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Original article

Prevalence of adverse reactions to intravenously administered originator biologics in patients with rheumatoid arthritis: A 5-year retrospective study

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ABSTRACT

Background: Few Saudi studies have examined adverse drug reactions (ADRs) in patients with rheumatoid arthritis (RA) receiving intravenous (IV) originator biologics. Therefore, this study aimed to evaluate the prevalence, types, and predictors of ADRs following long-term IV originator biologic use in patients with RA.

Patients and methods: This retrospective, single-center study included adult patients with RA who received IV originator biologics between 2015 and 2020. Medical records were reviewed and data regarding ADRs were collected and evaluated for causality using the Naranjo scale. Binary logistic regression analysis was performed to identify the odds for and factors associated with developing ADRs for each biologic.

Results: A total of 129 patients (87.6% women) with a mean (standard deviation) age of 54 (13) years were included in this study. A total of 1963 doses of tocilizumab (38.76%), rituximab (38.76%), abatacept (13.95%), and infliximab (8.53%), were administered during the study period. ADRs with a Naranjo score ≥ 1 were experienced by 103 (78%) patients, with an average of 2.2 events per patient. Infection (26.6%) and skin and mucous membrane disorders (14.18%) were the most commonly reported ADRs. Abatacept was associated with a significantly higher risk of multiple ADRs than the other biologics (adjusted odds ratio: 3.145, 95% confidence interval 1.004–9.854, p = 0.049).

Conclusion: There was a high prevalence of ADRs among patients with RA receiving biologics. Abatacept was associated with a greater risk of multiple ADRs than other biologics. Infection was the most common ADR. Future multicenter longitudinal studies are warranted.

1. Introduction

The introduction of biological disease-modifying anti-rheumatic drugs (bDMARDs) has revolutionized the treatment of rheumatoid arthritis (RA). The American college of rheumatology Guidelines have recommended these drugs as effective therapies for patients with moderate or high disease activity (Singh et al., 2016). Various routes of administration are available. The intravenous (IV) route is used when biologics are to be administered infrequently, and it is usually selected based on the physician's treatment plan and the patient's preference, particularly in patients who desire improved safety through drug administration in the hospital (Huynh et al., 2014).

Biologic use has been found to be associated with an increased risk of adverse drug reactions (ADRs) (Boyman et al., 2014). The World Health Organization (WHO) defines an ADR as "any response to a drug which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis or treatment" (World Health Organization. Department of Essential

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Drugs and Medicines Policy, 2002). Infection and infusion site reactions are the most commonly reported ADRs related to bDMARDs (van Vollenhoven et al., 2013). bDMARDs are more effective than conventional synthetic DMARDs (csDMARDs) for the treatment of RA. However, they have a high rate of serious ADRs (Curtis and Singh, 2011).

Causality assessments have been specifically designed to identify ADRs. Along with prevalence data, they aid treatment selection (Macedo et al., 2005). Furthermore, obtaining baseline information on the ADRs to biologics is crucial for future bioequivalence studies of biosimilars (Chingcuanco et al., 2016). The loss of patency of certain originator biologics and introduction of biosimilars poses a new challenge in the care of patients with RA. In fact, a negative perception of the safety and effectiveness of biosimilars in comparison with their originator biologics has led to the premature discontinuation of biosimilar use (Colloca and Miller, 2011). Consequently, and in light of the increased use of bDMARDs, this study aimed to determine the prevalence of ADRs associated with both long-term and short-term use of IV abatacept, infliximab, tocilizumab, and rituximab. We also evaluated the types and predictors of ADRs in patients with RA.

2. Materials and methods

2.1. Study design and setting

This retrospective study was designed to evaluate ADRs in patients with RA receiving IV bDMARDs at a tertiary hospital in Riyadh, Saudi Arabia. The manuscript has been prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology checklist for cohort studies (von Elm et al., 2007).

