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IN THIS ISSUE

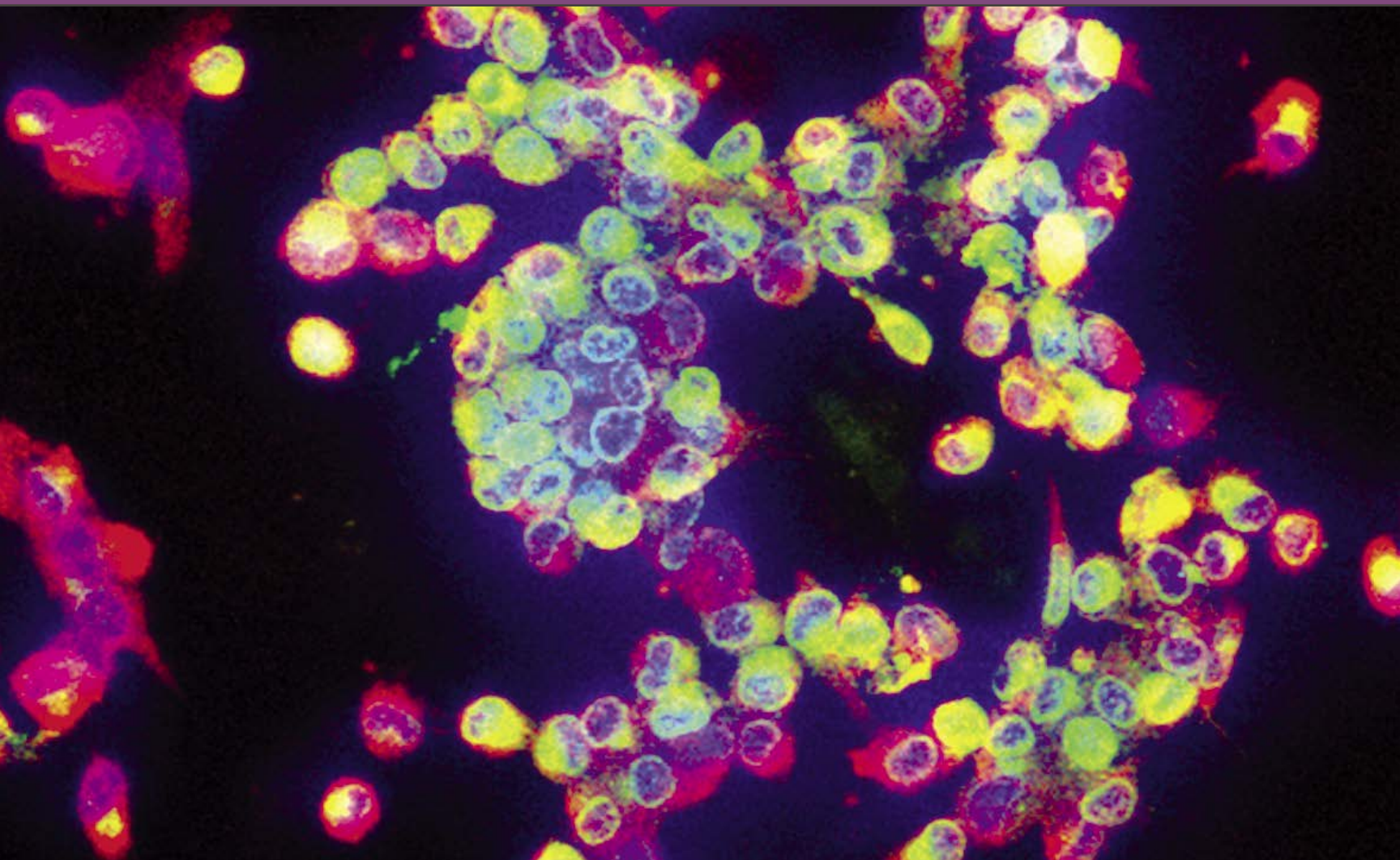
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Abatacept in GCA & TAK 3 | Checkpoint Therapy & Rheumatic Diseases 5 | SSc and Malignancy 7 | PRECISION Results 9  
Biologics Summit Recap 10 | Eosinophilic Granulomatosis with Polyangiitis 12 | Biologics for Metabolic Bone Disease 14  
HBV Reactivation After Immunosuppressives 16 | Thoughts on the ACR Workforce Study 18



# Rheumatology Connections

An Update for Physicians | Summer 2017



From the Chair of Rheumatic  
and Immunologic Diseases



## Dear Colleagues,

Few professional experiences compare with the focused, collaborative energy pulsing through the lecture halls and meeting rooms of an excellent conference or meeting. It's now easier than ever to collaborate from afar on research, education and even patient care, but there's something especially energizing about being present among colleagues that reignites the creativity and zest we sometimes lose in our day-to-day work lives.

While participating in the recent Biologic Therapies Summit VII, hosted by our own R.J. Fasenmyer Center for Clinical Immunology, I was reminded that this is such an exciting time in which we and our patients are living,

with what Leonard H. Calabrese, DO, calls "fundamental" changes in the way we treat immune-mediated inflammatory diseases (p. 10). Chad Deal, MD, in his examination of biologic treatments for metabolic bone diseases, illustrates this seismic shift (p. 14). Carol A. Langford, MD, MHS, who co-directed the Primary Vasculitides Presymposium with Rula Hajj-Ali, MD, and Dr. Calabrese, describes results from her most recent research, the first randomized, controlled trial examining Takayasu arteritis (p. 3).

Meeting speakers and participants reflected the truly interdisciplinary nature of our work as rheumatologists, and we've sought to capture that collaborative spirit in this issue of *Rheumatology Connections*. Dr. Hajj-Ali writes with a colleague in cardiovascular medicine and clinical genomics about the rare, chronic eosinophilic granulomatosis with polyangiitis (p. 12). In another collaboration with cardiovascular medicine, M. Elaine Husni, MD, MPH, discusses PRECISION trial results (p. 9). Dr. Calabrese discusses a recent study co-authored with a Cleveland Clinic Cancer Center colleague around checkpoint therapy (p. 5). Dr. Deal offers his thoughts on the American College of Rheumatology's 2015 Workforce Study, on which he collaborated with dozens of rheumatologists across disciplines and subspecialties (p. 18).

I always appreciate the opportunity to learn from esteemed colleagues from our and other institutions in meetings like these, as we seek to "educate those who serve," a critical part of Cleveland Clinic's tripartite mission. Two articles in this issue feature the cross-disciplinary work of our fellows, including the collaboration of Soumya Chatterjee, MD, MS, FRCP, and Pichaya OCharoen, MD, investigating systemic sclerosis and malignancy (p. 7) and the work of Cassandra Calabrese, DO, on checkpoint therapy (p. 5).

While this may not substitute for the in-person intellectual exchange of a great panel session, I hope this issue of *Rheumatology Connections* inspires your collaborative spirit, be it in caring for the sick, investigating their conditions or educating those who serve. I look forward to hearing your thoughts, feedback and questions.

Respectfully,

A handwritten signature in cursive script that reads "Abby Abelson".

Abby Abelson, MD  
Chair, Rheumatic and Immunologic Diseases  
216.444.3876 | [abelsoa@ccf.org](mailto:abelsoa@ccf.org)



Cleveland Clinic's Rheumatology Program is ranked among the top 3 in the nation in *U.S. News & World Report's* "America's Best Hospitals" survey.

*Rheumatology Connections*, published by Cleveland Clinic's Department of Rheumatic and Immunologic Diseases, provides information on leading-edge diagnostic and management techniques as well as current research for physicians.

**Please direct any correspondence to:**  
**Abby Abelson, MD**

Chair, Rheumatic and Immunologic Diseases

Cleveland Clinic/A50  
9500 Euclid Ave.  
Cleveland, OH 44195  
216.444.3876  
[abelsoa@ccf.org](mailto:abelsoa@ccf.org)

**Managing Editor:** Deborah Booth Summers

**Art Director:** Barbara Ludwig Coleman

**Photography:** Kenneth Baehr, Don Gerda,  
Willie McAllister Jr.

**Medical Illustration:** Beth Halasz, MFA, CMI

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# ABATACEPT IN GIANT CELL ARTERITIS AND TAKAYASU ARTERITIS

By Carol A. Langford, MD, MHS

**T**he results from two studies examining abatacept (CTLA4-Ig) in giant cell arteritis (GCA) and Takayasu arteritis (TAK) were recently published in *Arthritis & Rheumatology*.<sup>1,2</sup> These trials were conducted by the Vasculitis Clinical Research Consortium (VCRC) and funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).<sup>\*</sup> The results from these studies were interesting not only for their individual findings but also because they found a divergence in the effectiveness of abatacept between GCA and TAK.

