

RARE DISEASES REPORT: RHEUMATOLOGY

NOVEMBER 2020

SELECTED ARTICLES

Survey reveals special impact of COVID-19 on persons with rare disorders

Topical treatment tackles oral ulcers in Behçet's syndrome

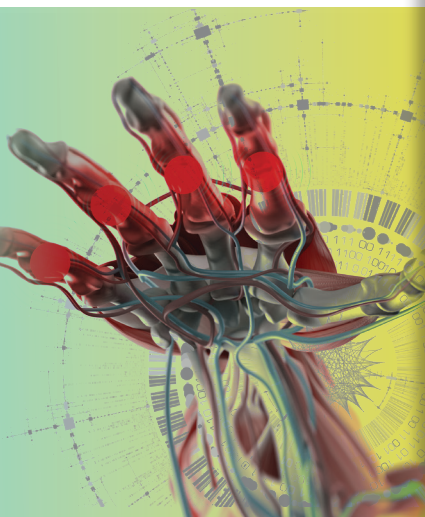
Managing the risk of congenital heart block in anti-Ro/SSA-positive women

Newly described lung disorder strikes children with systemic juvenile idiopathic arthritis



NORD
National Organization
for Rare Disorders

Rheumatology News



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EDITOR'S NOTE



Jeff Evans

Our second installment of *Rare Diseases Report: Rheumatology* comes at a challenging time for both patients with rare rheumatologic diseases and clinicians as we navigate through the COVID-19 pandemic. An article in this year's report details how these challenges have evolved for patients and their caregivers and how rheumatologists who care for them have adapted their practices to address the barriers and unique concerns of patients with rare diseases.

Rare rheumatologic disease can also strike people across a wide range of ages. You can read how hydroxychloroquine, a drug first touted and later discredited as a treatment for COVID-19, has proven to be a potential game-changer in the prevention of neonatal lupus and congenital heart block in infants born to women who are positive for anti-Ro/SSA antibodies. Another article chronicles how awareness of rare but striking pulmonary complications of children with systemic juvenile idiopathic arthritis has grown in pediatric rheumatology clinics across the United States and other parts of the world where early treatment with biologics has been in place.

Meanwhile, the various forms of vasculitis, most of which are rare, occur across a range of age groups. We learn that imaging has a big role to play in teasing out the clinico-pathologic patterns that may help to distinguish the middle- to older-aged adults who develop giant cell arteritis from patients who have Takayasu's arteritis, which may strike at younger age. An informative study of remission maintenance treatment regimens for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, another that can affect mid- to older-age adults, is also covered in the report.

Elsewhere in the report, we learn about treatments for oral ulcers in patients with Behçet's syndrome; evidence suggesting that chronic recurrent multifocal osteomyelitis and SAPHO syndrome are part of the same clinical entity; as well as predictors for progression from Raynaud's phenomenon to systemic sclerosis and atypical presentations of renal crisis in scleroderma.

I hope that you enjoy the report!

—Jeff Evans, Editor, *Rheumatology News*

A NOTE FROM NORD



Rebecca Aune

Welcome to the second issue of the *Rare Diseases Report: Rheumatology*! The National Organization for Rare Disorders is proud to collaborate with *Rheumatology News* and medical experts to bring you the most up-to-date information on timely topics related to caring for individuals affected by rare rheumatologic diseases. We value this opportunity to speak directly to the professionals who play such an important role in the lives of the patients and families whom we represent. At

this challenging time, we also appreciate the opportunity to share information on how COVID-19 is affecting the rare diseases community, with insights from medical experts on patient care during the era of COVID. Other topics covered in this issue – related to neonatal lupus, juvenile idiopathic arthritis, vasculitis, scleroderma, Behçet's syndrome, and other rare diseases – reflect that this is a time of unparalleled advances in the science of rare diseases. In 2019, 44% of the novel new drugs approved by the Food and Drug Administration were "orphan" drugs or ones for rare diseases. New rare diseases are being identified on a regular basis, and major advances are being made in diagnostic tools and treatment resources. To be able to convert today's rapidly expanding knowledge to earlier diagnosis and state-of-the-art care for patients requires constant communication with those on the "front lines" – the medical professionals caring for patients affected by rare medical conditions. NORD works closely with rare disease researchers and medical experts to promote awareness of these advances among physicians, other medical professionals, patients, and caregivers. We do this through our website (www.rarediseases.org), our rare disease database and video library, CME resources, free webinars, regional forums, and an annual conference known as the NORD Rare Diseases and Orphan Products Breakthrough Summit that takes place each year in October. We appreciate your interest in rare diseases, and we invite you to visit our website to learn more about the current status of rare disease management, new tools for generating better understanding of diseases, and new treatment options for adults and children affected by rare rheumatologic diseases.

—Rebecca Aune, Director of Education Programs, NORD

Survey reveals special impact of COVID-19 on persons with rare disorders

BY NEIL OSTERWEIL

It seems naive now, but in the early days of the COVID-19 crisis there was a debate among public health experts and media about whether to label it an “epidemic,” which affects only people within a specific population, community, or region, or a “pandemic,” an epidemic that spans continents and spreads rapidly throughout the world.

Today all reasonable doubts about the virulence and transmissibility of SARS-CoV-2, the virus that causes COVID-19, have been erased, along with the lives of more than 200,000 people in the United States and more than 1 million people worldwide as of this writing.

Among the myriad pernicious effects of the COVID-19 pandemic – social disruptions, financial chaos, the politicization of public health measures – the effects on health care have been especially severe, and perhaps nowhere more challenging than for patients with rare rheumatologic diseases and the clinicians who care for them.

The National Organization for Rare Disorders (NORD) has documented the barriers to care caused by the pandemic as well as the unique concerns of patients with rare diseases in a NORD Rare Insights report.¹

The advocacy group had previously published survey results revealing that people with rare diseases and their families suffered major disruption in their care and well-being in the early days of the pandemic.

The current report details the results of a second survey conducted in June 2020, including responses from 833 people, primarily

persons with rare diseases but also their family members and advocates.

“These unprecedented times have upset the balance of a health care system that already did not work in favor of most people with rare diseases,” the report says. “Patients and families typically face an uphill battle trying to find a diagnosis; often encounter a lack of treatment options; experience the hope and precariousness of participating in research or clinical trials; and travel extensively to be seen by disease-specific experts – all in the hope of gaining some relief or chance at improved well-being.”

In addition to finding that 92% of patients with rare diseases are still adversely affected by the pandemic, the report’s authors found that:

- More than three-fourths of respondents reported canceled medical appointments.
- One-third said they had challenges accessing medical care and treatment.
- Fourteen percent reported difficulties getting access to medical supplies, and two-thirds of the respondents to this

Continued



Sivia Lapidus, MD



Fatma Dedeoglu, MD

Dr. Sivia Lapidus and Dr. Fatma Dedeoglu have no relevant disclosures to report.

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question said they had trouble acquiring personal protective equipment (PPE), which is especially important for patients with immune disorders and those who are taking immunosuppressant therapies.

- More than one-third of respondents said that their households had been affected by a lack of income, and 27% reported job losses. Among those who lost jobs, 9% also lost health insurance.

Lessons from early epicenters

Sivia Lapidus, MD, a pediatric rheumatologist at the Joseph M. Sanzari Children's Hospital, and assistant professor of pediatrics at Hackensack Meridian School of Medicine in Hackensack, N.J., has seen firsthand the negative effects that the COVID-19 pandemic has had on patient care. Her hospital was the first in New Jersey to treat a patient with confirmed COVID-19 infection.

"We were flooded with COVID cases in Bergen County, where the hospital is, and a lot of New Jersey was flooded with cases during the peak," she said in an interview. "There was a lot of fear in the beginning because we just didn't know a lot about it, and initially our ability to see patients in person declined significantly because we didn't have rooms."

The hospital cafeteria became a makeshift intensive care unit, and pediatric inpatient units began accepting patients up to 80 years old in order to accommodate the surge, she said.

To compensate for their inability to see patients in person, Dr. Lapidus and colleagues began telemedicine visits in early March, and in-person patient visits were suspended altogether later that month.

"During that time we were encouraging our pediatric rheumatology patients to continue their medications and continue their follow-up, in order not to flare," she said.

In her group of six pediatric rheumatology specialists, who also see general pediatric rheumatology patients, "it was interesting that we did not see more amplified pain. I don't know whether it was due to patients being at home and comfortable or with less psychological distress, but we did not see more lupus or JIA [juvenile idiopathic arthritis] flares," she said.

When telemedicine visits began in earnest, however, Dr. Lapidus estimated that she was seeing a doubling or tripling in the number of patients with PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis) syndrome, a trend that appears to be reflected elsewhere in the United States and in Europe, based on postings to a rheumatology Listserv, she said.

Knowledge is power

In Boston, another early epicenter of COVID-19, Fatma Dedeoglu, MD, codirector of the autoinflammatory clinic in the rheumatology program of the division of immunology at Boston Children's Hospital and associate professor of pediatrics

at Harvard Medical School, Boston, was receiving calls from concerned patients.

"In general, the unknown is the major issue, because it's a new virus and was very difficult at the beginning," she said. "We didn't know how it was going to affect children, especially people who already have immune-related disease or immune-suppressing medications and such."

More than 6 months into the pandemic, the level of confidence about managing patients in the time of COVID-19 has risen substantially, and the risk of infection does not appear to be greater for children with rheumatologic disorders, even when they are taking immunosuppressive drugs, such as biologic agents or traditional disease-modifying antirheumatic drugs (DMARDs), she said.

"As long as the disease is under control and patients are not on long-term steroids, the problem seems to be under control," she said.

She noted that caregivers of patients who are immunosuppressed seem to be aware of the need for extra precautions, although there is evidence that some are beginning to let their guard down and becoming a little lax about social distancing.

Dr. Dedeoglu confessed to be initially somewhat concerned that telemedicine would greatly diminish the patient visit, because of the lack of hands-on, face-to-face contact.

"But having the telemedicine option actually has helped a lot, and it's been really, really important to have it," she said.

Patients are less likely to cancel or miss telemedicine appointments, compared with outpatient visits, because they don't have the logistical hurdles that coming to the hospital can entail. The parking is a whole lot cheaper, too.

Postpandemic care is likely to continue as a mix of remote and in-person visits, she said. For patients who experience flares, for example, the rheumatologist will likely need to physically examine joints and lymph nodes, and those patients will be asked to come into the clinic.

Not just phoning it in

Telemedicine is likely here to stay, both Dr. Dedeoglu and Dr. Lapidus acknowledged.

"There are times when telemedicine can be frustrating, and it can potentially delay care, but it depends on the circumstances," Dr. Lapidus said.

An American College of Rheumatology (ACR) guidance for the management of children with pediatric rheumatic disease during the COVID-19 pandemic includes telemedicine or telemedicine as an option for routine management, stating that "shared decision-making should occur between patients, families, and rheumatology providers to discuss additional measures to reduce interruptions in clinical care, particularly during

periods of increased community transmission. Such measures may include use of telemedicine for routine, regularly scheduled, and nonurgent clinical assessments, and physical therapy.²

The NORD report notes that “telemedicine has emerged as a bright spot for many people with rare diseases as a way to safely and confidently access medical care without risking exposure to COVID-19.”

The report shows a clear rise in the uptake and acceptance of telemedicine, with the proportion of respondents who reported being offered telemedicine visits at 83%, up from 59% in April 2020. Of those respondents who had medical appointments canceled because of the pandemic, 85% were offered a telemedicine alternative, compared with 65% in April.

Acceptance of telemedicine was also high, with 88% of those who said they had been offered a telemedicine visit agreeing to it, and 92% reporting their telemedicine visits as positive experiences.

