

[Clin Cosmet Investig Dermatol](#). 2022; 15: 2369–2382.

Published online 2022 Nov 6. doi: [10.2147/CCID.S388245](https://doi.org/10.2147/CCID.S388245)

PMCID: PMC9648179

PMID: [36387962](https://pubmed.ncbi.nlm.nih.gov/36387962/)

Cutaneous Reactions Following COVID-19 Vaccination: A Review of the Current Literature

COVID-19 ワクチン接種後の皮膚反応:現在の文献のレビュー

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<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9648179/>

抄録

2019年の新型コロナウイルス感染症(COVID-19)のアウトブレイクは、世界的な新たな課題であり、世界経済、健康全般および生活習慣に強い影響を及ぼした。それ以来、感染の拡大を抑えるためにいくつかの戦略が採用されている。その中でも、ワクチン接種は現在最も重要なパンデミック対策である。しかしながら、当初は、期待されたほどの導入の遅れ、限られたデータでの性急な承認、作用機序(特に mRNA ベース)、得られる予防効果の持続期間の不確実性など、いくつかの懸念が提起された。さらに、臨床試験で皮膚反応がまれにしか報告されていない場合でも、世界的な集団ワクチン接種により、当初は認識されなかったいくつかの皮膚反応が示されたため、皮膚科医はそれらの診断および治療方法を決定せざるを得なくなった。このシナリオでは、皮膚科医はこれらの臨床症状を直ちに認識できるように準備しておくべきである。そこで本稿の目的は、COVID-19 ワクチン接種後の皮膚反応(特に炎症性皮膚疾患)に関する最新の文献をレビューすることにより、臨床医がこれらの皮膚疾患をよりよく理解し、ワクチンに関連する全ての皮膚症状の広範な概要を把握できるようにすることである。

Keywords: cutaneous reactions, COVID-19 vaccinations, side effects

はじめに

2019年の新型コロナウイルス感染症(COVID-19)のアウトブレイクは、世界的な新たな課題であり、世界経済、健康全般および生活習慣に強い影響を及ぼした。[1]それ以来、感染拡大を抑制するためにいくつかの戦略が採

*本翻訳は MediTRANS(<http://www.mcl-corp.jp/meditrans/>)という機械(AI)翻訳エンジンによるものであり、人による翻訳内容の検証等は行っていません。従いまして本翻訳の利用に際しては、原著論文が正であることをご理解の上、あくまでも個人の理解のための参考に留めていただきますようお願いいたします。

用されてきた。[2],[3]皮膚科医は今回のパンデミックにおいて重要な役割を果たし、COVID-19 による皮膚反応、従来の治療法や生物製剤の有効性と安全性に対するこの時期の躊躇、個人防護具の着用によるいくつかの皮膚疾患の悪化、新しい生活習慣の導入など、いくつかの課題に取り組んだ。[4-6]実際、COVID-19 のパンデミック期間中にイタリア政府が採用した「自宅待機」政策と制限措置は、生活の質に大きな影響を与えた。[7]さらに、COVID-19 の制限措置は感染症や皮膚癌の疫学にも影響を及ぼす。[5][8-10]

COVID-19 の感染拡大を抑制するために策定された公衆衛生戦略の中で、現在ではワクチン接種がパンデミック対策として最も重要な対策となっている。しかし、当初は、期待されたほどの導入の遅れ、限られたデータでの性急な承認、作用機序(特に mRNA ベース)、得られた予防効果の持続期間の不確実性など、いくつかの懸念が提起された。[11],[12]幸いなことに、世界的なワクチン接種キャンペーンは成功を収め、COVID-19 の流行、疾患の進行、入院、死亡を予防・管理する上で最も効果的な手段であることが示された[13]。

2021 年 9 月 11 日にアクセスされた WHO の COVID-19 ダッシュボードによると、これまでに 6 億 800 万例以上の COVID-19 感染者が確認され、651 万人近くが死亡した。【14】現在、COVID-19 に対して認可されたワクチンでは、ウイルスベクタープラットフォーム、メッセンジャーリボ核酸、不活化ウイルスなどの核酸ベースのワクチン接種プラットフォームが使用されている。【13】

