UTILITY OF SERUM ANTI-CETUXIMAB IGE LEVELS TO IDENTIFY PATIENTS AT A HIGH RISK OF SEVERE HYPERSENSITIVITY REACTION TO CETUXIMAB

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Abstract:	Aim: To evaluate the utility of anti-cetuximab IgE detection to identify patients at risk of hypersensitivity reaction (HSR) to cetuximab. Methods: In this prospective, 3-year (2010 - 2013) trial carried out at 9 french centers, patients ready to receive a first cetuximab infusion were included. Pre-treatment anti cetuximab IgE levels were measured to classify patients into those with levels above (high levels) or below (low levels) 29 IgE Arbitrary Units (EAU). The incidence of severe HSR in the low levels subgroup was compared with that in a historical cohort in which pre-sensitization to cetuximab had not been measured prospectively. Results: Of the 301 assessable patients (mean age: 60.9±9.3 years, head-and-neck cancer: 77%), 66 patients (22%) had high anti cetuximab IgE levels, and 247 patients received cetuximab. Severe HSR occurred in 8 patients (grade 3 in 5 patients, and grade 4 in 3 patients). The incidence of severe HSR was lower in the low levels subgroup vs. the historical cohort [3/209 (1.4%) vs. 11/213 (5.2%), OR, 0.27, 95% CI, 0.07 to 0.97], and higher in high vs. low levels subgroup [5/38 (13.2%) vs. 3/209 (1.4%); OR, 10.4, 95% CI, 2.4 to 45.6]. Patients with severe HSR had higher anti-cetuximab IgE levels than patients who did not (median, 45 vs. 2 EAU, P = 0.006). No significant association was found between severe HSR and gender, age, history of allergies or tumor location. Conclusions: Detection of pretreatment anti-cetuximab IgE is feasible and helpful to identify patients at higher risk of severe cetuximab-induced HSR.

Dear Editor,

Along with my co-authors, I would like you to consider the attached manuscript, "**Utility of serum anti-cetuximab IgE levels to identify patients at a high risk of severe hypersensitivity reaction to cetuximab**" for publication in *The British Journal of Clinical Pharmacology* as an Original Article.

Hypersensitivity reactions (HSR) are observed at first infusion of cetuximab in 1 to 22% of the patients depending on the areas of the world. The HSR is essentially an anaphylactic reaction possibly due to pre-existing anti-cetuximab IgEs. Previously, we described a case report about fatal or near-fatal hypersensitivity reactions to cetuximab in order to expose the potential severity of this adverse event (Dupont et al., 2014, *Clin Med Insights Oncol,* 8: 91-4). We also reported the standardization of an ELISA-based testing of serum samples to measure the levels of anti-cetuximab IgEs and tested samples collected from cetuximab-treated patients (Mariotte et al., 2011, *MAbs*, 3: 396-401).
This new article is original and has not been previously published or is currently being considered for publication elsewhere. In the present study, we aimed at prospectively validate the interest of pretreatment anti-cetuximab IgE levels to identify patients more or less prone to develop a HSR at first infusion of cetuximab. In a population of 301 patients awaiting cetuximab treatment, we could observe a significant decrease of incidence of severe HSR in the subgroup of patients with low anti-cetuximab levels (<29 EAU, n = 209) as compared to that of the historic cohort. The analysis also shows that patients with high anti-cetuximab IgE levels were more likely to experience a severe HSR as those with low levels. Lastly, the pretreatment levels of anti-cetuximab levels was the only factor identified as related to the risk of severe HSR.

Thus, in continuation of our previous work, we now show that screening patients at increased risk of severe HSR at first administration of cetuximab is feasible, and would be useful in the clinical setting to provide individualized care to patients and reduce the incidence of HSR. The detection of anti-cetuximab IgE is part of a personalized medicine approach that seeks to define in advance the most appropriate treatment for each patient treated for cancer. In view of the current indications for cetuximab, we believe that the findings of this study are relevant to the scope of your journal and will be of interest to its readership.
All listed authors have worked and approved the final manuscript.

Thank you for your consideration.

