Spondylitis PLUS
Spring 2016

Spondyloarthritis: Autoimmune Or Autoinflammatory?
The New Biologic On The Block
Updated Medications Overview

My Surreal And Deeply Emotional Day - Jim’s Story

Spondylitis Association of America
Dear Readers,

There are some “new kids in town” in rheumatology. Biosimilars, as some of you may have heard, promise the potential to improve access to care, and at a lower cost. Many US rheumatologists, as well as your SAA, are cautiously optimistic about cost containment and the potential for increased access to care; however, we do believe that there is a significant need to understand the changing landscape.

In recent years, 20 biosimilar products have come to market, including the first one for spondyloarthritis, CT-P13, a monoclonal antibody, which is now available in more than 70 countries worldwide and approved in Europe in the treatment of RA and ankylosing spondylitis, psoriasis, Crohn’s disease and ulcerative colitis. While CT-P13 is not yet approved in the US, the FDA Arthritis Advisory Committee has recommended its approval. For the agency’s briefing document and information regarding the Advisory Committee meeting recommendations following a meeting held in February, 2016 please see (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM484859.pdf)

As of this writing only one biosimilar has been approved in the US, but it is not for spondyloarthritis. The FDA is moving forward as quickly as it can, however, to determine when, not if, these products will be approved for SpA.

So, what is a biosimilar and how does it differ from a replicated generic compounded drug? To explain broadly, biological products including TNF-a inhibitors are live medications that are complex to produce and unlike a compound such as an anti-inflammatory, cannot be identical in replication. Therefore, there is potentially an increased margin for error.

Time will tell as we move into new territory. It is forecasted that for patients, bringing biosimilars to market will increase affordability of treatment options and improve accessibility. Understandably, patient safety is paramount and evidence based information will be needed to inform choices. Patients should be kept informed and not transitioned without their knowledge.

Pharmacovigilance remains key to incorporating biosimilars into clinical practice which requires collection of safety data across nations to detect even the smallest safety signals.

We will keep you updated in these pages.

Laurie M. Savage  
Executive Director
“I love the Helpful Hints feature in the magazine. Years ago there was a tip to wear “slippery” pajamas to help move around in bed which was so helpful for me. I also find that smooth satin finish sheets are a big help to be able to roll over and move easily when I’ve become stiff and sore at night. I use a heating pad with my coffee in the morning and stiffness is nearly gone along with discomfort. On to exercise and the day goes well. Thanks for all the good tips in the magazine.”

~ Anne Maglisceau
Santa Fe, NM

“I received the Winter 2015 issue of Spondylitis Plus. I appreciate all of the research and information this magazine has for professionals and patients, and the priceless work of the Spondylitis Association of America; I also appreciate the doctors’ work, and updated advances... but at times this magazine just makes me want to quit. All the wonderful photos of healthy athletic people bring up feelings of inadequacies and guilt for not having achieved the same. Spondylitis is not always such a pretty disease. Fragile glass like bones and joints, bent bones, pain, exhaustion, frailties, and for some, other symptoms can make the activities depicted life altering if not lethal.

Keep up the good work of sharing research updates. I hope that in the future, you can publish more helpful advice on such issues as daily living, acupuncture for pain relief, safety issues and so on.”

~ Susie Cheek
San Diego, CA

Editor’s Note:

Dear Susie,

Your letter is something I will keep nearby as an additional reminder of the importance of keeping the balance between covering the inspirational stories and the more difficult and challenging aspects of life with SpA. We constantly strive to keep things balanced, but we can certainly do more on some of the important topics you mentioned.

As you noted, spondyloarthritis, being such a widely varied condition, affects people in different ways; some do indeed have more physical limitations than do others. Having anyone feel the way you did is by no means what we want. It is the exact opposite in fact. Please know that we understand that for many people a walk all the way around the block is equivalent to biking up a mountain for others; that every step and each minute doing something physical is a win.

Thank you for taking the time to share your thoughts.
Some physicians say that the challenge of being educated as a doctor is similar to mastering a foreign language. It’s certainly true that one’s vocabulary expands tremendously in medical school. To take the analogy a little further, languages and medical knowledge are both alive, meaning that they continuously change. I graduated from medical school in 1975. One word never mentioned was autoinflammatory. What is the distinction between autoinflammatory and autoimmune? Why is the concept of autoinflammatory relatively new? How does autoinflammatory apply to ankylosing spondylitis and related diseases?

To address these questions, I need to make each reader both a medical historian and a clinical immunologist. So be prepared for some complicated background information.

The major responsibility of the immune system is to protect you from danger such as a bacterial or viral infection. This is not a simple task. Your body plays host to trillions of bacteria. You also allow yeasts and a number of viruses to be passengers in your tissues. Your immune system must evaluate millions of signals from these microbes and decide which ones are potentially harmful and which are benign. It should not be all that surprising that there is an occasional mistake.
The major responsibility of the immune system is to protect you from danger such as a bacterial or viral infection."

An antigen is a substance that can be recognized by the immune system. In an autoimmune disease, the body’s immune system targets an antigen that is produced by your own body. “Auto”, as in auto-immune, means self. For example, in rheumatoid arthritis many experts now believe that an autoimmune response to an antigen known as CCP in your joints and elsewhere causes rheumatoid arthritis. In a number of diseases ranging from Graves’ disease to lupus to myasthenia gravis, autoantibodies are detectable. An autoantibody means that your body’s immune system has recognized an antigen that is made by your own body. Not every autoantibody results in a disease. But unless autoantibodies can be detected, the term autoimmune should not be used to describe the disease. And autoantibodies are not a typical feature of ankylosing spondylitis or related diseases like inflammatory bowel disease (such as Crohn’s disease and ulcerative colitis) or psoriasis. The immune system is clearly involved in these diseases, but it is seemingly targeting something other than one of the body’s own proteins.

"In an autoimmune disease, the body’s immune system targets an antigen that is produced by your own body. “Auto”, as in auto-immune, means self."

