Therapeutic targets in psoriatic arthritis

Despite their common use in treating psoriatic arthritis, there is little evidence supporting the use of conventional disease modifying agents such as methotrexate. Although treatment with inhibitors of TNF-α has brought significant benefit to certain patients with PsA, many do not respond. TNF-α inhibitors have also demonstrably failed to prevent new bone formation, a critical aspect to the changes in PsA that ultimately leads to joint destruction and disability. The identification of several new targets in PsA, and the advent of recently approved compounds inhibiting these targets, heralds a new dawn for PsA. The differential relevance of targets in rheumatoid arthritis and PsA underlines the need for a paradigm shift in how we name, describe and categorize rheumatic diseases.

Keywords: IL-17 pathway • molecular network • novel therapy • psoriatic arthritis

General considerations

Much has been learnt by the success of highly specific cytokine targeting, using biologic agents, in specific inflammatory diseases. However, even more has been learnt by noting the failure of these same agents in other inflammatory conditions, especially in instances where the responsive and the unresponsive diseases are thought to have a biological kinship. If Moll and Wright had difficulty persuading their colleagues at the time, of the existence of a phenotypically distinct entity to rheumatoid arthritis (RA) which we now know as psoriatic arthritis (PsA), their case would have had no adversaries today. The clinical phenotypic expression of PsA is now recognized to be quite different to that of RA. This is true at the microscopic level as well as during synovial examination with an arthroscope, where differing cellular infiltrates and vascular patterns are recognized [1,2]. More importantly, however, RA responds to a number of very specific cytokine blockades, where PsA does not (e.g., IL-17 antagonism). This underlines the importance of a varying cytokine hierarchy in the differing disease networks.

There is now a strong case to be made for developing a taxonomy of diseases (inflammatory and others) based not on clinical features, but rather on a more meaningful biological basis. This might begin with examining the varying levels of importance of certain cytokines in a given pathology [3]. A more advanced nomenclature and classifications approach would develop from a clinically and biologically meaningful system, based on a complete understanding of the disease networks [4].

The dawn of new era for PsA

Before late 2013, the last drug to be approved in Europe targeting a novel pathway in PsA was leflunomide, and even this was as far back as 1999. Furthermore, this was not itself a novel agent, simply an extension of existing licensed indications. Therefore, although it is true that over the last 15 years there have been additional agents targeting the TNF-α pathway, agents targeting truly novel pathways in PsA have been lacking. Both the European
Medicines Agency and the US FDA recognize that for those with PsA who have not responded adequately to TNF-α inhibition (TNFi), there are few alternatives. However, these past 18 months have seen two truly novel compounds meeting licensing requirements and reaching market, and at least one agent very likely to meet approval in the near future. All this makes for an exciting new era in the treatment of PsA.

Is PsA an important pathology?
PsA is the second most common inflammatory arthropathy [5], and it is now recognized that it is still both under recognized and under treated [6,7]. To address this, efforts have been made to improve recognition of PsA [8]. Since psoriasis precedes PsA in approximately 80% of cases, many of these efforts focus on the inflammatory dermatology clinics [9,10]. Importantly, PsA most frequently affects young people, with most studies reporting an age of onset in the 4th decade of life [11–13]. Quite apart from the short and medium-term deleterious effects of PsA on patients, as evidenced by measurements of pain and mental well-being, the disease itself is inherently destructive to bone, cartilage, enthesis and other soft tissues [14,15]. Furthermore, patients with PsA also have reduced longevity, principally due to increased cardiovascular mortality [16].

Understanding that PsA has a destructive nature is important, as failure to achieve satisfactory abrogation of the aberrant inflammatory response, may result in disability, with further implications for quality of life and the ability to remain in employment. In fact, patients with PsA have similar HAQ scores (a validated measure of disability) as patients with RA [17]. There is now some evidence suggesting that the same ‘window-of-opportunity’ exists early in the natural history of PsA as in RA, and it is therefore becoming increasingly important to treat these patients as quickly as possible after the diagnosis has become established [6].

