includes: Hygiene index (HI), Papillary bleeding index (PBI), Periodontal pocket depth (PD), Clinical attachment loss (CAL), Bleeding on probing (BOP) and the presence of recessions for each periodontal unit. The examination is performed with a specialized graduated periodontal probe, and six sites of each periodontal unit were explored. PISA Indicator (Periodontal inflamed surface area), which shows the amount of inflamed
ница в устата в шест точки. Определя се показателят PISA (Periodontal Inflamed Surface Area), който показва количеството на възпалена пародонтална повърхност, изчислено в mm² [4]. Изчисляването на PISA става чрез въвеждане на пародонтални измервания (CAL, PPD, BOP, ниво на гингивалния ръб) във върху специално създаден за целта файл на програмата Microsoft Excel. Според авторите PISA отразява тежестта и активността на пародонталното заболяване и може да се свърже с влиянието на П на други системни заболявания.

При пациентите с П (от първа и втора група) се изследват шест места в два квадранта с най-малко два засегнати зъба във всеки квадрант и всяко засегнато място е с дълбочина на джоба при сондирание PPD ≥ 5 mm, клинична загуба на аташман CAL ≥ 3 mm, кървене при сондирание BOP ≥ 20% от всички изследвани места (изследвани са шест места във възх). Участяват пациенти с П, определени по новата класификация като II, III и IV фаза [5]. Пациентите с П се класифицират с различна активност на заболяването на основата на показателя PISA. В трета и четвърта група пациентите са с пародонтално здраве. Здравите лица имат PBI ≤ 10% от всички изследвани места (изследвани са шест места във възх), дълбочина на джоба при сондирание PPD ≤ 3 mm на всички места, липса на места със загуба на аташман Clinical attachment loss (CAL ≥ 2 mm) [6].

От всички пациенти е събрана нестимулирана цялостна слюнка в съответствие с метода, описан от Navazesh [7] и модифициран съгласно IARC – International Agency for Research on Cancer (Collecting and Processing Saliva. The Molecular Methods database. Wed, 12/19/2012). Не се правят никакви интервенции в устата. Пациентът изплаква устата си с обикновена чешмичка вода (приблизително 10 ml) за 30 секунди и изплюва извън съда за събиране. Пет минути след устното изплакване всяко лице отделя слюнка в стерилен контейнер, поставен в съда с лед, за 10 минути. Целта е да се събере количество около 2 ml. Контейнерите със слюнка се транспортират в хладилна чанта до лабораторията, където подготовят материала в рамките на 2 часа. Слюнковият материал се центрифугира на 2600 x g за минута, за 15 минути, на t 4° C. Супернатантът се прехвърля в надписан криотуб със 1 μL от протеазния инхибитор (SigmaFast Protease inhibitor, Sigma-Aldrich Co, St. Louis, MO, USA) – 1 μL от протеазния инхибитор на всеки mL от слюнка.
ка. Всички проби се съхраняват на t –80° C до момента на анализа – количествено определяне на ACPA в слюнка чрез метода ELISA (enzyme-linked immunosorbent assay)(Euroimmun AG, Германия).

За статистическa обработка на данните се използват адекватни методи на медицинскa статистика: честотен анализ; вариационен анализ; кръстосване (взаимни честотни разпределения на две качествени променливи); проверка за нормалност на разпределение на количествени променливи – Kolmogorov-Smirnov;dисперсионен анализ: T-Test или ANOVA в зависимост от броя на категориите на групиращата променлива, когато променливите са нормално разпределени; непараметрични подходи (Mann-Whitney U test, когато групиращата променлива има две категории и Kruskal-Wallis test при повече от две категории на групиращата променлива), ако разпределението не е нормално; корелационен анализ: параметричен (Pearson Correlation) и непараметричен (Spearman’s rho). При проверка на хипотеза, нулевата хипотеза се отхвърля, ако p < 0,05.

Резултати

Резултатите показват значимо по-високи концентрации на ACPA в слюнка при пациентите от 3-та група (с RA) спрямо здравите лица от 4-та група (Mann-Whitney U test, p < 0,001), спрямо пациентите от 1-ва група (с P) (Mann-Whitney U test, p = 0,016) и спрямо пациентите от 2-ра група (с P и RA) (Mann-Whitney U test, p = 0,017). Установихме значимо по-високи концентрации на ACPA в слюнка при пациентите от 1-ва група (с P) спрямо здравите индивиди от 4-та група (Mann-Whitney U test, p < 0,001), както и на пациентите от 2-ра група (P и RA) спрямо здравите индивиди от 4-та група (Mann-Whitney U test, p < 0,001). Установихме, че пациентите с RA общо (от 2-ра и 3-та група) са със значително по-високи нива на ACPA в слюнка спрямо пациентите от 4-та група (без P и без RA) (Mann-Whitney U test, p < 0,0001). Установихме, че пациентите с P общо (от 1-ва и 2-ра група) са със значително по-високи нива на ACPA в слюнка спрямо пациентите от 4-та група (без P и без RA) (Mann-Whitney U test, p < 0,0001) (табл. 1).

При изследвания на пациенти с P (1-ва и 2-ра група) установихме статистически значими положителна корелация между концентрацията ACPA в слюнка и следните показатели: PISA; PD средно; BOP, съответно Spearman’s R = 0,525, p < 0,001, Spearman’s R = 0,290, p = 0,003, Spearman’s R = 0,263, p = 0,007 (фиг. 1, 2, 3). We found significantly higher concentrations of ACPA in saliva in patients in group 3 (with RA) compared to healthy subjects in group 4 (Mann-Whitney U test, p < 0.001), to the patients in group 1 (with P) (Mann-Whitney U test, p = 0.016) and the patients in group 2 (P and RA) (Mann-Whitney U test, p = 0.017). We found significantly higher concentrations of ACPA in saliva in patients in group 1 (with P) compared to healthy subjects in group 4 (Mann-Whitney U test, p < 0.001) as well as in patients in group 2 (P and RA) compared to healthy subjects in group 4 (Mann-Whitney U test, p < 0.001). We found that all the patients with RA (2nd and 3rd group) had significantly higher levels of ACPA in saliva than patients in group 4 (without P and RA) (Mann-Whitney U test, p < 0.0001). We found that all the patients with P (1st and 2nd group) had significantly higher levels of ACPA in saliva than patients in group 4 (without P and without RA) (Mann-Whitney U test, p < 0.0001) (Table 1).

In the studied patients with P (1st and 2nd group) we found significant positive correlation between ACPA concentration in saliva and the following indicators: PISA, mean PD, BOP, respectively (Spearman’s R = 0.525, p < 0.001), (Spearman’s R = 0.290, p = 0.003), (Spearman’s R = 0.263, p = 0.007) (Fig. 1, 2, 3). We found a tendency for a
3). Positive correlation between the ACPA concentration in saliva and the number of deep periodontal pockets (PD > 7 mm), as well as a tendency for a negative correlation between ACPA concentration in saliva and the number of shallow periodontal pockets (PD ≤ 3 mm) in all the patients with P (1\textsuperscript{st} and 2\textsuperscript{nd} group).

Таблица 1. Средни стойности на АСРА в слюнка в изследванияте групи

<table>
<thead>
<tr>
<th>Групи пациенти</th>
<th>Брой пациенти</th>
<th>Средна стойност ACPA в слюнка RU/ml</th>
<th>Стандартно отклонение</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-ва група / Group 1</td>
<td>26</td>
<td>9,750 RU/ml</td>
<td>± 8,65820</td>
</tr>
<tr>
<td>2-ра група / Group 2</td>
<td>28</td>
<td>11,301 RU/ml</td>
<td>± 14,45057</td>
</tr>
<tr>
<td>3-та група / Group 3</td>
<td>26</td>
<td>35,799 RU/ml</td>
<td>± 55,48167</td>
</tr>
<tr>
<td>4-та група / Group 4</td>
<td>25</td>
<td>2,770 RU/ml</td>
<td>± 1,61123</td>
</tr>
</tbody>
</table>

Fig. 1. Зависимост между концентрацията на АСРА в слюнка и показателя PISA при пациентите с П (1-ва и 2-ра група)

Fig. 1. Correlation between ACPA concentration in saliva and PISA in patients with P (1\textsuperscript{st} and 2\textsuperscript{nd} group)

Fig. 2. Зависимост между концентрацията на АСРА в слюнка и средна стойност на PD mm при пациентите с П (1-ва и 2-ра група)

Fig. 2. Correlation between ACPA concentration in saliva and mean PD mm in patients with P (1\textsuperscript{st} and 2\textsuperscript{nd} group)

Fig. 3. Зависимост между концентрацията на АСРА в слюнка и разпространението на BOP при пациентите с П (1-ва и 2-ра група)

Fig. 3. Correlation between ACPA concentration in saliva and BOP prevalence in patients with P (1\textsuperscript{st} and 2\textsuperscript{nd} group)
Установихме значима положителна зависи-
мост между концентрацията на АСРА в слюнка и
АСРА в серум при пациентите от 2-ра група (с П
и с RA) (Spearman’s R = 0.972, p < 0.0001) и при
пациентите от 3-та група (с RA) (Spearman’s R =
0.900, p < 0.0001), както и при всички пациенти с
RA от 2-ра и от 3-та група общо (Spearman’s R =
0.761, p < 0.0001) (фиг. 4).
Резултатите показват значима корелация
между концентрацията на АСРА в слюнка и кон-
cентрацията на RF в серум при пациентите от
2-ра група (с П и с RA) (Spearman’s R = 0.953, p
< 0.0001) и при пациентите от 3-та група (с RA)
(Spearman’s R = 0.911, p < 0.0001), както и при
пациентите с RA общо от двете групи (2-ра и 3-та
група) (Spearman’s R = 0.894, p < 0.0001) (фиг. 5).
Открихме значима положителна зависимост
между нивата на АСРА в слюнка и активността на
RA, отразена чрез DAS 28 (CRP) при пациентите
с RA общо от 2-ра и 3-та група (Spearman’s R =
0.353, p = 0.009) (фиг. 6).

We found a significant positive correlation be-
tween ACPA concentration in saliva and serum
ACPA concentration in patients of group 2 (with P
and RA) (Spearman’s R = 0.972, p < 0.0001) and
in patients of group 3 (with RA) (Spearman’s R =
0.900, p < 0.0001), as well as in all the patients with
RA (2nd and 3rd group) (Spearman’s R = 0.761, p <
0.0001) (Fig. 4).

Our results showed a significant correlation be-
tween ACPA concentration in saliva and serum RF
concentration in patients in group 2 (with P and RA)
(Spearman’s R = 0.953, p < 0.0001) and in patients
in group 3 (with RA) (Spearman’s R = 0.911, p <
0.0001), as well as in patients with RA in total, in
both groups (2nd and 3rd group) (Spearman’s R =
0.894, p < 0.0001) (Fig. 5).

We found a significant positive correlation be-
tween saliva ACPA levels and RA activity reflected
by DAS-28 (CRP) in patients with RA in total (2nd
and 3rd group) (Spearman’s R = 0.353, p = 0.009)
(Fig. 6).
Our results showed significantly higher levels of ACPA in saliva in patients with P and RA compared to healthy subjects, as well as in patients with P and without RA compared to healthy controls. We associate these results with the possibility that periodontal disease could be a source of citrullinated proteins that induce the synthesis of antibodies against them. In a previous study, Harvey et al. [8] found the presence of citrullinated proteins and antibodies against them in periodontal tissues and a positive correlation between the severity of gingival inflammation and the expression of citrullinated proteins. The authors found that most of the patients with high gingival crevicular fluid ACPA levels were in the periodontitis group compared to controls. According to these authors, ACPA production depends on the presence of generically existing citrullinated proteins in inflamed tissues, no matter the diagnosis gingivitis or periodontitis, and ACPA production depends on the genetic predisposition of the patients. We support this view. Our results showed in patients with periodontitis increased levels of ACPA in saliva, which are likely originate from periodontal tissues and result of two factors: increased production of citrullinated proteins in cases of periodontitis and genetically predisposed production of antibodies against increased citrullinated proteins.

