

Editorial

Recent Advances in Inflammatory Skin Diseases: Future Research on Viral Reactivations and Vaccine Improvement

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In recent decades, the knowledge on the pathogenesis, immune mechanisms, and molecular signaling pathway underlying inflammatory skin diseases has substantially improved, along with the management of such diseases. The use of antibodies neutralizing disease-associated cytokines and small molecules (such as the Janus kinase [JAK] inhibitors) targeting the intracellular pathways of cytokine production and transducing cytokine-mediated signals involved in the inflammatory process, is widely employed both in common chronic cutaneous diseases (psoriasis, atopic dermatitis) [1–4] and in rare dermatosis, like pyoderma gangrenosum [5]. Monoclonal antibodies may possibly offer therapeutic potential in treating chronic wounds (such as pyoderma gangrenosum, ulcerated necrobiosis lipoidica, hidradenitis suppurativa, and other atypical wounds) recalcitrant to standard therapies. However, the knowledge on their role is currently limited as well as their use as therapeutic options in vulnerable patients, like pregnant and breastfeeding women [6] and patients with infectious or neoplastic comorbidities [7,8].

Aiming to fill these knowledge gaps, the Special Issue "Recent Advances in Inflammatory and Infectious Skin Diseases" of the *Journal of Clinical Medicine* concerns a variety of topics in the field of inflammatory skin diseases describing the clinico-pathological findings of rare cutaneous diseases that occur in conditions of fragility such as pregnancy, postpartum, and hematoproliferative disorders (Table 1; Contributions 1 and 2).

The successful treatment modalities of pyoderma gangrenosum during pregnancy and lactation have been extensively reviewed in addition to the role of monoclonal antibodies in managing chronic wounds from 16 different etiologies (Contribution 3). In addition, the Special Issue explored some specific aspects of atopic dermatitis treatment: the occurrence of adverse events in patients undergoing anti-interleukin (IL)-4 and IL-13 drugs and the alternative therapeutic options (Contribution 4) as well as the role of the caregiver and the rising issue of corticophobia among parents of children with atopic dermatitis (Contribution 5).

The studies included in this Special Issue underscore the importance of the multidisciplinary management of the chronic inflammatory skin diseases. Interdisciplinary and multi-professional team care, involving dermatologists, gynecologists, oncologists, hematologists, ophthalmologists, and other specialists, is crucial to comprehensively manage conditions refractory to standard therapies, fragile patients, and adverse events [9].



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Table 1. Summary of the papers published in the Special Issue “Recent Advances in Inflammatory and Infectious Skin Diseases” of *Journal of Clinical Medicine*.

Contribution Number	Reference	Type of Publication	Number of Authors/Affiliation	Location of Authors' Affiliation
1	Matasariu D.R. et al. Pyoderma Gangrenosum, a Challenging Postpartum Diagnosis-Case Report and Literature Review. <i>J. Clin. Med.</i> 2024 Jun 22;13(13):3653. doi:10.3390/jcm13133653.	Review	10/6	Romania
2	Michelerio A. et al. Eosinophilic Dermatitis of Hematologic Malignancy: Emerging Evidence for the Role of Insect Bites-A Retrospective Clinico-Pathological Study of 35 Cases. <i>J. Clin. Med.</i> 2024 May 16;13(10):2935. doi:10.3390/jcm13102935.	Article	6/5	Italy
3	Manzo Margiotta F. et al. Monoclonal Antibodies in the Management of Inflammation in Wound Healing: An Updated Literature Review. <i>J. Clin. Med.</i> 2024 Jul 12;13(14):4089. doi:10.3390/jcm13144089.	Review	9/3	Italy
4	Paganini C. et al. Impact of Upadacitinib on Atopic Keratoconjunctivitis Exacerbated by Dupilumab Treatment in Atopic Dermatitis Patients: A Prospective Dermatological and Ophthalmological Clinical Evaluation in Common Clinical Practice. <i>J. Clin. Med.</i> 2024 Jun 28;13(13):3818. doi:10.3390/jcm13133818.	Article	8/3	Italy
5	Herzum A. et al. Corticophobia among Parents of Children with Atopic Dermatitis: Assessing Major and Minor Risk Factors for High TOPICOP Scores. <i>J. Clin. Med.</i> 2023 Oct 27;12(21):6813. doi:10.3390/jcm12216813.	Article	5/1	Italy

However, open questions on the knowledge of the comorbidities sometimes associated with inflammatory skin diseases already exist, and future research should be focused on the infectious complications that may occur with the use of immunosuppressive agents. Indeed, in cutaneous inflammatory diseases, the immune system may be compromised not only by the chronic inflammation involved in the pathogenesis of the diseases but also by the immunosuppressive treatments [10].

