Psoriasis: a systemic disease beyond the skin. Treating the skin or the patient?

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Conflict of interest

➢ I have received honorarium from Abbvie, GSK, Genesis-Pharma, Janssen-Cilag, LEO, MSD, Novartis, Pfizer and UCB for my participation as a speaker in satellite symposia, educational workshops or advisory boards

➢ I participated as an investigator in clinical trials conducted by Abbvie, MSD, Pfizer, Novartis, Amgen, Janssen-Cilag

➢ I have received honorarium from Novartis for this presentation
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- This presentation is accurate at the time of presentation.
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Psoriasis Is a Chronic, Disabling Disease

Affects 2–4% of population, more than 125 millions worldwide
• ~20% suffer from moderate to severe disease

Characterized by red, scaly plaques that are itchy and vary in severity from localized areas to complete body coverage

Manifestations of psoriasis include functional limiting sites such as palms and soles, scalp, nails, genital regions and body folds

Genetic and Environmental Factors Trigger Keratinocytes to Release Proinflammatory Cytokines

Genetic Predisposition

- Multiple genetic loci linked to psoriasis

Epidermal stress and inflammation

- Proinflammatory cytokines leading to dermal inflammation

Proliferation of keratinocytes

Psoriasis

Environmental Factors

- Systemic triggering factors in predisposed individuals

Elder JT, et al. JID 2010;130:1213
Traditional Model of Psoriasis Immunopathogenesis

**Initiation**
- **Keratinocyte**
  - TNF-α
  - IL-1β
  - IL-6
  - TNF-α
- **Natural killer T cell**
  - IFN-γ
- **Plasmacytoid dendritic cell**
  - IFN-α
- **Myeloid dendritic cell**
  - TNF-α

**Activation**
- **Th1 cell**
  - TNF-α
  - IFN-γ
- **Keratinocyte**
  - IL-12

**Perpetuation**
- **Th1 cell**
  - IL-17A
  - IL-17F
  - IL-22
- **Keratinocyte**
  - IL-1β
  - IL-6
  - TNF-α
  - S100
  - CXCL8
  - CXCL9
  - CXCL10
  - CXCL11
  - CCL20

Modified from: Nestle FO, et al. NEJM 2009;361:496
Psoriasis: clinical features

- Guttate psoriasis
- Plaque psoriasis
- Palmoplantar psoriasis
- Scalp psoriasis
Plaque psoriasis

- Most common variant (80%)
- Sharply defined erythematous, silvery scaly plaques (scalp, elbows, knees, buttocks)

Auspitz sign (pinpoint bleedings)

«Signe de la tache de bougie» (scratche on a wax candle)
Guttate psoriasis

- Young adults
- 2-4 weeks after strep infection
- Generalized (mainly on the trunk)

Photos from personal archive
Pustular psoriasis

Erythrodermic psoriasis

Psoriatic arthritis

Nail psoriasis
Erythrodermic and Generalized Pustular psoriasis

➢ Generalized erythema and scaling (onset acute or gradual)
➢ Skin painful, fever, patient feels ill
➢ Triggering factors: acute cessation of systemic steroids, infections, hypocalcemia, pregnancy
➢ AE: electrolytes disorder, temperature disorders, heart failure
➢ Needs hospitalization

➢ Generalized eruption with erythema and pustulation (Zumbusch pattern)
➢ Skin painful, fever, patient feels ill
➢ Triggering factors: same as in erythrodermic
➢ Severe, needs hospitalization
Genital psoriasis

Special localizations

Inverse psoriasis
Palmoplantar plaque psoriasis

mild

severe

Photos from personal archive
Clinical features specific to children:
- face involvement
- guttate / inverse psoriasis more often
- smaller plaques / thinner scale
- diaper rash is quite specific

Amode R et al. JEADV 2015,
Features of psoriasis strongly related with PsA

Scalp psoriasis
HR 3.89
95% CI (2.18-6.94)

Nail psoriasis
HR 2.93
95% CI (1.68-5.12)

Perianal or intrabuttock area
HR 2.35
95% CI (1.32-4.19)

CI, confidence interval; HR, hazard ratio.

