# Characterising infusion/injection-related reactions in patients with rheumatoid arthritis treated with biologic agents

J.-W. Kim[1], S.-K. Lee[2], K. Shin[3], J.-Y. Jung[1], C.-H. Suh[1], J. Kim[4], H.-A. Kim[1]

*[1]Department of Rheumatology, Ajou University School of Medicine, Suwon; [2]Department of Mathematics, College of Natural Sciences, Hanyang University, Seoul; [3]Division of Rheumatology, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul; [4]Division of Rheumatology, Department of Internal Medicine, College of Medicine, Chungnam National University, Daejeon, Republic of Korea.*

## Abstract

### Objective

*Biologic disease-modifying anti-rheumatic drugs (bDMARDs) have transformed the management of rheumatoid arthritis (RA), but their efficacy can be limited by infusion/injection-related reactions (IRRs). This study investigated demographic and clinical factors associated with IRRs in patients with RA using data from the Korean College of Rheumatology Biologics & Targeted Therapy (KOBIO) Registry.*

### Methods

*We analysed 1,832 patients with RA, categorising them into IRR and non-IRR groups. Demographic, disease characteristics, and treatment histories were compared. A Sankey plot visualised bDMARD switching patterns, and multivariable logistic regression identified IRR-independent predictors.*

### Results

*IRRs occurred in 9.7% of patients and were significantly associated with younger age (mean 49.9 vs. 54.9 years; OR=1.793, p=0.014), secondary Sjögren's syndrome (OR=2.175, p=0.035), and prior leflunomide use (OR=1.497, p=0.015). Abatacept (OR=0.263, p<0.001), tocilizumab (OR=0.419, p<0.001), and golimumab (OR=0.345, p=0.006) were associated with reduced IRR risk compared to infliximab. Following IRRs, use of etanercept, infliximab, and adalimumab declined, while tocilizumab and Janus kinase (JAK) inhibitors increased.*

### Conclusion

*IRRs are common among RA patients receiving bDMARDs, particularly in younger individuals or those with prior leflunomide use. Abatacept, tocilizumab, and JAK inhibitors represent safer alternatives, underscoring the need for individualised treatment strategies.*

**Key words**

rheumatoid arthritis, infusion/injection-related reactions, adverse reaction

*Ji-Won Kim, MD**
*Sun-Kyung Lee, PhD**
*Kichul Shin, MD, PhD*
*Ju-Yang Jung, MD, PhD*
*Chang-Hee Suh, MD, PhD*
*Jinhyun Kim, MD, PhD*
*Hyoun-Ah Kim, MD, PhD*

**Contributed equally.*

*Please address correspondence to:*
*Hyoun-Ah Kim*
*Department of Rheumatology,*
*Ajou University School of Medicine,*
*164 Worldcup-ro,*
*Yeongtong-gu,*
*Suwon 16499, Republic of Korea.*
*E-mail: nakhada@naver.com*
*ORCID iD: 0000-0003-2609-3347*

*Received on January 13, 2025; accepted in revised form on April 4, 2025.*



*Funding: this study was supported by a grant from Celltrion Corporation.*
*Competing interests: none declared.*

## Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by persistent synovial inflammation and progressive joint destruction, leading to significant disability and impaired quality of life. The pathogenesis of RA involves a complex interplay of genetic, environmental, and immunological factors, resulting in aberrant activation of the immune system and subsequent joint and organ damage (1). In recent decades, biologic disease-modifying anti-rheumatic drugs (bDMARDs) have revolutionised RA management, providing new hope for patients unresponsive to conventional synthetic DMARDs. bDMARDs effectively disrupt the inflammatory cascade by targeting specific immune system components, such as tumour necrosis factor (TNF), interleukins, and B cells (2, 3).

Despite their effectiveness, all bDMARDs administered intravenously or subcutaneously have a risk of infusion/injection-related reactions (IRRs) (4). These adverse events occur during or shortly after infusion and can range from mild symptoms such as fever, chills, and rash to severe reactions such as anaphylaxis, hypotension, and bronchospasm. Typically, IRRs are acute, with most reactions manifesting within minutes to hours of administration (5). While the majority of IRRs are mild to moderate and can be effectively managed with interventions such as reducing the infusion rate, premedication, or symptomatic treatment, severe IRRs, though less common, can be life-threatening and necessitate emergent medical intervention (6).

The incidence and severity of IRRs can vary depending on the specific bDMARD and the individual risk factors of patients (7). Previous studies indicated that some bDMARDs, particularly chimeric ones, have a higher propensity for inducing IRRs due to their immunogenic potential (8). Efforts to reduce the immunogenicity of chimeric antibodies have focused on partially or completely removing murine sequences to develop fully human or humanised monoclonal antibodies (9). Despite these improvements, patients continue to discontinue medications due to IRRs, and serious IRR rates in some bDMARDs are reported to occur more frequently in real-world data than in clinical trial reports (10). Understanding the precise mechanisms underlying IRRs and identifying predisposing factors are critical for optimising bDMARDs in clinical practice. Therefore, we used data from the Korean College of Rheumatology Biologics & Targeted Therapy (KOBIO) Registry to investigate the demographic and clinical characteristics of patients with RA with and without IRRs. Furthermore, we sought to identify factors associated with IRRs and examine their influence on treatment patterns.

## Materials and methods

### *Study population*

The KOBIO Registry is a nationwide, multicentre, web-based, observational cohort study launched in 2012 (11). Patients with RA (aged ≥19 years) who met the 1987 American College of Rheumatology (ACR) or 2010 ACR/European League Against Rheumatism RA classification criteria and initiated or switched to bDMARDs or targeted synthetic DMARDs were enrolled in South Korea (KOBIO-RA) (12, 13). The patients underwent annual follow-up assessments conducted by individual investigators.

From the 2,916 individuals registered in the KOBIO Registry until 19th June 2023, we selected an eligible population of 2,453 patients. Exclusions comprised 303 who were lost at follow-up and 160 who withdrew consent. Among these, 185 individuals with recorded adverse events related to IRR were categorised into the IRR group, with the remaining 2,268 classified into the non-IRR group. To maintain study integrity, we excluded Janus kinase (JAK) inhibitors from the analysis due to their limited relevance to IRR and potential bias to overall results. In the IRR group, we excluded cases where JAK inhibitors were implicated as causative agents (6 cases). Similarly, in the non-IRR group, we excluded cases involving the use of JAK inhibitors (549 cases) and those with unknown follow-up periods (Supplementary Fig. S1).

