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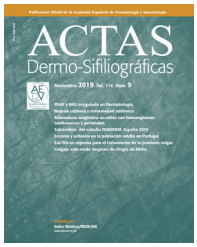

CASE AND RESEARCH LETTER

Effectiveness and safety in the use of Janus kinase inhibitors in combination with other classic or biological systemic treatments: real-world clinical practice experience

Efectividad y seguridad en el uso de inhibidores de Janus kinasa en combinación con otros tratamientos sistémicos clásicos o biológicos: experiencia en práctica clínica real

To the Editor,

While Janus kinase inhibitors (JAKi) have shown efficacy in the treatment of dermatologic conditions, a subset of patients may not achieve symptomatic control. In such situations, our approach may involve either switching to an alternative treatment or considering the addition of a different drug.

Given the limited literature available on the safety profile of combining JAKi with systemic immunomodulatory therapies to treat dermatologic conditions,[1,2] we conducted a retrospective review of patients undergoing simultaneous treatment in our department at a tertiary teaching hospital.

We identified a total of 18 patients (mean age, 43 years; 7 men and 11 women) treated with 22 different combination therapies. Twelve of these patients were prescribed a JAKi for alopecia areata (AA), 5 for atopic dermatitis (AD), and 1 for interstitial granulomatous dermatitis (IGD), in this case as an off-label treatment. A total of 15 patients received a median 21-month regimen of baricitinib 4 mg/day (range, 3–43 months). In 4 cases the given treatment was upadacitinib at a dose of 15 mg/day (in one case at 30 mg/day) for a median 20 months (range, 12–30 months).

The systemic therapies used in combination regimens were varied: methotrexate (12), prednisone (4), dupilumab (4), oral tacrolimus (1) and cyclosporine (1). The decision to combine treatments was based on several factors. The most common reason was a partial response to JAKi, where methotrexate was added in all cases, at a mean dose of 15 mg per week. This combination was used for a median 18 months. The second most frequent reason for combining therapies was a lack of response to JAKi monotherapy. In 2 cases, methotrexate was added, and in another, the combination included dupilumab 300 mg every 14 days and cyclosporine 100 mg twice a day for 6 months (cases #18 and #19; Table 1). Another reason for prescribing the combination therapy involved a patient with a kidney transplant, who was already on tacrolimus 2.5 mg/day plus oral prednisone 5 mg/day (cases #7 and #8; Table 1). Other reasons for prescribing the combination therapy included a transient relapse of atopic dermatitis, for which oral prednisone 40 mg/day was prescribed and tapered over 2 weeks, and a secondary loss of efficacy following the down titration of upadacitinib to 15 mg/day due to adverse effects, for which a 6-month regimen of dupilumab 300 mg every other week was prescribed. In 6 cases, patients who did not achieve complete response with classical immunosuppressive treatments or biologic therapies were initiated on JAKi. Two cases of AA and 1 of IGD who had been on methotrexate at doses of 15 mg/week for a median time of 16 months (range, 7–33 months) were prescribed baricitinib 4 mg/day. There was 1 patient with atopic dermatitis who had been on oral prednisone 30 mg/day for 1 month prior to starting upadacitinib 30 mg/day (case #16; Table 1) and another atopic patient who had been on dupilumab 300 mg every other week for 1 month and was added upadacitinib 15 mg/day to control a very severe flare (case #17; Table 1).

The mean duration of combination therapy was 14.8 months (with 4 patients still undergoing combined treatment to date). Complete responses were achieved in 8 patients diagnosed with AA and 3 cases of AD, representing 61.1%. However, 3 patients (17%), all diagnosed with AA (case #13, case #14 and case #15; Table 1) showed no significant improvement after a mean duration of 7 months of combination therapy with baricitinib and methotrexate at 15 mg/week. In 2 of these cases, adverse effects—mild lymphopenia and transaminitis—were also observed, leading to the interruption of both treatments and the initiation of another JAK inhibitor.

