Chronic Urticaria: New Management Options

FACULTY NAME

Financial Disclosures
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- Book Royalties (Walters, Kluwer, Lippincott, Williams & Wilkins)
- FDA Advisory Committees

Learning Objectives

After participation, the learner will be able to:

- Outline the assessment of disease activity
- Discuss the importance of treatment or avoidance of underlying causes and potentiating factors (e.g. heat)
- Describe guideline-driven therapy for chronic urticaria
- Discuss the rationale and efficacy of omalizumab and other alternative therapies for chronic urticaria
- Accurately apply evidence-based recommendations for the management of chronic urticaria in simulated patient encounters

Case Initial Visit

A 38-year old white female presents with a 5 month history of hives and swelling. She has seen a primary care physician and was placed on diphenhydramine 25 mg three times per day. Her hives improved slightly on this regimen, but she still has daily episodes. The hives come and go throughout the day and are made worse by a hot bath. She now presents to you for the possibility of an allergic cause to her hives and further treatment.

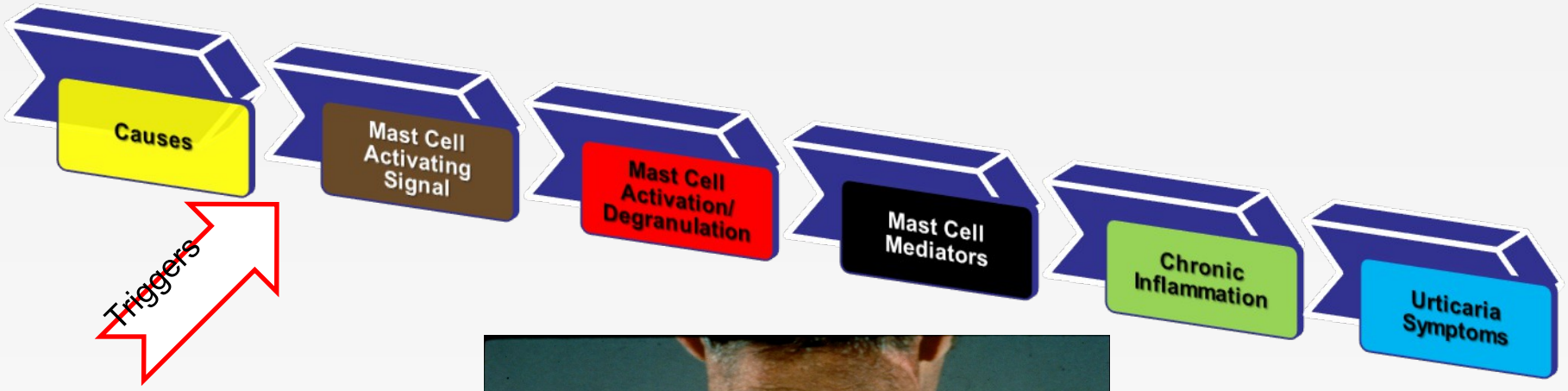
Based on her history, she most likely has:

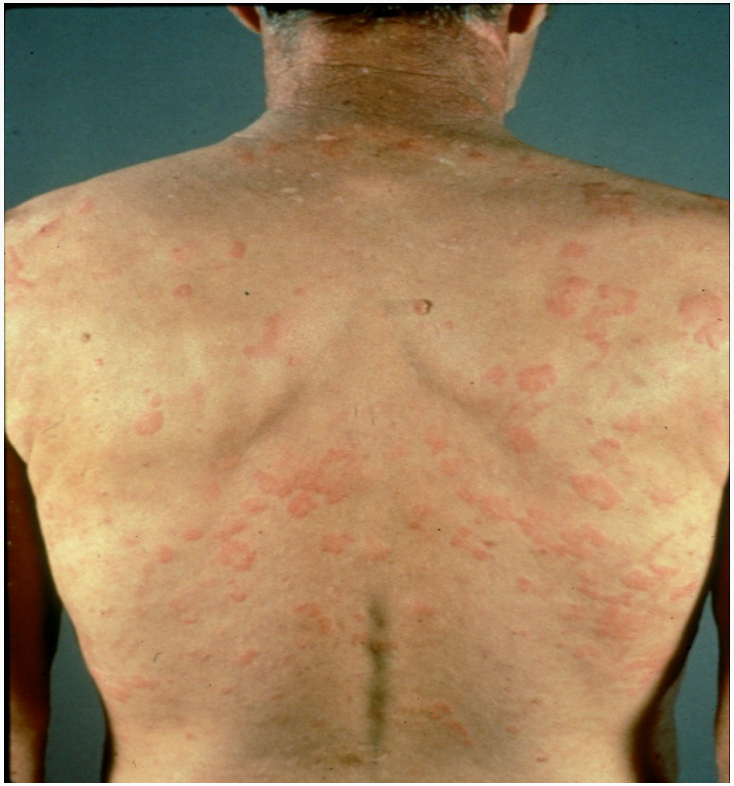
A. Acute allergic urticaria
B. Chronic idiopathic urticaria
C. Cholinergic urticaria
D. Urticarial vasculitits

Clinical features: Urticaria

- Repeated occurrence of short-lived cutaneous wheals accompanied by erythema and pruritus
  - Wheals range in size from a few millimeters to > several centimeters
  - Individual wheals typically last less than 24 hours
  - Lesions should resolve without any residual marks

Urticaria Progression





Urticaria Classification

- Chronic Urticaria (CU): > 6 weeks
  - Lesions several days/week or daily
  - May last months to years
  - Identifiable cause is usually not found (idiopathic)
  - IgE-mediated allergy to foods or drugs is rarely a cause of CU
  - Can be accompanied by angioedema
  - Considered a disease by itself

Chronic Urticaria

- Prevalence estimated to be between 0.6-5%
- No clear prevalence data in the U.S.
- More common in middle-age (not 1000 AD)
- More common in females
- Generally has prolonged duration > 1 yr in 70%

  1 to 5 years in about 9%

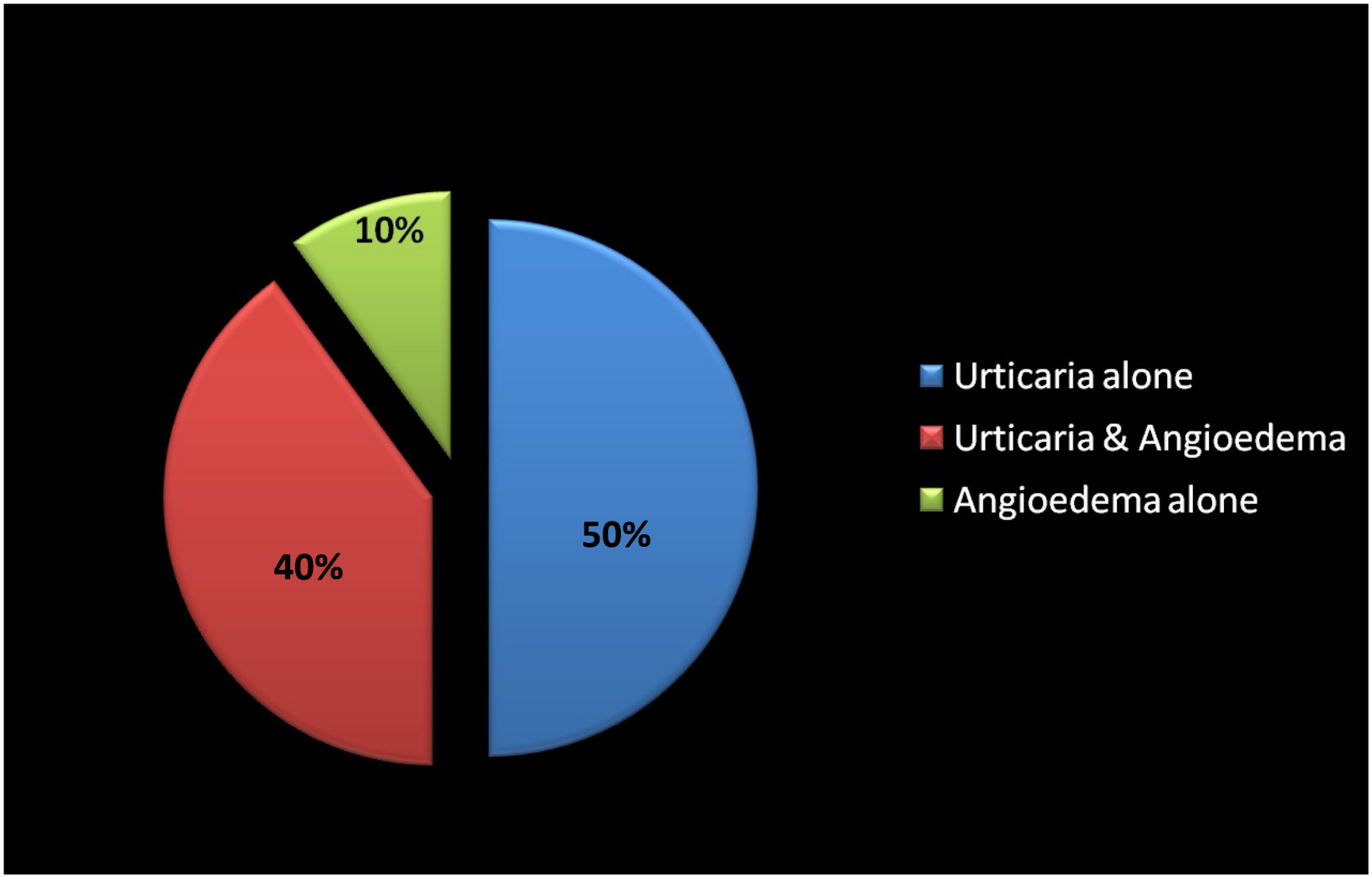
  > 5 yrs in 11-14%

Gaig, P., et al. J Investig Allergol Clin Immunol, 2004. 14(3): p. 214-20.
Jiamton, S., et al. J Med Assoc Thai, 2003. 86(1): p. 74-81.
Vazquez Nava F, et al. Rev Allerg Mex 2004;51:181-8.
Toubi, et al., Allergy, 2004;59(8):869-873.

