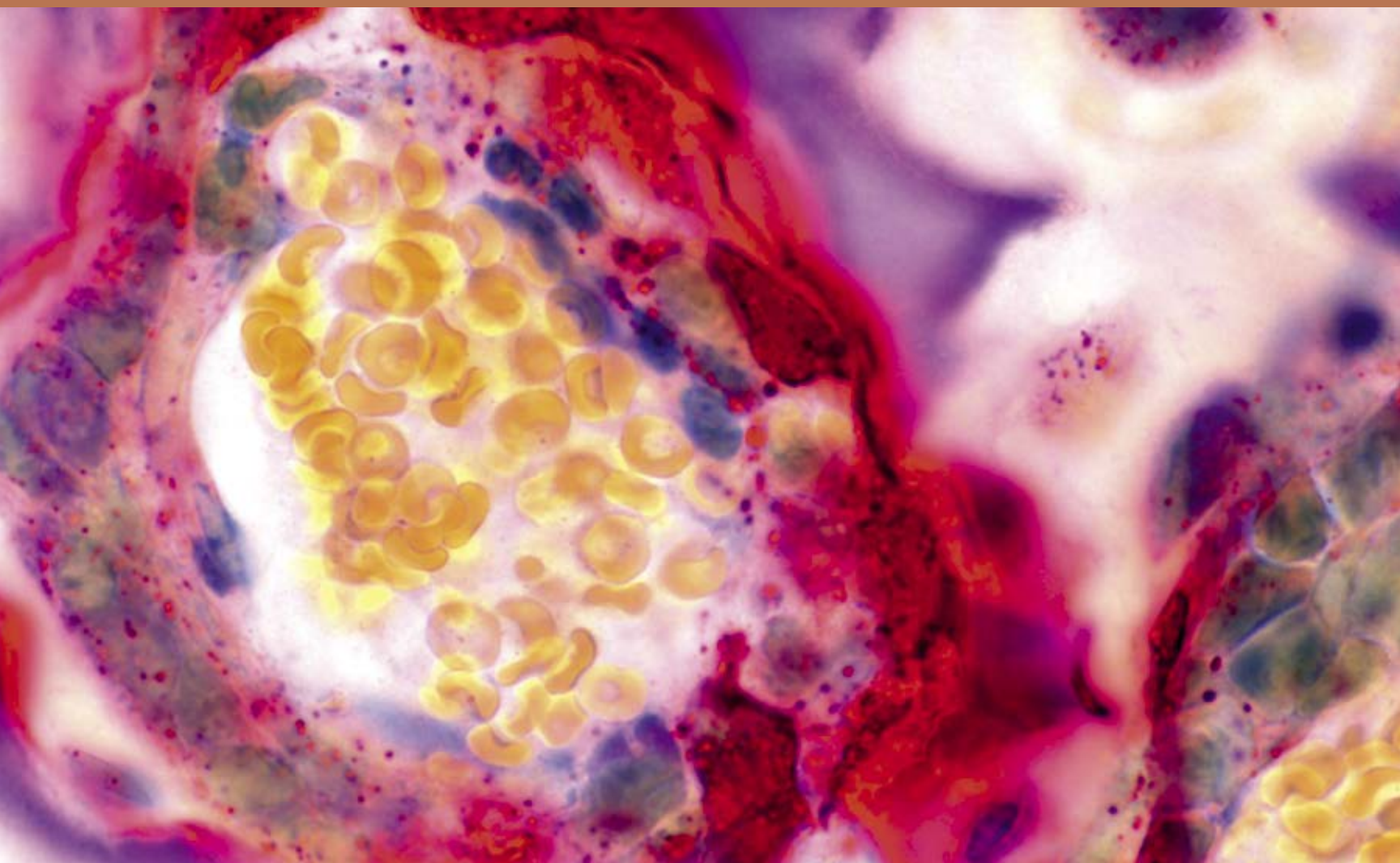
IN THIS ISSUE

Cleveland Clinic

Rheumatology Connections

An Update for Physicians | Winter 2019



Dear Colleagues,

From the Chair of Rheumatic and Immunologic Diseases

It is my pleasure to share with you the winter 2019 issue of *Rheumatology Connections* highlighting the clinical, research and educational expertise in the Department of Rheumatic and Immunologic Diseases. This issue powerfully demonstrates the Cleveland Clinic tripartite mission of caring for the sick, investigating their conditions and educating those who serve.

Two articles highlight our expertise in vasculitis. Dr. Rula Hajj-Ali offers an overview of Behçet's syndrome, a rare vasculitis on the rise in the United States (p. 3). Dr. Carol A. Langford details the optimal approach to orbital disease in granulomatosis with polyangiitis (p. 6).

Another pair of articles demonstrates the research and clinical work generated by our unique and rigorous fellowship offerings. Dr. Soumya Chatterjee presents a closer look at two uncommon autoimmune conditions — gastric antral vascular ectasia and antisynthetase syndrome — based on two fellows' abstracts from this year's American College of Rheumatology meeting (p. 16). Dr. Cassandra Calabrese, the first graduate of our combined fellowship in rheumatology and infectious disease, collaborates with a colleague in the Department of Allergy and Clinical Immunology to demonstrate the intersection of rheumatology, immunology and infectious disease (p. 12).

We also continue to excel in clinical and translational research. Dr. Emily Littlejohn's research proposes a way to distinguish flares from infection in our patients with systemic lupus erythematosus (p. 14). We also highlight the translational research of Dr. Elaine Husni on potential biomarkers for cardiovascular disease risk in patients with psoriatic arthritis (p. 11), and her clinical research on the safety of NSAIDs for patients with arthritis (p. 18). And for all our patients, we continue to drive quality and improvement through programs like MyRheum, a patient-reported outcomes interface (p. 8).

I am honored to work with these talented rheumatologists. I hope that you find in the stories that follow an opportunity to connect, collaborate or consult with our team.

Respectfully,

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Cleveland Clinic's Rheumatology Program is ranked among the top 2 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.

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On the cover: In this image of cartilage (purple and white) from a young mouse femur, osteoclasts (red) surround a blood vessel filled with red blood cells (yellow). In contrast to normal osteoclasts, the cells seen here have only a single nucleus due to the lack of a gene involved in osteoclast development. This research program aims to understand how large, bone-resorbing osteoclasts form, and whether preventing them from fusing together is a way to control bone loss in osteoporosis, arthritis or other conditions. Credit: Paul R. Odgren, PhD, University of Massachusetts Medical School. Image source: NIH Image Gallery. No changes were made.

UNDERSTANDING BEHÇET'S SYNDROME

Multisystemic inflammatory vasculitis on the rise in the U.S.

By Rula Hajj-Ali, MD

Behçet's disease or syndrome (BS) is a multisystemic inflammatory vasculitis characterized by recurrent oral and genital aphtha, ocular disease, skin lesions, gastrointestinal involvement, neurologic disease, vascular disease or arthritis. It is classified under systemic vasculitis and is the only vasculitis that can affect any vessel size as well as the arterial and venous systems.

BS is more common in the Mediterranean and Far East regions, but trend studies suggest an 18-fold increase in prevalence in the U.S. in recent years. The causes of this increase are unknown but could be partly attributed to population migration as well as increasing awareness of the disorder.

Some investigators regard BS as a disease. Others prefer the term "syndrome" due to its unknown pathogenesis, lack of clinically acceptable laboratory screening profile or definitive diagnostic test, and variability in prevalence and incidence. (Western patients tend to have a milder clinical course of BS than patients from Eastern countries). Today, it is known that BS is a more complicated entity affecting every tissue and organ in the body without exception.

Insufficient cross-sectional studies of different populations make it impossible to compare phenotypic differences around the globe. Clusters of various disease manifestations occur — for example, acne with arthritis, superficial thrombophlebitis with deep vein thrombosis (DVT), and oral ulcers (Figure 1A) with genital ulcers (Figure 1B) and erythema nodosum. These clusters (Figure 2) could imply that the pathogenesis of BS is complex, with more than one mechanism. Furthermore, BS has a more aggressive and severe course in young adult males in the Eastern Mediterranean and Middle and Far East regions as compared with Western countries. Genetic heterogeneity could explain this disparity.

How to diagnose BS

Diagnosing BS is based on pattern of clinical involvement, laboratory findings, tissue histology and imaging, usually in the context of:

- Recurrent aphthous ulcerations along with characteristic systemic manifestations, especially ocular disease (Figure 1C), panuveitis or retinal vasculitis.
- Neurologic disease, including characteristic central nervous system parenchymal findings.
- Vascular disease, particularly pulmonary artery aneurysms, Budd-Chiari syndrome and cerebral venous thrombosis.