Our results showed significant positive correlations between ACPA concentration in saliva and the mean PD, BOP, as well as a tendency for a correlation between ACPA concentration in saliva and the number of periodontal pockets with PD > 7 mm and a tendency for a negative correlation between ACPA concentration in saliva and the number of periodontal pockets with PD ≤ 3 mm. Previous studies have also found correlations between the expression of citrullinated proteins, antibodies against them in periodontal tissues, and the degree of inflammation [8, 9]. These data underlie the hypothesis of ongoing citrullination in periodontal tissues, which is dependent on the presentation of P and the possible local production of ACPA. The mechanism of these processes most likely being associated with the activity of P. gingivalis in protein citrullination and subsequent activation of ACPA-producing cells [8, 9, 10, 11]. In our opinion, increased salivary ACPA concentrations found in patients with higher periodontal
po-visoki показатели на П свързваме с локалната им продукция в тъканите на пародонта във връзка с активността на възпалението и послед- ващото им попадане в слюнката. Тези резултата си в подкрепа на хипотезата за евентуалната роля на П като извънствен източник на цитрулинирани протеини и антитела срещу тях, които биха могли при предразположени индивиди да допринасят за изява на РА, а при съществуващ РА да утежнят хода му [11].

Ние установихме наличие на АСРА в слюнката на всички участници в изследването, като концентрацията им е значително по-голяма при пациентите от 3-та група с РА в сравнение с пациентите от 1-ва група с П, пациентите от 2-ра група с РА и П и индивидите от 4-та група, които са здрави. Заедно с това установихме силна положителна корелация между концентрациите на АСРА в слюнка и АСРА в серум при пациентите от 2-ра група с РА и П и при пациентите от 3-та група само с РА, както и при 2-ра и 3-та група общо (всички пациенти с РА). Считаме, че едно обяснение за наличието на АСРА в слюнка и корелацията на концентрациите им в слюнка с тези в серум при пациенти с РА е дифузията им от серум. Подобни резултати са представени и в друго съвременно изследване [12], в което се установява силна зависимост между нивата на серумните и слюнчените АСРА при болни с РА, както и значимо по-високи нива на АСРА в слюнка при пациенти с РА в сравнение с нивата на АСРА в слюнка при здравите контроли.

Ние установихме силна положителна корелация между концентрациите на АСРА в слюнка и RF в серум (един от основните маркери за РА) при пациентите с РА – от 2-ра група с РА и П; от 3-та група с РА и общо от двете групи. Установихме положителна зависимост и между концентрацията на АСРА в слюнка и активността на РА, оценена чрез DAS 28 (CRP). Резултатите ни кореспондират с публикации, показващи значително по-високи стойности на показатели за РА, които се свързват с активността му – Erythrocyte sedimentation rate, plasma C-reactive protein, DAS 28, брой на подути стави и цялостна лекарска оценка на болестната активност при пациенти с РА, които са АСРА-позитивни в серум [3, 13]. Считаме, че тези резултати ни дават основание да обсъдим концентрацията на показателя АСРА в слюнка като евентуален диагностичен маркер за РА.

clinical measurements are associated with their local production in periodontal tissues, depending on the activity of inflammation and their subsequent entry into saliva. These results support the hypothesis for the possible role of P as an extraarticular source of citrullinated proteins and antibodies against them, which in susceptible individuals may contribute to the expression of RA, and in existing RA could complicate its course [11].

We found the presence of ACPA in saliva in all of the study participants, with a significantly higher concentration in patients in group 3 with RA compared to patients in group 1 with P, patients in group 2 with RA and P, and healthy individuals in group 4. In addition, we found a strong positive correlation between ACPA concentration in saliva and serum ACPA concentration in patients in group 2 with RA and P, and in patients in group 3 with RA, as well as in groups 2 and 3 in total (all patients with RA). We consider that the presence of salivary ACPAs and the correlation of salivary ACPA concentration with serum ACPA concentration in patients with RA may be due to their diffusion from serum. Similar results have been reported in another contemporary study [12], which found a strong correlation between serum and salivary ACPA levels in RA patients, and significantly higher levels of ACPA in saliva in RA patients compared to ACRA levels in saliva in healthy controls.

We found a strong positive correlation between ACPA concentrations in saliva and RF in serum (one of the major markers for RA) in patients with RA – group 2 with RA and P; group 3 with RA; and 2 and 3 groups in total. We also found a positive relationship between the concentration of ACPA in saliva and the activity of RA, assessed by DAS 28 (CRP). Our results correspond with publications showing significantly higher RA indicators, associated with its activity – Erythrocyte sedimentation rate, plasma C-reactive protein, DAS-28, number of swollen joints, and physician’s global assessment of disease activity in patients with RA who are ACPA-positive in serum [3, 13]. We believe that these results give us reason to suggest the saliva ACPA concentration as a possible diagnostic marker for RA.
Изводи

Получените резултати показват по-високи концентрации на ACPA в слюнка при пациенти с RA, както и положителна корелация на слюнчевите нива на ACPA със серумните нива на ACPA, серумните нива на RF и показателя DAS 28 (CRP) при пациентите с RA. На основата на установените зависимости може да се предложи високата концентрация на ACPA в слюнка като леснодостъпен показател за RA, но са необходими допълнителни изследвания, за да се верифицира като маркер за RA. Ние считаме, че ако ACPA бъдат открити в високи концентрации в слюнка преди клиничната изява на RA, то това би определило такива индивиди във висок риск от развитие на RA, тъй като ACPA са високоспецифични за RA.

Установената връзка между показателите за RA и ACPA в слюнка обосновава лечението на RA като начин за превенция и контрол на RA и потвърждава необходимостта от тясно сътрудничество между специалисти в двете области.

Благодарности

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Библиография / References

10. Rosenstein, ED et al. Hypothesis: the humoral immune response to oral bacteria provides a stimulus for the


ASSESSMENT OF KNOWLEDGE IN SAMPLE OF IRAQI PATIENTS WITH ANKYLOSING SPONDYLITIS

ОЦЕНКА НА ЗНАНИЯТА В ИЗВАДКА ОТ ПАЦИЕНТИ С АНКИЛОЗИРАЩ СПОНДИЛИТ ОТ ИРАК

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Abstract. The aim of the present study is to assess a level of knowledge in a sample of Iraqi patients with ankylosing spondylitis (AS) by a self-administered questionnaire. This is a cross-sectional study, including 200 Iraqi patients with AS, who have access to the Rheumatology Unit, Baghdad Teaching Hospital. AS Data collection was taking place between November 2017 and September 2018. Socio-demographic data were reported, including age, residence, marital status, smoking, educational level, occupation, and disease diagnosis duration. Patients had undergone an interview with a physician to assess their level of knowledge by a questionnaire, which included 4 knowledge areas: Area A includes general knowledge about AS, comprising etiology, symptoms musculoskeletal and extra musculoskeletal, and laboratory blood tests. Area B includes immuno-genetics test (HLA-B27 antigen) and inheritance. Area C includes general management, including pharmacological treatment and its side effects, physical therapy, and exercise (exercise type & proper duration and its role in treatment). Area D includes joints protection, pacing, and priorities. The clinical and demographic data were analyzed using descriptive statistics. The mean total questionnaire score is 16.28 ± 2.49, range (2-26). There is no significant statistical association between the mean total score and the gender (p = 0.14), age (p = 0.93), marital status (p = 0.73), smoking (p = 0.65), residence (p = 0.56), and BMI (p = 0.23), while there is a highly significant statistical relationship between mean total score and the level of education (p = 0.0004), and occupation (p = 0.0026). For Area A, the mean achieved score is 3.63 ± 1.61; the maximum possible score is 8. For Area B, the mean achieved score is 0.26 ± 0.51; the maximum possible score is 2. For Area C, the mean achieved score is 9.53 ± 2.42; the maximum possible score is 15. Area D, the mean achieved score is 2.87 ± 1.06; the maximum possible score is 4. The study showed that AS Iraqi patients have a low level of knowledge, unawareness, and wrong thoughts about specific aspects of their disease, which may reinforce the recommendation of this study.

Key words: ankylosing spondylitis; Iraq; musculoskeletal symptoms; chronic inflammatory disease

INTRODUCTION

Ankylosing spondylitis (AS) is an inflammatory, rheumatic disease from the group of spondyloarthropathies (SPAs), chronic in nature, which primarily involves the sacroiliac joint and spine, less frequently peripheral joints, and can also present with extra joint involvement [1]. AS is more prevalent in males, in the ratio of 2-4:1, and most symptoms occur between 20 and 35 years of age. It takes, on average, up to 8 years from the onset of back pain until a definite diagnosis of AS [2]. A positive family history increases the probability of AS pretest from 0.1% in the general population to approximately 10% for any first degree relative of an AS [3]. AS prevalence parallels closely with the frequency of HLA-B27 [4]. This holds for those B27 subtypes that are associated with the disease, but it is not true for populations in which the HLA-B2706 subtype, which lacks a strong association with AS [5, 6]. HLA-B27, an allele of the major histocompatibility complex, shows a strong association with AS and related SpA [7, 8]. HLA-B27 is found in approximately 8% of the general white population (western European) and more than 90% of patients with AS. In AS Iraqi patients, the estimated prevalence was 0.9%, with male to female ratio 9:1, and HLA-B27 was positive in 55% [9], while 2.1% of healthy Iraqi populations were HLA-B27 positive [10]. Genetic factors such as strong association with HLA-B27 that B*2705 is the strongest disease-associated subtype [4, 5]. Ramos et al., 2002 reported that B*2709 is weakly or not associated with ankylosing spondylitis [11]. HLA-B*2705 and B*2709 allotypes differ by a single D116H change. They suggested that weaker association of B*2709 with ankylosing spondylitis based on differential binding of a limited subset of natural ligands by this allotype [11, 12]. Other HLA-B*2706 is a relatively rare subtype of HLA-B27. In contrast to most...
HLA-B27 subtypes HLA-B*2705, some studies have reported HLA-B*2706 to be protective against AS [11, 12]. Regarding the immunological causes, the cytokine TNF-α is identified as an important mediator in the pathogenesis of AS [13]. IL-23 promotes the survival of TH17 CD4+ T cells. TH17 cells can play a major role in inflammatory responses by various pro-inflammatory cytokines production (like IL-17, IL-6, and TNF-α) and recruiting other inflammatory cells (like neutrophils) in inflammatory and infectious diseases. They may play an important role in the pathogenesis of AS and spondyloarthopathies [14]. Other causes could be environmental factors, HLA-B*2705 and nitrogenase from Klebsiella pneumoniae, which supports molecular mimicry as a possible mechanism for the induction of spondyloarthopathies in a host who is genetically susceptible via an environmental stimulus, including bacteria in the gastrointestinal tract [15]. To evaluate and monitor clinical disease activity in AS, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) has been used. This index is obtained by summing the values of a visual analog scale (VAS) that evaluates six items, namely: fatigue, axial pain, peripheral pain, enthesisis, duration, and intensity of morning stiffness. BASDAI values are internationally used (BASDAI ≥ 4 is deemed as high disease activity) [16]. Bath Ankylosing Spondylitis Functional Index (BASFI) is a set of 10 questions designed to decide the degree of functional limitation in AS patients. It is measured using a visual analogue scale (ranging from 0 being easy and 10 being impossible) and the questions are focused on the person's ability to perform specific functional tasks. The first 8 questions consider activities related to functional anatomy. The final two questions assess the patients' ability to cope with everyday life. It is included in the ASAS core sets for Ankylosing Spondylitis assessment. The mean of the ten questions gives the Bath Ankylosing Spondylitis Functional Index (BASFI) score, which is a set of 10 questions designed to decide the degree of functional limitations in AS patients [17]. The higher the BASFI score, the more the patient is functionally limited. The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a measure of axial spondyloarthritis (axSpA) disease activity with validated cut-offs endorsed by the Assessment of SpondyloArthritis international Society (ASAS) and OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials). The 2017 update of treat-to-target recommendations in axial and peripheral SpA state that the preferred measure to define the target in axSpA is the ASDAS. ASDAS cut-offs for disease activity states are 1.3 separating the inactive disease from moderate disease activity, at least 2.1, high disease activity, and more than 3.5 very high disease activity [18]. The cornerstone of the non-pharmacological treatment of patients with AS is patient education and regular exercise. Patient education is advised as an integral part of recommendations for the management of early arthritis and AS [19]. The primary goal of patient education is no longer only knowledge transfer and disease control, but also to help patients to manage their illness, adapt to their disease, and maintain quality of life. Knowledge is a palliative force against the damaging effects of chronic illness and a description of the tendency of patients to reconstruct stories to bridge a gap between medical explanations and their own understanding of etiology [20]. Knowledge acquisition is a complex procedure and depends on patient intelligence, level of education, motivation teaching style, and content. Different models have been identified to increase the level of knowledge, with educational courses and information booklets among the most common [21, 22]. Acquisition of specific disease knowledge and education programs can benefit patients with chronic conditions mainly through improvements in self-efficacy, which is defined as the expectation an individual has in their ability to achieve a beneficial change and allows patients to participate in their own care [23], improvement of compliance, changing behavior and, to a lesser extent increase or improve the level of knowledge. And by proper knowledge, we can build trusting therapeutic relationships between patients and the rheumatology team. Patients may have a certain amount of knowledge and concept or their understanding about their disease, but this may be flawed or overestimated and can never fully or get balance with the expertise of the medical consultation. Overestimating their knowledge about their illness could have two effects on patients: it may decrease their motivation to learn more about their condition because by their assessment they already know enough about their illness and have the best knowledge to manage it, and it may lead them to make choices about their health independently [24]. Patients may have multiple views, by careful collection, these views are tried to be more directed and specific, and by a discussion of the consequences of chronic illness on patients and the possible role of the level of knowledge, by all of these, patient's understanding of chronic AS.
illness and its experience will be deepened. The explanation of the process of spinal fusion or ankylosis to patients with AS will help to explain the associated pain, stiffness and restricted movement, and help patients to follow exercise programs and adhere to medication regimes in order to prevent ankylosis occurring. The same thing goes about extra skeletal symptoms, such as potential eye involvement. The importance of evaluating patients’ knowledge about their specific disease have recognized by several investigators and educators. This is the reason for multiple studies that developed tools to evaluate the knowledge of chronic diseases, such as rheumatoid arthritis [25, 26], fibromyalgia [27], low back pain [28, 29], and AS [30, 31]. With physical therapy, an education with effective corrected knowledge has been recommended as non-pharmacological treatment of the disease, according to EULAR (European League Against Rheumatism) recommendation, 2016 [32].

