

BRIEF ARTICLE

Safety and Efficacy of Combination Therapy of Upadacitinib and Biologic Agents for Treatment-Resistant Psoriasis and Psoriatic Arthritis

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ABSTRACT

Importance: Although there are many available treatments for psoriasis and psoriatic arthritis (PsA), there are patients resistant to standard conventional therapy. For these patients, combination therapy of biologic agents and upadacitinib may be a viable alternative option; however, there is limited data on concomitant usage.

Objective: To evaluate the safety and efficacy of combination therapy of upadacitinib and biologic agents for the treatment of refractory psoriasis and psoriatic arthritis.

Design: We report the results of a retrospective chart review of 3 patients in a single practice treated with a combination of upadacitinib and biologics for psoriasis and PsA. The risks, benefits, and safety warnings of combination therapy of upadacitinib and biologic agents were discussed before initiation. After shared decision-making with the provider, patients were placed on a trial of combination therapy.

Results: All three patients, previously refractory to monotherapy, experienced significant improvement of their symptoms while on combination therapy. No adverse reactions (malignancy, cardiovascular events, venous thromboembolism) occurred during treatment. However, one patient experienced a shingles outbreak and diverticulitis while on combination treatment. Further studies are needed to determine long-term efficacy with a larger sample size.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic autoimmune arthropathy characterized by pain and swelling in the joints and entheses.¹ PsA is associated with psoriasis (PsO), osteoporosis, uveitis, and an increased risk of cardiovascular disease.^{1,2} More than 20% of psoriasis patients will develop PsA with the onset of symptoms appearing around the ages of 40 and 50.² Both men and women are equally susceptible to the disease.²

The immune response in PsA and PsO is modulated by the secretion of cytokines (IL-6, IL-17, IL-23, and TNF- α) that promote inflammation and joint damage.³ Although there are many treatments focused on decreasing these inflammatory processes (conservative treatment and conventional biologic Disease Modifying Anti-Rheumatic Drugs (DMARD)), biologic DMARDs (such as brodalumab, ixekizumab, risankizumab) have focused on the inhibition of particular pathways involved in the pathogenesis of PsO and PsA.⁴ Tumor necrosis factor- α (TNF- α) blockers like etanercept,

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adalimumab, golimumab, infliximab, and certolizumab pegol are effective for PsA and PsO, but have boxed warnings for malignancy and infection.⁵ Brodalumab and ixekizumab, IL-17 inhibitors, are both highly effective with minimal side effects: primarily mild to moderate yeast infections, injection site reactions, and infrequent exacerbations of inflammatory bowel disease.^{6, 7, 8, 9} IL-23 inhibitors, guselkumab, and risankizumab, are highly effective for psoriasis and are approved for psoriatic arthritis as well.^{8, 10}

Another approved treatment for PsA, upadacitinib, a JAK-1 inhibitor, has been highly effective in patients with prior inadequate response of at least one DMARD (conventional or biologic).¹¹ Unlike biologic DMARDs, upadacitinib is an oral daily medication; however, its package insert carries boxed warnings for major cardiovascular (CV) events, malignancies, venous thromboembolism (VTE), infections, and death.^{12, 13, 14}

Biologics and Janus kinase (JAK) inhibitors are both commonly studied forms of treatment for PsO and PsA. However, there is limited research on the use of both biologics and JAK inhibitors together. Upadacitinib carries a safety warning stating that it should not be used in combination with biologic DMARDs due to insufficient data on concomitant usage.¹³ JAK inhibitors have, however, been used simultaneously with methotrexate, a drug that has more boxed warnings than biologics for psoriasis and is arguably more dangerous.¹⁵ Consequently, in patients with a previous inadequate response to monotherapy with biologics or JAK inhibitors, combination therapy may be an off-label option.

This case series evaluates the safety and efficacy of upadacitinib and biologic

combination therapy for the treatment of refractory psoriasis and psoriatic arthritis.

CASE REPORTS

Patient #1

A 68-year-old male with a history of anemia, hyperlipidemia, latent TB (positive PPD but multiple negative x-rays, and history of TB prophylaxis), Crohn's disease complicated by GI fistula and rectal abscess, and previously diagnosed psoriasis and psoriatic arthritis presented with left wrist swelling and scaly, erythematous plaques located on bilateral hands, lower extremities, feet, and ears.