The most commonly used criteria with the best sensitivity and specificity are the International Study Group (ISG) criteria for Behçet's syndrome (Table).[1] These criteria were developed to classify patients for research studies. Some investigators propose "strong" and "weak" elements in the definition of BS. A strong element, such as eye disease or vascular involvement, has unique features that distinguish BS from other pathological conditions. In contrast, weak elements, such as gastrointestinal involvement, point to more than one pathogenetic mechanism.

Treatment guidelines

BS typically runs a relapsing and remitting course. The goal of treatment is to promptly suppress inflammatory exacerbations and recurrences to prevent irreversible organ damage.

Treatment should be individualized according to age, gender, type and severity of organ involvement, and patient preferences. Ocular, vascular, neurological and gastrointestinal involvement may be associated with a poor prognosis. Disease manifestations may ameliorate over time in many patients.

The European League Against Rheumatism (EULAR) recently updated its 2008 evidence-based recommendations for the management of BS.[2] An expert committee defined the problem areas, performed a systematic literature search, and formulated a final set of recommendations and research questions. The committee included experts from several countries and specialists in all disciplines who care for patients with BS, as well as two patients with BS.

In addition to changing the title to "EULAR Recommendations for the Management of Behçet's Syndrome," updates include:

- Five new principles and one recommendation for the surgical management of arterial aneurysms.
- Adding apremilast as an option for mucocutaneous involvement. Apremilast is an oral phosphodiesterase-4 inhibitor that modulates inflammatory pathways and is approved in the U.S. for treatment of psoriasis and psoriatic arthritis — but it soon may be approved for treatment of BS as well. In a recent study presented at the 2018 American College of Rheumatology Annual Meeting, apremilast demonstrated consistent efficacy in reducing the number of oral ulcers over placebo through week 12.[3]
- Considering the use of anti-TNF (tumor necrosis factor) monoclonal antibodies in patients with refractory venous thrombosis. Anticoagulants may be added if the risk of bleeding is low in general, and as long as coexistent pulmonary artery aneurysms are ruled out.
- Emphasizing medical treatment with cyclophosphamide and corticosteroids before surgical interventions in patients with aortic and peripheral artery aneurysms, if the situation isn't urgent.

Further research is needed

Despite ongoing efforts, recommendations for the treatment of vascular, gastrointestinal and nervous system involvement in BS still rely mostly on observational and uncontrolled evidence and expert opinion. While there have been some randomized controlled trials involving several agents for mucocutaneous, joint and eye involvement, very few have been head-to-head trials. There also is a lack of research evaluating the efficacy of different treatment strategies for BS, such as a step-up versus step-down approach.

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More work in BS is needed. In particular, further research is warranted for controversial issues such as the role of anticoagulation in patients with thrombosis and the comparative efficacy of interferon alpha and TNF in patients with eye involvement.

References

1. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet*. 1990;335(8697):1078-1080.

2. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann Rheum Dis*. 2018;77(6):808-818.

3. Hatemi G, Mahr A, Ishigatsubo Y, et al. Efficacy of apremilast for oral ulcers associated with active Behçet's syndrome over 28 weeks: results from a phase III study [abstract]. *Arthritis Rheumatol*. 2018;70 (suppl 10). https://acrabstracts.org/abstract/efficacy-of-apremilast-for-oral-ulcers-associated-with-active-behcets-syndrome-over-28-weeks-results-from-a-phase-iii-study/. Accessed November 6, 2018.

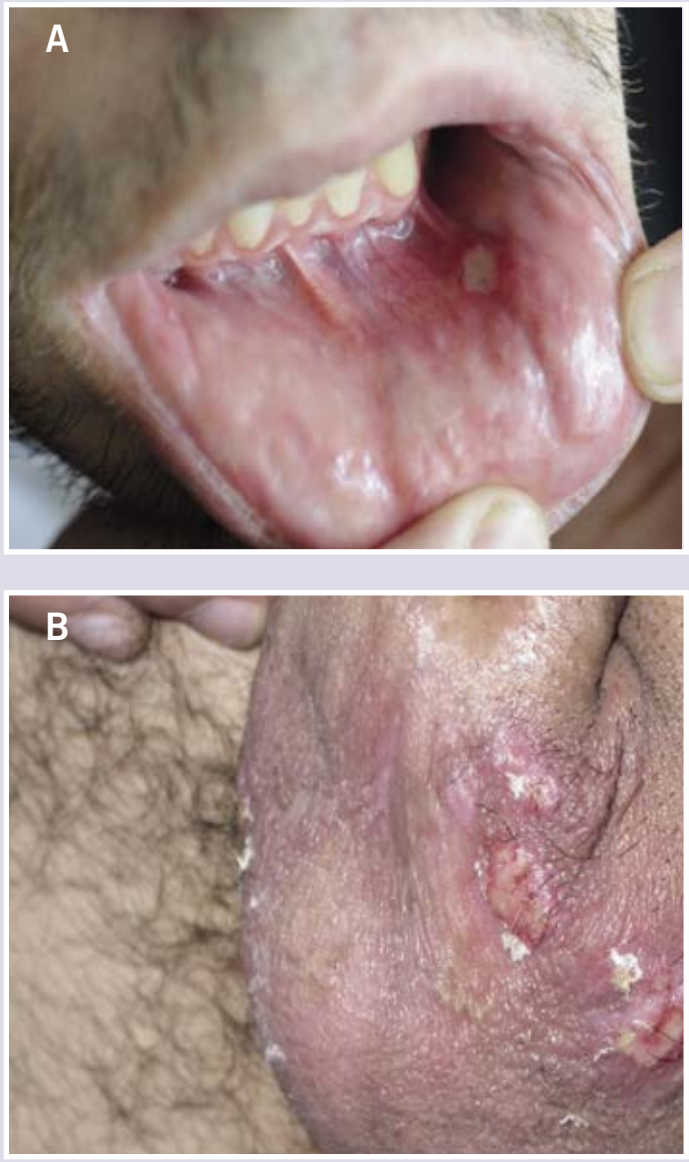
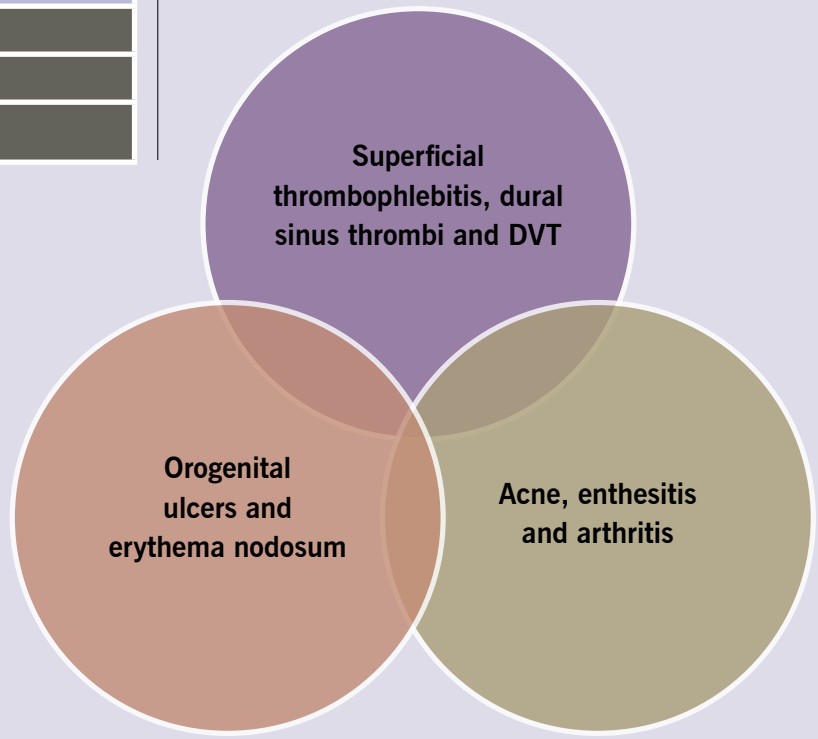


Figure 1. Three manifestations of Behçet's syndrome: oral ulcerations (A), genital ulcerations (B) and hypopyon (C).

TABLE. INTERNATIONAL STUDY GROUP (ISG) CRITERIA FOR BEHÇET'S SYNDROME[1]
• Recurrent oral ulcers (minor aphthous, major aphthous or herpetiform) at least three times in one 12-month period
PLUS TWO OF THE FOLLOWING:
• Recurrent genital ulcerations
• Eye lesions
• Anterior uveitis
• Posterior uveitis
• Cells in vitreous on slit-lamp examination
• Retinal vasculitis observed by qualified physician
• Skin lesions
• Erythema nodosum-like
• Pseudofolliculitis
• Papulopustular lesions
• Acneiform nodules
• Positive pathergy test read by a physician within 48 hours of testing, performed with oblique insertion of a 20-22 gauge or smaller needle under sterile conditions.
Sensitivity: 82.4%
Specificity: 96%
Accuracy of the ISG: 86.7%

Figure 2. Clusters of disease manifestations in Behçet's syndrome.



