A report on the adverse events of special interest from the Romanian Registry of Rheumatic Diseases in patients treated with biologic and targeted synthetic disease-modifying anti-rheumatic drugs during 2022

Corina Mogosan1,2, Claudiu C. Popescu1,2, Horatiu V. Popoviciu3, Elena Rezus4,5, Veronica Grigore6, Violeta C. Bojinca2,7, Ileana C. Filipescu8,9, Simona Rednic8,9, Catalin Codreanu1,2

1“Dr. Ion Stoia” Clinical Center for Rheumatic Diseases, Bucharest, Romania
2“Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
3Emergency County Hospital, Targu Mures, Romania
4“Grigore T. Popa” University of Medicine and Pharmacy, Iasi, Romania
5Rheumatology Department, Rehabilitation Hospital, Iasi, Romania
6Rheumatology, County Hospital, Sfantu Gheorghe, Romania
7Rheumatology, “Sfanta Maria” Hospital, Bucharest, Romania
8“Iuliu Hatieganu” University of Medicine and Pharmacy, Cluj-Napoca, Romania
9Rheumatology, Emergency County Hospital, Cluj-Napoca, Romania

ABSTRACT

Background. The evolution of the therapeutic arsenal in inflammatory rheumatic diseases has dramatically improved their evolution and prognosis. On the other hand, the information of the safety data, especially for conditions that may appear in a longer time of exposure, are not reflected by clinical trials, due to their limited time design. Patient registries are a valuable source of safety data applicable to real-world (unselected) patients. The evaluation of these data completes the evidence from the various development programs, with the aim of more concrete knowledge of each therapeutic class (therapeutic agent).

Aim. The present report descriptively presents the adverse events (AE) of special interest, recorded by the Romanian Registry of Rheumatic Diseases (RRBR), during 2022, in relation to the dynamics of the recent years.

Methods. The observational study included all AEs reported in the RRBR in 2022, their severity class, the relationship with exposure to the therapeutic agent.

Results. For a cohort of 10676 patients who were exposed to at least one course of treatment, with data in the RRBR during 2022, there were 669 AEs reported: 432 reports for patients with rheumatoid arthritis (RA), 195 records for patients with ankylosing spondylitis (AS) and 42 reports for patients with psoriatic arthritis (PsA). The most common AEs were infections, especially in RA patients. Of all AEs, 94 (14%) were serious AEs, the majority reported in the RA group (16%). A number of 15 MACE, 13 solid malignancy and 19 deaths were reported in the last year.

Conclusion. The distribution of EA by disease, the dominance in RA, as well as the distribution by therapeutic groups is in accordance with scientific data, with the exception of breast cancer, which is more frequently reported in RRBR. EA are underreported in the destined section in the RRBR, an aspect that gives a limit of this report. This represents an unmet need in terms of safety data reporting, that calls for increased knowledge of EA reporting requirements.

Keywords: biologics, Romanian Registry of Rheumatic Diseases, adverse events
**BACKGROUND**

Patient registries provide highly reliable data, challenged hierarchically only by randomized controlled trials. Although registries have been used in several fields of medicine for more than a century and a half, their key role is frequently overlooked and poorly recognized. Medical registries have evolved from calculating basic epidemiological data (incidence, prevalence, mortality) to diverse applications in disease prevention, early diagnosis and screening programs, data of efficiency and safety, disease control programs [1].

The Romanian Registry of Rheumatic Diseases (RRBR) is collecting data from all the population treated with biologics and targeted synthetic DMARDs in the country, as for the regulation of the National Insurance House, which stated that each patient who is upgraded to an innovative agent should be enrolled in the RRBR. The database follows a prospective observational cohort design, without a comparator arm, and started in 2013. To date it comprises data for the patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA). The reporting of the adverse events is at the discretion of the attending physician, it is not mandatory. The assignment of adverse events in severity classes follows the rules of clinical studies. The following report presents the adverse events of special interest registered in RRBR in 2022, in relation to the dynamics of their registrations in the last years.