欧州医薬品庁(European Medicines Agency:EMA)はこれまでに 4 つのワクチンを承認している:2 つの mRNA ベースのワクチン(Pfizer/BioNTech;BNT162b2 and Moderna;mRNA-1273)と 2 つのウイルスベクターベースのワクチン(AstraZeneca;AZD1222 and Johnson&Johnson;Ad26.COVS.2.S)である。【15】しかしながら、他の国では「CoronaVac」(Sinovac),「Sputnik V」(Gamaleya Research Institute),「Convidecia」(CanSino Biologics)など、他のワクチンも承認されている。【13】現在、53 億人以上が少なくとも 1 回は COVID-19 ワクチンの接種を受けている。【16】

他の薬剤と同様に、ワクチン接種後に疲労、頭痛、下痢、注射部位の発赤または疼痛、発熱、筋肉痛、悪寒などの軽度から中等度の有害事象が報告された症例もあった[17-19]。幸いなことに、ほとんどの副作用は限られたものであり、持続期間は数日間であった[17-19]。

臨床試験で皮膚反応がまれにしか報告されていない場合でも、世界的な集団ワクチン接種により、当初は認識されなかったいくつかの皮膚反応が示されたため、皮膚科医はそれらをどのように認識して治療するかを決定することになった。特に、広範囲の皮膚反応が報告されている[20]が、これらの反応の意義は依然として不明である。このシナリオでは、皮膚科医はこれらの臨床症状を迅速に認識できるように準備しておくべきであり、個別化医療ではこの点を考慮すべきである。[21],[22]

そこで本稿の目的は、COVID-19 ワクチン接種後の皮膚反応(特に炎症性皮膚疾患)に関する最新の文献をレビューすることにより、臨床医がこれらの皮膚疾患をよりよく理解し、ワクチンに関連する全ての皮膚症状の広範な概要を把握できるようにすることである。

材料と方法

今回のレビューでは、PubMed、Embase、Cochrane Skin、Google Scholar、EBSCO および MEDLINE のデータベースを用いて文献調査が実施された(2022年9月11日まで)。「COVID-19」、「vaccination」、「vaccine」、「cutaneous」、「side effects」、「adverse events」、「skin symptoms」、「mRNA」、「viral-vector」、「Pfizer/BioNTech」、「BNT162b2」、「Moderna」、「mRNA-1273」、「AstraZeneca」、「AZD1222」、「Johnson&Johnson」、「Ad26.COV2.S」、「atopic dermatitis」、「psoriasis」、「lichen planus」、「bullous disease」、「tempositis us」、「pemphigoids」、「hidradenitis suppurativa」、「urticaria」、「rash」、「ヘルペス」、「ばら色糝糠疹」、「しもやけ」、「白斑」、「erythematous eruption」、「alopecia」、「local-injection」、「angioedema」、「eczema」をキーワードとして調査を実施した。分析された論文には、メタアナリシス、レビュー、編集者への手紙、実生活での研究、症例シリーズおよび報告が含まれた。最も関連性の高い原稿が検討された。BNT162b2,mRNA-1273,AZD1222 および Ad26.COV2.S を用いた COVID-19 ワクチン接種(1回目と2回目の両方)後の皮膚反応に関する情報が得られた研究を選択した。他のワクチンの接種後に生じた皮膚反応や追加免疫後の皮膚反応は除外された。臨床試験で報告された皮膚反応に関する論文や症例が限られている論文は除外された。局所注射部位反応(即時型と遅延型の両方)、発疹または特定不能の皮疹、皮膚ヒアルロン酸充填剤に対する遅延型炎症反応を報告した文献は検討されなかった。また、皮膚反応を引き起こすワクチンが特定されていない論文は除外された。そこで本研究では、収集した論文のテキストと抄録を再検討することによって研究内容を洗練させた。参考文献も再検討され、見逃していた可能性のある記事が含まれた。英語の原稿のみが検討された。本稿は過去に実施された研究に基づくものであり、著者らが実施したヒトまたは動物を対象とした研究を含むものではない。対象とした試験の詳細を表1に示す。

