

Clinical characteristics of adverse events associated with therapeutic monoclonal antibodies in Korea

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ABSTRACT

Purpose The use of monoclonal antibodies (mAbs) is increasing in various clinical fields. Although mAb safety must be demonstrated prior to approval, targeted pharmacovigilance is essential for the recognition and assessment of adverse reactions. The purpose of this study was to identify the major clinical features of adverse reactions to mAbs in Korea.

Methods Spontaneous reports of adverse reactions attributed to 18 mAbs from January 2005 to December 2014 were extracted from the Korea Adverse Event Reporting System. We analyzed these reports for information relating to patient characteristics and the types of adverse reactions.

Results In total, 11 492 adverse reactions were reported in 7569 patients. Almost 19% of total study population showed suspected hypersensitivity reactions. Leukocyte abnormalities were reported frequently (10.0%), as well as infections (9.5%), drug eruptions (7.5%), and pruritus (5.0%). Furthermore, 3716 of the adverse reactions in 2538 patients were classified as serious; these included severe infections (18.2%), neutropenia (12.1%), visual dysfunctions (6.6%), and anaphylaxis (4.8%). The mAbs with the highest number of adverse reaction reports were rituximab (27.6%), adalimumab (17.5%), cetuximab (11.9%), and infliximab (10.7%).

Conclusions Hypersensitivity reactions were observed more frequently than expected, although no previously unrecognized reactions were observed. Adverse reactions occurred more frequently in children and in elderly patients. Close monitoring of adverse reactions to therapeutic mAbs is therefore warranted because these can potentially cause serious medical conditions or death. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—monoclonal antibody; adverse reaction; hypersensitivity; preferred term; neutropenia; pharmacovigilance

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INTRODUCTION

Biological products, defined by the US Food and Drug Administration (FDA) as drugs from natural sources that include humans, animals, and microorganisms,¹ have provided effective pharmaceuticals capable of targeting previously intractable diseases such as autoimmune diseases and cancer.^{2,3} In the last two decades, many biological agents including cytokines, monoclonal antibodies (mAbs), and fusion proteins have entered the drug market.⁴ Half of all new pharmaceutical products are estimated to be biological

products.⁵ In Korea, approximately 20 mAbs are currently registered and approved for the treatment of various diseases.

Biologic agents differ from traditional synthetic drugs.⁶ They are large, complex proteins, which are not metabolized in the liver and can only be administered parenterally.⁷ Biologic drugs have the potential to act as antigens or immunogens, generating humoral immune responses and forming anti-drug antibodies.^{8,9}

Biological agents may also differ from xenobiotics with regard to the clinical features of their adverse reactions.^{4,10,11} The disease for which the drug has been prescribed and concomitant treatments can both influence the adverse reactions to biological agents.¹² In recognition of these differences from xenobiotics, a new classification system for adverse reactions to

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biological products has been suggested; this consists of five types of reaction, which are denoted by Greek letters in order to distinguish them from the classical categorization of adverse reactions to traditional drugs.^{4,13} These five types are as follows: α reactions, which are associated with high cytokine levels; β reactions, which occur because of hypersensitivity; γ reactions, involving the immune imbalance; δ reactions caused by cross-reactivity; and ϵ reactions, which are not explained by the previous four classifications. Some previous reports have suggested that biologic product-induced adverse reactions often relate to immunomodulation, infection,^{14–16} and hypersensitivity reactions.^{17,18}

To protect public health and ensure drug safety, the Korean Ministry of Food and Drug Safety started to document spontaneous adverse events from 1988 onwards.¹⁹ The Korea Institute of Drug Safety and Risk Management (KIDS) was also established to expand national pharmacovigilance by monitoring adverse drug reactions observed in the Korean population and suggesting regulatory interventions. Currently, 27 Regional Pharmacovigilance Centers are affiliated with KIDS. On the basis of cumulative reports, the Korea Adverse Event Reporting System (KAERS) database was also established; this is compatible with international standards and the World Health Organization-Uppsala Monitoring Center (WHO-UMC) International Drug Monitoring Program.²⁰ The present study aimed to assess the clinical manifestations of spontaneously reported adverse reactions related to mAbs in the Korean population.

