Psoriasis Cardiovascular Comorbidities

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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Psoriasis Cardiovascular Comorbidities
F005
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Consultant and Advisory Boards
- Consultant (honoraria): AbbVie, Almirall, Amgen, Arena, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermavant, Dermira, Janssen, Leo, Eli Lilly, Kyowa Hakko Kirin, Medac, Meiji Seika Pharma, Sebela Pharmaceuticals, Menlo Therapeutics, Novartis, Pfizer, GlaxoSmithKline, UCB Pharma, Sun Pharma, Ortho Dermatologics/Valeant, Regeneron, Sanofi-Genzyme

Scientific Director

CORRONA Psoriasis Registry

The Metabolic Syndrome

• The presence of at least 3 of the following: 1,2
  • Increased waist circumference or abdominal obesity
  • Hypertension
  • Hypertriglyceridemia
  • Reduced high-density lipoprotein
  • Insulin resistance
  • Chronic inflammatory state 1,2
  • Associated with markedly increased cardiovascular mortality 1,2
  • United States: 35% of the population 7


Obesity, Waist Circumference, Weight Change, and the Risk of Psoriasis in Women

• Prospective examination of the Nurses’ Health Study II (N=76,626)
  • 14 years of follow-up
  • 892 incident cases of psoriasis
  • For body mass index (BMI) updated every 2 years compared with a BMI = 21.0-22.9 kg/m², the multivariate relative risks of psoriasis were statistically significant (P for trend <0.001)
    • 1.40 (95% CI, 1.13-1.73) for a BMI = 25.0-29.9 kg/m²
    • 1.48 (95% CI, 1.15-1.91) for a BMI = 30.0-34.9 kg/m²
    • 2.69 (95% CI, 2.12-3.40) for a BMI ≥ 35.0 kg/m²
  • Waist circumference, hip circumference, and waist-hip ratio were all associated with a higher risk of incident psoriasis (all P values for trend <0.001)

Prevalence of Cardiovascular Risk Factors in Patients with Psoriasis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prevalence (%)</th>
<th>Odds Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>7.1</td>
<td>1.39 (1.22-1.58)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20</td>
<td>1.16 (1.07-1.26)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>6</td>
<td>1.06 (1.05-1.07)</td>
</tr>
<tr>
<td>Obesity</td>
<td>20.7</td>
<td>1.47 (1.32-1.63)</td>
</tr>
</tbody>
</table>

* Severe psoriasis vs mild psoriasis.

Risk of Myocardial Infarction in Patients with Psoriasis

- Incidence per 1000 person-years (95% confidence interval [CI]):
  - Control: 3.58 (3.52-3.65)
  - Mild psoriasis: 4.04 (3.88-4.21)
  - Severe psoriasis: 5.13 (4.22-6.17)

Psoriasis may confer an independent risk of myocardial infarction (MI)

The relative risk (RR) was greatest in young patients with severe psoriasis

Potential Mechanisms for Risk of Cardiovascular Disease in Psoriasis

- Conventional Risk Factors
  - Family history
  - Smoking
  - Hypertension
  - Diabetes
  - Dyslipidemia
  - Obesity

Immune/Inflammatory Activity

Psoriasis and cardiovascular disease

- Even after controlling for risk factors associated with cardiovascular disease, severity of psoriasis correlates with the likelihood of a heart attack, particularly among patients who are younger

Prospective population-based cohort study (UK General Practice Research Database): Relative risk of myocardial infarction vs control patients

<table>
<thead>
<tr>
<th>Age 30 years</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild psoriasis</td>
<td>1.00</td>
</tr>
<tr>
<td>Severe psoriasis</td>
<td>1.29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 60 years</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild psoriasis</td>
<td>1.00</td>
</tr>
<tr>
<td>Severe psoriasis</td>
<td>3.10</td>
</tr>
</tbody>
</table>

Adjusted for age, age × psoriasis (interaction term), diabetes, family history of MI, hypertension, obesity, and smoking
**People With Psoriasis Die Earlier**