Why is there a need for novel targets?
PsA has been shown to be painful, destructive, disabling, and patients have a decreased life expectancy. The disease is, therefore, not dissimilar in many of these parameters to RA, but in RA, B-cells, IL-6 (IL-6) and the T-cell co-stimulatory molecule CD80/86, have all been shown to be relevant targets that have been exploited by approved biological therapies. In PsA, none of these agents have been approved. Despite the presence of B-cells in abundance in the synovium of patients with psoriatic arthritis [18], the results of an initial pilot study of rituximab in PsA was disappointing. No clinical trials have yet been performed evaluating tocilizumab for PsA, but there are a number of case reports with varying results [19–21]. There is already some evidence to support the use of abatacept to treat patients with PsA. In a phase IIb study of abatacept in PsA, a 3 mg/kg dose was associated with better skin response, while 10 mg/kg dose (the dose approved for RA) was associated with better ACR20 response [22]. Abatacept is now being studied, delivered subcutaneously, in a Phase III trial.

It is also worth noting that the primary outcome for most RCTs in PsA is ACR20, a very modest treatment benefit, and only 40–60% of patients achieve this.

PsA is, therefore, a significant burden to patients and a costly disease to the wider healthcare system, but has not been witness to the expansion of drugs with novel targets that RA has been the beneficiary of. Indeed, existing first-line therapies for PsA such as methotrexate and leflunomide lack an evidence base from randomized controlled trials (RCTs) [23].

Immunopathogenesis of PsA
The centrality that TNF-α and related Th1 response cytokines have in the immunopathogenesis of PsA is well recognized and exploited by targeted therapies. TNF-α is a critically important cytokine in PsA, and its presence has been demonstrated in the inflamed synovium, the enthesis, as well as in psoriatic skin [24,25]. TNFi has offered the most significant advance in treatment of PsA witnessed to date. TNF-α appears to be a key player operating as a ‘node’ in the disease network, and is responsible for the production of several other proinflammatory cytokines including IL-1, IL-6, IL-8 and IL-12, although it appears that these cytokines play a more minor role in the PsA phenotype than in the RA disease network [3,26,27].

The most promising novel targets that have been identified over the last decade concern protagonists in the IL-6 and the IL-23/IL-17 pathways.

IL-17 was first identified as inducing the production of IL-6 and IL-8 in human RA synoviocytes and skin fibroblasts from normal individuals, betraying its inherent proinflammatory characteristics [28,29]. It was then demonstrated that IL-17 was produced by RA synoviocytes, and that blockade in vitro (using specific IL-17 monoclonal antibody) could significantly reduce the production of IL-6 [30]. This set of experiments also demonstrated an important relationship concerning synergy between cytokines. In this case, it was observed that IL-17 must be in the presence of IL-1 and TNF-α, to maximize production of IL-6 [31]. The signaling of IL-17 through its major receptor (IL-17RA) is unique because it does not utilize JAK and STAT pathway, instead favoring an association of receptor with adaptor protein ACT1. The binding of IL-17 to its receptor thus activates NF-κB [32,33]. Quite apart...
from increasing proinflammatory cytokine expression in this manner, IL-17 receptor activation results in the stabilization of mRNA encoding for growth factors and chemokines [34,35].

A major source of IL-17 is a set of helper T cells quite distinct from the classical Th1 and Th2 types, known as Th17, after their signature cytokine [36,37]. These cells do not produce IFN-γ or IL-4, thus distinguishing them from classical helper T cells. Their differentiation from naïve T cells to specific Th17 cells is more complicated than originally thought. IL-23 increases the levels of IL-17 in naïve T cell culture [38], but there is no IL-17 receptor on naïve T cells. However, it has become clear that IL-23, which is produced by activated dendritic cells, is nonetheless important in TH17 cell differentiation, but that it is not the only pathway supporting this differentiation.

IL-23 is closely related to IL-12, sharing a common p40 subunit. Given the known importance of IL-12 in TH1 responses, it has been thought that targeting the shared p40 subunit may abrogate both TH1 and Th17 responses.

