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NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AS POTENTIAL DISEASE MODIFYING MEDICATIONS IN AXIAL SPONDYLOARTHRITIS

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line pharmacotherapy for patients with axial spondyloarthritis (axSpA). In the recent years, treatment options have expanded with the availability of biologics, including tumor necrosis factor inhibitors (TNFi) and IL-17 inhibitors. However, a treatment strategy that clearly prevents syndesmophyte formation has not been established. Observational studies of patients with ankylosing spondylitis indicated potential disease modifying effects of NSAIDs, but two randomized trials came to different conclusions. More broadly, whether any of the currently available medications for axSpA have an effect on spine radiographic progression, beyond symptom control, remains inconclusive. In this paper, we will review the clinical studies of NSAIDs and biologics on disease modification of axSpA, examine genetic, animal and clinical evidence of NSAID effects on bone formation, and discuss how future studies may investigate the question of disease modification in axSpA.

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory spine condition with a prevalence of 0.9 – 1.4% in the adult population (1). Patients with ankylosing spondylitis (AS), also called radiographic axSpA (r-axSpA), the prototypic form of axSpA, may develop features of new bone formation, such as ankylosis of the sacroiliac joints, syndesmophytes and even fusion of spine (2, 3). Pharmacotherapy for axSpA has significantly broadened beyond non-steroidal anti-inflammatory drugs (NSAIDs) in the past two decades with the availability of biologics, including tumor necrosis factor inhibitors (TNFi) and interleukin-17 (IL-17) inhibitors, and more recently, Janus kinase inhibitors (4).

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Despite these new treatments, NSAIDs remain as the first line and cornerstone for management of axSpA, including patients with early disease and patients with well-established AS. In observational cohorts of early axSpA, 73.0 – 92.8% of patients took NSAIDs (5) (6). Similarly, in a prospective cohort of established AS, 70.3% patients were using NSAIDs (7). These frequencies are not surprising given the efficacy of NSAIDs, as shown in many clinical trials. In a recent trial of full dose naproxen in patients with early axSpA with active inflammation of sacroiliac joints, 56.9% patients achieved a moderate response measured by Assessment in Spondyloarthritis International Society 40% response (ASAS40, Table 1 (8)), and 35.3% were in ASAS partial remission (Table 1), after 28 weeks of treatment (9). In an open label study of NSAIDs in patients with axSpA (including both radiographic and nonradiographic axSpA), 35% of participants achieved an ASAS40 response after 4-weeks of NSAID treatment (10). In comparison, in the major phase 3 clinical trials of biologics (TNFi and IL-17 inhibitors) in AS or r-axSpA, 39.4% to 58.1% participants achieved ASAS40 at 12 weeks to 24 weeks (11,12), indicating that the rest of participants, at least 40 – 60%, needed to optimize their NSAIDs use in addition to the study drugs or try a different biologic. Although these results were extracted from different studies, and cannot be compared directly, they support the notion that, for short-term symptom relief, NSAIDs are not only effective as a first line treatment, but are also important as combination therapy with biologics.

It is less clear, however, whether NSAIDs slow disease progression in patients with axSpA. In an early retrospective cohort of 40 patients with AS, continuous use of phenylbutazone delayed or arrested radiographic progression, compared to patients who did not use phenylbutazone or used it only intermittently (13). Two randomized trials examined the effects of continuous use versus on-demand use of NSAIDs on disease progression in AS, and came to opposite conclusions (14,15). The uncertainty prompted us to examine the clinical studies of disease modification in AS and the state of knowledge of NSAID effects on bone growth in general, and in axSpA in particular. In this paper, we will review the clinical evidence for NSAID and biologic effects on radiographic progression in patients with AS, examine *in vitro* and *in vivo* evidence of NSAID effects on bone formation, and discuss how future studies may evaluate disease modification in axSpA. Biomarkers for radiographic progression in axSpA theoretically may be used as surrogate endpoints for disease modification in clinical studies, however, it is a broad topic in itself, and will not be discussed in this review.

