VOL 5
ISSUE 4
2024

ISSN 2563-7673 (PRINT)
ISSN 2563-7681 (ONLINE)

CANADIAN DERMATOLOGY TODAY

TABLE OF CONTENTS

Canadian Dermatology Today is published 4 times per year in English and French.

To learn more please visit canadiandermatologytoday.com

The content in Canadian Dermatology Today qualifies for Section 2 (self-learning) credits towards the maintenance of certification. For information on how this activity fits in the Royal College Maintenance of Certification (MOC) Program, please visit the Royal College's website (royalcollege.ca/moc). For more personalized support, please contact the Royal College Services Centre (1-800-461-9598) or your local CPD Educator.

If you would like to contribute to a future issue of Canadian Dermatology Today please email us at info@catalytichealth.com.

EDITORIAL BOARD

PrCABTREO™

INTRODUCING

THE **FIRST + ONLY TRIPLE COMBINATION** TREATMENT INDICATED IN ACNE*

CABTREO (clindamycin phosphate, adapalene, and benzoyl peroxide) is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

C CLINDAMYCIN

A ADAPALENE

B BENZOYL PEROXIDE

ONCE-DAILY TOPICAL GEL

Consult the Product Monograph for complete details on recommended dosing and administration.

Scan here to learn more about CABTREO ›

Consult the Product Monograph at https://bauschhealth.ca/wp-content/uploads/2024/08/CABTREO-PM-E-2024-08-01.pdf for contraindications, warnings, precautions, adverse reactions, interactions, dosing and conditions of clinical use. The Product Monograph is also available by calling 1-800-361-4261.

* Comparative clinical significance unknown.
Reference: CABTREO Product Monograph. Bausch Health.

BAUSCH Health
bauschhealth.ca

MADE IN CANADA

REVIEWED BY PAAB

PrCABTREO™
(Clindamycin Phosphate, Adapalene and Benzoyl Peroxide) Gel
1.2%, 0.15%, 3.1% w/w

10.58931/cdt.2024.54128

ABOUT THE AUTHOR

Anastasiya Muntyanu, MD

Dr. Anastasiya Muntyanu is a Canadian and US board-certified dermatologist, currently practicing in Toronto. She completed her medical school at the University of Ottawa and graduated from the University of Toronto Dermatology Residency Program. She is completing her PhD focused on studying environmental triggers of autoimmune and inflammatory skin diseases including psoriasis, systemic sclerosis, atopic dermatitis. She has over 40 publications in high impact journals and has received numerous awards including from the Canadian Institutes of Health Research award, Canadian Dermatology Association, and American Dermato-Epidemiology Network. During her residency she was the co-chair of the Canadian Dermatology Association's Resident and Fellow Society and was a resident representative on numerous academic committees for which she received the Resident Leadership Award and the Resident Teaching Award from the Canadian Dermatology Association. Dr. Muntyanu's clinical areas of interest include medical and surgical dermatology with a focus on psoriasis, eczema, systemic sclerosis and morphea, and skin cancer.

Affiliations: Women's College Hospital, Toronto, ON
Canadian Dermatology Center, Toronto, ON

Systemic Sclerosis: Pathogenesis, Diagnosis, and Management

Anastasiya Muntyanu, MD

Background

Systemic sclerosis (SSc) is an autoimmune fibrosing disease with internal organ involvement leading to significant morbidity and mortality. The average age of diagnosis ranges from 33.5–59.8 years with a strong female predominance (3.8–15 times more common).[1]

Epidemiology

Previous studies in Canada have demonstrated a prevalence of 74.4 cases per 100,000 females and 13.3 cases per 100,000 males (Canadian SSc prevalence data, 2003), which accounts for approximately 2,500 males and 14,000 females who are affected by this debilitating condition in Canada.[2] The highest point prevalence reported in the world, 47/100,000 persons, was observed among Canadian First Nation residents. Globally, the prevalence of SSc is estimated to be between 7–489 cases per million individuals, with large variability, at least in part, due to differences in diagnosis and in the heterogeneity of the disease.[3] Consistently higher case numbers are reported in North America and Australia compared to continental Europe, the United Kingdom, and Japan.[3] In the United States, the estimated period prevalence is 50/100,000 persons, and the age-sex adjusted annual incidence was 5.6/100,000 person-years for the years 2003-2008.[4,5] Globally, the annual incidence has been estimated to be 0.6–5.6/100,000 adults. A recent updated study in Quebec, Canada, showed an overall age-standardized incidence rate of 4.14 cases per 100,000 person-years, with a 4:1 female predominance.[6] The age-standardized incidence rate increased steadily over time, with an average increase of approximately 4% each year.

Variable geographic distribution has been observed, suggesting that extrinsic/environmental factors may play a role in disease development. For example, in Europe, a north–south gradient was observed with an increased prevalence of SSc in

southern countries.[3] Small studies also reported clusters of SSc cases in boroughs near international airports in London, United Kingdom,[7] a rural community near Rome, Italy,[8] and in Libby, Montana, where mining activities are predominant.[9] Other reported clusters include Woodstock, Canada,[10] and the Kahnawake First Nations Community in Quebec, Canada.[11] These studies suggest a non-random distribution of SSc cases and highlight the need to further investigate the epidemiology and environmental risk factors for this disease.

Pathogenesis

The pathogenesis of SSc is not fully understood, but it is hypothesized to be due to an environmental trigger in a genetically susceptible host.[12] A three-step hypothesis has been proposed, which includes endothelial cell dysfunction/vasculopathy, inflammation due to immune system dysregulation, and fibrosis **(Figure 1)**.[1] The low concordance rate in monozygotic twins and the evidence of geographic clustering suggests the importance of an extrinsic factor leading to disease development.[13] The nature of such triggers and other factors accounting for the variability in SSc clinical severity and prognosis remains unknown.

Possible external factors that have been studied in SSc include infectious agents, chemicals, occupational or environmental pollutants, and medications/supplements, all of which could affect the immune response and trigger microvascular damage and inflammation, subsequently leading to fibrosis.[15] Air pollution, a frequently studied environmental factor, is known to negatively contribute to many diseases, and was designated by the World Health Organization (WHO) as the primary environmental threat to humanity. It accounts for at least 7 million deaths globally every year.[16] Currently, the highest level of evidence for extrinsic triggers for SSc points to occupational or environmental exposures to silica (18-fold increased risk) and organic solvents (2–4-fold increased risk).[14,17] Silica exposure was associated with lower survival rates and a more severe disease phenotype, including diffuse cutaneous systemic sclerosis (dcSSc), digital ulcers, interstitial lung disease (ILD), myocardial dysfunction, and positive anti-topoisomerase (ATA) antibodies.[14] Other occupational exposures proposed to increase SSc risk include epoxy resins, asbestos, and particulate air pollution.[14]

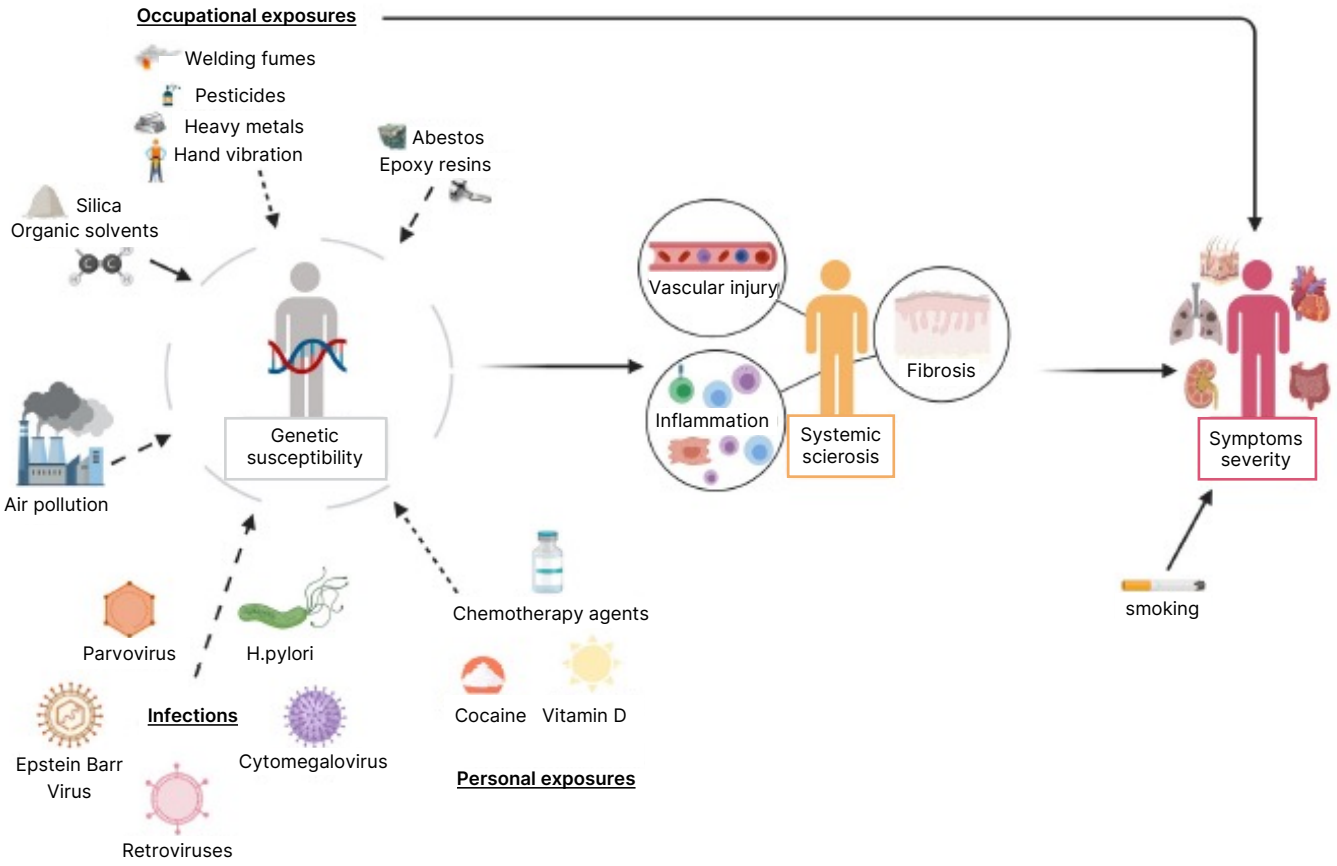


Figure 1. Pathogenesis of SSc and the role of occupational, environmental, and personal exposures to disease development. *H. pylori* - *Helicobacter pylori*. Thick lines—exposures increasing the incidence and/or severity of SSc risk based on observational studies. Dashed lines—exposures with probable increased incidence and/or severity of SSc (limited data). Dotted lines—exposures with anecdotal/unproven data only. Adapted from Ouchene et al.[14]

Clinical Presentation

Given that many manifestations of SSc are cutaneous, dermatologists play an important role in diagnosis, especially for early onset disease. The disease is classified into the following based on the extent of the skin fibrosis and the pattern of internal organ involvement: limited cutaneous (lcSSc) (the most common form) involving the distal limbs and face; dcSSc, involving the distal and proximal extremities, trunk and face; sine scleroderma, presenting without skin thickening but with internal organ involvement and serologic abnormalities; and overlap disease (e.g systemic lupus erythematosus, rheumatoid arthritis, polymyositis, or Sjögren's disease).[18] The most commonly affected organs are those with direct exposure to the environment such as the skin, gastrointestinal tract, and lungs.[19] In all forms, and especially in dcSSc, there is significant internal organ involvement leading to increased morbidity and mortality. The 10-year likelihood of survival is less than 65%,[19] and has remained unchanged for the last forty years.[20] In fact, SSc has one of the highest mortality rates of any rheumatic disease.[1]

Compared to females, SSc in males is more likely to present with a more severe phenotype including dcSSc, cardiomyopathy, ILD, and scleroderma renal crisis.[21] Whether these differences are related to sex-hormones or acquired risk factors (e.g. occupational/environmental) requires further investigation. On the other hand, females are more likely to have a younger age of disease onset and an increased rate of peripheral vascular disease and pulmonary arterial hypertension (PAH).[22]

Regarding ethnic differences, African American patients are more likely to develop the disease at a younger age and have more severe phenotypes including increased ILD and scleroderma renal crisis.[23]

Diagnostic Criteria

The diagnosis of SSc is based on the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) classification criteria, which includes clinical disease manifestations, such as bilateral, symmetric skin thickening proximal to the metacarpophalangeal joints (sufficient criterion), presence of SSc-related abnormalities (e.g. Raynaud's phenomenon, fingertip lesions, telangiectasias, SSc-specific antibodies, abnormal nailfold capillaroscopy) and internal organ involvement (e.g. ILD, PAH) **(Table 1)**.[24] Patients achieving a score of ≥9 are classified as having definite SSc.

Item	Sub Item	Weight/ Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)		9
Skin thickening of the fingers (only count the highest score)	Puffy fingers	2
	Sclerodactyly of the fingers (distal to MCP but proximal to the PIPs)	4
Fingertip lesions (only count the highest score)	Digital tip ulcers	2
	Fingertip pitted scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Lung Involvement (Maximum score is 2)	PAH	2
	ILD	2
Raynaud's phenomenon		3
Scleroderma related antibodies (Maximum score is 3)	ACA	3
	ATA	3
	RNAP3	3

Table 1. ACR/EULAR classification criteria for SSc. Patients with a total score of ≥9 are classified as having definite SSc. Adapted from van de Hoogen et al.[24]
Abbreviations: ACA: anti-centromere antibodies; **ATA:** anti-topoisomerasel/Scl-70 antibodies; **ILD:** interstitial lung disease; **MCP:** metacarpophalangeal joint; **PAH:** pulmonary arterial hypertension; **PIP:** proximal interphalangeal joint; **RNAP3:** anti-RNA polymerase III

Since internal organ involvement commonly occurs within the first 3 years, early diagnosis is important. In the last few decades, the availability of nailfold capillaroscopy, which reveals dilated capillary loops and drop out sign, as well as SSc-specific autoantibodies, have allowed an earlier diagnosis of SSc to be made. Very early diagnosis of SSc (VEDOSS) criteria were established in 2011.[25] These criteria include the presence of Raynaud's phenomenon, puffy fingers, and positive ANA as early disease features that predict progression to established SSc.[26] Hence, these early features could be helpful in establishing the diagnosis earlier, initiating treatment, minimizing end organ damage, and subsequently improving patient outcomes.