**METHODS**

The report is expressed as the total number of events and it is based on the information electronically included in the RRBR database with respect to any AE that occurred during 2022; it also looked at the figures of the last years. The entire cohort included patients exposed to at least one course of biologic or targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDs, tsDMARDs).

**RESULTS**

To date, the entire cohort with registered visits during 2022 consists of 10676 patients: 5396 with RA, 4315 with SA and 965 with PsA. From the year of RRBR launch a total number of 7759 AEs were reported and Figure 1 presents the evolution of AE registrations.

The pandemic of COVID-19 separated the number of reports of last 3 years from the previous years with a drop in the reported AEs, which was probably related with the reduction in the number of follow up visits, as telemedicine developed. On the other hand, evaluating the distribution of AEs for each condition, RA patients have the highest number of reports (Figure 2), which is relatively constant over the entire period.

The distribution of AEs into severity classes is presented in Table 1. Globally, to date, in RRBR is registered 1 serious adverse event (SAE) every 3 mild/moderate AEs. SAEs represent the most important category, as it implies either permanent disability, prolonged hospitalization, life-threatening complications or death. During the last year, the RRBR has registered 14% SAE.

The distribution if SAE between the rheumatological conditions during 2022 is presented in Figure 3.
RA registered the highest proportion of SAE (16%), compared to 10% in SA and only 6% in PsA patients.

Among all EAs, there are several categories grouped under the term EAs of special interest, among which are infections, MACE (major adverse cardiovascular events), thrombotic events, malignancies, mortality. With the expansion of the therapeutic arsenal in rheumatology, through the development of new therapeutic targets, biological or small molecules, reports regarding EA of special interest from different data sources, in different populations, triggered several discussions, debates, which continue even today.

Figure 4 displays the number of reported EAs of special interest in the RRBR, referring to the year 2022, in reverse order of the frequency. In the MACE

![Figure 2. Distribution of AEs during 2016-2022 in the RRBR](image)

<table>
<thead>
<tr>
<th>condition</th>
<th>RA (n)</th>
<th>SpA (n)</th>
<th>PsA (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>4470</td>
<td>4171</td>
<td>4407</td>
</tr>
<tr>
<td>SpA</td>
<td>2021</td>
<td>3187</td>
<td>3417</td>
</tr>
<tr>
<td>PsA</td>
<td>574</td>
<td>804</td>
<td>832</td>
</tr>
</tbody>
</table>

**TABLE 1.** Severity classes of all reported AEs during 2016 – 2022

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>7759</td>
<td>795</td>
<td>1083</td>
<td>1200</td>
<td>1107</td>
<td>638</td>
<td>901</td>
<td>669</td>
</tr>
<tr>
<td>2017</td>
<td>1873</td>
<td>225</td>
<td>296</td>
<td>280</td>
<td>170</td>
<td>109</td>
<td>240</td>
<td>94</td>
</tr>
<tr>
<td>2018</td>
<td>5886</td>
<td>570</td>
<td>787</td>
<td>920</td>
<td>933</td>
<td>529</td>
<td>661</td>
<td>575</td>
</tr>
<tr>
<td>2019</td>
<td>6432</td>
<td>690</td>
<td>677</td>
<td>383</td>
<td>432</td>
<td>343</td>
<td>338</td>
<td>271</td>
</tr>
<tr>
<td>2020</td>
<td>2019</td>
<td>234</td>
<td>3417</td>
<td>193</td>
<td>195</td>
<td>72</td>
<td>101</td>
<td>88</td>
</tr>
<tr>
<td>2021</td>
<td>2022</td>
<td>490</td>
<td>639</td>
<td>566</td>
<td>410</td>
<td>341</td>
<td>309</td>
<td>42</td>
</tr>
<tr>
<td>2022</td>
<td>2022</td>
<td>56</td>
<td>64</td>
<td>62</td>
<td>88</td>
<td>64</td>
<td>42</td>
<td>58</td>
</tr>
</tbody>
</table>
category there are included: heart failure hospitalized (n = 3), stroke (n = 7), acute coronary syndrome (n = 5).

