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Treatment with Janus kinase inhibitors in juvenile dermatomyositis: A review of the literature

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ABSTRACT

Background/Objectives: Janus kinase (JAK) inhibitors have been increasingly used in the treatment of juvenile dermatomyositis (JDM). This review aims to comprehensively analyze previous studies concerning the utilization of JAK inhibitors in JDM patients.
Methods: We conducted a thorough review of MEDLINE and Scopus databases, spanning from their inception to September 1st, 2023, to identify articles involving JDM patients treated with JAK inhibitors.
Results: Our literature search yielded 26 articles that encompassed 195 patients with JDM who received JAK inhibitors. The median (min-max) age of the patients was 4.9 (1–17) years (F/M:1.2). The most frequently used JAK inhibitor was tofacitinib (57.4 %), and improvement was achieved in 89.7 % of patients treated with tofacitinib. The improvement rate for ruxolitinib, which was the second most frequently used JAK inhibitor (27.2 %), was 69.2 %. For baricitinib (15.4 %), the improvement rate was 92.7 %. The most prevalent indication for JAK inhibitor use was resistant/recurrent skin involvement (34.7 %) followed by resistant/recurrent muscle involvement (28.6 %). Adverse events were reported in 72.1 % of the patients; an increase in infections (especially upper respiratory tract infections) was the most common side effect.
Conclusion: Our findings suggest that JAK inhibitors may be a good therapeutic option, particularly in the management of refractory JDM cases with an acceptable safety profile. However, further controlled studies are essential to establish a higher level of evidence for the optimal use of JAK inhibitors in JDM treatment.

Introduction

Juvenile dermatomyositis (JDM) is the most common idiopathic inflammatory myopathy in childhood. The most common findings are muscle weakness and erythematous rash. Less frequently, the lungs, gastrointestinal system (GIS), joints, and other organs are affected [1]. Corticosteroids and methotrexate are used in treatment. Complications such as calcinosis, lipodystrophy, interstitial lung disease, and joint contractures are difficult to manage [2]. Disease-modifying anti-rheumatic drugs (DMARDs) other than methotrexate, biologics, and small molecules are used in resistant cases [2].

Interferon (IFN) stimulated or regulated genes are upregulated in JDM, similar to systemic lupus erythematosus [3]. IFNs activate the Janus kinase (JAK)-signal transducer and transcription (STAT) pathway, which leads to the transcription of IFN-stimulated genes. This pathway is the target for the blockade of the transcription of IFN genes. Tofacitinib inhibits JAK1/3, while ruxolitinib and baricitinib inhibit JAK 1/2 [4]. Clinical trials regarding to use of specific JAK inhibitors in JDM are ongoing [5,6]. However, the use of JAK inhibitors in JDM is mostly limited to tofacitinib, ruxolitinib, and baricitinib.

In this review, we aimed to perform a detailed analysis of the published data regarding the use of JAK inhibitors in JDM treatment.

Search strategy for literature review

We conducted a systematic literature search following PRISMA guidelines and published guidance on narrative reviews [7], encompassing PubMed/MEDLINE and Scopus databases, spanning from their inception up to September 1st, 2023. We employed specific keywords, including “juvenile dermatomyositis”, “Janus kinase inhibitor”,

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"tofacitinib", "baricitinib", and "ruxolitinib" to identify pertinent articles. Our search was limited to articles in English and Spanish and exclusively included human studies. We examined case reports/series, original research articles, letters, editorials, and other articles involving patients with JDM (age at diagnosis <18 years) treated with JAK inhibitors. We did not include patients if the type of the JAK inhibitor was not clearly stated in the original report. Two authors (SS and VC) independently conducted the literature search, eliminating irrelevant literature, removing duplicates, and screening titles, abstracts, and full texts. Data extraction was performed independently by both authors, with any discrepancies resolved through consensus. Our evaluation encompassed various parameters from the included studies, such as age at diagnosis, gender, clinical manifestations, laboratory results, imaging [magnetic resonance imaging (MRI)] and electromyography (EMG)] and histopathological findings, treatment, and outcome. ''Improvement'' was defined as the complete resolution of disease-related clinical and serological findings after treatment; ''progression'' as no improvement and advance in disease-related findings after treatment compared to the pre-treatment period; ''stable disease'' as the absence of any improvement or progression in disease-related findings after treatment.