There are several specific autoantibodies that help with the diagnosis, clinical presentation, prognosis, and the exclusion of other conditions that present with skin thickening. ANA is positive in ~95% of patients.[1,27,28] SSc-specific-autoantibodies include anti-centromere

Antibody	Estimated Prevalence	Subtype of SSc	Main Systemic Associations
ACA	20–25%	lcSSc	• PAH (15–20%) • Esophageal dysmotility and gastrointestinal dysfunction • Low risk of ILD, cardiac and renal disease
ATA	20–30%	dcSSc >lcSSc	• High risk of ILD (early) • PAH • Scleroderma renal crisis • Cardiac • Myositis
PM/Scl	2–4%	Overlap Polymyositis/ lcSSc	• Myositis • ILD (50% by 15 years) • PAH (approximately 36% by 15 years) • Cardiac • Renal
To/Th ribonucleoprotein	<5%	lcSSc	• ILD (45%) • PAH (25%)
RNAP-III	1–22%	dcSSc (rapidly progressive)	• Scleroderma renal crisis (early) • Increased risk of malignancy within 3 years of diagnosis • Moderate risk of ILD • PAH (later) • Gastric antral vascular ectasia • Myositis • Less cardiac involvement
U1-RNP	5–10%	lcSSc, overlap syndromes (mixed connective tissue disease)	• Myositis • PAH • ILD
U3-RNP/ Fibrillarin	4–10%	dcSSc	• Early severe organ involvement: • PAH (highest risk) • ILD • Scleroderma renal crisis • Cardiac • Small bowel dysmotility • Myositis

Table 2. Summary of autoantibody profiles in SSc and corresponding key systemic associations. Adapted from Jerjen et al.[1]
Abbreviations: ACA: anti-centromere antibodies; **ATA:** anti-topoisomerase I/Scl-70 antibodies; **dcSSc:** diffuse cutaneous systemic sclerosis; **ILD:** interstitial lung disease; **lcSSc:** limited cutaneous systemic sclerosis; **PAH:** pulmonary arterial hypertension; **PM/Scl:** polymyositis/ scleroderma; **RNAP-III:** RNA polymerase III; **U1-RNP:** U1- ribonucleoprotein; **U3-RNP:** U3-ribonucleoprotein

System	Investigation	Explanation	Treatment
General	CBC with differential	Assess for anemia due to malabsorption, iron deficiency, or gastrointestinal blood loss	• Iron supplementation • Nutrition consultation
Lung Involvement	• HRCT of the chest • PFT with DLCO • Bronchoalveolar lavage and lung biopsy can be considered	To be completed at baseline and if clinical symptoms are present or worsening PFTs are identified	• Immunosuppression (mycophenolate mofetil, cyclophosphamide, rituximab) • Nintedanib, tocilizumab – FDA approved • Lung transplant • Autologous HSCT in rapidly progressive ILD
Pulmonary Arterial Hypertension	• Doppler echocardiography • Serum N-Tpro-BNP level • Right heart catheterization	This is recommended for initial screening for PAH	• O_2 • Anticoagulation • Endothelin receptor antagonist • Phosphodiesterase 5 inhibitor • Prostacyclin analogues • Prostacyclin receptor agonist • Soluble guanylate cyclase stimulant • Lung transplant
Cardiac Fibrosis	Echocardiography	Restrictive cardiomyopathy can occur secondary to PAH	•ACE inhibitors
• GI involvement • Esophageal dysmotility • Small bowel involvement	• Barium swallow with small bowel follow through • Manometry • Endoscopy	Evaluation should be guided by symptoms	• PPI • Promotility agent (ondansetron)
Renal crisis Hypertension	• Blood pressure measurement • Serum creatinine level • Urinalysis with urine sediment		• ACE inhibitors instituted for early treatment but not helpful for prevention
Overlap disease	• CK • Rheumatoid factor • Antibodies to CCP • Anti-double-stranded DNA and/or anti-Smith RNP antibodies	• May be elevated in patients with myopathy or myositis • These antibodies are relatively uncommon in patients with SSc and their presence points toward overlap syndromes with other systemic diseases • Usually in overlap cases there is more significant arthritis compared to SSc	

Table 3. Summary of screening recommendations and treatment approaches based on systemic involvement; *courtesy of Anastasiya Muntyanu, MD*
Abbreviations: ACE: angiotensin-converting enzyme; **CBC:** complete blood count; **CCP:** citrullinated peptides; **CK:** creatine kinase; **DLCO:** diffusing capacity for carbon monoxide; **GI:** gastrointestinal; **HRCT:** high-resolution computed tomography; **HSCT:** hematopoietic stem cell transplantation; **ILD:** interstitial lung disease; **PAH:** pulmonary artery hypertension; **PFT:** pulmonary function test; **PPI:** proton pump inhibitor; **RNP:** ribonucleoprotein; **Serum N-Tpro-BNP:** N-terminal pro-B-type natriuretic peptide; **SSc:** systemic sclerosis

antibodies (ACA), which is associated with lcSSc and PAH, ATA, associated with dcSSc and ILD, and anti-RNApolymerase (RNAP)-III antibodies, associated with malignancy and renal crisis **(Table 2)**.[1] The autoantibodies are typically mutually exclusive. Other autoantibody profiles include Polymyositis/Scl, To/Th ribonucleoprotein, U1-ribonucleoprotein (U1-RNP), and U3-RNP/fibrillarin.[1] A combination of autoantibodies can also help predict survival, timing, risk, and incidence of systemic complications.[1,29]

Systemic Involvement

Systemic manifestations include pulmonary (ILD or PAH), renal (i.e. scleroderma renal crisis or renal vasculopathy), cardiac (i.e. heart failure, arrythmias, pericardial effusion, and valve sclerosis), gastrointestinal (i.e. gastroesophageal reflux disease, impaired motility, gastric antral vascular ectasia), and urogenital (i.e. sexual dysfunction) involvement as well as an increased malignancy risk (i.e. cutaneous, breast, bladder, lung, liver, and hematological) **(Table 3)**.[1] Regular screening for lung involvement is mandatory and consists of pulmonary function tests as well as a high resolution CT scan (HRCT).[30] Cardiac involvement is more common in older patients and in those with ATA antibodies.[1,31] Scleroderma renal crisis is a severe manifestation that is less common now, given the knowledge that high dose prednisone can precipitate it, as well as the available preventative options such as angiotensin-converting enzyme (ACE) inhibitors.[32,33] Scleroderma renal crisis typically manifests within the first 5 years of the SSc diagnosis. The most commonly involved internal organ system is the gastrointestinal tract, and most patients with SSc are affected to some degree.[34]

Management

No curative treatments exist for SSc, and the available therapies may only have a limited effect on slowing disease progression, often with significant side effects.[35] Treatment is focused on the disease manifestations that are present. For skin fibrosis, immunosuppressive agents such as mycophenolate mofetil and methotrexate are typically used, with newer agents such as tocilizumab, rituximab, and brodalumab showing early promise in clinical trials.[30,36] Regarding brodalumab, a clinical trial of 100 patients randomized to brodalumab vs placebo reported that the treatment group showed a rapid, sustained, and significant reduction in skin sclerosis as measured by the modified Rodnan skin score (mRSS) up to 52 weeks.[37] Additionally, brodalumab exhibited therapeutic effects on lung/respiratory functions, formation of digital ulcers, the symptoms of gastroesophageal reflux disease, and quality of life indicators. No additional safety concerns were identified compared to treatment in other disease categories such as psoriasis.[37]

In recent years, autologous hematopoietic stem cell transplantation has provided tremendous hope.[38] This procedure reduces the number of aberrant immune cells and allows re-population with a self-tolerant immune system. This intervention continues to have the largest effect on skin fibrosis to date (e.g., a 10-point greater decrease in mRSS compared to 12 monthly infusions of cyclophosphamide).[39] While several studies have shown a decrease in skin involvement, improvements in organ function, quality of life measures, and overall survival,[40] this procedure is associated with significant risks, which limits its use to certain subsets of patients.

Conclusion

In conclusion, SSc is a complex, autoimmune fibrosing disease that significantly impacts morbidity and mortality due to its multi-organ involvement. The pathogenesis likely involves environmental triggers in genetically predisposed individuals, leading to immune dysregulation, endothelial damage, and progressive fibrosis. The variability in incidence/prevalence rates across regions and globally suggests that geographic/environmental factors could play a role.

Early diagnosis is essential for optimizing treatment, particularly as severe manifestations often develop within the first few years after disease onset. Recent advancements in diagnostic tools, such as nailfold capillaroscopy, SSc-specific autoantibodies, and VEDOSS classification facilitate earlier detection, which may improve outcomes. Management is tailored to specific organ systems, but little is known with regards to disease modification. Continued research is needed to better understand the underlying mechanisms of SSc and to develop targeted therapies that could help reduce the significant disease burden.

Correspondence

Anastasiya Muntyanu, MD
Email: anastasiya.muntyanu@mail.mcgill.ca

Financial Disclosures

None declared.

References

1. Jerjen R, Nikpour M, Krieg T, Denton CP, Saracino AM. Systemic sclerosis in adults. Part I: clinical features and

pathogenesis. J Am Acad Dermatol. 2022;87(5):937-954.
2. Bernatsky S, Joseph L, Pineau CA, Belisle P, Hudson M, Clarke AE. Scleroderma prevalence: demographic variations in a population-based sample. Arthritis Rheum. 2009;61(3):400-404.
3. Chifflot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. Semin Arthritis Rheum. 2008;37(4):223-235.
4. Zhong L, Pope M, Shen Y, Hernandez JJ, Wu L. Prevalence and incidence of systemic sclerosis: a systematic review and meta-analysis. Int J Rheum Dis. 2019;22(12):2096-2107.
5. Robinson D, Jr., Eisenberg D, Nietert PJ, Doyle M, Bala M, Paramore C, et al. Systemic sclerosis prevalence and comorbidities in the US, 2001-2002. Curr Med Res Opin. 2008;24(4):1157-1166.
6. Muntyanu A, Aw K, Kaouache M, Rahme E, Osman M, Baron M, et al. Epidemiology of systemic sclerosis in Quebec, Canada: a population-based study. Lancet Reg Health Am. 2024;35:100790. doi: 10.1016/j.lana.2024.100790
7. Silman AJ, Howard Y, Hicklin AJ, Black C. Geographical clustering of scleroderma in south and west London. Br J Rheumatol. 1990;29(2):93-96.
8. Valesini G, Litta A, Bonavita MS, Luan FL, Purpura M, Mariani M, et al. Geographical clustering of scleroderma in a rural area in the province of Rome. Clin Exp Rheumatol. 1993;11(1):41-47.
9. Diegel R, Black B, Pfau JC, McNew T, Noonan C, Flores R. Case series: rheumatological manifestations attributed to exposure to Libby Asbestiform Amphiboles. J Toxicol Environ Health A. 2018;81(15):734-747.
10. Thompson AE, Pope JE. Increased prevalence of scleroderma in southwestern Ontario: a cluster analysis. J Rheumatol. 2002;29(9):1867-1873.
11. Jacobs L. Kahnawake Scleroderma Support Group. Available from: https://sclero.org/scleroderma/support/groups/canada/quebec/kahnawake/a-to-z.html.
12. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med. 2009 360(19):1989-2003.
13. Feghali-Bostwick C, Medsger TA, Jr., Wright TM. Analysis of systemic sclerosis in twins reveals low concordance for disease and high concordance for the presence of antinuclear antibodies. Arthritis Rheum. 2003;48(7):1956-1963.
14. Ouchene L, Muntyanu A, Lavoue J, Baron M, Litvinov IV, Netchiporouk E. Toward understanding of environmental risk factors in systemic sclerosis. J Cutan Med Surg. 2021;25(2):188-204.
15. De Martinis M, Ciccarelli F, Sirufo MM, Ginaldi L. An overview of environmental risk factors in systemic sclerosis. Expert Rev Clin Immunol. 2016;12(4):465-478.
16. World Health Organisation 2020. How air pollution is destroying our health. 2018. Available from: https://www.who.int/news-room/spotlight/how-air-pollution-is-destroying-our-health.
17. Zhao JH, Duan Y, Wang YJ, Huang XL, Yang GJ, Wang J. The influence of different solvents on systemic sclerosis: an updated meta-analysis of 14 case-control studies. J Clin Rheumatol. 2016;22(5):253-259.
18. Asano Y, Jinnin M, Kawaguchi Y, Kuwana M, Goto D, Sato S, et al. Diagnostic criteria, severity classification and guidelines of systemic sclerosis. J Dermatol. 2018;45(6):633-691.
19. Joven BE, Almodovar R, Carmona L, Carreira PE. Survival, causes of death, and risk factors associated with mortality in Spanish systemic sclerosis patients: results from a single university hospital. Semin Arthritis Rheum. 2010;39(4):285-293.
20. Dolcino M, Pelosi A, Fiore PF, Patuzzo G, Tinazzi E, Lunardi C, et al. Gene profiling in patients with systemic sclerosis reveals the presence of oncogenic gene signatures. Front Immunol. 2018;9:449. doi: 10.3389/fimmu.2018.00449
21. Calderon LM, Pope JE. Scleroderma epidemiology update. Curr Opin Rheumatol. 2021;33(2):122-127.
22. Peoples C, Medsger TA, Jr., Lucas M, Rosario BL, Feghali-Bostwick CA. Gender differences in systemic sclerosis: relationship to clinical features, serologic status and outcomes. J Scleroderma Relat Disord. 2016;1(2):177-240.
23. Morgan ND, Shah AA, Mayes MD, Domsic RT, Medsger TA Jr, Steen VD, et al. Clinical and serological features of systemic sclerosis in a multicenter African American cohort: analysis of the genome research in African American scleroderma patients clinical database. Medicine (Baltimore). 2017;96(51):e8980. doi: 10.1097/MD.0000000000008980
24. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013;65(11) 2737-2747.
25. Avouac J, Fransen J, Walker UA, Riccieri V, Smith V, Muller C, et al. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. Ann Rheum Dis. 2011;70(3):476-481.
26. Minier T, Guiducci S, Bellando-Randone S, Bruni C, Lepri G, Czirjak L, et al. Preliminary analysis of the very early diagnosis of systemic sclerosis (VEDOSS) EUSTAR multicentre study: evidence for puffy fingers as a pivotal sign for suspicion of systemic sclerosis. Ann Rheum Dis. 2014;73(12):2087-2093.
27. Domsic RT. Scleroderma: the role of serum autoantibodies in defining specific clinical phenotypes and organ system involvement. Curr Opin Rheumatol. 2014;26(6):646-652.
28. Valentini G, Iudici M, Walker UA, Jaeger VK, Baron M, Carreira P, et al. The European Scleroderma Trials and Research group (EUSTAR) task force for the development of revised activity criteria for systemic sclerosis: derivation and validation of a preliminarily revised EUSTAR activity index. Ann Rheum Dis. 2017;76(1):270-276.
29. Nihtyanova SI, Sari A, Harvey JC, Leslie An, Derret-Smith EC, Fonseca C, et al. Using autoantibodies and cutaneous subset to develop outcome-based disease classification in systemic sclerosis. Arthritis Rheumatol. 2020;72(3):465-476.
30. Ouchene L, Muntyanu A, Assayag D, Veilleix E, Abril A, Ferrara G, et al. Skin disorders and interstitial lung disease: Part II-the spectrum of cutaneous diseases with lung disease association. J Am Acad Dermatol. 2023;88(4):767-782.
31. Kahan A, Coghlan G, McLaughlin V. Cardiac complications of systemic sclerosis. Rheumatology. 2009;48(suppl_3):iii45-iii8.
32. Caron M, Hudson M, Baron M, Nessim S, Steele R, Canadian Scleroderma Research Group. Longitudinal study of renal function in systemic sclerosis. J Rheumatol. 2012;39(9):1829-1834.
33. Woodworth TG, Suliman YA, Li W, Furst DE, Clements P. Scleroderma renal crisis and renal involvement in systemic sclerosis. Nat Rev Nephrol. 2018;14(2):137.
34. Shreiner AB, Murray C, Denton C, Khanna D. Gastrointestinal manifestations of systemic sclerosis. J Scleroderma Relat Disord. 2016;1(3):247-256.
35. Matucci-Cerinic M, Bellando-Randone S, Lepri G, Bruni C, Guiducci S. Very early versus early disease: the evolving definition of the 'many faces' of systemic sclerosis. Ann Rheum Dis. 2013;72(3):319-321.
36. Jerjen R, Nikpour M, Krieg T, Denton CP, Saracino AM. Systemic sclerosis in adults. Part II: management and therapeutics. J Am Acad Dermatol. 2022;87(5):957-978.
37. Fukasawa T, Yoshizaki A, Kagebayashi H, Sato S. POS0881 Efficacy and safety of subcutaneous brodalumab, a fully human anti–il-17ra monoclonal antibody, for systemic