Sincerely,

Dr. Benoît Dupont

UTILITY OF SERUM ANTI-CETUXIMAB IGE LEVELS TO IDENTIFY PATIENTS AT A HIGH RISK OF SEVERE HYPERSENSITIVITY REACTION TO CETUXIMAB

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Competing Interest

KBL had a consulting or advisory role for Sanofi and Merck Serono. FDF received honoraria from Roche, Sanofi, Amgen and Merck Serono. MPG had a consulting or

advisory role for Roche, Sanofi, Amgen and GlaxoSmithKline. RS had a consulting or advisory role for Roche. All the remaining authors have declared no conflicts of interests.

ABSTRACT

Aim: To evaluate the utility of anti-cetuximab IgE detection in order to identify patients at risk of hypersensitivity reaction (HSR) to cetuximab.

Methods: In this prospective, 3-year (2010 - 2013) trial carried out at 9 french centers, patients ready to receive a first cetuximab infusion were included. Pre-treatment anti-cetuximab IgE levels were measured to classify patients into those with levels above (high levels) or below (low levels) 29 IgE Arbitrary Units (EAU). The incidence of severe HSR in the low levels subgroup was compared with that in a historical cohort in which pre-sensitization to cetuximab had not been measured prospectively.

Results: Of the 301 assessable patients (mean age: 60.9±9.3 years, head-and-neck cancer: 77%), 66 patients (22%) had high anti-cetuximab IgE levels, and 247 patients received cetuximab. Severe HSR occurred in 8 patients (grade 3 in 5 patients, and grade 4 in 3 patients). The incidence of severe HSR was lower in the low levels subgroup *vs.* the historical cohort [3/209 (1.4%) *vs.* 11/213 (5.2%), OR, 0.27, 95% CI, 0.07 to 0.97], and higher in high *vs.* low levels subgroup [5/38 (13.2%) *vs.* 3/209 (1.4%); OR, 10.4, 95% CI, 2.4 to 45.6]. Patients with severe HSR had higher anti-cetuximab IgE levels than patients who did not (median, 45 *vs.* 2 EAU, $P = 0.006$). No significant association was found between severe HSR and gender, age, history of allergies or tumor location.

Conclusions: Detection of pretreatment anti-cetuximab IgE is feasible and helpful to identify patients at higher risk of severe cetuximab-induced HSR.

What is already known about this subject:

- Hypersensitivity reactions (HSR) are not rare and potentially life-threatening adverse events associated with cetuximab.
- HSR appears to be an IgE-mediated anaphylactic mechanism because of a cross-reactivity with galactose-α-1,3 present on cetuximab.
- High pretreatment levels of anti-cetuximab IgE have been observed in patients who experienced HSR.

What this study adds:

- HSRs reported in the study were immediate-onset, implying the presence of pre-existing anti-cetuximab IgEs
- A strong association is prospectively verified between the presence of circulating anti-cetuximab IgE and the risk of HSR
- Anti-cetuximab IgE detection could be helpful to physicians in order to identify patients at higher risk of severe HSR

INTRODUCTION

Hypersensitivity reactions (HSR) are adverse events often associated with cetuximab use [1]. The frequency of severe HSR to cetuximab was found to be <5% [2-5], although it appears to vary according to the geographical region. A higher incidence of 14 to 30% has been observed in the states of Arkansas, North Carolina, and Tennessee in the USA [6-9], and even fatal reactions have been reported [10-13].

Several approaches have been attempted to identify patients at a higher risk of HSR to cetuximab. Smokers, men, and patients with a history of allergy were suggested to be at a higher risk of HSR [8, 14], while no clear relationship was found with tumor location [8-10, 14, 15]. Importantly, the link between these factors and the risk of HSR to cetuximab is not strong enough to help clinicians identify patients at a high risk of severe HSR [15].

High pretreatment levels of anti-cetuximab IgE have been observed in patients who experienced HSR at the first cetuximab administration [6]. The basis for the HSR appears to be an IgE-mediated anaphylactic mechanism because of a cross-reactivity with galactose-α-1,3 (alpha-gal), a mammalian epitope that is present on cetuximab [16].

In a previous retrospective study, conducted between October 2005 and March 2009 at our center, we described the standardization of an ELISA test to detect serum anti-cetuximab IgE [17]. In that historical cohort, the overall incidence of severe HSR reactions was 5.2% (11/213 patients). Statistical analysis indicated a value of 29 anti-

cetuximab IgE arbitrary units (EAU) as the cut-off above which patients may be considered at a higher risk of severe HSR to cetuximab [17].