One theoretical attraction of this axis is the realization that this pathway can lead to the expression of all four features typical of psoriatic arthritis: skin and joint inflammation, erosive bone disease and pathological new bone formation. Thus by inhibiting the IL-23/17 axis at any of several levels, improvements in each parameter may be expected (see Figure 1).

**TNF-α**

There are now five TNFi agents approved in Europe for PsA, and their efficacy in treating the disease has a good evidence base, whether used with or without conventional DMARDs [23,39,40]. However, despite the availability of five individual TNFi, collectively they target a single pathway, and there is no evidence to support significant differences in their efficacy on articular, enthesial or axial disease, or indeed any major differences in safety profiles [41–44].

The use of TNFi has the additional benefit of efficacy in treating spinal symptoms where conventional DMARDs show little efficacy [45], however, whether this symptomatic improvement is reflected in a true retardation of the destructive process in the axial spine is contested. There certainly appears to be a reduction in axial inflammation as evidenced by decreased pain, decreased acute phase reactants and greater lumbar spine flexibility, but the progression of radiographic findings is a more complicated matter.

One important consideration regarding the use of TNFi in PsA relates to the differences observed in bone changes between RA and PsA, in the natural history of the respective diseases. In contrast to RA where only erosive changes are seen in bone, both anabolic and catabolic effects on bone are observed in PsA, and can be assessed using widely available imaging modalities.

Firstly, the bone erosions are architecturally distinct in PsA where the erosions are themselves associated with new bone formation, resulting in smaller erosions with significant periosteal bone proliferation, thereby giving them an ‘inverted omega’ appearance [46]. Secondly, new bone formation also tends to occur at the site of the enthesis, distal from the erosive sites. The effects of the new bone formation in PsA must at least be considered of equal importance in the development of functional impairment as the development of erosions. For example, in severe cases proliferating bone develops over the entire circumference of a small joint, giving the appearance of the so-called ‘bony corona’ on imaging, and resulting in significant disability [47]. In addition, since the enthesis is the principal site of new bone formation, and is also the junction where inflamed periarticular tissue and the bone surface meet, changes here effecting the attachment of tendons and their muscles to bone can lead to significant disability [48].

We concentrate here on the anabolic effects observed in PsA, because it is increasingly recognized that preventing this will be as important as preventing erosive disease in treating PsA. However, the TNFi have consistently failed to demonstrate any efficacy in achieving a reduction in the progression of new bone formation, and this is now seen as a significant failing of TNFi [47]. Moreover, radiographic scores in PsA focus on bone erosions, and will need to address the issue of new bone formations as well [49].

There is a clear biological basis for the lack of efficacy of TNFi on new bone formation. While TNF-α promotes osteoclast differentiation by inducing the expression of receptor activator of NF-κB ligand in the joints [50] (the essential differentiation factor for osteoclasts), it is also a potent suppressor of osteoblast differentiation [51]. Consist with this biology, the antagonism of TNF-α in PsA does not retard new bone formation [46], and indeed similar results are seen in ankylosing spondylitis (AS), where new bone formation has long been understood to be an important pathological process [52,53]. The importance of IL-22 in promoting new bone formation via activation of STAT3 and subsequent upregulation of genes regulating bone formation has only recently begun to be understood, and thus far, no agents have specifically targeted this pathway [54]. However, one report over a longer period of time (8 years) in AS, with a retrospective design and small numbers, suggests there may be less new bone growth in those treated with TNFi [55].
Figure 1. Resident DCs when activated secrete IL-12 and IL-23. IL-12 facilitates differentiation of Th1, IL-23, together with other cytokines facilitate differentiation of Th17 cells, which in turn secrete IL-17 as well as IL-21, IL-22 and IL-23. Inflammatory effects are seen at skin and synovium due to the actions of the proinflammatory cytokines IL-1, IL-6, IL-8 as well as TNF-α. Cartilage and bone degradation occurs due to the production of MMPs by synovial fibroblasts and macrophages. New bone formation occurs via IL-22 phosphorylation of STAT3 which activates expression of genes regulating bone formation.

