SPARTAN
Spondyloarthritis Research and Treatment Network

SPARTAN NEWS

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JOURNAL CLUB: Critical Review Of The Literature

T Hunter, K Schroeder, D Sandoval, A Deodhar. **Persistence, Discontinuation, and Switching Patterns of Newly Initiated TNF Inhibitor Therapy in Ankylosing Spondylitis Patients in the United States.** Rheumatol Ther (2019) 6:207-215 https://doi.org/10.1007/s40744-019-0148-4

TNF inhibitor (TNFi) therapy has become a mainstay of treatment in patients with ankylosing spondylitis (AS). In this retrospective commercial claims database analysis, Hunter et al. aimed to assess treatment patterns in the 2 years following initiation of TNFi therapy. Using the IBM MarketScan Commercial Claims database, 1372 patients with diagnostic codes ICD 9 720.0 and or ICD 10 M 45.x were initiated on TNFi from January 1, 2009 to December 31, 2013. 847 males and 526 females met the inclusion criteria with mean ages of 44.3 years and 42.3 years respectively.

The first biologic for the majority of patients was adalimumab (44.6% males/43.3% females), followed by etanercept (40.4% males/41.6% females), infliximab (10.4% males/10.8% females), golimumab(4.6% males/3.8% females), and certolizumab pegol (0.0% males/0.4% females).

During the 2 year follow-up period, 33.1% of patients were persistent (in therapy greater than 90 days) on their index TNFi, 40.7% discontinued their index TNFi and did not restart a TNFi (at least a 90 day gap in therapy) , and 26.1% switched to a second TNFi. Patients prescribed cDMARDs were more likely to be persistent on their initial TNFi; while females and opioid users were less likely to be persistent on their first TNFi. 32.8% of males and 43.6% of females switched to a second TNFi. Females and non-opioid analgesic users were more likely to switch to a second TNFi.

This study suggests that approximately 67% of male AS patients and 77% of female AS patients newly initiating a TNFi do not remain on their initial therapy after 2 years . This decreased persistence of TNFi therapy in AS (66.9%) is consistent with a prior 3 year study of US veterans with AS which reported 25 % persistence at 3 years(Bekele et. al) and Walsh et. Al in which 59.4% of AS patients that discontinued their index TNFi within 12 months and 21.4% switched to a second TNFi.

Limitations to the study may be attributable to the differences in follow-up period or reflect differences in the patient populations in the IBM Marketscan database, the lack of over-the-counter medication data (such as NSAIDs) and lack of reasons for discontinuation from a Commerical Claims database analysis.

- Elizabeth Chang, MD

S Tan, A Dasgupta, J A Flynn, M A Ward. **Aortic-Vertebral Interaction in Ankylosing Spondylitis: Syndesmophyte Development at the Juxta-Aortic Vertebral Rim**. Ann Rheum Dis (2019 78:922-928

Michael Ward and colleagues at the NIH performed a brilliant study examining the hypothesis that syndesmophyte growth (and perhaps, by extrapolation, other abnormal bone growth) in AS subjects may be affected by factors other than local inflammation. Multiple studies support this hypothesis as a principle to be examined - clinical studies that show bone growth in AS patients related to overall mechanical stress, animal studies revealing unloading of limbs reducing bone growth in spite of inflammation - and finally his own studies showing that syndesmophytes are more likely to develop in the spine where mechanical stress is most evident such as the posterior vertebral rim. Finally, the suggestion is made by Dr. Ward that the relationships between vertebral osteitis with fat metaplasia and subsequent bone formation based on MRI longitudinal observations has only modest sensitivity and specificity. Thus, Ward and colleagues hypothesized that the anatomic proximity of the aorta to the vertebral rims at different locations along the spine would influence syndesmophyte growth in AS much as it has been observed to be the case in diffuse skeletal hyperostosis (DISH) where it has been assumed that aortic pulsations have inhibited bone growth on the side next to the aorta.
The group at the NIH examined thoracolumbar CT scans in 60 subjects along with 22 additional subjects that provided data on the mid-thoracic spine. It appears that all data was utilized from patients who had syndesmophytes on CT in the neighborhood of the aorta in at least one intervertebral segment, and each segment was considered a unit of analysis. The aortic syndesmophyte association was measured in multiple ways including the positions along the rim of the vertebrae, the distance to the aorta, and the disc level. Using very complicated (at least for me) statistics, they showed quite convincingly in multiple types of analyses that the height and frequency varied with the distance to the aorta around the rim of the disc in the 180-degree range of each vertebral body, and that if the aorta-vertebral distance was miniscule, there were no syndesmophytes. This relationship occurred at each level examined.
Dr. Ward notes that his findings are similar to what is observed in DISH where paravertebral ossification in DISH develops largely contralateral to the aorta. Here is where the interpretations comparing AS to DISH get a little murky. Exactly how does the inhibition of bone growth take place in each environment? One assumes that a type of mechano-transduction takes place at a molecular level, possibly related to the HLA-B27 status of the subject. Although not discussed in Dr. Ward's paper, there have been conflicting studies looking at the status of DISH incidence or severity related to B27 positivity. Further, Dr. Ward's studies do demonstrate vertebral "flattening" at the thoracolumbar junction where the aorta comes very close to the vertebral bodies, exerting a possible direct effect of aortic pulsations on bone growth inhibition. But, is the relationship here straightforward or is it complicated? Dr. Ward likes complicated, and he points out in the discussion that forces of different nature could either promote or inhibit syndesmophyte growth. Forces within the skeletal system, compared to forces from without, may have different effects. What about the dramatic heterotopic bone formation that occurs in critically immobilized ICU patients? Dr. Ward suggests that extrinsic forces on bone (such as from the aorta) are different from forces generated within the musculoskeletal system such as, for example, normal exercise. Finally, Dr.

