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Wybrane aspekty kliniczne i psychospołeczne chorych na przewlekły wyprysk rąk

ROZPRAWA DOKTORSKA

Cykl publikacji powiązanych tematycznie

PROMOTOR:

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Pragnę złożyć najszczersze podziękowania mojemu promotorowi,
Panu ***prof. dr. hab. n. med. dr. h.c. Jackowi Szepietowskiemu****,*
Kierownikowi Katedry i Kliniki Dermatologii, Wenerologii i Alergologii
Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu za wsparcie,
wyrozumiałość, każdą wartościową uwagę,
nieskończone pokłady cierpliwości
i bezcenną pomoc na wszystkich etapach tworzenia pracy.

Najbliższym

oraz wszystkim Przewodnikom

na mojej dermatologicznej ścieżce.

Spis treści

1. CYKL PRAC STANOWIĄCYCH ROZPRAWĘ DOKTORSKĄ

1. **Zalewski A**, Szepietowski JC. Topical and systemic JAK inhibitors in hand eczema - a narrative review. Expert Rev Clin Immunol. 2023 Apr;19(4):365-373.
   IF = 4,4; **Punkty MEiN = 100**

2. **Zalewski A**, Krajewski PK, Szepietowski JC. Prevalence and Characteristics of Itch and Pain in Patients Suffering from Chronic Hand Eczema. J Clin Med. 2023 Jun 21;12(13):4198.
   IF = 3,9; Punkty MEiN = 140

3. **Zalewski A**, Krajewski PK, Szepietowski JC. Psychosocial Consequences of Hand Eczema-A Prospective Cross-Sectional Study. J Clin Med. 2023 Sep 3;12(17):5741.
   IF = 3,9; Punkty MEiN = 140

Sumaryczny IF: 12,2
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2. WYKAZ SKRÓTÓW

6-ISS	Skala Stygmatyzacji (ang. *6 Item Stigmatization Scale*)
CHE	Przewlekły wyprysk rąk (ang. *chronic hand eczema*)
DLQI	Dermatologiczny Kwestionariusz Oceny Jakości Życia (ang. *Dermatology Life Quality Index*)
DSM-IV	Klasyfikacja Zaburzeń Psychicznych Amerykańskiego Towarzystwa Psychiatrycznego – IV Edycja (ang. *Diagnostic and Statistical Manual of Mental Disorders IV Edition*)
GAD	Zespół Lęku Uogólnionego (ang. *Generalized Anxiety Disorder*)
GAD-7	Kwestionariusz Lęku Uogólnionego GAD-7 (ang. *Generalized Anxiety Disorder-7*)
HADS-M	Szpitalna Skala Lęku i Depresji – Zmodyfikowana (ang. *Hospital Anxiety and Depression Scale - Modified*)
HADS-M (A)	Szpitalna Skala Lęku i Depresji – Zmodyfikowana (Lęk) (ang. *Hospital Anxiety and Depression Scale – Modified (Anxiety)*)
HADS-M (D)	Szpitalna Skala Lęku i Depresji – Zmodyfikowana (Depresja) (ang. *Hospital Anxiety and Depression Scale – Modified (Depression)*)
HECSI	Wskaźnik Nasilenia Wyprysku Rąk (ang. *Hand Eczema Severity Index*)
IGA-CHE	Skala Globalnej Oceny Badacza dla Przewlekłego Wyprysku Rąk (ang. *Investigator Global Assessment for Chronic Hand Eczema*)
JAK	Kinazy janusowe (ang. *Janus activated kinases*)
JAK-STAT	Szlak Sygnałowy Kinazy Janusowe - Transduktor Sygnału i Aktywator Transkrypcji (ang. *Janus kinase - Signal Transducer and Activator of Transcription*)
NRS	Numeryczna Skala Oceny (ang. *Numerical Rating Scale*)
PHQ-9	Kwestionariusz Zdrowia Pacjenta PHQ-9 (ang. *Patient Health Questionnaire-9*)

3. OMÓWIENIE ROZPRAWY DOKTORSKIEJ

3.1. Wstęp

Przewlekły wyprysk rąk (CHE) to jedna z najczęściej występujących w populacji ogólnej dermatoz zapalnych, ze średnią zapadalnością w ciągu roku na poziomie 9,7% i sięgającą aż 20% populacji w skali całego życia. Pomimo stosunkowo wysokiej częstości występowania, brak jest wciąż badań obrazujących tę grupę chorych czy też charakteryzujących świąd i ból w przebiegu CHE. Schorzenie stanowi nie tylko wyzwanie diagnostyczno-terapeutyczne, ale wpływa także znacząco na psychospołeczne aspekty życia pacjentów. Świąd i ból, będące najczęściej zgłaszanymi objawami CHE, sprawiają zarówno fizyczny dyskomfort, jak i stanowią istotny czynnik wpływający na jakość życia pacjentów, która to definiowana jako subiektywna ocena ogólnej sytuacji życiowej jednostki, stała się ważnym wskaźnikiem skuteczności terapii i poziomu dobrostanu pacjentów. Ponadto, związek pomiędzy przewlekłym wypryskiem rąk a zaburzeniami depresyjnymi oraz lękowymi jest przedmiotem coraz bardziej intensywnych badań.

W świetle rosnącego zainteresowania psychosomatycznymi aspektami chorób skóry, analiza wpływu świądu i bólu na stan psychiczny pacjentów staje się nieodzownym krokiem w doskonaleniu holistycznego podejścia do opieki nad chorymi z CHE. Co więcej, identyfikacja mechanizmów tych związków oraz analiza czynników determinujących jakość życia pacjentów może dostarczyć istotnych wskazówek dotyczących optymalizacji terapii, prowadząc do poprawy fizycznego i psychicznego komfortu ich życia. Zrozumienie tych powiązań jest kluczowe nie tylko dla lekarzy dermatologów, ale także dla profesjonalistów zajmujących się zdrowiem psychicznym, mając na celu stworzenie bardziej skutecznych strategii leczenia i wsparcia pacjentów. Interdyscyplinarna perspektywa w zakresie terapii może wpłynąć również na poprawę kondycji psychicznej chorych na CHE.

W ostatnich latach znaczącą rolę w leczeniu CHE odgrywać zaczęły inhibitory kinaz janusowych (JAK), które stanowią nową klasę farmaceutyków opisywanych szeroko jako "leczenie szyte na miarę". Mechanizm ich działania opiera się na blokowaniu sygnalizacji komórkowej przez kinazy janusowe, co ma wpływ na odpowiedź immunologiczną. Analiza skuteczności i bezpieczeństwa stosowania tych leków, potencjalnych działań niepożądanych oraz możliwości rozwoju terapii przy użyciu JAK inhibitorów może stanowić istotny wkład w rozwój nowoczesnych strategii leczenia tej dermatozy. Wprowadzenie inhibitorów kinaz

janusowych do arsenału terapeutycznego otwiera nowe perspektywy dla pacjentów z CHE, podkreślając znaczenie innowacyjnych podejść w dziedzinie dermatologii klinicznej.

3.2. Cel badań i problemy badawcze

Celem niniejszej rozprawy doktorskiej było dokonanie klinicznej charakterystyki populacji pacjentów chorujących na przewlekły wyprysk rąk, ze szczególnym uwzględnieniem dwóch najczęściej występujących jego objawów – świądu i bólu. Ponadto zbadana została jakość życia uczestników badania, ocenione były również potencjalnie występujące w tej grupie zaburzenia depresyjne i lękowe, poczucie stygmatyzacji oraz korelacje i zależności wiążące poszczególne aspekty choroby. Dodatkowym celem pracy była analiza aktualnie dostępnych nowoczesnych metod leczenia wyprysku dłoni w obrębie grupy inhibitorów JAK.

3.3. Cele szczegółowe:

3.3.1. Charakterystyka grupy pacjentów chorujących na przewlekły wyprysk rąk, ze szczególnym uwzględnieniem świądu i bólu.

3.3.2. Ocena obecności i stopnia nasilenia obciążenia psychospołecznego w grupie chorych na przewlekły wyprysk rąk, w tym stopnia stygmatyzacji, ubytku jakości życia oraz zaburzeń depresyjnych i lękowych.

3.3.3. Analiza korelacji pomiędzy stopniem nasilenia choroby, a stopniem nasilenia świądu i bólu oraz stopniem nasilenia świądu i bólu a stopniem nasilenia poczucia stygmatyzacji.

3.3.4. Analiza korelacji pomiędzy stopniem nasilenia choroby, a stopniem pogorszenia jakości życia oraz stopniem ciężkości zaburzeń depresyjnych i lękowych.

3.3.5. Ocena efektywności klinicznej oraz bezpieczeństwa stosowania leków z grupy inhibitorów JAK w populacji pacjentów chorujących na przewlekły wyprysk rąk.

3.4. Materiał i metody

W pierwszym etapie wykonano przegląd piśmiennictwa dotyczący zastosowania inhibitorów JAK w leczeniu przewlekłego wyprysku rąk. Analizie poddane zostały

publikacje z dwóch elektronicznych baz danych z dziedziny medycyny i nauk biologicznych („PubMed", „Scopus"), a także z bazy gromadzącej informacje dotyczące badań klinicznych finansowanych ze środków prywatnych i publicznych przeprowadzonych na całym świecie (clinicaltrials.gov). Wybrane zostały doświadczenia odnoszące się do pacjentów z wypryskiem dłoni. Kolejno wyłoniono badania skupiające się na wykorzystaniu inhibitorów JAK. Do przeglądu włączono sumarycznie 11 takich eksperymentów klinicznych.

Następnie wykonano badanie będące podstawą drugiej i trzeciej publikacji cyklu. Do badania kwalifikowano pacjentów z rozpoznanym na podstawie obrazu klinicznego wypryskiem rąk. Kryteria włączenia obejmowały także: wiek dorosły (≥18 lat) oraz przebieg choroby utrzymujący się powyżej 3 miesięcy, pozwalający na rozpoznanie przewlekłej postaci wyprysku rąk. Z badania wyłączono wszystkich pacjentów ze zmianami skórnymi przypominającymi CHE, bez jednoznacznego rozpoznania lub oczekujących na wynik badania histologicznego. Zgromadzono grupę 100 pacjentów hospitalizowanych w ramach oddziału szpitalnego lub pozostających w opiece poradni dermatologicznej Kliniki Dermatologii, Wenerologii i Alergologii we Wrocławiu w okresie pomiędzy 1 lutego 2022 r. a 31 stycznia 2023 r.

Ocena stopnia nasilenia zmian skórnych dokonywana była przez lekarza przy użyciu dwóch narzędzi: skali globalnej oceny badacza dla przewlekłego wyprysku rąk (IGA-CHE) oraz wskaźnika nasilenia wyprysku rąk (HECSI). Skala IGA-CHE klasyfikuje nasilenie CHE w pięciu kategoriach: "wolny od zmian" (IGA-CHE 0), "prawie wolny od zmian" (IGA-CHE 1), "łagodny" (IGA-CHE 2), "umiarkowany" (IGA-CHE 3) i "ciężki" (IGA-CHE 4). Skala HECSI bierze pod uwagę zarówno rozległość zmian (w skali od 0 do 4), jak i nasilenie objawów takich jak rumień, naciek, obecność zmian pęcherzykowych, pęknięcia naskórka, złuszczanie oraz obrzęk (w skali od 0 do 3). Zmiany ocenia się w pięciu obszarach: opuszki palców, palce (z wyłączeniem opuszków palców), powierzchnie dłoniowe rąk, grzbiety rąk i nadgarstki. Ostateczny wynik HECSI mieści się w zakresie od 0 do 360 punktów, gdzie 360 oznacza najwyższy poziom nasilenia choroby. Aby zakwalifikować pacjentów do grup ciężkości, ustalono następujące wartości odcięcia: brak zmian (0 punktów; HECSI 0), prawie wolny od zmian (1-16 punktów; HECSI 1), stopień umiarkowany (17-37 punktów; HECSI 2), stopień ciężki (38-116 punktów; HECSI 3) i stopień bardzo ciężki (117 punktów lub więcej; HECSI 4).