METHODS

Data collection

This study included spontaneously reported individual case safety reports (ICSRs) in Korea from January 2005 to December 2014 that involved patients receiving mAbs. These were identified within the KAERS database using their Anatomical Therapeutic Chemical code²¹. The study drugs selected are listed in Table 1. This study limited each report to the usual dose administered for therapeutic purposes in humans. ICSRs associated with mAbs as a concomitant medication, drug abuse, or medication errors were excluded.

The reports were inspected for patient age and sex; year of record; mAb indication and administration route; adverse reaction reporter diagnosis or description of the reaction by World Health Organization-Adverse Reaction Terminology (WHO-ART)²²; the reporter's profession; progress of adverse reactions; and causality assessment. Causality was assessed using the six categories delineated by WHO-UMC

criteria: certain, probable, possible, unlikely, conditional, and unassessable.²³ This was primarily assessed by the adverse drug reaction monitoring team in each Regional Pharmacovigilance Center and was subsequently reassessed and confirmed by KIDS healthcare professionals.

Patients were classified into four age subgroups: children (<12 years); adolescents (12 to 18 years); adults (19 to 64 years); and the elderly (≥ 65 years). The Korean Standard Classification of Diseases revision 6 (KCD-6) was applied to this analysis.²⁴ To reduce duplication of data, each adverse reaction was individually compared based on patient initials, age, sex, and source of report. If these factors were identical, reports were further examined for other information, including the reaction term and suspected drug; duplicate reports were then omitted. Patient records were anonymized prior to analysis.

According to the International Conference on Harmonization (ICH) E2D Guideline, all adverse reactions were categorized as either 'serious' or 'not serious'.²⁵ Adverse events that caused death, were life threatening, caused or prolonged hospitalization, induced a congenital anomaly, or were otherwise considered medically important were classified as serious. Outcomes were evaluated with respect to six different categories: patient recovered, patient not recovered, patient recovering, patient recovered with sequelae, patient with fatal damage, and unknown result.

Clinical symptoms were categorized using the WHO-ART system. Among the four-level hierarchical system structure, system-organ classes (SOCs) and preferred terms (PTs) were used in the analysis.²² In this study, hypersensitivity reactions were defined as including pruritus, rash, urticaria, itching, anaphylaxis, dermatitis, petechiae, purpura, local reactions at the injection site, toxic epidermal necrolysis, or Stevens–Johnson syndrome. All reports of suspected hypersensitivity reactions were reviewed and assessed for anaphylaxis using the World Allergy Organization diagnosis criteria in order to calculate the proportion of patients that showed hypersensitivity reactions.²⁶ In addition, we compared the clinical manifestations of ICSRs reported to KIDS in 2014 with respect to mAbs and xenobiotics.

ICSRs describing two or more PTs in one patient who was receiving one drug were treated as different adverse reactions. For those taking two or more medications at the same time, it was assumed that each medication was responsible for any reported adverse reactions. All ICSRs were also compared with domestic labeling information in order to detect unrecognized adverse reactions.²⁷

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Table 1. Kinds of monoclonal antibodies; object for this study. The table showed the detailed information on the monoclonal antibodies in our study