## GCA and TAK — unique and similar challenges

GCA and TAK are two forms of large vessel vasculitis that have unique differences but many similar challenges. GCA is the most common form of vasculitis and occurs in people over the age of 50, most often in their 70s. Since the 1950s, prednisone has been the foundation of treatment for GCA and has been proven to reduce the risk of blindness. However, this has been associated with significant toxicity. In contrast to GCA, TAK is one of the rarest forms of vasculitis, affecting about three to nine people per million, and predominantly affects young women. Prednisone has again been found to be effective, but the side effects have made this an often unacceptable option to patients.

The interest in investigating abatacept in GCA and TAK was based not only on this unmet need to identify treatment options beyond prednisone but also on the safety profile of this medication and its mechanism of action. Abatacept is comprised of the ligand-binding domain of CTLA4 plus a modified Fc domain derived from IgG1. As CTLA4 acts as a negative regulator of CD28-mediated T cell costimulation, abatacept inhibits T cell activation. Laboratory evidence suggests that GCA and TAK are antigen-

driven diseases, in which T lymphocytes play an important role. By interfering with the T cell activation, abatacept carried the potential to impact a mechanism involved in disease pathogenesis.

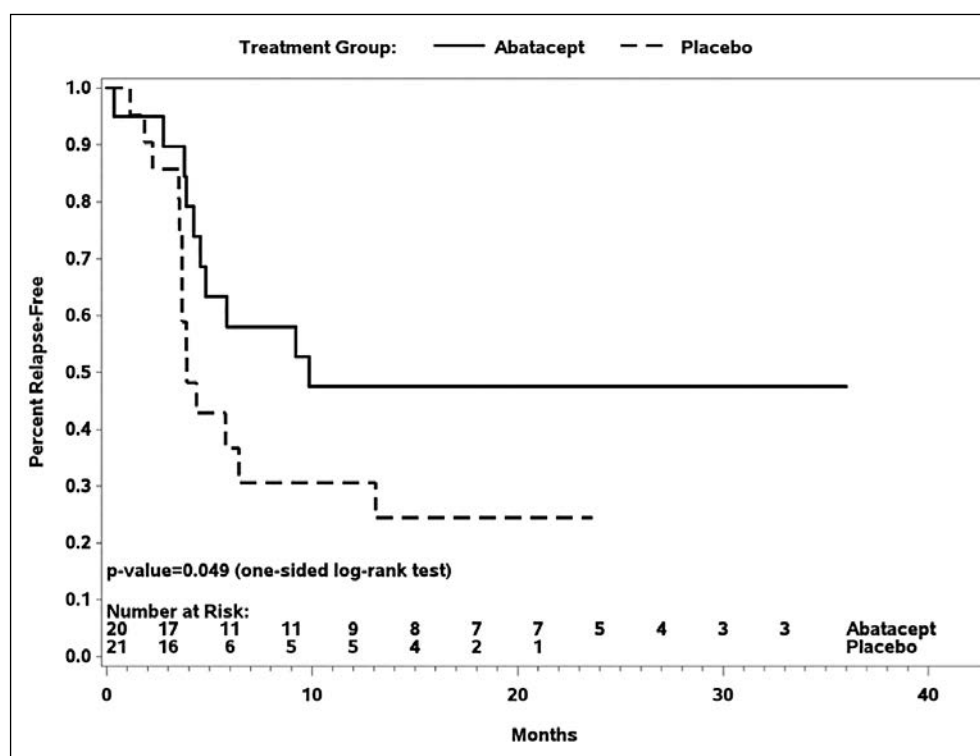
In these trials, patients were initially treated with abatacept and prednisone. At week 12 those in remission underwent a double-blinded randomization to remain on abatacept or be switched to placebo. All patients received a standardized prednisone taper with discontinuation of prednisone at week 28. Patients remained on their blinded treatment assignment until meeting a criteria for early termination or reaching the common close date, which was 12 months after randomization of the final patient with that disease. The primary endpoint was remission duration (relapse-free survival).

## Giant cell arteritis — a positive result in reducing relapse

In the GCA trial, 49 patients received the study drug, with 41 reaching randomization. The relapse-free survival at 12 months was 48 percent for those receiving abatacept and 31 percent for those receiving placebo ( $P = 0.049$ ) (Figure 1). A longer median duration of remission was seen with abatacept (9.9 months) compared with placebo (3.9 months,  $P = 0.023$ ). There was no difference in the frequency or severity of adverse events between treatment arms. These results demonstrated that in patients with GCA, the addition of abatacept to prednisone reduced the risk of relapse and was not associated with a higher rate of toxicity compared with prednisone alone.



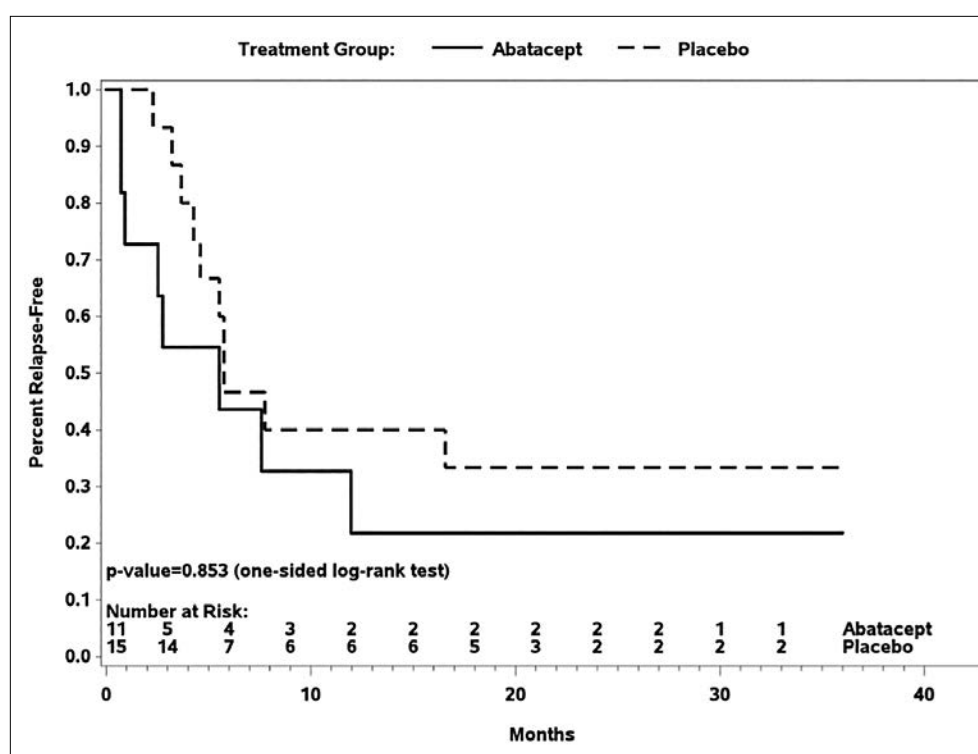
Dr. Langford (langfoc@ccf.org; 216.445.6056) is Director of the Center for Vasculitis Care and Research and Vice Chair for Research, Department of Rheumatic and Immunologic Diseases.



**Figure 1.** Relapse-free survival following randomization in giant cell arteritis. Republished with permission (see reference 1).



**Figure 2.** Relapse-free survival following randomization in Takayasu arteritis. Republished with permission (see reference 2).



### Takayasu arteritis — abatacept did not impact relapse-free survival

In the TAK trial, 34 patients received the study drug, with 26 reaching randomization. The relapse-free survival at 12 months was 22 percent for those receiving abatacept and 40 percent for those receiving placebo ( $P = 0.853$ ) (Figure 2). Treatment with abatacept in patients with TAK enrolled in this study was not associated with a longer median duration of remission (abatacept 5.5 months, placebo 5.7 months). There was once again no difference in the frequency or severity of adverse events between treatment arms. Therefore, in patients with TAK enrolled in this trial, the addition of abatacept to prednisone did not reduce the risk of relapse.

### Valuable messages from both trials — individually and together

Both of these trials provided important advancements to the field.

For GCA, the finding that abatacept combined with prednisone extended the duration of remission beyond treatment with prednisone alone was a

significant finding. With the ongoing need to identify additional treatment options in GCA, it is hoped that the results from this trial could lead to a novel therapeutic approach in this disease.

For TAK, although abatacept was not found to provide additional benefit beyond prednisone, the study was significant in being the first randomized trial to be conducted in this disease. By demonstrating that comparative studies in TAK are possible, this work will advance future investigations in TAK.

Another novel aspect of these studies is that these trials were designed to be conducted in parallel by the same investigator team using the same study protocol with the goal of exploring the similarities and differences between these two forms of large-vessel vasculitis. The observation of contrasting results raises intriguing questions about these diseases and highlights the importance of continued research in vasculitis.