By far, during 2022 infections were most frequently reported (45%). Top three localization of infections were: respiratory (n=134, 45% of all infections), followed by urinary tract infections (n=52, 17%) and skin infections (n=25, 8%).

The distribution of infections by disease is presented in Figure 5.

Coming back to the AEs registry section, Figure 6 displays the dynamic of severe infections during the years and Figure 7 displays the severe infections between the disease type.

According to literature data, the risk of infection is one of the most important factors when choosing a therapy, as it represents a substantial source of morbidity and mortality in RA patients [2]. On the other hand, recent data (a systematic review and meta-analysis of randomised controlled trials, open-label studies and observational studies) for PsA and axSpA mentioned that serious infections were rare events in RCTs and real-life studies. Non-serious infections were common adverse events, mainly in RCTs [3].

Only RA patients experienced serious infections during 2022, while there is no severe infections in AS and PsA group (Figure 7). Important to note, that even not severe infection reports in AS and PsA group, the mild/moderate infections could also be source of morbidity in a biologic treated patient.

The category of severe infections followed a slightly increasing trend up to year 2020 (year of pandemic) and decreased afterwards, as in 2022 there were only 18 reports (6% of all yearly infections). We have to mention that the reports of COVID-19 cases have lots of missing data; last year, there has been introduced a pop-up question related to CODIV-19 diagno-
sis and the severity of the disease (for year 2021). The association between the reported cases (in AEs section of the registry) and the reported ones as answers to the pop-up question was very low: in the registry there were 283 COVID-19 cases reported, much less than 1893 cases recognized after the direct question. Interestingly, for the cases reported in AEs registry section there were 15% severe forms, much more than the ones not fully reported (6% severe forms). We can comment that the more severe the AEs seem to be, the most likely it will be reported. This is not surprising for registries, as missing information is one of the common features of the real-world data.

Tumour necrosis factor (TNF) inhibitors are known to be associated with an increased risk of serious infection compared to conventional synthetic DMARDs (csDMARDs), with a time varying risk highest in the first 6-12 months of treatment [4,5].

The therapies behind the reported infections for all reports are displayed by Table 2.

From all serious infections reported in the RRBR during 2022, 39% were associated to exposure to TNF inhibitors, whereas no infections on Abatacept and IL17 inhibitors. There were 11 cases of herpes zoster, namely 9 cases (82%) of patients on JAK inhibitors and 2 cases in patients on TNF inhibitors. These ap-
peared in 82% in RA patients (n=9), 9% in AS group (n=1) and also 9% in PsA patients (n=1).

With respect to tuberculosis (TB), Romania has a special position being the country with the highest tuberculosis (TB) burden in the European Union/European Economic Area (EU/EEA) comprising almost a quarter (23.4%) of the reported patients in 2017, and a TB notification rate six times higher than the EU/EEA average. However the overall TB notification rate in Romania declined from 154/100.000 individuals to 66/100.000 individuals in the general population between 2002 and 2017 [6].

There is an increased incidence of TB among RA patients associated to the systemic Th1 defect associated with the disease [7]. Patients with the most advanced RA remain with Th1 systemic defects after TNF inhibitors treatment despite clinical improvement [8]. With respect to AS and PsA risk of TB, particularly under TNF inhibitor, there are data which demonstrate an elevated such risk, with large variations across the world, being higher in South Korea [9,10].

However, the rate of tuberculosis has fallen with the introduction of screening precautions, yet the continued risk of tuberculosis reactivation in TNF inhibitor-treated patients requires ongoing vigilance. The risk of TB reactivation appears lower with etanercept exposure compared with the monoclonal antibodies, as observed in registries data [11].

