FDA Symposium:
"Assessment of CV Toxicities in Immuno Oncology Trials

"Autoimmunity Associated With Therapies"

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Professor of Medicine
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December 1, 2017

Utz Conflict of Interest Disclosure (2012-2017):

Consultant:
Genentech (South SF, CA)
Gilead Sciences (Foster City, CA)
Gerson Lehrman Group (Boston, MA)
U.S.F.D.A. Arthritis Drugs Advisory Committee
Resolve Therapeutics (Seattle, WA)

SAB:
Genentech (South SF, CA)
GSK (London, UK)
UCB (Belgium)
Baxter Healthcare (Germany)
DNAX/Merck (Palo Alto, CA)
DynaVax (Berkeley, CA)
Genzyme (Cambridge, MA)
Novartis (Cambridge, MA)
Third Rock Ventures (Boston, MA)
5 am Venture Partners (Palo Alto, CA)

Co-Founder, Consultant:
BayHill Therapeutics (Palo Alto, CA)
Cardinal Therapeutics (Palo Alto, CA)
Tolerion, Inc (Portola Valley, CA)

Sponsored Research:
AMP RA/Lupus – Leadership Center and STAMP Tech Center
Amgen, Genentech, Intel, GSK, Sanofi-Aventis, Takeda
Novo Nordisk Fellowship Program

Private Stock Ownership: Gilead Sciences

Part Time Caddie: Dodge Kemmer

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Overview of Talk

- **Background on Tolerance and Autoimmunity**
- **Literature Review of Associated Autoimmune and Rheumatic Diseases**
- **Diagnostic and Treatment Recommendations**
- **Preclinical vs Clinical Autoimmunity**
- **Recommendations**

Tolerance

A selective lack of an immune response to targeted antigen(s) while leaving the normal immune response intact.

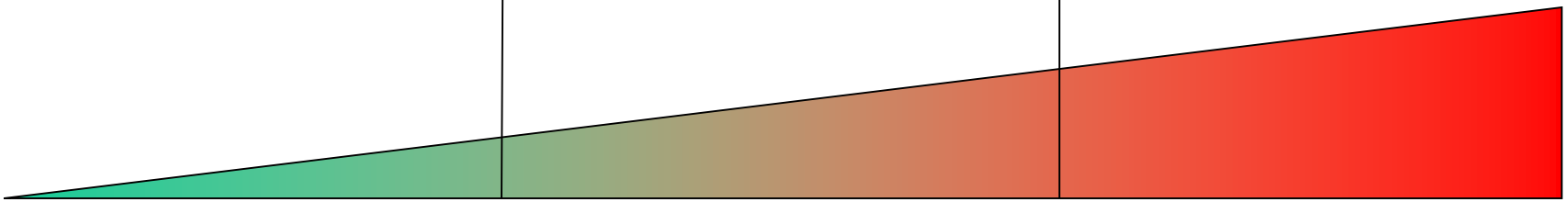
Autoimmunity

A breakage of tolerance in the immune system that results in the immune response attacking the body's own cells and tissues.

Where Tolerance and Autoimmunity Fit in with Immunology

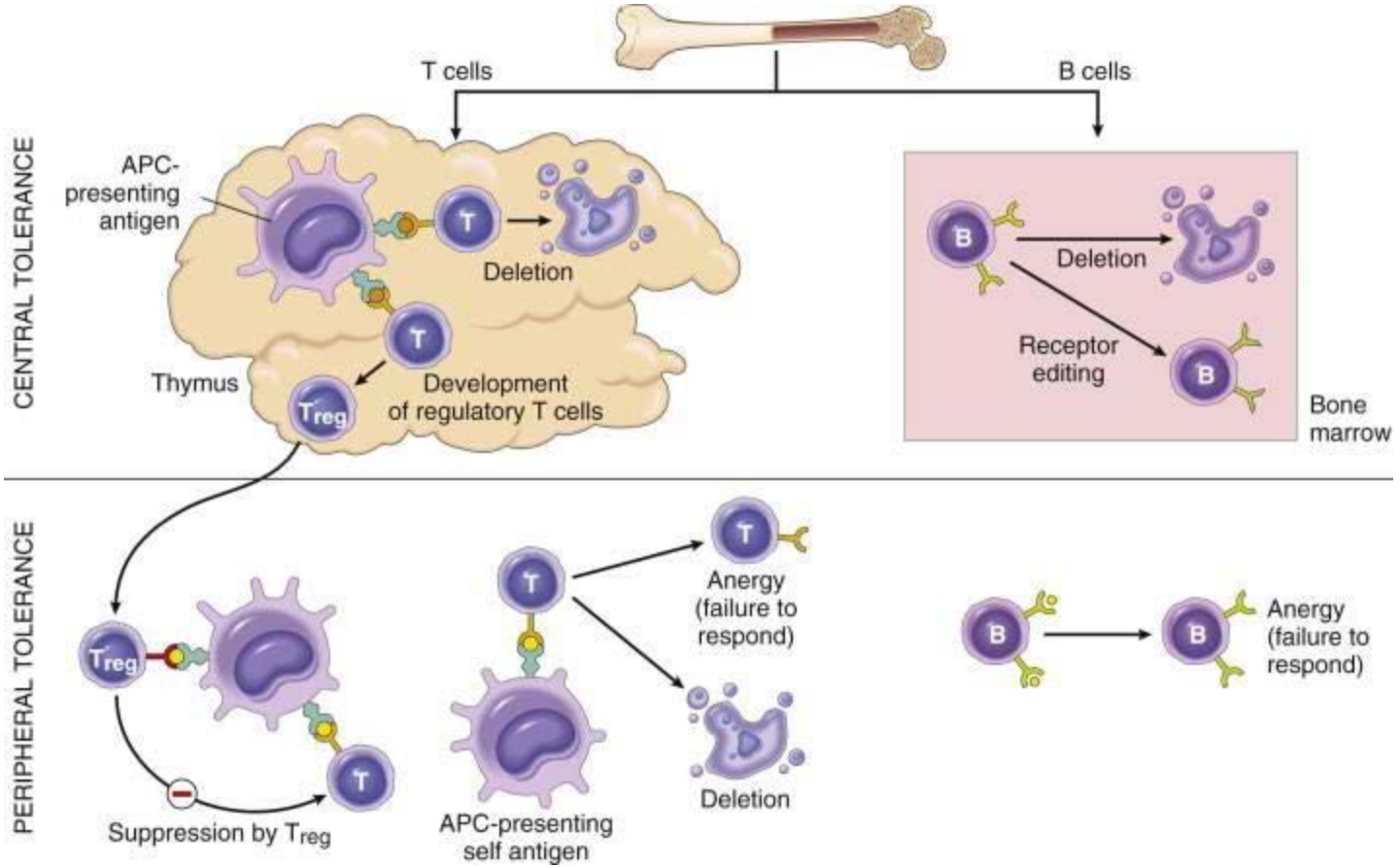
Immunodeficiency | Protective Immunity | Autoimmunity