The present study was conducted prospectively to evaluate the utility of pre-treatment measurement of serum anti-cetuximab IgE levels in patients naive to cetuximab to identify those who may be at a high risk of severe HSR.

METHODS

Study design

This was a multicenter, prospective, diagnostic trial carried out between January 2010 and February 2013, at 9 centers across France. Patients receiving a first infusion of cetuximab were included and classified according to their pre-treatment levels of serum anti-cetuximab IgE.

The primary objective was to compare the incidence of severe HSR at the first infusion of cetuximab in patients with low levels of anti-cetuximab IgE, to that observed in the historical cohort of 213 patients treated with cetuximab without prior testing for their anti-cetuximab IgE levels [17]. Secondary objectives were to compare the incidence of severe HSR to cetuximab between patients with low or high levels of anti-cetuximab IgE, and examine the association of previously reported risk factors for HSR to cetuximab in the present prospective cohort.

All patients provided a written informed consent before undergoing any study-specific procedures. The study was conducted in accordance with the principles of the

Declaration of Helsinki. The study was approved by the local Ethics Committee [Comité de Protection des Personnes (CPP) Nord-Ouest III, Caen, France]. This study is registered with ClinicalTrials.gov (NCT01436617) and with EudraCT (2009-016968-37).

Anti-cetuximab IgE assay

The detection of anti-cetuximab IgE was centralized at the Laboratory of Immunology and Immunopathology, Caen University Hospital, Caen, France, and was performed using an enzyme-linked immunosorbent assay (ELISA) as previously described [17]. The results were expressed as EAU using a standard calibration established with a control serum containing known concentration of anti-cetuximab IgE antibodies. Anti-cetuximab IgE levels ≤29 were defined as low, and levels >29 EAU as high.

Patients and treatment

Inclusion criteria for patients were age ≥18 years, histologically confirmed colon or head-and-neck cancer, naïve to cetuximab, and adequate liver, renal, and bone marrow functions to receive cetuximab and associated treatments. Cetuximab infusion, premedication, and concomitant treatments were applied according to the recommended protocols at each participating center. The serum anti-cetuximab IgE levels were determined in all patients before cetuximab infusion, and patients were excluded if these data were not available. Concerning the historical cohort, the premedication usually administrated before the cetuximab infusion was made up of a combination of corticosteroids and antihistamine.

The treating physician was informed of each patient's anti-cetuximab IgE levels before the first administration of cetuximab. Patients with low IgE levels were administered cetuximab according to the center's standard procedures. For patients with high IgE levels, the decision of cetuximab treatment was reevaluated in a multidisciplinary oncology experts meeting. In case of patients with high IgE levels, the two possible options were to provide cetuximab treatment as planned, or suggest another equally effective or less effective treatment. In all cases, the options and their consequences were clearly explained to the patient, who was then allowed to choose between the treatments. If the patient consented to receiving cetuximab treatment, the first and second (if applicable) infusions were monitored closely by a physician, with resuscitation equipment readily available in case of an HSR.

Clinical data

For each patient, data were collected on the following parameters: weight, age at cetuximab administration, site of primary tumor, date of diagnosis, previous tumor treatments, concomitant and previous medications, and location of metastases in case of metastatic disease. In addition, history of allergy (against drug, food, or insects), asthma, eczema, allergic rhinitis, and shock or angioedema were recorded.

In case of a HSR to cetuximab, the time interval between the beginning of the infusion and reaction, the clinical manifestation of the HSR, as well as the details of its management were recorded. Serum assays for histamine and tryptase were performed.

Case definition and grading system

HSRs to cetuximab were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0, in the same manner as in our previous retrospective cohort study [17]. The grades for all HSR were described by an independent clinician blinded to the anti-cetuximab IgE levels and to the grades given by the investigators. Severe HSR were defined as grades 3, 4, or 5.