ORBITAL DISEASE IN GRANULOMATOSIS WITH POLYANGIITIS

Active or damage and how to manage

By Carol A. Langford, MD, MHS

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

Two patients, similar lesions, different decisions?

A 56-year-old female with granulomatosis with polyangiitis (GPA) comes to see you for follow-up. She has had disease for nine years with past involvement of the sinuses, lungs, kidney and orbit. She describes sinus congestion and discolored drainage suspicious for infection. She has chronic periorbital pain and enophthalmos which are unchanged. Her visual acuity is normal which has not changed. In addition to starting her on antibiotics, you perform a CT sinus/orbit that shows sinus mucosal thickening and a left orbital lesion that are unchanged (Figure 1). After completing the antibiotics, she is feeling improved and back to her baseline. Is there anything you should do for the orbital lesion?

A 46-year-old male with a three-year history of GPA comes to see you for follow-up. He has had past disease involving the sinus, lung, nerve and skin and has been in remission on methotrexate. At his follow-up visit, he comments on new pressure around his left eye with doubling of his vision when looking up and to the left. On exam, his left eye appears slightly more proptotic with restricted left eye movement on left lateral gaze. CT sinus/orbit shows chronic sinus mucosal thickening with erosion of the medial orbital wall and new soft tissue fullness along the extraconal orbital space abutting the medial rectus muscle (Figure 2). Is there anything you should do for the orbital lesion?

Orbital disease: Why is it challenging?

Orbital disease is among the most challenging disease manifestations of GPA. It can occur either de novo within the orbit or, most commonly, as a result of erosion of the lamina papyracea along the medial orbital wall, allowing inflammatory soft tissue to extend into the orbit from the sinus.

Presenting symptoms/signs of orbital disease can include pressure or pain in, around or behind the eye, as well as swelling of the eyelid or periorbital tissues. When the lesion abuts the ocular muscles, it can affect their function, resulting in disconjugate gaze and diplopia. Lesions adjacent to the optic nerve can impact vision. The optic nerve is particularly vulnerable at the orbital apex, where the nerve leaves the orbit and enters the intracranial space. Lesions in this location can also result in other oculomotor cranial neuropathies with corresponding clinical manifestations.

There are two key reasons why orbital lesions are challenging. The first of these is the anatomical construct of the orbit in being a confined, bony space. Inflammatory lesions within the orbit are close to structures vital to vision, such that even small lesions and any associated edema can have a profound impact. The second challenge is the rapid development of scarring that accompanies the inflammatory process and becomes permanent damage. This can result in chronic symptoms, signs and persistent radiologic changes. Over the course of time, scar tissue can retract, resulting in enophthalmos which can also impact vision in some patients.

Treatment of orbital disease in GPA

Treatment of orbital lesions is pursued with the goal of preventing progression and with the hope of halting inflammation that has not yet progressed to scar. The medications used for active orbital disease are the same as for other GPA manifestations and consist of glucocorticoids combined most commonly with rituximab, methotrexate or cyclophosphamide. Although some studies raised concern about the effectiveness of rituximab for orbital disease, others have supported benefit, reflecting the general difficulty in managing this manifestation. Orbital lesions can be particularly sensitive to changes in glucocorticoid dose, and some patients require long-term prednisone.

Surgery has limited if any role in management of orbital disease in GPA. Because of their composition of inflammatory cells and fibroblasts, orbital lesions can become adherent to adjacent structures. Surgical manipulation of lesions abutting the optic nerve can impact nerve function and result in vision loss. Because of this risk, surgery is almost always avoided in patients who have normal visual acuity.

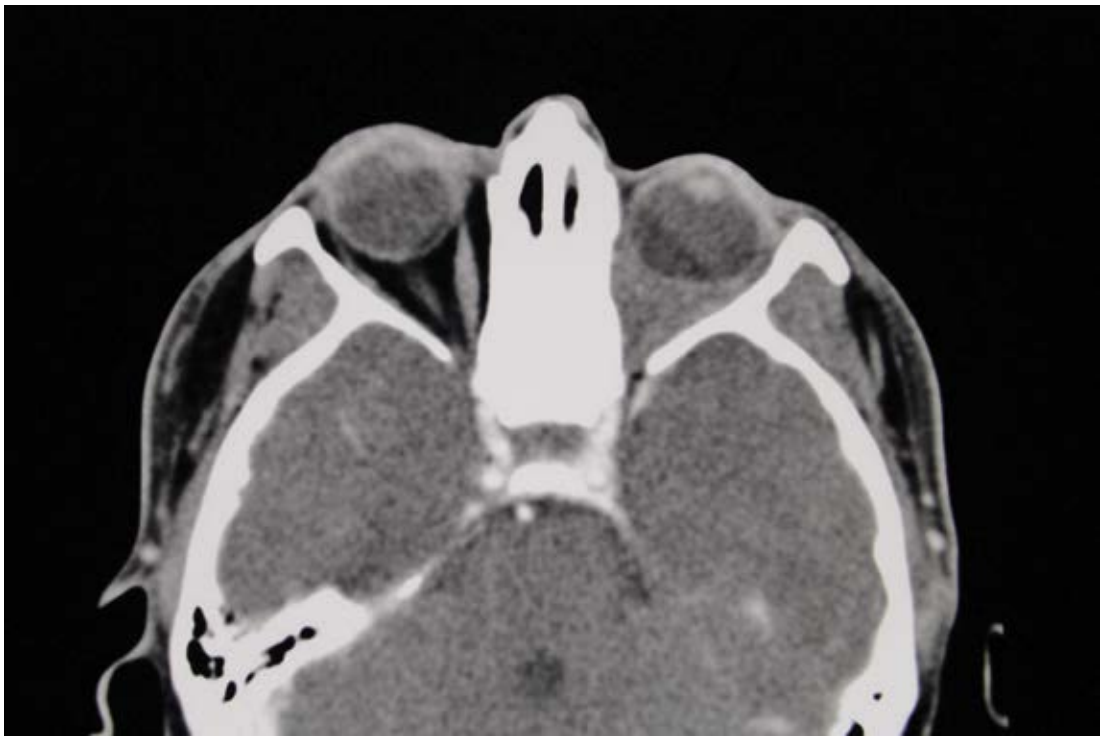
Injecting glucocorticoids directly into the orbital lesion has no proven benefit, and radiation therapy has no role in treatment.

Returning to the patients

In the absence of other features of active GPA, determining whether to treat an orbital lesion is based on whether this is felt to reflect active inflammation or damage from scarring. This can be difficult to determine and is largely based on objective evidence from a careful ophthalmologic exam and changes in imaging. A persistent orbital lesion can occur as a result of damage from scarring and in the absence of growth is usually not an indication for treatment.

For patient one who had a known orbital lesion that had not changed, this was felt to reflect damage, and treatment was not pursued. For patient two, as there was development of a new orbital lesion, this was treated as active disease.

Orbital disease in GPA can be challenging for both patients and physicians. Effective management of these patients requires regular assessments by an ophthalmologist and intermittent imaging by CT or MRI, particularly in the setting of new symptoms. Preservation of visual acuity, minimizing chronic symptoms and avoiding treatment-related toxicity are the cardinal objectives, which can be achieved in many patients through careful multidisciplinary care.



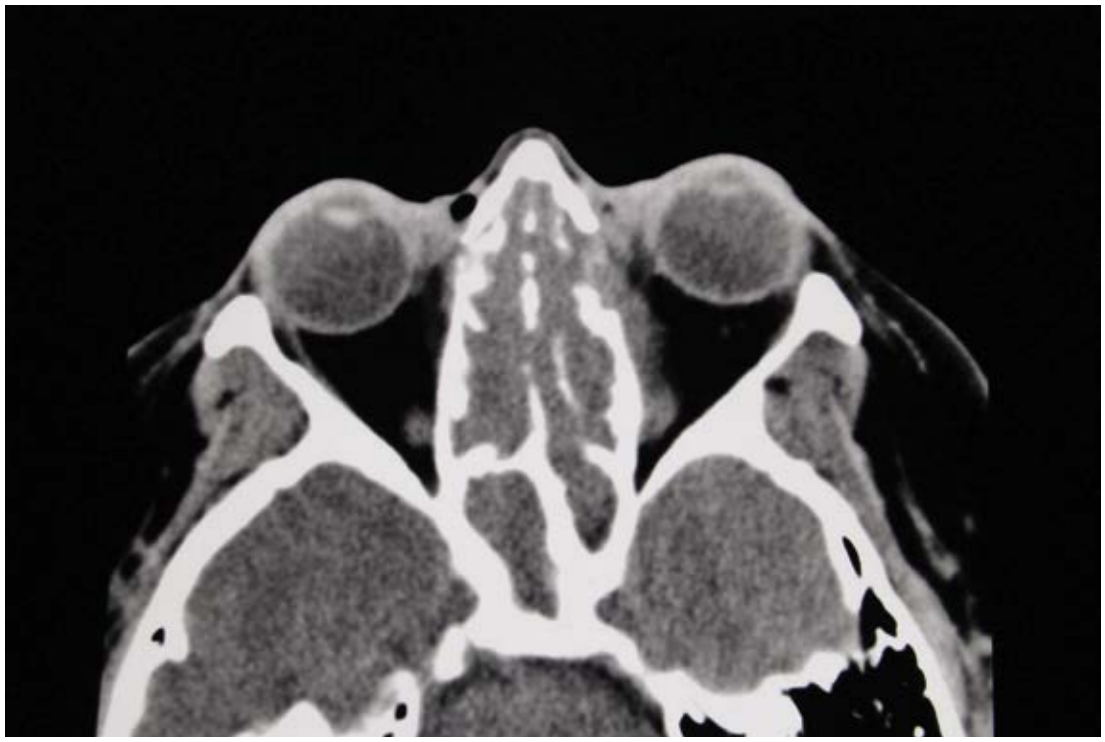


Figure 1. (Above) CT sinus/orbit shows a left orbital lesion that is filling the intraconal orbital space.

