Ref: Ro J Rheumatol. 2023;32(4)
DOI: 10.37897/RJR.2023.4.3

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 Mogosan[1,2], Claudiu C. Popescu[1,2], Horatiu V. Popoviciu[3], Elena Rezus[4,5], Veronica Grigore[6], Violeta C. Bojinca[2,7], Ileana C. Filipescu[8,9], Simona Rednic[8,9], Catalin Codreanu[1,2]

[1]"Dr. Ion Stoia" Clinical Center for Rheumatic Diseases, Bucharest, Romania
[2]"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[3]Emergency County Hospital, Targu Mures, Romania
[4]"Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania
[5]Rheumatology Department, Rehabilitation Hospital, Iasi, Romania
[6]Rheumatology, County Hospital, Sfantu Gheorghe, Romania
[7]Rheumatology, "Sfanta Maria" Hospital, Bucharest, Romania
[8]"Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania
[9]Rheumatology, 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 10,676 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 AE 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. AE are underreported in the designated 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 AE reporting requirements.

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

Corresponding author:
Claudiu C. Popescu
E-mail: claudiu.popescu@reumatologiedrstoia.ro

Article History:
Received: 19 December 2023
Accepted: 26 December 2023

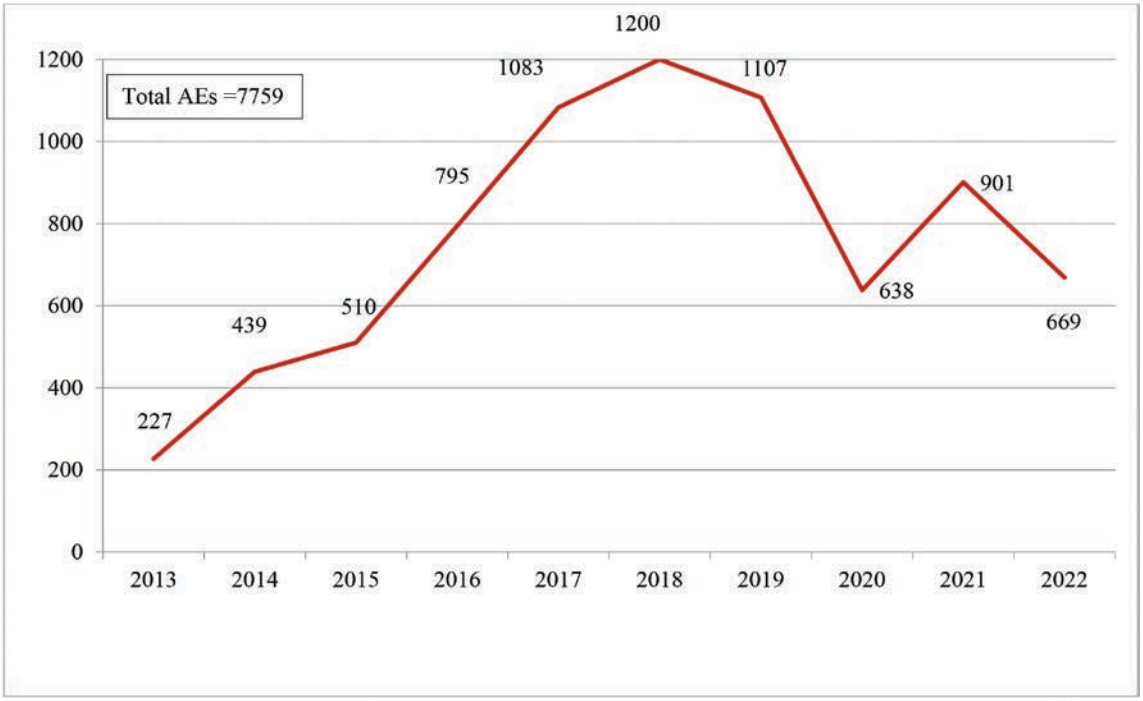


FIGURE 1. The total number of reported AEs in the RRBR since it was released

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).

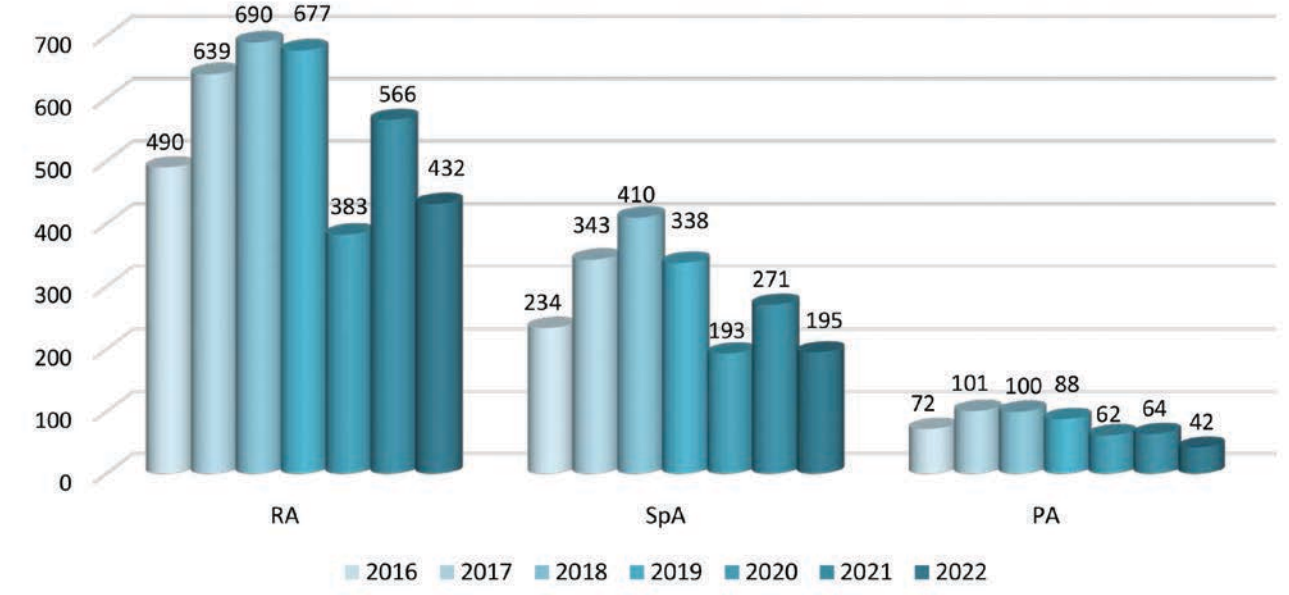
RESULTS

To date, the entire cohort with registered visits during 2022 consists of 10,676 patients: 5,396 with RA, 4,315 with SA and 965 with PsA. From the year of RRBR launch a total number of 7,759 AEs were reported and Figure 1 presents the evolution of AE registrations.

