

# Managing Cetuximab Hypersensitivity-Infusion Reactions: Incidence, Risk Factors, Prevention, and Retreatment

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**D**evelopment of monoclonal antibodies (MoAbs) and small molecules that can inhibit the epidermal growth factor receptor (EGFR) has ushered in a new era of biologic targeted therapies for advanced cancer treatment. Cetuximab (Erbix) and panitumumab (Vectibix) are MoAbs that inhibit the EGFR. Cetuximab is a chimeric mouse-human (30:70) IgG1 (immunoglobulin 1) molecule approved by the US Food and Drug Administration (FDA) for use in colorectal (CRC) and head and neck (H&N) cancers. Panitumumab is a fully humanized IgG2 protein approved for use only in CRC. A major difference between the two drugs is the reported incidence of hypersensitivity-infusion reactions (HIRs). These HIRs confer moderate morbidity and potential mortality.

According to the manufacturers of these drugs, severe HIRs occur in a small percentage of patients: 3% for cetuximab and < 1% for panitumumab.<sup>1,2</sup> Although a low incidence was initially reported, several groups have recently cited wide variations in HIRs associated with clinical practice and geographic distribution. For instance, reported incidence rates of severe HIRs now range

**Abstract** Cetuximab is an anti-epidermal growth factor receptor (EGFR) monoclonal antibody approved by the US Food and Drug Administration for the treatment of colorectal (CRC) and head and neck (H&N) cancers. Hypersensitivity-infusion reactions (HIRs) confer moderate morbidity and potential mortality. HIRs have a wide geographic incidence with few identifiable risk factors. Limited data regarding risk-reduction interventions for HIR or post-HIR retreatment are available. All patients treated with cetuximab at a single Veterans Affairs facility were monitored for development of HIRs, with baseline clinical, demographic, and supportive care data recorded. All received standard premedication based on cohort assignment. A total of 51 consecutive patients (30 CRC; 21 H&N) received at least one dose of cetuximab. Grades II–IV HIRs occurred in 14 patients (27%; 6 grade II, 6 grade III, 2 grade IV). There was no grade V HIR. All HIRs occurred during the first infusion. There were no differences between age, race, diagnosis, stage, concurrent chemotherapy, or radiotherapy with cetuximab, allergy history, or military service era of patients developing HIRs versus those who did not. There were no identifiable risk factors that predicted the severity of HIR. Neither premedication modifications ( $P = 0.34$ ) nor bronchodilator use ( $P = 0.12$ ) impacted the incidence or severity of HIR. A cetuximab test dose successfully elicited an HIR and resulted in an 87% cost savings. None of five patients receiving subsequent retreatment with anti-EGFR MoAb had recurrence of an HIR. An HIR during cetuximab infusion can be a serious and underestimated toxicity. The relatively high incidence reported here is consistent with that previously identified in the Southeastern United States. No clinical, demographic, or historic variables reliably predicted HIR in our population. Use of a test dose to elicit a HIR appears to be feasible and cost-effective. Use of panitumumab after a cetuximab HIR in select patients with CRC appears to be feasible and safe.

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Manuscript submitted November 12, 2009; accepted January 29, 2010.

Presented in part at the 2009 Gastrointestinal Cancers Symposium; January 15–17, 2009; San Francisco, California.

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J Support Oncol 2010;8:72–77

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between < 1% in New York to as high as 22% in North Carolina and Tennessee.<sup>3</sup> Such variability has been hypothesized to be related to regional environmental exposures to rodents, plant-based antigens, and an allergenic patient phenotype.

