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Title:

Applying Early Intervention Strategies to Autoimmune Skin Diseases. Is the window of opportunity pre-clinical? A dermato-rheumatology perspective.

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Abstract

Many inflammatory skin diseases exhibit a chronic course with unsatisfactory long term outcomes. Insights into early intervention approaches in other autoimmune contexts could improve the trajectory of life-long diseases in terms of sustained remission or minimal disease activity, reduced requirement for therapy and medical resource use, and improved quality of life. In both rheumatoid arthritis and psoriatic arthritis we have learned that the timing and intensity of early interventions can influence later outcomes. Investigation into early RA, PsA and SLE have has shown that the optimal “window of opportunity” may even extend into asymptomatic preclinical phases of disease. Notably, early and preclinical disease may have pathogenic mechanisms and therapeutic targets that differ from the established disease. We here review the literature on these insights and discuss how similar research and therapeutic strategies may be investigated in cutaneous autoimmunity. We highlight the contribution of skin resident cells to diseases that were previously thought to be initiated in the primary and secondary lymphoid organs of the immune system. We focus on two dermato-rheumatology conditions; lupus and psoriasis that share the commonality that effective early cutaneous disease therapy may have far reaching implications on abrogating potentially severe systemic disease.

Background

The traditional dermatology approach to treating chronic inflammatory skin conditions such as psoriasis, eczema and cutaneous lupus has been to "follow the disease" – starting with topical treatment and escalating to systemic immunosuppression as disease progresses. A change in approach is seen in some prototypic autoimmune conditions such as pemphigus vulgaris – where B-cell depletion therapy is recommended in recent guidelines as a first line approach for moderate to severe clinical presentations (Chen *et al.*, 2020; Lee *et al.*, 2020).

In any chronic, lifelong condition, success must be measured by a combination of outcomes including symptom burden, flares, treatment toxicity, health economic impact and quality of life. The priority of these factors may change over the course of the disease. Over time, irreversible tissue damage or glucocorticoid toxicity may progressively overwhelm more reversible features. The maxim "joint damage = inflammation x time" applied to rheumatoid arthritis (RA) in the 1990s may also translate to other long-term diseases. In systemic lupus erythematosus (SLE), glucocorticoids are a major predictor of damage, morbidity and mortality (Gladman *et al.*, 2003; Ruiz-Irastorza *et al.*, 2009). Conversely, sub-optimally controlled, chronic inflammation may increase cardiovascular, metabolic and mental health complications even in immunologically disparate diseases including psoriasis and SLE. A key question is therefore whether earlier, more intensive therapy would increase therapy-associated complications, or where guided by better diagnostics and understanding of early disease, could result in a better trajectory that improves all longer-term outcomes.

What can we learn from Rheumatoid arthritis? The early arthritis window of opportunity

Recent decades witnessed a paradigm shift in the clinical approach to RA. The historical treatment escalation moving stepwise from analgesia through to glucocorticoids and ultimately disease modifying anti-rheumatic drug (DMARD) therapy was based on an understanding that the early phases of inflammation were more benign than now believed, and that immunosuppressive therapies were more toxic. Historically DMARDs were initiated when joint damage was already radiographically apparent and irreversible (Quinn and Emery, 2003). There is now however firm evidence that early intensive treatment strategies lead to better outcomes and rapid attainment of remission or low disease activity is now central to clinical guidelines (Singh *et al.*, 2016; Smolen *et al.*, 2020). A real-world intensive treatment approach, while incurring higher DMARD and biologic prescribing, still achieves lower disability and higher quality of life, even among those in whom remission is not sustained (Gullick *et al.*, 2019).

Accrual of irreversible radiographic damage, which correlates with disability, is now recognised to begin in early disease where bone oedema and erosions detected by MRI significantly precede x-ray changes (Conaghan *et al.*, 2003). High resolution imaging now facilitates earlier case detection and treatment initiation by identifying erosions, subclinical synovitis and vascularity in the context of clinically suspect arthralgia without definitive arthritis (Di Matteo *et al.*, 2020a).

