Mechanisms and Clinical Features of Immune Checkpoint Inhibitor-induced Rheumatic Disease

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Conflict of Interest Disclosure

- I disclose the following financial relationships with commercial entities that produce health care-related products or services relevant to the content I am presenting:

Company	Relationship	Content Area
BMS	Consultant, Research Grant	IRAEs

- I will discuss the off-label use of immunomodulatory therapies, specifically TNF inhibitors and IL6-inhibitors to treat immune-related adverse events (IRAEs).

Evidence-based Medicine

- Cappelli LC et al, (Hopkins Case Series), *Ann Rheum Dis* 2017; 76(1): 43-50 [2016 Jun 15]
- Calabrese L, Velcheti V. (Editorial) *Ann Rheum Dis* 2017;76(1):1–3 [2016 Aug]
- Cappelli LC et al, (Review) *RMD Open* 2016 Sept; 2(2):e000321
- Cappelli LC et al, (Review) *Rheum Dis Clin North Am* 2017; 43(1) 65-78 [2016 Oct]
- Cappelli LC et al, (Systematic Review) *Arthritis Care Res (Hoboken)* 2017 Nov;69(11):1751-1763; [2016 Dec]
- Cappelli LC et al, (Treatment approach). *Immunotherapy* 2017 Jan; 9(1):5-8
- Suarez-Almazor ME et al. (Review) *Arthritis Rheumatol* 2017 Apr ; 69(4) 687–699 [2017 Jan]
- Calabrese C et al, (Cleve Clinic Case Series) *RMD Open.* 2017 Mar 20;3(1):e000412.
- Abdel-Wahab M et al, (Review) *Adv Exp Med Biol*. 2017 Mar;995:155-174.
- Naidoo J et al. (Treatment Approach) *The Oncologist* 2017 Jun;22(6):627-630.
- Belkhir R et al (French Series); *Ann Rheum Dis* 2017 Jun, doi:10. 1136/ annrheumdis-2017-211216
- Kim ST et al (M D Anderson Case Series, TCZ Rx), *Ann Rheum Dis* 2017 Aug, doi:10.1136/annrheumdis-2017-211560

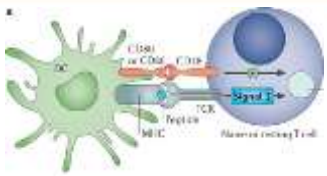
Objectives

- At the conclusion of this lecture, participants should be able to:
  - Describe immune checkpoints and their roles as targets for cancer treatment
  - Recognize the spectrum of immune-related adverse events (IRAEs) associated with ICI therapy
  - Recognize newly described rheumatic IRAEs
  - Appreciate the need for collaborative management of these disorders with oncologists

The Immune Response is Carefully Regulated

- Activation pathways are often balanced by naturally occurring inhibitory pathways
- Dampen and control response to prevent and/or limit host and tissue injury

The first phase of immune responses: T cells Require 2 Signals for Activation

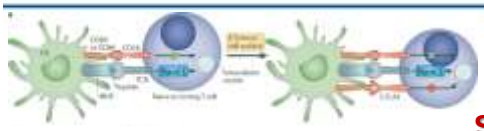


Antigen presenting cell (APC)

GO

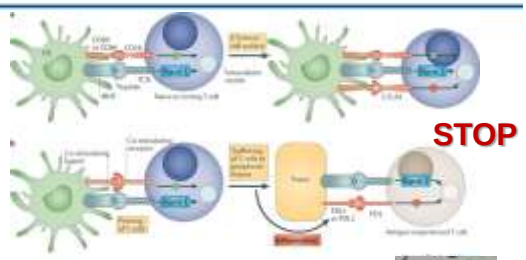
Pardoll DM, *Nature Reviews Cancer* 2012; 22: 252-64
wikihow

