Review

Clinical implications of peripheral new bone formation in psoriatic arthritis: a literature-based review

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ABSTRACT

While the destructive changes of peripheral articular damage of psoriatic arthritis (PsA) are extensively studied, the productive modifications have been somewhat neglected.

This literature-based study focuses on the clinically relevant aspects of peripheral bone proliferation in PsA.

New bone proliferation frequently occurs as juxta-articular and entheseal apposition in PsA patients but also in psoriatic patients without arthritis, the Psoriatic Arthritis Ratingen Score is the only radiographic method to evaluate peri-articular new bone formation, numerous ultrasound systems to score entheseal changes have been proposed, several serum biomarkers of bone-turnover have been associated with PsA and psoriasis but they do not have clinical relevance. The effects of the biologics on peripheral new bone formation remains to be elucidated as well as the contribution of peripheral bone apposition to disability.

Many aspects of peripheral osteoproliferation in PsA have not yet been properly addressed and represent clinical unmet needs of this rheumatic disorder.

Introduction

Whilst erosion is the typical feature of bone damage in rheumatoid arthritis (RA) and bone formation (syndesmophytes and enthesophytes) is the distinctive trait of ankylosing spondylitis (AS), the structural damage of psoriatic arthritis (PsA) is characterised by the combination of both, providing a distinctive identity to this inflammatory disease (1-4).

In addition to enthesophytes and syndesmophytes, patients with PsA may show periosteal thickening and bony ankylosing of the joints, suggesting a relevant role of new bone formation in PsA articular damage (5). In contrast to other inflammatory joint diseases, these typical expressions of new bone apposition might be caused by different pathogenetic mechanisms (6, 7). The relevance of bone apposition in PsA was also shown by the CASPAR study, where the juxta-articular new bone formation was the only radiographic feature predictive of PsA as opposed to other inflammatory rheumatic diseases; hence, it was included among the classification criteria (8).

Despite its relevance, articular damage progression due to new bone apposition has never been addressed by the randomised controlled trials (RCTs) evaluating the effects of new drugs in patients with PsA; therefore, during the 18° Target Therapies Meeting 2016, this issue was recognised as a primary unmet need of PsA and placed in the translational science field alongside other key aspects related to disease pathogenesis and cytokines inter-relationship, and the development of predictive markers of disease onset and progression (9). A previous consensus forum on unmet needs in PsA had already highlighted the need for a more comprehensive assessment of PsA progression (10).

Given the role of pathological new bone formation in PsA and the paucity of data on the clinical relevance of this feature, we carried out a literature search to address this topic.

Methods

The literature search was performed using two Internet engines (PubMed and EMBASE databases), selecting the items with the following criteria:

- Limits: humans, time window: 1980-February 2018.
- Inclusion criteria: phase-III RCTs, observational studies (prospective or

retrospective cohort studies, case-control studies, and case series studies), and English language publications.
- Exclusion criteria: studies in languages other than English, case reports, letters, editorials, and grey literature.

An additional literature search was carried out by hand searching in the reference lists of articles obtained by internet engines, seeking among the articles published in the main Rheumatology journals, abstracts of 2014, 2015, 2016 and 2017 EULAR and ACR meetings.
The key words were: psoriatic arthritis, bone damage, bone apposition, juxta-articular bone formation, bone spur formation, bone remodelling, osteoproliferation, enthesophytes, bone formation biomarkers, imaging, radiography, DMARDs, biological drugs.
The process of literature screening and the output obtained for this review is showed in Figure 1.

