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was made with SPSS version 16.0. 53 patients were screened, 5 did not meet the inclusion criteria; 47 enrolled, 5 withdrawn from the study, 42 analyzed.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

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
Дизайн на проучването: едноцентрово, обсервационно, открито, проспективно, неинтервенционално, фармакоепидемиологично проучване на клинични серии от случаи на изява на НЛР при българска популация пациенти с ревматоиден артрит, анкилозиращ спондилит и псориатичен артрит, провеждащи лечение с биологични лекарствени продукти. Проучването е проведено в периода март 2015 г.–октомври 2016 г., по предварително изготвен протокол. Всички участници са подписали информирано съгласие. Протоколът и информираното съгласие са изготвени в съответствие с изискванията на ЗЛПХМ, Закона за здравето при спазване на етичните принципи, заложени в Декларацията от Хелзинки, и Ръководството за добра клинична практика [7-11]. Проучването е съобразено и с изследователските практики, описани в Добра фармакоепидемиологична практика на Международното общество по фармакоепидемиология (ISPE) [12].

Пациентите, включени в изпитването, трябва да имат едно от следните заболявания: ревматоиден артрит (РА), анкилозиращ спондилит (АС), псориатичен артрит (ПсА), и да са определени като подходящи за лечение с някои от следните лекарствени продукти по международни непатентни наименования (INN): etanercept, adalimumab, golimumab, certolizumab pegol, rituximab, включително със или без methotrexate.

Inclusion criteria: Patients included in the study 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, гологумумаб, цертолизумаб пегол, ритуксимаб. Изключение от това изискване е допус-тимо за пациенти, които ще провеждат лечение с ритуксимаб. Те обичайно са лекувани преди това с един или повече 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 биоподобни лекарствени продукти; 5. Да отговорят 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 РА, АС или ПсА, провеждали предхождащо лечение с БЛП; 4. Пациенти с РА, АС или ПсА, провеждали предхождащо лечение с биоподобни 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. Прочуването 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 така, както са установени в предрегистрационния период.

Оценката на безопасността е направена чрез анализ на събранията информация, получена от анкетните карти на пациентите. Безопасността на биологичното лечение при всеки пациент бе проследявана през 6 месеца до 12-ия месец включително. Определихме големината на популацията и получени данни за НЛР по брой пациенти, заболявания, демографски показатели и др. Проведохме 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 по всяко време или да отпадне по преценка на изследователя.

Въвеждането на данните, техните начална обработка, графичното представяне и статистическите изчисления са направени със SPSS, версия 16.0. Използвахме следните ста-
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**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.
Получените резултати показват висок относителен дял на случаите, при които биологичното лечение е преустановено – 25.5% (от 47 пациенти 7 отпадат поради сериозни НЛР, 5 отпадат поради други причини).

Тежестта на установените сериозни НЛР е оценена по общи терминологични критерии за НЛР (Common Terminology Criteria for Adverse Events by National Cancer Institute – CTCAE version 4.03, June 14, 2010) [20]. 3 от НЛР са оцениeni като 3 степен на тежест, а останалите 4 – като 4 степен на тежест.

Анализ на резултатите при пациенти с АС. Данните на пациентите са оценени по основни демографски показатели – възраст, пол, възрастови групи, вид на провежданото биологично лечение по лекарствен продукт, средна възраст на проследените пациенти. Групата с АС включва 18 пациенти – 15 (10 мъже и 5 жени) са наблюдавани и проследени за пълен едногодишен период. Всички пациенти са проехли цикъл от 12-месечен период, средна възраст на проведеното лечение е 45.8 год. При двама пациенти е прекратено лечение поради сериозни НЛР. Анализът на демографските показатели показва, че мъжете са 2 пъти повече от жените, като това се наблюдава във всички възрастови групи. Средната възраст на проследяваните мъже и жени в групата с АС е изравнена – средната възраст на мъжете е 45.6 год., а на жените е 45.6 год. Във възрастовата група над 65 няма пациенти с АС (таблица 1).

Пациентите в групата с АС са провеждали лечение с 3 вида БЛП – etanercept, adalimumab и golimumab. Най-голям дял заема групата пациенти на лечение с adalimumab, докато само един пациент е на лечение с golimumab.

НЛР са систематизирани по системо-органната класификация по MedDRA, версия 12.0 [21]. 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].
Prognostic study of adverse drug reactions...  

The frequency distribution is presented in Fig. 3 and their typing is presented in Fig. 4. The total number of reported and confirmed ADRs was 74. Of them, there were 2 serious ADRs (leading to the withdrawal of the study), of which 1 ADR met the definition of SUSAR, and the second one fell into the group of suspected ADRs; there were nine unexpected ADRs and 64 suspected ADRs.

Table 1. Demographic data of patients with AS

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Men (26.66%)</th>
<th>Women (13.33%)</th>
<th>Total (40.0%)</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 &gt; 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>
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.
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>
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<tbody>
<tr>
<td>Age 18-45 years</td>
<td>1 (7.1%)</td>
<td>1 (7.1%)</td>
<td>2 (14.2%)</td>
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<tr>
<td>Age 46-65 years</td>
<td>1 (7.1%)</td>
<td>6 (42.9%)</td>
<td>7 (50.0%)</td>
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<tr>
<td>Age ≥ 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 изчисленi
Due to the low number of men, median and mode are not calculated
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.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Men n = 4</th>
<th>Women n = 2</th>
<th>Total n = 6</th>
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<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>
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<tr>
<td>Average</td>
<td>51.5</td>
<td>50.0</td>
<td>51.0</td>
</tr>
<tr>
<td>Median</td>
<td>61.0</td>
<td>–</td>
<td>59.0</td>
</tr>
<tr>
<td>Mode</td>
<td>56.0</td>
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<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 им 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), prosedened 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.

![Fig. 12. Grades of the severity of ADRs](image)

![Fig. 13. Types of relations between treatment and ADRs](image)
И. Първова, А. Рангелов, Е. Христов и др. I. Parvova, A. Rangelov, E. Hristov et al.

Демографската характеристика на включени-те в проспективното проучване пациенти отгова-ря на епидемиологичните данни за България, ти-пична е за българската популяция и съответства на данните за европеидната раса.

Adalimumab и etanercept са най-предписвани-те БЛП в България и заемат дял от 77% от общо-то предписание на биологични продукти, а оста-налите продукти заемат дял от 23%.

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

Установихме много висок относителен дял – 17,0%, на изявя на сериозни НЛР, довели до прекратяване на лечението. Проспективно уста-новената честота на НЛР е 3,80/пациент. Този ре-зултат извежда честотата на идентифицираните НЛР като много чести по системо-органната класификация по MedDRA.

**Обсъждане**

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.

<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**

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

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