sclerosis with moderate-to-severe skin thickening: a multicenter, randomized, placebo-controlled, double-blind phase 3 study. Annals of the Rheumatic Diseases. 2022;81(Suppl 1):736. doi: 10.1136/annrheumdis-2022-eular.2519

38. Spierings J, Chiu YH, Voortman M, van Laar JM. Autologous stem-cell transplantation in systemic sclerosis-associated interstitial lung disease: early action in selected patients rather than escalation therapy for all. Ther Adv Musculoskelet Dis. 2021;13:1759720×211035196. doi: 10.1177/1759720X211035196
39. Pope JE, Denton CP, Johnson SR, Fernandez-Codina A, Hudson M, Nevskaya T. State-of-the-art evidence in the treatment of systemic sclerosis. Nat Rev Rheumatol. 2023;19(4):212-226.
40. Del Papa N, Pignataro F, Zaccara E, Maglione W, Minniti A. Autologous hematopoietic stem cell transplantation for treatment of systemic sclerosis. Front immunol. 2018;9:2390. doi:10.3389/fimmu.2018.02390

When your patient presents with moderate-to-severe plaque psoriasis,

SAY TREMFYA®[1]

TREMFYA® provincial funding is now available in most provinces for patients with PsO or PsA.[1,2-10*]

Restrictions may apply. Refer to the respective provincial listings for full coverage details and restrictions.[2-10*]

TREMFYA® (guselkumab) is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[1]

TREMFYA® is also indicated for the treatment of adult patients with active psoriatic arthritis. TREMFYA® can be used alone or in combination with a conventional disease-modifying antirheumatic drug (cDMARD) (e.g., methotrexate).[1]

JANSSEN BIO ADVANCE® Program

ONE dedicated BioAdvance® Coordinator supports your patients with getting started on TREMFYA®.

Learn more about TREMFYA® at **Janssenpro.ca**

Please consult the Product Monograph at www.janssen.com/canada/our-medicines for important information relating to warnings, precautions, adverse reactions, interactions, dosing, and conditions of clinical use that has not been discussed in this piece.

The Product Monograph is also available by calling 1-800-567-3331.

PsO=psoriasis; PsA=psoriatic arthritis.

* Alberta, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario (EAP or Limited Use code required), Prince Edward Island, Saskatchewan. Please refer to the respective listings for coverage information and restrictions.[2-10]

References: 1. TREMFYA®/TREMFYA ONE-PRESS® (guselkumab injection) Product Monograph. Janssen Inc. January 17, 2024. **2.** Alberta Health. Drug benefit list. Formulary Search Results. October 13, 2023. **3.** Manitoba Pharmacare. Manitoba Drug Benefits Formulary Bulletin #129. December 21, 2023. **4.** New Brunswick (NB) Drug Plans Formulary Update. Bulletin #1122. December 18, 2023. **5.** Newfoundland and Labrador Prescription Drug Program Bulletin #234. December 13, 2023. **6.** Nova Scotia Formulary. November 16, 2023. **7.** Ontario Ministry of Health. Exceptional Access Program Reimbursement Criteria for Frequently Requested Drugs. December 18, 2023. **8.** Ontario Drug Benefit Formulary. Limited Use Note(s): Guselkumab. September 29, 2023. **9.** Health PEI. PEI Pharmacare Formulary. November 2023. **10.** Saskatchewan Drug Plan. Formulary Search Results. November 16, 2023.

Tremfya® (guselkumab) | JANSSEN BIO ADVANCE®

The image depicted contains models and is being used for illustrative purposes only.

Janssen Inc. 19 Green Belt Drive | Toronto, Ontario | M3C 1L9 | **www.janssen.com/canada**

catalytic health
communications • advertising • strategy

15 years

Medical minds gather here.

As the largest independent medical publisher in Canada, our peer-reviewed open access scientific journals are a practical resource for Canadian healthcare practitioners. We currently publish specialty journals in the areas of allergy & immunology, dermatology, hematology, ophthalmology, diabetes & endocrinology, gastroenterology, primary care, women's health, rheumatology, oncology, respirology and our press is constantly growing with new titles planned for 2025.

10.58931/cdt.2024.54129

ABOUT THE AUTHOR

Nikolas MacLellan, MD, FRCPC, DABD

Dr. Niko MacLellan is a board-certified dermatologist in Canada and the United States. He completed both his Bachelor of Science degree in Biochemistry and Molecular Biology and his Doctor of Medicine at Dalhousie University, followed by his Dermatology residency at the University of Toronto where he served as co-chief resident in his final year. He holds independent licensure in Ontario and Nova Scotia, and he started practice as a locum Assistant Professor in Dalhousie University's Division of Dermatology. He currently practices in multiple community clinics in Toronto, Ontario. He is a co-author on multiple publications in peer-reviewed journals, and is actively involved in medical education, including teaching residents and medical students in dermatology. His areas of interest include inflammatory skin conditions, skin cancer, and aesthetic dermatology.

Affiliations: FACET Dermatology, Toronto, ON
Sage Dermatology, Toronto, ON
Rosedale Dermatology, Toronto, ON

New treatments for acne vulgaris over the past decade

Nikolas MacLellan, MD, FRCPC, DABD

Introduction

Acne vulgaris is a prevalent, chronic inflammatory condition of the pilosebaceous units, commonly affecting adolescents and young adults, though it can persist or develop later in life. Conventional treatments such as retinoids, benzoyl peroxide, antibiotics, and hormonal therapies remain staples in managing acne vulgaris **(Figure 1)**. Advances in the past decade have introduced novel treatments for acne vulgaris that may be more effective and tolerable for select populations.

Novel topical therapies

Topical retinoids:

Topical retinoids remain a first-line treatment for managing acne vulgaris. Two newer topical retinoid formulations used to treat acne vulgaris are trifarotene 50 mcg/g cream and tazarotene 0.045% lotion.

Trifarotene was approved in 2019 by Health Canada for the topical treatment of acne vulgaris of the face and/or trunk in patients 12 years of age and older.[1] Unlike other topical retinoids, trifarotene is a 4th generation topical retinoid that specifically targets the retinoic acid receptor (RAR) gamma, which is the most common RAR isoform, making it more selective than other retinoids. It also has the most clinical data on safety and efficacy in treating truncal acne.[2] Adverse events are similar to those of other topical retinoids associated with cutaneous irritation that improves with continued therapy.

Tazarotene is a potent topical retinoid that remains highly effective in targeting inflammatory lesions of acne vulgaris. Although tazarotene lotion at doses of 0.05% and 0.1% were approved to treat acne vulgaris, these formulations resulted in more significant side effects given their high potency and are no longer routinely available in Canada to treat acne. Tazarotene 0.045% lotion was approved in 2021 by Health Canada for the topical treatment of acne vulgaris in patients 10 years of age and older.[3] Unlike previous formulations, tazarotene 0.045% lotion is formulated with a polymeric emulsification system that helps to

reduce dryness of the skin through its hydrating and moisturizing properties.[4]

Topical clascoterone:

Clascoterone 1% cream was approved by Health Canada in 2023 to treat acne vulgaris in patients 12 years of age and older.[5] It is the first topical hormonal therapy approved by Health Canada for acne vulgaris. It is an androgen receptor inhibitor that may reduce sebaceous gland activity. Patients treated with clascoterone applied topically twice daily for 12 weeks in two randomized control trials (RCTs) achieved higher investigator global assessment (IGA) scores compared to those using the vehicle. In addition, they experienced few local side effects, similar to those using the vehicle.[6] Unlike other hormonal therapies used to treat acne vulgaris, clascoterone is safe for use in both men and women. The most common side effects were local skin reactions, such as erythema, scaling and pruritus, but these reactions were reported at similar rates in patients taking the vehicle alternative. Systemic symptoms such as hypothalamic-pituitary-adrenal (HPA) axis suppression and hyperkalemia were not reported with prescription strength therapy.

Topical clindamycin/adapalene/benzoyl peroxide triple-combination:

The latest topical therapy approved by Health Canada to treat acne vulgaris in individuals 12 years of age and older is a gel containing clindamycin phosphate 1.2%, adapalene 0.15%, and benzoyl peroxide 3.1%.[7] This is the first triple-combination therapy approved by Health Canada, offering three mechanisms of action, including antibiotic, retinoid, and antibacterial. It is applied once daily to the affected areas, which may allow for better compliance than alternative topical regimens that require twice-daily application of multiple products. In two clinical trials, the triple-combination therapy was found to be significantly more effective at reducing both inflammatory and non-inflammatory lesions by week 12 compared to the vehicle. The most frequent side effects were mild local reactions, similar to those observed with other topical therapies used for acne vulgaris.

Topical minocycline:

While not approved by Health Canada, topical minocycline 4% foam is a topical antibiotic that received approval in the United States in 2019 from the Food and Drug Administration (FDA) to treat non-nodular lesions of acne vulgaris in patients 9 years of age and older.[8] Two clinical trials revealed significant reductions in IGA in patients treated with topical minocycline over 12 weeks, with continued improvement over 52 weeks. The most common side effect reported in these clinical trials was headache. Further, systemic absorption is low, and serious adverse reactions associated with oral minocycline were not observed in clinical studies.

9 y.o.
- Adapalene 0.1% & BPO gel 2.5%[15]

10 y.o.
- Tazarotene 0.045% lotion (*age 10-12: face only*) without other oxidizing agents[3]

12 y.o.
- Adapalene 0.1% or 0.3% gel[16]
- Adapalene 0.3% & benzoyl peroxide 2.5% gel[15]
- Benzoyl peroxide 3% or 5% & clindamycin 1% gel[17]
- Clascoterone 1% cream or solution[18]
- Clindamyin 1.2% & tretinoin 0.025% gel[19]
- Clindamycin 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%[7]
- Dapsone 5% gel[20]
- Tretinoin 0.01%/0.025% gel or 0.01%/0.025%/0.05%/0.1% cream[21]
- Trifarotene 50 mcg/g cream (*facial or truncal acne*)[1]
- PO cyproterone acetate & ethinyl estradiol (*after menarche*)[22]
- PO isotretinoin (micronized, non-micronized)[14]

14 y.o.
- PO drospirenone & ethinyl estradiol[23]
- PO levonorgestrel & ethinyl estradiol[24]

15 y.o.
- PO norgestimate & ethinyl estradiol[25]

Figure 1. Health Canada-approved pharmacologic therapies for acne vulgaris based on age of approval; *courtesy of Nikolas MacLellan, MD, FRCPC, DABD*

Novel oral therapies

Sarecycline:

Although not available in Canada, sarecycline is a tetracycline-class oral antibiotic approved by the FDA in 2018 to treat acne vulgaris in individuals 9 years of age and older.[9] Unlike other tetracycline-based antibiotics, sarecycline has a narrow spectrum of action and demonstrates a lower propensity for inducing antimicrobial resistance and gut microbiome alterations while still achieving a similar therapeutic efficacy to other antibiotics for treating acne.[10] While the most common adverse event reported was nausea, it seems to be associated with fewer instances of diarrhea, fungal overgrowth, and vaginal candidiasis compared to alternate tetracycline antibiotics.

Micronized isotretinoin:

Oral isotretinoin remains the gold standard for treating severe acne vulgaris. However, some oral formulations are poorly absorbed when taken with a low-fat diet, which may result in lower efficacy in selected patients. A new micronized formulation of isotretinoin was approved by Health Canada in 2023 to treat severe nodular and/or inflammatory acne, acne conglobata, and recalcitrant acne in patients 12 years of age and older.[11] The micronized formulation provides enhanced bioavailability that results in a comparable rate of absorption and extent of drug exposure under both fasting and fed conditions. This may be a more effective treatment option for younger patients who are on a diet or undergoing intermittent fasting and are unable to achieve the target cumulative dose of at least 120 mg/kg.[12] The side effect profiles are similar between micronized and non-micronized isotretinoin. It is recommended to start micronized isotretinoin at a dose of 0.4-0.8 mg/kg body weight daily, increasing to 1.6 mg/kg per day for a 15- to 20-week duration.

