1. Introduction

Psoriatic arthritis (PsA) is a progressive inflammatory syndrome associated with psoriasis [1, 2]. It encompasses highly variable manifestations (including inflammatory arthritis, spondylitis, enthesitis, dactylitis), occurring in up to 30% of people with psoriasis [1-3]. There has been a rapid expansion in therapeutic options available for PsA over recent years [1, 4]. However different drugs, with different modes of action, present new challenges when considering therapy selection for PsA and its wide-ranging clinical manifestations. Evidence is lacking to guide individual therapeutic decisions and therefore how to best offer a personalised approach to PsA management [1, 4].

Current practice generally follows a stepwise approach using conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), followed by biologic disease-modifying anti-rheumatic drugs (bDMARDs), if their response is inadequate [1, 2]. However newer guidelines (American College of Rheumatology (ACR) and National Psoriasis Foundation) recommend the use of bDMARDs as first-line treatment (tumour necrosis factor alpha inhibitors (TNFi)) [5]. Extending past csDMARDs, key treatment groups include three key bDMARDs: TNFi; interleukin (IL)-17A inhibitors; IL-12/-23 inhibitors; IL-23 inhibitors; and two small molecule targeted-synthetic disease-modifying anti-rheumatic drugs (tsDMARDs): janus kinase inhibitors; and apremilast (phosphodiesterase-4inhibitor) [1].

Some patients with inadequate responses to first-line bDMARDs, sequentially respond well to drugs with different modes of action [1, 6]. Others may sequentially respond to drugs within the same class [1]. This may represent different disease pathogenesis or evolution, potentially in response to varying sequential trials of bDMARDs [1]. These unpredictable responses can result in suboptimal therapy with potential delays and negative outcomes. These drugs are generally tolerated well however potential adverse events should be considered with bDMARDs, including reactivation of latent tuberculosis, opportunistic infections and skin site reactions from drug infusion or injection [7].

2. Current domain-based approach

Therapeutic decisions for bDMARDs and tsDMARDs are generally based on patients' limited clinical phenotype, physician familiarity and cost [1, 4]. Phenotypic focus is generally based on musculoskeletal or dermatological manifestations. Most rheumatological drug trials focus on patients with peripheral arthritis achieving 20% improvement in baseline ACR responses (ACR20) as their primary outcome [1]. Spondylitis, dactylitis and enthesitis, in contrast, tend to be included as secondary endpoints, rather than in specific research studies powered to evaluate these domains [1].

A small number of head-to-head studies have been performed in PsA allowing us to compare different therapies. A 52-week trial (SPIRIT head-to-head (NCT03151551)) compared the efficacy of ixekizumab (IL-17A inhibitor) and adalimumab (TNFi) in bDMARD-naïve patients with active PsA [8]. Patients were randomised 1:1 to either drug, and stratified by either concomitant csDMARDs therapy and co-existent moderate-to-severe plaque psoriasis [8]. Ixekizumab superiority was found, where a significantly higher proportion of patients achieved combined ACR50 (50% improvement from baseline in ACR responses) and PASI (Psoriasis Area and Severity Index)-100 responses, when compared to adalimumab (39.2% versus 26.1%, respectively; $p<0.001$) [8]. Significant achievement of PASI100 was higher in the ixekizumab arm, compared to adalimumab (64.3% versus 41.3%; $p<0.001$) [8]. Ixekizumab non-inferiority was demonstrated evaluating ACR50 alone ($p=0.924$) [8]. Secondary endpoints highlighted ixekizumab superiority to various composite disease measures, generally pertaining to skin disease [8]. Similar efficacy was observed for measures of enthesitis resolution (including Spondyloarthritis Research Consortium of Canada (SPARCC) ($p=0.097$) and Leeds Enthesitis Index ($p=0.392$)) and dactylitis resolution (Leeds Dactylitis Index-Basic ($p=0.620$)) [8]. Whilst these data demonstrate IL-17A suppression is effective in patients with co-existent skin and joint disease, it remains unclear which mechanism is preferred for extra-articular PsA features.

Another IL-17A inhibitor (secukinumab) was compared with adalimumab in a phase 3b trial (EXCEED NCT02745080), in active PsA [9]. The trial failed to meet its primary endpoint (ACR20) and secukinumab superiority was not achieved, with no significant difference observed between either treatment ($p=0.0719$) [9].

