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CONCISE COMMUNICATION

Biological and JAK inhibitor therapy outcomes for severe psoriasis in trisomy 21

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Abstract

Little is known about biological outcomes for severe psoriasis in trisomy 21 (T21). Our aim was to review outcomes of patients with T21 and severe psoriasis treated with biologic or Janus kinase inhibitors (JAKi). Information on demographics, co-morbidities, and therapeutic responses was retrospectively collated. Twenty-one patients were identified (mean age 24.7 years). Ninety percent (18/20) of TNFα inhibitor trials failed. Almost two-thirds (7/11) of patients achieved an adequate response with ustekinumab. All three patients treated with tofacitinib achieved an adequate response following at least three biologic failures. The mean number of biologic/JAKi therapies received was 2.1 with overall survival of 36%. Eighty-one percent (17/21) of patients required conversion from their index biologic treatment due to failure. In patients with T21 and severe psoriasis, failure of TNFα inhibition is common and ustekinumab therapy should be considered as first-line therapy. The role of JAKi is emerging.

KEYWORDS
arthritis, immunology, obesity, Psoriasis, trisomy 21

1 | INTRODUCTION

Trisomy 21 (T21) is associated with autoimmunity, related to abnormal monocyte and circulating cytokine populations.[1] There are defects in innate and adaptive immunity in T21 with higher levels of tumor necrosis factor-α (TNFα), interleukin- (IL) 1β, and interferons (IFN).[1] However, the prevalence of psoriasis in T21 is similar to the general population with no clear signal for increased severity.[2] T21-associated immune dysregulation may have implications for efficacy, safety, and drug survival of biologic medications. Other common dermatological disorders in T21 include xerosis, seborrheic and atopic dermatitis, keratosis pilaris, folliculitis, hidradenitis suppurativa, alopecia areata, vitiligo, onychomycosis, and scabies; and other papulosquamous disorders such as crusted scabies or pityriasis rubra pilaris.[2] Ireland has one of the highest incidences of T21 with 1 in 444 live births affected, and approximately 110 infants with T21 born annually in Ireland.[3] There have been six published reports of biologic use for psoriasis in T21: five for TNFα-inhibitors and one for ustekinumab (Table 1). There has been no report of Janus kinase inhibition (JAKi) for psoriasis in T21.

The aim of this study was to review the outcomes of patients with T21 and severe psoriasis treated with biologic agents or JAKi in our region. Given the cytokine dysfunction described above, our hypothesis was that TNFα inhibition should provide clinical benefit for severe psoriasis in T21.

TABLE 1 Previously reported outcomes for biologic therapy for severe psoriasis in trisomy 21.

Year	Authors	Sex	Age	Failed agents	Successful agents	Follow-up
2008	Alcaide et al.	Male	30	Top	ETAN	<9 months
2012	Talamonti et al.	Unknown	31	ADA, ETAN	USTE	N/A
2012	Marmon et al.	Male	12	Top	ADA	2 years
2012	Marmon et al.	Male	20	MTX, ETAN	ADA	3 years
2017	Adamczyk et al.	Female	12	Top, CSA	ETAN	10 weeks
2021	Madani et al.	Male	33	Top	ADA	7 months

Abbreviations: ADA, adalimumab; CSA, ciclosporin; ETAN, etanercept; MTX, methotrexate; N/A, not applicable; Top, topical; USTE, ustekinumab.

2 | METHODS

Ethical approval was granted by our clinical research and ethics committee (ECM 4 (oo) 22/02/2022). Patients were identified by searching the databases of three dermatology departments in Munster, Ireland. The research was also advertised through the social media channels of the Down Syndrome Ireland network. Retrospective reviews were performed using a uniform data collection sheet, collating information on demographic details, comorbidities, previous therapies, current therapies, and response to therapies. Severe psoriasis was defined as a Psoriasis Area Severity Index score of more than 10 or body surface area of more than 10%. Adequate response to treatment was defined as a Physician Global Assessment score of 0 (indicating clear skin), or 1 (indicating almost clear skin).