Monoclonal antibody	Target	ATC code third level	Approved indications in Korea
Abciximab	Platelet glycoprotein IIb/IIIa	Antithrombotic agents	Percutaneous coronary intervention Unstable angina
Adalimumab	TNF- α	Immunosuppressants	Rheumatoid arthritis, Ankylosing spondylitis Crohn's disease, Ulcerative colitis, Psoriatic arthritis, Psoriasis
Basiliximab	Interleukin-2 receptor- α	Immunosuppressants	Organ rejection
Bevacizumab	VEGF	Antineoplastic agents	Metastatic colorectal cancer Metastatic or unresectable non-small cell lung cancer Metastatic or advanced renal cell carcinoma Progressive glioblastoma
Brentuximab vedotin	CD30	Antineoplastic agents	Hodgkin lymphoma
Cetuximab	EGFR	Antineoplastic agents	Metastatic colorectal cancer Squamous cell cancer of head and neck cancer
Eculizumab	Complement protein C5	Immunosuppressants	Paroxysmal nocturnal hemoglobinuria
Golimumab	TNF- α	Immunosuppressants	Rheumatoid arthritis, Ankylosing spondylitis Ulcerative colitis, Psoriatic arthritis
Infliximab	TNF- α	Immunosuppressants	Rheumatoid arthritis, Ankylosing spondylitis Crohn's disease, Ulcerative colitis, Psoriatic arthritis, Psoriasis
Omalizumab	IgE Fc region	Systemic drugs for obstructive airway diseases	IgE-mediated asthma
Palivizumab	RSV protein F	Immunoglobulins	Prevention of RSV
Pertuzumab	HER2	Antineoplastic agents	Breast cancer
Ranibizumab	VEGF-A	Ocular vascular disorder agents	Age-related macular degeneration (intravitreal)
Rituximab	CD20	Antineoplastic agents	Non-Hodgkin's lymphoma, Rheumatoid arthritis Chronic lymphocytic leukemia, GPA, MPA
Tocilizumab	Interleukin-6 receptor	Immunosuppressants	Rheumatoid arthritis
Trastuzumab	HER2/neu	Antineoplastic agents	Breast cancer
Trastuzumab emtansine	HER2/neu	Antineoplastic agents	Breast cancer
Ustekinumab	Interleukin-12, Interleukin-23	Immunosuppressants	Psoriasis, Psoriatic arthritis

ATC, anatomical therapeutic chemical, FDA, food and drug administration, GPA, granulomatosis with polyangiitis, MRA, microscopic polyangiitis, TNF, tumor necrosis factor, VEGF, vascular endothelial growth factor, EGFR, epidermal growth factor receptor, IgE, immunoglobulin, Fc, fragment crystallizable, RSV, respiratory syncytial virus, HER, human epidermal growth factor receptor, CD, cluster of differentiation.

Statistical analysis

The demographic and clinical characteristics of study participants were analyzed using means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Chi-squared test or Fisher's exact test was used to compare categorical variables between groups and $p < 0.05$ was considered statistically significant. Data analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

General characteristics and clinical outcomes of mAb-related adverse reactions

In total, 20037 ICSRs in 9620 patients were obtained from January 2005 to December 2014. No duplicates were identified, although 5115 reports were excluded where the mAb was a concomitant drug and 3430 were eliminated because they reported a symptom that

had previously been reported in the same patient (tracking reports).

Finally, 11492 reports relating to 7569 patients were analyzed, involving 631 PT adverse reaction terms. The number of ICSRs increased each year and there was a 295-fold increase from 11 reports in 2005 to 3241 reports in 2014. Notably, for cetuximab, the ICSRs increased rapidly by more than 518-fold over these 10 years. A rapid rise was also seen for other mAbs (Figure 1). Approximately 70% of the ICSRs were reported by healthcare providers. Doctors were the dominant reporters of adverse reactions (41.7%), followed by nurses (19.7%), and pharmacists (5.4%). Reports by consumers represented 11.4% of all ICSRs in this study. Dosage information was accessible in 42.8% of the ICSRs. The study identified 4681 reports where complete recovery was achieved, 827 reports where the patient had not recovered, 333 reports where the patient was still recovering, 22 reports of recovery with sequelae, and 331 cases had fatal outcomes at the time of reporting. The outcomes were not

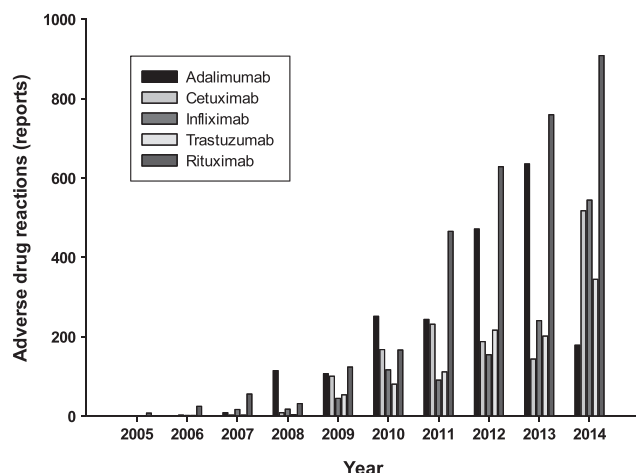


Figure 1. Number of adverse drug reaction reports of five common monoclonal antibodies in Korea. The increase rate of adverse drug reactions related five common monoclonal antibodies is much higher than the increase rate of whole monoclonal antibodies