Immune Checkpoints Regulate T-cell Activation: CTLA-4



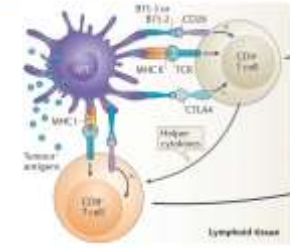
Pardoll DM, *Nature Rev Cancer* 2012

Immune Checkpoints Regulate T-cell Activation: PD1/PDL1



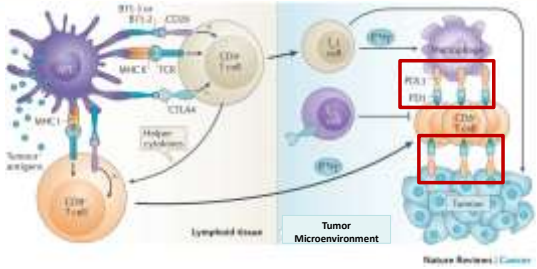
Pardoll DM, *Nature Rev Cancer* 2012

Tumors Express Checkpoint Ligands and Dampen T-Cell Responses



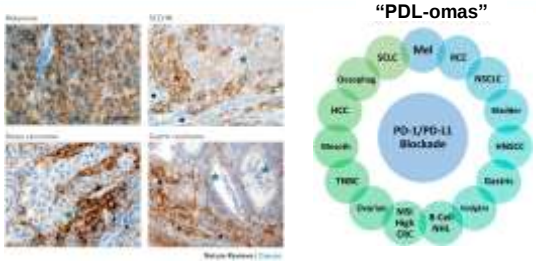
Topolian SL et al, *Nature Reviews Cancer* 2016; 16: 275-87

Tumors Express Checkpoint Ligands and Dampen T-Cell Responses



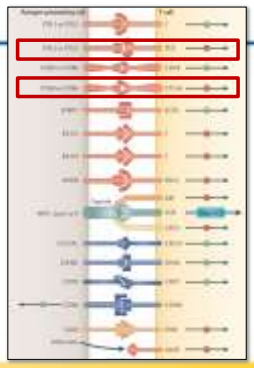
Topolian SL et al, *Nature Reviews Cancer* 2016; 16: 275-87

PD-L1 Expression in Cancers



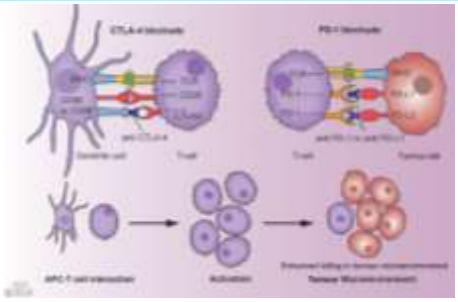
Topolian SL et al, *Nature Reviews Cancer* 2016; 16: 275-87

There are multiple immune checkpoints



Pardoll DM, *Nature Rev Cancer* 2012

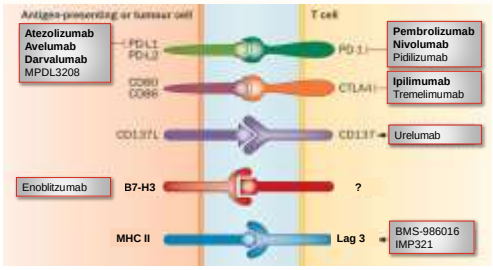
Immune Checkpoint Inhibitors (ICIs) Enhance Anti-Tumor Responses



Calabrese L, Velcheti V. *Ann Rheum Dis.* doi: 10.1136/annrheumdis-2016-209782.

Cancer Immunotherapy in the News

Current Targets of Cancer Immunotherapy



Adapted from Gangadhar TC. & Vonderheide RH. (2014) *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2013.245

FDA-approved Immune Checkpoint Inhibitors (ICIs)

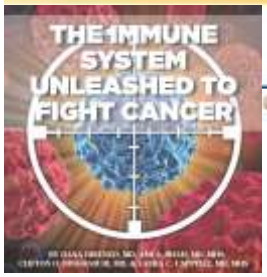
Target	FDA-approved
CTLA-4	**Ipilimumab** (Yervoy)- melanoma
PD-1 (CD-279)	**Nivolumab** (Opdivo)- melanoma, NSCLC, head and neck squamous, renal cell, Hodgkin, urothelial **Pembrolizumab** (Keytruda)- melanoma, NSCLC, head and neck, urothelial, Hodgkin, microsatellite instability-high
PDL-1 (CD-274, B7-H1)	**Atezolizumab** (Tecentriq)- urothelial, NSCLC **Avelumab** (Bavencio) –Merkel cell, urothelial **Durvalumab** (Imfinzi)- urothelial