**Patients and methods**

This is a cross-sectional study. Patients with an established diagnosis of ankylosing spondylitis, depending on fulfilling modified New York criteria 1984, who have access to the Rheumatology Unit at Baghdad Teaching Hospital, are included in the study.

A consecutive sample of 200 Iraqi patients with established AS diagnosis were recruited, with disease onset after the age of 16 years, and disease diagnosis duration at least 6 months. AS Data were collected between November 2017 and September 2018. The study protocol was approved after review, and official permission was obtained from the Iraqi Board for Medical Specializations. Written consent was obtained from 197 participants, and fingerprint was obtained from the illiterate 3 participants, by a pre administered letter emphasizing the anonymous and confidential nature of the questionnaire. Privacy was assured during the personal interview, and all identifying information was concealed during statistical analyses.

Socio-demographic data were taking (age, name, gender, BMI (the equation BMI = weight kg/height m²), residence, marital status, smoking (smoker, X-smoker and non-smoker), with different educational level (illiterate, read & write, primary school, secondary school, and university level), occupation and disease duration (6 months at least). Patients were on different medications (NSAIDs, bDMARDs as monotherapy, or combination with sDMARDs). Disease activity measurement was done by BASDAI [16]; functional disability by BASFI [17], for all patients and its association with the level of knowledge was included. Patients had interviewed and answered a questionnaire, which was including 4 knowledge Areas:

- **Area A.** General Knowledge about AS, comprising etiology, symptoms musculoskeletal and extra musculoskeletal, and laboratory blood tests.
- **Area B.** Immuno-genetics test (HLA-B27 antigen) and inheritance.
- **Area C.** General Management, including pharmacological treatment and its side effects, physical therapy and exercise (exercise type & proper duration and its role in treatment).
- **Area D.** Joints protection, pacing, and priorities.

The questionnaire contained 18 questions, in total, with multiple possible responses or answers, one or two would be correct responses in each question. One point for each correct answer, then the points of all areas was summed to give a final score. The total correct score was 29 from 92 total possible responses. A ‘don’t know’ response was added to enhance compliance of reluctant patients.

In **Area A**, total questions were 4, with the total correct score of 8. In **Area B**, total questions were 2, with total correct score 2. In **Area C**, total questions were 9, with a total correct score of 15. In **Area D**, total questions were 3, with total correct score 4, as shown in table 2.

All areas questions were answered during interviews at the rheumatology unit in Baghdad teaching hospital. Patients made free choices after reading, translating, and explanation of each question by a doctor. All 200 AS patients were keen to participate, and no patient had help from the family or the Health providers. Patients had received their knowledge or information about their disease AS, from different sources such as websites, rheumatologists, and even from discussion with each other.

The clinical and demographic data were analyzed using descriptive statistics of the participants’ data, and knowledge scores were computed, a mean and standard deviation for numerical variables, and frequency and percentage for categorical variables were calculated. Student’s t-test and Pearson’s correlation coefficient for numerical data and univariate correlation by the Spearman correlation coefficient were used, in order to correlate the results from the questionnaire of knowledge with the clinical and demographic parameters of the participants. Pearson’s chi-squared test ($\chi^2$) is used to determine whether there is a significant difference between the expected frequencies and the observed frequencies in one
or more categorical data. The statistical significance level was set at $p < 0.05$. The standard error of a correlation coefficient is used to determine the confidence intervals around a true correlation of zero. It has a value between (+1) and (−1), where (1) is total positive linear correlation, (0) is no linear correlation, and (−1) is total negative linear correlation. The interaction which describes noncausal associations were considered in the context of regression analyses or factorial experiments, and by simple setting in which interactions were analyzed using Analysis of variance (ANOVA). The results were disclosed by using Microsoft Office 2010 for windows. The data analyzed using Statistical Package for Social Sciences (SPSS) version 25.

**Results**

All patients knew that their diagnosis was AS (no other diagnoses). Eighteen females and 182 males participated. Body mass index (BMI) mean was 28.95 ± 4.04 kg/M² (range 18-43). Their mean age was 36.89 ± 9.65 (range 18-74), and the mean disease diagnosis duration was 8.45 ± 7.54 years, (range 6 months – 40 years). Patients had different educational levels (3 illiterate, 2 read and write, 60 primary school, 74 secondary school and 61 university level), and different occupations (housewife, wage earner, policeman, military soldier, driver, employee, teacher, engineer, and retired). One hundred fourteen were smokers, 15 were X-smokers, and 71 non-smokers, all socio-demographic data are shown in table 1. Their treatments were: 168 (84%) of patients on biologics mono-therapy. 23 (11.5%) on combination of sDMARD + bDMARD, and 9 (4.5%) on NSAID only. The mean total score of the questionnaire was 16.28 ± 2.49 (range 2-26). Total possible responses or answers were 92, total correct responses were 29, and every correct response takes one point. There was no significant statistical association between the mean total score and the gender ($p = 0.14$), as shown in fig. 1; age ($p = 0.93$), marital status ($p = 0.73$), as shown in fig. 2; smoking ($p = 0.65$), as shown in fig. 3; residence ($p = 0.56$), BMI ($p = 0.23$), BASDAI ($p = 0.42$), and BASFI ($p = 0.81$), table 1. While between the mean total score and the level of education, occupation, and engineer job, there was a highly significant statistical relationship, $p$-values respectively were 0.0004, 0.002, and 0.04, as shown in fig. 4, fig. 5, resp. There were no statistical correlations between the mean total score of the questionnaire and BASDAI, BASFI, age, and disease diagnosis duration.

**Area A: General knowledge, etiology, symptoms, and laboratory blood tests.** The mean total score is 3.63 ± 1.61. The maximum possible score is 8. The maximum achieved score is 7, as shown in table 2 and fig. 6.

In area A, 65 (32.5%) have been recognized that the cause of their disease is unknown or autoimmune. 74 (37%) have thought of back injuries of heavy exercise, which may cause AS. 49 (24.5%) don’t have any idea about the cause. 12 (6%) of patients thought that AS is an infectious disease. 49 (24.5%) know that AS can involve more than one member in the same family. 151 (75.5%) don’t know that AS can be presented in more than one member of the same family. All patients recognized that the main feature is back pain, 153 (76.5%) don’t know the first presentation could not be in the back. 160 (80%), recognized that AS is a chronic disease. 14 (7%), thought that AS is a curable disease, while 26 (13%) don’t know the attitude of AS. 127 (63.5%) get worse in cold weather. About eye and lung involvement in AS, 79 (39.5%) get the correct answer. Only 3 (1.5%) made a correct choice of CRP and ESR as a routine blood test used to assess disease activity.

**Area B: HLA-B27 antigen and inheritance.** The maximum possible score is 2. Mean achieved score is 0.26 ± 0.51 (0-2), the maximum total score is achieved by just 6 (3%), as shown in table 2 and fig. 6.

Only 43(21.5%), recognized that HLA-B27 is a useful blood test to assess the tendency to develop AS. The inheritance of AS is a cause of confusion with the majority of participants, 194 patients (97%) don’t know.

**Area C: Drug treatment and physical therapy.** The maximum possible score is 15, the mean achieved score (9.53 ± 2.42), (0-14), as shown in table 2 and fig. 6.

Area C shows, 131 (65.5%) of patients considered medications as a pain killer & anti-inflammatory, and 69 (34.5%) thought, they are just a pain killer. bDMARDs, side effects make a difficult question to the patients; just 48 (24%) recognized that reactivation of latent TB, HBV, and HCV could be one of the Side effects, and 8 (4%) of 200 patients know that bDMARDs can rarely cause malignancy. About eye involvement medications, only 14 (7%) know that doctors can use NSAID, sDMARDs, bDMARDs as a treatment of eye involvement in AS. About exercise role in AS management, the majority of patients 186 (93%), know that exercise is an important part of management, and regular daily exercise is a wise approach to keep
active. The majority of patients identified the role of good posture and knew that fluctuations of disease with spells of remission and flares might occur. No patient considered exercises as a cure or a potential for damage, and all patients are aware that even with regular exercise, normality will not be restored. A percent of correct responses about the most suitable activities for people with AS is found in approximately half no. Q11. In fact, swimming and muscle-strengthening exercises are chosen by 103 (51.5%). Nobody considered acupuncture as a cure, the question concerning the beneficial effect of exercise in water is answered by the majority of patients, 190 (95%), and 122 (61%) don’t know the proper duration of the exercise. Regarding Kyphosis reverse exercise, which is lying down on the face for 15-30 min. few times in a day can reverse or prevent kyphosis, the correct answer is recognized by only 63 (31.5%).

Area D: Joint protection, pacing, and priorities. The maximum possible score is 4, minimum to maximum are (0-4), mean score (2.87 ± 1.06), the full score is achieved by 67 (33.5 %), as shown in table 2 and fig. 6.

Rest in AS Question 8 (two responses) is correctly identified by 128 (64%), they answered correctly that, a spell off work or in the hospital may be necessary when the disease is very active rather than rest in bed for most of the day, 147 (73.5%) of patients identified that lying on the front for sometime before going to bed and before rising in the morning, is a good attitude for back stiffness. Regarding an ideal bed for patients with AS, the correct answer (firm) is identified by 107 (53.5%). Carry out range of movement exercises within pain-free limits, as the one activity which should be carried out when all joints are painful and stiff, as in acute flare, this question is recognized correctly by the majority of patients 191 (95.5%).

**Information sources of the 200 AS patients**

There were multiple sources of information that AS Iraqi patients based on their responses, 50% got their information from a rheumatologist, 5% depended on multiple websites, 2% of patients depended on discussion with each other, 5% got information from a rheumatologist, websites, and discussion. From rheumatologists and websites, information sources frequency was 32%, rheumatologists and discussion with each other was 6%, as shown in fig. 7.