Patient with all 3 clinical features

Photos from personal archive
Nail psoriasis

- 20-60% in patients with psoriasis
- 50% ☻ 50% ☼
- 80%-90% in patients with PsA
- Only nail psoriasis is rare (1-5%)

Nail psoriasis

27%
Only upper extremities

16%
Only lower extremities

57%
In both upper and lower extremities

1 or more nails
mean > 5,9 fingernails
> 5,2 toenails

Nail bed

Splinter haemorrhages

Subungual hyperkeratosis

Oil drop

Onycholysis

Nail psoriasis

Photos from personal archive
Psoriatic Arthritis is a Chronic, Heterogeneous Immune-Mediated Arthropathy Associated with Psoriasis

- Approximately 30–40% of psoriasis patients will develop PsA
- Age of onset: ~20 to 60 years
- Male/female ratio 1:1
- Skin psoriasis typically manifests prior to articular disease
  - The lag time of from the onset of psoriasis to diagnosis of PsA is approximately 7–12 years
- Nail dystrophy is considered to be a clinically significant predictor of PsA; it is reported in 63% to 83% of PsA patients
- Axial joints are affected in up to 40% of PsA patients

Nail psoriasis is strongly related with subclinical enthesopathy in early stages

Enthesopathy is one of the early findings of PsA

Psoriasis patients with nail disease have a greater magnitude of underlying systemic subclinical enthesopathy than those with normal nails
Psoriasis and PsA

- Prevalence: 6 – 24%
- Patients with both Ps and PsA have worst QoL that patients with Ps only

Cumulative risk of manifestation of PsA

<table>
<thead>
<tr>
<th>Time</th>
<th>Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years</td>
<td>1.7%</td>
<td>1.0 - 2.3%</td>
</tr>
<tr>
<td>10 years</td>
<td>3.1%</td>
<td>2.2 - 4.1%</td>
</tr>
<tr>
<td>20 years</td>
<td>5.1%</td>
<td>3.7 - 6.6%</td>
</tr>
</tbody>
</table>

Psoriasis and Comorbidities

- **Psoriatic arthritis 5%–40%**
  - Spondyloarthropathies

- **Ocular inflammation**
  - (Iritis/Uveitis 7-20%/Episcleritis)

- **Crohn’s disease 0.5–1%**
  - Ulcerative colitis 0.4%

- **Non-alcoholic fatty liver disease**

- **Nail psoriasis 40%–50%**

- **Metabolic syndrome 26–44% (severe Ps)**
  - Arterial hypertension 9–44%
  - Dyslipidaemia 6.5–50%
  - Insulin-resistant diabetes 2.5–37%
  - Obesity 22–37%
  - ⇒higher CVD risk (coronary disease ⇒4–8%)

- **Psychosocial burden**
  - Reactive depression 10–62%
  - Higher suicidal ideation
  - Alcoholism

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References:
Is there a psoriatic march that leads to comorbidities and irreversible changes?

Psychological Impact of Psoriasis Similar to Other Chronic Diseases

Conditions assessed by SF-36 Mental Component Score
Lower score indicates more disability
**Psoriasis beyond the skin: an expert group consensus on the management of psoriatic arthritis and common co-morbidities in patients with moderate-to-severe psoriasis**


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<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>Prevalence in psoriasis</th>
<th>Hazard*/odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriatic arthritis</td>
<td>8–73%10–14</td>
<td>–</td>
</tr>
<tr>
<td>Psychological co-morbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>15–62%21,22</td>
<td>1.39∗–1.4919,20</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>15–30%26–29</td>
<td>3.10–3.6129,31</td>
</tr>
<tr>
<td>Smoking</td>
<td>30–51%12,30</td>
<td>1.31–2.9630–32</td>
</tr>
<tr>
<td>Cardiovascular co-morbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>8–41%12,30,50,51</td>
<td>1.18–5.4934</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7–41%12,30,50</td>
<td>1.20–2.8034</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>16–40%12,52</td>
<td>1.30–5.9234</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13–50%21,30,50,53,54</td>
<td>1.09–3.2734</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>6–61%2,30,53,54</td>
<td>1.00–2.0934</td>
</tr>
</tbody>
</table>
People with psoriasis suffer from multiple medical and psychological comorbidities