Comparison of Acute and Chronic Urticaria

	Acute Urticaria	Chronic Urticaria
Urticarial lesions	✔	✔
Associated with Angioedema	✔	✔
Affects up to 20% population	✔	
Duration < 6 weeks	✔	
Etiology often identified	✔	
Often symptom of IgE-mediated allergy	✔	
Considered a disease		✔
Potential for anaphylaxis	✔	
Associated with autoantibodies		✔

CU Presentation



Urticaria -- History

- Onset (e.g. timing of symptoms with any change in medication or other exposures)
- Frequency, duration, severity, and localization of wheals and itching
- Dependence of symptoms on the time of day, day of the week, season, menstrual cycle, or other pattern
- Known precipitating factors of urticaria (e.g. physical stimuli, exertion, stress, food, medications)
- Relation to occupation and leisure activities

Bernstein J, et al. **The Diagnosis and Management of Acute and Chronic Urticaria: 2013 Update. Submitted.**

Medical History

You take a detailed history from the patient and find that she has hives throughout the day and night. She has no history of fevers, night sweats, weight loss or other constitutional symptoms. However, she does complain of being tired all day. She still is menstruating, but has no associated change in the hives with her menstrual cycle.

Based on this new information, what history would be most appropriate to obtain now?

A. **Allergies to aeroallergens**
B. **Whether she has used a new detergent**
C. **Allergies to food**
D. **Medications she is taking**

Urticaria -- History

- Associated angioedema, systemic manifestations (headache, joint pain, gastrointestinal symptoms, etc.)
- Detailed medication list
  - Rx, OTC, supplements
- Known allergies, intolerances, infections, systemic illnesses or other possible causes
- Family history of urticaria and atopy
- Degree of impairment of quality of life
- Response to prior treatment

Bernstein J, et al. **The Diagnosis and Management of Acute and Chronic Urticaria: 2013 Update. Submitted.**

Physical Examination

Physical Exam and Evaluation

The patient states that she does not have pollen allergy, but dust and cats make her sneeze. When she drinks wine, she thinks her hives get worse. She has not switched detergents recently. Her current medications are a multi-vitamin daily, and Tylenol occasionally for headaches.

On physical examination, she is a healthy appearing 38-year old white female with normal vital signs. Her exam is unremarkable, including no lymphadenopathy or organomegaly. Skin showed approximately 50 urticarial lesions that blanche with pressure and she has some mild angioedema above the eyelids.

The most appropriate next step in her evaluation is:

A. Skin biopsy
B. ANA
C. Allergy skin testing
D. Complete blood count with differential

Urticaria – Physical Exam

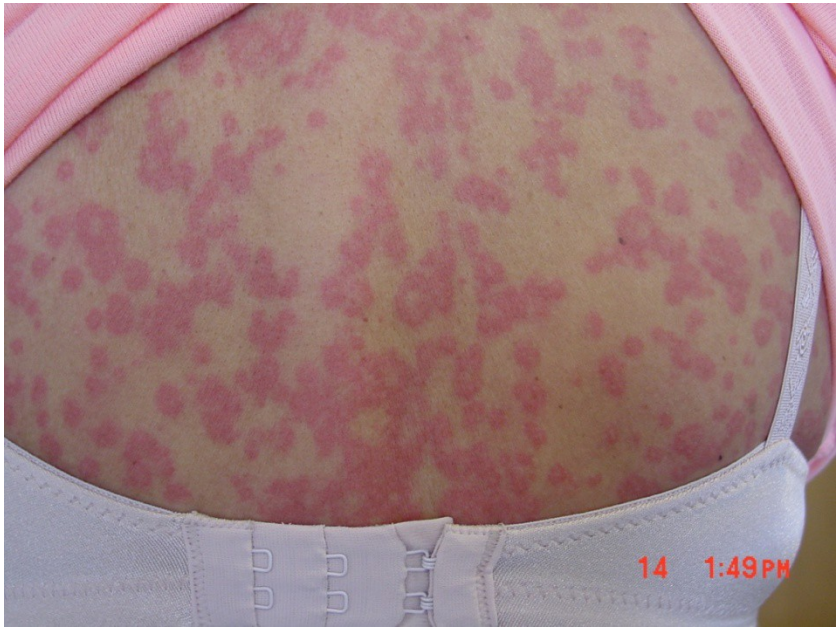
- Lesions are typically edematous pink or red wheals of variable size and shape, with surrounding erythema, and are generally pruritic.

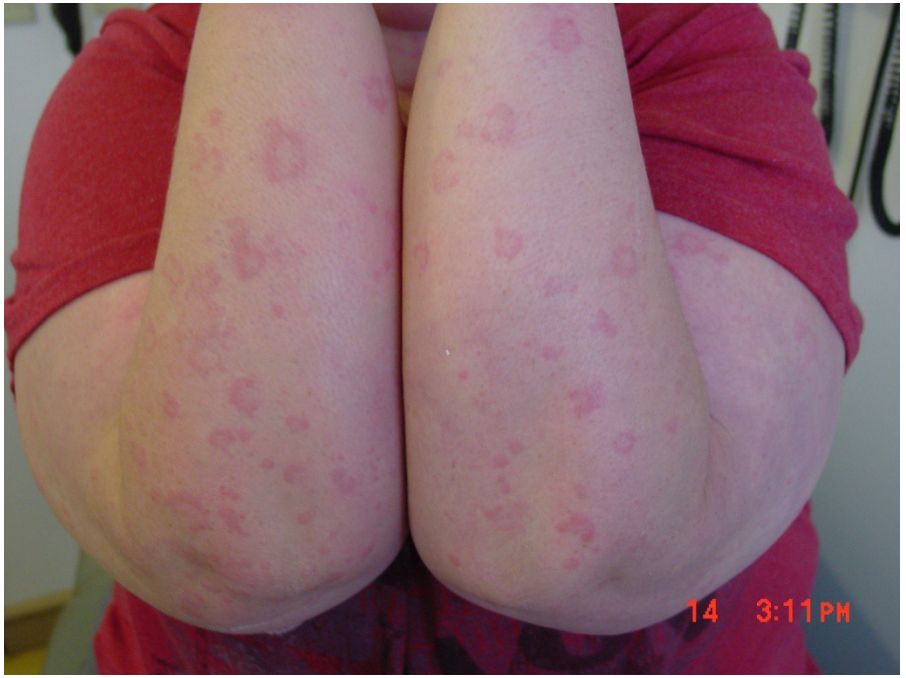
- A painful or burning dysesthesia suggests presence of a cutaneous vasculitis.

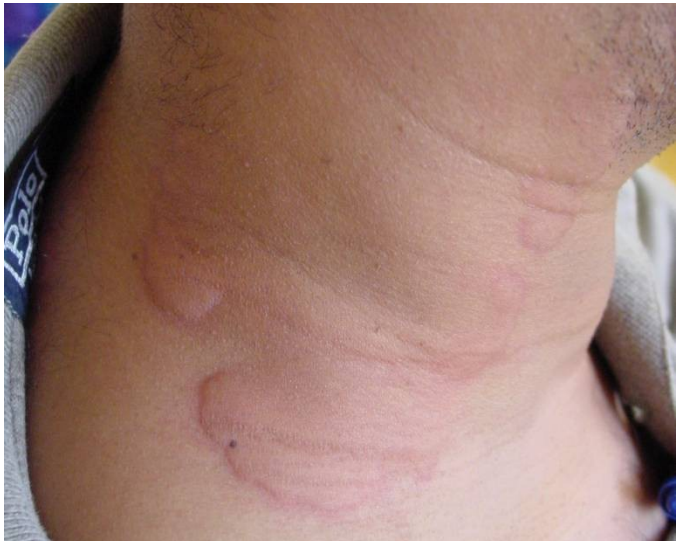
- Lesions usually fade within 24-48 hours; vasculitis lesions may span several days or more, and are often followed by residual hyperpigmented changes

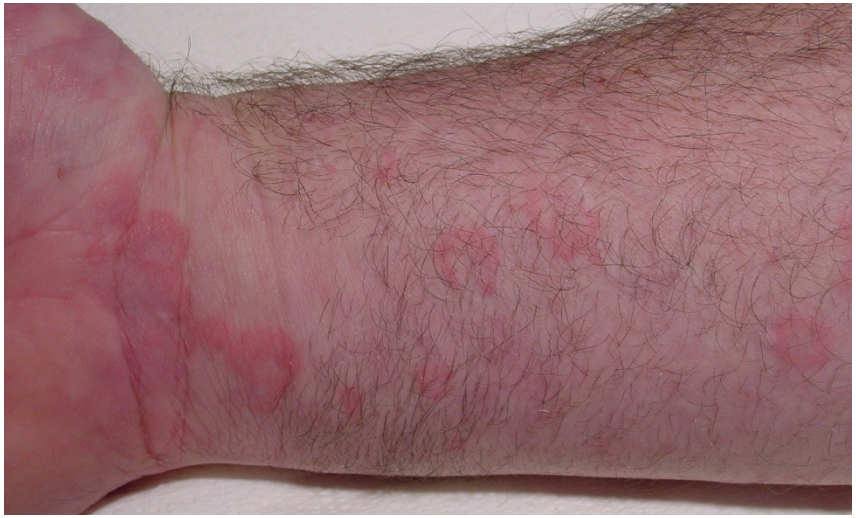
Bernstein J, et al. **The Diagnosis and Management of Acute and Chronic Urticaria: 2013 Update. Submitted.**

Urticaria









Evaluation Of Urticaria: US Guidelines

- Routine evaluation: Testing should be selective.

- A majority of members of the Practice Parameters Task Force expressed a consensus for the following routine tests in CIU:
  - Complete blood count with differential
  - Erythrocyte sedimentation rate
  - Liver enzymes
  - Thyroid stimulating hormone

- The utility of performing the above tests routinely for CU patients has not been established.