One respondent told NORD that “My daughter’s appointments at Boston Children’s were all canceled. Telehealth was very helpful as it allowed us to move forward with a trial drug therapy that would have been delayed another year despite her progressive decline in health.”

Dr. Lapidus said that she has some patients with recurrent fever who live several hours’ travel away from her center and may not have pediatric rheumatologists in their area, and for those patients telemedicine has been a boon.

The report goes on to add, however, that the use of telemedicine has declined since its peak in mid-April 2020.

“NORD has and will continue to advocate for people with rare diseases to have the best possible options and access to medical care,” the report states.

PPE and medications

Even before the COVID-19 pandemic, nearly half of all respondents regularly used PPE to help them manage infection risks associated with their diseases, and about 1 in 5 of these respondents said they required PPE continually.

In addition, many respondents reported widespread lack of precautions by others they came in contact with, such as failure or refusal to wear face masks or to follow common and well-understood social distance guidelines.

“Most people in my area refuse to wear masks. I wish they would so that I would feel more comfortable in venturing out,” one respondent wrote.

Equally troubling for many was the difficulty in getting access to medications, such as the DMARD hydroxychloroquine, which is considered one of the safest agents in its category because it does not increase the risk of serious infections and is not associated with either increased hepatotoxicity or renal dysfunction.³

When hydroxychloroquine was publicly – and wrongly as it turns out – touted by President Trump and others as an effective prophylactic and/or therapeutic against COVID-19, the result was a run on pharmacies by people clamoring for the drug, which caused the wholesale price of the active ingredient, hydroxychloroquine sulfate, to skyrocket.⁴

Other patients responded that they experienced delays in receiving medications in concert with the widely reported disruptions in the U.S. mail linked to budget cutbacks.

Social and economic stress

The concerns of patients with rare rheumatologic disorders during the pandemic have been compounded by social stresses such as isolation when family and friends can’t or won’t visit out of concern for transmitting disease, worries about social interactions with people who don’t follow public health and social distancing protocols, and coping with family and friends who don’t understand why a person with a rare disorder might need to self-isolate.

Equally troubling are income loss and job losses – including for some the loss of health insurance. Many at-risk people reported worrying about having to choose between their health and their jobs if their employers insist on a return to the workplace full- or part-time.

“Some of our patients, the parents lost their jobs and are going on Medicaid when they were previously middle class or upper middle class, and now they’re in a financially difficult situation,” Dr. Lapidus said.

Clinicians feel it too, she added, noting that in the early days of the pandemic staff members were unsure whether they would be pressed into service in other hospital areas, and of course worried about the possibility of becoming infected themselves or transmitting infections to family and friends.

To help people with rare diseases, NORD has created a COVID-19 resource center, available at rarediseases.org/covid-19, which offers links for on-demand videos and webinars, information and tools for advocacy, disease-specific resources for patients, and links to other sources of information that may be helpful for patients and caregivers.

REFERENCES

1. COVID-19 community follow-up survey report. *National Organization for Rare Disorders*. Published 2020 Aug 2.
2. Wahezi DM et al. *Arthritis Rheumatol*. 2020 Jul 23. doi: 10.1002/art.41455.
3. Benjamin O et al. StatPearls: Disease Modifying Anti-Rheumatic Drugs (DMARD). Updated 2020 Jul 4. <https://www.ncbi.nlm.nih.gov/books/NBK507863>.
4. Silverman E. A key ingredient that compound pharmacies need for hydroxychloroquine skyrockets in price. *STAT News*. 2020 Apr 10. <https://www.statnews.com/pharmalot/2020/04/10/compound-pharmacies-hydroxychloroquine-price-hike/>.

Topical treatment tackles oral ulcers in Behçet's syndrome

BY SARA FREEMAN

Oral ulcers that are a hallmark of Behçet's syndrome responded well to treatment with a novel gel containing pentoxifylline in a recent pilot trial, with improved healing time and substantially fewer detectable ulcers by day 4 of the 2-week treatment when used in combination with colchicine versus colchicine alone.

The trial's "strongly encouraging results," according to the study's authors, were coupled with a propensity for the gel to cause a bad taste in the mouth in three-quarters of patients, however, which was strongly linked to nausea in over half of the patients who were treated.

Now the company that is working on the product is trying to make it taste better to improve its tolerability, said Gülen Hatemi, MD, professor, Istanbul University – Cerrahpasa.

The trial's participants had to fill their mouths with the gel and keep it in the mouth as long as possible before swallowing. It was the taste of the actual drug that was the problem. "If they could give it a toothpaste-like taste it will be more tolerable," Dr. Hatemi suggested.

Oral ulcer-related disability

Oral ulcers can be a particularly disabling characteristic of Behçet's syndrome; patients may develop as many as 10 new ulcers each month. This is significant if you consider that some of these ulcers may be developing while others are still healing.

"Oral ulcers will heal on their own in around 7-10 days, but then when the patient has a few of them each month, it means that constantly they have oral ulcers in their mouth," Dr. Hatemi observed. "They cause an important disability, impairment in quality of life, because they are painful." The pain can stop people from eating and drinking and, in severe cases, lead to weight loss.

"It's a problem in their social life and work life because it makes it difficult to speak. Overall, it's really a disabling condition," Dr. Hatemi said.

In northern European countries, Behçet's syndrome has been reported to affect fewer than 1 in 100,000 people, and around 5 in 100,000 in the United States. However, it has a much higher prevalence in Mediterranean countries, notably

Turkey, where as many as 420 people per 100,000 may be affected, and where the topical pentoxifylline gel trial was conducted.¹

Topical gel effective, tolerability troublesome

The trial was an open-label, phase 2, "proof-of-concept" study in which 41 patients being treated with colchicine at Dr. Hatemi's institution were recruited and randomized to continue colchicine alone (n = 21) or together with topical pentoxifylline (n = 18).

"Colchicine is considered the first-line treatment for oral ulcers. Although it is not really very effective for oral ulcers, it is quite safe compared to the alternatives and may be effective for other Behçet's lesions such as genital ulcers or nodular lesions," and it's fairly inexpensive in most countries other than the United States, Dr. Hatemi noted.

Seeking a more effective alternative to colchicine was part of the rationale for the pilot study, and pentoxifylline was an attractive option because it had previously been shown to have an immunomodulatory effect and possibly to be a mild tumor necrosis factor (TNF)-alpha blocker.

Recruitment into the trial was completed between March and August 2019, with 60 patients. The trial was halted early, however, at the behest of the trial sponsor, Silk Road Therapeutics, after the first interim analysis showed a good enough response to move forward to a phase 3 trial, albeit with the need to improve the gel's tolerability.

The interim findings were presented by Dr. Hatemi during a poster session at the annual European Congress of Rheumatology.² Key results comparing the pentoxifylline-colchicine-treated patient with those who received only colchicine were a faster ulcer shrinkage time – at about 1 versus 3 days – and a shorter duration of ulcers in the mouth of about 3.5 versus 6.5 days.



Gülen Hatemi, MD

Dr. Gülen Hatemi has received grants for research, honoraria for consulting activities, or both from various pharmaceutical companies, including AbbVie, Bayer, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Mustafa Nevzat, Novartis, Silk Road Therapeutics, and UCB. The pilot study with pentoxifylline gel she discussed was sponsored by Silk Road Therapeutics. The phase 2 and phase 3 studies with apremilast were sponsored by Celgene.

The average number of oral ulcers from the start to end of 2 weeks' treatment were 0.81 and 0.67 in the pentoxifylline-colchicine group of patients and 1.89 and 1.71 in the colchicine group of patients. Furthermore, 50% of patients in the pentoxifylline-colchicine group had no detectable oral ulcers by day 4 of the study, compared with 10% of the colchicine group. The number of painful ulcers also fell, with greater mean changes in pain scores with pentoxifylline-colchicine than colchicine alone from day 1.

Adverse events affecting tolerability

Dysgeusia was reported by 11 (55%) of the pentoxifylline-colchicine-treated patients, a side effect not seen in the colchicine group. Nausea was reported in 15 (75%) of the pentoxifylline-colchicine-treated patients and 2 (10%) of the colchicine-treated patients. Vomiting occurred only in the experimental arm, affecting two (10%) patients. Although no serious side effects were seen, two patients in the pentoxifylline-colchicine group had to withdraw because of dysgeusia and nausea, one of whom experienced vomiting.

Despite the tolerability, this was enough to proceed to a larger, multicenter, possibly multinational trial, Dr. Hatemi said, with the proviso that it would need to be "with a better-tasting agent."

How to treat oral ulcers?

So where does that leave the treatment of oral ulcers currently? Recommendations produced by the European League Against Rheumatism provide some guidance.³ First published in 2008 and recently updated, these state that "topical measures such as steroids should be used for the treatment of oral and genital ulcers." They go on to say that because of its "safety and good tolerability," colchicine should be the first choice for the prevention of recurrent mucocutaneous lesions.

"For patients who have frequent recurrences of ulcers despite colchicine, systemic treatment modalities should be considered," said Dr. Hatemi, who was involved in the EULAR recommendations' development. "The agents that can be used are azathioprine, interferon- α , thalidomide, TNF-blockers, and apremilast [Otezla]."

Aside from drug treatment, patients with recurrent oral ulcers should be advised to avoid certain foods, such as anything crunchy like nuts, that might aggravate the lining of the mouth, she advised.

Apremilast provides oral ulcer pain relief

Apremilast is a relatively recent addition to the list of recommended systemic treatments for Behçet's syndrome, being already approved for use in psoriasis and psoriatic arthritis in both the United States and Europe. Just recently, on the back of the phase 3 RELIEF study,⁴ the Food and Drug Administration gave it the green light for use in the treatment of oral ulcers due to Behçet's syndrome.

"In 2015, we published the phase 2 data,"⁵ Dr. Hatemi said, adding that combined with the recent phase 3 data, the findings showed "that it is quite beneficial in managing oral ulcers; it decreases the number of oral ulcers and also the pain of oral ulcers."

RELIEF had the usual design requirements for a phase 3 trial – randomized, double-blind, placebo-controlled, multicenter – and it involved a substantial number of patients for a rare disease, 207 in total. The primary efficacy endpoint for the trial was the area under the curve (AUC) for the total number of oral ulcers during a 12-week placebo-controlled period. The AUC for the number of oral ulcers was much reduced with apremilast versus placebo, at 129.5 versus 222.1, with a mean difference of -92.6 (P less than .001).

"This measure reflects the number of oral ulcers over time and accounts for the remitting and relapsing course of oral ulcers in Behçet's syndrome," Dr. Hatemi and coinvestigators wrote in their publication for the trial.

During the EULAR e-congress, Dr. Hatemi presented further findings from the RELIEF trial, showing a reduction in painful oral ulcers.⁶ Compared to a 15.9-point reduction in visual analog scale (VAS)-rated pain at 12 weeks with placebo, patients who received apremilast showed a 40.7-point reduction (P less than .001).

Greater percentages of patients treated with apremilast than with placebo achieved a minimal clinically important difference in pain scores of 10 mm (78% vs. 49%), 30 mm (74% vs. 43%), and 50 mm or more (67% vs. 37%).

"These results indicate a clinically meaningful treatment effect of apremilast on oral ulcers associated with Behçet's syndrome," Dr. Hatemi said in presenting the findings.



An oral ulcer of Behçet's syndrome after treatment with colchicine.

Courtesy Dr. Hatemi

Time to treat oral ulcers more seriously

“Behçet’s syndrome is quite a severe disease,” she noted in an interview. It is a systemic disease that can affect multiple organs, from the skin and mucosa to the joints, vascular, nervous, and gastrointestinal systems. It can also affect the eyes, causing uveitis that can lead to blindness. So there is a host of issues that physicians have to contend with, Dr. Hatemi acknowledged.

