ABOUT THE AUTHOR

Patrick Fleming, MD, MSc, FRCPC, FCDA

Dr. Patrick Fleming is a certified dermatologist practicing in Toronto and an Assistant Professor of Medicine at the University of Toronto. He is a clinical associate at University Health Network where he sees inpatient consultations. Dr. Fleming works actively at Toronto-based COVID-19 Assessment and Vaccination Centres. He holds a master's degree in community health and also completed the Global Clinical Scholars program in advanced epidemiology at Harvard Medical School. He is a fellow of the Royal College of Physicians and Surgeons of Canada and the Canadian Dermatology Association. He is a member of the editorial board of the *Journal of Cutaneous Medicine* and Surgery and Board of Governors for the Canadian Dermatology Foundation.

WHAT TO KNOW ABOUT COVID-19 AND ITS IMPACT ON PATIENTS WITH PSORIASIS

Introduction:

Coronavirus disease 2019 (COVID-19) is an acute systemic illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This novel coronavirus was first identified in Wuhan, China in late 2019 and has since had a major impact on global health after being declared a pandemic in the spring of 2020 by the World Health Organization. To date, there have been over 180 million confirmed infections and over 4 million deaths worldwide across multiple 'waves'.[1]

COVID-19 has had a major impact on dermatology practice in Canada with a shift towards virtual care and a reluctance to prescribe some immunosuppressive medications.[2] However, since those early days, there has been growing comfort with continuing such medications in most cases.

The primary objective of this article is to review the impact of both COVID-19 and COVID-19 vaccination on patients with psoriasis who are taking oral agents and biologics (anti-tumour necrosis factor (TNF), anti-interleukin (IL)-17 and anti-interleukin (IL)-23 inhibitors).

Impact of COVID-19 On Patients with Psoriasis on Oral Agents or Biologics:

Psoriasis is a chronic and immune-mediated skin disease that affects 2-3% of the population.[3] It can range from mild to severe with worse cases often requiring systemic immunomodulatory therapy. This may include oral small molecules (apremilast, methotrexate, cyclosporine) and injectable biologics (TNF-α, IL-17 and IL-23 inhibitors).

Early in the pandemic, it was unknown what impact psoriasis may have on COVID-19, especially for those patients taking oral or biologic therapy. As data has begun to emerge, it has become clear that certain co-morbidities may predict a worse outcome for patients with COVID-19 such as cardiac disease, diabetes mellitus, and obesity, all of which are more common in psoriasis patients.[4] Several studies have shed light on the use of oral and biologic medications including a large and sophisticated cohort study which was conducted by examining over 50 million unique patient records across multiple countries to evaluate the impact of methotrexate and anti-TNF agents on COVID-19-related outcomes.[5] The researchers identified 214 patients within their database with COVID-19 who had recent anti-TNF or methotrexate exposure compared with 31,862 with COVID-19 who had not had recent methotrexate or anti-TNF exposure. Using propensity matching, the researchers did not identify any increased risk of COVID-19 hospitalization between the anti-TNF group vs no anti-TNF group (anti-TNF: risk ratio (RR) = 0.73 [95% CI 0.47 to 1.14], p = 0.1594) nor for those in the methotrexate group vs the no methotrexate group (RR = 0.87 [95% CI 0.62 to 1.23], p=0.4272). Similarly, a large cohort in Northern Italy found similar results.[6] This retrospective cohort study followed a large number of patients with chronic plaque psoriasis taking biologic therapy (n = 6501). The authors found that the incidence rate of hospitalization from COVID-19 was similar among the general population compared to those with psoriasis taking biologics (11.7 per 10,000 person-months in patients with psoriasis (95% CI, 7.2 to 18.1) vs 14.4 in the general population (95% CI, 14.3 to 14.5). Interestingly, the risk of death from COVID-19 trended lower among those on biologics (1.3 per 10,000 person-months in patients with psoriasis (95% CI, 0.2 to 4.3) vs 4.7 in the general population (95% CI, 4.6 to 4.7).[6]

Currently, the National Psoriasis Foundation does not recommended withholding or delaying treatment due to the pandemic in patients without active COVID-19 infection.[7] Based on these and other studies it appears there are no clear safety signals among patients using immunomodulatory therapy without active signs of infection.

