Psoriatic arthritis: embracing pathogenetic and clinical heterogeneity?

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Received and accepted on June 29, 2016.

Clin Exp Rheumatol 2016; 34 (Suppl. 98): S9-S11.

Key words: psoriatic arthritis, biologic therapy, strategy, pathogenesis

Competing interests: I.B. McInnes has received honoraria or research support from BMS, Abbvie, Pfizer, Novartis, Janssen, Celgene.

ABSTRACT

Psoriatic arthritis (PsA) is a clinically heterogeneous condition of skin, joint, enthesis and bone that provides considerable unmet therapeutic need. Recent treatment advances have offered new opportunities to improve quality of life and long term well being for afflicted patients. It is timely therefore, to consider the underlying heterogeneity inherent in the disease from a pathologic aspect so as to best optimise the choice and order of therapeutic application over time. Herein I will discuss the various contributions made by immune pathways to discrete tissue compartments that in turn might allow a more targeted approach to the management of PsA in which different tissues express variable severity of involvement.

Introduction

Psoriatic arthritis (PsA) is a complex syndrome comprising inflammatory disease of the skin, enthesis and synovium. Associated bone lesions are similarly complex, and perplexing, comprising erosion and structural damage, but also new bone formation leading to spondylosis, especially of the axial skeleton, although peripheral joints can also be affected. This in turn is reflected in varied and sometimes characteristic imaging features on plain x-ray, *e.g.* pencil and cup erosion, neoossification, through to ultrasound (*e.g.* neovascularisation) and MRI (*e.g.* enthesitis, tenosynovitis). Patients with PsA exhibit high levels of systemic comorbidities including cardiovascular disease, metabolic syndrome, osteoporosis and psychologic dysfunction. Reflecting its classification within the spondyloarthropathy (SpA) spectrum, PsA is also characterised by propensity to develop 'parallel' inflammatory 'diseases' including uveitis and inflammatory bowel disease. Moreover, the clinical course across the SpA spectrum is varied in terms of age of onset, gender bias and rate/severity of progression.

PsA is therefore a disease of remarkable clinical, imaging, prognostic and functional heterogeneity. A critical series of questions therefore arise: do each of the clinical lesions/affected tissues arise from common overarching pathogenesis, or unifying molecular pathways? Even if such a common pathogenetic origin exists, can we make assumptions that a distinct tissue will 'respond' to this given pathogenetic insult with an equivalent pathology? By corollary, should we expect a given therapeutic, particularly if monospecific (particularly a biologic antibody or receptor construct), to yield broad efficacy, exhibited at similar magnitude across a variety of affected tissues? These are questions of fundamental importance as we seek novel therapeutics. They are also pivotal as the move to apply therapeutic strategies develops momentum – analogous to the successful 'Treat to Target' philosophy that has substantially improved outcomes in people with rheumatoid arthritis (RA). How should we best combine modes of action in individuals with a common diagnosis, namely PsA, but anatomically discrete distribution, or magnitude of tissue involvement?

More than a decade ago, TNF blockade delivered a major success that advanced PsA management (1). A significant proportion of patients achieved clinical responses, with around 40-50% reaching minimal disease activity states over time. However, relapse, and/or loss of response is common and in a disease of relatively young age of onset, requiring treatment over decades, there remains considerable unmet need. We have learned subsequent, important lessons about pathogenesis via GWAS, *ex vivo*, and experimental studies. Built in part upon these advances, we witnessed the arrival of novel treatment modalities

targeting cytokines *e.g.* IL-12/23p40, IL-17A and intracellular signal pathways *e.g.* PDE4, JAK family (2, 3). The key challenge is now to optimise the strategic therapeutic value of these agents, and almost certainly the others that will be required, to maximise the levels of response achieved across tissues. We seek thereby to increase the number of patients ultimately achieving meaningful clinical remission and abrogation of disease progression.

In the following paragraphs, I shall address these fundamental questions drawing upon recent pathogenetic studies, interwoven with a perspective on the outcome of pathway-specific clinical trials when evaluated from the point of view of tissue specific responses. Perusal of the same reveals rather different responses, both in qualitative and quantitative terms, reflected in the outcomes that can be achieved in distinct tissues.

Tissue specific responses in the context of autoimmunity?

It has been recognised for some time that the immune system requires to balance the magnitude of host danger posed by an invading organism, to that level of tissue damage that can ensue upon elaboration of a response. The ideas contained in the original 'danger hypothesis' (4) have been elegantly revisited recently based on numerous recent advances, and might usefully inform the clinical conundrum offered by PsA (5).

It is likely that both pathogens, and cellular/structural elements within the affected host tissue, determine the nature of effector immune response(s), including the differentiation of T cell linages that emerge from the earliest local tissue and draining lymph node-dependent interactions. 'Sterile' inducers of inflammation, as likely occur in the context of autoimmunity, should therefore be subject to the same rules - thus tissues may differentially direct the phenotype and qualitative or quantitative nature of a local response in the context of autoimmunity. To state the obvious, there are likely to be fundamentally different demands placed on the immune response as it defends the gastrointestinal tract or skin as opposed to the exquisitely functionally sensitive microenvironment of the anterior chamber of the eye, or for that matter the normally sterile environment of the joint. A series of decisions made within tissues (including those influenced by stromal cells that themselves are now recognised to offer considerable tissue specific heterogeneous subsets) presumably influence the critical balance of host defence *versus* damage. This means that we should not assume that the pathologic pathways that govern pathology in the skin, joint or enthesis should be identical, even if there is a common overarching 'cause' of the disease.