The COVID-19 pandemic separated the number of reports of the last 3 years form 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.



condition		RA (n)	SpA (n)	PsA (n)
year	2016	4470	2021	574
	2017	4171	3187	804
	2018	4407	3417	832
	2019	4755	3651	849
	2020	4752	3767	861
	2021	5074	4047	900
	2022	5396	4315	965

FIGURE 2. Distribution of AEs during 2016-2022 in the RRBR

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

Year	Total	2016	2017	2018	2019	2020	2021	2022
Number of AEs (n)	**7,759**	795	1,083	1,200	1,107	638	901	669
SAE in RRBR (n) %	**1,873** **24%**	**225** **28%**	**296** **27%**	**280** **23%**	**170** **15%**	**109** **17%**	**240** **27%**	**94** **14%**
AEs (mild +moderate) (n) %	**5,886** **76%**	570 72%	787 73%	920 77%	933 85%	529 83%	661 73%	575 86%
RATIO mild+moderate AE : SAE	**3:1**	2.5:1	2.6:1	3.2:1	5.5:1	4.8:1	2.75:1	6:1

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

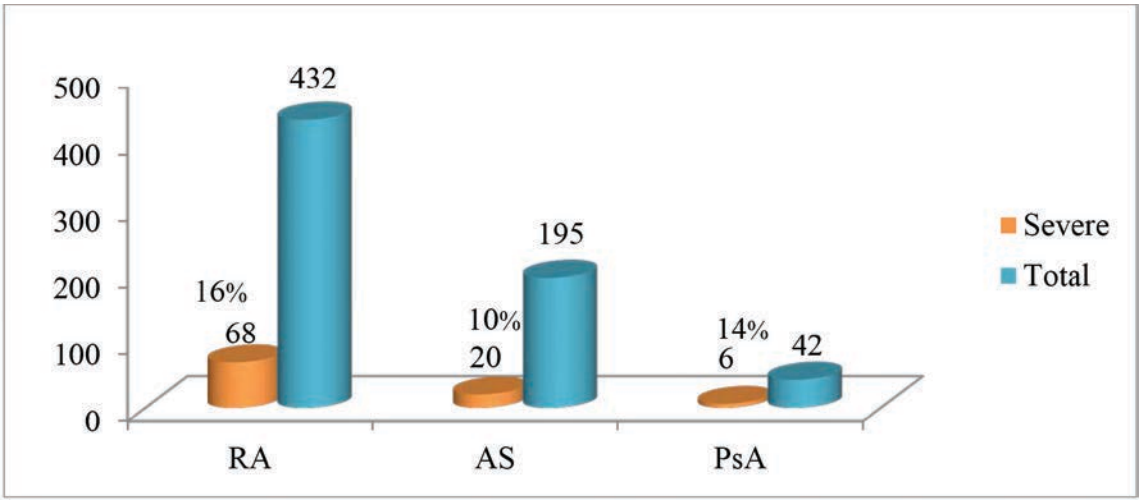


FIGURE 3. Severity classes of AEs in 2022 in RRBR

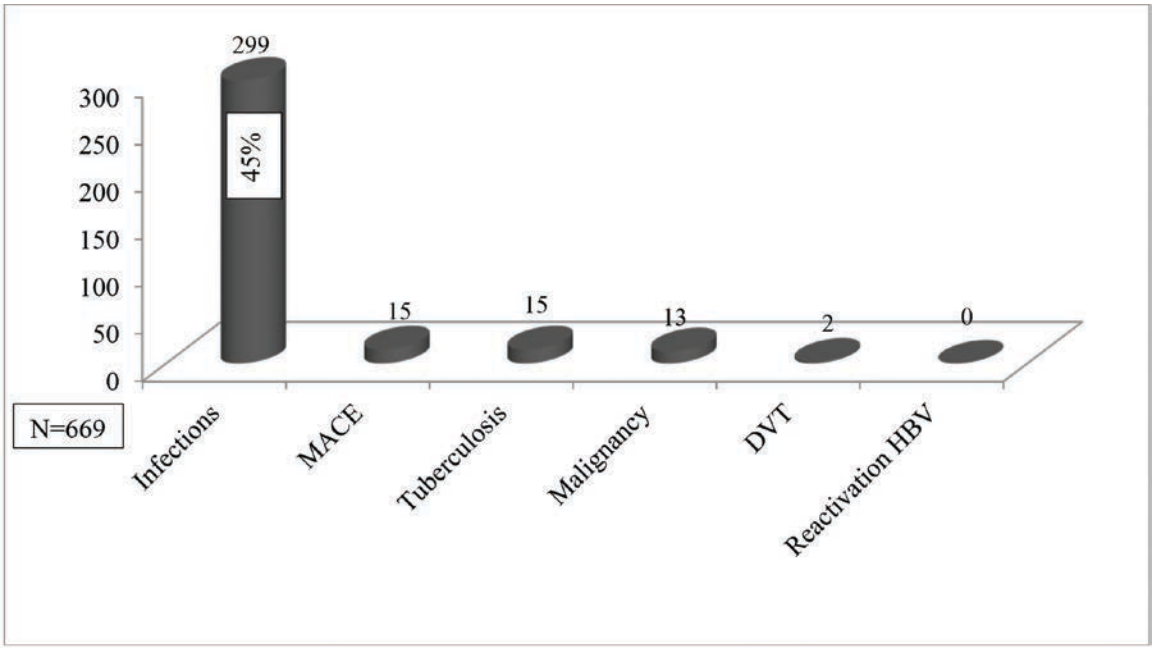


FIGURE 4. The reported AEs of special interest in RRBR in 2022

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 randomized 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 were no severe infections in AS and PsA groups (Figure 7). Important to note, that even non-severe infection reports in AS and PsA group, the mild/moderate infections could also be the 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-

