

Adverse events from the Romanian Registry of Rheumatic Diseases in patients treated with biologic and targeted synthetic disease-modifying anti-rheumatic drugs during 2019

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ABSTRACT

Background. The novel therapies in inflammatory rheumatic diseases have changed dramatically the evolution of these conditions, improving patient outcomes, as well as the quality of life. Nevertheless, the efficacy data continuously needs safety reports, on short and long term.

Aim. The present study reports adverse events (AEs) captured by the Romanian Registry of Rheumatic Diseases (RRBR, in Romanian), during 2019.

Methods. This observational study included all AEs reported in RRBR in 2019, the severity class, outcome and previous exposure to the therapeutic agent.

Results. For the active cohort of 9,255 patients that had at least one visit during 2019, there have been 934 reported AEs: 568 cases for rheumatoid arthritis (RA) patients, 291 cases for ankylosing spondylitis (AS) patients and 75 cases for psoriatic arthritis (PsA) patients. The most prevalent AEs were infections, especially in RA patients. Of all AEs, 102 (11%) were serious AEs, with an equal impact of 11% in RA and AS groups. A number of 25 deaths were reported during the last year.

Conclusion. AEs seem to be under-reported in the RRBR database, in accordance with literature data for registries which not do have a standardized method for AE reporting. This is an unmet need for safety data that also requires improving the knowledge about AE reporting requirements.

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

BACKGROUND

The requirements for methods to monitor the side-effects and any drug-related problem gained global attention in the early 1960's when the Australian doctor William McBride reported that thalidomide use in pregnancy was associated with birth defects (1).

Clinical registries may play an important role in the future monitoring of drug safety and efficacy. Registries are being recognised as an important mechanism in quality assurance in terms of being able to identify and detect high quality and poor performance in patient management involving the delivery of drugs or devices (2).

It is highly likely that registries will have an increasingly important role to play in post-marketing drug safety surveillance. Spontaneous reporting

schemes should continue to provide the opportunity for patients and healthcare professionals to voluntarily report adverse events, however, a systematic registry-based approach will facilitate our understanding of long-term safety outcomes in monitoring the incidence of events such as cancers. Randomised controlled trials remain the gold standard to provide evidence of efficacy; however, they are limited in their ability to inform on rare events and long-term safety. The increasing developments to harness the potential of electronic health records and record linkage may help to offset the major challenge associated with the costs of outcome data collection for long-term drug registry surveillance. However, further research into improving the quality of data collected through these mechanisms is required before they will become the mainstay of future safety surveillance programs (3).

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The Romanian Registry of Rheumatic Diseases (RRBR) is a prospective observational cohort study of biologic therapy starters in rheumatoid arthritis (RA) (since 2013), ankylosing spondylitis (AS) (since 2015) and psoriatic arthritis (PsA) (since 2015), without a comparator arm. The adverse events (AE) reports do not follow a mandatory standard of notification, being at the clinician’s decision of reporting. The following report aims to describe AEs reported during 2019 in the RRBR, in comparison with time trend distribution of all AEs.

METHODS

Data were gathered electronically from the RRBR database. The cohort included all active patients exposed to biologic and targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDs, tsDMARDs) at least once. An active patient refers to any case that has at least one visit uploaded in the RRBR during 2019.

RESULTS

From 2013 a total number of 12,215 patients were included, from which, during 2019, 9,255 patients had at least one visit reported, as follows: 4,755 RA patients, 3,651 AS patients and 849 PsA patients. The total number of AE reports since the release of RRBR is presented in Figure 1.

Evaluating the distribution of AEs for each condition, RA patients have the highest number of reports (Figure 2), which is relatively constant over the last 3 years.

During 2019, the distribution of AEs into severity classes is presented in Figure 3.

Serious AEs (SAEs) represents the most important category of all as it could imply severe consequences, such as permanent disability, prolonged hospitalization, life-threatening conditions or fatal events. During the last year, the RRBR has captured SAE in 11% of cases.