Background

Measurement of disease progression in AS

Syndesmophyte formation and ankylosis of the spine are the key features of AS, and are associated with long-term functional impairment; thus, disease modification to slow or stop syndesmophyte growth is an important goal. The modified Stoke AS Spine Score (mSASSS) has been widely used to describe syndesmophyte growth and radiographic progression. mSASSS is a semi-quantitative scoring system based on features of the anterior vertebral corners on lateral projections of cervical and lumbar spine radiographs. Each of the 24 corners (12 in the cervical spine and 12 in the lumbar spine) is graded as 0 to 3, with 0 being

normal, 1 being erosion, sclerosis or squaring, 2 being syndesmophyte, and 3 being bony bridging between adjacent vertebrae, for a total possible score of 0–72 (16). Radiographic progression is usually defined as mSASSS increase of 2 or more units; alternatively, mSASSS absolute change from baseline has been commonly used as a radiographic endpoint (16). When assessed longitudinally, in 2 years, 30 – 40% of patients demonstrate any increase in mSASSS, and about 20% of patients have an increase of mSASSS of 2 or more (16–19). The rate of mSASSS change ranges from about 1.0 unit in two years to 0.98 unit/year (17, 18, 21). The spine has been used as the preferred site to assess radiographic progression, rather than the sacroiliac joints, because it provides a greater range and most patients are eligible to demonstrate change, while changes in joint space or fusion of the SI joints are difficult to detect.

Although the mSASSS has been shown to have face and construct validity, its reliability and sensitivity to change have been challenged. When assessing progression over 2 years, two readers were in agreement in only 54% cases (18). Inter-reader reliability of mSASSS change over 2 years was poor to moderate, ranging from 0.17 to 0.67 (19,20,22,23). Assessing the films in chronological sequence also affects the reading, and results in higher apparent progression (17). In addition, it was estimated that in a 2-year randomized controlled trial, a sample size of 100 in each arm would be needed to detect a difference between arms (24), reflecting the slow progression of the disease and relative insensitivity to change of the method.

Risk factors for disease progression in AS

Using mSASSS as the measure, several risk factors have been associated with disease progression in longitudinal studies, including presence of syndesmophytes at baseline (25–28), elevated inflammatory markers (25,27), smoking (25–27), low bone mineral density (26), and high disease activity measured by the Ankylosing Spondylitis Disease Activity Score (ASDAS, Table 1) (29). In addition, mechanical stress has been associated with worse radiographic outcomes, both in AS cohorts and animal studies (30–32). Certain occupational and physical activities, such as bending, twisting and stretching, as well as exposure to whole body vibration, were associated with worse radiographic outcomes, and physically demanding jobs seem to amplify the radiographic progression (30).

Heterogeneity in syndesmophyte growth

Increasing evidence suggests that radiographic progression and syndesmophyte growth in AS is a highly heterogeneous process, both temporally and spatially. In a study that evaluated 12-year radiographic progression in patients with AS, new syndesmophytes, detected based on mSASSS change, were observed in about 60% of patients and 40% of time intervals. At the same time, in about 24% of patients and 40% of time intervals, no radiographic progression was observed, indicating high variability in individual patients, and at different time intervals (21). At the syndesmophyte level, within the same intervertebral disk spaces, some syndesmophytes were seen to grow substantially while others did not grow, suggesting that local factors, possibly including mechanical forces and local pro- and anti-proliferation factors, influence syndesmophyte growth (33). This heterogeneity adds further challenges to studying radiographic progression in AS.

Long-term effect of NSAIDs and Biologics on Disease Modification

Observational studies and clinical trials of a disease modification effect of NSAIDs

As there are more than 20 different NSAIDs used in various dosages, an NSAIDs intake index has been developed to quantify the dosage in equivalency and duration of NSAIDs use, with a range of 0 – 100 (34). For example, daily NSAID use equivalent to 150mg diclofenac over the whole study period is scored as 100. Using this index, in the German Spondyloarthritis Inception Cohort (GEPSIC), the odds of mSASSS increase over 2 years was much less (odds ratio = 0.15, 95% confidence interval (CI) 0.02 – 0.96) in patients with high NSAID intake (index >= 50) compared to those with low NSAID intake (index < 50) (total n=88) (35). The results support the hypothesis that NSAIDs have a protective effect on spine radiographic progression in patients with AS. In this study, a similar protective effect was not observed between patients with high versus low AS activity measured by Bath AS Disease Activity Index (BASDAI, Table 1) (35), suggesting that subjective symptoms may not be directly associated with radiographic progression, or that the mechanisms by which NSAIDs may act on progression are other than symptom control.