The technology to identify the specific cause of rare genetic diseases has progressed rapidly. In 1999 Dan Kastner, a rheumatologist at the National Institutes of Health, led a large group of scientists who studied a puzzling, rare inherited disease characterized by recurrent episodes of fever and inflammation. The group was able to show that the affected patients had an abnormality in the DNA that codes for the receptor for TNF, also known as tumor necrosis factor. TNF is the same protein that is targeted by many of the biologic drugs used to treat ankylosing spondylitis. For TNF to be active, it must be recognized by a protein known as a receptor on the surface of a cell. The inherited change in the TNF receptor caused inflammation because it resulted in TNF being overly active. In this case, the faulty receptor was like a faulty lock which left the door continually unlocked. Their discoveries were reported in the journal, Cell, and the title of the manuscript called this disease autoinflammatory. The term was apt because the body was behaving as if it were responding to a danger signal, but no autoantibodies were present. Since this report, a growing number of inherited illnesses have been called autoinflammatory because they are characterized by recurrent episodes of inflammation and the absence of autoantibodies.

The immune system has an adaptive arm and an innate arm. The adaptive arm makes the antibodies which result in a highly targeted response like a perfectly aimed guided missile. But it takes time, a week or more, to make specific antibodies. So the body also has an innate arm which can respond more rapidly but less specifically. The innate arm is able to recognize and respond to bacterial and viral products. The innate arm makes proteins like TNF to respond to this potential danger. Autoinflammatory diseases are almost always caused by mutations in proteins that have a major role in the innate immune system.

"Unless autoantibodies can be detected, the term autoimmune should not be used to describe the disease."

So what about ankylosing spondylitis, autoimmune or autoinflammatory? The current thinking is: a little bit of both, as most diseases fall somewhere along a continuum from autoimmune to autoinflammatory. In some mouse and rat models that resemble ankylosing spondylitis, the disease can be transferred from one animal to another by taking the lymphocytes [a type of white blood cell] from the diseased animal and injecting them into a healthy animal. This argues in favor of an autoimmune disease because lymphocytes make the targeted response characteristic of the adaptive immune system. HLA-B27 affects how lymphocytes function and that also argues for an autoimmune disease. But bacteria are suspected by some to cause ankylosing spondylitis and that argues for an autoinflammatory disease. As does the absence of autoantibodies. And TNF is made by many cells, but mostly by cells like macrophages that are major contributors to the innate immune system. So if blocking TNF helps ankylosing spondylitis, some argue that ankylosing spondylitis must be autoinflammatory.

I think that what most of us have been correctly saying is, “Don’t call it autoimmune.” I agree with that advice, but the subtlety is that even though it should not be called autoimmune, there can be aspects of autoimmunity contributing to it. The terms, autoimmune and autoinflammatory, have become useful concepts as a way to try to understand immune-mediated diseases. But many immune system diseases do not fit into a perfect label; most show some aspects typical of autoimmunity and some aspects of autoinflammation. The concept is proving useful as a theoretical way to understand ankylosing spondylitis and related diseases like psoriatic arthritis and reactive arthritis.

And medical knowledge has thankfully progressed a great deal since the day I graduated medical school.
One of the valuable benefits of attending a Spondylitis Educational Support Group meeting is hearing suggestions and tips from people in the room. We asked our volunteer support group leaders to send in helpful hints shared by their group members. Below is a selection of hints received.

From the Sonoma, CA support group:

- I found a blog dedicated to finding and reviewing comfortable shoes! https://www.barkingdogshoes.com. While the creator of this site has RA, she covers a variety of foot issues such as those that impact people with spondylitis. Mainly geared toward women, though there is a small section dedicated to men’s shoes.
- The “MultiFlex Adjust-A-View Safety Mirror” is a large, uniquely adjustable rear view mirror that works great for me! Find it at http://multiflexmirror.com/

From The Woodlands, TX support group:

- I use a timer to remind myself to stretch throughout the day since my job requires a lot of sitting.
- Monitoring my diet to identify foods that tend to increase joint pain and trigger migraines has been really helpful.
- Do some kind of activity every day. Walking on the treadmill for 10 minutes a day really helps me. I got a dog so I can walk around my neighborhood more. Keep active but don’t overdo it, and stay encouraged as you go.
- Heating pad prior to going to bed and prior to getting up.
- I journal about other things in my life I am thankful for when my pain gets extreme.
- I have found essentrics.com, which is a program to assist with strength and flexibility. Once on the site, click on videos, then scroll to the many workouts; there are a few helpful ones: soothe your joints and relieve your pain, etc. While I cannot do all of the positions, there are several poses which are gentler that I use. As always, you should check with your doctor before starting any exercise program. My physical therapist gave me an alternative to one of the hamstring stretches, given my issues in my lumbar spine.

From the Hollywood, FL support group:

- I back into all of my parking spaces. This way I’m able to use my big side mirrors while parking, and don’t have to turn my neck when leaving the parking space since I’m just driving out forward.
- The most helpful thing for me is to get in a heated pool. I had a physical therapist who showed me a 30 minute water stretching program; we printed and laminated the exercises and I still use them today.
- I started taking fish oil tablets for high cholesterol and after about a month and a half noticed that my pain and inflammation was reduced. Fish oil and turmeric have been shown to help reduce inflammation in RA, and I believe they work for spondylitis as well.
HELPFUL HINTS

SAA’s support groups wouldn’t exist without our dedicated volunteer group leaders. We thank each and every one of these caring and committed volunteers for their service to their communities. You’ve touched countless lives and you have our immense gratitude and respect.

From the Lansing, MI support group

- Recently I was able to convince my doctor to refer me to someone who does food allergy testing. Since that visit, I have found myself to be highly allergic to whole wheat, and also mildly allergic to peanuts and English walnuts. Since omitting caffeinated beverages, spicy, fatty foods, along with the wheat, peanuts and walnuts, I am noticing a reduction in pain, better breathing and less irritants in my throat.