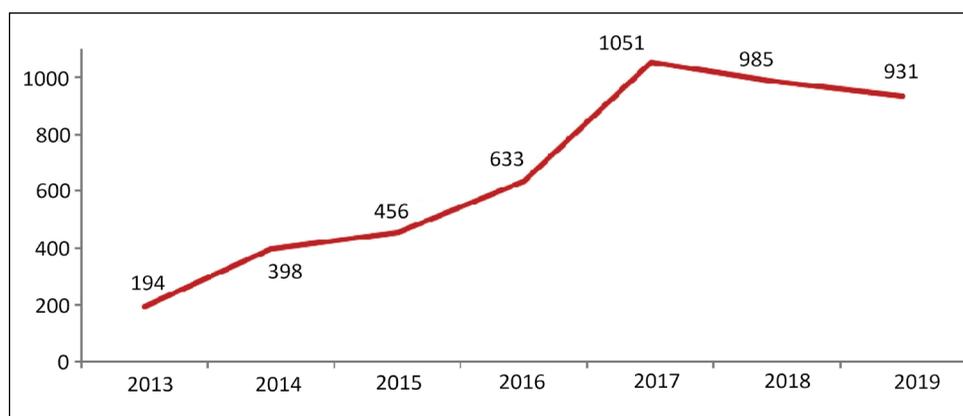
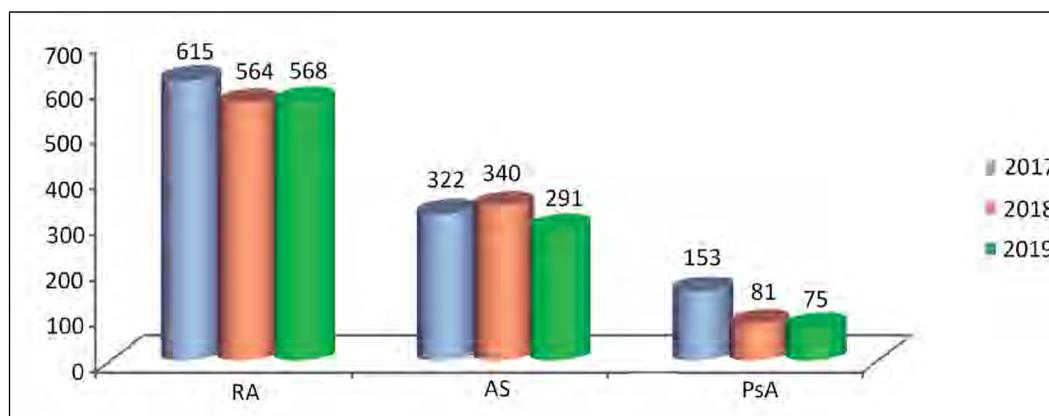


FIGURE 1. The total number of reported AEs in the RRBR in 2019



condition	RA			AS			PsA		
year	2017	2018	2019	2017	2018	2019	2017	2018	2019
number	4171	4407	4755	3187	3417	3651	804	832	849