Knowing the centrality that TNF-α occupies in the inflammatory cascade of PsA, and witnessing the success TNFi has on the abrogation of the inflammatory disease in patients, it is clearly disappointing that little or no effect is seen on new bone formation. This may be evidence of ‘uncoupling’ of inflammation from radiographic progression. However, it has also been suggested that there must be other cytokines involved (such as IL-22), that are important to this critical manifestation of PsA. Other than the role IL-22 plays, remarkably little is known about the biological mechanisms underlying the development of new bone in PsA, and while serum CRP and TNF-α are soluble markers of erosive disease, no such markers have yet been developed to measure new bone formation in PsA, which might allow the identification of potential therapeutic targets.

Questions remain about whether monotherapy with TNFi is any different than combination therapy (TNFi with methotrexate), and it is hoped that more data will be available on this in the near future. The design of trials to date do not allow for a comparison of monotherapy with combination therapy. From the limited data available, Mease's and Gladman's group's found no difference in structural progression between etanercept and adalimumab, respectively, each alone or in combination with methotrexate [56,57]. Others have found that there was no clinical benefit to the addition of methotrexate to TNFi, but that TNFi survival may be increased in those receiving combination therapy [58,59]. Another interesting concept is the selective targeting of more than one cytokine in a disease process, usually selecting cytokines that act synergistically. This might be achieved by combining existing biologic therapies [60]. To date, safety fears in relation to the risk of infections and neoplasms have meant that studies involving a combination of biological therapies are few. Ustekinumab antagonizes both IL-12 and IL-23, and is the first licensed biologic with more than one target.

IL-12/IL-23

Our understanding of the pathophysiology of PsA, and in particular the recognition of role that the IL-17 and IL-12/IL-23 axis plays, has provided for an exciting...
planned integrated analysis was reported using data from the two studies together because radiographic outcomes required higher numbers to be enrolled to be appropriately powered. This is a challenge in clinical trials where the primary or secondary outcomes are measured by radiographic scores over a relatively short period of time. However, there are important points to note here; again no radiological study examining axial progression is reported, and the scoring method of plain films of hands and feet is imperfect, not taking full account of new bone formation [49]. In the end, only long-term follow will be able to make a determination as to whether inhibition of IL-12/IL-23 can retard new bone formation, and have a truly disease modifying effect on the axial skeleton.

IL-17
Secukinumab is a fully human anti-IL-17A monoclonal antibody, already licensed for psoriasis in Europe earlier this year. Importantly, secukinumab at two doses performed better than etanercept for psoriasis in the FIXTURE head-to-head trial [63]. This is not only important from a drug selection and marketing point of view, but also informs us on the hierarchy of cytokines in specific inflammatory diseases, although we cannot extrapolate anything from this in relation to PsA.

There is now a growing body of evidence to suggest that secukinumab is efficacious in PsA. An initial small proof-of-concept study including 42 patients for 24 weeks, although failing to meet the primary endpoint (ACR20 at week 6), reported significant improvements in secondary outcomes [64]. The subsequent FUTURE 1 and 2 phase III RCTs have met their primary endpoints of ACR20 response at week 24, FUTURE1 demonstrating a 50.5 and 50.0% ACR20 response to secukinumab at 75 mg and 150 mg, respectively, and FUTURE2 demonstrating 29.3, 51.0 and 54.0% ACR20 response for doses at 75, 150 and 300 mg, respectively, versus 15.3% for placebo [65,66].