Figure 2. (Bottom) CT sinus/orbit shows sinus mucosal thickening with erosion of the medial orbital wall and soft tissue fullness extending into the left medial extraconal orbital space.

MyRheum: NEW REVELATIONS ON PATIENT-REPORTED OUTCOMES

A step closer to understanding MCID in immune-mediated diseases

By Abby Abelson, MD, and Chad Deal, MD

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Standardizing assessment of healthcare through patient-reported outcomes (PROs) is a national priority. Outcome measures evaluate the results of care and are therefore considered the most valid metrics for measuring and comparing clinical care and driving quality and improvement.

There is growing recognition of the value of measuring PROs in patients with rheumatologic conditions. Clinical disease activity measures are important for making treatment decisions but sometimes do not measure the domains of health important to patients. PROs measured at the point of care can enhance shared decision-making and facilitate treatment decisions, although the ability to collect and report PROs in real time can be challenging because of technology and workflow barriers.

Through support from Cleveland Clinic and an information technology team, the Department of Rheumatic and Immunologic Diseases developed a patient-entered data (PED) system using validated measurements that assess physical and mental function, social health and well-being, and disease activity, as well as a rheumatology-oriented review of systems. This PED system, called MyRheum, allows the clinician to evaluate patient-reported health measures at the point of care, engage patients in their care and make better treatment decisions based on patient-centric data.

At the 2018 American College of Rheumatology's Annual Meeting, several staff members presented compelling data on their recent experience with MyRheum.

Developing and implementing MyRheum

In "Development and Implementation of a Patient-Reported Outcomes Measurement Information System (MyRheum)," authors Chad Deal, MD; Abby Abelson, MD; Leonard Calabrese, DO; database designer Greg Strnad; Irene Katzan, MD; and M. Elaine Husni, MD, presented a behind-the-scenes look at MyRheum.

MyRheum was deployed throughout Cleveland Clinic's health system, with 27 rheumatologists in 10 locations, in August 2016. Since then, patients have used it at each rheumatology clinic visit.

When developing MyRheum, the team assessed the feasibility, patient/provider compliance and utility of electronically collecting PROs using Patient-Reported Outcomes Measurement Information System (PROMIS®) Global Health (GH), PHQ-9, RAPID3 or SLAQ; pain, fatigue and physical function PROMIS domains; and a review of systems (ROS). PROMIS allows measurement of health domains important for rheumatology patients as well as comparison with the general U.S. population.

With MyRheum, PROs are collected at the patient's visit on a tablet computer or prior to the visit through a patient portal (MyChart, Epic Systems) integrated with their electronic health record (EHR). PROMIS domains are administered using computer adaptive testing, and scores are standardized on a T scale with a mean of 50 and standard deviation of 10. Results are displayed within the EHR at the time of the visit (Figure 1). The ROS is administered at every visit. PHQ-9, if normal, is administered yearly, and the remaining scales are completed at least three months apart.

Through June 2018, approximately 160,000 MyRheum questionnaires (including nearly 50,000 PROMIS, nearly 90,000 RAPID3, more than 20,000 PHQ-9 and nearly 600 SLAQ) had been completed by 35,700 unique patients. Approximately 40 percent of questionnaires were completed by the patient on MyChart, at home before their visit.

Cross-departmental comparisons of diseases (PROMIS-10 T-scores) showed rheumatology patients had the second-lowest self-reported physical health score (Figure 2), demonstrating the impact of rheumatic diseases and the need to measure PROs.

Figure 1. How results display to patients.

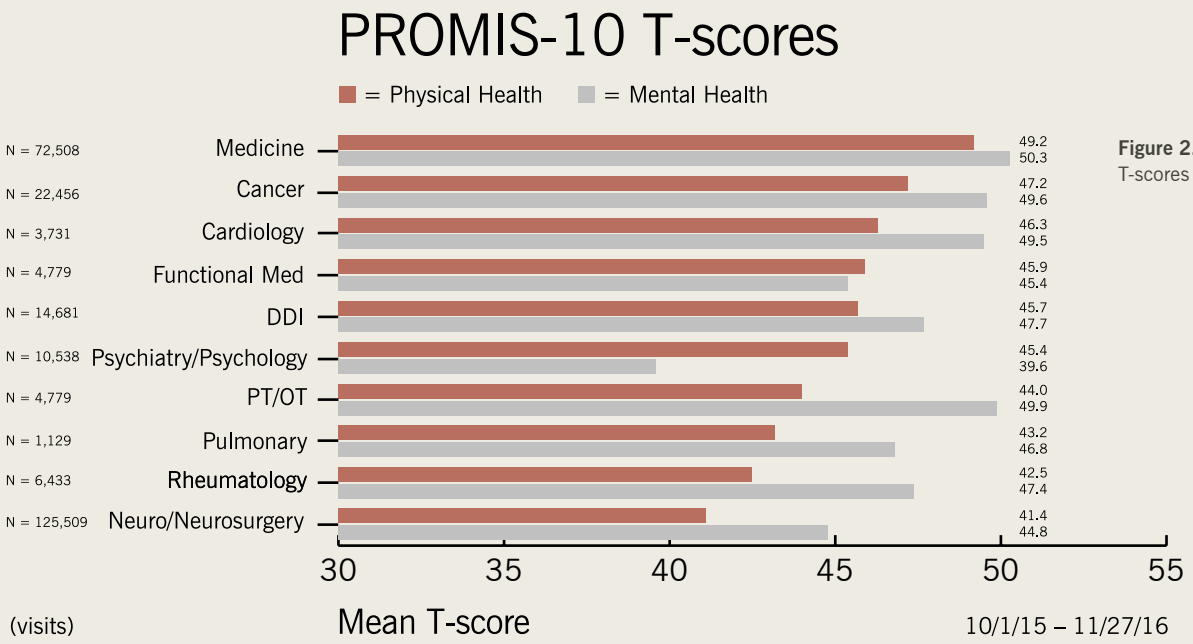

Figure 2. Comparison of T-scores by department.

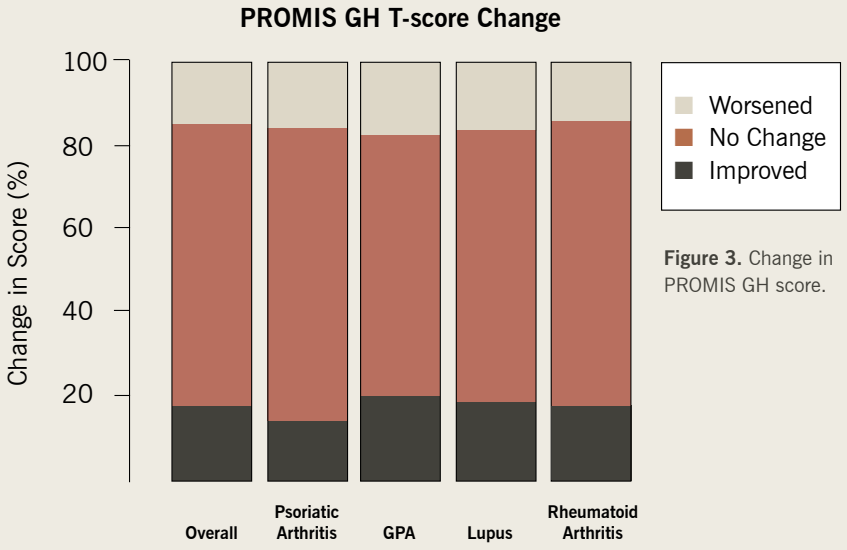

Figure 3. Change in PROMIS GH score.