FIGURE 2. Distribution of AEs during 2017-2019 in the RRBR

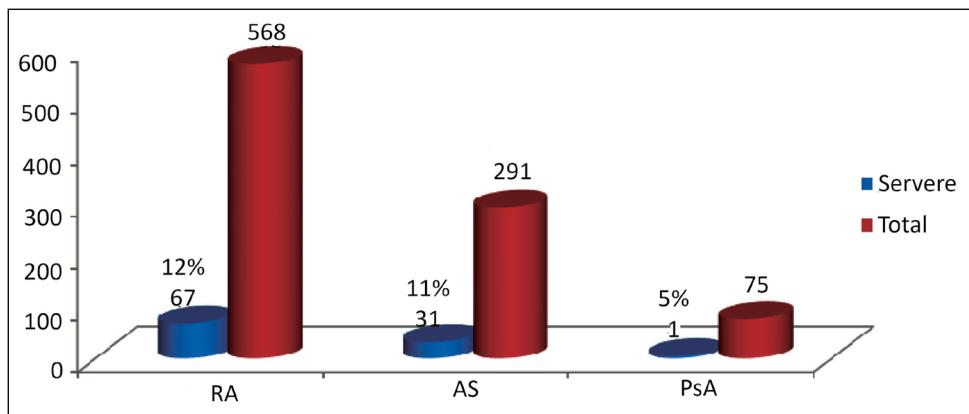


FIGURE 3. Severity classes of AEs in 2019 in RRBR

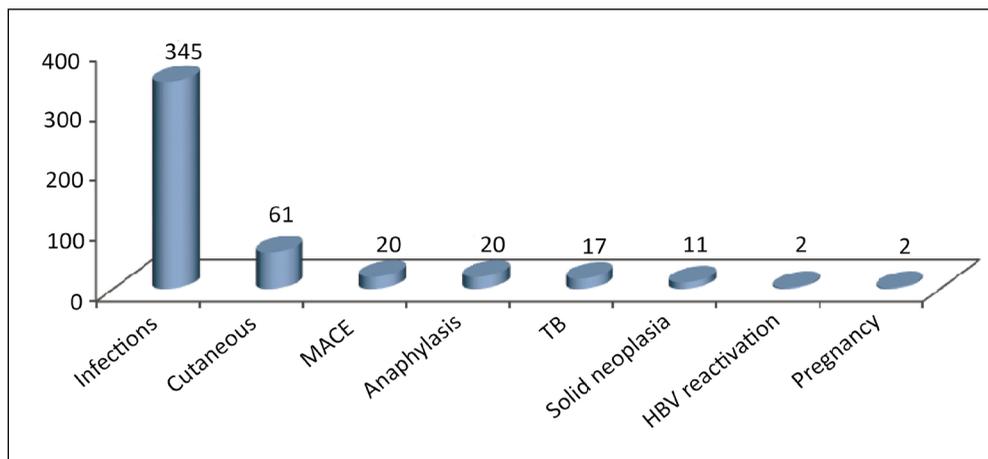


FIGURE 4. The most frequently reported AEs in RRBR in 2019. MACE (major adverse cardiovascular events): heart failure (n = 9), stroke (n = 4), acute coronary events (n = 7)

Classification of all reported AEs in 2019 is displayed in Figure 4 and Table 1.

Infections were reported most frequently (38%), as in previous years, followed by cutaneous AEs (6.5%), major adverse cardiovascular events (2%), anaphylaxis (2%), tuberculosis (1.8%), solid neoplasia (1.1%) and rare cases of hepatitis B infection and pregnancy (2 cases each). Respiratory infection was the most frequent (52%), followed by the urinary tract infections (21%) and skin infections (9.5%). 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 (4). As expected, RA patients experienced more severe infections, followed by AS, while there were no severe infections in the PsA group (Figure 5).

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 (5,6).

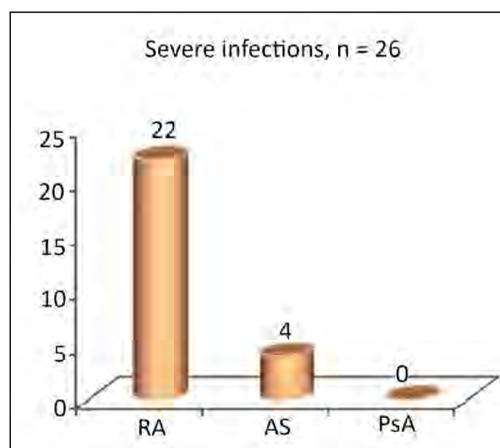


FIGURE 5. Severe infections reported in RRBR in 2019

From all serious infections registered in the RRBR during 2019, 77% were related to TNF inhibitors: etanercept (n = 7), adalimumab (n = 6), certolizumab (n = 3), infliximab (n = 3), golimumab (n = 1). There were 9 cases of herpes zoster, namely 6 cases in patients on TNF inhibitors and 3 cases in patients on tsDMARDs.

An infection that appears to have a clear differential risk across available TNF inhibitors is tuberculosis. 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 and investigation in any patient with symptoms suggestive of active tuberculosis regardless of their pre-b/tsDMARD screening results. The risk of tuberculosis reactivation appears lower in etanercept-treated patients compared with the monoclonal antibodies such as infliximab and adalimumab, as observed in several studies (7,8). In 2019, a number of 17 cases of tuberculosis were reported in the RRBR: 8 cases in RA patients, 7 cases in AS patients and 2 cases in PsA patients. Regarding clinical manifestations, 16 cases (94%) had pulmonary tuberculosis and only 1 case had extra-pulmonary tuberculosis. Of the 17 cases of tuberculosis, 12 cases (70%) were treated with TNF inhibitors (5 patients on adalimumab, 4 patients on golimumab, 2 patients on etanercept, 1 patient on infliximab) and 5 cases with bDMARDs with other modes of action: 3 patients on secukinumab and 2 patients on tocilizumab. Of all

tuberculosis patients, 3 cases had prophylactic treatment with isoniazid (before bDMARD start). The tuberculosis rate varied during the last 4 years in RRBR, as depicted in Figure 6.