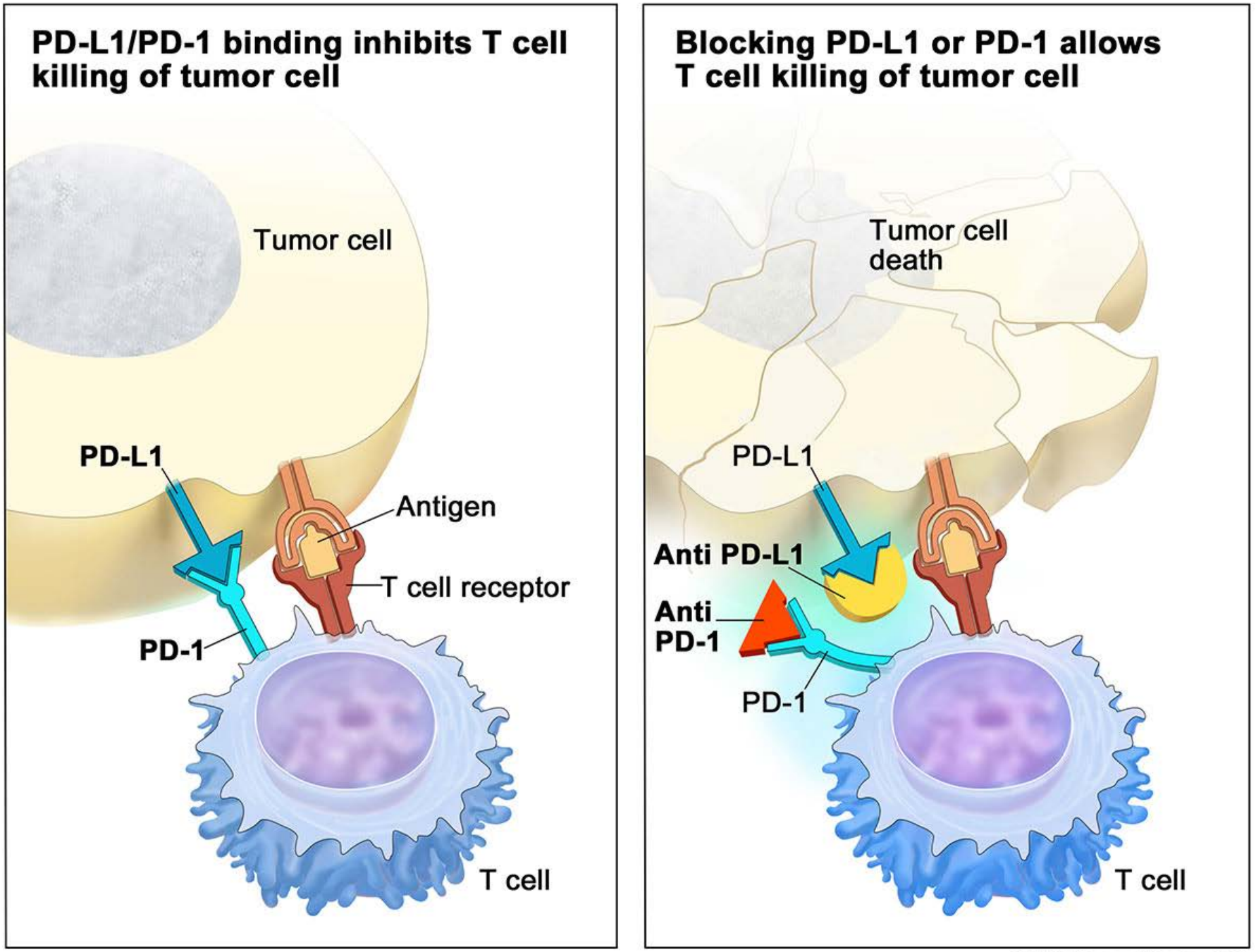
Cancer | Transplant Rejection | Allergy

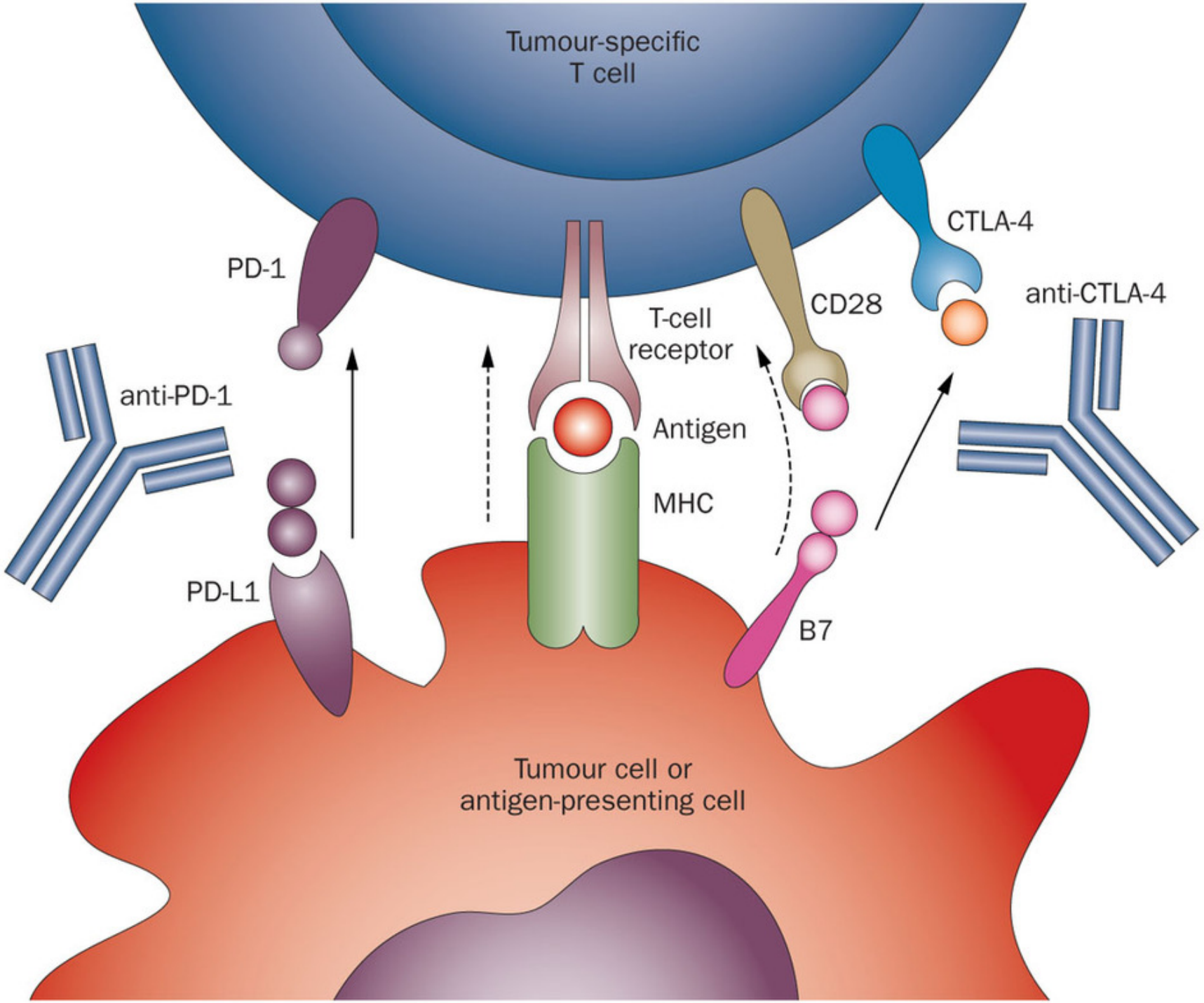


Magnitude of Immune Response

Central Tolerance vs Peripheral Tolerance






Tumour-specific
T cell
PD-1
CTLA-4
CD28
anti-CTLA-4
T-cell
receptor
anti-PD-1
Antigen
MHC
PD-L1
B7
Tumour cell or
antigen-presenting cell

Peripheral Tolerance: Immunotherapies = Trading Cancer for Autoimmune Diseases

Table 1. Immunotherapy Toxicity

Type of Immunotherapy	General Symptoms	Skin Toxicity	GI Toxicity	Hepatotoxicity	Endocrinopathy	Other Toxicities
Vaccines	Fevers, chills, lethargy	Maculopapular, vitiligo[1]	Rare diarrhea[5]	Rare[5]	None	Local reactions, back pain,[8] rare hypotension[5]
Cytokines: IFN	Fevers, chills, and flu-like symptoms[19]	Maculopapular[19]	Nausea, diarrhea, and rare vomiting[22]	Elevated LFTs common[23]	Thyroiditis; often associated with benefit[24]	Congestive heart failure,[19] anemia,[25] thrombocytopenia,[26] leukopenia,[24] depression[21]
Cytokines: IL-2	Fevers, chills, and lethargy[21]	Petechial and macular[31]	Transient nausea, vomiting, and diarrhea[31]	Elevated LFTs and bilirubin common[31]	Thyroiditis; often associated with benefit[36]	Pulmonary edema,[32] hypotension,[32] azotemia,[32] myocarditis,[32] altered mental status[31]
Cell therapy: TILs	Fevers, chills, and fatigue[43-45]	Maculopapular[43]	Rare diarrhea[43-45]	Elevated LFTs rare[43-45]	Thyroiditis; often associated with benefit[43-45]	Prolonged lymphopenia, CMV infections[43-45]
Cell therapy: CAR	Fevers, chills, and lethargy	Maculopapular	Rare diarrhea	Elevated LFTs with CA-IX CAR[66]	None	Cytokine release with tachycardia, hypotension, oliguria; B-cell aplasia[64]; pulmonary edema[66]
Cell therapy: TCR	Fevers, chills, and lethargy[47]	Maculopapular,[47] vitiligo[62]	Colitis with CEA TCR[63]	Elevated LFTs rare[47]	None	Encephalopathy[59] and carditis[60] with MAGE-3 TCR
Checkpoint protein inhibition: CTLA-4	Fevers, chills, and lethargy[62]	Maculopapular[62]	Diarrhea and colitis with ulceration[62]	Elevated LFTs[62]	Hypophysitis, thyroiditis, and adrenal insufficiency[62]	Neuropathy, nephritis, Guillain-Barré, myasthenia gravis, sarcoid, and thrombocytopenia all rare[62,63]
Checkpoint protein inhibition: PD-1	Fevers, chills, and lethargy[69-72]	Maculopapular[69-72]	Diarrhea and colitis with ulceration: uncommon[69-72]	Elevated LFTs uncommon[69-72]	Hypophysitis, thyroiditis more common, adrenal insufficiency[69-72]	Pneumonitis not common; neuropathy, Guillain-Barré, myasthenia gravis, nephritis, all rare[69-72]
Checkpoint protein inhibition: PD-L1	Fevers, chills, and lethargy[81,82]	Maculopapular[81,82]	Diarrhea and colitis with ulceration: rare[81,82]	Elevated LFTs rare[81,82]	Hypophysitis, thyroiditis more common, adrenal insufficiency[81,82]	Pneumonitis rare; anemia rare[81,82]
Combination checkpoint protein inhibition	Fevers, chills, and lethargy[100]	Maculopapular[100]	Diarrhea and colitis with ulceration; pancreatic lab elevation common[100]	Elevated LFTs common[100]	Hypophysitis, thyroiditis more common, adrenal insufficiency[100]	Pneumonitis not common[100]; neuropathy, Guillain-Barré, myasthenia gravis, nephritis, all rare[100]

Abbreviations: CA-IX, carbonic anhydrase IX; CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; CMV, cytomegalovirus; IFN, interferon; IL-2, interleukin-2; LFTs, liver function tests; TCR, T-cell receptor; TILs, tumor-infiltrating lymphocytes.

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Toxicities of Immunotherapy for the Practitioner

Jeffrey S. Weber, James C. Yang, Michael B. Atkins, and Mary L. Disis

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Abbreviations: CA-IX, carbonic anhydrase IX; CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; CMV, cytomegalovirus; IFN, interferon; IL-2, interleukin-2; LFTs, liver function tests; TCR, T-cell receptor; TILs, tumor-infiltrating lymphocytes.

Literature Review (255 papers 12/1/17)

GI
- Colitis
- Hepatitis
- Esophagitis
- Gastritis

Neuro
- CNS Vasculitis
- Limbic encephalitis
  - Hu
  - Contactin-associated protein-like 2
- MS
- Myasthenia Gravis (New, Flare)

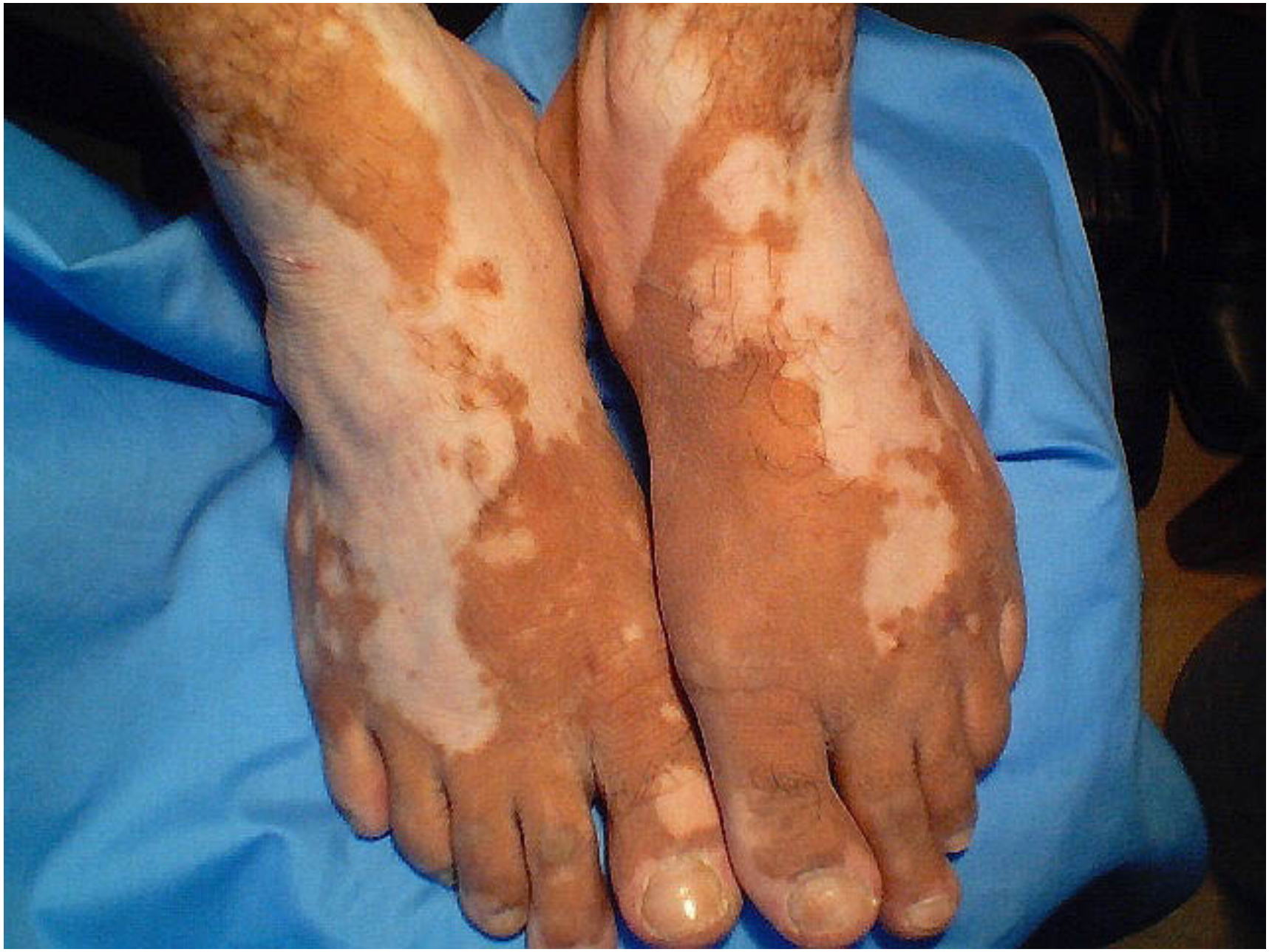
Derm
- Psoriasis
- Psoriasiform dermatitis
- Alopecia areata
- Bullous pemphigoid flare
- Vitiligo

Endocrine
- Primary adrenal failure
- Hypophysitis
- Thyroid disease
- T1D

Renal
- Acute GN
- Interstitial nephritis

Heme
- Pure red cell aplasia
- Hemolytic anemia

Miscellaneous
- Uveitis
- Autoimmune inner ear disease
- Severe myocarditis
- Pneumonitis
- Vasculitis (GCA, uterine, retinal)



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Fulminant Myocarditis with Combination Immune Checkpoint Blockade

