Immunotherapy side effects: Recommendations for management

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Disclosures

• **Advisory Board:** Abbvie, Boehringer Ingelheim, Bristol Myers Squibb, Roche-Genentech, Lilly, Merck

• **Steering Committee Member:** Bayer, Bristol Myers Squibb, Janssen, Roche-Genentech, Xcovery

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irAEs with Immunotherapy

Eye:
- Uveitis
- Iritis

Endocrine
- Hypo or hyper-thyroidism
- Adrenal insufficiency
- Hypophysitis

Skin
- Dermatitis exfoliative
- Vitiligo
- Alopecia
- Pruritis

Gastrointestinal
- Colitis
- Hepatitis

Neurologic
- Autoimmune neuropathy
- Guillain-Barre
- Encephalitis

Cardiac
- Myocarditis

Pulmonary
- Pneumonitis

Renal
- Nephritis

Average is 6-12 wks after initiation of therapy Can occur within days of the first dose, after several months of treatment, and after discontinuation of therapy.
# PD-1 Checkpoint Inhibition Phase III Trials - Toxicities

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Rx-Related AEs – All &amp; Grade 3/4</th>
<th>Most Common Rx-Related AEs</th>
<th>Pneumonitis Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Checkmate 017</td>
<td>Nivolumab</td>
<td>58% 7%</td>
<td>Fatigue – 16% appetite – 11% Asthenia – 10%</td>
<td>All – 5% Gr 3/4 – 0%</td>
</tr>
<tr>
<td>Checkmate 057</td>
<td>Nivolumab</td>
<td>69% 10%</td>
<td>Fatigue – 16% Nausea – 12% appetite – 10%</td>
<td>All – 3% Gr 3/4 – 1%</td>
</tr>
<tr>
<td>Keynote 010</td>
<td>Pembrolizumab 2 mg/kg dose</td>
<td>63% 13%</td>
<td>Fatigue – 20% Pruritis – 11% appetite – 11%</td>
<td>All – 5% Grade 3-5 – 2% 2 deaths</td>
</tr>
<tr>
<td>OAK</td>
<td>Atezolizumab</td>
<td>64% 15%</td>
<td>Fatigue - 25% Nausea – 18% Diarrhea – 15%</td>
<td>All – 1% Grade 3-4 – 0.7%</td>
</tr>
</tbody>
</table>

Not all Immune-related side effects are listed in the CTCAE and grades may not clearly define the severity of the side effects

Awareness Is Key

- Immune-related side effects are similar across PD-1/PD-L1 checkpoint inhibitors

- Incidence varies by agent(s) and may also vary by disease.

- Combinations of immunotherapy agents are likely to have higher incidence of immune-related side effects than single agents.

- Immune-related side effects can occur during treatment or weeks to months after discontinuation.

  Early recognition and differential diagnosis is paramount
Frequency of Immune-Mediated Toxicities

Occasional (5% to 20%)

- **Fatigue**, headache, arthralgia, fevers, chills, lethargy
- **Rash**: maculopapular, pruritus, vitiligo
  - Topical treatments
- **Diarrhea/colitis**
  - Initiate steroids early, taper slowly
- Hepatitis, liver/pancreatic enzyme abnormalities
- Infusion reactions
- **Endocrinopathies**: thyroid, adrenal, hypophysitis

Rare (< 5%)

- **Pneumonitis**
  - Grade 3/4 toxicities uncommon
  - Low grade reversible with steroids and discontinuation
- Anemia

Kinetics of Appearance of irAEs With Checkpoint Blockade

- Data from pts receiving anti–PD-1 antibodies q2w for ≥ 3 yrs show most irAEs occur by Wk 24 (6 mos)
- Toxicities with PD-1/PD-L1 agents may take longer to resolve than with ipilimumab, so long-term surveillance is recommended

### Time to Onset of First Treatment-related Select AE With Nivolumab by Category (Any Grade)

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Number of Patients with First Event in Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3</td>
<td>131</td>
</tr>
<tr>
<td>&gt;3–6</td>
<td>112</td>
</tr>
<tr>
<td>&gt;6–12</td>
<td>85</td>
</tr>
<tr>
<td>&gt;12–24</td>
<td>52</td>
</tr>
</tbody>
</table>

- **Pts still on study, n**: 131
- **Pts still on treatment, n**: 131
- **Total pts with first event, a**: 124

The majority of patients who experienced treatment-related select AEs with nivolumab experienced their first event within the first 3 months of treatment.