### Table 1. Frequency distribution of the 200 AS Iraqi patients by socio-demographic variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total no. = 200</th>
<th>%</th>
<th>Mean ± SD</th>
<th>P-Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>36.89 ± 9.65</td>
<td>0.93*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-40/ &gt; 40y</td>
<td>139/61</td>
<td>69.50%/30.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>0.14*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male/Female</td>
<td>182/18</td>
<td>91%/9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td>0.73**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/unmarried/divorce</td>
<td>158/41/1</td>
<td>79%/20.5%/0.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residency</td>
<td></td>
<td>0.56*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baghdad/other governorates</td>
<td>134/66</td>
<td>67%/33%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td>0.002**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>housewife</td>
<td>15</td>
<td>7.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>wage earner</td>
<td>80</td>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Policeman/military soldier</td>
<td>5/11</td>
<td>2.5%/5.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Driver/Baker</td>
<td>25/1</td>
<td>12.5%/0.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employee/student</td>
<td>21/14</td>
<td>10.5%/7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teacher/retired</td>
<td>21/3</td>
<td>10.5%/1.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>engineer</td>
<td>4</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td>0.04*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker, X-smoker, non-smoker</td>
<td>114 , 15 , 71</td>
<td>57%, 7.5%, 35.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td>0.65**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate/read and write</td>
<td>3/2</td>
<td>1.5%/1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary/Secondary school</td>
<td>60/74</td>
<td>30%/37%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University level</td>
<td>61</td>
<td>30.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease Diagnosis duration 6 months/8m- 40y</td>
<td>2/198</td>
<td>1%/99%</td>
<td>8.45 ± 7.54</td>
<td>0.32*</td>
</tr>
<tr>
<td>BASDAI/BASFI</td>
<td></td>
<td>2.9 ± 1.32 ± 1.7</td>
<td>0.42/0.81**</td>
<td></td>
</tr>
</tbody>
</table>

No = number, SD = standard deviation, P value = probability value, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Disease Functional Index, sec = secondary. (P value < 0.05 is considered significant).

* Student’s t test; **Analysis of variance (ANOVA)
Table 2. The mean score of the questionnaire’s areas. Mean ± SD in 200 AS sample of Iraqi patients

<table>
<thead>
<tr>
<th>Knowledge Areas</th>
<th>Mean ± SD</th>
<th>Minimum score</th>
<th>Maximum possible score</th>
<th>Maximum achieved score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (general knowledge)</td>
<td>3.63 ± 1.61</td>
<td>0</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>B (HLA-B27 and inheritance)</td>
<td>0.26 ± 0.51</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>C (treatment options)</td>
<td>9.53 ± 2.42</td>
<td>0</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>D (joints protection)</td>
<td>2.87 ± 1.06</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 3. Comparison between the current study and the other three studies conducted in the UK, France, and Brazil by using similar questionnaire

<table>
<thead>
<tr>
<th>Variables</th>
<th>Current study</th>
<th>UK study</th>
<th>French study</th>
<th>Brazilian study</th>
</tr>
</thead>
<tbody>
<tr>
<td>The mean total score</td>
<td>16.28 ± 2.49</td>
<td>19.45 ± 3.23</td>
<td>16.4 ± 4.8</td>
<td>17.33 ± 3.4</td>
</tr>
<tr>
<td>Area A</td>
<td>3.63 ± 1.61</td>
<td>7.23 ± 0.23</td>
<td>49 ± mean % of correct answers</td>
<td>5.17 ± 1.70</td>
</tr>
<tr>
<td>Area B</td>
<td>0.26 ± 0.51</td>
<td>2.63 ± 0.52</td>
<td>48 ± mean % of correct answers</td>
<td>0.97 ± 0.85</td>
</tr>
<tr>
<td>Area C</td>
<td>9.53 ± 2.42</td>
<td>8.81 ± 0.54</td>
<td>64 ± mean % of correct answers</td>
<td>7.2 ± 1.05</td>
</tr>
<tr>
<td>Area D</td>
<td>2.87 ± 1.06</td>
<td>4.74 ± 0.57</td>
<td>41 ± mean % of correct answers</td>
<td>3.43 ± 1.04</td>
</tr>
<tr>
<td>Gender</td>
<td>p = 0.14*</td>
<td>p = 0.19</td>
<td>Female p = 0.03</td>
<td>p = 0.71</td>
</tr>
<tr>
<td>Age</td>
<td>p = 0.93*</td>
<td>p = 0.4</td>
<td>p &gt; 0.05</td>
<td>48.4 ± SD 9.5</td>
</tr>
<tr>
<td>Educational level</td>
<td>p = 0.0004**</td>
<td>p = 0.57</td>
<td>p = 0.018</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>Occupation</td>
<td>p = 0.002** / Engineer 0.04*</td>
<td>Not included</td>
<td>Not included</td>
<td>Not included</td>
</tr>
<tr>
<td>Residence</td>
<td>p = 0.56*</td>
<td>Not included</td>
<td>Not included</td>
<td>Not included</td>
</tr>
<tr>
<td>BASDAI</td>
<td>p = 0.8**/cor-0.04***</td>
<td>Not included</td>
<td>Not included</td>
<td>No significant relationship</td>
</tr>
<tr>
<td>BASFI</td>
<td>p = 0.52**/cor-0.13***</td>
<td>Not included</td>
<td>Not included</td>
<td>No significant relationship</td>
</tr>
<tr>
<td>Information sources</td>
<td>Rheumatologist, websites, and discussion</td>
<td>ARC booklets</td>
<td>No formal sources</td>
<td>No formal sources</td>
</tr>
<tr>
<td>Sample number</td>
<td>200</td>
<td>62</td>
<td>90</td>
<td>60</td>
</tr>
<tr>
<td>Disease duration</td>
<td>p = 0.62*</td>
<td>p = 0.78</td>
<td>p &gt;0.05</td>
<td>p = 0.30</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Not included</td>
<td>Not included</td>
<td>Not included</td>
<td>p = 0.02</td>
</tr>
</tbody>
</table>

D = standard deviation, p = probability value, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, ARC = Arthritis and Rheumatism Council booklet

*Student’s t-test; **Analysis of variance (ANOVA); *** Spearman’s correlation coefficient

Fig. 1. The relationship between the mean total score of the questionnaire and gender in 200 AS Iraqi patients

Fig. 2. The relationships between the mean total score of the questionnaire and marital status in 200 AS Iraqi patients
Fig. 3. The relationship between the mean total score of the questionnaire and smoking in 200 AS Iraqi patients

Fig. 4. The relationship between the mean total score of the questionnaire and educational level in 200 AS Iraqi patients

Fig. 5. The relationship between the mean total score of the questionnaire and occupation Engineer job in 200 AS Iraqi patients

Fig. 6. The mean score of the 4 knowledge areas, mean ± SD in 200 AS Iraqi patients

Fig. 7. Information sources with frequencies of the 200 AS Iraqi patients, who undergo a self-administered questionnaire
**Discussion**

This study used a questionnaire with a physician interview to assess the level of knowledge in a sample of AS Iraqi patients. This questionnaire was based on a previously validated one for AS [30] and showed a high index of readability, reliability, and consistency so that it could allow a provision of reliable information. This study showed that Iraqi AS patients had a low level of knowledge, or they displayed limited knowledge of AS, with different wrong beliefs on specific aspects of their disease. Many conclusions can be drawn from these results, strongly suggests poor quality of patients' information sources, due to lack of regular, informative, proper, logic, and simplified educational program. Iraqi AS patients depend on multiple sources of information about their disease, including rheumatologists, different websites, and even discussion with each other. The current study revealed a significant statistical relationship between the mean total score of the questionnaire and the educational level and occupation; for example, engineers show a high level of knowledge and seem to be more interested in their disease. They might have easy access to a specific and accurate source of information. The study didn't show any statistical relationship or correlation between the mean total score of the used questionnaire and BASDAI [16], BASFI [17]. The mean score of Area A, which included general knowledge about AS, etiology, skeletal and extraskeletal symptoms, and laboratory blood tests, was 3.63 ± 1.61 (the maximum possible score was 8). The main explanation of this low level of knowledge is poor or lack of informative, simplified educational programs and the weak communication between patients and rheumatologists. In Area B, the majority of AS patients did not recognize the importance of HLA-B27 as a marker of disease susceptibility. The mean score was 0.26 ± 0.51 (the maximum possible score was 2). HLA-B27 test will not answer whether the patient's children will develop the disease or not; however, the relationship between this marker and AS inheritance is still not well known. So area B made a confusing state and was a very difficult, unexpected part for the majority of patients. This result is due to a lack discussion with rheumatologists about AS causes and associations. In Area C, which included drug treatment and physical therapy, the mean score was 9.53 ± 2.42 (the maximum possible score was 15). Patients had a moderate level of knowledge about treatment in AS, including anti-inflammatory and pain killer medications. But, they barely knew about the side effects of their drugs, which currently use, and they disclosed a very low level of knowledge about used medications in cases with eye involvement. Patients had a high level of knowledge in the area of physical treatment, reflected by their responses on posture and exercise. The majority of patients knew that exercise is an important part of treatment for AS, and regular daily exercise is a wise approach to keep them active. They had acceptable information about sport types, proper duration of sports, and kyphosis reverse exercise. The explanation is that most patients had received physical therapy at some time during their disease, and exercises undoubtedly relieve pain and stiffness in AS so that the proper concept will be well received with exercise. Moreover, exercises may give rapid, objective results in a pleasant atmosphere (e.g., pool, group exercises), thus increasing the readiness of patients to learn more and more about AS. In Area D, about half of the AS patients sample identified the role of good posture and the advantage of a firm bed. The majority knew that fluctuations of disease with spells of remission and flares might occur. No patient considered exercises as a cure for damage, and most of the patients knew that even with regular exercise, normality would not be restored. In a UK study which was published in 1998 [29], the level of knowledge was higher than the level in the present study, the mean total score of questionnaire was high (19.45 ± 3.23, range 6-24). Patients in the UK showed a good level of knowledge in areas A, C, and D; and a moderate level of knowledge in area B, which made some difficulty to the participants. There was no significant statistical relationship between the mean total score and age, gender, disease duration, or level of education. AS patients had a high level of knowledge with minimal wrong beliefs on specific aspects of the disease. The good level of observed knowledge may be attributed to the fact, that UK patients had read the Arthritis and Rheumatism Council booklet ARC booklet on AS at least once and due to the good quality of the ARC booklet, which was apparently written in a logical and simple way, allowing easy comprehension of the subject. Furthermore, many patients had also attended physiotherapy and special education courses held by NASS (the British National AS Society), run by physiotherapists, so undoubtedly gaining useful advice. In 2004, another study was published in France [32], which was done at six rheumatology departments in tertiary care hospitals throughout France for assessment of AS knowledge and to identify factors associated with this knowledge. 90 AS patients were receiving follow
up in France, completed a disease knowledge self-administered questionnaire and showed a Correct Answer Score CAS, and a Correct Item Score CIS. Correlations between these scores and other factors were assessed. Mean CAS was 16.4 ± 4.8, and mean CIS was 7.3 ± 3.1, which indicated a low level of knowledge like the resulted score in the current study. Female gender and higher educational level showed a better level of knowledge compared to male and those with lower educational level, and that might be due to female, and those with higher education levels read about AS, being aware of AS support groups, and had received longer tertiary care at hospital management. In the France multivariate analysis study, only three factors were associated independently with the level of knowledge: reading about AS, level of general education, and awareness of an AS support group. Level of knowledge in AS French patients was also low because none of French AS patients had followed classes on AS, and only a small sample had read about their disease; furthermore, the AS informative booklets that are now widely distributed in France, were not available before 2004. A study in Brazil was published in 2016 [33], it assessed the level of knowledge in 60 AS Brazilian patients, in two groups (adaptation and reliability). Most of the patients who were evaluated had not completed a high school education. The study found a strong correlation between educational level and the level of knowledge. In the cultural adaptation phase, there was a statistically significant difference between ethnic groups regarding knowledge; white participants disclosed a higher level of AS knowledge compared with black or brown ones. Brazilian observed that low level of knowledge about AS was correlated with ethnicity, (which was not included in the current study) and with educational levels (similar to the result in the current study), which reflected the racial and educational situation in Brazil. In Area A, the mean achieved score was 5.17 ± 1.70, which was more than area A in the present study. The level of knowledge was low, mainly in area B, and had a mean of 0.97 ± 0.85 and seem to be similar to area B in the present study. The question about HLA-B27 and its association with AS inheritance in area B gave rise to the greatest amount of confusion among the Brazil sample AS patients. While other areas showed average percentages of correct answers of greater than 60%. In Area C, the majority of Brazil AS patients correctly answered the questions about the most appropriate type of physical activity for AS, also obtained 100% correct answers to the question about the importance of exercise. The reasons might be most of the patients included in the Brazilian study had already undergone physiotherapy or had participated in other previous studies on physical activity related to AS. Area D showed a mean score of 3.43 ± 1.04. A conclusion that might be getting from this area is that patients with greater impairment had higher levels of knowledge. The translated questionnaire copy that used in the assessment of Brazil AS patients’ knowledge made clear the individual need of education about AS disease, facilitating the evaluation and guidance of what should be done to each patient, optimizing the conduct regarding education and knowledge improvement.