From the Spokane, WA support group:

- Get a recumbent exercise bike and use it at least 3-4 days a week. I can go 5 miles now!
- Massages as often as possible and trying to keep weight off.
- Self-work such as: Working on a positive attitude and patience with yourself on the not-so-good days.
- Staying busy and keeping the mind alert. Helping others.

From the Oakland, CA support group:

- Look into Nordic Walking! This is essentially walking with two walking sticks. Adds stability, takes some pressure off sore spots, and has been great for me. http://skiwalking.com/ has good quality Nordic Walking poles.
- Keep moving and stay loose. I have an alarm set on my Fitbit that reminds me every hour to get up and walk around.
- Prioritize your time, considering pain and energy levels realistically when making plans. Don’t over commit yourself, and plan days off after things that you know you may need to recover from.

Helpful Hints is a recurring feature in Spondylitis Plus dedicated to your helpful hints, tips, and tricks on different aspects of life with spondyloarthritis.

Have a helpful hint to share with other readers? Send it in and we might publish it in our next issue. Please send your hints to Elin@spondylitis.org

Please note that SAA does not endorse or recommend any specific medications or products for SpA and always advises that you seek the counsel of a physician before initiating treatment. The opinions expressed in the Helpful Hints feature are solely those of our readers and our community.
Dietary supplements are products that contain a “dietary ingredient” intended to provide additional nutrients to complement the diet. They are also used by some to complement treatment of disease. These ingredients often include vitamins, minerals, herbs, botanicals, amino acids, and substances like enzymes, organ tissues, and metabolites. Unlike medications, manufacturers of supplements are not required to conduct research studies to prove the dietary supplements’ safety and efficacy. That puts the onus on patients, their physicians, and other healthcare providers to determine the appropriateness of complementing the diet and traditional medicinal treatments with supplements.

For people with spondyloarthritis (SpA), using dietary supplements as an adjunct to more traditional medications can be enticing. Physicians, however, urge caution when using these supplements, as some have unproven benefits and others may interact with common SpA medications, including nonsteroidal anti-inflammatories (NSAIDs), opioids, steroids, disease-modifying antirheumatic drugs (DMARDs), and biologics.

Little data are available on many of the supplements used for SpA symptom relief, including how effectively they address symptoms and whether they have adverse interactions with any of the drug families used to treat the disease. Let’s look at three supplements commonly used by those with SpA: omega-3 fatty acids, vitamin D, and turmeric.

Omega-3 fatty acids are essential for a number of bodily functions. Studies have shown that omega-3 fatty acids, found in foods such as tuna and salmon and also sold as dietary supplements, can help to reduce inflammation in people with rheumatoid arthritis, a condition related to SpA. Few studies have focused on omega-3s and SpA; however, a 2006 Swedish study found that higher doses of these fatty acids significantly decreased disease activity. About 2.6 grams of omega-3s twice a day is generally considered sufficient.

Certain omega-3s, such as cod liver oil, can interact with NSAIDs and cause bleeding problems, including gastrointestinal (GI) bleeding and difficulty forming blood clots. All NSAIDs,
including prescription drugs like celecoxib (Celebrex) and over-the-counter NSAIDs such as aspirin, can potentially damage tissue lining the gastrointestinal tract, which can lead to intestinal bleeding and hinder blood clot formation. Likewise, omega-3s can inhibit the activity of platelets, a component of blood considered the body’s “bandages” because they stop bleeding by clumping together and clotting blood vessel injuries. In addition, omega-3 fatty acids can decrease the production of fibrinogen, a protein that aids in the formation of blood clots.

“Certain omega-3s, such as cod liver oil, can interact with NSAIDs and cause bleeding problems, including gastrointestinal (GI) bleeding and difficulty forming blood clots.”

People who bruise easily, have a bleeding disorder, or take aspirin, which also functions as a blood thinner, should use omega-3s cautiously. Experts say high doses of omega-3 fatty acids can increase the risk of bleeding even in people with no history of a bleeding disorder or who are not taking other medications.

Calcium and vitamin D are important nutrients for people with SpA, as the condition can cause low bone density and brittle bones. Because the human body is designed to get vitamin D through the skin (via exposure to sunlight), few foods are a rich source of the nutrient. Some people get extra vitamin D from fortified foods, such as milk, and dietary supplements.

While vitamin D is essential for healthy bones, steroid medications, which are often used by SpA patients to treat short-term flare-ups and reduce pain and stiffness, can interfere with vitamin D metabolism. A 2011 study by the Albert Einstein College of Medicine found that people taking oral steroids are twice as likely as the general population to have a vitamin D deficiency, which, if severe enough, can lead to osteomalacia (softening of the bones), a potentially disastrous situation for SpA patients.

Another supplement that can be beneficial for SpA patients is turmeric, the main spice found in Indian curry. Turmeric has been used for thousands of years for a number of medicinal purposes. The bright yellow color of turmeric comes primarily from pigments known as curcuminoids, the most plentiful of which in turmeric is curcumin. A 2006 Arizona Health Sciences Center study found that turmeric extract blocked inflammatory pathways and prevented action by a protein that triggers swelling and pain. In addition, curcumin may inhibit Cox2, an enzyme that speeds up the activity of pro-inflammatory chemical messengers.

Like omega-3s, turmeric can increase the risk of bleeding when used with NSAIDs. Studies have found that curcumin can inhibit platelet clumping, which suggests that curcumin supplementation may increase the risk of GI bleeding in people taking anti-coagulants such as aspirin or warfarin.

“A 2011 study by the Albert Einstein College of Medicine found that people taking oral steroids are twice as likely as the general population to have a vitamin D deficiency.”

Curcumin does, however, have a positive effect when used with opioid medications. A 2015 study in the Journal of Pharmacology and Experimental Therapy discovered that curcumin prevented physical dependence on opioids. In the study, University of Illinois researchers found that relatively low doses of curcumin weakened opioid tolerance, a phenomenon that occurs over time when an individual requires greater amounts of a drug to continue to receive its desired therapeutic effect. The findings suggest that curcumin may help patients in need of opioids to stay on the drugs longer, without developing a dependence on them.