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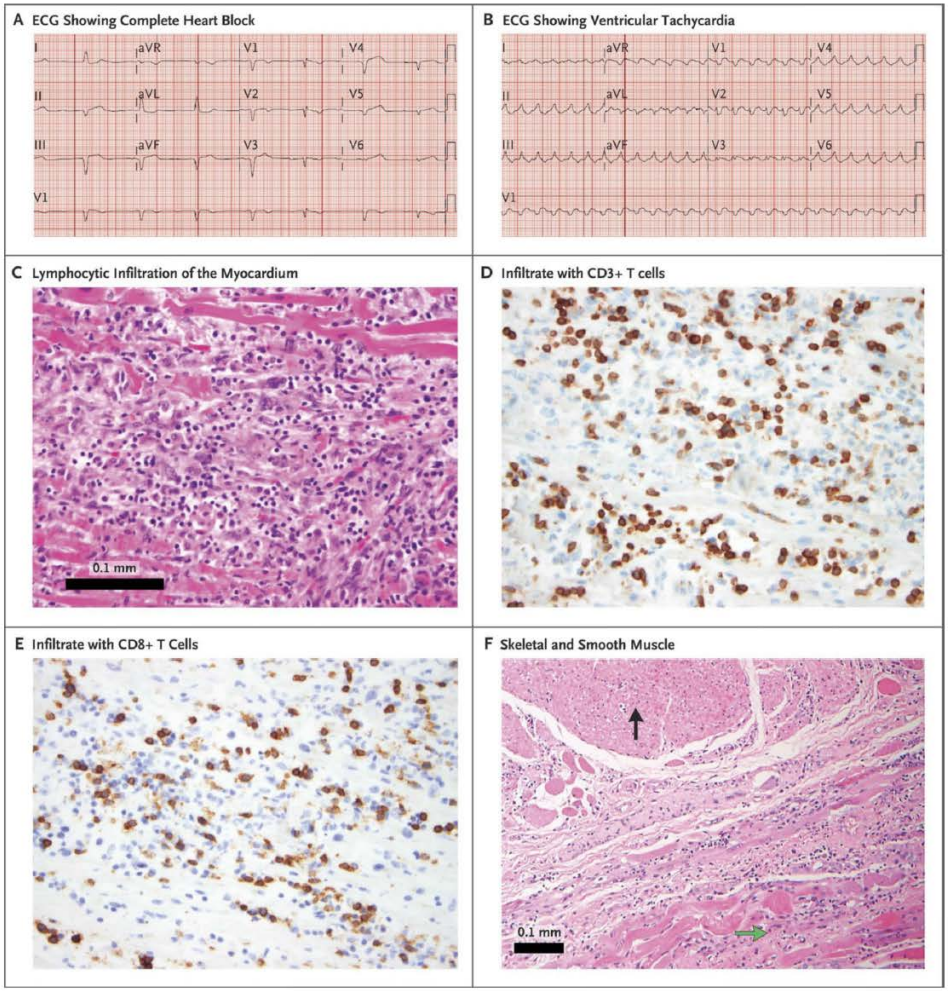

Figure 1.

Electrocardiographic and immune effects on cardiac muscle following ipilimumab and nivolumab treatment. Patient 1's ECG rapidly progressed to complete heart block (Panel A) followed by ventricular tachycardia (Panel B). Autopsy demonstrated lymphocytic infiltration in myocardium (intraventricular septum pictured, Panel C). Inflammatory infiltrate was comprised of CD3 positive T lymphocytes (Panel D), many of which were positive for CD8 (Panel E). Only cardiac and skeletal muscle were affected; smooth muscle and other tissue were spared (Panel F). The black arrow denotes esophageal smooth muscle

Endocrine side effects of cancer immunotherapy

Priscilla Cukier[1], Fernando C Santini[2], Mariana Scaranti[2] and Ana O Hoff[1]

Table 2 Reported frequencies of endocrine immune-related adverse events observed with immunotherapies.

	Endocrinopathies				
Monoclonal antibodies	Hypophysitis (%)	Hypothyroidism (%)	Hyperthyroidism (%)	Primary adrenal insufficiency (%)	Type 1 DM (%)
Anti-CTLA-4					
Ipilimumab[a]	1.5–17	1.5–6.8	4	0.8–1.6	NR
Tremelimumab[b]	0.4–2	2.3	0–3	1	NR
Anti-PD-1					
Nivolumab[c]	0.6–1.5	9–10.8	2.7	1	0.9
Pembrolizumab[d]	0.6–1	7–9.1	3.4–7.8	NR	0.2
Anti-PD-L1					
Avelumab[e]	NR	5	0.4	0.5	0.1
Atezolizumab[f]	0.2	2.5–4.2	0.6–1.1	0.4	0.2–0.3
Durvalumab[g]	<0.1	5.5–9.6	4.9–5.7	0.5–0.9	0.1
Combined therapy					
Nivolumab + ipilimumab[h]	4–12.8	4–27	4.3–14	4–8*	NR
Pembrolizumab + ipilimumab[i]	9.1	6–13.6	4.5–6	6*	NR
Durvalumab + tremelimumab[j]	NR	5.9	NR	NR	NR

*Comprises primary and secondary adrenal insufficiency.

CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein-1; PD-L1, PD-1 ligand molecule; NR, not reported.

[a]Phan *et al.* 2003, Attia *et al.* 2005, Maker *et al.* 2006, Downey *et al.* 2007, Yang *et al.* 2007, Weber *et al.* 2008, 2009, 2017, Ansell *et al.* 2009, Hodi *et al.* 2010, Ku *et al.* 2010, O'Day *et al.* 2010, Royal *et al.* 2010, Wolchok *et al.* 2010, Di Giacomo *et al.* 2011, Hersh *et al.* 2011, Sarnaik *et al.* 2011, Margolin *et al.* 2012, Altomonte *et al.* 2013, Slovin *et al.* 2013, Chiarion-Sileni *et al.* 2014, Kwon *et al.* 2014, Ryder *et al.* 2014, Larkin *et al.* 2015, Postow *et al.* 2015, Eggermont *et al.* 2016; [b]Ribas *et al.* 2005, Camacho *et al.* 2009, Chung *et al.* 2010, Kirkwood *et al.* 2010, Ralph *et al.* 2010, Ribas *et al.* 2012, 2013, Sangro *et al.* 2013, Aglietta *et al.* 2014, Calabrò *et al.* 2015; [c]Brahmer *et al.* 2010, Topalian *et al.* 2012, Weber *et al.* 2013, 2015*a*,*b*, 2017, Topalian *et al.* 2014, Ansell *et al.* 2015, Bauer *et al.* 2015, Brahmer *et al.* 2015, El-Khoueiry *et al.* 2015, Gettinger *et al.* 2015, Hamanishi *et al.* 2015, Motzer *et al.* 2015, Nishio *et al.* 2015, Paz-Ares *et al.* 2015, Rizvi *et al.* 2015*b*, Robert *et al.* 2015*a*; [d]Hamid *et al.* 2013, Robert *et al.* 2014, Doi *et al.* 2015, Garon *et al.* 2015, Le *et al.* 2015, Ott *et al.* 2015, Ribas *et al.* 2015, Robert *et al.* 2015*b*, Varga *et al.* 2015, Reck *et al.* 2016, Seiwert *et al.* 2016; [e]Disis *et al.* 2015, Gulley *et al.* 2015, Kelly *et al.* 2015, Shitara *et al.* 2015, Yamada *et al.* 2015; [f]Cho *et al.* 2013, Hamid *et al.* 2013, Herbst *et al.* 2013, Spigel *et al.* 2013, Powles *et al.* 2014, Petrylak *et al.* 2015, Spira *et al.* 2015; [g]Lutzky *et al.* 2014, Segal *et al.* 2014, 2016, Iguchi *et al.* 2015, Rizvi *et al.* 2015*a*; [h]Wolchok *et al.* 2013, Antonia *et al.* 2015*a*,*b*, Hammers *et al.* 2015, Hodi *et al.* 2015, Larkin *et al.* 2015, Postow *et al.* 2015; [i]Atkins *et al.* 2015, Patnaik *et al.* 2015; [j]Antonia *et al.* 2015*a*,*b*.

Diseases a Rheumatologist Might Encounter

- **Polyarthritis/Arthralgia**
  - **RA**
  - **PMR**
  - **Psoriatic Arthritis**

- **Vasculitis**
  - **Uterine**
  - **Retinal**
  - **GCA**

- **Connective Tissue Diseases**
  - **Systemic Sclerosis (Scleroderma)**
  - **Myositis**
  - **Eosinophilic fasciitis**
  - **SLE – associated manifestations, eg GN, IN, HA**
  - **Sicca (mimicking Sjögren's Disease)**

- **Sarcoidosis**

RA and PMR

CONCISE REPORT

Rheumatoid arthritis and polymyalgia rheumatica occurring after immune checkpoint inhibitor treatment

Rakiba Belkhir,[1] Sébastien Le Burel,[2] Laetitia Dunogeant,[3] Aurélien Marabelle,[4] Antoine Hollebecque,[4] Benjamin Besse,[5] Alexandra Leary,[5] Anne-Laure Voisin,[6] Clémence Pontoizeau,[7] Laetitia Coutte,[8] Edouard Pertuiset,[9] Gaël Mouterde,[10] Olivier Fain,[11] Olivier Lambotte,[2,12] Xavier Mariette[1,13]

Belkhir R, *et al*. *Ann Rheum Dis* 2017;**76**:1747–1750. doi:10.1136/annrheumdis-2017-211216

Table 1 Characteristics of patients with RA after ICI treatment for cancer

Patients	Sex/age, years	Type of cancer	ICI	Date of first ICI exposure	Date of IrAE	Type of rheumatic IrAE	IrAE response to treatment	Autoantibody results before ICI	Autoantibody results	Tumour response
1	F 55	Squamous cell carcinoma of the vagina	Nivolumab	October 2015	October 2015	RA	Resolution with NSAIDs	CCP: 61 U/mL RF:negative	CCP:671 U/mL RF:18 UI/mL	Progression death
2	F 66	Endometrial adenocarcinoma	Pembrolizumab	March 2016	April 2016	RA	Resolution with prednisone 10 mg/day	Not available	CCP:233 U/mL RF:180 UI/mL	Stable disease
3	M 59	Lung adenocarcinoma	Nivolumab	May 2016	July 2016	RA	Resolution with prednisone 10 mg/day	Not available	CCP:61 U/mL RF:47 UI/mL	Good response
4	F 56	Metastatic melanoma	Pembrolizumab	August 2015	September 2015	RA	NSAIDS and HCQ 400 mg/day:good response	CCP:22 U/mL RF:negative	CCP:18 U/mL RF<15 UI/mL	Stable disease
5	M 80	Metastatic melanoma	Nivolumab	April 2016	April 2016	RA	Prednisone 15 mg/day and HCQ 200 mg/day:good response	CCP:negative RF:not available	CCP:42 U/mL RF<15 UI/mL	Stable disease
6	M 68	Lung adenocarcinoma	Nivolumab	June 2015	July 2015	RA	NSAID: no effect stopping nivolumab and MTX 10 mg/week:good response	Not available	CCP:>300 U/mL RF:246 UI/mL	Stable disease

CCP, cyclic citrullinated peptide; F, female; HCQ, hydroxychloroquine; ICI, immune checkpoint inhibitor; IrAE, immune-related adverse event; M, male; MTX, methotrexate; NSAIDs, non-steroidal anti-Inflammatory drugs; RA, rheumatoid arthritis; RF, rheumatoid factor.

