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Safety of Ramucirumab Regimen Without H1-antihistamine Premedication in Patients With Solid Cancers

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Abstract. *Background/Aim: To prevent infusion-related reactions (IRRs), H1-antihistamines (H_1AT) are recommended as a premedication for monoclonal antibodies, such as Ramucirumab (RAM), even though there are H_1AT-related side effects, such as drowsiness and dizziness. Here, we investigated the safety of H_1AT-free RAM regimens in patients with solid cancer. Patients and Methods: We retrospectively reviewed the patients with solid cancer receiving RAM without H_1AT at Osaka Medical College Hospital between 2015 and 2019. Results: Among the 123 registered patients, 58 were identified as eligible. The total number of RAM infusions was 291, and the median number of RAM administration was 4 cycles (range=1-23 cycles). IRRs were not observed in any patient. Conclusion: Although our data are preliminary and limited, H_1AT-free RAM regimens may be a treatment option for cancer patients having a significant risk of developing H_1AT-related side effects. Further studies are needed to confirm the safety of H_1AT-free RAM regimens.*

Monoclonal antibodies (mAbs) have been widely used for the treatment of various malignancies (1-3). As most mAbs show lower toxicity than conventional anticancer agents, they are generally better tolerated (2-4). However, like other infused anticancer agents, mAbs may cause infusion-related reactions (IRRs) (1-3). Most IRRs are mild with symptoms such as chills, fever, nausea, skin rash, and pruritus. Although severe side effects are less frequent, they may be fatal without appropriate intervention care. The incidence of IRRs varies by agent, mostly during the first or second infusion (4-6). Although the exact etiology of IRRs remains unclear, they may arise *via* either immunoglobulin E (IgE)-dependent or -independent mechanisms. The mAbs interact with their molecular targets on circulating blood cells, tumor cells, or effector cells recruited to the tumor site, thereby promoting the release of inflammatory cytokines (6, 7). When released into the circulation, cytokines can produce a wide range of symptoms, characteristic of IRRs. Premedication with H1-antihistamines (H_1AT), acetaminophen, or corticosteroids is a common practice to prevent IRRs associated to mAb use (1, 5). It is difficult to evaluate adverse events, such as IRRs, through prospective studies due to the unexpected nature of these events. In a previous observational study, the rate of IRRs did not change with dexamethasone (DEX) reduction as a premedication in cetuximab treatment (8). The underlying nature of IRRs needs to be characterized in order to identify patients at risk, as well as provide optimal prophylactic measures and symptom management.

Ramucirumab (RAM) is a fully human mAb (IgG1) directed against the vascular endothelial growth factor receptor 2 (VEGFR2), developed for the treatment of solid cancers (9). IRRs occur in 1%-7% of patients who receive RAM, and high-grade (Grade 3 and 4) reactions occur in <1% of patients (9-14). Although IRRs are rarely observed in clinical practice during RAM infusions, H_1AT premedication is still recommended to reduce the risk of IRRs during RAM treatment. In fact, as stated in the package insert of RAM in the United States, H_1AT are recommended as the sole anti-allergy prophylactic premedication to treat

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Key Words: Ramucirumab, infusion-related reactions, H1-antihistamines, monoclonal antibodies.