Dietary and other supplements are a growing part of healthcare in the United States. The National Institutes of Health, however, says people should not take supplements in place of medications prescribed by their physician and that they should discuss with their healthcare provider which supplements they are taking so their effectiveness and potential adverse interactions can be monitored.
Updated Spondyloarthritis Medications Overview

Tell your doctor about all your prescription and over-the-counter medications, vitamins, minerals, herbal products, and drugs prescribed by other physicians. Do not start or stop a medication without telling your doctor. This list is not intended to be exhaustive, but is intended to be used as a general guide.

### NSAID (Non-Steroidal Anti-Inflammatory Drug) Therapy

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic Name</th>
<th>Pill Dose &amp; Frequency</th>
<th>Long Acting Formulation Dose &amp; Frequency</th>
<th>Usual Dose for AS</th>
<th>Maximum Daily Dose</th>
<th>Prescription Required?</th>
<th>FDA Approval for Ankylosing Spondylitis</th>
<th>Special Circumstances for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indocin</td>
<td>Indomethacin</td>
<td>25-50 mg 3-4 x/day</td>
<td>75 mg ER 2x/day</td>
<td>75 mg ER 2x/day</td>
<td>150-200 mg</td>
<td>Yes</td>
<td>Yes</td>
<td>Continuous use may reduce spinal fusion.</td>
</tr>
<tr>
<td>Naprosyn</td>
<td>Naproxen</td>
<td>250-500mg 2x/day</td>
<td>500-750 mg 1x/day</td>
<td>500-750 mg 1x/day</td>
<td>1000 mg</td>
<td>Yes</td>
<td>Yes</td>
<td>Vimovo Monograph (esomeprazole/naproxen combo) for NSAID stomach intolerance.</td>
</tr>
<tr>
<td>Aleve</td>
<td>Naproxen</td>
<td>220 mg 2x/day</td>
<td>N/A</td>
<td>440mg 2x/day</td>
<td>880 mg</td>
<td>No</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Voltaren</td>
<td>Diclofenac</td>
<td>25,50mg 2-4/day</td>
<td>100 mg ER 1-2x/day</td>
<td>75 mg DR 2x/day</td>
<td>200 mg</td>
<td>Yes</td>
<td>Yes</td>
<td>Arthrotec © (diclofenac/misoprostol combo) for NSAID stomach intolerance. Voltaren gel cream. Pennsaid drops topically for peripheral joint pain. Continuous use may reduce spinal fusion.</td>
</tr>
<tr>
<td>Clinoril</td>
<td>Sulindac</td>
<td>150,200 mg 1-2x/day</td>
<td>N/A</td>
<td>200mg 1x/day</td>
<td>200-400 mg</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Feldene</td>
<td>Piroxicam</td>
<td>10,20 mg 1x/day</td>
<td>N/A</td>
<td>20mg 1x/day</td>
<td>20 mg</td>
<td>Yes</td>
<td>No</td>
<td>Continuous use may reduce spinal fusion.</td>
</tr>
<tr>
<td>Lodine</td>
<td>Etodolac</td>
<td>200, 300, 400, 500 mg 2x/day</td>
<td>400,500,600 mg ER 1-2x/day</td>
<td>400mg ER 2x/day</td>
<td>1000 mg</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Mobic</td>
<td>Meloxicam</td>
<td>7.5,15 mg 1x/day</td>
<td>N/A</td>
<td>15mg 1x/day</td>
<td>15 mg</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Celebrex</td>
<td>Celecoxib</td>
<td>100,200,400 mg 1-2x/day</td>
<td>N/A</td>
<td>200 mg 1x/day</td>
<td>400 mg</td>
<td>Yes</td>
<td>Yes</td>
<td>COX-2 inhibitor has less propensity for stomach ulcers. Continuous use may reduce spinal fusion.</td>
</tr>
<tr>
<td>Motrin/Advil</td>
<td>Ibuprofen</td>
<td>200,400,600,800mg 3-4x/day</td>
<td>N/A</td>
<td>600-800 mg 3x/day</td>
<td>3200 mg</td>
<td>No</td>
<td>No</td>
<td>Duexis@ (famotidine/ibuprofen combo) for NSAID stomach intolerance. Continuous use may reduce spinal fusion.</td>
</tr>
<tr>
<td>Relafen</td>
<td>Nabumetone</td>
<td>500,750 mg 1x/day</td>
<td>N/A</td>
<td>1000-1500 mg/day</td>
<td>1000-2000 mg</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
### DMARDs (Disease Modifying Anti-Rheumatic Drugs)

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic or Brand Name</th>
<th>Dose</th>
<th>Frequency</th>
<th>Total Dose for AS</th>
<th>Route of Administration</th>
<th>FDA Approval for Ankylosing Spondylitis</th>
<th>Special circumstances for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azulfidine</td>
<td>Sulfasalazine</td>
<td>500-1500 mg</td>
<td>2-3 times/day</td>
<td>2000-4000 mg/day</td>
<td>Oral</td>
<td>No. Approved for ulcerative colitis.</td>
<td>Used for peripheral arthritis in AS and related illness.</td>
</tr>
<tr>
<td>Rheumatrex</td>
<td>Methotrexate</td>
<td>7.5-25 mg</td>
<td>One or two divided doses weekly</td>
<td>25 mg weekly</td>
<td>Oral or subcutaneous injection</td>
<td>No. Approved for seronegative SpA &amp; psoriasis.</td>
<td>Used for peripheral arthritis in AS and related illness; steroid sparing drug for uveitis.</td>
</tr>
<tr>
<td>Trexall</td>
<td>Methotrexate</td>
<td>7.5-25 mg</td>
<td>One or two divided doses weekly</td>
<td>25 mg weekly</td>
<td>Oral or subcutaneous injection</td>
<td>No. Approved for seronegative SpA &amp; psoriasis.</td>
<td>Used for peripheral arthritis in AS and related illness; steroid sparing drug for uveitis.</td>
</tr>
<tr>
<td>Rosuvo</td>
<td>Methotrexate</td>
<td>7.5-25 mg</td>
<td>One or two divided doses weekly</td>
<td>25 mg weekly</td>
<td>Oral or subcutaneous injection</td>
<td>No. Approved for seronegative SpA &amp; psoriasis.</td>
<td>Used for peripheral arthritis in AS and related illness; steroid sparing drug for uveitis.</td>
</tr>
<tr>
<td>Imuran</td>
<td>Azathioprine</td>
<td>50-100 mg</td>
<td>One or two divided doses daily</td>
<td>200 mg daily</td>
<td>Oral</td>
<td>No</td>
<td>Used for peripheral arthritis in AS and related illness; used to manage colitis in SpA.</td>
</tr>
<tr>
<td>Otezla</td>
<td>Apremilast</td>
<td>10-30 mg</td>
<td>Divided doses daily</td>
<td>10-30 mg 2x/day</td>
<td>Oral</td>
<td>No. Approved for psoriasis and psoriatic arthritis.</td>
<td>Used for peripheral arthritis in AS and related illness.</td>
</tr>
</tbody>
</table>

