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CASE REPORT

Tofacitinib as a Novel Therapeutic Option for Pemphigus Vulgaris: A Case Report and Mechanistic Insights

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Abstract: Pemphigus vulgaris (PV), a life-threatening autoimmune blistering disorder mediated by pathogenic anti-desmoglein antibodies, manifests clinically with extensive cutaneous and mucosal vesicles, bullae, and erosions. While corticosteroids remain first-line therapy, a substantial subset of patients develop refractory disease requiring advanced therapies. Tofacitinib, an oral Janus kinase (JAK) 1/3 inhibitor, demonstrates broad immunomodulatory effects through interference with cytokine signaling pathways. We report the case of a 50-year-old male with recalcitrant PV who achieved sustained remission following adjunctive tofacitinib therapy. Combination therapy with tofacitinib (5 mg twice daily) and prednisone (60 mg/day) enabled successful corticosteroids withdrawal within 5 months, achieving complete clinical remission (PDAI=0) and serological improvement (Dsg1/Dsg3 antibodies reduced by 64.5%/75.8%). Longitudinal immunohistochemistry (IHC) revealed attenuated phospho-STAT3 and phospho-STAT6 in post-treatment lesional skin compared to baseline. Proteomic profiling of PV lesions (n=3) versus healthy controls (n=3) identified 198 differentially expressed proteins (fold change >1.5, $p<0.05$), with KEGG pathway analysis revealing predominant enrichment in JAK-STAT signaling, IL-17-mediated inflammation, and lymphocyte differentiation pathways. Independent validation in an expanded cohort (5 PV vs 5 controls) confirmed constitutive JAK-STAT hyperactivation: phospho-STAT3 (7.2±1.64 vs 1±0, $p<0.001$) and phospho-STAT6 (9.6±1.34 vs 1.2±0.45, $p<0.001$) were markedly elevated in untreated PV lesions. These findings posit tofacitinib as a promising steroid-sparing agent in PV management, potentially through multimodal inhibition of pathogenic cytokine networks. Large-scale randomized controlled trials are warranted to validate these observations.

Keywords: pemphigus vulgaris, JAK-STAT pathway, tofacitinib, targeted immunotherapy, proteomic profiling

Introduction

Pemphigus vulgaris (PV), characterized by IgG autoantibodies against desmoglein (Dsg) 1 and 3, disrupts epidermal adhesion through complex immune dysregulation.[1] Emerging evidence implicates Th2/Th17 cytokine polarization (IL-4, IL-17, IL-21) and downstream JAK-STAT signaling in sustaining autoantibody production and inflammatory cascades.[2–5] Tofacitinib mechanistically targets this axis by selectively inhibiting JAK1 and JAK3, thereby disrupting signaling pathways critical for B-cell activation and differentiation into autoantibody-producing plasma cells, including those mediated by IL-4, IL-10, and IL-21.[6,7] Despite theoretical rationale, clinical evidence supporting JAK inhibition in PV remains limited to anecdotal reports.[8,9] This study provides the first comprehensive characterization of tofacitinib's therapeutic potential in steroid-dependent PV, coupled with mechanistic insights from proteomic and phosphoprotein analyses.

Case Report and Analysis of Molecular Mechanism

Case Report

A 50-year-old male with a 5-year history of PV presented with recurrent erosive lesions involving the trunk and limbs. The diagnosis was histologically confirmed through hematoxylin-eosin staining demonstrating suprabasal acantholysis,

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direct immunofluorescence showing IgG/C3 deposition, and elevated serum anti-Dsg1/Dsg3 antibody titers (173.5 U/mL and 175.67 U/mL, respectively). Despite previous therapies including cyclophosphamide, mycophenolate mofetil, and azathioprine, the patient experienced repeated relapses during prednisone tapering (40–25 mg/day). At current presentation, physical examination revealed extensive erythematous plaques with multiple ruptured vesicles and crusted erosions, corresponding to a Pemphigus Disease Area Index (PDAI) score of 19 (Figure 1a and b).