Laboratory Evaluation

- **Routine evaluation. Testing should be selective. There is an honest difference of opinion concerning the appropriate tests that should routinely be performed for patients with CU in the absence of etiologic considerations raised by a detailed history and careful physical exam.**
- **A majority of members of the Practice Parameters Task Force expressed a consensus for the following routine tests in managing a patient with CU without atypical features:**
  - Complete blood count with differential
  - Erythrocyte sedimentation rate
  - Liver enzymes
  - Thyroid stimulating hormone

The utility of performing the above tests routinely for CU patients has not been established.

Extensive routine testing for exogenous and rare causes of CU, or immediate hypersensitivity skin testing for inhalants or foods, is not warranted.

Benstein J et al. The Diagnosis and Management of Acute and Chronic Urticaria: 2013 Update (submitted).

Recommended Diagnostic Tests In Chronic Urticaria: EAACI

Routine Diagnostic Tests (recommended)

- Differential blood count and ESR or CRP
- Omission of suspected drugs (e.g. NSAID)

Extended Diagnostic Program /Tests (suggested) if indicated

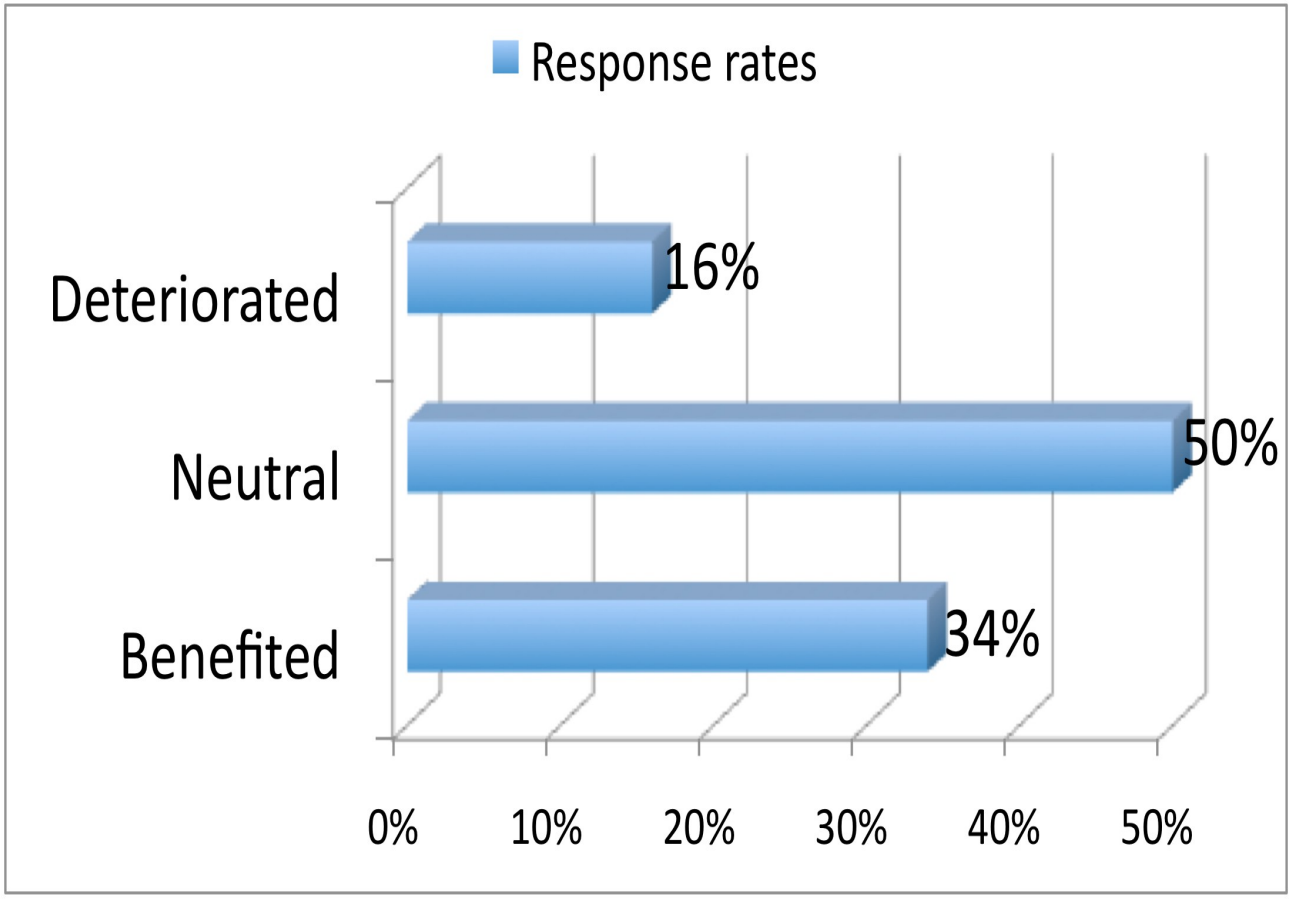
- Infectious diseases (eg H pylori)
- Type I allergy (eg latex)
- Functional autoantibodies, anti-FcεR test or ”CUI
- Thyroid hormones /autoantibodies
- Physical urticaria tests
- Pseudoallergen-free diet for 3 wks
- Autologous serum skin test
- Lesional skin biopsy

T. Zuberbier, Allergy 2009: 64: 1417–1426 2009

Pseudoallergen Free Diet

"Psuedoallergens" = substances that induce intolerance reactions: food additives, vasoactive substances, fruits, vegetables, spices.

Days 1-7
-Usual foods
Days 8-10
-rice, potatoes, bread, butter, salt, olive oil, coffee, tea
Days 11-31
-pseudoallergen free



Zuberbier T, et al. Allergy 2010; 6578-83.

Initial Therapy

The patient's complete and differential blood counts are normal. Her erythrocyte sedimentation rate is 30 (normal 0-20). Her liver enzyme and thyroid stimulating hormone levels are normal.

The next best step in the management of this patient is:

A. Increase diphenhydramine to 50 mg 4 x daily

B. Discontinue diphendydramine & switch to cetirizine 10 mg twice daily

C. Add cimetidine at 400 mg twice per day

D. Add dapsone 50 mg orally at night

H-1 Antihistamines

High Quality Evidence

- Preferred 1st line therapy for patients with chronic urticaria/angioedema.
- H1-antihistamines efficacious in numerous published RCTs since 1950s.
- 1st generation agents associated with risk for sedation and anti-cholinergic effects
- 2nd generation agents also efficacious and in most patients are better tolerated

Strong Recommendation

Step-Up Therapy

After three weeks, the patient returns to you and states that after discontinuation of diphendydramine she is more alert and less tired, but the cetirizine did not appear to be any better for her hives.

The most appropriate next therapeutic step is:
A. Increase cetirizine to 10 mg 4 x daily
B. Add hydrochloroquine 400mg daily
C. Add sulfasalazine 500mg daily
D. Add colchicine 0.6mg daily

Management Of Chronic Urticaria

Step 1

- Avoidance of triggers
- Monotherapy with second generation antihistamine

Step 2

- Dose advancement of 2nd generation antihistamine used in Step 1
- Add another second generation antihistamine
- Add H_2- antagonist
- Add leukotriene receptor antagonist
- Add 1st generation antihistamine (at bedtime)

Step 3

- Dose advancement of potent antihistamine (e.g. hydroxyzine or doxepin) as tolerated

Step 4

- Anti-inflammatory agent
- Immunosuppressant
- Biologics

Urticaria Practice Parameter Update

Antihistamines: H1 Combined with H2

- Evidence difficult to interpret
  - Small numbers of patients studied
  - Different H1 antihistamines used
  - Dose of H2 antihistamine variable
    - Cimetidine 800-1200 mg/day
    - One study: cimetidine 400 mg QID
- Superior efficacy
  - *Clin Allergy* 8:429, 1978
  - *Br J Dermatol* 117: 81; 1987
- No advantage
  - *Br J Dermatol* 99: 675; 1978
- Drug-Drug interaction: Hydroxyzine & Cimetidine
  - Simons EF, et al. *J Allergy Clin Immunol* 1995; 95: 685-93