Two separate randomized trials, one with the COX-2 selective NSAID celecoxib, and the other with the non-selective NSAID diclofenac, examined the efficacy of NSAIDs on radiographic progression (Table 2). In the celecoxib trial, TNFi naïve patients with AS were randomized to continuous use vs. on-demand use of celecoxib 100mg twice daily or higher. After 2 years, patients in the continuous use group had less radiographic progression compared to on-demand group (p=0.002) (14). Post hoc analysis of this trial showed that slowing of progression with continuous treatment was greater in patients with elevated inflammatory markers (erythrocyte sedimentation rate or CRP) (36). The diclofenac trial (Effects of NSAIDs on RAdiographic Damage in Ankylosing Spondylitis (ENRADAS)) used a similar design, in that TNFi naïve patients with AS were randomized to continuous use vs. on-demand use of diclofenac 150mg daily for two years. However, in contrast to the findings in celecoxib study, the continuous group had more progression numerically over two years (p = 0.39). Findings were similar in subgroups of patients with or without syndesmophytes at baseline and in those with or without elevated CRPs (15). The authors stated that despite the fact that “not even a trend for less radiographic progression was seen for the continuous group in our study, it is rather unlikely that inclusion of more patients would have changed the result.”

The results from both studies might suggest that only COX-2 selective NSAIDs have a disease modification effect, but several caveats should be considered. First, absence of a dose effect makes the trial results difficult to interpret. When using mSASSS change as the study outcome, at least two years are proposed to detect a significant change with a sample size of 100 patients in each treatment arm. Because it would be unethical to conduct placebo-controlled trials lasting 2 years, both NSAIDs trials compared continuous use versus on-demand use, to approximate the ideal placebo-controlled study, with the intention to see whether the difference in NSAID intake between the two groups was correlated with the difference in mSASSS increase. The result from the celecoxib trial did show a lower rate of mSASSS increase with continuous use, however, a dose effect of NSAIDs was not

demonstrated. The average dose in the continuous group (243mg) was only modestly higher than the on-demand group (201mg), despite the significant difference in the outcome (mean mSASSS change +0.4 in the continuous group vs. +1.5 in the on-demand group). The diclofenac trial groups had a difference in NSAID dose, with NSAIDs indices of 77 in the continuous group vs. 44 in the on-demand group, but did not show a corresponding decrease in radiographic progression (mean mSASSS change +1.3 in the continuous group vs. +0.8 in the on-demand group).

Further, in the event of imbalance in randomization, risk factors that are associated with spine radiographic progression could lead to bias when assessing treatment effects. For example, in the diclofenac study, the continuous use group had a significantly higher proportion of current smokers at baseline, compared to the on-demand group. Whether the difference in smoking between the groups was enough to overwhelm a potential inhibitory effect of continuous diclofenac use is unclear (15).

A third clinical trial (CONSUL trial, NCT02758782), which evaluates the effect of celecoxib with golimumab compared to golimumab alone on radiographic progression in patients with AS, is ongoing.

Disease modification effects of biologics

With regard to biologics, two strategies have been taken to retrospectively analyze radiographic data from long-term extensions of clinical trials. The first strategy was to compare the radiographic progression among participants in biologic trials to that of biologic-naïve, historical cohorts (Table 2) (19,20,23,37,38). Most of these studies used mSASSS change over 2 years as the primary radiographic endpoint, and did not find any significant difference in radiographic progression between groups. One of the studies, secukinumab vs. ENRADAS cohort used the proportion of patients with no radiographic progression (defined as least square mean change of mSASSS <= 0) as the endpoint, and reported a suggestion toward more non-progressors in the secukimunab group (60.7% vs 52.2%, $p = 0.2430$). Notably, the inter-reader agreement for mSASSS change of this study was poor ($k = 0.17$), and ENRADAS cohort had a much higher percentage of smokers (23).

The second strategy, similar to the NSAIDs trials, was to compare different dosing regimens with the question of whether there was a dose effect (Table 2) (39,40). However, this approach has not shown associations between the dose of biologics and progression. In the 4-year secukinumab study (Braun 2018), although the 150mg group had marginally less radiographic progression than the 75mg groups by mSASSS, the 75mg groups had higher mSASSS at baseline, which is a risk factor for radiographic progression (40). In addition, similar proportions of patients in each dosing group (78.9% vs. 78.6%) had no radiographic progression (mSASSS change <= 2)., in the open label extension of Certolizumab study, 80.6% patients had no radiographic progression at 4 years, although there was no comparison group (41).

Two observational studies examined the effect of TNFi on spine radiographic progression, with somewhat conflicting results. In a prospective cohort of 334 patients with AS in North America, after adjustment for baseline mSASSS and propensity to receive TNFi, patients

who were on a TNFi had a 50% lower odds of progression compared to those who never received TNFi. Also, patients who took TNFi for a larger proportion of their disease course had less mSASSS progression (42). In contrast, in a recent observational study of 432 patients with AS from the Swiss Clinical Quality Management Cohort, no contemporaneous association between TNFi use and radiographic progression (43). Instead, treatment with TNFi prior to the radiographic interval was protective, as was longer duration of prior use of TNFi. The data did not detect an association with TNFi during the radiographic interval, perhaps indicating that prolonged treatment is needed to see an effect (43).