Results

New bone formation in peripheral joints and entheses

Bony nodules in digit joints are the expression of new bone formation, typically found in areas different from those where erosions are usually seen. This observation suggests that osteoblast-mediated unbalanced bone turnover is not necessarily linked to osteoclast-disrupted homeostasis (5). This anatomical uncoupling between bone resorption and bone growth may also be detected in a single patient, possibly reflecting a different pattern of cytokines and growth factors in different musculoskeletal sites (11). The main occurrence of bone apposition was demonstrated at the entheses insertions, resulting in the formation of enthesophytes and syndesmophytes (12, 13). A comparative study of 30 RA and 58 PsA patients on the structural changes in the metacarpophalangeal (MCP) joints of the dominant hand, evaluated by high-resolution micro-computerised tomography (CT), showed that PsA periarticular bone changes are different from RA lesions (13). Although PsA patients had the same number of bone erosions as RA patients, they were smaller in size and depth. Moreover, while RA erosions appeared U-shaped, PsA erosions were F- and tubule-shaped and more evenly distributed. In PsA patients osteophytes (as they were defined by the authors) were more numerous, more extended toward the radial and ulnar sites with a tendency to involve the whole circumference of the periarticular bone surface ("bony corona"). A study evaluating the effect of adalimumab on the progression of bone damage in 41 PsA patients, found that at baseline, using standard radiography, 73% of patients had erosions, 85% joint space narrowing, and 68% new bone formation (14).
In digit joints, the inflammation of capsular and local ligament attachments to the perichondral bone seems to be the main pathophysiologic mechanism underlying enthesophyte formation and consequent bony nodules, with an osteoarthritis (OA)-like pattern (15). Although a high-resolution quantitative CT study of the MCP joints showed that in PsA and OA bone spurs are present in different sites (16), a synergistic overlap of these two articular disorders might occur in patients with both a psoriatic and an osteoarthritic trait (17).
The association between psoriasis (without PsA) and new bone formation around the MCP joints was proved by two micro-CT studies, suggesting that this psoriasis is a predisposing factor for bone apposition (18, 19). In these studies, periarticular enthesophytes were much more frequent in psoriatic patients than in healthy controls. Moreover, a higher prevalence of subclinical inflammatory lesions was found in psoriatic patients without PsA (20).
In PsA patients, new bone apposition may occur in any entheseal site. The CASPAR study assessed the sensitivity and specificity of plain radiograph features of peripheral enthesopathy at major sites in 588 PsA patients and 525 patients with other inflammatory diseases. New bone formation at sites of attachment of inguinal ligament, sartorius and rectus femoris muscles to the ilium was significantly more frequent in PsA patients (OR 3.01, 95% CI 1.13-8.02) than in patients with other inflammatory diseases (21). A recent study has shown that bony changes at hand flexor tendon insertions were significantly more frequent in 37 PsA patients than in 47 RA patients and 10 healthy controls (22). All these findings are in line with the widely recognised notion that bony spurs secondary to enthesitis are the hallmark of the spondyloarthritides (SpAs) and that they may be found at any entheseal insertion.
In addition to iuxta-articular bone apposition, psoriatic patients without arthritis also have more peripheral enthesophytes than normal subjects, as showed by several ultrasound (US) studies (23, 24, 25).
The effects of PsA on bone mineralisation are still a matter of debate. In a study of 32 RA and 32 PsA patients (95% in cDMARD therapy, 12.5% RA and 34.5% PsA patients also taking tumour necrosis factor inhibitors (TNFis)), at 12 month follow-up, hand periarticular bone mineral density measured by digital x-ray radiogrammetry showed a significant bone loss in RA patients but a significant bone gain in PsA patients (26). A study evaluating bone microstructure and volumetric BMD by high-resolution peripheral quantitative CT of the distal radius in 50 PsA patients showed that these patients had less bone changes than seropositive RA patients (27). However, using the same imaging technique, it was found that 50 PsA patients had a lesser degree of mineralisation than healthy controls and psoriatic patients without arthritis (28).

Imaging and scoring of new bone formation

In PsA, articular imaging is an essential tool for diagnosis, disease assessment, and treatment response. Since ultrasonography (US) and magnetic resonance imaging (MRI) can detect overall musculoskeletal inflammation and bone changes, they have been widely considered the most reliable instruments for an early diagnosis. However, radiography is still the tool used to score joint damage and to measure its progression (29), and it may help diagnosis and classification. For instance, radiographic evidence of a new bone formation may be the only sign pointing to PsA in patients with arthritis seronegative for the rheumatoid factor (30) and radiographic juxta-articular bone formation is included

in the CASPAR criteria (8). The recent EULAR recommendations for the use of imaging in SpAs diagnosis and clinical management, state that conventional radiography should be used to monitor structural damage of peripheral SpA and that MRI and US may provide additional information (31).

Scoring systems based on standard radiography

Most of the radiographic scoring systems aimed at evaluating bone damage in PsA are derived from existing scoring methods for RA and AS. The following systems have been proposed to evaluate peripheral joint damage in PsA (Table I): the modified Steinbroker method, the modified Sharp score, the modified Sharp-van der Heijde score (SHS), and the Psoriatic Arthritis Ratingen Score (PARS) (32, 33).