Novel physical therapies

1726-nm laser:

Physical therapies have played a role in managing acne vulgaris for decades. These include photodynamic therapy, visible light therapy, and other surgical methods such as the injection of intralesional triamcinolone acetonide or comedone extraction. In 2023, Health Canada approved a new diode laser with a 1726 nm wavelength to treat acne vulgaris due to its high selectivity for sebaceous glands.[13] It is postulated to be the first treatment since isotretinoin that significantly reduces sebaceous gland activity while being more tolerable than isotretinoin. The treatment is delivered in 3 sessions every 3 weeks. A prospective, open-label, single-arm institutional review study that included 104 participants demonstrated that the treatment is safe and effective across all skin types, as observed at 4, 12, and 26 weeks. The study showed a significant, durable reduction in acne lesions in up to 87.3% of participants 6 months post-treatment. Some patients experienced an initial transient eruption in the first 2 to 21 days post treatment (similar to the eruption that occurs after isotretinoin), and some patients experienced temporary perilesional erythema; however, there were no reports of residual erythema, edema, blistering, crusting, or dyspigmentation.

Conclusion

The treatment of acne vulgaris has evolved significantly in recent years, with new therapies offering patients more personalized and targeted options. Health Canada has approved several new treatments for the pharmacologic management of acne, including trifarotene, tazarotene 0.045% lotion, clascoterone, clindamycin/adapalene/benzoyl peroxide triple combination therapy, micronized isotretinoin, and the 1726-nm laser. These treatments offer effective options with improved safety profiles. Additionally, laser and light therapies, along with newer therapies approved by the FDA such as topical minocycline foam and oral sarecycline, offer innovative ways to tackle acne with less systemic involvement and enhanced patient outcomes. As research continues, it is likely that even more effective and safer treatments will emerge, offering renewed hope for patients with acne vulgaris who have long struggled with the psychological and physical impacts of this condition.

Correspondence

Nikolas MacLellan, MD, FRCPC, DABD
Email: nmaclellan@dal.ca

Financial Disclosures

Consultant/Advisor or Speaker and/or Grants: Abbvie, UCB, RBC Consultants

References

1. Aklief™ (trifarotene). Galderma Canada Inc., Thornhill, ON: Product Monograph. Health Canada website. .[Updated 2019 Nov 25; cited 08 Nov 2024]; Available from: https://pdf.hres.ca/dpd_pm/00054047.PDF
2. Tan J, Chavda R, Baldwin H, Dreno B. Management of Acne vulgaris with trifarotene. J Cutan Med Surg. 2023;27(4):368-374. doi:10.1177/12034754231163542. .
3. Arazlo™ Bausch Health, Canada Inc., Laval, QC. Product Monograph. Health Canada website. [Updated 07 Jul 2021; cited 08 Nov 2024]; https://bauschhealth.ca/wp-content/uploads/2021/07/Arazlo-PM-E-2021-07-08.pdf..

4. Latter G, Grice JE, Mohammed Y, Roberts MS, Benson HAE. Targeted topical delivery of retinoids in the management of acne vulgaris: current formulations and novel delivery systems. Pharmaceutics. 2019;11(10):490. doi:10.3390/pharmaceutics11100490.
5. Winlevi® Sun Pharma Canada Inc., Brampton ON. Product Monograph. Health Canada website. [Updated 15 Jun 2023; cited 08 Nov 2024]; Available from: https://pdf.hres.ca/dpd_pm/00071308.PDF..
6. Hebert A, Thiboutot D, Stein Gold L, Cartwright M, Gerloni M, Fragasso E, et al. Efficacy and safety of topical clascoterone cream, 1%, for treatment in patients with facial acne: two phase 3 randomized clinical trials. JAMA Dermatol. 2020;156(6):621-630. doi:10.1001/jamadermatol.2020.0465
7. Cabtreo® Bausch Health Canada Inc., Laval, QC. Product Monograph. Health Canada website. [Updated 14 Aug 2024; cited 08 Nov 2024]; Available from: https://pdf.hres.ca/dpd_pm/00076715.PDF..
8. Paik J. Topical Minocycline foam 4%: a review in acne vulgaris. Am J Clin Dermatol. 2020;21(3):449-456. doi:10.1007/s40257-020-00523-1. PMID: 32468355.
9. Seysara® (sarecycline) tablets. Allergan, Inc. Irvine CA. U.S. Food and Drug Administration website. [Updated 01 Oct 2018; cited 08 Nov 2024]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209521s000lbl.pdf.
10. Graber EM. Treating acne with the tetracycline class of antibiotics: a review. Dermatol Rev. 2021;2(6):321-330. https://doi.org/10.1002/der2.49
11. Absorbica LD® Sun Pharma Canada Inc. Brampton ON. Product Monograph. Health Canada website. [Updated 23Aug 2023; cited 08 Nov 2024]; Available from: https://pdf.hres.ca/dpd_pm/00071353.PDF.
12. Del Rosso JQ. Rationale for use of micronized isotretinoin for treatment of acne vulgaris: practical considerations and therapeutic advantages. J Clin Aesthet Dermatol. 2023;16(9):20-24.
13. Alexiades M, Kothare A, Goldberg D, Dover JS. Novel 1726 nm laser demonstrates durable therapeutic outcomes and tolerability for moderate-to-severe acne across skin types. J Am Acad Dermatol. 2023;89(4):703-710. doi:10.1016/j.jaad.2023.05.085
14. Tactipump™ andTactipumpTM Forte Galderma Canada Inc., Thornhill ON. Product Monograph. Health Canada website. [Updated 29 Jun 2018; cited 08 Nov 2024]; Available from: https://pdf.hres.ca/dpd_pm/00046183.PDF
15. Differin® (XP) Galderma Canada Inc., Thornhill, ON. Product Monograph. Health Canada website. [Updated December 5, 2018; cited 08 Nov 2024]; Available from: https://pdf.hres.ca/dpd_pm/00048625.PDF.
16. Benzaclin® Topical Gel Valeant Canada LP, Montreal QC. Product Monograph. Health Canada website. [Updated 29 Feb 2012; cited 08 Nov 2024]; Available from: https://pdf.hres.ca/dpd_pm/00015735.PDF.
17. Taro-Clindamycin Taro Pharmaceuticals Inc., Brampton, ON. Product Monograph. Health Canada website. [Updated 19 Oct 2020.cited 08 Nov 2024]; Available from: https://pdf.hres.ca/dpd_pm/00058691.PDF.
18. Biacna™ Topical Gel Valeant Canada Limited, Montreal QC. Product Monograph. Health Canada website. [Updated 29 Nov 2010; cited 08 Nov 2024]; Available from: https://pdf.hres.ca/dpd_pm/00012024.PDF.
19. Aczone® Bausch Health, Canada Inc., Laval, QC. Product Monograph. Health Canada website. [Updated 03 Jun 2020; cited 08 Nov 2024]; Available from: https://pdf.hres.ca/dpd_pm/00057223.PDF
20. Retin-A Micro® Valeant Canada LP., Laval QC. Product Monograph. Health Canada website. [Updated 21 Mar 2012; cited 08 Nov 2024]; Available from: https://pdf.hres.ca/dpd_pm/00024577.PDF.
21. Ran™-Cyproterone/Ethinyl Estradiol Ranbaxy Pharmaceuticals Canada Inc., Brampton ON. Product Monograph. Health Canada website. [Updated 08 Jun 2016; cited 08 Nov 2024]; Available from: https://pdf.hres.ca/dpd_pm/00035244.PDF
22. Yaz® Plus Bayer Inc., Mississauga, ON. Product Monograph. Health Canada website. [Updated 02 Mar 2017; cited 08 Nov 2024]; Available from: https://pdf.hres.ca/dpd_pm/00038327.PDF
23. Alesse® 21 and Alesse® 28 Pfizer Canada Inc., Kirkland, QC. Product Monograph. Health Canada website. [Updated 26 Jun 2018; cited 08 Nov 2024]; Available from: https://pdf.hres.ca/dpd_pm/00046064.PDF.
24. Tri-Cyclen® Lo Janssen Inc., Toronto, ON. Product Monograph. Health Canada website. [Updated 14 June 2018; cited 08 Nov 2024]; Available from: https://pdf.hres.ca/dpd_pm/00045949.PDF

HAVE CONFIDENCE IN DUPIXENT®

Indicated in patients aged 6+ months with moderate-to-severe atopic dermatitis (AD) and in adult patients with moderate-to-severe prurigo nodularis (PN) whose disease is inadequately controlled with topical prescription therapies[1]

First and only treatment indicated in PN[1,2]*

THE FIRST AND ONLY BIOLOGIC INDICATED IN PATIENTS 6 MONTHS AND OLDER WITH MODERATE-TO-SEVERE AD[1]*

ATOPIC DERMATITIS (AD)

DUPIXENT® (dupilumab injection) is indicated for the treatment of patients aged 6 months and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable[1]

- DUPIXENT® can be used with or without topical corticosteroids

PRURIGO NODULARIS (PN)

DUPIXENT® (dupilumab injection) is indicated for the treatment of adult patients with moderate-to-severe prurigo nodularis (PN) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable[1]

- DUPIXENT® can be used with or without topical corticosteroids

Please consult the Product Monograph at http://products.sanofi.ca/en/dupixent-en.pdf for contraindications, warnings, precautions, adverse reactions, interactions, dosing, and conditions of clinical use. The Product Monograph is also available by calling 1-800-589-6215.

* Clinical significance is unknown.

References: 1. DUPIXENT® Product Monograph, sanofi-aventis Canada Inc., July 12, 2023. **2.** Data on file, sanofi-aventis Canada Inc., September 1, 2023.

sanofi | REGENERON®

MEMBER OF INNOVATIVE MEDICINES CANADA

REVIEWED BY PAAB

Pr DUPIXENT® (dupilumab) Injection

10.58931/cdt.2024.54130

ABOUT THE AUTHOR

David O. Croitoru, MD

Dr. David Croitoru is a full-time Clinician Investigator at University Health Network, Toronto, Canada, with an interest in autoimmune and inflammatory dermatoses as well as cutaneous manifestations of chemotherapy. He is cross appointed at Women's College Hospital where he practices Wound Care and is the medical lead of specialized Pyoderma Gangrenosum and Hidradenitis Suppurativa surgery clinics. To further resident engagement with research, he is the co-chair of the CIHR-funded SKiN Canada's trainee development committee as well as for the SPoT (Skin Pathophysiology Therapeutics).

Affiliations: Temerty Faculty of Medicine, University of Toronto, Toronto, ON.
Division of Dermatology, Department of Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, ON.
Division of Dermatology, Department of Medicine and Research and Innovation Institute, Women's College Hospital, Toronto, ON.
Division of Dermatology, Department of Medicine, University Health Network, Toronto, ON.

Paradoxical Psoriasis Induced by TNF Inhibitors and Beyond: A Review

David O. Croitoru, MD

Introduction

Paradoxical psoriasis (PP) represents an uncommon but well-documented adverse effect that occurs following exposure to tumour necrosis factor-alpha (TNF-α) inhibitors.[1] There is growing evidence that this reaction may not be class-specific, as the indications for biologic interventions (interleukin [IL]12/23, IL23, IL17, IL4/13) broaden in chronic inflammatory diseases. However, cumulative evidence amongst other classes remains limited to case reports.[2,3]

The pathogenesis of this reaction to TNF inhibitors has been postulated and experimentally supported as a switch toward interferon (IFN) production by antigen-presenting cells, however, the mechanism with other biologics remains elusive.[4] The baseline association of classical psoriasis (non-drug induced) with the seronegative rheumatic and gastrointestinal inflammatory diseases treated by TNF inhibitors, initially made this reaction a challenge to define and study. As evidence has grown, PP has been defined as psoriatic lesions that arise *de novo* or as morphologically atypical exacerbations of pre-existing known psoriasis during TNF-α therapy. These lesions may persist and worsen unless treated, commonly requiring systemic therapeutic adjustments. This review explores the epidemiology, pathogenesis, clinical manifestations, and management of PP, with an emphasis on patient outcomes and recommendations based on primary data, systematic reviews, and contributions from key researchers in the field.

Epidemiology

The incidence of PP varies by therapeutic agent, clinical context, and patient demographic. Anti-TNF agents, such as infliximab, adalimumab, and etanercept, are frequently implicated. A systematic review conducted in 2022 involving 2,049 cases found that infliximab accounted for over half of the reported cases.[5] Studies suggest that up to 5% of patients on TNF inhibitors experience PP, with higher rates observed in inflammatory bowel disease (IBD) patients compared to those with other autoimmune diseases. Among patients with IBD, those with Crohn's disease are at over a 1.5 times greater risk of developing PP than those with ulcerative colitis.[6] Females appear more predisposed to PP, comprising approximately 60-70% of cases.[6,7] Anti-IL-17 therapies, often prescribed for psoriasis, psoriatic arthritis, and ankylosing spondylitis, are also associated with PP, though the number of reported cases has been significantly lower than that observed with anti-TNF agents. Among the approximately 30 documented cases, most involve IL-17A-specific inhibitors such as secukinumab, with fewer reports for agents such as ixekizumab, the

IL-17A/F inhibitor bimekizumab, and the receptor antagonist brodalumab.[8] While p19 and p40 inhibitors of Il-12 and IL-23 pathways are commonly described in the treatment of TNF-induced PP, they have also been occasionally described as potential culprits.[2] Recently, IL-4/IL-13 inhibitors, such as dupilumab, have also been described with a lower frequency of PP following exposure (1-2%) with an increased risk noted in those with a familial or personal history of psoriasis, suggesting that this may represent an 'unmasking' of psoriasis in predisposed patients.[3]

Pathogenesis

The pathogenesis of PP is distinct from idiopathic psoriasis and hinges on the tight immunological regulation of TNF, IFN, and likely IL-4/13 and Il-17. Evidence suggests that the mechanism for TNF-α induced PP occurs due to TNF inhibition, which causes an overcompensation in interferon-alpha (IFN-α) activity via plasmacytoid dendritic cell activation. This causes a T-cell independent, innate psoriasiform inflammatory response, as well as the recruitment of Th17 and Th1 cells.[4,9] In contrast, emerging data on the pathogenesis of IL-4/IL-13-induced PP supports the theory that dysregulation of the homeostasis of Th17 and Th2 inflammation is the underlying event for these agents.[10,11] Both IL-4-Rα and specific IL-13 inhibition have been demonstrated to shift toward a Th1/Th17 phenotype, resulting in the development of PP. Patients with this presentation have demonstrated increased relative Il-17A levels in peripheral blood, along with a corresponding increase in IL-23 in lesional skin. Conceptually, it is believed that psoriasis and atopic dermatitis may represent two poles of an interrelated immunological spectrum, with switches hinging on Il-17; emerging translational data may support baseline Il-17A levels as predictive of this immunological switch.[12]

Clinical Manifestations

PP presents with a spectrum of clinical forms, often mirroring classical psoriasis but with some variations. The most frequently observed morphologies include plaque-type (vulgaris) and palmoplantar pustulosis, which can occur either in isolation or with corporal involvement. Other documented forms include inverse, guttate, psoriasiform dermatitis and generalized pustular forms.[6] Palmoplantar pustules, observed in approximately one-third of cases, may be seen in conjunction with other morphologies simultaneously. Despite the predilection for pustular eruptions, generalized pustulosis is a rare occurrence with <3% of cases described in larger cohorts.[13] A notable feature of TNF-induced PP, which occurs in a minority of patients (approximately 10%), is the potential for scalp involvement with regional alopecia, which is not observed in classical psoriasis.[6,7] This scalp involvement typically manifests as psoriatic erythematous, hyperkeratotic, and sometimes exudative/pustular lesions.