\*These projects were funded in whole or in part with federal funds from the

National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, and Department of Health and Human Services, under Contract HHSN2682007000036C.

Physicians with questions about these studies, ongoing research in vasculitis at Cleveland Clinic, or for referrals should contact Dr. Langford.

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# IMMUNE-RELATED ADVERSE EVENTS: CHECKPOINT THERAPY AND RHEUMATIC DISEASES

By Leonard Calabrese, DO, and Cassandra Calabrese, DO

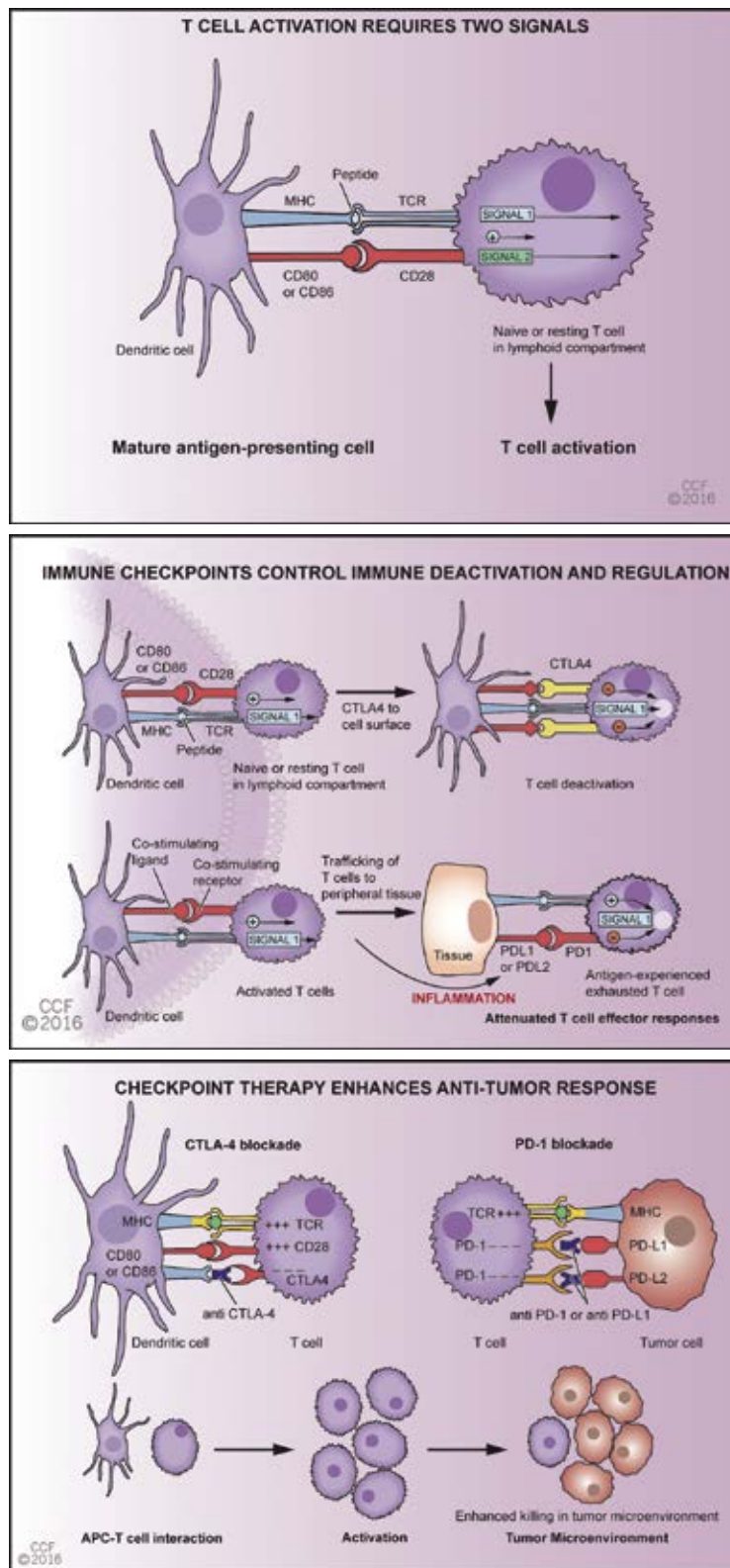
For a generation, those of us in the field of immuno-oncology have dreamed of harnessing the power of the immune system to fight cancer. After many failed trials of agents associated with poor outcomes or unacceptable toxicity, the introduction of new immunotherapies for a variety of cancers has energized the field in the past decade.

Currently there are four FDA-approved agents: ipilimumab, nivolumab, pembrolizumab and atezolizumab (Table). These therapies have produced significant and sometimes dramatic survival benefits in patients with metastatic melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma and urothelial carcinoma, and they are under investigation for many others. In addition, many other agents targeting different sites of immune-control pathways are now entering clinical trials.

## Mechanism of action

The agents' underlying biology and mechanism of action exploit the adaptive immune response to restrain itself in situations in which a danger signal endures despite robust effector cell pathway activation. Two situations serve as classic examples of this phenomenon: chronic viral infections such as HIV, where the pathogen may persistently replicate and challenge the host day after day for decades, and malignancies that are perceived as a danger signal but evade host defenses. Figure 1 depicts the two pathways that are currently the focus of approved agents.

Recently, a number of complex and challenging rheumatic disorders have been described that add to the more common dermatologic, gastroenterologic, pulmonary and endocrine immune-related adverse events (irAEs). While the exact incidence and prevalence have yet to be described, we estimate that rheumatic complications occur in about 5 percent of patients. Rheumatic complications have included polyarthritis, vasculitis, polymyalgia rheumatica, inflammatory myositis, sicca syndrome and more. In a recent analysis of our early experience, we found serious rheumatic



Dr. L. Calabrese (calabrl@ccf.org; 216.444.5258) is Director of the R.J. Fasenmyer Center for Clinical Immunology in Cleveland Clinic's Department of Rheumatic and Immunologic Diseases.



Dr. C. Calabrese is a fellow in the Department of Rheumatic and Immunologic Diseases.

Figure 1. Republished with permission from Calabrese et al., Ann Rheum Dis. 2017;76:1-3.

Table. FDA-approved immunotherapeutic agents.

AGENT	MOLECULAR TARGET	MALIGNANCY APPROVED FOR	YEAR APPROVED
Pembrolizumab	PD-1	Non-small cell lung cancer	2015
		Melanoma	2014
Nivolumab	PD-1	Hodgkin lymphoma	2016
		Renal cell carcinoma	2015
		Non-small cell lung cancer	2014
		Melanoma	2013
Atezolizumab	PDL-1	Urothelial carcinoma	2016
Ipilimumab	CTLA-4	Melanoma, in combination with nivolumab	2014
		Melanoma	2011

complications, the majority requiring glucocorticoids and even a second biologic agent. In almost all cases, these symptoms required interruption of immunotherapy for the underlying cancer and thus are truly life-threatening. We currently lack consensus on optimal therapy. We addressed these issues in detail at the recent Biologic Therapies VII Summit.

While the exact incidence and prevalence have yet to be described, we estimate that rheumatic complications occur in about 5 percent of patients.

**Virtual clinic, ongoing research**  
With Vamsidhar Velcheti, MD, of Cleveland Clinic Cancer Center, we have

created a virtual clinic where physicians and advanced practitioners can electronically share and triage patients with irAEs to the appropriate specialist. The clinic also serves as an excellent platform for research.

The integrated Cleveland Clinic team has been prospectively and longitudinally collecting data on a cohort of patients with rheumatic irAEs. These data were presented at the national meeting of the American College of Rheumatology in 2016 and were recently published in *Rheumatic & Musculoskeletal Diseases*.<sup>1</sup>

In these reports we described a series of 15 patients, including two patients with established rheumatic disease evaluated in anticipation of immunotherapy, and 13 patients without pre-existing autoimmune disease who subsequently developed rheumatic irAEs on therapy. Our initial experience reflects a broad spectrum of rheumatic disorders including inflammatory arthritis, sicca syndrome, polymyalgia rheumatic-like symptoms and inflamma-

tory myositis. We observed that the majority of patients developed rheumatic irAEs within 12 weeks of starting immunotherapy, and that most often these symptoms persisted despite cessation of therapy.

All patients required at least moderate doses of glucocorticoids to treat their rheumatic symptoms, and three required additional therapy with antitumor necrosis alpha, intravenous immunoglobulin or hydroxychloroquine. Current plans include accruing new patients into the database as well as longitudinal follow-up of incident cases, as the long-term outcomes of these complications are not well-understood.