Despite pathophysiologic differences between anaphylactic hypersensitivity reactions and anaphylactoid infusion reactions, there are no significant differences in clinical manifestations or

immediate management. The former is mediated through antigen-antibody (IgE) reactions, whereas the latter is mediated via cytokines. Currently, the presence of a preexisting serum IgE antibody that cross-reacts with cetuximab is the only laboratory-based assay that may predict HIRs (ie, true hypersensitivity), but it is not yet commercially available.<sup>4</sup> HIRs present a serious challenge to patients, providers, and oncology practices.<sup>5,6</sup> Prevention of HIRs through premedication modification has been postulated, with combinations of histamine 1 (H<sub>1</sub>) and 2 (H<sub>2</sub>) -receptor antagonists and steroid modulations purported to reduce hypersensitivity reactions.<sup>7,8</sup> The use of a test dose of cetuximab is recommended in H&N patients, but it is not common practice in patients receiving cetuximab for CRC.<sup>9</sup> Additionally, limited data exist on retreatment with anti-EGFR therapies after development of HIRs.

This study was conducted to determine the incidence and risk factors for development of HIRs in former US military patients within a single healthcare system. Secondary goals were to characterize the symptoms and timing of HIRs, determine whether systematic premedication modifications reduced or modified the development of these reactions, and assess the clinical and pharmacoeconomic impact of routine use of a test dose for cetuximab. Outcomes following select patient retreatment with anti-EGFR MoAb therapies following HIRs were also described.

## Methods

This was a retrospective cohort designed study whereby all patients treated with cetuximab at a single Florida Veterans Affairs facility were monitored for development of HIRs. Baseline clinical, demographic, and supportive care data were recorded. HIRs were graded by the National Cancer Institute–Common Toxicity Criteria for Adverse Events (NCI–CTCAE) definitions for both hypersensitivity and acute infusion reactions (Table 1).<sup>10</sup> Allergy history was defined as documentation of drug-induced rash or anaphylactic symptoms, bee sting or food allergy, asthma, eczema, or nonsedative antihistamine

use in an electronic medication record. Bronchodilator use included inhaled albuterol and/or ipratropium. Post-HIR therapy and outcomes were documented.

Patient cohort assignment was conducted prospectively as part of a systematic quality improvement (QI) program aimed at reducing the risk of cetuximab-induced HIR. Cohort 1 included all patients treated with standard premedications up until the start of the QI program. All patients received premedication 30 minutes prior to cetuximab infusion based on cohort assignment. Cohorts included diphenhydramine (50 mg intravenously [IV]) plus assignment to one of the following groups: 1) dexamethasone (20 mg IV), 2) hydrocortisone (100 mg IV), 3) dexamethasone (20 mg IV) and ranitidine (50 mg), or 4) cohort 3 plus a test dose of cetuximab. A test dose was 100 mg administered IV over 30 minutes. Vitals and oxygen saturations were obtained at baseline and then at every 10–15 minutes. After an additional 30-minute observation period, if no HIR was elicited, the remainder of the prescribed dose was infused over 2 hours. Staff monitored patients closely with one-on-one observation during the test dose and observation phase. Retreatment with an EGFR MoAb was at the discretion of the treating physician.

Statistical analysis was performed with Minitab (Minitab, Inc., State College, PA). The relationship between suspected risk factors, the impact of premedication modifications, and HIRs were evaluated with the Fisher's exact test. Results were considered significant, with a *P* value of < 0.05 on a two-sided test. Institutional review board approval and informed consent was obtained for the study.

## Results

### PATIENTS

Between May 2004 and August 2008, 51 consecutive patients (30 CRC; 21 H&N) received at least one dose of open-label cetuximab. The median age was 61 years (range, 43–82 years), 98%

**Table 1**

### Grading of Hypersensitivity-Infusion Reactions

| ADVERSE EVENT                                       | GRADE                                                                          |                                                                                                                                                                                                |                                                                                                                                                                      |                                                           |       |
|-----------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-------|
|                                                     | 1                                                                              | 2                                                                                                                                                                                              | 3                                                                                                                                                                    | 4                                                         | 5     |
| Hypersensitivity (allergic reaction)                | Transient flushing or rash; drug fever < 38 °C                                 | Rash; flushing; urticaria; dyspnea; drug fever ≥ 38 °C                                                                                                                                         | Symptomatic bronchospasm, with or without urticaria; parenteral medications indicated; allergy-related edema/angioedema; hypotension                                 | Anaphylaxis                                               | Death |
| Cytokine release syndrome (acute infusion reaction) | Mild reaction; infusion interruption not indicated; intervention not indicated | Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours | Prolonged; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) | Life-threatening; pressor or ventilator support indicated | Death |