Przygotowana została autorska ankieta, w której zawarto pytania dotyczące danych demograficznych, czasu trwania choroby, liczby zaostrzeń, dotychczasowej diagnostyki i leczenia oraz predyspozycji atopowych. Dodatkowo zbadano poszczególne cechy kliniczne świądu, takie jak dotknięty obszar (tylko w obrębie zmian skórnych lub w obrębie zmian skórnych i skóry zdrowej). Intensywność świądu i bólu oceniana była za pomocą numerycznej skali oceny (NRS). Wszystkich uczestników badania poproszono o wskazanie nasilenia najcięższego świądu i bólu w ciągu ostatnich 3 dni oraz najcięższego świądu i bólu w całym okresie choroby. W zależności od wyniku nasilenie świądu zostało podzielone na łagodne (1–3 punktów), umiarkowane (4–6 punktów), ciężkie (7–8 punktów) i bardzo ciężkie (≥9 punktów). Do oceny bólu autorzy zdecydowali się przyjąć następujące punkty odcięcia wartości NRS: ≤5 – ból łagodny; >5–7 – ból umiarkowany; >7–10 – ból silny. Pacjentów proszono także o podanie lokalizacji zmian skórnych (tylko dłonie; dłonie i stopy; dłonie, stopy i inne okolice – zmiany rozsiane).

Uczestnicy badania wypełniali dodatkowo zwalidowaną polską wersję Dermatologicznego Kwestionariusza Oceny Jakości Życia (DLQI). DLQI to narzędzie oceniające objawy i doznania, czynności codzienne, aspekty życia związane z czasem wolnym, pracą i szkołą, relacje oraz skutki uboczne leczenia w ciągu ostatnich 7 dni. Ankieta składa się z 10 pozycji, każda oceniana w skali od 0 do 3 punktów (0 – „wcale/nie dotyczy"; 1 – „trochę", 2 – „bardzo" 3 – „bardzo mocno"). Wszystkie indywidualne wyniki są sumowane uzyskując wynik mieszczący się w przedziale 0–30 punktów. Wynik 0–1 wskazuje na brak wpływu, wynik 2–5 punktów oznacza niewielki wpływ, 6–10 punktów oznacza umiarkowany wpływ, 11–20 punktów wskazuje na duży wpływ, a 21–30 punktów - niezwykle duży wpływ choroby na jakość życia pacjenta. Do określenia poziomu stygmatyzacji i jej wpływu na życie chorych wykorzystano skalę stygmatyzacji (6-ISS). Narzędzie to wymaga od pacjentów udzielenia odpowiedzi na 6 pytań, korzystając z jednej z czterech odpowiedzi ocenianych w skali od 0 do 3 punktów („nie", „czasami", „bardzo często" i „zawsze"). Im wyższy wynik, tym większa percepcja stygmatyzacji (w zakresie 0–18 punktów). Grupa przebadana została również pod kątem obecności oraz nasilenia zaburzeń depresyjnych oraz lękowych. Wykorzystany został kwestionariusz zdrowia pacjenta PHQ-9 będący dziewięcioelementowym narzędziem, służącym do wykrywania depresji. Pacjenci mają za zadanie ocenę częstości występowania każdego z dziewięciu głównych kryteriów rozpoznania depresji (na podstawie Podręcznika diagnostycznego i statystycznego zaburzeń

psychicznych, DSM-IV). Odpowiedzi są punktowane następująco: 0 („wcale nie dokuczały"), 1 („kilka dni"), 2 („więcej niż połowę dni") i 3 („niemal codziennie"). Do interpretacji wyników użyte zostały standardowe punkty odcięcia wynoszące 5, 10, 15 i 20 punktów, reprezentujące odpowiednio łagodną, umiarkowaną, umiarkowanie ciężką i ciężką depresję. W badaniach przesiewowych wynik 10 lub więcej punktów definiowany jest jako diagnostyczny punkt odcięcia i umożliwia rozpoznanie epizodu depresyjnego (czułość i swoistość na poziomie 88%). Oceniając zaburzenia lękowe zastosowano kwestionariusz lęku uogólnionego GAD-7 będący testem przesiewowym pozwalającym na ocenę obecności uogólnionego zaburzenia lękowego (GAD) oraz poziomu lęku. Składa się on z siedmiu komponentów, z których każdy jest stwierdzeniem opisującym ogólne napięcie somatyczne lub zmartwienie i oceniany jest w 4-punktowej skali Likerta, punktującej częstotliwość objawów w zakresie od 0 („wcale nie dokuczały") do 3 („niemal codziennie"). Im wyższy uzyskany wynik, tym wyższe jest natężenie objawów. Jako wartości odcięcia odpowiednio dla łagodnego, umiarkowanego i silnego lęku przyjęto sumę 5, 10 i 15 punktów. Punktem odcięcia pozwalającym określić prawdopodobieństwo wystąpienia uogólnionego zaburzenia lękowego jest wynik 8 lub więcej. Ostatnim z zastosowanych kwestionariuszy jest zmodyfikowana wersja szpitalnej skali lęku i depresji (HADS-M). Kwestionariusz zbudowany jest z 16 pytań (7 pytań dotyczących zaburzeń depresyjnych, 7 pytań dotyczących zaburzeń lękowych, 2 pytania dotyczące poziomu rozdrażnienia), z punktacją za każde pytanie od 0 do 3 punktów. Najwyższe możliwe do osiągnięcia wyniki dla zaburzeń depresyjnych i lękowych to po 21 punktów każdy. Wyniki w przedziale od 0 do 7 wskazują na stan prawidłowy, zakres od 8 do 10 punktów sygnalizuje poziom graniczny, natomiast wyniki w przedziale od 11 do 21 uznawane są za wartości nieprawidłowe, wskazujące na zaburzenia. W kolejnych etapach pracy analizowano obecność korelacji pomiędzy m. in. stopniem ciężkości choroby, a płcią lub wiekiem pacjentów, stopniem ciężkości choroby a nasileniem objawów o charakterze świądu i bólu czy nasileniem choroby, a nasileniem objawów depresyjnych, lękowych lub ubytkiem jakości życia.

Wyniki badań poddane zostały analizie statystycznej do której wykorzystano oprogramowanie IBM SPSS Statistics v. 26 (SPSS Inc., Chicago, IL, USA). Wszystkie dane oceniono pod kątem rozkładu parametrycznego lub nieparametrycznego za pomocą testu normalności Kołmogorowa – Smirnowa lub Shapiro–Wilk. Obliczono wartości minimalne, maksymalne, średnie, odchylenia standardowe, kwartyle i zakresy. Opierając się na teście normalności rozkładu, analizowane zmienne ilościowe oceniano za pomocą testu t-Studenta

lub testu U Manna-Whitneya, odpowiednio dla danych parametrycznych i nieparametrycznych. W zależności od normalności danych do oceny korelacji wykorzystano korelacje Spearmana i Pearsona. Do danych jakościowych wykorzystano test Chi2. Różnice w analizowanych danych pomiędzy więcej niż dwiema grupami oceniano, w zależności od rozkładu normalności, za pomocą ANOVA lub jednokierunkowej analizy wariancji rang Kruskala-Wallisa. Dla obu testów przeprowadzono analizę post-hoc z poprawkami Bonferroniego. $P < 0,05$ uznano za istotne statystycznie.

3.5. Podsumowanie wyników

W pierwszej publikacji wchodzącej w skład niniejszej rozprawy doktorskiej omówiono wykorzystanie inhibitorów JAK w kontekście leczenia przewlekłego wyprysku rąk. Wyniki analizy wskazują, że inhibitory JAK stanowią obiecującą opcję terapeutyczną, a ich zastosowanie może zrewolucjonizować podejście do leczenia pacjentów z CHE, regulując szlak sygnałowy kinazy Janusowe - transduktor sygnału i aktywator transkrypcji (JAK-STAT), istotny dla układu odpornościowego. Wyniki podkreślają potrzebę spersonalizowanej terapii, uwzględniającej profil bezpieczeństwa leków, co może przyczynić się do optymalnie długiego ich stosowania. Obecnie prowadzone są intensywne badania nad inhibitorami JAK, stosowanymi zarówno doustnie, jak i miejscowo, co budzi duże zainteresowanie wśród społeczności dermatologicznej. Lepsze zrozumienie szlaków patogenetycznych CHE będzie dodatkowo pozwalało dostosować terapię do indywidualnych potrzeb pacjentów. Inhibitory JAK wykazują szybki początek działania, co wydaje się być niezwykle istotnym, zwłaszcza w kontekście łagodzenia świądu, jednego z głównych objawów wpływających na jakość życia pacjentów z CHE. Wskazano dodatkowo na obiecujące perspektywy związane z zastosowaniem inhibitorów JAK w leczeniu CHE podkreślając jednocześnie konieczność prowadzenia dalszych badań czy monitorowania pacjentów. W procesie terapeutycznym istotne są także aspekty ekonomiczne i jakość życia związane z prowadzeniem terapii.

W kolejnym etapie pracy wykonano badanie mające na celu scharakteryzowanie populacji chorującej na CHE a także analizę częstości występowania i charakterystyki świądu i bólu towarzyszących chorobie. Badaniem objęta została populacja 100 pacjentów z rozpoznanym przewlekłym wypryskiem rąk, z których 60% stanowiły kobiety, a 40% mężczyźni w wieku od 18 do 80 lat (średnia wieku 46,0 ± 17,23 lat). Średni czas trwania choroby wynosił 42,5

miesiąca, a średnia liczba zaostrzeń w ciągu ostatnich 12 miesięcy wynosiła 4,7 ± 3,6. Spośród uczestników badania 71% było wcześniej leczonych z powodu choroby, z przewagą kobiet (78,3%) w porównaniu z mężczyznami (60%), różnica była istotna statystycznie. Predyspozycje atopowe, takie jak astma, alergiczny nieżyt nosa i atopowe zapalenie skóry, stwierdzono u 45% pacjentów. Tylko 27% pacjentów było wcześniej diagnozowanych z wykorzystaniem testów płatkowych, a u 14% rozpoznano alergie kontaktowe. Ponadto u 16 kobiet (26,7%) i 12 (30,0%) mężczyzn stwierdzono związek pomiędzy pracą zawodową a występowaniem schorzenia. Analizowano także palenie tytoniu jako czynnik zaostrzający chorobę - nie stwierdzono korelacji pomiędzy aktywnym paleniem i liczbą wypalonych papierosów a ciężkością choroby. Podział pacjentów z uwzględnieniem skali IGA-CHE wykazał, że 15% badanych (n = 15) należało do grupy 1 IGA-CHE, 25,0% (n = 25) do grupy 2 IGA-CHE, 37,0% (n = 37) do grupy 3 IGA-CHE, a 23,0% (n = 23) do grupy 4 IGA-CHE. Biorąc pod uwagę IGA-CHE z uwzględnieniem podziału z uwagi na płeć, większość mężczyzn uzyskała wyniki lokujące ich w grupach 1 i 2 IGA (n = 11; 27,5% w obu grupach), natomiast w grupie 3 IGA dominowały kobiety (n = 28; 46,7%). W skali HECSI średnia wartość wyniosła 35,0 ± 27,8 punktu, co można przełożyć na umiarkowany stopień nasilenia choroby.