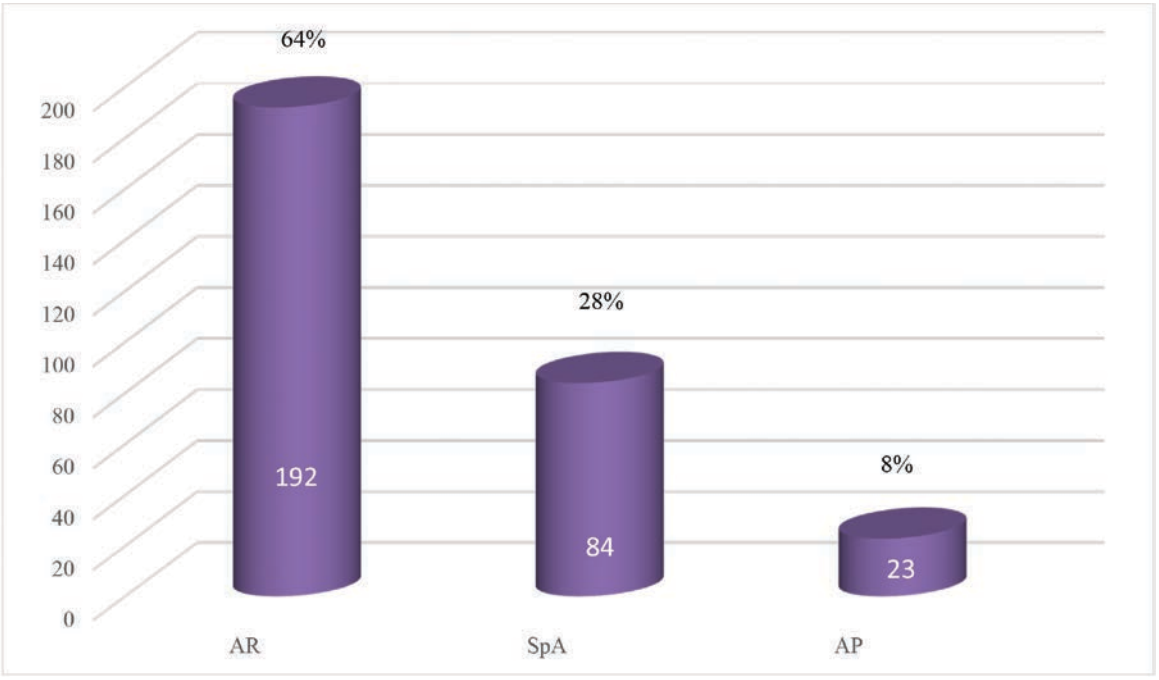


FIGURE 5. Infections number of reports during 2022

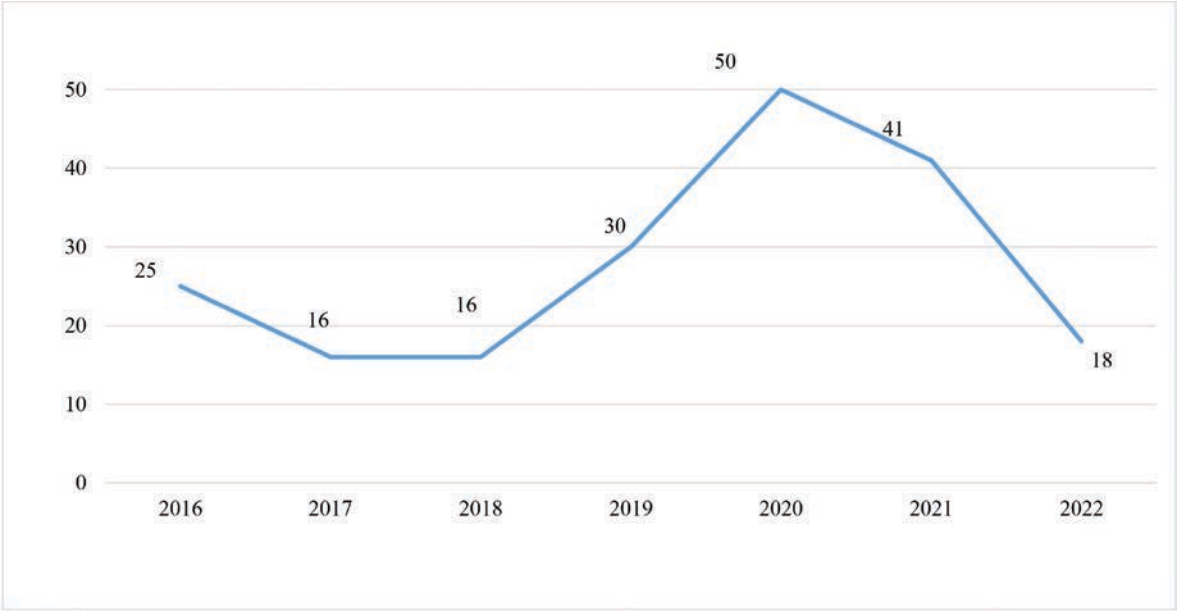


FIGURE 6. Severe infections - number of events between 2016-2022 in the RRBR

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 1,893 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.