For instance, atopic dermatitis is characterized by epidermal barrier defects, decreased antimicrobial peptide expression, and altered innate and adaptive immunity in the setting of T-helper (Th) 2-skewed inflammation, which can increase susceptibility to infections [11]. Indeed, the administration of immunosuppressive therapies in patients with atopic dermatitis and with other skin immune-mediated diseases further increases the risk of acquiring infections and/or the risk of reactivation of latent viruses. The awakening of viruses from latency can cause different cutaneous manifestations, ranging from self-limiting exanthematous diseases, like pityriasis rosea due to the endogenous systemic reactivation of human herpesvirus (HHV)-6 and HHV-7 [12], to more painful and disabling conditions like herpes zoster caused by the reactivation of Varicella Zoster virus (VZV) [12] or erythema nodosum and Stevens–Johnson syndrome associated with acute Epstein–Barr virus infection [13].

The systemic reactivation of herpesviruses is a well-known, dreaded complication in immunocompromised patients receiving hematopoietic stem cell transplant (HCT). After an HCT and myeloablative conditioning regimen, HHV-6 reactivates in 30–70% of patients between 2 and 4 weeks, and it could be an important cause of fever, hepatitis, encephalitis

or central nervous system dysfunction, bone marrow suppression, acute graft-versus-host disease, pneumonitis, nephrotoxicity, rash, and mortality in a small proportion of patients [14–16]. Occasionally, HHV-6 reactivation may also cause delayed engraftment and allograft dysfunction [17–19].

Furthermore, EBV and Cytomegalovirus (CMV) reactivation has been associated, mainly under immunosuppression, with lymphoproliferative disorders, malignancies (B-cell lymphomas and nasopharyngeal carcinoma), pneumonia, ulcers, and fever, respectively [20–22].

In contrast to HCT patients who are routinely monitored for herpesvirus plasma load to precociously detect viral reactivation and related complications [10], the patients suffering from chronic skin diseases under immunosuppressive treatment have not yet been studied in detail from this point of view.

A recent interesting study screened 206 patients suffering from chronic skin diseases (psoriasis, atopic dermatitis, urticaria, bullous pemphigoid, pyoderma gangrenosum, and others) to investigate whether the subclinical reactivation of EBV and CMV may have clinical relevance. The authors found that patients under immunosuppressive therapy with treatment-refractory disease showed the reactivation of EBV and CMV infection, differently from non-immunocompromised patients [10]. Immune dysfunction in these patients is also demonstrated by the fact that T cells isolated from lesional skin had an increased proliferation (up to 14-fold) with the production of T helper type 1 and type 17 cytokines upon stimulation with viral proteins, providing evidence for possible aggravation of the underlying skin diseases by the viral infections. Moreover, immunocompromised patients with treatment-refractory disease and reactivation of CMV showed improvement of skin lesions via specific antiviral treatment (ganciclovir) [10].

These data emphasize the usefulness of investigating the viral reactivations in cases of therapy-refractory chronic skin diseases. Virologic investigations could be expanded to include not only EBV and CMV, as described in the study by Speth P. et al. [10], but also herpes simplex virus 1 and 2, varicella zoster virus, HHV-6, HHV-7, and HHV-8. Indeed, early the detection of viral reactivation could reduce morbidity and health care costs [10].

Future research should also emphasize the importance of preventing infections and viral reactivations in immunosuppressed dermatologic patients promoting the available vaccinations based on the most updated version of the National Vaccine Prevention Plan [23]. It is noteworthy to mention that a recent survey conducted among Italian oncologists highlights the urgent issues of training oncologists in vaccine-preventable diseases and vaccine awareness and the necessity to increase a network of multidisciplinary collaborations [24], possibly involving, among others, dermato-venereologists.