The patient was initiated on combination therapy with tofacitinib 5 mg twice daily and prednisone 60 mg daily. Progressive clinical improvement was observed during follow-up: by the third month of treatment, prednisone had been successfully tapered to 10 mg daily with resolution of active blistering, and complete clinical remission (PDAI=0) was achieved by month five (Figure 1c and d). Concomitant serological analysis revealed a 64.5% reduction in anti-Dsg1 (61.6 U/mL) and 75.8% reduction in anti-Dsg3 (42.52 U/mL) antibody levels. Despite persistent seropositivity exceeding normal thresholds, prednisone was discontinued at month five while maintaining tofacitinib monotherapy (5 mg twice daily). Notably, no new lesions emerged throughout the treatment course, with sustained remission observed during subsequent follow-up. The therapeutic regimen demonstrated favorable tolerability, with no hematologic abnormalities, hepatic dysfunction, or infectious complications reported over six months of observation.

Molecular Mechanisms Underlying the Efficacy of Tofacitinib Treatment

Immunohistochemical (IHC) analysis of lesional skin biopsies obtained from the patient before treatment and at 5-month follow-up (PDAI=0) demonstrated reduced expression of phospho-STAT3 and phospho-STAT6 following combinational administration (Figure 2a–d).

Proteomic profiling of lesional skin from 3 PV patients and 3 healthy controls identified 198 differentially expressed proteins (fold change >1.5, $p<0.05$). Notably, STAT1, STAT3, and STAT6 were upregulated in PV lesions compared to controls (Figure 3a and Table S1). KEGG pathway analysis revealed enrichment of these proteins in immune-related

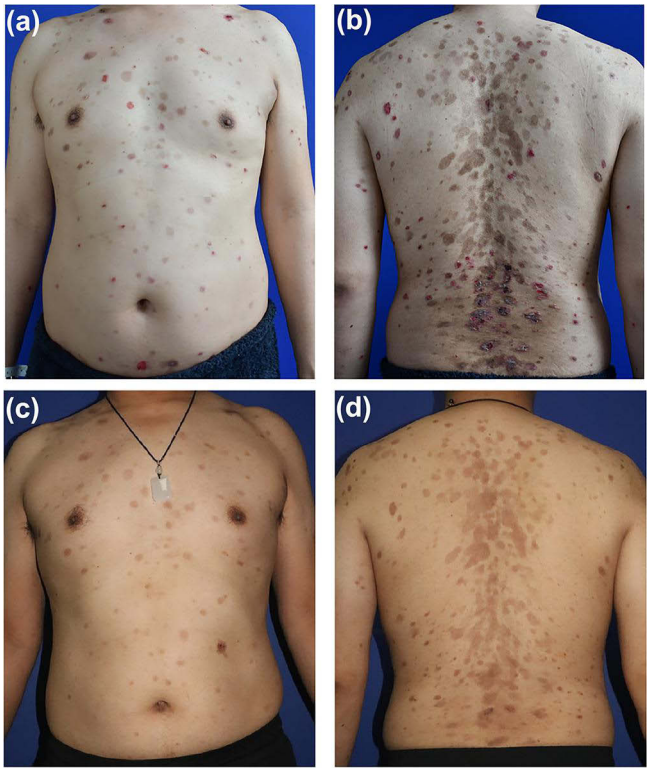

Figure 1 Tofacitinib Therapy-Induced Clinical Remission in this Patient. Clinical photography revealed erythema, vesicles, erosions, and crusts on the chest and abdomen (**a**) and back (**b**) at baseline. Clinical images revealed pigmentation on the chest and abdomen (**c**) and back (**d**) after five months of tofacitinib treatment.