indicated in the remaining ICSRs. Three hundred and fourteen patients reported adverse reactions after repeated drug administration. Reports were classified as certain (496 cases), probable (3271 cases), possible (2243 cases), unlikely (110 cases), unclassified (81 cases), or unassessable (1007 cases) using the WHO-UMC causality assessment. Causality was not assessed in the remaining reports because of a lack of information.

Patient demographic characteristics

The median age of the study participants was 53.0 years (Table 2). A subgroup analysis of the ICSRs revealed that the adult group was the largest. Females comprised 51.4% of all patients, with similar proportions in the children, adult, and elderly groups, whereas less than 40% of the adolescent subgroup was female; this represented a significant difference from the other age groups ($p < 0.001$). Almost all of

Table 2. Patient demographics

Characteristics	
Number of patients	7569
Female, <i>n</i> (%)	3648 (51.4 %)
Age, median (range)	53.0 (28 days–90.0 years)
Age, <i>n</i> (%)	
Children (<12 years)	113 (1.5%)
Adolescent (12 to 18 years)	140 (1.8%)
Adults (19 to 64 years)	4208 (55.6%)
Elderly (≥65 years)	1527 (20.2%)
Adverse drug reactions per patient (mean)	1.53
Number of patients with severe events, <i>n</i> (%)	2538 (33.5%)

the patients (96.4%) reported one adverse event while taking only one kind of mAb.

Types of adverse reactions by clinical symptoms

The SOC's most affected were the skin and appendages, followed by the body as a whole, and the gastrointestinal system (Table 3). The pattern of clinical manifestation differed between patient age groups (Figure 2). Visual abnormalities were reported more often in elderly patients ($p < 0.001$). In accordance with the PT system, the most frequent events were abnormal white blood cell counts (1150 events, 10.0%), followed by infection (1088 events, 9.5%), and skin rash (854 events, 7.4%). Hypersensitivity reactions were reported by 1466 patients (19.4%), who mainly experienced skin rash, urticaria, and pruritus. The majority of these individuals (1134 patients) had only one hypersensitivity symptom. Adults represented the largest subgroup of patients with hypersensitivity reactions (23.1%), followed by the elderly (16.8%), adolescents (16.4%), and children (9.7%). Patients with anaphylactic reactions to mAbs accounted for 2.4% of the total study group.

To investigate the differences in the clinical manifestations of adverse events to xenobiotics and mAbs, we analyzed the proportion of PT terms of ICSRs for the same time period. This indicated evident differences between the adverse events associated with these two medication types. The most common adverse event in patients receiving a xenobiotic was nausea, while the most common mAb-related adverse event was neutropenia (Figure 3).

During this study period, the rarest events (affecting less than 0.1%) involved collagen, the autonomic

Table 3. List of adverse drug reactions caused by monoclonal antibodies according to system organ class and frequency. Skin and appendages is the most dominant body system that is affected by adverse drug reactions of monoclonal antibodies

System organ class	Number of reports	% of reports
Skin and appendages	2148	18.7
Body as a whole-general	2119	18.4
Gastrointestinal system	1341	11.7
White cell and RES system	1151	10.0
Respiratory system	897	7.8
Central and peripheral nervous system	602	5.2
Application site	436	3.8
Vision	394	3.4
Resistance mechanism	297	2.6
Musculo-skeletal system	280	2.4
Psychiatric	247	2.1
Liver and biliary system	188	1.6
Urinary system	175	1.5

RES, reticuloendothelial system.