Whilst skin disease is generally measured as a secondary outcome in PsA trials, head-to-head studies exist evaluating chronic plaque psoriasis alone. Evaluating efficacy of treating skin disease is important, as controlling for all domains of psoriatic disease is the aim of optimal treatment. The ACCEPT phase three trial (NCT00454584) compared the efficacy of ustekinumab (IL-12/23-p40 subunit inhibitor) with etanercept (TNFi) in the treatment of moderate-to-severe psoriasis at 12 weeks [10]. Patients were randomly assigned to receive ustekinumab at 45mg or 90mg; etanercept (50mg); or placebo [10]. Significantly higher proportions of patients in the ustekinumab arms achieved PASI-75 responses, when compared with etanercept ($p=0.01$ and $p<0.001$, correspondingly) [10]. Physician's global assessment of clear or minimal skin disease were observed in both ustekinumab arms (compared to etanercept, $p<0.001$ each) [10].

The CLEAR phase 3b study (NCT0274982) established secukinumab superiority in achieving PASI-90 and PASI-100 responses ($p<0.0001$ and $p=0.0103$, respectively), in patients with moderate-to-severe psoriasis, when compared with ustekinumab [11]. Another study (IXORA-S NCT02561806) similarly found superior efficacy of IL-17A inhibition (ixekizumab) over ustekinumab [12]. Alongside these data, additional studies show superior efficacy of IL-23-p19 inhibitors (in addition to IL-17A suppression) over both TNF inhibition and ustekinumab, in treating skin disease [8, 10-14].

The ECLIPSA study (EudraCT 2017-003799-29) demonstrated that p40-IL-12/23 inhibition may be superior to that of TNFi in enthesitis-driven PsA [15]. Patients with active enthesitis (with previous inadequate responses to methotrexate, regardless of arthritic joint count) received either ustekinumab or a TNFi [15]. By week-24, significantly more patients receiving ustekinumab achieved enthesitis clearance (as per SPARCC=0), compared to those receiving a TNFi ($p=0.018$) [15]. There was no significant difference between either drug in the treatment of arthritis [15]. However, ustekinumab superiority was observed in terms of improvement of skin disease [15].

Differential efficacy may be particularly key in axial disease, as evidenced by trials in ankylosing spondylitis (AS). Data support the efficacy of TNFi and IL-17A inhibitors, both currently licensed in AS treatment [16]. However, AS trials evaluating other therapeutic modes have failed to achieve their primary outcomes [17-19]. Risankizumab (IL-23-p18 inhibitor) failed to achieve its primary endpoint of 40% improvement in Assessment in SpondyloArthritis International Society responses at week-12, when compared with placebo, in a proof-of-concept phase two trial (NCT02047110) [17]. Ustekinumab similarly failed to meet primary outcomes (versus placebo) in three multicentre studies evaluating its efficacy in AS [18]. Failure to meet the primary endpoint in the POSTURE trial (NCT01583374) was similarly observed evaluating the efficacy of apremilast in active AS [19].

From these data, our understanding of the mechanisms responsible for axial disease remain limited. Whilst genetic associations between IL23R-polymorphisms and AS are recognised, this does not correspond to the lack of efficacy observed with ustekinumab and risankizumab, and is reminder of the pathogenetic complexity of chronic inflammatory diseases. This polymorphism is also associated with inflammatory bowel disease, which may be linked to PsA, and seems to respond to TNFi and IL-23 suppression, but less effectively with IL-17 inhibition [20, 21].

2.1 Future approaches

Beyond the clinical phenotypic approach to personalised medicine in PsA, few data currently exist demonstrating precision medicine in rheumatology in general. Tissue-based therapeutic approaches already exist in oncological specialities, which could be a strategy applied in PsA.

One open-label trial addressed personalised medicine in PsA, stratifying treatments based on patients' baseline T-helper (T_H) cell immunophenotypes and their responses [22]. Four strategic treatment subgroups were defined, based on markers of T_H17 and T_H1 cell activation (both implicated in PsA pathogenesis), and predetermined upper and lower quartile parameters (from healthy controls) in the estimated proportion of activated T_H17 (above or below 1.5%) and T_H1 (above or below 1.2%) cells of the CD4 population [22]. These immunophenotypic subgroups (and their strategic bDMARD treatments) comprised: T_H1-predominant (ustekinumab); T_H17-predominant (secukinumab); both T_H1/T_H17 high proportions (TNFi for major joint involvement or secukinumab for major skin involvement); both T_H1/T_H17 low proportions (TNFi) [22].