Results of the literature review

The schematic overview of the included articles was presented in Fig. 1. We identified 26 articles describing 195 patients with JDM treated with JAK inhibitors during our literature search [8–33]. The characteristics of all patients were summarized in Table 1 and the detailed data were presented in Supplementary Table 1.

The median (min-max) age at diagnosis of the JDM patients treated with JAK inhibitors was 4.9 (1–17) years (F/M:1.2) (Table 1). Myopathy and skin involvement were present in 77.2 % and 90.2 % of patients, respectively. Other than these, the most frequently involved systems were pulmonary (26.1 %) and gastrointestinal (25 %).

The most frequently used JAK inhibitor was tofacitinib (n = 109, 57.4 %) (Table 2) [10,11,13,14,16,17,22-29,31-33], followed by ruxolitinib (n = 53, 27.2 %) [8,11-13,18,20] and baricitinib (n = 29, 15.4 %) [9,18,19,21,30]. The duration of treatment with JAK inhibitors was mentioned for 77 patients, and the median (min-max) duration was 1.4 (0.1–2.5) years.

Most patients treated with JAK inhibitors had previously and/or concomitantly used at least one immunosuppressive drug (Table 2). Corticosteroids (100 %), methotrexate (79.4 %), and intravenous immunoglobulin (IVIG) (70.7 %) were the most frequently used other treatments in these patients.

Treatment indications of JAK inhibitors, response to these drugs, and associated adverse events were presented in Table 3. The most common treatment indication was resistant/recurrent skin involvement (n = 34/98, 34.7 %), followed by resistant/recurrent muscle involvement (n = 28/98, 28.6 %). Improvement was achieved in 58/67 patients (86.6 %) (Table 1). The improvement rates for tofacitinib, ruxolitinib, and baricitinib were 89.7 % (n = 52/58), 69.2 % (n = 9/13), and 92.7 % (n = 38/41), respectively (Table 3). Among the improved patients, relapse under JAK inhibitors was detected in 4/55 cases (7.3 %).

Side effects were observed in 31/43 patients (72.1 %) treated with JAK inhibitors [12,15,18,24,30,33]. Most of these were upper respiratory infections (22/31, 70.9 %). GIS (n = 6) and musculoskeletal (n = 3) symptoms were also observed in a few cases. Additionally, some laboratory changes such as thrombocytosis (n = 1), anemia (n = 1),