Risk of Comorbid Diseases is Greater Among Patients with More Severe Psoriasis

Phenotype of a typical Ps patient

Metabolic Syndrome:
(at least 3 of 5)

1. **Hypertension**
   (BP >130/85 mmHg) or under medication

2. **Increased TG levels**
   (>150mg/dl) or under medication

3. **Low HDL**
   (♂<40mg/dl; ♀<50mg/dl) or under medication

4. **Fasting Glu** > 100mg/dl or under medication

5. **Central obesity**
   (waist circ ♂>102cm; ♀>88cm)

National Heart, Lung, and Blood Institute (NHLBI)
American Heart Association (AHA)
Myocardial Infarction Is a Risk in Patients With Severe Psoriasis

Gelfand JM et al. JAMA. 2006;296:1735-1741.
Compared to Controls Without Psoriasis, Patients With Psoriasis Have an Increased Incidence of Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mild Group</th>
<th>Severe Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n = 496,666)</td>
<td>Psoriasis (n = 129,143)</td>
</tr>
<tr>
<td>Follow-up time, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>4.2 ± 3.3</td>
<td>4.4 ± 3.3</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>3.5, 1.5, 6.6</td>
<td>3.7, 1.6, 6.9</td>
</tr>
<tr>
<td>Number of subject-years</td>
<td>2,108,718</td>
<td>570,815</td>
</tr>
<tr>
<td>Number of new stroke cases (%)</td>
<td>8535 (1.72%)</td>
<td>2100 (1.63%)</td>
</tr>
<tr>
<td>Incidence per 1000 subject-years (95% CI)</td>
<td>4.05 (3.96, 4.13)</td>
<td>3.68 (3.52, 3.84)</td>
</tr>
</tbody>
</table>

Gaps in Diagnosis and Treatment of Cardiovascular Risk Factors in Patients with Psoriatic Disease: An International Multicenter Study

Lihi Eder, Paula Harvey, Vinod Chandran, Cheryl F. Rosen, Jan Dutz, James T. Elder, Proton Rahman, Christopher T. Ritchlin, Sherry Rohekar, Richard Hayday, Snezana Barac, Joy Feld, Devy Zisman, and Dafna D. Gladman

**ABSTRACT.** *Objective.* We aimed to estimate the proportion of underdiagnosis and undertreatment of cardiovascular risk factors (CVRF) in an international multicenter cohort of patients with psoriasis and psoriatic arthritis (PsA).

*Methods.* A cross-sectional analysis was conducted of patients with psoriatic disease from the

**Conclusion.** In real-world settings, a large proportion of patients with psoriasis and PsA were underdiagnosed and undertreated for HTN and dyslipidemia. Strategies to improve the management of CVRF in psoriatic patients are warranted. (J Rheumatol First Release February 1 2018; doi:10.3899/jrheum.170379)

**Results.** A total of 2234 patients (68.3% PsA, 31.7% psoriasis) from 8 centers in Canada, the United States, and Israel were included. Their mean age was 52 ± 13.8 years and 53% were men. Of the patients, 87.6% had at least 1 modifiable CVRF, 45.1% had HTN, 49.4% dyslipidemia, 13.3% diabetes, 75.3% were overweight or obese, 54.3% central obesity, and 17.3% were current smokers. We found 59.2% of patients with HTN and 65.6% of patients with dyslipidemia were undertreated. Undertreatment was associated with younger age (≤ 50 yrs), having psoriasis, and male sex.

**Conclusion.** In real-world settings, a large proportion of patients with psoriasis and PsA were underdiagnosed and undertreated for HTN and dyslipidemia. Strategies to improve the management of CVRF in psoriatic patients are warranted. (J Rheumatol First Release February 1 2018; doi:10.3899/jrheum.170379)
Evidence of systemic inflammation in patients with psoriasis

Images courtesy of N.N.M., National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA.