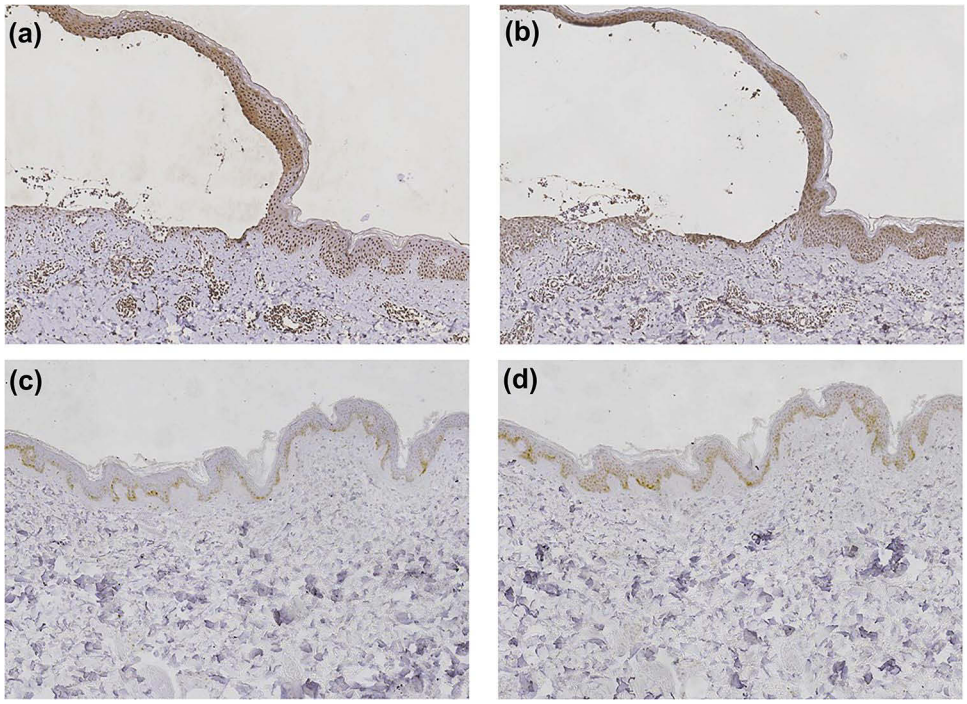

Figure 2 Immunohistochemical (IHC) analysis of phospho-STAT3 (pSTAT3) and phospho-STAT6 (pSTAT6) levels in skin lesions before and after five months of tofacitinib treatment. IHC staining analysis of skin lesion biopsies for pSTAT3 (**a**) and pSTAT6 (**b**) before treatment. IHC staining for pSTAT3 (**c**) and pSTAT6 (**d**) after five months of tofacitinib treatment (original magnification ×100).

pathways including JAK-STAT signaling, IL-17-mediated inflammation, and lymphocyte differentiation pathways (Figure 3b and Table S2).

To validate these findings, IHC quantification was performed on an independent cohort of 5 PV patients and 5 healthy controls. PV lesions exhibited significantly higher staining intensity scores for phospho-STAT3 (7.2 ± 1.64 vs 1 ± 0, $p<0.001$) and phospho-STAT6 (9.6 ± 1.34 vs 1.2 ± 0.45, $p<0.001$) compared to normal skin (Figure 3c–g). These results corroborate the proteomic data, confirming hyperactivation of JAK-STAT signaling in PV pathogenesis.

Discussion

Tofacitinib's therapeutic potential in PV may stem from its capacity to simultaneously block multiple cytokine pathways implicated in disease pathogenesis. Experimental studies have demonstrated this JAK1/3 inhibitor effectively suppresses signaling of IL-4, IL-6, IL-17, and IL-21 - key cytokines driving Th2/Th17 polarization and autoantibody production in PV.[10–12] Our clinical observations align with Tavakolpour's hypothesis proposing JAK inhibition as a viable strategy for refractory PV.[7] To date, only two cases of JAK inhibitor treatment in PV patients have been reported: one with nail improvement[8] and the other with oral mucosal lesion amelioration.[13] This case represents the first reported use of corticosteroid combined with tofacitinib for managing refractory PV, wherein adjunctive tofacitinib therapy enabled successful prednisone tapering to discontinuation (from 60 mg/day to 0 over 5 months) while maintaining complete clinical remission through tofacitinib monotherapy.

Mechanistically, our integrated analysis reinforces the role of JAK-STAT dysregulation in PV pathogenesis. Juczynska et al previously demonstrated elevated JAK/STAT proteins expression in both cutaneous and mucosal PV lesions compared to healthy tissues,[14,15] a finding corroborated by our proteomic data showing STATs upregulation in skin lesions and validated through cohort-level phosphoprotein quantification. The observed attenuation of STAT3/6 phosphorylation post-tofacitinib treatment aligns temporally with clinical remission, suggesting JAK-STAT pathway modulation as a plausible contributor to therapeutic efficacy. However, causality requires further validation given potential off-target effects or involvement of parallel pathways.

