Chemotherapy and Monoclonal Antibody Hypersensitivity: Evaluation and Management

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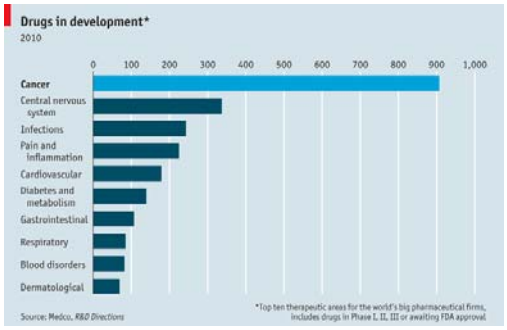
Disclosures

- None

Objectives

- Review common adverse/hypersensitivity reactions encountered with increased use of chemotherapeutics and monoclonal antibodies
- Provide effective tools to evaluate reactions to chemotherapeutics and monoclonal antibodies
- Discuss treatment strategies to manage reactions

Introduction



- Rapid expansion of the use of chemotherapeutics and biologics has resulted in an increase in hypersensitivity reactions
- All biologics have the potential to induce immunogenicity
  - Degree of humanization, pattern of glycosylation, episodic administration

Allergy vs. Side Effect

- Most side effects in chemotherapy are predictable such as hair loss, mucositis, nephrotoxicity, hepatotoxicity, ototoxicity, immunosuppression are caused by the chemotherapy affecting the non-cancerous "normal" cells in the body
- Hypersensitivity reactions are not common, are unpredictable, and unrelated to the known pharmacologic reactions of the chemotherapeutic agent

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Incidence of Reactions

Agent	Overall	Grade 3-4
Carboplatin (Paraplatin®)	2 %	none
Cetuximab (Erbitux®)	15-20%, dependent on tumor type	3%
Docetaxel (Taxotere®)	5-12%	2%
Eloxatin (Oxaliplatin®)	15-33%	2-3%
Paclitaxel (Taxol®)	41%	2%
Rituximab (Rituxan®)	77% First infusion, 30% fourth infusion, 14% eighth infusion	10%

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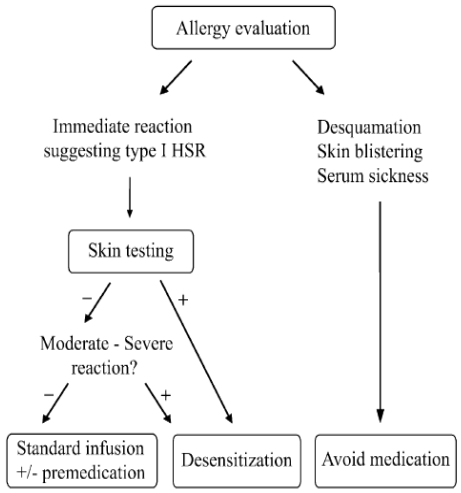
Vogel, CJON 2010

Evaluation of a Patient with HSR



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Brennan et al., JACI 2009

Decrease the Risk of a HSR

- Premedication
  - Steroids
  - Antihistamines
- Slowed infusion rates
- Desensitization

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Carboplatin Hypersensitivity

- Ovarian cancer is the most fatal gynecologic malignancy
  - Majority of patients will develop recurrent ovarian cancer
- For women with recurrent ovarian cancer, repeat treatment with carboplatin is frequently recommended.
  - Increased risk of hypersensitivity reaction (HSR)
    - 1% with 6 or less exposures to carboplatin
    - Approximately 25% with 7 or more exposure

Incidence of hypersensitivity reactions in patients receiving Carboplatin

Standard Infusior	Study	Type of Cancer	Frequency of HSR	Number of Previous cycles of carboplatin
	Markman, M et al (1999)	Gynecologic	22/83 (27%)	7 Cycles or greater
	Gaducci, A et al (2008)	Recurrent Ovarian	15/60 (25%)	6 cycles or greater
	Schwartz, JR et al (2007)	Gynecologic	55/118 (47%)	Cycle 6-13 (mean cycle 9)
	Caerbhaill, R et al (2010)	Epithelial ovarian, fallopian tube, or primary peritoneal	111/555 (20%)	7 Cycles or greater
	MGH Historical Data			
	For year 2013 to date	Gynecologic	14/59 (24%)	7 Cycles or greater

