# Hit hard and early: Can the march of psoriasis be halted?

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## ABSTRACT

Psoriasis is increasingly considered a systemic disease with comorbidities. There is sufficient evidence that systemic inflammation lies at the heart of these developments. Considering the chronic nature of psoriasis and its comorbidities, timely manipulation of systemic inflammation could avert both mortality and morbidity. Data from retrospective studies suggest that aggressive treatment of psoriasis with traditional systemic agents and/or biologic drugs improves health outcomes. To maximize treatment outcomes, severe psoriasis needs to be managed as a systemic disease with likely comorbidities.

**Key words:** Comorbidities, psoriasis, psoriatic march, systemic inflammation

*"Hit hard, hit fast, hit often"* Fleet Admiral William Frederick Halsey, Jr., United States Navy, legendary World War II admiral (who also suffered from severe psoriasis).

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## BACKGROUND

More than 2000 years ago, psoriasis was considered to be a form of leprosy. It was not until 1841 that Dr. Ferdinand von Hebra used the term "psoriasis." In the 1960s, psoriasis was described as a disease of epidermal proliferation, and in the 1980s as a disease of the immune system. Today, psoriasis is considered a systemic disease with comorbidities.[1]

Patients with psoriasis are at increased risk of developing diabetes, hypertension, hyperlipidemia, obesity, and smoking, which are known cardiovascular risk factors. It is believed that psoriasis constitutes an independent risk for developing myocardial infarction and stroke, particularly in young patients and those with severe disease.[2,3] Patients with severe psoriasis on average die about five years younger than those without the disease.[4]

## PSORIASIS AND SYSTEMIC INFLAMMATION

There is increasing awareness that systemic inflammation lies at the heart of these developments.[5] Elevated levels of inflammatory biomarkers, vascular endothelial growth factor (VEGF),[6] C-reactive protein,[7] and P-selectin[8] have been described in severe psoriasis. The last two also represent increased cardiovascular risk. Further, it has been hypothesized that psoriatic systemic inflammation causes insulin resistance that triggers endothelial cell dysfunction, atherosclerosis, and myocardial infarction or stroke. Although this "psoriatic march" needs further confirmation,[9] its import for sufferers of the disease cannot be overlooked. It would seem logical to screen and follow up patients with severe psoriasis for cardiovascular events. Even those with a borderline risk profile must receive a physician's evaluation, mindful of their inflammatory psoriatic burden,.

## HIT HARD AND EARLY

Considering the chronic nature of psoriasis and the ensuing cardiovascular risk, timely manipulation of psoriatic inflammation could avert both mortality and morbidity. Does primary immunosuppressive therapy curb the "psoriatic march"?

## BIOLOGICS VERSUS TRADITIONAL SYSTEMIC DRUGS

It is reasonable to speculate that certain antipsoriatic drugs may be more potent to check

relapses and stop the progression of comorbidities than others, depending on their mode of action.[2] TNF-alpha seems to be a particularly attractive target as it is known to induce endothelial cell dysfunction and atherosclerosis. A retrospective study of the TNF-alpha blocking drug, etanercept, in psoriasis documented a reduction of C-reactive protein as a biomarker for cardiovascular risk.[10] There is some evidence that IL-12/IL-23 targeted by ustekinumab may also play a role in attenuation of atherosclerosis.[11] In a recent study, major cardiovascular event rates among ustekinumab-treated patients with psoriasis were found to be lower than similar estimates from the general population.[12] Biologic drugs could thus be effective in limiting both cutaneous and systemic impact of psoriasis. In the context of the metabolic syndrome, they have the advantage of fewer contraindications and less drug interactions.

Amelioration of chronic systemic inflammation of psoriasis, however, demands continuous immunosuppression for which traditional systemic drugs may be better suited. In general, methotrexate (MTX), acitretin, cyclosporine, and others have been available for far longer than biologics (MTX was approved for psoriasis in 1971), with toxicity profiles that are well known. Traditional systemic agents are given orally (MTX may also be given by injection) and are also less expensive than injectable biologic agents. A large retrospective analysis concluded that continuous systemic therapy with MTX for psoriasis also reduced risk for myocardial infarction.[13] Recent evidence suggests that diabetes risk is mitigated in patients with psoriasis on disease-modifying antirheumatic drugs (DMARDs).[14] A small study on psoriasis patients receiving continuous dose fumaric acid esters documented improvement in endothelial cell function, and hence, cardiovascular risk at 24 weeks.[15] Another study documented a 26% reduction in cardiovascular mortality among psoriasis patients receiving more than the mean number of PUVA treatments[16] suggesting that aggressive treatment of psoriasis might improve health outcomes.

It must be borne in mind, however, that acitretin and cyclosporine may aggravate pre existing dyslipidemia or hypertension. Intake of statins (for dyslipidemia) along with cyclosporine could also lead to rhabdomyolysis and renal failure.

For psoriatic arthritis (PsA) however, because of its propensity to hamper physical function, therapies are shifting from mere interference with its inflammatory response (traditional systemic drugs) to abrogation and halting of joint damage (biologics).[17] Data on the use of infliximab in PsA[18,19] suggest that therapeutic intervention early in the disease course limits joint destruction. Results from the Respond trial[20] that investigated an aggressive treatment strategy in early, severe polyarticular PsA indicate that patients receiving a combination of infliximab and MTX showed more profound levels of disease suppression than infliximab alone, lending weight to a “hit early and hard” treatment paradigm in PsA.

## MONITORING

Against a background of systemic inflammation, clinical metrics alone (Psoriasis Area Severity Index (PASI)/American College of Rheumatology (ACR) criteria) may not be enough for gauging disease severity and response to treatment. Inflammatory markers, particularly, P-selectin,[8] C-reactive protein and to a lesser extent, fibrinogen and ESR, have been shown to be useful in this regard.[9] A combination of selected inflammatory markers and PASI might reflect the inflammatory status in psoriasis more accurately than each one separately.

## CONCLUSION

Severe psoriasis needs to be managed as a systemic disease with likely comorbidities. Early systemic therapy continued in effective dosage will check disease progression and conceivably prevent cardiovascular events, thus maximizing treatment outcomes.

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