He previously tried various treatments, including guselkumab (100 mg every four weeks [q4w]), certolizumab pegol (400 mg q4w), adalimumab (40 mg q2w), ixekizumab (80 mg q4w), infliximab, acitretin, narrowband UVB phototherapy, and tofacitinib (11 mg qd). Upadacitinib treatment (15 mg qd) was initiated while continuing the existing treatment of methotrexate (MTX) 15 mg weekly and celecoxib (200 mg bid). After six months of treatment, he noticed his psoriasis worsening (BSA<20%), and upadacitinib was increased to 30 mg daily. He shortly reported improved joint pain but the psoriasis continued to worsen. Methotrexate was tapered, and risankizumab 150 mg and atorvastatin (10 mg daily) were initiated. After 16 weeks of combination therapy, he experienced significant improvement in PsO and PsA with decreased pain, increased mobility (joint flexion), and increased skin clearance.

However, seven months after combination treatment initiation, the patient experienced an outbreak of herpes zoster infection and was treated with famciclovir (500 mg tid) and gabapentin. Upadacitinib treatment was held

for one week. He also developed diverticulitis (13 months after combination therapy) that resolved.

After 15 months of combination therapy, the patient continues the regimen of risankizumab 150 mg q12w and upadacitinib 30 mg daily. There were no reported VTE, upper respiratory infections, or malignancies. His anemia has been stable and is unchanged from before starting upadacitinib.

Patient #2

An 80-year-old male with a history of hypertension (HTN), hyperlipidemia, coronary artery disease, aortic stenosis with aortic valve replacement, and diabetes mellitus (DM) presented with a longstanding history of resistant psoriasis and psoriatic arthritis. He had erythematous, well-demarcated scaly plaques on his back, arms, and legs and swollen finger joints. The patient was previously treated with ixekizumab (80 mg q4w), apremilast (30 mg bid), etanercept, adalimumab, tildrakizumab (100 mg once), secukinumab, and certolizumab pegol. He was started on brodalumab 210 mg q2w and acitretin 25 mg daily. However, acitretin was discontinued due to hair loss, gastrointestinal (GI) symptoms, and hypertriglyceridemia.

His psoriasis significantly improved with brodalumab treatment, but his psoriatic arthritis worsened: marked swelling of joints (PIP, MCP, MTP), deformities (PIP and MCP joints), and arthralgia (ankles, knees). A trial of deucravacitinib 6 mg daily was added to brodalumab after pain progressed in the hands and feet after 23 weeks but later failed to improve symptoms. The patient presented 28 weeks later with progressed symptoms of severe, swollen, erythematous joints in the ankles, knees, hips, shoulders, fingers, and wrists. The swelling was most pronounced on

the first and second PIP joints on the right hand, and MCP joints on multiple fingers.

After discussing several options to treat the patient's severe PsA and receiving cardiology approval (low risk of interaction with rosuvastatin), upadacitinib (15 mg daily) was started in combination with brodalumab. Before upadacitinib initiation, the patient developed thrombocytopenia (104) and anemia (Hgb 12.2), which returned to normal after initiating upadacitinib. After six weeks of combination therapy, he experienced reduced morning stiffness and joint pains (ankles, knees, hips, shoulders, fingers, wrists) but still had swelling present on multiple PIP and MCP joints. Psoriasis continued to remain controlled. Thrombocytopenia has remained stable (104).

The patient has been on combination therapy for 11 weeks and remains on a regimen of brodalumab 210 mg every two weeks and upadacitinib 15 mg daily. No adverse reactions (CV events, malignancy, VTE) occurred during combination treatment.

Patient #3

A 45-year-old female with a history of polycystic ovarian syndrome (PCOS), psoriasis flare-ups (scalp, ears), eczema, and asthma presented with a longstanding history of treatment-resistant psoriatic arthritis, severely affecting multiple joints (hands, heel) and tendons (Achilles). Even when PsA was managed with ixekizumab 80 mg, she experienced multiple swollen and erythematous PIP joints. She has an extensive history of therapies including brodalumab, adalimumab, infliximab, secukinumab, etanercept, cyclosporine, and prednisone.