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Oxaliplatin Hypersensitivity

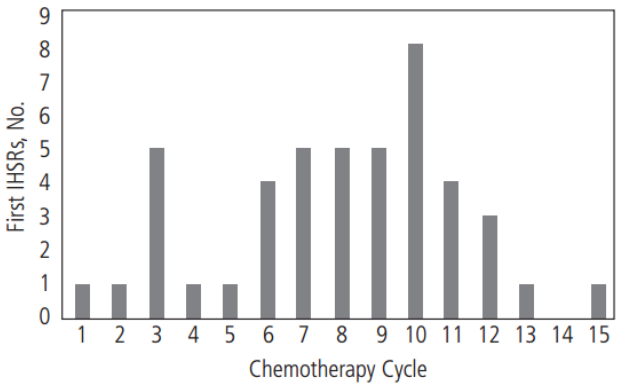

Figure 3. Number of chemotherapy cycles when first immediate hypersensitivity reaction (IHSR) to oxaliplatin occurred.

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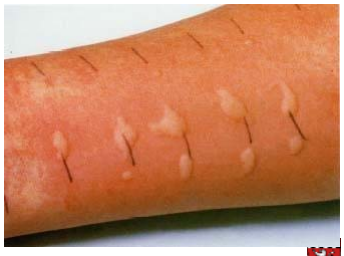
Park et al., JIACI 2016

Skin Testing for Platinum Agents

- Skin testing for platinum agents well-validated
  - Skin prick (epicutaneous) testing
  - Intradermal testing
- Patient must not receive anti-histamines for 5 days prior and should hold beta-blockers
- Patient has results same day



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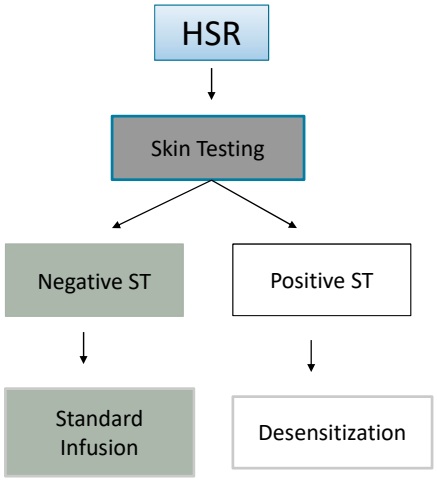
Is there a role for skin testing?



- 98-99% positive predictive value
- False negative rates as high as 8.5%

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Zanotti, et al. J Clin Oncol 2001
Gomez, et al. Int J Gynecol Cancer 2009

Carboplatin Desensitization is Safe and Effective

Solution	Dose in each solution (mg)[a]	Volume	Solution concentration
A	5	100 ml	0.05 mg/ml
B	50	100 ml	0.50 mg/ml
C	500	100 ml	5.00 mg/ml

Step	Solution	Rate (ml/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	A	2	15	0.025	0.025
2	A	5	15	0.063	0.088
3	A	10	15	0.125	0.213
4	A	20	15	0.250	0.463
5	B	5	15	0.625	1.088
6	B	10	15	1.250	2.338
7	B	20	15	2.500	4.838
8	B	40	15	5.000	9.838
9	C	10	15	12.500	22.338
10	C	20	15	25.000	47.338
11	C	40	15	50.000	97.338
12	C	75	64.4	402.663	500.000
		Total time = 3.8 h		Total dose = 500 mg	

- >2000 successful desensitizations at MGH and BWH
- Majority tolerated without any reactions

Lee et al., Gynecol Oncol 2004
Lee et al., Gynecol Oncol 2005
Castells et al., J Allergy Clin Immunol 2008
Hesterberg et.al. J Allergy Clin Immunol 2009

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Mechanism of HSR to Carboplatin

- Exact mechanism remains unclear
  - Markman et al., suggest that the patient may be sensitized during first-line treatment (6 courses)
  - Retreatment with the same drug provides the additional immunological stimulation
- Felt likely to be IgE mediated
- Skin testing has been validated

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Markman et.al. J Clin Oncol 1999