2.2. Participants and measurements

We included patients with RA who fulfilled the 2010 European League Against Rheumatism/American College of Rheumatology classification criteria (Aletaha et al., 2010), were $\geq$ 18 years of age, and had received $\geq$ 1 dose of IV abatacept, infliximab, tocilizumab, or rituximab. The medical file numbers of all patients who had received IV originator bDMARD therapy from the year of inception of electronic medical records (January 2015) to January 2020 were identified from the medical day care unit logbooks at the study site. Based on previous studies, we created a list of commonly reported ADRs to IV biologics (Downey, 2016; Singh et al., 2011; van Vollenhoven et al., 2013; Weisman et al., 2006; Westhovens et al., 2009). ADRs were documented and assessed for causality using the Naranjo scale (Naranjo et al., 1981). All ADRs reported in this study met the WHO definition (World Health Organization. Department of Essential Drugs and Medicines Policy, 2002). The medical records of patients with RA were reviewed, and any ADR that developed (at least one ADR or multiple ADRs), the type of ADR, and the time taken for the ADR to develop were recorded. These data were used to determine the prevalence of ADRs. We also collected data regarding patient demographics; IV biologic use, including pre-medications, concomitant medications, frequency, date of administration, laboratory information; and Charlson comorbidity index (CCI) (Charlson et al., 1987). All ADRs were assessed for quality using the Naranjo scale (Naranjo et al., 1981), which was scored based on 10 questions with different point values (−1, 0, +1, +2). The resulting combined score (−10 to + 20) was interpreted as doubtful (score: < 1), possible (score: 1–4), probable (score: 5–8), and definite (score: $\geq$ 9) (Naranjo et al., 1981). Any ADR with a Naranjo score $\geq$ 1 was considered to be caused by the administered IV bDMARD and included for analysis. In addition, seriousness of the ADRs according to World Health Organization definition "any event that Is fatal, life-threatening, permanently/significantly disabling, requires or prolongs hospitalization, causes a congenital anomaly or requires intervention to prevent permanent impairment or damage" was documented and reported (World Health Organization. Department of Essential Drugs and Medicines Policy, 2002).

2.3. Statistical analysis

Data were coded, entered, and analyzed using the Statistical Package Software for Social Sciences (IBM Corp., 2020). Each patient was assigned a unique study number to ensure complete patient confidentiality. Medications were classified according to the British National Formulary version 76 (Joint formulary Committee, 2018). Normally distributed data are presented as means and standard deviations. Skewed data are presented as medians and interquartile ranges (25th and 75th percentile values). The baseline characteristics of patients with and without ADRs to IV bDMARDs were compared using the *t*-test for normally distributed data and the Mann–Whitney *U* test for non-normally distributed data. The baseline characteristics of patients receiving different IV biologics were compared using one-way analysis of variance for normally distributed data and the non-parametric Kruskal–Wallis test for non-normally distributed data. Binary logistic regression analysis was performed to determine the adjusted odds ratio (AOR) for factors associated with ADRs. Regression analysis was performed using age, sex, and other factors that showed significant differences in the bivariate analysis as confounding variables. Binary logistic regression analysis was also performed to determine the AOR for each IV bDMARD and the resulting odds of experiencing at least one ADR with a Naranjo score $\geq$ 1. The AOR was separately calculated for each originator biologic, and the resulting odds of experiencing more than one adverse event were determined. Less than 3% of the values for marital status and body mass index (BMI) were missing, and they were replaced with the most common value. Other analyses were performed on complete data. The CCI includes blood disorders; therefore, they were not adjusted for in the analysis to avoid collinearity. However, fibromyalgia and infection are not included in the CCI, and they were used as covariates in regression analysis.

2.4. Ethical approval

The study was approved by the Institutional Review Board of our institution (approval project number E-18-3621). The need for informed consent was waived due to the retrospective, non-interventional nature of the study. Nevertheless, no patient identifiers were used or recorded to ensure confidentiality.