Ward's astute analysis suggests to this reviewer that there may be conflicting pathways of bone formation in AS patients and this may explain why it has been difficult to show concordance between syndesmophyte growth and vertebral inflammation on MRI. We have much more to learn and Dr. Ward has done a great service in pointing this out.

- Michael Weisman, MD

Rheumatology and Spondylitis Organizations Release Updated Treatment Guideline for Axial Spondyloarthritis

On August 22, 2019, the American College of Rheumatology (ACR), in partnership with the Spondylitis Association of America (SAA) and the Spondyloarthritis Research and Treatment Network (SPARTAN), released the 2019 Update of the Recommendations for the Treatment of Ankylosing Spondylitis (AS) and Nonradiographic Axial Spondyloarthritis (nr-axSpA). The guideline includes 86 recommendations that provide updated and new guidance for the management of patients with AS and nr-axSpA in the areas of pharmacologic and non-pharmacologic treatment options; AS-related comorbidities; and disease activity assessment, imaging, and screening.

"These guidelines update those from four years ago by consolidating the expert thought around the use of the newest therapeutic agents and modifying a number of recommendations from the 2015 guideline to reflect recent evidence. They provide patients and the medical community with clear recommendations for spondyloarthritis management using a rigorous approach, and SPARTAN is proud to endorse them," said Dr. Liron Caplan, chair of SPARTAN.

"SAA is proud to be a co-sponsor of these updated guidelines. SAA is committed to expanding treatment options and ensuring that both spondyloarthritis patients and the medical practitioners that are entrusted with their care have the best resources to aid in their decision-making," said Cassie Shafer, chief executive officer of the SAA.

Axial SpA, which is comprised of AS and nr-axSpA, is the main form of chronic inflammatory arthritis affecting the axial skeleton. This condition is characterized by back and hip pain, peripheral joint pain, and fatigue, all of which can vary in severity. According to the SAA, as much as 1 percent of the adult US population may have axial SpA. This means that as many as 2.7 million adults may be affected by the disease.

The ACR's previous guideline, published in 2015, provided recommendations for pharmacological treatments, management of selected comorbidities, disease monitoring, and preventive care. The 2019 update

builds on these recommendations by adding information on new medications, managing biologic and biosimilars usage in patients, and best practices for utilizing imaging (MRI and radiographs).

"Based on the literature, we felt it was important to address topics such as sequencing biologics for patients with active AS despite NSAID usage, whether to taper or discontinue biologics in the setting of remission, and clearer guidelines on when to obtain images - particularly in instances when results would likely lead to a change in treatment," said Michael Ward, MD, MPH, researcher at the National Institute of Arthritis and Musculoskeletal and Skin Diseases and principal investigator of the guideline. "We hope this new information will help get patients on an effective treatment faster and ultimately improve patients' health status and quality of life."

To update the guideline, a team of experts conducted a systematic literature review for 20 clinical questions on pharmacological treatment addressed in the 2015 guidelines along with 26 new questions on pharmacological treatment, treat-to-target strategy, and the use of imaging. The results of this review were then discussed by a separate voting panel and crafted into recommendations that were labeled conditional or strong based on the evidence available. A few of the recommendations from the guideline include:

- A strong recommendation to treat adults with active AS despite treatment with NSAIDs with a TNFi (no preferred choice) over no treatment with a TNFi.
- A conditional recommendation to treat with a TNFi over treatment with secukinumab, ixekizumab or tofacitinib, and a conditional recommendation to treat with seukinumab or ixekizumab over tofacitinib.
- A strong recommendation to continue treatment with the originator biologic over mandated switching to its biosimilar for adults with stable AS.
- A conditional recommendation against obtaining repeat spine radiographs at a scheduled interval as a standard approach for adults with active or stable nr-axSpA on any treatment.