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# SYSTEMIC SCLEROSIS AND MALIGNANCY

By Pichaya OCharoen, MD, and Soumya Chatterjee, MD, MS, FRCP

**T**he increased incidence of malignancies in systemic sclerosis (SSc) accounts for about 10 percent of the mortality in this disease.<sup>1</sup> In 1886, Hildebrand reported the first case, where a patient with SSc died from metastatic cutaneous squamous cell carcinoma. After the 1950s, more cases of malignancy were reported in SSc patients. In 1979, Duncan et al. published a study showing that 4 percent of SSc patients developed cancer, most commonly breast cancer, followed by lymphoma/leukemia, gastrointestinal malignancy and cervical cancer.<sup>2</sup> Subsequent studies demonstrated high standardized incidence ratios (SIR) of overall cancer; lung, bladder and liver cancer; and hematologic malignancies.<sup>3</sup> Lung cancer was found to be related to interstitial lung disease, lower forced vital capacity, positive anti-topoisomerase I (Scl-70) antibody and cyclophosphamide use.<sup>4</sup>

## Association with specific scleroderma autoantibodies

The three main autoantibodies associated with SSc are anticentromere, anti-Scl-70 and anti-RNA polymerase III (RNAP III). Prior studies have shown that patients with RNAP III tend to have a close temporal correlation between onset of cancer and SSc.<sup>5,6</sup> Breast cancer was the most common cancer reported in these studies.

RNA polymerase III is involved in protein synthesis and cell growth, and was found to be overexpressed in both metastatic and neoplastic cells. Nucleolar staining of RNA polymerase III was found exclusively in breast and ovarian cancer tissue from RNAP III-positive SSc patients, but not from RNAP III-negative SSc patients or normal controls.<sup>6</sup> This finding suggests that RNA polymerase III expression in tumor cells might trigger the autoantibody response. Mutations in the *POLR3A* gene were found in tumors from some patients

with positive RNAP III. Mutated RNA polymerase III was shown to generate RNAP III that cross-reacted with wild-type RNA polymerase III. Interestingly, mutated RNA polymerase III also triggered specific T cell response.<sup>7</sup>

The interval of SSc onset at breast cancer diagnosis was much shorter in RNAP III-positive patients compared with anticentromere and anti-Scl-70 antibody-positive patients.

## Proposed pathogenic mechanisms of oncogenesis in SSc

Several hypotheses have been proposed to explain the pathogenesis of malignancy in SSc.<sup>8</sup> Malignant transformation could occur secondary to chronic inflammation and fibrosis. For example, lung cancer has been associated with interstitial lung disease. Similarly, esophageal adenocarcinoma occurs in patients with long-standing gastroesophageal reflux disease leading to Barrett's esophagus. Moreover, immunosuppressive medication use, particularly cyclophosphamide, has been associated with bladder cancer and hematologic malignancies. Although mycophenolate mofetil is increasingly being used in scleroderma patients, its association with development of malignancy is unknown at this time. The close temporal correlation between cancer diagnosis and SSc onset in patients with positive RNAP III

raises the possibility that in this autoantibody subset, SSc may occur as a paraneoplastic phenomenon.

In addition to SSc, patients have also been reported to develop scleroderma-like skin changes after receiving radiation therapy or certain chemotherapeutic agents such as bleomycin, carboplatin, gemcitabine and paclitaxel. Finally, there could be a shared genetic susceptibility or environmental exposure between malignancy and SSc.

## Systemic sclerosis and breast cancer

There are conflicting reports of incidence of breast cancer in SSc. Some studies have shown an increased incidence, with SIR ranging from 1.62 to 6.1.<sup>9</sup> Other studies have failed to show this increased incidence. In addition, two studies demonstrated a close temporal correlation between the onset of SSc and breast cancer: 11.5 months<sup>9</sup> and 2.5 years,<sup>10</sup> respectively. However, in other studies, the median interval between onset of breast cancer and that of SSc was more than five years. To clarify these reported discrepancies, our group became interested in studying the development of breast cancer in SSc patients and comparing these patients with a nonscleroderma cohort of breast cancer patients.

We conducted a retrospective chart review to analyze the relationship between breast cancer and scleroderma in patients who were seen at Cleveland Clinic between January 2006 and May 2016. We compared 51 SSc patients who developed breast cancer (identified by ICD-9 and ICD-10 codes) with 102 patients with breast cancer alone. We excluded patients with mixed connective tissue disease or scleroderma-myositis overlap.

In our study, all patients were females, and most of them were Caucasian in their late 50s. Most patients had limited



Dr. OCharoen is a fellow in the Department of Rheumatic and Immunologic Diseases.



Dr. Chatterjee (chattes@ccf.org; 216.444.9945) is Director of the Scleroderma Program, Department of Rheumatic and Immunologic Diseases.

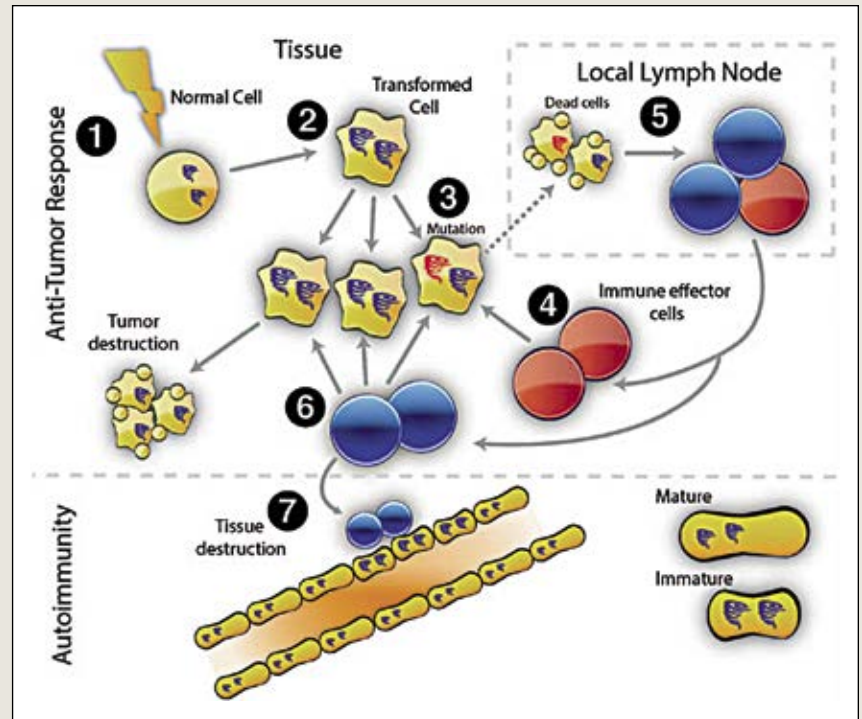


cutaneous SSc, with positive anticentromere antibody. This was followed in prevalence by RNAP III and anti-Scl-70 antibody, respectively. About a fifth of patients with positive RNAP III developed SSc within three years of breast cancer diagnosis. We found that the interval of SSc onset after breast cancer diagnosis was much shorter in RNAP III-positive patients compared with anticentromere and anti-Scl-70 antibody-positive patients. However, this association did not achieve statistical significance, probably because of small sample size.

SSc patients who subsequently developed breast cancer received less radiation therapy compared with patients with breast cancer alone. Also, patients with breast cancer and SSc had much higher mortality compared with patients with breast cancer alone. Further investigations with larger sample sizes are necessary to explore the relationship between SSc and malignancy.

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Model for cancer-induced autoimmunity. Transformation of normal cells (1) may result in gene expression patterns that resemble immature cells involved in tissue healing (2). Occasionally, autoantigens become mutated (3); these are not driver mutations, and not all cancer cells have them. The first immune response is directed against the mutated form of the antigen (4), and may spread to the wild-type version (5). Immune effector cells directed against the mutant (depicted in red) delete exclusively cancer cells containing the mutation (6). Immune effector cells directed against the wild type (depicted in blue) delete cancer cells without the mutation and also cross-react with the patient's own tissues (particularly immature cells expressing high levels of antigen, found in damaged/repairing tissue) (7). Once autoimmunity has been initiated, the disease is self-propagating. Immature cells (expressing high antigen levels) that repair the immune-mediated injury can themselves become the targets of the immune response, sustaining an ongoing cycle of damage/repair that provides the antigen source that fuels the autoimmune response. *Republished with permission from Shah AA, Casciola-Rosen L, Rosen A. Review: cancer-induced autoimmunity in the rheumatic diseases. Arthritis & Rheumatol. 2015;67:317-326.*

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# PRECISION RESULTS = PRECISELY TAILORED ARTHRITIS TREATMENT

Ten-year data show celecoxib noninferior to NSAIDs

By M. Elaine Husni, MD, MPH

**T**he aptly named PRECISION trial results challenged many assumptions about the use of nonselective NSAIDs versus selective COX-2 inhibitors when they were released in November 2016. Many osteoarthritis (OA) and rheumatoid arthritis (RA) patients rely on celecoxib, the only COX-2 inhibitor still marketed in the U.S., but we assumed that they faced a greater risk for cardiovascular (CV) disease.

