

The need for clarity on the use of glucocorticoids for people with psoriatic arthritis: A call for consensus.

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**This editorial refers to the article ‘Systemic glucocorticoid use and the occurrence of flares in psoriatic arthritis and psoriasis: a systematic review’, published by Nanette LA Vincken and colleagues [1].**

Glucocorticoids have long been an essential tool in the therapeutic armamentarium against inflammatory arthritis but our relationship with them has been a difficult one over the years as we wrestle with the risk benefit ratio in an evolving treatment landscape. In spite of the long list of potential risks we often find ourselves prescribing systemic glucocorticoids to achieve rapid disease control. However, there is always a moment of additional doubt as the rheumatologist reaches for their prescription pad for someone with psoriatic arthritis (PsA). What is the risk that glucocorticoids will flare the skin disease, how do I explain this risk and do I have a dermatologist on hand if the psoriasis does flare? It is on this background that we welcome a timely and important systematic review on the use of systemic glucocorticoids in PsA and the occurrence of flares in psoriatic arthritis and psoriasis in this issue of the journal [1].

Glucocorticoids are just one of a long list of drugs that may flare psoriasis (alongside lithium, beta blockers, hydroxychloroquine, interferons and ACE inhibitors amongst others). Baker and colleagues first reported glucocorticoids as a potential trigger for psoriasis in 1968, identifying 104 patients who developed pustular psoriasis included one third associated with abrupt corticosteroid withdrawal [2] Vincken and colleagues have systematically reviewed the risks of psoriasis flare amongst people with PsA prescribed systemic glucocorticoids in this edition of the journal [1]. The authors identified eleven retrospective cohorts including 6,727 people with PsA (37,82%) and 1,460,793 (35,17%) people with psoriasis who had been were treated with any type of systemic glucocorticoid and identified very low rates of psoriasis flare. The authors go on to critically review the seminal case series from Baker *et al*, discussing potential sources of bias including recall bias, the absence of psoriasis measurement and the fact that ten of the 19 cases were prescribed systemic glucocorticoids for the treatment of psoriasis, raising the possibility the pustular psoriasis was part of the psoriasis exacerbation and therefore could have evolved independently of the glucocorticoids. There are challenges interpreting the limited literature on this subject. By example the authors report one study by Carubbi *et al* comparing efficacy and safety of systemic glucocorticoids and TNF intra-articular treatment. No adverse events were reported after 52 weeks follow up but it is notable that skin disease was not included as an endpoint and psoriasis flare, if present, may not have been recorded. The authors conclude that the evidence to recommend against systemic glucocorticoids is based on insufficient evidence and their use should be considered in view of a low risk of skin flaring. This is a view shared in a recent study and review from the dermatology perspective.[3]

What is the evidence that local and systemic glucocorticoids are effective in PsA?

Data from observational cohorts indicate glucocorticoids are commonly prescribed in PsA. A study published in 2005 evaluated a cohort of 1306 Italian patients with PsA treated in 37 centres and showed that 41.2% had been administered systemic glucocorticoids at some point in their care. The authors noted that the systemic glucocorticoids were well-tolerated (92.2%), and efficacy rates were high (95.0%).[4] Analyses from the Tight Control of PsA (TICOPA) study of 206 patients with early PsA followed for a year identified 111 doses of intramuscular (IM) steroids and 50 intra-articular (IA) injections. There were no cases of psoriasis related adverse events but there was an 8% risk of PASI increasing by  $\geq 2$  and this risk was greater with higher steroid doses (120mg depomedrone vs 80mg or lower).[5] It is noteworthy that most participants in TICOPA had mild skin disease and were taking conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), usually methotrexate. The authors conclude that IM and IA glucocorticoids are a useful treatment options and have given an estimate of flare from a real world early arthritis clinic population. IA or soft tissue glucocorticoid