Suggested Treatment Goals in Psoriasis According to European Guidelines

• Clear skin and increased quality of life are important to patients and both are reflected in current treatment goals:

- **ΔPASI <50%**
  - DLQI >5
  - Inadequate response*: Modify treatment
    - Modification Strategies:
      - Increase the dose
      - Reduce dose intervals
      - Combination therapy
      - Change the drug

- **ΔPASI 50–75%**
  - DLQI ≤5
  - Adequate response: Continue treatment

- **ΔPASI ≥75%**

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Significant Advances in the Treatment of Psoriasis

**Approval in Psoriasis**

- Goeckerman Regimen
- Topical steroids
- UVB/PUVA
- Methotrexate
- Retinoids
- Topical vitamin D
- Fumaric acid esters
- Cyclosporine
- TNF inhibitors
- IL-12/IL-23 inhibitors
- PDE4 inhibitors
- IL-17 inhibitors

Timeline:
- 1920
- 1970
- 1990
- 2000
- 2020
Overview of modern targeted treatments

- **Ustekinumab**
  - IL-12/23 inhibitor

- **Secukinumab**
- **Ixekizumab**
- **Brodalumab**
  - IL-17 pathway inhibitors

- **Guselkumab**
- **Tildrakizumab**
- **BI 655066**
  - IL-23 inhibitors
Conclusions

Our data provide pathophysiological evidence that anti-inflammatory biologic treatment may prevent asymptomatic coronary atherosclerosis progression in patients with moderate-to-severe psoriasis.
ORIGINAL ARTICLE

Anti-tumor necrosis factor-alpha therapy improves endothelial function and arterial stiffness in patients with moderate to severe psoriasis: A 6-month prospective study

Trinitario PINA,¹,† Alfonso CORRALES,¹,† Raquel LOPEZ-MEJIAS,¹ Susana ARMESTO,² Marcos A. GONZALEZ-LOPEZ,² Ines GÓMEZ-ACEBO,³ Begoña UBILLA,¹ Sara REMUZGO-MARTÍNEZ,¹ M. Carmen GONZALEZ-VELA,⁴ Ricardo BLANCO,¹ Jose L. HERNÁNDEZ,⁵ Javier LLORCA,²,‡ Miguel A. GONZALEZ-GAY¹,‡

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journal homepage: www.elsevier.com/locate/atherosclerosis

Treatment with tumor necrosis factor inhibitors restores coronary microvascular function in young patients with severe psoriasis

Stefano Piaserico a,¹, Elena Osto b,¹, Giulia Famoso c, Irene Zanetti a, Dario Gregori c, Anna Poretto c, Sabino Iliceto c, Andrea Peserico a, Francesco Tona c,∗
Cardiovascular disease event rates in patients with severe psoriasis treated with systemic anti-inflammatory drugs: a Danish real-world cohort study

O. Ahlehoff¹,², L. Skov³, G. Gislason¹, J. Lindhardsen¹, S. L. Kristensen¹, L. Iversen⁴, S. Lasthein⁵, R. Gniadecki⁶, T. N. Dam⁷, C. Torp-Pedersen¹ & P. R. Hansen¹

Our results indicate that treatment with biological agents or methotrexate is associated with reduced risk of death and cardiovascular disease events in patients with severe psoriasis. It is interesting that
Secukinumab Reduces Endothelial Dysfunction in Subjects with Moderate to Severe Plaque Psoriasis Over 52 Weeks: Results of the Exploratory CARIMA Study

E von Stebut¹, K Reich², D Thaçi³, W Koenig⁴a–c, A Pinter⁵, A Körber⁶, T Rassaf⁶,⁷, A Waisman¹, V Mani⁸, D Yates⁹, J Frueh¹⁰, C Sieder¹¹, N Melzer¹¹, T Gori¹

¹University Medical Center Mainz, Germany; ²Dermatologikum Hamburg and SCIderm Research Institute, Germany; ³University Hospital Schleswig-Holstein, Germany; ⁴aUniversity of Ulm Medical Center Ulm, Germany; ⁴bDeutsches Herzzentrum München, Germany; ⁴cTechnische Universität München, Germany; ⁵University Hospital Frankfurt, Germany; ⁶University Hospital Essen, Germany; ⁷Dept of Cardiology and Vascular Medicine, West-German Heart and Vascular Center, Germany; ⁸Icahn School of Medicine at Mount Sinai, New York, USA; ⁹Novartis Institutes for Biomedical Research, USA; ¹⁰Novartis Pharma AG, Basel, Switzerland; ¹¹Novartis Pharma GmbH, Nürnberg, Germany
Multidisciplinary approach to the patient with severe psoriasis

Thank you for your attention!!