Patient-Specific Characteristics in the Treatment of Chronic Urticaria: Does it Matter?



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### Disclaimer

I have received honoraria from, have carried out clinical research with, and/or have served as a consultant for: AstraZeneca, Genentech/Novartis, GlaxoSmithKline, Meda, Merck.

My presentation will include discussion of off-label uses of a number of FDA approved products, but not agents that are not FDA-approved.

## Learning Objectives

After participation, the learner will be able to:

Relate and critically appraise several factors that may influence the management of patients with chronic urticaria.

### Case - JM

- 56 year-old attorney with a 4 month history of daily episodes of pruritus and "hives".
- erythematous wheals
  - range from pencil-eraser to quarter in size
  - duration < 24 hours, no residual bruising</li>
- She experienced several episodes of facial swelling, but denied episodes of throat constriction.
- She was "hive-free" while taking two oral steroid courses, but then relapsed.
- No history c/w physical urticaria/angioedema.
- Medications: OTC antihistamine prn.

### Quality of life in patients with urticaria

David R. Weldon, M.D.

#### ABSTRACT

Patients with chronic urticaria have a poor quality of life (QOL). Chronic pruritus with variable appearance of urticaria and/or angioedema are typical of the uncertainty that compromise their QOL. Other issues such as fatigue, cost of therapy, and social isolation further contribute to the frustration that patients experience. Various instruments are available to measure the quality of life of patients with urticaria and can be adjunctive in the continued assessment of patients with this variable condition. In comparison with other dermatological and medical conditions, patients with chronic urticaria have a significantly worse QOL. (Allergy Asthma Proc 27:96–99, 2006)

## What If Your Patient, JM ...

has a low vitamin D level?
has urticaria and angioedema?
has a physical urticaria/angioedema syndrome?

is older than 65 years of age?

**Does it Matter?** 

## Vitamin D and Urticaria/Angioedema

Sources: sunlight, dietary (fish, mushrooms, dairy products), supplementation.

Regulates growth and differentiation of multiple cell types and displays immunoregulatory and anti-inflammatory properties.

### Vitamin D is an Immunomodulator

Cell	Action	Mechanism	References	
Macrophages/monocyte	Promotes differentiation Inhibit dendritic cell differentiation Reduced inflammatory Cytokines Reduces co-stimulatory molecules	<ul> <li>↑ 1α hydroxylase</li> <li>↑ 1α hydroxylase</li> <li>↓ IL-6,8,12, TNF*</li> <li>↓ CD40, CD80, CD86 and HLA-DR*</li> </ul>	[13,14,18-20]	
T cells	Homing to inflamed tissue Homing to skin Increased T regulatory cells Reduced inflammatory cytokines	↑CCR5, CXCR3, CXCR6* ↑CCR10 ↑IL-10, TLR-9* ↓ IL-17, IL-2, IFN-gamma	[13,14,16,18,20]	
endritic cells Increased T cell regulation Reduced immune response Reduced co-stimulatory molecules Reduced cytokine release		↑ IL-10, TGFß ↓ IL-17 ↓ CD1a, CD14, CD40, CD86 ↓ IL-12, IL-23	[12,13,14,18,20]	
Mast cells	Stabilise mast cell Reduces IgE dependant pro-inflammatory mediators	↓ histamine release ↑ IL-10	[18,21,23]	

Varney and Warner, J Allergy Ther 2014, 5:6

#### Serum 25-hydroxyvitamin D levels lower in patients with chronic urticaria



Grzanka et al. J Inflamm 2014; 11: 2

# VIDA (Vitamin D add on therapy enhances corticosteroid responsiveness in asthma)

- Adult asthma patients: 25-OH Vitamin D < 30ng/ml.</p>
- RDBPGPC study: Oral Vitamin D3 x 1, then 4000 IU/day for 28 weeks or Placebo, added to Ciclesonide 320 µg/day → tapered when asthma controlled.
  - Primary outcome: time to 1<sup>st</sup> asthma treatment failure.
    - Decline in lung function
    - Increases in use of beta agonist, oral steroid, and health care utilization



Castro M, et al. JAMA 2014; 311: 2083-91

### Vitamin D and Urticaria/Angioedema

- RDB study: 42 subjects with chronic urticaria randomized to high (4000 IU/day) or low (600IU/ day) vitamin D3 supplementation for 12 weeks.
- All subjects treated with cetirizine, ranitidine, and montelukast.
- Main outcomes = Medication use and USS score at week 12.
- Triple therapy associated with 33% reduction in total USS in 1<sup>st</sup> week in both groups (p = 0.001), and then a further reduction in USS in the high but not the low dose group (p=0.052).