That said, “oral ulcers are generally not taken as seriously as they should be,” she suggested. “While trying to manage these more serious things, according to the physicians, oral ulcers are usually thought to be something minor and not taken as seriously as they should be.”

Patients may have oral ulcers at every visit that severely impact their quality of life, she added, suggesting that

physicians need to consider stepping up therapy as appropriate and including oral ulcers in their decision-making process.

“It’s important to listen to the patient’s perspective, preferences, and priorities, and for oral ulcers we do have targeted treatments to help manage patients.”

REFERENCES

1. Topical Pentoxifylline Gel on Behçet’s Disease Oral Ulcers, ClinicalTrials.gov Identifier: NCT03888846; <https://clinicaltrials.gov/ct2/show/NCT03888846>.
2. Hatemi G et al. *Ann Rheum Dis.* 2020;79(Suppl 1):1072-3.
3. Hatemi G et al. *Ann Rheum Dis.* 2018;77:808-18.
4. Hatemi G et al. *N Engl J Med.* 2019;381:1918-28.
5. Hatemi G et al. *N Engl J Med.* 2015;372:1510-8.
6. Hatemi G et al. *Ann Rheum Dis.* 2020;79(Suppl 1):20-1.

Managing the risk of congenital heart block in anti-Ro/SSA-positive women

BY CHRISTINE KILGORE

Anti-Ro/SSA antibodies in pregnant women have long been associated with complete (third-degree) congenital heart block – an irreversible feature of neonatal lupus erythematosus – and earlier expressions of the disease.

Now, the antibodies have a place in the American College of Rheumatology’s first guideline on the management of reproductive health, with conditional advice that women who are antibody positive be treated with hydroxychloroquine (HCQ) during pregnancy in order to try to prevent the rare but potentially fatal condition, and that they be serially monitored with echocardiography for early cardiac changes.¹

An estimated one-fifth of children with complete heart block die in utero or in the first year of life, and most of the children who survive require lifelong pacing.

For some rheumatologists, the ACR’s recommendation mirrors what they have practiced in recent years in response to findings from small retrospective studies and case series and from the 25-year-old Research Registry for Neonatal Lupus, founded and run by Jill Buyon, MD, a rheumatologist at New York University Langone Health.^{2,3,4}

For other rheumatologists, the new guideline published in March 2020 – as well as findings from the PATCH study, a

pertinent prospective study of HCQ published several months later – may spur more interest in using the drug as they work with ob.gyns. (often maternal-fetal medicine specialists) to manage the risk of congenital heart block (CHB) in women with anti-Ro/SSA and/or anti-La/SSB antibodies, say physicians who served on the guidelines panel.⁵

“In patients with lupus, [taking HCQ] has become a nonissue, since the risk for a short period of time is very minimal and since being on Plaquenil improves both maternal and fetal outcomes. But I also have discussions with all of my Ro-positive patients,” said Lisa R. Sammaritano, MD, a rheumatologist at Weill Cornell Medicine and the Hospital for Special Surgery in New York who led the ACR’s guideline committee.



Jill Buyon, MD



Lisa R. Sammaritano, MD

All physicians interviewed for this story reported having no relevant disclosures.

PATCH study provides strong evidence for prevention

Evidence of benefit is strongest for anti-Ro/SSA-positive women who have had a previous pregnancy complicated by CHB. In fact, it is likely, she said, that the “conditional” classification of the ACR’s HCQ recommendation (such a classification reflects limited data) would have instead been a “strong recommendation” for this group of women if the open-label, prospective PATCH study had been published while the guideline was under development.

Recurrence of CHB was reduced to 7.4% from the expected historical recurrence rate of 18% – a more than 50% drop – in the multicenter PATCH (Preventive Approach to Congenital Heart Block with Hydroxychloroquine) study.⁵ The study, led by investigators at NYU Langone, involved 54 women who had anti-SSA/Ro antibodies with or without anti-SSB/La antibodies and a previous pregnancy complicated by CHB. The women took HCQ 400 mg/day starting by 10 weeks of gestation.

The findings were presented at the annual meeting of the ACR in November 2019 and were published in the *Journal of the American College of Cardiology* in July.

Had the ACR guideline panel been permitted to consider unpublished findings, “I think we might have subdivided our recommendation,” said Dr. Sammaritano, director of the Rheumatology Reproductive Health Program at the Barbara Volcker Center for Women and Rheumatic Disease and professor of clinical medicine at Weill Cornell Medicine.

Either way, with or without a history of CHB, “it’s now well within the standard of care to discuss [the use of HCQ] in women who are positive for anti-SSA, anti-SSB antibodies,” said D. Ware Branch, MD, a maternal-fetal medicine specialist at the University of Utah, Salt Lake City, and a member of the ACR guideline panel. However, in the absence of any history of CHB (in the context of retrospective data only), it’s especially important that “the patient and physician make a shared decision regarding whether to take the medication or not,” he emphasized.

Complete CHB occurs in an estimated 2% of pregnancies exposed to anti-Ro/SSA with or without anti-La/SSB antibodies – significantly less than the recurrence risk of 18%. (The PATCH investigators chose this recurrence rate because it came from the largest study to date – an analysis of data from the Research Registry for Neonatal Lupus – but estimates from other researchers have ranged from 13% to 20%.)

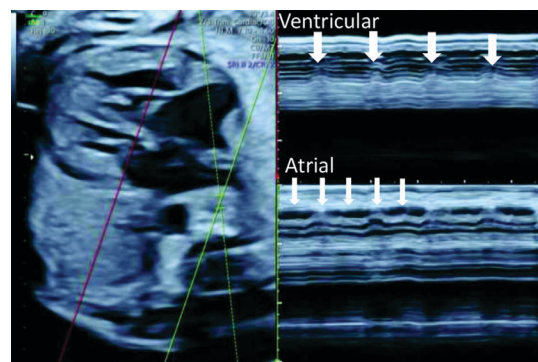
Regarding the safety of HCQ, “most experts in the realm of rheumatic disease in pregnancy consider HCQ relatively safe in pregnancy. ... This is what’s been written in all the major textbooks,” said Dr. Branch, a professor of ob.gyn. at the university who has coauthored textbook chapters on autoimmune

diseases in pregnancy. In his practice, “many but not all patients consider using the medication.”

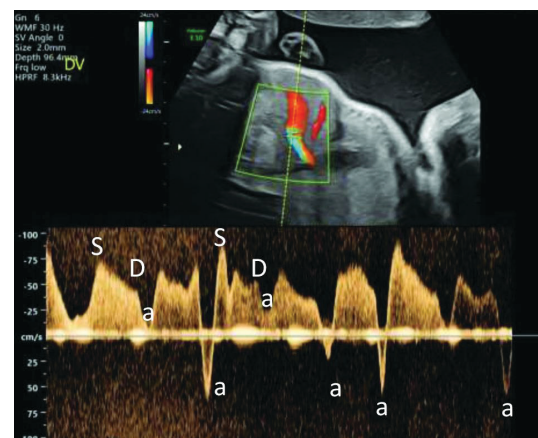
Prolonged use of HCQ carries a risk of maculopathy, he noted. Follow-up retinal examinations in the PATCH study offspring who have reached age 5 are ongoing. “That’s an important follow-up,” Dr. Branch said. “I look forward to those results.”

The value of serial echocardiography – particularly, again, for antibody-positive women who do not have a history of a pregnancy complicated by CHB – is where the larger controversy lies, both he and Dr. Sammaritano said. Serial echoes are time-consuming, expensive, and, Dr. Branch said, “there’s a lot of debate about whether periodic fetal echo can possibly alter outcomes.”

Within the world of maternal-fetal medicine, Dr. Branch said, “there are people on both sides of whether you should or should not do periodic echoes, and whether [you should or should not] prescribe HCQ in mothers who haven’t had a baby with congenital heart block.” Given all the uncertainties about the pathogenesis



Echocardiography in an anti-SSA and anti-SSB positive mother shows complete heart block and a thick and echogenic heart in a fetus at 33 weeks, with an atrial rate of 125 bpm and ventricular rate of 50 bpm.



Ductus venosus waveform in the setting of complete congenital heart block shows no regular ventricular systole (S), ventricular diastole (D), and atrial contractions (“a” wave).

Images courtesy of Dr. Turan.

and treatment of this rare disease – one that affects an estimated 1 in 15,000 pregnancies – “that’s not surprising,” he added.

Practicing with uncertainties

The ACR guideline strongly recommends testing for maternal anti-Ro/SSA and anti-La/SSB (one time, before or early in pregnancy) in women with systemic lupus erythematosus or SLE-like disorders, Sjögren’s syndrome, systemic sclerosis, and RA – the rheumatologic disorders “most likely to have the anti-Ro/La antibodies,” Dr. Sammaritano said.

Anti-Ro antibodies have been found in asymptomatic women as well, Dr. Buyon emphasized, often in the context of bradycardia detected in the fetus during the mid-to-late second trimester. “The term ‘neonatal lupus’ may be throwing some people for a loop,” she said. Physicians must appreciate that CHB, or atrioventricular block, “is a disease that’s associated with an antibody, and not with a disease in the mother.”

The antibodies cross the placenta, bind to fetal antigens in the developing atrioventricular node, and cause inflammation as the bound maternal antibodies are consumed by macrophages. This local inflammation, it is believed, can lead to irreversible scarring in the atrioventricular node. Plaquenil interrupts the macrophage Toll-like receptor signaling. (Conduction disease is the most characteristic part of cardiac neonatal lupus, but the

The greatest challenges for antibody-positive women without a history of CHB complications come with decision-making regarding the frequency of echocardiography.

spectrum also includes myocarditis, cardiomyopathies, valvular abnormalities, and endocardial fibroelastosis.)⁶

Anti-Ro antibodies play the central role in CHB. “The contribution of La antibodies [to CHB] is not so clear,” said Dr. Buyon, also an author of the ACR’s guideline on reproductive health. Alone, they rarely impose risk, she said. But in combination with anti-Ro/SSA, they may increase risk.

More clarity exists regarding an association of higher anti-Ro/SSA antibody titers with higher levels of risk for CHB; this has been documented in studies such as the PRIDE study (PR Interval and Dexamethasone Evaluation Prospective Study) on cardiac evaluation and treatment.⁷ Dr. Sammaritano said this information can be valuable for patients who struggle with decision-making about whether to take HCQ.

“I do raise this with some patients. I explain that in my experience and based on the published literature, they probably have a greater risk when antibody titers are high,” she

said, noting that studies are needed to identify cutoff values for higher-risk titer levels in commercial testing.

The greatest challenges, she and others said, come with decision-making regarding the frequency of serial echocardiography. ACR’s guideline conditionally recommends such monitoring weekly starting at 16-18 weeks and continuing through 26 weeks for antibody-positive women who have had a pregnancy complicated by CHB.

For women without such a history, the ACR conditionally advises monitoring during this time frame, but at some interval (“not determined”) that is less than weekly.

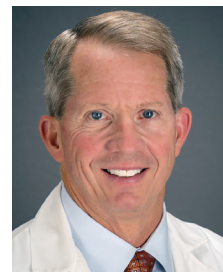
The goal is to detect and treat incomplete heart block before it becomes fully advanced and irreversible. Cost and resource considerations, physician judgment, and patient values all play a role in monitoring decisions. Dr. Sammaritano suggests echoes every 2 weeks for her antibody-positive patients who don’t have prior affected offspring, but as she acknowledged, “no data support this.”

The ob.gyns. caring for her patients or the pediatric cardiologists who perform the test will sometimes change the frequency, she said. “If there’s any concern with this, we discuss it with each other and with the patient.”