*Definition of infusion/injection-related reactions*

The KOBIO Registry adopted the Medical Dictionary for Regulatory Activities (MedDRA) to facilitate reporting adverse events, allowing researchers to select preferred terms online easily (11). IRRs were defined as reactions involving rash, urticaria, or systemic symptoms related to injection or infusion. The severity of IRRs was classified into three grades: mild/grade 1, moderate/grade 2, and severe/grade 3. Mild/grade 1 IRRs involve symptoms that are present but tolerable, do not interfere with daily activities, and are transient without needing treatment or medical intervention. Moderate/grade 2 IRRs cause mild discomfort and interfere with daily activities, but they usually improve with simple treatment. Severe/grade 3 IRRs significantly limit daily activities, typically require systemic drug therapy or medical intervention and often necessitate hospitalisation and functional assistance. Our study utilised data from the KOBIO Registry, which collects adverse event data using predefined criteria specifically established for consistent classification of IRRs.

Adverse events during treatment were defined and evaluated using the MedDRA (version 20.0 [Maintenance and Support Services Organisation, McLean, VA, USA]); those occurring in the interim periods between assessments were also included.

*Data collection*

Clinical information of the enrolled patients was collected from data uploaded to the KOBIO web server (http://www.rheum.or.kr/kobio/) between December 2012 and June 2023. Demographic data, previous or current medications, comorbidities, and extra-articular manifestations were extracted. Laboratory data collected included rheumatoid factor, anti-cyclic citrullinated peptide antibody positivity, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), haemoglobin, and haematocrit. Evaluation of tender and swollen joint counts, pain visual analogue scale score, and patient and physician global assessment scores were done at initiation or switch of bDMARDs and at each 1-year follow-up visit. Quantitative measurements of RA disease progression, such as disease activity scores of 28 joints (DAS28) based on ESR and CRP and the clinical disease activity index (CDAI), were calculated. Information on comorbidities or extra-articular manifestations was obtained from the KOBIO data.

**Table I.** Demographic and clinical characteristics comparison between RA with IRR and RA without IRR in the KOBIO registry.

| Variable | Total (n=1,832) | IRR (n=179) | No IRR (n=1,653) | *p*-value |
|---|---|---|---|---|
| Demographics | | | | |
| Age, years | 56 [46, 64] | 52 [41, 59] | 56 [47, 64] | **<0.001** |
| Sex, n (%) | | | | 0.337 |
| Male | 324 (17.7) | 27 (15.1) | 297 (18.0) | |
| Female | 1,508 (82.3) | 152 (84.9) | 1,356 (82.0) | |
| BMI, median [IQR] | 22.5 [20.4, 24.7] | 22.5 [20.1, 24.3] | 22.5 [20.4, 24.8] | 0.444 |
| Smoking, n (%) | | | | 0.335 |
| Ex-smoker | 179 (9.8) | 23 (12.9) | 156 (9.4) | |
| Current smoker | 140 (7.6) | 14 (7.8) | 126 (7.6) | |
| Never | 1,513 (82.6) | 142 (79.3) | 1,371 (82.9) | |
| Comorbidities, n (%) | | | | |
| Diabetes mellitus | 225 (12.3) | 15 (8.4) | 210 (12.7) | 0.094 |
| Hypertension | 566 (30.9) | 48 (26.8) | 518 (31.3) | 0.214 |
| Cardiovascular disease | 456 (24.9) | 39 (21.8) | 417 (25.2) | 0.312 |
| Cancer | 9 (0.5) | 2 (1.1) | 7 (0.4) | 0.217 |
| Extraarticular manifestations, n (%) | | | | |
| Scleritis or episcleritis | 2 (0.1) | 0 (0.0) | 2 (0.1) | >0.999 |
| Secondary Sjögren's syndrome | 64 (3.5) | 10 (5.6) | 54 (3.3) | 0.108 |
| Subcutaneous rheumatoid nodule | 45 (2.5) | 8 (4.5) | 37 (2.2) | 0.075 |
| Cutaneous vasculitis | 4 (0.2) | 0 (0.0) | 4 (0.2) | >0.999 |
| Pleuritis | 6 (0.3) | 0 (0.0) | 6 (0.4) | >0.999 |
| Interstitial lung disease | 109 (6.0) | 5 (2.8) | 104 (6.3) | 0.060 |
| Disease status | | | | |
| Disease duration, years, median [IQR] | 5.2 [1.6, 11.5] | 4.7 [1.4, 10.7] | 5.3 [1.7, 11.6] | 0.408 |
| RF positivity, n (%), (n=1,762) | 1,463 (83.0) | 146 (82.5) | 1,317 (83.1) | 0.839 |
| Anti-CCP Ab positivity, n (%), (n=1,540) | 1,309 (85.0) | 125 (82.8) | 1,184 (85.2) | 0.421 |
| Tender joint count, median [IQR] | 7 [4, 12] | 7 [4, 12] | 7 [4, 12] | 0.900 |
| Swollen joint count, median [IQR] | 6 [3, 10] | 5 [3, 10] | 6 [3, 10] | 0.931 |
| Patient global assessment, median [IQR] | 7 [6, 8] | 7 [6, 8] | 7 [6, 8] | 0.624 |
| Physician global assessment, median [IQR] | 7 [5, 8] | 7 [5, 8] | 7 [5, 8] | 0.253 |
| ESR, mm/hr, median [IQR] | 45 [28, 66] | 41 [26, 59] | 45 [29, 67] | 0.075 |
| CRP, mg/dL, median [IQR] | 1.3 [0.5, 2.9] | 1.1 [0.2, 2.4] | 1.3 [0.5, 2.9] | **0.009** |
| DAS28-ESR, median [IQR] | 5.5 [5.0, 6.3] | 5.5 [5.0, 6.2] | 5.5 [5.0, 6.3] | 0.521 |
| DAS28-CRP, median [IQR] | 4.9 [4.2, 5.6] | 48 [4.1, 5.5] | 4.9 [4.2, 5.6] | 0.317 |
| SDAI, median [IQR] | 27.7 [21.4, 36.1] | 26.9 [21, 36.1] | 27.7 [21.4, 36.1] | 0.712 |
| CDAI, median [IQR] | 25 [20, 34] | 25 [19, 34] | 25 [20, 34] | 0.857 |
| Radiographic erosions, n (%) (n=1,281) | 713 (55.7) | 72 (54.1) | 641 (55.8) | 0.709 |
| Function | | | | |
| RAPID3, median [IQR] | 15.7 [11.3, 19.3] | 14.7 [11, 19.3] | 15.7 [11.3, 19.3] | 0.472 |

Values are expressed as number (%) or median [interquartile range (IQR)].
RA: rheumatoid arthritis; IRR: infusion/injection-related reaction; KOBIO: Korean College of Rheumatology Biologics Registry; BMI: body mass index; RF: rheumatoid factor; Anti-CCP Ab: anti-cyclic citrullinated peptide antibody; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; SDAI: Simplified Disease Activity Index: CDAI: Clinical Disease Activity Index; RAPID3: routine assessment of patient index data 3.

