Q&A With A Medical Professional: Rheumatologist Edition

HLA-B27 & ERAP Genes In Ankylosing Spondylitis

Your Stories: Burning Man And My Disease
Dear Readers,

“Ankylosing Spondylitis, what’s that?” I’ve been hearing that question for as far back as I can recall. Well, things may be changing as we speak due to the courage and determination of a young man with a big audience and an even bigger heart. Dan Reynolds is the lead singer of Imagine Dragons, a very popular rock band hailing from Las Vegas.

Dan approached us and one of our industry partners, last year to find out how he could help get the word out so that others would not suffer the extreme pain and frustration still often associated with delayed diagnosis.

Soon after, we were in NYC for meetings when one of our corporate members, Novartis Global, approached us, asking if we would like to partner on a two year, celebrity-driven awareness campaign to get the word out into the general population regarding AS. They didn’t name the celebrity, but pitched the idea of video chats focused on disease self-management and lifestyle choices such as diet, exercise, and the importance of family and friends in coping with a chronic illness.

The celebrity was Dan. And, of course, we were delighted to jump right in to collaborate on what was to become This AS Life Live!

As many of you are aware, when diagnosed early enough, there are many tools that can influence the course of the disease and make for better outcomes. With proper self-management and a healthy lifestyle, as well as, when appropriate, the powerful medications that recently have shown the ability to slow disease progression in some individuals, AS patients can affect positive change.

We are very grateful that Dan jumped in with both feet, lending his star power to raise awareness, and encourage people to lead healthier lives. Thank you, Dan! We are so proud of you and look forward to our continued collaboration for the betterment of the AS and spondylitis communities.

Bravo!!!
“A few months ago I responded to an SAA survey requesting content ideas or suggestions for the Spondylitis Plus Magazine. My request was a piece on SSDI. I WAS THRILLED to see a Q&A piece with Richard Feingold on the topic in my inbox during the early hours of December 22nd.

I have been quite stressed and anxious about going through this process alone and was hoping SAA could provide me information and resources to make it less stressful.

After reading the article, I phoned Richard Feingold early the next morning. He returned my call late the evening of Friday the 23rd, before leaving his office and heading out for a few days. We plan to speak immediately after the New Year.

In the few minutes that Richard and I spoke, my confidence in him grew. As it turns out, his practice is less than five miles from my house!!!

While I know there will be some stress in starting the SSDI process, I’m fairly certain that I am in good hands with Mr. Feingold going forward.

Once underway, I’d be happy to give my perspective of the process to any SAA members along the way. THANK YOU for listening!! Your article was the absolute best gift I received this year for Christmas!!!

Wishing you and the entire SAA community Peace, Joy, Health, and many Blessings in 2017.”

~ Jill Miller
Evanston, IL

“I’ve enjoyed the restructured website - so much good info, though some of the personal stories are so effective, they bring tears. Makes my own situation, even though it’s getting worse, not seem so bad. Perhaps having a rock star (Dan Reynolds) on the TV show “The Doctors” discussing his AS, as they showed on the site, will help get the word out even more.”

~ Bonnie Smith
Support Group Leader of the Northern Great Plains Spondylitis Educational Support Group
Hettinger/Bismarck, ND

Editor’s Note: Imagine Dragons lead singer, Dan Reynolds, appeared on March 8th on the syndicated talk show “The Doctors” to speak about living with ankylosing spondylitis. Dan also hosts his own online talk show on AS, called “This AS Life Live!,” a series created in partnership with the Spondylitis Association of America and Novartis Pharmaceuticals, that brings together people with AS to share their stories with the world. You will find more information (and videos!) on both the online series and “The Doctors” appearance in our website’s news section, at www.spondylitis.org/updates.

LETTERS TO THE EDITOR
We want to hear from you! Send your thoughts, questions, opinions, and rebuttals.

Please send letters to:
Elin@spondylitis.org
Letters to the Editor/SAA
P.O. Box 5872, Sherman Oaks, CA 91413

Please note that we reserve the right to edit for space and clarity.
We hear so much about customized medicine in the media. We know they can test for whether a mood altering drug, such as Zoloft or Prozac, will be metabolized well or not. These tests can categorize whether they will probably reach the therapeutic dose, or whether it’s likely not to work. Is there any work being done in this regard with biologic medications?

There are commercially available tests for a couple of the biologics (infliximab and adalimumab) to determine what the level is in the blood and whether a patient has developed antibodies to the drug. This is routinely assessed in inflammatory bowel disease and the gastroenterologists have guidelines of what to do in various situations. They also have a target drug level they aim for. There is less evidence in rheumatology as to what the level should be and what to do in the various scenarios.
The emerging data is that taking a TNF inhibitor like adalimumab (Humira) is associated with a significant reduction in spinal progression. We do not believe it simply treats symptoms, though proving the effects are causal has been challenging.

Q I read recently that taking an anti-inflammatory with a TNF inhibitor like Humira can stop the progression of spondylitis. My rheumatologist says they don’t stop the progression, that they merely treat symptoms. Which is true?