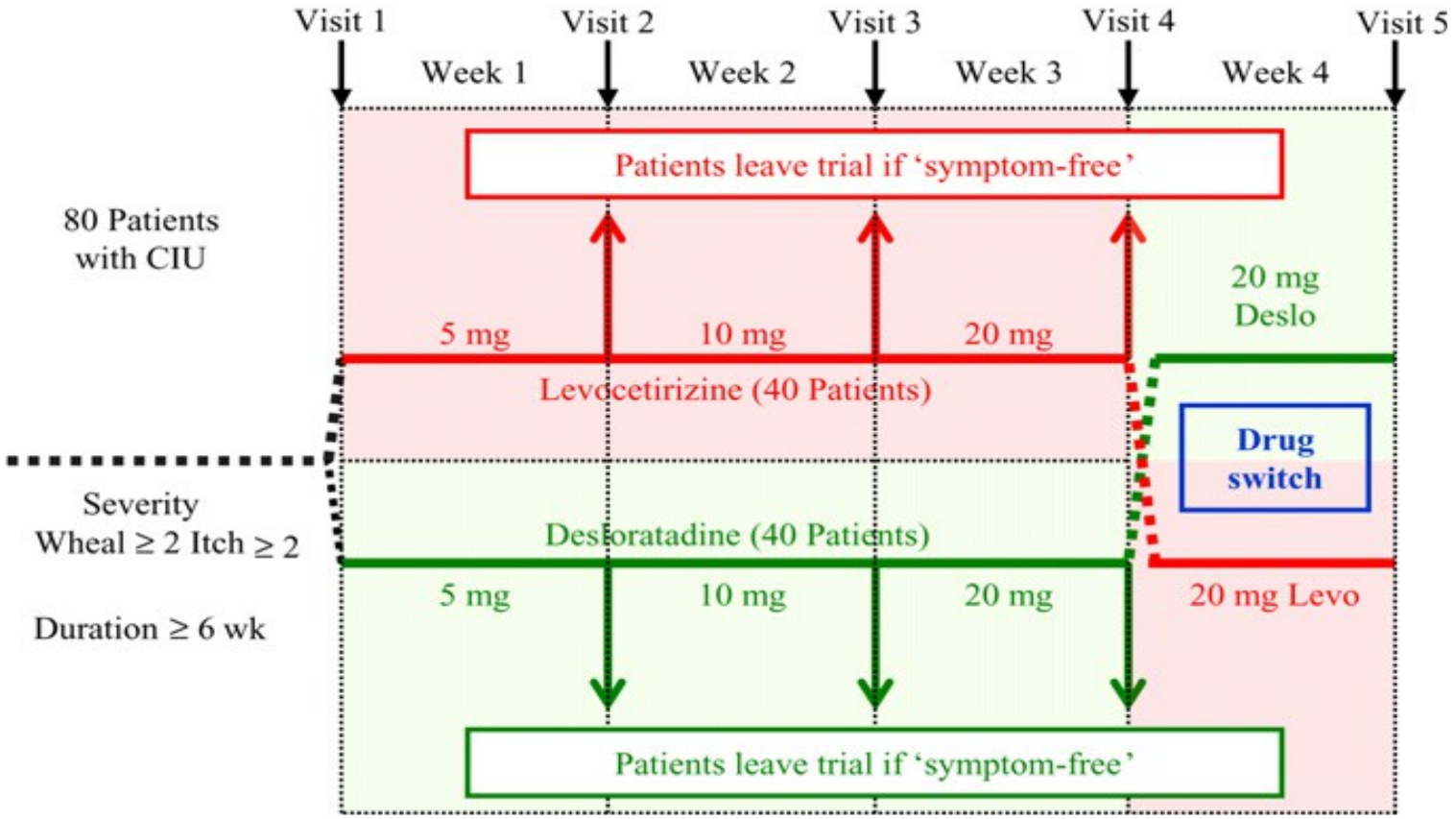
Anti-Leukotrienes

- Montelukast/Zafirlukast/Zileuton
- Substantial safety advantage compared with other “alternative” or “steroid sparing” agents
- RCTs
  - 5: favorable
  - 1: no advantage
- Data suggest salutary effect more likely
  - ASA-exacerbated urticaria/angioedema
  - Physical Urticaria/Angioedema
  - Positive Autologous Serum Skin Test

Morgan M, Khan D. Ann Allergy Asthma Immunol 2008; 100: 403-11

Dose Advancement of 2nd Generation Antihistamines

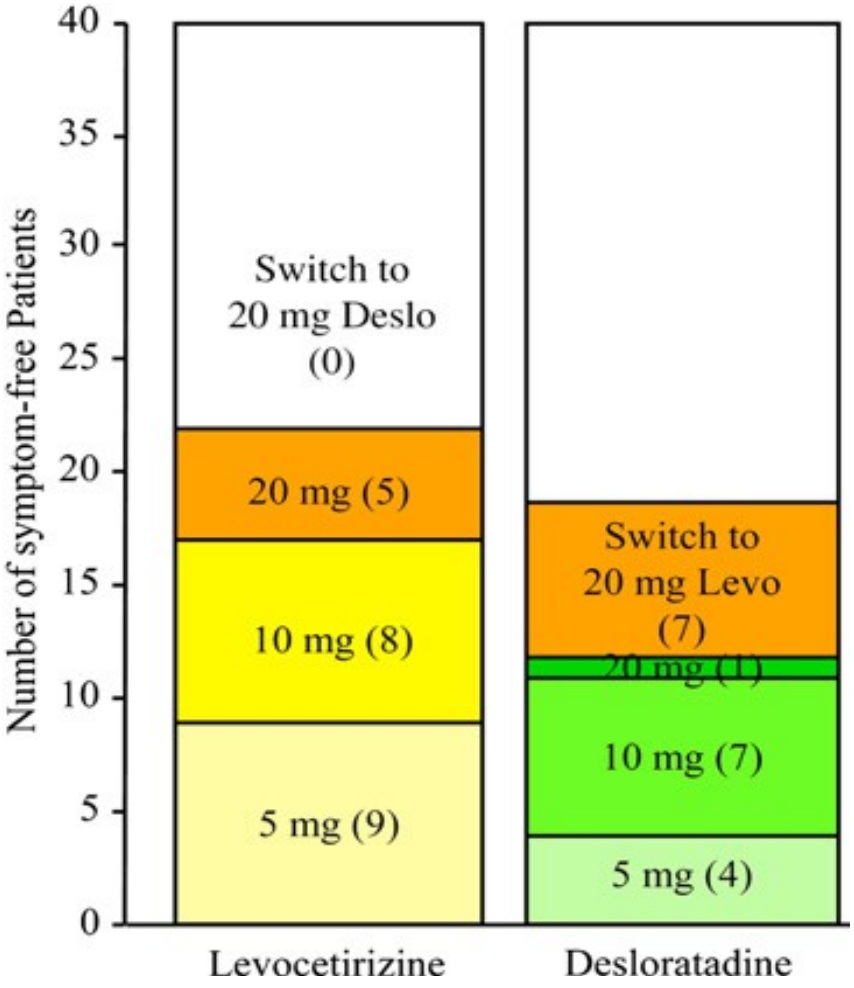
- 80 patients with refractory urticaria, 72% previously treated with steroids
- Randomized to antihistamine, with dose advancement to 4x standard dose



Staevska M, et al. J Allergy Clin Immunol 2010; 125: 676-82

Dose Advancement of 2nd Generation Antihistamines

- Patients whose symptoms were relieved with levocetirizine or desloratadine

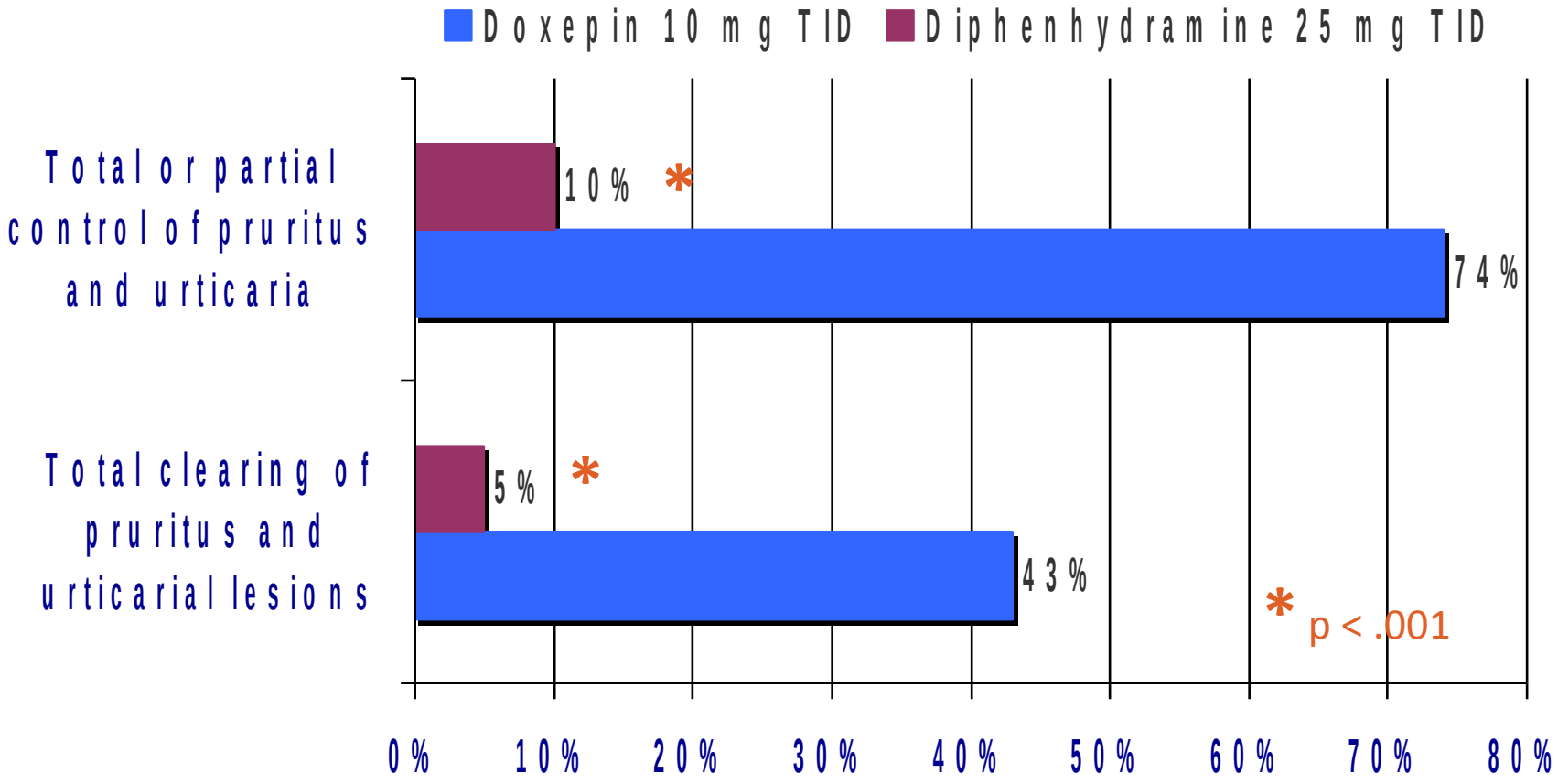


- Approximately 75% were responders to higher than conventional doses.