In comparison with the original methods, these PsA versions were modified to account for typical features of this disease such as distal interphalangeal (DIP) joint involvement and osteolytic changes. The PARS is the only system specifically developed for PsA and, in contrast to the others, includes the evaluation of new bone formation (33). This method measures separately bone destruction and proliferation in 40 hands and feet joints. Each evaluated joint is scored from 0 to 5 for bone erosion and from 0 to 4 for bone proliferation (regardless of the type of bone apposition), for a total score ranging from 0 to 360 (0-200 for erosion and 0-160 for proliferation). These scoring systems proved to have a good feasibility, reliability, and sensitivity to change in PsA (34). The PARS had been validated by a previous study in 20 PsA patients whose radiographs were evaluated at a mean interval time of three years (33). This study showed a weak correlation between the destructive and proliferative changes suggesting the uncoupling between bone resorption and bone growth. A single-centre observational study in 72 patients with early PsA evaluated with the PARS at baseline and after five years revealed that the proliferation score contributed more than the destruction score to the change in the total score (35).

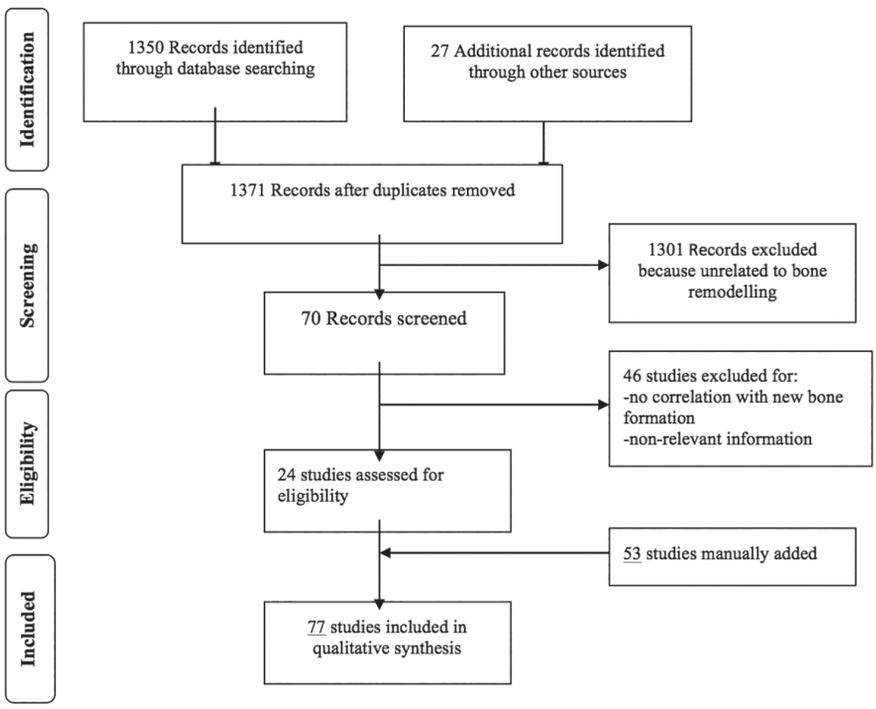

Fig. 1. Flow chart for the review studies selection.

Despite the importance of bone proliferation in PsA peripheral joint damage, the modified SHS, which measures only bone and cartilage destruction, has become the most used method to assess the progression of joint damage in RCTs evaluating new drugs in PsA.

In a recently published proof-of-concept study, a new simplified scoring method combining the SHS and PARS was applied on 22 joints (121 points) of hands and feet. This method encompassed all of the three typical features of PsA bone damage (erosions, joints space narrowing, and new bone formation) and showed sensitivity comparable to the SHS (36).

In contrast to the peripheral involvement, the radiographic systems used to score PsA axial damage mainly evaluate bone apposition (syndesmophytes). Both the modified Stoke Ankylosing Spondylitis Spine Score (mSASS) and the Bath Ankylosing Spondylitis Radiographic Index (BASRI) have been validated for PsA spondylitis (37). A modified version of the BASRI (the PASRI), which includes the facet joints of three cervical vertebras, has been proposed to assess PsA spine damage (38). The reliability of these scoring methods in axial PsA has been confirmed by a study, which also showed that the PASRI might perform better than other systems (39).

Scoring systems based on US, MRI and CT

In addition to the traditional radiographic methods, the assessment of bone damage (including bone formation) in patients with PsA may benefit from newer imaging techniques such as, US, MRI, and micro-CT, which can detect the typical features of structural modifications in joints, periarticular tissues and spinal structures (40, 41, 42). These imaging methods are more sensitive than standard radiography (43), but reliable and feasible scoring systems based on them are not extensively used.