NSAIDs = nonsteroidal anti-inflammatory drugs

Adapted from Cancer Therapy Evaluation Program.<sup>10</sup>

**Table 2****Case Characteristics of Hypersensitivity-Infusion Reactions (HIRs)**

| DX  | AGE | RACE | TREATMENT         | HIR GRADE | HIRs TIMING DURING INFUSION (min) | REACTION (R) AND INTERVENTION (I)                                                                                                                                                                                                                                             | DURATION OF SYMPTOMS (min) |
|-----|-----|------|-------------------|-----------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| CRC | 65  | W    | Cmab + irinotecan | II        | 15                                | (R) Groin itching and tickle in back of throat followed by lip numbness, chest pain, facial hyperemia, and palm urticaria<br>(I) Infusion stopped; methylprednisolone (125 mg IV), aspirin (325 mg PO), ranitidine (50 mg IV), diphenhydramine (50 mg IV), oxygen, and fluids | 180                        |
| CRC | 72  | W    | Cmab + irinotecan | II        | 120                               | (R) Warm sensation with scalp itching and facial flushing; urticaria on hands and arms<br>(I) Infusion stopped; methylprednisolone (125 mg IV), oxygen, and fluids                                                                                                            | 120                        |
| CRC | 57  | W    | Cmab + irinotecan | II        | 30                                | (R) Generalized pruritus with face and trunk flushing; slight nausea, dizziness<br>(I) Infusion stopped; dexamethasone (20 mg IV) and fluids                                                                                                                                  | 30                         |
| CRC | 63  | W    | Cmab + irinotecan | III       | 10                                | (R) Flushed, diaphoretic, tachycardic, hypoxic, and hypotensive<br>(I) Infusion stopped; hydrocortisone (100 mg IV), ranitidine (50 mg IV), diphenhydramine (25 mg IV), lorazepam (0.5 mg IV), and oxygen                                                                     | 180                        |
| CRC | 72  | W    | Cmab + irinotecan | III       | 30                                | (R) Coughing, hives, hypertension, and chills<br>(I) Infusion stopped; diphenhydramine (50 mg IV) and dexamethasone (20 mg IV)                                                                                                                                                | 120                        |
| CRC | 70  | W    | Cmab              | III       | 60                                | (R) Hypertension, acute SOB, tachycardia, and diaphoresis<br>(I) Infusion stopped; methylprednisolone (125 mg IV), fluids, and oxygen                                                                                                                                         | 120                        |
| CRC | 75  | W    | Cmab + irinotecan | IV        | 25                                | (R) Hypotension, diaphoresis, and poor inspiratory effort with subsequent unresponsiveness<br>(I) Infusion stopped; code called, patient admitted to MICU for continued management                                                                                            | NR                         |
| CRC | 77  | W    | Cmab + irinotecan | IV        | 10                                | (R) Unresponsive, apneic<br>(I) Infusion stopped; code called, patient admitted to MICU for continued management                                                                                                                                                              | NR                         |
| H&N | 60  | AA   | Cmab + XRT        | II        | 45                                | (R) Hypotension and chest tightness with itching near IV site; generalized pruritus<br>(I) Infusion stopped; methylprednisolone (125 mg IV) and fluids                                                                                                                        | 120                        |
| H&N | 60  | W    | Cmab + XRT        | II        | 60                                | (R) Face, chest, and abdomen hyperemia; hypotension; nausea; and episode of emesis<br>(I) Infusion stopped; methylprednisolone (125 mg IV) and fluids                                                                                                                         | 30                         |
| H&N | 50  | W    | Cmab + XRT        | II        | 12                                | (R) Generalized pruritus and face and neck flushing; rash on upper trunk<br>(I) Infusion stopped; methylprednisolone (125 mg IV), diphenhydramine (50 mg IV) and fluids                                                                                                       | 30                         |
| H&N | 74  | W    | Cmab + cisplatin  | III       | ONSET                             | (R) Generalized pruritus, hypoxia, chest pain, and hypotension<br>(I) Infusion stopped; diphenhydramine (50 mg IV), ranitidine (50 mg IV), methylprednisolone (125 mg IV), and fluids                                                                                         | 360                        |
| H&N | 62  | W    | Cmab + XRT        | III       | ONSET                             | (R) Rash, itching, and wheezing<br>(I) Infusion stopped; hydrocortisone (100 mg IV) and albuterol respiratory treatment                                                                                                                                                       | 120                        |
| H&N | 63  | W    | Cmab + XRT        | III       | 15                                | (R) Dry throat with coughing and clear sputum production; tachycardia, hypotension, and pulmonary distress<br>(I) Infusion stopped; hydrocortisone (100 mg IV), fluids, oxygen, and albuterol respiratory treatment                                                           | 60                         |