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References

1. Welsch, K.; Holstein, J.; Laurence, A.; Ghoreschi, K. Targeting JAK/STAT signalling in inflammatory skin diseases with small molecule inhibitors. *Eur. J. Immunol.* **2017**, *47*, 1096–1107. [[CrossRef](#)] [[PubMed](#)]
2. Sugumaran, D.; Yong, A.C.H.; Stanslas, J. Advances in psoriasis research: From pathogenesis to therapeutics. *Life Sci.* **2024**, *355*, 122991. [[CrossRef](#)] [[PubMed](#)]
3. Ramakrishna, C.; Mason, A.; Edwards, C.J. Tyrosine kinase 2 inhibitors in autoimmune diseases. *Autoimmun. Rev.* **2024**, *28*, 103649. [[CrossRef](#)] [[PubMed](#)]
4. Martora, F.; Tommasino, N.; Brescia, C.; Potestio, L.; Battista, T.; Megna, M. Hidradenitis Suppurativa in Elderly Patients: Clinical and Therapeutical Outcomes-A Review of the Literature. *Medicina* **2024**, *60*, 1465. [[CrossRef](#)] [[PubMed](#)]
5. Manzo Margiotta, F.; Michelucci, A.; Fidanzi, C.; Granieri, G.; Salvia, G.; Bevilacqua, M.; Janowska, A.; Dini, V.; Romanelli, M. Monoclonal Antibodies in the Management of Inflammation in Wound Healing: An Updated Literature Review. *J. Clin. Med.* **2024**, *13*, 4089. [[CrossRef](#)]