Rorie, et al. Ann Allergy Asthma Immunol 2014; 112(4):376-82



Rorie, et al. Ann Allergy Asthma Immunol 2014; 112(4):376-82



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### Vitamin D and Multiple Health Outcomes

#### **Health Outcomes**

- Osteoporosis
- Cardiovascular disease
- Metabolic disorders
- Infectious diseases
- Autoimmune disorders
- Diabetes
- Hypertension
- Stroke
- Alzheimer's disease
- Mortality

#### **Cancer Outcomes**

- Breast cancer
- Colon cancer
- Non-Hodgkin's lymphoma
- Ovarian cancer
- Pancreatic cancer
- Prostate cancer
- Rectal cancer
- Renal cancer

### Vitamin D and Multiple Health Outcomes

- Umbrella review of evidence across systematic reviews (107) and meta-analyses (74) of observational studies of Vitamin D and metaanalyses (87) of RCTs of Vitamin D supplementation.
- Explored relation between vitamin D and 137 outcomes.

Conclusion: "Despite a few hundred systematic reviews and meta-analyses, highly convincing evidence of a clear role of vitamin D does not exist for any outcome, but associations with a selection of outcomes are probable."

Outcome	Participants	Studies	Relative risk	Relative risk
Vitamin D			(95 % Ci)	()) /0 ()
Cardiovascular disease <sup>130</sup>	-	2		0.95 (0.86 to 1.05)
Low birth weight <sup>61</sup>	507	3		0.40 (0.23 to 0.71)
Small for gestational age <sup>61</sup>	305	2		0.67 (0.40 to 1.11)
Preterm delivery <sup>61</sup>	529	2		0.77 (0.35 to 1.66)
Bone pain in CKD patients <sup>121</sup>	109	4	***	0.29 (0.03 to 2.63)
Fractures in CKD RD <sup>121</sup>	181	4		1.00 (0.06 to 15.41)
Mortality (CKD NRD) <sup>120</sup>	477	4		1.40 (0.38 to 5.15)
Mortality (CKD RD) <sup>121</sup>	233	5		1.34 (0.34 to 5.24
Parathyroidectomy (CKD RD) <sup>121</sup>	133	2	+ · · · · · · · · · · · · · · · · · · ·	0.82 (0.05 to 12.47)
Risk of hypercalcaemia (CKD NRD) <sup>120</sup>	612	7		3.04 (1.17 to 7.90)
Risk of hypercalcaemia (CKD RD) <sup>121</sup>	182	5		3.80 (0.90 to 16.12)
Risk of hyperphosphataemia (CKD NRD) <sup>1</sup>	20 245	2		1.58 (0.47 to 5.30)
Risk of hyperphosphataemia (CKD RD) <sup>121</sup>	59	2		1.57 (0.97 to 2.54)
Risk of requiring dialysis (CKD NRD) <sup>120</sup>	301	4		0.76 (0.36 to 1.62)
Subperiosteal erosions (CKD RD) <sup>121</sup>	120	3		0.41 (0.07 to 2.38)
Vascular calcification (CKD RD) <sup>121</sup>	103	2		1.09 (0.45 to 2.67)
Vitamin $D_2$ or $D_3$ or UV therapy				
Dental caries <sup>128</sup>	1513	38		0.53 (0.43 to 0.65)
Vitamin $D_2$ or $D_3$ or active D (or + calcium)				*
Non-vertebral fractures <sup>5</sup>	7130	5		0.79 (0.63 to 0.99)
Vitamin D <sub>3</sub>				
Mortality <sup>110</sup>	12 824	9		0.91 (0.82 to 1.02)
Vitamin D <sub>2</sub> , D <sub>3</sub> or D				
Fractures <sup>107</sup>	25 0 1 6	10	+	1.01 (0.93 to 1.09)
Hip fractures <sup>107</sup>	24749	9		1.15 (0.99 to 1.33)
Vertebral fractures <sup>107</sup>	9138	5		0.90 (0.42 to 1.92)
Vitamin D <sub>2</sub>				
Mortality <sup>110</sup>	17 079	8	-	1.04 (0.97 to 1.11)
		0	0.2 0.4 0.5 0.6 1 1.5 2 2.5	

*Theodoratou E, et al, BMJ 2014; 348:g2035 doi:* 

### What If Your Patient ...

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is older than 65 years of age?