In conclusion, the present study disclosed that AS Iraqi patients have a low level of knowledge, high ignorance, unawareness, and wrong thoughts about specific aspects of their disease, which may reinforce the recommendation of this study. It’s recommended to spend more time listening to the AS patients’ thoughts; make sure you response carefully to their questions. Advice to improve the low, wrong patients’ concepts, by easily readable booklets, leaflets, videos or, group rather than individualized educational health sessions, by using simplified, informative materials. They are helping patients to organize the treatment options and to acquire the abilities necessary for self-management of the consequences of AS. Although education should be offered to all AS patients, the need may be focused on those with impaired school or low educational level.

Acknowledgment
We would like to thank Prof. Sami Salman, Ass. Prof. Faiq Gorial; Ass. Prof. Sabeeh Mashhadani for their insightful comments, motivations, and encouragement.

Conflict of interest: No.

References


INTERSTITIAL PNEUMONIA WITH AUTOIMMUNE FEATURES – WHAT DO WE KNOW?

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Abstract. In recent years, the attention of pulmonologists and rheumatologists was focused on the link between interstitial lung disease (ILD) and systemic connective tissue disease (CTD). The development of precise criteria has become a major aim due to the growing number of patients diagnosed with ILD, the variety of antibodies, and characteristic features of various rheumatic diseases. Diagnosing interstitial lung disease associated with systemic connective tissue disease, as well as identifying idiopathic interstitial pneumonia, is still a challenge due to the many nosological units in which there is significant heterogeneity in the disease phenotype between different populations. Immunological tests play an important role in the recognition of underlying CTD in patients with ILD, especially in the presence of discrete skin, joint, or muscle involvement. However, there is no algorithm or consensus to determine which immunological tests should start the diagnostic process. For the aforementioned reasons, in 2015, the European Respiratory Society/American Thoracic Society proposed the term "autoimmune interstitial pneumonia" to classify patients who are clinically indeterminate and cannot be included in any group. The proposed classification criteria have been thoroughly discussed by multidisciplinary teams, but are still subject to wide discussion and are updated over time.

Key words: interstitial lung disease, idiopathic interstitial pneumonia, systemic connective tissue diseases, classification
Difusne parenhimi naselobrani zaboljavani protitchat s vraplenie i/fibrozha na belite drobotove. Porad sходната klinichna karta, radiografski izrazeni, fiziolohichni ili patologichni pravyi chesto stego klassificirat v jedna grupa kao intersistiinalni naselobrani zaboljavani (ILD) [1, 2, 3]. Te predstavljat heterogena grupa, pri kоято bolenstata proces mozhe da byde initiiran ot razlichni faktori na okолнata sreda, profesionalski vrednosti, sarkoiida, naselobrana histicцитоза, limfan-gioliomyomatоза, sistemi zaboljavani na съединителната тъкън и значително po-rядko – системни вакулить [4]. Diagnostiquaneto na pъrvichnite intersistiinalni pnevmonii iziskva izchuvanieto na izvestnite prichini, tъt katova tova vliyay kako vrhu lechenieto, takva i vurku prognozata [5, 6, 7].

Chast ot sistemiите revmatichni zaboljavani protitchat s intersistiinalno naselobrano zaboljavane. Vъzможni sa tri varianti: 1) intersistiinalno naselobrano zaboljavane pri pacienti s цhеve dokazano sistemno revmatichno zaboljavane; 2) sistemno revmatichano zaboljavane, koeto debü-tira s intersistiinalno naselobrano zaboljavane i 3) intersistiinalno naselobrano zaboljavane s diskretni pravyi na sistemno revmatichano zaboljavane, za koeto lippvat dostatchno kriterii, za da mohe sъs sigurnost da se postavi diagnozata.

Edna ot dobre pozнатite klinichni pravyi na sistemiите zaboljavani na съединителната тъкън (CTD) e intersistiinalna pnevmonia. Naj-chesto ta vъznika v konteksta na usisatana CTD, no ne са рядкост i slucaitse, pri koeto in-terstiinalnata pnevmonia e пъrvata i vepotano edinstvenata pravva na inache okultna CTD [8-11]. Identiﬁkiraneto na podlejashchoto sistem-но zaboljavane na съединителната тъкън e pre-dizvikativosteto, особено v slucaite, kogato edna ot пъrrvite pravvi na болестта e idiopatichna intersistiinalna pnevmonia (IIP) [12-18]. Osnovnata prichina sa neisnites granici meeskoto CTD-ILD i IIP. Kъm momenta nema obshiriet poход за ochenka na takiva pacienti, no spered naстоящи-te medzunadnoti preporoki e zadlyжitelno da se izklicu sistemno zaboljavane na съединител-ната тъкън, za da se priemee diagnozata idiopatichna intersistiinalna pnevmonia [2, 19].

Cвьseme naskorо European Respiratory Society/American Thoracic Society predlozi termina „intersistiinalna пневmonia с autoimmune характер“.
Интерстициална пневмония с автоимунна характеристика: ИПАХ (Interstitial pneumonia with autoimmune features – IPAF) за класифициране на пациентите, които са клинично неопределени и не могат да бъдат включени в никаква група [4, 20]. За целта са създадени класификационни критерии, които са динамични и се актуализират с времето. По литературни данни пациентите с IPAF са 7,3-34,1% от пациентите с интерстициална белодробна болест [4].

Критерите за IPAF се променят динамично, като основните изменения са свързани с редовното актуализиране на съществуващите класификационни критерии за CTD и още по-често идентифициране на нови биомаркери. Най-важният ефект от тези критерии е идентифицирането на сива зона на недобре дефинирани ревматични състояния, например антисинтетазния синдром (ASSD) [21, 22].

След търсене в електронните бази данни за научна литература PubMed, Medline и Scopus са идентифицирани 35 научни публикации, които използват ключовите думи: интерстициална пневмония с автоимунна характеристика, интерстициална белодробна болест, класификационни критерии.

Класификационни критерии за IPAF

European Respiratory Society/American Thoracic Society сформира международна работна група от 13 членове, седем от които пулмонолози, четири – ревматолози, един – рентгенолог и един – белодробен патолог, с оглед изготвянето на Консенсус и придружаващата го номенклатура и класификация на пациентите с предполагаема интерстициална белодробна болест, асоциирана със заболявания на съединителната тъкан (CTD-ILD). Изготвеният становищ е притесняващ или недобре дефинирано състояние, например антисинтетазния синдром (ASSD) [21, 22].

IPAF CLASSIFICATION CRITERIA

The European Respiratory Society/American Thoracic Society formed an international working group of 13 members, seven of whom were pulmonologists, four rheumatologists, one radiologist, and one lung pathologist, with a view to drawing consensus and the accompanying nomenclature and classification of patients with suspected interstitial lung disease – connective tissue disease (CTD-ILD). The draft opinion proposes the following: 1) a new term „interstitial pneumonia with autoimmune features” (IPAF) in order to describe patients with ILD and the combination of clinical, serological and/or pulmonary morphological features that are thought to result from the underlying systemic autoimmune disease, but do not meet the current criteria characterizing CTD; and 2) a description of the proposed IPAF classification criteria [4].
To diagnose a patient with IPAF, interstitial pneumonia must be demonstrated by high-resolution computed tomography (HRCT) and/or by surgical lung biopsy. It is recommended that all known causes of interstitial pneumonia should be excluded by in-depth clinical evaluation. Patients should not meet the criteria for a particular connective tissue disease [4].

The classification criteria include the presence of a combination of features (presented in Table 1) in three areas:

1. Clinical domain consisting of specific extrathoracic features;
2. Serological domain consisting of specific autoantibodies;
3. Morphological domain consisting of specific lung images, histopathological, or pulmonary physiological characteristics.

At least one indication of at least two areas must be available for an IPAF diagnosis to be accepted.

<table>
<thead>
<tr>
<th>Classification criteria for interstitial pneumonia with autoimmune features according to the European Respiratory Society/American Thoracic Society [4]</th>
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<tbody>
<tr>
<td><strong>Clinical domain</strong></td>
</tr>
<tr>
<td>1. Distal digital fissuring (i.e. &quot;mechanic hands&quot;)</td>
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<tr>
<td>2. Distal digital tip ulceration</td>
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<tr>
<td>3. Inflammatory arthritis or polyarticular morning joint stiffness ≥ 60 min</td>
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<tr>
<td>4. Palmar telangiectasia</td>
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<td>5. Raynaud’s phenomenon</td>
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<td>6. Unexplained digital oedema</td>
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<tr>
<td>7. Unexplained fixed rash on the digital extensor surfaces (Gottron’s sign)</td>
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<tr>
<td><strong>Serologic domain</strong></td>
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<tr>
<td>1. ANA ≥ 1:320 titre, diffuse, speckled, homogeneous patterns or</td>
</tr>
<tr>
<td>a. ANA nucleolar pattern (any titre) or</td>
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<tr>
<td>b. ANA centromere pattern (any titre)</td>
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<tr>
<td>2. Rheumatoid factor ≥ 2× upper limit of normal</td>
</tr>
<tr>
<td>3. Anti-CCP</td>
</tr>
<tr>
<td>4. Anti-dsDNA</td>
</tr>
<tr>
<td>5. Anti-Ro (SS-A)</td>
</tr>
<tr>
<td>6. Anti-La (SS-B)</td>
</tr>
<tr>
<td>7. Anti-ribonucleoprotein</td>
</tr>
<tr>
<td>8. Anti-Smith</td>
</tr>
<tr>
<td>9. Anti-topoisomerase (Scl-70)</td>
</tr>
<tr>
<td>10. Anti-RNA synthetase (e.g. Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, IRS)</td>
</tr>
<tr>
<td><strong>Morphologic domain</strong></td>
</tr>
<tr>
<td>1. Suggestive radiology patterns by HRCT:</td>
</tr>
<tr>
<td>a. Non-specific interstitial pneumonia (NSIP)</td>
</tr>
<tr>
<td>b. Organising pneumonia (OP)</td>
</tr>
<tr>
<td>c. NSIP with Organising pneumonia overlap</td>
</tr>
<tr>
<td>d. Lymphoid Interstitial Pneumonia (LIP)</td>
</tr>
<tr>
<td>2. Histopathology patterns or features by surgical lung biopsy:</td>
</tr>
<tr>
<td>a. NSIP</td>
</tr>
<tr>
<td>b. OP</td>
</tr>
<tr>
<td>c. NSIP with OP overlap</td>
</tr>
<tr>
<td>d. LIP</td>
</tr>
<tr>
<td>e. Interstitial lymphoid aggregates with germinal centres</td>
</tr>
<tr>
<td>f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)</td>
</tr>
<tr>
<td>g. Multi-compartment involvement (in addition to interstitial pneumonia):</td>
</tr>
<tr>
<td>a. Unexplained pleural effusion or thickening</td>
</tr>
<tr>
<td>b. Unexplained pericardial effusion or thickening</td>
</tr>
<tr>
<td>c. Unexplained intrinsic airways disease® (by PFT, imaging or pathology)</td>
</tr>
<tr>
<td>d. Unexplained pulmonary vasculopathy</td>
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</tbody>
</table>
CLINICAL FEATURES OF PATIENTS WITH IPAF

Specific clinical signs suggestive of CTD are included in this area. Although they are specific findings, their presence alone does not allow the diagnosis of a specific systemic connective tissue disease. Raynaud’s phenomenon, palmar telangiectasias, distal finger ulcers, and digital edema are specific physical findings that are commonly observed in systemic sclerosis [23, 24, 25] but are rarely seen in IIP [4].