A total of 13 distinct adverse events (AEs) were reported in 10 different patients. Two-thirds of these AEs occurred in 5 patients who were on methotrexate 15 mg/week plus baricitinib 4 mg/day to treat alopecia areata. These events appeared after a mean 9 months (range, 1–23 months) of using the combination therapy. The reported AEs included oral intolerance (1), arthralgia (1), gout episode

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Table 1 Patients on a combination therapy with a JAK inhibitor and other immunomodulatory treatment.

Case	Sex	Age (years)	Comorbidities	Disease	Previous failed systemic therapies prior to JAKi	JAK inhibitor and dose	JAKi monotherapy efficacy	Reason for combination therapy	Systemic immunomodulatory therapies and dose	Combination therapy duration (months)	Combination therapy efficacy	Reason for ending combination therapy	Cause of JAKi discontinuation and following treatment	Adverse effects of combination therapy and treatment attribution
1	Woman	29	None	Alopecia areata	Oral corticosteroids, intralesional corticosteroids, cyclosporin	Baricitinib 4 mg/day	Partial response	Partial response	Methotrexate 15 mg/week (orally)	20	Partial response	Lack of response improvement	Partial response, switched to upadacitnib 30 mg/day monotherapy	None
2	Woman	27	Adaptative disorder	Alopecia areata	Oral corticosteroids, methotrexate, cyclosporin	Baricitinib 4 mg/day	Partial response	Partial response	Methotrexate 15 mg/week (orally)	9	Partial response	Adverse effects	Uninterrupted	Oral intolerance (methotrexate)
3	Man	42	Hypertension	Alopecia areata	Oral corticosteroids, Intramuscular corticosteroids, cyclosporin,	Baricitinib 4 mg/day	Partial response	Partial response	Methotrexate 15 mg/week (orally)	31	Complete response	Complete response	Uninterrupted	None
4	Woman	35	Hypothyroidism, attention deficit/hyperactivity disorder	Intersticial granulomatous dermatitis	Azathioprine, cyclosporin, tacrolimus, oral corticosteroids, methotrexate, adalimumab, etanercept,	Baricitinib 4 mg/day	Not valorable	Uncontrolled with classic immunosupressors	Methotrexate 15 mg/week (subcutaneous)	8 (ongoing)	Complete response	Uninterrupted	Uninterrupted	None
5	Woman	33	None	Alopecia areata	Oral corticosteroids, methotrexate, cyclosporin	Baricitinib 4 mg/day	Complete response	Uncontrolled with classic immunosupressors	Methotrexate 15 mg/week (subcutaneous)	22	Complete response	Complete response	Uninterrupted	None
6	Man	55	None	Alopecia areata	Oral corticosteroids, methotrexate, cyclosporin	Baricitinib 4 mg/day	Partial response	Partial response	Methotrexate 15 mg/week (orally)	20	Complete response	Complete response	Uninterrupted	None
7	Man	45	Renal trasplantation (IgA nephropathy)	Alopecia areata	Intralesional corticosteroids	Baricitinib 4 mg/day	Unassessable	Renal transplant	Prednisone 5 mg/day	24 (ongoing)	Complete response	Uninterrupted	Uninterrupted	Herpes simplex oral infection (baricitinib)
8	Man	45	Renal trasplantation (IgA nephropathy)	Alopecia areata	Intralesional corticosteroids	Baricitinib 4 mg/day	Unassessable	Renal transplant	Tacrolimus 2.5 mg/day	24 (ongoing)	Complete response	Uninterrupted	Uninterrupted	Herpes simplex oral infection (baricitinib)
9	Woman	50	None	Alopecia areata	Oral corticosteroids, methotrexate	Baricitinib 4 mg/day	Partial response	Partial response	Methotrexate 15 mg/week (orally)	19	Complete response	Complete response	Uninterrupted	None
10	Woman	67	None	Alopecia areata	Oral corticosteroids, intralesional corticosteroids, cyclosporin	Baricitinib 4 mg/day	Partial response	Partial response	Methotrexate 15 mg/week (orally)	13	Complete response	Complete response	Uninterrupted	None

Table 1 (*Continued*)