A The emerging data is that taking a TNF inhibitor like adalimumab (Humira) is associated with a significant reduction in spinal progression. We do not believe it simply treats symptoms, though proving the effects are causal has been challenging. (References: Haroon et al Arth Rheum 2013 and Gensler LS et al ACR supplement 2016)

Q What are the latest risks of lymphoma or other cancers from biologics (from FDA testing through aftermarket reporting?) People are still scared by the warnings on the packages, but I hear that the incidences are really much lower since we have many more users now.

A There has never been a study in spondylolharthritis to show an increased risk of any kind of solid cancer or blood cancer in patients using TNF inhibitors. The original study showing this association has not been reproduced. Many people believe that these data (performed in rheumatoid arthritis) were biased in that those patients were more severe from longstanding untreated disease and therefore at higher risk for lymphoma to begin with. In fact there may be emerging data in cancer research that TNF itself may drive cancer, so this may shift the entire paradigm of how we look at the risk in patients with rheumatic diseases. I generally think the risk of cancer in spondylolharthritis is far outweighed by the benefits of TNF inhibitors in those with active arthritis. There may be a slight increase in non-melanoma skin cancers, but these are generally not dangerous and can usually be removed if they arise. If they occur, there are often other risk factors like UV exposure and fair skin, so UV protection should be considered.

Q What is the long term effect of methotrexate on my body? What should I be concerned about? Also, I usually need one to two prednisone taper treatments a year if I flare up. What are the long term effects on my body with prednisone use?

A Methotrexate is one of our oldest rheumatology medications and is usually well-tolerated long term. It can affect the liver, and liver function should be measured every three months. It is metabolized in the kidney and if the kidneys do not work well, then methotrexate may not be a good option. This is especially true because as it builds up in the system it can suppress the bone marrow from producing cells (like a chemotherapy) and this can be dangerous. None of these are usually issues with regular blood monitoring. It does suppress the immune system and is associated with infections, but this is especially true if combined with biologics and prednisone. It does not need to be stopped during joint surgeries like knee and hip replacement.

Prednisone long term can have more significant side effects including infection, bone loss leading to osteoporosis and fracture. Fracture is a serious complication because AS patients are at risk for fracture and adding prednisone to that risk likely escalates it further. Prednisone causes weight gain which is bad for AS, but stopping prednisone does not help weight loss. With more chronic use, patients can get thinning of the skin and the adrenal glands can shut down because the body is being supplied by an exogenous source of steroids (with the prednisone). This makes it difficult to taper prednisone quickly, leading to more side effects. Other complications include steroid induced hyperglycemia (diabetes), lipid problems, fluid retention, glaucoma, and muscle weakness called myopathy. In general, the guidelines recommend against the use of oral or injectable prednisone for AS because the doses needed are high and the side effect profile often outweighs the benefit.

Q Is there any way to prevent recurrences of uveitis for a patient with AS?

A Some patients will not have recurrences of uveitis, however some will and sometimes frequently. In patients with frequently recurrent uveitis and active AS warranting a biologic, using certain biologics (the TNF inhibitors

www.stopas.org
There are many reasons why patients lose response to biologics. If, when the biologic is first used, the response is very positive and then this decreases, it could be that the patient has developed an antibody against the drug, causing it to be cleared more quickly and therefore decreasing its effectiveness.

I have dormant TB. What medication can I take? Any biologics?

Dormant tuberculosis (TB), otherwise known as latent TB, should not preclude treatment for axial spondyloarthritis/ankylosing spondylitis. However, if the TB test is positive by the blood test or the skin test (one of which is required to be performed in all patients before starting biologics) then TB antibiotics should be administered for at least two weeks before starting the biologic and continued for up to nine months (depending on medication used). This is most relevant with TNF inhibitors (where the risk for reactivation is the highest).

I have taken various biologic drugs over the years, but each one keeps losing effectiveness after a couple of years and so I have to keep switching. Can you explain why this keeps happening? Will I likely ever find a biologic that works for many years?

There are many reasons why patients lose response to biologics. If, when the biologic is first used, the response is very positive and then this decreases, it could be that the patient has developed an antibody against the drug, causing it to be cleared more quickly and therefore decreasing its effectiveness. In this setting, adding a low dose of a medication like methotrexate may help prevent this from happening. Not all of the biologics are prone to this happening. Infliximab is most strongly associated with this phenomenon but it rarely happens in etanercept. It may also be that patients stop responding as well because the disease becomes more active or progresses and the damage is what is causing the pain. The patient’s rheumatologist should evaluate the patient to determine the most likely cause of the reduction in response. I believe we will keep developing more effective drugs with fewer side effects; I therefore believe you will find a medication that works for you for long-term.

Can advanced ankylosing spondylitis affect the heart? If so how?