表 1

COVID-19 ワクチン接種後にみられる主な皮膚反応

Cutaneous Reaction	Cases	Authors and Number of Cases	Overall Reported Cases by Vaccines
New-onset psoriasis	17	Tran et al ¹²³ (3), Ouni et al ¹²⁴ (2), Nagrani et al ¹²⁵ (1), Song et al ¹²⁶ (1), Frioui et al ¹²⁷ (1), Cortonesi et al ¹²⁸ (1), Lehmann et al ¹²⁹ (1), Elamin et al ¹³⁰ (1), Wei et al ¹³¹ (1), Lamberti et al ¹³² (1), Romagnuolo et al ¹³³ (1), Ruggiero et al ¹³⁴ (1), Ricardo et al ¹³⁵ (1), Pesqué et al ¹³⁶ (1).	BNT162b2: 10 mRNA-1273: 3 AZD1222: 3 Ad26.CO2: 1
Flare of psoriasis	81	Huang et al ¹³⁷ (15), Sotiriou et al ¹³⁸ (14), Koumaki et al ¹³⁹ (12), Megna et al ¹⁴⁰ (11), Wei et al ¹⁴¹ (6), Ruggiero et al ¹⁴² (4), Durmaz et al ¹⁴³ (2), Tran et al ¹⁴⁴ (2), Piccolo et al ¹⁴⁵ (2), Bostan et al ¹⁴⁶ (1), Nagrani et al ¹⁴⁷ (1), Pavia et al ¹⁴⁸ (1), Durmus et al ¹⁴⁹ (1), Fang et al ¹⁵⁰ (1), Krajewski et al ¹⁵¹ (1), Trepanowski et al ¹⁵² (1), Mieczkowska et al ¹⁵³ (1), Lopez et al ¹⁵⁴ (1), Perma et al ¹⁵⁵ (1), Tsunoda et al ¹⁵⁶ (1), Nia et al ¹⁵⁷ (1), Pesqué et al ¹⁵⁸ (1).	BNT162b2: 43 mRNA-1273: 17 AZD1222: 21 Ad26.CO2: 0
Cutaneous lichen planus	16	New-onset: Merhy et al ¹⁵⁹ (1), Camela et al ¹⁶⁰ (1), Kato et al ¹⁶¹ (1), Diab et al ¹⁶² (1), Zagaria et al ¹⁶³ (1), Awada et al ¹⁶⁴ (1), Picone et al ¹⁶⁵ (1), Hlaca et al ¹⁶⁶ (1), Zengarini et al ¹⁶⁷ (1), Masseran et al ¹⁶⁸ (1), Gamonal et al ¹⁶⁹ (1), Ahravashdeh et al ¹⁷⁰ (1), Shakoei et al ¹⁷¹ (1). Flare: Hiltun et al ¹⁷² (1), Herzum et al ¹⁷³ (1), Hlaca et al ¹⁷⁴ (1).	BNT162b2: 8 mRNA-1273: 1 AZD1222: 7 Ad26.CO2: 0
New-onset atopic dermatitis/eczema	7	Rerknimitr et al ¹⁷⁵ (3), Holmes et al ¹⁷⁶ (1), Leasure et al ¹⁷⁷ (1), Bekkali et al ¹⁷⁸ (1), Larson et al ¹⁷⁹ (1).	BNT162b2: 3 mRNA-1273: 1 AZD1222: 3 Ad26.CO2: 0
Flare of atopic dermatitis/eczema	14	Potestio et al ¹⁸⁰ (11), Leasure et al ¹⁸¹ (1), Niebel et al ¹⁸² (1), Larson et al ¹⁸³ (1).	BNT162b2: 8 mRNA-1273: 3 AZD1222: 3 Ad26.CO2: 0
Hidradenitis suppurativa	6	Martora et al ¹⁸⁴ (5), Alexander et al ¹⁸⁵ (1).	BNT162b2: 2 mRNA-1273: 3 AZD1222: 1 Ad26.CO2: 0
Urticaria	98	Magen et al ¹⁸⁶ (39), Potestio et al ¹⁸⁷ (15), Rerknimitr et al ¹⁸⁸ (12), Riad et al ¹⁸⁹ (10), Sidlow et al ¹⁹⁰ (3), Peigottu et al ¹⁹¹ (2), Niebel et al ¹⁹² (2), McMahon et al ¹⁹³ (2), Holmes et al ¹⁹⁴ (2), Fernandez-Nieto et al ¹⁹⁵ (2), Bianchi et al ¹⁹⁶ (2), Corbeddu et al ¹⁹⁷ (2), Baraldi et al ¹⁹⁸ (1), Choi et al ¹⁹⁹ (1), Patruno et al ²⁰⁰ (1), Buriando et al ²⁰¹ (1), Thomas et al ²⁰² (1).	BNT162b2: 71 mRNA-1273: 12 AZD1222: 15 Ad26.CO2: 0
Alopecia areata	24	Scollan et al ²⁰³ (9), Babadjouni et al ²⁰⁴ (3), Rossi et al ²⁰⁵ (3), Chen et al ²⁰⁶ (2), Abdalla et al ²⁰⁷ (1), Gamonal et al ²⁰⁸ (1), Ho et al ²⁰⁹ (1), Su et al ²¹⁰ (1), Gallo et al ²¹¹ (1), May Lee et al ²¹² (1), Essam et al ²¹³ (1).	BNT162b2: 14 mRNA-1273: 4 AZD1222: 6 Ad26.CO2: 0
Pemphigus vulgaris	26	Martora et al ²¹⁴ (7), Zou et al ²¹⁵ (3), Gui et al ²¹⁶ (2), Rouatou et al ²¹⁷ (2), Aryanian et al ²¹⁸ (1), Koutlas et al ²¹⁹ (1), Knecht et al ²²⁰ (1), Ong et al ²²¹ (1), Yildirim et al ²²² (1), Singh et al ²²³ (1), Norimatsu et al ²²⁴ (1), Agharbi et al ²²⁵ (1), Almási-Nasrabadi et al ²²⁶ (1), Corrá et al ²²⁷ (1), Solimani et al ²²⁸ (1).	BNT162b2: 15 mRNA-1273: 6 AZD1222: 5 Ad26.CO2: 0
Pemphigoids	40	Maronese et al ²²⁹ (21), Maronese et al ²³⁰ (3), Hali et al ²³¹ (3), Gambichler et al ²³² (2), Shanshal et al ²³³ (1), Desai et al ²³⁴ (1), Fu et al ²³⁵ (1), Alshammari et al ²³⁶ (2), Hung et al ²³⁷ (1), Pauluzzi et al ²³⁸ (1), Dell'Antonia et al ²³⁹ (1), Pérez-López et al ²⁴⁰ (1), Agharbi et al ²⁴¹ (1), Young et al ²⁴² (1), Nakamura et al ²⁴³ (1).	BNT162b2: 29 mRNA-1273: 5 AZD1222: 6 Ad26.CO2: 0
Morphea	9	Paolino et al ²⁴⁴ (4), Antofanzas et al ²⁴⁵ (2), Oh et al ²⁴⁶ (1), Metin et al ²⁴⁷ (1), Aryanian et al ²⁴⁸ (1).	BNT162b2: 6 mRNA-1273: 1 AZD1222: 2 Ad26.CO2: 0