We now have more options given the similar CV risk profiles of these commonly used NSAIDs and can offer a more nuanced approach depending on individual patient factors such as comorbidities.

PRECISION data tell us that's not so. The randomized controlled trial of 24,081 patients is aptly named because the findings allow rheumatologists to offer more individualized treatment to patients on chronic NSAIDs. PRECISION found celecoxib to be as safe as naproxen and ibuprofen in terms of cardiovascular risk. A few key findings from secondary analyses impact how we treat patients with OA and RA.

## KEY FINDINGS: OSTEOARTHRITIS

In patients with OA (mean age 63.5 years), celecoxib:

- Carries less CV risk than ibuprofen (HR = 0.84, 95% CI 0.72-0.98,  $P = 0.03$ ) and similar risk to naproxen.
- Has less gastrointestinal risk than ibuprofen (HR = 0.68, 95% CI 0.51-0.91,  $P = 0.01$ ) and naproxen (HR = 0.73, 95% CI 0.55-0.98,  $P = 0.04$ ).
- Had fewer renal adverse events than ibuprofen and similar rates with naproxen (HR = 0.58, 95% CI 0.40-0.82,  $P = 0.003$ ).
- Was similar to both ibuprofen and naproxen in all-cause mortality.

## KEY FINDINGS: RHEUMATOID ARTHRITIS

For patients with RA (mean age 60.7 years):

- The study found no difference in the rates of major CV and renal adverse events among the three drugs.
- Found a lower but statistically insignificant rate of GI adverse events with celecoxib than with naproxen and ibuprofen.
- Found a doubling of all-cause mortality in patients who used naproxen vs. celecoxib (HR = 0.47, 95% CI 0.25-0.88,  $P = 0.02$ ).

### Limitations and implications for practice

These subgroup analyses are hypothesis-generating rather than definitive, but we can extrapolate some of these differences to help guide a more tailored treatment approach for our arthritis patients. We now have more options given the similar CV risk profiles of these commonly used

NSAIDs and can offer a more nuanced approach depending on individual patient factors such as comorbidities.

The PRECISION trial results have challenged the medical community and highlight the need to perform prospective randomized trials to obtain more accurate answers to pressing clinical questions.



Dr. Husni (husnie@ccf.org; 216.445.1853) directs both the Arthritis and Musculoskeletal Treatment Center and Cleveland Clinic's disease-specific biorepositories.

# BIOLOGICS SUMMIT CONTINUES TO GROW

Over 300 attendees address breakthroughs in translational immunology

**H**ealthcare providers from 10 countries and 33 states recently gathered in Cleveland for the seventh annual Biologic Therapies Summit and the Primary Vasculitides Presymposium. Physicians, scientists and advanced practice providers from virtually every medical specialty and scientific field heard their colleagues on the leading edge of this work highlight the hopes and challenges of precision medicine for the nearly 50 million people in the U.S. with disorders of immunity.

"In 2005, we started the summit to coincide with the opening of the R.J. Fasenmyer Center for Clinical Immunology and serve part of our threefold mission to educate other physicians, healthcare workers and the general public regarding immunologic diseases," says Leonard H. Calabrese, DO, Director of the center and the summit. "What started out as a local meeting grew to regional, then national, and now is broadcast and simulcast internationally as one of the top meetings in the field."



Dr. Calabrese, Director of the summit, converses with attendees.

## PRESENTERS FROM THE DEPARTMENT OF RHEUMATIC AND IMMUNOLOGIC DISEASES AT CLEVELAND CLINIC INCLUDED:

- **Cassandra Calabrese, DO**
- **Tiffany Clark, CNP**
- **Chad Deal, MD**
- **Rula Hajj-Ali, MD**
- **Alexandra Villa-Forte, MD, MPH**
- **Leonard Calabrese, DO**
- **Carol A. Langford, MD, MHS**
- **Carmen Gota, MD**
- **M. Elaine Husni, MD, MPH**

## HIGHLIGHTING THE COLLABORATIVE NATURE OF THE DEPARTMENT'S WORK AND THE WIDE RANGE OF APPLICATIONS IN BIOLOGIC THERAPIES, OTHER CLEVELAND CLINIC PARTICIPANTS INCLUDED:

- **Anthony Fernandez, MD, PhD, Dermatology & Plastic Surgery Institute**
- **Heather Gornik, MD, W.H. Wilson Tang, MD, Sydell and Arnold Miller Family Heart & Vascular Institute**
- **Fred Hsieh, MD, Michael S. Machuzak, MD, Joseph Parambil, MD, Respiratory Institute**
- **Carlos Isada, MD, Department of Infectious Disease, Medicine Institute**
- **Stephen Jones, MD, PhD, Imaging Institute**

Iain McInnes, PhD, gave the R.J. Fasenmyer Annual Lectureship, titled "Cytokine Profiles in Health and Disease — What Can They Inform Us?" Dr. McInnes is Muirhead Professor of Medicine, ARUK Professor of Rheumatology and Director of the Institute of Infection Immunity and Inflammation at the University of Glasgow.

The summit's growth illustrates the impact of biologics on the field. "I believe that biologics have changed rheumatology and the treatment of immune-mediated inflammatory diseases fundamentally," says Dr. Calabrese.

"They've raised the bar; we are no longer satisfied with small outcomes ... these great responses in patients improve quality of life and productivity and increase longevity."

This issue of *Rheumatology Connections* includes insights from several summit presentations, including Drs. Hajj-Ali and Tang's collaboration on eosinophilic granulomatosis with polyangiitis (p. 12), Dr. Deal's discussion of biologics in the treatment of metabolic bone disease (p. 14) and Dr. Calabrese's examinations of hepatitis B reactivation (p. 16) and immune-related adverse events (p. 5).



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**Photo 1.** Dr. Calabrese opens the summit with a brief history of Cleveland Clinic.

**Photo 2.** Dr. Hajj-Ali presents on EGPA during the summit (see p. 12).

**Photo 3.** The cross-disciplinary conference featured experts like Dr. Parambil from the Respiratory Institute speaking on idiopathic pulmonary fibrosis.

**Photo 4.** Dr. Husni presents on the controversies and best practices in cardiovascular disease across IMIDs on the final day of the summit.

**Photo 5.** Dr. Deal presents on advances in biologics for metabolic bone disease (see p. 14).



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# EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS: A DISEASE AT THE CROSSROADS

## Classification, diagnosis and treatment

By Rula Hajj-Ali, MD, and W.H. Wilson Tang, MD



Dr. Hajj-Ali  
(hajjalr@ccf.org;  
216.444.9643) is  
Associate Director  
of the Center for  
Vasculitis Care  
and Research.



Dr. Tang  
(tangw@ccf.org;  
216.444.2121) is  
Director of the  
Center for Clinical  
Genomics and staff  
in the Miller Family  
Heart & Vascular  
Institute.

**E**osinophilic granulomatosis with polyangiitis (EGPA) is considered a rare, orphan type of antineutrophilic cytoplasmic antibody (ANCA)-associated vasculitis. The disease is chronic with major morbidities involving vital organs including the heart, nervous system and kidneys. Asthma exacerbations remain a problematic manifestation that often do not respond to immunosuppressive treatment and thus require high doses of glucocorticoids.

I recently discussed the challenges of and prognosis for this peculiar disease at the crossroads of primary systemic vasculitides and hypereosinophilic disorders at the Primary Vasculitides Presymposium hosted by Cleveland Clinic. I also asked my colleague W.H. Wilson Tang, MD, Director of the Center for Clinical Genomics and staff in the Miller Family Heart & Vascular Institute, to discuss EGPA and the heart.

### EGPA the disease

EGPA is an eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract. This necrotizing vasculitis predominantly affects small to medium vessels and is often associated with asthma and eosinophilia, with common findings of nasal polyps and granulomatous and nongranulomatous extravascular inflammation. Formerly called Churg-Strauss syndrome, this multisystemic disease mostly affects patients between 40 and 60 years old, and its prevalence is 10.7 to 13 cases per million. Often, the diagnosis of EGPA is complex and requires collaboration from different disciplines including pulmonology, rheumatology, allergy and cardiology.