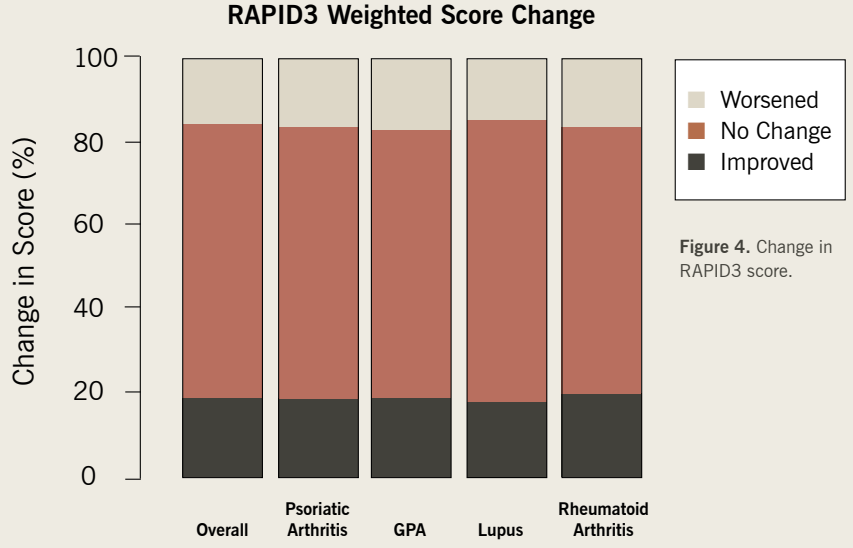

Figure 4. Change in RAPID3 score.

The creation of this large PRO biomarker databank demonstrates its practicality and provides a powerful platform for clinical care, research and value-based healthcare initiatives.

Evaluating PROs in immune-mediated diseases

In "Using Patient Reported Outcomes at Point of Care in Immune-Mediated Diseases: Minimal Clinically Important Differences," authors Drs. Husni, Deal, Calabrese and Abelson, Strnad and biostatistician James Bena shared how MyRheum helped evaluate PROs in several immune-mediated diseases.

Minimal clinically important differences (MCID) are patient-derived scores that reflect changes in clinical care that are meaningful to the patient. Little is known about MCID in many immune-mediated diseases, as small differences in PROs may be statistically significant yet clinically unimportant for the patient.

Using MyRheum, data were collected from patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), lupus and granulomatosis with polyangiitis (GPA) who had completed PROMIS GH and RAPID3 at two separate visits, six months apart. Paired t-tests assessed the changes between visits. Important differences were identified by a PROMIS MCID change of 5 and RAPID3-weighted score of 1.2 (improvement or worsening).

The authors found:

- The change in PROMIS score was statistically significant overall ($P < 0.001$) as well as for those with either GPA ($P = 0.030$) or RA ($P < 0.001$), but not for lupus ($P = 0.67$) or PsA ($P = 0.36$).
- The change in RAPID3 score was significant overall ($P < 0.001$), as was the change for lupus ($P = 0.048$) and RA ($P < 0.001$), but not for GPA ($P = 0.11$) or PsA ($P = 0.17$).
- Thresholds for clinically meaningful change in PROMIS GH were most significant for GPA and RA compared with PsA and lupus, and in RAPID3 were most significant for lupus and RA compared with PsA and GPA.
- Approximately 15-20 percent of patients showed an improvement or worsening of MCID by six months; 60-70 percent had no change between visits (Figures 3 and 4).

On average, there was improvement in PROMIS and RAPID3 scores among all immune-mediated diseases after two visits. However, this study indicates that it is unlikely for a single MCID value to be applicable across all chronic diseases.

The variability in MCID implies that some patients improve while others worsen. This study presents an opportunity to better understand patient characteristics and therapies that may explain these changes.

Capturing what matters most

The greatest advantage of measuring PROs is capturing what matters most to patients and allowing clinicians to use this information at the point of care.

Now, with MyRheum, most rheumatology providers at Cleveland Clinic start each clinical visit with a review of PROs. This focuses each visit on what is important to the patient, which helps guide treatment decisions.

In addition to facilitating patient engagement, MyRheum is providing rheumatology caregivers with objective, quantitative measures of treatment outcomes — assuring them when treatments are working.

PON1 ACTIVITY CORRELATES WITH SYSTEMIC INFLAMMATION, DISEASE ACTIVITY AND CVD RISK IN PSA

Paraoxonase-1 a potential biomarker for CVD risk

By M. Elaine Husni, MD, MPH

Patients with psoriatic arthritis (PsA) are known to have increased cardiovascular (CV) morbidity and mortality not completely explained by traditional CV risk factors. Recent research has sought to expand the understanding of the mechanisms through which PsA is linked to enhanced pathogenesis of atherosclerotic heart disease. Researchers have found evidence of increased oxidative stress in both psoriatic disease and atherosclerosis. Paraoxonase-1 (PON1), a family of antioxidant enzymatic proteins located on HDL cholesterol particles, helps inhibit lipid oxidation. Decreased PON1 activity is considered a biomarker for increased systemic oxidative stress and increased conversion of HDL to a dysfunctional proinflammatory and proatherogenic state, and has been associated with the development of cardiovascular disease.

In addition, decreased PON1 enzymatic activity has been demonstrated to predict the development of major adverse cardiovascular events in the general population. A significant reduction in PON1 activity has been reported in patients with systemic inflammatory diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

My recent study with colleagues W.H. Wilson Tang, MD, and Stanley Hazen, MD, PhD, from Cleveland Clinic's Sydell and Arnold Miller Family Heart & Vascular Institute reported for the first time on serum PON1 enzymatic activity and its association with both psoriatic disease activity and CV disease burden in a psoriatic disease population.[1] The results for psoriasis (PsO) and PsA were compared.

Measuring PON1 activity level

This study, involving 343 adult patients with PsO and PsA and 345 controls, was conducted as part of Cleveland Clinic's Cardiometabolic Outcome Measures in Psoriatic Arthritis Study (COMPASS). Various baseline data were assessed and recorded, including gender, BMI, current disease-modifying antirheumatic pharmaceutical regimens, PsA disease activity (DAS-28, CDAI, joint counts), pre-existent cardiovascular disease (CVD) and CVD risk factors (diabetes, dyslipidemia, hypertension, smoking), Framingham risk score, quality of life (QOL) measures and labs (ESR/CRP, lipid profiles).

We further assessed CV disease burden by identifying patients with metabolic syndrome, and a subgroup of patients with PsA underwent carotid duplex high-resolution B-mode ultrasound imaging and were screened for carotid intima-media thickening (CIMT) and the presence of plaque. A subgroup underwent a second carotid duplex ultrasound two years later. The serum PON1 activity level was measured by two methods: paraoxonase activity (using paraoxon as substrate) and arylesterase activity (using phenyl acetate as substrate). The levels of PON1 activity in the PsA and PsO cohorts were compared 2-to-1 with an age- and gender-matched healthy human cohort.

PON1 activity levels and correlation with disease activity

Mean arylesterase activities were significantly lower in the PsO ($P < 0.001$) and PsA ($P < 0.001$) subjects when compared with healthy controls. In addition, the PsO cohort showed significantly lower mean arylesterase activity when compared with the PsA cohort ($P = 0.003$). No significant difference in median paraoxonase activity between the PsO and PsA cohorts was detected, although median paraoxonase activity showed a trend of lower levels in the PsA and PsO cohorts when compared with controls.

PsA patients with moderate to high disease activity (defined as either a DAS28-ESR > 3.2 or a DAS28-CRP > 2.67) showed a statistically significant lower arylesterase activity than those with low disease activity (defined by DAS28-ESR < 3.2 or DAS28-CRP < 2.67). In addition, PsA patients with moderate to high disease activity had a greater percentage of CVD risk factors than those with low disease activity as measured by DAS28 scores.

PON1 activity correlates with CV burden and prevalent CV disease

Both PsO and PsA cohorts had significantly lower serum arylesterase activity when compared with healthy controls ($P = 0.001$). Specifically, the PsA cohort demonstrated that lower arylesterase activity, but not paraoxonase activity, of PON1 was associated with elevated disease activity measures, increasing CVD burden and worse QOL measures. These associations were not seen in the PsO cohort.

While epidemiologic studies have shown that patients with PsA can be seen as a high-risk group for developing atherosclerosis, these measures of HDL-associated PON1 enzymatic activity may provide the mechanistic link between increased oxidative stress and CVD burden.

Reference

1. Husni ME, Wilson Tang WH, Lucke M, et al. Correlation of high-density lipoprotein-associated paraoxonase 1 activity with systemic inflammation, disease activity, and cardiovascular risk factors in psoriatic disease. *Arthritis Rheumatol*. 2018;70(8):1240-1250.

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AT THE INTERSECTION OF AUTOIMMUNE AND INFECTIOUS DISEASE

Case study shows value of interdisciplinary collaboration

By Cassandra Calabrese, DO, and James Fernandez, MD, PhD

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Complex immunologic disease requires intense collaboration across subspecialties for optimal care. For that reason, Cleveland Clinic's Department of Rheumatic and Immunologic Diseases recently developed the nation's first combined fellowship in rheumatology and infectious disease (ID), designed to train physicians to practice in both of those specialties.