COVID-19 Vaccination & Psoriasis:

Currently four vaccines are approved in Canada for inoculation against SARS-CoV-2. The two mRNA-based vaccines use a lipid nanoparticle that encodes for the SARS-CoV-2 spike protein. The Pfizer-BioNTech (BNT162b2) vaccine is delivered as a series of two doses (0.3mL each) 21 days apart.[8] Phase III studies (n=43,448) demonstrated 95% efficacy in preventing COVID-19 (95% CI: 90.3 to 97.6) . National-level real world data from Israel demonstrates a similar efficacy level of 94% for symptomatic infection.[9] The Moderna (mRNA-1273) vaccine showed similar results in their phase III study (n=30,351) with 94.1% efficacy in preventing COVID-19 (95% CI, 89.3 to 96.8%; P<0.001) with two 0.5 mL doses at weeks 0 and 4.[10] Both vaccines are well-tolerated with injection site reactions, fatigue, and headache being the most common adverse effects.

Two adenovirus vector vaccines are available that both use replication-deficient chimpanzee adenoviral vector that encodes for part of the SARS-CoV-2 spike protein. The University of Oxford and AstraZeneca developed a two-shot vaccine (AZD1222). In the pivotal clinical trial (n=23,848) participants had a reported 70.4% efficacy (95.8% CI: 54.8–80.6; 66.9%; adjusted 95% CI, 59.0 to 73.4).[11] Johnson & Johnson also developed a one-shot vaccine based on similar technology.[12] Due to concerns about vaccine-induced immune thrombotic thrombocytopenia (VITT), adenovirus vector vaccines are not being commonly administered in Canada.[13]

It is unclear at this time if biologic therapy should be interrupted for COVID-19 vaccination. Theoretically, since these vaccines work partially through T-cell immunity, there may be a reduced immune response. A study of inflammatory bowel disease patients (n=48) in New York examined vaccine antibody response in patients receiving either anti-TNF or IL-23 inhibitors[14] and found that in those who completed two-doses, all subjects produced an immune response above the level thought to confer protection from COVID-19. A subgroup analysis in patients who received 2 vaccine doses revealed no association between timing of infusion and antibody response.

In contrast to biologics, there is some data to suggest that methotrexate may reduce immune response to vaccination. A cohort study in New York of patients (n=51) who received the Pfizer-BioNTech mRNA vaccine examined the antibody response of patients taking methotrexate for immune-mediated inflammatory diseases, including psoriasis.[15] The

a priori hypothesis included the assumption that antibody response would be attenuated in patients receiving a mRNA vaccine for COVID-19 since similar effects had been observed with the influenza vaccine. The authors found that there was a significantly lower level of 'adequate' antibody titres in those taking methotrexate with immune-mediated inflammatory diseases vs those not taking methotrexate with immune-mediated inflammatory diseases (92.3% vs 72.0%, p<0.001).

Vaccine Recommendations for Patients on Oral or Biologic Therapy:

The current guidelines from the National Psoriasis Foundation recommend that "patients who are to receive an mRNA-based COVID-19 vaccine continue their biologic or oral therapies for psoriasis and/or psoriatic arthritis in most cases".[7] The guidelines note that although there may be some reduced response to influenza vaccination in patients on methotrexate and/or anti-TNF agents, there is no apparent similar effect for anti-IL-12/23 or IL-17 inhibitors. Because patients on immunomodulatory therapy were excluded from clinical trials for COVID-19 vaccination, we have minimal data at this time.

In contrast, the American College of Rheumatology (ACR) recommends holding methotrexate for one week after receiving mRNA-based vaccines.[16] The ACR based their recommendation on the same data showing reduced antibody response to influenza vaccination and additional data suggesting no major disease flares. In addition, they recommend patients taking biologic therapy continue treatment as they normally would.

Direct Impact of COVID-19 Vaccination on Skin Disease in Psoriasis:

COVID-19 has the potential to flare skin disease. Anecdotal reports from patients suggest that there can be mild, transient flares of pre-existing skin disease such as psoriasis and atopic dermatitis. A single case report of a patient in his 40s with psoriasis who had a severe flare of inflammatory psoriasis, became febrile and required admission to the hospital, despite being on a TYK2 inhibitor, has been reported.[17] This flare occurred a few days after his second dose of the Pfizer-BioNTech mRNA vaccine. Thus far, such severe reactions appear rare.

