Spondyloarthropathy: A critical management analysis

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Abstract
Spondyloarthropathy, a group of overlapping disorders of chronic inflammatory diseases of autoimmune nature has undergone critical changes in its management, specially with introduction of newer biologics and targeted synthetic DMARDs. Secukinumab and Tofacitinib are newer additions to proper management targeting various cytokines. Cost being an important factor in developing world, conventional synthetic DMARDs are being advocated to be used in situations where patient can not afford the treatment with biologics / small molecules i.e. JAK Inhibitors. It is heartening to know that methotrexate can achieve 20% remission in psoriatic arthritis almost equivalent to some biologics. Drug antibody is also a challenging problem in management with biologics.

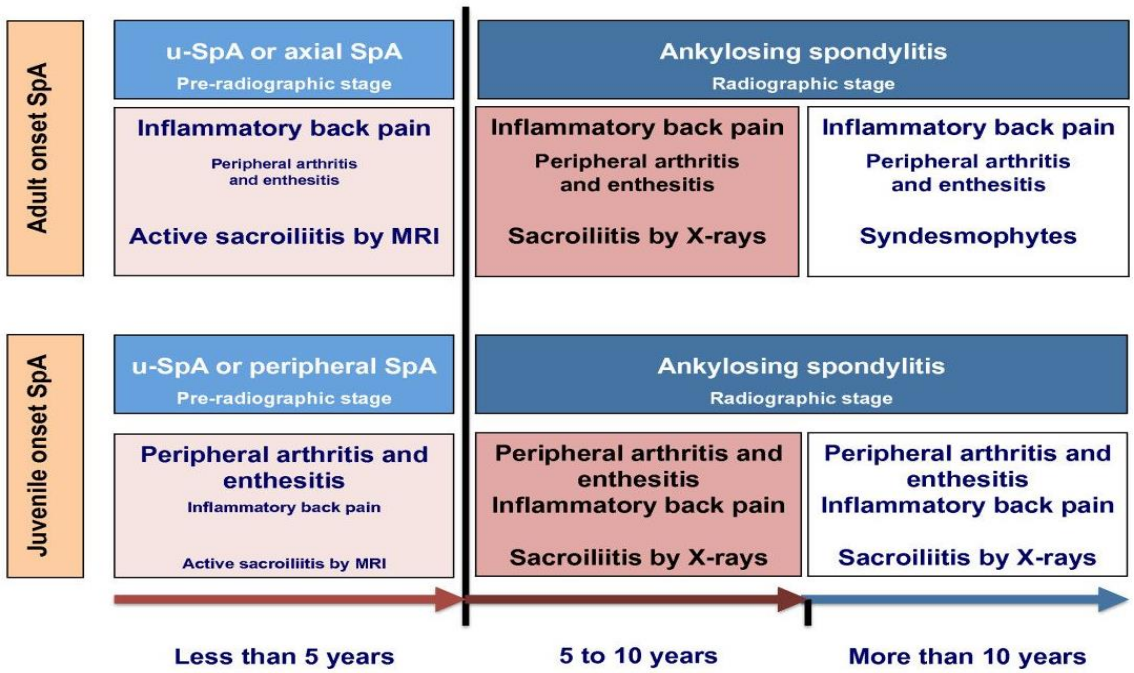
Keywords: Biologic, DMARDs, Secukinumab, Tofacitinib, JAK Inhibitors, Cost.

Introduction
Spondyloarthropathy cannotes sero-negative spondyloarthropathy implying absence of rheumatoid factor. SpA is a group of overlapping disorders of chronic inflammatory diseases of autoimmune nature sharing certain clinical features and common genetic associations with HLA-B27.[1]

Broadly it is grouped as axial spondyloarthropathy and peripheral arthropathy.

Among axial-spondyloarthropathy, initially it presents as non-radiographic spondyloarthropathy (nr-axSpA) which finally progresses to ankylosing spondylitis in a span of five to ten years, whereas in some cases it might continue to remain non-radiographic SpA. This progression is evident overtime in the following tables in adult onset and juvenile onset:-

SpA: Progression of SpA overtime 2



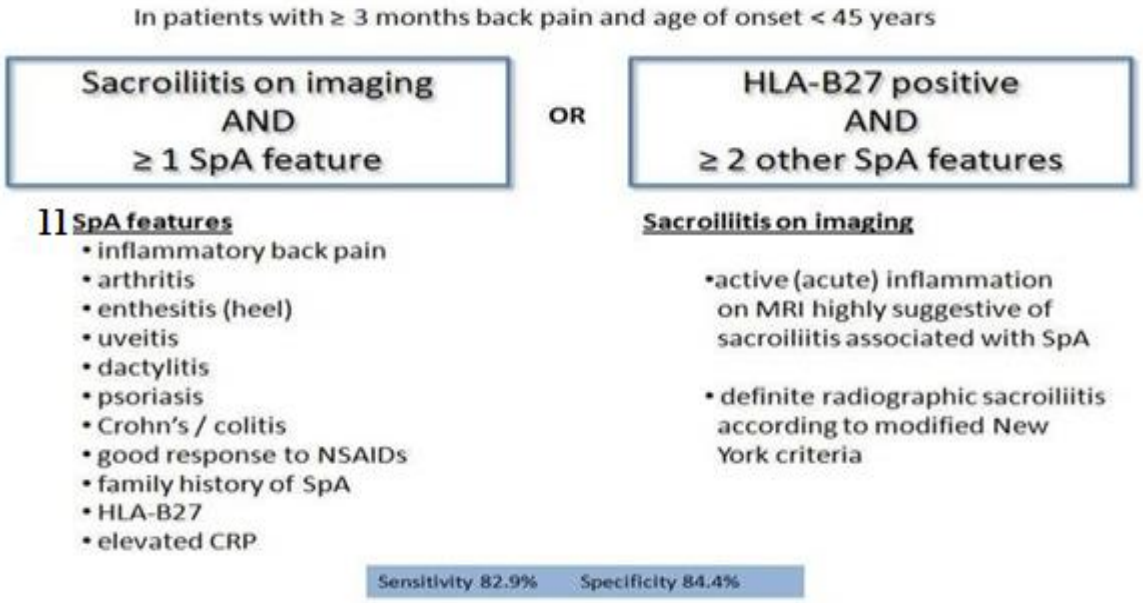
Transition of AxSpA into as? When
Evolution of the disease process from AxSpA into ankylosing spondylitis is marked only when ankylosis

typical of ankylosing spondylitis appears over a period of more than ten years.