Long standing AS is associated with inflammation and inflammation is not good for the heart. The most common heart effects in AS are coronary artery disease and atherosclerosis. This may be associated with an increased risk of heart attack and/or stroke. The older literature suggested AS patients also developed inflammation and leakiness of the aortic valve. In more recent studies, when compared to an age matched healthy population, this association has not been detected. It may be that by treating inflammation with the newer medications like the biologics, we are preventing some of the cardiovascular complications.

Is there a surgical procedure to correct kyphosis?

There is a surgical procedure called a spinal osteotomy. This is a relatively high risk surgery and should only be performed with severe kyphosis where the patient’s horizontal gaze may be compromised, and only at specialized centers that have significant experience with this procedure.

I have AS and osteoporosis. Will bisphosphonates cause a worsening of bony exostoses? My hand joints are already extremely distorted by the bony growths. Will a bisphosphonate make them worse?
Bisphosphonates turn off bone loss from osteoporosis, but they do not turn on bone growth. They should not cause extra bone growth or ankylosis.

Q Does the benefit of long term use of a bisphosphonate outweigh the risk of osteonecrosis for a 40 year old patient with osteopenia?

A I would rarely treat a 40 year old with bisphosphonates in the setting of AS because the usual cause is inflammation and stiffness and these can be treated with AS medications like TNF inhibitors. In addition the reason to treat is really because of the risk of osteoporosis and fracture. Since younger patients (40 is young) are at lower risk for fall, they are also lower risk for this outcome. When AS patients are treated with TNFi, bone density increases as inflammation is suppressed. There are occasional times when we do use bisphosphonates in younger patients. The risk of jaw osteonecrosis from oral bisphosphonates in patients without a history of radiation to the head/neck and with good dentition is quite rare, so when truly indicated, the benefit to bone health outweighs the risk of osteonecrosis. We do not like to use bisphosphonate for too many years without a break.

Q What is the current status of ustekinumab (Stelara) for the treatment of ankylosing spondylitis? My rheumatologist has recommended it to me. I had disastrous reactions to both Enbrel and Humira.

A A small proof of concept study suggested that ustekinumab may be helpful in AS. Phase three trials are underway both in patients that have never used biologics, and in those that did not respond or did not respond well to TNF inhibitors. Results are not yet available. Ustekinumab was recently FDA approved for Crohn’s disease and is approved for psoriasis and psoriatic arthritis.

Q What treatment do you recommend for enthesitis pain? Enbrel and NSAIDs don’t help me with this ongoing issue in many of my joints (I’m female and HLA-B27 negative); topical NSAIDs help only temporarily.

A NSAIDs and biologics are the only medications expected to work. If there is no relief with these agents, then making sure this is enthesitis causing the pain would be important. Enthesal pain does not necessarily come from inflammation and the above mentioned medications only work by suppressing inflammation.

Q How many patients with AS also suffer from Crohn’s disease? What about the percentage of Crohn’s patients who develop AS? Is there any difference in these populations based on gender?

A About 20% of patients with inflammatory bowel diseases (IBD), of which Crohn’s is one, develop AS or some amount of sacroiliitis. About 8% of AS patients have IBD, but the majority of AS patients without any gastrointestinal symptoms have some amount of microscopic inflammation in the gut supporting the strong relationship between these two conditions. There is no data to suggest a gender difference in the setting of IBD and AS.

Q Does a difficult or stressful childbirth contribute to triggering the onset of spondylitis symptoms in the child? Any research on this?

A There is no data to suggest that a baby born under stressful conditions is more at risk for spondyloarthritis. We do know that the vaginal microbiome is important for babies as they are delivered. Babies born via cesarean section will miss this exposure.
LEAVING A LEGACY

Cure This, Pronto!
By Richard Howard, MBA

Alan Fraser lived with AS; he was also part of the quest to cure spondyloarthritis and empower those affected to live life to the fullest. To speed that quest along, he asked questions, searched for solutions, and supported the SAA. Alan made 75 separate donations to the SAA, the last one in his will. He would sometimes write notes with his donations; notes such as: “Please find a very safe and very effective cure - treatment for AS pronto, as in yesterday, cause last night and this morning were VERY BAD.”

Alan would call SAA’s office to talk about a study he just read, or something he experienced that made him wonder if others with AS had as well. What better place to call than the place that is exploring the same issues every day, every year.

For a while there Alan would email four or five articles or questions to SAA every week. At one time or another, he spoke with everyone on staff. Alan would call SAA’s office to talk about a study he just read, or something he experienced that made him wonder if others with AS had as well. What better place to call than the place that is exploring the same issues every day, every year. Often, Chris Miller on our staff would take the call and follow up by sending additional articles related to the specific topic of the day (published research on adrenaline, neuropathy, vitamin D;) Alan even wondered if other people’s AS symptoms lessened after dealing with a bout of food poisoning. Chris was also curious and just as interested. They had lively conversations as co-explorers. This was an ongoing conversation that lasted years.

That’s how understanding works for many of us. We articulate our thoughts, and as we discuss them with others, things become clearer and new ideas emerge. Finding the answer to a question or expressing an idea often has the potential for raising new questions. “Why did that occur in the first place? How exactly does that happen? What can be done to change that process?”