Statistical Design and Analyses

All incidences of HSR were analyzed in patients who received cetuximab. A cohort of interest was defined as patients with low pretreatment levels of anti-cetuximab IgE (<29 EAU). The study was designed to test whether the incidence of severe HSR (grade 3 or above) in the cohort of interest would be lower than that observed in the historical cohort (11/213 = 5.2%) in which the pretreatment anti-cetuximab IgE levels had not been determined. Assuming that the severe HSR incidence in the cohort of interest would be 1.2% or lower (*i.e.* lower by at least 4-percent compared with the historical cohort), 135 patients would be needed in the cohort of interest to detect this difference as significant with a one-sided Fisher's exact test ($\alpha = 5\%$, $\beta = 20\%$). As the main objective was related to patients belonging to the cohort of interest from the same geographical region [2-9, 18, 19] as the historical cohort (Basse-Normandie, France), we decided to include at least 285 patients in the entire study population, to account for those from other geographical areas, those who may not receive cetuximab, and those who may have high levels of anti-cetuximab IgE.

The comparison of the incidence of severe HSR in the present prospective cohort with that in the historical cohort was done in a stepwise manner. In the first step, the

incidence in the cohort of interest specifically from the region of Basse-Normandie was compared with the historical cohort which had been entirely from this region by a one-sided Fisher's exact test. Secondly, the incidence was compared between the cohort of interest from Basse-Normandie and that from outside this region by a two-sided Fisher's exact test. Lastly, if no geographical disparity is found in the second step, then the incidence would be compared between the entire cohort of interest from the present prospective cohort and the historical cohort by a one-sided Fisher's exact test. The odds ratio (OR) of the incidence of severe HSR in a given cohort of interest to that in the historical cohort was determined with a two-sided 95% confidence interval (CI). The sensitivity and the negative predictive value (NPV) of anti-cetuximab IgE assay associated with the risk of severe HSR were estimated with exact binomial 95% CI. As it was possible for patients with high levels of anti-cetuximab IgE, not to receive cetuximab, specificity and positive predictive value could not be calculated.

The following factors that have been reported as possibly related to the occurrence of a severe HSR were investigated as described below. Mean age was compared by a Student's *t* test, levels of anti-cetuximab IgE by a Mann-Whitney *U* test, and qualitative factors (gender, history of allergy, premedication, and site of cancer) were compared by a Fisher's exact test. *P*-values and CI are two-sided unless otherwise specified. Significance was set at $P \leq 0.05$. The statistical software R version 3.0.1 (R foundation for statistical computing, Vienna, Austria) was used for all analyses.

RESULTS

Patient population

Three hundred three patients were included in the study (Figure 1). Of these 303 patients, 2 patients were excluded because of previous cetuximab treatment or lack of data on pretreatment anti-cetuximab IgE levels. Of the 301 assessable patients, 66 patients (21.9%) had high levels of anti-cetuximab IgE and 235 patients had low levels.

The baseline characteristics of the present study population were similar to those of the historical cohort [17], except for the site of tumor (Table 1). The proportion of patients treated with cetuximab for head-and-neck cancer was relatively higher in the present prospective cohort than in the historical cohort probably because of the later addition of this type of tumor to cetuximab indications.

Hypersensitivity reactions to cetuximab

Among the 247 patients who received cetuximab for the first time, 12 patients (4.9%) experienced a HSR, of which 8 patients (3.2%) had a severe reaction (5 patients had grade 3, and 3 patients had grade 4 reaction). There were no deaths due to a HSR to cetuximab. All HSRs occurred within one hour after the beginning the first cetuximab administration. The 12 cases of HSR to cetuximab and their management are described in Table 2.

Anti-cetuximab IgE levels and risk of hypersensitivity reaction to cetuximab

The incidence of severe HSR to cetuximab in the cohort of interest (low levels subgroup) from the Basse-Normandie region was lower than that in the historical cohort (2/138 = 1.4% *vs.* 11/213 = 5.2%, one-sided $P = 0.060$; OR, 0.27, 95% CI,

0.06 to 1.24; two-sided $P = 0.087$), indicating a difference of −3.8% in the observed incidence.

There was no geographical disparity in the incidence of severe HSR between the cohort of interest from Basse-Normandie and that from outside this region (2/138 = 1.4% *vs.* 1/71 = 1.4%, $P = 1$). The overall incidence in the cohort of interest from the entire study population was lower as compared with the historical cohort (3/209 = 1.4% *vs.* 11/213 = 5.2%, one-sided $P = 0.029$; OR, 0.27, 95% CI, 0.07 to 0.97; two-sided $P = 0.053$, Figure 2).