Staevska M, et al. J Allergy Clin Immunol 2010; 125: 676-82

Efficacy: Doxepin vs Diphenhydramine

DB, X-over study, 50 patients with chronic idiopathic urticaria



Green SL, et al. J Am Acad Dermatol 1985 12: 669-75

Immune Response Modifiers

The patient returns three weeks later and states that after increasing cetirizine to 4 x daily, she is only slightly better. The hives are very problematic for her and embarrassing. The most appropriate next therapeutic step would be to add:

A. Mycophenolate
B. Cyclophosphamide
C. Cyclosporine
D. Omalizumab

Management Of Chronic Urticaria

Step 1

- Avoidance of triggers
- Monotherapy with second generation antihistamine

Step 2

- Dose advancement of 2nd generation antihistamine used in Step 1
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- Add 1st generation antihistamine (at bedtime)

Step 3

- Dose advancement of potent antihistamine (e.g. hydroxyzine or doxepin) as tolerated

Step 4

- Anti-inflammatory agent
- Immunosuppressant
- Biologics

Urticaria Practice Parameter Update

Refractory Urticaria/Angioedema

- Colchicine
- Sulfasalazine
- Mycophenolate
- Methotrexate
- Dapsone
- Sirolimus
- Anti-TNF
- Stanozolol
- IVIG
- Hydroxychloroquine
- Omalizumab
- Tacrolimus
- Cyclosporine
- Others…

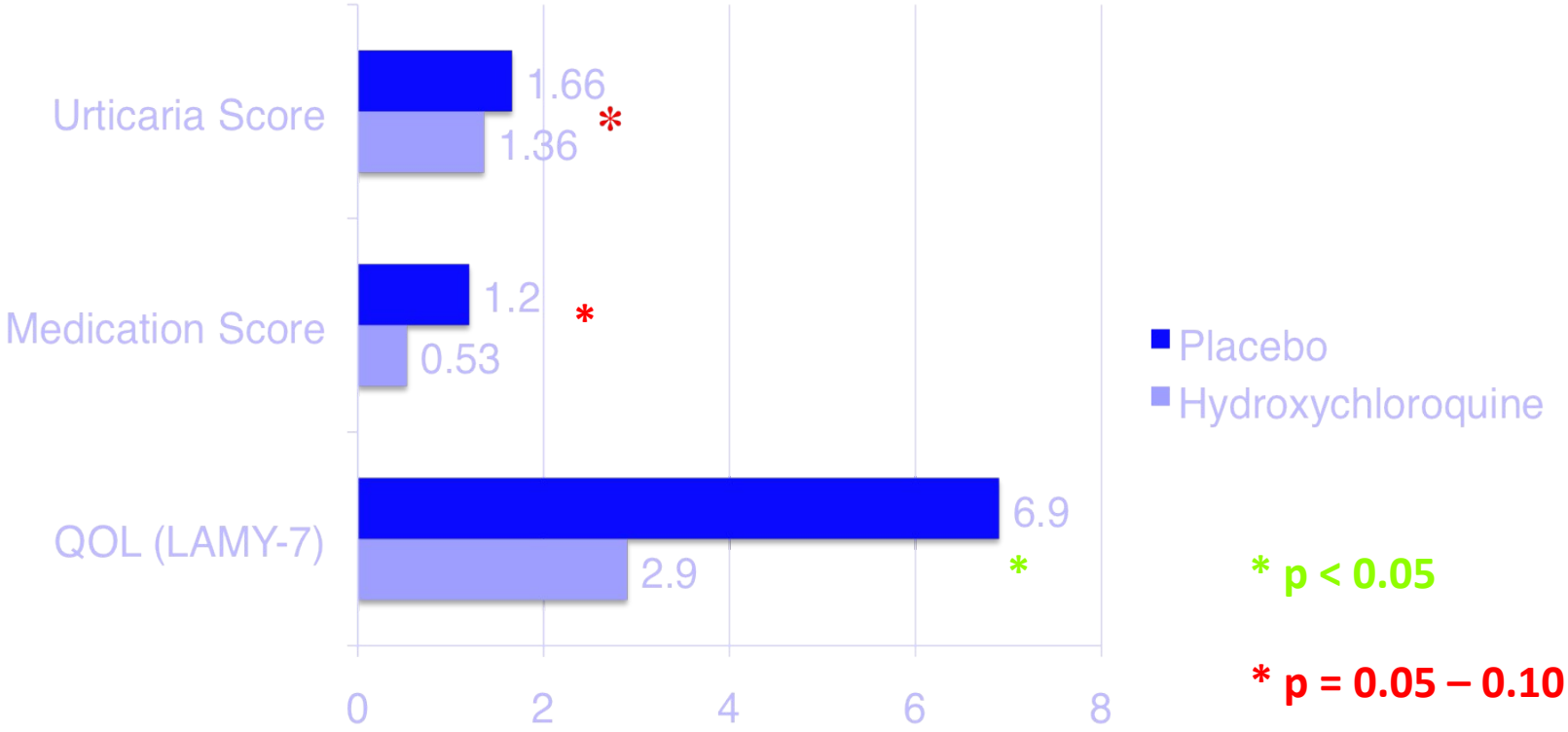
Evaluating Therapeutic Utility of Alternative Agents for Refractory CU/Angioedema

- Case Series and Case Reports are subject to bias, and do not provide high quality evidence.

- Only three agents have been studies in randomized controlled trials:
  - Hydroxychloroquine
  - Cyclosporine
  - Omalizumab

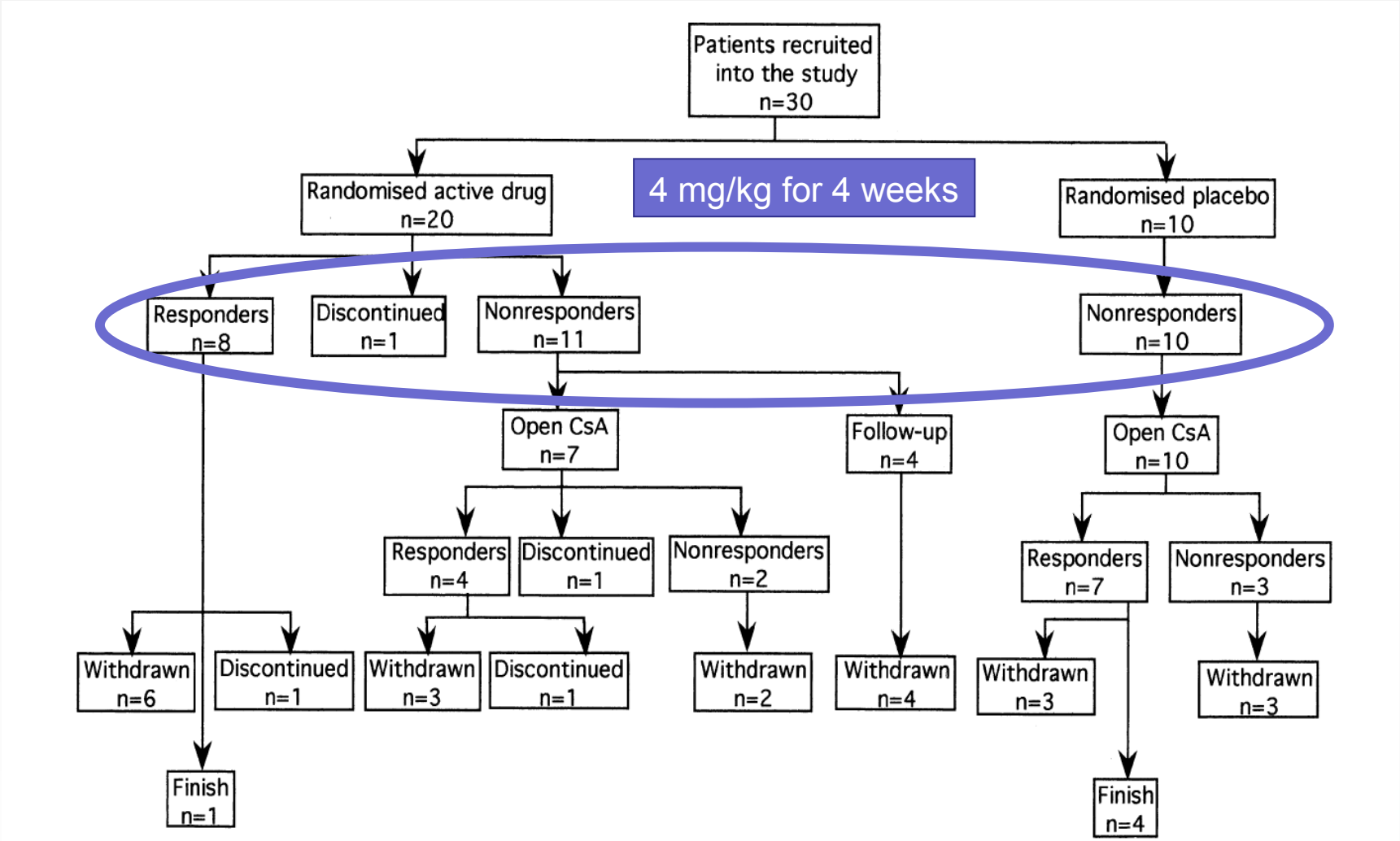
RCT: Hydroxychloroquine

- 21 patients with chronic urticaria/angioedema, randomized to Hydroxychloroquine or placebo for 12 weeks, in addition to other medications for urticaria (H1 & H2 antihistamines, doxepin, corticosteroids).
- Med taper q 2 weeks if well controlled; 18 completed trial, ITT analysis.



Reeves GEM, et al. Intern Med J 2004; 34: 182-6.