Większość badanej populacji (87,0%, n = 87) zgłaszała, że świąd występował jedynie w obrębie zmian skórnych, natomiast 13,0% ankietowanych odczuwało go dodatkowo w obszarach niezmienionych chorobowo. U wszystkich respondentów zgłaszających ból, był on zlokalizowany wyłącznie w obrębie zmian skórnych. W ciągu ostatnich 3 dni przed badaniem, 81% pacjentów zgłaszało świąd, a 53% odczuwało ból, z wyższym odsetkiem kobiet w obu przypadkach (świąd: 53 kobiety (88,3%) vs. 28 mężczyzn (70%), p = 0,022; ból: 47 kobiet (78,3%) vs. 16 mężczyzn (40,0%), p = 0,033). W tym okresie dla całej badanej grupy intensywność świądu oceniona została na 3,9 ± 2,9 punktów w skali NRS, co rozpoznaje się jako łagodny świąd. W całym okresie choroby 100% pacjentów zgłaszało świąd, oceniony na 6,4 ± 2,7 punktów w skali NRS, co odpowiada świądowi umiarkowanemu. Nasilenie bólu w ciągu ostatnich 3 dni i całego okresu choroby i oceniono na odpowiednio 2,6 ± 3,1 punktu i 4,6 ± 3,2 punktu (w obu przypadkach wynik odpowiada bólowi o łagodnym nasileniu). Oceniając wyniki pod kątem punktów odcięcia i analizując cały okres choroby, grupę świądu "bardzo nasilony" istotnie częściej reprezentowały kobiety w porównaniu z mężczyznami (22 (36,7%) kobiety vs. 5 (12,5%) mężczyzn; p = 0,008), natomiast w grupie ze świądem „umiarkowanym" dominowali mężczyźni (21 (52,5%)

mężczyzn vs. 19 (31,7%) kobiet; p = 0,037). Stwierdzono dodatnią korelację pomiędzy nasileniem świądu i bólu a stopniem nasilenia choroby w skali IGA-CHE (odpowiednio r = 0,307, p = 0,002; r = 0,350, p < 0,001; dla całego okresu choroby). Wyniki skali HESCI korelowały także z nasileniem świądu i bólu w całym okresie choroby (odpowiednio: r = 0,255, p = 0,01; r = 357, p < 0,001). Nasilenie świądu i bólu korelowało co więcej ze zmniejszoną jakością życia mierzoną za pomocą DLQI. Wykazano także dodatnią korelację pomiędzy poziomem poczucia stygmatyzacji a nasileniem świądu w okresie ostatnich 3 dni (r = 0,221; p = 0,027). U 28 (46,7%) kobiet wpływ na jakość życia był bardzo duży, co było najczęstszym wynikiem, natomiast u mężczyzn najczęściej był to wpływ umiarkowany (n = 17; 42,5%). Stopień upośledzenia jakości życia korelował ze stopniem nasilenia choroby.

Ostatnia analiza, oceniająca psychospołeczne konsekwencje CHE, wykazała, że dla większości badanych CHE miał umiarkowany (33%) lub bardzo duży (39%) wpływ na ich jakość życia (mierzony przy pomocy DLQI). Dodatkowo, aż co dziesiąty pacjent ocenił ten wpływ na wyjątkowo duży. Średnią wartość DLQI dla całej grupy określono na poziomie 11,62 ± 6,35 punktów. Wykazano także statystycznie istotne różnice w średnich wartościach wyników pomiędzy kobietami i mężczyznami, odpowiednio: 13,27 ± 6,67 punktów; 9,15 ± 4,95 punktów; p = 0,023. U 28 (46,7%) kobiet wpływ choroby na jakość życia był bardzo duży, co było najczęstszym wynikiem w tej grupie, natomiast u mężczyzn najczęściej był to wpływ umiarkowany (n = 17; 42,5%). Spadek jakości zycia korelował dodatnio z ciężkością choroby mierzoną w skali IGA-CHE (r = 0,617; p < 0,001) i HECSI (r = 0,579; p < 0,001). Co więcej, wynik DLQI korelował dodatnio z nasileniem obu ocenianych objawów, świądu i bólu, w ciągu 3 dni poprzedzających okres badania (odpowiednio r = 0,436, p < 0,001 i r = 0,305, p = 0,002).

W kontekście depresji, na podstawie punktacji odcięcia skali PHQ-9 (≥10 punktów) w całej badanej populacji u 17 pacjentów (17%) udokumentowano możliwość rozpoznania zaburzenia depresyjnego. Częściej występowała ona u kobiet (n = 13; 21,7%) niż u mężczyzn (n = 4, 10%), jednak różnica między obiema grupami była nieistotna statystycznie. W odniesieniu do całej grupy średni wynik w skali PHQ-9 wyniósł 6,3 ± 4,9 punktów co przekłada się na łagodne zaburzenia depresyjne. Korelację pomiędzy nasileniem objawów depresyjnych a nasileniem CHE wykryto zarówno dla skali HECSI (r = 0,264; p = 0,008), jak i dla IGA-CHE (r = 0,329; p = 0,001). Pacjenci uzyskujący wyższe wyniki

w kwestionariuszu PHQ-9 zgłaszali także większe nasilenie świądu ($r = 0,363$; $p < 0,001$) i bólu ($r = 0,445$; $p < 0,001$) w ciągu ostatnich 3 dni przed badaniem. Wyniki PHQ-9 korelowały również ze spadkiem QoL ($r = 0,537$; $p < 0,001$). Ponadto stwierdzono dodatnią korelację pomiędzy wynikami PHQ-9 a wynikami oceny w innych skalach oceniających nie tylko depresję (HADS-D: $r = 0,664$; $p < 0,001$), ale także lęk: GAD-7 ($r = 0,617$; $p < 0,001$) i HADS -A ($r = 0,690$; $p < 0,001$). Dla całej grupy średnia wartość wyników w skali HADS-M (D) wyniosła 4,7 ± 3,1 punktów. Wśród kobiet oceniono ją na 5,22 ± 3,29 punktów, natomiast u mężczyzn na 3,83 ± 2,74 punktów. Różnica była istotna statystycznie ($p = 0,029$). Natężenie objawów depresyjnych mierzone w skali HADS-M korelowało dodatnio z ciężkością choroby (odpowiednio dla IGA-CHE: $r = 0,283$; $p = 0,004$ i HESCI: $r = 0,228$; $p = 0,004$), a także z intensywnością świądu ($r = 0,237$; $p = 0,017$) i bólu ($r = 0,287$; $p = 0,004$).

Oceniając zaburzenia lękowe, zgodnie z kryteriami rozpoznania zaburzeń lękowych podążając za kwestionariuszem GAD-7 (8 punktów i więcej) zaburzenia lękowe można było rozpoznać u 25% całej grupy ($n = 25$): 17 kobiet (28,3%) i 8 mężczyzn (20,0%). Różnica nie osiągnęła istotności statystycznej. Średni wynik GAD-7 dla całej badanej populacji oceniono na 5,8 ± 4,0 punktów. Co ciekawe, zaobserwowano związek pomiędzy nasileniem bólu a obecnością rozpoznania zaburzeń lękowych. Średnie nasilenie bólu u pacjentów ze zdiagnozowanym lękiem wyniosło 3,48 ± 3,31 punktu, natomiast u pacjentów bez lęku – 2,24 ± 2,93 punktu, oba mierzone w skali NRS. Różnica była istotna statystycznie ($p = 0,034$). W przypadku świądu nie zaobserwowano takiej zależności ($p > 0,05$). Nasilenie objawów lękowych korelowało z nasileniem bólu ($r = 0,248$; $p = 0,013$). Nie udokumentowano takiego związku pomiędzy oceną lęku a intensywnością świądu ($p > 0,05$). Oceniając wyniki uzyskane przy użyciu skali HADS-M (A) średnia wartość wyniosła 5,3 ± 3,0 punktów, biorąc pod uwagę całą populację badaną (5,87 ± 3,36 punktów wśród kobiet; 4,40 ± 2,12 punktów wśród mężczyzn; $p = 0,001$). Zaobserwowano dodatnią korelację pomiędzy nasileniem objawów lękowych a ciężkością choroby ($r = 0,230$; $p = 0,022$). Podobnie jak w przypadku kwestionariusza GAD-7, wyniki HADS-M (A) korelowały z natężeniem bólu ($r = 0,342$; $p = 0,001$). Wartą podkreślenia obserwacją jest także fakt, że nasilenie objawów lękowych wykazywało ujemną korelację z czasem trwania choroby ($r = −0,215$; $p = 0,032$).

3.6. Etyka

Projekt pracy doktorskiej opartej na poniższych publikacjach został zatwierdzony przez Komisję Bioetyczną Uniwersytetu Medycznego we Wrocławiu - Nr KB 234/2023. Badanie przeprowadzono przestrzegając zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej Światowego Stowarzyszenia Lekarzy przyjętą przez 18 Zgromadzenie Ogólne Światowego Stowarzyszenia Lekarzy (WMA), w Helsinkach w czerwcu 1964 r., a zmienionej przez 64 Zgromadzenie Ogólne WMA, w Brazylii w październiku 2013 r. Badania zostały przeprowadzone z zachowaniem anonimowości uzyskanych danych.

3.7. Wnioski

1. Inhibitory JAK stanowią nowoczesną grupę leków w przewlekłym wyprysku rąk, prezentując obiecujące rezultaty terapeutyczne. Wykazują one dobrą biodostępność i tolerancję zarówno w miejscowej, jak i doustnej formie podania, co stanowi ich niewątpliwą zaletę.

2. Inhibitory JAK nie zostały dotychczas zarejestrowane do leczenia wyprysku rąk przez żadną z instytucji odpowiedzialnych za rejestrację produktów leczniczych. Istnieje pilna potrzeba dalszych badań nad tą grupą leków, aby osiągnąć najlepsze efekty terapeutyczne przy jednoczesnym minimalizowaniu ryzyka poważnych działań niepożądanych.

3. Świąd stanowi jeden z najczęstszych objawów istotnie wpływających na wszystkie aspekty życia pacjentów z przewlekłym wypryskiem rąk. Jego występowanie koreluje z nasileniem choroby i często towarzyszy jej zaostrzeniom.

4. Oprócz świądu, istotnym objawem przewlekłego wyprysku rąk jest również ból w obrębie zmian skórnych, który zgłaszany jest przez znaczną grupę chorych.

5. Zarówno świąd, jak i ból mają wyraźny wpływ na dobrostan psychofizyczny pacjentów, co podkreśla znaczenie konieczności poszukiwania nowych rozwiązań

terapeutycznych. Redukcja objawów subiektywnych może niewątpliwie poprawić jakość życia chorych i zmniejszyć poziom stygmatyzacji związanej z chorobą.

6. Przewlekły wyprysk rąk jest schorzeniem niosącym istotne konsekwncje dla zdrowia pacjenta w każdym z jego wymiarów.

7. Zrozumienie, w jaki sposób choroba wpływa na życie pacjentów, może być cenne dla lekarzy, przyczyniając się do doskonalenia ich podejścia diagnostyczno-terapeutycznego i wczesnej identyfikacji zaburzeń depresyjnych i lękowych.

8. Konieczne jest wdrożenie podejścia wielodyscyplinarnego w diagnostyce i leczeniu przewlekłego wyprysku rąk, co może nie tylko pozytywnie wpłynąć na tworzenie nowych schematów postępowania, ale także zoptymalizować i uefektywnić współpracę pacjenta z lekarzem.