The peripheral spondyloarthropathy (A certain pattern of peripheral joint involvement, usually asymmetric monoarthritis or oligoarthritis affecting major joints of lower extremities) encompasses psoriatic arthropathy, associated with inflammatory bowel disorder (i.e. Crohn's disease and ulcerative colitis), associated with anterior uveitis, reactive arthritis (Reiter's Disease). Sometimes to start with, it can not be differentiated into a particular pattern and hence, is called undifferentiated spondyloarthritis. Similar presentation in children is aptly coined as juvenile spondyloarthropathy. Enthesitis and dactylitis are commonly associated extra-articular manifestations in this group, apart from axial involvement.

In patients younger than 45 years presenting with ≥ 3 months of back pain ASAS criteria classifies them for diagnosis of SpA. Patient has to be submitted for MRI of sacroiliac joint. Active (acute) inflammation therein suggesting presence of sacroiliits or presence of a definite radiographic sacroiliitis showing one or more of the eleven SpA features is diagnostic of SpA. Conversely, in presence of HLA-B27 positive, two or more SpA features out of the eleven are also diagnostic of SpA.[3]

ASAS criteria for axSpA



The following modified New York criteria for classification of ankylosing spondylitis has been replaced with the above ASAS criteria.

Modified New York Criteria for classification of Ankylosing Spondylitis[4]

Clinical

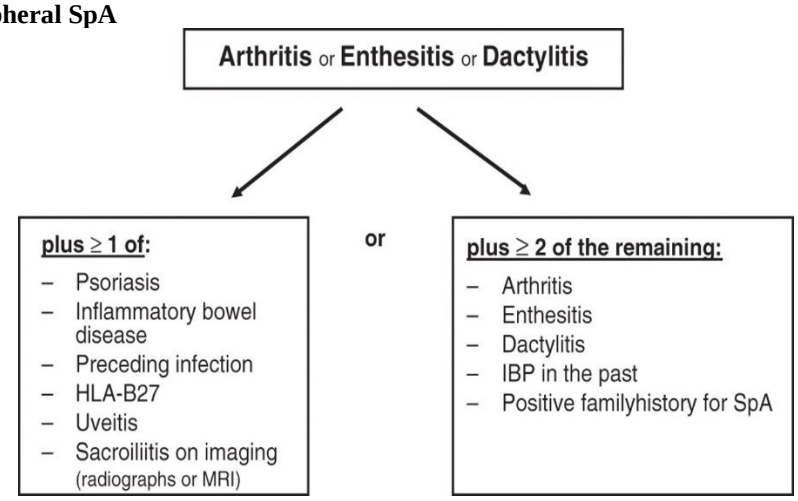
Low back pain and stiffness for more than 3 months that improves with exercise but is not relieved by rest.
Limitation of motion of the lumbar spine in the sagittal and frontal planes.
Limitation of chest expansion to 2.5 cm (1 inch) or less, measured at the level of the fourth intercostal space.

Radiographic

Sacroiliitis: Unilateral grade 3 (sclerosis and erosions of the joint margins) or grade 4 (fusion across the joint).
Bilateral grade 2 (sclerosis of joint margins) to 4.

Definite ankylosing spondylitis: unilateral grade 3 or 4, or bilateral grade 2 to 4 sacroiliitis and any of the clinical criterion.

ASAS criteria for Peripheral SpA



MRI for diagnosis of SpA

The introduction of MRI of the sacroiliac joints (SIJs) has led to a major shift in recognition of the disorder. MRI detects the initial inflammatory processes, in particular osteitis depicted by bone marrow oedema, even in patients who have not yet developed structural lesions. Interpretation of MRI lesions in daily practice depends on the clinical context

Characteristic lesions in Spine and SIJs depicted by MRI[5]

Inflammatory changes	Structural changes
SIJs	
Sacroiliitis—bone marrow edema/osteitis in one or both part of the sacroiliac joint (iliac or sacral)	Subchondral sclerosis
Synovitis	Erosions
Capsulitis	Backfill/subchondral fat metaplasia Bony bridges
Enthesitis	Ankylosis
Spine	
Anterior/posterior spondylitis—bone marrow edema/osteitis mainly in the vertebral corners	Fat metaplasia
Spondylodiscitis	Erosions
Arthritis of costovertebral joints	Syndesmophytes
Facet joints arthritis	Ankylosis
Enthesitis of spinal ligaments	

Treatment options of SpA including biologics

Treatment aims at potential deceleration of the disease process resulting into control symptoms and inflammation thereby maintaining health-related quality of life. Prevention and arrest of structural progression should ultimately result into remission or low-disease activity.

NSAIDs

NSAIDs constitute first-line therapy for active ankylosing spondylitis (AS). Continuous use of NSAIDs (2 NSAIDs for 3 months) is generally accepted but its continued use is controversial because of the apprehension of its unwarranted end organ complications[6]. Hence, in stable disease, on-demand NSAIDs is to be preferred.

NSAIDs have shown satisfactory evidence of symptom control and functional improvement but there are only some evidences in favour of achieving slower radiographic progression on continuous use.