**Select AEs**: AEs with potential immunologic etiology that require frequent monitoring/intervention.

Based on December 2014 DBL. Includes events reported between first dose and 30 days after last dose of study therapy.

Within each time interval, patients with ≥1 event were counted only once in each category but could be classified into more than one category.

*Reckamp et al., WCLC 2015*
Immune Adverse Events

• Onset:
  • Average is 6-12 wks after initiation of therapy
  • Can occur within days of the first dose, after several mos of treatment, and after discontinuation of therapy

• Pt complaints are autoimmune and drug related until proven otherwise
  • Rule out infections, metabolic causes, tumor effects, etc

• Early recognition, evaluation, and treatment are critical
Toxicity Guidelines for Immune Checkpoint Inhibitors

- TFTs, CBCs, LFTs and metabolic panels should be obtained at each treatment and q6-12 wks for 6 mos posttreatment in all pts receiving checkpoint protein antibodies.
- ACTH, cortisol should also be checked in pts with fatigue and nonspecific symptoms, plus testosterone in men.
- Frequency of follow-up testing should be adjusted to individual response and AEs that occur.
- Corticosteroids can reverse nearly all toxicities associated with these agents, but should be reserved for grade 3/4, or prolonged grade 2, infusion-related AEs (irAEs).

Endocrinopathies

• Hypo or hyperthyroidism most common
• Monitor TSH routinely
• If out of range for two consistent measurements, then add Free T4 as clinically indicated
• Continue treatment with immunotherapy while treating thyroid disease ie hormone replacement for hypothyroidism and Propylthiouracil or methimazole for symptomatic hyperthyroidism
• Hyperthyroidism will turn into hypothyroidism at some point

Presented by: Julie R. Brahmer, M.D., M.Sc.
Case One

46 year old, Caucasian male smoker with stage IV non-small cell lung cancer, adenocarcinoma histology, pan mutation negative is on a first line trial with nivolumab and ipilimumab. He comes into clinic with nausea, fatigue and states he feels like “he is going to die”

What is the differential diagnosis?

1. Treatment related fatigue
2. Anemia
3. Autoimmune thyroiditis or Hypophysitis
4. Treatment-related Fatigue, Hypophysitis, Hypothyroidism, Autoimmune thyroiditis
5. Hypophysitis or Hypothyroidism
Case One Continued

He is admitted to hospital for evaluation. CBC and CMP unremarkable. TSH is 22 (normal ), ACTH is (normal) and Testosterone is 20 (normal ). What do you do?

1. Start hydrocortisone, thyroid and testosterone replacement
2. Start prednisone
3. Consult endocrinology
4. Do nothing it will improve on its own if he holds his treatment
5. Obtain MRI of pituitary glad
Symptom Management: Hypophysitis

- Prompt therapy ameliorates symptoms and permits continued therapy
- 25% of pts with hypophysitis have normal pituitary MRI

**Diagnostic Workup:**
- Serial TSH, FT4 +/- T3
- MRI pituitary for suspected hypophysitis

**Management**
- Endocrine consultation
- Hormonal replacement
- Physiologic steroid replacement may be sufficient
- Higher-dose in symptomatic pts (headaches and vision changes)
# Endocrine Issues

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade 2</th>
<th>Grade 3 or Grade 4</th>
<th>Withhold or discontinue and administer corticosteroids and hormone replacement as clinically indicated</th>
<th>Withhold and administer corticosteroids and hormone replacement as clinically indicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophysitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Administer replacement hormones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Manage with thionamides and beta-blockers as appropriate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>Administer insulin for type 1 diabetes, and withhold KEYTRUDA and administer anti-hyperglycemics in patients with severe hyperglycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case Two Immune-Related Dermatitis

76 year old woman with metastatic squamous cell lung cancer on anti-PD1 therapy for 14 months with partial response to therapy. Initially she reports itchy palms on therapy. At week 64 she develops rash on therapy over arms and legs that is pruritic.

What do you do?