6. Wanberg, L.J.; Gorman, B.G.; Theis-Mahon, N.; Goldfarb, N.; Alavi, A. Management of pyoderma gangrenosum during pregnancy and breastfeeding: A systematic review. *Int. J. Dermatol.* **2024**. Epub ahead of print. [[CrossRef](#)] [[PubMed](#)]
7. Megna, M.; Lauletta, G.; Tommasino, N.; Salsano, A.; Battista, T.; Ruggiero, A.; Martora, F.; Potestio, L. Management of Psoriasis Patients with Serious Infectious Diseases. *Adv. Ther.* **2024**, *41*, 2099–2111. [[CrossRef](#)]
8. Lambert, J.L.W.; Segaert, S.; Ghislain, P.D.; Hillary, T.; Nikkels, A.; Willaert, F.; Lambert, J.; Speeckaert, R. Practical recommendations for systemic treatment in psoriasis in case of coexisting inflammatory, neurologic, infectious or malignant disorders (BETA-PSO: Belgian Evidence-based Treatment Advice in Psoriasis; part 2). *J. Eur. Acad. Dermatol. Venereol.* **2020**, *34*, 1914–1923. [[CrossRef](#)]
9. Amerio, P.; Ferrucci, S.M.; Galluzzo, M.; Napolitano, M.; Narcisi, A.; Levi, A.; Di Fino, S.; Palladino, C.; Patruno, C.; Rossi, M.A. Multidisciplinary Approach Is Beneficial in Atopic Dermatitis. *Dermatol. Ther.* **2024**, *14*, 1443–1455. [[CrossRef](#)]
10. Speth, P.; Jargosch, M.; Seiringer, P.; Schwamborn, K.; Bauer, T.; Scheerer, C.; Protzer, U.; Schmidt-Weber, C.; Biedermann, T.; Eyerich, S.; et al. Immunocompromised Patients with Therapy-Refractory Chronic Skin Diseases Show Reactivation of Latent Epstein-Barr Virus and Cytomegalovirus Infection. *J. Invest. Dermatol.* **2022**, *142*, 549–558.e6. [[CrossRef](#)]
11. Wan, J.; Shin, D.B.; Syed, M.N.; Abuabara, K.; Lemeshow, A.R.; Gelfand, J.M. Risk of herpesvirus, serious and opportunistic infections in atopic dermatitis: A population-based cohort study. *Br. J. Dermatol.* **2022**, *186*, 664–672. [[CrossRef](#)] [[PubMed](#)]
12. Drago, F.; Broccolo, F.; Ciccarese, G. Pityriasis rosea, pityriasis rosea-like eruptions, and herpes zoster in the setting of COVID-19 and COVID-19 vaccination. *Clin. Dermatol.* **2022**, *40*, 586–590. [[CrossRef](#)]
13. Ciccarese, G.; Trave, I.; Herzum, A.; Parodi, A.; Drago, F. Dermatological manifestations of Epstein-Barr virus systemic infection: A case report and literature review. *Int. J. Dermatol.* **2020**, *59*, 1202–1209. [[CrossRef](#)] [[PubMed](#)]
14. Yamane, A.; Mori, T.; Suzuki, S.; Mihara, A.; Yamazaki, R.; Aisa, Y.; Nakazato, T.; Shimizu, T.; Ikeda, Y.; Okamoto, S. Risk factors for developing human herpesvirus 6 (HHV 6) reactivation after allogeneic hematopoietic stem cell transplantation and its association with central nervous system disorders. *Biol. Blood Marrow Transplant.* **2007**, *13*, 100–106. [[CrossRef](#)] [[PubMed](#)]
15. Zerr, D.M.; Fann, J.R.; Breiger, D.; Boeckh, M.; Adler, A.L.; Xie, H.; Delaney, C.; Huang, M.L.; Corey, L.; Leisenring, W.M. HHV-6 reactivation and its effect on delirium and cognitive functioning in hematopoietic cell transplantation recipients. *Blood* **2012**, *117*, 5243–5249. [[CrossRef](#)] [[PubMed](#)]
16. Flamand, L.; Lautenschlager, I.; Krueger, G.; Ablashi, D. *Human Herpesviruses HHV-6A, HHV-6B, and HHV-7 Diagnosis and Clinical Management*, 3rd ed.; Elsevier: Amsterdam, The Netherlands, 2014; pp. 81–92.
17. Kampouri, E.; Handley, G.; Hill, J.A. Human Herpes Virus-6 (HHV-6) Reactivation after Hematopoietic Cell Transplant and Chimeric Antigen Receptor (CAR)- T Cell Therapy: A Shifting Landscape. *Viruses* **2024**, *16*, 498. [[CrossRef](#)] [[PubMed](#)]
18. Kampouri, E.; Zamora, D.; Kiem, E.S.; Liu, W.; Ibrahimi, S.; Blazevic, R.L.; Lovas, E.A.; Kimball, L.E.; Huang, M.L.; Jerome, K.R.; et al. Human herpesvirus-6 reactivation and disease after allogeneic haematopoietic cell transplantation in the era of letermovir for cytomegalovirus prophylaxis. *Clin. Microbiol. Infect.* **2023**, *29*, 1450.e1–1450.e7. [[CrossRef](#)]
19. Sedlak, R.H.; Hill, J.A.; Nguyen, T.; Cho, M.; Levin, G.; Cook, L.; Huang, M.L.; Flamand, L.; Zerr, D.M.; Boeckh, M.; et al. Detection of Human Herpesvirus 6B (HHV-6B) Reactivation in Hematopoietic Cell Transplant Recipients with Inherited Chromosomally Integrated HHV-6A by Droplet Digital PCR. *J. Clin. Microbiol.* **2016**, *54*, 1223–1227. [[CrossRef](#)]
20. Andrei, G.; Trompet, E.; Snoeck, R. Novel therapeutics for Epstein-Barr virus. *Molecules* **2019**, *24*, 997. [[CrossRef](#)] [[PubMed](#)]
21. Sanguenza-Acosta, M.; Sandoval-Romero, E. Epstein-Barr virus and skin. *An. Bras. Dermatol.* **2018**, *93*, 786–799. [[CrossRef](#)]
22. Cook, C.H. Cytomegalovirus reactivation in “immunocompetent” patients: A call for scientific prophylaxis. *J. Infect. Dis.* **2007**, *196*, 1273–1275. [[CrossRef](#)] [[PubMed](#)]
23. Ciccarese, G.; Drago, F.; Herzum, A.; Atzori, L.; Dattola, A.; Galluzzo, M.; Maronese, C.; Patrizi, A.; Piraccini, B.M.; Recalcati, S.; et al. Anti-Herpes zoster vaccination in patients with dermatologic diseases: A position statement from the Italian SDeMaST group of sexually transmitted, infectious and tropical diseases. *Ital. J. Dermatol. Venerol.* **2024**, *159*, 375–379. [[CrossRef](#)] [[PubMed](#)]
24. Lasagna, A.; Brunello, A.; Silvestris, N.; Pedrazzoli, P.; Di Maio, M.; Cinieri, S. Italian oncologists and vaccinations against infectious diseases: Results of a survey of the Italian Association of Medical Oncology. *Tumori* **2024**, *110*, 60–68. [[CrossRef](#)] [[PubMed](#)]

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