A PsA MRI scoring system (PsAMRIS) has been developed by the Outcome Measures in Rheumatology Clinical Trials (OMERACT) group to assess inflammatory and structural changes, including bone proliferation, in PsA hands (44, 45). An exercise conducted in a cohort of PsA patients treated with TNFis to test the performance of the PsAMRIS showed moderate/good reliability for most of the inflammatory features but a poor/untestable agree-

Table I. Main radiographic scoring systems used in PsA.

System	Joint scored	Features scored	Score
Modified Steinbroker	42 of hands and feet, scale 0-4	Juxta-articular osteopenia, soft tissue swelling, erosion, JSN, joint destruction (lysis or ankylosis)	0-168
Modified Sharp	42 hands, 12 feet, scale 0-5 JSN and for erosions	JSN, discrete erosion, joint involvement by erosion, extensive destruction	0-486
Modified Sharp-van der Heijde (SHS)	42 hands, 10 feet, scale 0-5 for JSN and erosions	JSN, discrete erosion, large erosion not passing/passing midline, combination of above	0-528
Psoriatic Arthritis Ratingen Score	30 hands, 10 feet scale 0-5 for destruction 30 hands, 10 feet scale 0-4 for proliferation	Erosion, destruction Bony proliferation, bony ankylosis	0-360 0-160

JSN: joint space narrowing

ment for bone proliferation (46). However, the results of this exercise were undermined by the very low values of structural damage. In a study evaluating adalimumab efficacy in reducing the evolution of bone damage in 41 PsA patients, using CT as a standard reference, sensitivity and specificity for bone proliferation were 40% and 93% for the PsAMRIS, and 26% and 96% for the PARS (14).

In PsA, US imaging is widely employed to evaluate both joint and entheseal involvement, but scoring methods based on this technique have been developed only for enthesitis. Up until now numerous methods that evaluate simultaneously inflammatory activity and soft tissue damage and structural damage of bone have been proposed (47). These methods are heterogeneous in terms of entheseal sites to investigate and lesions grading, and an agreement on which to use has not been reached. A composite US score encompassing both joints and entheses and inflammatory as well structural lesions has been proposed (48); however, given its complexity, feasibility and reproducibility of this method need to be established.

CT should be the most sensitive and specific imaging method to score joint and entheseal bone changes, including osteo-proliferation, but scoring systems for peripheral PsA based on this technique are not available.

MRI is the current gold standard to detect inflammatory changes in sacroiliac joints and spine of patients with axial SpA. A number of scoring methods based on MRI has been used to evaluate the effect of various drugs on axial inflammation (31). Some of them also measure bone damage but MRI, as well as CT, is not a recommended instrument to assess axial new bone formation in daily practice (31).

Biomarkers of new bone formation

Soluble biomarkers may be helpful for early diagnosis, assessment and monitoring of PsA activity, prognosis, and prediction of treatment response. As tissue remodelling is characteristic of PsA, most of the research in this field has focused on the products of bone, cartilage, and tendon turnover (49). The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) identified biomarkers as one of its research priority (50), especially with regard to the prediction of structural damage (51). Nevertheless, the topic of biomarkers of articular tissue remodelling in PsA has been the subject of a limited number of investigations. A summary of the results of some of these studies is reported in Table II.

In a controlled study, 52 patients with psoriasis, 26 of whom with PsA according to the CASPAR criteria, were compared with 26 healthy controls (52). Serum levels of receptor activator of nuclear factor-κB ligand (RANKL), TNF super family member 14 (TNFSF14), matrix metallo-proteinase (MMP)-3 and cartilage oligometric matrix protein (COMP) were independently associated with psoriasis ($p<0.05$), while hsCRP, osteoprotegerin (OPG), MMP-3 and C-propeptide of type II collagen (CPII):C2C ratio segregated PsA from psoriasis without arthritis ($p<0.03$) (52). Serum levels of OPG, leptin, dickkopf-1(Dkk-1), osteopontin (OPN), and sclerostin (SOST) were significantly higher in 60 patients with PsA than in patients with psoriasis without arthritis (53). In a study enrolling patients with PsA (n=38), psoriasis (n=10), and healthy controls (n=12), patients were stratified according to peripheral joint bone changes on standard imaging. Macrophage-colony stimulating factor (M-CSF) and RANKL concentration were positively associated with radiographic bone destructive changes but no correlation was found between the number of joints with new bone formation and serum concentration of mediators of bone remodelling and other factors (54). In this study, Dkk-1 serum levels were significantly higher in psoriatic patients but they did not correlate with bone changes (54).