1. Continue medication and monitor
2. Start high dose oral steroids
3. Hold therapy and monitor
4. Continue medication with high dose steroids
5. Refer to dermatology
Case Two Immune-Related Dermatitis

Her treatment is held for four weeks and she is given topical steroids. She resumes therapy and develops a more diffuse rash that is not pruritic.

What do you do?

1. Continue medication and monitor
2. Start high dose oral steroids
3. Hold therapy and monitor
4. Continue medication with high dose steroids
5. Refer to dermatology
Immune-related Dermatitis

- Most common AE
- 20-40% of patients receiving an anti-PD-1 agent
- Grade 3/4 are rare
- < 5% cases lead to treatment discontinuation

- **Grade 1**: Asymptomatic, <10% BSA
  - Topical steroid/oral antihistamines
- **Grade 2**: Symptomatic, 10-20% BSA,
  - Hold Tx
  - Oral steroid/antihistamines
- **Grade 3+**: Severe, >30% BSA
  - Derm consult, Skin biopsy
  - Hospitalize/IV fluid/burns unit

Naidoo et al, Ann Oncol 2015
Case Three

68 year old male with stage IV non-small cell lung cancer, adenocarcinoma histology, pan mutation negative, PD-L1 80%. He is started on pembrolizumab. He comes to clinic with abdominal pain, cramping, and 6-7 bowel movements a day for the last 3 days

What do you do?

1. Check stool cultures, ova and parasites, rule out c-dif
2. CT scan of the abdomen
3. GI consult for colonoscopy and biopsies
4. Start methylprednisolone 1-2 mg/kg daily
5. All of the above
6. Give loperamide and send home
Case Three Continued

He is admitted to hospital, started on steroids. A CT scan of the abdomen demonstrates colitis. Biopsies are positive for

He would like to resume therapy as he has been responding. What do you tell him?

1. He can start as soon as he is out of hospital
2. He cannot have the medication again it is not safe
3. He can start once he is off steroids
4. He can start once he is down to prednisone 10 mg daily
Diarrhea: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
<td>Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline</td>
<td>Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Death</td>
</tr>
</tbody>
</table>

NB: Assess severity not only by the number of stools per day, but also by clinical symptoms such as cramping, fever, malaise, blood in stool, etc.
# Autoimmune Hepatitis: Graded by liver function test

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2: AST or ALT &gt; 3.0 to ≤ 5 x ULN and/or T. bili &gt; 1.5 to ≤ 3 x ULN</td>
<td>Hold I-O therapy. Initiate steroids promptly 0.5-1 mg/kg of steroids. Taper over ≥ 4 weeks. Evaluate alternate etiology. Close monitoring</td>
<td>If resolves may consider resuming I-O therapy. Prophylactic antibx &amp; PPI</td>
</tr>
<tr>
<td>Grade 3 / 4: AST or ALT &gt; 5 x ULN and /or T.bili &gt;3 x ULN</td>
<td>Discontinue I-O therapy. Hospitalize. Initiate high dose steroids (1-2 mg/kg). If no improvement in 48-72 hours consider alternate immunosuppressants; Mycophenolate mofetil (Infliximab is NOT used in irAE hepatitis). Evaluate alternate etiology.</td>
<td>If returns to grade 2 taper steroids over ≥ 4 weeks.</td>
</tr>
</tbody>
</table>

Teply,B & Lipson,E. Cancer Network: Oncology Journal: Identification and Management of Toxicities from Immune Checkpoint Blocking Drugs
Hepatitis Management

AST/ALT > 3-5 x ULN or total bilirubin > 1.5 – 3 x ULN
Withhold IO agent and administer steroids
Grade 3 or greater permanently discontinue

AST/ALT ≥ 5 x ULN or > 50% increase from baseline lasting ≥ 1 week in patients with baseline liver dysfunction
Permanently discontinue IO agent and administer steroids
Case Four

54 year old female with stage IV squamous cell lung cancer on second line nivolumb presents to clinic with generalized fatigue and pruritis. Lab work indicates creatinine of 4.8 (previously 0.6)

What do you do?