Summary: Hypersensitivity to Platinum Agents

- Patient receiving multiple doses of platinum agents can become sensitized
- Consequently, these patients are often denied what is the best systemic therapy
  - results in the use of less effective second generation agents
- Skin testing is useful, but there remains a concern for false negative results
- Desensitization protocols have been successfully used to overcome HSR to platinum agents

Docetaxel and Paclitaxel Hypersensitivity

- HSRs to docetaxel and paclitaxel are primarily due to cremophor (polysorbate 80)
- HSRs occur in 30% of patients decreasing to <4% with premedication using antihistamines and steroids
- Reactions are dose- and rate-dependent and most often occur within the first few min of the 1st or 2nd infusions
- Symptoms include dyspnea, hypotension, bronchospasm, urticarial and erythematous rash
  - Clinical presentations similar to IgE mediated reactions

Abraxane

- There is a cross-reactivity rate of 90% between docetaxel and paclitaxel, therefore, substitution of the two is not recommended
- Cremophor-free formulations of albumin-bound paclitaxel decrease HSR risk

Management of Paclitaxel HSRs

- Slowed infusions
- Increase premedications
- Risk stratification
  - Allow patients to safely receive paclitaxel
  - Reduce the number of unnecessary desensitizations

Other Chemotheraputic Agents

- PEG-aspariginase
  - Risk factors include IV admin, interval >1 week between admins and previous exposure to L-aspariginase
- Procarbazine
  - Type 1, 3 and 4 associated reactions with an incidence of 6% to 18%
- Etoposide
  - HSRs are thought to be caused by polysorbate 80
  - Can be prevented through adequate premedication and slow infusion rates

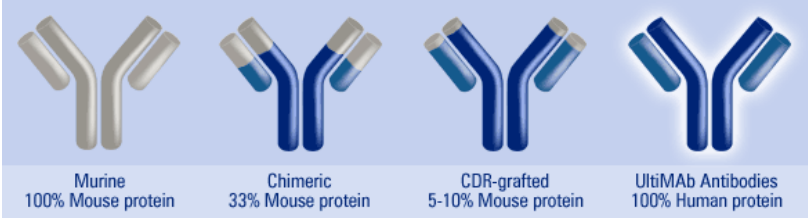
Commonly Used Biologicals

Table 1
Biologicals grouped according to their therapeutic principle

Biological Group	Examples
Cytokines	INF-α, GM-CSF
Monoclonal antibodies against	
Cytokines	Infliximab (anti–TNF-α)
Cell surface molecules	Rituximab (anti-CD20)
IgE	Omalizumab (anti-IgE)
Tumor antigens	Cetuximab (anti-EGFR)
Fusion proteins	
Soluble cytokine receptors	Etanercept (TNF-α-RII-IgG1)
Soluble cellular ligands	Abatacept (CTLA4-IgG1)

Hausmann et al., Med Clin N Am 2010

Evolution of Therapeutic Antibodies



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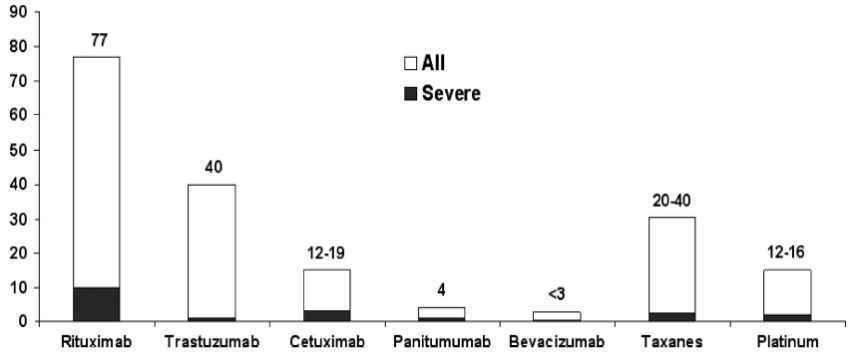
Incidence of Infusion Reactions