別のウィンドウで開く

略語: BNT162b2, Pfizer Oxford 162 b 2; mRNA-1273, Moderna mRNA-1273; AZD1222, AstraZeneca-Oxford AZD1222; Ad26.CO2, Johnson&Johnson Ad26.CO2.S.mRNABNT

結果

文献検索により計 1922 件の報告が最初に発見された。その後、523 件の論文と 71 件の原稿が、それぞれ重複であることと英語以外の言語であることから除外された。その後、選択基準および除外基準に従って文献レビューが洗練された。最後に、今回のレビューでは 456 人の患者を対象とした合計 183 の論文が選択された。主な所見を表 1 に要約する。

炎症性皮膚疾患の新規発症または増悪が数例報告されており(図 1),これらの反応を引き起こしたワクチンの種類も検討されている(図 2)。乾癬に関しては、COVID-19 ワクチン接種後の乾癬に関する報告が計 98 件報告された[23-54]。特に、既存疾患の再燃が 81 例、新規発症が 17 例で報告された。さらに、乾癬のいくつかの表現型が報告されており、プラークの亜型が最も多くみられた。注目すべきことに、生物学的製剤による治療が乾癬の管理における有効性と安全性の点で優れた結果を示したとしても[55-58],リスクをゼロにすることなく、ワクチン接種後に疾患が悪化する可能性を低下させるようである。さらに、生物製剤による治療を受けている患者における COVID-19 ワクチンの有効性についても議論がある。[59][,][60]

