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BRIEF COMMUNICATION

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Treatment of Generalized Granuloma Annulare With Biologics and Oral JAK Inhibitors: A Case Series

Benjamin Gerstein BS, Isabel Silva BS, Saakshi Khattri MD

Kimberly and Eric J. Waldman Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY

INTRODUCTION

Granuloma annulare (GA) is a granulomatous inflammatory skin condition of unknown etiology, often presenting as annular plaques or papules.[1] Generalized GA (GGA) is a rare subtype of GA characterized by its widespread distribution and resistance to conventional treatments such as topical or intralesional corticosteroids.[2] The rarity of the disease and lack of evidence-based treatment guidelines pose a unique management challenge. Biologics and oral JAK inhibitors have increasingly been used for refractory GGA cases.[3] We sought to characterize the outcomes of these therapies used for GGA in a large academic center.

GA is characterized by an upregulation of Th1, Th2, Th17, Th22, and JAK-STAT pathways. There is an increased expression of cytokines such as TNF-α, IL-1β, IFN-γ, IL-12/23p40, IL-4, and IL-31.[2] Due to the upregulation of these inflammatory pathways in GA, therapies that target these pathways have been used off-label to treat GGA.[4] Several reports have shown improvement or remission with systemic therapies, including JAK inhibitors, TNF-α inhibitors, IL-4 blockers, and IL-23 blockers.[4]

We conducted a retrospective case series of adult GGA patients treated with a biologic or oral JAK inhibitor at a single academic dermatology clinic (November 2016 to January 2025). Patient demographics, medical history, disease extent, and treatment response, assessed by changes in erythema, induration, and lesion count were obtained via medical records (Table 1).

CASE SERIES

We identified 22 patients (mean age 59.4 years; range 32–77), 90% (n=20) females, and 77% white (Table 2). All patients had recalcitrant disease, having previously attempted corticosteroids (topical, intralesional, or oral), topical ruxolitinib (n=4), hydroxychloroquine (n=6), oral antibiotics (n=6), and phototherapy (n=3).

Adalimumab was the most prescribed therapy (n=11), 63.6% experienced marked response or remission. Dupilumab (n=8) led to moderate or better responses in 62.5% of patients, and one achieved remission. All patients on upadacitinib (n=5) had a positive response, with 80% noting a marked response or remission. Among the 2 patients on abrocitinib, one achieved

TABLE 1.

Summary of Response of Patients With Generalized GA by biologic/oral JAK Inhibitor

Drug	Patients Treated	Drug Class	Clinical Response	Average Response Time	Adverse Events
Adalimumab	11	TNF-α inhibitor	Clinical remission (n=5) Marked response (n=2) Moderate response (n=1) Minimal response (n=2) No response (n=1)	6–7 months	Psoriasiform eruption (n=1)
Dupilumab	8	IL-4 and IL-13 blocker	Clinical remission (n=1) Marked response (n=0) Moderate response (n=4) Minimal response (n=1) No response (n=2)	4–5 months	None
Upadacitinib	5	JAK 1 inhibitor	Clinical remission (n=1) Marked response (n=3) Moderate response (n=1) Minimal response (n=0) No response (n=0)	7–8 months	Bloating, constipation, weight gain, acne (n=1)
Abrocitinib	2	JAK 1 inhibitor	Clinical remission (n=1) Marked response (n=0) Moderate response (n=0) Minimal response (n=1) No response (n=0)	3–4 months	Hives/ eczema outbreak (n=1)
Certolizumab	1	TNF-α inhibitor	Clinical remission (n=1)	4 months	None

Clinical Response:
1. 0% (no response)
2. <25% (minimal response)
3. >25%, <75% (moderate response)
4. >75%, <100% (marked response)
5. 100% (clinical remission)

*Because this was a retrospective study, data for patients were recorded when patients returned for visits. In many cases, the condition improved before follow-up visits.

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TABLE 2.

Patients With Generalized GA Treated With Biologics or Oral JAK Inhibitors and Their Clinical Response