In summary, current evidence for a disease-modifying effect of biologics, including TNFi and IL-17 inhibitors, is lacking; and the effect of the different classes of biologics on radiographic progression has not been compared directly. A direct comparison of secukinumab to an adalimumab biosimilar on radiographic progression is on-going (NCT03259074).

NSAIDs and Bone Formation

The inconclusive results from AS clinical studies of the effect of NSAIDs on radiographic disease progression prompts a review of pre-clinical, biological evidence that would support an inhibitory effect of NSAIDs on syndesmophyte formation in AS.

At the genetic level, in an experiment-wide genetic association study that examined genes related to radiographic severity in AS, a single nucleotide polymorphism (SNP) rs1236913 was found to have a protective association with the degree of radiographic damage (44). This SNP lies in the *PTGS-1* gene, encoding Prostaglandin-Endoperoxide Synthase 1, also known as COX-1. Although extensive functional studies are not available, the association at least suggests that COX-1 might be involved in radiographic progression in AS.

NSAIDs are COX inhibitors, blocking the synthesis of prostaglandin (PG) G_2/H_2 from arachidonic acid, the main precursor of prostanoids. Arachidonic acid is first hydrolyzed by secretory or cytoplasmic phospholipase A_2, then oxygenated to PGG_2/H_2 by COX, which is then further converted to PGD_2, PGE_2, PGF_2, PGI_2 or thromboxane A_2 by different synthases (45). Among them, PGE_2 is the most studied prostanoid involved in inflammation and bone formation. Local administration of PGE_2 into long bones in rats stimulates bone formation by increasing osteoblast number and activity, and systemic administration of PGE_2 has been shown to increase the osteogenic capacity of bone marrow in ex vivo culture systems (46, 47). However, in some experimental systems, PGE_2 is also a potent stimulator of bone resorption, by inducing receptor activator of nuclear factor kappa B ligand (RANKL) expression in primary osteoblastic cell cultures via the EP2/EP4 receptor (48,49). Figure 1 illustrates the prostaglandin pathway and effects on bone metabolism.

Prostaglandin pathway and bone metabolism: In vitro evidence

Two isoenzymes, COX-1 and COX-2, are traditionally considered the main rate-limiting enzymes in the generation of PGE_2. COX-1 is constitutively expressed, while COX-2 expression is induced under certain conditions. Proinflammatory cytokines, including interleukin-1 (IL-1), TNF, and IL-17, have been shown to induce COX-2 expression and

PGE_2 production in bone marrow cultures and osteoclast precursors, osteoblastic cells, and synoviocytes (50–52). In addition, mechanical loading of human osteoblastic cell line and primary bone cell cultures derived from the iliac crest triggered expression of COX-2 and prostaglandin synthesis, and induced bone nodule formation (53, 54). In human periodontal ligament cells, cyclic tension force increased PGE_2 expression as well as RANKL mRNA expression, but not osteoprotegerin expression, in a COX-2 dependent manner, suggesting a potential for increased osteoclastogenesis (55, 56). However, as the skeletal system constantly undergoes remodeling, and COX-2, triggered by proinflammatory cytokines and mechanical force, regulates PGE2 expression in osteoblasts as well as osteoclasts, these *in vitro* experiments did not address the net effect of these factors on osteogenesis and osteoclastogenesis.

Cyclooxygenases inhibition and bone formation: In vivo evidence

COX-1−/− and *COX-2−/−* mice are useful tools to study the net effect of inhibition of COX on bone formation. Using fracture healing models in these mice, COX-2 was shown to be critical for fracture healing, but COX-1 was not (57, 58). Consistent with these findings, both non-selective COX inhibitors, e.g. diclofenac, indomethacin, ketorolac, and selective COX-2 inhibitors, e.g. celecoxib, rofecoxib, valdecoxib, exerted a delayed or inhibitory effect on fracture healing in rat or rabbit models when given over 4–10 weeks (58 – 63). Interestingly, when treated with one to two weeks of COX-selective NSAIDs (rofecoxib, valdecoxib), or one week of diclofenac, the inhibitory effect of NSAIDs on bone growth was either reversible or less profound (64–66), suggesting a temporal effect of NSAIDs on bone formation.