Tumor 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-

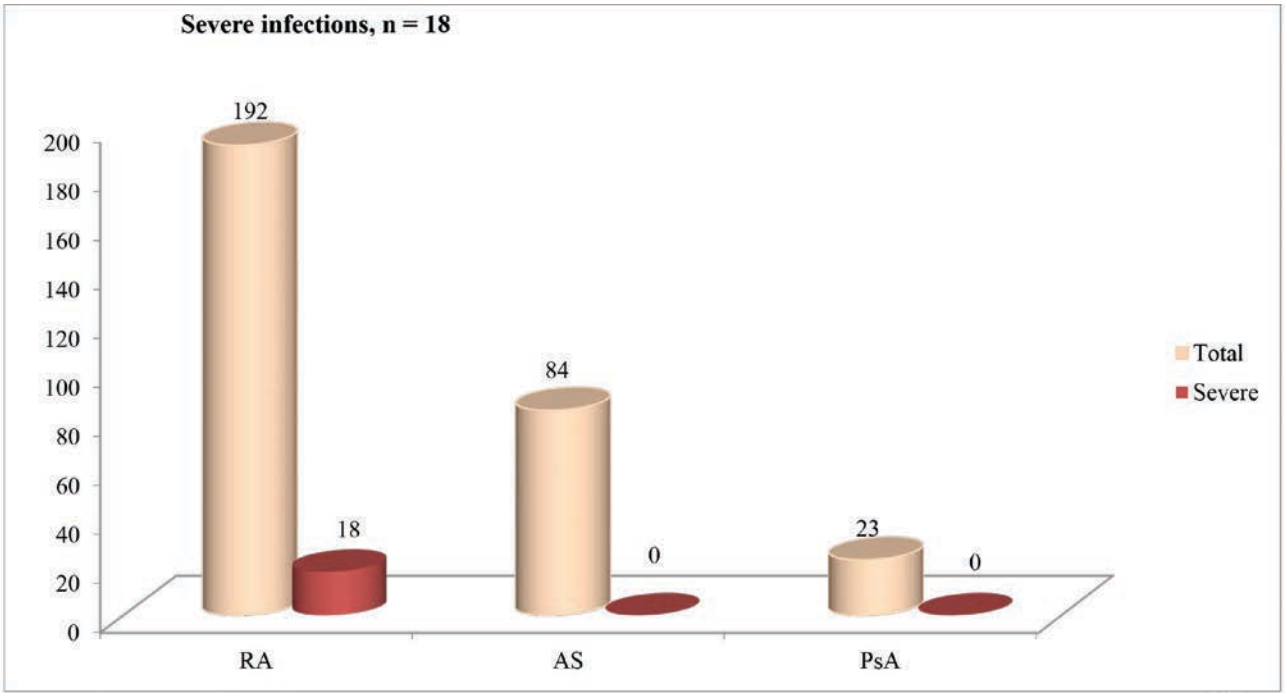


FIGURE 7. Severe infections reported in RRBR in 2022

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

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

**3 cases associated with exposure to csDMARDs: leflunomide (2), sulphasalazine (1)*

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 a 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 WHO 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

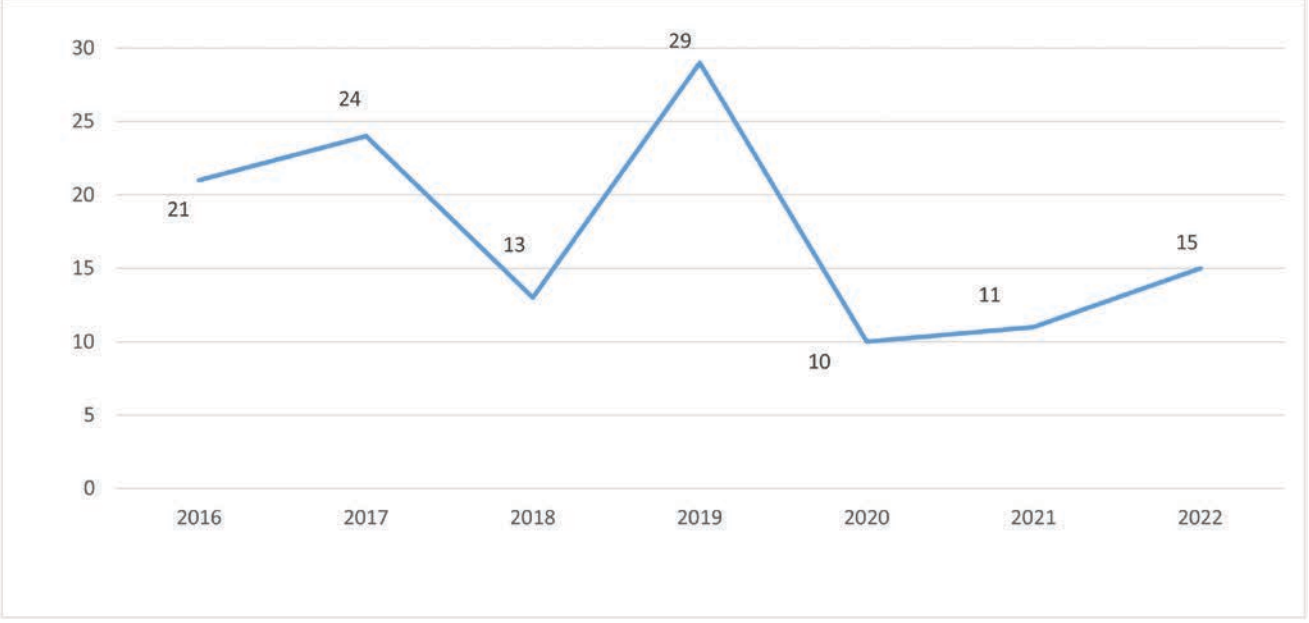


FIGURE 8. Tuberculosis number of events between 2016-2022 in the RRBR

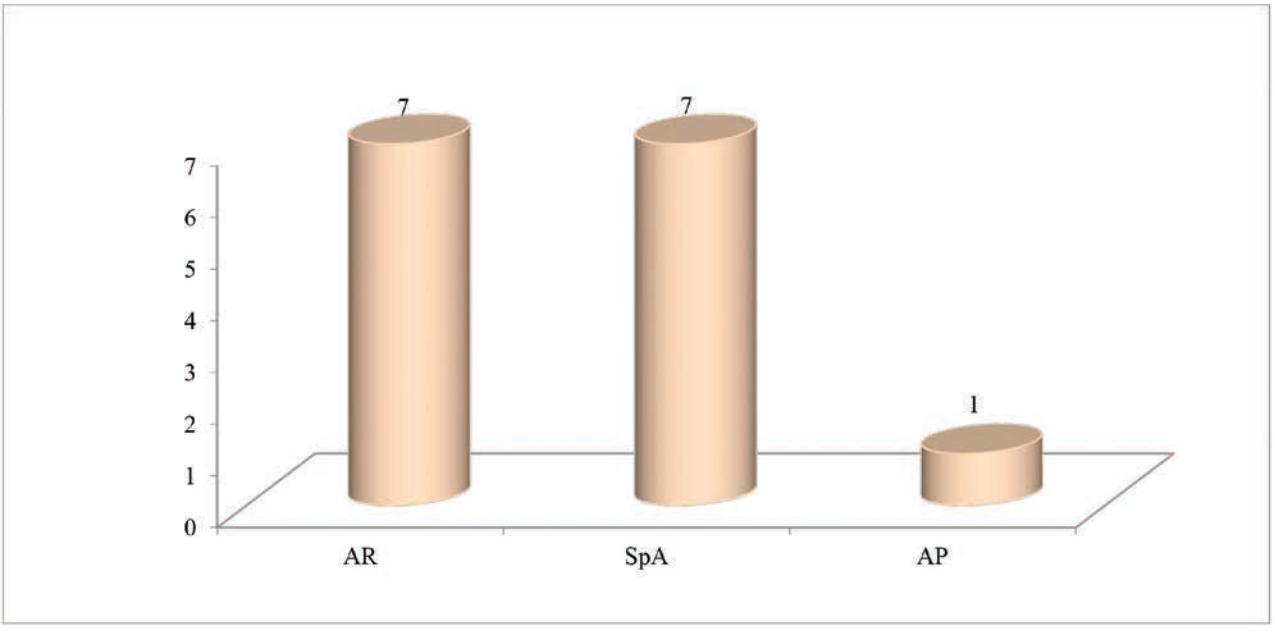


FIGURE 9. Tuberculosis number of events during 2022 in the RRBR

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, there was no case reported for any disease.