**Attributable and Excess Risk of Mortality Associated With Severe Psoriasis Increases With Age**

<table>
<thead>
<tr>
<th>Age Group, y</th>
<th>Mortality Rate per 1000 Patient-Years</th>
<th>Attributable Risk, No. or Deaths per 1,000 Patients-Year</th>
<th>Excess Risk, No. of Deaths (patients per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>12.6</td>
<td>1.9</td>
<td>14.5</td>
</tr>
<tr>
<td>50-59</td>
<td>2.0</td>
<td>4.5</td>
<td>16.5</td>
</tr>
<tr>
<td>60-69</td>
<td>6.4</td>
<td>9.6</td>
<td>16.0</td>
</tr>
<tr>
<td>70-79</td>
<td>10.5</td>
<td>12.9</td>
<td>13.8</td>
</tr>
<tr>
<td>80-89</td>
<td>15.7</td>
<td>16.9</td>
<td>13.8</td>
</tr>
</tbody>
</table>

Men and women with severe psoriasis died 3.5 and 4.4 years younger, respectively, than patients without psoriasis.

**iHOPE: All-cause mortality rates based on objective measures of psoriasis severity in patients with psoriasis**

<table>
<thead>
<tr>
<th>Mortality rate</th>
<th>All-cause mortality associated with psoriasis and other risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>2.0</td>
</tr>
<tr>
<td>Age and sex</td>
<td>1.5</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>1.4</td>
</tr>
</tbody>
</table>

**Risk of death for patients with psoriasis vs controls**

<table>
<thead>
<tr>
<th>BSA</th>
<th>Mortality rate, per 1000 pt-y (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3% BSA</td>
<td>3.25 (3.07–3.44)</td>
</tr>
<tr>
<td>3%–10% BSA</td>
<td>3.00 (2.32–3.88)</td>
</tr>
<tr>
<td>&gt;10% BSA</td>
<td>2.81 (2.04–3.86)</td>
</tr>
</tbody>
</table>

- Patients with BSA >10% had an increased risk of death vs age- and sex-matched adults without psoriasis.
- Further worse than smoking.
- Results were robust to adjustment for the Charlson Comorbidity Index, suggesting underlying medical comorbidities are not solely responsible for increased risk.
- Preventive efforts should be targeted to psoriasis with BSA >10%.

**Methotrexate Reduces Incidence of Vascular Disease in Veterans with Psoriasis or Rheumatoid Arthritis**

- Retrospective cohort study that analyzed computerized records at the Veterans Integrated Service Network 8.
- 3,869 outpatients with psoriasis
- 6707 outpatients with rheumatoid arthritis
- Patients prescribed methotrexate had a significantly reduced risk of vascular disease compared with those who were not prescribed methotrexate:
  - Psoriasis: RR, 0.73; 95% CI, 0.55–0.98
  - Rheumatoid arthritis: RR, 0.83; 95% CI, 0.71–0.96
- Reduction most evident in patients prescribed a low cumulative dose of methotrexate.
- Concomitant use of folate acid further reduced the incidence of vascular disease in patients prescribed methotrexate.

Cardiovascular disease event rates in patients with severe psoriasis treated with systemic anti-inflammatory drugs: Danish real-world cohort study

- Retrospective longitudinal cohort study
- Denmark 2007-2009. Individual-level linkage of nationwide administrative databases to assess the event rates associated with use of biological agents, methotrexate or other systemic therapies
- Primary study end-point: composite of death, myocardial infarction and stroke
- Secondary end-point: cardiovascular death, MI, stroke
- 2400 patients with severe psoriasis:
  - 693 patients treated with biological agents
  - 799 treated with methotrexate
  - Maximum follow-up was 3 years, mean follow-up of approximately 18 months.


105 individual primary outcome events (death, MI, stroke) were recorded:
- 6 and 33 events occurred in patients treated with biological agents and methotrexate, respectively.

54 individual secondary outcome events (cardiovascular death, MI, stroke) were recorded:
- 4 and 15 events occurred in patients treated with biological agents and methotrexate, respectively.
- In contrast to the primary analysis, patients treated with both methotrexate and biological agents had the lowest risk estimate (HR 0.30; 95% CI 0.07–1.26).
- The results were not qualitatively affected by multivariable adjustment for baseline comorbidity, use of various medications and socioeconomic status.
- The lower risk associated with the use of biological agents and methotrexate was confirmed after exclusion of subjects with a history of hospitalization and/or cardiovascular drug use.