The evolution of TB cases in the RRBR is displayed by Figure 8, while Figure 9 is presenting the number of events during year 2022.

In 2022, a number of 15 cases of tuberculosis were reported in the RRBR: 7 cases in RA cohort, 7 cases in AS group and 1 case in PsA patients. Regarding clinical manifestations, 14 cases (93%) had pulmonary form of the disease and only 1 case (7%) had extra-pulmonary TB. Of the 15 cases of TB, 12 cases (84%) were treated with TNF inhibitors (adalimumab -6, etanercept -3, certolizumab -2, infliximab -1), 2 cases with other mode of action biologics (IL17 inhibitor) and 1 case was exposed to JAK inhibitors.

On the other hand, according to an OMS study report, Romania faces a high burden of chronic viral hepatitis in the general population. Insufficient infection control in health-care settings decades ago was the cause of increased infections. A national survey among adults estimated a prevalence about double the regional average for hepatitis C (at 3.2%), or triple the average for hepatitis B (at 4.4%) [12].

A recent report on hepatitis B virus (HBV) reactivation in the RRBR underlined that it appeared more often on a chronic infection state, especially without

**TABLE 2.** The therapies associated with reported infections for all diseases

<table>
<thead>
<tr>
<th></th>
<th>TNFi</th>
<th>JAKi</th>
<th>Tocilizumab</th>
<th>IL17 inhibitors</th>
<th>Rituximab</th>
<th>Abatacept</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL* n=299</td>
<td>180</td>
<td>51</td>
<td>30</td>
<td>14</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>17%</td>
<td>10%</td>
<td>5%</td>
<td>5%</td>
<td>1.7%</td>
</tr>
<tr>
<td>SEVERE Infections n=18 (6%)</td>
<td>7</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>39%</td>
<td>22%</td>
<td>28%</td>
<td>0</td>
<td>11%</td>
<td>0</td>
</tr>
</tbody>
</table>

*3 cases associated with exposure to csDMARDs: leflunomide (2), sulphasalazine (1)
antiviral prophylaxis, with no cases of fulminant hepatitis. Rituximab exposure was most commonly associated with RA cases and HBV reactivation, while in the AS group all HBV reactivations appeared in patients exposed to TNF inhibitors; HBV reactivation in the PsA cohort had a very low rate [13].

Figure 10 displays the number of cases with HBV reactivation during 2016-2022. Of note, during the last year no case reported for any disease.

As for cumulative data, there is an increase risk for MACE and VTE for patients with inflammatory rheumatic diseases. On behalf of the French Society of Rheumatology, there was recently published recommendations for assessing the risk of cardiovascular disease (CVD) and venous thromboembolism before the initiation of targeted therapies for chronic inflammatory rheumatic diseases. According to that, in one overarching principle, the treating rheumatologist has a major role in evaluating the risk factors for cardiovascular disease and also for thromboembolic events, on start of the therapies and also on a regular basis [14].

In the RRBR, MACE category comprises heart failure, stroke and acute coronary events. Figure 11 is presenting the reported MACE – as number of events, between 2016-2022.

In 2022, there were 15 reports for MACE, mostly in RA patients (73%), as presented in Figure 12. Of all reported MACE, 9 cases (60%) were exposed to TNF inhibitors, 3 cases (20%) to JAK inhibitors, 2 cases
Patients with RA are at increased risk of cancer overall, mainly due to an increased occurrence of lung cancer and malignant lymphoma [15]. Increased risks of non-melanoma skin cancer (NMSC) have been reported in patients with RA [16] and also in patients with psoriatic arthritis (PsA) [17]. Studies on cancer risks with biological disease-modifying antirheumatic drugs (bDMARDs) such as tumour necrosis factor inhibitors (TNFi) and other (non-TNFi) bDMARDs have overall been reassuring [18,19], but also pointed to signals of potential risk increases, with individual drugs and for individual cancer sites, for example, NMSC [20]. Concerning to therapy exposure, recent data adds evidence to suggest a possible increased risk for non-melanoma skin can-

(13%) to rituximab and 1 case (7%) to tocilizumab. Of all MACE events, 5 (33%) were fatal, all cases belonged to RA cohort (2 cases acute coronary event, 3 cases with stroke). The therapies associated with MACE and death were TNF inhibitors (3 cases, 60%), tocilizumab (1 case, 20%), rituximab (1 case, 20%).