### Biologic Medications

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Generic or Brand Name</th>
<th>Dose</th>
<th>Frequency</th>
<th>Total Dose for AS</th>
<th>Route of Administration</th>
<th>FDA Approval for Ankylosing Spondylitis</th>
<th>Special circumstances for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enbrel</td>
<td>Etanercept</td>
<td>25-50 mg</td>
<td>Once weekly</td>
<td>50 mg/week</td>
<td>Subcutaneous injection</td>
<td>Yes. Also approved for psoriatic arthritis and juvenile idiopathic arthritis.</td>
<td>Not effective in colitis associated with AS. Not as effective in iritis associated with AS. May reduce spinal fusion.</td>
</tr>
<tr>
<td>Remicade</td>
<td>Infliximab</td>
<td>3-10 mg/kg</td>
<td>Every 4-8 weeks</td>
<td>200-800 mg every 4-8 weeks</td>
<td>Intravenous infusion</td>
<td>Yes. Also approved for psoriatic arthritis.</td>
<td>Effective for AS patients with co-existing colitis and iritis. Has a mouse protein as part of drug molecule which can cause infusion reactions. May reduce spinal fusion.</td>
</tr>
<tr>
<td>Humira</td>
<td>Adalimumab</td>
<td>40 mg</td>
<td>Every 2 weeks</td>
<td>40 mg</td>
<td>Subcutaneous injection</td>
<td>Yes. Also approved for psoriatic arthritis and juvenile idiopathic arthritis.</td>
<td>Effective for AS patients with co-existing colitis and iritis. May reduce spinal fusion.</td>
</tr>
<tr>
<td>Simponi</td>
<td>Golimumab</td>
<td>50 mg</td>
<td>Every 4 weeks</td>
<td>50 mg</td>
<td>Subcutaneous injection</td>
<td>Yes. Also approved for psoriatic arthritis.</td>
<td>Effective for AS patients with co-existing colitis and iritis. May reduce spinal fusion.</td>
</tr>
<tr>
<td>Simponi Aria</td>
<td>Golimumab</td>
<td>2 mg/kg</td>
<td>Baseline, At 4 weeks, then every 8 weeks</td>
<td>50-150 mg/8 weeks</td>
<td>Intravenous infusion</td>
<td>No</td>
<td>Approved for rheumatoid arthritis.</td>
</tr>
<tr>
<td>Cimzia</td>
<td>Certolizumab pegol</td>
<td>200-400 mg</td>
<td>Every 4 weeks</td>
<td>400 mg monthly</td>
<td>Subcutaneous injection</td>
<td>Yes. Also approved for psoriatic arthritis.</td>
<td>Effective for AS patients with co-existing colitis and iritis. May have less hematological side-effects. Does not cross placental barrier. May reduce spinal fusion.</td>
</tr>
<tr>
<td>Stelara</td>
<td>Ustekinumab</td>
<td>45-90 mg</td>
<td>Baseline, At 4 weeks, then every 12 weeks</td>
<td>&lt;100 kg 45 mg, &gt;100 kg 105 mg</td>
<td>Subcutaneous injection</td>
<td>No. Approved for psoriatic arthritis.</td>
<td>Used for spinal inflammation, peripheral arthritis &amp; colitis in AS and related illness.</td>
</tr>
<tr>
<td>Cosentyx</td>
<td>Secukinumab</td>
<td>150-300 mg</td>
<td>150 mg weekly</td>
<td>150 mg weekly</td>
<td>Subcutaneous injection</td>
<td>Yes. Also approved for psoriatic arthritis.</td>
<td>Loading and maintenance dose of 300 mg if there is co-existing moderate to severe psoriasis. New onset of or flare-up of Crohn’s or colitis bears caution.</td>
</tr>
</tbody>
</table>
The New Biologic On the Block: How Is Secukinumab Different?

Editor’s Note: The first biologic medication to be approved for ankylosing spondylitis was the TNF-alpha inhibitor, Enbrel, approved in 2003. While four additional TNF-alpha (TNF-a) inhibitors have been approved for ankylosing spondylitis and other spondyloarthritis conditions since then, TNF-a inhibitors had been the sole biologic medications available for these conditions until recently. In January of this year the FDA approved a brand new kind of biologic medication for ankylosing spondylitis and psoriatic arthritis. Secukinumab (Cosentyx®) is the first spondyloarthritis medication to target Interleukin 17 (IL-17) cytokines; thus, it is an IL-17 inhibitor, rather than a TNF-a inhibitor.

{Note, Ustekinumab (Stelara), an IL-12/23 inhibitor, was approved for psoriatic arthritis in 2013.}

TNF-alpha (TNF-a), Interleukin 17 (IL-17), Interleukin 12 (IL-12), and Interleukin 23 (IL-23), all of which will be discussed below, are inflammatory cytokines (cell signaling molecules) that, as the name implies, signal to activate inflammation throughout the body, modulating or altering the immune system response. Inflammatory cytokines play an important role; however, when there is an overabundance of these, as has been described in inflammatory disease, they can cause harm to the body if left unchecked.