The two studies differed in their methodology for loading doses, as well as in subsequent dosing regimens, which may in part account for the differences in response rates seen at the 75-mg dose between the two studies. Data presented at EULAR’s annual congress in 2015 reported on response rates to secukinumab in patients naive to prior treatment with TNFi, compared with those TNFi nonresponders. As might be expected, better responses were seen in the naive group overall. Only those TNFi nonresponders receiving the 300-mg dose saw a statistically significant benefit when compared with placebo [67]. Notwithstanding the problems reporting radiographic outcomes in PsA discussed earlier, further data suggest that secukinumab may be able to retard...
such as TNF-α-protection. In this manner, blockading two cytokines presents important failsafe immune mechanisms in host appropriate inflammatory responses in PsA, actually representing a difference in PsA. Perhaps what we witness as frustrating redundancy in our attempts to abrogate inappropriate inflammatory responses in PsA, actually represents important failsafe immune mechanisms in host protection. In this manner, blockading two cytokines such as TNF-α and IL-1, which have broadly similar effects, will not increase efficacy of treatment, but could predictably increase incidence of infections.

Small molecular inhibitors
Apremilast is a small molecular inhibitor (compounds with a molecular weight of less than 1 kDa) licensed in Europe since February 2015, and it constitutes another major advance in the treatment of PsA. Small molecular inhibitors have the benefit of being delivered orally, and are expected to be produced at a much lower cost than biological compounds [76]. Their targets in inflammation are usually intracellular signaling, principally kinases, which represent an attractive therapeutic target. These kinases act upstream of mediators such as TNF-α, and thus selective inhibition may inhibit several inflammatory processes [77,78]. The most notable success in this regard has been tofacitinib, where efficacy in RA has been established, and the agent is licensed in the USA (but not in Europe) for this indication [79]. Although many compounds have been studied, few have made it as far as phase III study. Apremilast inhibits phosphodiesterase 4 (PDE4), one of 11 phosphodiesterases widely expressed in a heterogeneous array of cell types, and it hydrolyses and degrades cyclic AMP [80,81]. PDE4 is involved in modulating inflammatory processes downstream from protein kinase A, changing the cytokine profile in varying cell types [82]. Apremilast inhibits the production of TNF-α, IL-12, as well as the chemokines CXCL9, CXCL10 and CCL4, in human peripheral mononuclear cells stimulated with bacterial lipopolysaccharide. In T cells, apermilast decreases the expression of IFN-γ, and in neutrophils inhibits the production of IL-8 [83,84].

The PALACE Phase III trials compared two doses of apermilast with placebo in those with active disease despite prior treatment with DMARDs or biologics, and each demonstrated better performance than placebo in reaching ACR20 [85]. Two-year follow-up data presented recently, in open label extension for...
the PALACE3 trial demonstrated sustained ACR20 responses \[86\]. There were no new safety concerns, although tolerability due to GI disturbances can be an issue in the short-term, and there was a less pronounced effect on dactylitis and enthesitis when compared with ustekinumab and secukinumab \[87\].

There is a biological basis that tofacitinib may be beneficial in PsA, with recent data demonstrating that it inhibits proinflammatory mechanisms in both in vitro and in vitro synovial models \[88\]. There are currently three clinical trials of tofacitinib in PsA, and it is hoped that they will validate the JAK-STAT pathway as a relevant target in PsA. Tofacitinib has been shown to inhibit IL-4 dependent Th2 differentiation. It also interferes with Th17 differentiation, inhibiting the expression of the IL-23 receptor and the signature cytokines of Th17 cells including IL-17, and IL-22, when naive T cells were stimulated with IL-6 and IL-13, but this was rescued when the same cells were stimulated in the presence of TGF-β. In a model of established arthritis, tofacitinib improved disease, inhibiting the production of inflammatory mediators and suppressing STAT1-dependent genes in joint tissue \[89\]. There is very limited data on the effect the small molecular inhibitors have on radiographic progression in the context of PsA. The biology of small molecular inhibitors is complex as their targets often represent ubiquitous intracellular signaling pathways that are incompletely understood and are essential for both physiological and pathological processes. Some concern exists about how truly selective these molecular inhibitors are, and about the safety in relation to both serious infection and malignancy risks.

As outcomes such as resolution of dactylitis and enthesitis have been reported as secondary outcomes in the trials of both the biologic agents and small molecular inhibitors, it is not possible to draw conclusions as to which agent performs best for patients with a high burden of a specific presentation of the disease. Only ustekinumab has data on radiographically detected bone changes in Phase III trials \[62\].