ACR guidelines are currently developed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology, which creates rigorous standards for judging the quality of the literature available and assigns strengths to the recommendations. Due to limited data in some areas, the quality of evidence was most often low, very low or occasionally moderate. This led to nearly all recommendations being conditional, with only a few strong recommendations in cases in which there was sufficient evidence.

The updated and expanded recommendations, supporting PICO questions and evidence report are available on the ACR website.

Critical Review from SPARTAN Annual Meeting:
Low radiation CT and advances in MRI for detection of lesions in axSpA

Dr. Robert Lambert's review of low dose CT (LD-CT) and MRI in axSpA was a highlight of the meeting. In summary, low dose CT (LD-CT) is excellent for evaluating bony changes in the sacroiliac (SI) joints. The radiation risk of 0.42 mSv is minimal. (For reference, a standard abdomen and pelvic CT is 10 mSv and a chest radiograph is 0.1 mSv). LD-CT demonstrates subtle bony changes better than radiographs and may also be used to resolve equivocal bony findings on MRI T1. The role of LD-CT in the spine may be more limited. LD-CT of the spine is better than radiographs for detecting progression of bony changes, particularly in the thoracic spine, but the radiation dose (~4 mSv) is higher than LD-CT of SI joints. LD-CT has also been studied for quantifying syndesmophyte circumferential height, but this application is currently limited to research because interpretation is time-consuming and the radiation dose is higher (~8 mSv). For evaluating inflammatory lesions in the SI joints, dual energy CT was not shown to be useful (unable to distinguish bone marrow edema from healthy red bone marrow). Dr. Lambert concluded that LD-CT of the SI joints is under-utilized, and LD-CT of the spine is a powerful research tool that may be clinically useful for addressing specific questions in individual patients.

Several MRI techniques have been evaluated in axSpA. For detecting inflammatory lesions, multiple water-sensitive sequences are effective; Short Tau Inversion Recovery (STIR) and T2 spin echo with spectral presaturation for fat (T2FS) are probably the best. Other water-sensitive sequences studied in axSpA include T1FS with gadolinium enhancement (T1FS+Gd), Dixon T2, and diffusion weighted imaging (DWI). T1FS+Gd is advantageous for detecting enthesitis, capsulitis, and synovitis, but T1FS+Gd was inferior to T2FS and STIR (less sensitive) for detecting bone marrow edema. Dixon T2 involves a post-acquisition deconvolution of fat and water components and is theoretically attractive since T1 sequences may not be necessary. However, the 'water only' images were no better than STIR/ T2FS and the other T2 sequences were not useful in axSpA. DWI did not perform better than STIR for identifying SI joint inflammation and variance in MRI systems/interpretations are a concern. For detecting SI joint erosions, a T1 sequence with fat suppression or water excitation (similar to fat suppression) "is the way to go." These T1 sequence options may include 3D volumetric breath-hold sequence (VIBE), Dixon T1, or spin echo T1.

This scientific session was received with much interest from an audience eager for better alternatives to our current imaging options of SI joint radiographs (difficult to interpret) and MRIs (expensive and potentially over-sensitive). The excellent visualization of structural changes and minimal risk of LD-CT raised the question of whether LD-CT should replace SI joint radiographs in axSpA. The conclusion was that LD-CT is a better alternative to SI joint radiographs, but cost remains uncertain and availability is currently limited. LD-CT of the spine offers an exciting alternative for quantifying structural progression in research, particularly in the thoracic spine, but radiation risk and costs are expected to limit its use in clinical practice. Multiple new MRI techniques are effective in evaluating axSpA, but none have been shown to surpass the standard STIR/T2FS and T1FS sequences.

- Jessica Walsh, MD

IGAS Meeting report

Alternating with the biannual Spondylo Conference in Gent, Belgium, the IGAS Meeting has become a premier venue for the scientific exchange between basic and translational researchers in the SpA field. This year's meeting was held in Versailles, France, from September 12 to 14. The Waldorf Astoria Trianon Palace, the hotel where the Treaty of Versailles was drafted in 1919, served as conference venue, and Versailles with the legendary palace of Sun King Louis 14th provided a stylish backdrop for a fantastic meeting.