4. ARTYKUŁ PIERWSZY:

TOPICAL AND SYSTEMIC JAK INHIBIOTORS IN HAND ECZEMA – A NARRATIVE

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Topical and systemic JAK inhibitors in hand eczema – a narrative review

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REVIEW

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Topical and systemic JAK inhibitors in hand eczema – a narrative review

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ABSTRACT

Introduction: Hand eczema is a chronic inflammatory skin disease characterized by significant prevalence and impact on patients' Quality of Life (QoL). Because of its complex and diverse clinical picture, HE management requires patient-specific treatment which may constitute a challenge. First described in the 1990s, Janus kinase inhibitors (JAK inhibitors) state a group of modern therapeuticals, which exhibit good bioavailability and are well tolerated by patients in both – topical and systemic – routes of administration. They are an immunomodulating small molecules, impacting JAKs' enzymatic activity.

Areas covered: This review provides a summary of available data concerning JAK inhibitors' use in HE patients, regarding also clinical trials for the HE treatment.

Expert opinion: Recent studies are introducing JAK inhibitors as an alternative for other topical and systemic therapies in HE patients. Treatment targeting specific immune pathways enables precise management and extends range of potential therapeutic options. Despite early promising results, future studies need to evaluate JAK inhibitors' safety, potential risks and benefits resulting from the treatment, as well as impact of the therapy on patients' QoL.

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ARQ-252; baricitinib; delgocitinib; gusacitinib; hand eczema; JAK inhibitors; ruxolitinib; upadacitinib

1. Introduction

Hand eczema (HE) is a chronic inflammatory skin disorder of high prevalence and a significant social importance which often has severe, prolonged, and negative impact on patients' quality of life (QoL), as well as on their social status [1,2]. In 2021 Quaade et al. [3] analyzed sixty-six studies performed between 1964 and 2019, comprising 568100 individuals, in terms of prevalence, incidence and severity of HE in general population. Their study demonstrated that the pooled estimates for lifetime, 1-year, and point prevalence were 14.5% (CI: 12.6–16.5), 9.1% (CI: 8.4–9.8), and 4.0% (CI: 2.6–5.7), respectively, which identifies HE as a highly prevalent disease worldwide [3]. The spectrum of HE clinical manifestations, severity, and course of the disease is remarkably broad. It is usually described as a heterogeneous condition occupying surface of the hands and/or wrists, sometimes also related to eczematous lesions on the feet [1,4]. Clinical picture varies from erythematous macules, single, disseminated, or merged papules, edema, and vesicles to hyperkeratosis and linear fissures or erosions, depending on the stage of the disease [4,5]. Two most often described and most burdensome symptoms experienced by HE patients are localized itch and pain [6]. Other symptoms such as sleep and mood disturbances have also been reported [1]. Because of the above-mentioned disease diversity, therapeutic approach needs to be individual and is frequently challenging. The management of the HE requires a combination of pharmacological and/or physical treatment, a major change of patient's behavior together with a proper patient-physician communication and compliance [4,5,7,8].

2. Materials and methods

Preparing this paper, authors wanted to gather most current data covering the use of JAK inhibitors in HE patients. To evaluate available therapeutic options concerning JAK inhibitors we reviewed data from two electronic databases ('PubMed,' 'Scopus').

We also retrieved data from a database of privately and publicly funded clinical studies conducted worldwide (clinicaltrials.gov), screening for all studies concerning hand eczema patients. Subsequently, we manually chose research on JAK inhibitors, collecting 11 studies in total (Table 1).

3. HE pathogenesis

Allergic contact dermatitis, irritant contact dermatiti,s and atopic dermatitis of hands are distinguished to be the most common causes of HE [20]. Also a mixed, overlapping etiology is considered – endogenous predisposition (atopy) along with causative environmental factors triggering disease exacerbations [2,21]. The pathogenesis of HE is thus complex and comprises diverse elements.

There are numerous factors that can possibly influence the function of the skin barrier such as immune dysregulation, modified composition of intracellular lipids of epidermal stratum corneum, or skin microbiome imbalance [22–25]. Dysfunction of a skin barrier in both AD and HE leads to increased cutaneous penetration of irritants, allergens or microbial agents [20,22,23]. Easier antigen penetration results in stimulation of antigen-presenting cells and enhanced innate immune response. Tissue damage and/or an altered

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Article highlights

- Hand eczema is a chronic inflammatory skin disease impacting severely on patients' Quality of Life (QoL).
- Janus kinase inhibitors (JAK inhibitors) are modern therapeuticals characterized by good bioavailability and tolerance.
- JAK inhibitors may state an alternative for other topical and systemic therapies in HE.
- Further studies, especially in non-AD-related HE patients group, need to be performed to evaluate this group of pharmaceuticals.
- JAK inhibitors have not been yet approved for hand eczema diagnosis by either FDA or EMA.

microbial profile promote pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) secretion and thereby consolidate inflammation of the tissue. Additionally, antigen stimulation provokes a secretion of Th2-promoting cytokine (such as IL-25 or IL-33) [24].

Filaggrin is a protein which is strictly associated with proper skin barrier function. It is responsible for promoting adequate structure and hydration of the stratum corneum. Polymorphisms in the filaggrin (FLG) gene may result in loss of protein production and thereby increase transepidermal water loss (TEWL) and transepidermal antigen transfer [22,26,27]. Study of de Jongh et al. [26] indicated also that FLG null allele carriage possibly results in higher susceptibility to chronic irritant contact dermatitis. A heterozygosity for nonfunctional FLG gene mutations may promote a decreased resistance to exogenous damage and contribute to a specific HE subtype development which is a combination of allergic and irritant contact dermatitis [21].

Atopic dermatitis (AD) seems to be one of the most important risk factors for the HE, most of all in a pediatric population [3,7]. Additionally, according to the studies of Ruff et al. [28] patients with AD seem to be more prone to experience HE during their life time. An imbalance in immunity in course of the AD involves i.a. lymphocyte T-cells, such as Th1, Th2, Th17, Th22 and Treg as well as cytokines produced and released by them [29–31]. Levels of expression of type 2 immune cytokines, e.g. IL-4 and IL-13 are significantly higher within AD skin lesions and play a crucial role in chemokine production and skin barrier dysfunction [30,32–34]. Koga et al. [35] demonstrated an elevated number of Th17 cells in peripheral blood and acute lesional skin of AD patients. Moreover, IL-17 was reported to reduce HE expression of filaggrin and involucrine [36]. It induces also IL-4 and interferon-γ-mediated proliferation of keratinocytes which may lead to hyperkeratosis – a classical clinical symptom of HE [22,37]. Associated with skin barrier dysfunction IL-22 expression is found to be upregulated in AD patients skin biopsies [38]. Importantly, IL-4, IL-5, and IL-13 are described to be activators of the Janus kinase-Signal Transducer and Activator of Transcription proteins (JAK-STAT) pathway, which regulates Th2-cell differentiation [39,40].

4. Janus-activated kinases

First described in the early 1990s, Janus-activated kinases (JAK) are proteins composed of two domains – one performing the kinase activity, and another – negatively regulating the activity of the first domain. They are defined as an intracellular, non-receptor tyrosine kinase [41]. There are four representatives of the JAK family: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) [42–45]. STAT proteins are a group of latent cytoplasmic intracellular transcription factors that mediate many processes of cellular immunity, cell growth, and differentiation or apoptosis. Seven types of STATs can be distinguished: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. Their primary activation occurs with the involvement of receptor-associated JAK-kinases [46,47]. STAT signaling cascade is an example of a direct pathway in which STAT protein is bound to receptors at the surface of the cell and translocated toward nucleus, where they act as gene activating transcription factors [46].

The JAK-STAT pathway is a classical intracellular signal transduction pathway which is involved in numerous biological processes such as cell proliferation or immune response [39,48]. It is described as a human immune system central communication node, being engaged in transducing signals of over 50 cytokines and growth factors [45]. Despite the mechanism of its signaling being rather uncomplicated, the results of the pathway are considered to be complex. Activation of the JAK-STAT is preceded by binding a ligand to a corresponding JAK-receptor. Subsequently, tyrosine in the receptor is phosphorylated, which enables STAT binding. It consecutively leads to STAT' phosphorylation by JAK, releasing it from the receptor and translocating its dimerized form into nucleus in which it can moderate gene expression [44,49]. Data from the literature indicate a substantial role of JAK-STAT in the pathogenesis of AD and consequently, HE, with IL-4 being considered a crucial cytokine [39]. JAK2, TYK2, and STAT4 take part in IL-12 signaling pathway and Th1-cell differentiation, whereas JAK1, JAK3, and STAT6 – IL-4-pathway compounds – are responsible for regulating similar process in Th2-cell-line. Moreover, JAK2 takes part in activation of Th2-associated IL-5 receptor. STAT3 regulates Th17 differentiation and alongside with STAT5 plays a role in IL-4 signaling pathway [49,50].

5. JAK-inhibitors

In 1995 first descriptions of JAKs involvement in the etiology of diseases were presented. A mutation in JAK3 (loss-of-function) which was associated with severe combined immunodeficiency (SCID) was identified [51,52]. Similar discoveries stimulated researchers to explore this entirely novel branch of medical knowledge and demonstrated JAKs as an attractive pharmaceutical target, which led to the development of JAK-inhibitors (Jakinibs). Jakinibs are a group of small molecules that impacts on JAKs' enzymatic activity [53]. First approved by the Food and Drug Administration (FDA) in the United States of America (USA) in 2011, Jakinibs are now representing an interesting option of immunomodulating agents which may be a possible alternative for biological treatment [53,54]. Initially used in hematology and transplantology, over the course of time Jakinibs found their place in AD, alopecia areata, or graft-versus-host disease therapy [55–58]. Recently, the use of Jakinibs in HE patients has also been investigated. In Table 1 we gathered all available clinical trials on the use of topical and systemic JAK-inhibitors in HE patients. Of most commonly reported systemic adverse effects of JAK-inhibitor treatment, headaches, gastrointestinal disturbances, and upper respiratory tract infections along with nasolaryngitis

Table 1. Clinical trials on use of topical and systemic JAK-inhibitors in HE patients (according to *clinical.trialas.gov*).