KPSC retrospective cohort study: Association between TNF inhibitor therapy and risk of major CV events in patients with psoriasis

- 50,497 KPSC members were assessed for eligibility
- 15,074 were not eligible:
  - 284 had a prior MACE
  - 8672 were enrolled at KPSC <1 year prior to psoriasis diagnosis
  - 5120 had <1 medical encounter every 3 years
  - 399 were diagnosed with conditions other than psoriasis that may justify TNFi use (eg, Crohn’s disease, RA)
  - 599 were younger than 18 years at psoriasis diagnosis
  - 69 were excluded due to UST use in study period
- Findings were robust to multiple sensitivity analyses when looking at phototherapy or methotrexate alone

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
<th>No. of events</th>
<th>Incidence rate</th>
<th>Unadjusted HR (95% CI)</th>
<th>Propensity score-adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical</td>
<td>78,191</td>
<td>922</td>
<td>11.79</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Oral/phototherapy</td>
<td>25,799</td>
<td>300</td>
<td>11.63</td>
<td>0.98 (0.86–1.11)</td>
<td>0.98 (0.86–1.11)</td>
</tr>
<tr>
<td>TNFi</td>
<td>13,490</td>
<td>114</td>
<td>8.45</td>
<td>0.71 (0.59–0.86)</td>
<td>0.60 (0.48–0.76)</td>
</tr>
</tbody>
</table>

- TNFi was associated with a significantly lower risk of MACE vs topical agents or oral/phototherapy
- Outstanding questions:
  - Severity of disease and post-treatment success were not accounted for (oral/phototherapy group looked like topical group)
  - Was the effect specific to TNFi only, or would other biologics show the same effect?
  - What about patients with a history of CVD?
  - Does not account for concomitant medications such as aspirin (largest risk reduction in CVD events)
Gelfand JM. AAD 2017, Presented during symposium S030

VIP and VIP-E: Phase 4, randomized, double-blind, placebo-controlled trial of the effect of adalimumab for psoriasis on vascular inflammation

VIP and VIP-E: Baseline demographics and psoriasis endpoints following treatment with adalimumab

VIP and VIP-E: Change in total aortic vascular inflammation from entire aorta assessed on ¹⁸F-DG-PET/CT

MarketScan® claims database: Effect of cumulative TNF inhibitor exposure on the risk for major CV events

- Psoriasis patients treated with TNF inhibitors were associated with a statistically significant lower risk of experiencing MACE compared with patients treated with MTX
- Cumulative exposure to TNF inhibitors was associated with a reduced hazard for MACE over time

Baseline demographics

<table>
<thead>
<tr>
<th>Baseline demographics</th>
<th>Week 12</th>
<th>Week 12</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phototherapy</td>
<td>Placebo</td>
<td>Phototherapy</td>
</tr>
<tr>
<td>Male (%)</td>
<td>23 (77)</td>
<td>23 (77)</td>
<td>23 (77)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>22 (23)</td>
<td>22 (23)</td>
<td>22 (23)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.4 (5.1)</td>
<td>27.4 (5.1)</td>
<td>27.4 (5.1)</td>
</tr>
<tr>
<td>Psoriasis duration, mean</td>
<td>32 (22)</td>
<td>32 (22)</td>
<td>32 (22)</td>
</tr>
<tr>
<td>Age (y), mean</td>
<td>44 (6)</td>
<td>44 (6)</td>
<td>44 (6)</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>24 (75)</td>
<td>24 (75)</td>
<td>24 (75)</td>
</tr>
</tbody>
</table>

Psoriasis endpoints

<table>
<thead>
<tr>
<th>Psoriasis endpoints</th>
<th>Week 12</th>
<th>Phototherapy</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PASI 75, n (%)</td>
<td>13 (41)</td>
<td>13 (41)</td>
<td>13 (41)</td>
</tr>
<tr>
<td>PGA clear, n (%)</td>
<td>15 (47)</td>
<td>15 (47)</td>
<td>15 (47)</td>
</tr>
<tr>
<td>PGA clear/almost clear, n (%)</td>
<td>14 (44)</td>
<td>14 (44)</td>
<td>14 (44)</td>
</tr>
<tr>
<td>Complete clearance, n (%)</td>
<td>18 (55)</td>
<td>18 (55)</td>
<td>18 (55)</td>
</tr>
</tbody>
</table>