Biologics

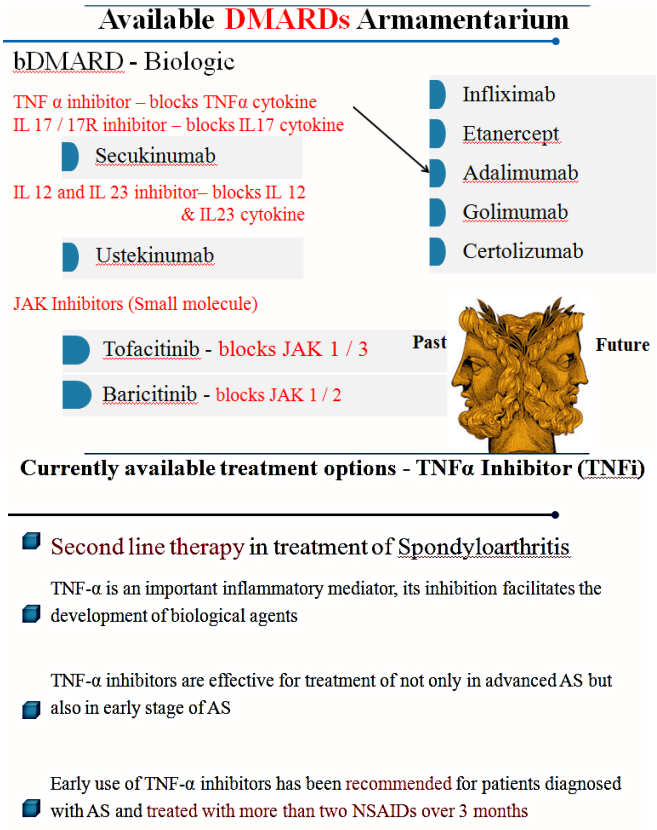
Introduction of biologics have revolutionized the management of spondyloarthropathy. This armamentarium has considerable expansion of ability to control the disease by specifically targeting the immune system. It considerably avoids other end organ toxicity. It provides satisfactory evidence based symptom control and functional improvement. There is growing body of evidence regarding

slowing or stopping radiographic progression on its long-term use.

The available biologic armamentarium[7]

a. Targeting TNFα cytokine-Infliximab, Etanercept, Adalimumab, Golimumab and Certolizumab.
b. Targeting IL 17 cytokine- Secukinumab
c. Targeting IL 12 and IL 23 cytokine- Ustekinumab
d. JAK1 inhibitors-

Targeting JAK1 and JAK 3– Tofacitinib
Targeting JAK1 and JAK 2– Baricitinib
Targeting PDE4 – Apremilast



Secukinumab: Clinical considerations

Secukinumab is a fully human anti-interleuking IL-17A monoclonal antibody. It shows sustained improvements in signs and symptoms of ankylosing spondylitis with a low rate of structural radiographic progression. It has sustained efficacy through a total 3 years of treatment. Sings and symptoms of AS (assessed by ASAS20) gets lower at week 6 and is sustained at week 28 through 2 years along with decreased inflammation as assessed by MRI.[8,9]

Targeted synthetic DMARD (tsDMARD)

These oral small Molecule-JAK inhibitors are chemically more related to traditional methotrexate than to biological DMARD. They act like biological DMARDs in their mode of action of suppression of cytokines. It targets multiple cytokines and inhibit intracellular signaling of cytokines and growth factors, whereas TNFα inhibitors target a single cytokine and work within extra cellular space targeting cell surface receptors. These small molecules also target increased biologic disease activity across multiple pathways. Their onset of response occurs within two weeks and efficacy is maintained up to five years.

Heralding the transition to new era of treatment with small molecule, first JAK inhibitor, Tofacitinib has been approved by USA FDA since November 2012 and is recommended for use in spondyloarthropathy.

Candidates of spondyloarthropathy requiring biologic treatment[10-11]

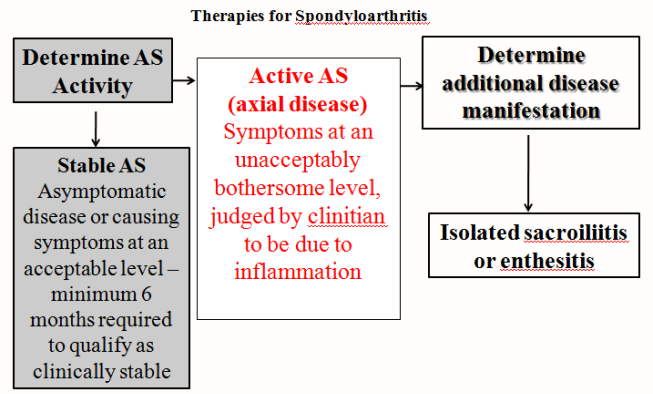
1. Patients for whom conventional therapy with non-steroidal anti-inflammatory drugs (NSAIDs) has failed.
2. When two different NSAIDs aren't much effective and helping the patient.
3. NSAIDs causing GI problems or other medical conditions and patients still have high pain and stiffness.
4. Disease having a big impact on patient's life or might be affecting work, family life etc.
5. Non Responder / Failure of 1st line csDMARDs in peripheral SpA.

2019 ACR Recommendation[12]

Biological Therapies for Spondyloarthritis

From time-to-time recommendations for biological therapies have been changing but the most current ACR recommendations have finally come to a conclusive set of recommendations.