3. Results

3.1. Baseline demographics and primary outcome variable

Between January 2015 and January 2020, there were 15,000 patient visits to the medical day-care unit. Approximately 25% of these visits (3000 visits) were for IV therapy in patients with RA. Of the 129 eligible patients, 38.76%, 38.76%, 13.95%, and 8.53% received tocilizumab, rituximab, abatacept, and infliximab, respectively. A total of 1963 doses were administered, including 381 (19%) doses of abatacept, 993 (50%) doses of tocilizumab, 284 (14%) doses of infliximab, and 305 (16%) doses of rituximab. Longest duration of use was in rituximab group with a median of 42 months and the lowest was in the abatacept group with a median of 5 months. The mean (standard deviation) age and BMI of the study participants were 54 (13) years and 31.3 (6.6) kg/m^2, respec-

Table 1
Baseline demographic characteristics of the patients with rheumatoid arthritis by type of biologic received.

Characteristics	Abatacept (n = 18)	Tocilizumab (n = 50)	Infliximab (n = 11)	Rituximab (n = 50)	Total (n = 129)	p-value
Age, years, mean (SD)	53 (12)	52 (14)	50 (12)	57 (12)	54 (13)	0.201
Female sex, n (%)	16 (88.9)	47 (94.0)	9 (81.8)	41 (82.0)	113 (87.6)	0.296
BMI, kg/m^2, mean (SD)	32.4 (6.3)	31 (6.4)	33.1 (7.8)	30.8 (6.7)	31.3 (6.6)	0.655
BMI categorical, n (%)						
Obese n (%)	11 (61)	30 (60)	6 (54.5)	27 (54.0)	74 (57.4)	0.916
Married, n (%)	12 (66.7)	39 (78)	9 (81.8)	46 (92.0)	106 (82.2)	0.077
Living in Riyadh, n (%)	16 (88.9)	47 (94.0)	9 (81.8)	38 (76.0)	110 (85.3)	0.080
Saudi nationality, n (%)	18 (100.0)	49 (98.0)	11 (100.0)	49 (98.0)	127 (98.4)	0.899
CCI, mean (SD)	3 (1)	2 (1)	2 (1)	3 (1)	2 (1)	0.024*
Medication used						
Methotrexate, n (%)	11 (15.3)	26 (36.1)	7 (9.7)	28 (38.9)	72 (55.8)	0.927
Oral glucocorticoids, n (%)	5 (15.2)	11 (33.3)	3 (9.1)	14 (42.4)	33 (25.6)	0.899
Other DMARDs, n (%)	4 (22.2)	11 (22.0)	0 (0.0)	14 (28.0)	29 (22.5)	0.205
Other medications, n (%)	18 (100.0)	48 (96.0)	11 (100.0)	49 (98.0)	126 (97.7)	0.722
Non-steroidal anti-inflammatory drugs and non-opioid analgesics, n (%)	11 (12.9)	35 (41.2)	8 (9.4)	31 (36.5)	85 (65.9)	0.730
Seropositive, n (%)	12 (66.7)	37 (74.0)	7 (63.6)	43 (86.0)	99 (76.7)	0.196
ESR, mm/h, mean (SD)	29.44 (15.29)	35.09 (29.30)	32.09 (19.18)	42.17 (26.74)	36.67 (26.00)	0.267
CRP level, mg/L, mean (SD)	6.10 (5.22)	13.73 (29.80)	6.60 (7.61)	11.97 (14.48)	11.42 (21.02)	0.568
Duration of use, month, median (IQR)	5 (3—6)	20 (15-27)	36 (26-54)	42 (30—42)	28 (21—35)	<0.001*
ADRs with Naranjo score ≥ 1, n (%)	15 (833)	39 (78.0)	10 (90.9)	36 (72.0)	100 (77.5)	0.501
Multiple ADRs, n (%)	13 (72.2)	23 (46.0)	8 (72.7)	19 (38.0)	63 (48.8)	0.030*
Time till first ADR, days, median (IQR)	84 (42–171)	187 (146–275)	326 (83–389)	279 (183–537)	188 (162–258)	0.002*

ADR, adverse drug reactions; BMI, body mass index; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; DMARDs, disease-modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; IQR, interquartile range; SD, standard deviation.
*p < 0.05 (one-way analysis of variance or chi-square test).

tively. Most of the patients were women (87.6%), married (79%), Saudi (98%), and living in Riyadh (85%). There were significant differences in the CCI of patients receiving different biologics (p = 0.024) (Table 1).