Dx = diagnosis; CRC = colorectal cancer; W = white; Cmab = cetuximab; IV = intravenous; PO = by mouth; SOB = shortness of breath; MICU = medical intensive care unit; NR = not reported; H&N = head and neck cancer; AA = African-American; XRT = radiation therapy

were male, 45 patients were white, and 7 received cetuximab as monotherapy. Military service included the World War II, Korean, post-Korean, Vietnam, and Persian Gulf eras. No patients had a documented history of exposure to Agent Orange.

**HIRs**

Grades II–IV HIRs occurred in 14 patients (27%; 6 grade

II, 6 grade III, 2 grade IV). There was no grade V HIR. All HIRs occurred during the first infusion (median, 30 minutes; range, 1–120 minutes). All HIRs eventually resolved with immediate discontinuation of cetuximab and supportive medical management (Table 2); two of the five patients requiring hospitalization needed care in a medical intensive care unit. There were no differences between developing a HIR versus

**Table 3****Development of Hypersensitivity-Infusion Reactions (HIRs) with Differing Premedication Cohorts**

| COHORT | COHORT PREMEDICATION  | SIZE (N) | HIR (%)  | HIR GRADES                          | P VALUE <sup>a</sup> |
|--------|-----------------------|----------|----------|-------------------------------------|----------------------|
| 1      | B + D                 | 27       | 5 (18.5) | 1 grade II; 3 grade III; 1 grade IV | 0.34 <sup>b</sup>    |
| 2      | B + H                 | 8        | 3 (37.5) | 1 grade II; 1 grade III; 1 grade IV | 0.34                 |
| 3      | B + D + R             | 7        | 3 (42.8) | 3 grade II                          | 0.31                 |
| 4      | B + D + R + test dose | 9        | 3 (33.3) | 1 grade II; 2 grade III             | 0.38                 |

B = diphenhydramine (50 mg IV); D = dexamethasone (20 mg IV); H = hydrocortisone (100 mg IV); R = ranitidine (50 mg IV); test dose = cetuximab (100 mg IV)

<sup>a</sup> Relative to cohort 1

<sup>b</sup> Overall test for global difference

not developing one with regard to age (median, 64 vs 60;  $P = 0.17$ ), race ( $P =$  nonsignificant [NS]), cancer type, stage, concurrent chemotherapy or radiotherapy, or military service era of patients. There was no relationship between allergy history and development of an HIR ( $P =$  NS). There also were no identifiable risk factors that predicted the severity of an HIR.

