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Letter to the Editor

Apremilast in comorbidities associated with psoriasis

Sir,

Psoriasis (PsO) is a multifactorial inflammatory disorder frequently associated with comorbidities such as cardiovascular disease (CVD), metabolic syndrome (MetS), and type 2 diabetes mellitus (DMII).[1] Several studies have demonstrated a strong correlation between PsO and MetS, suggesting shared inflammatory mechanisms. Chronic inflammation contributes to both conditions, with cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-17, and IL-10 playing central roles.[2] IL-17, in particular, modulates the interface between inflammation and metabolism by influencing glucose homeostasis and adipocyte function.[2] Elevated TNF-α and IL-6 levels, characteristic of PsO, are implicated in insulin resistance, while IL-6 additionally promotes adipose lipolysis and hepatic gluconeogenesis, exacerbating metabolic dysfunction.[2]

Apremilast, an oral phosphodiesterase-4 (PDE-4) inhibitor, elevates cyclic adenosine monophosphate (cAMP) levels, thereby reducing pro-inflammatory cytokines and enhancing anti-inflammatory mediators like IL-10.[3] Beyond improving psoriatic disease activity, apremilast has been linked to weight reduction and decreased haemoglobin A1c (HbA1c) levels, possibly through glucagon-like peptide-1 (GLP-1) modulation.[2-5] Emerging evidence also suggests vascular benefits, including enhanced endothelial function, indicating that PDE-4 inhibition may confer additional cardiometabolic advantages beyond its anti-inflammatory effects.[2]

Apremilast reduces plasma levels of IL-17A, IL-17F, IL-22, and TNF-α in patients with moderate to severe plaque PsO, potentially mitigating inflammatory pathways common to both PsO and MetS. Conversely, low IL-10 levels-an anti-inflammatory cytokine involved in lipid metabolism-are linked with MetS.[2] By enhancing intracellular IL-10 expression, apremilast may help restore metabolic balance, warranting further investigation into its pleiotropic effects.[2]

Beyond its dermatologic efficacy, apremilast has shown promise in improving metabolic parameters related to MetS.[6-8] PDE-4-mediated cAMP signalling is integral to glucose and lipid metabolism, and apremilast may positively influence insulin sensitivity and lipid homeostasis.[6,7] Recent findings suggest an additional role via activation of the sirtuin-1 (SIRT1) pathway, promoting cholesterol efflux and reducing atherosclerotic risk.[2,9] Increased cAMP levels induced by PDE-4 inhibition also enhance lipolysis.[2] Pooled analyses from phase 3 trials (ESTEEM, PALACE, and LIBERATE) demonstrated greater HbA1c reduction among patients on concomitant antidiabetic therapy receiving apremilast versus placebo.[2,10] Similarly, improved PsO clearance in patients with diabetes supports the bidirectional relationship between metabolic and inflammatory processes.[2]

Apremilast has also been reported to improve oxidized LDL-induced endothelial dysfunction and lower lipid and glucose levels over 52 weeks, suggesting potential cardiometabolic benefits and synergy with statins in managing dysmetabolism among psoriatic patients with MetS.[2]

Apremilast represents an effective oral, non-immunosuppressive therapy for PsO patients with metabolic and systemic comorbidities. Its mechanism-targeting the IL-23/Th17 axis through PDE-4 inhibition-extends anti-inflammatory benefits beyond the skin, with emerging evidence of improvements in BMI, HbA1c, and lipid parameters. While its efficacy is moderate compared with biologics, its favourable safety profile makes it particularly suitable for patients in whom biologic therapy is contraindicated or poses safety concerns.

Future research should focus on large-scale, comorbidity-specific trials evaluating cardiovascular outcomes, longitudinal safety, and patient-reported measures to better define apremilast's role in the evolving paradigm of personalized PsO care.

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