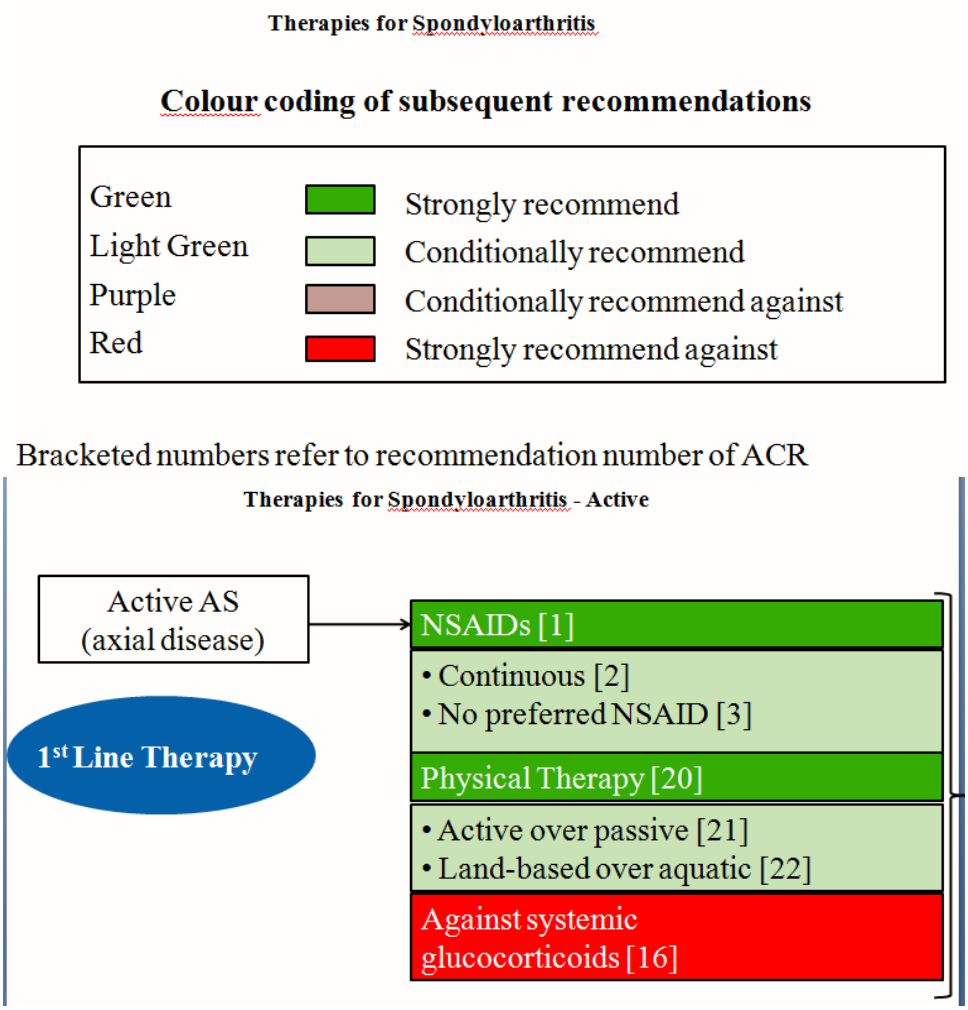
As a first step, the disease activity is to be assessed whether the axial disease is active AS or stable AS. The active disease is further looked for additional disease manifestations and presence of isolated sacroiliitis or enthesisits is taken note off.

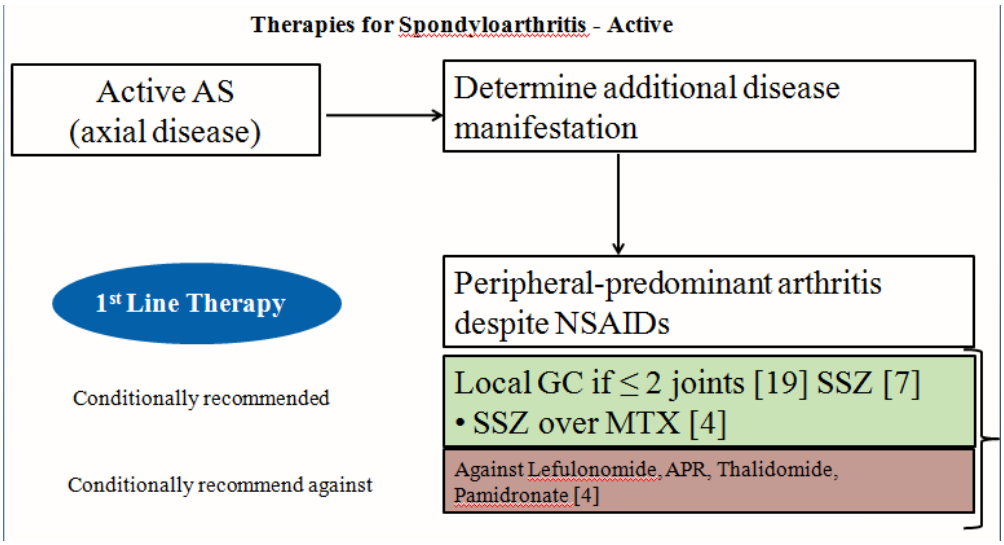


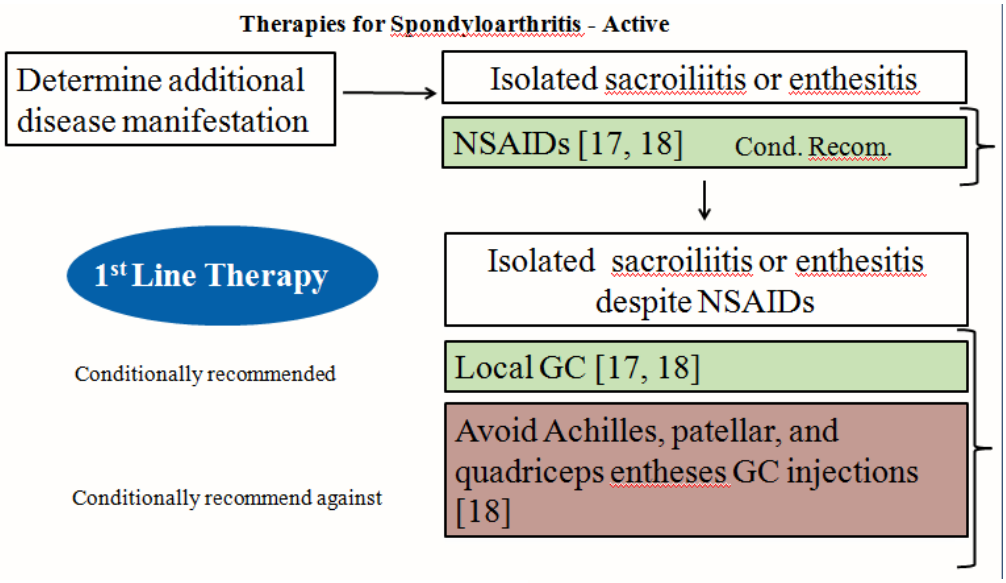
The recommendation for active AS has been put forward into three lines of therapy as under:-