### Difficulties with diagnosis

A major area of controversy in EGPA includes classification in the absence of

proven vasculitis or in the presence of ANCA or other vasculitis surrogate markers. Multiple studies have classified EGPA based on phenotype and presence or absence of ANCA, with a consensus of association of ANCA positivity with kidney and peripheral nervous system involvement and constitutional symptoms. ANCA are present in about 40 percent of cases of the disease and are more frequent when glomerulonephritis is present. Limited expressions of EGPA confined to the upper or lower

As difficult as this  
disease can be to classify  
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proved difficult to treat.

respiratory tract may occur and may pose a diagnostic challenge with other eosinophilic-associated diseases. ANCA alone may not be sufficient to diagnose vasculitis in EGPA patients. Further, it is clear that EGPA is a polygenic disease with different gene susceptibility in ANCA-positive and ANCA-negative patients.

### EGPA and the heart

Dr. Tang emphasized in the symposium that heart involvement in EGPA carries a major prognostication. The presence of cardiomyopathy is associated with a worse prognosis and should always be evaluated when diagnosis of EGPA is confirmed. Cardiac involvement usually warrants more aggressive immunosuppressive therapy, and may occur even when patients do not present with symptoms.

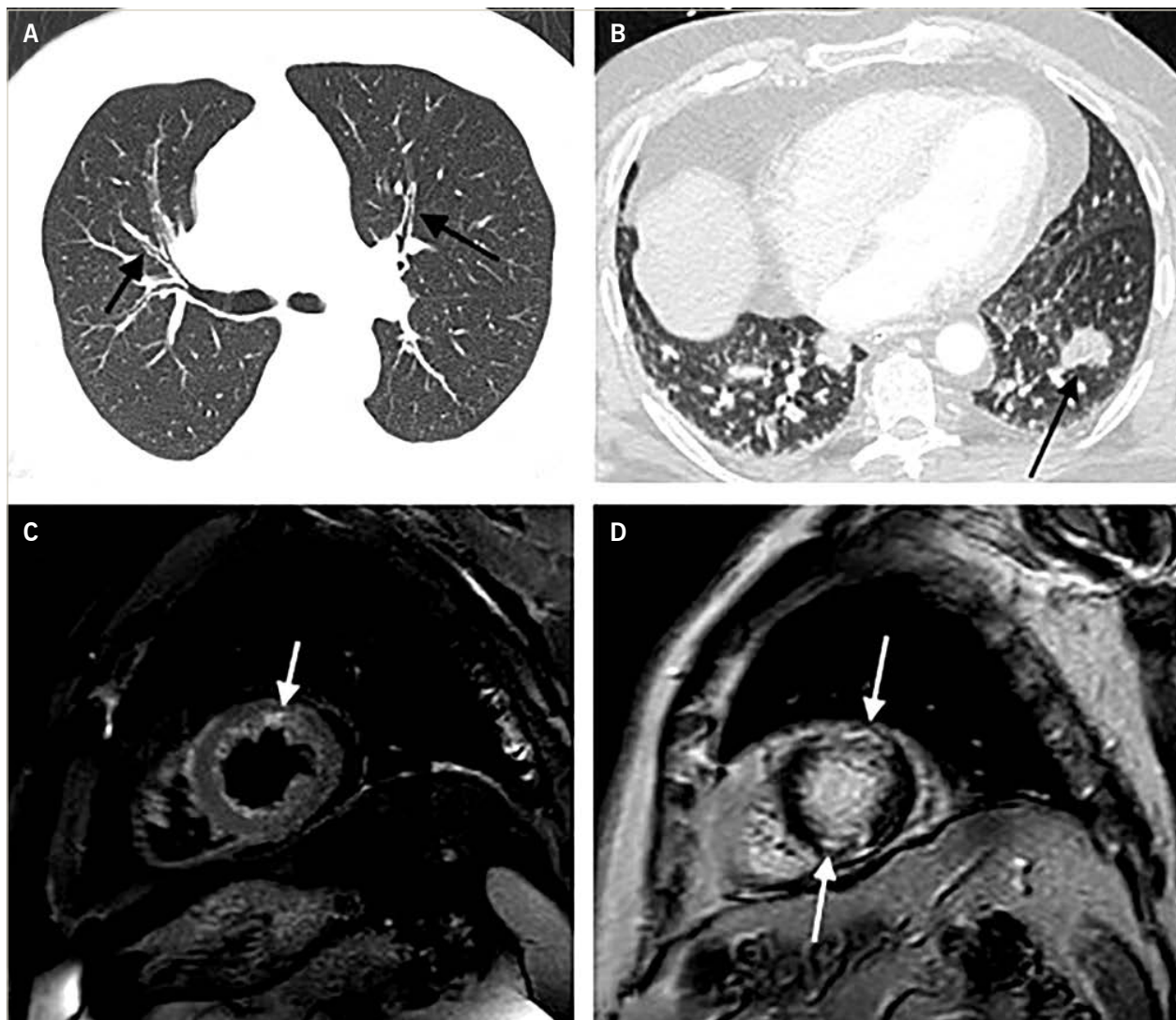
The EGPA Consensus Task Force recommends evaluation for possible heart involvement even when patients are asymptomatic. We routinely assess for cardiac involvement once a diagnosis of EGPA is established. Advances in cardiac imaging have improved the sensitivity of detecting earlier cardiac involvement (Figure).

### Treating EGPA

Because controlled trials in EGPA are sparse, diagnostic and therapeutic principles are often adapted from other ANCA-associated vasculitides. During the symposium, Michael Wechsler, MD, MMSc, Professor of Medicine at National Jewish Health, shared major advances in the pathogenesis of EGPA. Dr. Wechsler discussed the role of interleukin 5 (IL5) in EGPA. Higher IL5 levels have been found in EGPA-cultured eosinophils as compared with controls; IL5 is also important in promoting eosinophil adhesions to vascular endothelium.

These findings led to a multisite clinical trial in which Cleveland Clinic participated. This randomized, double-blind, phase 3 study (MIRRA) investigated the efficacy and safety of mepolizumab, an IL5 inhibitor, in treating relapsing or refractory EGPA. The MIRRA study is the first placebo-controlled study testing the use of mepolizumab as a steroid-sparing agent in EGPA.

Data from the MIRRA trial are being analyzed, and if the results are positive, it will be a breakthrough in the treatment of EGPA. As difficult as this disease can be to classify and diagnose, it has also proved difficult to treat. We are cautiously hopeful for a breakthrough for our patients.



**Figure.** A 54-year-old man with EGPA and lung and cardiac involvement. **A:** Axial CT image shows diffuse bronchial wall thickening (arrows). **B:** CT image on the same patient 3 months later shows a new peribronchovascular nodular opacity in the left lower lobe (arrow); these fleeting opacities are typical of EGPA. **C:** T2 STIR short-axis cardiac MR image shows increased signal in the distal anterior wall suggestive of myocardial inflammation (arrow). **D:** Corresponding phase-sensitive inversion recovery (PSIR) delayed enhancement MR short-axis image shows mid-myocardial enhancement in the apical anterior and inferior segments consistent with myocarditis (arrows).

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# BIOLOGIC THERAPIES FOR METABOLIC BONE DISEASE

## Beyond bisphosphonates

By Chad Deal, MD



Dr. Deal  
(dealc@ccf.org;  
216.444.6575)  
is Head of the  
Center for Osteoporosis  
and Metabolic  
Bone Disease.

**R**heumatologists have used biologic agents for inflammatory arthritis since etanercept was introduced in 1998. The biologic era for the treatment of low bone mass began with the introduction of denosumab in 2010. Romosozumab, a second biologic for metabolic bone disease, has a Prescription Drug User Fee Act (PDUFA) date of July 2017 and may be available in late 2017.

I recently presented an update on the use of biologic therapies for metabolic bone disease at the Biologic Therapies Summit VII hosted by Cleveland Clinic's R.J. Fasenmyer Center for Clinical Immunology. Denosumab and romosozumab work on different pathways but offer new options for patients with low bone mass as primary therapy and for those unresponsive to or contraindicated for bisphosphonates.

### **Denosumab: big benefits, but no holidays**

Denosumab is a fully human monoclonal antibody directed against rank ligand, a key cytokine required for both osteoclast development and function. The FREEDOM trial<sup>1</sup> showed denosumab reduced the risk of vertebral fractures by 68 percent, hip fractures by 40 percent and nonvertebral fractures by 20 percent, all clinically significant. The FREEDOM extension trial enrolled over 4,500 patients for 10 years, giving clinicians important information on the long-term efficacy and safety of denosumab.