1. Admit to hospital and start methylprednisolone 1-2 mg/kg daily
2. Consult nephrology
3. Discontinue drug permanently
4. All of the above
# Autoimmune Nephritis: graded by creatinine level

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
<th>Follow up</th>
</tr>
</thead>
</table>
| Grade 1: Creatinine 1-1.5 X ULN | • Continue I-O therapy per protocol  
• Monitor creatinine weekly | If creatinine returns to baseline  
resume routine monitoring.  
If worsens, treat as > Grade 2 |
| Grade 2: Creatinine 1.5-3 X ULN | • Delay I-O therapy per protocol  
• Monitor creatinine every 2-3 days  
• steroids  
• Consider renal biopsy | Taper steroids >1 month,  
prophylactic antibiotics should be renal sparing |
| Grade 3 (>3-6 X ULN) / Grade 4 (>6 X ULN) | Discontinue I-O therapy per protocol  
• Monitor creatinine daily  
• steroids  
• Consult nephrologist  
• Consider renal biopsy | Taper steroids >1 month,  
prophylactic antibiotics should be renal sparing  
Extended follow up |
Case Five

54 year old male, former smoker diagnosed with stage IV squamous cell lung cancer two years prior, treated with carboplatin and gemcitabine, docetaxel, started on therapy with anti-PD-1 antibody. He is responding well to therapy with 60% reduction in disease burden on imaging at 8 weeks. After 6 months of therapy he presents with increasing dyspnea, cough and new oxygen requirement.

What do you do?

1. Order a PFTs in clinic
2. Order a chest CT scan in clinic
3. Add a chest CT scan to next appointment in two weeks
4. Request a pulmonary consult
5. Unsere
Case Five Continued

CT scan shows diffuse ground glass opacities. What do you do?

A. Continue nivolumab and administer steroids
B. Continue nivolumab, administer steroids +/- antibiotics, monitor as an outpatient
C. Discontinued nivolumab administer steroids +/- antibiotics, monitor as an out patient
D. Consulting pulmonary and ensure they are seen within two weeks
Pneumonitis and NSCLC

• Severe drug-related pneumonitis
  • PD-1 Antibody 2%
  • Erlotinib 1.6-4.5%
  • Gefitinib 3.5%
  • Docetaxel 4.6%
  • Gemcitabine 1-2%
  • Pemetrexed – 2 reports in the literature

• Radiation pneumonitis - 13%

• Treatment = Steroids

Pneumonitis Diagnosis in NSCLC is Complicated

• Possible pre-existing poor cardiopulmonary reserve in NSCLC
  • COPD, DVT/PE, tumor effects, pleural/pericardial effusions, infections and cardiovascular disease

• Broad differential of cough, tachypnea, hypoxia with inflammatory – ground glass changes on CT
  • Infection? Pulmonary edema, ? progression? Tumor inflammation? PE?, COPD?

• Stop therapy or continue?
• Early identification, high clinical suspicion, early treatment
Retrospective Study of Pneumonitis

- Retrospective search AE records MSKCC and MIA (Sydney)
- All patients received anti-PD-1/
  - PD-L1 therapy alone, or
  - with anti-CTLA-4 therapy
- Pneumonitis cases identified:
  - Clinico-pathologic data collected
  - Dedicated Radiology Assessment (MSKCC)
  - Pathology review (MSKCC)

<table>
<thead>
<tr>
<th>Pneumonitis Cases vs. Controls</th>
<th>Yes (n=44)</th>
<th>No (n=871)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single agent vs. Combination*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>25 (3%)</td>
<td>693</td>
</tr>
<tr>
<td>Combination</td>
<td>19 (10%)</td>
<td>178</td>
</tr>
<tr>
<td>PD-1 vs. PD-L1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-1</td>
<td>41 (6%)</td>
<td>701</td>
</tr>
<tr>
<td>PD-L1</td>
<td>3 (2%)</td>
<td>170</td>
</tr>
<tr>
<td>Treatment Regimen**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-1 monotherapy</td>
<td>23 (4%)</td>
<td>543</td>
</tr>
<tr>
<td>PD-1 combination</td>
<td>18 (10%)</td>
<td>158</td>
</tr>
<tr>
<td>PD-L1 monotherapy</td>
<td>1 (5%)</td>
<td>20</td>
</tr>
<tr>
<td>PD-L1 combination</td>
<td>2 (1%)</td>
<td>150</td>
</tr>
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</table>