First line of therapy are NSAIDs. In peripheral SpA not improving on NSAIDs, local infilteration of glucocorticoid is conditionally recommended if upto two joints are involved and additionally sulfasalazine is preferred over methotrexate. Leflunomide, Apremilast, Thalidomide and Pamidronate are conditionally recommended against their

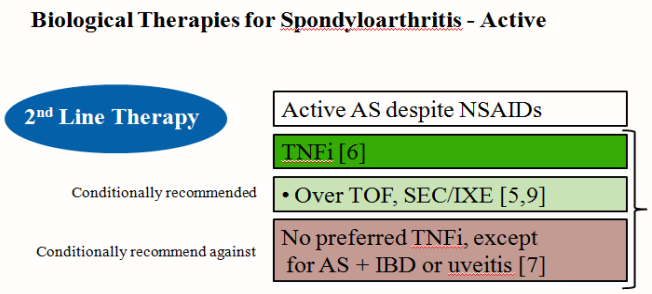
use. There are strong recommendations against use of systemic glucocorticoids. For isolated sacroiliitis or enthesitis, local glucocorticoid injection is conditionally recommended (avoid glucocorticoid injection at achilles, patellar, and quadriceps entheses) but conditional recommendation against use of glucocorticoid parenteral injection is there.

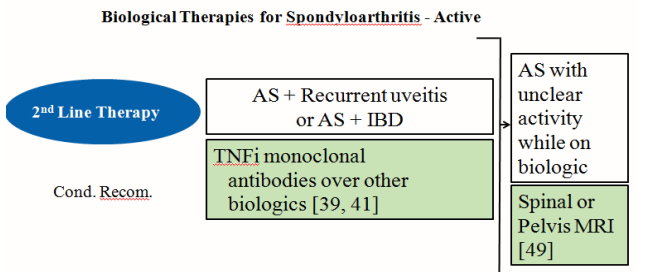


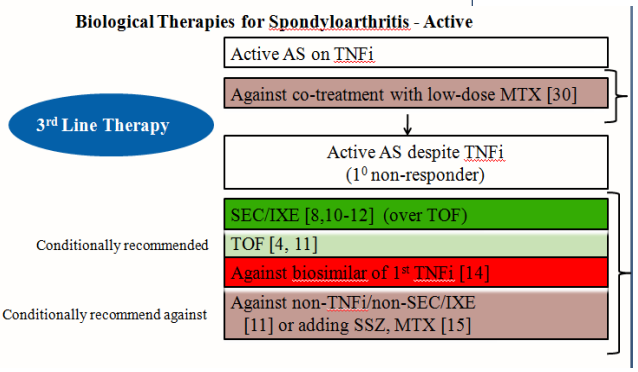


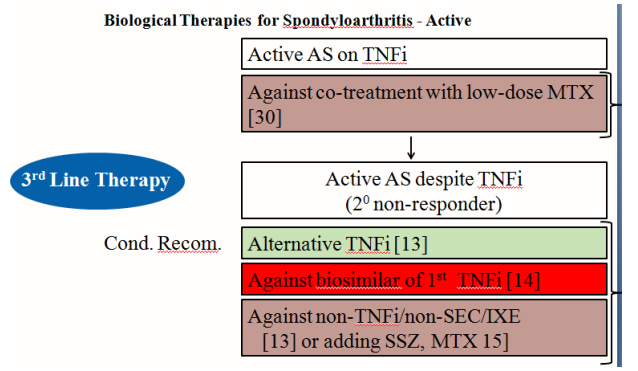


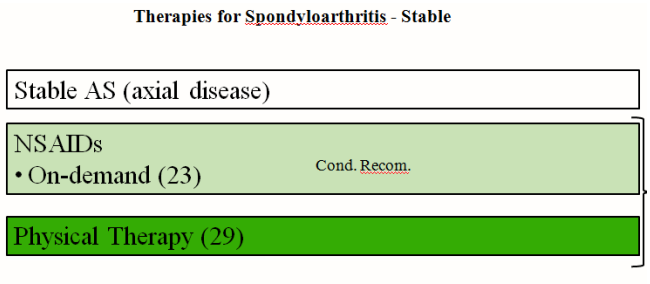
Second line of therapy is exclusively TNFα inhibitors. Conditionally recommended biologic is Secukinumab over Tofacitinib. In case of AS with IBD or uveitis, the conditionally recommended biologic is monoclonal TNFα inhibitor. Spinal or pelvic MRI is recommended if AS is present with unclear activity on biologic.











Third line therapy has conditional recommendation against co-treatment with low-dose methotrexate when the patient is on TNFα inhibitor therapy. In case of 1st degree non-responder (Active AS despite TNFi), Secukinumab and Ixekizumab are recommended over Tofacitinib. Tofacitinib is conditionally recommended. There is conditional recommendation against non-TNFi/non-SEC/IXE or adding SSZ, MTX. There are strong recommendation against biosimilar of 1st TNFα inhibitor.