Dr. Sammaritano noted that patient members of the ACR guideline panel expressed concerns that weekly testing can be costly, inconvenient, and anxiety inducing for some women. “We need to take that into consideration,” she said. In her own experience, however, “if it’s not too onerous for the patient, [the testing] can serve primarily as reassurance.”

Shifa Turan, MD, who directs the fetal heart program at the University of Maryland, Baltimore (and who was not a member of the ACR guideline panel), said that the pediatric cardiologists in her program currently perform weekly monitoring for all antibody-positive patients – sometimes up to 28 weeks’ gestation, or longer in the presence of certain findings.

And at the University of Utah, Dr. Branch said he and the other specialists involved in risk management for CHB plan to meet soon to hash out the uncertainties over echocardiography and to “get on one page about how we can counsel patients.”



D. Ware Branch, MD

Moving forward on risk management

The premise of serial fetal echocardiography is that full expression of autoimmune-associated CHB occurs over a sequential progression from normal rhythm to first-degree atrioventricular heart block (prolonged AV interval as assessed on echo) and then second-degree block (irregular rhythm or bradycardia),

culminating in third-degree block. Practices often administer oral dexamethasone 4 mg daily when first- and second-degree block are detected (most commonly for second-degree block) for variable periods of time and based on limited and inconsistent data on efficacy.⁸

Dr. Buyon and other experts now hypothesize based on studies of fetal heart rate and rhythm monitoring that there is a critical and brief transition period – a period as short as 12 hours from normal rhythm to third-degree block, and several hours from second-degree to complete block – that marks a window of opportunity for anti-inflammatory treatment to restore normal rhythm.

In a recently registered clinical trial awaiting full funding (STOP BLOQ), Dr. Buyon and pediatric cardiologist Bettina Cuneo, MD, of the University of Colorado at Denver, Aurora, plan to screen women for high-titer anti-Ro, have them monitor fetal heart rate and rhythm three times daily at home, and then rapidly treat mothers whose abnormal findings are confirmed by echo.⁹ A study led by Dr. Cuneo and published in 2018 showed that “women could actually pick up abnormalities (with home monitoring), and that there were very few false positives,” Dr. Buyon said.¹⁰

Dr. Sammaritano said “it would be wonderful” if the study supports efficacy of home fetal monitoring, since “presumably

this would allow intervention with steroids at the earliest moment, when it might make more of a difference.”

As for the efficacy of using HCQ in anti-Ro-positive women without a history of an affected child, “it would be wonderful to answer that question through a large prospective study,” she said. “But complete heart block is so rare that enrolling the number of patients needed would be extremely difficult.”

REFERENCES

1. Sammaritano LR et al. *Arthritis Rheumatol.* 2020;72:529-56. doi: 10.1002/art.41191.
2. Izmirly PM et al. *Circulation.* 2012;126:76-82. doi: 10.1161. CIRCULATIONAHA.111.089268.
3. Izmirly PM et al. *Ann Rheum Dis.* 2010;69:1827-30. doi: 10.1136/ard.2009.119263.
4. Tunks RD et al. *Am J Obstet Gynecol.* 2013;208:64.e1-7. doi: 10.1016/j.ajog.2012.09.020.
5. Izmirly P et al. *J Am Coll Cardiol.* 2020;76:292-302. doi: 10.1016/j.jacc.2020.05.045.
6. Izmirly P et al. *Curr Opin Rheumatol.* 2017;29:467-72. doi: 10.1097/BOR.0000000000000414.
7. Friedman DM et al. *Circulation.* 2008;117:485-93. doi: 10.1161/CIRCULATIONAHA.107.707661.
8. Clowse MEB et al. *Rheumatology.* 2018;57[suppl 5]:v9-7. doi: 10.1093/rheumatology/key141.
9. <https://clinicaltrials.gov/ct2/show/NCT04474223>.
10. Cuneo B et al. *J Am Coll Cardiol.* 2018;72:1940-51. doi: 10.1016/j.jacc.2018.07.076.

Are CRMO and SAPHO syndrome one and the same?

BY BRUCE JANCIN

EXPERT ANALYSIS FROM RWCS 2020

MAUI, HAWAII – Chronic recurrent multifocal osteomyelitis (CRMO) in children and SAPHO syndrome in adults may well be a single clinical syndrome.

That contention, recently put forth by Austrian investigators, resonates with Anne M. Stevens, MD, PhD, a pediatric rheumatologist at the University of Washington, Seattle, and senior director for the adaptive immunity research program at Janssen Pharmaceuticals.

“Is CRMO just for kids? No,” she asserted at the 2020 Rheumatology Winter Clinical Symposium.

First off, she noted that the nomenclature is shifting: The more familiar acronym CRMO is giving way to CNO (chronic

nonbacterial osteomyelitis) in light of evidence that roughly 30% of patients with CRMO start out with a single characteristic bone lesion, with the disease turning multifocal in the subsequent 4 years in the great majority of cases.

SAPHO syndrome – an acronym for synovitis, acne, pustulosis, hyperostosis, and osteitis – a formerly obscure disease entity first described in 1987 in France, has suddenly become a trendy research topic, with three small studies



Anne M. Stevens, MD, PhD

Dr. Anne M. Stevens reported research collaborations with Kineta and Seattle Genetics in addition to her employment at Janssen Pharmaceuticals.

presented at the 2019 annual meeting of the American College of Rheumatology.

CNO is a pediatric autoinflammatory bone disease characterized by sterile bone lesions, most often on the clavicle, spine, mandible, and lower extremities. It is marked by prominent focal bone and/or joint pain, worse at night, with or without swelling. With no agreed-upon diagnostic criteria or biomarkers, CNO is a diagnosis of exclusion. Two-thirds of the time the condition is initially misdiagnosed as bacterial osteomyelitis or a malignant tumor.

Austrian investigators at the University of Graz recently conducted a retrospective comparison of 24 pediatric patients diagnosed with CNO and 10 adults with SAPHO syndrome. The median age at diagnosis of CNO was 12.3 years versus 32.5 years for SAPHO syndrome. The two groups shared compelling similarities in mean number of bone lesions, prevalence of skin involvement, and other aspects of initial clinical presentation, as well as laboratory and histopathologic findings on bone biopsy.¹

There were, however, several notable clinical differences in this small dataset: CNO bone lesions affected mainly the lower extremities, clavicle, spine, and mandible, while SAPHO syndrome more commonly involved the sternum (50% vs. 8%) and vertebrae (50% vs. 21%). Also, the most frequent cutaneous manifestation was palmoplantar pustulosis in adults with SAPHO syndrome, while severe acne predominated in children with CNO. In both children and adults, the skin lesions most often arose after the bone symptoms, making early diagnosis a challenge.

Another similarity: Although there have been no randomized treatment trials in either CNO or SAPHO syndrome, case series suggest the same treatments are effective for both, with NSAIDs as first line, followed by nonbiologic disease-modifying antirheumatic drugs, tumor necrosis factor (TNF) inhibitors, or bisphosphonates.

CNO diagnosis, treatment, and follow-up

Various investigators have pegged the sensitivity of physical examination for diagnosis of CNO at 31%, radiographs at a lowly 13%, and bone scintigraphy at 74%, all in comparison with MRI.

“Our go-to now is MRI with STIR [short tau inversion recovery],” according to Dr. Stevens. “There’s no contrast – so no IV – no radiation, and it’s fast, 20 minutes for a whole body MRI in a little kid, 45 minutes in a big one.”

Insurers are reluctant to pay for serial whole-body MRIs for patient follow-up, so it’s often necessary to order a series of images covering different body parts.

Her University of Washington colleague Dan Zhao, MD, PhD, is developing infrared thermal imaging as an inexpensive,

convenient alternative to MRI that could theoretically be done at home. In a pilot study in 30 children with CNO and 31 controls, inflamed leg segments showed significantly higher temperatures. Larger studies are planned.²

Dr. Stevens advised leaning toward a diagnosis of CNO with avoidance of bone biopsy in a patient with multifocal osteomyelitis at the typical sites, a normal CBC, the typical extraosseous manifestations, and normal or only mildly elevated erythrocyte sedimentation rate and C-reactive protein in an otherwise well-appearing child. In contrast, strongly consider a bone biopsy to rule out malignancy or infection if the child has unexplained highly elevated C-reactive protein and erythrocyte sedimentation rate, cytopenia, high fever, excessive pain, lymphadenopathy, hepatosplenomegaly, or suspicious imaging findings.

German rheumatologists have developed a clinical score for diagnosis of CNO. A normal blood cell count gets 13 points; symmetric bone lesions 10; lesions with marginal sclerosis 10; a normal body temperature 9; two or more radiologically proven lesions 7; a C-reactive protein of 1 mg/dL or greater 6; and vertebral, clavicular, or sternal lesions 8. A score of 39 points or more out of a possible 63 had a 97% positive predictive value for CNO in a retrospective study of 224 children with CNO, proven bacterial osteomyelitis, or malignant bone tumors. A score of 28 points or less had a 97% negative predictive value for CNO. An indeterminate score of 29-38 warrants close monitoring.³

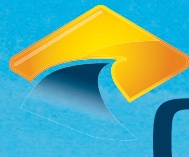
The scoring system hasn’t been validated, but most pediatric rheumatologists agree that it’s useful, according to Dr. Stevens.

The Childhood Arthritis and Rheumatology Research Alliance (CARRA) is in the process of developing standardized diagnostic and classification criteria and treatment plans for CNO. Dr. Zhao was first author of a CARRA consensus treatment plan for CNO refractory to NSAID monotherapy. The plan for the first 12 months includes three options: methotrexate or sulfasalazine, TNF inhibitors with or without methotrexate, and bisphosphonates.⁴

“The main point of this is you try a medicine and then wait 3 months. If they’re not responding then, switch medicines or add another drug. Monitor every 3 months based upon pain,” she said.

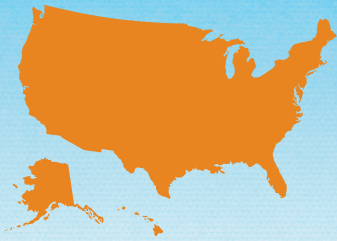
REFERENCES

1. Skrabl-Baumgartner A et al. *Pediatr Rheumatol Online J*. 2019 Jul 23. doi: 10.1186/s12969-019-0353-2.
2. Zhao Y et al. *Arthritis Care Res*. 2019 Nov;71(11):1430-5.
3. Jansson AF et al. *Arthritis Rheum*. 2009 Apr;60(4):1152-9.
4. Zhao Y et al. *Arthritis Care Res*. 2018 Aug;70(8):1228-37.



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INDICATIONS

Otezla[®] (apremilast) is indicated for the treatment of adult patients with active psoriatic arthritis.

Otezla is indicated for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

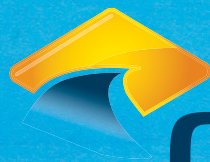
IMPORTANT SAFETY INFORMATION

Contraindications

- Otezla[®] (apremilast) is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation

Please see Important Safety Information and Brief Summary of Full Prescribing Information on the following pages.

Reference: 1. Data on file, Amgen Inc.