After diagnosis, focussed treatment intensification in RA supresses disease activity, reduces radiographic progression, improves physical function and quality of life (Grigor *et al.*, 2004; Klarenbeek *et al.*, 2011). Conversely, later intervention is associated with greater treatment resistance (Green *et al.*, 1999). A delay of as little as three months from symptom onset to treatment initiation impairs rates of remission achieved by DMARD monotherapy and necessitated greater use of combination therapy which is potentially more burdensome (Möttönen *et al.*, 2002). Very early referral and treatment initiation retards radiographic joint destruction and boosts odds of achieving treatment-free remission (Nell *et al.*, 2004; van der Linden *et al.*, 2010) but failure to reduce disease activity by 50% or more after 12 weeks of treatment substantively diminishes the prospect of remission thereafter (Aletaha *et al.*, 2016). These findings have shaped the understanding that seemingly mild early arthritis cannot not be viewed as an entirely benign entity and RA is the phenotypic endpoint of a disease continuum where the 'window of opportunity' to avert persistent inflammation is highest in the early stages. Indeed this concept of disease interception now extends to treatment of subjects with minimal inflammation and without clinically discernible tissue damage. Optimal targeting of the earliest stages of RA currently hinges around the concept that clinically suspicious arthralgia in anti–citrullinated protein antibody (ACPA) positive patients with imaging evidence of synovitis are most likely on a trajectory towards clinically defined RA and may be targetable with existing DMARD therapy towards arthritis interception.

RA – early disease mechanisms and biomarkers

While established RA is recognised as almost entirely confined to the joint, studies into the preclinical phases of disease have revealed different insights into pathogenesis. ACPA, which are highly specific to RA are not directed solely against synovial targets but against ubiquitous antigens; self-proteins that carry the post-translational citrullination modification. ACPA are retrospectively detectable years before overt arthritis (Nielen *et al.*, 2004) and their specificities escalate in the years leading to disease onset through epitope spreading (van de Stadt *et al.*, 2011; van der Woude *et al.*, 2010). Later in established RA the ACPA repertoire stabilises (van der Woude *et al.*, 2010) suggesting RA is the culmination of evolving autoimmune processes occurring predominantly in the pre-clinical phase. These findings have formulated

the concept of ‘imminent RA’ and another earlier ‘window of opportunity’ for intercepting or aborting the pre-clinical disease process in ‘at-risk’ individuals (Mankia and Emery, 2016).

Evidence now suggests autoimmunity and generation of ACPA in RA has origins outside of the joint environment and immunological derangements at mucosal barrier surfaces are evident before the onset of arthritis. Cigarette smoking which has strong epidemiological association with RA, promotes peptide citrullination and the same ACPA targets are detectable in both the lungs and synovial fluid of patients with RA. The oral and gut mucosa are other sites of interest (Zhang *et al.*, 2015). Dysbiosis in the periodontal (Cheng *et al.*, 2021; Mankia *et al.*, 2019) and gut microbiome (Wells *et al.*, 2020) is apparent before clinically manifest RA. Periodontal disease is associated with RA and the oral pathogen *Porphyromonas gingivalis* is capable of protein citrullination, generating novel epitopes and potential targets of autoimmunity (Mankia and Emery, 2016). Notably, higher levels of subgingival *P. gingivalis* are already detectable in ACPA positive individuals ‘at-risk’ of RA (Cheng *et al.*, 2021; Mankia *et al.*, 2019). Thus - as emerging for other chronic inflammatory diseases - novel biomarkers derived from the mucosal microbiome and local immune response may ultimately provide a tool for refining and accelerating stratification of at-risk patients. The “second hit” that causes asymptomatic epithelial surface-related autoimmunity to switch to a chronic, highly synovial-specific inflammatory disease remains unknown. However, once synovitis is established, it rapidly develops into a chronic and potentially treatment-resistant disease. Early mild histological inflammation progresses to organised immune structures enriched for plasma cells and such histological changes predict resistance to some therapies in established disease (Humby *et al.*, 2021).

Targeting pre-clinical disease

Efforts to understand the natural history of early RA disease continuum and characterise ‘at-risk’ status have brought the field of RA to the threshold of preventative strategies which could be both risk- and cost- acceptable. High risk patients can be identified; Individuals with arthralgia (Bos *et al.*, 2010) or non-specific musculoskeletal symptoms who are positive for high-titre ACPA, show high rates of progression to definitive RA (Di Matteo *et al.*, 2020b; Nam *et al.*, 2016; Rakieh *et al.*, 2015). This group is now the focus of clinical trials testing strategies for RA prevention. The PRAIRI study randomised ACPA and rheumatoid factor positive ‘at-risk’ individuals without arthritis to treatment with B-cell depletion using a single dose of rituximab. This reduced clinical progression to arthritis by 55% at 12 months (Gerlag *et al.*, 2019) indicating it may indeed be possible to modify the disease process, at least temporarily with pre-clinical B-cell targeted intervention. Further trials are ongoing including StopRA and APIPPRA, respectively evaluating hydroxychloroquine and abatacept in ‘at-risk’ RA (Al-Laith

et al., 2019). Importantly, these studies have cross-speciality relevance as they will provide new insights on the design and implementation of trials in the pre-clinical phase of autoimmune diseases.