Other specific symptoms are cracks on the fingers (‘mechanic’s hands’) (Figure 1) and a fixed rash on the extensor surfaces of the fingers (Gotron’s sign) – which is a hallmark of anti-synthetase syndrome or systemic scleromyositis, which are associated with positive anti-PM-Scl [18, 26-33].

Capillaroscopy finds application in cases of established Raynaud’s phenomenon in order to prove non-specific changes that could have a predictive value for the development of systemic connective tissue disease [4, 34].

Inflammatory arthropathy (arthritis) is included as a criterion for IPAF and is characterized by symptoms or signs of synovitis of the peripheral joints. However, arthralgias in the joints alone are not included as a criterion due to a lack of specificity. Other non-specific features, such as alopecia,
CEREOLOGICHI CHARAKTERISTIKI NA PACIENTITE S IIPAF

В този домейн са включени специфични циркулиращи автоантитела (за които е известно, че са свързани с CTD), оценени като част от оценката на пациента с предполагаема IIP. По-малко специфични серологични маркери, като нискотитърни антинуклеарни антитела (ANA), ревматоиден фактор с нисък титър (RF), скорост на утаяване на еритроцитите, C-реактивен протеин или креатинфосфокиназа, не са включени в критерияте [4].

За ANA позитивност с дифузен, хомогенен или петнист имунофлуоресцентен образ се изисква титър най-малко 1:320, тъй като това е в съответствие с повечето експертни указания за изследване на ANA [35]. Ниските титри на ANA с тези модели на ,,светене“ са изключени, тъй като нискотитърна ANA позитивност е наличие при много неревматични пациенти и дори при „здрави“ контролни популации, особено при възрастните хора [35-38]. Независимо от титъра, ANA позитивността с нуклеоларен или с центромерен тип на ,,светене“ е включена като IPAF критерий. Всяко от двата модела притежава силна асocioация със системна склероза [4, 35]. При липса на други признаки обаче нито единия, нито другият модел на светене е диагностичен за системна склероза. В съответствие с настоящите насоки за изследване на ANA предпочитаният метод за анализ е чрез непряка имунофлуоресценция [39], която позволява да се оценят титърът на ANA и моделът на имунофлуоресцентния образ. Изследването на ANA по метода ELISA е по-малко надеждно поради фалшовоотрицателния резултат, фоточувствителност, язви в устата, загуба на тегло, сика синдром, миалгия или артралгия, също не фигурират в клиничния домейн.

КАТО ЦЯЛО ПАЦИЕНТИТЕ С CTD-ILD СА ЖЕНИ В ПО-МЛАДА ВЪЗРАСТ, НЕПУШАЧИ, В СРАВНЕНИЕ С ТЕЗИ С ИДИОПАТИЧНА ИНТЕРСТИЦИАЛА ПНЕВМОНИЯ [23]. ДЕМОГРАФСКИТЕ ХАРАКТЕРИСТИКИ, КОИТО МОГАТ ДА БЪДАТ ПО-ЧЕСТО СРЕЩАНИ ПРИ CTD, НЕ СА ВКЛЮЧЕНИ В НОВИТЕ КРИТЕРИИ, ПРЕДВИЗАНАТА НА СПЕЦИФИЧНОСТ [4].

В идеалния случай оценката за екстраторакалните характеристики се осъществява чрез обстоятелна анамнеза и физикален преглед, извършен от добре подготвени клиницисти, включително ревматологи, и не се основава единствено на самооценката (например самооценяващ въпросник) [4].

SEROLOGICAL CHARACTERISTICS OF PATIENTS WITH IIPAF

This domain includes specific circulating autoantibodies (known to be associated with CTD), evaluated as part of the assessment of the patient with suspected IIP. Less specific serological markers, such as low titers of antinuclear antibodies (ANA), rheumatoid factor with low titer (RF), erythrocyte sedimentation rate, C-reactive protein or creatine phosphokinase, are not included in the criteria [4].

For ANA positivity with a diffuse, homogeneous, or speckled staining pattern, a titer of at least 1:320 is required, as this is in line with most expert guidelines for ANA testing [35]. Low ANA titers with these staining models are excluded, as low-titer ANA positivity is present in many non-rheumatic patients and even in „healthy“ control populations, especially in the elderly [35-38]. Regardless of the titer, ANA positivity with a nucleolar or centromere staining pattern is included as an IPAF criterion. Each of the two patterns has a strong association with systemic sclerosis [4, 35]. In the absence of other signs, however, neither staining is diagnostic of systemic sclerosis. In accordance with the current guidelines for the study of ANA, the preferred method of analysis is by indirect immunofluorescence [39], which allows the assessment of the ANA titer and staining pattern. ELISA analysis for ANA testing is less reliable due...
Interstitial pneumonia with autoimmune features...

...tation, which is often obtained in subgroups of patients with systemic sclerosis [40].

Due to the possibility of error in the diagnosis when reporting low titers of ANA, specific requirements for the type of staining and the titer of antibodies in the serological domain are indicated. Only high RF values (defined as greater than or equal to twice the upper limit of normal) meet the IPAF criteria. Weakly positive RF is present in many non-rheumatic patients, and not infrequently in some „healthy“ individuals [36-38].

For other circulating autoantibodies that are listed in the serological domain, any value above the upper limit of normal is considered positive serology. It is recognized that in clinical practice, there may be a repeat serological test for various reasons, such as when the autoantibody titer is borderline positive. However, for the purposes of the IPAF criteria, repeated serological tests are not required if positive.

Literature reports the presence of antineutrophil cytoplasmic antibodies (ANCA) in patients with isolated interstitial lung disease [22, 41, 42]. However, this group of patients did not meet the criteria for the classification of vasculitis or those for IPAF, but certainly gave grounds to accept autoimmune-mediated ILD. It remains to be decided whether this group of patients will be included in the IPAF criteria, even at some risk of ANCA-associated vasculitis being diagnosed with possible disease progression [22]. Sambataro and colleagues suggest that the type of patients described above to be excluded from the IPAF classification [43]. There is currently no consensus on this issue, which is why, in the future, this group of diseases is waiting to be more clearly defined through a multidisciplinary approach.

Sambataro et al. correctly suggest that rheumatologists and pulmonologists should share their experience in order to optimize the classification of patients affected by CTD and ILD, as well as any autoimmune conditions that are potentially underlying ILD [43]. Furthermore, it is worth noting that the IPAF classification criteria include ILD with antibodies such as anti-MDA5 and PM-Scl, but not anti-Ku and anti-Th-To. In recent years, it has been suggested that anti-MDA5 antibodies are specific for myositis autoantibodies associated-
The morphological domain consists of three sections:

1) models of interstitial pneumonia detected by HRCT images;
2) histopathological features identified by surgical lung biopsy, or evidence of further lung involvement, by diagnostic imaging, histopathological findings, right cardiac catheterization (RHC), or lung function testing.
3) involvement of various structures (in addition to interstitial pneumonia): unexpected pleural effusion or thickening of the pleura; unexpected pericardial effusion or thickening of the pericardium; unexplained disease of the internal respiratory tract (proven by FID, imaging or pathology); unexpected pulmonary vasculopathy.

The radiological models included in the IPAF criteria are non-specific interstitial pneumonia (NSIP), organized pneumonia (OP), NSIP with OP, and lymphoid interstitial pneumonia (LIP). These models are commonly found in CTD-ILD, and their presence with the onset of rapidly progressive interstitial lung disease, which severely affects patient survival (40-55% after six months) [43, 44]. For this reason, the classification of these borderline conditions in IPAF raises concerns, not only because it may lead to the wrong selection of patients for inclusion in clinical trials, but also because it may mislead the therapeutic approach. This area is further complicated by the fact that patients cannot be classified as polymyositis or dermatomyositis, as the new classification criteria of the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) do not include anti-MDA5 antibodies, thus excluding early forms of myositis in patients. In addition, the new criteria require more than 6 months of disease duration before application, and they do not include ILD among the identified symptoms [45]. In anti-MDA5 positive patients, early diagnosis is crucial, and it is almost impossible to wait a period of 6 months due to the rapid progression of pulmonary changes, which often lead to severe lung failure.
Interstitial pneumonia with autoimmune features...

should increase the suspicion of underlying autoimmune disease [46, 47].

The findings on HRCT are defined as bilateral reticular changes, traction bronchiecasis, peribronchovascular extensions, bilateral mainly basal ground-glass attenuation, correspond to fibrous non-specific interstitial pneumonia (Fig. 2) [4, 48]. Diagnosis requires a surgical biopsy, with histological outcome confirming interstitial inflammation and fibrosis [4, 49].

The results of HRCT with bilateral areas of consolidation with predominantly subpleural and basal localization in the lungs indicate organized non-specific interstitial pneumonia (Fig. 3) [4, 48]. The histological finding revealed intraalveolar fibrin deposition and associated organizing pneumonia [50]. The classic hyaline membranes of diffuse alveolar damage (DAD) are missing.

Great variability was observed in the HRCT finding characteristic of lymphoid interstitial pneumonia. Typical are centrilobular and subpleural nodules, thickened bronchovascular connections, nodular opacities of the ground-glass type, and cystic structures. In adults, the diagnosis requires a lung biopsy with a demonstration of thickening of the alveolar septa from infiltrates of lymphocytes and other immune cells (plasma cells, immunoblasts, histiocytes) [4]. Immunohistochemical staining is required to rule out lymphoma. In LIP infiltrates are polyclonal (with the presence of T- and B-cells), unlike lymphomas. Other common findings are germinal centers and multinucleated giant cells with non-caseating granulomas (Fig. 4).

**Fig. 2.** Fibrous non-specific interstitial pneumonia (NSIP) (Fischer A, Antoniou KM, Brown KK, et al. [4])

**Fig. 3.** Organized non-specific interstitial pneumonia (Fischer A, Antoniou KM, Brown KK, et al. [4])
The distinction between CTD-ILD and IIP is critical and has important implications for prognosis and treatment. The long-term prognosis of CTD-ILD is usually milder than that of the most common IIP, namely idiopathic pulmonary fibrosis (IPF).

A better understanding of the underlying disease and its mechanisms will lead to increasingly targeted therapeutic strategies. Approved for clinical use in 2014, new antifibrotic drugs nintedanib and pirfenidone have been shown to slow the development of IPF and are now available in many countries [51]. However, in recent years, IPAF can be seen more as a working diagnosis than as an independent entity. Additional prospective studies are needed to answer the many unanswered questions.


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ДЪЛГОСРОЧЕН ЕФЕКТ НА ХУМАНИЗИРАНО МОНОКЛОНАЛНО АНТИТИЛО СРЕЩУ РЕЦЕПТОРА ЗА ИНТЕРЛЕВКИН-6 ПРИ ПАЦИЕНТ С АРТЕРИИТ НА ТАКАЯСУ

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A LONG-TERM EFFECT OF A HUMANIZED ANTI-INTERLEUKIN-6 RECEPTOR ANTIBODY IN A PATIENT WITH TAKAYASU ARTERITIS

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Резюме. Артериитът на Такаясу (ТАК) се отнася към групата на васкулитетите, засягащ големите съдове, като засяга аортата и основните й клонове. Съществуват доказателства, че повишеният продукция на интерлейкин-6 (IL-6) има ключова роля в патогенезата на ТАК. Представяме клиничен случай на жена с рефрактерен ТАК, при която започнахме терапия с тойлизумаб – моноклонално антитяло срещу рецептора за IL-6. В резултат на лечението настъпи подобряние на клиничните симптоми и на лабораторните показатели, което даде възможност да се редуцира дозата ГКС без последващ релапс на болестната активност за периода на проследяване от 2 години. Тези резултати показват, че инхибирането на IL-6 пътя може да бъде част от терапевтичната стратегия при пациентите с рефрактерен ТАК.

Ключови думи: артериит на Такаясу, биологично лечение, интерлейкин 6 (IL-6), тойлизумаб

Abstract. Takayasu arteritis (TAK) is a large-sized vessel vasculitis that involves the aorta and its major branches. The overproduction of interleukin-6 (IL-6) has been proved to play a major role in the pathogenesis of TAK. The following case report describes a 21-year-old woman with refractory TAK, treated with tocilizumab – IL-6 receptor antibody. As a result of the treatment, the clinical manifestations and the abnormal laboratory findings were improved, which allowed the tapering of the glucocorticoids without a consequent relapse of the disease for a follow-up period of 2 years. The results suggest that inhibition of the IL-6 pathway may be a possible treatment option for patients with refractory TAK.