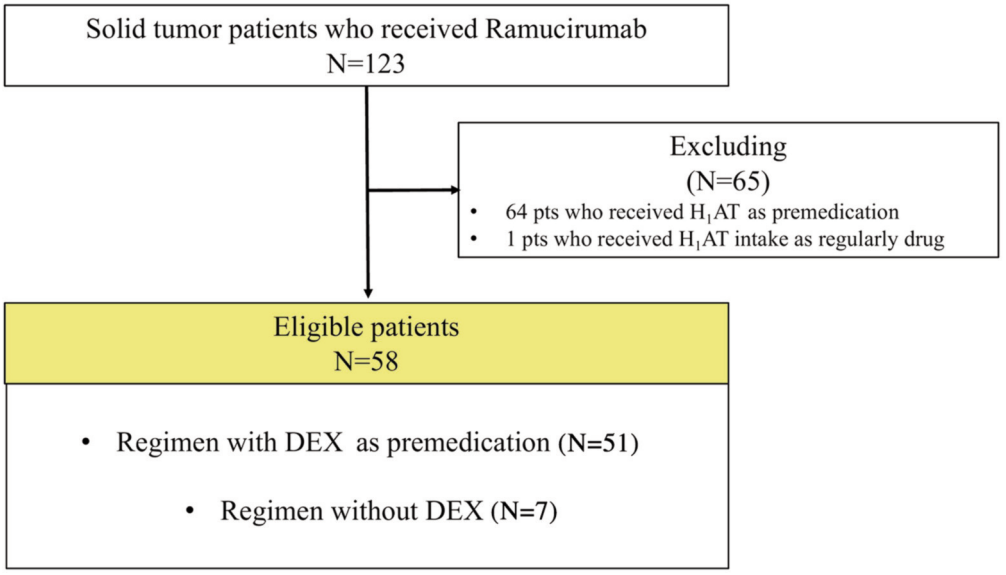

Figure 1. *CONSORT diagram. H1AT: H1-antihistamine; DEX: dexamethasone.*

IRRs caused by RAM. However, H_1AT may cause several side effects, including drowsiness and dizziness (15), and therefore, their use should be carefully administered in the elderly and those who need to drive. To date, it is unclear whether H_1AT-free RAM regimens can be considered safe for the patients with cancer. Therefore, our aim was to investigate the safety of H_1AT-free RAM regimens in patients with solid cancers.

Patients and Methods

Study subjects. We retrospectively reviewed the patients with solid cancer who received RAM-containing regimens with or without H_1AT at the Osaka Medical College Hospital from June 1, 2015 to July 7, 2019. We selected patients who met the following four inclusion criteria: i) being >20 years old, ii) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, iii) having histologically confirmed cancers, and iv) receiving RAM without H_1AT. The exclusion criterion was having daily use of H_1AT due to allergic diseases. Antiemetic steroids for cytotoxic chemotherapy were acceptable.

Evaluation. The incidence of IRRs during the infusions within the first cycle and the total number of cycles, as well as the incidence of other adverse events (allergic and RAM-related) was investigated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Each chemotherapy regimen, including dose and duration, was determined by the corresponding physician. Generally, patients received intravenous RAM (8 mg/kg) for 1 hour every 7 or 14 days with or without other chemotherapeutics.

Data analysis. Bivariate analyses, chi-square tests, or Fisher's exact probability tests were used to evaluate the significance of incidence of IRRs. All data were analyzed using JMP® 14 (SAS Institute Inc., Cary, NC, USA), and $p<0.05$ was considered statistically significant.

Results

Patient characteristics. Out of 123 registered patients, 58 were identified as eligible subjects for this retrospective study (Figure 1). Fifty-one patients received RAM with DEX as premedication and 7 patients did not have DEX. Patient characteristics are listed in Table I. Median age was 72 (range=39-83) years old, 58% were male, 26% had a history of allergies, and patients who had lung cancer, gastric cancer, and colorectal cancer were 48.4%, 44.8%, and 6.9%, respectively.

Incidence of IRRs and premedication. Regimens were categorized into Groups A-E, according to the combination and doses of DEX. Premedication in regimens A, B, D, and E was 6.6 mg of DEX, while regimen C had no premedication (Table II). The total number of RAM infusions was 291. Moreover, the median cycle number per patient was 4 (range=1-23 cycles), and the median dosage of RAM for all patients was 470 mg (range=164-892 mg). The overall incidence of IRRs was 0% (0/291) (Table III).

Other adverse events. Toxicities associated with an initial treatment are listed in Table IV. Although there were no IRRs, other RAM-related adverse events did occur. Proteinuria and hypertension were experienced by 32.8% and 13.8% of the patients, respectively. Severe toxicities of grade 3 or 4 included proteinuria (6.9%), hypertension (1.7%) and bleeding (1.7%).