Two and a half days of dense programming included sessions on various aspects of SpA pathogenesis. It would be impossible to comprehensively cover everything that was presented or discussed. A few (admittedly subjective) meeting notes:

- Not surprisingly, HLA-B27 played a role in several sessions. No new hypotheses to explain the association between HLA-B27 and SpA were put forth. But the time might be ripe for a fresh look at the peptide hypothesis and CD8+ T cells as disease initiators. One of the major arguments against a role of these cells has been the finding that HLA-B27 transgenic rats (reviewed by Joel Taurog, Dallas) develop disease in the absence of CD8+ T cells. However, several lines of evidence support a potential role of CD8+ T cells in humans. For instance, Robert Inman, Toronto, presented mass cytometry data which identified an expanded unique population of αEß7 integrin expressing CD8+ T cells in joints of patients with AS. Aimee Hanson, Brisbane, presented TCR ß chain sequencing data showing evidence for expanded clonotypes in AS. Interestingly, some of these sequences had previously been identified by other groups suggesting antigen-driven clonal expansion of CD8+ T cells with shared specificity between AS patients. Have the transgenic rats been leading us in the wrong direction?
- Matt Brown, newly appointed Director of the National Institute for Health Research (NIHR) Biomedical Research Centre in London, reviewed GWAS data. Nothing new to report. As the power of GWAS relies on large numbers, Matt Brown's group is working on pooling a variety of data sets. However, compatibility and quality control issues pose significant challenges. Since most recent GWAS meta-analysis from 2016, the number disease-associated loci has been 115 explaining 28% of the genetic variance of AS.
- Dirk Elewaut, Gent, presented a recently published study on the role of mechanical stress in mouse arthritis. His group had previously published that tail suspension, which mechanically unloads the hindlimbs, reduced experimental arthritis severity in mice. They now showed, using the reciprocal and more physiological approach, that voluntary treadmill running aggravated experimental arthritis. This was shown to depend on secretion of the chemokine CCL2 by mesenchymal cells. A provocative study: Is exercise bad for patients with SpA?
- Bob Colbert, NIH, reported interesting experiments with osteoblast progenitors generated by reprogramming pluripotent stem cells isolated from the skin. Progenitor cells from AS patients demonstrated increased osteogenic potential in vitro compared with cells from controls. These results are consistent with and go beyond findings recently published by another group that analyzed bone-derived cells from the spine. Bon Colbert's data suggest that patients with AS may have a genetic predisposition not just to inflammation but also to pathological new bone formation. Overproduction of IL-1a by mesenchymal cells seems to explain at least some of the observed phenotype. Additional mechanistic

studies are ongoing.

- Several talks discussed potential new treatment targets. Paul Bowness, Oxford, is currently conducting a small randomized trial of the anti-GM-CSF antibody Namilumab. This study is based on published data from his group showing an expansion of GM-CSF producing T cells in SpA patients. Enrollment for the trial (42 patients with axial SpA randomized 6:1 to Namilumab vs. Placebo) has been completed, so we can expect results early next year. Other potential treatment targets include inhibitors of RORγt, the transcription factor controlling the development of Th17 cells and other innate-like lymphocytes with potential role in SpA pathogenesis. Mauricio Pacifici, Philadelphia, discussed the pathogenesis and treatment of Fibrodysplasia Ossificans Progressiva (FOP), a devastating monogenetic disease characterized by widespread heterotopic ossification. He made a passionate plea to try Palovarotene, a highly selective retinoic acid receptor gamma agonist with promising results in clinical trials in FOP, in animal models of AS. Open for discussion: Is there a need for inhibitors of new bone formation in AS or is inhibition of inflammation all that is needed to prevent spinal ankylosis?

While IGAS (International Genetics of Ankylosing Spondylitis) started out as a consortium for genetic studies in AS, the IGAS acronym in 2019 might just as well stand for ImmunoGenetics of Axial Spondyloarthritis. Much remains to be learned about the pathogenesis of this disease. The IGAS meeting in Versailles also highlighted the fact that the number of basic and translational researchers working in the SpA field is quite small. To grow this community and accelerate scientific progress will require nurturing junior research talents as well as recruiting established researchers from outside the SpA field. SPARTAN should continue expanding its research grant program. I suggest to include a travel stipend program so that junior SPARTAN researchers can mingle with the leaders in the field at future Spondylo and IGAS meetings.

- Joerg Ermann, MD

ACR September 10 - 13

We've summarized the SpA related ACR programming for your convenience.

Read more here >> SpA sessions
Here is the full schedule

UPCOMING SPONDYLOARTHRITIS EVENTS

SPARTAN–GRAPPA Symposium
October 5, 2019
Troy, Michigan
registration

ACR
November 8–13, 2019
Atlanta, Georgia

CLASSIC Study Investigators Meeting

November 10, 2019
Atlanta

SPARTAN-GRAPPA-ASAS Symposium
November 13, 2019
Omni Hotel | Atlanta
registration

SPARTAN Board Meeting
January 16, 2020
Houston

Annual ASAS Workshop
January 17-18, 2020
Houston

SPARTAN-GRAPPA Symposium
February 2, 2020
Los Angeles

April 4, 2020
Cleveland

April 18, 2020
Chicago

SPARTAN Trainee Symposium
May 14, 2020
Madison

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