These dual-trained specialists will be well-suited to engage in clinical care and research in a multitude of areas, including:

- Diagnosis and management of serious and opportunistic infections in patients on advanced immunosuppressive regimens.
- Infection prevention and vaccinology in at-risk populations.
- Diagnosis and management of patients in primary immunodeficiency states, especially those with infectious and autoimmune manifestations.

Rheum-ID hybrids also will be well-poised to sort out the complexities of the growing list of rheumatic complications of infections, such as spirochetes; blood-borne viral illnesses such as HCV, HBV and HIV; and the emerging field of arboviruses.

Below we share two situations at the intersection of rheumatology/immunology and infectious disease.

Case study: Patient with primary C7 deficiency

An 18-year-old female presented for evaluation of possible immunodeficiency. She was in her usual state of health until two years prior, when she was admitted for meningococcal meningitis. She was treated and recovered. One year later, she presented with flu-like symptoms and was diagnosed again with meningitis secondary to *Neisseria meningitidis* (Figure). Her history is also notable for frequent upper respiratory tract infections.

The patient's laboratory evaluation revealed a complement deficiency assay (CH50) of 0, C7 deficiency (< 5 U/mL) and absent AH50 without evidence of humoral immune deficiency. She was diagnosed with primary C7 deficiency.

Complement plays a key role in protection against a variety of infections. Activation of terminal complement components (or membrane attack complex: C5-C9) is crucial for controlling infections with encapsulated organisms, such as *Neisseria spp.* Patients with genetic deficiencies of terminal complement, such as the patient presented here, have a significantly increased risk of recurrent invasive meningococcal infection.[1]

The patient was educated on methods to reduce her infection risk, including revaccination against all five available meningococcal serotypes every three to five years. She has done well since.

Eculizumab therapy and its risks

Eculizumab is a monoclonal anticomplement C5 antibody that is FDA-approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (both diseases that involve uncontrolled activation of the complement system). Not surprisingly, eculizumab is associated with a significantly increased risk of meningococcal disease — 1,000 to 2,000 times greater than that of a healthy person.[2]

The rheumatology community will be increasingly exposed to eculizumab, as it also is used to treat refractory lupus nephritis.[3] Therefore, it is crucial that rheumatologists become aware of the drug's unique risk, as well as the current recommendations to offset it.

A black box warning was added to the eculizumab package insert after two of 196 PNH patients developed meningococcal infections while using the drug during clinical trials.[4] The insert recommends meningococcal vaccines for recipients of eculizumab, although recent data show some patients developed meningococcal disease even after receiving vaccinations.[5]

Currently available are vaccines for the most common serotypes, the meningococcal conjugate vaccine (MenACWY) and a serogroup B meningococcal vaccine (MenB). While most eculizumab-associated meningococcal infections have been nongroupable *Neisseria meningitides*, both meningococcal vaccines should be given at least two weeks before the first dose of eculizumab, if possible.[4,6]

Interestingly, breakthrough infection has been reported,[5] so antibiotic prophylaxis is also required.

Opportunities for interdisciplinary collaboration

Both the case study and the use of eculizumab involve a significantly increased risk of systemic neisserial infection and are perfect examples of the opportunity for collaboration between rheumatology, immunology and infectious disease.

Rheumatology offers many more opportunities, as the specialty encompasses every organ system and diseases with protean manifestations. Patients with primary immunodeficiencies may also present with autoimmune conditions, such as connective tissue diseases, inviting even more interdisciplinary collaboration.

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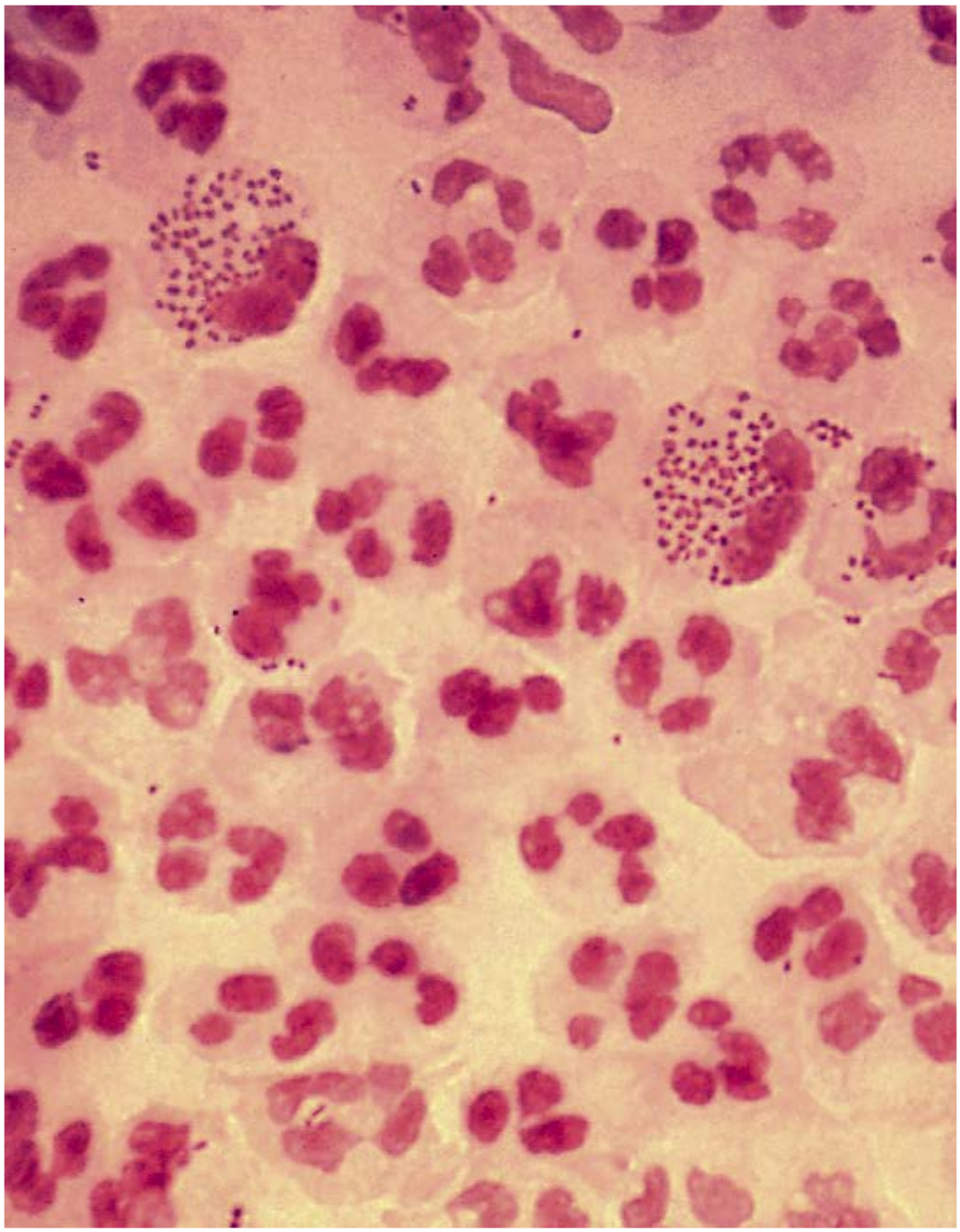

Figure. *Neisseria meningitidis*

THE FEVER THAT CRIES WOLF

Distinguishing the causes of fevers in patients with lupus

By Emily Littlejohn, DO, MPH

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A 25-year-old female with systemic lupus erythematosus (SLE) manifesting with class IV lupus nephritis, lupus cerebritis, antiphospholipid syndrome, hemolytic anemia, oral ulcers, alopecia and arthritis was recently evaluated in our clinic for follow-up. Current therapy included prednisone, hydroxychloroquine and rituximab intravenous infusions, with the last dose given two months prior to this visit. She presented after a complex hospitalization during which she was diagnosed with atypical hemolytic uremic syndrome and received eculizumab therapy.

At our visit the patient reported feeling chilled, with myalgia and gastrointestinal upset. Her vital signs revealed that she was tachycardic to 130 beats per minute with a temperature of 38.6°C (101.5°F). She was promptly admitted to the hospital where blood work revealed elevated sedimentation rate (ESR) and C-reactive protein (CRP), and leukopenia with stable hemoglobin and platelets.

Infection or flare? Using the ESR-to-CRP ratio

Rheumatic diseases and their treatments often put patients at increased risk of infections. This leaves us keenly aware and constantly inquiring about infectious signs and symptoms. Herein lies one of the most common dilemmas faced by rheumatologists: distinguishing the causes of fevers in patients with rheumatic diseases. This is particularly true in lupus, where fevers can be a common manifestation of a lupus flare.