**PREMEDICATION MODIFICATION AND TEST DOSE**

Bronchodilator use did not impact the development of an HIR ( $P = 0.12$ ). Systematic premedication modifications through cohort assignment did not impact the incidence or severity of an HIR ( $P = 0.34$ ; Table 3). In cohort 4, three of nine patients developed an HIR, and all were successfully elicited by a test dose of cetuximab of 100 mg. HIRs associated with the test dose were not significantly different from those that occurred without a test dose. However, discontinuation of further cetuximab infusion preparation based on a test dose associated with an HIR resulted in an 87% cost and inventory savings.

**POST-HIR CHALLENGE**

At the discretion of the treating physician, five patients (36%) with documented HIRs received subsequent retreatment with an anti-EGFR MoAb. One patient with H&N cancer was rechallenged with cetuximab (prior HIR, grade III), and four patients with CRC received panitumumab (prior

HIR, grades II, III, III, and IV). In each case, premedication administration was as performed in cohort 4, so as to maximize the premedication regimen and provision of test dose. No patient had recurrence of an HIR.

**Discussion**

Anti-EGFR MoAbs represent an important therapeutic class in the care of patients with CRC and H&N malignancies. However, the development of cetuximab HIRs represents a clinically significant and underestimated toxicity in the Southeastern United States. The relatively high incidence reported here (27%) is consistent with that previously described. Although mortality remains low overall, with the majority of cases resolving with supportive care, the development of HIRs disrupts patient care, poses patient and practice safety challenges, and utilizes limited infusion room and hospital resources.<sup>11</sup> Provider and patient concerns over the risk of HIR may limit the clinical use of these agents despite FDA-approved indications. A complete review of acute anaphylaxis management is beyond the scope of this article, but it has been previously reported.<sup>12,13</sup> Tumor testing for *KRAS* mutations should now be routinely incorporated to select patients who would derive no efficacy benefit from anti-EGFR MoAbs yet remain at risk for HIR.<sup>14</sup>

Grade II HIRs require infusion interruption and symptom management, including that of pulmonary complaints (ie, dyspnea). Therefore, grade II reactions are clinically relevant reactions for both patients and providers. HIRs occur via one of two mechanisms: IgE-dependent anaphylaxis and cytokine-mediated infusion reactions. Despite the pathophysiologic differences, there are no significant differences in the clinical manifestations or immediate management. However, confusion may occur in the reporting of an HIR as a result of inconsistent criteria and grading within the categories of cytokine release syndrome/acute infusion reaction or allergic reaction/drug hypersensitivity (Table 1).<sup>10</sup> As such, given these varied definitions, clinical trial reporting may underestimate the true incidence of HIRs in clinical practice. Revisions to this inconsistent reporting system have been called for and have been incorporated in the next NCI-CTCAE (v4.0).<sup>15</sup>

Prediction of individuals at risk for HIRs continues to remain a challenge. True risk factors remain inconclusive, but reports imply a geographic distribution in the Southeastern United States.<sup>3,16</sup> The incidence reported here is consistent with the previously suggested etiology being related to a geo-

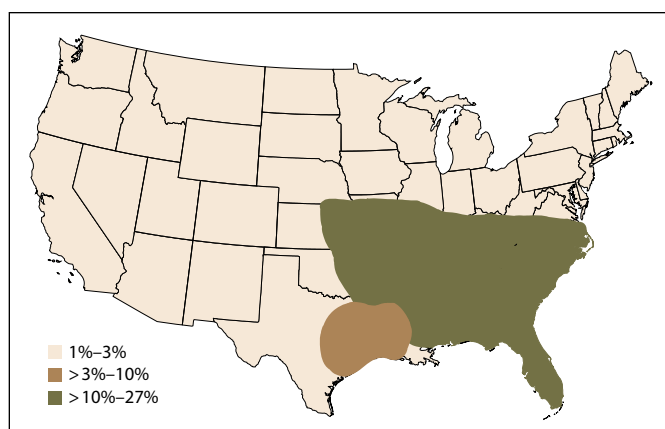


**Figure 1** Geographic Distribution of Incidence Rates of Hypersensitivity-Infusion Reaction in the Continental United States