The thromboembolic events (deep vein thrombosis – DVT and pulmonary embolism – PE) were started to be reported as a separate category in previous year. To date, 5 cases of TEV were reported: all 5 cases developed DVT: for 2021, 3 cases (1 in each disease group), for 2022, 2 cases (1 in RA group and 1 in SA). These patients were exposed to TNF inhibitors (3 cases), JAK inhibitors (1 patient) and IL17 inhibitors (1 patient).
cancers with JAKi as used in clinical practice for RA and PsA [21].

Since the RRBR started to register AEs, a number of 158 cases of solid malignancy were diagnosed during exposure to biologic agents; Figure 13 displays the evolution of solid malignancy diagnosis, along the years, which was quite linear.

Breast cancer is the most frequently reported cancer, with 23 (15%) cases. Lung cancer with 19 (12%) cases is the second cancer type reported in the RRBR, followed by non-melanoma skin cancer (NMSC) with a total of 15 (9%) reports.

Of these, 13 solid neoplasms were reported during 2022, with the following localizations: breast cancer (n = 3), lung cancer (n = 2), colon cancer (n = 2), NMSC (n=1), melanoma (n=1), central nervous system (n=1), pancreatic cancer (n=1), renal cancer (n = 1), ENT localization (n = 1). These events were reported in patients who were previously exposed to TNF inhibitors (n = 9, 69%), abatacept (n = 2, 15%), JAK inhibitors (n = 2, 15%).

Longitudinal studies averaging a standardised mortality ratio of 1.5 (95% confidence interval of 1.2-1.8) for RA patients compared to the general population [22]. On the other hand, data on mortality in AS is scarce; there are conflicting evidence on the mortality risk among patients with PsA; however, it is accepted that PsA patients do not have a significantly
A recent study conducted with RRBR data revealed that RA patients have a higher mortality risk compared to AS and PsA patients [24].

To date, there were 343 all-cause deaths reported in the RRBR, while during 2022 there were 19 fatal events reported. The evolution of mortality events in patients treated with biologics for rheumatic diseases is displayed in Figure 14.

The most frequently related cause of mortality is presented in Figure 15. In accordance with literature data, the mortality rate in RA is higher compared to other inflammatory diseases treated with biologics/JAK inhibitors. Infections and cardiovascular events are dominantly reported as causes of death for RA patients. It is worthy to note that a >50% of all-mortality is of unknown cause.

CONCLUSIONS

The number of reports for AEs is relatively over the last years, except for the pandemic period. The majority of AEs were reported for RA patients, in all severity classes. Infections, included serious infections, also MACE events were more frequently related to the RA group, compared to AS and PsA patients. From the perspective of HBV reactivation, there is a decrease in the number of cases over the last years. The most frequently reported type of solid malignancy is breast cancer, followed by lung cancer, also in RA group more prevalent. The first two causes of mortality are represented by infections and cardiovascular events.

Even if, generally the frequency of certain AEs look very similar with other registry evidence, there are several limitations that can influence the results of this report. As there is no standardised procedure...
across registries with respect to AEs reporting, the RRBR follows the physician decision in registration an event or not. It is highly probable that not all AEs that really occurred are registered in the destined section in the RRBR. This may modify the ratio be-

between mild/moderate AEs and serious ones. Persistence and efforts are needed to improve the unmet need of collecting as much information as possible for the medical evolution of patients exposed to any treatment, especially the innovative molecules.

Conflict of interest: none declared
Financial support: none declared

REFERENCES