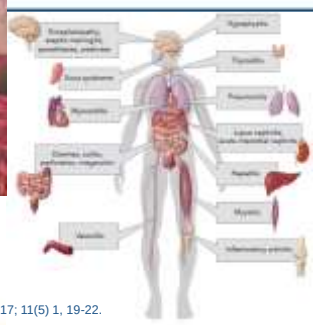
Why should a Rheumatologist care about Oncology drugs?

toonvectors.com

ICIs cause Immune-related Adverse Events (IRAEs)

- Unopposed general T-cell activation
- Off-target (non-tumor) tissue damage
- Disease and Drug Agnostic
  - Seen with all agents and across all indications
  - May be more common/severe with combination therapies
  - Some differences between agents are emerging
- Diverse phenotypes (multiple organs and systems)
  - Often more than one IRAE at same time or in sequence
- Severity from mild to life-threatening
- Temporality in relationship to ICI exposure is variable
- Many are monophasic
- Risk factors remain unclear



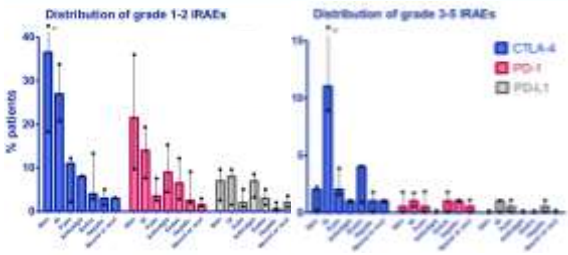


DiRenzo D, et al. *The Rheumatologist*, 2017; 11(5) 1, 19-22.

Commonly Recognized IRAEs

IRAE	Clinical Characteristics
Colitis	Diarrhea (30%), severe colitis (5-10%), perforation, usually develops earlier
Rash	Vitiligo, neutrophilic dermatoses, Psoriasis, TEN/SJS, usually early, up to 30-35%
Thyroiditis	Thyroiditis, Grave's, hypothyroid, often later, up to 20%, thyroid-specific Abs may be seen
Pneumonitis	Mild dyspnea/cough to respiratory failure, 1-5%, multiple patterns
Hypophysitis	Can affect all hormonal axes or can be selective, 0.5-10%
Hepatitis	Transaminitis, with or without ↑ bilirubin, 5-10%
CNS	Encephalitis, 1%; aseptic meningitis, transverse myelitis, MS, Posterior Reversible Encephalopathy Syndrome (PRES)
Peripheral NS	Peripheral neuropathy, Guillain-Barre syndrome, myasthenia

Distribution of IRAEs in Clinical Trials



Michot JM et al, Immune-related adverse events with immune checkpoint blockade: a comprehensive review. *European J Cancer* 2016; 54: 139-48

Histology and Findings

- Colon:
  - CTLA4: PMN w/ ↑ intraepithelial lymphs, crypt epi. cell apoptosis, few/no features of chronicity
  - Anti-PD-1:
    - Colitis with apoptosis (active inflammation, PMN, crypt micro-abscesses, crypt epi. cell apoptosis and atrophy/dropout)
    - Lymphocytic colitis (↑ intraepithelial lymphs in surface epithelium, surface epithelial injury, expanded lamina propria)
- Lung:
  - Cryptogenic organizing pneumonia (COP), nonspecific interstitial pneumonitis (NSIP), hypersensitivity pneumonitis (HP), usual interstitial pneumonitis (UIP)/pulmonary fibrosis (PF), sarcoidosis.
  - Mimics: pneumonia, lymphangitic spread, cancer progression, and diffuse alveolar hemorrhage.

