original contributions

Incidence and Management of Olaratumab Infusion-Related Reactions

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QUESTION ASKED: What have we learned about the nature and frequency of infusion-related reactions (IRRs) associated with olaratumab in clinical trials and postmarketing surveillance reports?

SUMMARY ANSWER: For almost all patients, the first IRR occurred during the first two cycles of treatment, and grade 3 or worse IRRs were reported during the first infusion only, usually within 15 minutes of the start of the infusion. An association was evident between grade 3 or worse IRRs and pre-existing immunoglobulin E anti–galactose-α-1,3-galactose (anti–α-Gal) antibodies, with a trend toward higher IRR rates in US geographies known to have a higher prevalence of anti–α-Gal antibodies.

WHAT WE DID: All nine olaratumab clinical trials conducted by sponsor Eli Lilly that were completed as of November 2016, as well as postmarketing surveillance reports through October 2017, were reviewed for IRRs, and blood samples from patients in the clinical trials were analyzed for pre-existing anti–α-Gal antibodies.

WHAT WE FOUND: The clinical nature and severity of IRRs observed for olaratumab in clinical trials and postmarketing surveillance reports were consistent, and the symptoms were similar to those reported for other monoclonal antibodies. Grade 3 or worse IRRs were observed exclusively during the first infusion of olaratumab, and there was an association between grade 3 or worse IRRs and pre-existing anti–α-Gal antibodies.

BIAS, CONFOUNDING FACTORS: The strength of the associations in this study cannot be reliably determined at this time, because the overall number of patients with grade 3 or worse IRRs in olaratumab clinical trials is still too small (only 11 patients) to draw valid conclusions. Clinical trial sites and their enrollments were not equally spread across the United States, and because soft tissue sarcoma (STS) is rare and often treated at regional sarcoma centers of excellence, geographic distribution of IRRs may be more localized to these centers than it would for common types of cancer that would involve larger numbers of patients treated in community settings.

REAL-LIFE IMPLICATIONS: All patients receiving olaratumab should be premedicated according to the local label, regardless of where they are treated, and monitored for signs and symptoms of IRRs in a setting where resuscitation equipment for treatment of IRRs is readily available. Olaratumab should be immediately and permanently discontinued if a patient experiences a grade 3 or worse IRR. Active monitoring for IRRs is ongoing in current clinical trials and postmarketing surveillance. The recent phase III ANNOUNCE study of olaratumab in combination with doxorubicin in patients with advanced or metastatic STS did not confirm the phase II results in STS. In light of this information, the US Food and Drug Administration recommended on January 24, 2019, that patients who are currently receiving olaratumab consult with their health care providers about whether to continue treatment and that olaratumab not be initiated in new patients outside of an investigational study.

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CARE DELIVERY

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abstract

PURPOSE Olaratumab is a human monoclonal immunoglobulin G1 antibody against platelet-derived growth factor receptor-α. We report the nature and frequency of infusion-related reactions (IRRs) with olaratumab in clinical trials and postmarketing reports.

METHODS Data from patients exposed to olaratumab across nine clinical trials were reviewed for IRRs. Blood samples were also analyzed for pre-existing immunoglobulin E anti–galactose-α-1,3-galactose (anti–α-Gal) antibodies.

RESULTS In the clinical trials, IRRs were identified in 70 of 485 patients (14.4%). The most frequent symptoms included flushing, fever or chills, and dyspnea. For 68 of 70 patients (97.1%), the first IRR occurred during the first two cycles of treatment. Grade 3 or worse IRRs were reported in 11 patients (2.3%), all during the first infusion and usually within 15 minutes of the start of the infusion. One IRR-related fatality (0.2%) occurred in a nonpremedicated patient with grade 3 or worse cardiac comorbidities. There was an association between grade 3 or worse IRRs and pre-existing anti–α-Gal antibodies, with a trend toward higher IRR rates in US geographies known to have a higher prevalence of anti–α-Gal antibodies. IRRs in postmarketing reports were consistent in nature and severity with those in the clinical trials.