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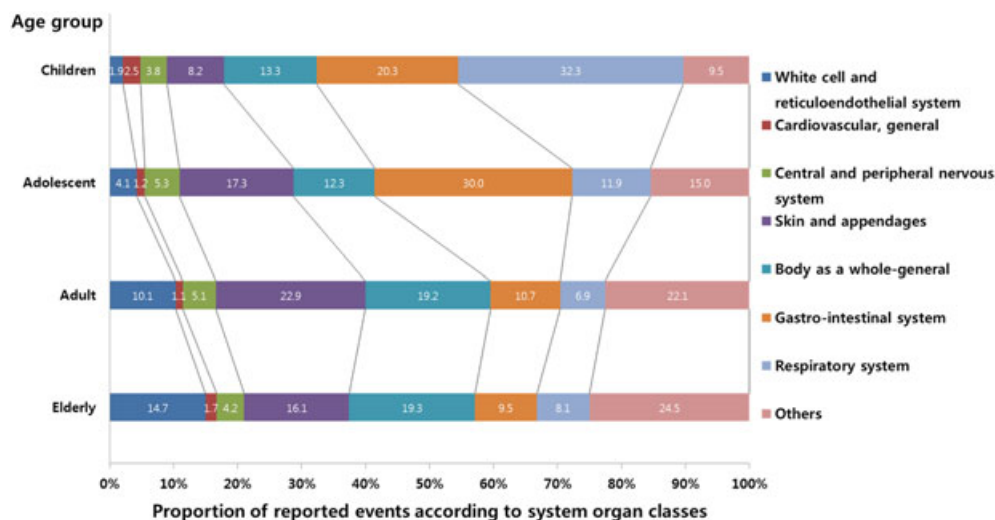


Figure 2. Frequent manifestations of monoclonal antibodies induced adverse drug reactions and distribution according to age. Clinical symptoms vary according to the age of the group

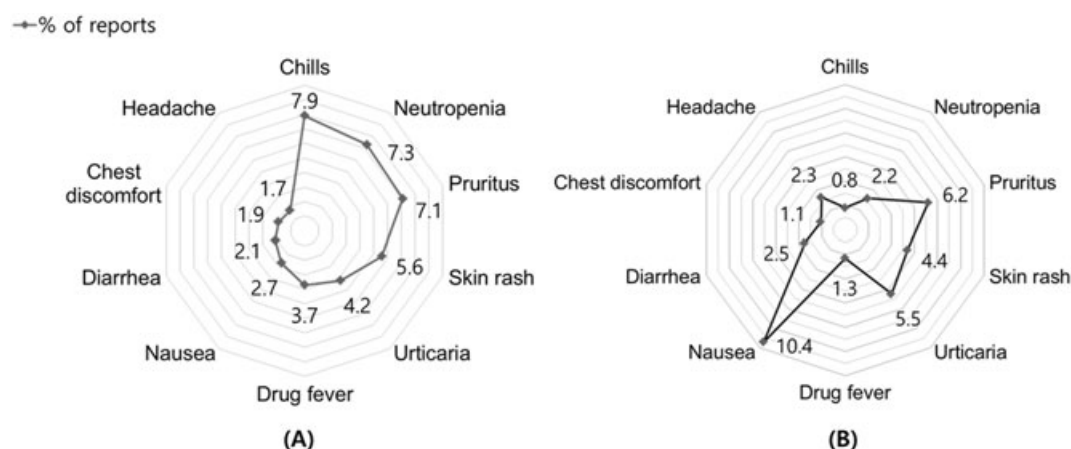


Figure 3. Comparison of the adverse drug reactions of monoclonal antibodies with entire set of adverse drug reactions to KIDS at 2014. (A: Adverse drug reactions of monoclonal antibodies, B: Entire set of adverse drug reactions) Adverse drug reaction caused by monoclonal antibodies is quite different from entire set of adverse drug reaction in clinical manifestations

nervous system, special sense, endocrine, cardiovascular, and male reproductive disorders. We did not identify any adverse reactions that were not covered by the product labeling.