What makes a TNF-a blocker medication different from an IL-17 blocker medication?

The various biologic medications currently available for spondyloarthritis block the signaling of specific cytokines as a way to attempt to limit the inflammation they cause. But how do they actually work? And what makes a TNF-a blocker medication different from an IL-17 blocker medication? How exactly is Secukinumab different?

Dr. David Hallegua and Dr. Lianne Gensler explain all of this and more, helping us dig much deeper.

The Immune pathways in the pathogenesis of inflammation in AS and related diseases

By David Hallegua, MD

The genesis of the autoimmune response may occur in any part of the body where the immune system sensory cells come into contact with the environment that we are immersed in. These environmental antigens include toxins or micro-organisms in the air, micro-organisms that reside in the digestive tract or enter the body through the mouth or through the skin. When the body isn’t able to regulate, or turn off the immune system’s inflammatory response to these environmental antigens, the result is a cascade of cell activation and variable inflammatory cytokine production.
In patients predisposed to spondyloarthritis, the immune sensory cells produce cytokines IL-12 and IL-23, which lead to other cytokines such as TNF-alpha and IL-17.

IL-12 and TNF-a predominance leads to bowel inflammation, spinal inflammation, and skin psoriasis. IL-23 and IL-17 pathway activation and predominance leads to spinal inflammation and skin psoriasis, yet offers relative protection from colitis.

Thus it becomes clearer how the approved blockers of these pathways help with the various disease manifestations:

- Blockers of TNF-alpha benefit patients with AS, colitis, and psoriasis.
- Blockers of IL-12/IL-23 also benefit patients with AS, colitis, and psoriasis.
- Blockers of IL-17, such as the newly approved secukinumab, benefit AS and psoriasis, but can worsen or bring on new cases of ulcerative colitis or Crohn’s disease by amplifying the IL-12 pathway which can lead to bowel inflammation.

"When the body isn’t able to regulate, or turn off the immune system’s inflammatory response, the result is a cascade of cell activation and variable inflammatory cytokine production."

Below is an excerpt from the Q&A Session of our webinar, Troubleshooting Spondylitis: Complications and Comorbidities, with Lianne Gensler, MD. You will find the full webinar recording on our website, at http://www.spondylitis.org/Seminar

Q: “Dr. Gensler, would you mind spending a few minutes sharing what we know at this point about Secukinumab? What it is, indications, contraindications, which patients may be ideal candidates for this, etc. and anything else you think is important to touch on briefly?”

A: “Sure. Secukinumab is the first biologic agent that’s specifically been approved for ankylosing spondylitis and psoriatic arthritis. It is the first one in ankylosing spondylitis that is specific in its target to what we think is the cause of the disease or the inflammatory pathway; this is important.

With the TNF inhibitors – we sort of got lucky with those drugs. We had them approved in rheumatoid arthritis first and then tried them in AS and they happened to work. And so we’ve used them for the last, what, 13 years. With Secukinumab, it actually does not work in rheumatoid arthritis and it specifically works in ankylosing spondylitis. That’s why this is very exciting; we’re working towards targeted therapy in a very different way with this medication.

When the body isn’t able to regulate, or turn off the immune system’s inflammatory response, the result is a cascade of cell activation and variable inflammatory cytokine production.

Some people with active AS who didn’t respond to a TNF inhibitor, may respond well to Secukinumab.

The studies for this drug look good. Phase III, randomized control trials were published in the New England Journal of Medicine just in the last few months.

The studies report that 60% of AS patients had a good response, or a response adequate to get approval by the FDA. Additionally, up to a third of the patients enrolled in the trial were inadequate responders to TNF inhibitors in the past, or had contraindications to using a TNF inhibitor. This means that some people with active AS who didn’t respond to a TNF inhibitor, may respond well to Secukinumab.

So, what we know about this drug is that it is fantastic for psoriasis and, in fact, that’s where it’s had the most robust response. Where we’ve had difficulty clearing psoriasis patients in the past - this drug really does mop the floor of the psoriasis.

Where I would urge caution is that if you have active inflammatory bowel disease, this is not a good drug for you. In fact, when it was tried in Crohn’s disease people actually had no response and maybe even more disease activity. So, if you have active inflammatory bowel disease, this is not the drug I would prescribe for you.”
We found Eve's recipe for Nasi Goreng (Dutch Spiced Rice) in the 1960 City of Hope Cookbook. My wife Karin was helping her friend Bonnie sort through her mother’s things. Bonnie’s mom Barbara had passed away recently; before she died, Bonnie wanted to make sure she had the recipe to her mother’s beloved brisket. Barbara loved to prepare home cooked brisket on Friday nights for the people she cared about the most. During the final days in the hospital, Barbara told Bonnie the recipe was in a City of Hope cookbook.

Flipping through the cookbook that was obviously put together as a fundraiser, they found the recipe that Barbara had submitted. On the opposite page was the recipe from Eve.

Eve is my mother-in-Law, Karin’s mom.

Barbara and Eve didn’t know each other at the time they each submitted recipes to raise money for City of Hope Hospital. It would only be later -- 15 years later -- that their daughters would become best friends. It just shows that when you put something out into the world, you never know how far it will travel or how close to home it might stay.

When we told her about the find, Eve had no recollection of donating the recipe for the cookbook but immediately recognized the dish. When we spoke of going through Barbara’s things, she said, “I’ve been thinking about my own legacy lately.”

Eve lost her cousin this year (a painter and sculptor) who left behind an abundance of artwork - which may be what got Eve thinking about what she herself would leave behind. Eve’s legacy, like Barbara’s, and yours, and mine, will go light years beyond a recipe in a cookbook. Each remnant is just a small part of the whole.