### **Does it Matter?**

## Chronic Urticaria/Angioedema



Etiology "unknown" in 79%

Champion, et al. Br J Derm 1969; 81: 588-97.

## **Duration of Illness**



FIG. 4.—The expected percentage of patients active, with 95% confidence limits, by the total duration of disease (log scale).

Champion, et al. Br J Derm 1969; 81: 588-97.

### **Response Rates**

#### 86 patients with chronic urticaria and/or angioedema



Quaranta, et al. Ann Allergy 1989; 62: 421-424.

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## Physical Urticaria/Angioedema

Up to 0.5% of the general population has been estimated to have a physical urticaria/angioedema condition

In an estimated 20% of patients with chronic urticaria/angioedema, a physical urticaria component is present

> Kontou-Fili, K., et al. Allergy, 1997. **52**(5): 504-13. Orfan, N.A. and G.B. Kolski. Ann Allergy, 1993. **71**: 205-12

### Physical Urticaria/Angioedema



### Challenge Procedures Let's Get Physical...

Syndrome	Challenge Procedure	Positive Result
Cholinergic	<ul> <li>Methacholine intradermal challenge</li> <li>Partial immersion using hot water (42 C).</li> </ul>	<ul> <li>Appearance of "satellite wheal"</li> <li>Urticaria (1-3 mm wheals) at challenge site</li> </ul>
Cold	Cold provocation testing (ice cube) on skin of forearm for 5 minutes	Development of urticaria at challenge site during rewarming of skin
Dermatographia	Stroking of skin with tongue blade	Erythema at site of stroking within 1-3 minutes
Delayed Pressure	Weights (15 lbs) suspended over shoulder for 10 or 15 minutes	Area of angioedema develops 2-12 hours later (peak = 4-6.5 hours) at site of pressure challenge.
Vibratory	Vortex mixer applied to forearm for 4 minutes	Development of angioedema sharply demarcated from normal skin

Lang DM, Hsieh F, Bernstein JA, Ann Allergy Asthma Immunol 2013; 111: 235-41.



Accessed at urticare.com, March 28, 2015







### Natural Course of Physical and Chronic Urticaria

- 220 patients enrolled
  - 132 women, 88 men
  - Mean age = 38 (range: 15-79) years
  - Follow-up: ≥ 1 year
- Physical Urticaria (73/220 = 33.2%)



Kozel MMA, et al.. J Am Acad Derm 2001; 45: 387-91.

### Natural Course of Physical and Chronic Urticaria

Free of Symptoms at 1 Year



Kozel MMA, et al.. J Am Acad Derm 2001; 45: 387-91.

### Step Care Management of Chronic Urticaria/Angieodema

#### **STEP 4**

Add an alternative agent

•Omalizumab or cyclosporine

•Anti-inflammatory agent (e.g. dapsone,

hydroxychloroquine, sulfasalazine)

•Other immunosuppressant or biologic agent

(e.g.mycophenolate)

#### **STEP 3**

Dose advancement of hydroxyzine or doxepin

#### **STEP 2**

One or more of the following:

- •Dose advancement of 2<sup>nd</sup> generation antihistamine used in Step 1
- •Add another second generation antihistamine
- •Add H<sub>2</sub>- antagonist
- •Add leukotriene receptor antagonist
- •Add 1st generation antihistamine to be taken at bedtime

#### **STEP 1**

Monotherapy with second generation antihistamine
Avoidance of triggers (e.g., NSAIDs) and relevant physical factors if physical urticaria/angioedema syndrome is present.