CONCLUSION Premedication with corticosteroids and antihistamines should occur in all patients before olaratumab infusion, as indicated in labels in the United States and the European Union. Patients receiving olaratumab should be monitored for IRRs in a setting where resuscitation equipment is available for the treatment of IRRs.

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INTRODUCTION

Monoclonal antibodies used for cancer treatment are nonendogenous proteins that are parenterally administered and therefore carry the inherent risk of infusion-related reactions (IRRs).[1,2] IRRs are type B (idiosyncratic) adverse drug reactions that are unrelated to dose or drug pharmacologic activity.[2] Most IRRs are mild to moderate in severity (grade 1 or 2 IRRs), with symptoms including chills, flushing, fever, headache, nausea, pruritus, and skin rash. Severe (grade ≥ 3 IRRs) presentations (eg, anaphylaxis or cytokine release syndrome) may occur infrequently; these grade 3 or worse IRRs can develop rapidly and be life threatening. Immediate and appropriate medical treatment and termination of antibody treatment are required in these cases.[3,4] IRRs most often occur during or after the first or second exposure to an antibody.[2,5] The reported incidence of IRRs during exposure for several commonly used monoclonal antibodies varies from 77% for rituximab to 40% for trastuzumab and from 15% to 21% for cetuximab.[4] Rates of grade 3 or worse IRRs for these monoclonal antibodies range from lower than 1% for trastuzumab to 10% or lower for rituximab.[5] Although the use of premedication might reduce the incidence of IRRs, grade 3 or worse IRRs, such as anaphylaxis, can still occur.[1,2,5]

Olaratumab is a recombinant fully human immunoglobulin G1 (IgG1) monoclonal antibody that specifically binds to platelet-derived growth factor receptor-α and blocks receptor activation, which has been shown in vitro and in vivo to lead to antitumor activity against

ASSOCIATED CONTENT

Appendix

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selected sarcoma cell lines and disrupted platelet-derived growth factor receptor-α pathway signaling in in vivo tumor implant models.[6] Olaratumab has two glycosylation sites: one in the variable Fab region and the other in the conserved heavy chain Fc region.[7] The Fab site of olaratumab is occupied by N-linked oligosaccharides capped with galactose-α-1,3-galactose (α-Gal) and/or N-glycolylneuraminic acid residues.[7] α-Gal glycosylation residues have been reported to be implicated in grade 3 or worse IRRs to other therapeutic antibodies containing α-Gal glycosylation (eg, cetuximab), particularly in patients with detectable levels of naturally occurring immunoglobulin E (IgE) antibodies directed against α-Gal.[8]

In a phase Ib/II study (I5B-IE-JGDG [JGDG]) of patients with advanced soft tissue sarcoma (STS), the addition of olaratumab to doxorubicin resulted in a significant improvement in overall survival compared with doxorubicin alone.[9] On the basis of the results of the JGDG study, olaratumab in combination with doxorubicin received accelerated or conditional approval from the US Food and Drug Administration and the European Medicines Agency in 2016 for the treatment of patients with advanced STS. Topline results from the confirmatory phase III ANNOUNCE study (I5B-MC-JGDJ) did not confirm the benefit for patients with STS observed in the phase II study.[10]

Here we provide a detailed analysis of IRRs across nine olaratumab studies, including an analysis of premedication, IRR management, and patients' pre-existing anti–α-Gal antibodies. We also analyzed reports of IRRs outside of clinical trials through postmarketing surveillance reports.

METHODS

Olaratumab Clinical Trials

Trials and treatments. Data were analyzed from nine olaratumab clinical trials conducted by Eli Lilly that were completed as of November 2016.[6,9,11-17] The trials were conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice E6.

Safety and IRR analysis. Safety in each clinical trial was assessed through clinical and laboratory evaluations according to their respective study protocols, as previously published.[6,9,11-17] Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0 or 4.0). A comprehensive strategy of 57 preferred terms was used to search for potential IRRs. Medical reviews were conducted to assess temporal relationships between olaratumab infusion, medical history, and associated concurrent symptoms or illnesses. Case narratives from Council for International Organizations of Medical Sciences forms were also evaluated, taking into consideration the investigator's opinion if an event was reported as a serious AE to the sponsor. Safety analyses were conducted in all patients who received at least one dose of olaratumab, including premedicated and nonpremedicated patients (safety population).