“"This fall, SAA will invite top researchers from the U.S. and overseas to hold those lively conversations, and ask those ‘why,’ ‘how,’ and ‘what’ questions, during our third Unmet Needs Conference.”

No one has all those answers yet. When we do, we will have the cure and prevent others from developing spondyloarthritis.

What we can do and will continue to do is keep asking questions.

This fall, SAA will invite top researchers from the U.S. and overseas to hold those lively conversations, and ask those ‘why,’ ‘how,’ and ‘what’ questions, during our third Unmet Needs Conference. 175 people will be on the National Institutes of Health (NIH) campus in Bethesda, Maryland for two days sharing their expertise and learning from one another. While we are of course including spondyloarthritis researchers, as well as people living with spondyloarthritis, the main goal of this conference is to expand our horizons and learn as much as possible from research conducted in related fields, which is, in some cases, ahead of where we are. Accordingly, leaders in fields complementary to spondyloarthritis are being invited to present innovative approaches and cutting edge research being conducted in their areas of expertise.

Each time SAA holds this conference new collaborations are built, new research areas are launched, and we get closer to a cure. Alan will be part of the conversation when we recognize his contribution. The entire gift from Alan’s will is being applied to the cost of this conference. When he left a donation in his will he planned for a better future for others, for people he may never know personally. Applying his donation to the upcoming SAA Spondyloarthritis 2017: Unmet Needs Conference III, seems a suitable tribute to someone who had asked SAA for “an effective cure-treatment, pronto.”

Please let us know if you have included SAA in your will or other estate plan, or if you are interested in including SAA in your plans. Please contact me at legacy@spondylitis.org or at (800) 777 – 8189, ext. 231. More information can also be found at www.spondylitis.org/quest.
The Quest Legacy Society

We gratefully acknowledge the generosity of the following individuals who have kindly remembered SAA in their estate plans. Members of the Quest Legacy Society help ensure that SAA will continue to fund research and to provide programs to empower future generations.

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* Remembered in perpetuity. (Year of donation.)
Thanks in no small part to the assistance of the Spondylitis Association of America, the genetic basis of this disease has been to a great extent ascertained. To date over 113 genetic factors have been found by our collaborative group, including genes important in the TH17 arm of the immune response, in CD8 T cell function, in sensing of germs such as bacteria, and, in particular, in the presentation of fragments of proteins that have been degraded in our cells, called peptides, to immune cells to stimulate an immune response.

The leading player in this category, of course, is HLA-B27, which is the 600 pound gorilla in the genetic susceptibility to AS, accounting for up to 80% of the known genetic cause. It is present in up to 90% of patients with AS, as well as in 7.5% of Caucasians in the United States. It is somewhat less common in Latinos (4.6%) and even less common in those of African descent (about 1%). Although we have known about the association of HLA-B27 with AS for nearly 45 years, only recently are we getting clues as to how it predisposes to AS.

The usual function of HLA-B27 proteins is to pick up peptides (breakdown products of degraded proteins in the cell) and to present them on the surface of the cell to other immune cells such as CB8 positive T lymphocytes and natural killer cells, which in turn stimulate an immune response. However, despite many studies looking for an “AS-causing peptide,” none have been found.

Another property that is rather unique to HLA-B27 is that it sticks to itself and forms a “double HLA-B molecule,” called a homodimer. A growing body of evidence shows that HLA-B27 can fold the wrong way, causing it to accumulate inside the cell and cause something that is called “an unfolded protein response,” which in itself can cause inflammation, especially in cells that produce interleukin 17 and 23. Alternatively, it has been shown that these HLA-B27 homodimers can get out to the cell surface and stimulate cells to do the same thing. Lastly, HLA-B27 positive people don’t handle certain infections as well as HLA-B27 negative people (see below) and this may contribute to AS by failing to eliminate certain microorganisms that may drive the disease.

Patients with AS who are HLA-B27 positive are much more likely to suffer from uveitis, have a younger age at disease onset, and are more likely to have family members who are similarly affected.

There are more types of HLA-B genes around the world than any other genetic factor; in fact, as of March 2017, there are over 3,400 known types of HLA-B proteins that have been identified. Why so many? Because HLA proteins mutate in response to external environmental challenges, such as infections, and those challenges vary widely in different parts of the world. Being HLA-B27 positive gives an advantage in fighting such viral infections as HIV-1, hepatitis C, and even possibly influenza. Before the introduction of highly active antiretroviral therapy, HLA-B27 positive people lived much longer than HLA-B27 negatives - in part to an exuberant immune response that HLA-B27 positive individuals have against the HIV-1 virus. The same is likely with other viruses. In fact, the reason why certain population groups such as Eskimos and certain other
Native American tribes and other populations in far northern climates have such a high frequency of HLA-B27 (up to 50%) could be that many years ago, an infection such as a flu epidemic could have preferentially attacked those who lacked HLA-B27. On the other hand, people who are HLA-B27 positive don’t handle other types of infections as efficiently, specifically certain bacteria that can get inside cells and otherwise escape immune surveillance, such as Chlamydia, Salmonella, etc. This may explain why HLA-B27 is now rare in the tropical parts of the world where malaria is common (malaria too is able to live inside cells).