*p=0.001  **p=0.002

<table>
<thead>
<tr>
<th>Complete Patient Database</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (915)</td>
</tr>
<tr>
<td>MSKCC (n=578)</td>
</tr>
<tr>
<td>MIA (n=337)</td>
</tr>
<tr>
<td>Pneumonitis</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>871 (95)</td>
</tr>
<tr>
<td>551 (95)</td>
</tr>
<tr>
<td>320 (95)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>44 (5)*</td>
</tr>
<tr>
<td>27 (5)</td>
</tr>
<tr>
<td>17 (5)</td>
</tr>
</tbody>
</table>

*p=0.001  **p=0.002  *95% CI 4-10%

Patients with Pneumonitis

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range)</td>
<td>67 (36-89)</td>
</tr>
<tr>
<td>Deaths</td>
<td>8</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Former</td>
<td>22 (50)</td>
</tr>
<tr>
<td>Never</td>
<td>21 (48)</td>
</tr>
<tr>
<td>Single agent vs. Combination</td>
<td></td>
</tr>
<tr>
<td>Monotherapy</td>
<td>25 (57)</td>
</tr>
<tr>
<td>Combination</td>
<td>19 (43)</td>
</tr>
<tr>
<td>PD-1 vs. PD-L1</td>
<td></td>
</tr>
<tr>
<td>PD-1</td>
<td>41 (93)</td>
</tr>
<tr>
<td>PD-L1</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Primary Disease Site</td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Malignant Melanoma</td>
<td>27 (61)</td>
</tr>
<tr>
<td>Hematologic Malignancy</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Bladder Carcinoma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Breast Carcinoma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Head and Neck SCC</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Pancreatic Carcinoma</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Median no. doses (range) 4 (1-38)
Median time to event (range) 2.9 mos. (9 days-19.2 mos.)
Treatment Outcomes by Grade

- **86%** Completely Resolved
- **14%** Improved
- **4/6 died:**
  - 1 = pneumonitis
  - 3 = infection

**Smoking status**
- Current/former: 17 (45), 21 (55)
- Never: 6 (100), 0 (0)
- p = 0.022

**Number of Pneumonitis Cases**

Pneumonitis

• **Symptoms**
  • New or worsening cough, shortness of breath

• **Signs**
  • Decrease in oxygen saturation

• **Radiographs**
  • New or changes in ground-glass changes, nodular or interstitial
# Pneumonitis Treatment

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
</tr>
</thead>
</table>
| Grade 1 \nRadiographic changes only | • Consider delay of I-O therapy  
• Monitor for symptoms every 2-3 days  
• Consider Pulmonary and ID consults |
| Grade 2 \nMild to moderate new symptoms | • Delay I-O therapy  
• Pulmonary and ID consults  
• Monitor symptoms daily, consider hospitalization  
• 1mg/kg/day of methylprednisolone IV or oral equivalent  
• Consider bronchoscopy, lung biopsy |
| Grade 3-4 \nSevere new symptoms; new/worsening hypoxia; life-threatening | • Permanently discontinue I-O therapy  
• Hospitalize  
• Pulmonary and ID consults  
• 1-2 mg/kg/day methylprednisolone IV or IV equivalent  
• Prophylactic antibiotics for opportunistic infections  
• Consider bronchoscopy, lung biopsy |
# Pneumonitis Treatment – Follow up

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
</tr>
</thead>
</table>
| Grade 1 Radiographic changes only | • Reassess every 3 weeks  
                                | • If improved, resume treatment when stable  
                                | • If worsens, treat as grade 2-4                                           |
| Grade 2 Mild to moderate new symptoms | • Reassess every 1-3 days  
                                      | • If improved to baseline – taper steroids over at least a month before resuming treatment  
                                      | • If not improving over 2 weeks, treat as grade 3 or 4                    |
| Grade 3-4 Severe new symptoms; new/worsening hypoxia; life-threatening | • If improving, taper steroids over atleast a month  
                                      | • If persists or worsens after 2 days of treatment, add non-corticosteroid immunosuppressive medication |
Case Six

62 year old man with stage IV NSCLC treated with Ipilimumab /nivolumab combination therapy on a clinical trial developed pain in R elbow, bilateral knees, with swelling. Plain X-Rays unremarkable.

What is the most likely diagnosis?