Table I. *Patient characteristics*.

Criteria	N=58 (%)
Age median (range)	72 (39-83)
Gender	
Male	34 (58.6)
Female	24 (41.4)
Origin	
Lung cancer	28 (48.3)
Gastric cancer	26 (44.8)
Colon cancer	4 (6.9)
PS	
0	20 (34.5)
1	38 (65.5)
History of allergies	
Medicine	11 (20.1)
Food	2 (3.4)
Food & medicine	2 (3.4)
Not applicable	43 (73.1)
Daily medicine	
Steroids	5 (8.6)
Not applicable	53 (91.4)

PS: Performance status.

Table II. *Treatment regimens, premedication, and total infusion*.

Regimen	N (%)	Premedication	Total infusion
A: Docetaxel+RAM	28 (47)	DEX 6.6 mg	139
B: Nab-Paclitaxel+RAM	18 (31)	DEX 6.6 mg	81
C: RAM monotherapy	7 (12)	-	29
D: FOLFIRI+RAM	4 (8)	DEX 6.6 mg	35
E: Irinotecan+RAM	1 (2)	DEX 6.6 mg	7

RAM: Ramucirumab; FOLFIRI: leucovorin calcium; 5-fluorouracil, and irinotecan; DEX: dexamethasone.

Table III. *Incidence of infusion-related reactions in H1AT-free ramucirumab regimens*.

Factors	Results
Total number of ramucirumab infusions	291
Number of cycles per patient, median (range)	4 (1-23)
Ramucirumab dosage, median (range), mg/kg	470 (164-892)
Incidence of IRRs at first cycle, % (95%CI)	0 (0-0.06)
Incidence of IRRs at all cycles, % (95%CI)	0 (0-0.07)

H_1AT: H1-antihistamines; CI: confidence interval.

Discussion

The present study investigated the safety of H_1AT-free RAM regimens in patients with solid cancers. On evaluating these regimens, we found that none of the patients receiving H_1AT-free RAM-containing regimens experienced IRRs.

These results are in conflict compared to RAM-induced IRRs in patients with solid cancer identified in the RAINBOW (5.8%) (10), REGARD (0.4%) (11), REVEL (3.7%) (12), REACH (6.1%) (13), REACH-2 (6.6%) (14) and RAISE (5.9%) (9) trials (Table V). The regimens for gastrointestinal cancer patients used in the RAINBOW (10) and RAISE (9) trials consisted of RAM combination therapy with cytotoxic drugs, and DEX as premedication. However, it is unclear whether H_1AT was used for the prevention of IRRs. The RAISE trial regimen consisted in RAM monotherapy without DEX, and only 57.8% of the patients received H_1AT (9). Although DEX was not used as premedication, the incidence of IRRs in the REGARD trial was lower than in the RAINBOW and RAISE trials. DEX and H_1AT are generally used as anti-allergy premedication (1, 5). However, the benefits of these drug combination are unknown, and suitable doses are not well established. In clinical practice, DEX and H_1AT are considered beneficial to reduce the occurrence of RAM-induced IRRs. Considering the rate of incidence of IRRs in the RAINBOW (5.8%) and RAISE (5.9%) trials, DEX and H_1AT premedication is likely to reduce the risk of IRRs. In contrast, although the use of H_1AT premedication was only 57.8% in the REGARD trial, IRRs were rarely observed.

Using molecular targeting agents, the MABEL trial (16) has reported that the incidence of IRRs using cetuximab (chimeric mouse-human mAbs) was higher in colorectal cancer patients who received H_1AT alone compared to patients who received H_1AT and DEX (any grade=25.6% *vs*. 9.6%; grade¾=4.7% *vs*. 1.0%, respectively). Data from the prospective and retrospective studies of panitumumab (fully humanized mAbs) and cetuximab showed that the frequency of IRRs was lower in the panitumumab group (17-19). Our findings are consistent with those of the previous reports concerning panitumumab and cetuximab, and with the hypothesis that fully humanized mAbs are less immunogenic than chimeric mAbs. As RAM is a fully humanized mAb, IRRs may occur at a lower rate.