Anti–α-Gal antibody assay. Blood samples, where available, for assessment of immunogenicity were evaluated for all nine trials before initiation of olaratumab treatment and after any known IRR occurred. Anti–α-Gal antibodies were measured by ViraCor Eurofins Laboratories (Lees Summit, MO), using an assay that was developed for screening red meat allergies.[8,18] Calibration of the assay was performed using IgE standards. The dynamic range of the assay was 0.10 to 100 kU/L of anti–α-Gal antibodies with a upper limit of normal of 0.35 kU/L.

Postmarketing Surveillance Reports

Postmarketing surveillance reports included AEs reported (unsolicited or spontaneous cases) to Eli Lilly by health care providers, non–health care providers, and regulatory agencies through October 2017. The methodology for identification of potential IRR cases was consistent with that used for clinical trials based upon information provided in the case description. An additional search of preferred terms was performed using Standardized MedDRA Queries for anaphylaxis (MedDRA version 20.0). Determination of the severity of IRRs was based on the nature of reported preferred terms. The estimated postmarketing reporting rate for IRRs was calculated using all the surveillance reports of IRRs and the estimated number of patient exposures based upon the total volume of olaratumab drug product released by distributors.

Statistical Analysis

The statistical analyses for this study were descriptive. Categorical variables were summarized using frequencies and percentages. Positive and negative predictive values for the presence of anti–α-Gal antibodies and grade 3 or worse IRRs were determined. The Clopper-Pearson method was used to calculate the 95% CIs for the positive and negative predictive values.[19]

RESULTS

Incidence and Severity of IRRs in Clinical Trials

Across the nine olaratumab trials, IRRs of any grade were reported for 70 of 485 patients (14%) who received at least one dose of olaratumab. A majority of IRRs were grade 1 or 2 (n = 59), and for a majority of patients (97%), the onset or first occurrence of the IRR was in cycle one or two. The most common terms reported for these events were IRR and hypersensitivity. When specific AE terms indicative of IRRs were reported, the most common were flushing; fever and/or chills; itching, pruritus, rash, or hives, back or abdominal pain, chest pain or tightness, and dyspnea.

TABLE 1. Olaratumab Clinical Trials Assessed for IRRs

Study	Phase	Primary End Point	Cancer Type	Study Treatment	ClinicalTrials.gov Identifier	Olaratumab Arm			Control Arm		
							No. (%) of IRRs*			No. (%) of IRRs*	
						No. of Patients	Any Grade	Grade ≥ 3	No. of Patients	Any Grade	Grade ≥ 3
JGDA	II	PFS	Ovarian cancer	Olaratumab + liposomal doxorubicin	NCT00913835	90	9 (10.0)	0	61	3 (4.9)	0
JGDB	II	PFS	NSCLC	Olaratumab + paclitaxel + carboplatin	NCT00918203	85	19 (22.4)	2 (2.4)	64	5 (7.8)	1 (1.6)
JGDC	I	Safety	Solid tumors and lymphoma	Olaratumab	NCT00768391	19	5 (26.3)	0	NA	NA	NA
JGDD	II	PFS	Prostate cancer	Olaratumab + mitoxantrone + prednisone	NCT01204710	81	9 (11.1)	4 (4.9)	59	0	0
JGDE	II	PFS	Glioblastoma	Olaratumab	NCT00895180	40	4 (10.0)	0	NA	NA	NA
JGDF	I	Safety	Solid tumors	Olaratumab	NCT01199822	16	0	0	NA	NA	NA
JGDG	Ib	Safety	STS	Olaratumab + doxorubicin	NCT01185964	15	2 (13.3)	0	NA	NA	NA
JGDG	II	PFS	STS	Olaratumab + doxorubicin	NCT01185964	94	14 (14.9)	4 (4.3)	65	2 (3.1)	0
JGDH	II	Tumor response	GI stromal tumors	Olaratumab	NCT01316263	21	5 (23.8)	0	NA	NA	NA
JGDI	I	PK	STS	Olaratumab + doxorubicin	NCT02326025	24	3 (12.5)	1 (4.2)	NA	NA	NA
Total						485	70 (14.4)	11 (2.3)	249	10 (4.0)	1 (0.4)