1. Rheumatoid arthritis
2. Seronegative Spondyloarthritis
3. Reactive arthritis
4. Septic Arthritis
5. Any of the above
Musculoskeletal and Rheumatic IRAES with Immunotherapy

- Poorly recognized from RCTs

- Present but diluted by lack of standardized reporting (e.g., arthralgia, arthritis, joint pain, joint effusion-aggregate >20%)

- CTCAE grading under calls severity of arthritis and autoimmune manifestations (significant disability or impaired self-care ADLs to reach Grade 3)

- No mention for monitoring or management in labels or information for patients, nurses, physicians

Cappelli et al, Ann Rheum Dis 2016 In Press
Rheumatologic AEs: Clinical phenotype

- **Seronegative Spondyloarthropathy**
  - Medium-large/ Axial joints
  - Synovitis +/- erosive
  - Autoab negative (HLAB27+)

- **Reactive Arthritis**
  - Conjunctivitis
  - Urethritis
  - Large joint predominant

- **Rheumatoid Arthritis**
  - MCP+PIP+Wrist
  - Autoab (Anti-RF and Anti-CCP) +/-
Rheumatologic AEs: Management

Seronegative Spondylo-

- Prolonged oral steroids (may not always respond)
- Intra-articular steroids
- Steroid-sparing non biologic DMARDs
- Anti-TNF
- Other DMARDs

Medium-large/ Axial joints
Synovitis +/- erosive
Autoab negative (HLA27+)

Rheumatoid Arthritis

MCP+PIP+Wrist
Autoab (Anti-RF and Anti-CCP) +/-

Cappelli et al, Ann Rheum Dis 2016 In Press
Proposed Management Algorithm
Immune-related Inflammatory arthritis

CTCAE Grade
- Mild joint pain
- Inflammatory symptoms*
- Joint swelling

1
- Mild/moderate joint pain
- Inflammatory symptoms
- Limiting instrumental ADLs

2
- Severe joint pain
- Inflammatory symptoms
- Joint swelling
- Limiting self-care ADLs
- +/-Irreversible joint damage,

CTCAE Grade
- Mild joint pain
- Inflammatory symptoms*
- Joint swelling

2
- Mild/moderate joint pain
- Inflammatory symptoms
- Limiting instrumental ADLs

3+
- Severe joint pain
- Inflammatory symptoms
- Joint swelling
- Limiting self-care ADLs
- +/-Irreversible joint damage,

Investigations
- Rheumatologic Clinical examination
  - Number of swollen/tender joints
  - Assessment of functional status
- Laboratory Tests (Inflammatory markers)
  - ANA
  - RF
  - CCP
  - HLA-B27
- Radiologic Assessment
  - Plain X-rays of affected joints
  - Consider musculoskeletal ultrasound
  - Consider MRI

Management
- Continue Immunotherapy
  - NSAIDs**
  - Consider prednisone 10 - 20 mg daily x 4 weeks, if NSAIDs ineffective
  - Consider intra-articular steroids

Follow-up
- Serial rheumatologic examinations, at 2 weeks and 4 weekly
- Functional assessment
- If not improving in 2-4 weeks, escalate to grade 2 management

- Continue immunotherapy
  - Oral prednisone 20 mg daily, increase to 1mg/kg/day or equivalent if no response after 6+ weeks and consider hold immunotherapy
  - Consider intra-articular steroids

- Hold immunotherapy
  - Oral prednisone 1mg/kg/day or equivalent x 4 weeks or until improve to grade 1
  - Consider TNF-inhibitors#
  - Consider methotrexate in refractory cases^

- Hold immunotherapy
  - Oral prednisone 1mg/kg/day or equivalent x 4 weeks or until improve to grade 1
  - Consider TNF-inhibitors#
  - Consider methotrexate in refractory cases^
Case Six continued

- 40 mg Prednisone, Intra-articular steroids with partial response
- Prednisone tapered off over 6 weeks, worsening of symptoms

- ‘Progressive joint involvement: small joints of the hands MCPs, PIPs

- Immunotherapy stopped (disease progression), 40 mg Prednisone
- Continued symptoms with disproportionate worsening of left elbow

- Repeat imaging showed metastatic lesion in left distal humerus
- Died of cancer 4 months after initial symptoms of inflammatory arthritis
Immune Mediated Myocarditis

• Rare event (<1% of patients)
• Two patients with after therapy within two weeks of first dose of nivolumab and ipilimumab.
• Post mortem analysis showing intense, patchy lymphocytic infiltrate within the myocardium and skeletal muscles, and tumor

Who Not to Treat with Checkpoint Inhibitors
Are Preexisting Autoimmune Disorders Contraindications to Checkpoint Inhibitor Therapy?