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RESULTS

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Otezla[®] (apremilast) significantly increased ACR20 response at week 16 (primary endpoint) vs placebo (38% vs 19%; n = 168 for both; P = 0.0001) in PALACE[™] 1.¹⁻³

PALACE 1-3 clinical trial program

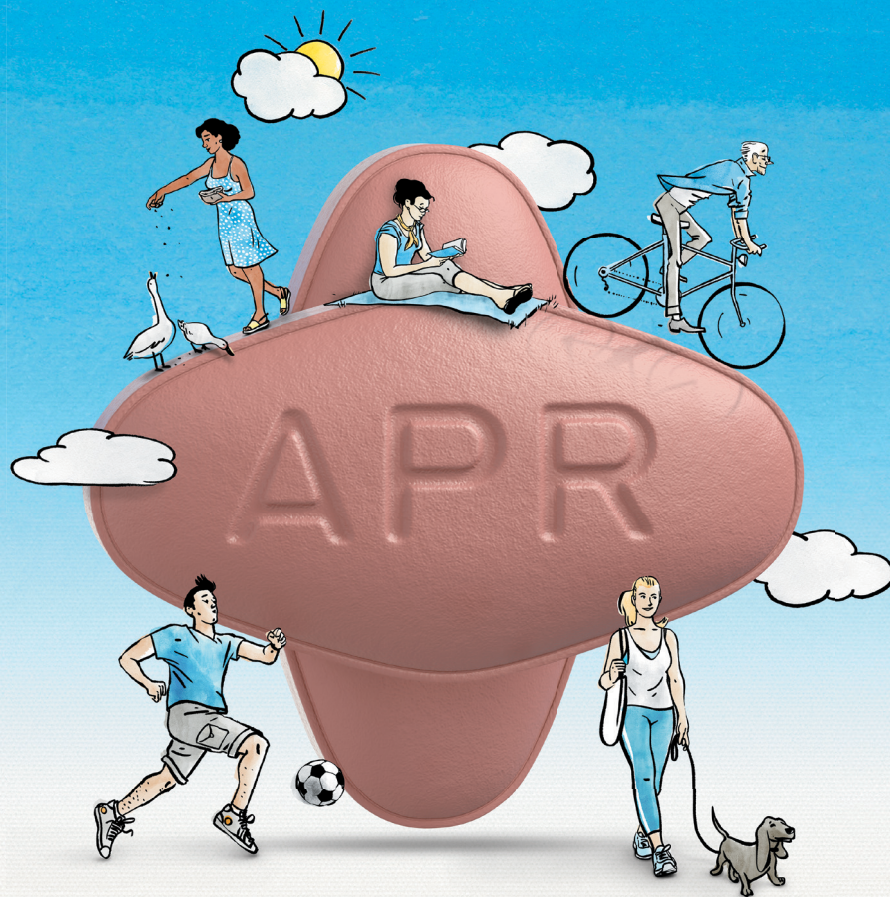
- Otezla was studied in 3 multicenter, randomized, double-blind, placebo-controlled trials of similar design. 1493 adults with active psoriatic arthritis (≥ 3 swollen and ≥ 3 tender joints), despite prior or current DMARD therapy, were randomized to placebo, Otezla 20 mg twice daily, or Otezla 30 mg twice daily, after a 5-day titration period¹
- Patients who failed >3 small molecules or biologics or >1 TNF- α inhibitor were excluded¹
- Significant ACR20 responses also seen with Otezla in Studies 2 and 3^{1,2,4,5}

ACR, American College of Rheumatology; DMARD, disease-modifying antirheumatic drug; PALACE, Psoriatic Arthritis Long-Term Assessment of Clinical Efficacy; TNF, tumor necrosis factor

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions

- **Diarrhea, Nausea, and Vomiting:** Cases of severe diarrhea, nausea, and vomiting have been reported with the use of Otezla. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting; advise patients to contact their healthcare provider. Consider Otezla dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting
- **Depression:** Treatment with Otezla is associated with an increase in depression. During clinical trials, 1.0% (10/998) reported depression or depressed mood compared to 0.8% (4/495) treated with placebo. Suicidal ideation and behavior was observed in 0.2% (3/1441) of patients on Otezla, compared to none in placebo-treated patients (0/495). Carefully weigh the risks and benefits of treatment with Otezla for patients with a history of depression and/or suicidal thoughts/behavior, or in patients who develop such symptoms while on Otezla. Patients, caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and they should contact their healthcare provider if such changes occur
- **Weight Decrease:** Body weight loss of 5-10% was reported in 10% (49/497) of patients taking Otezla and in 3.3% (16/495) of patients taking placebo. Monitor body weight regularly; evaluate unexplained or clinically significant weight loss, and consider discontinuation of Otezla



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IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd)

- Drug Interactions: Apremilast exposure was decreased when Otezla was co-administered with rifampin, a strong CYP450 enzyme inducer; loss of Otezla efficacy may occur. Concomitant use of Otezla with CYP450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended

Adverse Reactions

- Adverse reactions reported in at least 2% of patients taking Otezla, that occurred at a frequency at least 1% higher than that observed in patients taking placebo, for up to 16 weeks (after the initial 5-day titration), were (Otezla%, placebo%): diarrhea (7.7, 1.6); nausea (8.9, 3.1); headache (5.9, 2.2); upper respiratory tract infection (3.9, 1.8); vomiting (3.2, 0.4); nasopharyngitis (2.6, 1.6); upper abdominal pain (2.0, 0.2)

Use in Specific Populations

- Pregnancy: Otezla has not been studied in pregnant women. Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Otezla during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972 or visiting <https://mothertobaby.org/ongoing-study/otezla/>
- Lactation: There are no data on the presence of apremilast or its metabolites in human milk, the effects of apremilast on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Otezla and any potential adverse effects on the breastfed child from Otezla or from the underlying maternal condition

- Renal Impairment: Otezla dosage should be reduced in patients with severe renal impairment (creatinine clearance less than 30 mL/min); for details, see Dosage and Administration, Section 2, in the Full Prescribing Information

*Following a 5-day titration, the recommended maintenance dosage is 30 mg twice daily.¹

[†]To receive a free Bridge supply of Otezla, patients must have an on-label diagnosis and be denied or waiting for coverage.

[‡]Certain restrictions apply; eligibility not based on income, must be 18 years or older. This offer is not valid for persons eligible for reimbursement of this product, in whole or in part under Medicaid, Medicare, or similar state or federal programs. Offer not valid for cash-paying patients. People who are not eligible can call 1-844-4OTEZLA to discuss other financial assistance opportunities.

References: 1. Otezla [package insert]. Thousand Oaks, CA: Amgen Inc. 2. Data on file, Amgen Inc. 3. Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. *J Rheumatol*. 2015;42(3):479-488. 4. Cutolo M, Myerson GE, Fleischmann RM, et al. *J Rheumatol*. 2016;43(9):1724-1734. 5. Edwards CJ, Blanco JC, Crowley J, et al. *Ann Rheum Dis*. 2016;75(6):1065-1073.

Please turn the page for Brief Summary of Full Prescribing Information.

OTEZLA® (apremilast) tablets, for oral use

RX Only

The following is a Brief Summary of the Prescribing Information; see Full Prescribing Information for complete product information.

4 CONTRAINDICATIONS

OTEZLA is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation [see *Adverse Reactions* (6.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea, Nausea, and Vomiting: There have been postmarketing reports of severe diarrhea, nausea, and vomiting associated with the use of OTEZLA. Most events occurred within the first few weeks of treatment. In some cases patients were hospitalized. Patients 65 years of age or older and patients taking medications that can lead to volume depletion or hypotension may be at a higher risk of complications from severe diarrhea, nausea, or vomiting. Monitor patients who are more susceptible to complications of diarrhea or vomiting. Patients who reduced dosage or discontinued OTEZLA generally improved quickly. Consider OTEZLA dose reduction or suspension if patients develop severe diarrhea, nausea, or vomiting.

5.2 Depression: Treatment with OTEZLA is associated with an increase in adverse reactions of depression. Before using OTEZLA in patients with a history of depression and/or suicidal thoughts or behavior prescribers should carefully weigh the risks and benefits of treatment with OTEZLA in such patients. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal thoughts or other mood changes, and if such changes occur to contact their healthcare provider. Prescribers should carefully evaluate the risks and benefits of continuing treatment with OTEZLA if such events occur.

Psoriatic arthritis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.0% (10/998) of subjects treated with OTEZLA reported depression or depressed mood compared to 0.8% (4/495) treated with placebo. During the clinical trials, 0.3% (4/1441) of subjects treated with OTEZLA discontinued treatment due to depression or depressed mood compared with none in placebo treated subjects (0/495). Depression was reported as serious in 0.2% (3/1441) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0/495). Instances of suicidal ideation and behavior have been observed in 0.2% (3/1441) of subjects while receiving OTEZLA, compared to none in placebo treated subjects (0/495). In the clinical trials, 2 subjects who received placebo committed suicide compared to none in OTEZLA-treated subjects.

Psoriasis: During the 0 to 16 week placebo-controlled period of the 3 controlled clinical trials, 1.3% (12/920) of subjects treated with OTEZLA reported depression compared to 0.4% (2/506) treated with placebo. During the clinical trials, 0.1% (1/1308) of subjects treated with OTEZLA discontinued treatment due to depression compared with none in placebo-treated subjects (0/506). Depression was reported as serious in 0.1% (1/1308) of subjects exposed to OTEZLA, compared to none in placebo-treated subjects (0/506). Instances of suicidal behavior have been observed in 0.1% (1/1308) of subjects while receiving OTEZLA, compared to 0.2% (1/506) in placebo-treated subjects. In the clinical trials, one subject treated with OTEZLA attempted suicide while one who received placebo committed suicide.

5.3 Weight Decrease: During the controlled period of the studies in psoriatic arthritis (PsA), weight decrease between 5%-10% of body weight was reported in 10% (49/497) of subjects treated with OTEZLA 30 mg twice daily compared to 3.3% (16/495) treated with placebo.

During the controlled period of the trials in psoriasis, weight decrease between 5%-10% of body weight occurred in 12% (96/784) of subjects treated with OTEZLA compared to 5% (19/382) treated with placebo. Weight decrease of $\geq 10\%$ of body weight occurred in 2% (16/784) of subjects treated with OTEZLA 30 mg twice daily compared to 1% (3/382) subjects treated with placebo.

Patients treated with OTEZLA should have their weight monitored regularly. If unexplained or clinically significant weight loss occurs, weight loss should be evaluated, and discontinuation of OTEZLA should be considered [see *Adverse Reactions* (6.1)].

5.4 Drug Interactions: Co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of efficacy of OTEZLA. Therefore, the use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with OTEZLA is not recommended [see *Drug Interactions* (7.1)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Psoriatic Arthritis Clinical Trials: OTEZLA was evaluated in 3 multicenter, randomized, double-blind, placebo-controlled trials [Studies PsA-1, PsA-2, and PsA-3] of similar design in adult patients with active psoriatic arthritis. Across the 3 studies, there were 1493 patients randomized equally to placebo, OTEZLA 20 mg twice daily or OTEZLA 30 mg twice daily. Titration was used over the first 5 days. Placebo patients whose tender and swollen joint counts had not improved by at least 20% were re-randomized 1:1 in a blinded fashion to either OTEZLA 20 mg twice daily or 30 mg twice daily at week 16 while OTEZLA patients remained on their initial treatment. Patients ranged in age from 18 to 83 years, with an overall median age of 51 years.

The majority of the most common adverse reactions presented below occurred within the first 2 weeks of treatment and tended to resolve over time with continued dosing. Diarrhea, headache, and nausea were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for patients taking OTEZLA were nausea (1.8%), diarrhea (1.8%), and headache (1.2%). The proportion of patients with psoriatic arthritis who discontinued treatment due to any adverse reaction was 4.6% for patients taking OTEZLA 30 mg twice daily and 1.2% for placebo-treated patients.

Adverse Reactions Reported in $\geq 2\%$ of Patients on OTEZLA 30 mg Twice Daily and $\geq 1\%$ Than That Observed in Patients on Placebo on Day 1-5 (Placebo %, OTEZLA %): Diarrhea^a (1.2%, 9.3%), Nausea^a (1.4%, 7.4%), Headache^a (1.8%, 4.8%), Upper respiratory tract infection^b (0.6%, 0.6%), Vomiting^a (0.4%, 0.8%), Nasopharyngitis^a (0.2%, 0.2%), Abdominal pain upper^c (0.0%, 0.6%).