Another group of genes that was discovered by our group to be important in susceptibility to AS are called endoplasmic reticulum aminopeptidases I and 2 (ERAP1 and 2). These enzymes trim peptides in the part of the cell called the endoplasmic reticulum to the right size to fit onto the HLA-B molecule. ERAP 1 is only associated with AS in HLA-B27 positive patients, whereas ERAP 2 is associated with AS in both HLA-B27 positives and negatives. Both genes sit right next to each other on chromosome 5. There are over 10 different types of ERAP1; the one associated with AS has been shown to result in decreased peptide trimming and interacts with HLA-B27 to influence disease susceptibility. The same type of ERAP1 that is associated with AS is also associated with psoriasis, where ERAP1 interacts with HLA-Cw6. Another type of ERAP1, one that is somewhat different functionally from the type associated with AS and psoriasis, is linked to an inflammatory disease that is most common in the Middle East and Asia, called Behcet’s disease, which results in inflammation of blood vessels called vasculitis, eye disease, painful ulcers in the mouth and genitalia, and skin lesions.

As in AS with HLA-B27, and psoriasis with HLA-Cw6, this type of ERAP1 interacts with HLA-B51 in Behcet’s disease to influence disease susceptibility. Given its primary association in HLA-B27 positive individuals, it is not surprising that the ERAP1 type associated with AS is particularly seen in AS patients who have uveitis.

The discovery of these newer genes has important therapeutic implications. The TH17 pathway, which includes IL-17, IL-23, and tumor necrosis factor (TNF), have already been effective therapeutic targets, with anti-TNF and anti-IL17 agents now being used in treatment, and anti-IL23 agents in clinical trials. Drug companies are also currently assessing ERAP1 and ERAP2 as targets. These genetic findings have allowed a great deal of new information and research into the causes of this disease. Hopefully, this may one day mean a cure, or at least stopping AS in its tracks before it can cause the pain and suffering of our patients.
The first time that I met Michael (back in the 90s) I became immediately privy to his outrageousness. His humor knocked me sideways each time he answered his phone, greeting me with a carnival announcer’s voice - his loud, beautifully projected actor’s voice announcing, “LAAAAURIEEE SAAVAAAAAGE!” I liked to pretend to myself that I was the only one who received a greeting like that from him, though of course I knew I wasn’t. That was our Michael.

Through the many years of our friendship, Michael and a core group of spondylitis trailblazers, including our close friend and online guru - spondy999, Tom Contrino, kindly took me under their collective wing in 1997 and proceeded to show me how not to do it; that I would not be up to the job unless I truly listened and took heed from those really in charge - those precisely whom we strive to serve. I have carried those lessons for two decades now, and they have served me, and our SAA well.

The last time Michael and I enjoyed laughter and deep affectation in person was during my most recent trip to NYC in June of 2016. I remember we had this huge, gigantic, awesomely delicious pizza in his office. He was kind as always and went along with my favorite toppings: spicy Italian, double provolone, tomatoes, and oodles of oregano. We laughed hard that day - our history, the spondylitis community’s future, stupid stuff, important stuff, gallows… Little did we know that he would fall soon after and make us all so sad. The gallows part would have likely tickled his fancy. I fell and fractured my own cervical spine shortly after his passing. I fell at home – same as Michael. Later I could hear him in my head, “LAAAAURIEEE SAAVAAAAAGE, pay attention stupid person!” I got lucky, my fracture is now repaired.

I love you, Michael. Please keep on sending me those nuggets of wisdom and strength, and please continue to kick butt.

~ Laurie Savage

Editor’s Note: The deeply loved and talented Michael Tracy Smith - tireless spondylitis advocate, friend to thousands, leading voice and constant presence in the spondylitis community, and writer of haikus (among many, many other things) - passed away on December 6th, 2016, at the age of 65, after having suffered a fall and a heart attack. With his 66th birthday one day away, he passed in the hospital, surrounded by loved ones. We would like to honor the life and many achievements of our dear friend, and offer our deepest condolences to his family and his many loving friends.

“I don’t feel discouraged
when your back’s against the wall…
you’ve found some support.”
~Michael Smith

“Footprints on the beach….
When I could not go on, God
drove me in his jeep.”
~Michael Smith

“Yes, you know my heart,
For we are kindred spirits,
Walking the same path.

But stay wary, my friend, for
Paths, like lover’s hearts, may turn.”
~ Michael Smith
In May, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) published its recommendations for the treatment of psoriatic arthritis (PsA). The updated recommendations represent advances in drug development and availability since previous recommendations published in 2009, as well as changes in treatment paradigms and the importance of associated aspects of the disease.

“Along with including the importance and treatment of comorbidities associated with PsA, the new recommendations include three new classes of drugs that have come to the market since the 2009 recommendations. These include interleukin 12- and 23-blocking drugs, an interleukin 17-blocking drug, and a small-molecule drug that inhibits phosphodiesterase 4.”