Incidence in Alaska and Hawaii, not shown on the map, is 1%–3%.

graphic or environmental exposure. However, the geographic region clearly extends beyond Appalachia (Figure 1). Besides geography, our study failed to demonstrate any clinical or demographic data associated with a risk of HIR. The population of patients in our study represents predominately white men, thus limiting the ability to clearly identify differences in risk factors such as gender or race. Indeed, white race has been purported to be a risk factor for HIR<sup>8</sup>; thus, our high incidence may represent a reflection of this variable.

One limitation of our study is the lack of incorporated serum testing for IgE antibody,<sup>4</sup> which may predict true hypersensitivity to cetuximab. The presence of IgE against cetuximab occurs in patients who have never been exposed to the drug. IgE binds to a specific sugar moiety (galactose- $\alpha$ 1,3-galactose oligosaccharide), which is located on the Fab end of cetuximab. However, given that this test has yet to be validated and cytokine-mediated (non-IgE) reactions are not detected by this assay, the clinical utility of this test remains unclear. Other potential markers of the risk of HIR include serum levels of platelet-activating factor (PAF) and PAF acetylhydrolase (the PAF-inactivating enzyme); however, they also remain investigational.<sup>17</sup>

Attempts to prevent or reduce the severity of HIRs have been suggested through premedication modification.<sup>7,8</sup> According to the package insert of cetuximab, routine premedication with a H<sub>1</sub> antagonist is recommended, although IV steroids have been incorporated into many clinical and research protocols (either as primary prevention of HIRs or as antiemetic therapy).<sup>13</sup> The role of steroids is akin to that used for other protein-based reactions (ie, serum sickness, transfusion reactions, etc.). The source of allergen on the cetuximab molecule has been speculated to be the murine component. Indeed, the carbohydrate moiety identified by the IgE that cross-reacts cetuximab is related to the murine cell line in which cetuximab is produced.<sup>4</sup>

Other recombinant murine-based MoAbs (ie, rituximab [Rituxan]) are associated with similarly high degrees of HIR, although the mechanism is postulated to be related to non-IgE (ie, cytokine-mediated) mechanisms.<sup>5,18,19</sup> Fully humanized MoAbs (ie, panitumumab, trastuzumab [Herceptin], bevacizumab [Avastin]) each have a low incidence of HIR, and premedication use is not routinely recommended with these drugs.<sup>2,20,21</sup> In our population, we were unable to demonstrate a significant statistical or clinical impact on the incidence or severity of HIRs with premedication modification, including the addition of an H<sub>2</sub> antagonist and IV steroid rotation. The relatively small number of patients tested in these cohorts limits definitive conclusions.

Given that prevention and modification of risk factors may not be effective, the incorporation of a test dose into the initial infusion of cetuximab may be both clinically reliable and cost-effective. HIRs occur early in the course of therapy.<sup>5</sup> Although not routinely recommended,<sup>1</sup> use of a test dose has been previously integrated into clinical protocols.<sup>9</sup> In our study, administration of a test dose with the initial cetuximab infusion successfully elicited an HIR. Despite being no less severe, the HIR