Like the bisphosphonates, denosumab is an antiresorptive agent, but it is unique in a number of aspects:

1. It is a monoclonal antibody and administered as an injection every six months.

2. The effect on bone turnover is short-lived. In patients who discontinue denosumab after two years, bone density returns to baseline without medication in 12 months. Patients who discontinue a bisphosphonate will maintain bone mass for years. This difference has important implications for drug holidays. Guidelines from the American Association of Clinical Endocrinologists suggest no holiday with denosumab. An investigator-initiated trial is underway using zoledronate at denosumab discontinuation.

Denosumab and romosozumab work on different pathways but offer new options for patients with low bone mass as primary therapy and for those unresponsive to or contraindicated for bisphosphonates.

3. While bisphosphonates are excreted by the kidney and not recommended in patients with a glomerular filtration rate of less than 35 mL/min/1.73 m<sup>2</sup>, denosumab is excreted by the reticuloendothelial system and can be used in patients in stage 3 or 4 of chronic kidney disease.

4. Denosumab increased the risk of cellulitis (12 cases in 3,800 patients) in the FREEDOM trial. The label states that patients on concomitant immunosuppressive agents may be at increased risk for infections. The risk-benefit profile should be considered prior to use. A recent analysis using Centers for Medicare & Medicaid Services claims data did not show an increased risk for hospitalization for infection in patients with rheumatoid arthritis on biologic DMARDs who had a dose of denosumab.<sup>2</sup>

5. In patients treated with bisphosphonates, bone density increases 7 percent in the lumbar spine for the first two to three years of treatment with minimal increases thereafter. In patients on denosumab, lumbar spine density continues to increase and is 20 percent higher after 10 years of treatment.

6. Denosumab has a greater effect on cortical remodeling and reduces cortical porosity to a greater extent than alendronate.

In addition to infection, hypocalcemia is a potential side effect of denosumab, especially in patients with severe renal impairment. These patients should be vitamin D-replete, treated with calcium and have serum calcium levels tested frequently after denosumab injection. Higher than normal calcium supplementation may be required as well as the use of calcitriol to maintain serum calcium levels.

### **Romosozumab: cautious optimism while awaiting approval**

Romosozumab is a fully human monoclonal antibody targeting sclerostin, an important inhibitor in the Wnt signaling pathway. While denosumab is



an antiresorptive agent, romosozumab is an anabolic agent. Unlike teriparatide, the currently available anabolic agent, romosozumab does not stimulate bone resorption and actually has an antiresorptive effect. The drug is given once per month for 12 months as a subcutaneous injection.

The FRAME trial<sup>3</sup> has been completed, and an application for drug approval has been submitted to the FDA. The trial was unique in that the control arm was placebo for only one year followed by denosumab for a second year, while the treatment arm was romosozumab for one year then denosumab for one year. All previous trials with osteoporosis drugs had a three-year placebo comparator.

A significant reduction in vertebral fracture was achieved at year one, but a reduction in nonvertebral fracture was not significant ( $P = 0.06$ ), in part related to the short active versus placebo phase for this trial.

An additional reason for the nonvertebral fracture results was that 43 percent of the patients were enrolled from Latin America, where fracture rates are significantly lower than in other regions of the world. Only 3 percent of the patients in FRAME were from the U.S. If Latin American patients are excluded from the analysis, nonvertebral fracture reduction is significant.

#### **A new era in low bone mass treatment?**

Both denosumab and romosozumab target pathways only recently identified as critical in bone turnover. The potential addition of a new anabolic agent is especially important since use of the currently approved agent is limited to 24 months. Biologic agents have opened a new therapeutic era in the



Dr. Deal presents on advances in biologics for metabolic bone disease at the Biologic Therapies Summit VII.

treatment of osteoporosis, offering new options for both primary therapy and for those patients for whom current treatments have been insufficient.

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# DEADLY BUT PREVENTABLE: HBV REACTIVATION AFTER IMMUNOSUPPRESSIVE TREATMENT

Patients with IMIDs particularly vulnerable

By Leonard Calabrese, DO



Dr. Calabrese (calabrl@ccf.org; 216.444.5258) is Director of the R.J. Fasenmyer Center for Clinical Immunology in Cleveland Clinic's Department of Rheumatic and Immunologic Diseases.

**H**epatitis B virus (HBV), while considered a de-emerging viral infection due largely to global immunization and blood screening, still chronically infects nearly 500 million people. In the U.S. alone, an estimated 1 million individuals are chronically infected.

Chronic HBV is often clinically silent and undiagnosed. When individuals with clinically unapparent HBV have concomitant immune-mediated inflammatory diseases (IMIDs), they are particularly vulnerable to HBV reactivation when immunosuppressed. HBV reactivation is defined as an abrupt increase in HBV replication in a patient with current or past HBV infection. HBV reactivation may range from asymptomatic rises in blood HBV viral load to fulminant hepatitis leading to death.

## HBV reactivation with immunosuppressive treatment for IMIDs

While HBV reactivation has been long recognized in the settings of cancer chemotherapy and organ transplantation, it is also clinically important for patients with IMIDs exposed to immunosuppression with conventional or biologic agents. TNF inhibitors were approved in the late 1990s, but only in 2006 did worldwide regulatory agencies issue a class warning for potentially lethal HBV reactivation. More recently, HBV reactivation has been associated with other biologics including abatacept and most importantly rituximab, which recently received a black box warning. HBV reactivation was part of a half-day session dedicated to comorbidities

of biologics use, including serious infections, at the Biologic Therapies Summit VII in April.

## Serology screening highly effective, unevenly utilized

Fortunately, we now recognize this risk and screen with serologies (hepatitis B [HB] surface antigen and antiHB core antibodies) to identify patients who will benefit from antiviral prophylaxis. Screening has been demonstrated as highly effective in numerous settings. Low rates of patient screening by

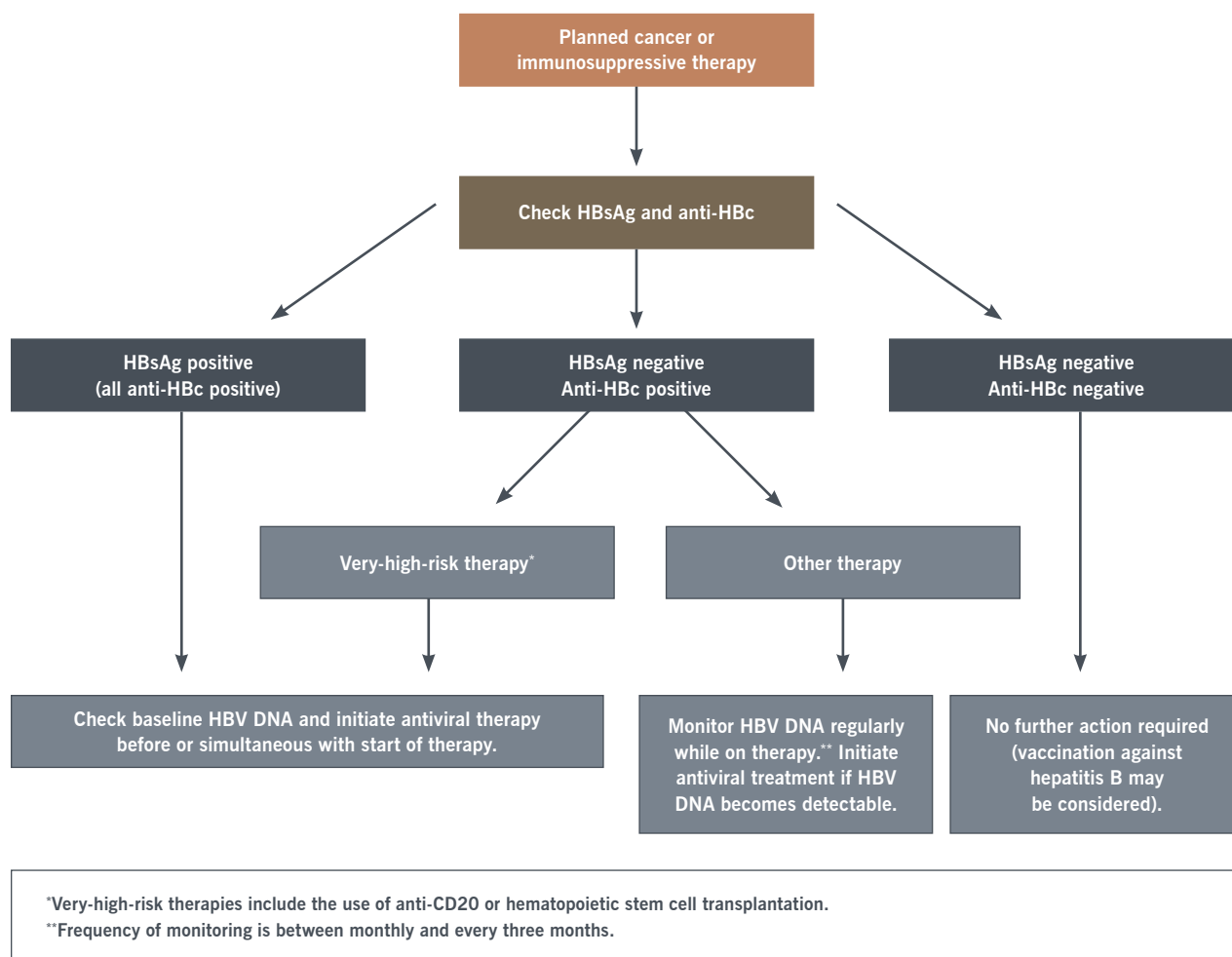
While HBV reactivation has been long recognized in the settings of cancer chemotherapy and organ transplantation, it is also clinically important for patients with IMIDs exposed to immunosuppression with conventional or biologic agents.