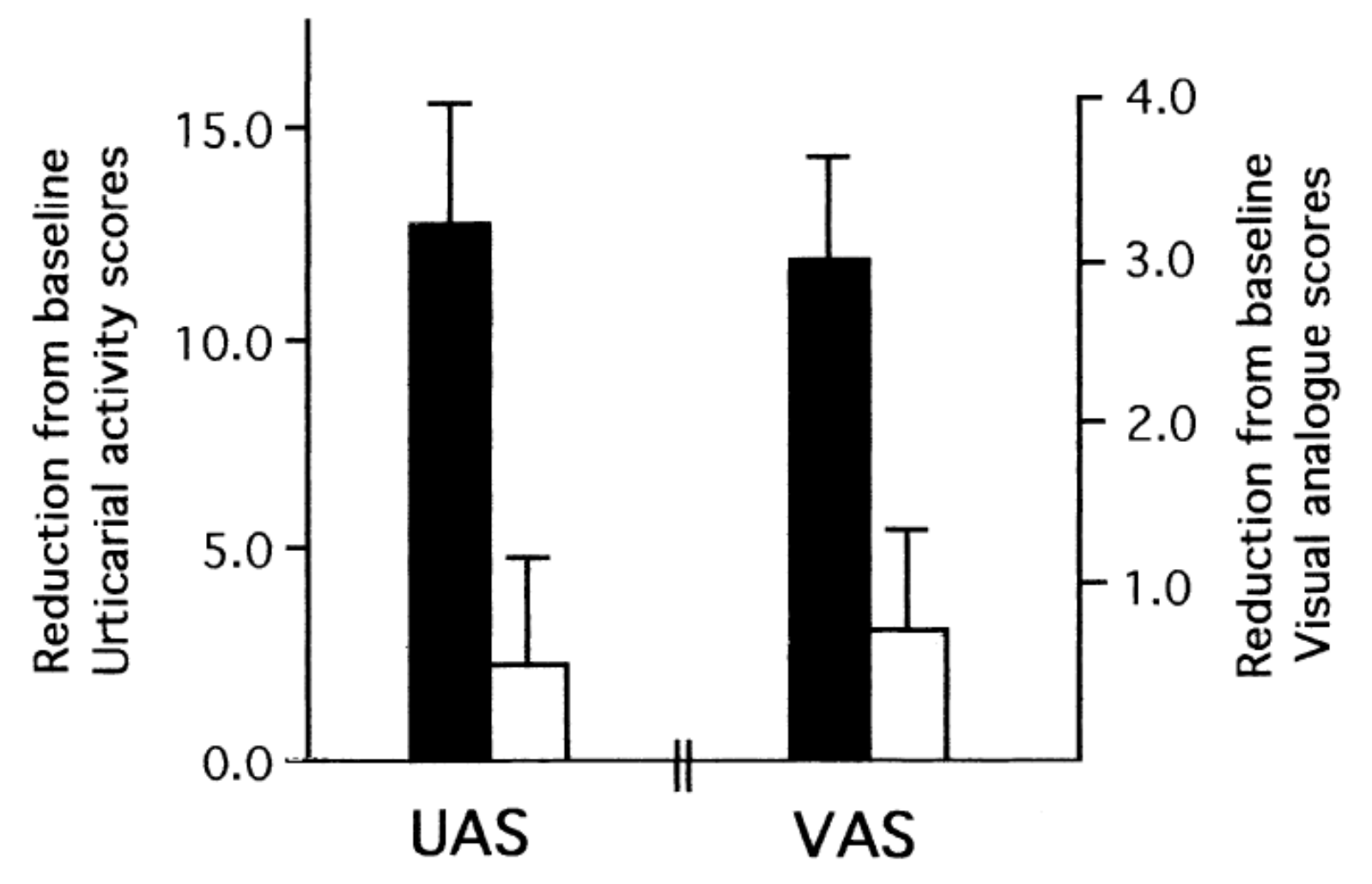
Study Flow Chart For Cyclosporine Trial



ure 1. Randomization and progress summary flow chart showing withdrawals and discontinuations.

Grattan et al, BJD, 2000

Cyclosporine Response at 4 Weeks



Grattan et al, BJD, 2000

Cyclosporine

- It is unclear whether the potential for desirable effects significantly outweighs the risk for undesirable effects, particularly with the lack of an appropriate comparator group (e.g., cetirizine 10-20 mg/day) enrolled in these studies.

- In the context of study limitations, potential harms and costs, the quality of evidence supporting cyclosporine administration is LOW -- leading to a WEAK RECOMMENDATION, based on current evidence.

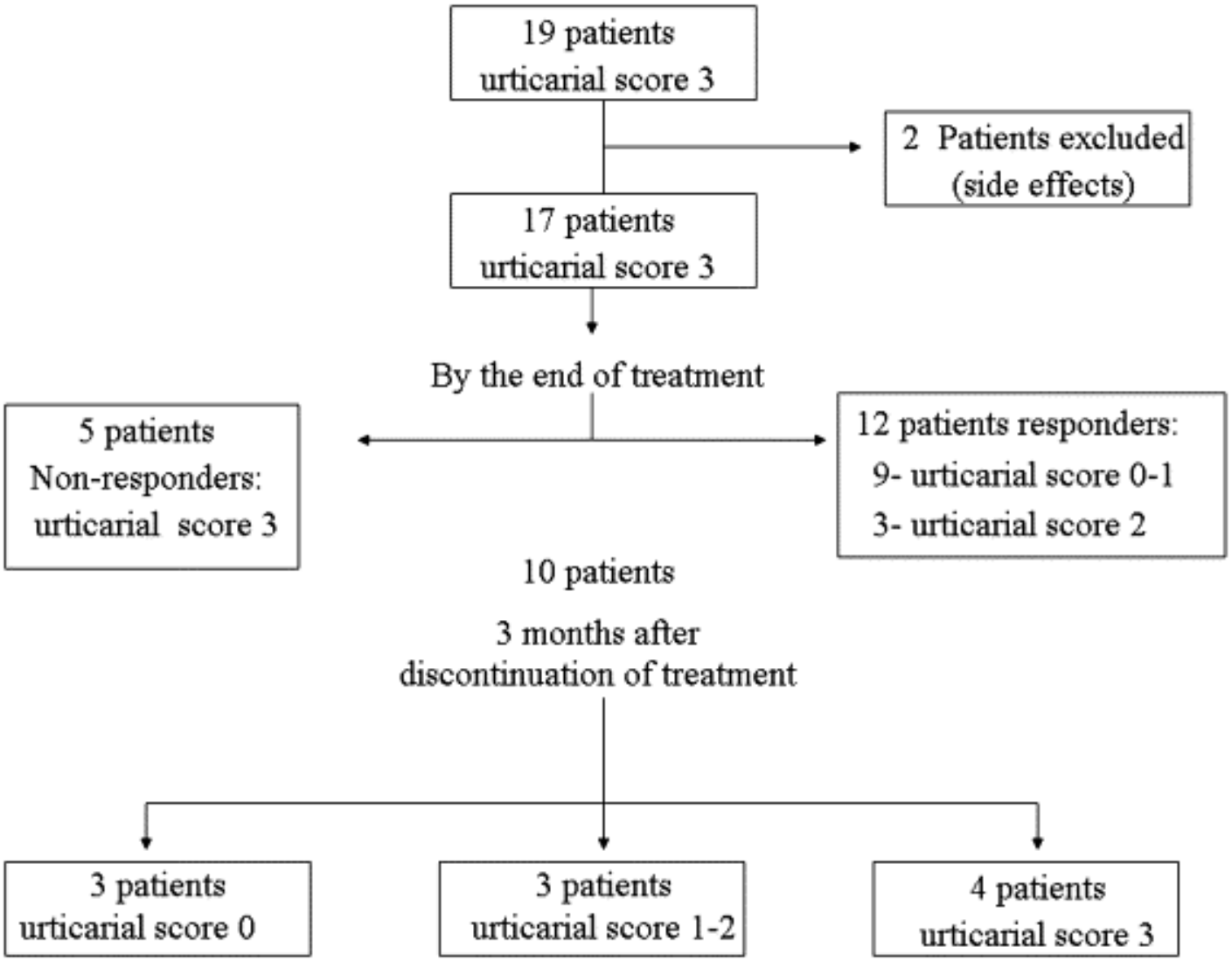
- This recommendation implies that future research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

•*Bernstein J, et al.* **The Diagnosis and Management of Acute and Chronic Urticaria: 2013 Update. Submitted**

Tacrolimus-Open Label 12 Week Trial

- J Am Acad Dermatol 2005;52:145-8
- “Clinical response in 12/17 patients over 3 months”
- Summary urticaria score (0 = no symptoms to 3 = severe urticaria)
- Tacrolimus (0.05-0.07mg/kg orally twice daily for 4 weeks then 0.025-0.035mg/kg daily for 6 weeks. Then tacrolimus was reduced to 1mg daily for 2 weeks.

TACROLIMUS IN ADULTS WITH UNREMITTING CIU



First of 3 DBRCT with Omalizumab

The NEW ENGLAND JOURNAL of MEDICINE

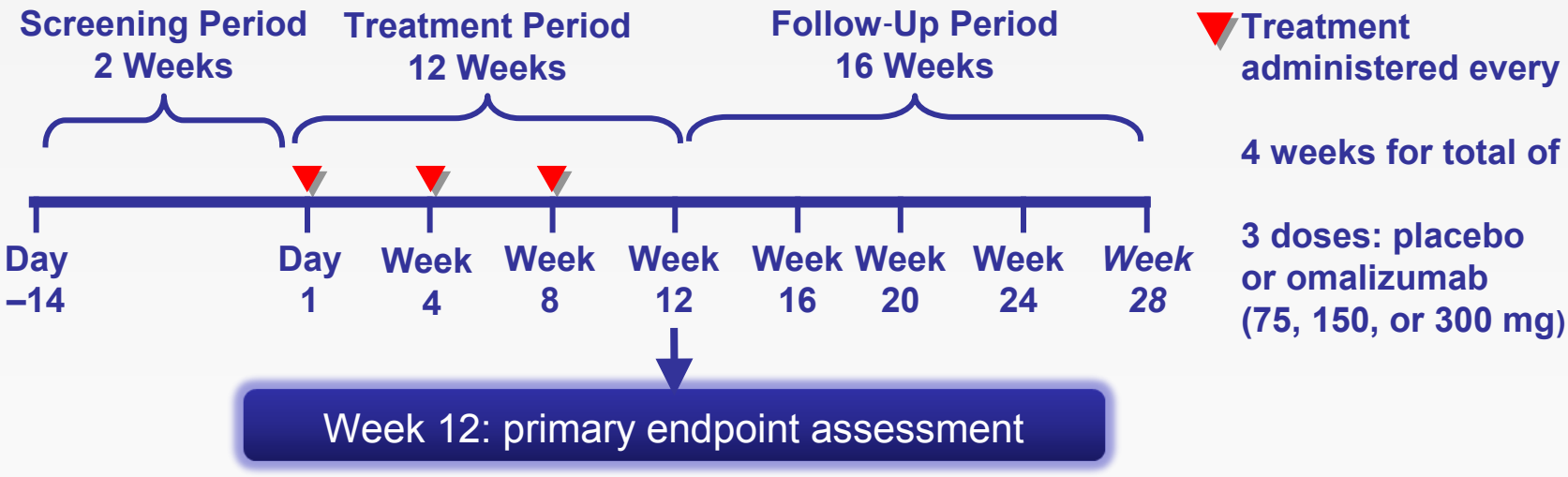
ORIGINAL ARTICLE

Omalizumab for the Treatment of Chronic Idiopathic or Spontaneous Urticaria

Marcus Maurer, M.D., Karin Rosén, M.D., Ph.D., Hsin-Ju Hsieh, Ph.D., Sarbjit Saini, M.D., Clive Grattan, M.D., Ana Gimenéz-Arnau, M.D., Ph.D., Sunil Agarwal, M.D., Ramona Doyle, M.D., Janice Canvin, M.D., Allen Kaplan, M.D., and Thomas Casale, M.D.