As for cumulative data, there is an increased 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 evaluation 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

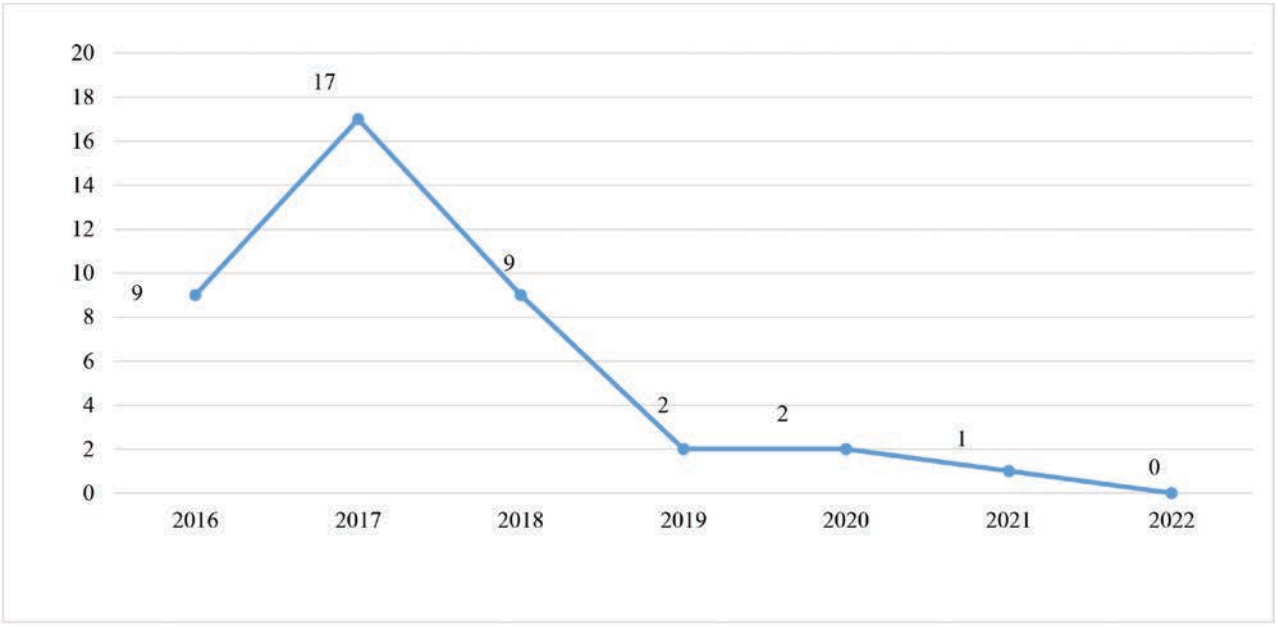


FIGURE 10. Hepatitis B virus reactivation number of events between 2016-2022 in the RRBR

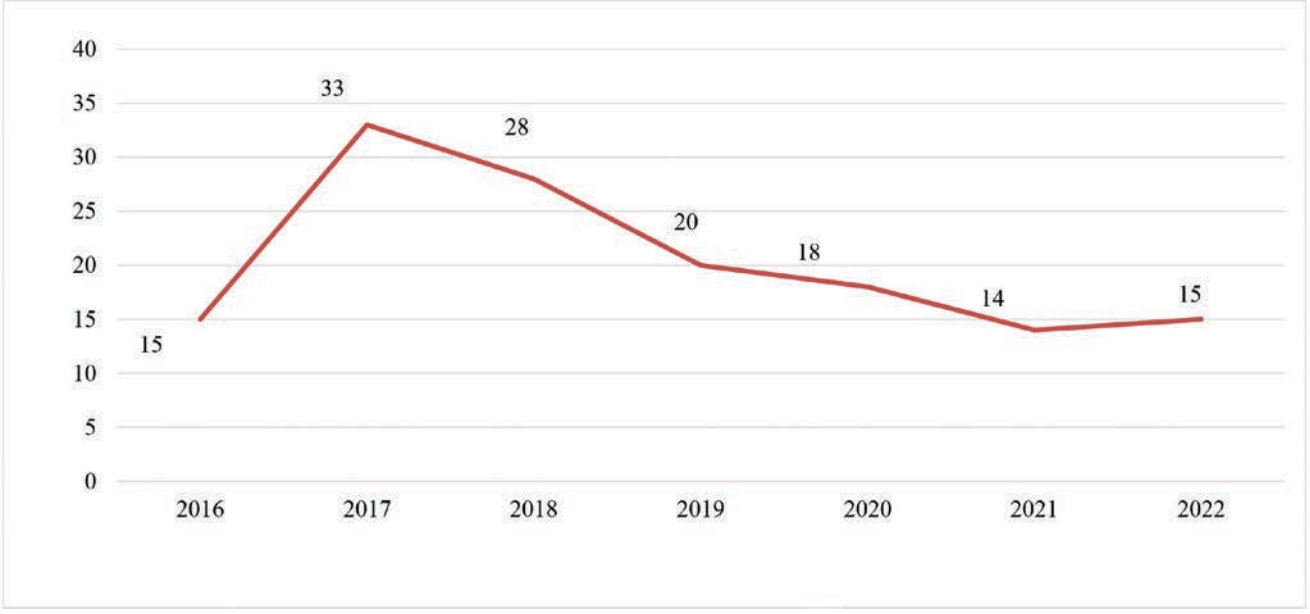


FIGURE 11. MACE number of events between 2016-2022 in the RRBR

(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 (3cases, 60%), tocilizumab (1case, 20%), rituximab (1case, 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).