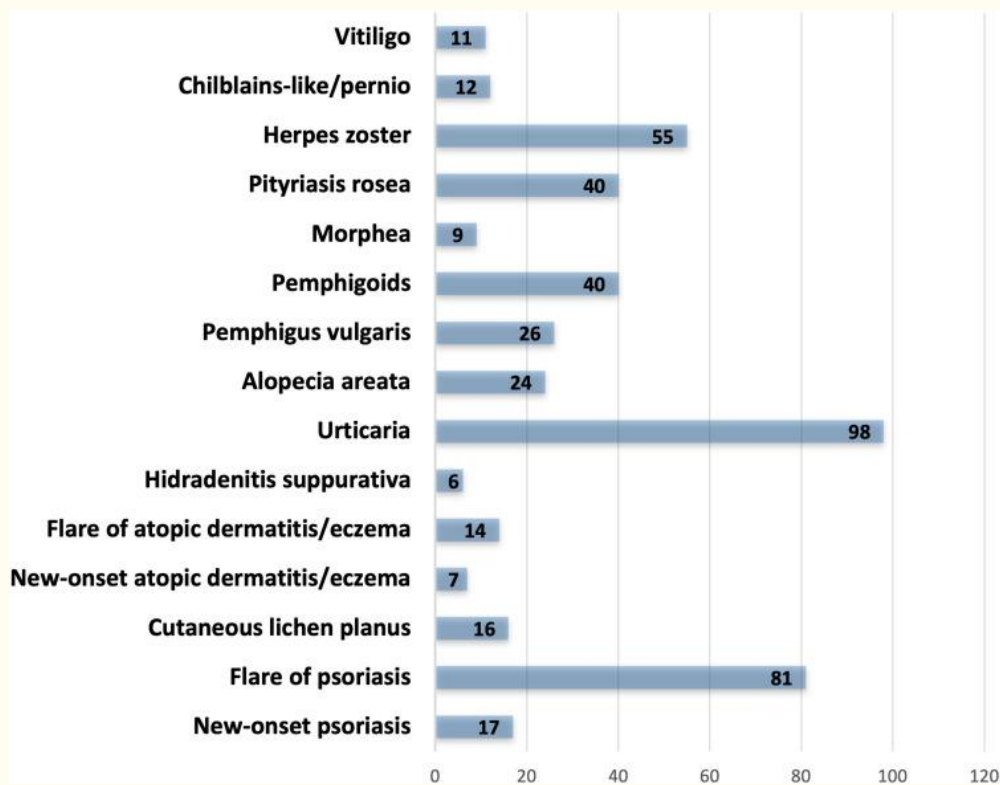


図 1

調査された皮膚反応と症例数

注:投与されたワクチンの数が異なることで、mRNA ベースのワクチンとウイルスベクターベースのワクチンで皮膚反応の数が異なることを説明できる可能性がある。

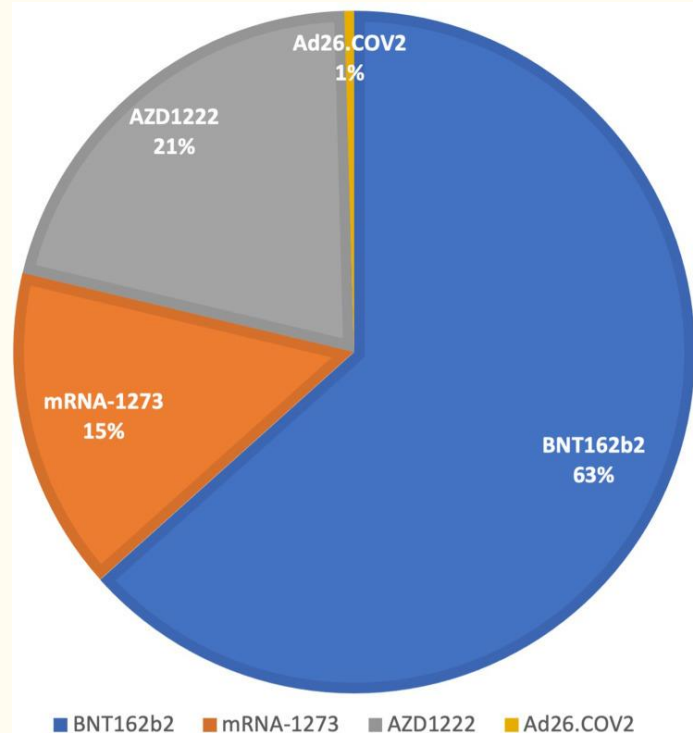


図 2

調査対象となったワクチンのうち、皮膚反応を引き起こしたものの割合。

略語: BNT162b2, Pfizer Oxford 162 b 2; mRNA-1273, Moderna mRNA-1273; AZD1222, AstraZeneca-Oxford AZD1222; Ad26.COV2, Johnson&Johnson Ad26.COV2.S.mRNABNT

扁平苔癬は、慢性、炎症性、自己免疫疾患であり、病因は不明である。[61]これまでに、皮膚扁平苔癬の新規発症例が 13 例、皮膚扁平苔癬の増悪例が 3 例報告されている。[62-76]乾癬と同様に、アトピー性皮膚炎や湿疹の新規発症例と再燃例も報告されている(それぞれ 7 例と 14 例)。[77-83]しかし、臨床表現型との間に明確な相関は認められていない。[84]さらに、デュピルマブによる治療を行っても、その有効性と安全が広く実証されているとしても、病気の再燃の可能性を防ぐことはできないようである。[85][,][86]ヤヌスキナーゼ阻害薬による治療を受けている患者でアトピー性皮膚炎が悪化したというデータはない。[87][,][88]化膿性汗腺炎については、現在のところ新規発症例(n=1)[89]または増悪例(n=5)はほとんどない。[90]しかしながら、化膿性汗腺炎の患者では、COVID-19 ワクチンに関連した有害転帰のリスクは高くない。[91],[92]