Of the 129 included patients, 103 (78%) experienced ADRs, with an average of 2.2 events per patient (282 ADRs). The number of ADRs for each biologic were as follows: 57 (20%), 103 (37%), 30 (11%), and 92 (33%) for abatacept, tocilizumab, infliximab, and rituximab, respectively. Infliximab users had the highest prevalence of ADRs with Naranjo $\geq$ 1 (91%), followed by abatacept users (83%, p = 0.501). Forty-nine percent of patients experienced multiple ADRs, with infliximab having the highest rate (73%), followed by abatacept (72%, p = 0.030). Due to the wide range of ADRs reported to occur with biologic DMARDs use, all mentioned ADRs were previously reported in the literature.

3.2. Baseline comorbidities and concurrent medications

The patients with RA had various comorbidities, mostly cardiovascular with percentage of patients using abatacept, tocilizumab, infliximab or rituximab having hypertension were 40%, 32%, 18%, and 4% respectively. Diabetes mellitus had overall lower percent and is distributed as follows abatacept 30%, tocilizumab 60%, infliximab 27% and rituximab 38%. Finally, hyperlipidemia was 20% in abatacept users, 18% in tocilizumab users, 9% in infliximab users and 16% in rituximab users. (Table 2) Consequently, they were receiving multiple concurrent medications, with proton pump inhibitors being the most common (64%, Table 2). Blood disorders were more common in patients receiving rituximab than in those receiving other biologics (n = 8 [72.7%], p = 0.002). Meanwhile, fibromyalgia was more common in patients receiving tocilizumab than in those receiving other biologics. There were significant differences among the groups in the number of patients using proton pump inhibitors and angiotensin-converting enzyme inhibitors (p < 0.05).

3.3. Types of ADRs with causality assessment

Infection (26.6%) was the most commonly reported ADR, followed by oral, skin, and mucous membrane reactions (14%). The rate of infection was the highest in the rituximab group (31.5%), followed by the tocilizumab (25%), abatacept (24.6%), and infliximab (20%) groups. The rate of oral, skin, and mucous membrane reactions was the highest in the infliximab group (20%), followed by the tocilizumab (19%), abatacept (14%), and rituximab (6.5%) groups. Of the reported ADRs about half of the participants experienced serious events (n = 69, 53.5%). On causality assessment using the Naranjo scale, it was found that most of the ADRs were either possibly or probably caused by the biologic (Table 3).

3.4. Odds of ADR development

The odds of developing at least one ADR and those of developing multiple ADRs are shown in Table 4. Analysis of many of the demographic characteristics did not yield statistically significant results. However, the erythrocyte sedimentation rate of participants who experienced multiple ADRs was significantly lower than those who did not, with an odds ratio (OR) of 0.984 (95% confi-

Table 2
Comorbidities and medications of the patients with rheumatoid arthritis by type of biologic received.