March 2013

Study Design – Asteria II



Patients continued stable doses of a licensed dose H1-antihistamine throughout treatment period and were permitted rescue DPH 25 mg up to 3 doses/day

DPH=diphenhydramine

Primary Endpoint: Change From Baseline in Weekly Itch-Severity Score At Week 12 (mITT)

- Significant improvements in weekly ISS with omalizumab 150 mg and 300 mg doses vs. placebo

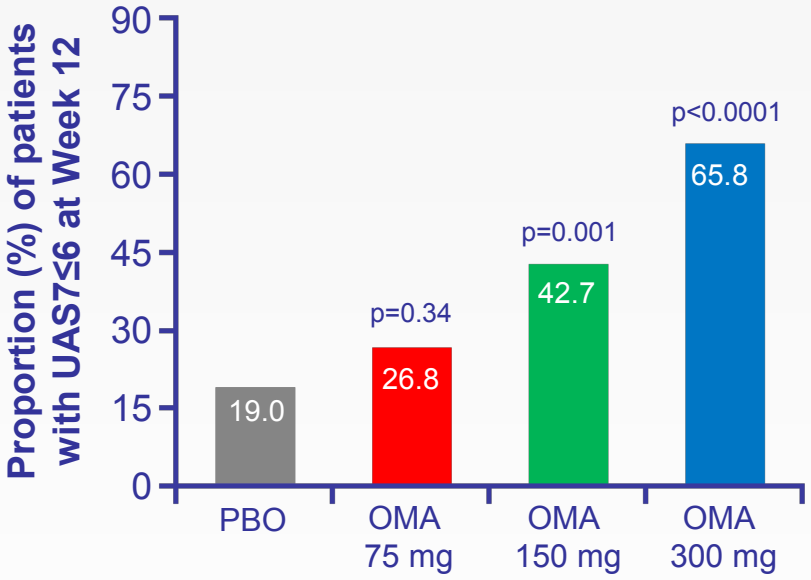
Change from baseline in weekly ISS at Week 12	Placebo (N=79)	Omalizumab 75 mg (N=82)	Omalizumab 150 mg (N=82)	Omalizumab 300 mg (N=79)
Mean (SD)	–5.1 (5.6)	–5.9 (6.5)	–8.1 (6.4)	–9.8 (6.0)
LSM treatment difference vs. placebo (95% CI)		–0.7 (–2.5, 1.2)	**–3.0 (–4.9, –1.2)**	**–4.8 (–6.5, –3.1)**
p value		0.4637	**0.0011**	**<0.0001**

CI=confidence interval; ISS=Itch-Severity Score; LSM=least squares mean; mITT=modified intention-to-treat population; SD=standard deviation

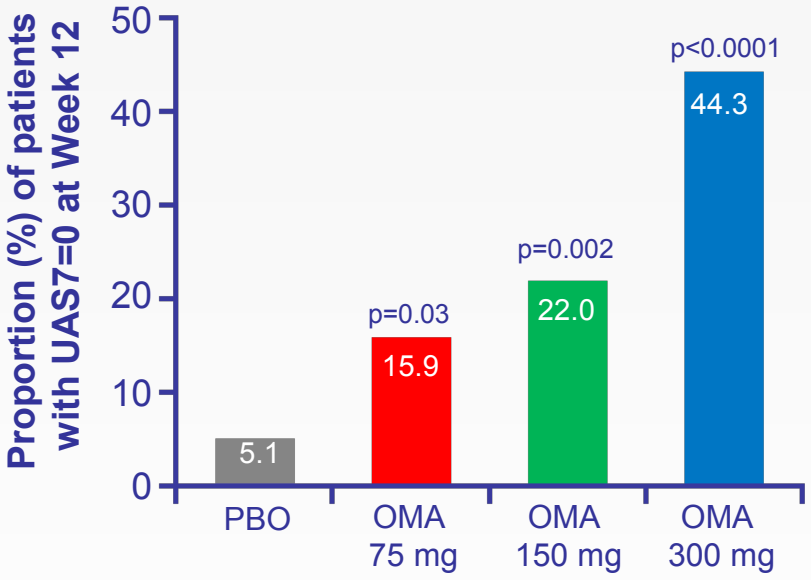
Responder Analysis (mITT)

- **Significantly higher proportion of patients in omalizumab 150 mg and 300 mg groups had symptoms which were well controlled (UAS7≤6) vs. placebo**
- **A large proportion of patients treated with omalizumab 300 mg were completely symptom free (UAS7=0) by Week 12**

UAS7≤6 (secondary endpoint)



UAS7=0 (post-hoc analysis)



mITT=modified intention-to-treat population; OMA=omalizumab; PBO=placebo; UAS7=weekly urticaria activity score

Summary of Efficacy and Safety of Omalizumab in Asteria II Study for CIU/CSU

- Omalizumab improved primary and secondary endpoints in a ***consistent dose-dependent*** fashion:
  - 300 mg improved all endpoints
  - 150 mg improved all endpoints except angioedema
  - 75 mg did not meet the primary endpoint
- Rapid onset of treatment effect
  - Within 1 week for 300 mg dose
- Symptom scores increased towards placebo after Week 12
- No new safety issues or concerns were identified compared to the known safety profile of omalizumab in the allergic asthma patient population

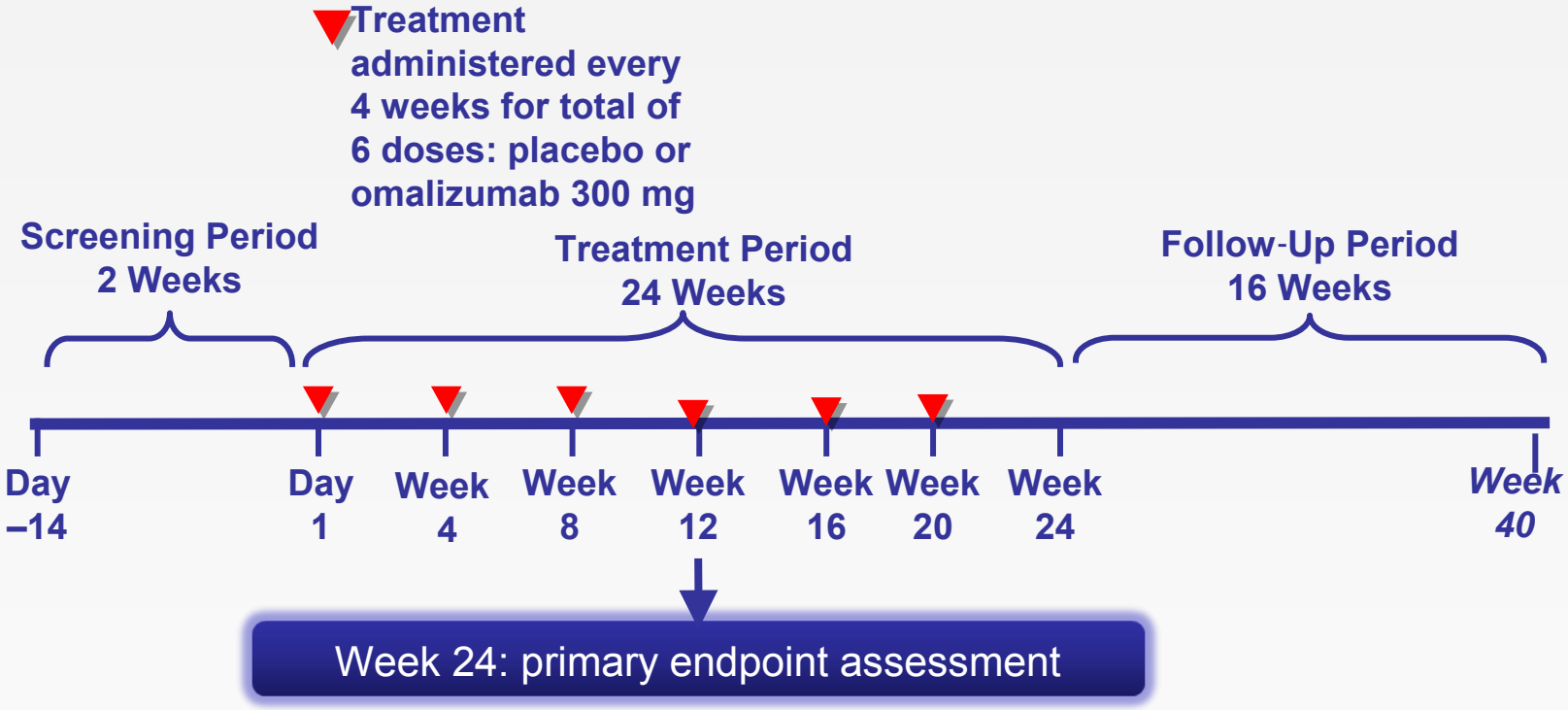
Omalizumab in Guideline-Driven Care

Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy

Allen Kaplan, MD,[a] Dennis Ledford, MD,[b] Mark Ashby, PhD,[c] Janice Canvin, MD, FRCPC,[d] James L. Zazzali, PhD,[c] Edward Conner, MD,[c] Joachim Veith, MD,[c] Nikhil Kamath, MD,[e] Petra Staubach, MD,[f] Thilo Jakob, MD,[g] Robert G. Stirling, MB, FRACP,[h] Piotr Kuna, MD, PhD,[i] William Berger, MD,[j] Marcus Maurer, MD,[k] and Karin Rosén, MD, PhD[c] *Charleston, SC, Tampa, Fla, South San Francisco and Mission Viejo, Calif, Horsham and Welwyn Garden City, United Kingdom, Mainz, Freiburg, and Berlin, Germany, Melbourne, Australia, and Lodz, Poland*