Distribution of mAbs in ICSRs

ICSRs relating to 17 mAbs were reported to KIDS. There were no reports of brentuximab-induced adverse reactions during the study period. The most prevalent causative drugs were rituximab (3176 events, 27.6%), adalimumab (2015 events, 17.5%), cetuximab (1367 events, 11.9%), and infliximab (1213 events,

10.7%). The highest number of serious events was associated with the administration of rituximab (777 events, 20.9%), followed by infliximab (536 events, 14.4%), adalimumab (466 events, 12.5%), and cetuximab (349 events, 9.4%). Subgroup analysis indicated that males were more vulnerable to cetuximab, ranibizumab, and ustekinumab than females using the same drugs ($p < 0.001$). In contrast, females were more vulnerable to eculizumab, omalizumab, pertuzumab, tocilizumab, trastuzumab, and emtasine ($p < 0.001$). Adverse reactions associated with infliximab were reported more frequently in adolescents than in the other age subgroups

($p < 0.001$). The proportion of neutropenia in patients prescribed with rituximab was 20.7%.

Serious adverse reactions

According to criteria defined by the ICH E2D Guideline, 3716 serious adverse reactions were identified in 2538 patients; 331 of these patients died, 73 experienced life-threatening events, 26 had persistent disability, 2183 were hospitalized, and 1393 were considered to have medically important conditions. None of the patients included in this study experienced fetal malformation. The severity of events did not differ across gender. The frequency of serious events was elevated in children and in the elderly; these age subgroups included 56.3% and 40.5% of these events, respectively, which was significantly more than was observed in the other age subgroups ($p < 0.001$). The most common serious adverse reaction was infection (677 events, 18.2%); white blood cell abnormalities (448 events, 12.1%), visual abnormalities (247 events, 6.6%), and anaphylactic reactions (182 events, 4.9%) were also observed relatively frequently.

Indications leading to administration of mAbs

Indications were reported in 52.5% of the ICSRs included in this study (6038 of 11 492). In the remainder, the indication was not mentioned in detail. The indication stated most frequently for mAb administration was inflammatory bowel disease (Table 4). Of 3477 patients, only half of those who experienced adverse reactions from mAbs had cancer (2045 patients, 58.8%).

Table 4. Common indications of therapeutic administration of monoclonal antibodies among patients reported adverse drug reactions. Autoimmune disease and malignancy comprised a large proportion

Disease	Number of reports	% of reports
Malignancies		
Malignancy of breast	558	9.2
Malignancy of colon	528	8.7
Secondary malignancy of colon	403	6.7
Malignancy of lung	74	0.7
Hematologic malignancy		
Diffuse large B cell lymphoma	486	8.0
Non-Hodgkin lymphoma	376	6.2
Chronic lymphocytic leukemia	168	1.2
Other malignancy	278	4.6
Autoimmune diseases		
Inflammatory bowel disease	658	10.9
Rheumatoid arthritis	601	10.0
Ankylosing spondylitis	373	6.2
Psoriasis	318	5.3
Degeneration of mucula	258	4.3
Other diseases	959	15.9

DISCUSSION

Although there have been previous studies of specific adverse reactions to clinical mAb use,^{15,17,28–30} few of these have reviewed all of the reported adverse reactions.³¹ To the best of our knowledge, this is the first comprehensive study of this type that employed a long monitoring period.

The present study identified a higher proportion of serious adverse reactions involving neutropenia, as compared with previous reports. Neutropenia can occur either as an adverse reaction during mAb administration or at a later stage in the treatment. It is therefore difficult to determine whether this is an adverse reaction to the mAb administration. In the previous studies, early-onset neutropenia rarely developed in patients receiving rituximab, which was most frequently associated with neutropenia in these patients.^{32,33} Although the present study did not allow us to analyze the time of neutropenia onset, relative to mAb administration, previous studies have indicated the late-onset neutropenia is commonly associated with rituximab administration.³⁴ Late-onset neutropenia is self-limiting and rarely associated with infections or other serious events.^{34,35} However, the present study found that in patients taking rituximab, a similar proportion of those with serious and non-serious adverse reactions had neutropenia. These results suggest that late-onset neutropenia might lead to serious adverse events. Neutrophil counts should therefore be carefully monitored in patients receiving rituximab.

A notable finding of this study was that a high proportion of the total adverse reactions was classified as serious. Comparison of our study with a previous Korean report relating to adverse reactions indicated that the proportion of serious events in patients receiving mAbs was markedly higher than the proportion observed in the entire patient population.¹⁹ Among the patients using anti-tumor necrosis factor- α , a substantial increase in opportunistic infections, such as tuberculosis and other serious infections leading to hospitalization, was reported.^{36–38} The proportion of infections was significantly higher in patients with serious adverse reactions, as compared to those with any level of adverse reaction. Anaphylactic reactions occurred more frequently than expected. The proportion of serious reactions in children and the elderly was significantly higher than in the other age groups. Therefore, mAbs should be administered cautiously in certain age groups and anaphylaxis should be closely monitored.