Key words: Takayasu arteritis, biologic treatment, interleukin-6 (IL-6), tocilizumab

Въведение

Артериитът на Такаясу (TAK) се отнася към групата на васкулитетите, засягащ големите съдове (large-sized vessel vasculitis – LVV), и се характеризира с възпаление на аортата и нейните главни клонове. ТАК е рядко заболяване в Европа и Северна Америка. Болестността е по-висока в Азия и Средния изток с честота в Япония приблизително в 60 случаи на милион, съобщено в Japan [24]. It is more common in young women, approx-
60 cases per million population [24]. The disease is more common among young women of the age of 20 years [10]. Symptoms vary depending on the type of involved vessels, the degree of disease progression and include systemic symptoms, as well as symptoms from organ ischaemia (upper limb and jaw claudication, headache, syncope, arterial hypertension, etc.) [24]. Persistent inflammation in patients with TAK can lead to severe vascular damage, thus leading to organ failure [5, 11]. There is an increase in the number of Th1 and Th17 cells in patients with TAK, as well as in the concentration of different cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-17A, IL-8, IL-18 and γ-interferon [3, 12, 18]. Evidence exists that elevated IL-6 levels are associated with increased disease activity [18].

Conventional angiography was the „gold standard” imaging method for the diagnosis and monitoring of patients with TAK, but it is no longer recommended due to the risks associated with the procedure [7]. According to the new 2018 EULAR recommendations for the use of imaging in LVV, magnetic resonance imaging (MRI) should be used as the first imaging test to make a diagnosis of TAK [7]. As an alternative imaging method, [18F] fluorodeoxyglucose positron emission tomography ([18F]FDG-PET), computed tomography (CT), and Colour Doppler Ultrasonography (CDUS) may be used for the diagnosis and follow-up of patients with TAK [7, 15].

According to the new 2020 EULAR recommendations for the management of LVV, glucocorticoids (GCs) are first-line treatment for patients with TAK and high dose glucocorticoid (GC) therapy (40-60 mg/day prednisone-equivalent) should be initiated immediately for induction of remission in active TAK [9]. GCs have long-term adverse effects, and disease relapse is frequent during GC tapering [13]. Non-biologic disease-modifying agents should be given in combination with GC in all patients with TAK according to the 2020 EULAR recommendations, although they have not shown major clinical benefits or any steroid-sparing effects [9, 13]. Unlike giant cell arteritis, where tocilizumab is preferred over methotrexate in refractory or relapsing disease, or the presence/ increased risk of GC related adverse effects, in TAK, Tocilizumab or
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хромна анемия с хемоглобин 105 г/л, и повишени острофазови реактанти (ОФР) – скорост на утаяване на еритроцитите (СУЕ) 115 мм/ч, C-реактивен протеин (CRP) 96 мм/л.

От извършената ехокардиография се установи дилатация на асцендентната аорта с диаметър 4.1 см. С артериография се констатира аневризмена дилатация от началото на асцендентната аорта до нивото на лиеналната артерия и стеноза на лявата подключична артерия.

Инициира се терапия с преднизолон 60 мг/дн. и антиагрегант. Проведоха се 3 пулса с циклофосфамид (респективно 400, 250 и 200 мг), след което се премина на поддържащ препарат. Един месец след началото на терапията с циклофосфамид, достигнахме до кумулативна доза на циклофосфамид 8,0 г. Поддържащата терапия се провежда с циклофосфамид 50 мг/дн., перорално. При последващ опит за намаляване на дозата на преднизолона до 25 мг/дн., настъпи възобновяване на симптомите и повишение на ОФР. От 2011 г. пациентката периодично е на лечение с пулсов метилпреднизолон (1,000 мг/дн. в продължение на 3 последователни дни) и циклофосфамид, достигати до кумулативна доза на циклофосфамид 8,0 г. Поддържащата терапия е перорален ГКС в доза поне 25 мг/дн., но нито един от приложените медикаменти не доведе до пълен контрол над болестната активност. Последната инфузия на циклофосфамид беше през ноември 2014 г. Един месец след нея пациентката получи значителна хематурия и беше приета в Клиниката по урология за извършване на цистоскопия. От хистологичното изследване се установи хроничен хеморагичен цистит, който беше интерпретиран като страничен ефект от лечението с циклофосфамид.

През месец юни 2015 г. пациентката се оплака от болка във врата, болка при натоварване и слабост на лява ръка, артериално кръвно налягане (дясна ръка – 110/70 mm Hg, лява ръка – 80/40 mm Hg), голямо тегло през последния месец със 7 кг на фон на терапия с 25 мг/дн. преднизолон. От физикалното изследване се установиха някои странични ефекти от продължителното лечение с ГКС (фациес луната), стрии по гърдите, корема и бедрата, както и разлика в артериалното кръвно налягане (дясна ръка – 110/70 mm Hg, лява ръка – 80/40 mm Hg), странични симптоми на нервна система. T. Sapundzhieva, R. Karaillova, A. Marinkov et al.
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dвустранно върху каротидните артерии, по-силен върху лявата, систолен шум върху лявата подключична артерия и върху абдоминалната арта. Ре- гистрира се СУЕ 86 мм/ч, серумно ниво на CRP 105 мг/л. От извършенията ехокардиография се установиха прогресиране на аневризменото раз- ширение на асцендентната арта и високостеpen- на обструкция на лявата подключична артерия. На КАТ на гръдна кош и на корем се визуализира циркулярна неправилна дилатация на стената на асцендентната и на десцендентната арта, която продължава до лиеналната артерия.

Поради честите релапси на заболяването, про- гресията на съдовото увреждане, описаните стра- нични ефекти от имуносупресорите и от ГКС се об- мисли добавяне към терапията на антигена срещу рецептора за IL-6. Лечението с тоцилизумаб беше одобрено от Етичната комисия при УМБАЛ „Кас- пела‘‘ и пациентката подписа информирано съгла- сие. При включване на тоцилизумаб към терапията (юни 2015 г.) дозата ГКС не се повиши.

Две седмици след инцидиране на терапия с подложен тоцилизумаб в доза 162 мг/седмично па- циентката съобщи за намаляване на болката във врата и лявата ръка и за повишен апетит. След едномесечно лечение СУЕ спадна до 32 мм/ч и нивото на CRP до 8 мг/L. Doppler ехокардиогра- фията установи повышен кръвоток в лявата под- ключична артерия. Преди започване на лечението пулсациите на лявата брахиална артерия бяха силно отслабени. На седмица 24 пулсациите на лявата брахиална артерия се палпираха по-лесно. Намаляването на дозата на преднизолон за- почна на седмица 4 след инцидиране на терапия- та с тоцилизумаб и беше успешно, без релапс на болестната активност. На седмица 16 (октомври 2015 г.) преднизолонът се изведе и пациентката остана само на терапия с тоцилизумаб. Клинич- ните симптоми и лабораторните показатели на па- циентката бяха мониторирани на всеки 3 мес. за период от 2 години, без да настъпи релапс на бо- лестната активност. По време на проследяването не се установиха признаци на биологична актив- ност на заболяването – пациентката не съобщи за възвръщане на симптомите и ОФР бяха в ре- ферентни стойности. Не бяха отчетени странични ефекти от терапията с тоцилизумаб.

Обсъждане

Лечението на ТАК цели контрол над болест- ната активност и предотвратяване на съдовата увреда при свеждане до минимум на дългосроч-
proximately half of the patients treated with steroids respond to treatment [21]. Immunosuppressive agents have not shown major clinical benefits in TAK. Due to the lack of universal success with conventional treatment for TAK and the frequent side effects of long-term GCs treatment, new therapeutic options are needed. In the biologic era, the evidence is accumulating regarding the effect of anti-IL-6 receptor antibody for the treatment of LVV and tocilizumab is included in the latest 2020 EULAR recommendations for the management of patients with LVV [1, 9].

In our case, tocilizumab led to a reduction of the clinical manifestations and laboratory markers of inflammation in our patient with refractory TAK, which allowed tapering and the consequent cessation of the corticosteroid without a disease flare for a follow-up period of 2 years. This confirms the major role of IL-6 in the pathogenesis of this vasculitis. In order to prevent irreversible organ damage, it might be more beneficial to introduce this biologic treatment early in the course of the disease.

Conclusion

IL-6 receptor antibody tocilizumab might be a therapeutic option for patients with refractory TAK. Further research is required to confirm the benefits of long-term treatment with IL-6 receptor antibody in patients with TAK.


Oligoarthritis associated with a “forgotten” IUD – a case report

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Abstract. Infection related arthritis has been defined as an aseptic inflammatory arthritis associated with a concomitant infectious disease. Usually, the symptoms develop during or soon after a symptomatic infectious disease, however, in both sexes genitourinary infections might be asymptomatic. Herein, we presented a case of a 68-year old woman with oligoarthritis associated with a “forgotten” intrauterine device (IUD). The IUD was successfully removed by laparoscopy leading to a full resolution of symptoms and improvement of inflammatory markers. The presented case shows that asymptomatic genital infection should be considered in case of suspected infection-related arthritis without clear etiological cause, especially in women with IUD. The in-depth training of patients regarding the proper use of contraception methods as well as the regular gynaecological examinations might help to prevent further similar cases.

Key words: IUD, infection related arthritis, reactive arthritis

Introduction

Reactive arthritis has been defined as an aseptic inflammatory arthritis developing during or soon after a concomitant infectious disease usually in genetic susceptible people [1, 2]. According to the recommendations of the 4-th International Workshop on Reactive Arthritis the term „reactive arthritis“ should
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be used if the clinical manifestations are associat-
ed with spondyloarthritis and HLA-B27 carrier status, whereas other cases should be described as „infection related arthritis (IRA)“ [3]. The potential triggers of IRA might be Gram-negative bacteria emerging from genitourinary, gastrointestinal, and rarely respiratory tracts [2]. The pathophysiological hypothesis suggests that bacterial fragments such as lipopolysaccharide and nucleic acids in the systemic circulation might induce an immune response. Thus, activated cytotoxic T-cells could attack the synovium and other self-antigens through molecular mimicry [2]. Typically, the asymmetric oligoarthritis develops one to three weeks after a symptomatic infectious disease; however, in both sexes genitourinary infections might be asymptomatic [5]. Therefore, in specific group of patients the development of oligoarthritis without clear cause might be a symp-
tom of serious underlying health problem.

Herein, we present a case of a woman with oli-
goarthritis, which has led to a discovery of “forgotten” intrauterine device (IUD).

**Case Report**

A 68-year old female patient was referred to Rheumatology clinic with complaints of severe pain in her right shoulder and elbow with a limitation of motion in both joints. The symptoms had developed about a week earlier and worsened gradually. Her temperature was normal, and she has no other com-
plaints or symptoms except for chronic back pain associated with thoracic and lumbar radiculopathy. Her medical history included well-controlled arte-
rial hypertension as well as partial resection of the thyroid gland thirty years ago with no subsequent disturbances. The patient reported nine pregnan-
cies including one miscarriage, two live births and six abortions. She had used an intrauterine device (IUD) for contraception since the age of 36 years, but claimed that the IUD had been removed. Her last menstrual period occurred at the age of 43 years and she has no gynecological complaints thereafter. However, in her outpatient medical records a recent plain X-ray of the pelvis was found, where the IUD was visible.

The laboratory values of the patient were consis-
tent with infection despite the good overall condi-
tion and the apyrexia (ESR 80 mm/h, Leu 10.0/12.5...

Представяме случай на жена с олигоартрит, довел до откриването на “забравена” интрауте-
ринна система (спирала) (intrauterine device – IUD).

Клиничен случай

Към Ревматологичнo отделение е насочена 68-годишна жена с оплаквания от остра болка в дясното рамо и десния лакът, с ограничен обем движение в двете стави. Симптомите са се развили около седмица по-рано, като впоследствие прогресивно са се влошили. Болната е афе-
брилна, без други оплаквания освен хронична болка, свързана с торакална и лумбална ради-
кулопатия. Миналите и придружаващи заболя-
вания включват артериална хипертония с добър
контрол под терапия и парциална резекция на
щитовидната жлеза преди 30 години без хормо-
нални нарушения впоследствие. Пациентката
съобщава за девет бременности (един спонтанен
аборт, две раждания и шест аборта по желание).