Lupus erythematosus (LE) – early disease and progress towards biomarkers

SLE is now also a focus for early intervention strategies. The imperative for this is potentially even higher than RA, since severe, sometimes fulminant SLE presentations frequently occur early after diagnosis. As in RA, seropositivity and epitope spreading (McClain *et al.*, 2005) for characteristic SLE nuclear autoantigens is established years in advance of diagnosis (Arbuckle *et al.*, 2003) supporting the view that a continuum of pre-clinical and clinically overt disease may be common to the pathogenesis of autoimmune disorders. Seropositivity and isolated clinical manifestations below threshold for SLE classification, frequently precede the diagnosis of SLE (Heinlen *et al.*, 2007) but can still be associated with significant end-organ damage (Bourn and James, 2015). Retrospective data indicate early introduction of hydroxychloroquine delays progression to classifiable SLE in this group and attenuates accrual of autoantibodies (James *et al.*, 2007) suggesting SLE pathogenesis could, like RA, be potentially modifiable in its earliest phase. Anti-nuclear antibody (ANA) positivity is however found in up to 25% healthy individuals (Wandstrat *et al.*, 2006) and, unlike ACPA positivity in RA, provides very low specificity for identifying imminent SLE.

IFN pathway activation is an important emerging biomarker in autoimmune rheumatic disease (Psarras *et al.*, 2017). It is implicated in cutaneous LE (CLE) and SLE pathogenesis through genetic susceptibility (Deng and Tsao, 2010), transcriptional signatures (Chiche *et al.*, 2014; Jabbari *et al.*, 2014; Tsoi *et al.*, 2019; Wenzel, 2019; Zahn *et al.*, 2011) and the therapeutic efficacy of IFN-blockade (Morand *et al.*, 2020). IFN-status measured by two IFN stimulated gene (ISG) expression scores was the second strongest independent predictor of progression to SLE among individuals harbouring positive ANA, after family history (Md Yusof *et al.*, 2018). Notably, IFN signatures derived from skin in ANA positive individuals at-risk of SLE may suggest a key role of the skin in disease initiation. IFN production is markedly dysregulated in ANA-positive individuals, with defective circulating sources and excessive production from the skin (Psarras *et al.*, 2020). In acute viral infections, the main source of type I IFNs is plasmacytoid dendritic cells (pDCs) and, since these have toll-like receptors (TLRs) that can recognise antibody-bound nuclear autoantigens, they have been assumed to be involved in SLE pathogenesis (Ronnblom and Alm, 2001). More recently pDCs have been shown to be defective in SLE patients and instead, type I IFN was found to predominantly arise from non-haematopoetic sources(Gall *et al.*, 2012; Psarras *et al.*, 2020) and this is also evident in

asymptomatic ANA-positive individuals, Further, SiMoA methods could detect IFN-α in pDCs in the monogenic interferonopathy STING, but not in SLE (Rodero *et al.*, 2017) and defective pDC function is also found in murine models of lupus (Macal *et al.*, 2018).

Among ANA-positive, at-risk subjects, elevated IFN signatures are more marked in skin than in peripheral blood (Md Yusof *et al.*, 2018). Moreover, expression of keratinocyte derived IFN-κ is observed in CLE lesions and non-lesional SLE skin and is sensitive to UV provocation (Psarras *et al.*, 2020). A similar profile was seen in the epidermis of SLE at-risk ANA-positive individuals indicating it becomes aberrant in advance of clinically manifest SLE (Psarras *et al.*, 2020). The notion, that the skin is an important peripheral organ for early disease activity which can progress to other organs in the natural disease course is supported by recent murine studies showing a link between skin UV exposure and subsequent kidney inflammation (Skopelja-Gardner *et al.*, 2021). Such observations could have far reaching consequences for targeting skin specific IFN dysregulation as a strategy to mitigate against severe end organ autoimmunity

A disease-specific transcriptional ISG signature is expressed in hair follicles from discoid lupus whereas hair follicles from psoriasis – which is an interfollicular skin disease – fails to show any inflammatory signature (Shalbaf *et al.*, 2019). Hence, the skin – previously described as a “target organ” in SLE, may play an active role in initiation of disease, and in promoting an autoimmune process that then affects distant other organs.

