Difficult Cases: Immunosuppressive Therapy

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History

• 17 year-old girl
• 4 weeks of urticaria
  – Pruritic, erythematous
  – Usually on the trunk
  – A couple of times a week
  – Lasts for hours
  – No residual marks
  – Responds poorly to Benadryl

History

No association with:
  – Menses
  – Food ingestions
  – Latex exposure
  – Insect stings
  – Tick bites

History

• Family History
  – The mother had hives and swelling as an adolescent that resolved spontaneously
  – A maternal aunt requires “thyroid medication”
• Medications: None
• Physical examination: No hives today

Urticaria: Definitions

• Urticaria:
  “Pruritic, erythematous, blanching, circumscribed macular or raised lesions involving the superficial layers of the skin”¹
• Chronic urticaria
  “Persistent or recurring over 6 weeks in duration”¹

History (continued)

The patient was started on cetirizine 10 mg daily with hydroxyzine for breakthrough.
Two Months Later...

- Hives 3–4 times a week
- Cetirizine 10 mg twice daily
- Primary care provider started prednisone
  - Some initial relief
  - Now up to 60 mg daily with recurrences

History & Exam

- No heat/cold intolerance, night sweats, weight loss, joint swelling, or other rashes
- No history concerning for physical urticaria
- The patient is not sexually active
- Physical examination: No hives, no dermatographism

Laboratory Testing

- Complete blood count with differential: normal, no eosinophilia
- Erythrocyte sedimentation rate: normal
- Serum C4 level: normal
- ANA titer: 1:40
- TSH: normal
- Thyroid antibodies: not detected
- Serum tryptase: 3 ng/mL
- Serum galactose alpha-1,3-galactose IgE: <0.35 kU/L
- Anti-IgE receptor antibody test (National Jewish): 20%

Immune Suppression

Randomized, controlled trials have been published for using which of the following to treat chronic urticaria?

A) Methotrexate
B) Tacrolimus
C) Mycophenolate
D) Cyclosporine
E) Cyclophosphamide

Cyclosporine

Cyclosporine is an FDA category C medication.

The patient was placed on depot medoxypregosterone acetate with no effect on the urticaria.

Cyclosporine RCT #1

- 30 subjects randomized to cyclosporine or placebo (double-blinded) for 4 weeks
- After 4 weeks:
  - Responders continued for another 4 weeks
  - Non-responders offered open-label cyclosporine for 4 weeks
- Dose was 4 mg/kg/day
- Primary measure: Urticaria activity score
  - Response: reduction of UAS to <25% of baseline
  - Relapse: return of UAS to >75% of baseline
- One subject (cyclosporine group) dropped out after 2 weeks: lack of efficacy
Cyclosporine RCT #1

• Weeks 0 – 4 (randomized, double-blinded)
  – 8 of 19 subjects in cyclosporine group responded
  – None of 10 subjects in placebo group responded

• Weeks 4 – 8 (open)
  – 4 of 7 in cyclosporine group continued and responded
  – 7 of 10 in placebo group started cyclosporine and responded

• Follow-up to 24 weeks: only 5 responders still well-controlled

Cyclosporine RCT #2

• 99 subjects randomized to cyclosporine or placebo (double-blinded) for 16 weeks
  – Group #1: cyclosporine for 16 weeks
  – Group #2: cyclosporine for 8 weeks, placebo for 8 weeks
  – Group #3: placebo for 16 weeks

• Dose:
  – 5 mg/kg/day, days 0 – 13
  – 4 mg/kg/day, days 14 – 27
  – 3 mg/kg/day, day 28 forward

• Primary measure: Severity score

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### Cyclosporine for Chronic Urticaria: What Duration?

For how long might you plan to treat this patient?