Table 2 Characteristics of patients with PMR after ICI treatment for cancer

Patients	Sex/age, years	Type of cancer	ICI	Date of first ICI exposure	Date of IrAE	Type of rheumatic IrAE	IrAE response to treatment	Autoantibody results	Tumour response
7	F 76	Mesothelioma	Anti-PDL1	June 2014	March 2015	PMR	Resolution with prednisone 20 mg/day then tapered	ANA, RF, CCP negative	Progression switch for pemetrexed
8	M 69	Gastric adenocarcinoma	Pembrolizumab	September 2016	October 2016	PMR	Resolution with prednisone 20 mg/day then tapered	ANA, RF, CCP negative	Progression
9	M 62	Colon adenocarcinoma	Nivolumab+ipilimumab (four cycles) then nivolumab alone	June 2015	October 2015	PMR	Resolution with prednisone 60 mg/day then tapered	ANA 1:320 with anti-ENA negative, RF, CCP negative	Stable disease
10	M 68	Metastatic melanoma	Nivolumab	August 2016	August 2016	PMR	Resolution with prednisone 40 mg/day then tapered	RF, CCP negative	Stable disease

ANA, antinuclear antibodies; anti-ENA, anti-extractable antibodies; CCP, cyclic citrullinated peptide; F, female; ICI, immune checkpoint inhibitor; IrAE, immune-related adverse event; M, male; PDL1, programmed cell death ligand protein 1; PMR, polymyalgia rheumatica; RF, rheumatoid factor.

ARD Online First, published on November 16, 2017 as 10.1136/annrheumdis-2017-212257

EXTENDED REPORT

Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer—clinical aspects and relationship with tumour response: a single-centre prospective cohort study

Marie Kostine,[1] Léa Rouxel,[1] Thomas Barnetche,[1] Rémi Veillon,[2] Florent Martin,[2] Caroline Dutriaux,[3] Léa Dousset,[3] Anne Pham-Ledard,[3] Sorilla Prey,[3] Marie Beylot-Barry,[3] Amaury Daste,[4] Marine Gross-Goupil,[4] Julie Lallier,[4] Alain Ravaud,[4] Edouard Forcade,[5] Bernard Bannwarth,[1] Marie-Elise Truchetet,[1] Christophe Richez,[1] Nadia Mehsen,[1] Thierry Schaeverbeke,[1] and on behalf of the FHU ACRONIM

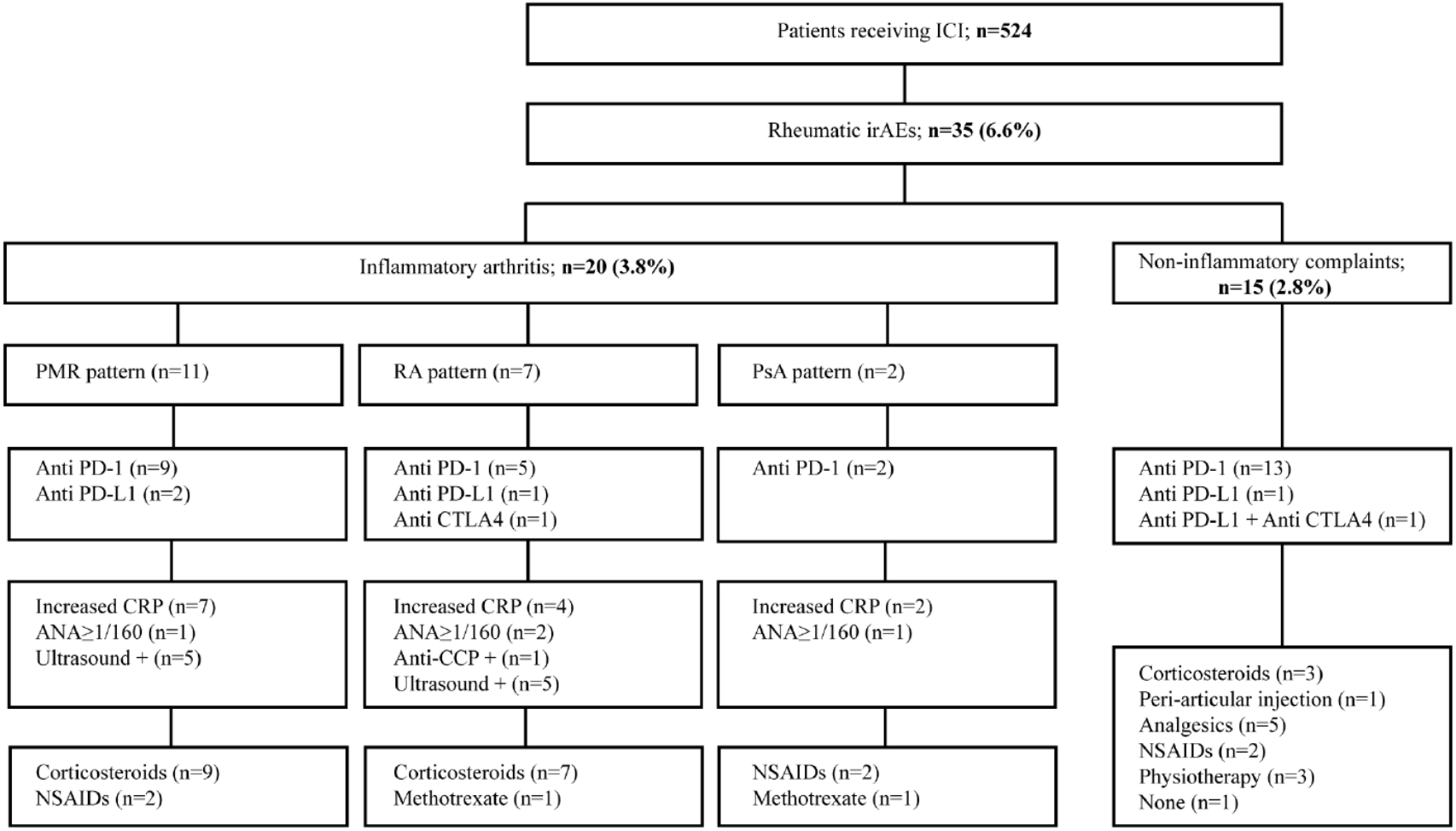

Figure 1 Description of rheumatic irAEs occurring with ICI treatment. ANA, antinuclear antibodies; CCP, cyclic citrullinated peptide; CRP, C reactive protein; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; irAEs, immune-related adverse effects; NSAIDs, non-steroidal anti-inflammatory drugs; PD-1, programmed cell death protein 1; PD-L1, PD-1 ligand 1; PMR, polymyalgia rheumatica; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

Inflammatory Arthritis and Sicca Syndrome

EXTENDED REPORT

Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab

Laura C Cappelli,[1] Anna Kristina Gutierrez,[1] Alan N Baer,[1] Jemima Albayda,[1] Rebecca L Manno,[1] Uzma Haque,[1] Evan J Lipson,[2] Karen B Bleich,[3] Ami A Shah,[1] Jarushka Naidoo,[2] Julie R Brahmer,[2] Dung Le,[2] Clifton O Bingham III[1]

Handling editor Tore K Kvien

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ABSTRACT

Objectives Immune checkpoint inhibitors (ICIs) targeting the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) pathways have demonstrated survival improvements in multiple advanced cancers, but also cause immune-related adverse events (IRAEs). IRAEs with clinical features similar to rheumatic diseases have not been well described. We report patients with inflammatory arthritis and sicca syndrome secondary to ICIs.

Methods We report patients evaluated in the Johns Hopkins Rheumatology clinics from 2012 to 2016 identified as having new rheumatological symptoms in the context of treatment with ipilimumab (anti-CTLA-4) and/or nivolumab (anti-PD-1) for solid tumours.

Results We identified 13 patients who received ICIs and developed rheumatological IRAEs. Mean age was 58.7 years. Cancer types included melanoma, non-small cell lung cancer, small cell lung cancer and renal cell carcinoma. ICI regimens included nivolumab or ipilimumab as monotherapy (n=5), or combination nivolumab and ipilimumab (n=8). Nine of 13 patients developed an inflammatory arthritis, 4 with synovitis confirmed on imaging (3 ultrasound, 1 MRI) and 4 with inflammatory synovial fluid. Four patients developed sicca syndrome with severe salivary hypofunction. Other IRAEs included: pneumonitis, colitis, interstitial nephritis and thyroiditis. Antinuclear antibodies were positive in 5 out of 13 patients. All 13 patients were treated with corticosteroids with varying response. Two patients were treated with methotrexate and antitumor necrosis factor therapy for inflammatory arthritis.

Conclusions As ICIs are increasingly used for a range of malignancies, new cases of rheumatic IRAEs are likely to emerge. Further research is required to understand mechanisms, determine risk factors and develop management algorithms for rheumatic IRAEs.

was approved for metastatic melanoma in 2013,[5] with pembrolizumab and nivolumab approved within the past year. Nivolumab and pembrolizumab are also FDA-approved for metastatic non-small cell lung cancer (NSCLC) in the second-line setting and for programmed death ligand 1 (PDL-1)-positive NSCLCs,[6] and nivolumab has approval for the treatment of renal cell carcinoma (RCC).[7] In addition, these and other agents targeting related immune pathways, including PDL-1, T-cell immunoglobulin and mucin domain 3 (TIM-3) and lymphocyte activation gene 3 (LAG-3), are currently being tested in a variety of cancers, from solid tumours to haematological malignancies.[8 9] Hundreds of trials of ICIs are ongoing in the USA.[10] Although ICI use continues to increase, consequences of these therapies as a result of inducing autoimmunity or through other mechanisms are only beginning to be understood.

A range of immune-related adverse events (IRAEs) have been described with these agents, ranging from severe and potentially life-threatening pneumonitis and colitis, to autoimmune thyroid disease, hypophysitis and vitiligo.[11] Rates of events have differed by drug and tumour type.[11 12] Rheumatic and musculoskeletal IRAEs have to date not been widely recognised or well characterised. Recognising the potential for ICIs to cause IRAEs that resemble more classical autoimmune diseases will become increasingly important to rheumatologists as more patients are referred for evaluation and management, and to oncologists who must recognise these toxicities in order to refer.

In this article, we report a series of patients evaluated in the Johns Hopkins Rheumatology outpatient clinics from 2012 to 2016 with inflammatory arthritis or sicca symptoms that occurred after the administration of ICIs. We report the clinical, auto-

Table 2 Autoimmune disease phenotype, antibodies and treatment for included patients