С оглед контрацепция на 36-годишна възраст е
поставена IUD, но болната смята, че спиралата
е била извадена няколко години по-късно. Тя е
в менопауза от 43-годишна възраст и оттогава
do момента не е имала симптоми на гинеколо-
gично заболяване. Въпреки това на представена
скоростна рентгенография на тазобедрени стави
catо случайна находка се забелязва IUD.

Лабораторните стойности при пациентката
показат инфекциозен процес, въпреки доброто
общо състояние и липсата на фебрилитет (СУЕ...
80 mm/h, leukocytes 10.0/12.5 x 10^9/L, granulocytes 7.5/9.1 x 10^9/L, C-reactive protein 183.8 mg/l, ALAT 79.3 U/L, GGT 158 U/L), rheumatoid factor was negative. The ultrasound of the shoulder showed a subdeltoid bursa effusion as well as a partial subscapular tendon rupture. The patient was treated with local corticosteroid application and non-steroidal anti-inflammatory drugs with partial improvement. Considering the IUD a gynecological examination was also performed and uterine hysteroscopy was strongly recommended. After obtaining a signed informed consent from the patient the hysteroscopy showed the IUD in the uterine cavity and the myometrium, which was successfully removed by laparoscopy. Chronic endometritis and cervicitis were also proven. The patient was treated with antibiotics and her laboratory values normalized (ESR 24 mm/h, Leu 6.8 x 10^9/L, Gran 4.4 x 10^9/L, normal liver enzymes). The pain and effusion in the right shoulder and elbow also disappeared rapidly and did not relapse in the next three years.

**Discussion and Conclusions**

The presented case describes the IRA diagnosis and clinical management in a patient with chronic endocervicitis and IUD associated uterine inflammation. The intrauterine devices provide reversible, safe and effective contraceptive options with an optimal risk-benefit ratio. Their main advantages include the long-acting contraceptive protection, the avoidance of systemic side effects related to estrogen and progestin components of commonly used oral contraceptives as well as better adherence profile [6]. Some types of IUD have been used not only for

![Image](image-url)
Олигоартрит, свързан със „забравена”... Oligoarthritis associated with a “forgotten”...

Procedures performed on the insertion of the IUD can increase the risk of pelvic inflammatory disease, but even in the first month, the incidence of infections is very low [10]. Nevertheless, a microbiological study of removed IUD-s showed that the long-term use might lead to a biofilm formation on the surface of devices containing different anaerobic and aerobic bacteria. A total of 62% of the investigated removed devices had positive culture results for aerobic and/or anaerobic bacteria. While the prevalence of sexually transmitted infections was very low in the investigated low-risk population, species associated with bacterial vaginosis were often found in the biofilm samples [11]. Several cases of IRA related to bacterial vaginosis have been described [12, 13], but the role of IUD-s for the development of infection related arthritis has not been clarified.

In 1977 a case of group A streptococcal septicemia with a monoarticular arthritis of the right shoulder, originating from an infected Lippe’s loop has been described [14]. Disseminated infection with necrotizing fasciitis of the right shoulder was also observed after insertion of a levonorgestrel-containing intrauterine system, and the cultures from the coil and vaginal swabs were positive for group A streptococcus [15]. In the opposite to these studies, in our case the right shoulder arthritis was aseptic and no clinical evidence of streptococcal toxic shock syndrome was available. Nevertheless, the “forgotten” IUD was considered as the most likely cause for the inflammatory response in our patient and the leading joint pain. The rapid improvement of our patient after the IUD removing and treatment of the inflammation supports the initial assumption.

The IUD was embedded in the uterine wall in our patient despite the lack of subjective complaints. Thus, she was at increased risk of perforation considering also her additional risk factors, e.g. high number of abortions as well as IUD persistence over 25 years [16]. According to the current studies, about 15% of the “lost” intra-abdominal IUD-s might lead to complications including abdominal pain,
and peritonitis [17]. Sporadic cases of aseptic arthritis, associated with a "forgotten" IUD. Unfortunately, we were not able to perform microbiological analysis of the IUD. Additionally, we did not investigate the HLAB27 status of the patient which could be helpful for the diagnosis of reactive arthritis.

Nevertheless, the presented case shows that asymptomatic genital infection should be considered in case of suspected IRA without clear etiological cause, especially in women with IUD-s, which have not been removed according to manufacturers’ recommendations. The in-depth training of patients regarding the proper use of contraception methods as well as the regular gynaecological examinations might help to prevent further similar cases.

The authors declare that the present article has not been submitted for publication or published in any other journal. None of the authors have any conflicts of interest regarding this article.

Библиография / References

13. Mezouar I, Abourazzak F, Aradoni N, Harzy T. Reactive arthritis induced by Gardnerella vaginalis. The Egyptian Rheu-
ИЗИСКВАНИЯ КЪМ АВТОРИТЕ

Приемат се за публикуване: оригинални статии, обзори, клинични случаи, реферати, рецензии, кратки научни съобщения (тписма до редактора и др.). Първите три жанра са обект на рецензирани (със стандартизирани формули), а останалите подлежат на експертна преценка от страна на редколегията.

Кореспондиращият автор посочва свои данни за контакт (електронен адрес, по желание – пощенски адрес и телефон) и декларира, че материалът не е публикуван досега, освен като резюме на съобщение, изнесен на научна промяна, и не е предложен за публикуция другаде. Авторите носят отговорност за съдържанието на публикацията. Представените материали и описанието в тях изследвания следва да съответстват на утвърдените етични стандарти относно провежданите етични изследвания, жертви и опитни животи. Не трябва да се споменават пациенти с техните имена, инициали или да се предоставя снимков материал, на който те могат да бъдат разпознати. Съблюдава се стриктното спазване на авторското право – текстове с над 10% дословно повторение на чужда публикация се връщат за преработка.

Приемат се файлове на програма MS Word. Няма специфични изисквания за размер и вид на шрифта, разстояние между редовете, полета и друго оформление.

Всяка статия започва със заглавие (без съкращения), имена на авторите (без посочване на академични и други титли), тяхната месторабота, обозначена с цифров индекс, резюмето в посочения обем, ключови думи. На английски език се превежда заглавието, резюмето, ключовите думи, местоработата, а имената на авторите се транскрибират.

В резюмето на всяка оригинала статия се посочват: цел и обект на изследването, основни данни за методиката, резултати и изводи. Резюмето към другите видове статии включва кратка информация без обособена структура. Ключовите думи за всеки вид публикация са между 3 и 8 на брой, като могат да бъдат единични думи или кратки словосъчетания, общоприети в конкретната област на познание.

Оригиналните научни статии имат задължително обособени раздели: „Въведение“, което включва цел на изследването, “Изследване“, “Резултати“, “Обсъждане“ и “Заключение“. Могат да бъдат добавени „Благодарности“ (към лица или институции, които са допринесли интелектуално или са оказали техническа, материала или финансова помощ и др.). Обзорите обикновено включват „Въведение“, тематични подразделени и „Заключение/изводи“. Клиничните случаи съдържат „Въведение“, „Описание на клиничния случай“, „Обсъждане“ и „Изводи“. Кратките научни жанрове следват приблизително структурата на оригиналната статия. Писмата до редактора обсъждат критично научен проблем, нерешен към момента, или дискутират друга публикация.

Цитиранятия на библиографските източници в текста се обозначават с цифри в квадратни скоби по реда на появата им. Библиографската информация се подрежда по реда на поява на източниците в текста. Изписването на всеки източник е на нов ред с арабска номерация. Даниите се оформят по следния начин (Ванкувър стил):

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</table>

Цитираните на библиографските източници в текста се обозначават с цифри в квадратни скоби по реда на поява им. Библиографската информация се подрежда по реда на поява на източниците в текста. Изписването на всеки източник е на нов ред с арабска номерация. Даниите се оформят по следния начин (Ванкувър стил):


Ако авторите са до трима, се изписват фамилиите, последвани от инициалите им (без точки). Когато авторите са повече от трима, след името на третия се пише “и др.” (за латиница – "et al."). Настойчиво се препоръчва цитирането (познаването) на български източници.

Илюстративният материал (таблици, фигури, снимки) се поставя на съответните места в текста със заглавия и мерните единици. Няма специфични изисквания за мерните единици, следвайки „Системата SI“. Приемат се за публикуване: оригинални статии, обзори, клинични случаи, реферати, рецензии.

Всяка статия започва със заглавие (без съкращения), имена на авторите (без посочване на академични и други титли), тяхната месторабота, обозначена с цифров индекс, резюмето в посочения обем, ключови думи. На английски език се превежда заглавието, резюмето, ключовите думи, местоработата, а имената на авторите се транскрибират.
INSTRUCTIONS TO AUTHORS

The following types of articles are accepted for publication: original article, review, clinical case, short scientific reports (letters to the editor, clinical image, etc.). All materials undergo a rigorous review process.

The corresponding authors provide their contact details (e-mail address; postal address and telephone number are optional) and declare that the material has not been published yet, except as an abstract presented at a scientific conference, and is not submitted for publication elsewhere. The authors are responsible for the content of the papers. The materials and studies should comply with established ethical standards for conducting clinical and/or experimental studies with humans (WMA Declaration of Helsinki) and experimental animals. Patients’ names, initials, or photographic, should not be recognized. Copyright is strictly observed - texts with more than 10% plagiarism will be returned for revision.

Word count (approximate) of proposed publications:

<table>
<thead>
<tr>
<th>Type of paper</th>
<th>Word count</th>
<th>Word count of the abstract</th>
<th>Number of references</th>
</tr>
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<tbody>
<tr>
<td>Original Article</td>
<td>2500-5000</td>
<td>200-300</td>
<td>30</td>
</tr>
<tr>
<td>Review</td>
<td>3000-6000</td>
<td>100-200</td>
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<tr>
<td>Clinical case</td>
<td>1000-3000</td>
<td>100-200</td>
<td>20</td>
</tr>
<tr>
<td>Short communication, letter to the editor, etc.</td>
<td>500-1000</td>
<td>-</td>
<td>10</td>
</tr>
</tbody>
</table>

MS Word files are only accepted. There are no specific requirements for font size and theme, line spacing, paper field sizes, and other layouts.

Each article begins with a title (no abbreviations), authors' names (without indicating academic and other titles), their affiliations, denoted with numbers, an abstract, and keywords.

The abstract of each original article shall indicate the purpose/objectives of the study, methodology, results, and conclusions. The abstracts of the other types of articles include brief information without a specific structure.

The keywords for each type of publication could be between 3-8 single words, or short phrases commonly accepted in a particular field of knowledge.

The original scientific papers should have the following separate sections: "Introduction," which includes the purpose of the study, "Material and methods," "Results," "Discussion," and "Conclusions / Conclusion." Acknowledgments may be given at the end of the article (to persons or institutions who have contributed intellectually or provided technical, material or financial assistance, etc.). Reviews typically include Introduction, specific sections on behalf of the authors, and Conclusions. Clinical cases include Introduction, Clinical Case Description, Discussion, and Clinical pearls. The brief scientific reports, short communications, etc., follow the structure of the original article closely. The letters to the editor discuss a critical scientific issue that has not yet been resolved or comment on another controversial publication.

Square brackets should indicate references in the text. The bibliography is arranged in the order of appearance in the text. Each new source should be listed with Arabic numerals and presented as follows (Vancouver style):


If the authors are up to three, the surnames are displayed, followed by their initials (without dots). When the authors are more than three, after the name of the third one is written "et al.". References should be written in the original language of the article. It is strongly recommended to be familiar with and to cite Bulgarian sources as well.

Illustrative material (tables, figures, photos) has to be placed in the text with titles and legends. The headings of the figures should not be included in the image. The figures and photos must be of good quality (at least 300 dpi) and in a suitable format (.jpg, .tif, .png). Tables should be provided in an editable format, not as images.

The specific abbreviations used in the text should be enclosed in brackets when the full name first appears.

The units of measurement should be in the SI system.

The materials have to be sent by e-mail to the organizational secretary of each journal.