• Historically excluded from trials
• Active vs History of ?
• No published data with PD-1 or PD-L1 inhibitors
• Data comes from Ipilimumab
Ipilimumab Therapy in Patients with Advanced Melanoma and Preexisting Autoimmune Disorders

Retrospective study of the clinical outcomes of 30 patients with preexisting autoimmune disorders (AiDs) who received ipilimumab (CTLA-4 antibody)

<table>
<thead>
<tr>
<th>Autoimmune Disorders (N = 30)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid arthritis (RA)</td>
<td>6 (20%)</td>
<td>Psoriasis (5/30)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>2 (7%)</td>
<td>Crohn disease or ulcerative colitis</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>3 (10%)</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>2 (7%)</td>
<td>Other</td>
</tr>
</tbody>
</table>

5 (17%)
Ipilimumab Therapy in Patients with Advanced Melanoma and Preexisting Autoimmune Disorders

- 15/30 patients (50%) experienced irAEs or flares of their underlying AiD, which were generally manageable with standard treatment
- 6/30 (20%) experienced complete or partial responses to therapy
- Median overall survival was 12.5 months
- Ipilimumab appears to be safe and effective for many patients with advanced melanoma and concurrent, preexisting AiDs
- Patients should be monitored closely for irAEs and autoimmune flares
<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Baseline Condition</th>
<th>Autoimmune Exacerbation</th>
<th>Treatment</th>
<th>Immune-Related Adverse Event</th>
<th>Treatment</th>
<th>Outcome Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Sarcoidosis</td>
<td>...</td>
<td>...</td>
<td>Glaucoma</td>
<td>Ocular steroids</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>RA</td>
<td>Joint pain</td>
<td>As for hypophysitis</td>
<td>Hypophysitis</td>
<td>Prednisone 1 mg/kg tapered over 6 wk; now receiving 7.5 mg</td>
<td>红色圆圈，Durable CR</td>
</tr>
<tr>
<td>4</td>
<td>RA</td>
<td>...</td>
<td>...</td>
<td>Thyroiditis</td>
<td>Prednisone 1 mg/kg tapered over 2 wk</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Psoriasis, Graves disease</td>
<td>Worsening plaques</td>
<td>As for colitis</td>
<td>Colitis</td>
<td>Methylprednisolone 2 mg/kg tapered over 6 wk</td>
<td>After 1 dose</td>
</tr>
<tr>
<td>6</td>
<td>Psoriasis, Graves disease</td>
<td>...</td>
<td>...</td>
<td>Hypophysitis</td>
<td>Prednisone 30 mg x 1 wk, transition to hydrocortisone over 5 d</td>
<td>PR</td>
</tr>
<tr>
<td>8</td>
<td>RA, polymyalgia rheumatica</td>
<td>Joint pain, myalgias</td>
<td>Prednisone 30 mg/d tapered over 1 mo</td>
<td>...</td>
<td>...</td>
<td>After 3 d</td>
</tr>
<tr>
<td>9</td>
<td>RA</td>
<td>Joint pain</td>
<td>Prednisone 15 mg/d down to 10 mg</td>
<td>...</td>
<td>...</td>
<td>After 7 mo</td>
</tr>
<tr>
<td>11</td>
<td>Transverse myelitis</td>
<td>...</td>
<td>...</td>
<td>Colitis</td>
<td>Prednisone 1 mg/kg tapered over 8 wk</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Crohn disease</td>
<td>...</td>
<td>...</td>
<td>Colitis</td>
<td>Methylprednisolone 1 mg/kg tapered over 8 wk</td>
<td>After 1 dose</td>
</tr>
<tr>
<td>14</td>
<td>Ulcerative colitis</td>
<td>Diarrhea, disease flare</td>
<td>Infliximab, dexamethasone 2 mg daily</td>
<td>...</td>
<td>...</td>
<td>PR</td>
</tr>
<tr>
<td>15</td>
<td>Inflammatory arthritis</td>
<td>Joint pain</td>
<td>As for colitis</td>
<td>Colitis</td>
<td>Prednisone 1 mg/kg tapered over 4 wk, infliximab</td>
<td>...</td>
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<tr>
<td>20</td>
<td>Psoriasis</td>
<td>...</td>
<td>...</td>
<td>Hypophysitis</td>
<td>Prednisone 50 mg x 1 dose, then 5 mg daily</td>
<td></td>
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<tr>
<td>23</td>
<td>Sarcoidosis</td>
<td>Hypercalcemia, renal insufficiency</td>
<td>Prednisone 25 mg/d, tapered to 20 mg after 4 wk</td>
<td>...</td>
<td>...</td>
<td>Ongoing SD</td>
</tr>
<tr>
<td>24</td>
<td>RA</td>
<td>Joint pain</td>
<td>Prednisone 10 mg/d, now receiving 8 mg/d</td>
<td>...</td>
<td>...</td>
<td>Ongoing PR</td>
</tr>
<tr>
<td>28</td>
<td>Psoriasis</td>
<td>...</td>
<td>...</td>
<td>Presumed colitis grade 5</td>
<td>Methylprednisolone 1 mg/kg</td>
<td>Patient died</td>
</tr>
</tbody>
</table>
Checkpoint Inhibitor in the Solid Organ Transplant Setting