Even with the addition and increasing doses of methotrexate (25 mg weekly) and celecoxib, arthralgia and swelling, especially in hand joints (MCP, PIP, and DIP joints), were poorly controlled. Skin continued to remain clear of psoriasis with intermittent flares on both ears.

The patient's ixekizumab dose was then increased to 80 mg q2w. However, after four months of treatment, she continued to experience dactylitis, tenderness, and swelling in the MCP joints. Due to insufficient improvement, ixekizumab was discontinued and the patient was started on upadacitinib 15 mg daily combined with 25 mg of methotrexate. She reported that joint pains were 50% less painful with improved flexion of hands after one month. However, the patient experienced hair loss attributed to methotrexate.

The treatment course was later complicated by pneumonia secondary to COVID-19 infection eight weeks after upadacitinib initiation, and the patient was treated with doxycycline and prednisone. Methotrexate was discontinued permanently, and upadacitinib was held for a month.

Although PsA was effectively managed, psoriasis was aggravated post-COVID-19. After discussing options with the provider, the patient was started on a combination therapy trial of ixekizumab (80 mg q4w) and upadacitinib 15 mg daily. She experienced significant improvement in her psoriasis (completely clear) and psoriatic arthritis. Her joint pain in the hands remained stable with mild pain in the lower back/SI joints after eight weeks of combination therapy. The patient reported an upper respiratory infection that self-resolved. Upadacitinib was increased to 30 mg daily.

The patient has been treated with combination therapy for six months and remains on a regimen of ixekizumab 80 mg q4w and upadacitinib 30 mg daily. During treatment, CBC, CMP, and lipid levels were within normal limits. Tuberculosis testing was negative, and there have been no adverse side effects (VTE or malignancies) during combination therapy.

DISCUSSION

The Janus Kinase (JAK/STAT) signaling pathway plays an essential role in the development of inflammatory diseases such as psoriatic arthritis and psoriasis.¹⁶ JAK1 inhibition prevents the recruitment, phosphorylation, and activation of STATs (STAT3/5), thereby reducing the release of pro-inflammatory cytokines, most notably IL-6 among γ -common chain cytokines (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21), and IFN γ .^{16, 17}

Elevated levels of IL-6 are present in patients with psoriatic arthritis. Higher levels of IL-6 are associated with increased PsA activity.^{18, 19, 20} One study showed a decrease in IL-6 and BD-2 (beta-defensin 2) proteins and joint improvement 12 weeks after upadacitinib treatment.²¹ It also showed that the IL-17 pathway, another important pathway in the pathogenesis of psoriatic arthritis, was independent of IL-6 modulation.²¹

Therefore, we hypothesize that combination therapy of upadacitinib and biologic DMARDs is effective in psoriatic arthritis due to the dual inhibition of independent pathways, STAT3/IL-6 (upadacitinib) and IL-17/IL-23 axis (biologic DMARDs). However, more studies are required to examine drug interactions and their effects on signaling pathways.

In our study, all our patients experienced significant improvement in their PsA with combination therapy, although the timing varied. However, providers should still exercise caution when placing patients on combination therapy and follow screening guidelines for each respective medication and monitor for respective side effects. One patient experienced a self-resolving URI, and another experienced an outbreak of herpes zoster and diverticulitis after starting combination therapy. Another patient experienced COVID-19-related pneumonia; however, they were only on upadacitinib and methotrexate at the time. One patient developed thrombocytopenia before initiating combination therapy but has remained stable. There were no incidences of cardiovascular events, VTE, anemia, malignancy, or hyperlipidemia while on combination therapy.

No conclusions can be made about the safety of this combination therapy as the study was limited by the number of patients in our sample size and the time spent on combination therapy. Considering that herpes zoster, a known adverse event seen in trials of JAK inhibitors, occurred in one of our patients, vaccination against herpes zoster should be considered before starting this combination therapy. Further studies are required to evaluate long-term safety and efficacy.

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