Patients with RA are at an 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 tumor 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-

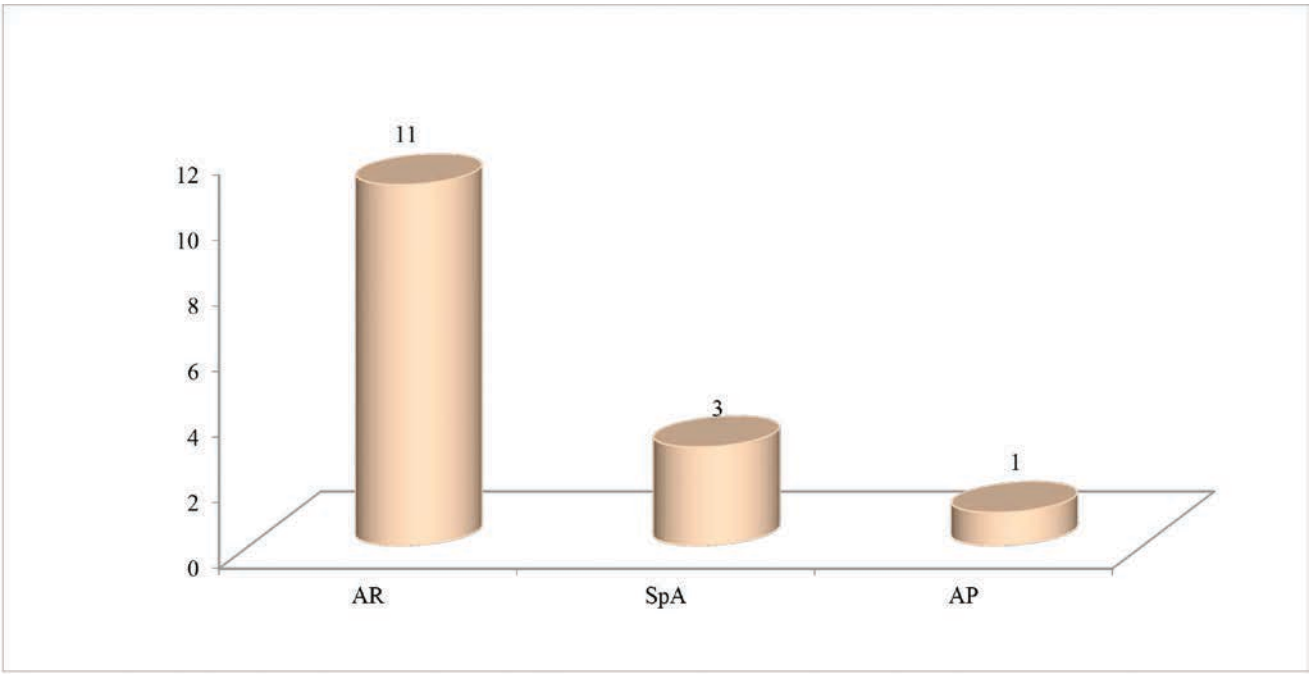


FIGURE 12. Major adverse cardiovascular events (MACE) during 2022 in the RRBR

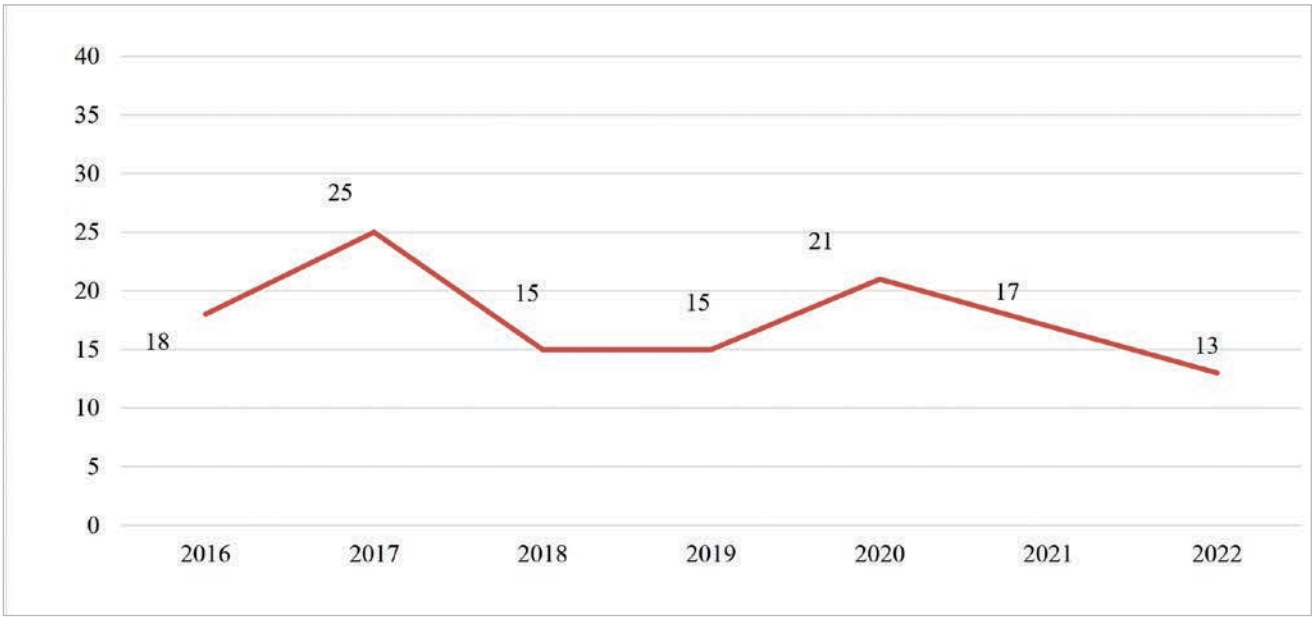


FIGURE 13. The solid malignancy number of events between 2016-2022 in the RRBR

cers 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 standardized 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

