Systemic Medications for the Dermatology Toolbox: Cyclosporine

Carolyn Bangert, MD
Associated Dermatologists, PC
DISCLOSURE OF RELEVANT
RELATIONSHIPS WITH INDUSTRY

Carolyn Bangert, MD
Systemic Medications for the Dermatology Toolbox:
Cyclosporine

I have no relevant conflicts of interest with any companies.

I will mention off-label use of medications.
Discussion Questions

- What are the best uses for cyclosporine?
- What are potential contraindications?
- What are the potential toxicities and monitoring guidelines?
Hospitalized Patient Consult

- **CC:** “I have a rash all over”
- **HPI:** 37 WF y/o with painful, pruritic eruption covering most of her body
  - Developed abruptly 7 days ago and rapidly spread
  - Has a history of similar rash – last flare in 2011, hospitalization in 2003
  - Positive for fevers, chills, joint pains
  - No preceding URI, major stressors or travel.
- **PMH:** childhood eczema
- **Meds:** benadryl
- **NKDA**
Acute Generalized Pustular Psoriasis

- Is cyclosporine a good treatment choice?
  - Effective for psoriasis
  - Rapid in onset
  - Relatively easy to obtain
- Does she have any contraindications for cyclosporine?
- What toxicities and monitoring do I need to do?
Cyclosporine Background

- Calcineurin inhibitor (along w/ tacrolimus, pimecrolimus)
- Originally isolated from soil fungus *Tolypocladium inflatum gams*
- Has modest antifungal properties
- Discovered as effective for psoriasis in 1979
- Effective for treatment of many dermatologic conditions and organ transplant rejection
- Rapid onset of action
- Not cytotoxic unlike most immunosuppressives
Indications

- Psoriasis (FDA-approved), severe psoriasis, recalcitrant tx–resistant psoriasis, disabling psoriasis
- Atopic dermatitis (approved in Australia and EU)
- Pyoderma gangrenosum
- Less commonly:
  - Prurigo nodularis, lichen planus, cutaneous lupus, dermatomyositis, chronic idiopathic urticaria among others
Indications

- Excellent for:
  - Rapid control of psoriasis in patients with diffuse disease (erythrodermic, pustular), often as a bridge to other therapies
  - Short courses for control of severe atopic dermatitis flares
  - Pyoderma gangrenosum
  - Chronic idiopathic urticaria
Efficacy for Psoriasis

  - 84 pts for 12 wks
  - 58% PASI change in MTX and 72% in CsA
Efficacy for Psoriasis

  - 88 pts for 16 wks on 15 mg MTX and 3 mg/kg CsA
  - Mean PASI score decrease same at 16 wks
Efficacy for Atopic Dermatitis

  - 63 pts treated at mean of 4.27 mg/kg/day
  - After 4 wks, 35% excellent outcome, good 29% poor 36%, better with eosinophilia
Efficacy for Pyoderma Gangrenosum

- Compared 59 pts with CSA 4 mg/kg/d to 53 pts with prednisolone 0.75 mg/kg/d x 6 mos
- Efficacy at 6 mos 47% in both
- Toxicity rates similar, but serious adverse events, including infection > prednisolone
Formulation

- Two forms:
  - Unmodified (Sandimmune)—cheaper
  - Modified cyclosporine (Neoral)—microemulsion form, more expensive, but better bioavailability and more consistently absorbed
    - 25, 100 mg tablets
    - 100 mg/ml solution
Pharmacology

- Absorption: modified CsA 10–54% more bioavailable than non-modified
- Metabolism:
  - Extensive CYP-450 3A4 metabolism
  - Excreted through bile and feces
  - Hepatic insufficiency may prolong half life
Mechanism of Action

- Inhibits IL-2 production by activated CD4+ T cells
- Inhibits IFN-γ production by T-cells
Dosing

- 2.5–5 mg/kg/day divided bid
- Metabolism: liver (CYP 3A4)
- Dose adjustments:
  - Hepatic insufficiency: reduce dose
  - Renal failure/dialysis: no significant dose adjustments
- Pregnancy category C
- Excreted in breast milk
Contraindications

<table>
<thead>
<tr>
<th>Absolute Contraindications</th>
<th>Relative Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal dysfunction</td>
<td>Controlled hypertension</td>
</tr>
<tr>
<td>Uncontrolled hypertension</td>
<td>Meds interfering with metabolism</td>
</tr>
<tr>
<td>Hypersensitivity to CsA</td>
<td>Other immunosuppressives</td>
</tr>
<tr>
<td>Malignancy, CTCL</td>
<td>Hx numerous skin cancers</td>
</tr>
<tr>
<td>Concurrent phototherapy or PUVA hx (&gt;200)</td>
<td>Pregnancy/lactation</td>
</tr>
<tr>
<td>Radiation treatment</td>
<td>Active infection</td>
</tr>
<tr>
<td></td>
<td>Poorly-controlled DM, obesity, elderly</td>
</tr>
</tbody>
</table>
Toxicity