Updated Recommendations

The 2015 updated recommendations were developed by a panel of GRAPPA rheumatologists, dermatologists and patients with PsA, which reviewed the current literature on treatment of key domains of PsA, including arthritis, spondylitis, enthesitis, dactylitis, skin disease, and nail disease. New to this update was the inclusion of a review to identify pertinent comorbidities associated with PsA and their effect on treatment.
Using a modified Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process, the panel then developed treatment recommendations for each disease domain (as well as comorbidities) and a schema that incorporated the overarching principles.1

Dr. Kavanaugh emphasized that these treatment recommendations are meant to help clinicians optimize their care for patients with PsA. The recommendations do not, however, provide clear guidance on exactly when to use each agent.

“I think that when recommendations come out there is a hope or aspiration that they may be more specific than they can be,” he says, “meaning that along with listing the recommended therapies, the specifics on when to use which drug first in a given patient [would] also [be] provided.”

“That would be nice, but we don’t have that information, so the clinician is left with clinical experience and patient choice,” he adds. “So that is partially why more patient involvement is included in these guidelines compared to older guidelines.”

Dr. Deodhar emphasizes that clinicians will want to know how to use these new drugs, whether as first-line treatment or as second-line treatment after anti-TNF inhibition failure. Given the lack of head-to-head studies on comparative efficacy of the drugs, he says that clinicians can look at their comparative safety profiles.

For example, when comparing the safety of methotrexate to the new small-molecule drug, apremilast [Otezla], he says apremilast seems to be extraordinarily safe except for stomach upset and diarrhea and appears not to be associated with the more severe side effects of liver function abnormalities or significant immunosuppression.

“However, we have 40 years of experience with methotrexate and only three years of experience with apremilast, so the side effects may appear later,” he cautions.

Of course, cost is also an issue, because the cost of the newer agents is extraordinary, he says.

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**Table 1** 1,3 Overarching principles and agreement by members of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

<table>
<thead>
<tr>
<th>Principle</th>
<th>Health care professional agreement, % (n=135)</th>
<th>Patient agreement, % (n=10)</th>
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</thead>
<tbody>
<tr>
<td>1. The ultimate goals of therapy for all patients with psoriatic arthritis (PsA) are as follows:</td>
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<tr>
<td>A) To achieve the lowest possible level of disease activity in all domains of disease; as definitions of remission and low or minimal disease activity become accepted, these will be included in the goal.</td>
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<td>B) To optimize functional status, improve quality of life and well-being, and prevent structural damage to the greatest extent possible.</td>
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<td>C) To avoid or minimize complications, both from untreated active disease and from therapy.</td>
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<tr>
<td>2. Assessment of patients with PsA requires consideration of all major disease domains, including peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis, and nail disease. The impact of disease on pain, function, quality of life, and structural damage should be examined. In addition, activity in other potentially related conditions should be considered, including cardiovascular disease, uveitis, and inflammatory bowel disease. Multidisciplinary and multispecialty assessment and management will be most beneficial for individual patients.</td>
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<tr>
<td>3. Clinical assessment ideally includes patient-reported measures with a comprehensive history and physical examination, often supplemented by laboratory tests and imaging techniques.</td>
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<td>4. A comprehensive assessment of relevant comorbidities (including but not restricted to obesity, metabolic syndrome, gout, diabetes, cardiovascular disease, liver disease, depression, and anxiety) should be undertaken and documented.</td>
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<tr>
<td>5. Therapeutic decisions need to be individualized, and are made jointly by the patient and his or her doctor. Treatment should reflect patient preferences, with the patients provided with the best information and relevant options provided to them. Treatment choices may be affected by various factors, including disease activity, structural damage, comorbid conditions, and previous therapies.</td>
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<tr>
<td>6. Ideally, patients should be reviewed promptly, offered regular evaluation by appropriate specialists, and have treatment adjusted as needed in order to achieve the goals of therapy. Early diagnosis and treatment is likely to be of benefit.</td>
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</tbody>
</table>

Health care professional agreement and patient agreement for the overarching principles of the guidelines for the assessment and management of patients with PsA.

