Use of biologics and chemotherapeutic agents in cutaneous emergencies: Focus on life-threatening forms of psoriasis

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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Current Consulting/Advisory Board Agreements/or Speakers Bureau:


Research/Educational Grants:

Janssen, Incyte
Agenda

• When is psoriasis an emergency?
  • Erythroderma
  • Generalized pustular psoriasis

• Treatments
  • Chemotherapeutic drugs (MTX, Acitretin, *Cyclosporine)
  • *Biologics

*not FDA approved for these indications
How does erythrodermic psoriasis present as an emergency?

• Increased infection which can lead to sepsis and shock, especially S. aureus*

• Temperature control abnormalities

• Fluid loss

• Loss of nutrients through the skin leads to anemia and electrolyte imbalance

• High output congestive heart failure

How does generalized pustular psoriasis present as an emergency?

- Increased infections which can lead to sepsis and shock
- Fluid loss
- Electrolyte imbalance, loss of nutrients through the skin
- Loss of temperature control
- Fever, tachycardia, hypotension
- High output congestive heart failure
- Death
Hospitalized patients with psoriatic erythroderma and generalized pustular psoriasis require:

• Bed rest
• Monitoring of temperature, vital signs (BP), urine output, weight, cardiac function, bloodwork
• Work up potential infections
• Emotional support: These conditions are frightening for the patients
• Emollients and Soaks
• Topical corticosteroids*
• Treatments which work quickly

Treatment of Erythrodermic Psoriasis
“There are few high quality studies available to make strong recommendations”

Rosenbach et al  Treatment of erythrodermic psoriasis: From the medical board of the National Psoriasis Foundation. JAAD 62: 655, 2009
Cyclosporine for Erythrodermic Psoriasis

• Open-label, multicenter study of 33 patients with psoriatic erythroderma
• Initial mean dose 4.2 mg/kg/d slowly tapered after clearance by 0.5 mg/kg q 2 weeks
• 67% cleared, 27% “significantly improved” at 2-4 months
• Relatively fast

Studio Italiano Multicentrico nella Psoriasi Dermatology 1993; 34:911.
Acitretin

• “...” is indicated for the treatment of severe psoriasis in adults” (FDA PI)
• Meta-analysis of 12 clinical trials of acitretin as a single agent
• 25-35 mg/d
• 83.3% of patients with erythrodermic psoriasis had “marked improvement or remission”

Geiger and Czarnetzki Dermatologica 1988; 176: 182.
Methotrexate

• “METHOTREXATE SHOULD BE USED ONLY IN LIFE THREATENING NEOPLASTIC DISEASES, OR IN PATIENTS WITH PSORIASIS OR RHEUMATOID ARTHRITIS WITH SEVERE, RECALCITRANT, DISABLING DISEASE WHICH IS NOT ADEQUATELY RESPONSIVE TO OTHER FORMS OF THERAPY.” (FDA PI)

• Best of 3 studies available summarized as follows:
  • Retrospective, single-center review of 26 years of experience
  • 36 patients with erythrodermic psoriasis treated with MTX
    • Initial dose 7.5-40 mg/wk
    • Maintenance dose 7.5-15 mg/week
  • Response to therapy noted within 1-4 weeks (? How defined)
  • 28/36 had good outcome; 6/36 had moderate outcome (definitions of good and moderate not provided)

Haustein and Rytter JEADV 2000; 14:382.
Infliximab

- Open label, single-center study of 28 patients; 5 with erythrodermic psoriasis
- Infliximab 5 mg/kg IV at weeks 0, 2, 6 and q 8 weeks
- 2 achieved PASI 90, 1 achieved PASI 75 at week 14
- Relatively fast and the fastest of all the TNF blockers

Treatment of Generalized Pustular Psoriasis

Robinson et al  Treatment of pustular psoriasis: From the Medical Board of the National Psoriasis Foundation. JAAD 2012; 67: 279.
Unopposed IL-36 activity promotes clonal CD4+ T-cell responses with IL-17A production in generalized pustular psoriasis; Arakawa et al JID published online DOI 10.1016/j.jid.2017.12.024.

