Impact of psoriasis biologics on cardiovascular risk: relevance for clinical practice

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Psoriasis and co-morbidities paradigm

Environmental risk factors
- Smoking
- Obesity

Genes and loci associated with psoriasis, diabetes and CV diseases
- PSORS2/3/4
- CDKAL1
- ApoE4
- TNFAIP3

Mediating factors
Pathophysiology
- Th1/17 inflammation (atherosclerosis, thrombosis, lipid metabolism)
- Epidermal proliferation (↑uric acid, oxidative stress)
- Angiogenesis (endothelial dysfunction)

Treatment
- Increase CV risk (e.g. cyclosporine, acitretin)?
- Decrease CV risk (e.g. methotrexate, TNF inhibitors)?

Psychosocial impact
- Depression, alcohol and smoking, lower socioeconomic status

Risk of Cardiometabolic Disease in Severe Psoriasis

**Clinical Significance:**

1. Increased risk of MI, stroke, cardiovascular death, diabetes
2. 5 years of life lost
3. 10 year risk of major CV event attributable to psoriasis= 6%
4. Risk of cardiovascular disease in patients with severe psoriasis similar to risk conferred by diabetes
5. Patients treated for severe psoriasis are 30X more likely to experience MACE (attributable to psoriasis) than to develop a melanoma

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adj. RR Mild</th>
<th>Adj. RR Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI¹</td>
<td>1.05</td>
<td>1.5</td>
</tr>
<tr>
<td>Stroke²</td>
<td>1.06</td>
<td>1.4</td>
</tr>
<tr>
<td>CV Death³</td>
<td>Not done</td>
<td>1.6</td>
</tr>
<tr>
<td>MACE⁴</td>
<td>Not done</td>
<td>1.5</td>
</tr>
<tr>
<td>Diabetes⁵</td>
<td>1.11</td>
<td>1.5</td>
</tr>
</tbody>
</table>

5. Azfar R, et al.. *Arch Derm* 2012; 148:995-1000
Psoriasis and CV risk knowledge is rapidly expanding

- 9 meta-analyses covering 500,000+ psoriasis patients and 29+ million controls
- An estimated 11,500 extra MACE events attributable to psoriasis in the US per year

Comparison of cardiometabolic outcomes: Psoriasis vs. RA


|                     | Psoriasis | RA  
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>CV Death (DMARD)</td>
<td>1.5</td>
<td>1.6</td>
</tr>
<tr>
<td>All cause mortality (DMARD)</td>
<td>1.8</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Prevalence of CVD increases with increasing body surface area affected by psoriasis (iHOPE N= 9000)

Psoriasis and CVD: Mechanistic insights

Metabolic and CV gene expression > cycle and inflammatory disease categories in lesional vs non lesional psoriasis biopsies

KC-Tie2 psoriasis skin specific inflammation mouse model demonstrates development of aortic inflammation and thrombosis


18-FDG PET CT Imaging biomarker demonstrates diffuse vascular inflammation in psoriasis

Youn SW J Dermatol. 2015 Jun;42(6):559-66
Naik HB et al Arterioscler Thromb Vasc Biol. 2015 Dec;35(12):2667-76
New Findings 2016-2017: Psoriasis and CV risk

1. Psoriasis is associated with increased arterial and subcutaneous fat inflammation based on FDG-PET/CT
2. Adipose under psoriasis plaques express miRNA’s that modulate lipid metabolism
3. IL-6 mediates psoriasiform associated thrombosis
4. HLA-C*06:02 is associated with a higher burden of atherosclerosis
5. Patients with psoriasis have similar CAC scores to diabetes, and is more strongly associated with metabolic syndrome and mortality than atopic dermatitis
6. Psoriasis is associated with an increased risk of atrial fibrillation and aortic aneurysm

Clinical Care Recommendations: Educate and Screen for CV risk factors

AJC Editor’s Consensus: Psoriasis and Coronary Artery Disease

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National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening

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Boston, Massachusetts; Toronto, Ontario, Canada; Philadelphia, Pennsylvania; Skokie, Illinois; Portland, Oregon; Cleveland, Ohio; Salt Lake City, Utah; and New York, New York

CV risk factors are under screened and under managed in psoriasis patients

- CDC US population data indicates poor screening rates for HTN by derms
- < 50% of US dermatologists report screening for hypertension, dyslipidemia, and diabetes
- 37% of newly screened psoriasis patients found to be at high CV risk and 46% had suboptimal CV RF management