Available evidence is consistent with this view though it is far from proven. For example, tissue transcriptomic evaluation of matched skin and synovial biopsies from PsA patients suggest intriguing differences in the expressed pathways (6) - the skin appearances are consistent with an IL-23/IL-17A dominant lesion whereas the synovial tissue has elements of IL-17A but also TNF driven pathways present by in silico pathway analysis. Examination of cellular subsets within the tissues also suggest subtle differences *e.g.* in the composition and expression profile of IL-17A expressing CD4 and CD8 T cells (7, 8). More comparative studies are urgently required. Equally, other influences may impose, or regulate emergence of 'tissue discrete' pathology - recent genetic studies describe loci that associate with PsA as opposed to psoriasis (without arthritis) and vice versa. Dense genotyping of immune related loci have uncovered new risk loci for PsA on chromosomes 1 and 5 (9). Others report 5 tissue exclusive loci - 3 associated with cutaneous psoriasis and 2 with PsA (10). Discrete impacts across different MHC class I loci are also now evident (11). The functional implications of such observations are not yet clear but will be important to unravel. Superimposed on this, there is increasing evidence for stromal cell heterogeneity within joints that may particularly define tissue locations (12). It is possible that discrete tissue programmes will influence the emerging inflammatory pathways and their phenotypic evolution. Future studies are needed to inform such possibilities.

A final and important consideration concerns discovery of the mechanisms that mediate significant co-morbidities in the PsA spectrum - there is generally considered to be increased risk of metabolic, vascular, psychologic and systemic bone morbidities in people with PsA that can adversely affect long term outcomes (13). Lessons from RA suggest that aggressive management of inflammatory disease is advantageous in this context. Whereas this is also a reasonable starting point in the management of PsA, it is worth noting that PsA patients in general present with higher BMI and potentially enhanced metabolic risk and it is not yet clear whether all of this metabolic risk is conferred by the inflammatory burden and as such comparison with RA could be misleading. For example, the IL-6 pathway that is partially implicated in altered lipid metabolism in RA is much less evident in PsA pathogenesis - CRP is often not a useful biomarker, clinical IL-6 blockade has been essentially unimpressive. The impact of skin and musculoskeletal diseases may also impose particular insult to the central nervous system (14) and as such psychologic risks should be better understood and aggressively managed once identified. Taken together this is a strong argument for clinical evaluation of the whole patient, with consideration given to the mechanisms driving disease in each tissue compartment, including co-morbidities, using tissue relevant disease activity measurements and thereafter offering treatment in a sequential and targeted manner.

Discrete responses seen in clinical practice and trials

Clinical trial data obtained thus far are also consistent with the foregoing discussion. Thus TNF inhibitors deliver robust and highly reproducible outcomes across the different agents thus far licenced for use (infliximab, adalimumab, certolizumab pegol, etanercept and golimumab). ACR20 response rates (primary outcomes at phase III) are in the order of 50-60% across stud-

ies (1). Similar response rates have now been observed in clinical trials evaluating biologic agents that involve novel modes of action, including ustekinumab (15) that targets the p40 subunit of IL-12 and IL-23, and secukinumab (16), that targets IL-17A, when administered to patients with PsA with active disease but in whom TNF inhibitors have not been previously tried. In those patients in prior receipt of a TNF inhibitor the response rates have been lower upon exposure to a new mode of action - the reason for this is not yet understood but may reflect a true biological refractory state, a variable clinical phenotype or as yet unidentified factors *e.g.* epigenetic alterations, stromal imprinting. Nevertheless, thus far different modes of action have not delivered high hurdle responses with sufficient frequency, nor have they differentiated on frequency of responders at any level.

In contrast, responses observed in cutaneous psoriasis are beginning to show intriguing differences, especially in the higher hurdle responses upon use of distinct modes of action. Thus whereas TNF inhibitors do indeed bring about improvements in clinical outcomes particularly as evaluated by PASI, that have been clinically useful – the magnitude of response, and the frequency of high hurdle responders (*e.g.* PASI90, PASI100), is proving higher in recipients of particularly IL-17A blockers (17). It is too early to determine whether IL-23 blockade can deliver similar impact. These clinical trial data are consistent with the notion that there are indeed discrete pathologies, or contributory factors ongoing in distinct tissues. An alternative, non-exclusive possibility is that the clinical outcome measures (including patient reported outcomes) that are used in skin and musculoskeletal disease trials respectively have different capacity to report on abrogation of the inflammatory tissue lesion itself - *e.g.* do other factors (*e.g.* residual damage, non-inflammatory pain pathways, cognitive distress) set a 'ceiling' on the level of response that can be achieved in the joints that do not apply to the detection and evaluation of severity of skin disease.

Conclusions

In the long term, we seek long lasting remission in PsA, or at least in medium term achievement of MDA status. The unique predictive power of having psoriasis in terms of incipient arthropathy raises rather interesting possibilities. Moreover, the existence of discrete tissue responses if confirmed provides for rational combinatorial targeting in future as we unravel tissue specific components of pathology. By this means we can reasonably seek to create tissue specific bespoke therapeutic regimens that can together provide definitive remission inducing therapeutics.

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