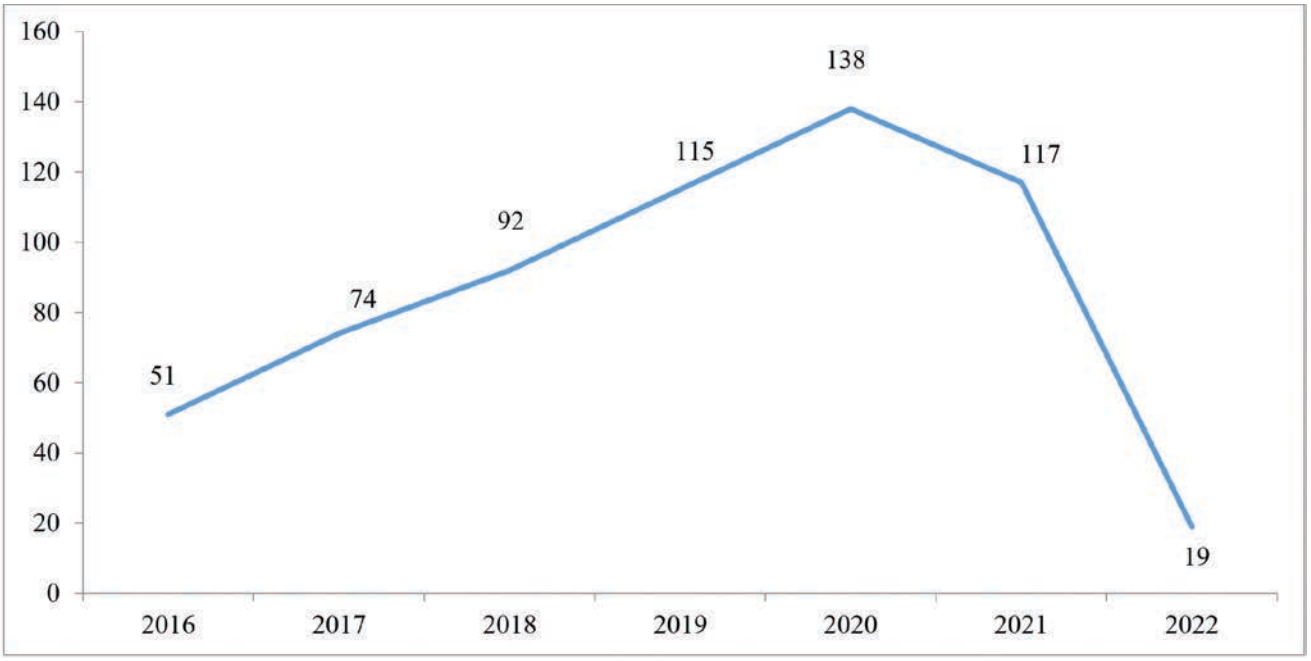


FIGURE 14. Mortality in the RRBR, expressed in reported number of events between 2016-2022

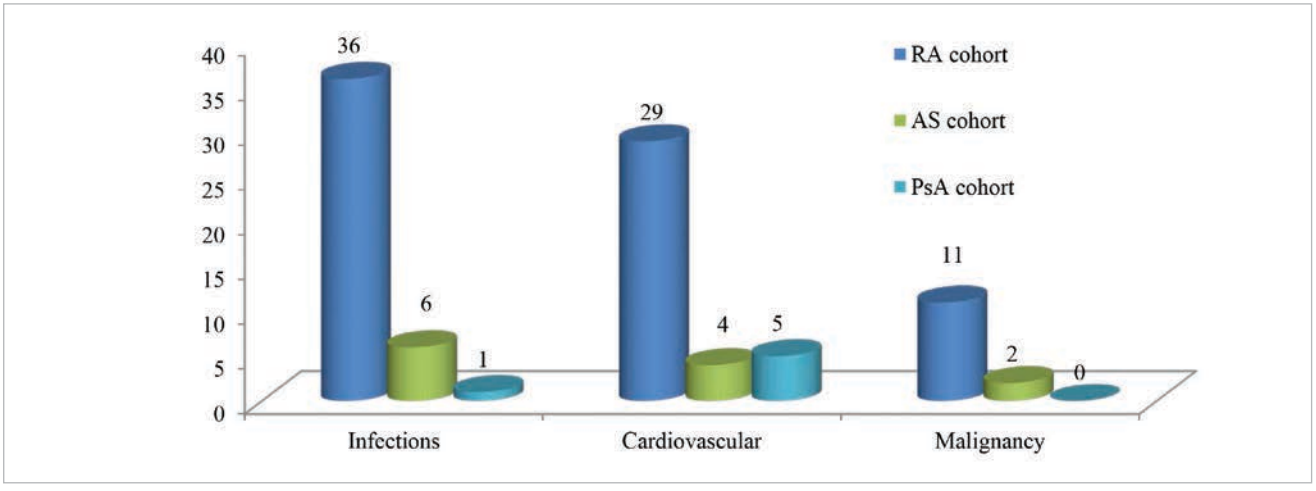


FIGURE 15. Top three all-cause known cause of mortality: number of events reported in the RRBR

elevated risk of mortality [23]. 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 standardized procedure

across registries with respect to AEs reporting, the RRBR follows the physician decision in registering an event or not. It is highly probable that not all AEs that really occurred are registered in the destinated section in the RRBR. This may modify the ratio 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