Abbreviations: IRR, infusion-related reaction; NA, not applicable; NSCLC, non–small-cell lung cancer; PFS, progression-free survival; PK, pharmacokinetics; STS, soft tissue sarcoma.
*IRRs are presented by maximum National Cancer Institute Common Terminology Criteria for Adverse Events grade.

Incidence of IRRs in each of the nine clinical trials is listed in Table 1.

Grade 3 or worse IRRs occurred in 11 patients (2.3%). All grade 3 or worse IRRs occurred during the first dose of olaratumab (Fig 1), and a majority occurred within 15 minutes of the start of the infusion of the first dose. For grade 3 or worse IRRs, symptoms reported included hypotension, hypersensitivity reaction, anaphylactic shock, or cardiac arrest. One of the IRRs resulted in a fatality. This patient in study JGDG had STS and an extensive cardiac history of ischemic cardiomyopathy with myocardial infarction, ventricular tachycardia requiring an implantable defibrillator, heart valve replacement, and doxorubicin-associated cardiac dysfunction. The patient discontinued doxorubicin monotherapy because of an AE of decreased ejection fraction. The patient crossed over to olaratumab monotherapy and experienced a fatal cardiac arrest approximately 10 minutes after the start of the first olaratumab monotherapy infusion. Of note, the patient did not receive any premedication before the olaratumab infusion.

Premedication Use in Clinical Trials

In early olaratumab studies, premedication was not required per protocol but administered at the investigators' discretion. To evaluate the role of premedication in preventing or mitigating olaratumab IRRs, IRR rate (all grade IRRs) was reviewed in premedicated (n = 243) and nonpremedicated patients (n = 242). The most common premedications included antihistamine (eg, H_1 antagonists such as diphenhydramine) and corticosteroids (eg, dexamethasone and hydrocortisone). Additional premedications administered at the investigators' discretion included H_2 antagonists (eg, ranitidine) and β_2 agonists via nebulizer (eg, albuterol), with some regional disparity. Both premedicated (n = 243) and nonpremedicated (n = 242) groups were reported to have any-grade IRRs at similar rates during the first dose of olaratumab (9.9% and 10.3%, respectively). Of the 11 patients experiencing a grade 3 or worse IRR, six did not receive premedication, for a grade 3 or worse IRR rate of 2.5%. The five premedicated patients with a grade 3 or worse IRR (grade ≥ 3 IRR rate of 2.1%) received different types of premedication, although all received corticosteroids, and four of five patients received diphenhydramine. In the subset of patients enrolled in the phase II study of STS, IRRs of any grade occurred in four of 64 premedicated patients (6.3%) at the first dose, compared with six of 29 nonpremedicated patients (20.7%).

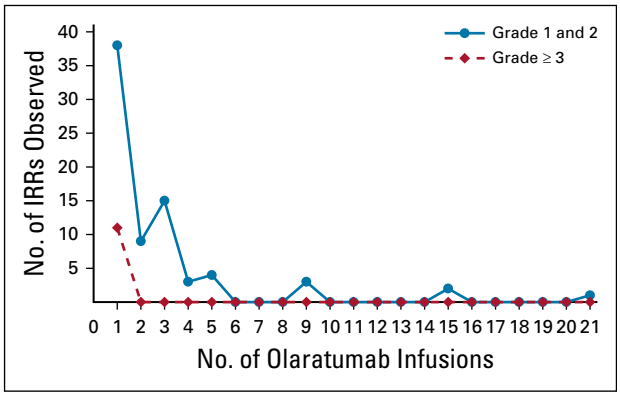

FIG 1. Number and timing of olaratumab infusion-related reactions (IRRs) in nine clinical trials.