Cutaneous Reactions to COVID-19 Vaccination:

Although COVID-19 vaccination is considered safe, there is a risk of cutaneous adverse effects. A large cohort study (n=414) in the United States tracked reactions to both the Pfizer-BioNTech and Moderna mRNA vaccines and found local reactions to be the most frequent reported adverse event.[18] Drug eruptions, either urticarial or morbilliform, were also common and there were a number of rare cutaneous reactions that resembled those reported with actual COVID-19 infection such as chilblains and pityriasis rosea. These were typically transient and resolved on their own. Less than half of patients who experienced these reactions after their first dose had a recurrence after their second dose.

Conclusion:

COVID-19 is a potentially serious and lethal infection that has impacted physical and mental health, and the global economy. Patients with severe psoriasis taking immunomodulatory agents appear to have similar outcomes as the general population. Effective and safe mRNA-based vaccines exist for COVID-19. At this time, medical organizations recommend these vaccines for patients taking either oral or biologic agents for psoriasis without interruption of treatment. The only exception is methotrexate which some suggest holding for one week. Local reactions to the vaccine are common and on occasion atypical cutaneous eruptions may occur which dermatologists should be aware of in the event that they arise.

References:

1. John Hopkins. Coronavirus Resource Centre. July 15, 2021. Accessed July 15, 2021, from https://coronavirus.jhu.edu/map.html

2. Leis M, Fleming P, Lynde CW. Impacts of COVID-19 on Dermatologic Practice, Disease Presentation, and Immunomodulator Prescriptions. Journal of Cutaneous Medicine and Surgery. 2021;25(1):106-108. doi:10.1177/1203475420960437

3. Gulliver W. Long-term prognosis in patients with psoriasis. Br J Dermatol 2008; 159(Suppl. 2):2–9.

4. Fu L, Wang B, Yuan T, et al. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: A systematic review and meta-analysis. J Infect. 2020;80(6):656-665. doi: 10.1016/j.jinf.2020.03.041

5. Yousaf A., Gayam S., Feldman S., Zinn Z., Kolodney M. Clinical outcomes of COVID-19 in patients taking tumor necrosis factor inhibitors or methotrexate: a multicenter research network study. J Am Acad Dermatol. 2021; 84:70–75.

6. Gisondi P, Piaserico S, Naldi L, et al. Incidence rates of hospitalization and death from COVID-19 in patients with psoriasis receiving biological treatment: A Northern Italy experience. J Allergy Clin Immunol. 2021;147(2):558-560.e1. doi:10.1016/j.jaci.2020.10.032

7. Gelfand JM, Armstrong AW, Bell S, Anesi GL, Blauvelt A, Calabrese C, Dommasch ED, Feldman SR, Gladman D, Kircik L, Lebwohl M, Lo Re V 3rd, Martin G, Merola JF, Scher JU, Schwartzman S, Treat JR, Van Voorhees AS, Ellebrecht CT, Fenner J, Ocon A, Syed MN, Weinstein EJ, Gondo G, Heydon S, Koons S, Ritchlin CT. National Psoriasis Foundation COVID-19 Task Force guidance for management of psoriatic disease during the pandemic: Version 2-Advances in psoriatic disease management, COVID-19 vaccines, and COVID-19 treatments. J Am Acad Dermatol. 2021 May;84(5):1254-1268. doi: 10.1016/j.jaad.2020.12.058. Epub 2021 Jan 7. PMID: 33422626; PMCID: PMC7788316.

8. Skowronski DM, De Serres G. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2021 Apr 22;384(16):1576-1577. doi: 10.1056/NEJMc2036242. Epub 2021 Feb 17. PMID: 33596348.

9. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, Hernán MA, Lipsitch M, Reis B, Balicer RD. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 2021 Apr 15;384(15):1412-1423. doi: 10.1056/NEJMoa2101765. Epub 2021 Feb 24. PMID: 33626250; PMCID: PMC7944975.

10. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J, Khetan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T; COVE Study Group. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021 Feb 4;384(5):403-416. doi: 10.1056/NEJMoa2035389. Epub 2020 Dec 30. PMID: 33378609; PMCID: PMC7787219.

11. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, Angus B, Baillie VL, Barnabas SL, Bhorat QE, Bibi S, Briner C, Cicconi P, Collins AM, Colin-Jones R, Cutland CL, Darton TC, Dheda K, Duncan CJA, Emary KRW, Ewer KJ, Fairlie L, Faust SN, Feng S, Ferreira DM, Finn A, Goodman AL, Green CM, Green CA, Heath PT, Hill C, Hill H, Hirsch I, Hodgson SHC, Izu A, Jackson S, Jenkin D, Joe CCD, Kerridge S, Koen A, Kwatra G, Lazarus R, Lawrie AM, Lelliott A, Libri V, Lillie PJ, Mallory R, Mendes AVA, Milan EP, Minassian AM, McGregor A, Morrison H, Mujadidi YF, Nana A, O'Reilly PJ, Padayachee SD, Pittella A, Plested E, Pollock KM, Ramasamy MN, Rhead S, Schwarzbold AV, Singh N, Smith A, Song R, Snape MD, Sprinz E, Sutherland RK, Tarrant R, Thomson EC, Török ME, Toshner M, Turner DPJ, Vekemans J, Villafana TL, Watson MEE, Williams CJ, Douglas AD, Hill AVS, Lambe T, Gilbert SC, Pollard AJ; Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021 Jan 9;397(10269):99-111. doi: 10.1016/S0140-6736(20)32661-1. Epub 2020 Dec 8. Erratum in: Lancet. 2021 Jan 9;397(10269):98. PMID: 33306989; PMCID: PMC7723445.

12. Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, Goepfert PA, Truyers C, Fennema H, Spiessens B, Offergeld K, Scheper G, Taylor KL, Robb ML, Treanor J, Barouch DH, Stoddard J, Ryser MF, Marovich MA, Neuzil KM, Corey L, Cauwenberghs N, Tanner T, Hardt K, Ruiz-Guiñazú J, Le Gars M, Schuitemaker H, Van Hoof J, Struyf F, Douoguih M; ENSEMBLE Study Group. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Engl J Med. 2021 Jun 10;384(23):2187-2201. doi: 10.1056/NEJMoa2101544. Epub 2021 Apr 21. PMID: 33882225; PMCID: PMC8220996.

13. An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI): Recommendations on the use of COVID-19 Vaccines. July 2, 2021.

14. Wong SY, Dixon R, Martinez Pazos V, Gnjatic S, Colombel JF, Cadwell K; ICARUS-IBD Working Group. Serologic Response to Messenger RNA Coronavirus Disease 2019 Vaccines in Inflammatory Bowel Disease Patients Receiving Biologic Therapies. Gastroenterology. 2021 Apr 20:S0016-5085(21)00648-X. doi: 10.1053/j.gastro.2021.04.025. Epub ahead of print. PMID: 33887219; PMCID: PMC8055494.

15. Haberman RH, Herati R, Simon D, et al Methotrexate hampers immunogenicity to BNT162b2 mRNA COVID-19 vaccine in immune-mediated inflammatory disease Annals of the Rheumatic Diseases Published Online First: 25 May 2021. doi: 10.1136/annrheumdis-2021-220597

16. Curtis JR, Johnson SR, Anthony DD, et al. American College of Rheumatology Guidance for COVID-19 Vaccination in Patients With Rheumatic and Musculoskeletal Diseases: Version 1. Arthritis Rheumatol. 2021;73(7):1093-1107. doi:10.1002/art.41734 021;84(5):1254-1268. doi:10.1016/j.jaad.2020.12.058

17. Krajewski PK, Matusiak Ł, Szepietowski JC. Psoriasis flare-up associated with second dose of Pfizer-BioNTech BNT16B2b2 COVID-19 mRNA vaccine. J Eur Acad Dermatol Venereol. 2021 Jun 16. doi: 10.1111/jdv.17449. Epub ahead of print. PMID: 34131967.

18. McMahon DE, Amerson E, Rosenbach M, Lipoff JB, Moustafa D, Tyagi A, Desai SR, French LE, Lim HW, Thiers BH, Hruza GJ, Blumenthal KG, Fox LP, Freeman EE. Cutaneous reactions reported after Moderna and Pfizer COVID-19 vaccination: A registry-based study of 414 cases. J Am Acad Dermatol. 2021 Jul;85(1):46-55. doi: 10.1016/j.jaad.2021.03.092. Epub 2021 Apr 7. PMID: 33838206; PMCID: PMC8024548.