蕁麻疹は、COVID-19 ワクチン接種後に報告される皮膚反応のうち、「Covid-arm」などの局所注射部位反応に次いで 2 番目に多くみられる。[93]世界的に、COVID-19 ワクチン接種後に発生した有痛性発疹の症例 98 例が我々のレビューで収集されており、[77][,][78][,][83][,][94-107]オマリズマブによる治療中にも発生していた。[108]

COVID-19 ワクチン接種後に円形脱毛症が発生したとの報告がある[109-119]。Nguyen らは、円形脱毛症を発症した患者(39 人)と疾患が悪化した患者(38 人)77 人を対象とした最大規模の研究を報告したが、残念ながら、円形脱毛症の発症とワクチンの種類を相関させることは不可能である[120]。

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水疱性疾患に関しては、COVID-19 ワクチン接種後に合計 26 例の尋常性天疱瘡が報告されており[121-135]、治療および管理にいくつかの意味がある[136]。さらに、40 例の pemphigoids が報告されている[137-151]。

COVID-19 ワクチン接種後に発生したその他の皮膚疾患としては、モルヘア、【152-157】ばら色靴擦疹、【158-177】帯状ヘルペス、【178-187】しもやけ、【188-197】および vitiligo【198-208】がそれぞれ 9,40,55,12,11 例報告されている。

最後に、データは限られているものの、他にもいくつかの皮膚疾患が報告されている。その中でも特に強調したいのは、毛孔性紅色靴擦疹、白血球破砕性血管炎、麻疹様発疹、蕁状皮斑、固定薬疹、遠心性環状紅斑、環状肉芽腫、筋膜の好中球性発疹、環状発疹、ヘノッホ-シェーンライン紫斑病、皮膚筋炎、ウイルス性疣贅の退縮、レイノー現象、発疹性血管腫症、線状苔癬、急性痘瘡状苔癬状靴擦疹、ローウェル症候群、先端チアノーゼなどであり、COVID-19 ワクチン接種によって様々なタイプの皮膚疾患が誘発される可能性が示唆されている。【209-221】しかしながら、これらのほとんどは 1~2 例の症例報告に限られている。