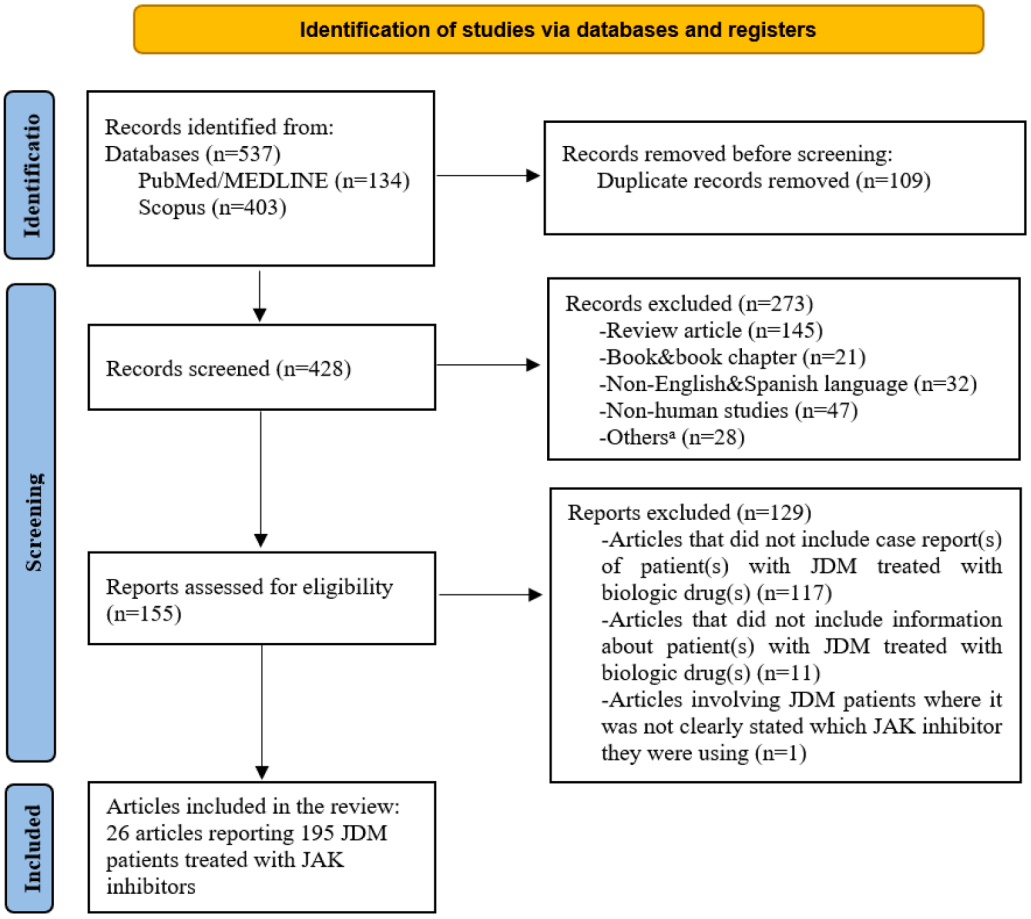

Fig. 1. The PRISMA flow diagram of literature screening regarding Janus kinase (JAK) inhibitor use in juvenile dermatomyositis (JDM).
[a]Others: letter, editorial, conference paper, short survey, comment, note

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Table 1
The general features and outcomes of the juvenile dermatomyositis (JDM) patients in the literature treated with Janus kinase (JAK) inhibitors.

	JDM patients (n = 195)
Age at diagnosis, years, median (min-max)	4.9 (1–17)
Gender, female, n (%)	52/92 (56.5)
Clinical findings, n (%)	
Musculoskeletal symptoms	71/92 (77.2)
Proximal muscle weakness	16/92 (17.4)
Arthritis/arthralgia	4/92 (4.3)
Myalgia	40/92 (43.5)
Skin findings	43/92 (46.7)
Gottron's papule	11/92 (11.9)
Heliotrope rash	21/92 (22.8)
Skin ulceration	5/92 (5.4)
Malar rash or facial erythema	40/92 (43.5)
Shawl sign	18/92 (19.6)
Other rashes	18/92 (19.6)
Calcinosis	26/92 (28.3)
Constitutional symptoms	14/92 (15.2)
Cardiopulmonary symptoms	4/92 (4.3)
GIS symptoms	1/92 (1.1)
MAS	
Neuropsychiatric symptoms	
Organ involvement, n (%)	
Skin	83/92 (90.2)
Pulmonary	24/92 (26.1)
GIS	23/92 (25)
Cardiac	2/92 (2.2)
CNS	1/92 (1.1)
Laboratory findings, n (%)	
Elevated muscle enzymes	36/46 (78.3)
Myositis-specific or associated antibodies	23/89 (25.8)
Anti-NXP2	22/89 (24.7)
Anti-MDA5	20/89 (22.5)
Anti-Ro52	16/89 (17.9)
Other antibodies[a]	
MRI findings suggesting JDM, n (%)	14/16 (87.5)
EMG findings suggesting JDM, n (%)	3/4 (75)
Histopathological proof of JDM, n (%)	27/28 (96.4)
Disease duration, years, median (min-max)	1.5 (0.1–18)
Outcome, n (%)	
Improvement	58/67 (86.6)
Progression	6/67 (8.9)
Stable disease	3/67 (4.5)

CNS, central nervous system; EMG, electromyography; GIS, gastrointestinal system; JAK, Janus kinase; JDM, juvenile dermatomyositis; MAS, macrophage activation syndrome; MRI, magnetic resonance imaging.