*Ethics approval*

Ethics approval for the KOBIO Registry was provided by the institutional

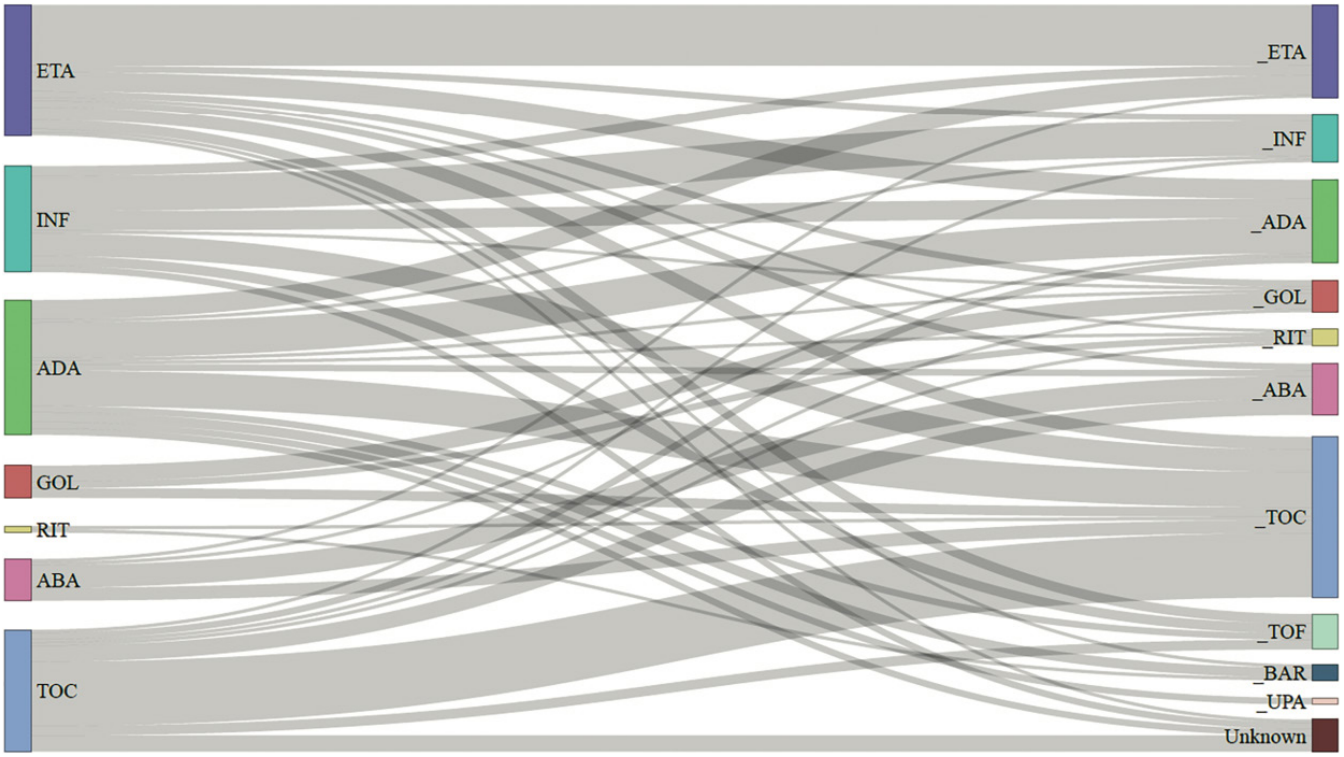


**Fig. 1.** Sankey plot illustrating the biologic usage patterns at the time of infusion-related reaction occurrence in the infusion-related group. Sankey plot visualises the flow of biologic drug usage patterns among patients who experienced infusion-related reactions (IRRs) within the IRR group. The plot illustrates transitions between different biologics when IRRs occurred, highlighting changes in treatment strategies following these events. Instances where subsequent follow-up data or biologic usage information was unavailable are denoted as 'unknown'.
ETA: etanercept, INF: infliximab, ADA: adalimumab, GOL: golimumab, RIT: rituximab, ABA: abatacept, TOC: tocilizumab, JAK: JAK inhibitors, TOF: tofacitinib, BAR: baricitinib, UPA: upadacitinib

review boards (IRBs) of all the 58 participating institutions. Ethics approval for this study and the use of KOBIO Registry data was provided by the IRB of the researchers' affiliated hospitals (AJOUIRB-DB-2023-410). This study was conducted in compliance with the principles of the Declaration of Helsinki. All the patients provided written informed consent to participate in the study.

*Statistical analysis*

Baseline demographic and clinical characteristics distinguishing between continuous and categorical variables were compared. Normality of continuous variables was assessed using the Shapiro-Wilk test, and as none of the variables satisfied the normality assumption, we applied non-parametric methods (*e.g.* Mann-Whitney U-test) for all comparisons. Continuous variables are presented as median [IQR], consistent with the non-parametric approach. Categorical variables were assessed using Chi-square or Fisher's exact test, with frequencies presented as counts and percentages.

The biological usage frequencies at the time points when adverse events related to IRRs occurred, along with subsequent administrations of biologics, are summarised in Table I. A Sankey plot (Fig. 1) was used to illustrate patterns of changes in biologic usage. Instances where there was no follow-up after IRR or information about subsequent biologics was unavailable were annotated as 'unknown'.

Logistic regression analysis was conducted to identify IRR risk factors. Continuous variables, such as CRP, ESR, and Physician's Global Assessment of Disease Activity, were binarised based on their respective third quartiles. Multivariable models included variables with $p$-values <0.2 from univariable models. Biologics included in the model were defined as medications contributing to the IRR occurrence in the IRR group and as drugs used at enrolment in the non-IRR group. We assessed multicollinearity using the Variance Inflation Factor (VIF) and the Condition Index (CI). All VIF values were below the commonly used threshold of 10, and the CI did not indicate any substantial concerns regarding multicollinearity. Based on these results, we conclude that multicollinearity does not significantly affect model stability. The corresponding VIF and CI values are presented in Supplementary Table S1.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and R 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). A $p$-value <0.05 was considered statistically significant.