	Study Title	NCT Number	Tested Drug Name	Way of administration/ drug dosage or concentration	Phase	Number Enrolled	Status
1	Efficacy and Safety of Delgocitinib Cream in Adolescents 12–17 Years of Age with Moderate to Severe Chronic Hand Eczema [9]	NCT05355818	delgocitinib/	Topical/ 20 mg/g	Phase 3	92	Recruiting
2	Topical Ruxolitinib in Chronic Hand Dermatitis [10]	NCT05293717	ruxolitinib	Topical/ 1.5%	Phase 1 Phase 2	15	Recruiting
3	A 24 Week Trial to Compare the Efficacy and Safety of Delgocitinib Cream 20 mg/g Twice-daily With Alitretinoin Capsules Once-daily in Adult Participants with Severe Chronic Hand Eczema [11]	NCT05259722	delgocitinib	Topical/ 20 mg/g	Phase 3	510	Recruiting
4	Topical Ruxolitinib Evaluation in Chronic Hand Eczema Study 2 [12]	NCT05233410	ruxolitinib	Topical/ 1.5%	Phase 3	0	Withdrawn
5	Topical Ruxolitinib Evaluation in Chronic Hand Eczema Study 1 [13]	NCT05219864	ruxolitinib	Topical/ 1.5%	Phase 3	0	Withdrawn
6	Open-label Multi-site Extension Trial in Subjects Who Completed the DELTA 1 or DELTA 2 Trials [14]	NCT04949841	delgocitinib	Topical/ 20 mg/g	Phase 3	600	Enrolling by invitation
7	Efficacy and Safety of Delgocitinib Cream in Adults with Moderate to Severe Chronic Hand Eczema (DELTA 2) [15]	NCT04872101	delgocitinib	Topical/ 20 mg/g	Phase 3	450	Active, not recruiting
8	Efficacy and Safety of Delgocitinib Cream in Adults with Moderate to Severe Chronic Hand Eczema [16]	NCT04871711	delgocitinib	Topical/ 20 mg/g	Phase 3	487	Completed
9	Safety and Efficacy of ARQ-252 Cream in Subjects with Chronic Hand Eczema [17]	NCT04378569	ARQ-252	Topical/ 0.1% vs. 0.3%	Phase 1 Phase 2	230	Completed
10	Study to Evaluate ASN002 in Subjects with Moderate to Severe Chronic Hand Eczema [18]	NCT03728504	gusacitinib	Oral/ 40 mg vs. 80 mg	Phase 2	97	Completed
11	Phase 2b Dose-ranging Trial to Evaluate Delgocitinib Cream 1, 3, 8, and 20 mg/g Compared to Delgocitinib Cream Vehicle Over a 16-week Treatment Period in Adult Subjects with Chronic Hand Eczema [19] Has Results	NCT03683719	delgocitinib	Topical/ 1 mg/g vs. 3 mg/g vs. 8 mg/g vs. 20 mg/g	Phase 2	258	Completed –

seem to be the most frequent ones [59–61]. Also other events are mentioned such as acne, herpes simplex, and herpes zoster infection or eczema herpeticum [59,62,63]. Some authors point to the association of JAK-inhibitors therapy and increased incidence of asthma exacerbations, reduced platelets count, or neutropenia [63,64]. Complications including deep vein thrombosis, pulmonary embolism, and arterial thrombosis described in several papers are regarded to be dose- and disease-dependent. Importantly, further studies are needed to assess those risks and explain their pathogenesis [59,65]. Table 2 presents a short comparison of molecules included in this review, regarding also common adverse events.

5.1. Topical JAK-inhibitors

5.1.1. Degocitinib

Delgocitinib (JTE-052; JTE-052A) is a small molecule – pan-JAK inhibitor targeting JAK1, JAK2, JAK3, and TYK2 [76]. Delgocitinib inhibits several signaling cascades mediated by the cytokines, which suppress inflammation. It is inhibiting innate and adaptive immune cells activation as well as Th-1, Th2-, Th17, and Th22-type inflammatory response. What is more, delgocitinib is described as an agent that modulates keratinocyte differentiation improving the skin barrier function, which is indicated by elevated concentrations of profilaggrin, filaggrin monomer, and locrin, and has antipruritic properties [8,77–80]. A Phase II, multicenter, randomized, vehicle-controlled clinical study performed by the group of Japanese researchers [81] showed a rapid and marked improvement in clinical signs and symptoms of adult AD patients (moderate to severe). Efficacy of all concentrations of the delgocitinib ointment (ranging from 0.25 to 3 %) was greater than vehicle, taking under consideration all parameters: modified Eczema Area Severity Index (mEASI), Eczema Area Severity Index (EASI), Investigator's Global Assessment (IGA), and pruritus Numerical Rate Scale (NRS) [81]. This trial concerned patients with AD, but it presented the potential role of delgocitinib in atopic dermatitis subtype HE patients treatment strategy. In 2020 0.5% delgocitinib cream was approved in Japan for AD treatment [82]. However, no registration of delgocitinib is yet available for HE patients.

In 2020 Worm et al. [78] published a study describing a clinical trial conducted by their group, assessing the efficacy and safety of topical delgocitinib in patients with chronic hand eczema. They gathered a group of 91 patients who received delgocitinib ointment 30 mg/g (applied twice daily) or vehicle ointment for 8 weeks. 5-point PGA was used to measure the treatment success (primary endpoint) and Hand Eczema Severity Index (HECSI) score (secondary endpoint). Forty-six percent of patients achieved treatment success (PGA 0–1), compared with 15% of those using vehicle ointment (odds ratio 4.89, 95% confidence interval (CI) 1.49–16.09; P = 0.009). Also, the value of adjusted mean HESCI score was lower with delgocitinib than with the vehicle (13.0 vs. 25,8). Both results were statistically significant. The therapy was well tolerated, adverse events incidence was comparable in both

Table 2. JAK-inhibitors – comparison of individual molecules.

	Drug name	Molecular weight ($g*mol^{-1}$)	Targeted JAK isoforms	Way of administration in HE patients	Inhibited cytokine signaling	Most common adverse effects
1	Delgocitinib	310.35 [66]	JAK1, JAK2, JAK3, TYK2	Topical	IL-2, −4, −6, −12, −13, −19, −20, −22, −23, −31, IFN-alfa, IFF-gamma, EPO [67]	Nasopharyngitis Headache [60]
2	Ruxolitinib	306.4 [68]	JAK1, JAK2	Topical	IL-2, −4, −6, −12, −19, −20, −22, −23, IFN-alfa, IFN-gamma, EPO [67]	Nasopharyngitis Upper respiratory tract infection Headache Application site burning [69]
3	ARQ-252	No data available	JAK1	Topical	No data available	No data available
4	Gusacitinib	460.5 [70]	JAK1, JAK2, JAK3, TYK2, SYK	Systemic	IL-4, −12, −13, −22, −31, S100 [31,71]	Headache Gastrointestinal disturbances Nasopharyngitis Back pain [72]
5	Baricitinib	371.4 [73]	JAK1, JAK2	Systemic	IL-2, −3, −4, −5, −6, −7, −9, −10, −11, −12, −13, −15, −19, −20, −22, −23, −27, −28, IL-31, TSLP, G-CSF, GM-CSF, INF-gamma [31,67,74]	Upper respiratory tract infection Gastrointestinal disturbances Headache [61]
6	Upadacitinib	380.4 [75]	JAK1	Systemic	IL-2, −4, −6, −7, −9, −10, −11, −12, −13, −15, −19 −20, −22, −23, −27, −28, Interferon- gamma [31,67,74]	Acne Worsening of atopic dermatitis Upper respiratory tract infection [62]

groups of patients, and after 8 weeks' efficacy plateau was not achieved which may imply that longer treatment can bring more promising results. Another study of this group [79] proved also that delgocitinib cream is presenting a dose-response relationship. On a population of 258 patients Worm et al. [79] showed that doses of 8 and 20 mg/g used twice daily for 16 weeks demonstrate a treatment effect vs. vehicle in all established endpoints – IGA for chronic hand eczema treatment success (IGA-CHE TS) [0 (clear) or 1 (almost clear) with a ≥ two-point improvement from baseline to week 16, time to IGA-CHE TS, and changes in HECSI. IGA-CHE TS was noticed in 36.5% of 8 mg/g-group and 37.7% of 20 mg/g-group, whereas only 8.0% of patients using placebo vehicle reported treatment success. A rapid and sustained reduction in itch and pain was also observed. No safety concerns were raised. Also a trial on using an oral form of delgocitinib was conducted. It was demonstrated that JTE-052 inhibited antigen-specific T cell activation and subsequent inflammation in acquired skin immunity such as contact hypersensitivity [83].

Upregulation of IL-31 can also induce the pruritus. Signaling of this cytokine is downregulated by inhibition of the JAK-STAT pathway, and it may be the explanation for an almost instant antipruritic effect of delgocitinib [84–86]. Taking under consideration that cytokines are related to molecular pathogenesis of pruritus, JAK-inhibitors may also play a crucial role in breaking the itch-scratch cycle and be an interesting therapeutic option for patients with HE-associated pruritus [58,87].

5.1.2. Ruxolitinib

Ruxolitinib is a selective JAK1 and JAK2 inhibitor. It was first described in 2010 by the team of Quintas-Kardama et al. [88] While working on this paper (on 20th of November 2022) we found that there is one ongoing clinical trial on use of ruxolitinib in subjects with HE [10]. During the intervention, 15 HE patients are receiving 1.5% ruxolitinib cream to apply twice daily for 12 weeks. Researchers are going to assess treatment success by achieving IGA score of 0 to 1, with at least 2-step improvement. An improvement in HESCI score is also taken under investigation. As the estimated study completion date is December 2024, no results have yet been published. Two similar trials have recently been withdrawn, because of business decisions, no safety concerns [12,13]. Topical formulation of ruxolitinib was also used in a few AD clinical studies in which promising results were obtained. Outcomes of two phase 3, randomized, double-blind studies revealed an antipruritic and anti-inflammatory effects in AD, confirming the results of phase 2 data [69,89,90]. Studied population comprised of 631 and 618 patients aged ≥ 12 years (631/577 were analyzed for efficacy). Significantly more patients reached the primary endpoint (IGA-TS) after 8 weeks of twice-daily-application of 0.75%-ruxolitinib cream (50.0%/39.0%) and 1.5%-ruxolitinib cream (53.8%/51.3%) compared with a vehicle cream (15.1%/7.6%). What is more, reduction in itch NRS scores within 12 hours of the first application of 1.5%-ruxolitinib cream was reported ($P < .5$). Reduction in itch that was clinically relevant (≥4 points reduction in NRS measured with worst itch level) occurred early in patients treated with ruxolitinib creams and improved continuously during the trial period. No differences in its tolerability based on lesion location were observed [69].

The antipruritic effect of ruxolitinib can be related to the fact that neuronal JAK-1 signaling pathway inhibition reduces not only inflammatory but also non-inflammatory itch and may represent a new approach to target pruritus [91]. What was confirmed in

murine Th-2 mediated dermatitis models, ruxolitinib application results in downregulation of T helper-driven inflammation, reduced skin thickening, and decreased itch [92].

5.1.3. ARQ-252

ARQ-252 is described as a topical JAK1 selective inhibitor. In April 2020 a study to investigate its efficacy and safety in HE patients was created [17]. Researchers constituted two cohorts: Cohort 1 – a multiple dose cohort – assigned with 0.3% ARQ-252 cream to be applied to both hands for 2 weeks and Cohort 2 – double-blind, vehicle-controlled group randomized to 0.3%- ARQ-252-, 0.1%-ARQ-252- or vehicle-cream to be applied to both hands for 12 weeks [17]. Unfortunately, the study did not meet its primary endpoints and none of the ARQ-252 groups achieved statistical significance compared with vehicle. However, ARQ-252 developers consider it as a drug of high potency and exceptionally high selectivity against JAK1 in comparison with JAK2, which may determine its safety and further tests are still ongoing [93,94].