Biological Therapies for Spondyloarthritis - Stable

Physical Therapy (29)

↓

Stable AS on biologic

Against discontinuation of biologic (26)
Against biologic tapering as a standard approach (27)

Therapies for Spondyloarthritis - Stable

Spinal fusion or advanced osteoporosis

Avoid spinal manipulation (34)

Advanced hip arthritis

Total hip arthroplasty (35)

Biological Therapies for Spondyloarthritis - Stable

Physical Therapy (29)

↓

Stable AS on TNFi + NSAID

Continue TNFi alone; stop NSAID (24)

Cond. Recom.

Active & Stable AS

Conditionally Recommend

General Adjunctive Management: at all stages
1. Unsupervised back exercises [31]
2. Formal group or individual self-management education [33]
3. Fall evaluation/counselling [32]
4. Monitor using validated AS disease activity measures, & CRP or ESR [42, 43] regularly

Biological Therapies for Spondyloarthritis - Stable

Physical Therapy (29)

↓

Stable AS on TNFi + oral small molecule

Continue TNFi alone; stop csARD (25)

Cond. Recom.

Active AS - Physical Therapy & Miscellaneous

Conditionally Recommend against

General Adjunctive Management:
1. Against using treat-to-target strategy with target of ASDAS < 1.3 or 2.1 over strategy based on provider assessment (44);
2. Against obtaining repeat spine radiographs at a scheduled interval (51)

Biological Therapies for Spondyloarthritis - Stable

Physical Therapy (29)

↓

Stable AS on TNFi

If on originator TNFi, do not switch to biosimilar TNFi as a standard approach (28)

Against co-treatment with low-dose MTX (30)

Stable AS

Conditionally Recommend against

General Adjunctive Management:
1. Against obtaining spinal or pelvis MRI to confirm inactivity

Therapies for Spondyloarthritis - Stable

Determine additional disease manifestation

↓

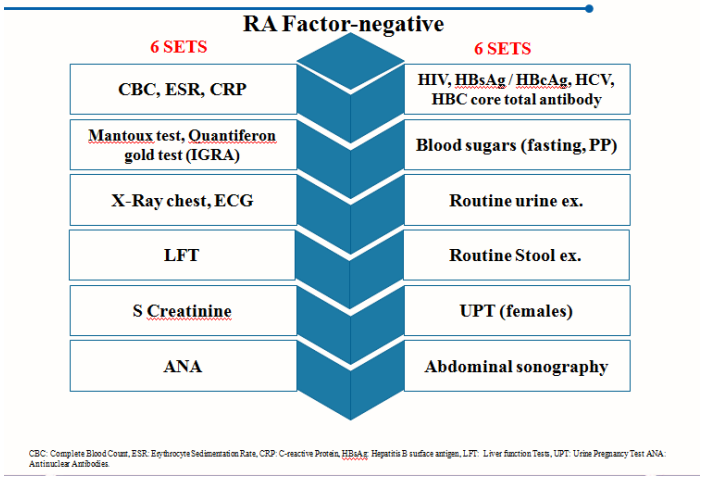
Severe kyphosis

Avoid spinal osteotomy (36)

Dose of biologics in AS & PsA[13-17]

Biologic	Dose	Route of Administration
Etanercept[1]	50 mg weekly	SC
Adalimumab[2]	Day 1- 40 mg; Day 15 - 40 mg every fortnight thereafter	SC
Infliximab[3]	5 mg/kg at 0, 2 & 6 wks thereafter every 8 wks	IV
Secukinumab[4]	AS-150 mg at weeks 0, 1, 2, 3, 4 monthly thereafter PsA-300 mg at weeks 0, 1, 2, 3, 4 monthly thereafter	SC
Golimumab[5]	50 mg monthly	SC

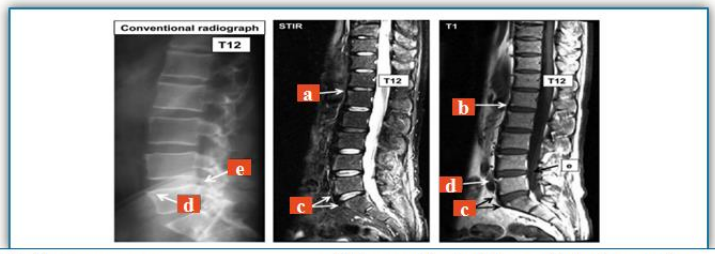
Investigations to be done before instituting biologics



CBC: Complete Blood Count, ESR: Erythrocyte Sedimentation Rate, CRP: C-reactive Protein, HBsAg: Hepatitis B surface antigen, LFT: Liver function Tests, UPT: Urine Pregnancy Test ANA: Antinuclear Antibodies

Types of lesions considered in the study[18]

Treated with anti-TNF agents
Long term observational study using MRI and conventional radiography



Typical lesions seen on	a. Inflam.-without evidence of fatty degeneration
	- hyperintense on STIR-weighted MRI
1. STIR-MRI	- hypointense on T1 -weighted MRI
2. T1-weighted MRI	b. FD without evidence of inflammatory lesion
3. Conventional Radiograph	c. Combination of inflammation & FD
	d. Fatty lesion combined with a syndesmophyte
	e. Posterior edges with fatty degenerative lesions

STIR-MRI: Short-TI Inversion Recovery magnetic resonance imaging, FD: fatty degeneration

Which of these spinal lesions progress to new bone formation?[18]

Treated with anti-TNF agents
Long term observational study using MRI and conventional radiography

Baseline		At 2 years		New syndesmophyte formation
Inflammation	Fatty degeneration	Inflammation	Fatty degeneration	RR (95% CI)
No	No	No	Yes	2.4* (1.1 to 5.2)
Yes	No	No	Yes	0.8 (0.2 to 4.4)
No	Yes	No	Yes	1.5 (0.6 to 3.8)
Yes	Yes	No	Yes	3.3* (1.3 to 8.1)