## Results

*Participant demographics and clinical characteristics*

The study enrolled 1,832 participants, who were classified into two groups based on the presence of IRRs. There were 179 and 1,653 participants in the IRR and non-IRR groups, respectively. Demographic and clinical characteris-

tics of the participants are summarised in Table I. The mean age of participants in the IRR group was significantly lower than in the non-IRR group (median 52 [41, 59] *vs*. 56 [47, 64], $p<0.001$). Both groups had a similar sex distribution, body mass index, smoking status, and prevalence of comorbidities, such as diabetes mellitus, hypertension, and cardiovascular disease.

The IRR group had a significantly lower CRP level than the non-IRR group (1.1 [0.2–2.4] mg/dL *vs*. 1.3 [0.5–2.9] mg/dL, $p=0.009$). Other clinical measures, including ESR, DAS28, DAS28-CRP, Simplified Disease Activity Index, and Clinical Disease Activity Index, had no significant differences between the groups.

*Coexisting symptoms and prognosis*

Coexisting symptoms and patient prognosis following IRRs are summarised in Table II. Most reactions were mild to moderate in severity, with severe cases being relatively rare (2.8%). Within the study cohort, 83 individuals (46.4%) experienced immediate IRRs within 24 h of receiving biologics. Only five patients (2.8%) required hospitalisation. The most common types of IRRs were skin-related, with 126 patients (70.4%) with skin rash. Specific types of rashes included generalised urticaria (29.6%), injection site rash or swelling (31.3%), drug rash with eosinophilia and systemic symptoms (DRESS) (6.1%), and angioedema (3.4%). Other notable reactions included itching (7.3%), chest discomfort (7.3%), fever (2.8%), arthralgia (3.4%), and nausea/vomiting (2.8%). Less common but significant adverse reactions included anaphylaxis (1.1%) and arrhythmia/tachycardia (1.1%). There were isolated reports of abdominal pain (1.1%), headache or dizziness (1.1%), and numbness (0.6%).

*Drug administration patterns*

Patterns of drug administration before and after the occurrence of IRRs in the IRR group are presented in Table III. The median duration from the initiation of biologic therapy to the onset of an IRR was 3 months, with an IQR of 1–10 months. Before the onset of IRRs, the most used biologics were etanercept (22.9%), adalimumab (23.5%), and tocilizumab (21.2%). Following an IRR, there was a noticeable switch in biologic therapy, with tocilizumab (27.9%) and adalimumab (14.5%) being the most frequently selected options.

**Table II.** Coexisting symptoms and prognosis of patients with IRR.

| | Infusion/injection-related reactions (n=179) |
|---|---|
| Severity, n (%) | |
| Mild/Grade I | 100 (55.9) |
| Moderate/Grade II | 74 (41.3) |
| Severe/Grade III | 5 (2.8) |
| Occurrence within 24 hours, n (%) | 83 (46.4) |
| Infusion number at reaction, n (%) | |
| 1 | 67 (37.4) |
| 2 | 18 (10.1) |
| 3 | 20 (11.2) |
| 4 | 16 (8.9) |
| 5 | 5 (2.8) |
| ≥6 | 45 (25.1) |
| missing | 8 (4.5) |
| Hospitalisation, n (%) | 5 (2.8) |
| Discontinue medication, n (%) | 129 (72.1) |
| Types of reaction, n (%) | |
| Skin rash | 126 (70.4) |
| Generalised urticaria | 53 (29.6) |
| Infusion/injection site rash, swelling | 56 (31.3) |
| DRESS syndrome | 11 (6.1) |
| Angioedema | 6 (3.4) |
| Fever | 5 (2.8) |
| Itching | 13 (7.3) |
| Nausea/vomiting | 5 (2.8) |
| Chest discomfort | 13 (7.3) |
| Anaphylaxis | 2 (1.1) |
| Arrhythmia/tachycardia | 2 (1.1) |
| Arthralgia | 6 (3.4) |
| Abdomen pain | 2 (1.1) |
| Headache/dizziness | 2 (1.1) |
| Numbness | 1 (0.6) |
| Unknown | 2 (1.1) |

Values are presented as number (%).
IRR: infusion/injection-related reaction; DRESS: drug rash with eosinophilia and systemic symptoms.

**Table III.** Drug administration patterns before and after infusion/injection-related reactions (IRRs) occurrence in the IRR group.

| | Biologics | Switched biologics |
|---|---|---|
| Duration from biologics administration to the onset of IRR (months), median [IQR] | 3 [1, 10] | |
| TNF inhibitors, n (%) | | |
| Etanercept | 41 (22.9) | 29 (16.2) |
| Infliximab | 33 (18.4) | 15 (8.4) |
| Adalimumab | 42 (23.5) | 26 (14.5) |
| Golimumab | 10 (5.6) | 10 (5.6) |
| Rituximab, n (%) | 2 (1.1) | 5 (2.8) |
| Abatacept, n (%) | 13 (7.3) | 16 (8.9) |
| Tocilizumab, n (%) | 38 (21.2) | 50 (27.9) |
| JAK inhibitors, n (%) | | 18 (10.1) |
| Tofacitinib | - | 11 (6.2) |
| Baricitinib | - | 5 (2.8) |
| Upadacitinib | - | 2 (1.1) |
| Unknown, n (%) | | 10 (5.6) |

Values are presented as number (%) or median [interquartile range (IQR)].
IRR: infusion/injection-related reaction; TNF: tumour necrosis factor; JAK: Janus kinase.

*Medication use and biologic withdrawal*

Patterns of medication use and reasons for biologic withdrawal are detailed in Table IV. Participants in the IRR group had a higher prevalence of prior use of methotrexate (98.3% *vs*. 94.5%, $p$=0.027) and leflunomide (60.3% *vs*. 52.2%, $p$=0.039). Additionally, the IRR group exhibited a significantly higher biologic withdrawal rate than the non-IRR group (69.8% *vs*. 43.9%, $p$<0.001). The predominant reason for biologic withdrawal in the IRR group was adverse events, accounting for 100% of the cases, indicating that IRRs are a major factor influencing treatment discontinuation.