The effect of NSAIDs on fracture healing in humans has been assessed in randomized controlled trials, case control studies and cohort studies, with somewhat different conclusions (table 3). Dodwell et al reported an increased risk of nonunion among NSAID-treated patients (odds ratio 3.0, 95% CI 1.6 – 5.6) in the pooled effect of all of the 11 studies, but no effect was observed when only including seven high-quality studies (67). Another meta-analysis by Wheatley et al also showed that NSAID use was associated with an increased risk of nonunion or delayed union (odds ratio 2.07, 95% CI 1.19 – 3.61), but similar to the temporal effect observed in the animal studies, no association was found in studies with a short duration of NSAID treatment (68). In addition, no association was observed in studies with low dose NSAIDs or in the pediatric groups (68). Neither of these two meta-analyses examined the difference in effects of COX-2 selective versus non-selective NSAIDs.

NSAID effects on bone formation have also been examined in the prevention of heterotopic ossification (HO), an abnormal localized growth of bone in muscles and tendons. Systematic reviews and meta-analysis of RCTs (table 3) have shown that post-operative use of NSAIDs, including indomethacin, naproxen, as well as COX-2 selective NSAIDs, was effective in preventing severe HO after total hip arthroplasty (69,70). In the most recent meta-analysis of NSAID effects on HO prevention, the effect of non-selective and COX-2 selective NSAIDs were directly compared, based on 7 RCTs and 1096 participants, and no difference was found between these classes in preventing post-operative HO (70).

The animal studies and clinical evidence from studies of fracture healing and HO formation support the notion that NSAIDs have an inhibitory effect on new bone formation, with no difference between selective and non-selective NSAIDs, at least as clinically evident in humans. A temporal effect of NSAIDs on bone formation has been suggested in animal and human fracture healing studies, i.e. that short duration of NSAID use had less profound or reversible effect on bone growth, but definitive proof is needed.

Future studies on disease modification in patients with axSpA

Whether NSAIDs or biologics have a disease modification effect, or more fundamentally, whether suppressing inflammation is sufficient to prevent bone formation in AS, remains unclear. Further studies on disease modification are needed to identify treatment strategies that effectively prevent radiographic progression with the least side effects. How can we improve future studies?

Radiographic outcome measures: new imaging modalities

In recent years, three-dimensional imaging modalities, including full-dose computed tomography (CT) and low dose CT (ldCT) of spine, have been evaluated to improve the measurement of radiographic progression of AS (Table 4) (71,72). The thoracic spine has been omitted from radiographic studies because of the difficulty in seeing vertebral changes on conventional radiographs. In contrast, CT scan methods provide a 360-degree evaluation of the entire vertebral body, and a better visualization of thoracic spine. Using CT scanning, it has been shown that syndesmophytes develop more commonly at thoracolumbar junction and thoracic spine, rather than lumbar spine, offering the potential to detect more patients with abnormalities (73,74). In the full dose CT scan method, syndesmophyte volume was directly quantified and compared over time using computer algorithm (75). In the ldCT method, a CT Syndesmophyte Score (CTSS) has been developed to measure the radiographic damage in the entire spine by human readers, with moderate inter-reader ICC for change score (74). Both CT methods have shown to be more sensitive to change than the mSASSS (74,75), which makes it possible to detect a treatment effect in a clinical trial with fewer participants and/or shorter study length. Notedly, the full dose CT scan method has a radiation exposure of 8 millisievert per scan, which is comparable to 3 years of natural background radiation, and about one third of a PET/CT scan, while the ldCT has a radiation exposure of 4 millisievert per scan. To date, no RCTs data have been reported using these new measurements for disease modification effects.

Magnetic Resonance Imaging (MRI) is a useful imaging tool to detect bone marrow edema in the spine and pelvis. However, it is less sensitive to signals from calcification, so is not as useful to measure new bone formation. A sequential process in which bone marrow edema proceeds the development of fat metaplasia and new bone formation has been proposed, but with mixed evidence (76,77). It is unclear whether presence of bone marrow edema or its resolution closely correlates with future development of syndesmophytes.

Participants: identifying subsets of disease

Studies have consistently shown that 30–40% of patients have an increase of mSASSS in a 2-year study. A handful of risk factors for radiographic progression have been identified from previous longitudinal studies, including male sex, HLA-B27 positivity, smoking status, elevated CRP, and presence of syndesmophytes at baseline. These risk factors can be used to identify the subset of potential candidates who are more likely to have disease progression, and hence, a higher chance of detecting a difference in radiographic progression in a given time frame. The trial design most likely to detect an NSAID effect would be a study of patients with high risk for progression treated with either minimal doses or full-dose NSAIDs and assessed with spinal CT.