The pleomorphic nature of PP coupled with the variable latency period from initial drug exposure can make the etiology of the eruption challenging to pinpoint. The timing of PP generally occurs within the first year of TNF inhibitor initiation, with an average onset of approximately 11 months in adults and 22 months in children.[14]

Factors that predict extensive or severe PP with alopecia include female sex, younger age, smoking, and having Crohn's disease, with a particularly elevated risk among patients on adalimumab.[6]

In rare cases, PP may involve articular manifestations, resembling both arthralgia secondary to IFN upregulation as well as true psoriatic arthritis with synovitis, associated with upregulations in IL-17 and IL-23 pathways.

An important diagnostic consideration for clinicians when managing patients with suspected PP on less commonly described agents (e. g., IL-17) is whether the eruption represents a breakthrough of classical psoriasis or multiple competing pathologies.

Management

Managing PP is often a multidisciplinary decision that involves a reassessment of biologic therapy, without a standard treatment ladder or published guideline. For mild cases, topical therapies may be considered as the first line of treatment, either alone or in conjunction with phototherapy.[15] These include vitamin D agonists, corticosteroids, calcineurin inhibitors, salicylic acid/retinoids, and more recently, phosphodiesterase inhibitors. Discontinuing or alternating biologic therapy is the most straightforward approach, with symptomatic resolution observed in many patients after cessation. However, this decision must be weighed against the risk of exacerbating the underlying inflammatory condition, particularly in patients with severe rheumatoid arthritis or Crohn's disease. Some clinicians will arrange for interval disease staging with synovial exams, serum and stool studies (fecal calprotectin), and/or imaging modalities to define the underlying disease before committing to a management strategy. For patients who cannot discontinue TNF inhibitors, alternative biologic therapies, such as IL-17 or IL-12/23 inhibitors, have shown promise.

In one systematic review on PP in patients with IBD following TNF inhibitor exposure, ustekinumab

resulted in a complete or partial resolution in 83.1% of patients (n=74/89), with 75.4% maintaining their IBD remission.[13,16] Clinical outcomes following interclass transitions vary, but they are generally favourable, with improved symptom control and reduced lesion progression.

Intraclass switches may also be of benefit but have been associated with persistence or worsening of their PP in large cohort studies. Therefore, this approach should be employed cautiously and on an as-needed basis.

Systemic agents, such as methotrexate or cyclosporine, may also be considered for moderate-to-severe cases using a treat-through approach, though the risk-benefit profile of these treatments must be assessed carefully. Studies underscore the importance of regular monitoring for side effects, particularly when systemic agents are prescribed concurrently with TNF inhibitors. For refractory cases, small-molecule inhibitors such as apremilast, which modulate intracellular inflammatory pathways, have shown potential in small cohort studies but require further validation in larger studies and trials.

Conclusion

PP presents a unique therapeutic challenge, reflecting the complexity of immune modulation through TNF-α inhibition and the polarization of Th17/Th2 immunity. This review highlights the unpredictable epidemiology, complex pathogenesis, and diverse clinical manifestations associated with this condition. Although TNF inhibitors are indispensable for treating various autoimmune disorders, the emergence of PP necessitates ongoing vigilance and a tailored management approach. Current therapeutic options, particularly IL-17 and IL-12/23 inhibitors, offer promising alternatives for managing PP while maintaining disease control of the primary autoimmune condition. Ongoing research into the immunologic mechanisms and long-term outcomes of PP is essential for refining treatment protocols and improving patient care.

Correspondence

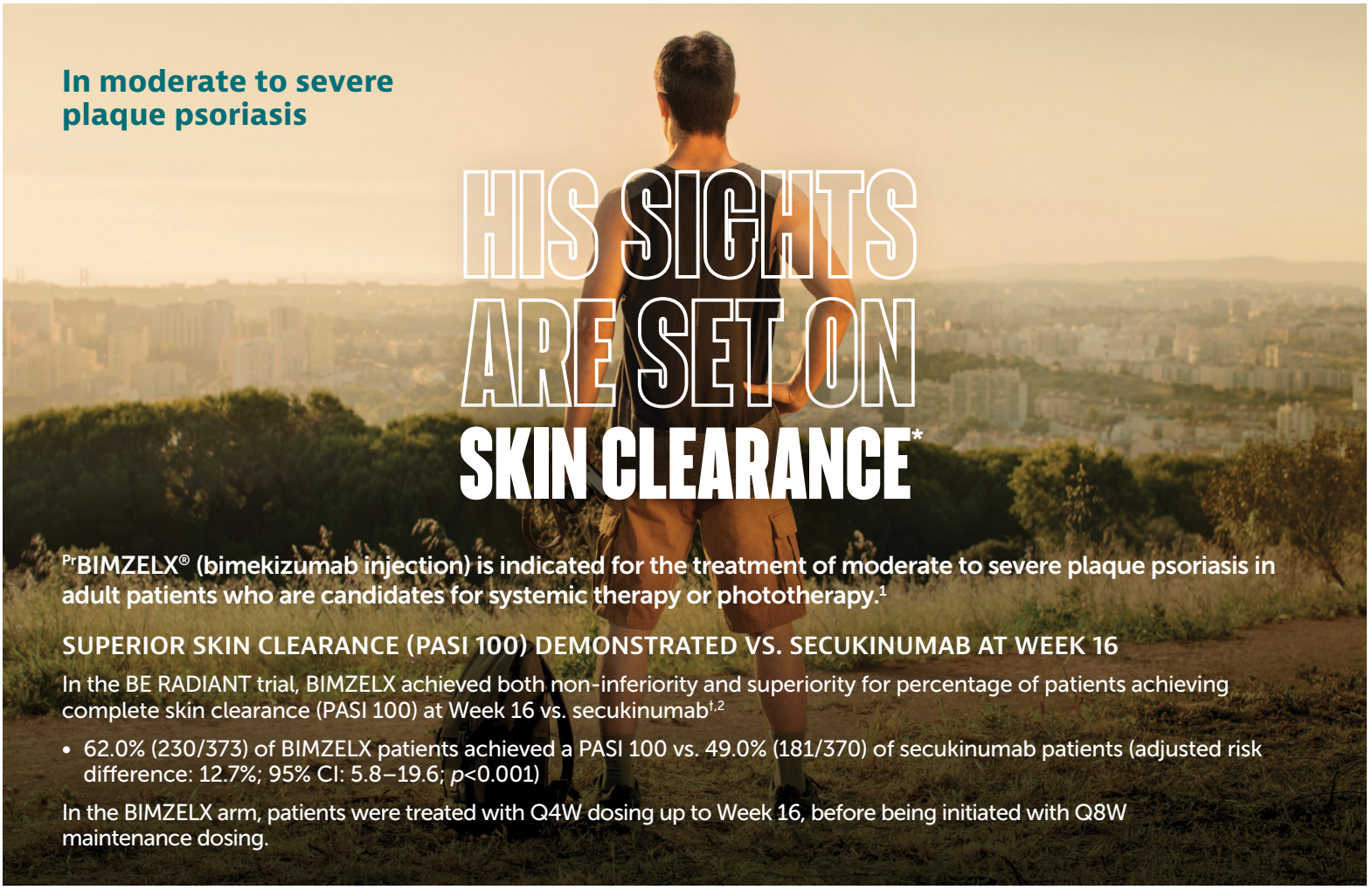
David O. Croitoru, MD
Email: david.croitoru@utoronto.ca

Financial Disclosures

Consultancy: AbbVie, Amgen, Bausch Health, BioJAMP, Boehringer-Ingelheim, Bristol Myers Squibb, Eli Lilly, Janssen, Leo, Novartis, Pfizer, Sanofi-Regeneron, Sun Pharma, and UCB.

References

1. Tillack C, Ehmann LM, Friedrich M, Laubender RP, Papay P, Vogelsang H, et al. Anti-TNF antibody-induced psoriasiform skin lesions in patients with inflammatory bowel disease are characterised by interferon-γ-expressing Th1 cells and IL-17A/IL-22-expressing Th17 cells and respond to anti-IL-12/IL-23 antibody treatment. Gut. 2014;63(4):567-577. doi:10.1136/gutjnl-2012-302853
2. Klimko A, Olteanu AO, Tieranu I, Orzan OA, Toma CV, Ionescu EM, et al. Paradoxical psoriasis induced by ustekinumab: a comprehensive review and case report. Medicina (Kaunas). 2024;60(1). doi:10.3390/medicina60010106
3. Brumfiel CM, Patel MH, Zirwas MJ. Development of psoriasis during treatment with dupilumab: a systematic review. J Am Acad Dermatol. 2022;86(3):708-709. doi:10.1016/j.jaad.2021.05.013
4. Conrad C, Di Domizio J, Mylonas A, Belkhodja C, Demaria O, Navarini AA, et al. TNF blockade induces a dysregulated type I interferon response without autoimmunity in paradoxical psoriasis. Nat Commun. 2018;9(1):25. doi:10.1038/s41467-017-02466-4
5. Murphy MJ, Cohen JM, Vesely MD, Damsky W. Paradoxical eruptions to targeted therapies in dermatology: a systematic review and analysis. J Am Acad Dermatol. 2022;86(5):1080-1091. doi:10.1016/j.jaad.2020.12.010
6. Croitoru DO, Brooks SG, Nathanielsz N, Silverberg O, Nicolau I, Drucker AM, et al. Predictors of severity in paradoxical psoriasis from biologic therapies: a systematic review. J Am Acad Dermatol. 2023;88(2):471-473. doi:10.1016/j.jaad.2022.06.019
7. Brown G, Wang E, Leon A, Huynh M, Wehner M, Matro R, et al. Tumor necrosis factor-α inhibitor-induced psoriasis: systematic review of clinical features, histopathological findings, and management experience. J Am Acad Dermatol. 2017;76(2):334-341. doi:10.1016/j.jaad.2016.08.012
8. Alnaqbi KA, Zeyoudi JA, Fazal F, Alhaj OM, Jassim I, Albreki FA. Paradoxical psoriasis and worsening spondylitis due to secukinumab in a patient with ankylosing spondylitis: a case report and literature review. Cureus. 2023;15(12):e50726. doi:10.7759/cureus.50726
9. Moran B, Gallagher C, Tobin AM, Fletcher JM. Enrichment of polyfunctional IL-17-producing T cells in paradoxical psoriasis skin lesions. J Invest Dermatol. 2020;140(5):1094-1097. doi:10.1016/j.jid.2019.10.010
10. Safa G, Paumier V. Psoriasis induced by dupilumab therapy. Clin Exp Dermatol. 2019;44(3):e49-e50. doi:10.1111/ced.13901
11. Ahmad M, Murphy MJ, Damsky W, Leventhal J. Dupilumab-induced psoriasis in the setting of pembrolizumab therapy: an analysis of cytokine expression. Int J Dermatol. 2023;62(8):e424-e426. doi:10.1111/ijd.16538
12. Guttman-Yassky E, Krueger JG. Atopic dermatitis and psoriasis: two different immune diseases or one spectrum? Curr Opin Immunol. 2017;48:68-73. doi:10.1016/j.coi.2017.08.008
13. Maronese CA, Valenti M, Moltrasio C, Romagnuolo M, Ferrucci SM, Gilliet M, et al. Paradoxical psoriasis: an updated review of clinical features, pathogenesis, and treatment options. J Invest Dermatol. 2024;144(11):2364-2376. doi:10.1016/j.jid.2024.05.015
14. Böhner A, Jargosch M, Müller NS, Garzorz-Stark N, Pilz C, Lauffer F, et al. The neglected twin: Nummular eczema is a variant of atopic dermatitis with codominant T(H)2/T(H)17 immune response. J Allergy Clin Immunol. 2023;152(2):408-419. doi:10.1016/j.jaci.2023.04.009
15. Mazloom SE, Yan D, Hu JZ, Ya J, Husni ME, Warren CB, et al. TNF-α inhibitor-induced psoriasis: a decade of experience at the Cleveland Clinic. J Am Acad Dermatol. 2020;83(6):1590-1598. doi:10.1016/j.jaad.2018.12.018
16. Karadeniz H, Ataş N, Avanoğlu Güler A, Tufan A. Treatment of anti-TNF-related paradoxic palmoplantar psoriasis in Behçet's disease with azathioprine. Clin Exp Rheumatol. 2019;37 Suppl 121(6):168.



PrBIMZELX® (bimekizumab injection) is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.[1]

SUPERIOR SKIN CLEARANCE (PASI 100) DEMONSTRATED VS. SECUKINUMAB AT WEEK 16

In the BE RADIANT trial, BIMZELX achieved both non-inferiority and superiority for percentage of patients achieving complete skin clearance (PASI 100) at Week 16 vs. secukinumab†,[2]

- 62.0% (230/373) of BIMZELX patients achieved a PASI 100 vs. 49.0% (181/370) of secukinumab patients (adjusted risk difference: 12.7%; 95% CI: 5.8–19.6; $p<0.001$)

In the BIMZELX arm, patients were treated with Q4W dosing up to Week 16, before being initiated with Q8W maintenance dosing.