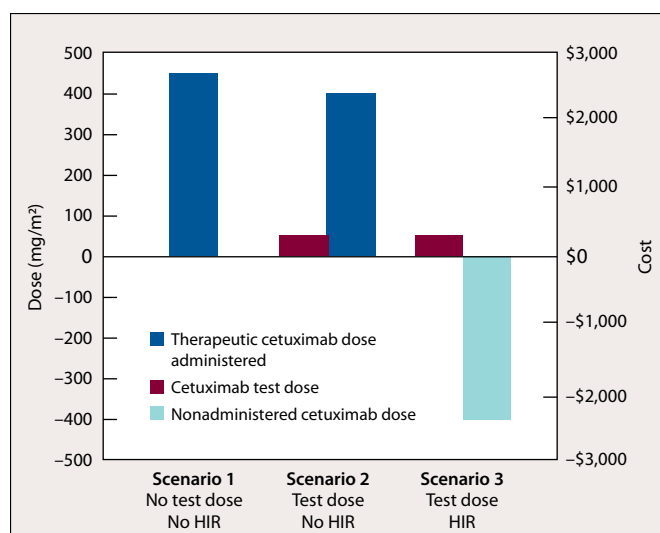


**Figure 2** Pharmacoeconomic Impact of Using a Test Dose of Cetuximab

HIR = hypersensitivity-infusion reaction

occurred in a finite period. Thus, increased supportive care, staff monitoring, and capable interventions could be appropriately focused.

Pharmacoeconomic and clinical outcomes may be improved with general incorporation of test dosing into a clinical algorithm (Figure 2). For patients who do not develop an HIR (scenario 1 or 2 in Figure 2), incorporation of a test dose adds only an additional 30 minutes of close observation between completion of the test dose and administration of the remaining infusion. However, if a test dose associated-HIR develops (scenario 3 in Figure 2), 87% of potentially lost drug inventory can be avoided. Financial savings are possible because the full prescribed infusion is not prepared until after the post-test dose observation period. Based on average wholesale price, use of a test dose would have equalled a \$46,560 savings if the data were extrapolated to our entire cohort. In this way, patient safety (increased monitoring), staff resources (finite and focused anticipation), and practice pharmacoeconomics are simultaneously addressed. This small pilot suggests that a test dose has the potential to identify a large portion of the HIR and save resources, but a larger trial will be needed to confirm these observations.

The safety and efficacy of retreatment with a MoAb after a HIR are clinically important issues for some patients. With careful patient selection, some individuals can be successfully retreated with anti-EGFR MoAbs, particularly panitumumab, without redevelopment of HIRs. Our experience here suggests further that the use of panitumumab after cetuximab-induced HIR appears feasible and safe.<sup>22-25</sup> Presumably, the fully humanized MoAb does not elicit a similar immune response; thus, the IgE hypersensitivity appears non-cross-reactive. For successful rechallenges of cetuximab, the implication is that HIRs are not based on hypersensitivity, but they may be related more to cytokine-mediated mechanisms.

Ultimately, a large post-marketing (phase IV) registry study

could provide valuable information on demographic risk factors, incidence, and other currently unidentified variables which place certain patients at risk for HIR. A correlative serum analysis looking for IgE against galactose- $\alpha$ -1,3-galactose oligosaccharide, PAF, and PAF acetylhydrolase in all patients would also help to determine the sensitivity and predictive value of these laboratory-based assays, which could be subsequently validated in a prospective study.

## Conclusion

This study provides further evidence that the clinically relevant rate of cetuximab HIR exceeds that initially reported. With a high incidence of such reactions in the Southeastern United States and few routine clinical, demographic, or historic variables reliably predicting HIRs, strong consideration must be given to refining clinical management of these patients. Incorporation of a test dose of cetuximab with close clinical monitoring for HIRs may provide a safe and effective way to

use staff and financial resources. Premedication use should include both H<sub>1</sub> antagonists and IV steroids. Alternatively, panitumumab may be considered a reasonable substitution for cetuximab in this high-risk geographic population, particularly for patients with CRC receiving palliative monotherapy. Additional research is needed prior to routine substitution of panitumumab for cetuximab. Further studies may help us to understand better the etiology of cetuximab HIR and to validate the benefit of test dosing. Results of prospective studies incorporating IgE testing are eagerly awaited; thus, reliable and reproducible laboratory-based assays may prospectively identify those at highest risk.

**Acknowledgments:** We are indebted to B. McMichael for administrative assistance with the formatting of this article. We wish to thank all current and former members of the US military and their families for their service and sacrifice for our country.

*Conflicts of interest:* None to disclose.

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