Takeshita, J et al. JAMA Dermatology 2015;151:161-9
Manalo IF et al JAAD 2015 73:872-4
Rutter BJD 2016;175:348-56
TNF inhibitors and methotrexate are cardioprotective in RA meta-analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TNF (RR)</th>
<th>MTX (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV all</td>
<td>0.70</td>
<td>0.72</td>
</tr>
<tr>
<td>MI</td>
<td>0.59</td>
<td>0.81</td>
</tr>
<tr>
<td>CHF</td>
<td>0.75 (NS)</td>
<td>0.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.52</td>
<td>0.78 (NS)</td>
</tr>
<tr>
<td>MACE</td>
<td>0.30</td>
<td>0.38 (NS)</td>
</tr>
</tbody>
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Impact of systemic psoriasis treatment on mortality and MACE

- Nationwide cohort study in Denmark using time varying approach adjusting for age, sex, comorbidity, pharmacotherapy, and year
- Reference group – severe psoriasis on “other therapies” such as topicals, and UV (n=3961)
- Outcome: Death, MI, Stroke, CV death

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mortality</th>
<th>MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologics (n=1137)</td>
<td>0.47 (0.25-0.88)</td>
<td>0.58 (0.30-1.10) NS</td>
</tr>
<tr>
<td>Methotrexate (n=3564)</td>
<td>0.56 (0.42-0.76)</td>
<td>0.53 (0.34-0.83)</td>
</tr>
<tr>
<td>Cyclosporine (n=244)</td>
<td>1.09 (0.4-2.97) NS</td>
<td>1.06 (0.26-4.27) NS</td>
</tr>
<tr>
<td>Retinoids (n=756)</td>
<td>1.38 (0.93-2.04) NS</td>
<td>1.80 (1.10-2.96)</td>
</tr>
<tr>
<td>TNF (n=959)</td>
<td>NR</td>
<td>0.46 (0.22-0.98)</td>
</tr>
<tr>
<td>Il 12/23 (n=178)</td>
<td>NR</td>
<td>1.52 (0.47-4.94) NS</td>
</tr>
</tbody>
</table>

Ahlehoff O et al. JEAADV 2015;29:1128-1134   NS: Not Significant NR: Not Reported
New Findings 2016-2017: Psoriasis treatment and CV risk

1. TNF treatment of psoriasis is associated with lower CV event risk compared to methotrexate
2. Anti-TNF treatment of psoriasis improves endothelial function, arterial stiffness, E-selectin levels, GlycA levels, aortic inflammation measured by FDG-PET/CT, improved echocardiographic data and coronary microvascular function

Biologics and CV Risk: Promise or Peril

1. Biologics lower CV risk 😊
   – Observational data support this theory for TNF inhibitors

2. Biologics raise CV risk 😞
   – Early phase trials found signal for IL-12/23 inhibitors that has not been confirmed

3. Biologics have no effect on CV risk

4. Risk associated with biologics varies by duration of treatment analogous to hormone replacement therapy 😊 😞
   – Purely theoretical- but stay tuned!

Hierarchy of evidence: Prevention requires strongest level!
RCTs evaluating impact of psoriasis treatment on CV risk

• **Vascular Inflammation in Psoriasis Trial (VIP) and VIP-Ustekinumab**
  – Does treatment with adalimumab or phototherapy lower vascular inflammation and improve lipid metabolism in patients with moderate to severe psoriasis? (NCT01553058)
  – Does treatment with ustekinumab lower vascular inflammation and improve lipid metabolism in patients with moderate to severe psoriasis (NCT02187172)
  – Does treatment with secukinumab lower vascular inflammation and improve lipid metabolism in patients with moderate to severe psoriasis (NCT02690701)

• **Cardiovascular Inflammation Reduction Trial (CIRT)**
  – Does methotrexate lower the risk of major vascular events in patients with a history of MI and diabetes or metabolic syndrome? (NCT01594333)
Psoriasis: Think beyond the skin

“... For the secret of the care of the patient is in caring for the patient.”

– Francis W. Peabody October 21 1925

To refer patients for the VIP trials: 215-662-SKIN or SkinVIP@upenn.edu
Acknowledgements

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