Of the VEs with inflammation at baseline, >70% resolved completely, 28.8% turned into FD after 2 years, but only 1 syndesmophyte developed within 5 years

RR: Relative Risk, VE: vertebral edges

Interesting points for consideration[19]

REMISSION

in axial-SpA

Consensus on definition of REMISSION → Inactive / LDA

Ankylosing Spondylosis (ASDAS) Disease Activity Score

1. Validated definition of low disease activity < 2.1

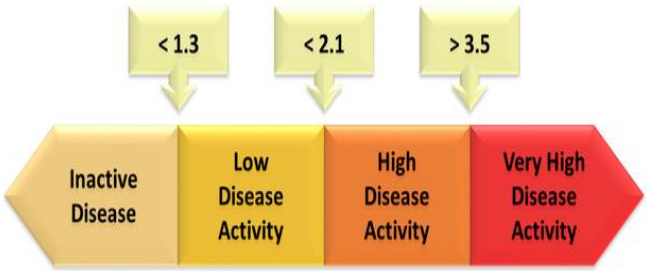
2. Inactive Disease <1.3 (in active disease)

serves as a target for therapeutic strategy

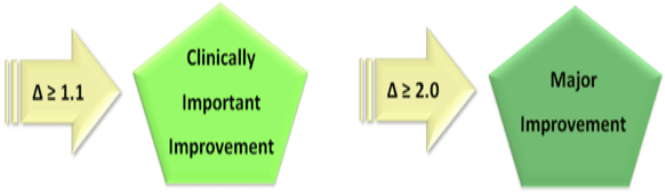
or

3. Reduction by at least 1.1 during treatment

Selected cut-offs for disease activity states



Selected cut-offs for improvement scores



MOA of the Biologics[20-23]

Mode of action	Biologics
TNF alpha blockers	**Etanercept, Infliximab, Adalimumab, Golimumab,** Certolizumab
IL 17 blockers	**Secukinumab,** Brodalumab, Ixekizumab
IL 12 and IL 23 blocker	Ustekinumab
IL 23 blocker	Tildrakizumab, Guselkumab, Risankizumab
Blocking co-stimulation between CD6 and ALCAM	Itolizumab

Vaccinations Recommended Before Initiating / During Therapy

	Killed Vaccine			Recombinant Vaccine	Live Vaccine
	Pneumococcal	Influenza (IM)	Hepatitus B	Human papilloma	Herpes Zoster
Before initiating therapy					
csDMARD bDMARD tsDMARD	√	√	√	√	√
While already on therapy					
csDMARD	√	√	√	√	√
bDMARD tsDMARD	√	√	√	√	Not recommended

Prophylactic immunization with live Zoster vaccine – not while on bDMARD

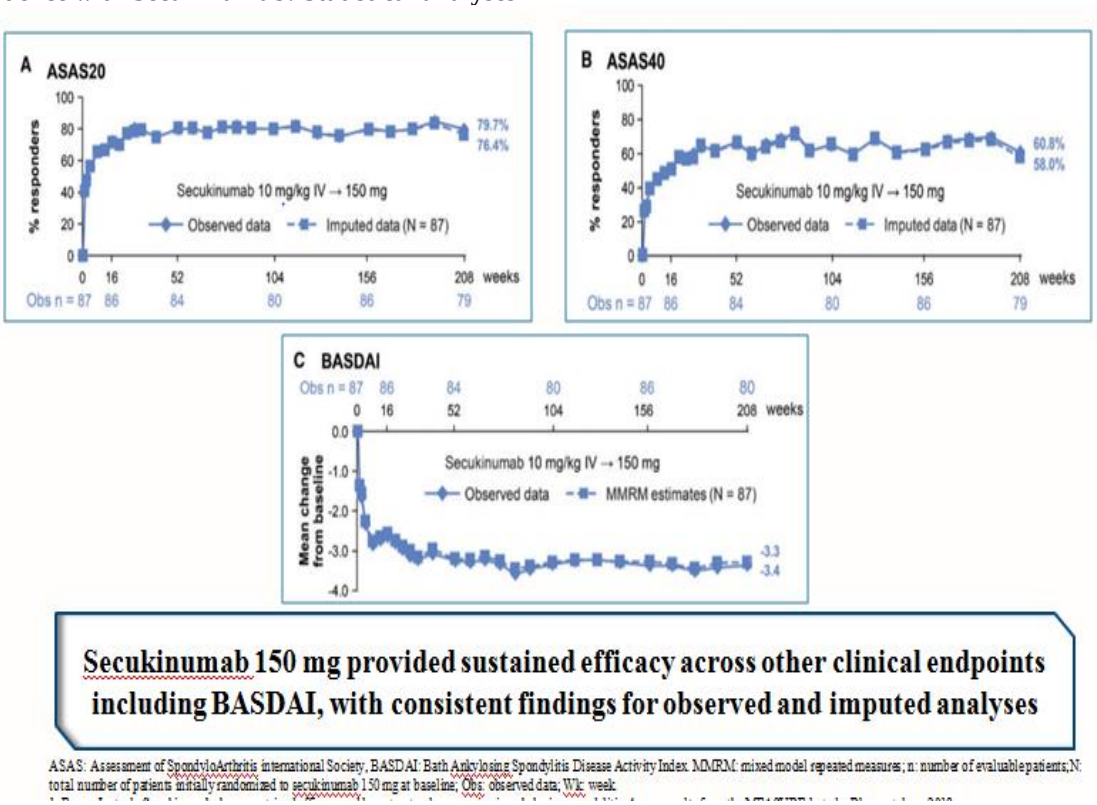
Recommendation for use of biologic therapy in perioperative period for elective surgery[24]

- TNF-a antagonists should be discontinued at least 4 half lives prior to major surgery
  - 2 weeks for Etanercept
  - 6-8 weeks for Adalimumab
  - 4-6 weeks for Infliximab
- It can be restarted post operatively if there is evidence of no infection and wound healing is satisfactory

Effect on Structural Progression[25]
Do anti-TNF therapy reduce progression in AS?