#### Proportion of Subjects in 3 Randomized Controlled Trials Evaluating the Efficacy of Omalizumab Who Became Hive and Itch Free

<u>Author and</u> <u>Year</u>	<u>Study</u> Duration	Randomized To <u>Omalizumab</u> <u>300 mg</u>	Randomi zed To <u>Placebo</u>	<u>300 mg</u>	<u>Placebo</u>
Maurer 2013	12 weeks	79	79	35 (44.3%)	4 (5.1%)
Kaplan 2013	24 weeks#	252	83	85 (33.7%)	4 (4.8%)
Saini 2015	24 weeks#	81	80	29 (35.8%)	7 (8.8%)
Totals		412	242	<b>NN</b> 149 (36.2%)	<b>T = 3.3</b> 15 (6.2%)

# Efficacy assessed at 12 weeks, trial duration 24 weeks. UAS 7 = Urticaria Activity Score over 7 days.

Drugs Today (Barc). 2015 Jun;51(6):367 -74

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## 1<sup>st</sup> Generation Antihistamines

With first generation antihistamines, prominent anticholinergic effects, including dryness of mouth and eyes, constipation, inhibition of micturition, and potential provocation of narrow angle glaucoma, may occur. Because of co-occurring conditions (e.g., increased intraocular pressure, benign prostatic hypertrophy, and pre-existing cognitive impairment) that may increase the potential risk associated with regular or even intermittent use, first generation antihistamines should be prescribed with caution in older adults

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## Efficacy: Doxepin vs Diphenhydramine

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



**\*** p < .001

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

## **Anti-Cholinergic Drugs**

- Frequently taken by older adults for GI spasm, overactive bladder, Parkinson's, etc.
- Other medications have unintended anticholinergic effects.
- Risk for acute cognitive impairment older age
  - Age related changes in pharmacokinetics
  - Reduced acetylcholine-mediated CNS transmission
  - Increased blood-brain barrier permeability
- ? Risk for irreversible impairment

Fox C, et al. J Am Geriatr Soc 2011; 59: 1477-83

## **Cognitive Impairment Ahead?**

- Prospective population based cohort study, integrated health care delivery system in Seattle, Washington.
- 3434 subjects, 65 and older enrolled with no dementia at study entry,
- Initial recruitment: 1994-1996 & 2000-2003.
- Followed up q 2 years; most recent: 2012.
- Computerized pharmacy data used to determine cumulative anticholinergic exposure, TSDD dispensed over 10 years.
- Determined rates of incident dementia and Alzheimer's.
- Most common anticholinergic classes:

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- Most common anticholinergic classes:
  - Triclyclic anti-depressants
  - 1<sup>st</sup> generation antihistamines

Gray SL, et al. JAMA Intern Med 2015; 175: 401-407.

Diagnosis, TSDD <sup>b</sup>	Follow-up Time, Person-years	No. of	HR (95% CI)		
		Events	Unadjusted <sup>c,d</sup>	Adjusted <sup>d,e</sup>	
Dementia					
0	5618	136	1 [Reference]	1 [Reference]	
1-90	7704	203	0.96 (0.77-1.20)	0.92 (0.74-1.16)	
91-365	5051	172	1.31 (1.04-1.65)	1.19 (0.94-1.51)	
366-1095	2626	102	1.39 (1.07-1.82)	1.23 (0.94-1.62)	
>1095	4022	184	1.77 (1.40-2.23)	1.54 (1.21-1.96)	
AD					
0	5618	112	1 [Reference]	1 [Reference]	
1-90	7704	168	0.96 (0.75-1.24)	0.95 (0.74-1.23)	
91-365	5051	128	1.21 (0.93-1.58)	1.15 (0.88-1.51)	
366-1095	2626	83	1.38 (1.03-1.85)	1.30 (0.96-1.76)	
>1095	4022	. 146	1.73 (1.34-2.24)	1.63 (1.24-2.14)	

#### Table 3. Association of Incident Dementia and AD With 10-Year Cumulative Anticholinergic Use<sup>a</sup>

#### Gray SL, et al. JAMA Intern Med 2015; 175: 401-407.

"Our findings suggest that a person taking an anticholinergic such as... doxepin 10 mg/day for more than 3 years would have a greater risk of dementia."

Gray SL, et al. JAMA Intern Med 2015; 175: 401-407.

## Validity Scale



### **Critical Appraisal: Internal Validity**

# Limitations Not a randomized trial!

### **Strengths**

- Clinical diagnosis of dementia determined by panel of experts as dependent variable.
- Minimized recall bias by using pharmacy claims data
- Dose gradient in magnitude of effect
- Risk similar comparing participants with remote and recent use.

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### **Does it Matter?**

has a low vitamin D level = ?
has urticaria and angioedema = YES
has a physical urticaria/angioedema syndrome = YES

is older than 65 years of age = YES