5.2. Systemic JAK-inhibitors

5.2.1. Gusacitinib

There are also systemic JAK-inhibitors, administered orally, that are suggested to enhance the range of therapeutic options in HE patients. An example of such medication is guscitinib (ASN002), JAK and spleen tyrosine kinase (SYK) signaling pathways inhibitor [71]. In 2019 Pavel et al. [71] investigated the effect of gusacitinib on inflammatory pathways in AD patients. They detected statistically significant suppression of Th1-, Th2-, Th17-, and Th22-related genes paralleled by reduction in levels of cytokines such as IL-12, IL-22, IL-31, and S100. Further, they described downregulation of genes related to T-cells/T-cell activation and general inflammation. Improvements in the epidermal barrier were also reported. Results corresponded to clinical response [71]. Gusacitinib is also presented as effective at improving signs and symptoms of AD and a well-tolerated drug. In a randomized double-blind placebo-controlled study adverse events (AE) of the treatment with 40 mg or 80 mg of ASN002 were similar to those reported in placebo group. AEs which occurred most frequently were headache, nausea, diarrhea, nasopharyngitis, back pain, mild hypertension, and lowering the levels of lymphocytes. A rapid onset of action on itch was noticed – on day 2, with a significant decrease on day 8 in patients using 80 mg of gusacitinib. What is intriguing, greater efficacy was observed in ASN002 40 mg group [72]. A phase 2b clinical trial that ended in 2020 evaluated the efficacy of gusacitinib in patients with severe chronic HE. Subjects were randomized (1:1:1) to receive ASN002 at 40 mg, 80 mg, or placebo once daily for 16 weeks. In the second part of the study all patients received 80 mg of gusacitinib for another 16 weeks, with 4 weeks of follow-up observation. The research revealed a dose-dependent improvements in modified Total Lesion Severity Score (mTLSS) and Physician's Global Assessment (PGA) in subjects receiving both 40 mg and 80 mg of ASN002, in relation to placebo. The dose of 80 mg resulted in decrease of 69% ($p < 0.005$) in mTLSS from baseline, in comparison with 49% in 40 mg-group and 33% in placebo receivers. Clinically significant decreases in mTLSS, PGA, and pruritus were reported as early as 4 weeks of treatment. AEs of the therapy were consistent with those mentioned in previous papers [18,95].

5.2.2. Baricitinib

Baricitinib, an oral selective JAK-1 and JAK-2 inhibitor, has been lately approved as a first-line systemic AD treatment [49]. Nonetheless, its impact on HE patients is poorly described. In the literature there are two case reports concerning baricitinib use in patients with severe chronic hand eczema. Both subjects were treated with 4 mg baricitinib, orally. To assess the severity of the disease, HECSI score was used, and quality of life impairment was measured with Quality of Life in Hand Eczema Questionnaire (QOLHEQ). After 16-week therapy, in both cases great improvement in clinical picture (decrease in HECSI from 55 points to 4 points in Case 1; and from 47 points to 8 points in Case 2) as well as in quality of life (improve from 'strongly impaired' to 'not at all impaired' in Case 1; and from 'moderately impaired' to 'not at all impaired' in Case 2) was observed [96].

5.2.3. Updadacitinib

Another example of small molecule used in dermatological treatment is upadacitinib. This reversible, selective JAK-1 inhibitor was indicated for the therapy of moderate to severe active rheumatoid arthritis, but it is now approved by the FDA as well as by the European Medicines Agency (EMA) for treating AD patients (adults and children 12 years and older) [97–100]. A meta-analysis concerning efficacy and safety of abrocitinib, baricitinib, and upadacitinib for moderate-to-severe AD demonstrated superiority of 30 mg upadicitinib, administered orally, over two others mentioned, regarding IGA and EASI response [98]. In 2021, two phase 3 clinical trials with upadacitinib showed significant improvements in mild-to-severe chronic HE in a group of patients with moderate-to-severe AD at 16 weeks, compared with placebo [101,102]. A high safety profile, low rates of AEs during the therapy, and rapid antipruritic effect explain a rising interest in selective JAK-1 inhibitors [103]. Studies concerning upadacitinib use in patients with HE not associated with AD are also still lacking.

6. Conclusions

JAK-inhibitors are a novel and modern group of medications with promising therapy outcomes. Taking under consideration a complex and difficult HE pathogenesis, JAK-inhibitors may become an important part of HE therapeutic regimen. What also cannot be forgotten is a fact that by the time this review was created, JAK inhibitors had not been yet approved for hand eczema diagnosis by either FDA or EMA. By the time of the approval their use in HE patients remains off-label management. Good bioavailability and tolerance of both topical and oral routes of administration are their indisputable advantages. Careful and alert monitoring during the therapy as well as post-treatment follow-up observation appears to be necessary. Nevertheless, more reliable data about their safety profile is still lacking. Importantly, there is a great need to investigate

possible interactions of JAK-inhibitors with other drugs and factors to obtain the best therapeutic effects and the least risk of severe adverse events. Having regard to the course of HE, improvement in patients' quality of life should also be an anticipated endpoint of our management.

7. Expert opinion

Recently pharmaceutical market has been influenced significantly by biological agents which brought new hopes and satisfying effects for patients suffering from different dermatoses, including HE patients. Further step in developing therapeutic options for HE treatment appears to be use of JAK inhibitors, which can undoubtedly revolutionize clinical approach to this group of patients, as the JAK-STAT signaling pathway is described as an essence of immune system regulation. More and more new studies concerning both oral and topical JAK inhibitors appear all over the world, which makes this topic one of the most frequently discussed, also in dermatological environment. While exploring pathogenetic pathways of HE we could determine which form of the therapy will be most appropriate for each individual as well as which particular drug to administer. An individualized, patient-adjusted therapy with a high level of safety is a paradigm which should be aimed for. Low rate of AEs influences also the duration of the treatment – the safer the drug, the longer it can be used. Most of available literature confirms high safety profile of JAK inhibitors in all formulations and ways of administration, which provides patients' trust and build confidence in physicians and care system. In HE patients this seems to be a major potential advantage of JAK inhibitors in terms of chronicity of the disorder. There are few steps that can be undertaken to even improve that safety. Before starting treatment, it needs to be obligatory to confirm the diagnosis and indications for initiation of the systemic treatment. Performing a baseline test should also be mandatory. As in all systemic therapies (including JAK inhibitors in other indications, e.g. AD), treatment monitoring is supposed to be conducted.

Exploring and extending the knowledge about JAK inhibitors allows also to take further steps and decisions in an effective therapeutic plan. Thanks to their specific way of action, JAK inhibitors may state an efficient and safe therapeutic option and help dermatologists to create a HE treatment somehow tailored to patients' needs and expectations.

Also every-day clinical experience with JAK inhibitors used in our patients (not as strictly selected as groups for clinical trials) will be crucial for better understanding and development of those pharmaceuticals.

Rapid onset of action is one of the most frequently underlined advantages of JAK inhibitors, especially when the pruritus is discussed, which is described as one of the most severely impacting HE patients' quality of life symptom. The itch relief occurring even before reduction of erythema or other visible symptoms can improve treatment compliance.

HE treatment can be characterized as a process causing an economic loss for patients as well as for the whole health care system. Only a patient's skin care with emollients consumes a large portion of one's budget. JAK inhibitors are so far expensive drugs. Therefore, their use needs to be considered in agreement with a patient, regarding the effects of medication prices on patient's social situation. Moreover, oral administration may also be beneficial from both patients' and health care system's point of view – it increases patients' independence and comfort of the therapy, simultaneously reducing health care costs associated with parenteral treatment.

In five-years perspective approach to HE treatment may be altered. If a new agent with better effect size and lower rate of unwanted side effects emerges, it is the one which is wanted to be used and is wanted to become a new therapy standard. If the early promising results are confirmed and with trials developing successfully, JAK inhibitor may take a place of a golden standard in HE management. However, long-term studies conducted on a large patient population are still lacking.

Declaration of interests

J Szepietowski acted as a global coordinator and principal investigator in the phase III studies of ruxolitinib cream: TRuE-AD1 [NCT03745638]; TRuE-AD2 [NCT03745651]. J Szepietowski also acted as: Advisory Board/Consultant: AbbVie, Leo Pharma, Novartis, Sandoz, Sanofi-Genzyme, Trevi, Viofor. Speaker: AbbVie, Janssen-Cilag, Eli-Lilly, Leo-Pharma, Sanofi-Genzyme. Clinical trials: AbbVie, Amgen, BMS, Galderma, Galapagos, Incyte, InfraRX, Janssen-Cilag, Menlo Therapeutics, Merck, Novartis, Pfizer, Regeneron, UCB, Trevi. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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5. ARTYKUŁ DRUGI:

PREVALENCE AND CHARACTERISTICS OF ITCH AND PAIN IN PATIENTS SUFFERING FROM CHRONIC HAND ECZEMA

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Prevalence and Characteristics of Itch and Pain in Patients Suffering from Chronic Hand Eczema

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Abstract: Background: Hand eczema (HE) is a frequent chronic inflammatory dermatosis. Itch and pain are considered two of the most common and burdensome symptoms of the disease. Yet, the data related to these symptoms are still limited. The aim of this study was to evaluate characteristics of itch and pain in adults suffering from HE. Methods: The study group comprised 100 adult HE patients. An original questionnaire designed by the authors was used to survey the patients. It included questions regarding demographic characteristics such as the duration of the disease, exacerbation count, past diagnostics and treatment, as well as atopic predispositions. Additionally, the itch and pain intensity (numerical rating scale—NRS) during '3 days prior to the study' and the 'entire disease' period was implemented. The clinical assessment of the disease severity was performed according to two specific measurement instruments: Investigator Global Assessment for Chronic Hand Eczema (IGA-CHE) scale and Hand Eczema Severity Index (HECSI). To assess patient quality of life (QoL), the DLQI tool was used and to determine the level of stigmatization and for its impact on patients' life the 6-Item Stigmatization Scale (6-ISS) was employed. Results: Within the period of 3 days prior to the examination, itch was reported by 81.0% of patients (n = 81), whereas 53.0% (n = 53) of them experienced pain. Both symptoms were reported more frequently in females (itch: p = 0.022; pain: p = 0.033). When sexes were compared, females reached higher scores in both IGA-CHE and HECSI. Itch and pain intensity correlated positively with disease severity. The intensity of itch and pain significantly influences HE patients' QoL. A positive correlation between the 6-ISS score and the intensity of itch in the 'last 3 days' period was revealed (r = 0.221; p = 0.027). Conclusions: Itch and pain are common symptoms in HE patients, significantly contributing to the feeling of stigmatization. Providing characteristics of itch and pain may improve HE management. Symptom-decreasing treatment would definitely have a positive influence on patients' well-being.

Keywords: hand eczema; itch; pain; chronic inflammation; inflammatory disease; quality of life; stigmatization

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1. Introduction

Hand eczema (HE) is a recurrent inflammatory dermatosis with a high 1-year prevalence reaching 9.7% [1] and lifetime prevalence ranging from 11.3% to 20% [2–5]. The incidence rate of the disease is reported to be 5.5–8.8 per 1000 person years [1,4,6,7]. HE is also presented as a disease that affects many diverse aspects of patients' life (i.e., physical, material, social and psychological) and impairs their quality of life (QoL) [3,8]. The term 'chronic' is commonly used in relation to HE (chronic hand eczema; CHE) and it describes a condition which persists for at least 3 months or reoccurs for a minimum of two times in a 12-month period [4,9]. There is debate on the many factors that take part in CHE etiopathogenesis and the course of the disease. The etiology of HE is complex and depends on both endogenous (e.g., genetic) and exogenous (e.g., environmental or occupational) agents [8,10]. Endogenous variables are predominantly associated with the dysfunction of the skin barrier, which is characteristic of atopic dermatitis (AD) patients. An increased risk of developing a severe type of HE in this group of individuals is described, especially

in coexistence with filaggrin mutation [11,12]. Exogenous factors contributing to HE development may be defined as forms of exposure leading to skin barrier deterioration. Among the most frequent, work in wet conditions (or water in general), irritants, toxic agents and mechanical irritation of the skin are suggested [7,13].