Adverse Reactions Reported in $\geq 2\%$ of Patients on OTEZLA 30 mg Twice Daily and $\geq 1\%$ Than That Observed in Patients on Placebo on Day 6-112 (Week 16) (Placebo %, OTEZLA %):

Diarrhea^a (1.6%, 7.7%), Nausea^a (3.1%, 8.9%), Headache^a (2.2%, 5.9%), Upper respiratory tract infection^b (1.8%, 3.9%), Vomiting^a (0.4%, 3.2%), Nasopharyngitis^a (1.6%, 2.6%), Abdominal pain upper^c (0.2%, 2.0%).

^a Of the reported gastrointestinal adverse reactions, 1 subject experienced a serious adverse reaction of nausea and vomiting in OTEZLA 30 mg twice daily; 1 subject treated with OTEZLA 20 mg twice daily experienced a serious adverse reaction of diarrhea; 1 patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction of headache.

^b Of the reported adverse drug reactions none were serious.

Other adverse reactions reported in patients on OTEZLA in clinical studies including extension studies:

Immune system disorders: Hypersensitivity. **Investigations:** Weight decrease. **Gastrointestinal Disorders:** Frequent bowel movement, gastroesophageal reflux disease, dyspepsia. **Metabolism and Nutrition Disorders:** Decreased appetite^d. **Nervous System Disorders:** Migraine. **Respiratory, Thoracic, and Mediastinal Disorders:** Cough. **Skin and Subcutaneous Tissue Disorders:** Rash [†] 1 patient treated with OTEZLA 30 mg twice daily experienced a serious adverse reaction.

Psoriasis Clinical Trials

The safety of OTEZLA was assessed in 1426 subjects in 3 randomized, double-blind, placebo-controlled trials in adult subjects with moderate to severe plaque psoriasis who were candidates for phototherapy or systemic therapy. Subjects were randomized to receive OTEZLA 30 mg twice daily or placebo twice daily. Titration was used over the first 5 days. Subjects ranged in age from 18 to 83 years, with an overall median age of 46 years.

Diarrhea, nausea, and upper respiratory tract infection were the most commonly reported adverse reactions. The most common adverse reactions leading to discontinuation for subjects taking OTEZLA were nausea (1.6%), diarrhea (1.0%), and headache (0.8%). The proportion of subjects with psoriasis who discontinued treatment due to any adverse reaction was 6.1% for subjects treated with OTEZLA 30 mg twice daily and 4.1% for placebo-treated subjects.

Adverse Reactions Reported in $\geq 1\%$ of Subjects on OTEZLA and With Greater Frequency Than in Subjects on Placebo; up to Day 112 (Week 16) (Placebo %, OTEZLA %):

Diarrhea (6%, 17%), Nausea (7%, 17%), Upper respiratory tract infection (6%, 9%), Tension headache (4%, 8%), Headache (4%, 6%), Abdominal pain^{*} (2%, 4%), Vomiting (2%, 4%), Fatigue (2%, 3%), Dyspepsia (1%, 3%), Decreased appetite (1%, 3%), Insomnia (1%, 2%), Back pain (1%, 2%), Migraine (1%, 2%), Frequent bowel movements (0%, 2%), Depression (0%, 1%), Bronchitis (0%, 1%), Tooth abscess (0%, 1%), Folliculitis (0%, 1%), Sinus headache (0%, 1%).

^{*}Two subjects treated with OTEZLA experienced serious adverse reaction of abdominal pain.

Severe worsening of psoriasis (rebound) occurred in 0.3% (4/1184) subjects following discontinuation of treatment with OTEZLA.

7 DRUG INTERACTIONS

7.1 Strong CYP450 Inducers: Apremilast exposure is decreased when OTEZLA is co-administered with strong CYP450 inducers (such as rifampin) and may result in loss of efficacy [see *Warnings and Precautions* (5.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to OTEZLA during pregnancy. Information about the registry can be obtained by calling 1-877-311-8972 or visiting <https://mothertobaby.org/ongoing-study/otezla/>.

Risk Summary: Available pharmacovigilance data with OTEZLA use in pregnant women have not established a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes, but these data are extremely limited. Advise pregnant women of the potential risk of fetal loss. Consider pregnancy planning and prevention for females of reproductive potential.

8.2 Lactation

Risk Summary: There are no data on the presence of apremilast or its metabolites in human milk, the effects of apremilast on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OTEZLA and any potential adverse effects on the breastfed child from OTEZLA or from the underlying maternal condition.

8.4 Pediatric Use: The safety and effectiveness of OTEZLA in pediatric patients less than 18 years of age have not been established.

8.5 Geriatric Use: Of the 1493 patients who enrolled in Studies PsA-1, PsA-2, and PsA-3 a total of 146 psoriatic arthritis patients were 65 years of age and older, including 19 patients 75 years and older. No overall differences were observed in the safety profile of elderly patients ≥ 65 years of age and younger adult patients < 65 years of age in the clinical studies.

Of the 1257 subjects who enrolled in two placebo-controlled psoriasis trials (PSOR 1 and PSOR 2), a total of 108 psoriasis subjects were 65 years of age and older, including 9 subjects who were 75 years of age and older. No overall differences were observed in the efficacy and safety in elderly subjects ≥ 65 years of age and younger adult subjects < 65 years of age in the clinical trials.

8.6 Renal Impairment: Apremilast pharmacokinetics were characterized in subjects with mild, moderate, and severe renal impairment as defined by a creatinine clearance of 60-89, 30-59, and less than 30 mL per minute, respectively, by the Cockcroft-Gault equation. While no dose adjustment is needed in patients with mild or moderate renal impairment, the dose of OTEZLA should be reduced to 30 mg once daily in patients with severe renal impairment.

8.7 Hepatic Impairment: Apremilast pharmacokinetics were characterized in subjects with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment. No dose adjustment is necessary in these patients.

10 OVERDOSAGE

In case of overdose, patients should seek immediate medical help. Patients should be managed by symptomatic and supportive care should there be an overdose.

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Newly described lung disorder strikes children with systemic juvenile idiopathic arthritis

BY MICHELE G. SULLIVAN

An uncommon but potentially deadly inflammatory lung disease is emerging among children with systemic juvenile idiopathic arthritis, and its history appears to coincide with the rise of powerful biologics as first-line therapy for children with the disease.

Most confirmed cases of systemic juvenile idiopathic arthritis with lung disease (sJIA-LD) are in the United States. But it's popping up in other places that have adopted early biologic treatment for sJIA – including Canada, South America, Europe, and the Middle East.

The respiratory symptoms are relatively subtle, so by the time of lung disease detection, the amount of affected lung can be extensive, said Elizabeth Mellins, MD, a Stanford (Calif.) University researcher who, along with first author Vivian Saper, MD, recently published the largest case series comprising reports from 37 institutions.¹ By the end of follow-up, 22 of the 61 children in her cohort had died, including all 12 patients who demonstrated excessively high neutrophil levels in bronchoalveolar lavage samples.

Another recent report, authored by Grant Schulert, MD, PhD, and colleagues of the Cincinnati Children's Hospital Medical Center, described 18 patients, 9 of whom were also included in the Stanford cohort.²

Both investigators have now identified new patients. "We are aware of 60 additional cases beyond what were included in our series," Dr. Mellins said in an interview, bringing her entire cohort to 121. Dr. Schulert also continues to expand his group, detailing 9 new cases at a recent private meeting.

"We are up to 27 now," he said. "The features of these new patients are all very similar: The children are very young, all have had macrophage activation syndrome in the past and very-difficult-to-control JIA. Reactions to tocilizumab [Actemra] were also not uncommon in this group."

Dr. Mellins also saw this association with allergic-type tocilizumab reactions, severe delayed hypersensitivity reactions



Vivian Saper, MD, left, and Elizabeth Mellins, MD



Grant Schulert, MD, PhD

to anakinra (Kineret) or canakinumab (Ilaris). Although serious lung disease in sJIA patients is not unheard of, this phenotype was virtually unknown until about a decade ago. Both investigators said that it's been rising steadily since 2010 – just about the time that powerful cytokine-inhibiting biologics were changing these patients' world for the better. After decades of relying almost solely on steroids and methotrexate, with rather poor results and significant long-term side effects, children were not only improving, but thriving. Gone was the life-changing glucocorticoid-related growth inhibition. Biologics could halt fevers, rash, and joint destruction in their tracks.

"For the first time in history, these kids could look forward to a more or less normal life," Dr. Schulert said.

But the emergence of this particular type of lung disease could throw a pall over that success story, he said. If sJIA-LD is temporally associated with increasing reliance on long-term interleukin-1/IL-6 inhibition in children with early-onset disease, could these drugs actually be the causative agent? The picture remains unclear.

Some of the 18 in his initial series have improved, while 36% of those in the Stanford series died. Most who do

The research groups were supported by grants from the sJIA Foundation, the Lucile Packard Foundation for Children's Health, Stanford graduate fellowships, the Life Sciences Research Foundation, the Bill & Melinda Gates Foundation, Cincinnati Children's Research Foundation, the Childhood Arthritis and Rheumatology Research Alliance, the Arthritis Foundation, and the National Institutes of Health. Many authors on both papers reported financial ties to Genentech, which markets tocilizumab, and other pharmaceutical companies. Dr. Nigrovic reported receiving consulting fees and research support from Novartis and other companies.

recover stay on their IL-1 or IL-6 blocking therapy with good disease control without further lung problems. Both investigators found compelling genetic hints, but nothing conclusive. Children with trisomy 21 appear especially vulnerable. Most patients are very young – around 2 years old – but others are school age. Some had a history of macrophage

“We’ve been going full bore toward early biologic therapy in sJIA and at the same time we are seeing more of this lung disease. Is it guilt by association? Or is there something more? The challenge for us is not to jump too soon to that conclusion.”

activation syndrome. Some had hard-to-control disease and some were clinically well controlled when the lung disease presented.

There are simply no answers yet. With so many potential links, all unproven, clinicians may question the wisdom of embarking on long-term biologic therapy for their children with sJIA.

Peter Nigrovic, MD, of Boston Children’s Hospital, addressed this in an accompanying editorial.³

“My take on this is that it’s a very worrisome trend,” he said in an interview. “We’ve been going full bore toward early biologic therapy in sJIA and at the same time we are seeing more of this lung disease. Is it guilt by association? Or is there something more? The challenge for us is not to jump too soon to that conclusion.”

Although the association is there, he said, association does not equal causation. And there’s no doubt that biologics have vastly improved the lives of sJIA patients. “The drugs might be causal, and I worry about that and think we need to study it. But we absolutely need stronger evidence before we change practice.”

“This is a new manifestation of the disease, and it’s coming at the same time we are changing the treatment paradigm,” Dr. Nigrovic continued. “It could be because of interleukin-1 or interleukin-6 blockade. There is biological plausibility for such a link. It could also be related to the fact that we are using less steroids and methotrexate, which might have been preventing this. The appearance of sJIA lung disease could also be a distinct secular trend unrelated to treatment, just as we saw amyloid come and go in this population in Europe. These

other therapies were actually preventing this. We just don’t know.”

Clinical characteristics

Children presented with similar symptoms. Respiratory symptoms are usually subtle and mild. These can include tachypnea, hypoxia (43% in the Stanford series), and pulmonary hypertension (30% in the Stanford series).

Digital clubbing, often with erythema, was a common finding. Some children showed pruritic, nonevanescient rashes. Eosinophilia occurred in 37% of the Stanford series and severe abdominal pain in 16%, although Dr. Mellins noted that belly pain may be underestimated, as it was only volunteered, not queried, information.