A) 1 – 2 months

B) 3 – 4 months

C) 4 – 6 months

D) 6 – 8 months

E) 8 months or more

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### Cyclosporine for Chronic Urticaria

• Open label trial of cyclosporine
  – 120 subjects

• Primary measure: Severity score

• Doses:
  – 3 mg/kg/day for 3 months
  – Weaned over 1 month for severity scores less than 3

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### Cyclosporine for Chronic Urticaria

• 38 subjects dropped out or withdrew
  – 8 in Group #1 (3 due to lack of efficacy)
  – 13 in Group #2 (8 due to lack of efficacy)
  – 17 in Group #3 (11 due to lack of efficacy)

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### Cyclosporine for Chronic Urticaria

<table>
<thead>
<tr>
<th>Group 1 (16 weeks)</th>
<th>Group 2 (8 weeks)</th>
<th>Group 3 (Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity score improvement (at 8 weeks)</td>
<td>62.5% (p &lt; 0.05)</td>
<td>62.1% (p &lt; 0.02)</td>
</tr>
<tr>
<td>Severity score improvement (at 16 weeks)</td>
<td>52.9% (p &lt; 0.05)</td>
<td>45.0% (p &lt; 0.05)</td>
</tr>
<tr>
<td>Severity score improvement (at 24 weeks)</td>
<td>41.7% (p &gt; 0.05)</td>
<td>46.9% (p &gt; 0.05)</td>
</tr>
</tbody>
</table>
Two Weeks Later…

- Scheduled follow-up assessment
- You had placed her on 4 mg/kg/day of cyclosporine divided BID
- Urticaria: improved
- Headaches
- Examination: BP 130/85, otherwise unremarkable
- Laboratory studies:
  - Complete blood count with differential: normal
  - Serum magnesium level: normal
  - Serum creatinine: normal

Cyclosporine for Chronic Urticaria: Adverse Events

- RCT #1:
  - Paresthesias (50%)
  - Headaches (40%)
  - Gastrointestinal upset (37%)
  - Malaise (30%)
- RCT #2:
  - Gastrointestinal upset (16%)
  - Paresthesias (14%)
  - Headaches (9%)
  - Elevated serum creatinine (9%)
  - 2 subjects withdrew due to hypertension
- Open label trial:
  - Peripheral neuropathy or “severe” headaches (9%)
  - Severe abdominal pain/diarrhea (8%)
  - No drug-related adverse events in subjects receiving cyclosporine for up to 5 – 10 years

References

4. Kessel A and Toubi E. *Allergy* 2010; 65:1478-82

History (continued)

Referral to Gastroenterology:
- Colonoscopy: active Crohn’s disease
- “Refractory”
- The gastroenterologist recommends starting infliximab (anti-TNF-α) therapy

History

- 29 year-old man with X-linked agammaglobulinemia
- 30 lb. weight loss, fatigue, and abdominal pain
- Past history: Crohn’s disease
  - Diagnosed at 13 years old
  - Symptoms mostly stable with occasional exacerbations responsive to steroid bursts
  - Abdominal obstruction requiring resections and stricturoplasties at 15, 17, 20, and 23 years of age
  - From ages 23 – 25, maintained on azathioprine 75 mg daily and sulfasalazine 1 gram twice daily
  - At 25 – 26 years of age, azathioprine increased to 200 mg daily (fatigue, diarrhea, weight loss)

Infliximab: Contraindications

4 CONTRAINDICATIONS

REMYCANE at doses 5 mg/kg should not be administered to patients with moderate to severe heart failure. In a randomized study evaluating REMYACEN in patients with moderate to severe heart failure: New York Heart Association (NYHA) Functional Class (III-IV), REMYACEN treatment at 5 mg/kg was associated with an increased incidence of death and hospitalization due to worsening heart failure, while it was noted that patients with known hypersensitivity to albumin components of the product or to any excipients should not be administered to patients with moderate to severe heart failure. Additionally, REMYACEN should not be administered to patients who have experienced a severe hypersensitivity reaction to REMYACEN. Additionally, REMYACEN should not be administered to patients with known hypersensitivity to albumin components of the product or to any excipients.
Infliximab: Black Box Warning