The incidence of severe HSR in patients with high levels of anti-cetuximab IgE was significantly higher than that in those with low levels (5/38 = 13.2% *vs.* 3/209 = 1.4%, $P = 0.0027$*;* OR, 10.4, 95% CI, 2.4 to 45.6). The sensitivity and the NPV of anti-cetuximab IgE assay associated with the risk of severe HSR were 5/8 = 63% (95% CI, 24 to 91%) and 206/209 = 98.6% (95% CI, 95.9 to 99.7%), respectively.

Patients with severe HSR had significantly higher levels of anti-cetuximab IgE than patients without severe HSR (median, 45 EAU; range, 3.5 – 220.5 *vs*. median, 2 EAU; range, 1 – 12, $P = 0.0059$*)*.

Factors related to severe hypersensitivity reactions

A comparison of various characteristics between patients who did not have a severe HSR and those who did (Table 3) revealed that high levels of anti-cetuximab IgE was the only factor significantly associated with the occurrence of severe HSR to cetuximab. No significant association was noted between severe HSR and gender,

age, history of allergies or tumor localization (Table 3). Further, none of these factors was found to be related to HSR of any severity grade (data not shown).

DISCUSSION

This is the first prospective study to confirm the strong association between the presence of circulating anti-cetuximab IgE before the first infusion of cetuximab, and the occurrence of hypersensitivity reactions to cetuximab. It demonstrates that assaying for pre-existing anti-cetuximab IgEs could help assess the risk of HSR and to tailor the therapeutic strategy accordingly. These considerations are clinically meaningful because prevention of severe allergic reactions to cetuximab is a major challenge, and also a financial burden, especially in regions with high incidence [12, 20].

The study was powered to detect a difference of at least −4% in the incidence of severe HSRs between patients with low pretreatment anti-cetuximab IgE levels from the present prospective cohort and the historical cohort that had not been prospectively screened for pre-sensitization to cetuximab [17]. However, the calculated difference was −3.8%, after verifying lack of geographical disparity. Although our statistical assumptions concerning the main objective were not fully reached (expected at least −4%, observed −3.8%), the decrease in the severe HSR incidence remains of clinical interest.

This study confirms that severe HSR to cetuximab is not a rare adverse event. In the historical cohort, the incidence was of 5.2%, an intermediate between low incidences from the pivotal studies of cetuximab (1%–3.5%) [2-5], and the high incidences

described in some areas such as North Carolina or Tennessee (up to 22%) [7, 8]. In the present prospective study, we noted an overall low incidence of severe HSR of 3.2%, accounting for 1.4% or 13.2% in subgroups of cetuximab-treated patients with low or high levels of anti-cetuximab IgE, respectively. This observed overall incidence is indeed biased because some patients with high levels of anti-cetuximab IgE declined cetuximab treatment (19/66), notably patients with an alternative treatment option.

Analysis of various patient characteristics did not show a correlation of any with the risk of HSR, except for high levels pre-existing anti-cetuximab IgEs. The results of this study do not support the indications from previous studies, such as that of association of HSR with allergies, head-and-neck cancer, or male gender [8-10, 14]. Indeed, several reports have described a higher incidence of HSR to cetuximab in patients treated for head-and-neck cancer or lung cancer[8-10], but these patients are usually more likely to have symptoms such as dyspnea or bronchospasm, which are confounding symptoms for HSR.

In our study, patients who had severe HSR had in fact received appropriate premedication, but this did not seem to prevent HSR to cetuximab unlike in previous studies [7, 21]. Given the mechanism of HSR involving pre-existing IgE, it is not surprising that premedication with corticosteroids and antihistamine was not sufficient to avoid anaphylactic reaction in patients with high anti-cetuximab IgE concentration.

The results presented here support the notion that cetuximab HSR is an IgE-mediated anaphylactic reaction in a pre-sensitized individual [22]. All HSRs reported here were immediate-onset, implying the presence of pre-existing IgEs [23].

The negative predictive value of testing for anti-cetuximab IgE would permit a better selection of patients for cetuximab treatment, so that patients with high IgE levels will not be exposed to the risk of a potentially fatal HSR. Therefore, rather than denying this treatment, it would be advisable to test for pre-sensitization to cetuximab and then provide the treatment taking all the necessary precautionary measures, especially during the first infusion. It is often the element of surprise that can cost the life of patients experiencing severe reactions [10, 11, 15]. Thus, screening for patients at a high risk of severe reactions would allow a better management of these cases.