- Limited data
- CTLA-4 blockade seems to be compatible with solid organ transplants.
  - Liver transplant Rx with Ipi and no rejection –
- PD-1 blockade does NOT seem to be compatible with solid organ transplants.
  - Severe rejection in renal transplant pts showing cell and antibody mediated rejection.
  - PD-1 signaling is important in maintaining graft tolerance
    - Boils CL et al Am J Transplant 2016 Mar 14
    - Lipson et al NEJM 2016 Mar 3
Immune Side Effect Management: Simplification

• Mild symptoms (grade 1): consider delay I-O, frequent re-assessment, & symptomatic treatment.

• Moderate symptoms (grade 2): delay I-O, evaluate early and frequently, consider steroids, once symptoms improve steroids are tapered over ≥ 4 weeks.

• Moderate to severe (grade 3-4): discontinue I-O, early assessment, corticosteroids, if no improvement within 3-5 days consider additional immuno-suppressants.

• When on steroids, patient should receive stomach protection & consider prophylactic antibiotics. During steroid taper, patient should be evaluated frequently and for an extended period of time.
General Principles of Management

• Management generally based on severity of symptoms:

  • Grade 1: supportive care ± withhold drug

  • Grade 2: withhold drug, consider redose if toxicity resolves to grade ≤ 1; low-dose corticosteroids (prednisone 1-2 mg/kg/day or equivalent)

  • Grade 3/4: discontinue drug; high-dose corticosteroids (prednisone 2-4 mg/kg/day or equivalent) tapered over ≥ 1 mo once toxicity resolves to grade ≤ 1
Monitoring At Every dose

Vital signs including:
T__ HR__ RR__BP___O2sat at rest____ O2sat walking____

Blood work including:
CBC w/diff__, CMP__, TSH___, free T4___

*Physical exam by provider
Neuro:___, CV:____, Resp:____, GI:____, GU:____, Derm:____
other_______

Patient education
• Symptoms of immune related toxicities
• When to call
• Contact information for day or night
• If you are admitted to Emergency, have them call provider
Instructing Patients “When to call”

• New or worsening cough, chest pain or shortness of breath
• Loose stools or increased frequency, blood in your stool or abdominal pain,
• Nausea, vomiting, drowsiness or significant fatigue, dark urine, or jaundice
• Decreased urine output, blood in urine, swollen ankles, loss of appetite
• Headaches, extreme tiredness, lightheadedness, confusion
• Change in vision
• Fever or chills
• Rash
• Joint or muscle pain or weakness
Best practices are ones that lead to early awareness, evaluation and treatment of immune-related side effects!

• Baseline evaluation
• Assessment before every dose
• Patient Education
• Effective management of irAe’s
• Frequent monitoring
• Extended follow up

Cancer network.com: Identification and Management of Toxicities from Immune Checkpoint-Blocking Drugs. Teply,Benjamin, and Lipson,Evan
Thank You