Accompanying the increased use of biological and non-biological antirheumatic drugs, a greater number of cases of hepatitis B virus (HBV) reactivation have been reported in inactive hepatitis B surface antigen (HBsAg) carriers and also in HBsAg-negative patients who had cured HBV infections (9). Romania has a high prevalence for HBV infection: according to a national epidemiological study conducted in 2013, 27.9% of Romanians have serological markers of resolved HBV infection, while 4.2% are inactive carriers of HBsAg (10). A recent reported on HBV reactivation in RRBR revealed that HBV reactivation appeared more often on a resolved infection state, especially without antiviral prophylaxis, without any cases of fulminant hepatitis. Most RA cases developed HBV reactivation when exposed to rituximab, while in the AS group all HBV reactivations appeared in patients exposed to TNF inhibitors, while HBV reactivation in the PsA cohort had a very low rate (11). In 2019,

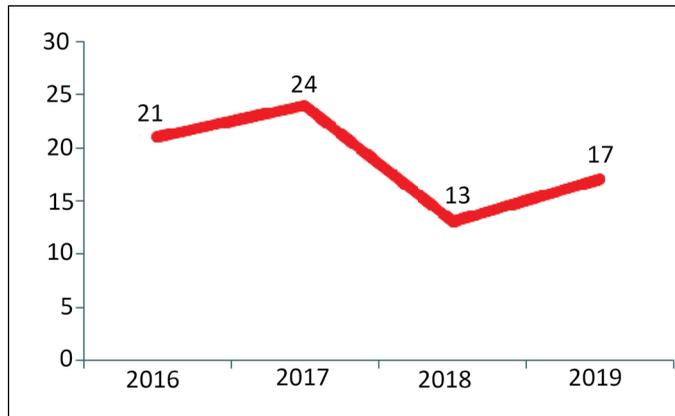


FIGURE 6. Tuberculosis rates during 2016-2019 in the RRBR

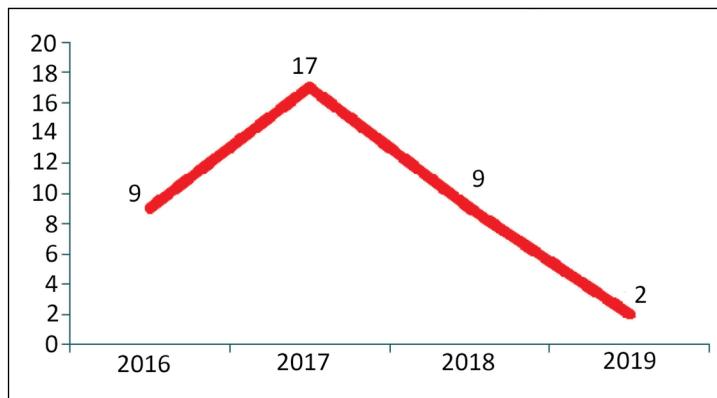


FIGURE 7. Hepatitis B virus reactivation rate during 2016-2019 in the RRBR

there were only 2 cases on HVB reactivation, both in AS patients previously exposed to etanercept. The HBV reactivation rate during 2016-2019 is presented in Figure 7.

RA is associated with increased risk of cardiovascular events and mortality, which is partly attributed to systemic inflammation that promotes premature atherosclerosis (12). According to a recent systematic literature review and meta-analysis, compared to TNF inhibitors, tocilizumab may be associated with reduced risk of major adverse cardiovascular events (MACE), whereas csDMARDs may be associated with increased risk of MACE and stroke (13). In the RRBR, MACE category comprises heart failure, stroke and acute coronary events. In 2019, there were 20 MACE reported, mostly in RA patients, as presented in Figure 8. Of all reported MACE, 11 (55%) cases were exposed to TNF inhibitors, while the rest were exposed to rituximab (n = 5), secukinumab (n = 2), abatacept (n = 1) and baricitinib (n = 1).