Case Presentation (continued)
- The patient was placed on a regimen of infliximab 4 mg/kg IV every other month and azathioprine 200 mg daily
- Crohn’s exacerbation at 31 years of age, responded to steroids but developed TPN requirement
- 34 years of age
  - 25 lb. weight loss over 1–2 months
  - Colonoscopy
    - No active Crohn’s disease
    - Viral cytopathic effect with stains positive for CMV in the ileum and colon

CMV Enteritis
- XLA: not an associated risk factor
- Crohn’s disease:
  - Unclear
  - More commonly associated with ulcerative colitis and even then CMV rarely found in colonic biopsies during exacerbations
- Azathioprine
  - Converts to 6-mercaptopurine, ultimately blocking purine synthesis (lymphocytes)
  - Theoretical risk factor

Infliximab and Infections
- M. tuberculosis
- Other mycobacteria
- Fungi: Histoplasma, Candida, Coccidioides, Cryptococcus, Aspergillus
- Pneumocystis jiroveci
- Listeria
- Legionella
- Nocardia
- Varicella zoster reactivation
- Epstein Barr virus reactivation
- Hepatitis B reactivation

Infliximab: Warnings and Precautions
- Infections
- Malignancies
- Heart Failure
- Rare:
  - Hepatotoxicity
  - Hypersensitivity
  - Neurologic reactions
  - Autoimmunity

CMV Enteritis
- One study of 9 subjects with latent CMV receiving infliximab (3 mg/kg) for rheumatoid arthritis found no reactivation
- 21 subjects receiving infliximab for steroid-resistant GVHD: 11 (52%) developed CMV viremia or cystitis
- Case report: a 63 year-old woman receiving infliximab for Crohn’s disease developed disseminated CMV vasculitis

Infliximab: Black Box Warning

WARNING: ADVERSE REACTIONS and MALIGNANCY
Be alert for the following information for complete boxed warning in INFliximab PACKAGE INSERT:
- Increased risk of serious infections leading to hospitalization or death, including tuberculosis (TB), listeriosis, histoplasmosis, coccidioidomycosis, nocardiosis, and infection due to other opportunistic pathogens.
- Precedence of TB, listeriosis, and coccidioidomycosis.
- Patients with latent TB, listeriosis, or coccidioidomycosis treated with INFliximab treated, while LTBI test is positive: (C.D.
- LIVER FUNCTION
- Symptoms and/or signs of cholestasis, jaundice, or other serious liver dysfunction
- Liver function tests
- Treat with INFliximab may be continued if no improvement after 4 weeks of medical treatment or if liver function tests return to normal.
- Patients with severe chronic hepatitis (including Budd-Chiari syndrome, autoimmune hepatitis) treated with INFliximab may be at increased risk of liver failure.
- Other injection site reactions
- Infusion reactions
- Hypersensitivity
- Inflammation of the pericardium (pericarditis)
- Pericardial effusion
- Theoretical risk of pneumonitis
- Theoretical risk of tuberculosis
- Theoretical risk of listeriosis
- Theoretical risk of coccidioidomycosis
- Theoretical risk of histoplasmosis
- Theoretical risk of nocardiosis
- CMV Enteritis
- One study of 9 subjects with latent CMV receiving infliximab (3 mg/kg) for rheumatoid arthritis found no reactivation
- 21 subjects receiving infliximab for steroid-resistant GVHD: 11 (52%) developed CMV viremia or cystitis
- Case report: a 63 year-old woman receiving infliximab for Crohn’s disease developed disseminated CMV vasculitis
Case Presentation (continued)

• The patient was started on ganciclovir; azathioprine was discontinued
• CMV enteritis resolved
• Infliximab was gradually titrated up to 10 mg/kg IV every other month
• Improvement over the next year: only 2 stools a day
• Then he returned...

Demyelinating Polyneuropathy: Etiology

• X-linked agammaglobulinemia
  – Enteroviral encephalitis is a known association
  – Demyelinating polyneuropathy: not reported
• IVIG therapy: no
• Crohn’s disease
  – Maybe
  – Study of 18 subjects with Crohn’s disease: 3 developed chronic inflammatory demyelinating polyneuropathy

Infliximab: reported

References