The most common primary lesions observed in HE patients are erythema, papules, oedema, vesicles or crusting. Additionally, signs of lichenification, areas of hyperkeratosis, scaling, fissures or erosions may appear. Manifestations of HE usually evolve in severity and clinical presentation over time. [8,14] Signs and complaints reported by patients predominantly include itching as well as pain, burning, stinging and mood and sleep disturbances. All of the above-mentioned complaints may lead to difficulties in everyday duties or the avoidance of social activities which involve hands [14–16]. Despite their high incidence, data related to itch and pain in HE are still lacking. A better overview and understanding of these symptoms may help physicians to improve diagnosis and management. It can also contribute to achieving better outcomes when it comes to increasing patients' QoL.

Itch can be defined as an unpleasant sensation which leads to scratching. It can be classified as acute or chronic, depending on time criteria (less or more than 6 weeks, respectively) [17,18]. Four different types of itch can be distinguished: neuropathic (a result of central or peripheral nervous system damage), systemic (caused by systemic diseases such as infections or metabolic disorders), psychogenic (of psychiatric or psychosomatic origin) and dermatological (triggered by an invasion of exogenous substances causing an inflammatory response such as an insect bite, scabies infestation or sunburn, or occurring as a result of a various dermatoses, e.g., lichen planus). Additionally, a combination of these types is possible as well as the coexistence of more than one type in a single patient [19–21]. Itch occurs frequently not only in the course of HE, but also in other inflammatory dermatoses.

Pain itself may be classified in various ways; for example, acute and chronic. The latter is described to affect over 30% of people worldwide [22]. Another classification of pain distinguishes between nociceptive pain (a result of tissue injury or a stimuli that may potentially lead to tissue damage), neuropathic (caused by nerve injury or a disease affecting the nervous system, and may be commonly associated with numbness or allodynia) and nociplastic pain (triggered by a sensitized nervous system, without objective tissue or nerve damage) [22–26]. The mixed pain phenotype is being increasingly recognized by clinicians and researchers as a combination of the above-mentioned types [22]. In patients suffering from various dermatoses (such as HE, AD, psoriasis, hidradenitis suppurativa (HS)) pain is described as one of the most frequently occurring symptoms. It may be limited to skin lesions or generalized, often also manifesting as musculoskeletal pain [26].

Assessment of QoL and health-related QoL (HRQoL) has become one of the most important means used to evaluate the effects of interventions in various studies or the impact of the disease on patients' well-being. The following types of HRQoL instruments can be distinguished: generic instruments—whose results may be compared across different disorders—such as EQ-5D, and disease-specific instruments—assessing the influence of a particular disease on QoL—namely the Quality of Life in Hand Eczema Questionnaire (QOLHEQ). Additionally, a skin-specific group is recognized, as represented by Dermatology Life Quality Index (DLQI) or Skindex-17 questionnaires [27]. Currently, there is no Polish version of QOLHEQ that is validated.

The aim of this study was to evaluate the prevalence and characteristics of itch and pain in a group of patients suffering from HE.

2. Materials and Methods

2.1. Studied Group

A cross-sectional, prospective study was conducted on a group of 100 consecutive patients from an inpatient (hospital ward) and outpatient clinic at the Department of Dermatology, Venereology and Allergology in Wroclaw, Poland, between 1 February 2022

and 31 January 2023. All patients were recruited by the authors of this research. The whole studied population was diagnosed with chronic HE, based on the clinical picture and time criteria. Inclusion criteria comprised adult age (≥18 years old) and a course of disease persisting for over 3 months, enabling a chronic form of HE diagnosis. All patients with skin lesions that resembled CHE without a definite diagnosis or those waiting for the result of the biopsy were excluded from the study. An original survey, in the form of an investigation sheet, concerning group characteristics was prepared by the authors of the research prior to the study. The survey comprised questions regarding data related to the demographic data, the duration of the disease, exacerbation count, past diagnostics and treatment and atopic predispositions. Additionally, particular clinical features of the itch were investigated such as affected area (only within skin lesions vs. skin lesions and healthy skin). Patients were also asked to report where the skin lesions were located (only hands; hands and feet; hands, feet and other regions—disseminated lesions) and to declare whether they smoked tobacco or not (if the answer was positive, patients were asked to indicate the number of cigarettes smoked daily). Patients completed questionnaires concerning itch and pain assessment, as well as validated Polish versions of the instruments assessing quality of life (Dermatology Life Quality Index; DLQI) and stigmatization level (6-Item Stigmatization Scale; 6-ISS).

The study was approved by the local ethics committee (consent no. KB-234/2023) and written informed consent was obtained from all studied individuals.

2.2. Disease Severity Assessment

The clinical assessment of the severity of the disease was performed according to English versions of two specific measurement instruments: Investigator Global Assessment for Chronic Hand Eczema (IGA-CHE) scale and Hand Eczema Severity Index (HECSI). All investigators were instructed and trained on their use prior to the study.

IGA-CHE (physicians' global assessment; PGA) distinguishes 5 categories of HE severity: 'clear', 'almost clear', 'mild', 'moderate' and 'severe' [28].

The HECSI is a tool employed to assess disease severity, combining the intensity, extent and clinical signs of HE. According to HECSI, both hands of the patient are divided into five areas: fingertips, fingers (except the fingertips), the palm of the hand, back of the hand and wrists. Within each area, the intensity of the following six clinical signs—erythema, induration/papulation vesicles, fissuring, scaling, and oedema—are graded on a scale as follows: 0 (no skin changes), 1 (mild disease), 2 (moderate disease), and 3 (severe disease). For each specific location, the total affected area (considering both hands) is given a score from 0 to 4 for the extent of clinical symptoms (0 = 0%, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, and 4 = 76–100%). Finally, the score given for the extent of clinical symptoms at each location is multiplied by the total sum of the intensity of each clinical feature and summated. The HECSI score ranges from 0 to 360 points (the maximum severity score) [29]. The following criteria for allocating patients into groups in relation to disease severity were used in our study: clear, 0; almost clear, 1–16; moderate, 17–37; severe, 38–116; very severe, ≥117 points [30].

2.3. Itch and Pain Assessment

Itch and pain intensity were evaluated using a numerical rating scale (NRS). All study participants were asked to assess the severity of the worst itch and pain during the last 3 days as well as the worst itch and pain during the entire period of the disease. The NRS is a unidimensional, brief symptom intensity measurement scale ranging from 0 (no itch/pain) to 10 (worst imaginable itch/pain). The scores of the itch NRS range from no (0 points), mild (1–3 points), moderate (4–6 points), severe (7–8 points), to very severe (≥9 points) [31]. In order to assess pain, the authors decided to use the following cut-off points for pain NRS, which were established at: ≤5—mild pain; >5–7—moderate pain; >7–10—severe pain, on the 0–10 rating scale [32].

2.4. QoL and Stigmatization Assessment

The validated Polish version of the DLQI questionnaire was implemented to assess issues related to quality of life [33]. DLQI is a dermatology-specific tool with a 1-week recall period, evaluating symptoms and feelings, daily activities, leisure, work and school aspects of life, relationships and side effects of treatment. It comprises 10 items, each scored from 0 to 3 points (0—'not at all'; 1—'a little', 2—'a lot' 3—'very much'). All individual scores are summed up and a total DLQI result is obtained, ranging 0–30 points. A score of 0–1 indicates no impact of the disease on QoL; a score of 2–5 points indicates a small impact; 6–10 points indicate a moderate impact; 11–20 points indicate a large impact; 21–30 points indicate an extremely large impact [33–35].

The 6-ISS (validated; in Polish) [36,37] was used to determine the level of stigmatization and its impact on patients' life [38]. This instrument requires patients to answer 6 questions using one of four responses scored from 0 to 3 points ('not at all', 'sometimes', 'very often', and 'always'). The higher the result, the greater the perception of stigmatization (ranging 0–18 points) [38].

2.5. Statistical Analysis

The statistical analysis of the acquired data was performed using IBM SPSS Statistics v. 26 (SPSS INC., Chicago, IL, USA) software. Firstly, all the data were assessed for parametric or non-parametric distribution using the Kolmogorov–Smirnov normality test. The minimum, maximum, mean, standard deviations and ranges were calculated. Based on the normality, analyzed quantitative variables were evaluated using the students t test or Mann–Whitney U test for parametric and non-parametric data, respectively. Depending on the normality, Spearman's and Pearson's correlations were used for the correlation assessments. For the qualitative data, the Chi^2 test was used. Differences in analyzed data between more than two groups were evaluated, depending on normality, with ANOVA or the Kruskal–Wallis 1-way analysis of variance in ranks. A 2-sided p value of ≤ 0.05 was statistically significant.

3. Results

The study group consisted of 60 women (60.0%) and 40 men (40.0%), with an age range of 18–80 (mean 46.0 $\pm$ 17.23) years. The mean disease duration time was assessed at 42.5 months (SD = 60.84) and ranged from 3 to 396 months. The total exacerbation count at 12 months prior to the study reached 4.7 $\pm$ 3.6. Out of 100 participants, 71 (71.0%) were reported to have been treated because of HE in the past, with a predominance of females (n = 47; 78.3%) compared to males (n = 24; 60.0%). The difference was statistically significant (p = 0.048). Importantly, 28.0% of the studied group (n = 28) was treated systemically with glucocorticosteroids, methotrexate or alitretinoin. Atopic predispositions in the past (a history of asthma, allergic rhinitis, or atopic dermatitis) were indicated by 45 patients (45.0%). Moreover, 16 females (26.7%) and 12 (30.0%) males showed a correlation between occupation and disease occurrence. Only 27.0% (n = 27) of our patients were previously diagnosed with the use of patch tests (prior to the first visit at our department) and in 14.0% (n = 14) of all cases an allergic contact background was detected. Out of the whole population included in the research, 15.0% of the participants were active smokers. The difference between males and females was statistically significant (p = 0.022)—25.0% of males (n = 10), and 8.3% of females (n = 5) admitted to smoking. Additionally, the difference in the mean number of smoked cigarettes was statistically significant (1.98 $\pm$ 4.60 for males; 0.83 $\pm$ 2.94 for females; p = 0.029). All data concerning group characteristics are presented in Table 1.

Table 1. Demographic characteristics, risk factors, previous treatment and lesion location. Gender division has been applied, with the indication of the statistical significance.

Characteristics	Whole Population (n = 100)	Females (n = 60)	Males (n = 40)	p
Age, years (mean ± SD)	46.0 ± 17.23	46.6 ± 18.27	36.9 ± 13.2	NS
Disease duration, months (mean ± SD)	42.5 ± 60.84	30.85 ± 40.34	27.7 ± 7.1	NS
Exacerbation count in last 12 months (mean ± SD)	4.67 ± 3.55	4.72 ± 2.98	4.60 ± 4.31	NS
Previous treatment	71 (71.0%)	47 (78.3%)	24 (60.0%)	0.048
Systemic treatment	28 (28.0%)	17 (28.3%)	11 (27.5%)	NS
History of atopy/allergy	45 (45.0%)	26 (43.3%)	19 (47.5%)	NS
Observed correlation between disease and occupation	28 (28.0%)	16 (26.7%)	12 (30.0%)	NS
Diagnosed allergic contact background	14 (14.0%)	8 (13.3%)	6 (15.0%)	NS
Previous patch testing	27 (27.0%)	13 (21.7%)	14 (35.0%)	NS
Smokers	15 (15.0%)	5 (8.3%)	10 (25.0%)	0.022
Cigarettes count, number (mean ± SD)	1.29 ± 3.71	0.83 ± 2.94	1.98 ± 4.60	0.029
Lesion location				
Only hands	65 (65.0%)	38 (63.3%)	27 (67.5%)	NS
Hands and feet	23 (23.0%)	15 (25.0%)	8 (20.0%)	NS
Disseminated lesions	12 (12.0%)	7 (11.7%)	(12.5%)	NS

NS—not significant.

