Systemic Inflammation in Psoriasis

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Silje Michelsen Solberg from the Department of Dermatology, Haukeland University Hospital defended her doctoral thesis titled *Systemic inflammation in psoriasis: Circulating immune cells and cytokines* at the University of Bergen on September 27, 2019. Her supervisors were Silke Appel, Yenan Bryceson and Lene Frøyen Sandvik. Charlotta Enerbäck from Linköping University, Sweden and Lone Skov from the University of Copenhagen, Denmark were first and second opponents. Available from: https://bora.uib.no/bora-xmlui/handle/11250/2826774.

Psoriasis is a common, chronic inflammatory skin disease associated with arthritis and multiple comorbidities. Autoantigens in the skin elicit a response in cytotoxic T cells, leading to local inflammation and recruitment of Th1 and Th17 cells from the blood. There is a complex immunological interplay between cytokines and cells from the innate and adaptive immune system, creating self-sustaining amplification loops. Increased levels of inflammatory cytokines and cells have been detected in blood from psoriasis patients. This notion, together with mechanistic similarities in establishment of psoriatic and atherosclerotic plaques, probably contributes to the increased prevalence of cardiovascular disease in psoriasis patients, however, this link needs to be further elucidated.

No cure for psoriasis exists, and treatments aim at amelioration of symptoms. If topical treatments or UV-light are not effective enough, systemic medication including methotrexate, ciclosporin, fumarate or acitretin can be tried. Biological drugs specifically targeting the key cytokines TNF, IL-12/23 and IL-17 are available if conventional treatment is insufficient or contraindicated. However, these newer drugs are not accompanied by similarly precise laboratory analyses to aid selection of a specific drug for individual patients. As adverse events and loss of effect can be encountered, the switching from original to cheaper biosimilar drug has been controversial.

The overall aim of this thesis was to study the blood immune system in psoriasis during active inflammation and treatment with biological drugs, in the search for disease specific immune signatures and biomarkers. In Study I, Luminex® Technology was used to investigate if serum cytokine levels could reflect psoriasis activity (1). In Study II, we compared impact of switching from original TNF inhibitor infliximab to biosimilar CT-P13 in psoriasis patients, both evaluating clinical parameters and effect on peripheral blood cells and their intracellular signalling, measured by phosphoflow cytometry (2). In Study III, single cell analysis of blood immune subsets, with special emphasis on the T-cell lineage and intracellular signaling, was explored by use of mass cytometry (3). In all studies, clinical parameters including Psoriasis Area and Severity Index and Dermatological Life Quality Index were incorporated in analyses.

From left to right: Tor Hervig (acting dean), Lone Skov (2nd opponent), Charlotta Enerbäck (1st opponent), Silje Solberg and Einar Klæboe Kristoffersen (member of the evaluation committee).

The results indicate that cytokine and single cell analysis of blood can be useful methods for describing the complex systemic immunological picture in psoriasis. In Study I, logistic regression revealed higher risk of having severe psoriasis with increased IL-17A. Increase of IL-2 positively correlated with improvement of PASI and DLQI. Moreover, increase of IL-5, IL-10, IL-12, IL-22 and GM-CSF correlated with treatment effect.

In Study II, intracellular phosphorylation levels in peripheral blood mononuclear cells were increased in psoriasis patients compared to healthy controls. This increased signalling activity decreased during continued treatment with infliximab,

but did not completely normalize despite clinical remission. Switching from original to biosimilar infliximab did not affect laboratory findings, like cell abundance and phosphorylation levels, or clinical parameters.

Study III revealed that biological therapy of psoriasis facilitated a shift in the balance of Th1 and Th2 cells in blood, transition from naïve/effector to memory predominance, reduction of circulating Th17, Th22, Th9 and CD8 cells and enhancement of inhibitory PD-1 expression on T cells. In the monocyte compartment, changes in favour of reduced cardiovascular risk were observed. Intracellular phosphorylation of blood immune cells was higher in psoriasis patients compared to healthy controls and in non-responders to treatment compared to responders.

In conclusion, multiple aberrancies in circulating cells and cytokines were detected in patients with severe psoriasis, confirming that systemic inflammation is a trait of psoriasis. Further research can highlight the role of cytokines and peripheral blood mononuclear cells as potential tools for stratification of patients for personalized treatment. Optimized therapeutic strategies might alter the chronic course of psoriasis with positive implications on quality of life and long-term comorbidities

List of original publications

I. Solberg SM, Sandvik LF, Eidsheim M, Jonsson R, Bryceson YT, Appel S. Serum cytokine measurements and biological therapy of psoriasis – Prospects for personalized treatment? Scand J Immunol 2018; 88: e12725.

II. Aarebrot AK, Solberg SM, Davies R, Bader LI, Holmes TD, Gavasso S, et al. Phosphorylation of intracellular signalling molecules in peripheral blood cells from patients with psoriasis on originator or biosimilar infliximab. Br J Dermatol 2018; 179: 371–380.

III. Solberg SM, Aarebrot AK, Sarkar I, Petrovic A, Lene Frøyen Sandvik L, Bergum B, et al. Mass cytometry analysis of blood immune cells from psoriasis patients on biological therapy. Eur J Immunol 2021; 51: 694–702.