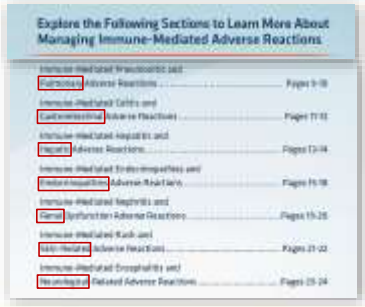
Treatment of IRAEs

- Steroids- 0.5-1 mg/kg initially, up to 2-3 mg/kg depending on severity
- Infliximab- colitis refractory to steroids (often only 1-2 doses needed)
- MMF and azathioprine have been used for autoimmune hepatitis and dermatoses

- Hold ICI treatment (Grade 3 AEs)
- Discontinue ICI treatment (Grade 4 AEs)
- Referral to "organ specialist" at Grade 3

Michot JM et al. *European Journal of Cancer* 2016; 54: 139-148

Educational Material for Providers and Patients regarding ICIs



Musculoskeletal and Rheumatic IRAEs with Immunotherapy

- Poorly recognized or described in RCTs
- Present but diluted by lack of standardized reporting
- Arthritis is rarely life-threatening, infrequent requirement for hospitalization (relevant to grading of AEs)
- Oncology AE grading under-calls arthritis and autoimmune manifestation severity
- Poor awareness in general Oncology community
- No mention for monitoring/management in labels or information for patients, nurses, MDs for any approved drugs

Systematic Review: Rheumatic and Musculoskeletal IRAEs

- Inclusion: PD-1, PD-L1, and/or CTLA-4 inhibitor, MSK or rheumatic IRAE mentioned, original data
- Data from 33 clinical trials:
  - Arthralgia 1-43% (n=24), myalgia 2-20% (n=12)
  - Arthritis reported in only 5/33 trials, 1-7%
  - Xerophthalmia, xerostomia 3-24%
  - Isolated reports of vasculitis, sarcoid etc.
- Case reports, series
  - Inflammatory arthritis, myositis, vasculitis, PMR/GCA, lupus nephritis
- Since the SLR additional cases: psoriasis/PsA, PMR, eosinophilic fasciitis, many others coming…

Cappelli LC et al. *Arthritis Care and Research*. E-pub Dec 2016, doi: 10.1002/acr.23177..

How Does an Oncologist Code a Swollen Joint? Confusion w/in CTCAE

Joint Effusion

- Gr1: Asymptomatic, clinical or diagnostic evaluation, no intervention
- Gr2: Symptomatic limiting instrumental ADL
- Gr3: Severe symptoms limiting self-care ADL, elective operative intervention indicated, disabling

Arthritis

- Gr1: Mild pain with inflammation, erythema or joint swelling
- Gr2: Moderate pain with inflammation, erythema, swelling limiting instrumental ADL
- Gr3: Severe pain, limiting self care ADL, disabling, **irreversible damage**

Arthralgia

- Gr1: Mild pain
- Gr2: Pain limiting instrumental ADL
- Gr3: Severe pain limiting self care ADL

Pain in extremity…
Periarthritis…
MSK pain…

Oncology AE Grading May Not Detect Clinically Significant Rheumatic AEs

CTCAE v 4	OMERACT RCTCAE v 2.0
Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention	**Grade 1** Mild; asymptomatic or transient, short duration < 1 wk, No change in lifestyle, None or OTC
Grade 2 Moderate; minimal, local or noninvasive intervention indicated; **limiting instrumental ADL**.	**Grade 2** Moderate; symptomatic, 1-2 weeks, **alter lifestyle occasionally**, OTC or Rx meds
Grade 3 Severe or medically significant but not immediately life-threatening; **hospitalization or prolongation of hospitalization** indicated; **disabling; limiting self care ADL**.	**Grade 3** Severe; prolonged symptoms, reversible, major **functional impairment**, prescription meds give partial relief, hospitalization < 24h
Grade 4 Life-threatening consequences; urgent intervention indicated.	**Grade 4** Includes life threatening; at risk of death, **sustained disability, Hospitalized > 24 hr**

Woodworth T, Furst DE, Alten R, Bingham CO 3rd, et al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0. *J Rheumatol*. 2007 Jun;34(6):1401-14.

Case

- 35 year old man with stage IIIb melanoma
- One dose of ipilimumab (anti-CTLA4)/nivolumab (anti-PD1)
- Develops colitis, responds to prednisone, tapered off after 1 month
- One subsequent dose of nivolumab monotherapy
- Develops severe conjunctivitis and sterile urethritis

Case, continued

- Within weeks, develops joint pain and swelling
- Initial significant synovitis in bilateral ankles and knee effusions, then wrists
- ***Prednisone 120 mg/d,*** tapered to 40 mg/d over 2 weeks
- Some improvement in swelling and stiffness, but persistent symptoms, difficulties with ADLs
- Synovial fluid: 11950 WBCs (92% PMN)
- Adalimumab → one dose, marked improvement. But then….