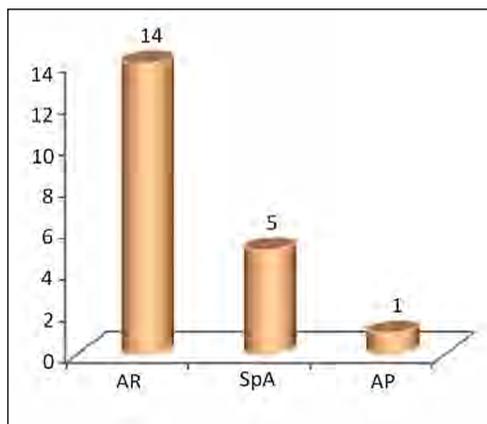


FIGURE 8. Major adverse cardiovascular events (MACE) during 2019 in the RRBR

Considering the continuous widespread use of biological agents to treat chronic inflammatory conditions, and the concern that immunomodulation may alter cancer risk and progression, the limited available data on use of these therapies as used in clinical practice and cancer risks are a concern. According to a nationwide cohort study from Sweden, the overall risk of cancer among RA patients initiating TNF inhibitors as first or second bDMARDs, tocilizumab, abatacept, or rituximab does not differ substantially from that of biologic-naïve patients, csDMARD-treated patients with RA, although altered risks for specific cancer types, or those with longer latency, cannot be excluded, with the possible exception of an increased risk of squamous cell skin

cancer risk in patients treated with abatacept (14). Since RRBR registers AEs, a number of 94 cases of solid malignancy were diagnosed during exposure to biologic agents. Breast cancer is the most frequently reported cancer, with 17(18%) cases. Non-melanoma skin cancer is the second cancer type reported in the RRBR, with a total of 13 (14%) cases, followed by lung cancer with 12 (13%) reports. Of these, 11 solid neoplasms were reported during 2019, with the following localizations: breast cancer (n = 3), genital cancer (n = 2), lung cancer (n = 2), kidney cancer (n = 1), skin cancer (n = 1), larynx cancer (n = 1) and central nervous system cancer (n = 1). These events were reported in patients who were previously treated with TNF inhibitors (n = 7, 64%), tocilizumab (n = 1), baricitinib (n = 1) and rituximab (n = 1).

It was documented that RA is associated with increased mortality, with 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 (15). In contrast, information on mortality in AS is scarce, whereas there are conflicting reports of the mortality risk among patients with PsA, although it is accepted that patients with PsA do not have a significantly elevated risk of mortality (16). A recent study conducted with RRBR data revealed that RA patients have a higher mortality risk compared to AS and PsA patients (17).

To date, there were 117 all-cause deaths reported in the RRBR, while during 2019 there were 25 fatal events reported. The evolution of mortality rates in patients treated with biologics for rheumatic diseases is displayed in Figure 9.

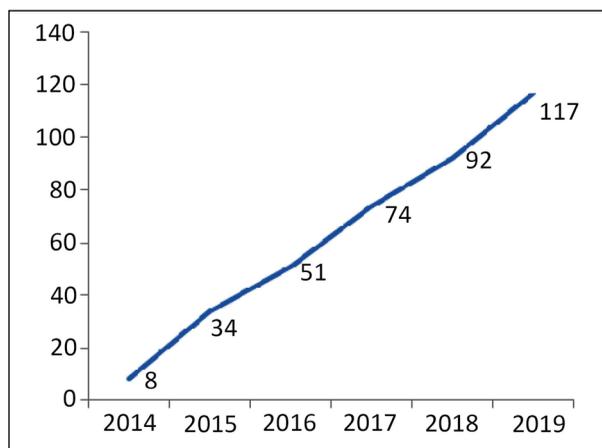


FIGURE 9. Mortality rate in RRBR, expressed in reported number of events

All-cause mortality is detailed in Figure 10. In accordance with literature data, the mortality rate in