“There are some red flags that should raise suspicion even without obvious respiratory symptoms,” Dr. Mellins said. These include lymphopenia, unexplained abdominal pain, eosinophilia, an unusual rash, and finger clubbing with or without erythema.

Findings on imaging were consistent in both series. Several key clinic features emerged: pleural thickening, septal thickening, bronchial wall or peribronchovascular thickening, “tree-in-bud” opacities, “ground-glass” opacities, peripheral consolidation, and lymphadenopathy.

“The imaging findings correspond to two things,” Dr. Schulert said. “The first is inflammation in the interstitium, which is evidence of chronic and ongoing inflammation. The other thing is that the alveoli are filled with a lipoproteinaceous material which is actually surfactant that’s not being normally recycled by the lung macrophages. You can see these features in other conditions where there’s a problem with lung macrophages, like pulmonary alveolar proteinosis, genetic and autoimmune disorders, infections, or inhalants.”

Pathology showed alveolar filling – a location in the lung that hides usual symptoms until the lung disease is advanced. Prior drug reactions were common. Tocilizumab anaphylaxis occurred in close to 40% of the Stanford series – a surprising finding given the 0.6% reaction incidence in the drug’s sJIA trials. Dr. Schulert saw a similar story.

“In our cohort we also observed a striking number of adverse events to cytokine-targeted biologics exposure,” Dr. Schulert said. “Most of these reactions were to tocilizumab, and were described variously from pain and feeling unwell, to difficulty breathing, to anaphylaxis.”

In a risk analysis, Dr. Schulert determined that adverse events to cytokine-targeting biologics increased the likelihood of lung disease more than 13 times (odds ratio, 13.6).

“We also identified a statistically significant association with history of macrophage activation syndrome when compared to controls (OR, 14.5),” Dr. Schulert and associates wrote.

Genetics

Both the Cincinnati and Stanford teams conducted genetic analyses on some of their patients.

Among eight lung biopsy samples, Dr. Schulert found 37 differentially expressed genes: 36 with increased expression and 1 with decreased expression. Many of the up-regulated genes are involved in interferon-gamma response. Two (CXCL10 and CXCL9) are interferon-induced chemokines associated with macrophage activation syndrome. The down-regulated gene, PADI4, modulates immune response in lupus, and has been associated with the risk of interstitial lung disease in RA.

Dr. Mellins and her team analyzed whole-exome sequencing data from 20 patients and found some rare protein-altering gene variants in genes related to pulmonary alveolar proteinosis, all of which were heterozygous and shared with a healthy parent. But none of them could be directly tied to the disorder.

Another genetic puzzle demands attention, she said. About 10% of the children had trisomy 21 – a stark contrast to the typical 0.2% prevalence among a control group of sJIA patients without any known lung disease in the Childhood Arthritis and Rheumatology Research Alliance Registry cohort, similar to the background population rate. There were suggestions of more aggressive lung disease in all six of these children. Four presented with hypoxia, and two showed advanced interstitial fibrosis. Children with trisomy 21 also seemed more susceptible to infections; 83% had a viral or fungal lung infection at diagnosis, compared with 29% of those without trisomy 21.

Prior exposure to cytokine inhibitors

Parenchymal lung disease and pulmonary hypertension complicating sJIA was first highlighted in a series of 25 cases reported by Kimura et al. in 2013.⁴ These authors raised the question of the possible relationship of this and the increasing use of anti-IL-1 and anti-IL-6 biologics in sJIA treatment.

Following this lead, Dr. Mellins started looking into this new clinical entity in 2015. By then, she was identifying some past cases by autopsy records and current cases by clinical presentation. She saw a dramatic shift over time. From 2002 to 2011, she identified four cases, half of which had been exposed to IL-1/IL-6 inhibitors. From 2012 to 2014, eight new cases came to light, and seven had been exposed to those drugs. The crescendo continued from 2015 to 2017. During those years, Dr. Mellins and associates identified 10 new patients, 7 of whom had taken interleukin-inhibiting biologics. The mean time from initial drug exposure to diagnosis was a little more than 1 year.

An adjusted analysis comparing sJIA-LD patients and sJIA patients without lung disease didn't find any significant difference in drug exposure. However, children with lung disease were more likely to have taken anakinra before the symptoms developed. Additionally, the symptoms of clubbing, abdominal pain, eosinophilia, hyperenhancing lymph nodes, and pulmonary alveolar proteinosis were much more common in children who'd taken the drugs.

The authors pointed out that this association does not prove causality and is confounded by the concomitant reduction in glucocorticoids with IL-1/IL-6 inhibitor use. And the vast majority of children with sJIA take cytokine inhibitors with no problems.

“Possibly, drug exposure may promote lung disease in a subset of children with sJIA, among the substantially larger group of patients who derive striking benefit from these drugs,” Dr. Mellins said, “Importantly, our results argue strongly for more investigation into a possible connection.”

Survival

After a mean follow-up of 1.7 years, the Stanford group saw high mortality. The 5-year survival rate translated to a mortality incidence of 159 deaths per 1,000 person-years, compared with 3.9 per 1,000 person-years in a historical cohort of sJIA patients who required biologic therapy.

Diffuse lung disease was the cause of 12 deaths; 5 of these patients also had macrophage activation syndrome at the time of death. Factors significantly associated with shortened survival included male sex, hypoxia at presentation, and neutrophilic bronchoalveolar lavage with more than 10 times the normal count. In an adjusted analysis, all of these variables fell out. However, none of the children with excessively high neutrophilic bronchoalveolar lavage survived.

Does it affect adults?

Could adults be experiencing the same disorder? There is some evidence to support it. The Food and Drug Administration adverse event website shows alveolar disease or pulmonary hypertension in 39 adults who have been exposed to IL-1 or IL-6 inhibition. Of these, 23 had RA, 11 adult-onset Still's disease, and 5 unclassified rheumatic disorders.

REFERENCES

1. Saper V et al. *Ann Rheum Dis.* 2019;78:1722-31. doi: 10.1136/annrheum-dis-2019-216040.
2. Schulert GS et al. *Arthritis Rheumatol.* 2019 Nov;71(11):1943-54. doi: 10.1002/art.41073.
3. Nigrovic PA. *Arthritis Rheumatol.* 2019 Nov;71(11):1773-5. doi: 10.1002/art.41071.
4. Kimura Y et al. *Arthritis Care Res.* 2013 May;65(5):745-52. doi: 10.1002/acr.21889.

Be vigilant for scleroderma renal crisis

BY BRUCE JANCIN

FROM SOTA 2020

Scleroderma renal crisis is often the most challenging type of scleroderma emergency to identify promptly, according to Francesco Boin, MD, professor of medicine and director of the scleroderma center at the University of California, San Francisco.

“Fortunately, it’s not a frequent event. But it’s severe enough that all rheumatologists should be aware of it,” he said at the virtual edition of the American College of Rheumatology’s 2020 State-of-the-Art Clinical Symposium.

Atypical presentations occur in 30%

Scleroderma renal crisis (SRC) occurs in 5%-10% of scleroderma patients. A vexing feature of this emergency is that not uncommonly it actually precedes the diagnosis of scleroderma. Indeed, 20% of patients with SRC present with sine scleroderma – that is, they have no skin disease and their renal crisis is their first symptom of scleroderma. In contrast, critical digital ischemia – the most common scleroderma emergency – is invariably preceded by worsening episodes of Raynaud’s, and impending intestinal pseudo-obstruction – also among the most common scleroderma emergencies – is heralded by an established history of dysmotility, loss of appetite, abdominal bloating, small intestinal bacterial overgrowth, and bowel distension.

While sine SRC often poses a formidable diagnostic challenge, SRC occurs most often in patients with early, rapidly progressing diffuse scleroderma skin disease. Indeed, the median duration of scleroderma when SRC strikes is just 8 months. The use of glucocorticoids at 15 mg or more per day, or at lower doses for a lengthy period, is an independent risk factor for SRC. Detection of anti-RNA polymerase III antibodies warrants increased vigilance, since 60% of patients with SRC are anti-RNA polymerase III antibody positive. Other autoantibodies are not a risk factor. Neither is preexisting hypertension nor a high baseline serum creatinine.

The classic textbook presentation of SRC is abrupt onset of blood pressures greater than 20 mm Hg above normal for that individual, along with sudden renal failure; a climbing creatinine; proteinuria; and expressions of malignant hypertension such as pulmonary edema, new-onset heart failure, encephalopathy, and/or development of a thrombotic microangiopathy.

Notably, however, 30% of individuals with SRC don’t fit this picture at all. They may present with abrupt-onset severe hypertension but no evidence of renal failure, at least early on. Or they may have sudden renal failure without a hypertensive crisis. Alternatively,

they may have no signs of malignant hypertension, just an asymptomatic pericardial effusion or mild arrhythmias.

“Also, the thrombotic microangiopathy can be present without the other features of scleroderma renal crisis, so no renal failure or hypertensive emergency. Be aware of the possibility of atypical presentations, and always suspect this unfolding problem in the right individuals,” the rheumatologist urged.

Anyone with scleroderma who presents with new-onset hypertension needs to begin keeping a careful home blood pressure diary. If the blood pressure shoots up, or symptoms of malignant hypertension develop, or laboratory monitoring reveals evidence of thrombotic microangiopathy, the patient should immediately go to the ED because these events are often followed by accelerated progression to renal crisis.

Inpatient management of SRC is critical. “In the hospital we can monitor renal function in a more refined way, we can manage the malignant hypertension, and early on, hospitalization provides the opportunity to do a renal biopsy. I always consider doing this early. The pathologist often pushes back, but I think it’s relevant. It confirms the diagnosis. We’ve had patients where we were surprised: We thought it was scleroderma renal crisis, but instead they had interstitial nephritis or glomerulonephritis. Most important, biopsy has major prognostic implications: You can measure the extent of damage and therefore have a sense of whether the patient will be able to recover renal function,” Dr. Boin explained.

Prognosis and predictors

Outcome of SRC is often poor: the 1-year mortality is 20%-30%, with a 5-year mortality of 30%-50%. Normotensive SRC with renal crisis, which accounts for about 10% of all cases of SRC, is particularly serious in its implication, with a 1-year mortality of 60%. Half of patients with SRC require hemodialysis, and only one-quarter of them recover spontaneous renal function.

Predictors of worse outcome include older age at onset of SRC, male gender, a serum creatinine level above 3 mg/dL at presentation, incomplete blood pressure control within the first 3 days of the crisis, and normotensive SRC. Use of an ACE inhibitor prior to SRC is also an independent predictor of poor outcome, possibly because by keeping the blood pressure under control the medication blunts recognition of the unfolding renal crisis.

“This is why experts don’t recommend prophylactic ACE inhibitors in patients who are at risk for SRC,” according to Dr. Boin.

Dr. Francesco Boin reported having no financial conflicts regarding his presentation.

VEDOSS study describes predictors of progression to systemic sclerosis

BY JEFF CRAVEN

REPORTING FROM ACR 2019

ATLANTA – Patients with Raynaud’s phenomenon and puffy fingers, disease-specific antibodies, and/or nailfold video capillaroscopy abnormalities were more likely to progress to systemic sclerosis within 5 years than were patients without those features, according to recent results from the Very Early Diagnosis Of Systemic Sclerosis (VEDOSS) study presented at the annual meeting of the American College of Rheumatology.

“Our data show that thanks [to a] combination of the signs that characterize the various phases of the disease, patients can be diagnosed [with systemic sclerosis] in the very early stages,” first author Silvia Bellando-Randone, MD, PhD, assistant professor in the division of rheumatology at the University of Florence (Italy), said in her presentation.¹

Dr. Bellando-Randone and colleagues performed a longitudinal, observational study of 742 patients (mean 45.7 years old) at 42 centers in a cohort of mostly women (90%), nearly all of whom had had Raynaud’s phenomenon for longer than 36 months (97.5%). Data collection began in March 2012 with follow-up of 5 years.