JACI, July 2013

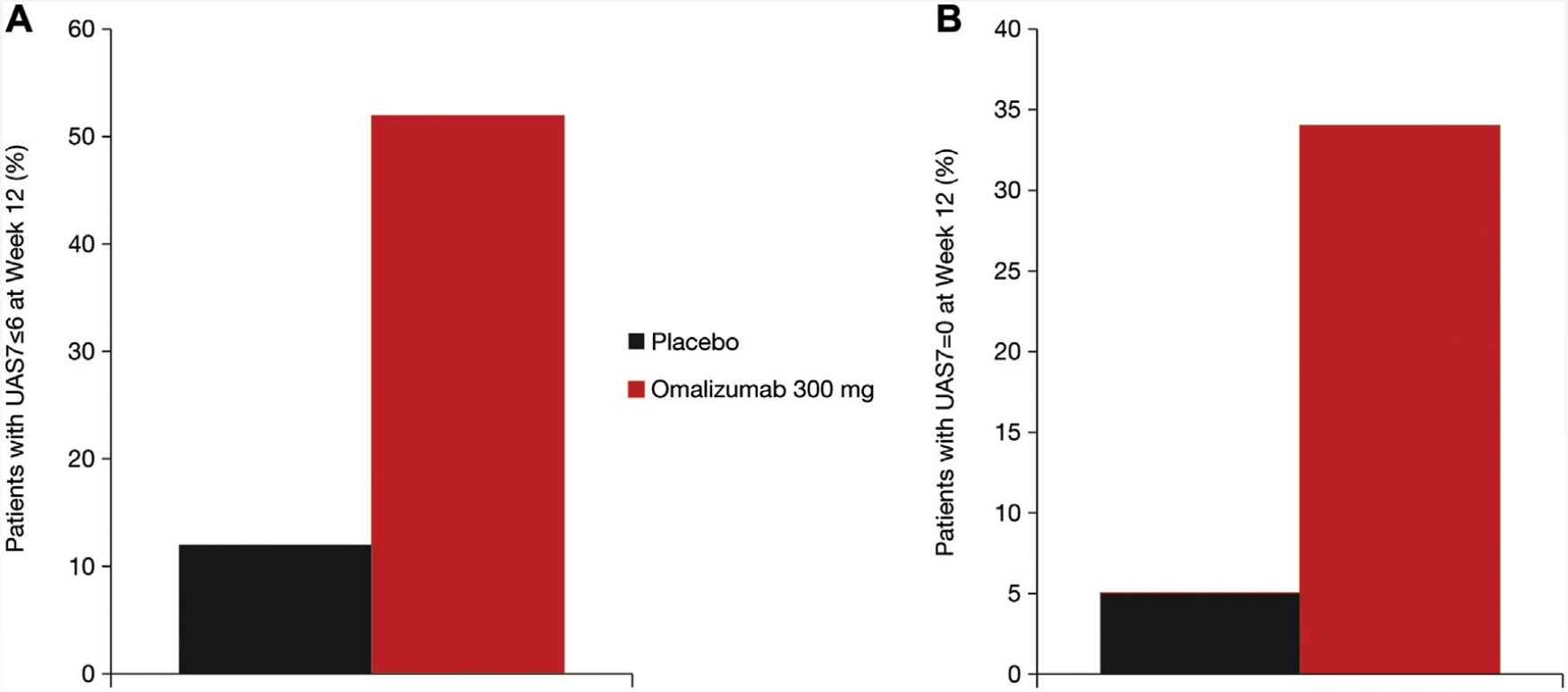
Study Design



Patients continued stable doses of H1-antihistamines, H2 antihistamines and/or LTRA throughout treatment period and were permitted rescue DPH 25 mg up to 3 doses/day

DPH=diphenhydramine

Omalizumab Responder Analysis



SUMMARY STATEMENT 88:

… Relative to other biologic agents, the therapeutic utility of omalizumab has been supported by findings from double-blind randomized controlled trials and is the preferred biologic agent for refractory CU

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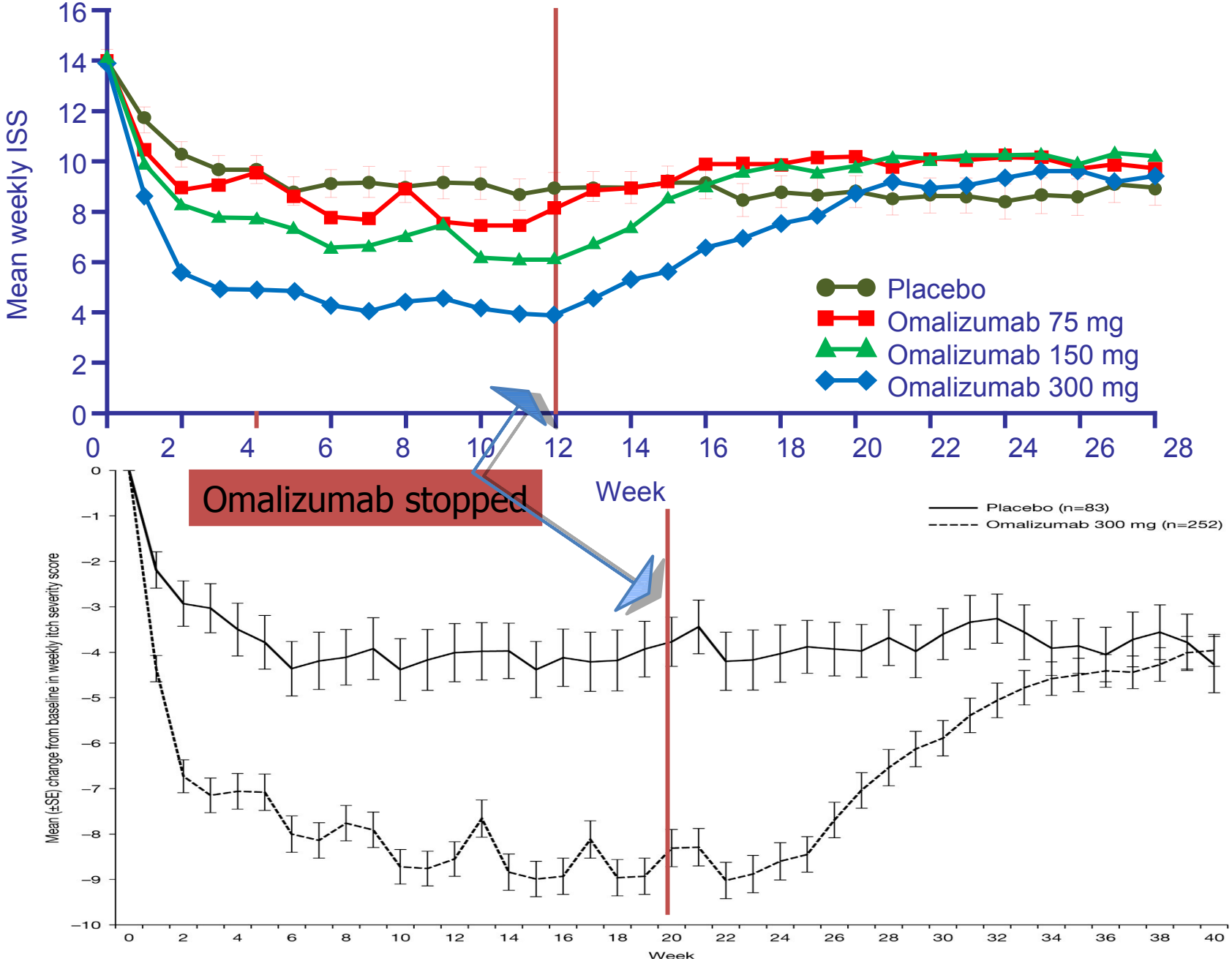
Patient Follow-up

The patient returns 12 weeks after starting omalizumab and states she feels much better. Her hives have completely gone away and she has no angioedema. Her energy level and spirits are much improved. The most appropriate next therapeutic step would be to:

A. Stop cetirizine
B. Stop omalizumab
C. Stop both cetirizine and omalizumab
D. Continue the same regimen

Omalizumab Duration of Action



CU Summary and Conclusions

- Antihistamines, the mainstay of therapy, are ineffective in as many as 50% of CU patients.
- Systemic corticosteroids, although effective in many patients, have predictable systemic toxicities especially with chronic use.
- A number of therapeutic alternatives have been evaluated to treat antihistamine-refractory CU in order to reduce the need for systemic corticosteroids.
- Limited evidence for many alternative therapies in antihistamine refractory CIU patients and some require monitoring for adverse effects
  - Omalizumab data support placement in therapy of anti-histamine-resistant CU

Algorithm For Antihistamine Refractory CIU
Non-Evidence Based

Step 1
- Continue high dose 2nd generation H1-blockers
- Eliminate triggers

Step 2
- Consider biopsy
- If neutrophilic, trial of dapsone or colchicine

Step 3
- Omalizumab 150 mg/month
  - If partial (or no) response increase to 300 mg/month
  - If no response, consider cyclosporine

Step 4
- Use whatever works with the best safety profile and least cost

Conclusion

Don’t be afraid to make rash decisions!!!