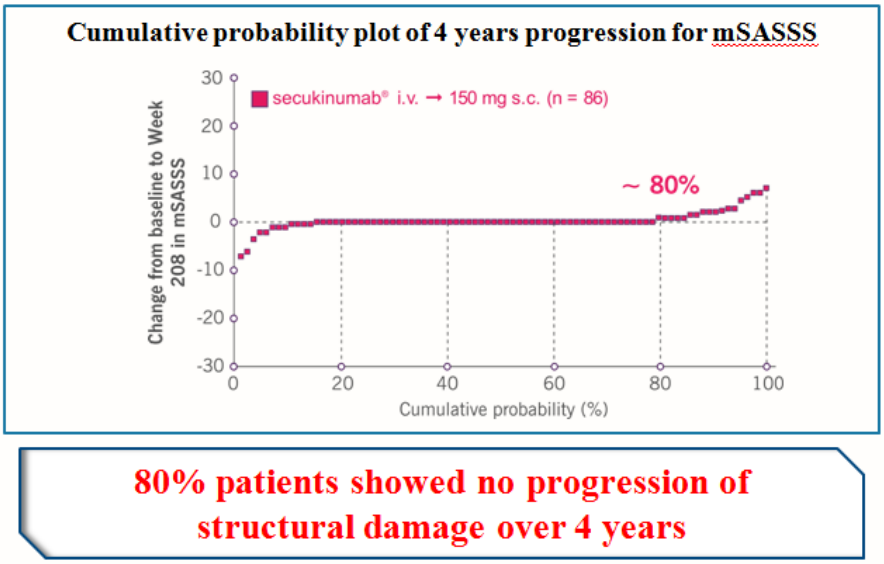
Adults with established AS on anti-TNF therapy produced mixed results but have not shown a clear reduction in spinal radiographic progression when compared to historical cohorts never treated with anti-TNF

Clinical evidence with Secukinumab: Statistical analyses[8]



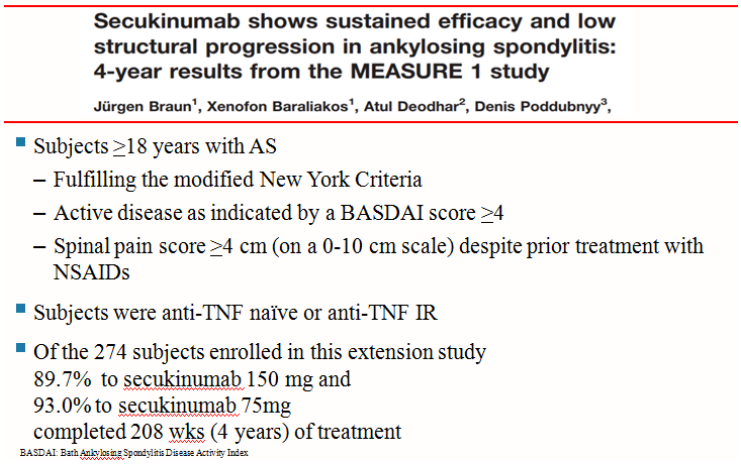
ASAS: Assessment of SpondyloArthritis international Society, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index. MMRM: mixed model repeated measures; n: number of evaluable patients; N: total number of patients initially randomized to secukinumab 150 mg at baseline; Obs: observed data; Wk: week

Clinical evidence with Secukinumab:Clinical efficacy and end results[8]

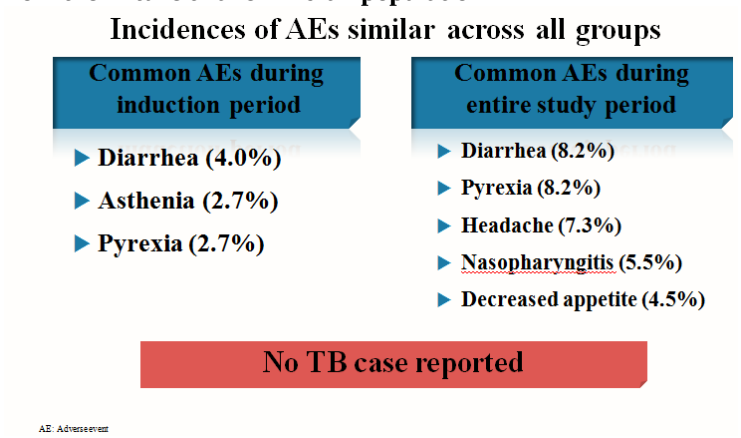


mSASSS: modified Stoke Ankylosing Spondylitis Spine Score

Clinical evidence with Secukinumab[8]



Secukinumab Indian data from the fixture trial on Indian population[26]



Traditional DMARDs

In developing world, where cost is a constraint, rheumatologists must first initiate treatment with csDMARDs (the traditional) such as sulfasalazine and methotrexate. These medications should be used in higher dosage to achieve improvement in peripheral spondyloarthropathy and also to some advantage in axial spondyloarthropathy. In clinical practice, most widely used traditional DMARDs are having different levels of evidence-

Methotrexate - B level
Sulfasalazine – A level
Leflunomide – A level
Cycolosporine – B level

Efficacy of these agents in inhibiting joint erosions is not assessed in controlled studies and their effectiveness in controlling enthesitis and dactylitis is controversial. It is recommended to use them following biologic therapy whenever cost is a constraint or from the very beginning in higher dosage.

Sulfasalazine even otherwise, has potent anti-inflammatory effect and for this reason of its behavior as NSAID, it is recommended for use even in axial SpA and definitely in peripheral SpA.

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