The researchers determined the positive predictive values (PPV) and negative predictive values (NPV) of clinical features, systemic sclerosis-specific antibodies, and nailfold video capillaroscopy (NVC) abnormalities on progression from Raynaud’s phenomenon to systemic sclerosis.

Overall, 65% of patients were positive for antinuclear antibodies (ANA). Other baseline characteristics present in patients that predicted systemic sclerosis included positive anticentromere antibodies/anti-Scl-70/anti-RNA polymerase III antibodies (32%), NVC abnormalities such as giant capillaries (25%), and puffy fingers (17%).

Rates and predictors of progression

Using Kaplan-Meier analysis, the researchers found 7.4% of 401 patients who were ANA positive progressed to meet ACR-EULAR 2013 criteria, and the percentage of these patients increased to 29.3% at 3 years and 44.1% at 5 years. When the researchers considered disease-specific antibodies alone, 10.6% of 90 patients progressed from Raynaud’s phenomenon to systemic sclerosis within 1 year, 39.6% within 3 years, and 50.3% within 5 years. When the researchers analyzed disease-specific

antibodies and NVC abnormalities together, 16% of 72 patients progressed to systemic sclerosis within 1 year, 61.7% within 3 years, and 77.4% within 5 years.

Puffy fingers also were a predictor of progression, and 14.4% of 69 patients with puffy fingers alone progressed from Raynaud’s phenomenon to systemic sclerosis at 1 year, 47.7% at 3 years, and 67.9% at 5 years. Considering puffy fingers and disease-specific antibodies together, 20% of 27 patients progressed at 1 year, 56.3% at 3 years, and 91.3% at 5 years. No patients with puffy fingers and NVC abnormalities together progressed to systemic sclerosis at 1 year, but 60.4% of 22 patients progressed at 3 years before plateauing at 5 years. For patients with NVC abnormalities alone, 7.1% progressed to systemic sclerosis from Raynaud’s phenomenon at 1 year, 39.4% at 3 years, and 52.7% at 5 years.

“Regarding capillaroscopy, we have to say that not all centers that participated were equally screened in capillaroscopy, and so we cannot assume the accuracy of this data,” she said.

Dr. Bellando-Randone noted that patients were more likely to have a history of esophageal symptoms if they progressed to systemic sclerosis (37.3%), compared with patients who did not progress (23.6%; $P = .003$).

Puffy fingers alone were an independent predictor of systemic sclerosis (PPV, 78.9%; NPV, 45.1%) as well as in combination with disease-specific antibodies (PPV, 94.1%; NPV, 43.9%). The combination of disease-specific antibodies plus NVC abnormalities also independently predicted progression to systemic sclerosis (PPV, 82.2%; NPV, 50.4%). In a Cox multivariate analysis, disease-specific antibodies (relative risk, 5.4; 95% confidence interval, 3.7-7.9) and puffy fingers (RR, 3.0; 95% CI, 2.0-4.4) together were strongly predictive of progression from Raynaud’s phenomenon to systemic sclerosis (RR, 4.3; 95% CI, 2.6-7.3).



Silvia Bellando-Randone, MD, PhD,

REFERENCES

1. Bellando-Randone S et al. *Arthritis Rheumatol*. 2019;71(suppl 10). Abstract 2914.

Dr. Silvia Bellando-Randone and her coinvestigators reported having no conflicts of interest.

Imaging reveals different clinico-pathologic patterns in Takayasu's, giant cell arteritis

BY MICHELE G. SULLIVAN

FROM ANNALS OF THE RHEUMATIC DISEASES

While the symptoms of Takayasu's and giant cell arteritis do not differ greatly, they are associated with different imaging findings of vascular inflammation and luminal damage, a retrospective cohort study has found.

"Clinical symptoms were not sensitive markers of underlying vascular pathology but were specific when present," Despina Michailidou, MD, PhD, and colleagues wrote in *Annals of the Rheumatic Diseases*.¹ "Vascular imaging should be considered in the management of these patients since reliance on the presence of clinical symptoms may not be sensitive to detect vascular pathology within an acceptable window to prevent or minimize damage."

Dr. Michailidou and her coauthors in the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) examined the relationships between clinical presentation and imaging findings in 110 patients involved in an ongoing observational cohort study at the National Institutes of Health, including 56 with Takayasu's arteritis (TAK) and 54 with giant cell arteritis (GCA). Dr. Michailidou conducted the study while she was a research fellow at NIAMS, but she is now a rheumatology fellow at the University of Washington, Seattle.

The team looked at 11 symptoms (lightheadedness, positional lightheadedness, carotidynia, arm claudication vertigo, frontotemporal and posterior headache, posterior neck pain, blurred vision, vision loss, and major CNS events, including stroke, transient ischemic attack, or syncope). These were related to findings on MR angiography (MRA) and 18F-fluorodeoxyglucose PET (FDG-PET).

Patients with TAK had significantly higher rates of carotidynia (21% vs. 0%), lightheadedness (30% vs. 9%), positional lightheadedness (29% vs. 5%), major CNS events (25% vs. 9%), and arm claudication (52% vs. 28%). Arm claudication was the most common symptom in those with TAK (52%), and blurred vision the most common in patients with GCA (37%).

On the day of evaluation, 8% of patients with TAK reported carotidynia; none of the GCA patients reported this. On FDG-PET, carotidynia was more strongly associated with inflammation of the carotid artery than with damage of the carotid artery on MRA.

The sensitivity of this association was low, but specificity was high for both FDG-PET and MRA, suggesting that carotidynia was

strongly associated with corresponding carotid artery abnormalities on both FDG-PET and MRA.

More of those with GCA than those with TAK reported posterior neck pain (18% vs. 7%). It was significantly associated with vertebral artery inflammation in GCA, but not TAK, patients. However, there was no association with vertebral artery damage.

While sensitivity was low for posterior neck pain and imaging abnormalities, specificity was very high in both groups, which indicates "the presence of posterior neck pain was strongly associated with corresponding vertebral artery abnormalities on both FDG-PET and MRA."

Posterior headache was present in 5% of GCA patients and was significantly associated with vertebral artery damage, but it was not associated with such damage in patients with TAK.

About 6% of patients with TAK and 10% of those with GCA reported frontotemporal headache. The headache was not associated with carotid PET activity or damage in either group of patients.

Arm claudication was the most commonly reported symptom overall: 52% with TAK and 28% with GCA. It was more strongly associated with subclavian artery damage on MRA than with inflammation on FDG-PET.

The investigators also assessed the association between specific clinical symptoms and the number of affected neck arteries. Patients with large vessel vasculitis and an increased number of damaged neck arteries on MRA were significantly more likely to experience lightheadedness (odds ratio, 2.61), positional lightheadedness (OR, 3.51), or a major CNS event (OR, 3.23). But those with large vessel vasculitis and inflamed neck arteries on FDG-PET were more likely to experience posterior headache (OR, 2.84).

"These findings may help clinicians predict imaging pathology in specific vascular territories based on patient-reported symptoms and may inform which type of imaging modality would be the most useful to obtain in certain clinical scenarios, recognizing that additional sequences to detect wall morphology may augment the ability of MR-based assessments to detect vascular inflammation in addition to luminal damage."

REFERENCES

1. Michailidou D et al. *Ann Rheum Dis*. 2019 Oct 24. doi: 10.1136/annrheumdis-2019-216145.

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Rituximab tops azathioprine for relapsing ANCA-associated vasculitis remission maintenance

BY M. ALEXANDER OTTO

REPORTING FROM ACR 2019

ATLANTA – Rituximab (Rituxan) is superior to azathioprine (Imuran) for preventing ANCA-associated vasculitis relapses in patients with histories of previous relapses, according to a randomized trial of 170 patients presented at the annual meeting of the American College of Rheumatology.¹

Rituximab has been previously shown to be the superior remission maintenance option in the French MAINRITSAN trial, but mostly in newly diagnosed patients after cyclophosphamide induction.² The results expand the finding to those with relapsing disease who previously had remission induced with rituximab, said lead investigator Rona Smith, MD, a clinical lecturer at Cambridge (England) University.

Subjects in the RITAZAREM trial (rituximab versus azathioprine as therapy for maintenance of remission for antineutrophil cytoplasmic antibody [ANCA]-associated vasculitis) were enrolled during a relapse of either granulomatosis with polyangiitis or microscopic polyangiitis and underwent remission induction with rituximab 375 mg/m² per week for 4 weeks coupled with prednisone, either 1 or 0.5 mg/kg per day at provider discretion.

After successful induction – defined as a Birmingham Vasculitis Activity Score for Wegener’s Granulomatosis of 1 point or less on no more than 10 mg/day prednisone – 85 patients were randomized to rituximab 1 g every 4 months for 20 months and 85 to azathioprine 2 mg/kg per day for 20 months, followed by a taper. Prednisone was tapered per protocol to discontinuation at 20 months.

Eleven rituximab patients (13%) relapsed during the 20-month maintenance phase; two relapses were major. There were 32 relapses (38%) in the azathioprine group, 12 of them (38%) major (hazard ratio for rituximab versus azathioprine, 0.3; 95% CI, 0.15-0.60; *P* less than .001). ANCA type, glucocorticoid induction regimen, and severity of the enrollment relapse did not affect the outcomes.

Also, “there was an increase in the proportion of patients who became ANCA negative” in the rituximab arm, while “there was really no change” with azathioprine. In short, “rituximab is superior to azathioprine for prevention of disease relapse,” Dr. Smith said.

Her audience had a few questions about the rituximab regimen. The French MAINRITSAN trial dosed rituximab every

6 months instead of every 4, for a cumulative dose of 2.5 g, not 5 g, which an audience member said is the standard approach.

Dr. Smith explained that she and her colleagues have seen relapses with rituximab maintenance at 5 and 6 months, so they wanted to move to a shorter schedule. As for the higher dose, they wanted to “achieve complete B-cell depletion for the duration of the treatment period” to see if it trans-

lates into longer lasting remissions. “We will hopefully be able to address that question” with further analysis, she said.

There were no new safety signals; 19 rituximab patients (22%) and 31 azathioprine subjects (36%) had at least one serious adverse event; an infection requiring hospitalization occurred in 7 rituximab patients (8%) and 11 azathioprine patients (13%). Twenty-five (29%) rituximab and 21 (25%) azathioprine subjects developed hypogammaglobulinemia (IgG less than 5 g/L), and about half of each group developed an infection that required antibiotics, but not hospitalization.

There was one death in the azathioprine arm from malignancy, and three in the rituximab group, one from infection and two as of yet unclassified.

The groups were well balanced. Subjects were a median of 59 years old, with a median disease duration of 5.3 years. Refractory patients – those who had not achieved remission during a previous relapse – were excluded, as were patients who had received a B cell-depleting treatment in the previous 6 months and those with eosinophilic granulomatosis with polyangiitis or a malignancy in the past 5 years. Among patients in the study, 72% had tested positive for anti-proteinase 3 ANCA, and 28% for myeloperoxidase ANCA.



Rona Smith, MD

REFERENCES

1. Smith R et al. *Arthritis Rheumatol*. 2019;71(suppl 10), Abstract 806.
2. Guillevin L et al. *N Engl J Med*. 2014 Nov 6;371(19):1771-80. doi: 10.1056/NEJMoa1404231.

The work was funded by Versus Arthritis (formerly Arthritis Research UK), the National Institutes of Health, and the makers of rituximab, Roche/Genentech. Dr. Rona Smith reported ties to Roche, Sanofi, and MedImmune.



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