Identifying novel risk factors and potential interactions

Another methodological aspect is to identify potential risk factors and their interactions, and include them as covariates in future observational studies. Recent cross-sectional studies have shed light on several new possible risk factors for disease progression, such as crystals, PTH and Vitamin D, and adipokines, but these have not been examined in longitudinal studies. Monosodium urate (MSU) microcrystals have been shown to induce COX-2 expression in human monocytes and osteoblast-like cells, and have a synergistic effect with IL-1 on osteoblasts to overexpress COX-2 (78,79). In patients with AS but not a clinical diagnosis of gout, urate crystal deposition at the sacroiliac joint was associated with progression of sacroiliac joint fusion (80). Both PTH and Vitamin D have direct and indirect effects on cyclooxygenase expression, and hence PGE_2 level. A systematic review of cross-sectional studies showed that patients with AS commonly have low vitamin D levels (81). In a cross-sectional study, serum PTH levels were found to be significantly higher in patients with AS than in healthy controls (82). Consistent with this finding, PTH was reported to modulate the response to mechanical stress in osteoblast-like cells (76). Syndesmophyte formation and its association with serum adipokine levels have been investigated in several studies, but the results were inconsistent (84, 85).

Conclusion

Despite new therapies that are effective in relieving symptoms in patients with axSpA, treatments to prevent radiographic progression remains elusive. Observational studies have suggested that NSAIDs might slow syndesmophyte formation in patients with AS, however, two clinical trials had inconsistent results. Genetic and animal studies suggested potential effects on NSAIDs on bone formation, and clinical studies have indicated that NSAIDs may potentially modify disease progression, particularly in patients with higher risk of syndesmophyte growth. Better quantification of syndesmophyte growth, disease subsets with higher risk for radiographic progression, and potential risk factors and their interactions should be considered when designing future studies on disease progression in patients with axSpA.

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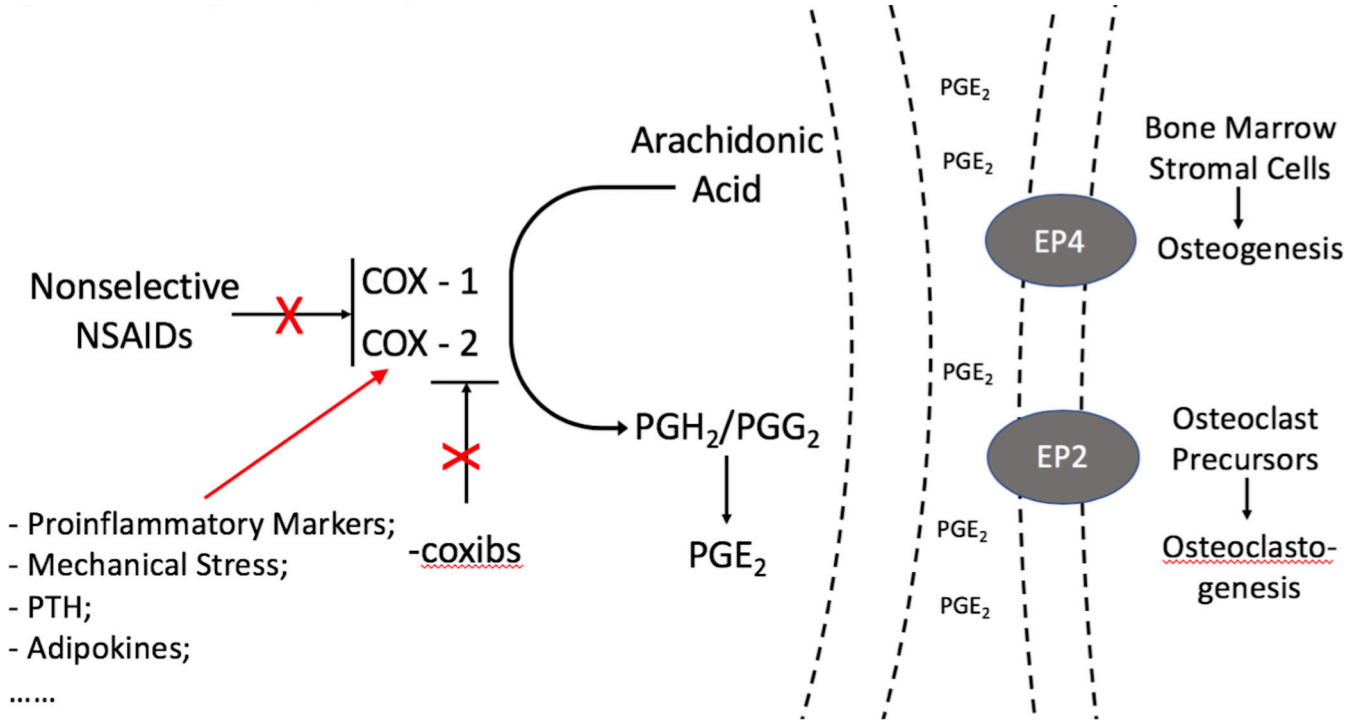

Figure 1. Prostaglandin pathway and bone metabolism.