In conclusion, anti-cetuximab IgE detection appears to be an effective tool to help clinicians predict allergic accidents to cetuximab, and should be considered as a part of a comprehensive approach to personalized cancer treatment. In addition to testing for *RAS* and *RAF* mutations to predict the effectiveness of treatment with cetuximab in colon cancer, assaying anti-cetuximab IgE levels will predict a patient's tolerance to treatment [24, 25] and avoid fatal events.

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FIGURES LEGENDS

Figure 1. Study flowchart

CTX: Cetuximab; IgE: Immunoglobulin E

Figure 2. Incidence of severe hypersensitivity reactions to cetuximab. Incidence of severe hypersensitivity reactions (bold line) and two-sided 95% confidence interval (thin line) in the historical retrospective cohort and the present prospective cohort, according to the levels of anti-cetuximab IgE (low levels, ≤29, or high levels, >29 EAU).

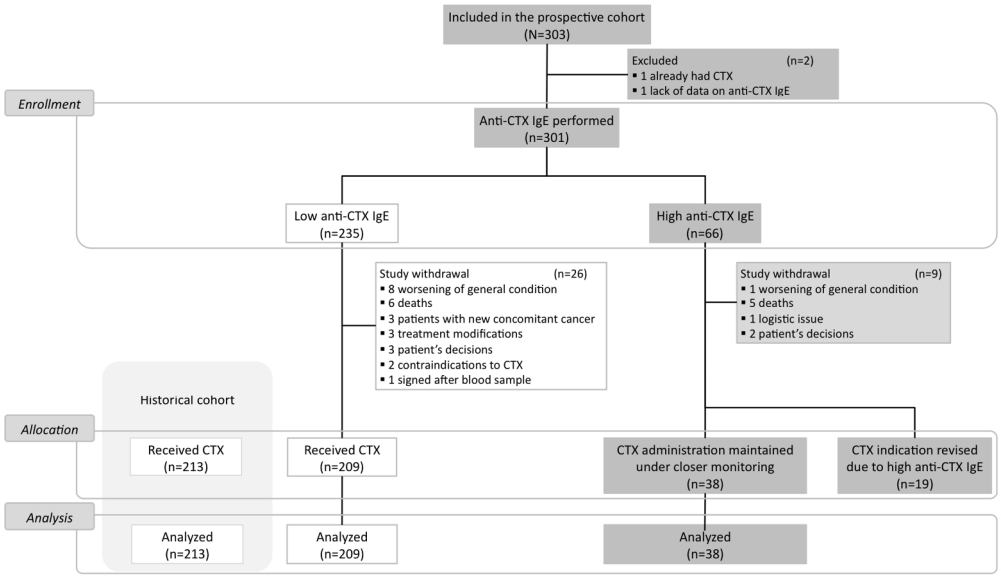

Figure 1. Study flowchart
694x416mm (72 x 72 DPI)