---
Peripheral arthritis, DMARD-naive
DMARDs (MTX, SSZ, LEF), TNFi
Recommended (strong)
Recommended (conditional)
Not recommended (strong)
No recommendations due to lack of evidence
Peripheral arthritis, inadequate response to DMARDs
TNFi, IL-12/23i, PDE-4i
NSAIDs, oral CS, IA CS, PDE-4i
IL-12/23i, IL-17i
Peripheral arthritis, inadequate response to biologic treatment
TNFi
NSAIDs, oral CS, IA CS, IL-12/23i, IL-17i, PDE-4i
Axial PsA, biologic-naive
NSAIDs, physiotherapy, simple analgesia, TNFi
IL-17i, SI joint CS injections, bisphosphonates, [IL-12/23i]
Axial PsA, inadequate response to biologic treatment
Physiotherapy, simple analgesia
NSAIDs, TNFi, IL-12/23i, IL-17i
DMARDs, IL-6i, CD20i
Enthesitis
TNFi, IL-12/23i
NSAIDs, physiotherapy, CS injections (with extreme caution since injecting CS in weight-bearing entheseal sites can lead to rupture of entheses), PDE-4i, IL-17i
DMARDs
Dactylitis
TNFi (infliximab, adalimumab, golimumab, CZP)
CS injections, DMARDs (MTX, SSZ, LEF), TNFi (etan.), IL-12/23i, IL-17i, PDE-4i
Psoriasis (plaque)
Topical therapies, phototherapy, DMARDs (MTX, LEF, CSA), TNFi, IL-12/23i, IL-17i, PDE-4i
Topical therapies, procedural therapies, DMARDs (CSA, LEF, acitretin, MTX), IL-17i, PDE-4i
Nail psoriasis
TNFi, IL-12/23i
Recommended (strong)
Recommended (conditional)
Not recommended (strong)
No recommendations due to lack of evidence

Table 2 1,3 Summary of GRADE recommendations for PsA therapies, by disease domain

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended (strong)</th>
<th>Recommended (conditional)</th>
<th>Not recommended (strong)</th>
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<td>Enthesitis</td>
<td>TNFi, IL-12/23i</td>
<td>NSAIDs, physiotherapy, CS injections (with extreme caution since injecting CS in weight-bearing entheseal sites can lead to rupture of entheses), PDE-4i, IL-17i</td>
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<td>Dactylitis</td>
<td>TNFi (infliximab, adalimumab, golimumab, CZP)</td>
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<td>Psoriasis (plaque)</td>
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</tbody>
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a Italicized text signifies conditional recommendations for drugs without current regulatory approvals or for which recommendations are based on data published in abstract form only; italicized text in brackets signifies conditional recommendations based only on data from a small open-label proof-of-concept trial, published in abstract form only.

GRADE = Grading of Recommendations, Assessment, Development and Evaluation; PsA = psoriatic arthritis; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; SSZ = sulfasalazine; LEF = leflunomide; TNFi = tumor necrosis factor inhibitor; NSAIDs = nonsteroidal antiinflammatory drugs; CS = corticosteroids; IA = intraarticular; PDE-4i = phosphodiesterase 4 inhibitor (apremilast); IL-12/23i = interleukin-12/23 inhibitor; SI = sacroiliac; CZP = certolizumab pegol; etan. = etanercept; CSA = cyclosporin A; CD20i = CD20 inhibitor.

Live Document

Another update to the current recommendations isn’t too far off. Both Drs. Kavanaugh and Deodhar emphasize that the rapid evolution of changes in the understanding and treatment of PsA mandates the need to update these recommendations continuously.

“In such a rapidly changing field, it is good to be on the lookout for new recommendations, because even though the current recommendations are brand new, there is already new information on the short horizon that will be useful,” says Dr. Kavanaugh.

Calling the recommendations a live document, Dr. Deodhar says he hopes the recommendations will be updated on an ongoing basis to meet the rapid pace of drug discovery and new questions that arise for the clinician on how to implement these drugs.

One pressing issue already, he says, is the need to provide clinicians with guidance on how to use the recently approved biosimilars to treat PsA.

Dr. Kavanaugh acknowledges the need for continual updating to meet the ongoing challenge presented by the rapid pace of change. “The challenge is that there are newer therapies and treatment strategies that are being tested in ongoing studies, and there is a lag time between when the results are presented at an international meeting and when they are published.” He says part of the challenge is to adhere to producing evidence-based guidelines while not spending too much time and effort on a document that will be outdated soon after it is published. Given this, Dr. Kavanaugh says the next version of the recommendations should probably start soon.

Editor’s Note: Preliminary work on the next version of the recommendations has already begun as of this writing, and is anticipated to be completed in 2018. We will keep you updated in these pages.

References

The original article appeared online, on The-Rheumatologist.org and in print, in The Rheumatologist publication.
An oft-used quote at my alma mater, Meredith College, is: “From the outside looking in, you can never understand it. From the inside looking out, you can never explain it.”

This year I went to Burning Man, an arts, music, and alternative lifestyle festival in Black Rock Desert in Nevada. Upwards of 70,000 people come together every year the week leading up to Labor Day to party, play, explore, gift, create, and survive in the middle of a desert complete with dust storms, extreme temperatures, and limited access to resources. You just have to experience it.

Aside from a desire to engage in a society where clothes are optional, costumes are revered, and money is virtually outlawed; I needed an escape from my life which, in short, has never been easy. I needed a spiritual retreat.