[a] Anti-TIF-1 gamma (n = 5), anti-PL7 (n = 3), anti-Pm-Scl-75 (n = 2), anti-Mi-2 beta (n = 1), anti-Jo-1 (n = 1), anti-SSA (n = 1), anti-SRP (n = 1), anti-Ku (n = 1), anti-PL12 (n = 1).

neutropenia (n = 1), basophilia (n = 1), basophilopenia (n = 1), lymphocytosis (n = 1), elevated liver enzymes (n = 3), creatine kinase (n = 2), lactate dehydrogenase (LDH) (n = 2), total cholesterol (n = 1), triglycerides (n = 1), creatinine (n = 1) and uric acid (n = 1) levels were among the reported side effects. Two patients who had herpes zoster infection after using JAK inhibitors were hospitalized [18,30]. In one of these cases, the JAK inhibitor was temporarily discontinued [30]. In another patient with increased BK viremia, the JAK inhibitor dose was temporarily reduced until the viremia resolved [12].

Discussion

Small molecules like JAK inhibitors, which have been introduced to the treatment of JDM during the last decade, have contributed to the improvement of disease outcomes. Our results revealed that JAK inhibitors were frequently preferred in JDM patients with resistant/recurrent skin involvement (34.7 %) and resistant/recurrent muscle involvement (28.6 %). However, in these cases, JAK inhibitors were not usually the first choice, and other immunosuppressive agents were used first in the majority. JAK inhibitors were started especially in the absence of response to other agents or in the presence of toxicity associated with other agents. The most frequently used JAK inhibitor in JDM patients was tofacitinib (57.4 %), followed by ruxolitinib (27.2 %). Improvement rates were also good for all JAK inhibitors (~70 %). Side effects were observed in 72.1 % of patients treated with JAK inhibitors, but most were mild upper respiratory tract infections (70.9 %).

Table. 2
All treatments of juvenile dermatomyositis (JDM) patients treated with Janus kinase (JAK) inhibitors in the literature.

All treatments, n (%)	JDM patients (n = 195)
JAK inhibitors	
Tofacitinib	112 (57.4)
Ruxolitinib	53 (27.2)
Baricitinib	30 (15.4)
Other treatments	
Corticosteroid	92/92 (100)
Methotrexate	50/63 (79.4)
IVIG	65/92 (70.7)
Mycophenolate mofetil	25/63 (39.7)
Cyclophosphamide	20/63 (31.7)
Rituximab	20/63 (31.7)
Cyclosporine A	18/63 (28.6)
Hydroxychloroquine	14/63 (22.2)
ASCT	9/63 (14.3)
Tacrolimus	8/63 (12.7)
Infliximab	6/63 (9.5)
Abatacept	6/63 (9.5)
Plasma exchange	4/63 (6.3)
Thalidomide	3/63 (4.8)
Bisphosphonate	3/63 (4.8)
Anakinra	2/63 (3.2)
Tocilizumab	2/63 (3.2)
Azathioprine	1/63 (1.6)
Adalimumab	1/63 (1.6)
Sirolimus	1/63 (1.6)
Etoposide	1/63 (1.6)
Unknown biologic agents	1/63 (1.6)

ASCT, autologous stem cell transplantation; IVIG, intravenous immunoglobulin; JAK, Janus kinase; JDM, juvenile dermatomyositis.

Studies on JDM pathogenesis have underscored the excessive activation of the type 1 interferon pathway [34]. Type 1 IFNs exert their effect via signaling through their receptors which are connected to JAKs [34]. In line with emerging evidence that JAK inhibitors may benefit patients with JDM by reducing type I IFN signaling, JAK inhibitors are being used in JDM treatment. While ruxolitinib and baricitinib can only inhibit JAK 1/2, tofacitinib can inhibit JAK 1/3 [35]. Although pathogenetic pathways are important in drug preference, side effects should also be taken into consideration.

JAK inhibitors have been successfully used for the treatment of rheumatoid arthritis, psoriasis, and inflammatory bowel disease [36]. However, JAK inhibitors are not currently approved by the Food and Drug Administration (FDA) for the treatment of dermatomyositis (DM) or JDM. We use them as off-label treatment. Unfortunately, this situation limits the clinical use of JAK inhibitors in JDM treatment. However, after the necessary indication is determined by clinicians, especially in resistant cases, JAK inhibitors can be obtained through off-label applications.