Our legacies are immortal in the accomplishments of our children and grandchildren; the memories that live on after we are gone; the lessons we have taught through our achievements and through our failures. We all leave legacies through our daily acts; legacies that reflect aspects of our lives, our values.

For me, and for many of you, one important aspect is spondylitis. In SAA’s annual reports and website you’ll find names of people who remembered the Spondylitis Association of America in their wills or through other planned gifts. My name and Karin’s are there. This will not be our entire legacy - our children and eventual grandchildren will carry on much of what we’ve passed on to them. But like every good recipe, every ingredient makes the finished dish more savory and rich.

Please consider a planned gift to the Spondylitis Association of America. As with Eve’s recipe, you never know how far it will travel, or whom it may touch.

Contact me to hear easy ways to make a gift - legacy@spondylitis.org, (800) 777-8189, ext. 231, or let us know of your planned gift by calling, emailing or using the enclosed envelope.

P.S. Feel free to also email me for my favorite brisket recipe. You won’t be sorry!
Contesting Insurance Denials

I t happened. Your doctor filed a claim for something you both thought was necessary, and covered by your health insurance, but the company denied the claim. So what now? What recourse do you have to get the insurer to reverse its decision?

Know your rights, gather the necessary information, and appeal the denied claim. Here are five tips to help you along the way.

1) Why exactly was your claim denied?

Your insurance company is required to explain in a timely fashion why they denied your claim. They will likely do this through the standard Explanation of Benefits (EOB) form which uses a key code to explain how and why the company made the decision to deny. If the explanation on the form is not sufficient, or you are not sure you fully understand what it means, call the company to ask for clarification. The insurer is obligated to explain this in terms that make sense to you.

2) Crossing your t’s and dotting your i’s.

Sometimes the reason for a denial is human error and can be easily fixed. Read all documentation closely and keep an eye open for errors such as: an incorrect insurance ID number; wrong date of service or date of birth; a misspelled name; inaccurate diagnostic or service code; etc. If you do find an error, ask the party responsible to correct the problem. Your medical provider may need to re-submit the claim if the error was theirs.

3) Preparing for the Internal Appeal.

Review your policy to see what they should cover, understand the insurance company’s internal appeals process, and follow the steps outlined to overturn a denial. Make sure you obtain and complete all forms required to start your appeal. You might want to gather evidence to show that the service you are requesting payment for is medically necessary, and that you’ve followed the appropriate steps to secure approval. Things like referrals, past prescriptions and medical procedures, a letter from your doctor, and other relevant details from your medical history may help you argue your case. Referencing your health plan’s Clinical Policy Bulletin (CPB) for the specific service may also be a good idea. The CPB details the services and procedures the insurance company finds medically necessary, cosmetic, or experimental and unproven, and can be found on your insurance company’s website. Keep copies of any and all submitted or signed paperwork related to the claim, the denial, and your appeal. Document all phone conversations noting dates, names and titles, and important details of the conversations. You will need all of this should your internal appeal be denied.

Note, you must file your internal appeal within six months (180 days) of receiving the denial notice. If you have an urgent health situation you can simultaneously request the internal appeal and an external review.

4) What comes next? The External Review.

So you’ve submitted all documents and forms, and stated your case to your insurance company; what happens now?

The insurance company has 30 days to complete the internal appeal for a service you haven’t yet received, and 60 days for a service you’ve already received. If the insurance company denies your appeal, you can ask for an external review. The insurance company’s written denial of your appeal must tell you how to ask for this third party review, and provide the contact information of the entity that will handle your external review.

All insurance companies operating in the US must abide by these consumer protections under the Affordable Care Act. The right to information about why a claim has been denied, the right to an internal appeal, and the right to an independent/external review are guaranteed to you by law. For further details about your rights to appeal a health plan decision, and the insurance company’s obligations to you, please see https://www.healthcare.gov/appeal-insurance-company-decision/appeals/.

5) Additional help and resources.

If you’re not getting the results you need, or feel the insurance company is not meeting their obligations under the law, your state’s Insurance Commissioner’s Office can help. Insurance Commissioners advocate for consumer protections, regulate and license insurance providers, handle complaints, and enforce state insurance laws. You can find your state’s insurance commissioner through the National Association of Insurance Commissioners at: https://eapps.naic.org/cis/fileComplaintMap.do.

You can file a complaint directly with your state insurance department at: https://eapps.naic.org/cis/fileComplaintMap.do.

In addition, many states assist consumers with health insurance problems through The Center for Consumer Information and Insurance Oversight. The programs offer direct help with problems or questions about health coverage, by phone and email. You can find your state’s programs at: https://www.cms.gov/CCIIO/Resources/Consumer-Assistance-Grants.
I did not see this coming. I bubbled up with tears of joy as I left a meeting room this afternoon... Here is the story, personal and from the heart. I am in a warm place tonight.

In 1984 after about ten years of strange, intermittent, and unpredictable incidents of severe hip and heel pain, with relatively minor low back pain and stiffness, my general practitioner, Dr. Grant, sent me to the University of Minnesota for a consultation which led me to the diagnosis of Ankylosing Spondylitis. The old saying, “It was the best and worst day of my life,” is exactly how I felt. Great to finally know I was not crazy, and yet, because of my mother’s advanced condition staring me in the face, soul flattening knowing what my future held.

My entire life had me watching my mother suffer beyond anything I could truly understand. I was NOT going to end up like my mother.

About a week later I was sitting in Dr. Grant’s office, staring at a Target store sign across the street. I was waiting to discuss the self-hatched treatment plan of a strong, athletic, intelligent, and highly motivated person. My entire life had me watching my mother suffer beyond anything I could truly understand. I knew well the high stakes of this battle and vowed to cure myself with diet, exercise, and positive personal energy. I was NOT going to end up like my mother, and frankly, I knew I was not strong enough to live as she had been forced to in her 40s and 50s.

I was desperate. Dr. Grant patiently listened to my plan. Then he said these words, “You must live well and stay active no matter what.” He followed with something like, “but make no mistake, you have a severe case of an incurable disease. You’re going to have to change your occupation, your expectations, and prepare for a future that is not going to be one you would choose. You are going to need to take strong medications to treat this disease.”