*IRR risk factors*

Logistic regression analysis was conducted to identify risk factors for IRRs among patients with RA, with results presented in Table V. In the RA population, younger age (odds ratio [OR]=2.201, $p$=0.001), prior use of methotrexate (OR=3.418, $p$=0.038), prior use of leflunomide (OR=1.392, $p$=0.039), adalimumab (OR=0.66, $p$=0.09), golimumab (OR=0.376, $p$=0.01), abatacept (OR=0.242, $p$<0.001), and tocilizumab (OR=0.397, $p$<0.001) were associated with IRRs. In the multivariable analysis, significant risk factors for developing IRRs included younger age (adjusted OR=1.793, $p$=0.014), presence of secondary Sjögren's syndrome (adjusted OR=2.175, $p$=0.035), prior use of sulfasalazine (adjusted OR=1.406, $p$=0.036), and prior use of leflunomide (adjusted OR=1.497, $p$=0.015). Additionally, biologics such as golimumab, abatacept, and tocilizumab had lower odds of IRRs than infliximab, indicating a possible variation in IRR risk depending on the specific biologic agent used.

**Table IV.** Comparison of medication use and biologic withdrawal between RA patients with IRR and RA without IRR in the KOBIO registry.

| Variable | Total (n=1,832) | IRR (n=179) | No IRR (n=1,653) | $p$-value |
|---|---|---|---|---|
| Medication | | | | |
| Previous treatments, n (%) | | | | |
| Prior use of methotrexate | 1,738 (94.9) | 176 (98.3) | 1,562 (94.5) | **0.027** |
| Prior use of sulfasalazine | 736 (40.2) | 84 (46.9) | 652 (39.4) | 0.052 |
| Prior use of leflunomide | 971 (53.0) | 108 (60.3) | 863 (52.2) | **0.039** |
| Prior use of csDMARDs | | | | 0.524 |
| None | 41 (2.2) | 2 (1.1) | 39 (2.4) | |
| One csDMARD received | 815 (44.5) | 83 (46.4) | 732 (44.3) | |
| Two or more csDMARDs received | 976 (53.3) | 94 (52.5) | 882 (53.4) | |
| Concomitant treatments | | | | |
| Methotrexate, n (%) | 1,153 (62.9) | 108 (60.3) | 1,045 (63.2) | 0.448 |
| Sulfasalazine, n (%) | 18 (1.0) | 2 (1.1) | 16 (1.0) | 0.693 |
| Leflunomide, n (%) | 74 (4.0) | 6 (3.4) | 68 (4.1) | 0.623 |
| Corticosteroid use, n (%) | 1,567 (85.5) | 151 (84.4) | 1,416 (85.7) | 0.637 |
| Corticosteroid dosage, mg/day | 5 [2.5, 7.5] | 5 [2.5, 7.5] | 5 [2.5, 7.5] | 0.576 |
| Prior use of biologic agents, n (%) | | | | 0.432 |
| 0 | 119 (6.5) | 14 (7.8) | 105 (6.4) | |
| 1 | 1,303 (71.1) | 120 (67.0) | 1,183 (71.6) | |
| ≥2 | 410 (22.4) | 45 (25.1) | 365 (22.1) | |
| Number of prior biologic agents | 0.3 ± 0.8 | 0.3 ± 0.6 | 0.3 ± 0.8 | 0.605 |
| Initial withdrawal | | | | |
| Treatment duration (month), median [IQR] | 46 [12, 89] | 6 [2, 21] | 50 [15, 92] | **<0.001** |
| Withdrawal, n (%) | 851 (46.5) | 125 (69.8) | 726 (43.9) | **<0.001** |
| Discontinuation | 445 (50.2) | 34 (21.3) | 411 (56.6) | |
| Switching | 441 (49.8) | 126 (78.8) | 315 (43.4) | |
| Withdrawal reason, n (%) | | | - | **<0.001** |
| Clinical remission | 41 (4.8) | 0 (0.0) | 41 (5.7) | |
| Inefficacy | 287 (33.7) | 0 (0.0) | 287 (39.5) | |
| Adverse events | 296 (34.8) | 125 (100.0) | 171 (23.6) | |
| Other reasons | 227 (26.7) | 0 (0) | 227 (31.3) | |

Values are presented as number (%), mean ± standard deviation (SD), or median [interquartile range (IQR)]. $p$-values were calculated using chi-square test, Student's t-test, or Wilcoxon rank-sum test.
Bold indicates statistically significant values.
RA: rheumatoid arthritis; IRR: infusion/injection-related reaction; KOBIO: Korean College of Rheumatology Biologics & Targeted Therapy Registry; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs.
Corticosteroid dose is presented as prednisone-equivalent.

## Discussion

In RA treatment, adverse events significantly influence the retention rate of bDMARDs. Given the administration routes and characteristics of these agents, IRRs are an unavoidable adverse event and a crucial issue to consider (14, 15). While previous studies have primarily examined the risk of IRRs associated with individual biologic agents, comprehensive analyses that assess the overall incidence and risk factors across various biologics in RA treatment are lacking. To the best of our knowledge, this study is the first to utilise national registry data to provide a broad overview of IRR incidence and associated risk factors in patients receiving biologic therapies, offering a unique and valuable contribution to the field.

In our study, we observed a 9.7% IRR incidence, consistent with previous reports indicating a range of 5–25% among patients administered bDMARDs for RA treatment (6, 16-18). While most reactions in our cohort were mild to moderate, over 70% of patients discontinued treatment due to IRR, underscoring the significant impact of these events on adherence, consistent with findings from other studies in South Korea, where adverse events are more frequently cited than inefficacy as reasons for discontinuation, with IRRs being the most common cause (19). Several factors may have contributed to the high discontinuation rate of bDMARDs. Mild IRRs can cause significant distress, particularly when occurring during or after infusion, leading to anxiety and concerns about future treatments (20). This distress, combined with the long-term nature of RA therapy, may prompt patients and physicians to discontinue bDMARDs due to an unwillingness to endure ongoing discomfort and its potential impact on quality of life (21). Additionally, the