DISCOVER BIMZELX

NOW INDICATED IN PSORIATIC ARTHRITIS

PrBIMZELX® (bimekizumab injection) is indicated for the treatment of adult patients with active psoriatic arthritis. BIMZELX can be used alone or in combination with a conventional non-biologic disease-modifying antirheumatic drug (cDMARD) (e.g. methotrexate).

CI: confidence interval; PASI 100: 100% improvement from baseline in Psoriasis Area and Severity Index; Q1W: every week; Q4W: every four weeks; Q8W: every eight weeks

*Fictional patient. May not be representative of the general population.

†BE RADIANT: A phase IIIb multicentre, randomized, double-blind, active comparator-controlled study comparing the efficacy and safety of BIMZELX vs. secukinumab in adult patients with moderate to severe plaque psoriasis (N=743). Patients were randomized 1:1 to BIMZELX 320 mg Q4W through Week 16 (n=373), or secukinumab 300 mg Q1W through Week 4 followed by secukinumab 300 mg Q4W through Week 48. Patients who completed the 48-week double-blind period could enrol in an ongoing 96-week open-label extension period. At Week 16, patients receiving BIMZELX 320 mg Q4W were re-randomized 1:2 to receive either BIMZELX 320 mg Q4W (off-label maintenance arm) or 320 mg Q8W through Week 48. The primary endpoint was 100% reduction from baseline in the PASI score at Week 16.

Conditions of clinical use:
- Not authorized for use in pediatrics (< 18 years of age)

Relevant warnings and precautions:
- Inflammatory bowel disease
- Serious hypersensitivity reactions
- Vaccinations
- Infections, including tuberculosis
- Pregnant or nursing women
- Women of childbearing potential

For more information:
Please consult the Product Monograph at https://www.ucb-canada.ca/en/bimzelx for important information relating to adverse reactions, drug interactions, and dosing information that has not been discussed in this piece. The Product Monograph is also available by calling 1-866-709-8444.

References: 1. BIMZELX Product Monograph. UCB Canada Inc. March 11, 2024. **2.** Reich K, Warren RB, Lebwohl M, et al. Bimekizumab versus secukinumab in plaque psoriasis. *N Engl J Med.* 2021;385(2):142–152.

PrBimzelx® (bimekizumab)

Inspired by patients. Driven by science.

REVIEWED BY PAAB

CA-BK-2400086

10.58931/cdt.2024.54131

ABOUT THE AUTHOR

Annie Langley, MD, MSc, FRCPC, DABD

Dr. Annie Langley completed her residency training in dermatology at the University of Ottawa and is a board-certified dermatologist in both Canada and the United States. She completed her medical training and an MSc in Epidemiology at Queen's University and undergraduate studies in Cell Biology at McGill University. She has a combined hospital/community practice in medical dermatology in Ottawa. Her clinical interests are broad and include cutaneous drug reactions, atopic dermatitis, psoriasis and hidradenitis suppurativa.

Affiliations: Lecturer, University of Ottawa, Division of Dermatology

Highlights from the 33rd Congress of the European Academy of Dermatology and Venereology (EADV)

Annie Langley, MD, MSc, FRCPC, DABD

Introduction

The 33rd congress of the European Academy of Dermatology and Venereology (EADV) was held in Amsterdam, the Netherlands from Sept 24–28, 2024. With over 17,000 participants, this meeting had the highest attendance of any EADV congress to date. The meeting featured over 160 symposia and 20 subspecialty sessions and provided updates and data on new and emerging therapies for a number of skin conditions. This article will highlight interesting findings in atopic dermatitis, psoriasis, and hidradenitis suppurativa (HS).

Reducing the risk of disease comorbidities in psoriasis and atopic dermatitis through biologic therapies

An interesting theme discussed in several late-breaking sessions was the possibility for biologic therapies in atopic dermatitis and psoriasis to reduce the risk of disease comorbidities. Below, I will review presentations by Drs. Armstrong and Irvine, who presented data examining the association of biologic therapy in psoriasis and the risk of subsequent development of psoriatic arthritis,[1] as well as the impact of biologic therapy in atopic dermatitis and the risk of growth suppression.[2]

Biologics for psoriasis and the risk of future psoriatic arthritis

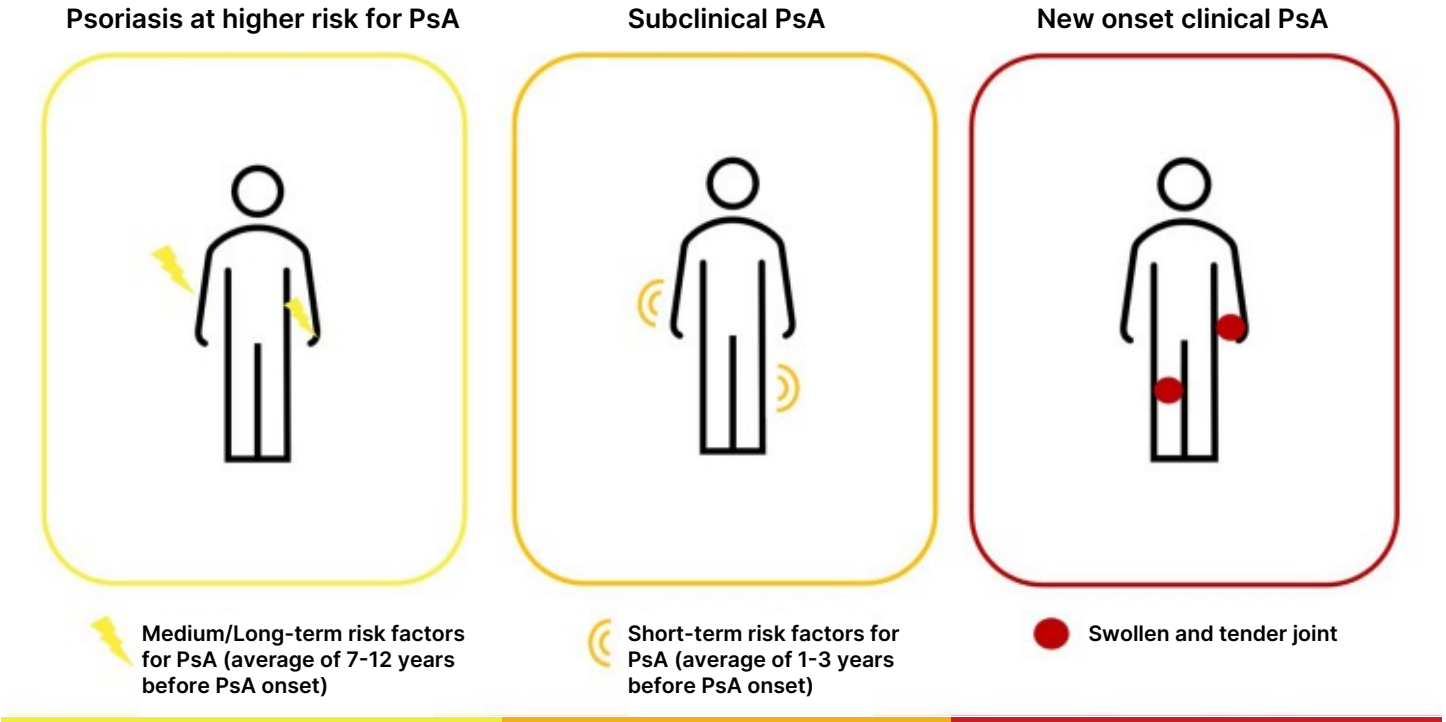
Observational studies suggest that approximately one-third of patients with psoriasis develop psoriatic arthritis, with joint changes usually occurring following psoriasis development.[1] This temporal progression from skin to joint involvement was initially described in the nomenclature put forth by the European Alliance of Associations for Rheumatology (EULAR) task force,[3] which has been revised by Errichetti and Zabotti, 2023[4] in **Figure 1**.

Given this temporal progression and the shared inflammatory mediators in the pathophysiology of psoriasis and psoriatic arthritis, it is biologically plausible that early use of biologic agents in this timeframe may delay or prevent the progression to psoriatic arthritis.

However, the literature to date on this topic is unclear. While many studies show a reduction

of psoriatic arthritis among psoriasis patients on biologics,[5-8] some studies show an increased risk.[9] In her presentation, Dr. Armstrong discussed how significant biases may be impacting these later findings, namely, 1) protopathic bias and 2) survival time bias. For instance, if you consider a typical severe psoriasis patient in your practice who reports joint issues, it is conceivable that you might be more likely to prescribe a biologic agent that also addresses psoriatic arthritis, which could create the impression that the biologic is increasing the risk of psoriatic arthritis. This is referred to as protopathic bias, which is a type of confounding by indication. This bias is likely also at play when comparing different biologic classes. Retrospective studies show that interleukin (IL)-23 agents have the lowest risk of progression to psoriatic arthritis.[9] However, a more likely explanation is that this medication class was chosen for these patients due to a perceived lower risk of psoriatic arthritis. Lastly, survival time bias may explain why psoriatic arthritis occurs earlier among psoriasis patients on biologics.[9] Usually, we prescribe biologics to more severe patients who have "survived" longer with their psoriasis, and are further along on the temporal progression from skin to joint involvement compared to those receiving other treatments.[2]

Overall, while the evidence to date is inconclusive, it is biologically plausible that biologics for psoriasis might reduce the risk of progression to psoriatic arthritis. Ideally, prospective controlled studies are required to further elucidate this potential association.



Psoriasis at higher risk for PsA	Subclinical PsA	New onset clinical PsA
Severe skin involvement	Arthralgia	Peripheral pattern
Nail psoriasis	Imaging evidence of synovio-entheseal inflammation	Oligoarthritis pattern
Obesity		Articular erosions pattern
Familial history for PsA		

Figure 1. Biologics for psoriasis and the risk of future psoriatic arthritis.
Legend: The transition from psoriasis to clinical psoriatic arthritis (PsA) occurs through two stages: (1) "psoriasis at higher risk for PsA," including patients with a medium-long-term risk (average of 7–12 years) of developing PsA (i.e., those with severe skin involvement, nail psoriasis, obesity, and/or familial history for PsA); (2) "subclinical PsA," including patients with a short-term risk (average of 1–3 years) of developing PsA (i.e., those with arthralgia and/or imaging evidence of synovio-entheseal inflammation). Such phases precede "clinical PsA," which may present with three main patterns, including "peripheral," "oligoarthritis," and "articular erosions"
Source: Errichetti and Zabotti, 2023[4]

Biologics for atopic dermatitis and the risk of growth suppression

It is well known that patients with severe atopic dermatitis are predisposed to growth suppression.[10] Potential mechanisms for this include chronic inflammation, stress, sleep disruption, and the effects of systemic/systemically absorbed topical corticosteroids. Dr. Irvine from Ireland presented a post hoc analysis from the Liberty-AD PEDS phase 3 trial looking at the role of dupilumab on the growth of children with severe atopic dermatitis.[2] Children aged 6 to 11 years with severe atopic dermatitis were randomized 1:1 to receive either placebo or dupilumab 300 mg subcutaneously every 4 weeks (both groups were also allowed mild-to-moderate topical corticosteroids). Height was measured at baseline and after 16 weeks of treatment. While growth is expected over this timeframe in children of this age group, the proportion of patients showing at least a five percentile increase in height was consistently and statistically significantly higher in the dupilumab group vs the placebo group. This was observed across all baseline height percentiles (ranging from <25th height percentile to <50th height percentile). Notably, the difference in the proportion of patients reaching this five percentile height increase was quite striking, with some groups reaching over a 25% difference in just a 16-week period.[2]

Overall, this rigorous and controlled data provides compelling evidence that early treatment with dupilumab for severe AD in childhood can have a quick and meaningful impact on improving growth, which may offer lifelong benefits for these patients **(Figure 2)**.

Treatment update for hidradenitis suppurativa

Biologics & small molecules

A number of new biologics and small molecules for HS were reviewed including IL-17, IL-1, tyrosine kinase, and Janus kinase (JAK) inhibitors.

Izokibep is a novel IL-17A inhibitor small molecule therapy designed to overcome limitations of traditional monoclonal antibodies. Izokibep is approximately one-tenth the size of monoclonal antibodies, which enables it to reach higher drug concentrations typically only achievable with intravenous administration. Dr. Papp presented data from a phase 3 trial demonstrating an improvement in the HS Clinical Response of 75% (HiSCR75) of 33% (compared to 21% in the placebo arm) after just 12 weeks of treatment.[11]

Dr. Hunger provided a review of several new and emerging biologics and small molecules for treating HS, including sonelokimab, lutikizumab, remibrutinib and upadacitinib.[12] Sonelokimab is an IL-17A and IL-17F inhibiting nanobody composed of three domains, two with high affinity for IL-17A and IL-17F, and a third that binds to human albumin, allowing for higher drug concentrations to be reached at sites of inflammatory edema. In a phase 2 trial with 24 weeks of follow-up,[13] HiSCR75 was achieved in 56.9% of patients (placebo data for 24 weeks was not reported, but 12-week data previously published shows HiSCR75 29% change compared to placebo).[14] Lutikizumab, the first IL-1 inhibitor studied for HS, is a dual-variable domain IL-1 alpha/IL-1 beta antagonist. In phase 2 studies, lutikizumab reached HiSCR75 in 45.9% of patients compared to 17.5% in the placebo group.[15] Remibrutinib, the first agent studied for HS that specifically targets B-cells, is an oral Bruton's tyrosine kinase inhibitor that prevents B-cell conversion to plasma cells. In Phase 2 studies, HiSCR75 was achieved in 42.4% of patients compared to 18.4% in the placebo group.[16] Lastly, data from a retrospective cohort study on upadacitinib was reviewed, showing a HiSCR75 response rate of over 90% after 12 weeks of therapy. Prospective, controlled trials are required to verify this impressive response.[17]