Case, continued

- Develops sinus congestion/periorbital swelling, Adalimumab held
- 2 courses of antibiotics w/out improvement
- Sinus CT shows pan-sinusitis w/out air-fluid levels
- New Atrial fibrillation requiring cardioversion x 2
- Arthritis recurrent in spite of 40 mg prednisone
- No evidence of melanoma recurrence
- Restarted Adalimumab with prompt resolution of all symptoms (joint, sinus, and cardiac)
- MTX started, TNF inhibitor tapered
- No recurrence of other IRAEs
- Maintains complete response to melanoma
- Required ongoing arthritis Rx > 18 months after onset

Rheumatic IRAEs at Hopkins: Initial case series

- Case Series: 9 pts w/inflammatory arthritis, 4 sicca
- Melanoma, Lung, Bladder Ca
- Mono Rx (PD1/PDL1) and Combo Rx (CTLA4/PD1)
- None with prior diagnosed autoimmunity
- Response (radiographic RECIST 1.1)
  - 7 partial response, 5 stable disease, 1 progression
- Other IRAEs (occurred in 7/13)
  - Colitis, pneumonitis, thyroiditis
  - First IRAE w/in 9mo after ICI initiation; 62% w/in 3mo, 23% w/in 1mo
  - Time between ICI and rheumatic presentation: 2-13 months
- Additional cases seen at the time but not reported as patients were participants in ongoing trials

Cappelli LC , *Ann Rheum Dis*. 2017 Jan;76(1):43-50 [Epub 2016 Jun].

Inflammatory Arthritis: Presentation

- Joint involvement
  - For many, medium-large joints first (knee, ankle, shoulder)
  - Many evolved to small joints (MCPs, PIPs, wrists)
  - Others have predominant RA-like small joint predominance
  - Reactive arthritis: conjunctivitis, urethritis, arthritis, dactylitis
- Serologies
  - RF/CCP rare, occasional ANA low titer
- Inflammatory Synovial Fluid (WBC 9-28K, PMNs)
- Imaging
  - Effusion, proliferative synovitis (highly vascular), extensive tendon inflammation, erosions

Cappelli LC et al, *Ann Rheum Dis*. 2017 Jan;76(1):43-50.

Notable Arthritis Features (n>35)

- 2 Major patterns observed based on Rx
  - PD1/PDL1 monoRx vs CTLA4+PD1/PDL1 Combo
- Combo: earlier onset, assn. with colitis, initial large joints, higher CRP, “reactive arthritis”
- Mono: later onset, initial small joints, arthritis may be only IRAE, “RA-like”
- Both: early erosions, highly vascularized tenosynovitis
- Among these patients, autoantibodies have been rare and low titer (RF/CCP in 3), no B27

Cappelli, Bingham, Shah et al, ACR2017

Published Arthritis Series from Other Groups

- Cleveland Clinic[1] (n=8)—RF in 1/ANAs in 3, small and large joints, requirement for higher dose steroids, TNFi in 2, associated with other IRAEs
- France[2] (n=6)—all CCP-positive (2 antecedent) 4 RF, 3 required HCQ/MTX,
- MD Anderson[3] (n=3)—1 RF low pos, 1 ANA/Ro, symmetric small joint, 1 erosive, steroids, all required TCZ

1. Calabrese C, *RMD Open* 2017 Mar 20;3(1):e000412. 2. Belkhir R, *Ann Rheum Dis* 2017 Jun, doi:10.1136/ annrheumdis-2017-211216. 3. Kim ST, *Ann Rheum Dis* 2017 Aug, doi:10.1136/annrheumdis-2017-211560

Sicca Syndrome

- Initial case series: 4 patients
- Dry mouth more severe than dry eyes
- Parotitis in one, responded to prednisone 40 mg tapered off over 6 weeks
- Serologies have been variable, ANA low-mod titer in some, rare Ro/La, rare RF
- >9 patients now seen and evaluated at our center
- Salivary gland biopsies in all

Cappelli LC et al, Ann Rheum Dis. 2017 Jan;76(1):43-50.