	Abatacept (n = 18)	Tocilizumab (n = 50)	Infliximab (n = 11)	Rituximab (n = 50)	Total (n = 129)	p-value
Comorbidities, n (%)						
Hypertension	8 (17.4)	16 (34.8)	2 (4.3)	20 (43.5)	46 (35.7)	0.428
Diabetes mellitus	6 (14.0)	15 (34.9)	3 (7.0)	19 (44.2)	43 (33.3)	0.820
Hyperlipidemia	4 (18.2)	9 (40.9)	1 (4.5)	8 (36.4)	22 (17.1)	0.824
Asthma	5 (23.8)	7 (33.3)	1 (4.8)	8 (38.1)	21 (16.3)	0.684
Musculoskeletal disorders	3 (12.0)	9 (36.0)	3 (12.0)	10 (40.0)	25 (19.4)	0.897
Gastrointestinal disorder	1 (10.0)	1 (10.0)	1 (10.0)	7 (70.0)	10 (7.8)	0.158
Blood disorder	0 (0.0)	0 (0.0)	3 (27.3)	8 (72.7)	11 (8.5)	0.002*
Psychological disorder	0 (0.0)	4 (33.3)	2 (16.7)	6 (50.0)	12 (9.3)	0.333
Respiratory disorder	1 (11.1)	3 (33.3)	0 (0.0)	5 (55.6)	9 (7.0)	0.646
Endocrine disorder	3 (14.3)	8 (38.1)	2 (9.5)	8 (38.1)	21 (16.3)	0.998
Infection	1 (5.9)	6 (35.3)	5 (29.4)	5 (29.4)	17 (13.2)	0.010*
Skin/mucous membrane disorder	2 (20.0)	2 (20.0)	3 (30.0)	3 (30.0)	10 (7.8)	0.062
Renal disorder	2 (28.6)	2 (28.6)	0 (0.0)	3 (42.9)	7 (5.4)	0.573
Cardiac disorder	1 (11.1)	1 (11.1)	1 (11.1)	6 (66.7)	9 (7.0)	0.263
Autoimmune disorder	2 (15.4)	5 (38.5)	1 (7.7)	5 (38.5)	13 (10.1)	0.998
Fibromyalgia	0 (0.0)	9 (60.0)	4 (26.7)	2 (13.3)	15 (11.6)	0.003*
Other comorbidities	0 (0.0)	4 (25.0)	1 (6.3)	11 (68.8)	16 (12.4)	0.051
Medications, n (%)						
Proton pump inhibitors	12 (14.6)	25 (30.5)	8 (9.8)	37 (45.1)	82 (63.6)	0.046*
Inhaled corticosteroids	4 (20.0)	9 (45.0)	1 (5.0)	6 (30.0)	20 (15.5)	0.680
Selective β2 agonists	3 (20.0)	5 (33.3)	0 (0.0)	7 (46.7)	15 (11.6)	0.504
Selective β1 blockers	3 (30.0)	2 (20.0)	1 (10.0)	4 (40.0)	10 (7.8)	0.438
Non-selective β blockers	0 (0.0)	1 (20.0)	0 (0.0)	4 (80.0)	5 (3.9)	0.243
Minerals	5 (23.8)	8 (38.1)	1 (4.8)	7 (33.3)	21 (16.3)	0.562
Hypoglycemic agents	5 (13.9)	11 (30.6)	1 (2.8)	19 (52.8)	36 (27.9)	0.105
Vitamins	16 (15.7)	39 (38.2)	9 (8.8)	38 (37.3)	102 (70.1)	0.932
Antidepressants	4 (17.4)	7 (30.4)	4 (17.4)	8 (34.8)	23 (17.8)	0.410
Angiotensin converting enzyme inhibitors	1 (8.3)	1 (8.3)	1 (8.3)	9 (75.0)	12 (9.3)	0.038*
Antifoaming agents	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)	2 (16)	0.430
Antacids	8 (15.4)	17 (32.7)	3 (5.8)	24 (46.2)	52 (40.3)	0.308
Anti-tuberculosis drugs	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)	2 (1.6)	0.175
Anti-epileptics	3 (15.8)	9 (47.4)	3 (15.8)	4 (21.1)	19 (14.7)	0.351
Calcium channel blockers	5 (26.3)	6 (31.6)	1 (5.3)	7 (36.8)	19 (14.7)	0.444
Other medications	8 (16)	13 (26)	6 (12)	23 (46)	50 (38.76)	0.115

*p < 0.05 (one-way analysis of variance or chi-square test).

Table 3
Adverse drug reactions to various biologics and causality assessment using the Naranjo scale.