Sixty-four patients with methotrexate-resistant PsA were allocated to receive either standard bDMARD treatment (n=38); or one of the aforementioned strategic bDMARD treatments (n=26) (based on their immunophenotyping) [22]. After six months, significant decreases from baseline were observed in the Simple Disease Activity Index (SDAI); 28-joint Disease Activity Score (DAS28)-erythrocyte sedimentation rate (ESR); and PASI responses in the overall strategic group ($p<0.05$) [22]. There were significant improvements in low disease activity measures (SDAI, DAS28-(ESR) and ACR20) in the strategic treatment group, compared with the standard treatment group ($p<0.05$) [22]. However, there was no significant difference in PASI achievement between the two groups [22].

These results demonstrate the efficacy of bDMARD selection according to T_H cell immunophenotyping. Albeit small, this is the first study to enact the concept of baseline immunophenotyping in PsA. There are however various limitations. The small study size was not powered to effectively compare the groups, nor was a prespecified primary endpoint stated. It is not fully clear how the T_H cell markers and their parameters were selected for formulating the immunophenotypic subgroups, nor the rationale for their allocation of respective therapeutic agents. The T_H1 percentages did not differ between the healthy controls and PsA patients, raising the question of the significance of the T_H1-predominant subgroup [4, 22]. Nonetheless, this proof-of-concept study exemplifies a promising approach and exciting potential for personalising PsA therapy, especially in the context the expanding treatment choices.

Further research is required to optimise our understanding and accuracy of PsA immunophenotyping. Questions have been raised about potential immunophenotypic stability and evolution, in the context of time or prior DMARD exposure [4]. Future suggestions for personalised medicine are broad, including advanced blood and tissue immunophenotyping processes; larger, carefully-designed trials; complex statistical methodologies; and evolving our understanding of immunocompetent cells in PsA. These advances however pose challenges to researchers. Blood analysis, whilst practical, may not reflect the same pathogenic process at tissue level. However tissue analysis, whilst more specific, is more expensive and incurs a more invasive approach.

3. Summary

The expanding range of treatments for PsA is welcome but poses challenges for selecting the best therapeutic mode, given its heterogeneity. The beginnings of personalised medicine, in the form of proof-of-concept immunophenotyping, is one novel and exciting approach. This, combined with complex statistical analyses, is a potential step in the right direction to help re-define the PsA treatment algorithm and therefore optimise patients' treatment without delay.

Declaration of interest:

Funding: Laura C Coates is an NIHR Clinician Scientist and Senior Clinical Research Fellow funded by a National Institute for Health Research Clinician Scientist award. The research was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflict of interest: LCC has received research funding and/or honoraria from Abbvie, Amgen, Biogen, BMS, Boehringer Ingelheim, Celgene, Gilead, Janssen, Lilly, Medac, Novartis, Pfizer and UCB.