PG: prostaglandin; COX: cyclooxygenase; NSAIDs: non-steroidal anti-inflammatory drugs; EP2: prostaglandin E receptor 2; EP4: prostaglandin E receptor 4; PTH: parathyroid hormone.

Table 1.

Major outcome measures in clinical research of ankylosing spondylitis or radiographic axial spondyloarthritis.

Measures	Description
ASDAS (8)	A composite score, including assessment of total back pain, patient global of disease activity, peripheral pain and swelling, duration of morning stiffness, and C-reactive protein or erythrocyte sedimentation rate.
BASDAI (8)	A six-question, self-administered questionnaire, assessing fatigue, spinal pain, peripheral arthritis, enthesitis, intensity and duration of morning stiffness
ASAS40 response criteria (8)	On a scale of 10, improvement of >= 40% and >=2 units in at least three of the four domains (patient global, pain, function, inflammation*), and no worsening in any scores.
ASAS partial remission (8)	On a scale of 10, the score in each domain (patient global, pain, function and inflammation*) not above 2 units.

ASDAS: ankylosing spondylitis disease activity score; BASDAI: Bath ankylosing spondylitis disease activity index; ASAS: Assessment of SpondyloArthritis International Society.

*average score of severity and duration of morning stiffness in BASDAI.

Table 2.

Comparison of studies on radiographic progression in patients with ankylosing spondylitis.

Author, year	Study groups	Number of Participants	Study Length	Baseline mSASSS, mean (SD)	Smoking status (%)	Male (%)	HLA-B27 positivity (%)	mSASSS change, mean (SD)
NSAIDs [Randomized controlled Trials]								
Wanders, 2005 (14)	Continuous celecoxib	76	2 years	7.9 (14.7)	NR	66	88	0.4 (1.7)
	On-demand celecoxib	74	2 years	9.3 (15.2)	NR	70	88	1.5 (2.5)
Sieper, 2015 (15)	Continuous diclofenac	62	2 years	10.9 (15.5)	59 *	71.0	88.7	1.3 (0.7–1.9)
	On-demand diclofenac	60	2 years	16.4 (18.2)	33 *	66.7	91.7	0.8 (0.2–1.4)
TNFi [Retrospective analyses of clinical trials/long-term extension of clinical trial data]								
Baraliakos, 2005 (37)	Infliximab	41	2 years	12.1	NR	63	90	0.4(2.7)
	GESPIC cohort	41	2 years	5.9	NR	71	85	0.7(2.8)
van der Heijde, 2008 (19)	Infliximab	201	2 years	17.7 (17.9)	NR	78.1	86.5	0.9 (2.6)
	OASIS	192	2 years	15.8 (18.1)	NR	67.7	84.4	1.0 (3.2)
van der Heijde, 2008 (38)	Etanercept	257	2 years	16 (18.3)	NR	75.5	78.2	0.91 (2.45)
	OASIS	175	2 years	14 (17.6)	NR	69.1	71.1	0.95 (3.18)
van der Heijde, 2009 (20)	Adalimumab	307	2 years	19.8 (19.3)	NR	76.5	NR	0.8 (2.6)
	OASIS	169	2 years	15.8 (17.6)	NR	69.2	NR	0.9 (3.3)
Braun, 2014 (39)	Placebo -> Golimumab 50mg	66	208 weeks	16.1 (18.7)	NR	NR	NR	2.1 (5.2)
	Golimumab 50mg	111	208 weeks	11.7 (16.4)	NR	NR	NR	1.3 (4.1)
	Golimumab 100mg	112	208 weeks	13.5 (18.9)	NR	NR	NR	2.0 (5.6)
IL-17A inhibitor [Retrospective analyses of clinical trials/long-term extension of clinical trial data]								
Braun, 2018 (40)	Secukinumab 75mg	61	208 weeks	10.7 (17.82)	39.3	87.0	NR	1.6 (5.67)
	Secukinumab 75mg -> 150mg	23	208 weeks		34.8	70.5	NR	1.8 (4.32)
	Secukinumab 150mg	71	208 weeks	8.6 (16.23)	29.6	63.4	NR	1.2 (3.91)
Braun, 2019 (23)	Secukinumab	168	2 years	NR	25	73.2	82.9	60.7% *
	ENRADAS cohort	69	2 years	NR	44.9	66.7	88.4	52.2% *