Management of IRRs

In olaratumab clinical trials, most of the 59 patients with grade 1 or 2 IRRs had their infusions interrupted (n = 39; 66.1%) and/or their infusion rate decreased (n = 20; 33.9%). Treatment administered included antihistamines, acetaminophen, and corticosteroids. In patients with a grade 3 or worse IRR, olaratumab infusions were immediately stopped, and patients received medical treatment as indicated for IRRs. The most common drugs administered included antihistamines (81.8%), corticosteroids (72.7%), and epinephrine (54.5%). Other reported treatments included other vasopressors (45.5%; including norepinephrine and dobutamine), oxygen (36.4%), and salbutamol (27.3%). Patients with a grade 3 or worse IRR were permanently discontinued from olaratumab per study protocols.

Patients with grade 1 or 2 IRRs were eligible to continue receiving olaratumab upon resolution of IRR symptoms at a 50% reduced infusion rate. Before subsequent olaratumab infusions, patients were premedicated with antihistamines, acetaminophen, and corticosteroids. Of the 59 patients who received additional olaratumab doses, 47 (79.7%) did not experience a second IRR upon olaratumab re-exposure. None of the 12 patients (20.3%) with reported recurrence of an IRR to olaratumab had a grade 3 or worse IRR (Table 2).

IRRs and Presence of Anti–α-Gal Antibodies

Data for pre-existing anti–α-Gal antibodies were available from 425 olaratumab-treated patients in the nine clinical trials. Nine patients (2.1%) had detectable anti–α-Gal antibodies above the manufacturer-specified upper limit of normal (ULN), with seven of these nine patients experiencing a grade 3 or worse IRR. Of the 416 patients with anti–α-Gal antibodies below the ULN, two experienced a grade 3 or worse IRR. On the basis of the small number of patients who experienced a grade 3 or worse IRR, anti–α-Gal antibodies above the ULN had a positive predictive value of 77.8% (95% CI, 40.0% to 97.2%) and a negative predictive value of 99.5% (95% CI, 98.3% to 99.9%) for grade 3 or worse IRRs. Including patients with detectable anti–α-Gal antibodies above the assay lower limit of quantification, grade 3 or worse IRRs occurred in eight (47.1%) of 17 patients with detectable anti–α-Gal antibodies compared with one grade 3 or worse IRR in 408 patients (0.2%) with no detectable anti–α-Gal antibodies (Appendix Table A1, online only).

TABLE 2. Rechallenge of Patients With Olaratumab IRRs in Nine Clinical Trials

	No. (%) of Olaratumab-Treated Patients		No. (%) of Recurrent IRRs		
Study*	Experienced IRR	Redosed After Initial IRR†	Any Grade	Grade 1 or 2‡	Grade ≥ 3‡
JGDA	9	9 (100)	1 (11.1)	1 (11.1)	0
JGDB	19	18 (94.7)	2 (11.1)	2 (11.1)	0
JGDC	5	5 (100)	2 (40.0)	2 (40.0)	0
JGDD	9	5 (55.6)	1 (20.0)	1 (20.0)	0
JGDE	4	4 (100)	0	0	0
JGDG	16	12 (75.0)	3 (25.0)	3 (25.0)	0
JGDH	5	5 (100)	3 (60.0)	3 (60.0)	0
JGDI	3	1 (33.3)	0	0	0
Total	70	59 (84.3)	12 (20.3)	12 (20.3)	0

Abbreviation: IRR, infusion-related reaction.

*No patients in JGDF study experienced IRRs.

†Patients with a documented IRR were analyzed to determine if they experienced adverse events that were consistent with an any-grade IRR in a subsequent cycle.

‡Patients were only counted once. If they had multiple recurrences of IRRs or multiple adverse events associated with a single occurrence of an any-grade IRR, they were only counted once, and their highest-grade event was used.

