Rheumatic Immune-Related Adverse Events

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I have no disclosures
Overview

1. Inflammatory arthritis
2. Sjogren’s
3. Myositis
4. Patients with underlying rheumatic diseases
Cl-associated inflammatory arthritis - incidence

- Prospective observational single-center study
  - 524 Cl-treated patients
- 3.8% referred to rheumatologists
  - for inflammatory arthritis
Inflammatory arthritis
PD-1/L1 vs. CTLA-4 blockade

• Clinical trials: odds ratio 3.5 with PD-1/L1
  Khoja. Ann Oncol 2017

• Head to head trials
  • [PD-1 vs. CTLA-4 vs. combo] = [7.7% vs. 6.1% vs. 10.1%]
  Larkin NEJM 2015

PD1/PDL1 introduced later, used longer in individual patients
CI-arthritis: onset

• 1-93 weeks after CI initiation

• Delay in referrals

Cappelli L. Semin Arthritis Rheum 2018  (N=30)
Hospital for Special Surgery (HSS)  
CI-Arthritis Registry – (N=37)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>67  [59, 77]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>60%</td>
</tr>
<tr>
<td>Smoker</td>
<td>49%</td>
</tr>
<tr>
<td>Months to onset</td>
<td>2.8  [0.9, 12]</td>
</tr>
<tr>
<td>Months to presentation</td>
<td>5.0  [1.0, 10]</td>
</tr>
<tr>
<td>Checkpoint discontinued</td>
<td>61%</td>
</tr>
</tbody>
</table>
HSS CI-Arthritis Registry – Cancers

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>14 (38%)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Renal cell</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>Urothelial</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (32%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination CTLA-4/PD1</td>
<td>12 (32%)</td>
</tr>
<tr>
<td>PD-1 or PD-L1 alone</td>
<td>25 (68%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response Status</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission</td>
<td>9 (26%)</td>
</tr>
<tr>
<td>Stable</td>
<td>11 (31%)</td>
</tr>
<tr>
<td>Partial Remission</td>
<td>7 (20%)</td>
</tr>
<tr>
<td>Progression</td>
<td>8 (23%)</td>
</tr>
</tbody>
</table>

Median follow up 5.4 [2.5,15] months
## HSS CI-Arthritis Registry – Serologies

<table>
<thead>
<tr>
<th>Test</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA +</td>
<td>22 (67%)</td>
</tr>
<tr>
<td>RF +</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>CCP +</td>
<td>8 (23%)</td>
</tr>
<tr>
<td>RF or CCP</td>
<td>10 (29%)</td>
</tr>
</tbody>
</table>
## HSS CI-Arthritis Registry – Phenotypes

<table>
<thead>
<tr>
<th></th>
<th>Small joint</th>
<th>Large joint only</th>
<th>Arthralgia</th>
<th>PMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22 (59%)</td>
<td>5 (14%)</td>
<td>8 (22%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Prednisone &gt;20 mg</td>
<td>9 (41%)</td>
<td><strong>3 (60%)</strong></td>
<td>4 (50%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Biologic</td>
<td>5 (23%)</td>
<td>1 (20%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>RF or CCP</td>
<td>6 (30%)</td>
<td><strong>0 (0%)</strong></td>
<td>3 (38%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Duration arthritis (mos)</td>
<td>18 [3.0,34]</td>
<td>13.0 [13,13]</td>
<td>8.8 [5.5,12]</td>
<td>3.0 [3.0, 3.0]</td>
</tr>
<tr>
<td>Tenosynovitis/enthesitis*</td>
<td>1 (5%)</td>
<td><strong>3 (60%)</strong></td>
<td>5 (63%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Wrists, patellar, quadriceps, triceps tendon*
Pathology

• Similar to RA:
  • Macrophages (CD68+)
  • B cells (CD20+)
  • Memory T cells
    • (CD3+ CD45RO+)

• Difference from RA:
  • Markedly elevated TNFα
FlowSOM on CD8 ViSNE- synovial fluid

Wang ...Bass, Rao. ACR abstract 2019
General approach to treatment

• Grade 1: NSAIDS, intraarticular injections, consider prednisone 5-20mg, try to taper over the month.
  • see back in 3-4 weeks
  • If unable to taper, add hydroxychloroquine (Plaquinil) or sulfasalazine

• Grade 2-3: Prednisone 20-120 mg
  • see back in 1-2 weeks
  • If not dramatically better at follow up, strongly consider TNFi
  • MTX can also be used but slow onset
Cl-associated Sjogren’s

• 20 patients, 14M/6F
  • 10 melanoma, 3 thymic, 4 respiratory papillomatosis
  • 17 monotherapy, 3 combination CI
  • 3/20 cancer progression
Cl- associated Sjogren’s

• Sicca: dry mouth predominant
  • Onset 70 days (30–206).
  • 5 grade 1, 15 grade 2
  • Some Candidiasis, some oral burning

• Serology:
  • 3 ANA, 2 RF/SSA, 1 Scl70

Warner Oncologist 2019;24:1–11
Salivary gland biopsy

A

H&E  CD3  CD4  CD8  CD20  PD-1  PD-L1  MASSON
HV  5x

B

ICI  FS: 1
5x

C

ICI  Severe  Sialadenitis
5x

D

Sjögren's  Syndrome  FS: 6
5x

T cells  B cells  Warner Oncologist 2019;24:1–11
Sjogren’s treatment

• Trial of corticosteroids - 20 mg or more
  • some symptomatic improvement but not resolution
  • salivary flow unchanged