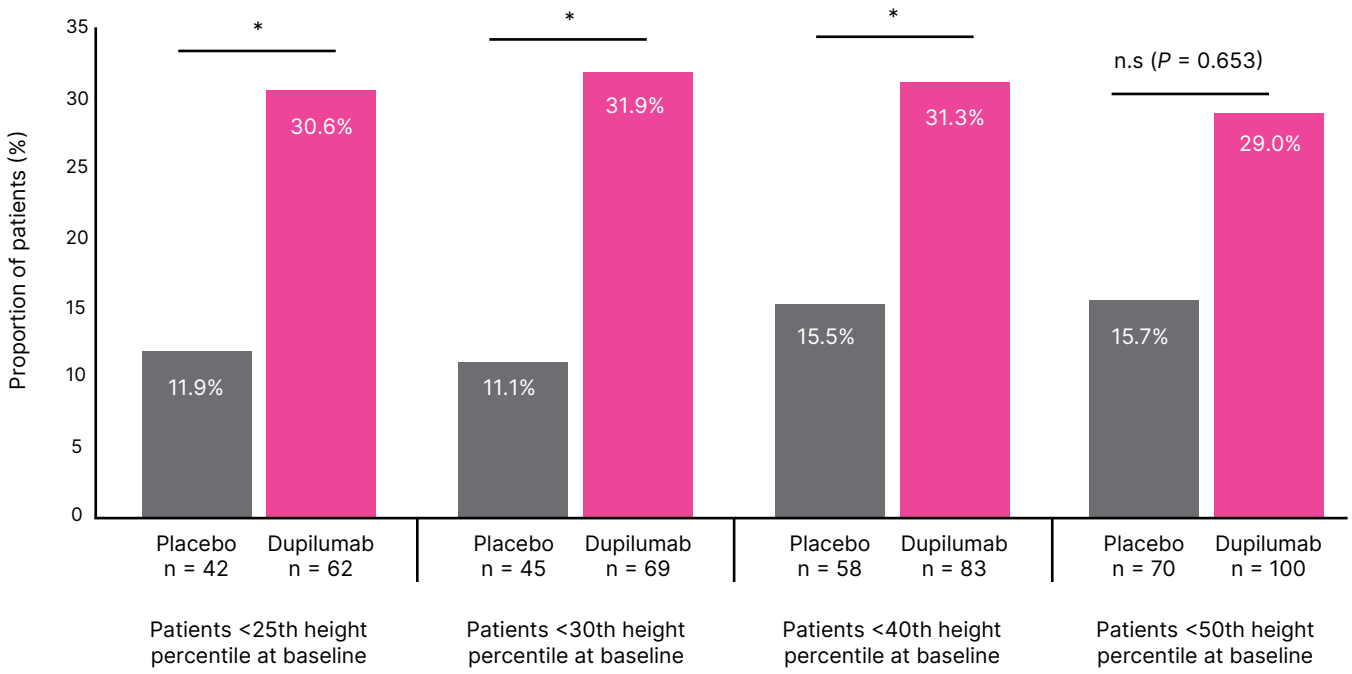
Supportive agents for weight loss

Several sessions examined new supportive therapies for HS, including novel agents to assist in symptom improvement through weight loss. Hughes et al.[18] presented the first published data for the use of semaglutide in HS during a poster presentation. In this retrospective, non-controlled study, thirty HS patients of all severities on various conventional HS therapies were concomitantly treated with semaglutide for weight loss over a mean period of 8.2 months. The mean weight loss was 6.1 kg, with one-third of patients losing at least 10 kg. Patient-reported HS flares decreased from a mean of once every 8.5 weeks to once every 12 weeks, and one-third of patients experienced at least a four point reduction in the Dermatology Life Quality Index (DLQI). Of note, the mean dose of semaglutide used in this study (0.8 mg weekly) is far below the 2.4 mg weekly licenced dose for weight loss (the authors stated supply issues).

In the session by Dr. Hunger described above,[12] the use of oral roflumilast was reviewed in a single-centre prospective study.[19] While weight loss was not the intent of this treatment, it is a common side effect of roflumilast and likely contributed to the improvement in HS scores. The weight loss observed was quite striking and far greater than the semaglutide study described above over a shorter follow-up period (median <4 months). Sixteen patients with HS with insufficient response to topical therapy and oral antibiotics were treated with oral roflumilast at a dose of 500 mcg once daily. They achieved a median weight loss of 9 kg and a corresponding median DLQI

Results

Proportion of patients 6 to 11 years with **lower stature** at baseline, showing a **≥5-percentile improvement in height** following 16 Weeks **treatment with dupilumab**



*P < 0.05 vs placebo BL, baseline; DUPI, dupilumab; PBO; placebo

Figure 2. Dupilumab vs placebo and growth
Legend: Liberty-AD PEDS phase 3 trial of dupilumab 300mg subcutaneous every 4 weeks vs placebo among patients aged 6-11 years with severe atopic dermatitis with lower stature at baseline. Over 16 weeks of observation, the percentage of patients acheiving at least a 5 percentile increase in growth was consistently and statistically significantly higher in the dupilumab group. This was observed across all baseline height percentiles.
Source: Irvine 2024[2]
License: none

improvement of 12 points. While these studies with different populations and study designs are not directly comparable, the data suggest that both semaglutide and oral roflumilast may be considered as weight loss agents in HS, with greater potential weight loss with roflumilast.

Correspondence

Annie Langley, MD, MSc, FRCPC, DABD
Email: alangley@toh.ca

Financial Disclosures

Honoraria: Abbvie, Arcutis, Bausch, Biojamp, Boehringer Ingelheim, Ceravae, Galderma, Jansen, Kenvue, Leo, L'oreal, Lilly, Novartis, Pfizer, Sanofi, SUN-pharma, UCB, Vichy

References

1. Armstong A. Does psoriasis treatment prevent the development of psoriatic arthritis? In: Proceedings of the 33rd EADV 2024 Congress, 2024 Sept 24-28. Amsterdam, Netherlands
2. Irvine, A. Growth analysis in children aged 6 to 11 years with severe atopic dermatitis and impact of 16 weeks of dupilumab treatment on height. In: Proceedings of the 33rd EADV 2024 Congress, 2024 Sept 24-28. Amsterdam, Netherlands
3. De Marco G, Zabotti A, Baraliakos X, Iagnocco A, Aletaha D, Gisondi P, et al. Characterisation of prodromal and very early psoriatic arthritis: a systematic literature review informing a EULAR taskforce. RMD Open. 20239(2):e003143. doi: 10.1136/rmdopen-2023-003143.
4. Errichetti E, Zabotti A. Biologics in prevention of psoriasis to psoriatic arthritis transition: the need of prospective analyses and stratification according to time-related risk factors. Dermatol Ther (Heidelb). 2024;14(1):1-3. doi: 10.1007/s13555-023-01072-1.
5. Watad A, Zabotti A, Patt YS, Gendelman O, Dotan A, Ben-Shabat N, et al. From psoriasis to psoriatic arthritis: decoding the impact of treatment modalities on the prevention of psoriatic arthritis. Rheumatol Ther. 2024;11(4):963-976. doi: 10.1007/s40744-024-00680-3.
6. Acosta Felquer ML, LoGiudice L, Galimberti ML, Rosa J, Mazzuoccolo L, Soriano ER. Treating the skin with biologics in patients with psoriasis decreases the incidence of psoriatic arthritis. Ann Rheum Dis. 2022;81(1):74-79. doi: 10.1136/annrheumdis-2021-220865.
7. Gisondi P, Bellinato F, Targher G, Idolazzi L, Girolomoni G. Biological disease-modifying antirheumatic drugs may mitigate the risk of psoriatic arthritis in patients with chronic plaque psoriasis. Ann Rheum Dis. 2022;81(1):68-73. doi: 10.1136/annrheumdis-2021-219961.

8. Singla S, Putman M, Liew J, Gordon K. Association between biological immunotherapy for psoriasis and time to incident inflammatory arthritis: a retrospective cohort study. Lancet Rheumatol. 2023;5(4):e200-e207. doi: 10.1016/S2665-9913(23)00034-6.
9. Meer E, Merola JF, Fitzsimmons R, Love TJ, Wang S, Shin D, et al. Does biologic therapy impact the development of PsA among patients with psoriasis? Ann Rheum Dis. 2022;81(1):80-86. doi: 10.1136/annrheumdis-2021-220761.
10. Paller A, Geng B, Irvine A, Adams B, Ardeleanu M, Zhang A, et al. Growth analysis in children aged less than 12 years with moderate-to-severe atopic dermatitis. Journal of the American Academy of Dermatology. 2024;91(3), AB1. doi:10.1016/j.jaad.2024.07.015.
11. Papp K, Bachara FG, Porter ML, Forman S, Sofen H, Szepietowski J, et al. Efficacy and safety of izokibep, a novel IL-17A inhibitor, in moderate-to-severe hidradenitis suppurativa: Week 12 results from a randomized, double-blind, placebo-controlled, multicenter, phase 3 study. In: Proceedings of the 33rd EADV 2024 Congress, 2024 Sept 24-28. Amsterdam, Netherlands.
12. Hunger R. Focus on hidradenitis suppurativa- new and emerging treatments. In: Proceedings of the 33rd EADV 2024 Congress, 2024 Sept 24-28. Amsterdam, Netherlands
13. Kimball A, Ackerman L, Lima H, et al. A phase 2 multicenter randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of lutikizumab in adult patients with moderate-to-severe hidradenitis suppurativa who have failed anti-TNF therapy. In: American Academy of Dermatology Annual Meeting. 2024 Mar 8-12. San Diego, CA.
14. MoonLake Immunotherapeutics. MoonLake Immunotherapeutics achieves landmark milestone with positive Phase 2 results for Nanobody® sonelokimab in hidradenitis suppurativa. 2023 June 25 [cited 2024 Nov 15]. Available from: https://ir.moonlaketx.com/news-releases/news-release-details/moonlake-immunotherapeutics-achieves-landmark-milestone-positive
15. Kimball AM, Kirby B, Bechara GF, et al. Efficacy and safety of the IL-17A- and IL-17F-inhibiting Nanobody® sonelokimab in patients with moderate-to-severe hidradenitis suppurativa (HS): Week 24 results from the Phase 2 MIRA trial. In: American Academy of Dermatology Annual Meeting, 2024 Mar 8-12. San Diego, CA.
16. Kimball AB, Prens EP, Bechara FG, et al. Efficacy and safety of the oral Bruton's tyrosine kinase inhibitor, remibrutinib, in patients with moderate-to-severe hidradenitis suppurativa in a randomized, phase 2, double-blind, placebo-controlled platform study. In: American Academy of Dermatology Annual Meeting, 2024 Mar 8-12. San Diego, CA.
17. Kozera E, Flora A, Frew JW. Real-world safety and clinical response of Janus kinase inihibitor upadacitinib in the treatment of hidradenitis suppurativa: a retrospective cohort study. J Am Acad Dermatol. 2022;87(6):1440-1442. doi:10.1016/j.jaad.2022.07.047.
18. Hughes R et al. Semaglutide for weight loss in obese patient as an adjunctive treatment for hidradenitis suppurativa: its impact on disease control and quality of life. Proceedings of the 33rd EADV 2024 Congress. 2024 Sept 24-28. Amsterdam, Netherlands.
19. Nielsen, VW, Holgersen NK, Ring HC, Thyssen JP, Gyldenløve M, Thomsen SF, et al. Effectiveness and safety of oral roflumilast in patients with hidradenitis suppurativa: a prospective single-center study. Journal of the American Academy of Dermatology. 2024;91(3), AB192. doi:10.1016/j.jaad.2024.07.765.

For patients with moderate-to-severe plaque psoriasis

Consider

Pr ILUMYA®
tildrakizumab
Injection 100 mg/mL

for the

Treatment Journey

Now publicly covered in Ontario, Alberta, Manitoba, Saskatchewan, and the Atlantic provinces (restrictions may apply)

Enrol your patients in the Sun Patient Support Program for ILUMYA® – designed to help you and your patients every step of the way

PrILUMYA® (tildrakizumab injection) is indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

For more information:
Please consult the Product Monograph at: info.ilumya.ca/Product_Monograph for important information relating to contraindications, warnings, precautions, adverse reactions, interactions, dosing and conditions of clinical use.

The Product Monograph is also available by calling our medical information department at: 1-844-924-0656.

REFERENCE:
Current ILUMYA® Product Monograph,
Sun Pharmaceutical Industries Limited.

PM-CA-ILY-0072

REVIEWED BY PAAB

SUN PHARMA

10.58931/cdt.2024.54132

ABOUT THE AUTHOR

Geneviève Gavigan, MSc, MD, FRCPC

Dr. Genevieve Gavigan is a Canadian dermatologist in Ottawa, Ontario. She specializes in pediatric dermatology, complex medical dermatology, and hidradenitis suppurativa. She earned her medical degree and completed her dermatology residency at the University of Ottawa. An award-winning educator, Dr. Gavigan is dedicated to teaching and mentoring future dermatologists. She focuses on personalized patient care, understanding each individual's unique needs.

Affiliations: The Ottawa Hospital, Department of Medicine, Division of Dermatology, Ottawa, ON
The Children's Hospital of Eastern Ontario (CHEO), Department of Pediatrics, Division of Rheumatology and Dermatology, Ottawa, ON

Practical Tips for Treating Pediatric Dermatology Patients

Geneviève Gavigan, MSc, MD, FRCPC

The purpose of this paper is to provide strategies to help deliver quality care that meets the unique needs of children and their families in a dermatology outpatient clinic setting. The tools highlighted are simple and fast to implement in a dermatologic office setting. Five separate tips are presented herein.

Tip 1: Dispensing 2 supplies for children living in multiple homes

Many children that we treat live in more than one primary home. Often this means that the family must remember to shuttle treatments back and forth between the homes with the child. This becomes a barrier to proper care, as the family or child could easily forget to bring the treatment to the other home, causing lapses in treatment, and contributing to uncontrolled skin disease. A simple solution is to dispense sufficient medication so that the child has all the necessary treatments at each home, thereby removing the need to shuttle medications between locations. This approach is especially well suited for topical treatments. For example, when treating a child with atopic dermatitis who lives in 2 primary homes, it is beneficial to dispense 2 sets of topical medications–one for flare treatment and one for maintenance treatment–at each home simultaneously. This helps to streamline things for the family involved as well.

Tip 2: Cryotherapy simplified with an otoscope speculum

The use of otoscope specula for cryotherapy is not new. In her paper, Fern (2004)[1] described a clinical technique where a disposable otoscope speculum was used to focus the spray from the liquid nitrogen canister onto the target skin lesion. In this manner, the disposable otoscope speculum is placed directly on the target lesion and acts to shield the surrounding skin from the liquid nitrogen spray.