	Date of first ICI exposure	Autoimmune disease phenotype	Date of IRAE	Treatment of IRAE	IRAE response to treatment	Imaging, synovial fluid and other findings	Autoantibody results
1	21/2/2014	Colitis	21/3/2014	Prednisone 120 mg daily, tapered off over 3 months. ICI held for 3 months	Resolution of colitis. Able to go back on ICI		
		Inflammatory arthritis	2/2015: reported 16/6/2015: seen	Prednisone 10 mg daily with suboptimal response. ICI stopped and prednisone increased to 40 mg daily. Continued disease activity, so MTX 15 mg weekly and adalimumab weekly added to regimen with improvement	Improvement with adalimumab and MTX. Able to come off prednisone	MRI: tibiotalar and subtalar joint effusions with marked synovitis	ANA, RF, CCP, Ro, La, dsDNA, RNP, Sm, myositis panel*, Scl70, HLA-B27 negative
2	7/2013	Colitis (on anti-CTLA-4)	10/2013	Prednisone 1 mg/kg/day	Resolution of colitis		
		Thyroiditis/hypothyroid	10/2013	Prednisone 40 mg, tapered to 7 mg/day MTX	Poor response to steroids (4 months) Poor response to MTX (5 months)	Synovial fluid: WBC 12 700 (75% PMN)	
		Inflammatory arthritis (on anti-PD-1)	8/2014	Infliximab Etanercept	Initial response to infliximab, d/c due to AE (nausea, chills) Marked response to etanercept	Ultrasound: Doppler-positive synovitis in the right ankle	RF, CCP negative
3	14/11/2014	Inflammatory arthritis	3/8/2015—reported 17/9/2015—seen	Intra-articular triamcinolone Prednisone 40 mg daily, tapered off over 1 month. ICI stopped, resumed 40 mg prednisone	Temporary relief from intra-articular triamcinolone, partial relief from 40 mg prednisone but not smaller doses	Ultrasound: Doppler-positive synovitis and erosions at elbow Subsequently developed metastatic lesion at distal humerus	ANA, RF, CCP, Ro, La, RNP, Sm, dsDNA, P-ANCA, C-ANCA, HLA-B27, Scl70, RNA pol III, cardiolipin, β-2-glycoprotein antibodies negative
4	21/10/2015	Colitis	11/2015	Prednisone starting at 160 mg daily tapered off over 1 month	Resolved		
		Inflammatory arthritis	1/2016–	Prednisone 120 mg daily tapered down to 40 mg daily Intra-articular triamcinolone Adalimumab initiated	Initial steroid treatment with no improvement, after 2 weeks high-dose steroids some improvement in pain and swelling. Marked improvement with adalimumab allowing steroid taper	Synovial fluid: 11 950 WBCs (92% PMN)	ANA, RF, CCP, Ro, La, RNP, Sm, dsDNA, P-ANCA, C-ANCA, HLA-B27, Scl70, cardiolipin antibodies, β-2-glycoprotein antibodies negative
5	26/3/2015	Inflammatory arthritis	21/5/2015—reported 25/6/2015—seen	Prednisone 10 mg daily, tapered to 7.5 mg daily after 3 months	Good response with improvement of symptoms	None available	ANA 1:80 (speckled) Anti-Ro positive RF, CCP, RNP, Sm, Scl70, myositis panel negative
6	3/2012	Colitis	5/2013	Prednisone 80 mg/day tapered to 20 mg/day	Initial response high dose steroids, recurrence with steroid taper Resolved with infliximab	Colonoscopy: mild, left-sided colitis (descending colon, sigmoid colon and rectum notable for mild erythema without ulceration)	
			5/2/2014 (recurrence after re-dosing with ICI 1 month prior) 20/12/2013	Infliximab (one dose) Prednisone 80 mg/day tapered to 20 mg/day Infliximab (two doses) Adalimumab Hormone replacement	Poor response to high dose steroids Adverse event (pneumonia) Resolved Initial response to prednisone 40 mg, with recurrence of joint pain and stiffness at 10 mg/day	Knee radiographs: large suprapatellar effusion, no erosions	
		Hypothyroidism Reactive arthritis (inflammatory arthritis, conjunctivitis)	5/1/2014—seen 7/3/2014 (flare after infliximab)	Prednisone 40 mg/day tapered over 1 months to 10 mg/day Intra-articular triamcinolone Prednisone 1 mg/kg/day Intra-articular triamcinolone	Improved with steroid injection Improved with steroids Improved with adalimumab	Synovial fluid analysis: WBC 28455 (70% PMNs)	ANA, RF, CCP, antihistone negative

Continued

Table 2 Continued

	Date of first ICI exposure	Autoimmune disease phenotype	Date of IRAE	Treatment of IRAE	IRAE response to treatment	Imaging, synovial fluid and other findings	Autoantibody results
7	3/3/2015	Inflammatory arthritis Thyroiditis/ hypothyroidism	19/11/2015—reported 7/12/15—seen 17/4/2015	Prednisone 10 mg daily Intra-articular triamcinolone Colchicine 0.6 mg daily Propranolol initially, Levothyroxine for subsequent hypothyroidism	Improvement of symptoms on 10 mg prednisone, but progressive symptoms involving the shoulder, knee, wrist and elbow requiring 40 mg prednisone for relief	Ultrasound: Synovitis with positive Doppler signal in knee, elbow Synovial fluid: 9854 WBC (86% PMN, 14% mononuclear, monosodium urate crystals present)	ANA, RF, CCP, Ro, La, RNP, Sm, dsDNA, P-ANCA, C-ANCA, HLA-B27, Scl70, RNA pol III, cardiolipin antibodies, β-2-glycoprotein antibodies negative
8	26/2/2015	Inflammatory arthritis	5/2015—reported 9/12/2015—seen	Dexamethasone 8 mg daily for brain metastasis, no additional corticosteroids added	Improvement of joint symptoms on dexamethasone	None	ANA, RF, CCP, Ro, La, RNP, Sm, dsDNA, P-ANCA, C-ANCA, HLA-B27, Scl70, RNA pol III, cardiolipin antibodies, β-2-glycoprotein antibodies negative
9	16/7/2015	Inflammatory arthritis	12/2015—reported 2/2016—seen	Celecoxib twice daily, intra-articular triamcinolone		None available	ANA, RF, CCP, Ro, La, RNP, Sm, dsDNA, P-ANCA, C-ANCA, Scl70, cardiolipin antibodies, β-2-glycoprotein antibodies negative
10	1/5/2015	Pneumonitis Acute sicca	23/7/15 9/7/15—reported 30/7/15—seen	Prednisone 80 mg daily, tapered over 2 months Pilocarpine for symptoms	Improvement of imaging and symptoms Improvement of xerostomia	None available	ANA 1:320 (nucleolar) RF 38 (ULN 35) Anti-EJ antibodies positive, rest of myositis panel negative. Ro, La, RNP, Sm, Scl70 negative
11	24/4/2015	Acute sicca	6/2015	Prednisone 0.5 mg/kg/day, increased to 1 mg/kg/day, tapered to until discontinued Cevimeline for symptoms	No improvement No benefit		ANA 1:320 homogenous Ro, La, RF negative
12	6/9/2011 nivolumab 8/3/2013 ipilimumab	Acute sicca Interstitial nephritis Insulin-dependent diabetes Colitis	1/5/2012 22/5/2012—seen 1/5/2012 3/2013 4/2013	Prednisone 1 mg/kg/day Prednisone 1 mg/kg/day Insulin Dexamethasone 8 mg twice a day tapered then discontinued	Improvement in xerostomia Improvement in creatinine Maintained on insulin Resolved with steroids	Creatinine 3.1 BUN 36 Renal biopsy: acute and evolving chronic interstitial inflammation with some T cells and focally numerous eosinophils suggesting a hypersensitivity reaction. The T-cell-rich lymphocytic infiltrate in the interstitial kidneys suggested an autoimmune interstitial nephritis	ANA 1:80 speckled Ro, La, RF, P-ANCA, C-ANCA negative
13	1/4/2015	Acute sicca with parotid swelling	12/2015	Prednisone 40 mg daily Cevilemine for symptomatic relief of xerostomia	Improved parotid swelling, prednisone tapered off over 6 weeks	Ultrasound bilateral parotid glands: hypoechoic foci consistent with lymphocytic aggregates, >50% of gland involved	La/SSB antibodies positive. ANA, Ro, RNP, Sm, RF, CCP, myositis panel, anti-dsDNA, P-ANCA, C-ANCA negative

*Myositis panel tests for antibodies to Jo-1, SRP, EJ, OJ, PL-7, PL-12, Mi-2, Ku.
AE, adverse events; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic autoantibody; BUN, blood urea nitrogen; CCP, cyclic citrullinated peptide; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HLA, human leucocyte antigen; ICI, immune checkpoint inhibitor; MTX, methotrexate; PMN, polymorphonuclear leucocytes; RF, rheumatoid factor; RNP, ribonuclear protein antibody; ULN, upper limit of normal; WBC, white blood cells.

Vasculitis

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REVIEW | *Inflammation, Immunity, and Cardiovascular Disease*

Immune checkpoint dysfunction in large and medium vessel vasculitis

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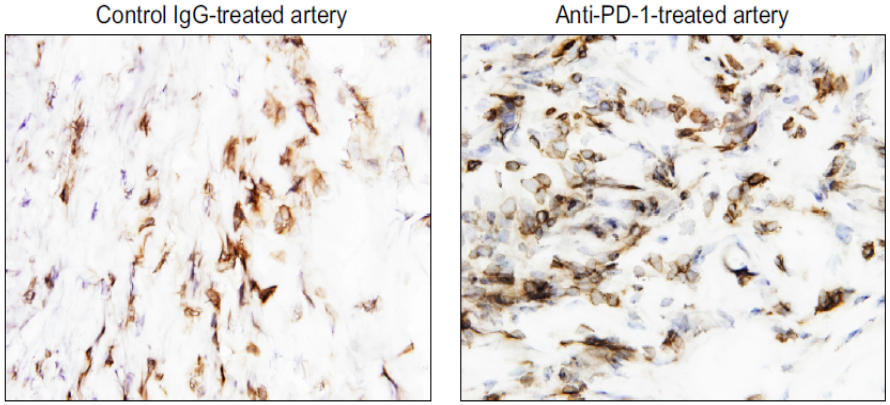

Fig. 4. Checkpoint inhibition with anti-PD-1 antibody treatment exacerbates vasculitis. Human arteries were engrafted into immunodeficient nonobese diabetic NSG-γ mice. To induce vasculitis in the engrafted vessels, chimeric mice were reconstituted with peripheral blood mononuclear cells from patients with GCA. Two weeks later, the human arteries were explanted, and the intensity of vasculitis was determined by immunostaining for human $CD3^+$ T cells in tissue sections. Before harvesting of the human arteries, the chimeric mice were treated with anti-PD-1 antibodies (100 μg) or control IgG by alternative-day intraperitoneal injections. Anti-CD3-binding T cells (brown) in the tissue were visualized with horseradish peroxidase-conjugated goat anti-rabbit secondary antibodies. Compared with the IgG control (*left*), PD-1 blockade (*right*) markedly increased the density of the vascular T cell infiltrate. Original magnification: ×600.

Table 1. *Consequences of an impaired PD-1 checkpoint in vasculitis*

Biological Pathway	Clinical Consequence
T cell activation and polarization	Density of the T cell infiltrate
	Interferon-γ, IL-17, and IL-21 production
	IL-7 and IL-15 production
Macrophage activity	IL-1β, IL-6, IL-23, and TNF-α production
Intramural neoangiogenesis	Density of the microvascular lumina
Intimal hyperplasia	Thickness of the intimal layer

Systemic Sclerosis (Scleroderma)

Scleroderma Induced by Pembrolizumab: A Case Series

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Abstract

Immune checkpoint inhibitors are approved for select cancer treatment and have shown survival benefit in patients with advanced melanoma. Adverse events, including immune-related adverse events, are common and potentially life-threatening. We describe cases of 2 patients with scleroderma (patient 1 had diffuse scleroderma, and patient 2 had limited scleroderma) that developed while they were receiving pembrolizumab therapy for metastatic melanoma. Prompt recognition and treatment of immune-related adverse events may improve tolerance to immune checkpoint inhibitors and contribute to an understanding of the manifesting autoimmune disease.