• Consider hydroxychloroquine

• Pilocarpine (Salagen) and cevimeline (Evoxac)
  • can cause sweating, abdominal pain, flushing and increased urination
  • Can’t use with asthma or small angle glaucoma

• Dental hygiene

• Anti-fungal agents if needed for thrush

<table>
<thead>
<tr>
<th>Grade 2–3 severity</th>
<th>Grade 1 severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hold ICI</td>
<td>Maintain adequate hydration</td>
</tr>
<tr>
<td>Prednisone 20–40 mg qd for 2–4 weeks, followed by taper</td>
<td>OTC dry mouth products</td>
</tr>
<tr>
<td></td>
<td>Systemic sialogogue</td>
</tr>
</tbody>
</table>
Cl-associated myositis

- Onset 2-7 weeks
- Proximal muscle weakness and elevated CPK
  - Occasional myalgia, dyspnea, dysphagia, hypophonia
- Myocarditis – can be concomitant
- Features of myasthenia gravis
  - Dysarthria, ptosis, opthalmoplegia, facial paresis, orbicularis oculi weakness
  - Anti-striated muscle antibodies

- Uncommon:
  - ILD not reported
  - Dermatomyositis very rare
Figure 1 Clinical features, treatment, and outcome of patients with irMyositis

Touat M. Neurology 2018; 91:e985-e994
myophagocytosis
necrotic myofibers

macrophages
CD3
CD8
CD4
PD-1 lymphocytes
PD-L1 macrophages

Touat M. Neurology 2018; 91:e985-e994
Treatment

• Grade 1: myalgia no weakness: NSAIDS, prednisone 10-20 mg
  • Advance to grade 2 if weakness or elevated CPK

• Grade 2: moderate pain or weakness: prednisone 20-60
  • Watch for bulbar weakness, myocarditis
  • Advance to grade 3 if no response 2-4 weeks

• Grade 3 -4: moderate to severe weakness and/or pain
  • Methylprednisolone 1 gm IV daily x 3 days
  • Consider IVIG, plasmapheresis (Plex)
  • Consider MMF, AZA, MTX
  • Consider TNFi or Rituximab
Cases and case fatality rates – Global Pharmacovigilance – WHO Vigibase

Wang DY. JAMA Oncol 2018
Preexisting autoimmune disease

• Are they at greater risk for IRAE?
• Is it safe to treat them with CI?
Preexisting autoimmune disease – Systematic literature review (SLR)

• 123 cases
  • 49 publications

• 46% active autoimmune disease

• 23% PsA, psoriasis
• 16% RA
• 11% IBD
• 9% Thyroid disease
• 5% Multiple sclerosis
• 4% Sarcoid
• 3% Myasthenia

Abdel-Wahab N. Ann Intern Med 2018; 168:121-130
Preexisting autoimmune disease – Treatment changes at time of CI initiation

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Before CI (%)</th>
<th>At time of CI initiation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>29</td>
<td>21 (&lt; 10 mg)</td>
</tr>
<tr>
<td>DMARDs</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Biologics</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>No treatment</td>
<td>17</td>
<td>56</td>
</tr>
</tbody>
</table>

Abdel-Wahab N. Ann Intern Med 2018; 168:121-130
Preexisting autoimmune disease – IRAE

- Total irAE: 75%
  - Disease exacerbation: 50%
  - De Novo irAE: 34%

- CTLA-4: more de novo
- PD-1/PD-L1: more autoimmune disease flares

Abdel-Wahab N. Ann Intern Med 2018; 168:121-130
Preexisting autoimmune disease – IRAE

• Cancer response:
  • 50% with irAE, 36% without

• Lower rate of irAE
  • if on baseline treatment/immunosuppression

• Deaths:
  • 2 irAE [1 IBD: TEN/sepsis, 1 psoriasis: colitis]
  • 3 unrelated to irAE

Abdel-Wahab N. Ann Intern Med 2018; 168:121-130
Preexisting autoimmune disease –

- 75% overall rate of irAE –
  - 50% have a flare of their disease

- Yes, patients with autoimmune disease can receive CI
  - Stop immunosuppression at the time of CI initiation if at all possible
  - (Watch myositis patients carefully)
Thank you
Seropositivity and survival

Toi Y. 2018 JAMA Oncol.
Seroconversion overall - 19.2% (19/99) (ipilimumab)

**Figure 1.** Heatmap of antibody positivity pre- and post-ipilimumab treatment. Not shown: all patients were anti-ENA negative at baseline, while at follow-up, two patients became anti-ENA positive, specifically anti-SSA positive.

De Moel 2018 ACR ABSTRACT #23
Myositis & Myocarditis – T cell clones

Steroids: dosing and safety

- Low dose - probably safe
- High dose - may impact cancer survival

Risks
  - infection, osteoporosis
TNF inhibitors - safety

- No difference in survival
  - Steroids vs. steroids + infliximab
  - Study not powered

327 patients, multiple CI, multiple cancers

Wang. J ImmunoTherapy 2018; 6(37)
IL-6R blockade

- Multiple malignancies (most NSLC) - nivolumab

  - Safety unknown
    - Watch for colonic perforation
    - Much less experience than with TNFi
  - Reserve for refractory cases

Stroud. J Oncol Pharm Practice 2017
Safety of JAK/STAT blockade?

• Indirect evidence suggests they may NOT be safe.
  • Avoid JAK/STAT inhibitors for CI-associated irAE

• JAK/STAT important for regulation of PD-1 ligands and IFN-g signaling in tumors
• JAK1/2 mutations can cause anti-PD-1 resistance

Shin DA. Cancer Discov. 2017;7(2): 188–201