• Findings in this basic science paper suggest:
  • Role for both autoinflammatory pathways, e.g., IL-36 and IL-1 in the pathogenesis of generalized pustular psoriasis
  • Role for IL-17A in generalized pustular psoriasis
Acitretin, MTX and Cyclosporine Compared

- *385 cases of generalized pustular psoriasis from 325 Japanese hospitals
  - Retinoid (etretinate and acitretin) treatment effective (?definition) in 84.1% patients
  - MTX in 76.2%
  - Cyclosporine in 71.2%
- **Another study recommended oral acitretin 0.75-1.0 mg/kg/d with clinical response within 7 to 10 days; Maintenance dose 0.125 to 0.25 mg/kg/d for several months

Recommended MTX and Cyclosporine Dosing

• *MTX
  • Slow onset of action problematic
  • Start with 5-15 mg once weekly; lower doses in elderly. Increase by 2.5 mg weekly

• *Cyclosporine
  • 3.5-5 mg/kg/d to start. Improvement can be observed as early as 2 weeks. Taper dose by 0.5 mg every two weeks

**Infliximab**

- Combined study of erythrodermic and generalized pustular psoriasis in Japanese clinical practice
- Without washout, patients switched to infliximab at 5 mg/kg at weeks 0, 2, 6 and then every 8 weeks up to week 46
- Outcome measure was a global improvement score
- Global improvement in pustular psoriasis was between 66.7% and 100% during the 2-50 week period
- Global improvement in erythroderma was between 75% and 100% during the 2-50 week period

IL-17 inhibition in Generalized Pustular Psoriasis and Erythrodermic Psoriasis
Ixekizumab

• FDA approved for moderate to severe plaque psoriasis and for psoriatic arthritis
• Japanese open-label study of psoriasis patients treated with ixekizumab at USA-marketed dose up to 52 weeks
• 8 erythroderma; 5 generalized pustular psoriasis; 78 plaque type
• 75% of erythroderma patients achieved PGA 0,1 and 60 % of generalized pustular psoriasis patients achieved PGA 0,1 at week 52
• Second outcome measure: Global Improvement Score rated as Resolved in 12.5% of erythroderma and 40% of generalized pustular psoriasis patients
• No increased toxicity with these forms of psoriasis

Secukinumab

- FDA approved for both moderate to severe plaque psoriasis and for psoriatic arthritis
- Open-label, multicenter, single arm study in 12 Japanese patients with generalized pustular psoriasis
- Secukinumab 150 mg sc at baseline, weeks 1, 2, 3, 4 and every 4 weeks; Two non responders up-titrated to 300 mg dose.
- Outcome measure: change in clinical global impression of improvement (CGI) categorized as worsened, no change, minimally improved, much improved or very much improved
- At week 16, 83.3% were very much improved (n=9) or much improved (n=1)
- Erythema with pustules area started improving as early as week 1 and resolved by week 16 in most patients
- Responses sustained up to 52 weeks
- No increased toxicity with this form of psoriasis

Imafuku et al J. Dermatol. 2016, 43: 1011
Brodalumab: Anti-IL-17A Receptor

- Open-label, multicenter, long-term phase III Japanese study
- Brodalumab 140 mg at day 1 and weeks 1 and 2, then every 2 weeks until week 52; dose escalation to 210 mg at week 4 or later if Pustular Symptom Score (PSS) was moderate or severe
- Primary endpoint was the Clinical Global Impression of Improvement (CGI)
- PSS was a composite score evaluating areas involved with erythema, pustules, edema; systemic features: fever, WBC count, CRP, serum albumin used to grade severity of generalized pustular psoriasis (score ranges from 0-17; moderate 7-10, severe 11-17)
- 18 patients with erythrodermic psoriasis; 16 completed
- 12 patients with generalized pustular psoriasis; 10 completed
- At week 12, CGI remission or improvement was achieved in 83.3% patients with generalized pustular psoriasis and 100% with erythroderma
- At week 12, 66.7% of generalized pustular psoriasis patients achieved 0, 1 PSS score (mean baseline score was 4.4±2.4)
- 52 week data also reported
- No increased toxicity with these forms of psoriasis

These biologics work too slowly or no data were available to review

- Etanercept
- Adalimumab
- Certolizumab
- Ustekinumab
- Guselkumab
Treatments which work the fastest in psoriasis emergencies and for which data are available

• Cyclosporine
• Acitretin
• Infliximab
• IL 17 inhibitors