 ■ Mayo Clin Proc. 2017;92(7):1158-1163

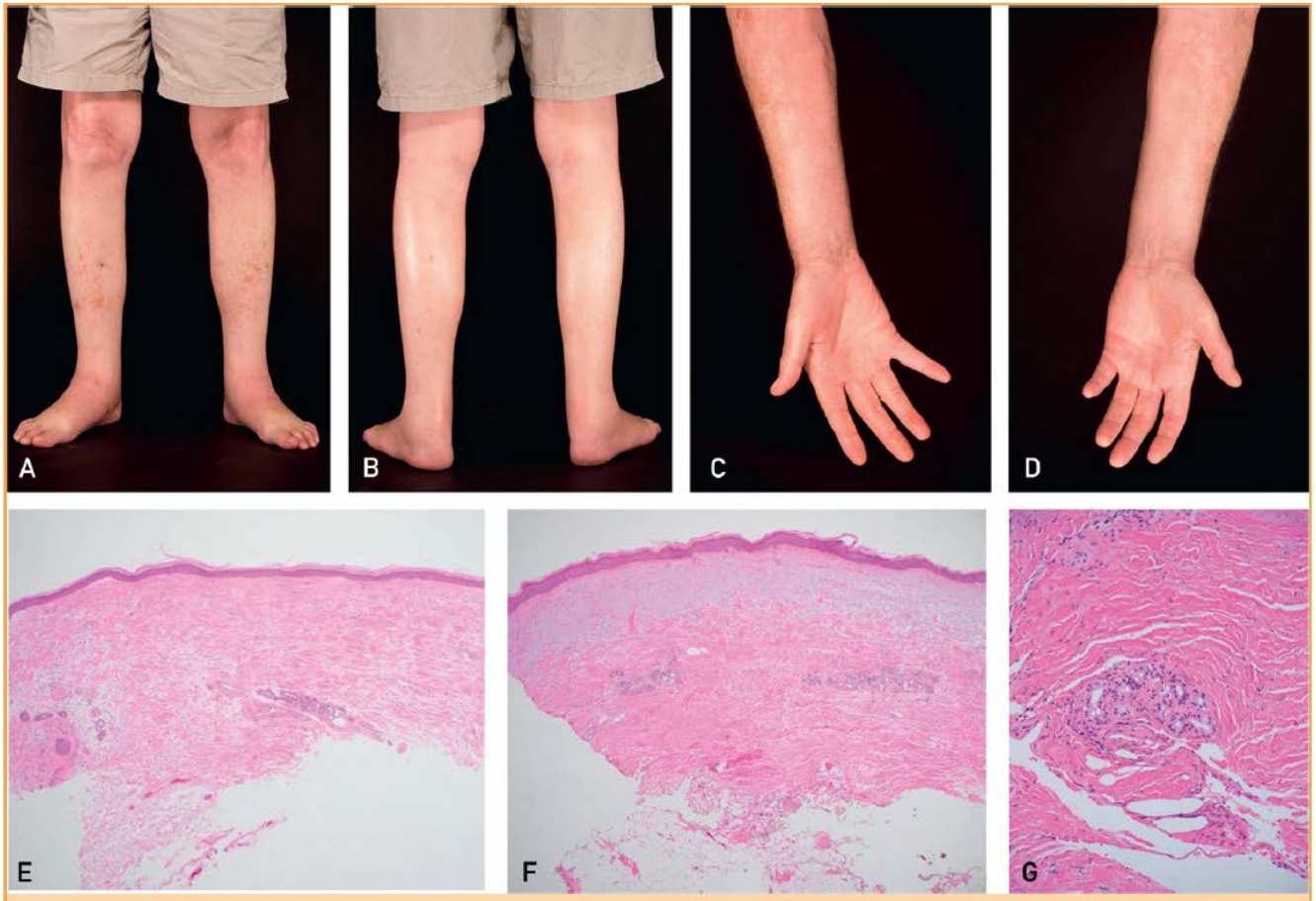

FIGURE 1. Bilateral skin tightening, consistent with scleroderma, is shown on the lower extremities and feet (A and B) and on the forearms and hands (C and D) of patient 1. Skin histology from the right medial shin (E) and right upper forearm (F) revealed mild dermal sclerosis with trapping of adnexal structures and minimal inflammation (hematoxylin-eosin, original magnification ×4). Higher magnification of the right upper forearm specimen (G) revealed deep dermal sclerosis (hematoxylin-eosin, original magnification ×20).

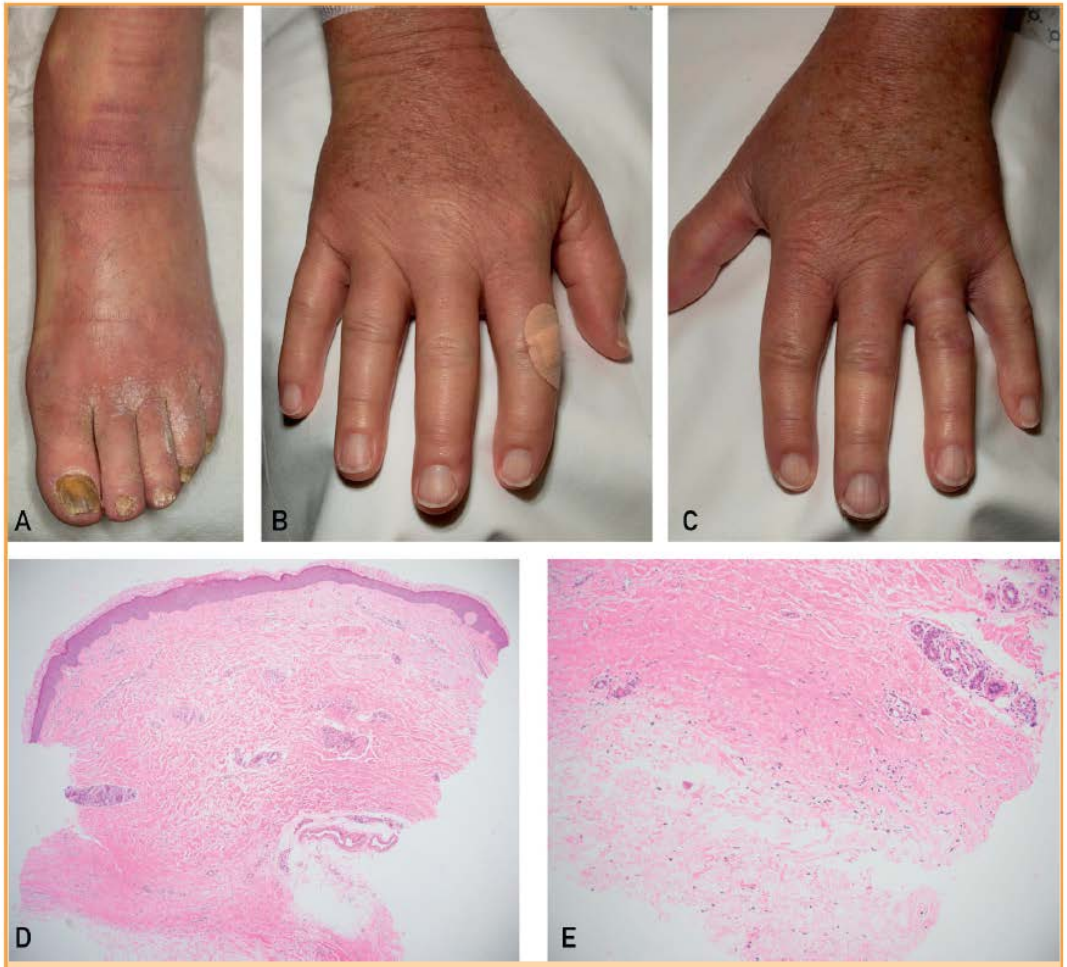

FIGURE 2. Acral skin tightening, consistent with scleroderma, is shown on the left foot (A) and hands (B and C) of patient 2. Skin histology from the left ventral wrist (D) revealed mild perivascular lymphocytic inflammation and deep dermal sclerosis, consistent with a sclerodermoid reaction (hematoxylin-eosin, original magnification ×4). Higher magnification (E) revealed deep dermal sclerosis (hematoxylin-eosin, original magnification ×10).

Clinical Management

Immune-Related Adverse Effects of Cancer Immunotherapy— Implications for Rheumatology

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Clifton O. Bingham III, MD

KEYWORDS

- Arthritis • Sicca syndrome • Immune checkpoint inhibitors • Malignancy
- Immune-related adverse events

KEY POINTS

- By blocking inhibitory pathways of T-cell activation, immune checkpoint inhibitors (ICIs) can cause immune-related adverse events (IRAEs), including inflammatory arthritis, myositis, vasculitis, and sicca syndrome.
- Treatment of ICI-induced rheumatic IRAE requires different considerations than treatment of classic rheumatic conditions.
- Using ICIs in those with preexisting autoimmunity is possible but with risk of causing a disease flare or a different IRAE.

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Table 3
Recommendations for evaluation of patients with suspected rheumatic immune-related adverse events

Suspected Immune-related Adverse Event	Clinical Examination	Laboratory Studies	Imaging, Other Studies
Inflammatory arthritis	Full joint examination Schober test	ESR, CRP, RF, CCP, ANA, HLA B27	Synovial fluid analysis Joint ultrasound or MRI
Sicca syndrome	Schirmer test Palpation of parotid glands Unstimulated salivary flow assessment	ESR, CRP, ANA, Ro, La	Parotid gland ultrasound Salivary scintigram Minor salivary gland biopsy
Myositis	Manual strength testing Dynamometry	CK, aldolase, ESR, CRP, ANA Myositis panel (Jo-1, PL-7, PL-12, EJ, OJ, Mi-2, SRP)	Electromyography MRI of affected muscle
Vasculitis	GCA: palpation of temporal arteries Palpation and auscultation of arteries Skin examination (purpura) Evaluation for mononeuritis multiplex	ESR, CRP, cANCA, pANCA, MPO, PR3, urinalysis	For GCA: temporal artery biopsy MRI or PET of suspected affected area

Abbreviations: ANA, anti-nuclear antibodies; cANCA, cytoplasmic anti-neutrophil cytoplasmic antibodies; CCP, cyclic citrullinated peptide antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; HLA, human leukocyte antigen; pANCA, perinuclear anti-neutrophil cytoplasmic antibodies; PR3, proteinase-3; RF, rheumatoid factor; MPO, myeloperoxidase.

Box Key messages for the practising rheumatologist

1. Musculoskeletal symptoms are likely to occur in 5%–10% of cancer patients being treated with immune checkpoint inhibitors (ICIs).
2. There are two distinct clinical manifestations: inflammatory arthritis (3.8%), mainly rheumatoid arthritis (RA), polymyalgia rheumatica (PMR) or psoriatic arthritis (PsA) , and non-inflammatory musculoskeletal conditions (2.8%).
3. Treatment options comprise:
   - For the inflammatory arthritis: non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and conventionnal synthetic disease-modifying antirheumatic drugs (csDMARDs). A biological DMARD may be considered if there is no improvement.
   - For the non-inflammatory conditions: NSAIDs, analgesics and/or physiotherapy.
4. Usually there is no need to stop or even to modify the ICI treatment.
5. Treatment of these musculoskeletal manifestations must be based on a shared decision between the rheumatologist and the referring oncologist.
6. Patients experiencing rheumatic manifestations or other immune-related adverse event(s) are likely to respond to ICI treatment (85%).

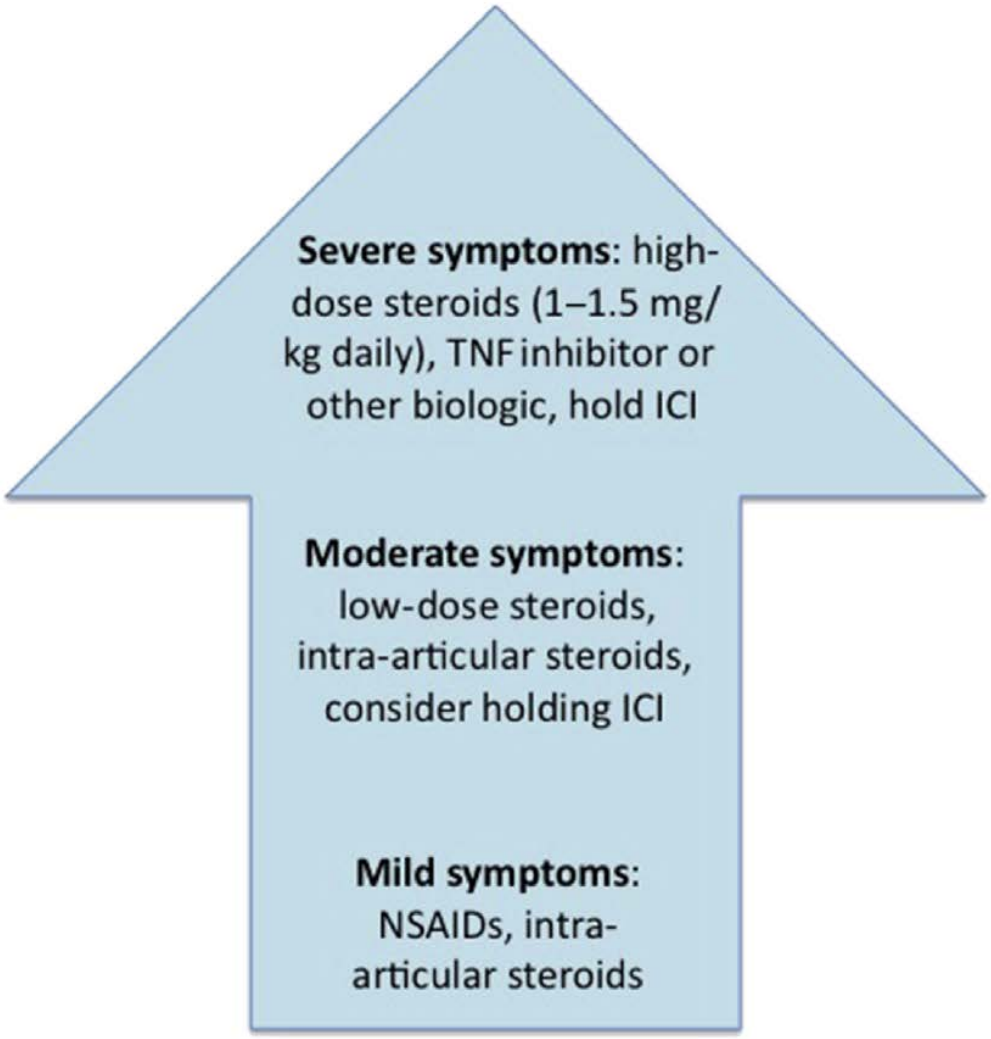

Fig. 2. Proposed treatment algorithm. If patients do not respond within 4 to 6 weeks of therapy, escalate to next level of treatment.