There are however different subtypes of CLE not all of which show transition into SLE. In one (Wieczorek *et al.*, 2014) prospective study of 77 patients with CLE only 17% went on to meet SLE classification criteria during the 4 year study. Patient who developed SLE were more likely to demonstrate higher baseline ANA titres compared to those whose disease remained restricted to the skin. Most patients who met SLE criteria did so based on mucocutaneous features. The risk of transition to SLE from ANA negative, localised chronic discoid LE still remains uncertain. Additionally, in SLE, response to B cell depletion therapy in the skin was variable, and related to CLE morphology. Some subtypes, such as discoid LE, were even observed to initiate or worsen in the absence of circulating B cells (Vital *et al.*, 2015) and further mechanistic understanding is needed.

Identification of “at risk” individuals with highest likelihood to progress to clinical LE remains a key challenge. The above findings raise the possibility that in ANA-positive individuals, the skin could be a better compartment to interrogate than blood. Interestingly, minimally-invasive approaches such as analysis of plucked hair follicles (Shalbaf *et al.*, 2019) or skin material obtained by tape stripping (Merola *et al.*, 2021) have been described but the reliability of epidermal mRNA sampling (as opposed to protein expression) by these methods is yet to be

demonstrated, particularly given the deeper dermo-epidermal interface involvement characteristic of LE.

Psoriatic disease and early treatment

In psoriatic disease 2 key questions are challenges for future trials. Firstly, can we ever attain psoriasis remission thus allowing discontinuation of systemic treatment which might influence the natural course of the disease? Secondly, can we prevent a psoriasis to PsA transition? Given the compelling evidence for early treatment of RA ongoing studies are exploring the benefit of treating new-onset psoriasis with early IL-17 blockade (Iversen *et al.*, 2018) though large cohorts will be needed to ascertain if early intervention indeed benefits all patients or preferentially those on a "natural" remission trajectory. In PsA a number of studies now suggest early treatment may indeed improve long term outcome (Coates *et al.*, 2015; Yan *et al.*, 2021). However, this area remains challenging as early biomarkers to expedite diagnosis and predict development of PsA are lacking.

Targeting the psoriasis to psoriatic arthritis transition

Psoriasis affects about 2% of the population and up to a third of psoriasis cases may ultimately develop PsA (Gisondi *et al.*, 2005; Gladman *et al.*, 2005; Ogdie *et al.*, 2013). Skin psoriasis, particularly with scalp and nail involvement is thus, the strongest known biomarker predicting development of PsA and (Wilson *et al.*, 2009). To date, no convincing molecular profile has helped identify the transition from skin psoriasis to PsA. Proposed psoriasis autoantigens including cytokeratin 16, LL37 and melaonocyte peptides appear to be confined to the skin and none have shown predictive value in larger clinical trials.

Mirroring observations in RA, arthralgia and imaging changes among patients with psoriasis confer an approximately 10-fold risk of developing PsA (Zabotti *et al.*, 2019). In psoriasis early treatment with IL12/IL-23 blockers may suppress progression of ultrasound identified subclinical enthesopathy (Savage *et al.*, 2019). Verification with long term prospective data is still needed. Three recent retrospective studies showed very low rates of PsA evolution when psoriasis was intensively treated with biological therapy (Acosta Felquer *et al.*, 2021; Gisondi *et al.*, 2021; Shalev Rosenthal *et al.*, 2021) however Meer et al could not confirm this in their retrospective cohort investigated (Meer *et al.*, 2021). Clearly, prospective studies are needed to inform on strategies for PsA prevention which is distinct from pre-clinical RA since psoriatic patients frequently merit systemic therapy on the basis of their psoriasis severity alone and consequently it incurs no extra costs or toxicity risks.

How could the treatment of psoriasis lead to PsA prevention? In experimental psoriasis models overactivaiton of keratinocytes may lead to systemic arthritis but this is not thought to be a key mechanism in humans. Unlike in SLE and RA, the skin and the entheses may share a common IL-23/17 immune axis and targeted therapies may diminish site specific inflammation. Recent investigations on tissue resident memory (TRM) cells residing in the skin and their role in "molecular scar signature" and flaring of psoriasis, indicate that some re-circulation of antigen-experienced TRM trained to produce IL-17 could reach other body sites (Leijten *et al.*, 2021; Penkava *et al.*, 2020). Thus, current data may suggest effective therapy of psoriasis at any stage of disease might theoretically prevent PsA development but as biologic treatment is currently reserved for patients with severe skin psoriasis – the need to identify early markers of PsA transition in those with mild to moderate psoriasis remains an important challenge.

