Personalised Medicine – a new reality in psoriatic arthritis?

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Since 1999, when the first biologics were licensed, the therapeutic options for psoriatic arthritis (PsA) have expanded rapidly. The first anti-TNF biologics targeting this predominantly myeloid-derived cytokine revolutionised the treatment of resistant PsA. In recent years, genome-wide association and functional immunology studies have informed the development of a number of different biologic therapies, in particular targeting interleukin (IL) 12/23 and IL-17 pathways (Nograles et al., 2009). Whilst this expansion of therapeutic options is welcome, there are few studies to guide therapeutic strategy, in particular the biologic choice in PsA.

We cannot currently predict why some people fail to respond to certain biologics but may respond with a switch to a different therapy. To date, our choice of biologic often rests on comorbidities, psoriasis severity (where differentiation between drugs has been shown) and in many healthcare settings, cost.

In an effort to address these issues, the authors of a recent study in Japan have trialled the use of baseline CD4 T cell immunophenotype characteristics to select an appropriate therapy in PsA. Th17 produce a number inflammatory cytokines including IL-17A and IL-17F and have high expression of the chemokine receptor CCR6 while Th1 cells express higher levels of the chemokine receptor CXCR3 (Crome et al., 2010). IL-12 is key cytokine for the differentiation Th1 cells and shares the p40 subunit with IL-23, a key differentiation factor for Th17. Ustekinumab neutralises p40 and this modulates both the Th1 and Th17 pathways. The authors first defined the peripheral blood Th1 and Th17 phenotypes based on CCR6 and CXCR3 expression on CD4 T cells and then measure co-expression of known T cell activation markers CD38 and HLA-DR (Kestens et al., 1994). They determine four groups based on the predetermined cut-offs (figure 1). Sixty-four PsA patients about to start biologic therapy were randomly divided into a standard care group (n=38) who were treated based on clinical features and a precision medicine group (n=26) where the choice of therapy was based on this peripheral blood lymphocyte analysis.

In the standard care group, the majority of patients (30/38) were treated with TNF inhibitors with only one receiving secukinumab. The precision medicine group showed more variation using TNF inhibitors (9/26), secukinumab (12/26) and ustekinumab (5/26). In both groups, there was a reduction in disease activity in both joints and skin. Outcomes were focused on peripheral arthritis (ACR, disease activity score [DAS] 28, clinical disease activity index [CDAI], simplified disease activity index [SDAI]) and skin (psoriasis area and severity index [PASI]). In the precision medicine group, significantly higher rates of ACR 20 response, SDAI and DAS28 low disease activity (LDA) were seen although other measures, including PASI responses, were not significantly different. The dropout rate was also higher in the standard care group with four patients discontinuing for drug reactions which seems surprisingly high.

This is the first study in PsA using baseline immunophenotype to select therapy and has shown some promising results despite the small numbers in each group. However the study has limitations suggesting strongly that further research is needed. The study is not powered to compare the two groups with no primary outcome stated. Whilst some outcomes were significantly different, this was not consistent raising issues of multiple testing. In particular, no difference in any PASI outcomes was seen despite the much higher use of secukinumab in the precision group which is surprising. It is not clear how the groups were randomly allocated and the differences between the groups, particularly with the small sample size may be relevant. There were more men (18/26) in the precision group who generally score lower on patient reported outcomes and at baseline this group had milder disease activity (making achievement of targets like LDA easier).

A number of key questions raised by this study need to be considered before adoption of this precision medicine strategy into clinical practice, in particular, the stability of the immunophenotype over time and in the context of synthetic DMARD therapies. Additionally, the rationale used for assigning the four immunophenotypes in the precision medicine group and the selection of

therapies is not clear. The authors demonstrate no difference in activated Th1 percentage between healthy donors and PsA patients, hence calling into question the relevance of the Th1 dominant group. Moreover, one might argue that ustekinumab should be the therapy selected for the Th1/Th17 co-dominant group since this monoclonal removes a common subunit from both pathways, yet this group was assigned to receive TNF blockade.

Yet despite these limitations, the novelty and potential applicability of the approach used in this paper is exciting. With the expanding treatment options in PsA, research is desperately needed to guide physicians on which drug may be optimal for each patient. In this study, TNF, IL12/23 and IL17A inhibitors were used in both groups, but it is clear from the standard care group that the majority of patients in routine practice still receive TNF inhibitors presumably due to longer term outcome data, physician familiarity and potentially cost with the advent of biosimilars. However 14 patients showed high levels of activated Th17 cells confirming the potential role of IL17 inhibitors which were used much more extensively in the precision group.

The challenge of optimising therapy will become more complex as more therapies are licensed for use. Beyond the therapies used in this study, we now have additional therapies such as JAK inhibitors and further molecules are in development. Moving forward we need to include and update treatment algorithms as new drugs become available and we need much larger datasets addressing this issue.

Currently in routine clinical practice we essentially randomly select therapies based on a limited clinical phenotype and personal experience. Why don't we randomly allocate patients to different therapies within carefully designed studies and integrate our knowledge of the immune pathways in PsA to optimise therapy? This study offers the first evidence for the potential success of such a precision medicine approach and could transform our treatment algorithms getting the right drug to the right patient each time.

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