Table 4
Potential immunosuppressive therapy for immune checkpoint inhibitors–induced rheumatic immune-related adverse events

Drug Options	Likelihood of Efficacy	Anticipated Time of Onset	Effect on Cancer Risk/Cancer Response	Potential Side Effects (Overlap with Immune Checkpoint Inhibitors)
HCQ	Low	Months	Likely no effect	None
Sulfasalazine	Low	Weeks–months	Likely no effect	Allergic reaction/ rash?
Methotrexate	Moderate	Weeks–months	Likely no effect	Liver toxicity
Leflunomide	Moderate	Weeks–months	Possible T-cell target	Liver toxicity
TNF inhibitors	High	Days–weeks	Possible melanoma risk	None
Abatacept	High	Weeks	*Likely impaired response*	None
Tocilizumab	High	Weeks	Unclear	*GI issues, colitis*
Tofacitinib (JAK inhibitors)	High	Weeks	Possible natural killer–cell target	*GI issues, colitis*
Azathioprine	Moderate	Months	Possible T-cell target	GI issues?
Mycophenolate	Moderate	Weeks–months	Possible T-cell target	GI issues?
Anakinra	Moderate	Days	Likely no effect	None
Secukinumab	Moderate	Weeks	Likely no effect	None

Drugs to avoid are listed in italic.
Abbreviation: GI, gastrointestinal.

De Novo Autoimmunity vs Evolution of Preclinical Autoimmunity?

Immune Checkpoint Inhibition and the Prevalence of Autoimmune Disorders Among Patients With Lung and Renal Cancer

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Table 1. Autoimmune disorders in patients with lung and renal cancer between the years 2009 and 2013.

AUTOIMMUNE DISORDER	AMONG PATIENTS WITH LUNG CANCER WITH AUTOIMMUNE DISEASE, NO. (%)	AMONG PATIENTS WITH RENAL CANCER WITH AUTOIMMUNE DISEASE, NO. (%)
Rheumatoid arthritis	2653 (20.2)	1490 (18.1)
Psoriasis	527 (4.0)	402 (4.9)
Systemic lupus erythematosus	225 (1.7)	120 (1.5)
Systemic sclerosis	78 (0.6)	20 (0.2)
Sicca syndrome	115 (0.9)	70 (0.9)
Autoimmune NOS	37 (0.3)	20 (0.2)
Autoimmune hepatitis	59 (0.5)	72 (0.9)
Primary biliary cirrhosis	38 (0.3)	33 (0.4)
Celiac disease	71 (0.5)	51 (0.6)
Ankylosing spondylitis	506 (3.9)	402 (4.9)
Polymyalgia rheumatica	227 (1.7)	141 (1.7)
Addison's disease	357 (2.7)	196 (2.4)
Ulcerative colitis	352 (2.7)	238 (2.9)
Crohn disease	258 (2.0)	208 (2.5)
Ménière disease	89 (0.7)	67 (0.8)
Hashimoto disease	89 (0.7)	67 (0.8)
Polyarteritis nodosa	174 (1.3)	89 (1.1)
Giant-cell arteritis	93 (0.7)	45 (0.6)
Pernicious anemia	710 (5.4)	301 (3.7)
Autoimmune hemolytic anemia	39 (0.3)	22 (0.3)
Idiopathic thrombocytopenic purpura	152 (1.2)	82 (1.0)
Thyrotoxicosis	157 (1.2)	100 (1.2)
Multiple sclerosis	200 (1.5)	103 (1.3)
Iridocyclitis	280 (2.1)	209 (2.5)
Pemphigus	32 (0.2)	33 (0.4)
Eczema	312 (2.4)	288 (3.5)
Alopecia Areata	34 (0.3)	26 (0.3)
Vitiligo	18 (0.1)	29 (0.4)
Wegener granulomatosis	28 (0.2)	21 (0.3)
Dermatopolymyositis	33 (0.3)	10 (0.1)
Myasthenia gravis	89 (0.7)	58 (0.7)
Scleroderma	62 (0.5)	47 (0.6)
Antiphospholipid	3 (0.0)	5 (0.1)
Guillain-Barré syndrome	28 (0.2)	23 (0.3)
Type 1 diabetes mellitus	1507 (11.5)	1189 (14.5)
Hypothyroidism	7334 (55.8)	4661 (56.7)
Hyperthyroidism	157 (1.2)	100 (1.2)
Sweet syndrome	215 (1.6)	183 (2.2)
Sjögren syndrome	115 (0.9	70 (0.9)
Pyoderma gangrenosum	7 (0.1)	1 (0.0)
Sarcoidosis	249 (1.9)	129 (1.6)

Abbreviations: NOS, Not Otherwise Specified.

Table 2. Characteristics of baseline characteristics and comorbidities between patients with lung and renal cancer with or without autoimmune disease.

	CANCER WITH AUTOIMMUNE (21 373)	CANCER WITHOUT AUTOIMMUNE (59 759)	*P* VALUE
	NO. (%)	NO. (%)	
Age categories, y			
<65	8393 (39.3)	25 672 (43.0)	<.0001
65-74	6439 (30.1)	16 762 (28.1)	<.0001
75-80	3545 (16.6)	9276 (15.5)	<.0001
>80	2996 (14.0)	8049 (13.5)	<.0001
Gender (F)	12 133 (56.8)	25 140 (42.1)	<.0001
CHF	2938 (13.8)	6860 (11.5)	<.0001
Arrhythmias	5530 (25.4)	13 659 (22.9)	<.0001
Valvular disease	2986 (14.0)	6920 (11.6)	<.0001
Pulmonary circulation	1150 (5.4)	2953 (4.9)	.0119
Peripheral vascular	5812 (27.2)	14 187 (23.7)	<.0001
Hypertension uncomplicated	13 814 (64.6)	35 614 (59.6)	<.0001
Hypertension complicated	2375 (11.1)	5067 (8.5)	<.0001
Paralysis	211 (1.0)	584 (1.0)	.899
Other neurological	1919 (9.0)	4231 (7.1)	<.0001
Chronic pulmonary	9063 (42.4)	25 053 (41.9)	.2219
Renal failure	3085 (14.4)	6130 (10.3)	<.0001
Liver disease	2528 (11.8)	6767 (11.3)	.047
Peptic ulcer disease	308 (1.4)	772 (1.3)	.1032
HIV/AIDS	33 (0.2)	116 (0.2)	.2445
Metastatic cancer	4340 (20.3)	15 952 (26.7)	<.0001
Coagulopathy	1145 (5.4)	2332 (3.9)	<.0001
Obesity	1598 (7.5)	3402 (5.7)	<.0001
Weight loss	1599 (7.5)	4778 (8.0)	.0165
Fluids and electrolytes	3549 (16.6)	8679 (14.5)	<.0001
Blood loss anemia	990 (4.6)	2075 (3.5)	<.0001
Deficiency anemia	1358 (6.4)	2835 (4.7)	<.0001
Alcohol abuse	278 (1.3)	1087 (1.8)	<.0001
Drug abuse	246 (1.2)	624 (1.0)	.1933
Psychoses	397 (1.9)	1148 (1.9)	.5595
Depression	2713 (12.7)	5888 (9.9)	<.0001
CHD	5791 (27.1)	14 702 (24.6)	<.0001

Abbreviations: CHF, congestive heart failure; CHD, coronary heart disease; HIV, human immunodeficiency virus.

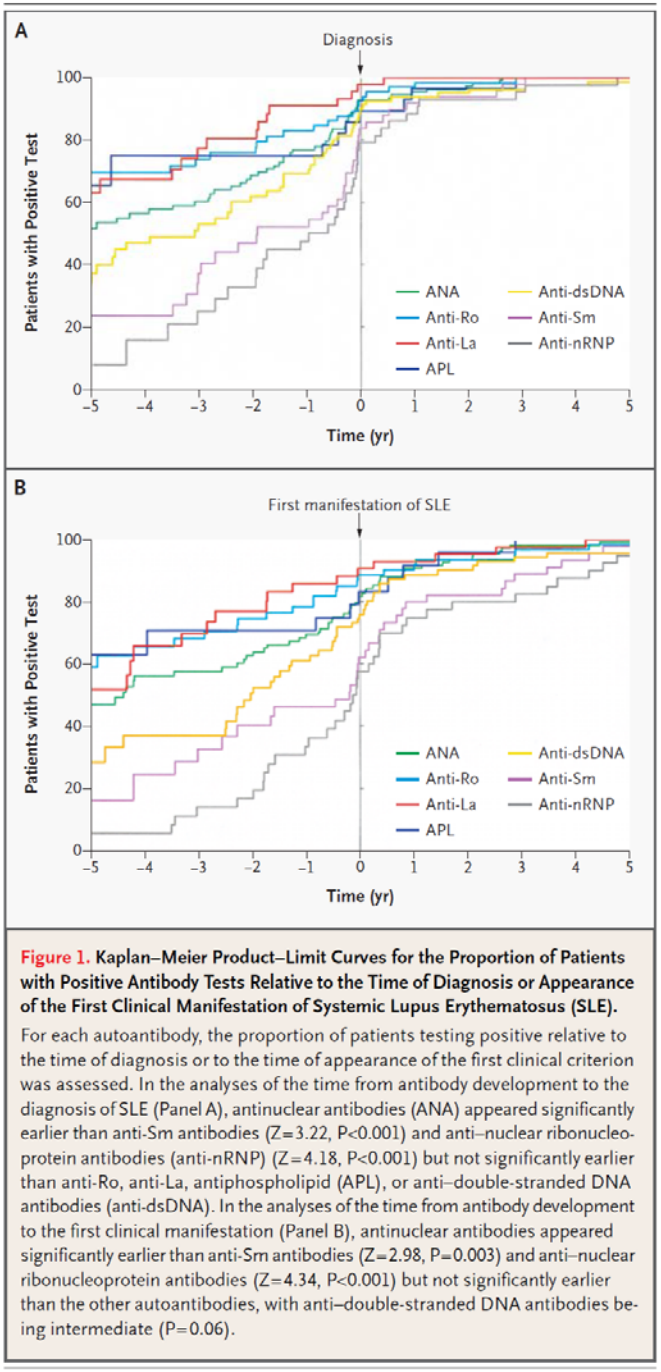


Figure 1. Kaplan–Meier Product–Limit Curves for the Proportion of Patients with Positive Antibody Tests Relative to the Time of Diagnosis or Appearance of the First Clinical Manifestation of Systemic Lupus Erythematosus (SLE).