This technique is advantageous when using cryotherapy to treat children as well. Verruca vulgaris and molluscum contagiosum are benign cutaneous viruses that commonly infect children. A child may develop a verruca on the eyebrow, the vermilion border of the lip, or in the naris. If active intervention is desired, one option is cryotherapy. Using an otoscope speculum to direct the spray in these situations allows for trickier locations to be treated, as it shields the surrounding skin and structures. Furthermore, children are moving targets and cannot be relied upon to remain still during treatment with cryotherapy. The addition of the otoscope speculum provides a direct touch point

between the young patient and the healthcare provider, as the healthcare provider holds the speculum directly on the patient's skin lesion. This allows the provider's hand to stabilize the speculum and react and move in response to the child's movements. The cryotherapy spray from the liquid nitrogen canister is directed into the otoscope speculum, which channels the spray onto the target lesion **(Figure 1)**.

Tip 3: Procedural distraction

Dermatological procedures, such as skin biopsies, are frequently accompanied by a degree of pain; for example, pain associated with the infiltration of local anesthesia. These procedures can be challenging in children and adolescents, but at times they are necessary. Procedural sedation may not be possible or desired in an outpatient setting. The process of overwhelming the senses can help distract the child from the pain of a needle poke in this situation. The goal of overwhelming the senses is to provide abundant sensory stimuli so that the brain does not focus on the pinch or pain from the infiltrating local anesthetic. Examples of potential options to achieve this include listening to music, watching a video, holding a hand or a stuffed animal, singing, or eating a special treat such as a lollipop or popsicle. Ideally several stimuli should be employed simultaneously.

All children are different, and it is important to mention that this quantity of sensory stimulation would not be appropriate for all children. Also, these techniques for overwhelming the senses and distraction should not replace other strategies to minimize the pain of local anesthesia infiltration, (i.e., such as selecting a smaller needle diameter, slow speed of infiltration, etc.)

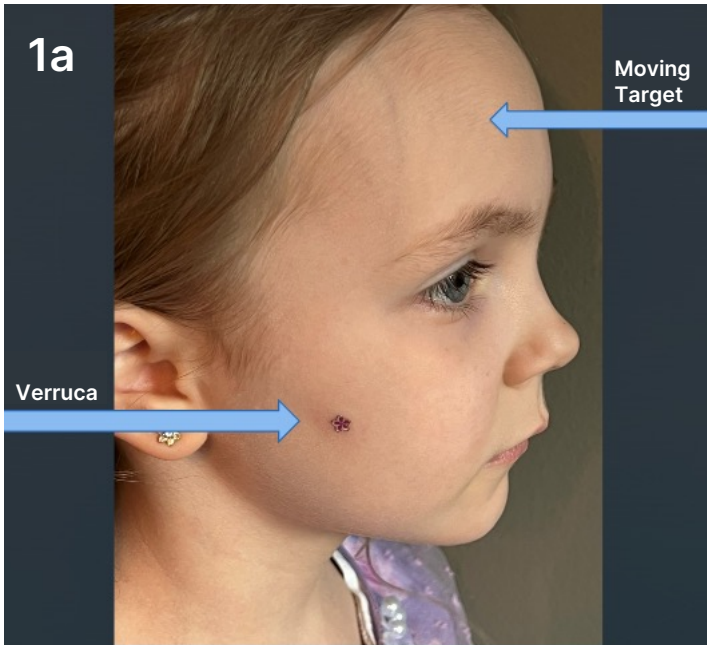
Tip 4: Table salt for the treatment of pyogenic granulomas

Pyogenic granulomas are benign acquired vascular neoplasms that can be problematic because of their tendency to grow quickly and bleed. The standard of care for treatment is surgical removal. This allows for histopathologic confirmation of the diagnosis, and distinction from malignant neoplasms.

Sometimes, non-surgical treatment options are desired. Effective non-surgical treatment of pyogenic granulomas with topical beta-blockers, such as topical timolol applied twice daily, is well documented. Topical imiquimod is another option, however, the resulting inflammatory reaction limits its clinical application.[2]

Recently, table salt has been investigated as a therapeutic option for pyogenic granulomas. Daruwalla et al.[3] described the use of topical table salt for this purpose **(Figure 2)**. In their study, soft paraffin was used to create a well around the target pyogenic granuloma, and topical table salt was placed within the well. This was then secured with tape. This process was repeated daily. Their study of 50 patients included 15 pediatric patients. The results indicated a decrease in bleeding by day 3.7 (mean). They achieved 100% resolution of pyogenic granulomas after a mean of 14.7 days, with a single recurrence of pyogenic granuloma reported 11 months later. Adverse events included difficulty with the application site, mild burning if the pyogenic granuloma was eroded, and surrounding eczema.

Table salt has also been demonstrated as an effective treatment for umbilical granulomas in infants.[4] In a study of 17 infants, table salt was applied to a cleaned area with a wet toothpick in the clinic. The treated area was secured with surgical adhesive



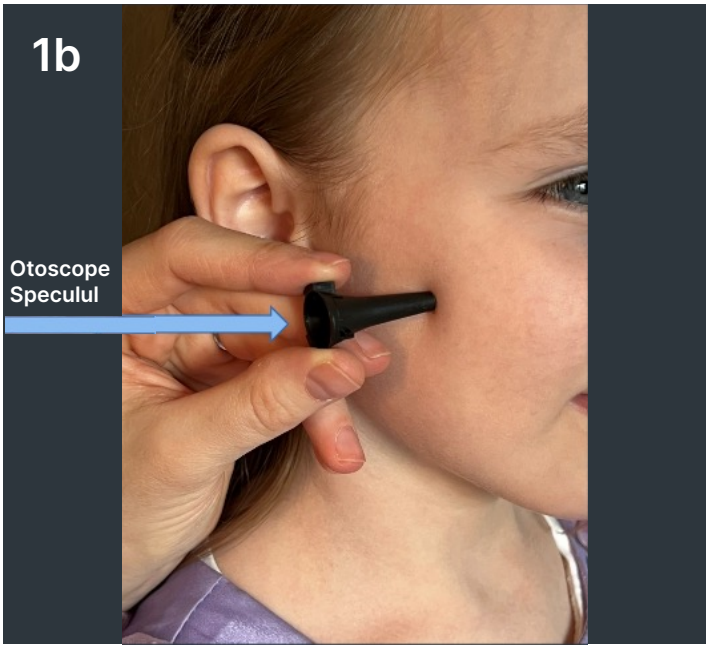


Figure 1 A-C: Using cryotherapy with an otoscope speculum; *courtesy of Genvieve Gavigan, MD.*

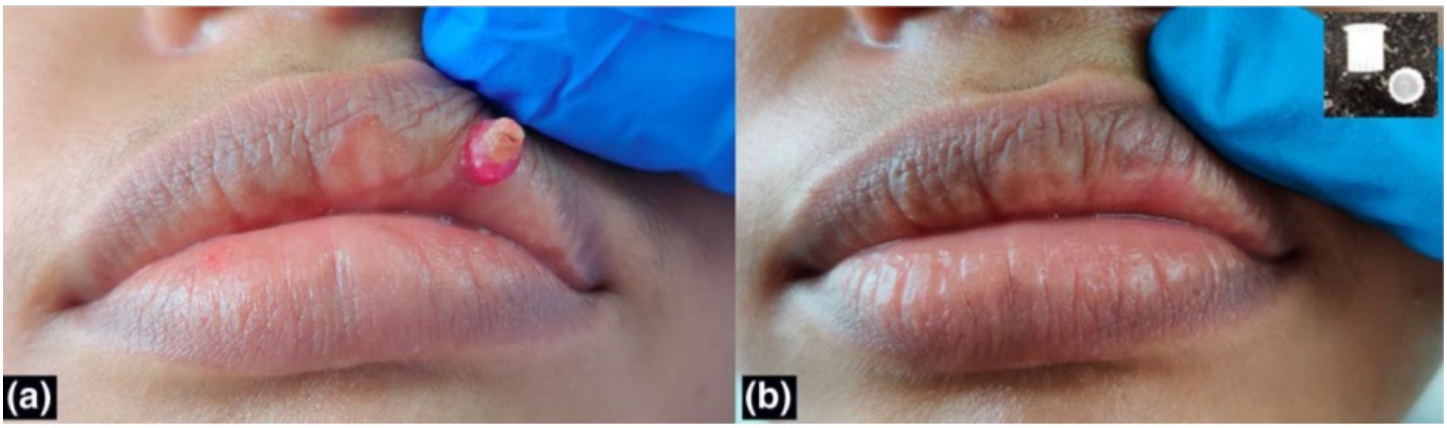


Figure 2 A-B: The use of common salt for the treatment pyogenic granuloma; *from Daruwalla et al., 2021*

tape. After 24 hours, all 17 infants showed complete resolution of their umbilical granulomas.

The mechanism of action by which salt treats pyogenic granuloma and umbilical granuloma is through the creation of a hyperosmolar environment, which desiccates and shrinks the pyogenic granuloma or umbilical granuloma.[3,4]

Tip 5: Tools to learn how to swallow pills

Learning to swallow medication pills is a life skill. Yet, it can be scary and difficult to master for many children. Dr. Bonnie Kaplan has created an online learning program, based on her research to assist children and their families to learn this problematic skill. Her video, "How to Swallow Pills by Dr. Bonnie Kaplan", is available in YouTube. In it, she outlines a stepwise method that can be practiced at home. At first, children practise swallowing water while positioning their heads in 5 different ways (head turned to the left, head turned to the right, head looking up, head looking down, and head looking straight ahead). Next, the same 5 head positions are used when swallowing a small hard candy. It is recommended to spend 30 minutes to learn the technique and to practice for 14 days (about 5 minutes each day) to achieve the skill of swallowing pills. This video also describes possible pitfalls and additional methods to help remedy them.[5]

In conclusion, five practical and easy-to-implement tips were reviewed. Taken together, these tips may ameliorate the tolerability of cryotherapy and skin biopsies in children, providing real-world strategies for treating dermatologic conditions and prescribing medications to children.

Correspondence

Genvieve Gavigan, MSc, MD, FRCPC
Email: genevieve.gavigan@gmail.com

Financial Disclosures

Honoraria: Amgen, AbbVie, Bausch, Beiersdorf, Biojamp, Bristol Myers Squibb, Galderma, Lilly, Medexus Pharma, Novartis, L'Oreal Canada, Pfizer, Sanofi, Sun Pharma, UCB, Valeant

References

1. Nelson FP. Surgical pearl: a novel adaptor for cryotherapy. J Am Acad Dermatol. 2004;51(6):980-981.
2. Malik M, Murphy R. A pyogenic granuloma treated with topical timolol. Br J Dermatol. 2014;171(6):1537-1538.
3. Daruwalla SB, Ghate S, Dhurat R. Establishing the efficacy and safety of the novel use of common salt for the treatment of pyogenic granuloma. Clin Exp Dermatol. 2021;46(7):1243-1247
4. Bagadia J, Jaiswal S, Bhalala KB, Poojary S. Pinch of salt: a modified technique to treat umbilical granuloma. Pediatr Dermatol. 2019;36(4):561-563
5. B Kaplan. How to swallow pills by Dr. Bonnie Kaplan. YouTube·UCalgaryMedicine·Oct 9, 2019. Available from: https://www.youtube.com/watch?v=Zxqs7flHJQc

TAKE ON MODERATE-TO-SEVERE ATOPIC DERMATITIS WITH THE POWER OF CIBINQO®

INCLUDING RELIEF OF PRURITUS

CIBINQO is indicated for the treatment of patients 12 years and older with refractory moderate-to-severe atopic dermatitis, including the relief of pruritus, who have had an inadequate response to other systemic drugs (e.g., steroid or biologic), or for whom these treatments are not advisable.

A new, highly selective oral JAK1 inhibitor for moderate-to-severe AD*

Clinical use

Can be used with or without medicated topical therapies for atopic dermatitis.

Limitations of use: use in combination with other JAK inhibitors, biologic immunomodulators, or potent immunosuppressants, such as methotrexate and cyclosporine, has not been studied and is not recommended.

Most serious warnings and precautions

Serious infections: patients may be at increased risk for developing serious bacterial, fungal, viral and opportunistic infections that may lead to hospitalization or death; more frequently reported serious infections were predominately viral. If a serious infection develops, interrupt treatment until the infection is controlled. Risks and benefits of treatment should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Monitor for signs and symptoms of infection during and after treatment, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Malignancies: lymphoma and other malignancies were observed in patients taking JAK inhibitors to treat inflammatory conditions and were more frequently observed in patients with rheumatoid arthritis (RA) during a clinical trial with another JAK inhibitor versus TNF inhibitors.

Thrombosis: including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients taking JAK inhibitors to treat inflammatory conditions. Many of these events were serious; some resulted in death. Consider risks and benefits prior to treating patients who may be at increased risk. In a clinical trial in patients ≥50 years of age with RA, a higher rate of all-cause mortality and thrombosis occurred in patients treated with another JAK inhibitor versus TNF inhibitors. Patients with symptoms of thrombosis should be promptly evaluated and treated appropriately.

Major adverse cardiovascular events (MACE): including non-fatal myocardial infarction, were observed more frequently in patients ≥50 years of age with RA during a clinical trial comparing another JAK inhibitor versus TNF inhibitors.

Other relevant warnings and precautions

- Driving or operating machinery
- Dose-dependent increase in blood lipid parameters, lipid monitoring and management
- Hematological abnormalities
- Use with potent immunosuppressants
- Vaccination
- Monitoring and laboratory tests
- Fertility
- Women of childbearing potential
- Pregnancy and breastfeeding
- Geriatrics

For more information

Consult the Product Monograph at http://pfizer.ca/pm/en/CIBINQO.pdf for important information regarding adverse reactions, drug interactions and dosing information, which have not been discussed in this piece. The Product Monograph is also available by calling 1-800-463-6001.

AD=atopic dermatitis; JAK1=Janus kinase 1.
* Clinical significance unknown.

Reference: CIBINQO Product Monograph, Pfizer Canada ULC.

Contact your Pfizer representative to learn more about CIBINQO

Pfizer

MEMBER OF INNOVATIVE MEDICINES CANADA

REVIEWED BY PAAB

Patient Support Program
PfizerFlex
Experienced, Dedicated Team

NEW
PrCIBINQO®
abrocitinib tablets

Canadian Dermatology Today
Science for the Real World

canadiandermatologytoday.com

Canadian Dermatology Today is published four times per year
(ISSN 2563-7673) under the terms of the Creative Commons
Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0)
license by Catalytic Health in Toronto, Ontario, Canada.

VOL 5
ISSUE 4
2024

Register for future digital and print issues by visiting us at catalytichealth.com/cdt

Looking for more?
All back issues are available online at canadiandermatolgytoday.com