Change in vascular inflammation

- Change in total vascular inflammation from baseline to Week 12:
  - Phototherapy: Mean −6.40 (95% CI: −7.90 to −4.90)
  - Placebo: Mean −2.50 (95% CI: −4.00 to −1.00)
- Change in total aortic vascular inflammation from baseline to Week 12:
  - Phototherapy: Mean −3.80 (95% CI: −5.80 to −1.80)
  - Placebo: Mean −1.84 (95% CI: −3.84 to 0.16)
- No evidence of an effect of adalimumab on aortic vascular inflammation, but treatment effects were statistically significant

VIP and VIP-E: Phase 4, randomized, double-blind, placebo-controlled trial of the effect of adalimumab for psoriasis on vascular inflammation

- Inclusion criteria:
  - Diagnosis of psoriasis
  - Baseline demographic risk factors
  - Baseline vascular inflammation:
    - Baseline aortic inflammation:
      - Baseline global change: −5.8 ± 4.1%
      - Baseline regional changes:
        - Baseline psoriasis:
          - Baseline global change: −5.84 ± 3.47%
          - Baseline mean change: −6.78 ± 3.95%
    - Baseline PSORT

- Exclusion criteria:
  - Candidate for systemic immunosuppressive therapy
  - Candidate for systemic antibiotic therapy

- Global change
  - Global change: −5.8 ± 4.1%
  - Regional changes: −5.84 ± 3.47%
  - Mean change: −6.78 ± 3.95%

- No evidence of an effect of adalimumab on aortic vascular inflammation, but treatment effects were statistically significant

VIP and VIP-E: Change in total aortic vascular inflammation from entire aorta assessed on ¹⁸F-DG-PET/CT

- No evidence of an effect of adalimumab on aortic vascular inflammation, but treatment effects were statistically significant

- Placebo group had a decrease of 2.5% in vascular inflammation, comparable effect of lifestyle changes
- Age was not compared with other vascular inflammation trials
- Not all patients achieved a NAD 75 response when imaged following therapy
- Sensitivity analysis for patients with high BMI, high baseline vascular inflammation, and ≥2 CV risk factors were not performed
Phase 4, randomized, placebo-controlled study to evaluate the effect of adalimumab on vascular inflammation in patients with psoriasis

Participants
- BSA ≥5%
- Ascending aorta atherosclerotic plaque inflammation TBR ≥1.6
- Psoriasis treatments washouts included:
  - Biologics: 12 weeks
  - Oral medication: 4 weeks
  - UVB treatment/topical treatment: 2 weeks
- No history of myocardial infarction, acute coronary syndrome or percutaneous coronary intervention, stent installation, or carotid revascularization within 12 weeks of Day 0

Bissonette R, et al. AAD 2017, Late breaking clinical trial 5257

Primary endpoint: change from baseline to Week 16 in target-to-background ratio (TBR) from the ascending aorta

Adalimumab
Placebo

Week 16
Baseline (Day 0)

1:1
N=107, 4 sites in Canada

FDG-PET

Phase 4 study: Effect of adalimumab on vascular inflammation in patients with psoriasis

Baseline demographics

Vascular inflammation (ascending aorta)

Mean maximum TBR

Baseline
Week 16

Placebo
ADA

Before treatment
52 weeks of treatment

No difference in vascular inflammation over 16 weeks for patients treated with adalimumab or placebo

• Modest increase in vascular inflammation in carotid arteries after 52 weeks of treatment with adalimumab

• However, a difficult area to measure without contrast enhancement

Vascular and systemic inflammation assessed by 18FDG-PET/CT following treatment with ustekinumab in Korean patients with psoriasis

Effect of systemic and biologic drug treatment on carotid intima-media thickness in patients with moderate to severe psoriasis

- Biologics may decrease CVD – data are conflicting
- Observational study of 53 psoriatic patients assigned to either ustekinumab or methotrexate
- There was a trend towards decreased IMT values for patients treated with biologic drugs with a significant decrease in levels of glucose and insulin


Effect of MTX on IMT

Effect of UST on IMT

VIP-U: Phase 4, randomized, double-blind, placebo-controlled trial of the effect of ustekinumab for psoriasis on aortic vascular inflammation

- **Objectives:**
  -1,153 patients
  - Double-blind, placebo-controlled trial
  - Randomized, parallel-group design
  - Efficacy, safety, tolerability
  - For up to 52 weeks

- **Outcomes:**
  - Baseline demographics
  - Psoriasis outcomes
  - 18FDG-PET/CT total aortic vascular inflammation at Week 12

- **Randomization:**
  - Ustekinumab (n=22)
  - Placebo (n=21)