In clinical practice, *d*-Chlorpheniramine maleate is a type of H_1AT commonly used to prevent the occurrence of IRRs during the administration of RAM regimens (8). The use of *d*-Chlorpheniramine maleate poses several known risks. The intake of 2 mg of *d*-Chlorpheniramine maleate causes loss of concentration, and decreases the judgment and work efficiency to an extent comparable with drinking three glasses each containing 90 ml of whiskey (15). An intravenous injection of 5 mg of *d*-Chlorpheniramine maleate occupies 87% of the averaged values of available histamine H1 receptors in the frontal cortex. In addition, impaired performance of the central nervous system is significantly correlated with the concentration of plasma chlorpheniramine

Table IV. *Incidence of adverse events for ramucirumab.*

	NC/NA	Grade 1	Grade 2	Grade 3	Grade 4	All
Proteinuria	39	10 (17.2%)	5 (8.6%)	4 (6.9%)	0	19 (32.8%)
Hypertension	50	0	7 (12.0%)	1 (1.7%)	0	8 (13.8%)
GI perforation	58	0	0	0	0	0
Bleeding	57	0	0	1 (1.7%)	0	1 (1.7%)
Pneumonia	57	0	0	0	1 (1.7%)	1 (1.7%)

NC/NA: No change from baseline/no adverse event; GI: gastrointestinal.

(20). These results suggest that due to the adverse side effects of H_1AT premedication, which include drowsiness and dizziness, it may be advisable to restrict its use in the elderly and those who need to drive.

Our results did not reveal a clear benefit of premedication with H_1AT, as IRRs were not observed with either the H_1AT-free RAM monotherapy or the combination therapy regimens. To the best of our knowledge, this is the first report demonstrating the safety of RAM infusion without H_1AT premedication, suggesting H_1AT-free RAM-containing therapies may be safe in terms of IRRs development. However, our study has some limitations. First, this was a single-center population and a retrospective nonrandomized study with a small sample size. The RAM regimen was selected according to the physician's choice, which may have introduced a selection bias. Second, data on the pharmacokinetics of RAM were not obtained. Third, our study included patients with different treatment regimens, resulting in differences in terms of premedication. Fourth, our study did not include patients with hepatocellular carcinoma who have been reported to have more IRRs in RAM (13, 14). Finally, patients with allergic diseases could have been excluded.

The H_1AT-free RAM regimens may be considered as a treatment option for the patients with cancer who risk developing H_1AT-related side effects. Given that this was a retrospective analysis, caution must be exercised in the interpretation of these data, which require a formal confirmation in a prospective study.

Conflicts of Interest

MG: Eli Lilly, TAIHO Pharmaceutical Co., LTD., Daiichi Sankyo, Yakult Honsha Co., LTD., CHUGAI PHARMACEUTICAL CO., LTD., ONO PHARMACEUTICAL CO., LTD., Eisai, NIPPON KAYAKU, MSD, Sumitomo Dainippon Pharma Co., AstraZeneca, outside the submitted work. All other Authors have declared no conflicts of interest regarding this study.

Authors' Contributions

MY initiated this project. EG, TY, NH, MG, MN, KU, and YR designed the study protocol and wrote the manuscript. EG, NH and TY collected clinical information and performed statistical analysis.

Table V. *Comparison of infusion-related reactions rates between our study and previous prospective trials.*

Trial	N	All Grades	Grade 3	Grade 4
RAINBOW (10)	327	19 (5.8%)	2 (0.6%)	0
REGARD (11)	236	1 (0.4%)	0	0
RAISE (9)	529	31 (5.9%)	4 (0.8%)	0
REVEL (12)	627	23 (3.7%)	2 (0.3%)	3 (0.5%)
REACH (13)	277	17 (6.1%)	3 (1.0%)	0
REACH-2 (14)	197	13 (6.6%)	0	0
Our study	58	0	0	0

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