3 | RESULTS

Twenty-one patients were identified (age range 6–48 years; Table 2). Most (62%, $n=13$) were male and most (76%, $n=16$) did not have a first degree relative with psoriasis. Overall, 33% of patients had arthritis, but all children ($n=6$) had arthritis, while only 7% ($n=1$) of adults had arthritis. A small proportion of patients had known comorbid nail disease (14%), ischaemic heart disease (5%), inflammatory bowel disease (5%), or hepatic steatosis (10%). Nearly half of patients (48%) were obese, defined as a body mass index (BMI) over 30 in adults or a BMI over the 95th centile in children. In terms of non-biologic therapies, a third ($n=7$) had received narrow band ultraviolet B phototherapy, over half ($n=13$) had been treated with methotrexate, and smaller numbers had received ciclosporin ($n=1$), acitretin ($n=3$), fumaric acid esters ($n=2$), and apremilast ($n=2$). Patients had been treated with a mean of 2 (range, 0–5) of these therapies prior to transition to biologic/JAKi treatment.

In terms of biologic therapy (Table 3), 90% (18/20) of TNFα inhibitor trials failed with five etanercept failures, nine adalimumab failures, two golimumab failures, and two infliximab failures. The two patients who responded to adalimumab were children with comorbid psoriatic arthritis, who also had a parent with psoriasis. Almost two-thirds (7/11) of patients achieved persistently clear/almost clear skin with ustekinumab. IL-17 inhibition was successful for one third (2/6) of patients and IL-23 inhibition was successful for two thirds (2/3) of patients. IL-6 inhibition with tocalizumab was not helpful for two children. All three patients (one adult, two children) who had comorbid arthritis treated with the JAKi tofacitinib achieved an adequate response following at least three biologic failures. The mean number of biologic/JAKi therapies received in this population ($n=21$) was 2.1 (range, 1–5) with an overall biologic survival rate of 31%, suggesting a treatment-resistant population. Overall, 81% (17/21) of patients required a switch from their index biologic treatment. The four patients who remained on their index biologic treatment were all started on ustekinumab. No patient had therapy withdrawn because of adverse events. Primary failure (21/29) was more common than secondary failure (8/29), suggesting mechanistic failure rather than immunogenicity.

TABLE 2 Demographic details of patients with trisomy 21 on biologic therapy for severe psoriasis.

$n=21$	Variable	n (%)
Sex	Male	13 (61.9)
	Female	8 (38.1)
Age	Mean	24.7 years
	Range	6–48 years
Family history psoriasis[a]	Yes	5 (23.8)
	No	16 (76.2)
Comorbidities	Arthritis	7 (33.3)
	Nail involvement	3 (14.3)
	Ischaemic heart disease	1 (4.8)
	Inflammatory bowel disease	1 (4.8)
	Hepatic steatosis	2 (9.5)
	Obesity	10 (47.6)

[a]Family history of psoriasis was defined as a first-degree relative (parent or sibling) with psoriasis.

4 | DISCUSSION

This is the largest series of patients with T21 and severe psoriasis treated with biologic/JAKi therapy. In adults, the rate of comorbidities was relatively low with less than 15% having arthritis or nail

TABLE 3 Outcomes for biologic therapies and the janus kinase inhibitor tofacitinib in 21 patients with trisomy 21 and severe psoriasis.