**Table V.** Logistic regression analysis for risk factors of IRR among RA patients.

| Variable | Univariable | | Multivariable | | |
|---|---|---|---|---|---|
| | OR (95% CI) | *p*-value | Adjusted OR (95% CI) | *p*-value | Variance inflation |
| Young age (*vs*. ≥65 years) | 2.101 (1.364 – 3.384) | **0.001** | 1.793(1.145 – 2.927) | **0.014** | 1.38 |
| Sex (*vs*. male) | 1.233 (0.817 – 1.929) | 0.338 | | | |
| High ESR (*vs*. <66 mm/hr) | 0.797 (0.543 – 1.145) | 0.232 | | | |
| High CRP (*vs*. <2.9 mg/dL) | 0.77 (0.521 – 1.112) | 0.176 | 0.803 (0.539 - 1.169) | 0.264 | 1.36 |
| Diabetes mellitus | 0.628 (0.349 – 1.053) | 0.097 | 0.707 (0.388 - 1.203) | 0.226 | 1.18 |
| Secondary Sjögren's syndrome | 1.752 (0.827 – 3.358) | 0.113 | 2.175 (1.001 - 4.316) | **0.035** | 1.05 |
| Subcutaneous rheumatoid nodule | 2.043 (0.872 – 4.239) | 0.073 | 2.134 (0.878 - 4.644) | 0.071 | 1.02 |
| Interstitial lung disease | 0.428 (0.150 – 0.962) | 0.068 | 0.75 (0.256 - 1.75) | 0.548 | 1.12 |
| Prior use of methotrexate | 3.418 (1.266 – 14.012) | **0.038** | 3.212 (1.167 - 13.293) | 0.052 | 5.05 |
| Prior use of sulfasalazine | 1.358 (0.995 – 1.850) | **0.053** | 1.406 (1.022 - 1.932) | **0.036** | 1.31 |
| Prior use of leflunomide | 1.392 (1.019 – 1.914) | **0.039** | 1.497 (1.085 - 2.078) | **0.015** | 2.08 |
| Concomitant corticosteroid use | 0.903 (0.598 – 1.407) | 0.634 | | | |
| Biologics that induced SIRR or were used at enrolment (*vs*. Infliximab) | | | | | |
| TNF inhibitors | | | | | 3.94 |
| Etanercept | 0.751 (0.457 – 1.241) | 0.259 | 0.804 (0.483 - 1.345) | 0.402 | |
| Adalimumab | 0.66 (0.404 – 1.087) | **0.099** | 0.638 (0.387 - 1.059) | 0.08 | |
| Golimumab | 0.376 (0.17 – 0.765) | **0.010** | 0.345 (0.155 - 0.709) | **0.006** | |
| Rituximab | 0.625 (0.096 – 2.339) | 0.544 | 0.613 (0.094 - 2.319) | 0.530 | |
| Abatacept | 0.242 (0.12 – 0.462) | **<0.001** | 0.263 (0.128 - 0.513) | **<0.001** | |
| Tocilizumab | 0.397 (0.241 – 0.656) | **<0.001** | 0.419 (0.252 - 0.699) | **<0.001** | |

Values are presented as odds ratio (OR) with 95% confidence intervals (CI) calculated using logistic regression analysis.
Bold indicates statistically significant *p*-values.
IRR: infusion/injection-related reaction; RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein: TNF: tumour necrosis factor; SIRR: systemic infusion/injection-related reaction.

emergence of alternative therapies, particularly oral medications such as JAK inhibitors, has become a viable option for patients to change their treatment when experiencing the risks associated with infusion or injection risks (22).

In analysing the patterns of treatment switching among patients experiencing IRRs, our study found that approximately 10% of patients transitioned to JAK inhibitors after encountering an IRR event. Given that registry data has been collected since 2012, this relatively high rate of switching to JAK inhibitors – considered a more recent treatment option – suggests an increasing acceptance of these therapies in clinical practice. Contrary, the switch to other TNF inhibitors, excluding golimumab, has significantly declined. Previous studies indicated that infliximab and adalimumab have a high frequency of anti-drug antibody (ADA) formation, and patients with ADA have an increased risk of immediate hypersensitivity reactions (23, 24). Furthermore, it has been reported that the incidence of dermatologic events is more than twice as high in patients using TNF inhibitors compared with that of the TNF-naive group, with golimumab having an incidence of approximately 9%, while other TNF inhibitors have a significantly higher incidence of approximately 15% (17, 25). Paradoxical skin reactions are the most prevalent among TNF inhibitors, treatment patterns that are possibly reflected in these findings (26).

Rituximab was identified as the only non-TNF biologic not associated with a reduced incidence of IRRs in this study. This can be attributed to the rituximab mechanism of action, where exposure leads to rapid lysis of B cells and subsequent cytokine release, which is central to cytokine release syndrome and contributes to the higher incidence of IRRs compared with that of the other non-TNF biologics (27, 28). Furthermore, in South Korea, rituximab is prescribed exclusively for patients who have failed TNF inhibitors, often including those with preexisting ADAs, which may explain why the incidence of IRRs with rituximab does not significantly differ from that of TNF inhibitors. Abatacept and tocilizumab among non-TNF biologics exhibit a notably lower risk of IRRs, with most studies to date reporting very low incidences of these events (10, 29). This can primarily be attributed to their mechanisms, which involve cytokine modulation rather than hypersensitivity related to complement activation or ADAs (30).

IRRs have indeed been extensively studied in the field of cancer chemotherapy before research expanded to biologic treatments such as those for autoimmune diseases (31). The incidence of IRRs in cancer chemotherapy varies with the drug type, with monoclonal antibodies such as rituximab and cetuximab posing a higher risk, while agents such as platinum-based compounds (*e.g.* cisplatin) also cause hypersensitivity reactions, though typically less frequently (32). Among these, comparing rituximab, which is used in cancer therapy and autoimmune diseases such as RA, demonstrates notable differences in the incidence of IRRs between these two fields. In cancer treatment, particularly lymphoma, IRRs are reported in up to 77% of patients after the first infusion, while in RA, the rate is significantly lower at approximately 25%, with severe IRRs occurring in approximately 10% of patients with cancer compared to approximately 1% in patients with RA (33, 34). This difference is likely due to the more frequent use of concomitant corticosteroids and

immunosuppressive therapies, which may also explain why the incidence of IRRs in patients with systemic lupus erythematosus after rituximab, approximately 18%, is similar to that in RA (35).

Conversely, in our study, the immunomodulatory effects of methotrexate, sulfasalazine, and leflunomide did not produce the expected protective effect, leading to a paradoxical increase in IRR rates. Although the concomitant use of these medications typically reduces ADA formation, the fact that they were previously administered rather than used concurrently may account for the different outcomes observed (36). These drugs are often prescribed to patients with higher disease activity, which could contribute to elevated IRR rates due to persistent inflammation and immune dysregulation. Additionally, prolonged exposure to various treatments may impact the immune system's ability to recognise and react to foreign antigens, adding to the higher incidence of IRRs (37). Similarly, younger patients exhibited a higher incidence of IRRs, which could be explained by their more active immune systems potentially producing more ADAs (38). Additionally, in patients with RA with secondary Sjögren's syndrome, abnormal B cell activation and autoantibody production may heighten hypersensitivity reactions during infusions, potentially through complement activation, further increasing IRR incidence (39).