I was in denial – staring out the window at the Target sign across the street thinking, “I’ll prove him wrong. I’m not a fool; I know it will be hard, but I also know that alternative and naturopathic treatment combined with my resolve will beat this thing. I will be able to fix this. My mother could have done this if she had known what I know in these modern times of the 1980s.”

Over the next few years I would follow my own treatment plan of an unyielding and fanatical approach to diet, exercise, pushing through pain, supplements, fasting and more. I would explore every healer’s theories (new and old); investigate possible causes such as bugs (I prayed it was simply Lyme disease), bacteria, food or environmental allergies, viral infections, fungus, and more. However, as I painfully learned, each great new cure I would investigate was usually a failed and repackaged theory of the past.

I got progressively worse; my pain had become constant...
and debilitating. My future began to look bleak, and my mother’s crippled posture became one I now understood more than I ever could have dreamed. I could see the “how could that happen” question being slowly and painfully answered. I was losing to this disease and it didn’t seem that anything could really touch its root or calm it down. I had seen x-rays of my scarred and narrowed hip joints, my fused SI joints, and fusing lumbar vertebra. I had been shown the glowing radioactive images of my entire spine, inflamed like a Christmas tree pelvis to neck.

It was 1988; I was back in Dr. Grant’s office staring at that same Target sign waiting for him to come in. The discussion was very frank - it was time to go to the Mayo clinic and start accepting that I was not in control, this disease was. I had started to use NSAIDs, and finally Prednisone which became my go-to drug and would remain so for 20 years. Yes, the disease was indeed in control; it had become very aggressive and progressed considerably over those last four years. I had been bedridden by pain for months on end. I could barely walk due to hip and foot pain; my spine had daggers of pain taking hold. I was in serious danger of losing my job and had already left my love of land surveying behind for a less physical job in traffic control inspection and design.

“I felt so totally cheated and defeated. I was losing everything and I so missed my old physical self. I looked at the damn Target sign and wished I had a gun.”

As I stared out the window at the Target sign Dr. Grant was talking about hip replacements and wheelchairs being in my future. How I needed to find a low stress office job; that my hours would need to be cut back and/or my work schedule would need to be more flexible. I was 30 years old. I was also advised to think ahead, and plan my finances for a move to full disability. Dr. Grant then told me that he was leaving for San Diego and that he’d refer me to a new doctor in his clinic. After we finished up he said goodbye wishing me well. We’d had a very good relationship and I think he truly cared for me beyond simply as a patient. I broke down, I felt so totally cheated and defeated. I was losing everything and I so missed my old physical self. I looked at the damn Target sign and wished I had a gun. It was the first time I had ever thought (seriously) about taking the easy way out... I was now beyond my denials and had dived right into hopelessness.

The Mayo visit in 1988 was a game changer for me. I met with a very passionate and knowledgeable rheumatologist who was able to rekindle my hope with promises of future advancements in medicine. He said they were years from release, but showed tremendous promise at a cellular level. We talked at length about strategies to keep moving and working. He warned me that I needed to stay away from narcotics, always keep moving, and learn to rest ONLY when needed. He couldn’t promise that I’d save my hip joints or avoid full fusion, but he said I could save my posture and that I was doing a great job considering how much fusion I already had. He then prescribed a disease modifying drug (Sulfasalazine) that, while taking months to take hold, eventually got me back on my feet. It was all that was available at the time short of gold salts which I refused to take.

Yoga, breath work, bicycle riding, swimming... I quit drinking, and committed to a balanced, healthy diet and lifestyle - the strategies that emerged from my years of self-treatment and my disease control delusions. I moved with a job transfer and began a relationship with a great primary care physician, whom I still see today. I was very fortunate to maintain employment in a relatively low stress, flexible, research and design, environment.

This is not to say that the next 27 years didn’t include terrible pain, frustrations, and challenges, but the road was understood. I accepted that I didn’t have control of the disease, but that I could, with help from good doctors, be a good manager of the disease. I will not be able stop it, but I can have a positive role in my long range prognosis. I’ve lost 18” of colon, I’ve been within hours of death due to infections, I’ve had surgical corrections of my feet, I’ve got aortic scarring from inflammation, I’ve had my eyes impacted, I’m fused from hip to neck including my rib cage, my neck is a mess — it sounds like busted glass rolling around in there and it barely moves enough to safely drive. In the late 1990s cancer drugs were prescribed to knock down my overactive immune system; they made me very sick and did not help.
“My reward for all my decades of hard work fighting my demons and this disease is not that I have survived and prospered, but who I have become.”

Then in 2001 I went on a biologic drug (TNF inhibitor) that changed my life; I can say without hesitation that I am a Remicade poster boy – in part I feel because I have lived well and stayed active as I waited for my miracle drug to be born.

Today, some 28 years after I had wished for a gun, I found myself sitting in that very same office looking at that very same Target sign. It’s no longer a doctor’s office, but an engineering office and I was there as a Sr. Project Manager, advising and reviewing preliminary designs for a new light rail transit line being planned and built by the Metropolitan Council.

After the meeting was finished I stayed in the room to reflect on the emotions that were bubbling up as I gazed out the window at that same Target sign from 30 years ago. I thought about Dr. Grant and those very scary first years on this journey to a now satisfied mind, and the odds of me finding myself sitting here today in that same office, nearly pain free, fulfilled, and truly happy. I did not know the precise location of this meeting until I walked into the building and easily climbed a set of steel blue stairs, stairs I had struggled mightily to climb back in 1986 with my feet screaming in pain at every gingerly taken step because I was too stubborn to take the elevator.

This was a special day I never saw coming. As I left the room, taking a last glance at the Target sign, I had tears of joy bubbling up and a soul overflowing with thanks. I am truly blessed. AS is not something I would wish on anyone, but I understood today that my reward for all my decades of hard work fighting my demons and this disease is not that I have survived and prospered, but who I have become.
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