What does the prevention approach require? Clinical study requirements

Experience in RA reveals what will be necessary to an early intervention and disease interception approach. Firstly, a robust characterisation on the manifestations and natural history of early disease, discerning spontaneously remitting from poor prognosis disease. Secondly, sensitive and reliable early diagnostics, paralleling ultrasound and MRI in RA, to expedite treatment in the early disease 'window of opportunity'. Thirdly, studies with sufficient follow up to ascertain the benefit at both patient and health economic level. Finally, the pre-clinical 'window of opportunity' requires a research agenda focussed on prognostic biomarkers for risk-acceptable stratification of preventative interventions.

Treatment modalities and therapeutic targets.

Ample literature support the notion that more chronic inflammatory skin diseases as more treatment refractory. Hypotheses to account for this include autoantibody memory consolidation and epitope spreading in autoantibody mediated conditions. However other factors at tissue level are emerging. Firstly the role of tissue memory and TRM (Mehta *et al.*, 2021; Ryan *et al.*, 2021). Skin TRMs seem to be long lived and keratinocyte derived IL-15 may be important to their persistence along with expression of the skin homing molecule cutaneous lymphocyte antigen (CLA). In cutaneous lupus TRM appear higher in number among patients refractory to antimalarials (Zeidi *et al.*, 2019). TRM allow fast immune activation upon re-encountering their specific antigen. TRM may recirculate and conceivably contribute to systemic disease. Re-circulation of CLA positive memory cells following tonsillar streptococcal infection has been implicated in initiating psoriasis (Ferran *et al.*, 2013). Furthermore, long lived TRM may also undergo epigenetic modifications enabling them to contribute to "trained immunity" of their residing tissue in addition antigen specific responses. Exogenous fatty acids

(Pan *et al*., 2017) and / or keratinocyte derived IL-15, upon which TRM are dependent have now been postulated as novel therapeutic targets. Epigenetically determined trained immunity refers to mechanisms by which non-leukocyte resident cells can be primed for increased responsiveness to a repeated “environmental trigger” (Naik *et al*., 2017). While dividing keratinocytes may not maintain new epigenetic information this is different for the epidermal stem cells and the dermal compartment. Interestingly, methotrexate may impact epigenetic changes. Low-dose methotrexate has been reported to alter the epigenome in a folate-independent manner, via direct inhibition of S-adenosyl-methionine synthesis, the intracellular methyl carrier used during DNA methylation (Nesher *et al*., 1991; Wang and Chiang, 2012). Intriguingly this suggests that MTX could also modulate cell-type specific epigenetic modifications, which may even persist following cessation of treatment via a phenomenon termed transcriptional memory (Foley *et al*., 2009) possibly explaining the extended disease-free state observed in some psoriasis patients. However, more in depth mechanistic investigation is needed.

Summary and Conclusions

The pathogenesis and clinical features of the diseases described are diverse, but some common themes may inform approaches in other diseases (Figure 1). The autoimmune process may begin years before symptom onset and pathogenesis in pre-clinical phases may differ to the established disease, and involve different sites. In this phase the disease is asymptomatic and offers a window of opportunity for prevention. Non-specific initial symptoms leading to diagnostic delays may allow epigenetic processes and histological advancement of disease into more resistant forms by the time of diagnosis. In established disease, reversible inflammation amenable to immunosuppression progresses, but later the cumulative effects of the chronic disease may eventually dominate. Hence key areas for research include the pathogenesis in preclinical phases, pre-disease or early diagnostic tools, and the efficacy of early intervention on longer-term outcomes. While there is no guarantee that similar insights and outcomes will be achieved in other autoimmune skin diseases, the area warrants investigation. Understanding disease initiation in the skin may allow early identification of patients with imminent autoimmunity, reveal new therapeutic targets, and allow interventions to prevent both skin and systemic autoimmunity.

Author contributions

Conceptualisation: MW, EMV, LC; Writing – original draft: LC, MW, EMV; Writing – review & editing: LC, MV, EMV, DM; Visualization; EMV.

Conflict of Interests

The authors declare no conflicts of interest.

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Figure Legends

Figure 1. The window of opportunity in the autoimmune disease continuum.

Autoimmune disease spans a continuum from an 'at-risk' state influenced by genetic and environmental factors, through to a pre-clinical state where asymptomatic autoimmune response and inflammation are initiated, ultimately to clinically overt symptomatic disease at diagnosis. Chronic inflammation, cumulative irreversible tissue damage and treatment toxicity dominate the established disease state. Sequential transitions in pathogenic mechanisms may underlie this continuum as tissue homeostasis is surpassed by target adaptive autoimmunity. A window of opportunity to intercept or modify the disease is present in the earliest phases. Diagnostic and therapeutic strategies in this early and pre-clinical disease state differ from those of established disease.