Serum levels of OPG, COMP, and IL-20 were significantly higher in psoriatic patients than healthy controls, irrespective of the simultaneous presence of PsA (55). In a small study 11 PsA patients had lower serum levels of osteocalcin (OCN) and higher levels of cathepsin K (CTSK), C-telopeptide of type I collagen (CTX-1), CTX-1/OCN and CTX-1/CTSK ratios than 8 patients with psoriasis and 14 healthy controls (51). In a longitudinal study, baseline serum levels of acute phase serum amyloid A (A-SAA) were independently associated with radiographic progression in RA (n=45) and PsA (n=17) patients. As A-SSA might stimulate the production of MMPs and TNF-α by synovial tissue, its effects on joint damage might occur through these substances in both the diseases (56).

Table II. Main clinical studies regarding biomarkers of new bone formation in PsA.

Reference	Type of study	n./type of patients	Intervention	Results/Conclusions
Chandran, 2010	Cross-sectional	52 26 PsA and Pso; 26 Pso; 26 HCs	Serum levels of IL-12, IL-12p40, IL-17, TNFSF14, MMP-3, RANKL, OPG, COMP, CPII, C1-2C, hsCRP.	Serum levels of hsCRP, OPG, and MMP-3, CPII:C2C ratio independently associated with PsA in patients with psoriasis.
Abij, 2014	Cross-sectional analysis	120 60 PsA; 60 Pso	Serum levels of Dkk-1, FGF23, IL-6; IL-1β, leptin, OCN, OPG, OPN, SOST and TNF-α.	Serum levels of OPG, leptin, Dkk-1, OPN, and SOST higher in PsA patients.
Dalbeth, 2010	Cross-sectional	60 38 PsA; 10 Pso, 12 HCs	Serum levels of Dkk-1, M-CSF, OPG and RANKL; patients stratified for appendicular bone changes	M-CSF and RANKL concentrations associated with bone destruction; no association found with bone proliferations
Connolly, 2012	Longitudinal	62 45 RA; 17 PsA	ESR and serum levels of A-SAA, CRP, MMP-1), MMP-2, MMP-3, MMP-9, MMP-13, TIMP-1), VEGF), C2C, C1,2C	A-SAA associate with bone damage progression in RA and PsA

Bone proliferation and biologics

Notwithstanding biologic disease-modifying anti-rheumatic drugs (bDMARDs) are considered the most efficacious agents for the therapy of PsA, their possible effect on bone damage is only partially known (5) and their impact on new bone formation has been scarcely studied. The phase III RCTs of all the TNFis available for the therapy of PsA showed that these drugs are capable of retarding radiographic progression as measured by the mSHS in the short and long term (57-66). However, as this scoring method includes only erosions and joint space narrowing, these trials do not provide data on the effect of TNFis on the new bone formation.

Given the known capacity of TNF-α to promote osteoclastogenesis and inhibit bone formation mainly through the Dkk-1/Wnt mechanism (11, 67-69), not surprisingly the suppression of this cytokine may reduce the destructive bone damage. However, data on the effects of TNFis on the serum levels of soluble factors involved in bone turnover are scarce and unclear. TNFi influence on serum Dkk-1, RANKL and OPG was assessed in 27 PsA and 25 RA patients treated with these agents (70). After 12-month treatment, the serum levels of Dkk-1 and RANKL had not changed while OPG levels were significantly higher only in RA patients. At this time point, Dkk-1 levels were lower in PsA than in RA patients but the difference was not significant. RANKL levels were higher at all time points in PsA patients (70).

In a small study of 41 patients with PsA, treatment with methotrexate (MTX) or TNF did not condition the pathological new bone formation at the metacarpophalangeal joints, as measured by high-resolution micro-CT at 1 year (71). The size of the bony spurs significantly increased from baseline to one year regardless of the therapy (mean ±SEM change +0.23±0.02 and +0.27±0.03 in the TNFis and MTX group, respectively) (71). In contrast, in an open-label trial 41 PsA patients treated with adalimumab did not show a progression in erosive or proliferative hand bone changes after 48 weeks as measured by PARS, PsAMRIS, and CT (14).