Type of biologic	Type of ADR	Number of ADRs	% of patients experiencing ADRs	Naranjo score		
				Possible (1–4)	Probable (5–8)	Definite (≥9)
Abatacept	Infection	14	24.6	6	6	2
	Oral, skin, and mucous membrane disorders	8	14.0	3	4	1
	Miscellaneous	9	15.8	9	0	0
	Gastrointestinal disorders	5	8.8	5	0	0
	Hematological disorders	9	15.8	0	8	1
	Renal disorders	3	5.3	3	0	0
	Ophthalmological disorders	2	3.5	1	1	0
	Allergy and infusion site reactions	0	0	0	0	0
	Musculoskeletal disorders	0	0	0	0	0
	Cardiovascular disorders	1	1.8	1	0	0
	Neurological and psychological disorders	0	0	0	0	0
	Respiratory disorders	6	10.5	5	1	0
	Endocrine disorders	0	0	0	0	0
Tocilizumab	Infection	26	25.2	6	19	1
	Oral, skin, and mucous membrane disorders	20	19.4	12	5	3
	Miscellaneous	12	11.7	7	5	0
	Gastrointestinal disorders	9	8.7	5	3	1
	Hematological disorders	9	8.7	3	5	1
	Renal disorders	2	1.9	2	0	0
	Ophthalmological disorders	1	1.0	1	0	0
	Allergy and infusion site reactions	4	3.9	1	2	1
	Musculoskeletal disorders	3	2.9	1	1	1
	Cardiovascular disorders	3	2.9	2	1	0
	Neurological and psychological disorders	0	0	0	0	0
	Respiratory disorders	13	12.6	9	4	0
	Endocrine disorders	1	1.0	0	1	0
Infliximab	Infection	6	20.0	3	1	2
	Oral, skin, and mucous membrane disorders	6	20.0	4	2	0
	Miscellaneous	4	13.3	3	1	0
	Gastrointestinal disorders	5	16.7	4	1	0
	Hematological disorders	0	0	0	0	0
	Renal disorders	0	0	0	0	0
	Ophthalmological disorders	2	6.7	1	1	0
	Allergy and infusion site reactions	1	3.3	0	1	0
	Musculoskeletal disorders	2	6.7	1	1	0
	Cardiovascular disorders	0	0	0	0	0
	Neurological and psychological disorders	0	0	0	0	0
	Respiratory disorders	4	13.3	1	3	0
	Endocrine disorders	0	0	0	0	0
Rituximab	Infection	29	31.5	8	8	13
	Oral, skin, and mucous membrane disorders	6	6.5	1	2	3
	Miscellaneous	16	17.4	9	6	1
	Gastrointestinal disorders	14	15.2	2	5	7
	Hematological disorders	8	8.7	4	1	3
	Renal disorders	2	2.2	1	1	0
	Ophthalmological disorders	4	4.4	3	1	0
	Allergy and infusion site reactions	1	1.1	0	0	1
	Musculoskeletal disorders	2	2.2	2	0	0
	Cardiovascular disorders	1	1.1	0	0	1
	Neurological and psychological disorders	2	2.2	1	1	0
	Respiratory disorders	6	6.5	4	0	2
	Endocrine disorders	1	1.1	1	0	0

ADR: Adverse drug reaction.

dence interval [CI] 0.977–0.999, p = 0.034). There were no significant differences among the groups in the OR and AOR for having at least one ADR. Patients receiving abatacept had a significantly higher OR (3.17, 95% CI 1.059–9.501, p = 0.039) and AOR (3.15, 95% CI 1.004–9.854, p = 0.049) for developing multiple ADRs than those receiving other biologics.

4. Discussion

This study highlights the comparability of the safety of four IV bDMARDs in patients with RA in Saudi Arabia. Reported prevalence of ADRs data were variable (13%-79.9%) between published studies (D'Arena et al., 2017; De Camargo et al., 2019; Elmedany et al., 2019; Harigai et al., 2016; Harrold et al., 2016; Jones et al., 2010; Krintel et al., 2013; Salmon et al., 2018). However, different methodologies including type of study, and definition of ADRs, populations including disease and gender, the type and route of administration for bDMARDS, follow-up period, and analytical technique of causality assessment were observed in these studies. The most similar ADRs rate to our study was observed in a 24 weeks multinational randomized trial (Jones et al., 2010); where 79.9% of RA patients developed ADRs following IV tocilizumab therapy in the USA, Canada, and Israel. A local longitudinal study in Saudi Arabia by Elmedany and colleagues found that the prevalence of ADRs in RA patients reached 60.29% and 28.13% with

Table 4
Unadjusted and adjusted odds of developing single and multiple adverse drug reactions in patients with rheumatoid arthritis receiving intravenous biologics.