**Conclusion**

PsA is an important disease and is still underrecognized. Our recent advances in understanding the underlying pathophysiology of this disease have contributed to our understanding of inflammatory biology in general. The recognition of the differences in cytokine biology, as well as in molecular networks between differing inflammatory diseases, underscores the inadequacies of current disease taxonomy. A complete understanding of these networks, and knowledge of the important nodal differences between them, promises to allow better prognostication, the identification of better biomarkers, as well as more rational selection of treatments. Mapping these networks may also reveal further putative targets.

For now, however, the emergence of drugs targeting IL-12/23 and IL-17 represents the most significant advance in recent years, and together with the more recent emergence of apremilast as a proven agent, these agents represent an exciting dawn of a new age in PsA.

**Future perspective**

Although discreet phenotypes of PsA are well described based on their clinical features, a more meaningful categorization of these may be achievable by a fuller understanding of the disease network(s). It no longer makes sense to pursue the established clinical nomenclature, and this should be dispensed with in favor of describing diseases by their disease network. An understanding of the importance of the cytokine hierarchy is the first step toward this more meaningful classification system.

It is also notable that current strategies at identifying targets in PsA are still focusing on treatment, rather than prevention. Isolating the biological processes around the time of loss of self-tolerance, may introduce the possibility cure, or even prevention in the future.

What is clear is that for the moment, physicians and patients must employ a treatment strategy that is rational, and evidence-based, utilizing therapies that are already available and maximizing the benefit that these can offer. Unfortunately, there is a dearth of evidence to inform physician. For example:

- Which nonbiological DMARD should be commenced as first line therapy.
- Whether to switch to biologic therapy after failure of a single nonbiological DMARD, or add/change another DMARD.
- What novel agent is best (lack of head-to-head trials).

However, new evidence suggests that even with the currently limited (though expanding) armamentarium, regular review using an aggressive treat-to-target strategy in PsA, results in better outcomes \[90\].

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Executive summary

- A significant number of patients with psoriatic arthritis do not respond adequately to TNFi.
- PsA is an inherently destructive disease, which causes articular changes early in the disease course and results in disability, with patients reporting similar HAQ scores to RA patients.
- The number of targets therapeutically exploited in PsA has failed to keep pace with those in RA.
- A novel approach to classification and nomenclature in describing rheumatic diseases is required. This must take account of new developments in our understanding of rheumatic diseases, as technologies advance and provide a more complete understanding of disease molecular networks. Such a system must integrally apply a biologically meaningful template to describe disease.
- Undoubtedly the most important development in our understanding of the pathogenesis of PsA concerns the IL-17 inflammatory pathway. There are clearly important differences in the nature of the inflammatory process in PsA when compared with other inflammatory conditions such as RA, and it is necessary to investigate these further to fully understand the disease network.
- The IL-23/IL-17 pathway is an attractive target in PsA because the downstream molecules all participate in at least one of the key pathological features of PsA.
- New agents will hope to tackle the characteristic pathological new bone formation which is peculiar to the spondyloarthropathies, and leads to deformity and disability.
- There is likely significant functional redundancy in the pro-inflammatory cytokine networks, leading to similar results in inflammatory indices and other outcomes between TNFi and inhibition of novel molecular targets such as IL-17.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

•• A clear description of the relevance of cytokine hierarchies in various inflammatory diseases.
•• Seminal paper demonstrating the utility of mapping the disease networks, even incompletely.
Excellent overview of IL-17 biology.


Review of the problem of pathological new bone formation in PsA.
Future science group

Review Orr & Veale

• Demonstrates the presence of IL-23+ cells at the enthesis, underlying the importance of both the enthesis and the IL-23 pathway in PsA.


Weinblatt M, Schiff M, Goldman A et al. Selective costimulation modulation using abatacept in patients with...


• Summary of evidence for adopting a treat-to-target approach in PsA.