JAK inhibitors are also preferred in adult DM patients, especially in resistant/recurrent diseases. In a systematic literature review by Paik et al. [37], 84 DM cases treated with JAK inhibitors were identified. The most frequently used JAK inhibitor in adult patients was tofacitinib (79.8 %). Significant improvements in skin lesions, muscle strength, and interstitial lung disease were observed in most of the included studies. Sixty-one patients with refractory skin disease (73 %) had significant improvement in their cutaneous symptoms after the treatment with JAK inhibitors. All 16 patients with refractory muscle disease (19 %) had improvement in their muscle symptoms after the treatment. In addition, 31 of 33 adult DM patients (94 %) complicated by interstitial lung

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Table 3
The treatment indications of Janus kinase (JAK) inhibitors, response to these drugs, and associated adverse events in patients with juvenile dermatomyositis (JDM).

JAK inhibitors	No. of patients	Treatment duration, years, median (min-max)	Indications for the treatments[a]	Responses to the treatments	Relapse under the treatment (among improvements)	Adverse events
Tofacitinib	112	1.5 (0.1–2.4)	Resistant/recurrent muscle involvement[b] (n = 16/57, 28.1 %)	Improvement (n = 15) No improvement (n = 1)	1/24 (4.2 %) NA=28	- Upper respiratory infections (n = 22/43, 51.2 %) - GIS symptoms (n = 6/43, 13.9) - Herpes zoster (n = 4/43, 9.3 %) - Musculoskeletal symptoms (n = 3/43, 6.9 %) - Increased BK viremia (n = 3/43, 6.9 %) - BK viruria (n = 1/43, 2.3 %) - HSV meningitis (n = 1/43, 2.3 %) - Skin abscess (n = 1/43, 2.3 %) - Paronychia (n = 1/43, 2.3 %) - Viral gastroenteritis (n = 1/43, 2.3 %) - Weight gain (n = 1/43, 2.3 %) - Dizziness (n = 1/43, 2.3 %) - Dysuria (n = 1/43, 2.3 %) - Dysmenorrhea (n = 1/43, 2.3 %) - Thrombocytosis (n = 1/43, 2.3 %) - Anemia (n = 1/43, 2.3 %) - Neutropenia (n = 1/43, 2.3 %) - Basophilia (n = 1/43, 2.3 %) - Basophilopenia (n = 1/43, 2.3 %) - Lymphocytosis (n = 1/43, 2.3 %) - Elevated creatine kinase (n = 2/43, 4.7 %), LDH (n = 2/43, 4.7 %), aldolase (n = 1/43, 2.3 %), GGT (n = 1/43, 2.3 %), liver enzymes (n = 1/43, 2.3 %), cholesterol (n = 1/43, 2.3 %), triglycerides (n = 1/43, 2.3 %), creatinine (n = 1/43, 2.3 %), and uric acid (n = 1/43, 2.3 %) levels
			Pulmonary involvement (n = 16/57, 28.1 %)	Improvement (n = 12) No improvement (n = 4)		
			Resistant/recurrent skin involvement[c] (n = 12/57, 21.1 %)	Improvement (n = 12)		
			Joint involvement (n = 6/57, 10.5 %)	Improvement (n = 6)		
			Calcinosis (n = 3/57, 5.3 %)	Improvement (n = 3)		
			MAS (n = 2/57, 3.5 %)	Improvement (n = 1) No improvement (n = 1)		
			Cardiac involvement (n = 2/57,3.5 %)	Improvement (n = 2)		
			NA (n = 85)	Improvement (n = 1) NA (n = 84)		
Ruxolitinib	53	1.2 (0.3–1.9)	Resistant/recurrent muscle involvement[b] (n = 2/3, 66.7 %)	Improvement (n = 2)	1/8 (12.5 %) NA=1	
			Calcinosis (n = 1/3, 33.3 %)	Improvement (n = 1)		
			NA (n = 54)	Improvement (n = 6) No improvement (n = 4) NA (n = 44)		
Baricitinib	30	1.4 (0.2–2.5)	Resistant/recurrent skin involvement[c] (n = 22/38, 57.9 %)	Improvement (n = 22)	2/23 (8.7 %) NA=15	
			Resistant/recurrent muscle involvement[b] (n = 10/38, 26.3 %)	Improvement (n = 9) No improvement (n = 1)		
			Calcinosis (n = 3/38, 5.2 %)	Improvement (n = 3)		
			Pulmonary involvement (n = 3/38, 5.2 %)	Improvement (n = 2) No improvement (n = 1)		
			NA (n = 3)	Improvement (n = 2) No improvement (n = 1)		