According to a review from the Spanish Society of Rheumatology, hypersensitivity reactions account for 0.5% of all adverse reactions.³⁹ However, we found

that the proportion of patients with hypersensitivity reactions was significantly higher than that reported previously.^{39,40} Even if some of the hypersensitivity reactions reported in this study were false positives, this result has significant implications for mAb-related hypersensitivity reactions. We also found marked differences between the adverse reactions to mAbs and the adverse reactions to xenobiotic administration submitted to KIDS in 2014. These results might reflect the obvious differences in clinical manifestation of adverse reaction between mAbs and xenobiotics.⁴¹

Patient age influenced the mAb-related adverse reactions. The relationship between aging and adverse reactions has been found to reflect differences in co-morbidity, medical care utilization, and drug prescription rates.⁴² A retrospective cohort study of pediatric patients who experienced an adverse reaction over a 10-year period reported similar results as the present study.⁴³ The clinical symptoms of adverse reactions were also affected by sex. In this study, the proportion of female study participants was fairly similar to that reported in previous epidemiological studies of the distribution of adverse drug reactions.^{33,44} There were similarities with data from previous studies, which showed a preponderance of adverse reactions in female patients.^{45–47}

This study had several limitations. First, the data resulted from spontaneous reporting, which has a tendency to underestimate the true rate of adverse drug reactions, contains heterogeneous reports from a range of sources, and can lack information.⁴⁸ This meant that we could not perform statistical analyses that controlled for confounding factors in the group comparisons. In addition, our exclusion of reports associated with mAb use as a concomitant medication may have led to an underestimation. Second, we could not produce a reliable estimate of the overall incidence of adverse reactions in patients receiving mAbs because of a lack of information on the total usage of mAbs in Korea. However, the goal of this study was to investigate the clinical manifestation of these adverse reactions, rather than to estimate their incidence. Third, this retrospective study could not investigate the frequency of long-term complications of mAb usage, such as malignancy. Some previous studies reported that patients using mAbs had an increased incidence of malignancy.^{49–51}

mAbs represent a current trend in the pharmaceutical industry and can provide valuable tools in clinical medicine. With their increasing clinical use, the total number of adverse reaction reports in patients receiving mAbs is expected to increase. This study indicated that there is a need to collate information on these adverse events because limited data is available on

clinical manifestations that are identified after the drug approval process.

CONCLUSION

The present study found that reports of adverse events related to mAb usage increased during the study period, with a higher proportion of severe reactions reported in patients receiving mAbs. Although previous studies identified mild neutropenia and a low incidence of hypersensitivity reactions, our study found that neutropenia could be present in patients with serious adverse events and that hypersensitivity occurred more frequently than expected. The pattern of adverse reactions related to mAb usage also differed between age groups. Severe adverse reactions developed more frequently in children and the elderly, and anaphylaxis was not rare in these age groups. Consequently, there is a need for intensive monitoring when administering mAbs to children or elderly patients. As the use of mAbs increases, heightened awareness of healthcare professionals and patients will be required to predict, identify, and manage adverse drug reactions.

AUTHORS' DISCLOSURE

The authors declare no conflicts of interest. Pharmacovigilance data was provided by the Korea Institute of Drug Safety & Risk Management (Ministry of Food and Drug Safety). This study was supported by the Severance Regional Pharmacovigilance Center (Seoul, Korea).

KEY POINTS

- Nineteen percent of patients reported type β adverse reactions to monoclonal antibodies.
- The pediatric and aging populations are more vulnerable to serious adverse reactions.
- Intensive monitoring of vital signs is important during treatment of patients with monoclonal antibodies because of the high proportion of hypersensitivity reactions.

ETHICS STATEMENT

The Institutional Review Board of Yonsei University College of Medicine approved this study (IRB No. 4-2015-0590) and waived the requirement for informed consent.

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