Research that can provide physicians with tools to elucidate the cause of fevers in lupus patients is ongoing. SLE activity measures — such as anti-double-stranded DNA antibodies, complements and the complete blood count — can be helpful, although these measures do not always track or change with lupus activity and certainly can be abnormal in the setting of infection. CRP and ESR, both nonspecific markers of systemic inflammation, are potentially useful biomarkers in this frequently encountered clinical scenario.

Table. Nonspecific markers of inflammation corresponding to episodes of flare vs. infection.[11]

	Lupus flare (N = 28)	Infection (N = 25)	*P* Value
ESR (mm/hour)	50.7 (31.3)	53.4 ± (34.5)	NS
CRP (mg/dL)	5.4 (6.5)	11.2 (7.2)	0.0035
ESR:CRP Ratio			0.000
≤ 2	0 (0)	3 (12.0)	
2 – 15	13 (46.4)	21 (84.0)	
≥ 15	15 (53.6)	1 (4.0)	
WBC > 10K/mm^3	6 (21.4)	5 (20)	NS

Interestingly, where ESR elevations are strongly associated with disease exacerbations in SLE,[1] CRP levels do not tend to correlate with markers of disease activity, such as anti-double-stranded DNA antibodies and complement levels.[2] The blunted CRP response in SLE patients may be due to the effects of interferon-α, a molecule highly expressed in lupus patients, by inhibiting CRP promoter activity and CRP secretion in hepatocytes.[3]

Since ESR rises both with lupus activity and with infection, alone it is too nonspecific to distinguish between lupus flare and infection.[4] CRP values of > 6.0 mg/dL in SLE patients have been associated with infectious processes,[5-7] and higher CRP levels have been observed in SLE infection compared with SLE flare without infection.[8,9] When CRP is elevated during a flare, flares of serositis (pleuritis, pericarditis, pneumonitis) and flares involving nephritis or myositis present with a significantly higher CRP than other types of SLE flares.[10]

In an article recently published in *Lupus,* the medical records of hospitalized patients with SLE were reviewed to assess the usefulness of the ESR-to-CRP ratio in distinguishing infection from flare in lupus patients presenting with fever.[11]

Eligible hospitalizations for this study were those in which patients presented with a temperature of > 37.9°C (100.3°F) or with subjective fever as a chief complaint upon admission. Collected at admission were clinical and laboratory data, including patient symptoms, the infectious workup (X-rays, blood cultures, urine cultures), basic labs (including complete blood count), ESR and CRP.

We found that ESR levels were similar in patients with flares and infections. CRP levels were significantly higher in infections compared with flares (Table). The ESR-to-CRP ratio was positively associated with flare, where each unit increase in the ESR-to-CRP ratio was associated with a 13 percent increase in the odds of fever

etiology being attributed to SLE flare versus infection. The proportion of flares versus infections varied according to the ratio of ESR to CRP (Table and Figure), with infections predominant for ratios of ≤ 2, and flares predominant for ratios of ≥ 15 (P = 0.000).

How the ESR-to-CRP ratio guided treatment

Our patient was promptly admitted to the hospital, where blood work revealed elevated ESR of 27 mm/hr (normal range 0-20 mm/hr) and CRP of 2.3 mg/dL (normal < 0.9 mg/dL), with an ESR-to-CRP ratio of 11.7. Complements were normal, and anti-double-stranded DNA antibodies also were normal. Her complete blood count showed leukopenia, with both lymphopenia and neutropenia. Blood cultures grew methicillin-resistant *Staphylococcus epidermidis*, and our patient received a full course of IV antibiotics, which resolved her fevers and normalized her cytopenias.

In summary, our patient was one with difficult-to-control, multi-organ-involved lupus, receiving ongoing immunosuppression and presenting with a temperature of 38.6°C (101.5°F). Blood work on admission was difficult to interpret, and there was a high suspicion of both infection and SLE flare. The ESR-to-CRP ratio was a useful tool in helping to guide the clinical acumen and delay use of high-dose glucocorticoids or other immunosuppressive SLE medications.

This precarious situation between treating an infection versus flare is not foreign to rheumatologists. In analyzing the usefulness of the ESR-to-CRP ratio, we hope to shed light on a potentially useful tool that can guide management in this common clinical conundrum.

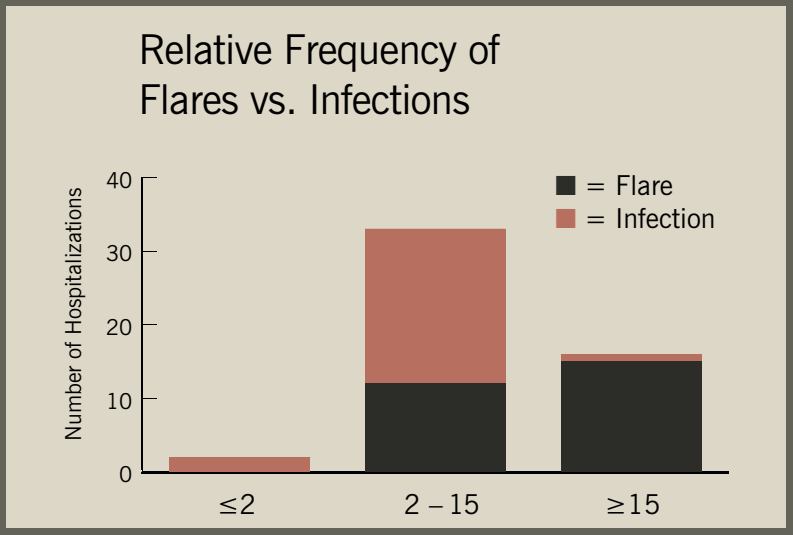

Figure. Relative frequency of flares versus infections according to the ratio of erythrocyte sedimentation rate (ESR) to C-reactive protein (CRP) (categorized as ≤ 2, 2-15 or ≥ 15). There was a significant difference in the distribution of flares versus infections according to the ESR to CRP ratio (P = 0.000).[11]

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A CLOSER LOOK AT TWO RARE AUTOIMMUNE CONDITIONS

Gastric antral vascular ectasia in systemic sclerosis and serositis in antisynthetase syndrome

By Soumya Chatterjee, MD, MS, FRCP

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At the 2018 American College of Rheumatology Annual Meeting in Chicago, Cleveland Clinic rheumatology fellows presented research on two rare autoimmune conditions. Their findings shed new light on these little-understood diseases.

Gastric antral vascular ectasia in systemic sclerosis

Second-year rheumatology fellow Rabeea Mirza, MD, compared gastric antral vascular ectasia (GAVE) in systemic sclerosis (SSc) with GAVE in other diseases.

Background. GAVE is a pathologic angioectasia with a characteristic endoscopic appearance. Rugal folds with dilated blood vessels radiate from the antrum and converge at the pylorus, resembling watermelon stripes, supporting the name "watermelon stomach" (Figure 1). GAVE can cause anemia and significant morbidity; hence there is need for surveillance.

GAVE has been associated with cirrhosis of the liver, autoimmune diseases (e.g., SSc, rheumatoid arthritis, primary biliary cholangitis), end-stage renal disease, hypertension, heart failure, hypothyroidism and chronic pulmonary disease. It also can occur after hematopoietic stem cell transplantation. Prevalence of SSc-associated GAVE is highly variable, ranging from 1 to 76 percent of patients with SSc. Prevalence of GAVE in other associated diseases and its long-term outcomes are still unknown.

Methods. We conducted a retrospective chart review of patients with GAVE and evaluated those diagnosed between 2012 and 2017. We initially identified 145 GAVE patients and separated them into cohorts of those with SSc and those with other diseases. We selected 37 consecutive SSc and 37 consecutive non-SSc patients from the GAVE database. Outcomes were defined by number of transfusions, number of recurrences of GAVE bleeding diagnosed endoscopically, and death.

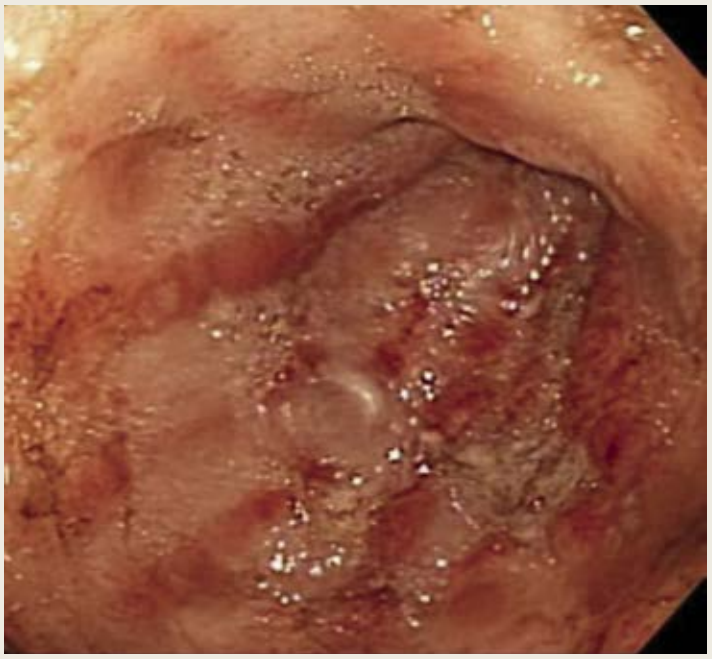

Figure 1. A 55-year-old female with diffuse systemic sclerosis presenting with severe iron deficiency anemia (hemoglobin 7.5 g/dL). Upper endoscopy shows gastric antral vascular ectasias (GAVE).