Our study, which comprehensively analyses the incidence and risk factors of IRRs among Korean patients with RA using national registry data, can significantly assist in medication selection for patients who experience IRRs. However, this study had several limitations. The retrospective design introduces potential selection bias and confounding factors. While national registry data provides a broad overview, individual allergy or skin disease histories were not verified, nor were the use of medications such as acetaminophen or non-steroidal anti-inflammatory drugs collected, which may influence IRR occurrences. Additionally, the analysis grouped patients receiving golimumab and infliximab intravenously and subcutaneously, preventing the assessment of differences considering administration routes. Future studies should focus on prospective designs and include detailed mechanistic analyses to explore pre-treatment strategies that can further mitigate IRR risk in patients with RA.

## Conclusions

This study provides important insights into the incidence and risk factors associated with IRRs in patients with RA. We observed a 9.7% IRR incidence, which is comparable to rates in autoimmune diseases, including RA globally, but lower than those seen in conditions such as cancer. Using national registry data, we identified that younger age, prior use of methotrexate and leflunomide, and the presence of secondary Sjögren's syndrome are significant risk factors for IRRs. Additionally, certain biologics such as golimumab, abatacept, and tocilizumab were associated with a lower risk of IRRs than infliximab, highlighting the need for tailored treatment strategies to minimise IRR risk and improve medication adherence in patients with RA.

## Acknowledgment

We thank the KOBIO study team for aiding the data management and preparation.

## References

1. SMOLEN JS, ALETAHA D, BARTON A *et al*.: Rheumatoid arthritis. *Nat Rev Dis Primers* 2018; 4: 18001. https://doi.org/10.1038/nrdp.2018.1
2. CHAUDHARI K, RIZVI S, SYED BA: Rheumatoid arthritis: current and future trends. *Nat Rev Drug Discov* 2016; 15(5): 305-6. https://doi.org/10.1038/nrd.2016.21
3. SPARKS JA, HARROLD LR, SIMON TA *et al*.: Comparative effectiveness of treatments for rheumatoid arthritis in clinical practice: a systematic review. *Semin Arthritis Rheum* 2023; 62: 152249. https://doi.org/ 10.1016/j.semarthrit.2023.152249
4. VULTAGGIO A, MAGGI E, MATUCCI A: Immediate adverse reactions to biologicals: from pathogenic mechanisms to prophylactic management. *Curr Opin Allergy Clin Immunol* 2011; 11(3): 262-68. https://doi.org/10.1097/aci.0b013e3283464bcd
5. DOESSEGGER L, BANHOLZER ML: Clinical development methodology for infusion-related reactions with monoclonal antibodies. *Clin Transl Immunol* 2015; 4(7): e39. https://doi.org/10.1038/cti.2015.14
6. CHOQUETTE D, FARAAWI R, CHOW A, RODRIGUES J, BENSEN WJ, NANTEL F: Incidence and management of infusion reactions to infliximab in a prospective real-world community registry. *J Rheumatol* 2015; 42(7): 1105-11. https://doi.org/10.3899/jrheum.140538
7. KAPETANOVIC MC, LARSSON L, TRUEDSSON L, STURFELT G, SAXNE T, GEBOREK P: Predictors of infusion reactions during infliximab treatment in patients with arthritis. *Arthritis Res Ther* 2006; 8(4): R131. https://doi.org/10.1186/ar2020
8. LICHTENSTEIN L, RON Y, KIVITY *et al*.: Infliximab-related infusion reactions: systematic review. *J Crohns Colitis* 2015; 9(9): 806-15. https://doi.org/10.1093/ecco-jcc/jjv096
9. CALOGIURI G, VENTURA MT, MASON *et al*.: Hypersensitivity reactions to last generation chimeric, humanized and human recombinant monoclonal antibodies for therapeutic use. *Curr Pharm Des* 2008; 14(27): 2883-91. https://doi.org/10.2174/138161208786369786
10. SALMON JH, PEROTIN JM, MOREL J *et al*.: Serious infusion-related reaction after rituximab, abatacept and tocilizumab in rheumatoid arthritis: prospective registry data. *Rheumatology* (Oxford) 2018; 57(1): 134-39. https://doi.org/10.1093/rheumatology/kex403
11. KIM J, KOH JH, CHOI SJ *et al*.: KOBIO, the first web-based Korean biologics registry operated with a unified platform among distinct disease entities. *J Rheum Dis* 2021; 28(4): 176-82. https://doi.org/10.4078/jrd.2021.28.4.176
12. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69(9): 1580-88. https://doi.org/10.1136/ard.2010.138461
13. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31(3): 315-24. https://doi.org/10.1002/art.1780310302
14. EBINA K, HASHIMOTO M, YAMAMOTO W *et al*.: Drug retention and discontinuation reasons between seven biologics in patients with rheumatoid arthritis - The ANSWER cohort study. *PLoS One* 2018; 13(3): e0194130. https://doi.org/10.1371/journal.pone.0194130
15. LEE SK, SHIN K, JUNG JY, SUH CH, KIM JW, KIM HA: Retention rate and safety of biologic and targeted synthetic DMARDs in patients with ra-associated interstitial lung disease: a KOBIO Registry study. *BioDrugs* 2023; 37(2): 247-57. https://doi.org/10.1007/s40259-023-00578-6
16. CURTIS JR, CHAKRAVARTY SD, BLACK S *et al*.: incidence of infusion reactions and clinical effectiveness of intravenous golimumab versus infliximab in patients with rheumatoid arthritis: the real-world AWARE study. *Rheumatol Ther* 2021; 8(4): 1551-63. https://doi.org/10.1007/s40744-021-00354-4
17. LI M, YOU R, SU Y, ZHOU H, GONG S: Characteristic analysis of adverse reactions of five anti-TNF-α agents: a descriptive analysis from WHO-VigiAccess. *Front Pharmacol* 2023; 14: 1169327.