	At least 1 ADR			Multiple ADRs		
	Unadjusted odds ratio	95% confidence interval	p-value	Unadjusted odds ratio	95% confidence interval	p-value
Risk factors						
Age (years)	0.973	0.940–1.006	0.109	0.984	0.957–1.011	0.250
Female sex	1.173	0.348–3.957	0.797	0.948	0.333–2.702	0.921
Obese	2.311	0.996–5.365	0.051	1.864	0.918–3.783	0.085
Married	0.949	0.319–2.823	0.925	0.553	0.220–1.387	0.207
Living in Riyadh	0.362	0.078–1.667	0.192	0.873	0.316–2.219	0.720
Saudi nationality	3.536	0.214–58.340	0.377	0.954	0.058–15.585	0.974
CCI score	0.922	0.696–1.222	0.573	1.157	0.903–1.483	0.249
Medication used						
Methotrexate	1.433	0.592–3.470	0.425	0.923	0.448–1.900	0.828
Glucocorticoids	0.942	0.353–2.514	0.904	1.039	0.467–2.310	0.925
Other medications	7.333	0.641–83.958	0.109	1.973	0.171–21.914	0.593
csDMARDs	1.315	0.446–3.884	0.620	2.209	0.928–5.260	0.073
Seropositive	0.474	0.150–1.494	0.202	0.705	0.307–1.620	0.410
ESR, unit increase	0.994	0.978–1.010	0.461	0.984	0.977–0.999	0.034*
CRP level, unit increase	1.022	0.979–1.066	0.322	1.020	0.992–1.047	0.158
IV biologics						
Abatacept	1.529	0.411–5.967	0.527	3.171	1.059–9.501	0.039*
Tocilizumab	1.046	0.447–2.450	0.917	0.831	0.408–1.689	0.608
Infliximab	3.111	0.381–25.379	0.289	3.055	0.772–12.085	0.112
Rituximab	0.603	0.261–1.389	0.235	0.488	0.237–1.005	0.052
	Adjusted odds ratio	95% confidence interval	p-value	Adjusted odds ratio	95% confidence interval	p-value
Abatacept[¥]	1.513	0.386–5.936	0.553	3.145	1.004–9.854	0.049*
Tocilizumab[¥]	1.446	0.511–4.092	0.487	0.853	0.378–1.925	0.702
Infliximab[¥]	2.052	0.213–19.779	0.534	2.455	0.545–11.061	0.242
Rituximab[¥]	0.455	0.163–1.272	0.133	0.438	0.187–1.027	0.058

ADR, adverse drug reaction; BMI, body mass index; CCI, Charlson Comorbidity Index; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; IV, intravenous.
*$p < 0.05$.
[#] Naranjo score ≥ 1.
[¥] Adjusted for age, sex, Charlson comorbidity index, infection, fibromyalgia, proton pump inhibitor use, and angiotensin-converting enzyme inhibitor use.

tocilizumab and abatacept therapy, respectively (Elmedany et al., 2019). However, this study is limited by the short period of follow up (24 weeks) and inclusion of females only which limits the generazibility of the results (Elmedany et al., 2019). The only study used the WHO definition and causality assessment, as our study, was by De Camargo et al. longitudinal study in which the ADRs rate reached 43% in RA and psoriatic arthritis patients in Brazil (De Camargo et al., 2019). However, the study included subcutaneous and IV biologics (adalimumab, etanercept, infliximab, rituximab, abatacept, efalizumab, and tocilizumab), includes other patients group with RA, and followed the patients for 13–36 months (De Camargo et al., 2019). Other studies addressing the safety of bDMARDs included other diseases with RA (D'Arena et al., 2017), used single biologics (Krintel et al., 2013), subcutaneous and IV route(Harrold et al., 2016), and followed-up the patients for short period (20–52 weeks) (D'Arena et al., 2017; Harigai et al., 2016; Harrold et al., 2016; Krintel et al., 2013). In addition, all studies except one study (De Camargo et al., 2019)didn't used any causality assessment and the definition of ADR was either not reported (D'Arena et al., 2017; Elmedany et al., 2019; Jones et al., 2010; Krintel et al., 2013; Salmon et al., 2018) or used different definition for ADRs (Harigai et al., 2016). This heterogeneity in the used definition of ADRs between studies have limited the results of two previous systematic reviews and meta-analysis on the safety of both csDMARDs and bDMARDs (Gartlehner et al., 2006; Sepriano et al., 2020). Therefore, given the wide methodological variability in the previous studies, the direct comparison with our study is challenging.