References

1. Al-Mossawi H, Taams LS, Goodyear CS, et al. Precision medicine in psoriatic arthritis: How should we select targeted therapies? *The Lancet Rheumatology* 2019; 42(1): E66-E73. doi: https://doi.org/10.1016/S2665-9913(19)30008-6 (accessed 6 March 2021).
2. National Institute for Health and Care Excellence. *Etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis.* https://www.nice.org.uk/guidance/ta199 (accessed 6 March 2021).
3. Coates LC, Kavanaugh A, Mease PJ, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. Arthritis & *Rheumatology* 2016; 68(5): 1060-71.
4. Al-Mossawi H, Coates LC. Personalized medicine – a new reality in psoriatic arthritis? *Nature Reviews Rheumatology* 2018; 14(8):449-451. doi: 10.1038/s41584-018-0043-3 (accessed 7 March 2021).
5. Singh JA, Guyatt G, Ogdie A, et al. Special Article: 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis. *Arthritis & Rheumatology* 2019; 71(1): 5-32. doi: 10.1002/art.40726 (accessed 7 March 2021).
6. Fagerli KM, Kearsley-Fleet L, Watson KD, et al. Long-term persistence of TNF-inhibitor treatment in patients with psoriatic arthritis. *RMD Open* 2018;4:e000596. doi:10.1136/rmdopen-2017-000596 (accessed 8 March 2021).
7. Murdaca G, Colombo BM, Cagnati P, et al. Update upon efficacy and safety of TNF-alpha inhibitors. *Expert Opinion on Drug Safety* 2012; 11(1):1-5. doi: 10.1517/14740338.2012.630388 (accessed 11 May 2021).
8. Smolen JS, Mease P, Tahir H, et al. Multicentre, randomised, open-label, parallel-group study evaluating the efficacy and safety of ixekizumab versus adalimumab in patients with psoriatic arthritis naïve to biological disease-modifying antirheumatic drug: final results by week 52. *Ann Rheum Dis* 2020;79: 1310-1319. doi: 10.1136/annrheumdis-2020-217372. (accessed 2 March 2021).
9. McInnes IB, Behrens F, Mease J, et al. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. *The Lancet* 2020; 395(10235): P1496-1505. doi: https://doi.org/10.1016/S0140-6736(20)30564-X (accessed 23 March 2021).
10. Griffiths CE, Strober BE, van de Kerkhof P, et al. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med* 2010; 362(2): 118-28. (accessed 14 March 2021).
11. Blauvelt A, Reich K, Tsai TF, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study. *Journal of the American Academy of Dermatology* 2016; 76(1): P60-69.E9. doi: https://doi.org/10.1016/j.jaad.2016.08.008 (accessed 14 March 2021).
12. Reich K, Pinter A, Lacour, et al. Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. *British Journal of Dermatology* 2017; 177:1014-1023. doi: 10.1111/bjd.15666 (accessed 14 March 2021).
13. Gordon KB, Strober B, Lebwohl M, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *The Lancet* 2018; 392(10148): 650-661. doi: https://doi.org/10.1016/S0140-6736(18)31713-6. (accessed 14 March 2021).2
14. Blauvelt A, Papp KA, Griffiths CE, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *Journal of the American Academy of Dermatology* 2017; 76(3):405-417. doi: 10.1016/j.jaad.2016.11.041. (accessed 14 March 2021).
15. Araujo EG, Englbrecht M, Hoepken S, et al. Effects of ustekinumab versus tumor necrosis factor inhibition on enthesitis: Results from the enthesial clearance in psoriatic arthritis (ECLIPSA) study. *Seminars in Arthritis and Rheumatism* 2019; 48:632-637. https://doi.org/10.1016/j.semarthrit.2018.05.011 (accessed 15 March 2021).
16. Baeten D, Sieper J, Braun J, et al. Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. *New England Journal of Medicine* 2015; 373:2534-48. doi: 10.1056/NEJMoa1505066 (accessed 17 March 2021).

17. Beaten D, Ostergaard M, Wei JCC, et al. Risankizumab, an IL-23 inhibitor, for ankylosing spondylitis: results of a randomised, double-blind, placebo-controlled, proof-of-concept, dose-finding phase 2 study. *Ann Rheum Dis* 2018; 77:1295–1302. doi:10.1136/annrheumdis-2018-213328 (accessed 16 March 2021).
18. Deodhar A, Gensler LS, Sieper J, et al. Three Multicenter, Randomized, Double-Blind, Placebo-Controlled Studies Evaluating the Efficacy and Safety of Ustekinumab in Axial Spondyloarthritis. *Arthritis & Rheumatology* 2019; 71(2): 258-70. https://doi.org/10.1002/art.40728 (accessed 16 March 2021).
19. ClinicalTrials.gov. Study of Apremilast to Treat Subjects With Active Ankylosing Spondylitis (POSTURE). 2019. https://clinicaltrials.gov/ct2/show/results/NCT01583374 (accessed 16 March 2021).
20. Fauny M, Moulin D, D'Amico F et al. Paradoxical gastrointestinal effects of interleukin-17 blockers *Annals of Rheumatic Disease* 2020;79:1132–1138. doi:10.1136/annrheumdis-2020-217927 (accessed 3 May 2021).
21. Kashani A, Schwartz DA. The Expanding Role of Anti-IL-12 and/or Anti-IL-23 Antibodies in the Treatment of Inflammatory Bowel Disease. *Gastroenterology & Hepatology* 2019;15(5):255-265. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6589846/ (accessed 3 May 2021).
22. Miyagawa I, Nakayamada S, Nakano K, et al. Precision medicine using different biological DMARDs based on characteristic phenotypes of peripheral T helper cells in psoriatic arthritis. *Rheumatology* 2019; 58:336-344. doi:10.1093/rheumatology/key069 (accessed 1 March 2021).