My initiation to Black Rock City involved hugging a naked man, hitting a gong, and rolling in the dust. Immediately, I was Home.
I went to Burning Man intending to spend time at the Temple, where people leave things they need to release: prayers, tokens, fears, celebrations, memorials. There are weddings, funerals, meditations, and services; people crying and hugging and others alone in silent introspection. It seems the Temple consistently attracts a larger crowd than any other place in Black Rock City. It’s a place to take a breather from partying, to find a safe space from an overwhelming emotional experience, to celebrate or remember, or just stop and feel. As with all things Burning Man, the Temple does not stay. We cling to its temporal nature and wait for it to be set ablaze the final night, cleansing us of whatever we left there. It’s a symbol of transition and release.

At Burning Man I felt more human than I feel in my ordinary life. When people asked me what I do and I responded, “I’m disabled.” Their response was, “No, no – what do you DO?” I was caught off guard.

Aside from the physical enormity of Black Rock City and the pulsing energy I did not expect at the Temple, nothing else surprised me.

I rode a bicycle covered in an odd assortment of lights and unicorns. I peed in a plastic bottle at night. I jumped on trampolines and explored welded art installations during white-out dust storms. I blessed strangers in the middle of the night while sipping on whiskey and apple juice. I attended an Episcopal Church service at the Temple after three hours of sleep. I wrote “I love you” in sharpie on the Temple wall and I shared a picnic at Trash Fence while the sun was setting. I watched the Man burn amid raucous cheers Saturday night and I cried through the silent burning of the Temple the next night. And yes, I spent as much time as possible not wearing any clothes.

At first glance, this is an apt description of many a Burner’s experience; all that’s missing is dancing all night and perhaps some experimental drugs. But I am a minority at Burning Man. I’m disabled and sick – really sick. I won’t be dying tomorrow, but I don’t know what my health will be like next year, and the next after that. I didn’t go to party. I went to be saved and to be reborn.

In 2013, I was diagnosed with ankylosing spondylitis, a disease I inherited from my estranged father.

AS is characterized by rampant, widespread inflammation throughout the entire body. Extreme fatigue is common because the body is constantly fighting the inflammation. Movement helps decrease stiffness, yet too much movement can leave me in bed for days or weeks. I am stuck in a vicious cycle, ever trying to find a balance between movement and rest.

At best, AS is an annoyance to those of us who try our best to ignore the constant pain. At worst, AS leaves us with progressively debilitating pain and stiffness and, in extreme cases, with a hunched back fused together with knobby bone spurs. A “young person’s disease,” AS commonly begins before the age of 40, though it takes an average of a decade or more to be diagnosed. Its invisibility often leaves young, healthy-appearing people trying to explain or even hide their constant pain and fatigue, even around friends and family.

At Burning Man I felt more human than I feel in my ordinary life. When people asked me what I do and I responded, “I’m disabled.” Their response was, “No, no – what do you DO?” I was caught off guard. I was struck that my disability was not seen as a detractor from my humanity. I was reminded that I am not my disease. “What do you do?” really meant “Who are you?”
“Burning Man slowly began to heal the wounds I have sustained from a constant barrage of new symptoms, diagnoses, disability denials, and reminders that my health keeps me from being successful in the working world. For a few days in the desert I was able to celebrate the whole, complete person I am. I began to remember that I really love me.”

What’s more, when I began talking about AS, people actually listened. They didn’t try to fix me or tell me what I should do to treat it. Strangers didn’t judge me when I broke down in tears in the middle of a conversation, or rush me when I couldn’t find the words in the middle of a brain fog. It was a stark contrast to the “real world,” where I am defined by everything I cannot do or be. Burning Man slowly began to heal the wounds I have sustained from a constant barrage of new symptoms, diagnoses, disability denials, and reminders that my health keeps me from being successful in the working world. For a few days in the desert I was able to celebrate the whole, complete person I am. I began to remember that I really love me.

I didn’t partake in drugs like marijuana, acid, heroin, and other such things that have been hailed as magical to the experience of being Home at Black Rock City. Rather, I took my nightly prescription medication: a handful of pills and supplements to help me sleep and to feel slightly less pain. Everywhere I went I carried my medication and my cane. I wore a dog tag around my neck with emergency information. I gave in-case-I-don’t-make-it-out-alive instructions to one of my friends at home. Nothing was going to keep me from going to Burning Man, even though I was scared I might not come back.

I survived Burning Man. I more than survived, the burn saved me. It reminded me why I’m still alive and gave me a reason to keep living.

Unbeknownst to me, Burning Man also prepared me for the sudden death of my father. On the ride home, with the return of cell service came the news that he was very ill from complications after spine surgery. I screamed myself to exhaustion out of the car window into the darkness of the highway. I screamed in anger that I didn’t know him, that he gave me this horrible disease, and that he might die before I got a chance to have some questions answered. I didn’t know then that he was already dead. I would find out two days later he died the night the Temple burned.

Next year I’ll take him with me – some of his ashes, pictures, and the nearly-full carton of cigarettes he left behind. I’ll leave him at the Temple and I’ll watch him burn as I am reborn again, and again, and again, until there is nothing left of us both but dust.

Charis Hill is a chronic disease advocate, fashion model, and the leader of the Sacramento area SAA Sponsored Spondylitis Educational Support Group. You can read more of her writing on her blog, beingcharis.com
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