- **Double-blind period:**
  - 12 weeks

- **Open-label period:**
  - 64 weeks

- **Key endpoints:**
  - Global change in total aortic vascular inflammation compared with placebo at Week 12
  - Primary endpoint: Global change in total aortic vascular inflammation compared with placebo at Week 12

- **Physician-reported psoriasis endpoints (Week 12):**
  - PASI 75, n (%): 2 (10.5) vs 17 (77.3), P<0.001
  - PGA clear/almost clear, n (%): 2 (10.5) vs 14 (63.6%), P=0.001

- **Secondary endpoints:**
  - Change in aortic vascular inflammation:
    - Mean % change vs baseline (95% CI): −6.6 (−13.6 to 0.5) vs 12.1 (3.3 to 20.9), P=0.07 vs 0.010
  - Global change vs placebo (95% CI): −18.7 (−29.5 to −7.8), P=0.001

- **Inclusion criteria:**
  - ≥18 years
  - BSA ≥10%, PASI ≥12
  - Diagnosis of psoriasis ≥6 months, stable for 2 months
  - Candidate for systemic therapy

- **Exclusion criteria:**
  - Recent treatment with biologics
  - Active infection
  - History of malignancy

- **Safety monitoring:**
  - Regular assessments for adverse events
  - Laboratory tests

- **Conclusion:**
  - Ustekinumab shows promise in reducing aortic vascular inflammation in patients with psoriasis.

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VIP-S: Effect of secukinumab on aortic vascular inflammation in moderate to severe plaque psoriasis

- **Objectives:**
  - Randomized, double-blind, placebo-controlled trial
  - Secukinumab (n=46)
  - Placebo (n=45)

- **Double-blind period:**
  - 12 weeks

- **Open-label period:**
  - 64 weeks

- **Key endpoints:**
  - Total aortic vascular inflammation at Week 12
  - Primary endpoint: Neutral effect on aortic vascular inflammation at 12 weeks compared with placebo

- **Secondary endpoints:**
  - No clinically significant changes in cardiometabolic biomarkers
  - VIF analysis may be inappropriate readouts for cardioprotective actions of psoriasis therapies

- **Conclusion:**
  - Secukinumab does not significantly affect aortic vascular inflammation in moderate to severe plaque psoriasis.
IHOPE: Prospective, population-based study to determine all-cause mortality rate based on objective measures of psoriasis severity

The Health Improvement Network (THIN)
- Electronic medical records database in the UK
- Over 10 million individuals
- Broadly representative of the population
- Information entered by GPs

Study design and analysis
- Exposure: physician-confirmed diagnosis of psoriasis
- Outcome: death, from any cause (PPV >99%)
- Cox proportional hazards model
  - Start: survey (sent starting in 2/2009)
  - End: death, transfer out of a practice or end of data collection period (2/2015)
  - Average follow-up time: 4.25 years
- Covariates: age, sex, smoking, alcohol use, Charlson Comorbidity Index

Incident Health Outcomes and Psoriasis Events (iHOPE) cohort
- Psoriasis patients randomly selected from THIN (aged 25–64 years)
- Survey sent to GP
  - Confirm diagnosis
  - Assess extent of disease at last visit
  - 95.7% response rate
- Controls matched 10:1 for age category and GP practice

Summary
- Effective treatment of moderate-to-severe psoriasis may reduce the risk of MI, stroke and death.
- More corroborating studies, both epidemiological and mechanistic, are needed.

Questions
- What length of time is required for any given cardioprotective treatment in order to realize benefit?
- What degree of treatment response is required to assume there is cardioprotective benefit?
- Is cardioprotective benefit from treatment reserved for only specific ranges of severity?
- To what extent do the presence of one or multiple comorbidities (psoriatic arthritis, obesity, diabetes, etc.) mandate systemic, cardioprotective therapy?
  - For example, would lower skin severity with psoriatic arthritis be equivalent to higher skin severity without psoriatic arthritis?
- Will all biologics/effective therapy provide similar benefit?

Patients with BSA >10% had an increased risk of death vs age- and sex-matched adults without psoriasis.

Results were robust to adjustment for the Charlson Comorbidity Index, suggesting underlying medical comorbidities are not solely responsible for increased risk.

Preventive efforts should be targeted to psoriasis with BSA >10%.

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- Will all biologics/effective therapy provide similar benefit?
Thank you

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