clinicians who care for vulnerable patients have complicated the application of this effective strategy. Reasons for

low rates of screening are complex but include weak or unclear screening recommendations and conflicting guidelines issued by specialty societies and public health authorities. In rheumatology, the field labors under risk-based guidelines from 2008 that lack clarity and rationale.<sup>1</sup>

In January 2014, the American Association for the Study of Liver Diseases, in conjunction with the FDA, pharmaceutical companies and numerous specialty societies, including the American College of Rheumatology (ACR), American Dermatology Society, American Gastroenterology Association and American Society of Clinical Oncology, held an Emerging Trends Conference. I represented ACR at the meeting, and the resulting recommendations for a uniform and simplified screening strategy that could be used in any setting — including in the presence of IMIDs — were published in 2015.<sup>2</sup>

These important recommendations attempt to classify immunosuppressives based on their risk, propose a simple algorithm (Figure) that recommends serologic screening for all patients being considered for immunosuppressive therapy, and provide guidelines for management and referral. These recommendations obviate the use of risk factor-based screening, which is both insensitive and inefficient. We believe most if not all specialty societies will endorse these recommendations, as they are now considered a best practice in managing a deadly but preventable disease.



**Figure.** Recommended algorithm for HBV testing and treatment in patients undergoing immunosuppressive therapy. (Figure and caption republished from Di Bisceglie et al. with permission from John Wiley and Sons.)  
 HBsAg = hepatitis B surface antigen  
 Anti-HBc = antibody to hepatitis B core antigen

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# ALL SIGNS POINT TO SHORTAGE

## Thoughts on the 2015 ACR Workforce Study

By Chad Deal, MD



Dr. Deal  
(dealc@ccf.org;  
216.444.6575)  
is Head of the  
Center for  
Osteoporosis and  
Metabolic  
Bone Disease.

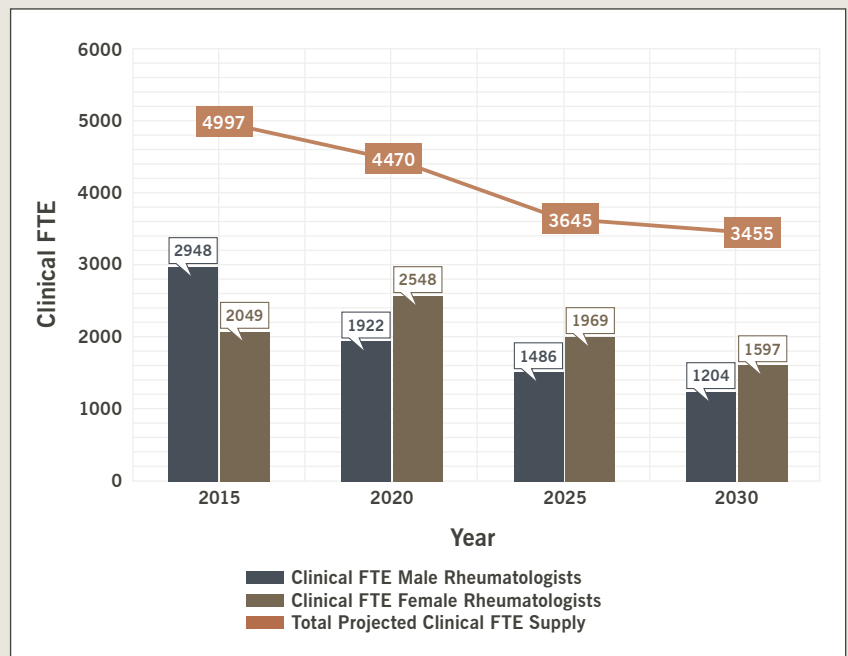
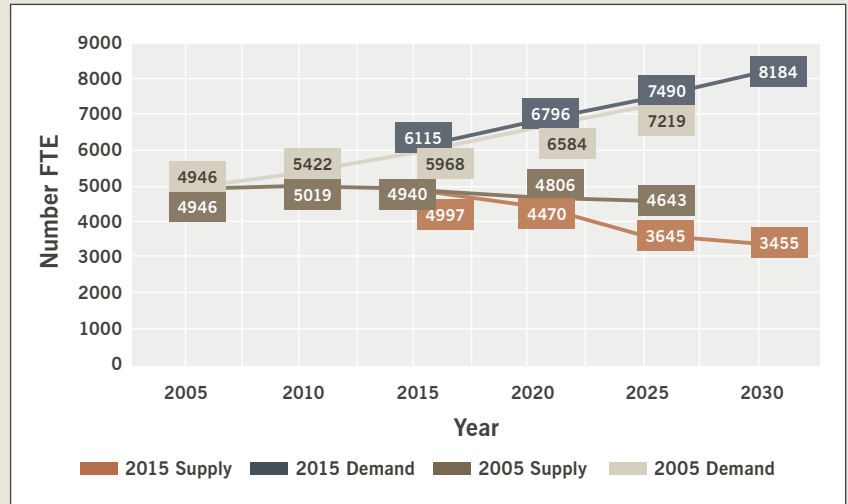
If projections are correct, demand for rheumatologists will more than double in the next 15 years. By 2030 the supply of rheumatologists will fall by 31 percent and demand will increase by 138 percent. That's an excess demand of over 4,500 rheumatologists by 2030. We would need to add another 350 adult fellowship graduates each year for the next 13 years just to meet that demand.

### Digging into the data

Under the guidance of Daniel Battafarano, DO, of San Antonio Military Medical Center, and the American College of Rheumatology (ACR) Workforce Committee, the 2015 ACR Workforce Study (WFS) was presented at the 2016 ACR annual meeting. Workforce studies are important to assess the current and future states of the rheumatology workforce and to provide data for recommendations and planning.

As a committee member, I studied the effects of age and gender on the rheumatology workforce. The data show that the rheumatology workforce in 2030 will be predominantly millennial (> 50 percent) and female (59 percent). Both millennial males and females see fewer patients compared with physicians in the 2005 WFS. There are many reasons for this, including emphasis on work/life balance and time out of the workforce for family. In the survey portion of the WFS, 18 percent of current fellows reported planning part-time employment, and of these, 90 percent were women.

Add these factors to those that increase demand, such as increases in healthcare utilization, access to care and per-capita income as well the aging of the population, and we are approaching a critical shortage of providers qualified to diagnose and treat rheumatic diseases.



**Figure 1.** Comparison of supply and demand of adult rheumatology workforce.

**Figure 2.** Projected clinical FTE by gender 2015-2030.

Figures republished with permission from John Wiley and Sons, from 2015 ACR WFS abstracts noted in references.

### Bridging the gap

While no projection or model is perfect, the 2005 WFS was largely accurate in its supply and demand predictions; with improved methodologies, the 2015 WFS

should reliably predict future supply and demand.

Our undeniable challenges are patient access, recruitment into rheumatology and support for the existing workforce.

We must continue to ensure that our fellowship slots are full. The ACR and the Rheumatology Research Foundation increased support for fellowship training after the 2005 WFS. However, we cannot train our way out of the impending shortage. Advanced practice clinicians will need to be recruited into rheumatology, although that is a challenge since we compete against all medical and surgical specialties for their services. Increasing the number of pediatric rheumatologists is also a challenge. The ACR has advocated for legislation for years that would pay off student loan debt for pediatricians as an incentive to go into pediatric rheumatology.

Practice redesign will be critical; we must work more efficiently, utilizing advanced practice clinicians, and we will need to make tough choices about who we should see based on disease category.

The problems we face are simple and straightforward — we do not have enough rheumatologists to meet demand, and the problem will only intensify as

We are approaching a critical shortage of providers qualified to diagnose and treat rheumatic diseases.

time advances. The solutions are complex and require the kind of volunteer work in advocacy, training, mentoring and recruitment that we do through professional organizations, often on our own time and after our other work is done.

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