injections are also known to be effective for arthritis, enthesitis or dactylitis in PsA. A prospective study of 133 people with polyarthritis, 79 received one injection and 54 received more than one, 41.6% achieved a clinical response with no swelling or tenderness at 12 weeks.[6] Systemic glucocorticoids appear to be more effective in Psoriatic Axial Spondyloarthritis (axPsA) than those with axial spondyloarthritis (axSpA). In a study of 15 people with axPsA axial symptoms, pain, quality of life and function improved significantly among patients with axPsA compared to patients with radiographic axSpA and controls two weeks after 80mg im triamcinolone.[7] A final, important consideration is that systemic glucocorticoids can improve psoriasis.[8] A review of case series conducted by Mrowietz and Domm identified psoriasis improvements in half of those administered systemic triamcinolone.[8] The evidence would therefore back up the clinical perception that systemic and local glucocorticoids appear to be effective of peripheral, axial and, occasionally, skin disease in people with PsA.

What do current PsA treatment guidelines recommend?

The theme across guidelines is caution when administering systemic glucocorticoids, in the relative absence of data. The European League Against Rheumatism (EULAR) evidence review did not include data relating to the risk of psoriasis flare with glucocorticoids. [9] The EULAR guidelines for the treatment of PsA state that local injections of glucocorticoids should be considered as adjunctive therapy in psoriatic arthritis; systemic glucocorticoids may be used with caution at the lowest effective dose, assessing the risk of skin flares related to systemic glucocorticoids. [10] The EuroGuiDerm guideline for the treatment of psoriasis offer clear advice suggesting local injection of glucocorticoids can be recommended in patients with active mono- or oligoarthritis, dactylitis and enthesitis. Systemic usage of glucocorticoids should not be standard for treatment but systemic steroids at the lowest effective dose may be used with caution and tapering of glucocorticoids should be done slowly and step-wise when feasible.[11, 12] The American College of Rheumatology (ACR), British Association of Dermatologists (BAD) and BSR PsA guidelines, soon to be published in the journal, all focus on immunomodulatory therapies and do not specifically comment on glucocorticoids. At the present time there are no consensus statements or strong recommendations on the use of systemic glucocorticoids amongst people with PsA.

What are the practice changing implications of the systematic literature review by Vincken et al?

The review highlights the paucity, and low quality, of evidence for psoriasis flares with use of glucocorticoids. We agree with the authors' conclusions that the perceived risks of psoriasis flare maybe greater than the received wisdom. The lack of a clear definition of what constitutes a skin

‘flare’ is also relevant to practice. Even if glucocorticoids are causally related to a deterioration in psoriasis – as reported by Coates *et al* - mild to moderate deterioration in psoriasis is likely to be manageable with simple interventions. Conversely generalised pustular or erythrodermic forms of psoriasis ‘flares’ as reported by Baker can be life threatening. Such forms of psoriasis are very rare and unlikely to be picked up using the study designs published to date. We know that disease causing loss of function mutations in IL36RN are prevalent in around 25% of the generalised pustular psoriasis population and it may be there is a subset of the PsA population where use of glucocorticoids confers particular risk. Studies that take into account the population exposed (for example including people with severe psoriasis), the nature of the glucocorticoid exposure (route, duration and with follow up post withdrawal) and at a scale that will capture rare, severe forms of psoriasis flares may better identify and quantify the risk – if any- if glucocorticoid use in the context of psoriasis. Finally, we need more understanding of the potential protective effect of concurrent biologic, targeted synthetic and csDMARD use on the risk of psoriasis flare with glucocorticoids, an area of dramatic change since the original Baker report in 1968.

In the meantime, findings from this review should be considered in the context of the known benefits of glucocorticoids, and the well-established risks (beyond the skin) in the context of prevalent diabetes, hypertension and obesity in the psA population to support shared decision making. [13] Rheumatologists need to consider skin disease when commencing or switching any therapy (including GC) and liaise closely with dermatology when needed. We call for a combined rheumatology dermatology consensus statement and decision making tool to offer practical guidance on the risks and benefits for patients and clinicians around the world for the use of local and systemic glucocorticoids in PsA.

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