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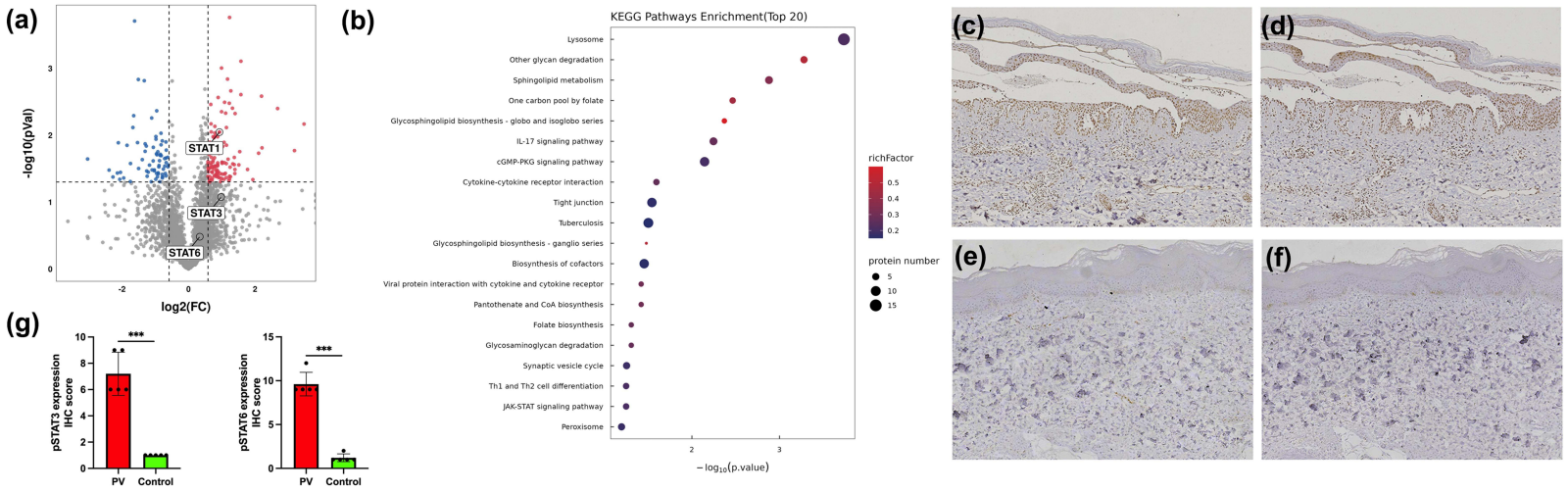

Figure 3 Proteomic and immunohistochemistry (IHC) analyses demonstrated activation of the JAK-STAT signaling pathway in Pemphigus vulgaris (PV) Patients. (**a**) Volcano plot of all detected genes in PV patients compared with health controls. Red dots indicate the up-regulated genes, and blue dots indicate the down-regulated genes (fold change >1.5, p<0.05). (**b**) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of dysregulated proteins. IHC analysis of phospho-STAT3 (pSTAT3) (**c** and **e**) and phospho-STAT6 (pSTAT6) (**d** and **f**) staining from a biopsy of PV (**c** and **d**) and healthy control skin (**e** and **f**) (original magnification ×100). (**g**) IHC scores for pSTAT3 and pSTAT6 in skin lesion samples from PV patients versus healthy controls. Error bars indicate mean standard deviation (SD). ***P < 0.001.

Several limitations merit emphasis. First, residual anti-Dsg antibody titers despite clinical remission highlight tofacitinib's preferential suppression of effector immune responses rather than elimination of autoreactive B-cell clones, necessitating long-term immunologic monitoring. Second, the single-arm design precludes definitive efficacy conclusions. Third, the 6-month follow-up period limits assessment of delayed adverse events, particularly given JAK inhibitors' known association with opportunistic infections and thromboembolic risks. Larger controlled trials are warranted to confirm these preliminary findings and establish safety profiles in PV populations.

Conclusion

This case demonstrates successful corticosteroid withdrawal and sustained remission in refractory PV through adjunctive tofacitinib therapy. Mechanistic analyses revealed JAK-STAT pathway hyperactivation in PV lesions, with tofacitinib attenuating STAT phosphorylation and modulating pathogenic cytokine networks, supporting its role as a steroid-sparing agent.

Ethics Statement

Approval for this study was obtained from the First Affiliated Hospital of Army Medical University. Informed consent for publication of the case details and clinical images was obtained from the patient.

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Disclosure

The authors declare no conflicts of interest for this article.

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