Polymyalgia rheumatica

- Hopkins Experience (n=3)
  - Classic Symptoms, Ages 59-73
  - Documented USG trochanteric/subacromial bursitis
  - All responded to 15 mg prednisone
- 3 Cases reported by Cleveland Group[1]
  - Responded to 20-40 mg prednisone
  - MRI in one patient with shoulder involvement
- 4 Cases reported by French Group[2]
  - Responded to 20-60 mg initial steroids

1. Calabrese C *RMD Open*. 2017 Mar 20;3(1):e000412. 2. Belkhir R; *Ann Rheum Dis* 2017 Jun, doi:10. 1136/ annrheumdis-2017- 211216

Myositis

- DM and PM reported
- Case w/ concomitant myesthenia reported
- Biopsy showed endomysial lymphocytic infiltrate
- Corticosteroids: IV and PO (30-120 mg/d)
- IVIG, plasma exchange reported in one case with no effect

Sheik Ali et al. *JAMA Dermatol*. 2015. Hunter et al. *Can J Neurol Sci*. 2009. Yoshioka et al. *J Dermatol*. 2015. Calabrese et al *RMD Open*. 2017. Suzuki et al. *Neurol*. 2017. John et al. *J Immunother Cancer*. 2017.

Other inflammatory, rheumatic, and musculoskeletal manifestations…

- Psoriasis/psoriatic arthritis
- Raynaud's
- Accelerated osteoporosis
- Myasthenia gravis
- Pan-sinusitis
- Giant Cell Arteritis
- Single Organ Vasculitis
- Lupus nephritis
- Scleroderma

Cappelli Ann Rheum Dis. 2017. Chan J Immunotherapy. 2015 Goldstein Arthritis Rheum 2014. Minor J Clin Onc 2013. Sheikh Ali JAMA Derm. 2014. Yoshioka J Derm. 2015. Fadel NEJM 2009. Bonigen J Eur Academ Dermatol Venerol. 2016. Law-Ping-Man Rheum (Ox). 2016. Barbosa Mayo Clin Proc. 2017. Calabrese RMD Open. 2017. Dien E, *J Immunotherapy* 2017

Rheumatologic IRAEs Abstracts ACR2017

- 116
- 850
- 1148
- 1156
- 1173
- 1184
- 1880
- 2095
- 2106
- 2119
- 2126
- 2128
- 2155
- 2902

Treatment Considerations

- Delay in referral for inflammatory arthritis
  - Potential functional impairment and irreversible damage
- Manage acute symptoms
- Symptom control is important to make decisions on ICI continuation
- Traditional step-up approaches for IA with conventional DMARDs and delayed onset of action may not achieve adequate timely control
- May need chronic management

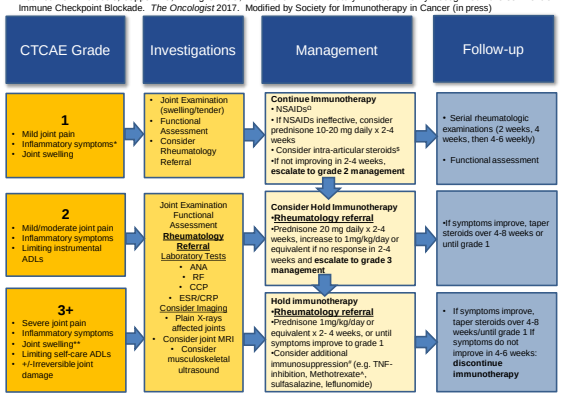
Potential Therapies for IRAEs and Anticipated Effects based on MOA

