Anti-TNF-Induced Dermatological Complications

Hermenio Lima, MD PhD  
FRCPC  
Division and Post-Grad Program Director of Dermatology  
Clinical Immunologist and Dermatologist  
Associate Clinical Professor of Dermatology  
McMaster University - Hamilton, Ontario  
Email: hlima@mcmaster.ca
Disclosures

• In accordance with the requirements of the General Code of Conduct.
  – Grant/Research Support:
    • Celgene, La Roche-Posay, Novartis.
  – Clinical Trials:
    • AbbVie (Abbott), Amgen, AstraZeneca, Bristol-Myers Squibb, Dermira, Eli Lilly, Janssen Research, Merck Sharp & Dohme, Novartis*, Pfizer, Regeneron*, Sanofi.
  – Speaker’s Bureau:
    • AbbVie, Novartis.
  – Consultant / Ad board:
    • AbbVie, Celgene, Novartis, Leo Pharmaceutics.

* Active clinical trials
LEARNING OBJECTIVES
Learning Objectives

• Discuss the dermatologic manifestations of anti-TNF therapy
  – Present a literature-based review of cutaneous reactions reported with anti-TNF treatment
  – Discuss their clinical presentation
  – Provide frequency of such reaction
  – Describe possible pathogenic mechanisms.
Skin manifestations are a common complication of inflammatory diseases.

**Table 2. Non-specific cutaneous manifestations of Crohn’s disease (CD)**

<table>
<thead>
<tr>
<th>Reactive cutaneous manifestations with immunological mechanisms related to CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aphthous stomatitis</td>
</tr>
<tr>
<td>Erythema nodosum</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
</tr>
<tr>
<td>Sweet’s syndrome</td>
</tr>
<tr>
<td>Bowel-associated dermatosis-arthritis syndrome (BADAS)</td>
</tr>
<tr>
<td>Pyostomatitis vegetans</td>
</tr>
<tr>
<td>Leucocytoclastic vasculitis</td>
</tr>
</tbody>
</table>

**Autoimmune cutaneous disorders associated with CD**

<table>
<thead>
<tr>
<th>Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary amyloidosis</td>
</tr>
<tr>
<td>Vitiligo</td>
</tr>
<tr>
<td>Acquired epidermolysis bullosa</td>
</tr>
<tr>
<td>Alopecia areata</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
</tbody>
</table>

**Secondary cutaneous manifestations/complications**

| Acrodermatitis enteropathica (zinc deficiency) |
| Purpura, angular cheilitis, hair and nail abnormalities |
Skin lesions induced by tumour necrosis factor inhibitors (TNFIs).

• Late 1990s, tumour necrosis factor inhibitors (TNFIs) introduced as Rx for inflammatory disorders.

  Hanauer, S. B. et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. The Lancet 359, 1541-1549,

• TNFIs have favourable safety profile when well indicated and comorbidities are taken into account.

True or False

• Skin conditions induced by TNFIs were reported in post-marketing surveillance and risk assessment programs (phase IV studies).
Cutaneous reaction associated with TNFIs

- First cases reported CD patient treated with infliximab
- Described with all the TNFIs: class effect
- Described in patients receiving treatment for diverse indications
  - (RA, IBD, psoriasis, psoriatic arthritis, ankylosing spondylitis and recently with HS)
- May lead to therapy discontinuation

Increasingly recognized side-effect of anti-TNF therapy in the literature

Ref:
Denadai, R., et al., Induction or exacerbation of psoriatic lesions during anti-TNF-α therapy for inflammatory bowel disease: A systematic literature review based on 222 cases. Journal of Crohn's and Colitis, 2012. 7(7): 517-524.
Skin adverse events in patients treated with TNFIs are classified as

- Local or systemic related to treatment
- Skin infection
- Malignancy
- Immune mediated
Skin adverse events

- **Local or systemic**
  - Infusion reaction
  - Injection site reaction

- **Skin infection**

- **Malignancy**

- **Immune**

Injection site reaction with the use of adalimumab.

**REF:** Mocci, G., et al., Dermatological adverse reactions during anti-TNF treatments: Focus on inflammatory bowel disease. Journal of Crohn’s and Colitis, 2013. 7(10): 769-779
Skin adverse events

- Local or systemic
- **Skin infection**
  - Bacterial cellulitis, erysipelas, abscess
  - HSV, VZV, CMV, HPV, MCV
  - Candida species
- Malignancy
- Immune.

Infections associated with anti-TNFalpha Rx

**REF:** Atzori, M.L.L., Cutaneous Adverse Reactions during Anti-Tnf Alpha Treatment for Inflammatory Bowel Diseases: The Experience of the Dermatology Clinic of Cagliari. Journal of Pharmacovigilance. 2015.
• Local or systemic
• Skin infection
• **Malignancy**
  – Melanoma and non-melanoma skin cancer
• **Immune.**

Hazard ratios (95% CI) for SSC and BBC

Skin adverse events

- Local or systemic
- Skin infection
- **Malignancy**
  - Melanoma and non-melanoma skin cancer
- Immune.

Pigmented BCC mimicking melanoma, typical BCC, Bowen’s

**REF:**


Skin adverse events

- Local or systemic
- Skin infection
- Malignancy
- Immune
  - Psoriasiform
Skin adverse events

• Local or systemic
• Skin infection
• Malignancy
• **Immune**
  – Psoriasiform
  – Pustular palmo-plantar psoriasis
Activation of autoreactive T-cells by IFNα.

- Source of IFNα is in the plasmacytoid dendritic cells.
- T-cells are recruited by IFNα-mediated upregulation of CXCR3 on T-cells.
- IFNα also activates the secretion of IL-12 and IL-23.

TNFIs induced PsO
Hypothesis II

Skin adverse events

- Local or systemic
- Skin infection
- Malignancy
- **Immune**
  - Psoriasiform
  - Pustular palmo-plantar psoriasis
  - Eczema like lesions
Skin adverse events

- Local or systemic
- Skin infection
- Malignancy
- Immune
  - Psoriasiform
  - Pustular palmo-plantar psoriasis
  - Eczema like lesions
  - Acneiform eruption
Skin adverse events

• Other Immune mediated reactions
  – Cutaneous lupus, lupus-like syndrome
  – Cutaneous vasculitis
  – Erythema multiforme
  – Stevens Johnson syndrome
  – Toxic epidermal necrolysis
  – Alopecia

• Other Immune mediated reactions
  – Cutaneous lupus, lupus-like syndrome
  – Cutaneous vasculitis
  – Erythema multiforme
  – Stevens Johnson syndrome
  – Toxic epidermal necrolysis
  – Alopecia

As the use of TNFIs continues to increase the diagnosis and management of cutaneous side-effects will become an increasingly important challenge.

- Counsel your patients about signs and symptoms of cutaneous reactions
- Advise properly about sun protection
- Refer patients to the Dermatologist