In geographic regions of the United States previously reported to have a higher prevalence of anti–α-Gal antibodies,[13,15] six of 56 patients (10.7%) enrolled in olaratumab clinical trials in Missouri, Tennessee, and North Carolina experienced a grade 3 or worse IRR. Among these six patients, all four who were evaluable for anti–α-Gal antibodies had detectable antibodies above the ULN at baseline.

Postmarketing Surveillance Reports

Since 2016, olaratumab has been available for the treatment of patients with advanced STS in combination with doxorubicin in a number of countries. Postmarketing surveillance reports were mostly from the United States, reflecting the earlier commercial availability of olaratumab in the United States. Review of postmarketing reports of IRRs received up to October 31, 2017, showed IRRs were consistent in severity and nature with those reported in the clinical trials. The reporting rate for severe IRRs from postmarketing reports was estimated to be 2.4%.

Most severe IRRs reported occurred within approximately 15 minutes of the start of the infusion of the first olaratumab dose. Additional symptoms described included reports of patients complaining of not feeling well, urgency, or syncope before a severe IRR. Similar to the clinical trials, the postmarketing reports described patients who received additional doses of olaratumab after the resolution of low-grade IRRs without any reoccurrence of IRRs.

DISCUSSION

This report provides an overview of the nature and incidence of olaratumab IRRs from nine olaratumab clinical trials and postmarketing reports. For almost all patients, the first IRR occurred during the first two cycles of treatment. Grade 3 or worse IRRs were reported during the first infusion only and usually occurred within 15 minutes of the start of the infusion.

As with other monoclonal antibodies, olaratumab requires administration of appropriate premedication per the label. Premedication resulted in a similar rate of IRRs across the nine clinical studies assessed, whereas in the subset of patients with STS enrolled in the JGDG study, there was a numerically lower rate of IRRs at the first olaratumab dose in premedicated patients. Confounding factors may have contributed to this discrepancy, including different premedications administered for chemotherapies evaluated in combination with olaratumab across trials (eg, corticosteroids for taxanes), as well as additional premedications administered before olaratumab according to local practice. For instance, investigators at Washington University in St Louis (St Louis, MO) administered 20 mg of famotidine, 100 mg of hydrocortisone, and 2.5 mg of albuterol nebulization in addition to protocol-required premedication with dexamethasone and diphenhydramine before the first olaratumab infusion. Premedications are reported to reduce the incidence and/or severity of IRRs to monoclonal antibodies.[1,2,5] Therefore, premedication recommendations as specified in the olaratumab label, including histamine H_1 antagonist (eg, diphenhydramine) and dexamethasone before olaratumab, seem prudent given the occurrence of IRRs associated with olaratumab administration.

Consistent with reports for other monoclonal antibodies,[20] several patients reported feeling odd or uncomfortable or expressed a need to urinate or defecate immediately before the onset of the IRR. These relatively nonspecific symptoms

should be evaluated and closely monitored, because they may be followed by the onset of grade 3 or worse IRRs. The consistent pattern of grade 3 or worse IRRs (ie, a rapid onset and the need for urgent medical attention) necessitates monitoring in a setting with available resuscitation equipment, such as airway and assisted breathing equipment, equipment for rapid intravenous fluid replacement, emergency medications, and equipment for defibrillation. For anaphylactic reactions, current guidelines highlight the importance of early use of epinephrine (eg, as an injection for intramuscular application) as first-line treatment.[21] Although discontinuation of olaratumab for patients who experience a grade 3 or worse IRR is required, data from clinical trials suggest that patients with grade 1 or 2 IRRs can be safely retreated with olaratumab, with no grade 3 or worse IRRs observed. Resumption of dosing at a reduced rate and proper premedication are recommended, consistent with European Society for Medical Oncology guidelines.[2]