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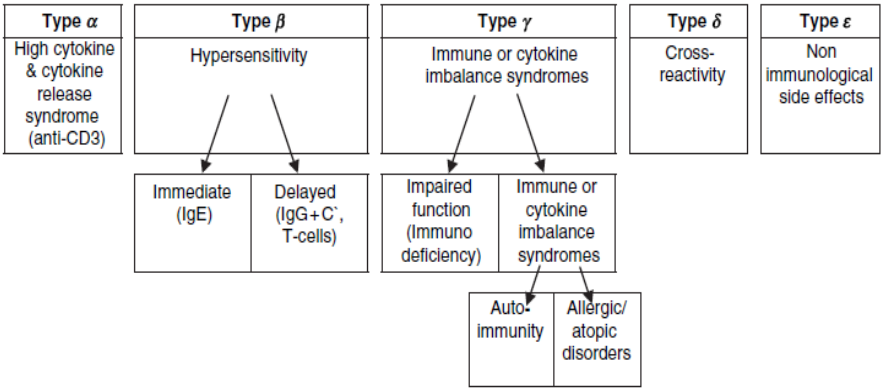
Chung CH. Oncologist 2008

Classification of HSRs to Biologics



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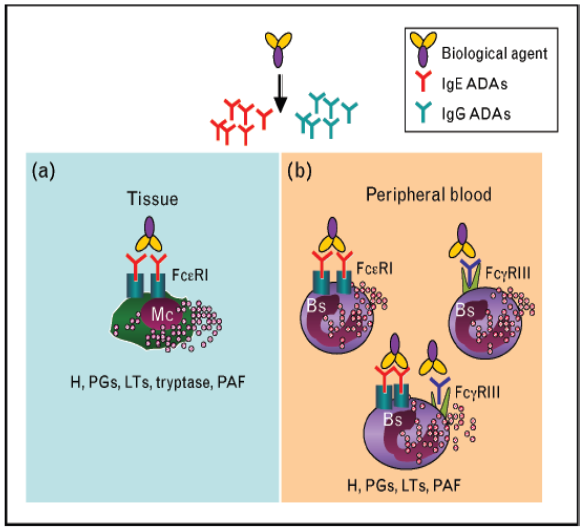
Pichler et al., Curr Opin Allergy Clin Immunol 2011

Mechanisms of Hypersensitivity Reactions

IgE and non-IgE mediated



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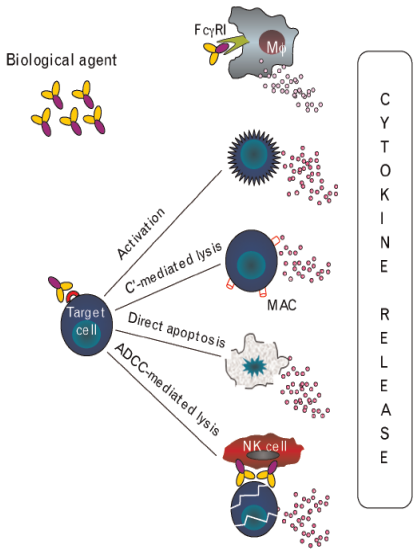
Vultaggio et al., Curr Opin Allergy Clin Immunol 2011

Mechanisms of Hypersensitivity Reactions
Cytokine Release

- Monoclonal antibodies have a unique potential for a nonallergic infusion reaction caused by cytokine release
- Recognition and expert management of a cytokine-release reaction may enable patients to be rechallenged with the monoclonal antibody



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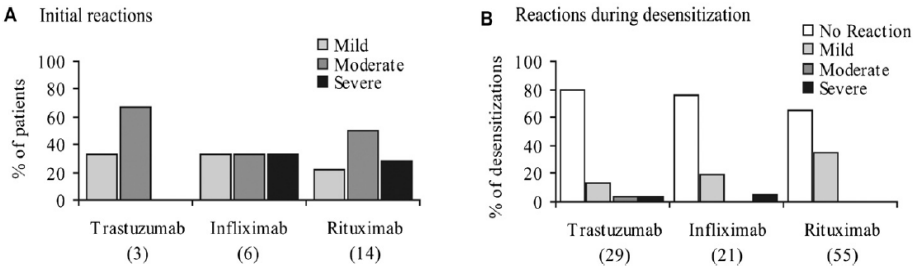
Vultaggio et al., Curr Opin Allergy Clin Immunol 2011

Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment

Patrick J. Brennan, MD, PhD,* Tito Rodriguez Bouza, MD,* F. Ida Hsu, MD, David E. Sloane, MD, and Mariana C. Castells, MD, PhD *Boston, Mass*