- Renal:
  - More common with prolonged use, in patients with preexisting renal dysfunction
  - More than 50% patients have this if tx > 2 yrs
  - Use drug for less than 1–2 yrs continuously
  - Reduce dose or discontinue for Cr elevations of 30% or more
  - Following these guidelines: no permanent kidney dz
Toxicity

- Hypertension:
  - Common, in 27% of CsA pts
  - Can treat HTN and continue drug
  - Treat with nifedipine, beta-blocker
  - Reversible with discontinuation
  - Mechanism: activation of renin–angiotensin systems, inhibit NO–induced vasoconstriction
Toxicity

- Hyperlipidemia:
  - Common, reversible
  - May be treated by diet and exercise, dose reduction
  - Can use lipid-lowering agents, but statins interact

- Neurologic:
  - Tremors, headache, paresthesias

- Others: nausea, malaise

- Hyperkalemia, hypomagnesemia, hyperuricemia

- Rare: hepatic toxicity, hematologic toxicity
Toxicity

- Cutaneous:
  - Hypertrichosis
  - Gingival hyperplasia
  - Acne
Toxicity

- Malignancy:
  - Increased risk of NMSC 6x in one study of 1252 pts
  - Unclear if increased risk of other malignancies in psoriasis patients
  - Avoid other immunosuppressives
  - Avoid concurrent phototherapy
  - Avoid with CTCL or other malignancy
No increase in opportunistic infections or TB
- Cited one comprehensive prospective study of 1252 pts showed increased risk of NMSC 6x, SCC:BCC 3:1
- Other malignancies not increased
- Numerous case reports of malignancy, particularly liquid tumors
Toxicity

- **Infection:**
  - Concern for infection and serious infection, particularly with long-term use
  - Reports of TB reactivation with drug
Compared data from large multi-center cohort of 2153 patients on biologics, MTX, acitretin, CsA over 3 yrs

Found that RR infection in CsA was 1.58 and serious infection 3.12
Hepatitis C

- CsA has potent anti-HCV effects:
  - Inhib of cyclophillins (impt for viral replication)
  - In conjunction with antiviral therapy, reduced viral load, risk of fibrosis
  - Reduced risk of HCV recurrence following liver transplant
- Limited data but CsA is probably safe in hep C + psoriasis patients, and useful to prevent IFN-induced flares
Drug Interactions

- CYP 3A4 inhibition (↑ CsA levels)
  - Amiodarone
  - Erythromycin >> clarithro > azaithro
  - Cipro
  - Ketoconazole >> itraconazole > fluconazole
  - Ritonavir, indinavir, other protease inhibitors
  - Diltiazem, nicardapine, verapimil
  - Grapefruit juice
  - Cimetidine
  - Fluoxetine, sertraline
Drug Interactions

- CYP 3A4 Induction (↓ CsA efficacy)
  - St. John’s wort
  - Nafcillin
  - Rifabutin, firampin, rifapentine
  - Carbamezepine, phenobarbital, phenytoin, VPA
  - Griseofulvin
  - Efavirenz
  - Bexarotene
Drug Interactions

- CsA can increase the toxicity of (CYP 3A4 inhib):
  - Calcium channel blockers (hypotension)
  - Sildenafil, etc. (risk of excess vasodilatation)
  - Statins (risk of rhabdo)
- Other:
  - Thiazides and allopurinol could increase toxicity
Dosing and Monitoring

- **Dosing:**
  - May begin 3 mg/kg/day and increase to max 5
  - May also begin at full-dose (4–5 mg/kg/day) for severe cases, and slowly taper

- **Monitoring**
  - Baseline CBC, CMP, UA, BP, lipids, Mg, uric acid
  - Q 2 weekly BUN/Cr, UA, BP x 1 mos
  - Monthly CBC, CMP, UA, lipids, Mg, uric acid, BP
Returning to Our Consult
Acute Generalized Pustular Psoriasis

- Is CsA a good treatment?
  - It’s effective for psoriasis, rapid in onset, usually easy to get
- What are the contraindications?
  - Uncontrolled hypertension
  - Renal dysfunction
  - Malignancy
  - Phototherapy or XRT
  - Hypersensitivity
- Other potential issues?
  - Pregnancy/lactation, active infection, drug interactions
Acute Generalized Pustular Psoriasis

- What monitoring do we do?
  - Check blood pressure
  - CMP, CBC, UA, lipids, Mg, uric acid
- How do I start?
  - Begin 4–5 mg/kg/day x 2 weeks
  - Follow up in 2 weeks for monitoring and blood pressure
Conclusions

- What are the best uses?
  - Rapid control of severe diseases (psoriasis, eczematous dz) and also useful for PG, urticaria

- What are potential contraindications?
  - Renal dz, HTN, malignancy, infection, phototherapy

- What are potential toxicities and monitoring guidelines?
  - Particularly with long-term use
  - Renal dz, HTN, electrolyte imbalances, lipids is required
References