Treatment	Success/trial	Success rate, %
TNFα-inhibitors	2/20	10
Etanercept	0/5	0
Adalimumab	2/11	18.2
Golimumab	0/2	0
Infliximab	0/2	0
IL-12/23 inhibitor		
Ustekinumab	7/11	63.6
IL-17 inhibitors	2/6	33.3
Secukinumab	1/4	25
Ixekizumab	1/2	50
IL-23 inhibitors	2/3	66.7
Guselkumab	1/2	50
Risankizumab	1/1	100
IL-6 inhibitor		
Tocilizumab	0/2	0
Biologics overall	13/42	30.9
Janus kinase inhibitor		
Tofacitinib	3/3	100

Abbreviations: IL, interleukin; TNF, tumor necrosis factor.

involvement. However, all children in the study had arthritis, probably related to the fact that children with psoriatic arthritis are more likely to start a biologic medication because of the potential for permanent joint damage. The rate of obesity was high, which is common in both T21 and severe psoriasis. Obesity is associated with a 25%–30% reduction in efficacy for biologic therapy.[4] There was a very poor response to TNFα inhibition, a good response to ustekinumab, and an excellent response to tofacitinib in the small number of patients treated in this series. Ustekinumab has the benefit of higher dosing for heavier patients, although it is rare for patients with T21 to weigh over 100 kg due to their relatively short stature. Ustekinumab may also be preferable to JAKi because of potentially reduced infectious, thrombotic, cardiovascular, and cancer risks. Two children who responded to TNFα inhibition had parents with severe psoriasis, which might suggest that their immunophenotype relates to genes other than those directly related to T21. Reassuringly, no patient required biologic cessation due to adverse events such as infection or abnormal blood tests.

Most treatments prescribed for severe psoriasis target cytokines, particularly interleukins such as 12/23, 17, and 22.[5] However, the IFN pathway is the major signaling cascade consistently activated by T21 in human cells.[6] Furthermore, signal transduction of IFN requires binding to its receptors (IFNAR1, IFNAR2, and IFNAR3), which are encoded on chromosome 21,[7] and are triplicated in T21. With the additional copy of chromosome 21, IFN sensitivity is increased. Therefore, patients with T21 have both higher levels of, and enhanced sensitivity to, IFN. This is similar to the immune profile seen in paradoxical psoriasis, which is also driven by aberrant IFN signaling,[8] and has been shown by Irish colleagues to affect downstream immune pathways.[9] If dysfunctional IFN is the underlying disorder, then interleukin-based therapies that target alternative pathway cytokines are less likely to be helpful. The rheumatology literature has already recommended that JAK inhibition, via direct effect on receptors which suppress IFN-signaling pathways, be considered as a first-line therapy for psoriatic arthritis in T21, given the IFN hyperactivation.[10] Other considerations include that the risks of major adverse cardiovascular events[11,12] and dementia[13] are higher in both T21 and in severe psoriasis, and that these risks may be modified by immunomodulatory therapy.[14]

Following the results of this study, our new hypothesis is that because of elevated levels of IFN, inhibitors of JAK/STAT signaling should provide benefit, but that IL-directed biologic agents (such as IL-12 and IL-23) may also provide benefit by interfering with IFN-mediated inflammation.

The Irish National Register for Children with Down Syndrome (https://nbci.ie/dsregister/) was established in 2015. We hope that this register will facilitate prospective immune-profiling and mechanistic studies investigating our hypothesis and help to formulate specific guidance for patients with T21.

Limitations of this study include the retrospective data collection, the relatively small number of patients given the examined outcome of treatment efficacy, and the lack of immune profiling to assess immunophenotypes objectively. Previous trials have shown that IL-17 inhibitors and IL-23 inhibitors are superior to TNFα inhibitors in terms of efficacy.[15] This trend was also seen in this study, so it is not possible to state that the results of this study are specific to patients with T21. Strengths include the size of the cohort, given the rarity of previously reported outcomes, and the long-term follow-up.

In summary, this is the largest series of biologic outcomes for severe psoriasis in T21, with almost four times the total number of cases previously reported. Failure of TNFα inhibition is common; ustekinumab therapy should be considered first line, and there is an emerging role for JAK inhibition, given the interferon hyperactivation seen in these patients. Future studies should examine immune parameters to verify these clinical outcomes.

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CONFLICT OF INTEREST STATEMENT

None declared.

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