https://doi.org/10.3389/fphar.2023.1169327
18. HARAOUI B, CIVIDINO A, STEWART J, GUÉRETTE B, KEYSTONE EC: Safety and effectiveness of adalimumab in a clinical setting that reflects Canadian standard of care for the treatment of rheumatoid arthritis (RA): results from the CanACT study. *BMC Musculoskelet Disord* 2011; 12: 261. https://doi.org/10.1186/1471-2474-12-261
19. KIM JW, SHIN K, JUNG J *et al*.: Uncovering risk factors for adverse events and infections in rheumatoid arthritis and rheumatoid arthritis with interstitial lung disease under treatment with biologics or targeted synthetic DMARDs: insights from the KOBIO Registry. *Clin Exp Rheumatol* 2024; 42(9): 1781-91. https://doi.org/10.55563/clinexprheumatol/6h1euo
20. SHAW Y, METES ID, MICHAUD K *et al*.: Rheumatoid arthritis patients' motivations for accepting or resisting disease-modifying antirheumatic drug treatment regimens. *Arthritis Care Res* (Hoboken) 2018; 70(4): 533-41. https://doi.org/10.1002/acr.23301
21. KATZ G, OGDIE A, BAKER JF, GEORGE MD: Association between depression, anxiety, chronic pain, or opioid use and tumor necrosis factor inhibitor persistence in inflammatory arthritis. *Clin Rheumatol* 2022; 41(5): 1323-31. https://doi.org/10.1007/s10067-021-06045-3
22. DE SOUZA S, WILLIAMS R, NIKIPHOROU E: Clinician and patient views on janus kinase inhibitors in the treatment of inflammatory arthritis: a mixed methods study. *BMC Rheumatol* 2024; 8(1): 1. https://doi.org/10.1186/s41927-023-00370-7
23. DOELEMAN MJH, VAN MAARSEVEEN EM, SWART JF: Immunogenicity of biologic agents in juvenile idiopathic arthritis: a systematic review and meta-analysis. *Rheumatology* (Oxford) 2019; 58(10): 1839-49. https://doi.org/10.1093/rheumatology/kez030
24. MURDACA G, SPANÒ F, CONTATORE M *et al*.: Immunogenicity of infliximab and adalimumab: what is its role in hypersensitivity and modulation of therapeutic efficacy and safety? *Expert Opin Drug Saf* 2016; 15(1): 43-52. https://doi.org/10.1517/14740338.2016.1112375
25. FLENDRIE M, VISSERS WH, CREEMERS MC, DE JONG EM, VAN DE KERKHOF PC, VAN RIEL PL: Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: a prospective study. *Arthritis Res Ther* 2005; 7(3): R666-76. https://doi.org/10.1186/ar1724
26. GARCOVICH S, DE SIMONE C, GENOVESE G, BERTI E, CUGNO M, MARZANO AV: Paradoxical skin reactions to biologics in patients with rheumatologic disorders. *Front Pharmacol* 2019; 10: 282. https://doi.org/10.3389/fphar.2019.00282
27. FOUDA GE, BAVBEK S: Rituximab hypersensitivity: from clinical presentation to management. *Front Pharmacol* 2020; 11: 572863. https://doi.org/10.3389/fphar.2020.572863
28. CÁCERES MC, GUERRERO-MARTÍN J, PÉREZ-CIVANTOS D, PALOMO-LÓPEZ P, DELGADO-MINGORANCE JI, DURÁN-GÓMEZ N: The importance of early identification of infusion-related reactions to monoclonal antibodies. *Ther Clin Risk Manag* 2019; 15: 965-77. https://doi.org/10.2147/tcrm.s204909
29. TERREAUX W, MASSON C, ESCHARD JP *et al*.: Incidence of paradoxical reactions in patients treated with tocilizumab for rheumatoid arthritis: data from the French registry REGATE. *Joint Bone Spine* 2018; 85(1): 53-57. https://doi.org/10.1016/j.jbspin.2017.01.002
30. PIZANO-MARTINEZ O, MENDIETA-CONDADO E, VÁZQUEZ-DEL MERCADO M *et al*.: Anti-drug antibodies in the biological therapy of autoimmune rheumatic diseases. *J Clin Med* 2023; 12(9): 3271. https://doi.org/10.3390/jcm12093271
31. LENZ HJ: Management and preparedness for infusion and hypersensitivity reactions. *Oncologist* 2007; 12(5): 601-9. https://doi.org/10.1634/theoncologist.12-5-601
32. ROSELLÓ S, BLASCO I, GARCÍA FABREGAT L, CERVANTES A, JORDAN K: Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines. *Ann Oncol* 2017; 28(Suppl_4): iv100-iv18. https://doi.org/10.1093/annonc/mdx216
33. D'ARENA G, SIMEON V, LAURENTI *et al*.: Adverse drug reactions after intravenous rituximab infusion are more common in hematologic malignancies than in autoimmune disorders and can be predicted by the combination of few clinical and laboratory parameters: results from a retrospective, multicenter study of 374 patients. *Leuk Lymphoma* 2017; 58(11): 2633-41. https://doi.org/10.1080/10428194.2017.1306648
34. GILABERTE REYZABAL S, ISENBERG D: Differences in the development of adverse infusion reactions to rituximab in patients with systemic lupus erythematosus, rheumatoid arthritis and non-Hodgkin's lymphoma-enigma variations. *Front Med* (Lausanne) 2022; 9: 882891. https://doi.org/10.3389/fmed.2022.882891
35. HENNESSEY A, LUKAWSKA J, CAMBRIDGE G, ISENBERG D, LEANDRO M: Adverse infusion reactions to rituximab in systemic lupus erythematosus: a retrospective analysis. *BMC Rheumatol* 2019; 3: 32. https://doi.org/10.1186/s41927-019-0082-7
36. STRAND V, BALSA A, AL-SALEH J *et al*.: Immunogenicity of biologics in chronic inflammatory diseases: a systematic review. *BioDrugs* 2017; 31(4): 299-316. https://doi.org/10.1007/s40259-017-0231-8
37. BAUER ME: Accelerated immunosenescence in rheumatoid arthritis: impact on clinical progression. *Immun Ageing* 2020; 17: 6. https://doi.org/10.1186/s12979-020-00178-w
38. PARIKH CR, PONNAMPALAM JK, SELIGMANN G *et al*.: Impact of immunogenicity on clinical efficacy and toxicity profile of biologic agents used for treatment of inflammatory arthritis in children compared to adults. *Ther Adv Musculoskelet Dis* 2021; 13. https://doi.org/10.1177/1759720X211002685
39. HE J, DING Y, FENG M *et al*.: Characteristics of Sjögren's syndrome in rheumatoid arthritis. *Rheumatology* (Oxford) 2013; 52(6): 1084-89. https://doi.org/10.1093/rheumatology/kes374