When assessing the odds of developing ADRs for each biologic, rituximab was the lowest compared with other biologics, which was similar to the findings of De Camargo et al. (De Camargo et al., 2019). Infliximab was the highest in our study and found to have a hazard rate of 5.06 with withdrawal due to ADR in Krintel and colleagues (Krintel et al., 2013). In regard to the types of developed ADRs, the incidence of infusion site reactions was lower than what reported in the literature (D'Arena et al., 2017; De Camargo et al., 2019; Elmedany et al., 2019; Harigai et al., 2016; Krintel et al., 2013; Salmon et al., 2018). However, the rate of infections was higher than four studies (De Camargo et al., 2019; Elmedany et al., 2019; Harigai et al., 2016; Harrold et al., 2016; Jones et al., 2010)and similar to D'Arena et al (D'Arena et al., 2017). One reason for the lower rate of infusion site reaction in the current study may be the standard pre-treatment protocol followed in patients receiving biologics. The pre-treatment protocol included administration of antihistamines and paracetamol prior to IV bDMARD administration. Another reason could be the poor documentation of ADRs in our setting as it is hypothesized that not all reactions are documented. The presence of multiple comorbidities affects the development of ADRs (Angamo et al., 2016). Therefore, we adjusted for the CCI in our analysis. Patients with chronic illnesses, such as those included, often use multiple medications for various comorbidities. Hence, controlling for these variables is essential when performing regression analysis.

4.1. Strengths and weaknesses

This study has several strengths. First, it is one of the first Saudi studies to reflect the real-world management of RA with a longitudinal study design and a wide range of collected variables. Second, the WHO definition (World Health Organization. Department of Essential Drugs and Medicines Policy, 2002) was used to define ADRs, and all undesirable events recorded in patient files during

the five-year period were included in the analysis. Third, the Naranjo scale was used to exclude ADRs for which the cause was uncertain (Naranjo score < 1) from the analysis to avoid generating misleading results and to enhance the accuracy of the causality assessment for each ADR. Finally, the patients were followed up for a long period, which enabled us to evaluate the most commonly used IV bDMARDs in patients with RA in a clinical setting. However, this study has some limitations. Although all eligible patients were included, the number of participants was relatively small and the bDMARDs used by them varied. The number of participants who were followed up was especially low in the infliximab group, making comparisons among the groups difficult and compromising the generalizability of our findings. Abatacept was the only medication associated with significantly increased odds of having multiple ADRs; however, it is possible that statistical significance was not achieved for the other medications because of an insufficient number of participants.

4.2. Recommendations and future directions

Given safety concerns and the higher reported prevalence in our data, it is encouraged to educate patient using bDMARDs to perform frequent monitoring and assessment. This could be done through adherence to follow-up appointments (Findeisen et al., 2021). Patients should also be educated on importance of proper life style and nutrition which could help reducing disease progression and could be an area for future research for its effect on prevalence of ADRs (Gioia et al., 2020). To add, the future is shifted towards the use of oral targeted therapy with recently approved Janus kinase inhibitors which may theoretically play a role in omitting or minimizing some ADRs of large molecule IV therapy. This might be true. However, larger longitudinal comparative safety trials are highly warranted.

4.3. Conclusion

There was a high prevalence of ADRs among patients with RA receiving IV biologics. Abatacept was associated with a greater risk of multiple ADRs than other biologics. Infection was the most common ADR. This study provides health care practitioners engaged in RA management with information on what to expect when IV originator biologics are administered to patients with RA. Future multicenter longitudinal studies are warranted.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Haya M. Almalag: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing. **Shiekha S. Alaujan:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Hawazin S. Alhazzani:** Writing – original draft. **Lamia A. Alzamel:** Writing – original draft. **Reem S. Tashkandi:** Writing – original draft. **Hussain F. Alarfaj:** Validation, Writing – review & editing. **Abdurhman S. Alarfaj:** Validation, Writing – review & editing. **Mohammed A. Omair:** Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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