Patient No. /Age/ Sex/Race	Comorbidities	Previous Therapies	Biologic/ Oral JAK Inhibitor	Therapy Duration	Skin Involvement	Clinical Response	Time Until Response	Adverse Events
1/ 64/ M/ White	Asthma	Topical steroids Ciprofloxacin Rifampin Pulsed minocycline	Adalimumab	6.5 months (discontinued)	Extremities, bilateral axillae, abdomen, back, groin	Minimal response	6.5 months	None
			Upadacitinib	16 months (ongoing)		Clinical remission	11 months	
2/ 58/ F/ White	Hashimoto's thyroiditis, hyperlipidemia	Topical steroids	Adalimumab	13 months (discontinued)	Legs, trunk	Minimal response	5 months	Bloating, constipation, weight gain, acne on upadacitinib
			Upadacitinib	2 months (discontinued)		Moderate response		
			Abrocitinib	7 months (ongoing)		Clinical remission		
3/ 65/ F/ Other	Hyperlipidemia, T2DM	Hydroxy-chloroquine Pentoxifylline Dapsone Phototherapy Oral minocycline Topical steroids IMTAC Acitretin Doxycycline	Adalimumab	5.5 months (discontinued)	Extensor forearms, left posterior thigh, trunk	Marked response, but discontinued due to drug eruption rash.	3 months	Psoriasiform eruption (TNF-α related drug reaction)
4/ 68/ F/ White	Hyperlipidemia	Topical steroids ILTAC	Upadacitinib	7 months (ongoing)	Right index finger, bilateral extensor elbows	Marked response	4 months	None
5/ 43/ F/ White	None	Oral steroids Doxycycline ILTAC Phototherapy	Adalimumab	4 yrs (ongoing)	Lower extremities, elbows	Clinical remission	6 months	None
6/ 68/ M/ Unknown	Atopic dermatitis	Topical steroids	Dupilumab	8 months (ongoing)	B/l Shoulders, arm, L arm, L thigh	Moderate response	7 months	None
7/ 58/ F/ White	Hashimoto's thyroiditis, Celiac disease, Atopic dermatitis	Hydroxy-chloroquine Topical steroids ILTAC	Abrocitinib	3 months (discontinued)	B/l upper extremities, medial thighs, lower legs, dorsum of feet bilaterally.	Minimal response, discontinuation due to hives/ eczema outbreak	2 months	Hives/ eczema outbreak
8/ 49/ F/ White	Atopic dermatitis	Topical steroids Topical ruxolitinib Oral steroids Dapsone	Dupilumab	26 months (ongoing)	Upper and lower extremities	No response	N/A	None
9/ 68/ F/ White	Psoriasis	Topical steroids ILTAC	Adalimumab	3.5 yrs (ongoing)	B/l ankles and lower legs	Clinical remission	7 months	None
10/ 32/ F/ White	Alopecia areata	Topical steroids Hydroxy-Chloroquine ILTAC Topical tofacitinib	Dupilumab	7 months (discontinued)	Trunk, back, and neck	Minimal response	4 months	None
11/ 67/ F/ Black	Dyshidrotic eczema, atopic dermatitis	Topical steroids Topical ruxolitinib	Adalimumab	11 months (ongoing)	Arms, thighs	Clinical remission, then flare	2 months	None
			Dupilumab	7 months (ongoing)		Clinical remission	3 months	
12/ 48/ F/ White	Hypothyroidism, seborrheic dermatitis	Topical steroids	Upadacitinib	11 months (ongoing)	Dorsal hands, chest, back	Marked response	9 months	None

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TABLE 2. (CONTINUED)

Patients With Generalized GA Treated With Biologics or Oral JAK Inhibitors and Their Clinical Response

Patient No. /Age/ Sex/Race	Comorbidities	Previous Therapies	Biologic/ Oral JAK Inhibitor	Therapy Duration	Skin Involvement	Clinical Response	Time Until Response	Adverse Events
13/ 54/ F/ White	Psoriasis	Topical steroids	Dupilumab	5 months (discontinued)	Abdomen, bilateral inner thighs	No response	N/A	None
			Adalimumab	15 months (discontinued)				
14/ 75/ F/ White	Ulcerative colitis	Topical steroids Hypochlorous acid NBUVB	Certolizumab pegol	6 yrs (ongoing)	Generalized	Clinical remission	4 months	None
15/ 63/ F/ White	Psoriasis	Topical steroids Doxycycline, Hydroxy-chloroquine	Adalimumab	11 months (discontinued)	B/l lower legs and forearms	Moderate response	12 months	None
16/ 54/ F/ White	Lichen sclerosis	Topical steroids Methotrexate Acitretin	Adalimumab	7 months (discontinued)	B/l lower extremities	Clinical remission	5 months	None
17/ 74/ F/ White	Sarcoid uveitis, psoriasis	Topical steroids Oral steroids Methotrexate UBUVB	Adalimumab	7 months (ongoing)	Chest, abdomen, B/l upper and lower extremities	Marked response	5 months	None
18/ 44/ F/ White	None	Topical steroids ILTAC Topical ruxolitinib	Adalimumab	27 months (ongoing)	Neck, chest, b/l arms	Clinical remission	6 months	None
19/ 66/ F/ Unknown	Atopic dermatitis	Topical steroids ILTAC	Dupilumab	26 months (ongoing)	Arms, chest	Moderate response	6 months	None
20/ 63/ F/ White	Atopic dermatitis	Ustekinumab Oral steroids Topical steroids	Dupilumab	16 months (ongoing)	Legs, arms, abdomen, face, buttocks	Moderate response	6 months	None
21/ 48/ F/ White	Atopic dermatitis, osteoporosis	Topical steroids Topical ruxolitinib Hydroxy-chloroquine Doxycycline	Dupilumab	6 months (ongoing)	Generalized	Moderate response	2 months	None
22/ 77/ F/ White	Hypothyroidism, hyperlipidemia	Topical steroids Minocycline, Ofloxacin Rifampin Hydroxy-chloro-quine Phototherapy	Upadacitinib	5 months (ongoing)	Bilateral anterior and posterior legs	Marked re-sponse	6 months	None