For each autoantibody, the proportion of patients testing positive relative to the time of diagnosis or to the time of appearance of the first clinical criterion was assessed. In the analyses of the time from antibody development to the diagnosis of SLE (Panel A), antinuclear antibodies (ANA) appeared significantly earlier than anti-Sm antibodies ($Z=3.22$, $P<0.001$) and anti–nuclear ribonucleoprotein antibodies (anti-nRNP) ($Z=4.18$, $P<0.001$) but not significantly earlier than anti-Ro, anti-La, antiphospholipid (APL), or anti–double-stranded DNA antibodies (anti-dsDNA). In the analyses of the time from antibody development to the first clinical manifestation (Panel B), antinuclear antibodies appeared significantly earlier than anti-Sm antibodies ($Z=2.98$, $P=0.003$) and anti–nuclear ribonucleoprotein antibodies ($Z=4.34$, $P<0.001$) but not significantly earlier than the other autoantibodies, with anti–double-stranded DNA antibodies being intermediate ($P=0.06$).

Arbuckle et al, NEJM, 2003 349(16):1526-33

Take Home Points

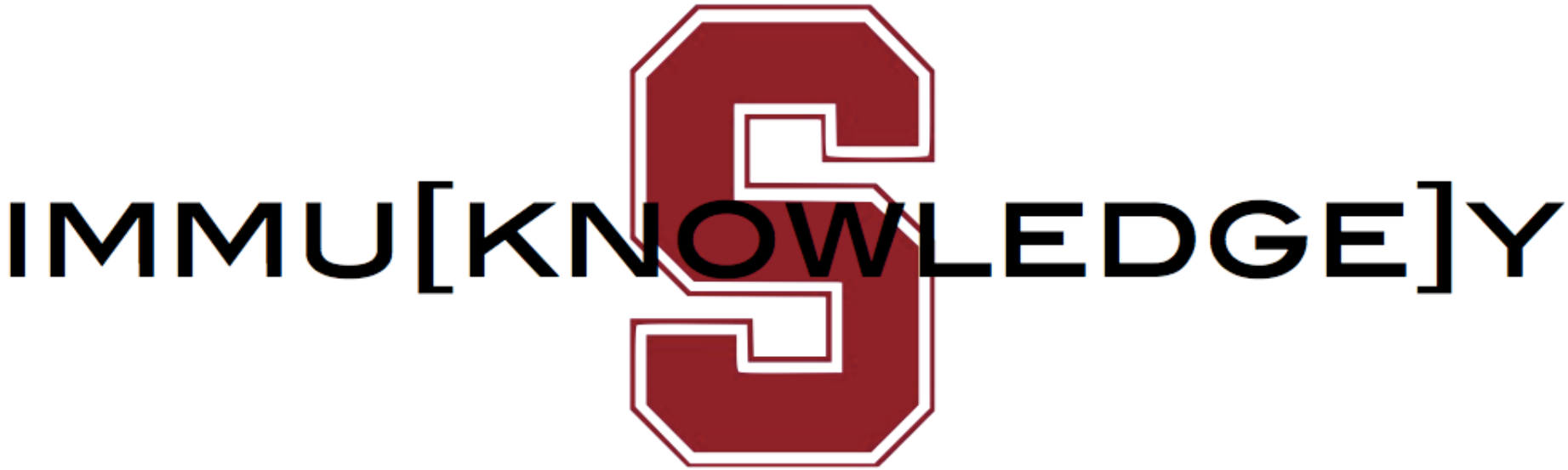
• Clear clinical association of rheumatic diseases and tumor immunotherapies

• Incidence will increase due to combination therapy, no longer excluding autoimmunity

• Autoimmune diseases (eg T1D, TA, SLE) clearly evolve over time and have preclinical phase

• Clinical autoantibody testing may predict adverse events

• What the field needs:
    - Registry of patients and baseline clinical samples
        - Serum
        - Plasma
        - PBMCs
        - RNA
        - DNA
    - Baseline tissue
    - Matching samples after adverse event (including controls)
    - Technologies to identify autoantigens, markers and predictors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ORIGINAL ARTICLE

Rheumatic and Musculoskeletal Immune-Related Adverse Events Due to Immune Checkpoint Inhibitors: A Systematic Review of the Literature

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Objective. Immune checkpoint inhibitors (ICIs) are improving prognoses in advanced stage cancers, but they also lead to immune-related adverse events (IRAEs). IRAEs targeting many organ systems have been reported, but musculoskeletal and rheumatic IRAEs have not been well-characterized. We systematically reviewed published literature on musculoskeletal and rheumatic IRAEs to better understand prevalence and clinical characteristics.

Methods. Medline and CENTRAL databases were searched for articles reporting rheumatic and musculoskeletal IRAEs secondary to ICI treatment. After screening abstracts and full texts in duplicate, clinical features, prevalence, and treatment data were extracted and summarized.

Results. A total of 1,725 unique abstracts were screened; 231 contained original data and were about ICIs and went to full-text screening. Fifty-two of these contained information about musculoskeletal or rheumatic IRAEs or about treatment with ICIs in preexisting autoimmune disease. Of these, 33 were clinical trials, 3 were observational studies, and 16 were case reports or series. Arthralgia prevalence in clinical trials ranged 1–43%, and myalgia was reported in 2–20%. Arthritis was reported in 5 of 33 clinical trials, and vasculitis was reported in only 2. One observational study and 3 case reports described patients with preexisting autoimmune disease treated with ICIs. Case reports included development of inflammatory arthritis, vasculitis, myositis, and lupus nephritis.

Conclusion. Arthralgia and myalgia have been reported commonly in patients treated with ICIs. The prevalence of rheumatic IRAEs such as inflammatory arthritis, vasculitis, and sicca syndrome is less clear from current evidence. There is limited observational and case-level evidence describing ICI use in patients with preexisting autoimmune disease.

Table 1. *(Cont'd)*

Author, year	Trial phase	Indication	No. exposed	Drug/s	Dose	Arthralgia	Arthritis	Dry eyes	Dry mouth	Myalgia	Muscle weakness	Vasculitis	Other
Yamazaki, 2015	2	Previously untreated advanced melanoma	15	IPI ± dacarb.	10 mg/kg	NR	NR	NR	NR	NR	NR	NR	Back pain: 4/15 (27%)
Yang, 2007	2	Metastatic RCC	47	IPI	Various	1/47 (2%)	NR	NR	NR	NR	NR	NR	NR
Calabro, 2014	2	Malignant mesothelioma	29	TML	DE	4 (14%)	NR	NR	NR	NR	NR	NR	NR
Ralph, 2010	2	Advanced gastric and esophageal adeno-carcinoma	18	TML	15 mg/kg	3/18 (17%)	NR	NR	NR	NR	NR	NR	NR
Sangro, 2013	2	HCC and hepatitis C	21	TML	15 mg/kg	NR	1/21 (5%)	NR	NR	NR	NR	NR	NR
Anti–CTLA-4 vs. anti–PD-1													
Robert 2015 (PMB)	3	Advanced melanoma	811	IPI vs. PMB	PMB: 10 mg/kg IPI 3 mg/kg	26/278 (9%) in Q2W PMB, 32 /277 (12%) in Q3W PMB, 13/256 (5%) in IPI	5/278 (2%) in Q2W, 1/277 (0.450 in Q2W)	NR	20/278 (8%) in Q2W PMB, 11/277 (4%) in Q3W PMB, 1/2,576 (0.4%) in IPI	19/278 (7%) in Q2W, 6/277 (2%) in Q3W, 2/256 (2%) in IPI	NR	NR	Myositis: 2/277 (1%) in Q3W, 1/256 (0.5%) in IPI MSK stiffness: 3/278 (1%) in Q2W, 2/277 (1%) in Q3W
Anti–PD-1													
Borghaei, 2015	3	NSCLC	287	NVL	3 mg/kg	46 (16%)	NR	NR	NR	18 (6%)	NR	NR	MSK pain: 39 (14%)
Brahmer, 2010	1	Refractory solid tumors	39	NVL	DE	2 (5%)	NR	NR	NR	NR	NR	NR	MSK "events": 6 (15%)
Brahmer, 2015	3	Squamous cell lung cancer	135	NVL	3 mg/kg	7 (5%)	NR	NR	NR	2 (2%)	NR	NR	NR
Gibney, 2014	1	Resected metastatic melanoma	33	NVL + peptide vaccine	DE	14 (43%)	NR	NR	8 (24%)	6 (18%)	4 (12%)	NR	"Eye disorders" (e.g., dry eyes) 8 (24%)
Motzer, 2015	2	Metastatic RCC	168	NVL	3 doses: 0.3 mg/kg, 2 mg/kg, 10 mg/kg	1/60 (2%) in 0.3 mg/kg, 4/54 (7%) in 2 mg/kg, 8/54 (15%) in 10 mg/kg	NR	NR	0.3 mg/kg: 2 /60 (3%), 2 mg/kg 3/54 (6%), 10 mg/kg 6/54 (11%)	NR	NR	NR	NR
Rizvi, 2015	2	Squamous NSCLC	117	NVL	3 mg/kg	NR	NR	NR	7/117 (6%)	6/117 (5%)	NR	NR	NR
Robert, 2015 (NVL)	3	Previously untreated stage III/IV melanoma	206	NVL	3 mg/kg	12/206 (6%)	NR	NR	NR	9/206 (4%)	NR	NR	Pain in extremity: 6/206 (3%)
Weber, 2015	3	Advanced melanoma; progressed after anti–CTLA-4	268	NVL	3 mg/kg	14/268 (5%)	NR	NR	NR	NR	NR	NR	NR
Ribas, 2015	2	IPI refractory melanoma	357	PMB	2 mg/kg, 10 mg/kg	13/178 (7%) in lower, 11/179 (6%) in higher	NR	NR	NR	9/178 (5%) in lower, 7/179 (4%) in higher	NR	NR	NR

Table 1. *(Cont'd)*

Author, year	Trial phase	Indication	No. exposed	Drug/s	Dose	Arthralgia	Arthritis	Dry eyes	Dry mouth	Myalgia	Muscle weakness	Vasculitis	Other
Robert, 2014†	1	Metastatic melanoma	173	PMB	2 mg/kg, 10 mg/kg	NR	NR	NR	NR	NR	1/89 (1%) in 2 mg/kg group	NR	MSK pain: 1/84 (1%) in 10 mg/kg group
Anti–PD-L1													
Brahmer, 2012	1	Advanced cancers	207	MDX-1105	DE	15 (7%)	NR	NR	NR	NR	NR	NR	Sarcoid: 1 (0.5%)
Combination anti–CTLA-4 and anti–PD-1													
Larkin, 2015	3	State III or IV melanoma	945	IPI, NVL, or comb.	3 mg/kg IPI 3 mg/kg NVL, 3 mg/kg IPI + 1 mg/kg NVL	NVL: 24/313 (7.7%), IPI 9/311 (6.1%), both 33/313 (10.5%)	NR	NR	NR	NR	NR	NR	NR
Postow, 2015	1	Metastatic melanoma	142	IPI ± NVL	DE	10/94 (10%) in comb., 4/46 (9%) in IPI	NR	NR	NR	9/94 (10%) comb., 6/46 (13%) in IPI	NR	NR	NR

* References for cited studies can be seen in Supplementary Appendix B, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23177/abstract. IPI = ipilimumab; DE = dose escalation; NR = not reported; dacarb. = dacarbazine; *Cancer Immunol Res = Cancer Immunology Research;* GCA = giant cell arteritis; *JAMA = Journal of the American Medical Association*; sargra. = sargramostim; comb. = combination/combined; MSK = musculoskeletal; GVAX = GM-CSF secreting cancer vaccine; NSCLC = non–small-cell lung cancer; IL-2 = interleukin-2; chemo. = chemotherapy; RCC = renal cell carcinoma; TML = tremelimumab; HCC = hepatocellular carcinoma; PMB = pembrolizumab; Q2W = every 2 weeks; Q3W = every 3 weeks; NVL = nivolumab.

† Only reported grade 3 or higher adverse events.