Case	Sex	Age (years)	Comorbidities	Disease	Previous failed systemic therapies prior to JAKi	JAK inhibitor and dose	JAKi monotherapy efficacy	Reason for combination therapy	Systemic immunomodulatory therapies and dose	Combination therapy duration (months)	Combination therapy efficacy	Reason for ending combination therapy	Cause of JAKi discontinuation and following treatment	Adverse effects of combination therapy and treatment attribution
11	Man	43	None	Atopic dermatitis	Oral corticosteroids, cyclosporin	Baricitinib 4 mg/day	Partial response	Transitory loss of efficacy	Prednisone 40 mg/day in gradual tapering (orally)	0.5	Partial response	Secondary failure to JAKi	Secondary failure, switched to upadacitnib 30 mg/day monotherapy	None
12	Man	44	None	Alopecia areata	Oral corticosteroids, methotrexate	Baricitinib 4 mg/day	Unassessable	Uncontrolled with classic immunosupressors	Methotrexate 15 mg/week (subcutaneous)	23	Complete response	Complete response	Uninterrupted	Hypercolesterolemia and hypertrigliceridemia (baricitinib), gout (methotrexate)
13	Woman	51	Hypertension	Alopecia areata	Oral corticosteroids, intralesional corticosteroids, cyclosporin	Baricitinib 4 mg/day	Transitory partial response	Partial response	Methotrexate 15 mg/week (orally)	11	None	No response and adverse effects	Primary failure, switched to ruxolitinib 20 mg/12 h monotherapy	Transminitis and mean corpuscular volume increase (methotrexate)
14	Woman	65	Osteoporosis	Alopecia areata	Oral corticosteroids, cyclosporin, methotrexate	Baricitinib 4 mg/day	None	No response	Methotrexate 15 mg/week (orally)	6	None	Adverse effects	Primary failure, switched to ruxolitinib 20 mg/12 h monotherapy	Lymphopenia and herpes simplex infection (baricitinib)
15	Woman	44	None	Alopecia areata	Oral corticosteroids, intramuscular corticosteroids, intralesional corticosteroids, cyclosporin, methotrexate,	Baricitinib 4 mg/day	None	No response	Methotrexate 10 mg/week (orally)	5	None	No response	Primary failure, switched to ruxolitinib 20 mg/12 h monotherapy	Artharlgia (methotrexate)
16	Man	21	Smoker, asthma	Atopic dermatitis	Oral corticosteroids, cyclosporin, dupilumab,	Upadacitinib 30 mg/day	Complete response	Uncontrolled with classic immunosupressors	Prednisone 30 mg/day in gradual tapering (orally)	0.5	Complete response	Complete response	Uninterrupted	None
17	Man	39	Glaucoma and cataracts	Atopic dermatitis	Oral antibiotics, oral corticosteroids, methotrexate, mycophenolate, cyclosporin, azathioprine, dupilumab	Upadacitinib 15 mg/day	Unassessable	Uncontrolled with biologic therapy	Dupilumab 300 mg/14 days	32 (ongoing)	Complete response	Uninterrupted	Uninterrupted	None

Table 1 (*Continued*)

Case	Sex	Age (years)	Comorbidities	Disease	Previous failed systemic therapies prior to JAKi	JAK inhibitor and dose	JAKi monotherapy efficacy	Reason for combination therapy	Systemic immunomodulatory therapies and dose	Combination therapy duration (months)	Combination therapy efficacy	Reason for ending combination therapy	Cause of JAKi discontinuation and following treatment	Adverse effects of combination therapy and treatment attribution
18	Woman	54	Environmental allergies, asthma, rheumathoid arthitis, pulmonar sarcoidosis	Atopic dermatitis	Oral corticosteroids, cyclosporin,	Baricitinib 4 mg/day	None	No response	Dupilumab 300 mg/14 days	6	Partial response	Lack of response improvement	Uncontrolled arthritis, switched to adalimumab 40 mg/2 weeks	Nausea (dupilumab)
19	Woman	54	Environmental allergies, asthma, rheumathoid arthitis, pulmonar sarcoidosis	Atopic dermatitis	Oral corticosteroids, cyclosporin, methotrexate	Baricitinib 4 mg/day	Unassessable	No response	Cyclosporin 100 mg/12 h	12	Partial response	Lack of response improvement	Uncontrolled arthritis, switched to adalimumab 40 mg/2 weeks	
20	Woman	55	Environmental allergies, asthma, rheumathoid arthitis, pulmonar sarcoidosis	Atopic dermatitis	Oral corticosteroids, cyclosporin, methotrexate	Upadacitinib 15 smg/day	Unassessable	Oral corticosteroid used to control arthritis	Prednisone 15 mg in gradual tapering (orally)	12	Complete response	Complete response	Uninterrupted	6 kg weight increase (upadacitinib)
21	Woman	27	Environmental allergies	Atopic dermatitis	Phototherapy, oral corticosteroids, methotrexate, azathioprine, cyclosporin	Upadacitinib 15 mg/day	Complete response	Loss of efficacy of JAKi monotherapy	Dupilumab 300 mg/14 days	6	Complete response	Patient preference	Patient preference	
22	Woman	27	Environmental allergies	Atopic dermatitis	Phototherapy, oral corticosteroids, methotrexate, azathioprine, cyclosporin, upadacitinib, dupilumab	Upadacitinib 15 mg/day	Unassessable	Uncontrolled with biologic therapy	Dupilumab 600 mg/14 days	3	Complete response	Unfunded combination	Unfunded combination	Neutropenia (upadacitinib)