JAK, Janus kinase; NB, narrowband; UV, ultraviolet; b/l, bilateral.

remission. One patient treated with certolizumab-pegol for 6 years achieved remission (Table 1). Two patients unresponsive to adalimumab achieved remission after switching to an oral JAK inhibitor. One patient on adalimumab relapsed and achieved remission upon addition of dupilumab combination therapy.

Three patients reported adverse events (Table 2). One patient reported a psoriasiform eruption on adalimumab, a reported side effect of TNF-α inhibitors, and therapy was discontinued. Another reported moderate GI discomfort, weight gain, and acne on upadacitinib, which are all reported side effects of oral JAK inhibitors, and therapy was discontinued. The last reported hives/eczema outbreak after 3 months on abrocitinib and therapy was discontinued. No serious adverse events were reported.

DISCUSSION

While the pathogenesis of GA is not fully understood, targeting the known inflammatory pathways in GA can lead to improvement or clinical remission in patients with recalcitrant GGA.

To our knowledge, this is the largest case series of patients with GGA treated with biologics or oral JAK inhibitors. Out of

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22 patients, nearly all experienced at least some improvement in erythema, induration, and the formation of GA lesions, with 13 (59.1%) patients experiencing a marked response or clinical remission. Most patients who experienced marked response or clinical remission were treated with adalimumab (63.6%, 7/11) or upadacitinib (80%, 4/5).

Adalimumab is a TNF-α inhibitor that has shown efficacy in the treatment of several granulomatous diseases, such as Crohn's disease and sarcoidosis.5 Upadacitinib is a selective JAK-1 inhibitor currently FDA-approved for the treatment of multiple autoimmune and inflammatory skin diseases.[6] Emerging reports suggest that biologics such as adalimumab and oral JAK inhibitors such as upadacitinib may also be effective treatment options for GGA.[7,8] However, most of these reports are confined to case reports and small case series'. We observed positive outcomes in 20 patients, and marked response or clinical remission in 13 patients. In addition, few reports have described treatment with biologics or JAK inhibitors after recurrence or failure on another biologic or JAK inhibitor. We observed clinical remission in two patients on oral JAK inhibitors (one on upadacitinib and one on abrocitinib) who had experienced minimal response to adalimumab.

The selection of a therapy of choice for GGA patients should involve a discussion between the dermatologist and the patient, taking into account safety, monitoring, patient expectations, patient comorbidities, and quality of life. This study is limited by its small sample size and retrospective nature; however, we have shown positive results in the treatment of GGA with biologic and oral JAK inhibitors. Clinicians should proceed with caution when considering any systemic therapy off-label, but we did not experience any safety concerns in our small sample size. Evidence-based treatment guidelines derived from randomized controlled trials are warranted, as the majority of published research is still confined to case reports, case series, and singular retrospective studies.

DISCLOSURES

Dr Saakshi Khattri is an employee of Mount Sinai and receives research funds from Leo Pharma, AbbVie, Bristol Myers Squibb, Pfizer, Celgene, and Acelyrin. Dr Khattri is also a consultant for Leo, AbbVie, Eli Lilly, Janssen, Regeneron, Sanofi, and UCB. Authors Gerstein and Silva have no conflicts of interest to declare.

IRB Approval Status: Institutional Review Board of the Mount Sinai School of Medicine, in accordance with Mount Sinai's Federal Wide Assurances (FWA#00005656, FWA#00005651), to the Department of Health and Human Services, approved the following human subject research.

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AUTHOR CORRESPONDENCE

Saakshi Khattri MD
E-mail:..... saakshi.khattri@mountsinai.org