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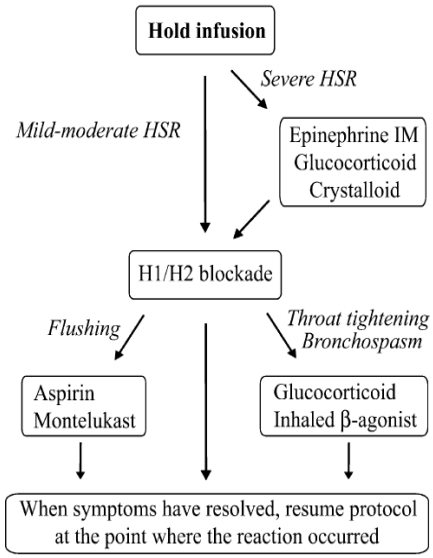
Brennan et al., JACI 2009

Management of Reactions during Desensitization



Brennan et al. JACI 2009

Case: Hypersensitivity Reaction to Rituxan

- JM is a 72 year old male recently diagnosed with Non-Hodgkin's Lymphoma, started on Rituxan therapy
- About one hour after starting his first infusion, he developed fever, chills and back pain
- Infusion was stopped and he received IV diphenhydramine and ranitidine
  - symptoms resolved within 35 minutes
- He refused rechallenge and presents today for your advice

How do you evaluate JM's symptoms as a possible hypersensitivity reaction to Rituxan?

Rituxan Hypersensitivity

- Chimeric murine/human mAb against CD20 on normal and malignant B lymphocytes
- Infusion reactions with fever, chills and rigor reported in 5-10%
- Usually first dose within 30 minutes to 2 hours
  - correlate with disease burden and decrease with subsequent infusions
- Often resolve with slowing of the infusion
- Most reactions are not thought to be IgE-mediated

Grillo-Lopez et al., Semin Oncol 1999
Dillman et al.,1999

Mechanisms for Hypersensitivity to Rituxan

- Cytokine Release Syndrome: fever, chills, nausea, vomiting, hypotension, dyspnea
  - Increased serum TNF, IL-6
- Tumor Lysis Syndrome: renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia
  - Usually within 12-24 hours of infusion
- Pseudoallergic Reactions: urticaria, bronchospasm, hypotension, flushing

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Rituxan Skin Testing

Epicutanous	**10 mg/mL**
Intradermal	**0.1 mg/mL**
Intradermal	**1 mg/mL**

- Performed at specific academic centers
- Little data on sensitivity and specificity with poor predictive value currently
- Reaction rate lower during desensitization in ST negative patients but reactions seen in both skin test positive and skin test negative patients

Mechanism of hypersensitivity is unclear

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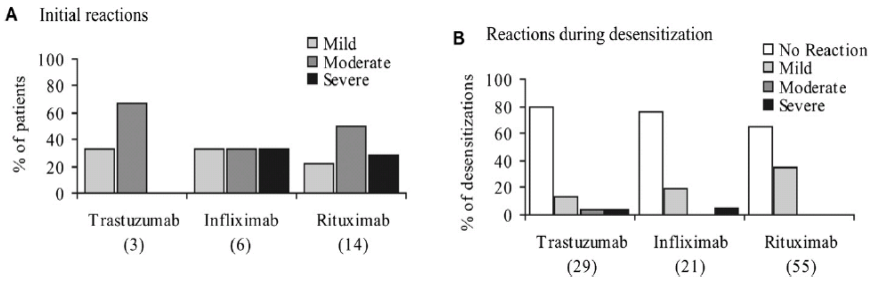
Brennan et al. JACI 2009

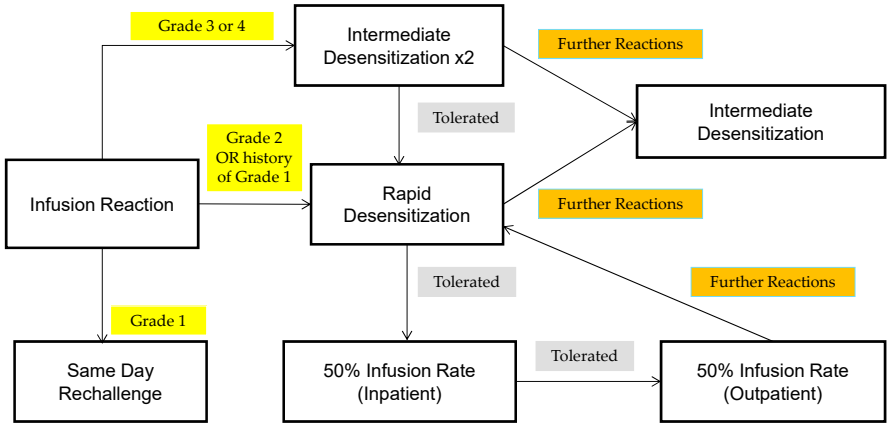
Management of Patients with HSR to Rituxan