Results. This study demonstrated that SSc patients with GAVE were significantly younger than those with non-SSc GAVE, and were mostly females. Patients were followed for a median of five years.

Clinical manifestations associated with GAVE in both SSc and non-SSc groups were telangiectasias, melena, hematemesis, fatigue, dyspnea and lightheadedness. When adjusted for pretransfusion hemoglobin, the difference in transfusion requirements was not statistically significant between the two groups. There was no difference in use of NSAIDs and anticoagulants between the two groups. There also was no difference in number of recurrences of GAVE. Two patients with cirrhosis of the liver died.

Further studies with larger cohorts of GAVE patients may be helpful in understanding its natural history and outcomes in specific diseases.

Serositis in antisynthetase syndrome

First-year rheumatology fellow Alexis Katz, DO, studied the prevalence of serositis in antisynthetase syndrome (ASS), its clinical significance and its association with specific ASS autoantibody subtypes.

Background. ASS is a relatively rare autoimmune disease characterized by interstitial lung disease, myositis, inflammatory arthritis, Raynaud phenomenon and mechanic's hands. Eight autoantibodies to aminoacyl-transfer RNA synthetases have been described so far: Jo-1, PL-7, PL-12, EJ, OJ, YRS, KS and Zo. Morbidity and mortality are mainly related to pulmonary complications. However, little has been reported about the

prevalence of serositis (pleural and/or pericardial effusions) in ASS other than in small cohort studies (15-20 patients) and case reports.

Methods. Clinical data were obtained by retrospective review of electronic medical records from 2004 to 2017. Our study included patients diagnosed with ASS by a rheumatologist. All patients had one of the following ASS antibodies: Jo-1, PL-7, PL-12, EJ or OJ. Pleural effusions were qualified as trace, small, medium or large, based on chest radiographs and thoracic CT scans. Pericardial effusions were classified as trace, small, medium, large or tamponade, based on echocardiographic findings (Figure 2).

Results. A total of 93 patients were included in this study. The mean age was 57.5 years; 63 percent were females.

Out of 90 patients with complete data available, 42.2 percent had pleural effusion(s) and 47 percent had a pericardial effusion, of which 10 percent were moderate to large. One patient had tamponade physiology. Anti-Jo-1 patients were significantly less likely to have pleural effusions when compared with patients with other antibodies. Anti-PL-12 patients had a higher frequency of pleural effusions relative to patients with anti-Jo-1, anti-PL-7 and all other antibodies combined.

More research is necessary to better understand, diagnose and treat both GAVE in SSc and serositis in ASS. Our work is intended to raise awareness of these conditions, share new insights and serve as a springboard for further investigation.

Figure 2. Echocardiogram in a 23-year-old female with anti-Jo-1 syndrome showing a large circumferential pericardial effusion.

PRACTICE-CHANGING PRECISION SUBANALYSES

What rheumatologists should know

By M. Elaine Husni, MD, MPH

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PRECISION trial results[1,2] have challenged many assumptions about the use of nonselective NSAIDs versus selective COX-2 inhibitors.

NSAIDs are normally classified by the relative selectivity of COX-1 and COX-2 enzymes. Nonselective NSAIDs, such as naproxen and ibuprofen, inhibit both COX-1 and COX-2. Selective NSAIDs, such as celecoxib, are COX-2-specific and were developed to spare COX-1 inhibition to allow more gastrointestinal (GI) protection.

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.

PRECISION data tell us that's not so. PRECISION found celecoxib to be as safe as naproxen and ibuprofen in terms of CV risk. In patients with OA, celecoxib carries less CV risk than ibuprofen and similar risk to naproxen, and less GI risk than ibuprofen and naproxen. Celecoxib was similar to both ibuprofen and naproxen in all-cause mortality. In patients with RA, the study found no difference in the rates of major CV and renal adverse events among the three drugs but found a doubling of all-cause mortality in patients who used naproxen versus celecoxib.

Since the original results were published, many subanalyses have dissected the data for relevance to particular populations or disease states. I find the below studies of particular relevance for practicing rheumatologists who frequently help patients balance the benefit of arthritis medications with the risk of comorbidities.

Aspirin coadministration and CV prevention in arthritis patients who use NSAIDs

An important PRECISION substudy[3] from our colleagues at Cleveland Clinic shows that adding aspirin attenuates celecoxib's safety advantage over the nonselective NSAIDs naproxen and ibuprofen, but that celecoxib with aspirin still has an equal or better safety profile (in regard to GI and renal events) relative to both agents. The study evaluated the trial's on-treatment population for both OA and RA, which consisted of 11,018 patients taking concomitant aspirin and 12,935 patients not on aspirin. Propensity score weighting was used to adjust for baseline characteristics, thereby increasing the validity of comparisons.

Another substudy published in *Rheumatology* tested the hypothesis that RA patients have a different risk-benefit profile for the use of aspirin in secondary CV risk prevention.[4] Of 1,852 subjects with RA in PRECISION, 540 reported using low-dose aspirin for CV prevention, and 1,312 did not. We observed major NSAID toxicity in 79 (6.0 percent) nonaspirin users and 37 (6.9 percent) aspirin users ($P = 0.50$). Thus, in the RA population, low-dose aspirin users experienced the same rate of primary outcome as nonaspirin users. The risk of a major adverse CV event was similar as well.

These findings highlight the importance of appropriately counseling arthritis patients on drug safety profiles, especially when they are taking multiple medications. Remember:

- There were very few CV events observed in arthritis patients on the studied NSAIDs over 18 months.
- Selective NSAIDs did not indicate a higher CV risk than nonselective NSAIDs.
- Using aspirin may decrease the CV safety advantage of selective NSAIDs — although there was no difference between aspirin users and nonaspirin users in the RA population.

GI safety in arthritis patients

Another subanalysis examined the overall GI safety of celecoxib, ibuprofen and naproxen in arthritis patients on concomitant esomeprazole and low-dose aspirin or corticosteroids. Our randomized, double-blind controlled trial published in *Alimentary Pharmacology & Therapeutics* found that celecoxib had a safer GI profile overall compared with ibuprofen or naproxen for patients with RA and OA.[5] The primary endpoints were clinically significant GI events (CSGIEs), including bleeding, obstruction, perforation events from the stomach downward or symptomatic ulcers, and iron deficiency anemia.

Patients received 100 to 200 mg celecoxib twice daily (N = 8,072), 600 to 800 mg ibuprofen three times daily (N = 8,040) or 375 to 500 mg naproxen twice daily (N = 7,969) as well as 20 to 40 mg esomeprazole for gastroprotection. CSGIEs occurred in 0.34, 0.74 and 0.66 percent of patients receiving celecoxib, ibuprofen and naproxen, respectively. There also was less iron deficiency anemia in patients on celecoxib than in those on naproxen or ibuprofen. *Helicobacter pylori* status was also studied but did not influence the outcome.

Interestingly, concomitant corticosteroid use increased total GI events and CSGIEs. Our data show that CSGIEs are infrequent in patients with OA and RA taking NSAIDs plus esomeprazole, but celecoxib has better overall GI safety than ibuprofen or naproxen at these doses regardless of concurrent low-dose aspirin or corticosteroid use.

As rheumatologists, we can be reassured that patients with OA and RA who may need prolonged use of NSAIDs for joint pain have relatively infrequent CSGIEs. These results allow us to consider celecoxib for patients at higher risk of CSGIEs.

Tailoring treatment for patients with multisystemic disease or high risk

These subgroup analyses are hypothesis generating rather than definitive, but they help address gaps in our knowledge related to chronic NSAID use in patients with OA and RA. First, the overall data allow us a more tailored

approach to treatment for patients using selective and nonselective NSAIDs, especially when the need may be chronic. Second, subanalyses allow us to offer a more nuanced approach for patients with comorbid GI and CV disease and/or increased risk, such as the elderly population or those on dual therapy with low-dose aspirin or corticosteroids.

Although several PRECISION substudies have generated interesting data, those mentioned above are particularly relevant to our daily practice as clinical rheumatologists and should inform our interactions with and recommendations for patients.

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