Drug options	Likelihood of efficacy	Time to Onset	Effect on cancer risk/response	Potential side effects (overlap ICI)	Use for IRAE reported
Hydroxychloroquine	low	3 mo	Likely no effect	None	Yes
Sulfasalazine	low	1-2 mo	Likely no effect	Rash, GI	Yes
Methotrexate	moderate	2 mo	Likely no effect	LFT ↑	Yes
Leflunomide	moderate	2 mo	Possible- T cell	GI/ LFT ↑	Yes
TNF inhibitors	high	weeks	Possible	None	Yes
Abatacept (T cell)	high	weeks	Likely impaired	None	No
Azathioprine	moderate	1-2 mo	Possible- T cell	GI/ LFT ↑	
Mycophenolate	low-mod	1-2 mo	Possible- T cell	GI issues	Yes
IL-6-- Tocilizumab/ Mavrilimumab	high	weeks	Unclear	LFT ↑, colitis	Yes
Tofacitinib (pan-Jak inhibitor)	high	weeks	Possible, NK inhib, T-cell function	LFT ↑, colitis	No
IL-1-- Anakinra	moderate	weeks	Likely no effect	None	No
IL-17- Secukinumab/ Ixekizumab	moderate	weeks	Some concerns of ICI efficacy	None	No
Rituximab (B cell)	low- mod	wk-mo	Likely no effect	Rash	No

Inflammatory Arthritis Treatment

- NSAIDS
- IA steroids
- Oral steroids (80%)—higher than usual doses
  - 20 mg to 120 mg/d for initial control
  - 7.5 mg daily to 40 mg daily for maintenance of response
- Conventional DMARDs (MTX) required in 33% of our patients (60% in ComboRx group)
- TNF-inhibitors in 50% of our patients with comboRx (2-16+ mo.)
- Use of IL-6 inhibitor recently reported by MD Anderson group
- Other groups have reported responses with HCQ/MTX
- No worsening of tumor response on DMARDs

Proposed Management Algorithm for Immune-related Inflammatory arthritis (Revised).
Modified from: Naidoo J, Cappelli LC, …Bingham CO, Brahmer JR. Inflammatory Arthritis: A Newly Recognized Adverse Event of Immune Checkpoint Blockade. *The Oncologist* 2017. Modified by Society for Immunotherapy in Cancer (in press)



ICIs in pre-existing autoimmunity

- 2 retrospective cohort studies
- 30 patients treated w/ ipilimumab
  - 8 (27%): exacerbation. 6 resolved w/ steroids, 2 required infliximab
  - 10 (33%) grade 3 + "conventional" IRAE
  - 15 (50%) neither flare nor IRAE
- 52 patients treated w/ PD-1 inhibitors
  - 20 (38%) flare requiring immunosuppression
  - 15 (29%) other IRAEs

Johnson et al. JAMA Onc. 2015. Menzies et al. Annals of Onc. 2017

What We Do Not Know

- Clinical phenotypes—continue to emerge
- Incidence
  - Numerator and Denominator difficult to define
- Associations between IRAEs
- Risks for development
- Best treatment: type, dose, duration
- Correlation with tumor response
- Underlying mechanisms

Putative Underlying IRAE Mechanisms

- T cell activation
  - Generalized and unchecked
  - Preferential upregulation of subpopulations (Th17, Treg, etc)
- Mixed T-cell and effector inflammatory cell infiltration at sites
- Tumor expression of self-antigens
- Pro-inflammatory cytokines

Hopkins Rheumatic IRAE Program

Rapid Evaluation, Collaborative Management, Coordinated Research

- **Rapid referral**: patients scheduled within 1 week
- Oncology groups using immunotherapy (particularly lung, melanoma, GI, GU)
- Sharing clinical data, banked specimens, complementary translational approach
- IRAE Evaluation/Treatment algorithm
- Common data collection forms (baseline and follow-up) to identify risks and increase detection
- IRAE Team—designated "disease-specialists" (GI, pulmonary, rheum, derm, endocrine, ophtho, etc.), expedite referrals, collaborative management, weekly case-review meetings

Summary

- IRAEs are common in patients treated with ICIs
  - Frequently multiple concurrent or consecutive events
- Inflammatory arthritis, PMR, sicca, and myositis most commonly reported
  - May become chronic, and persist after ICI discontinuation
- Incidence of rheumatic and musculoskeletal IRAEs will increase as ICI use grows
- Multidisciplinary integrated research/care models are required to characterize IRAEs, understand mechanisms, and optimize treatment
  - Traditional risk/benefit assessment and management algorithms require modification

Acknowledgements

Hopkins Rheumatology

- **Laura Cappelli MD MHS**
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