1. Pop B, Fetica B, Blaga ML, Trifa AP, Achimas-Cadariu P, Vlad CI, Achimas-Cadariu A. The role of medical registries, potential applications and limitations. *Med Pharm Rep*. 2019 Jan;92(1):7-14. doi: 10.15386/cjmed-1015. Epub 2019 Jan 15. PMID: 30957080; PMCID: PMC6448488.
2. Hazlewood GS, Bombardier C, Tomlinson G, Thorne C, Bykerk VP, Thompson A, et al. Treatment preferences of patients with early rheumatoid arthritis: a discrete-choice experiment. *Rheumatology* (Oxford). 2016 Nov;55:1959–68. doi: 10.1093/rheumatology/kew280. Epub 2016 Jul 31. PMID: 27477807
3. Aureal M, Seauve M, Laplane S, Lega JC, Cabrera N, Coury F. Incidence of infections in patients with psoriatic arthritis and axial spondyloarthritis treated with biological or targeted disease-modifying agents: a systematic review and meta-analysis of randomised controlled trials, open-label studies and observational studies. *RMD Open.* 2023 Sep;9(3):e003064. doi: 10.1136/rmdopen-2023-003064. PMID: 37714666; PMCID: PMC10510924.
4. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, et al.; BSRBR Control Centre Consortium; British Society for Rheumatology Biologics Register. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. *Rheumatology* (Oxford). 2011;50(1):124–31. doi: 10.1093/rheumatology/keq242. Epub 2010 Jul 31. PMID: 20675706; PMCID: PMC3105607.
5. Rutherford AI, Patarata E, Subesinghe S, Hyrich KL, Galloway JB. Opportunistic infections in rheumatoid arthritis patients exposed to biologic therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Rheumatology* (Oxford). 2018 Jun 1;57(6):997-1001. doi: 10.1093/rheumatology/key023. PMID: 29529307.
6. Munteanu I, Cioran N, van Hest R, Abubakar I, Story A, Chiotan D, et al. Tuberculosis Surveillance in Romania Among Vulnerable Risk Groups Between 2015 and 2017. *Ther Clin Risk Manag*. 2022 Apr 20;18:439-46. doi: 10.2147/TCRM.S347748. PMID: 35478731; PMCID: PMC9035834
7. Robert M, Miossec P. Reactivation of latent tuberculosis with TNF inhibitors: critical role of the beta 2 chain of the IL-12 receptor. *Cell Mol Immunol*. 2021 Jul;18(7):1644-51. doi: 10.1038/s41423-021-00694-9. Epub 2021 May 21. PMID: 34021269; PMCID: PMC8245521
8. Kosmaczewska A, Swierkot J, Ciszak L, Szteblich A, Chrobak A, Karabon L, et al. Patients with the most advanced rheumatoid arthritis remain with Th1 systemic defects after TNF inhibitors treatment despite clinical improvement. *Rheumatol Int.* 2014 Feb;34(2):243-53. doi: 10.1007/s00296-013-2895-9. Epub 2013 Nov 13. PMID: 24221190; PMCID: PMC3904036.
9. de Vries MK, Arkema EV, Jonsson J, Bruchfeld J, Jacobsson LTH, Askling J; ARTIS Study Group. Tuberculosis Risk in Ankylosing Spondylitis, Other Spondyloarthritis, and Psoriatic Arthritis in Sweden: A Population-Based Cohort Study. *Arthritis Care Res* (Hoboken). 2018 Oct;70(10):1563-1567. doi: 10.1002/acr.23487. Epub 2018 Sep 4. PMID: 29195024.
10. Lee SK, Kim SY, Kim EY, Jung JY, Park MS, Kim YS, et al. Mycobacterial infections in patients treated with tumor necrosis factor antagonists in South Korea. *Lung*. 2013 Oct;191(5):565-71. doi: 10.1007/s00408-013-9481-5. Epub 2013 Jun 1. PMID: 23728990.
11. Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A; B S R B R Control Centre Consortium; Symmons DP; BSR Biologics Register. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann Rheum Dis.* 2010 Mar;69(3):522-8. doi: 10.1136/ard.2009.118935. Epub 2009 Oct 22. PMID: 19854715; PMCID: PMC2927681.
12. https://www.who.int/europe/news/item/26-07-2018-universal-access-to-testing-and-treatment-is-key-to-eliminating-viral-hepatitis, accessed: 17 Dec 2023.
13. Mogosan C, Codreanu C, Predeteanu D, et al. Hepatitis B virus reactivation in a cohort of patients treated with biologics – data from the Romanian Registry of Rheumatic. *Ann Rheum Dis.*2019;78(Suppl2):A634.
14. Avouac J, Fogel O, Hecquet S, Daien C, Elalamy I, Picard F, et al.; on behalf of the French Society of Rheumatology. Recommendations for assessing the risk of cardiovascular disease and venous thromboembolism before the initiation of targeted therapies for chronic inflammatory rheumatic diseases. *Joint Bone Spine.* 2023 Sep;90(5):105592. doi: 10.1016/j.jbspin.2023.105592. Epub 2023 May 16. PMID: 37201575.
15. Wu X, Peng H, Wen Y, Cai X, Li C, Zhong R, et al. Rheumatoid arthritis and risk of lung cancer: meta-analysis and mendelian randomization study. Semin Arthritis Rheum. 2021 Jun;51(3): 565-575. doi: 10.1016/j.semarthrit.2021.03.015. Epub 2021 Apr 2. PMID: 33932788.
16. Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. *J Rheumatol.* 2005 Nov;32(11):2130–5. PMID: 16265690.
17. Egeberg A, Thyssen JP, Gislason GH, Skov L. Skin cancer in patients with psoriasis. *J Eur Acad Dermatol Venereol.* 2016 Aug;30(8):1349-53. doi: 10.1111/jdv.13619. Epub 2016 Mar 2. PMID: 26932589.
18. Dreyer L, Mellemkjær L, Andersen AR, Bennett P, Poulsen UE, Juulsgaard Ellingsen T, et al. Incidences of overall and site specific cancers in TNFα inhibitor treated patients with rheumatoid arthritis and other arthritides - a follow-up study from the DANBIO Registry. *Ann Rheum Dis.* 2013 Jan;72(1):79-82. doi: 10.1136/annrheumdis-2012-201969. Epub 2012 Sep 3. PMID: 22945500.
19. van Vollenhoven RF, Fleischmann RM, Furst DE, Lacey S, Lehane PB. Longterm Safety of Rituximab: Final Report of the Rheumatoid Arthritis Global Clinical Trial Program over 11 Years. *J Rheumatol.* 2015 Oct;42(10):1761-6. doi: 10.3899/jrheum.150051. Epub 2015 Aug 15. PMID: 26276965.
20. Wadström H, Frisell T, Askling J; Anti-Rheumatic Therapy in Sweden (ARTIS) Study Group. Malignant Neoplasms in Patients With Rheumatoid Arthritis Treated With Tumor Necrosis Factor Inhibitors, Tocilizumab, Abatacept, or Rituximab in Clinical Practice: A Nationwide Cohort Study From Sweden. *JAMA Intern Med.* 2017 Nov 1;177(11):1605-12. doi: 10.1001/jamainternmed.2017.4332. PMID: 28975211; PMCID: PMC5710271.
21. Huss V, Bower H, Hellgren K, Frisell T, Askling J; Behalf of the ARTIS group; behalf of the ARTIS group. Cancer risks with JAKi and

biological disease-modifying antirheumatic drugs in patients with rheumatoid arthritis or psoriatic arthritis: a national real-world cohort study. *Ann Rheum Dis.* 2023 Jul;82(7):911-19. doi: 10.1136/ard-2022-223636. Epub 2023 Mar 3. PMID: 36868796; PMCID: PMC10314043.

22. Dadoun S, Zeboulon-Ktorza N, Combescure C, Elhai M, Rozenberg S, Gossec L, Fautrel B. Mortality in rheumatoid arthritis over the last fifty years: systematic review and meta-analysis. *Joint Bone Spine.* 2013 Jan;80(1):29-33. doi: 10.1016/j.jbspin.2012.02.005. Epub 2012 Mar 27. PMID: 22459416.
23. Ogdie A, Haynes K, Troxel AB, Love TJ, Hennessy S, Choi H, Gelfand JM. Risk of mortality in patients with psoriatic arthritis, rheumatoid arthritis and psoriasis: a longitudinal cohort study. *Ann Rheum Dis.* 2014 Jan;73(1):149-53. doi: 10.1136/annrheumdis-2012-202424. Epub 2012 Dec 21. PMID: 23264338; PMCID: PMC3883139.
24. Codreanu C, Mogosan C, Predeteanu D, et al. Mortality Rate in patients treated with biologics: data from the Romanian Registry of Rheumatic Diseases. *Ann Rheum Dis.* 2019;78(Suppl2):A1394.