CK, creatinine kinase; CNS, central nervous system; GGT, gamma glutamyl transferase; GIS, gastrointestinal system; HSV, herpes simplex virus; LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; NA, not assessed.
[a] More than one indication may exist for a patient.
[b] Progressive and/or recurrent muscle involvement unresponsive to multiple immunosuppressive treatments.
[c] Progressive and/or recurrent skin involvement unresponsive to multiple immunosuppressive treatments.

disease improved with JAK inhibitor therapy. In our review, similar to adults, the most frequently used JAK inhibitor was tofacitinib and was frequently preferred in resistant/recurrent muscle involvement and pulmonary involvement. Similar to children, JAK inhibitors were used at a higher rate in adults due to pulmonary involvement.

In reported studies, JAK inhibitors were used at different doses in JDM patients [8–33]. Unfortunately, controlled studies on safe and effective doses of JAK inhibitors in children are lacking and there is no clear consensus on dosing in the literature. In the coming years, focusing on studies regarding the optimum dosage of JAK inhibitors in juvenile dermatomyositis will be very useful to close this gap in the literature.

The main side effects associated with the use of JAK inhibitors in DM are infections. Other side effects include hematologic abnormalities (such as anemia and leukopenia), GIS symptoms (such as vomiting, diarrhea, GIS perforation), hyperlipidemia, cardiovascular disease, nasopharyngitis, headache, and cancer [38,39]. Apart from these, no serious complication has been reported [36]. In our literature review, an increase in infection rate (especially upper respiratory infections) was the most common side effect in JDM patients treated with JAK inhibitors [12,15,18,24,30,33]. In a few cases, GIS and musculoskeletal symptoms, increased BK viremia and viruria, weight gain, dizziness, dysuria, dysmenorrhea, thrombocytosis, anemia, neutropenia, basophilia, basophilopenia, lymphocytosis, elevated liver enzymes, creatine kinase, LDH, cholesterol, triglycerides, creatinine and uric acid levels were

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reported [12,13,15,30].

Our review had some limitations. Important limitations were that many studies included in this review were open-label and consisted of small case report(s) and series. Systematic evaluations and controlled studies are lacking in the literature on this topic. Also, when evaluating the treatment indications and outcomes related to the use of JAK inhibitors, it should be taken into account that the patients included in these studies had previously or simultaneously used other immunosuppressive agents. Finally, there may be a potential overlap of patients since the patient(s) in the studies included in our systematic review might have been reported more than once in different studies.

Conclusion

JAK inhibitor treatment may lead to an improvement in a wide range of JDM symptoms. Also, the safety profile of JAK inhibitors seems to be good with a lack of serious adverse events. However, controlled studies in larger-scale JDM cohorts are needed to clearly determine the effectiveness and safety of these small molecules.

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CRediT authorship contribution statement

Seher Sener: Conceptualization, Formal analysis, Investigation, Resources. **Veysel Cam:** Data curation, Formal analysis, Investigation, Methodology, Methodology, Project administration, Resources, Visualization, Writing – original draft. **Seza Ozen:** Data curation, Resources, Supervision, Writing – original draft, Writing – original draft. **Ezgi Deniz Batu:** Conceptualization, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft.

Declaration of competing interest

Ezgi Deniz Batu receives payment for speakers' bureaus from Novartis. Seza Ozen receives consultancy fees and payment for speakers' bureaus from Novartis and Sobi. Other authors did not declare any conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152426.

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