Author, year	Study groups	Number of Participants	Study Length	Baseline mSASSS, mean (SD)	Smoking status (%)	Male (%)	HLA-B27 positivity (%)	mSASSS change, mean (SD)
								$p = 0.2430$

NSAID: non-steroidal anti-inflammatory drugs; TNFi: tumor necrosis factor inhibitor; IL-17A: interleukin-17A; GESPIC: German Spondyloarthritis Inception Cohort; OASIS: Outcomes in Ankylosing Spondylitis International Study; ENRADAS: Effects of NSAIDs on Radiographic Damage in Ankylosing Spondylitis; SD: standard deviation; NR: not reported.

* Proportion of patients with no radiographic progression (least squares mean change of mSASSS <= 0)

Table 3.

Meta-analyses of NSAIDs effect on fracture healing and heterotopic ossification.

Study	Condition	Study type	Length of follow up	Type of NSAIDs	number of studies and participants	Result
Dodwellet al, 2010 [67]	Fracture Healing	Mostly retrospective cohort; one prospective cohort study	5 month to 3.8 years	Diclofenac, indomethacin, ibuprofen, ketorolac, and not defined.	11 studies/2067 patients exposed to NSAIDs	Increased risk for non-union: OR = 3.0 (1.6 – 5.6); in 7 high-quality studies, no statistical significant risk, OR = 2.2 (0.8 – 6.3).
Wheatly, 2018 [68]	Fracture Healing	RCTs, cohort studies, and case-control studies	> 6 months	All type of NSAIDs	16 studies/3283 exposed bones to NSAIDs	Increased risk for delayed union or nonunion: OR = 2.07 (1.19 to 3.61). No risk for low dose (< 125mg/d diclofenac, 150mg/d of indomethacin or 120mg/d ketorolac) or shorter duration (< 1 week): OR = 1.68 (0.63 to 4.46)
Ma, 2018 [69]	Heterotopic Ossification	RCTs	1.5 to 12 months	Naproxen vs. Placebo	4 RCTs/total of 269 patients	Decreased risk for HO: RR = 0.21 (0.12 to 0.35) at 12 months.
Joice, 2018 [70]	Heterotopic Ossification	RCTs	3 – 24 months	Non-selective NSAIDs vs. Placebo	17 RCTs/ total of 4979 patients	Decreased risk for HO: Log OR = −1.35 (−1.83 to −0.86)
				Selective NSAIDs vs. Placebo	5 RCTs/ total of 628 patients	Decreased risk for HO: Log OR = −1.58 (−2.41 to −0.75)
				Non-selective vs. selective NSAIDs	7 RCTs/ total of 1096 patients	No difference in risk for HO: Log OR = 0.22 (−0.36 to 0.79)

NSAIDs: non-steroidal anti-inflammatory drugs; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk.

Table 4.

Comparison of radiographic measures for new bone formation in ankylosing spondylitis, or radiographic axial spondyloarthritis.[**]

	mSASSS	CTSS	Quantitative Syndesmophyte height volume
Imaging modality	spine radiograph	low dose CT	full dose CT
Spine segments	cervical and lumbar spine	cervical, thoracic and lumbar spine	thoracic and lumbar spine
Number of scored intervertebral disk spaces (IDS)	12 (C2/C3 to C7/T1, T12/L1 to L5/S1)	23 (C2/C3 to L5/S1)	13 (T3/T4 to L3/L4)
Number of scoring sites per IDS	2	8	circumferential
Total score	0 – 72	0 – 552	not applicable
Training human readers	needed	needed	not needed
Sensitivity to change (in 2 years)	mSASSS increase in 30 – 40% patients	any net change in 61 –76% patients; the SDC in 37 – 43% patients	volume increase in more than 70% patients
Inter-reader ICC of change scores	0.17 – 0.67	whole spine: 0.77 spine segments: 0.32–0.75	Not applicable: measured by computer algorithm, no human readers involved.
Radiation	1.5mSV[*]	4 mSV	8 mSV

mSASSS: modified Stoke AS Spine Score; CTSS: computed tomography syndesmophyte score; CT: computed tomography; SDC: smallest detectable change; ICC: Intraclass correlation coefficient; mSV: millisievert.

[*] 2 views.

[**] MRI scoring method is not included here because it does not measure new bone formation.