Earlier reports from patients treated with cetuximab, another antibody that contains an α-Gal glycosylation site, indicated an association between the presence of preformed anti–α-Gal antibodies in patients and the occurrence of grade 3 or worse IRR events, particularly for patients from the southeastern United States.[8,20,22] Preformed anti–α-Gal antibodies have been implicated in the occurrence of grade 3 or worse IRRs in response to therapeutic proteins. There seems to be some association between olaratumab-associated grade 3 or worse IRRs and anti–α-Gal antibodies and a trend toward higher IRR rates in US geographies associated with a higher prevalence of naturally pre-existing anti–α-Gal antibodies.[8,22] However, the strength of this association cannot be reliably determined at this time, because the overall number of patients with grade 3 or worse IRRs in olaratumab clinical trials is still too small (n = 11) to draw valid conclusions. Clinical trial sites and enrollment were not equally spread across the United States, and because STS is rare and often treated at regional sarcoma centers of excellence, geographic distribution of IRRs may be more localized to these centers than it would for common types of cancer that would involve larger numbers of patients treated in community settings. Patients in olaratumab clinical trials will continue to be monitored for IRRs as an AE of special interest to better understand any associations between anti–α-Gal antibodies and olaratumab-associated IRRs.

Of note, in contrast to cetuximab, which is a chimeric mouse-human IgG1antibody, olaratumab is a fully human antibody. Rituximab, another chimeric IgG1 antibody without any α-Gal glycosylation site, has a higher IRR rate than olaratumab, demonstrating that the immunogenicity of monoclonal antibodies is complex and needs to be carefully evaluated independently for each antibody. Most importantly, and taking into account the geographic mobility of patients, current data suggest all patients, regardless of where they are treated, maintain some risk of IRR and therefore should be premedicated according to the label and observed in settings where appropriate treatment of IRRs is available.

Postmarketing surveillance reports show IRRs with olaratumab are consistent in nature with those observed in clinical trials. In addition, the estimated reporting rate for severe IRRs (2.4%) is similar to that observed for grade 3 or worse IRRs across clinical trials (2.3%). A precise incidence of IRR in a real-world setting could only be estimated by an observational study in a large representative population, because inconsistency of information provided across reports, potential underreporting of events, and absence of a reliable denominator prevent translation of postmarketing information into an accurate estimate of incidence rate. However, this information can be used to complement clinical trial data while real-world data mature.

The recent phase III ANNOUNCE study of olaratumab in combination with doxorubicin in patients with advanced or metastatic STS did not confirm the phase II results in STS.[10] In light of this information, the US Food and Drug Administration recommended on January 24, 2019, that patients who are currently receiving olaratumab consult with their health care providers about whether to continue treatment and that olaratumab not be initiated in new patients outside of an investigational study. Although this limits the relevance of the data reported here for current clinical practice, clinical development continues for olaratumab, and our report details the current understanding of the numerous factors that may affect olaratumab-associated IRRs.

In conclusion, the clinical nature and severity of IRRs observed for olaratumab within clinical trials and postmarketing reports are consistent, and the symptoms are similar to those reported for other monoclonal antibodies. Grade 3 or worse IRRs were observed exclusively during the first infusion of olaratumab. All patients receiving olaratumab should be premedicated according to the local label, regardless of where they are treated, and monitored for signs and symptoms of IRRs in a setting where resuscitation equipment for treatment of IRRs is readily available. Active monitoring for IRRs is ongoing in current clinical trials and postmarketing surveillance.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JOP.18.00761.

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Incidence and Management of Olaratumab Infusion-Related Reactions

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APPENDIX

TABLE A1. IgE Anti–α-Gal Antibodies and Grade ≥ 3 Olaratumab IRRs

	No. of Patients	
Anti–α-Gal Antibodies	**Grade ≥ 3 IRR**	**No Grade ≥ 3 IRR**
> ULN	7	2
≤ ULN	2	414
> LLOQ	8	9
≤ LLOQ	1	407

NOTE. Data in the table represent a summary of 425 patients for whom anti–α-Gal antibody information was available. A total of nine patients had a grade ≥ 3 IRR.

Abbreviations: anti–α-Gal, anti–galactose-α-1,3-galactose; IgE, immunoglobulin E; IRR, infusion-related reaction; LLOQ, lower limit of quantification; ULN, upper limit of normal.