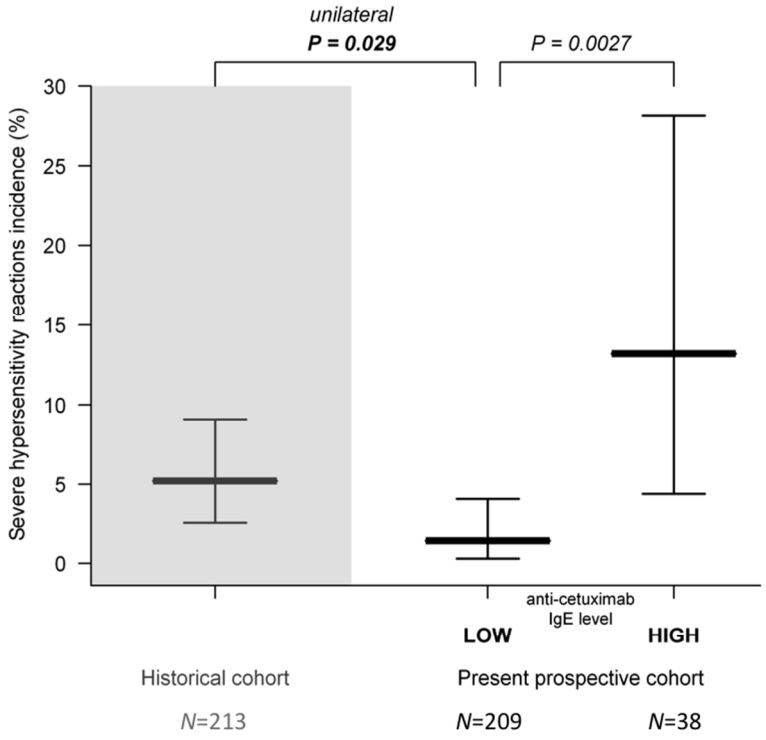

Figure 2. Incidence of severe hypersensitivity reactions to cetuximab.
352x264mm (72 x 72 DPI)

Table 1. Baseline Patient Characteristics

	Historical cohort *N* = 213	Present prospective cohort	
		Patients receiving cetuximab *N* = 247	Overall population *N* = 301
Age, years, (mean ± SD)	62.1 ± 10	61.1 ± 9.1	60.9 ± 9.3
Male	159 (76.6%)	197 (79.8%)	244 (81.1%)
History of allergy	36 (16.9%)	30 (12.1%)	41 (13.6%)
Type of cancer			
Head-and-neck cancer	100 (46.9%)	189 (76.5%)	232 (77.1%)
Colon cancer	107 (50.2%)	58 (23.5%)	69 (22.9%)

Data are presented as *N* (%) unless otherwise specified.

Table 2. Description of the cases of hypersensitivity reactions to cetuximab

Cases	Localization	Premedication dexchlorpheniramine + corticosteroids	Grade	Time (min)	IgE Value (EAU)	Anti-cetuximab IgE assay	Histamine (Normal <6 nmol/L)	Tryptase (Normal <12.5 µg/L)	Treatment*
									Medications
A	Colon	Yes	1	35	9	Low	ND	ND	-
B	Colon	Yes	1	15	1.5	Low	3.1	5.2	-
C	Head-and-neck	Only dexchlorpheniramine	2	40	15	Low	9.3	27.8	-
D	Head-and-neck	Yes	2	15	39	High	ND	ND	CORT
E	Colon	Yes	3	40	1.5	Low	3.8	5.1	CORT, TER, IPR
F	Head-and-neck	Yes	3	15	35	High	83.3	13.7	-
G	Head-and-neck	Yes	3	20	55	High	1.3	2	CORT, DEX, TER, IPR
H	Colon	Yes	3	25	2.5	Low	12	ND	CORT, DEX
I	Head-and-neck	Yes	3	15	490	High	ND	ND	DEX, CORT, TER
J	Head-and-neck	Yes	4	15	134	High	661	31.6	CORT, EPI
K	Head-and-neck	Yes	4	<1	480	High	100	64	CORT, EPI, TER
L	Head-and-neck	Yes	4	30	4	Low	20.8	8.6	EPI

* Treatment administered in addition to cetuximab infusion stop. In patient A, cetuximab infusion was stopped temporarily and resumed. ND, Not Determined.

CORT: corticosteroids; DEX: dexchlorpheniramine; TER: terbutaline; IPR: ipratropium; EPI: epinephrine; SD: standard deviation.

Table 3. Univariate analysis of factors related to the occurrence of a severe hypersensitivity reaction to cetuximab

	No severe HSR ***N*=239**	**Severe HSR** Grade 3 or 4 ***N*=8**	***P***
Age, years, *mean* ± *SD*	61.1 ± 8.9	62 ± 12.9	0.85
Male	191 (79.9%)	6 (75%)	0.67
History of allergy	28 (11.7%)	2 (25%)	0.25
Type of cancer			
Head-and-neck cancer	183 (76.6%)	6 (75%)	1
Premedication			
Dexchlorpheniramine	216 (91.5%)	8 (100%)	1
Corticosteroids	232 (98.3%)	8 (100%)	1
Anti-cetuximab IgE assay			
High	33 (13.8%)	5 (62.5%)	**0.0027**

HSR, hypersensitivity reaction, *SD* Standard Deviation
Data are presented as *N* (%) unless otherwise specified.