Similarly to the TNFis, ustekinumab, and secukinumab (two new bDMARDs targeting the IL-23/IL-17 pathway) proved to be effective on the progression of joint bone destruction but their effect on new bone formation was not studied (72, 73).

Discussion

This review focused on aspects of new bone formation, mainly in the appendicular skeleton, occurring in PsA patients that may have relevance in clinical practice. Exceeding bone can be found in the periarticular area of small joints and at the tendon insertions much more frequently in PsA patients than in RA patients and healthy controls. These bony changes may also be seen in patients with psoriasis without clinical arthritis, suggesting that this feature is a general characteristic of the psoriatic disease. In the literature, PsA abnormal bone proliferations in the peripheral skeleton have been referred to as enthesophytes, osteophytes, or bony spurs. As this various terminology may be confusing (osteophytes, for instance, are generally considered typical of OA), an agreement on the definitions should be reached. New bone formation in the peripheral skeleton is common in PsA, occurring at a periarticular level in about 70% of patients treated with TNFis and, at tendon insertion level, probably in nearly all the PsA patients.

As the relationship between peripheral osteo-proliferation and patients' disability has never been properly studied, the burden of this specific feature in PsA cannot be established. However, while enthesophytes at tendon insertions *per se* are not likely to lead to function impairment, new bone apposition in the joints may be responsible for various degrees of loss of articular movement up to joint ankyloses. It has been reported that, in the long term, new bone formation might contribute to total peripheral joint damage more than destructive changes (35).

Proliferative bony changes are clinically relevant not only for their possible impact on joint function but also for their diagnostic usefulness. In fact, in patients with undifferentiated peripheral arthritis, the detection of periarticular bony spurs may be indicative of PsA. Similarly, in psoriatic patients with

widespread chronic pain, enthesophytes at the tendon insertions might help distinguish PsA from fibromyalgia (74).

Standard radiography is still widely used to detect bony lesions in PsA, even if US, MRI, and CT are more sensitive. The PARS is the only validated scoring system that includes the evaluation of periarticular proliferative changes but, in virtually all of the PsA RCTs, the SHS was the method used to measure the progression of joint damage. The US is more sensitive than traditional radiography in revealing bony spurs and seems to be the best instrument to evaluate tendon insertions. While a number of scoring systems may be applied to measure entheseal involvement at the tendon insertions, no US-based method exists to quantify juxta-articular enthesophytes. MRI and CT are the most sensitive imaging methods to evaluate peripheral bone apposition and the PsAMRIS, a MRI-based system that includes proliferative changes, has been proposed. However, because of limited availability, complexity or lack of scoring methods and, for CT, high radiation dose, both MRI and CT will be likely restricted to research settings.

Serum biomarkers of bone turnover may represent an essential prognostic tool to early identify the most aggressive subtypes of PsA (75) and they are being actively studied. Unfortunately, though several biomarkers associated with peripheral osteo-proliferation have been discovered, robust confirming studies have not been performed. The development of multiplex assays of biomarkers, based on mass spectrometry able to quantitatively measure proteins, may provide a validation of the identified biomarkers (76). Whether serum biomarkers predicting peripheral bone apposition in PsA will ever be helpful in clinical practice remains unknown.

The inflammatory cytokines targeted by the bDMARDs currently available for the PsA therapy (TNF-α, IL-12/23, IL-17) are likely to play a relevant role in the pathophysiology of peripheral osteo-proliferation (77), but how their inhibition might alter this process has not been elucidated. Theoretically, TNF-α blocking might enhance new bone formation by the effect of this cytokine on the Dkk-1/Wnt interaction; however, as this mechanism might be counterbalanced by the anti-inflammatory effect of TNF-α inhibition, the final result of this inhibition remains obscure. Surprisingly enough, all of the pivotal RCTs that studied the effects of the bDMARDs in PsA have focused only on bone and cartilage destruction. TNFis, IL-12/23 inhibitors, and IL-17 inhibitor all proved their efficacy in reducing progression of joint erosions and space narrowing but their effect on new bone formation was not studied. The few existing studies on this issue do not provide enough data for evidence-based conclusions. The lack of information about the effects of the bDMARDs on peripheral bone proliferation can be considered an important unmet need in the field of the therapy of PsA.

In conclusion, periarticular and entheseal osteoproliferation has relevant clinical implications in PsA. Translational researches fully addressing this topic are needed.

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