- 23 patients underwent 105 successful desensitizations



Brennan et al. JACI 2009

Rituximab Risk Stratification



Infliximab

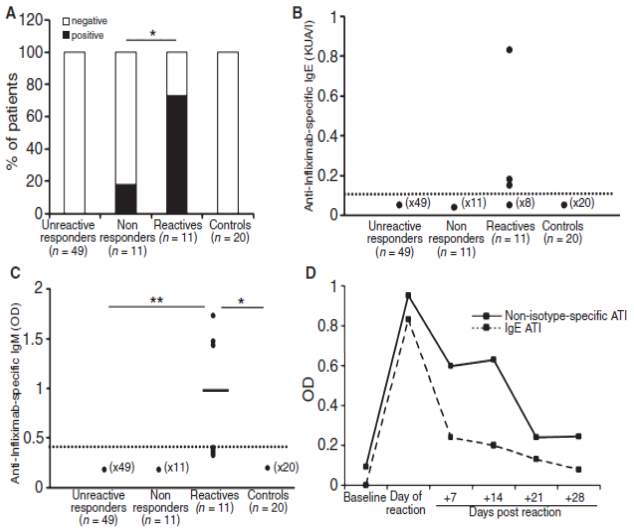
Chimeric Monoclonal Antibody TNFα

- Acute infusion reactions
  - Within 10 minutes to 4 hours
  - Can often continue with slowed infusions/premedication
  - With more severe reactions, desensitization has been successful
- Delayed infusion reactions
  - Usually 5-7 days later
  - Arthralgias, fevers, malaise, urticaria, myalgias, "serum-sickness" like

Antibodies to Infliximab

- Antichimeric antibodies (ATIs) are produced in a substantial number of patients
- Positive correlation between ATIs and both acute and delayed infusion reactions along with reduced efficacy of treatment
  - Concomitant administration of methotrexate reduces antibodies
- Not all patients with ATIs suffer from infusion reactions suggesting a role for other cofactors
- Shifting to another TNFα antagonist generally tolerated

Serum Anti-Chimeric Antibodies: Infliximab

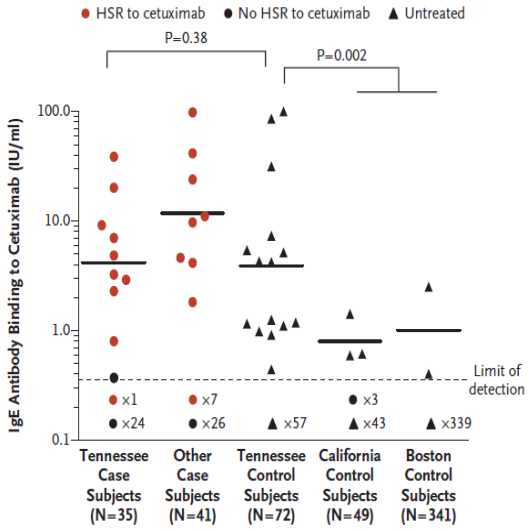


Vultaggio et al. Allergy 2010

Cetuximab

- Chimeric IgG1 monoclonal antibody EGFR
- HSRs reported in 1-22% of patients
  - Higher rates in certain regions
- HSR frequently reported within minutes of initial exposure
- Found to be related to antibodies specific for galactose-α-1,3-galactose present on F_{ab} portion of cetuximab

IgE Antibodies Binding to Cetuximab



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Chung et al. NEJM 2008

Summary

- Approach will vary by drug and mechanism of hypersensitivity
  - Discontinue drug and use reasonable alternative
  - Slowed infusion
  - Pre-medication regimen
  - Skin Testing
  - Induction of tolerance
  - Utility of risk stratification

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