討論

COVID-19 パンデミックは日々の臨床業務に革命をもたらした。実際、感染拡大を抑えるためにいくつかの戦略が採用された。[222]皮膚科医は、いくつかの病態(特に皮膚悪性腫瘍)の発見と治療の減少を避けるために、臨床業務を変更する必要があった。[223-227]その中でも遠隔皮膚科医は、医師が患者の皮膚疾患を継続的に支援することを可能にし、治療アドヒアランスと臨床アウトカムの面で優れた結果をもたらした。[228-230]ワクチン接種キャンペーンは、安全と有効性の面で優れた結果を示す最も重要な戦略である。[231][232]実際に、COVID-19 パンデミックの重症度と影響を軽減することができた。しかしながら、COVID-19 ワクチン接種によって誘発または増悪したいくつかの皮膚疾患が報告されている。幸いなことに、ほとんどの症例が軽症で自然治癒し、治療を必要としなかった。我々のレビューでは、乾癬、アトピー性皮膚炎、水疱性疾患など、COVID-19 ワクチン接種後にみられたいくつかの皮膚反応に焦点を当てた。具体的に調査されたわけではないが、ワクチン関連の皮膚有害事象として最も多く報告されたのは局所注射部位反応であった。注目すべきことに、mRNA ベースのワクチンとウイルスベクターベースのワクチンの両方で接種後に皮膚反応が報告されており、皮膚反応の基礎にある発病機序がワクチンの作用機序自体と直接関連していないことが示唆されている[99]。確かに、「リスクのある」被験者を特定して予防策を講じるためには、皮膚反応と COVID-19 ワクチン接種を関連付ける発病機序を解明するためのさらなる研究が必要である。

注目すべきことに、我々の研究でレビューした論文の中で、皮膚反応の診断はほとんどの症例で病理組織学的検査によって確認された。しかし、組織学的報告を評価したところ、共通の免疫プロセスは認められなかった。

全体として、mRNA ワクチン、特に BNT162b2 が皮膚反応と関連する頻度が最も高いようである。しかし、mRNA ワクチンは以前は世界中で認可され、生産され、投与されていた。したがって、投与されたワクチンの数が異なることで、mRNA ベースのワクチンとウイルスベクターベースのワクチンで皮膚反応の数が異なる理由を説明で

きる可能性がある。さらなる疫学的研究により、ワクチン接種後の皮膚反応の割合が2種類のワクチンのいずれかで有意に高いかどうか明らかにされ、臨床的な意味がある。

要約すると、今回のレビューでは、COVID-19 ワクチン接種後に増悪または発症したいくつかの皮膚疾患について分析を行った。しかし、ワクチン接種と皮膚反応の発現との時間的関連性は偶発的なものである可能性がある。

ワクチン接種の用量に関しては、1回目と2回目の両方で皮膚反応が報告された。さらに、同じ患者で両用量の投与後に皮膚反応が生じたことも報告されている。我々の意見では、臨床医は追加免疫後の皮膚反応にも備えておくべきである。【233】

長所と限界

我々のレビューの主な強みは、文献調査中に系統的な方法を用いたことと、分析された記事や皮膚反応の数が多かったことである。主な限界について考察すべきである。第一に、EMAによって承認された4つのワクチンのみが検討されている。さらに、登録ベースの研究を報告したいくつかの論文では、ワクチンの種類と皮膚反応との間に直接的な相関は認められなかった。最後に、COVID-19 ワクチン接種後に発生する皮膚症状は通常軽度であり、患者は医療機関を受診しない。

8

結論

ワクチン接種プログラムの世界的な進歩に伴い、いくつかの皮膚反応が報告されている。幸いなことに、投与されたワクチンの数と比較すると、これらの有害事象の割合は極めて低い。我々の意見では、COVID-19 ワクチン接種後に他の皮膚反応が報告されると思われる。さらに、ワクチン接種と皮膚反応を結びつける病原的機序を解明すべきである。臨床医は、ワクチンにより誘発された皮膚症状を迅速に認識し、他の臨床疾患と鑑別するために、ワクチン接種後に新たに発症したいくつかの皮膚疾患が増悪する可能性に留意すべきである。確かに、ワクチン接種を控えさせるべきではない。

情報開示

著者らはこの研究に利益相反がないことを報告している。

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