(1), relapse of oral herpes simplex (3), dyslipidemia (1), mild lymphopenia (810 cells/10$\hat{9}$/L) (1), transaminitis (alanine transaminase, 87.6 U/L; aspartate transaminase, 50.99 U/L) (1), and an increase in mean corpuscular volume to 106 fL (1).

In addition, 1 patient with AD on baricitinib 4 mg/day and dupilumab experienced several days of nausea after the first dose of dupilumab. Another patient, treated for 6 months with upadacitinib 30 mg/day and prednisone 10 mg, had a 6 kg weight gain, leading to a 50% down titration of the JAKi. A patient with AD on upadacitinib 15 mg/day and intensified dupilumab therapy (case #22; Table 1) developed mild neutropenia (1030 cells/10$\hat{9}$/L), nevertheless this patient had a prior history of neutropenia and had already down titrated upadacitinib by 50%. Finally, a renal transplant recipient experienced a recurrence of oral herpes 12 months into baricitinib while on immunosuppressive therapy with tacrolimus and prednisone (case #7 and case #8; Table 1).

In 7 patients who achieved complete responses, the classic immunosuppressant was withdrawn. In contrast, in 4 cases, both treatments were discontinued and replaced with another JAK inhibitor due to primary treatment failure. Three patients with AA who had been on baricitinib and methotrexate were switched to ruxolitinib 20 mg twice daily. Additionally, 2 patients were switched from baricitinib 4 mg/day to upadacitinib 30 mg/day—one due to a stationary response in an AA patient, and the other due to secondary failure of the JAK inhibitor in a patient with AD (case #1 and case #11; Table 1).

Based on our experience, combining JAKi with systemic immunomodulatory therapy seems to be a viable strategy for a substantial proportion of patients, particularly those unable to achieve complete responses in monotherapy or with specific comorbidities. Of note, side effects were observed around the 50% of patients, all of which were classified as mild. Only 2 patients discontinued the combination therapy, switching to another JAKi in monotherapy, not due to the severity of the events but because a viable alternative was readily available. Of note, no adverse events of special interest, such as venous thromboembolism, pulmonary embolism, major adverse cardiovascular events, neoplasms, serious infections, or non-melanoma skin cancers were reported at the follow-up.

While this combination therapy introduces new avenues for managing challenging cases of inflammatory skin conditions, the validation of our observations requires further prospective studies with larger cohorts and longer follow-ups.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT to optimize the word count of the article and orthographics. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Conflicts of interest

Clara Muntaner-Virgili declared to have received support for attending meetings from Lilly, and Sanofi.

Clara Torrecilla-Vall-llossera declared to have received support for attending congresses from Lilly, Sanofi, and LEO pharma.

Montserrat Bonfill-Orti declared to have received honoraria as a speaker for Lilly, Abbvie, LEO pharma, and Sanofi.

Ignasi Figueras-Nart declared to have received honoraria as speaker and advisor for Lilly, Abbvie, and Sanofi.

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