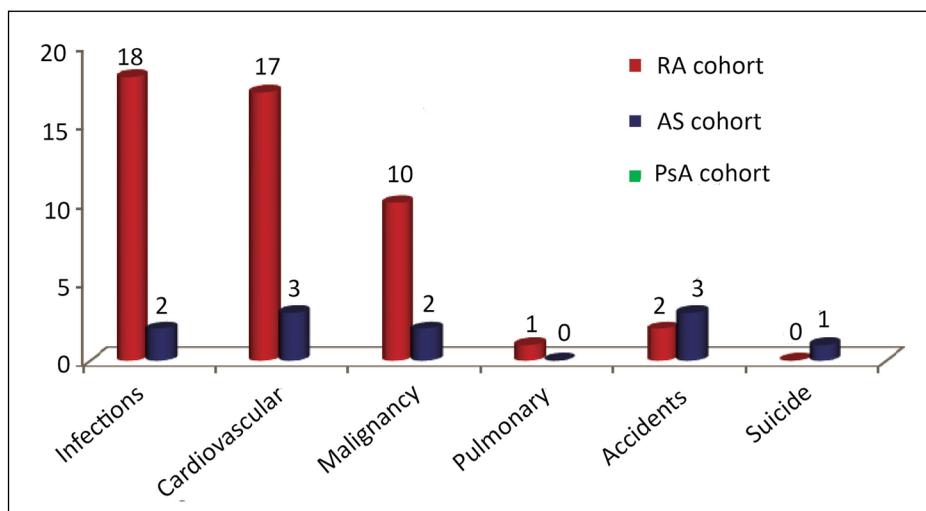


FIGURE 10. All-cause mortality rates reported in the RRBR. Deaths of unknown cause: RA – 49 cases (50%); AS – 5 cases (37%); PsA – 4 cases (100%)

RA is higher compared to other inflammatory diseases treated with biologics. Infections and cardiovascular events are equally reported as causes of death for RA patients. It is also noted that for RA patients 50% of all-cause mortality is of unknown cause, whereas for AS patients the rate of unknown causes of death is 37% and 100% for the PsA cohort.

Other categories of AEs are presented in Table 1, all being with mild severity.

TABLE 1. Other categories of AEs reported in 2019 in the RRBR

AE	RA	AS	PsA	total
metabolic	35	24	5	64
cardiovascular (non-MACE)	28	24	5	57
hepatobiliary	21	9	12	43
haematological	32	6	3	41
gastro-intestinal	18	17	0	35
musculo-skeletal	24	3	4	31
pulmonary	22	3	3	2
ocular	11	14	0	25
renal	15	9	0	24
dermatological	18	1	0	19
endocrine	6	4	3	13
psychiatrically	7	4	1	12
urological	3	5	1	9
ENT	5	2	0	7
gynaecological	2	1	0	3
immune	1	0	0	1

AE – adverse event; AS – ankylosing spondylitis; ENT – ear, nose, throat; MACE – adverse cardiovascular events; PsA – psoriatic arthritis; RA – rheumatoid arthritis, RRBR – Romanian Registry of Rheumatic Diseases

There are several limitations which can influence the significance of this report. One of the limitations of the current report is most probably related to the

insufficient number of reports for all AEs that occurred in RRBR, which makes, on one hand, all the figures seem smaller, and, on the other hand, it creates a disproportion in the severity class of all reported events. Efforts are needed to improve the unmet goal of collecting as much information as possible for all AEs.

Timely reporting and follow-up as necessary of AEs is a requirement described in the Good Pharmacovigilance Practices (Module 6) for marketing authorisation holders in case of post-authorisation studies based on primary data collection. This requirement cannot be fulfilled if applies to a registry. Moreover, there is no legal obligation to force investigators to report adverse drug reactions or to track patients. In some registries, such as EBMT (for haematopoietic transplant procedures) and Pharmachild (for juvenile idiopathic arthritis), processes have been put in place to inform investigators about the spontaneous reporting of AEs, but there is no standardised procedure across registries. In some cases, this is due to a lack of knowledge about reporting requirements (18).

CONCLUSIONS

The number of reports for AEs is stable over the last years. Most AEs were reported for RA patients, in all severity classes. Importantly, the rate of infections, including SAE and the rate of MACE, is more frequently related to the RA group, compared to AS and PsA patients. This is not surprising, considering the heterogenous inflammation pattern of the disease and the increased risk for infections and for cardio-

vascular events of the disease *per se*. Tuberculosis remains a great concern, for all diseases, especially related to TNF inhibitors. Given the high prevalence of HBV infection in our country, from the perspective of HBV reactivation, apparently there is a decrease in the number of cases over the last years. This could be related to better screening and monitoring of patients. The first two causes of mortality are represented by infections and cardiovascular

events; mortality rate is higher in RA patients, compared to the AS and PsA groups. The fact that AEs seem to be under-reported in the RRB database is accordance with literature data for registries which not do have a standardized method for AE reporting. This is an unmet need for safety data that also requires improving the knowledge about AE reporting requirements.

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