Considering the IGA-CHE, no patients were allocated in IGA-CHE group 0. Briefly, 15% of individuals (n = 15) belonged to IGA-CHE group 1, 25.0% (n = 25) belonged to IGA-CHE group 2, 37.0% (n = 37) belonged to IGA-CHE group 3, and 23.0% (n = 23) belonged to IGA-CHE group 4. Regarding the HECSI, the mean value was equal to 35.0 ± 27.8 points, with 29.3 ± 26.7 points for males and 38.8 ± 28.1 points for females. Table 2 presents the size of the particular HE severity groups, regarding the IGA-CHE, whereas Table 3 relates to the HECSI. When it comes to IGA-CHE scores for males and females, most of the men had scores falling within IGA groups 1 and 2 (n = 11; 27.5% in both groups), whereas women predominated in IGA group 3 (n = 28; 46.7%). No correlation between active smoking or the number of smoked cigarettes and disease severity was found.

Table 2. Prevalence of individual IGA-CHE severity groups among HE patients, considering gender division.

IGA-CHE Severity Group	Total Group Size/ Frequency (n = 100)	Females (n = 60)	Males (n = 40)	p
0	0 (0.0%)	0 (0.0%)	0 (0.0%)	NS
1	15 (15.0%)	4 (6.7%)	11 (27.5%)	0.004
2	25 (25.0%)	14 (23.3%)	11 (27.5%)	NS
3	37 (37.0%)	28 (46.7%)	9 (22.5%)	0.014
4	23 (23.0%)	14 (23.3%)	9 (22.5%)	NS

NS—not significant.

Table 3. Prevalence of individual HECSI severity groups among HE patients, considering gender division.

HECSI Severity Group	Total Group Size/ Frequency (n = 100)	Females (n = 60)	Males (n = 40)	p
clear	0 (0.0%)	0 (0.0%)	0 (0.0%)	NS
almost clear	34 (34.0%)	15 (25.0%)	19 (47.5%)	NS
moderate	27 (27.0%)	20 (33.3%)	7 (17.5%)	NS
severe	37 (37.0%)	23 (38.3%)	14 (35.0%)	NS
very severe	2 (2.0%)	2 (3.3%)	0 (0.0%)	NS
mean HECSI value	35.0 ± 27.8	38.8 ± 28.1	29.3 ± 26.7	0.037

NS—not significant.

Characteristics of the Itch and Pain

Within 3 days prior to the examination, the majority, 81.0% (n = 81), of individuals reported itching, whereas 53.0% (n = 53) of patients experienced pain during the same period of time. During the 'last 3 day' period both symptoms were reported more frequently in females (pruritus: 53 females (88.3%) vs. 28 males (70%), p = 0.022; pain: 47 females (78.3%) vs. 16 males (40.0%), p = 0.033). During the whole disease period, 100% of the studied group reported itching, including both males and females. In the same period, pain was perceived by 53 females (88.3%) and 29 males (72.5%). For the whole studied population itch intensity was assessed to be 6.4 ± 2.7 points, for the entire disease period, which corresponds to 'moderate' itch, and for the 'last 3 days' period, it was assessed to be 3.9 ± 2.9 points, representing 'mild' itch (both measured with NRS). The pain severity for the entire disease and the 'last 3 days' period was rated as 4.6 ± 3.2 points and 2.6 ± 3.1 points (both corresponding to 'mild' pain), respectively. Evaluating outcomes with regard to the cut-off values, analyzing the entire disease period, the 'very severe' itch group was significantly more often represented by females in comparison to males (22 (36.7%) females vs. 5 (12.5%) males; p = 0.008), while in the 'moderate' itch group the predominance of males was observed (21 (52.5%) males vs. 19 (31.7%) females; p = 0.037). The results of the itch and pain assessment are included in Tables 4 and 5, respectively.

Table 4. Results of itch assessment, considering 'last 3 days' period and entire disease period with gender division.

	Whole Population (n = 100)	Females (n = 60)	Males (n = 40)	p
Itch in last 3 days				
mean maximum itch severity, points (mean ± SD)	3.88 ± 2.93	4.77 ± 2.90	2.55 ± 2.45	0.002
no (0 points)	19 (19.0%)	7 (11.7%)	12 (30.0%)	NS
mild (1–3 points)	17 (17.0%)	6 (10.0%)	11 (27.5%)	0.003
moderate (4–6 points)	40 (40.0%)	27 (45.0%)	13 (32.5%)	NS
severe (7–8 points)	20 (20.0%)	16 (26.7%)	4 (10.0%)	NS
very severe (≥9 points)	4 (4.0%)	4 (6.7%)	0 (0.0%)	NS
Itch during the whole disease period				
maximum itch severity, points (mean ± SD)	6.35 ± 2.65	6.97 ± 2.65	5.43 ± 2.41	0.004
no (0 points)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NS
mild (1–3 points)	7 (7.0%)	3 (5.0%)	4 (10.0%)	NS

Table 4. *Cont.*

	Whole Population (n = 100)	Females (n = 60)	Males (n = 40)	p
moderate (4–6 points)	40 (40.0%)	19 (31.7%)	21 (52.5%)	0.037
severe (7–8 points)	26 (26.0%)	16 (26.7%)	10 (25.0%)	NS
very severe (≥9 points)	27 (27.0%)	22 (36.7%)	5 (12.5%)	0.008

NS—not significant.

Table 5. Results of pain assessment, considering 'last 3 days' period and entire disease period with gender division.

	Whole Population (n = 100)	Females (n = 60)	Males (n = 40)	p
Pain in last 3 days				
Maximum pain severity, points (mean ± SD)	2.55 ± 3.06	3.40 ± 3.35	1.27 ± 2.01	0.005
no pain	47 (47.0%)	23 (38.3%)	24 (60.0%)	NS
mild (1–5 points)	38 (38.0%)	23 (38.3%)	15 (37.5)	NS
moderate (>5–7 points)	11 (11.0%)	10 (16.7%)	1 (2.5%)	NS
severe (>7–10 points)	4 (4.0%)	4 (6.7%)	0 (0.0%)	NS
Pain during the whole disease				
Maximum pain severity, points (mean ± SD)	4.59 ± 3.21	5.33 ± 3.27	3.48 ± 2.81	0.005
no pain	18 (18.0%)	7 (11.7%)	11 (27.5%)	NS
mild (1–5 points)	51 (51.0%)	29 (48.3%)	22 (55.0%)	NS
moderate (>5–7 points)	18 (18.0%)	12 (20.0%)	6 (15.0%)	NS
severe (>7–10 points)	13 (13.0%)	12 (20.0%)	1 (2.5%)	NS

NS—not significant.

A positive correlation between itch as well as pain intensity and IGA-CHE was observed, when these parameters 3 days prior to the examination period were taken into account (r = 0.261, p = 0.009; r = 0.377, p = 0.002, respectively) (Figures 1 and 2). Additionally, similar correlations were found between itch and pain intensity during the entire disease period and IGA-CHE (r = 0.307, p = 0.002; r = 0.350, p < 0.001, respectively). Moreover, comparing the particular IGA-CHE severity groups, statistically significant differences in itch (p = 0.029) and pain (p = 0.002) intensity were found, only for the 'last 3 days' period. Results of the HESCI score also correlated with itch severity, in the entire disease period (r = 0.255, p = 0.01). No such correlation was found for the 'last 3 days' period. In the analysis of pain severity, a correlation with HECSI was found for both the 'last 3 days' and the entire disease period (r = 346, p < 0.001; r = 357, p < 0.001, respectively). No correlation between active smoking or the number of smoked cigarettes and itch or pain severity was found.

As for the localization of the lesions, in 65.0% (n = 65) of cases only hands were affected by eczematous lesions. Out of the whole population, 23.0% of patients reported foot skin involvement (n = 23). The remaining group (12.0%, n = 12) declared a disseminated form of the disease. Most of the investigated population (87.0%, n = 87) answered that itch was present only within skin lesions, whereas 13.0% of respondents experienced itching additionally in unaffected skin areas. No significant differences between sexes regarding the above-mentioned features were found. In all respondents reporting pain, it was localized only within skin lesions.

Severity of both itch and pain correlated with reduced QoL measured with DLQI (Table 6).

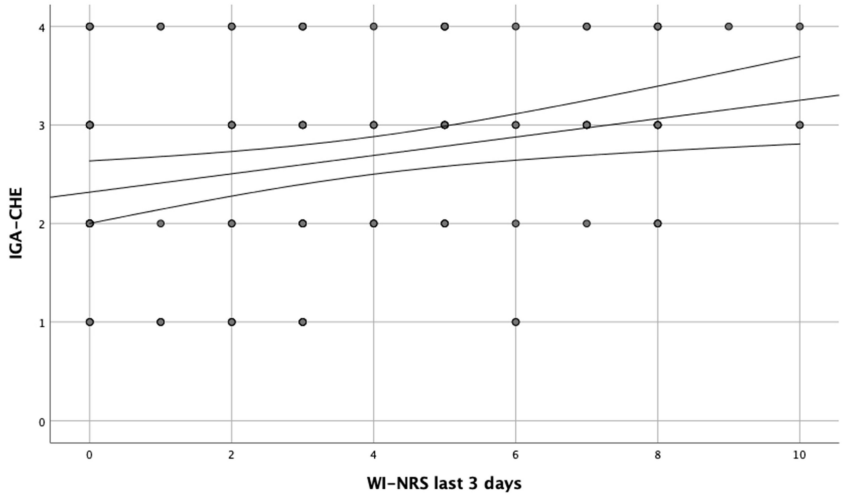

Figure 1. Correlation between worst itch (WI) in intensity of the last 3 days and IGA-CHE score.

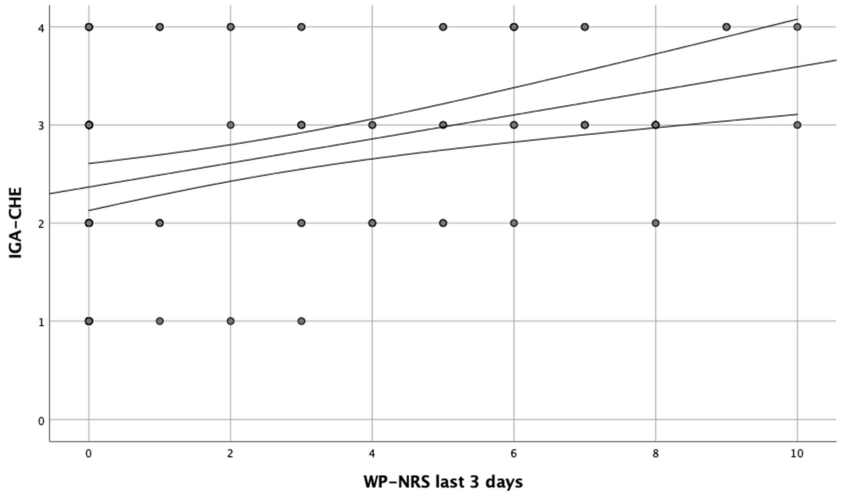

Figure 2. Correlation between worst pain (WP) in intensity of the last 3 days and IGA-CHE score.

Table 6. Correlations between itch/pain severity and DLQI.

	Correlation with DLQI (r)	*p*
Itch within last 3 days	0.436	<0.001
Pain within last 3 days	0.305	0.002
Itch during the whole disease	0.255	0.01
Pain during the whole disease	0.347	<0.001

Based on the level of stigmatization, a positive correlation between the 6-ISS score and the intensity of itching in the 'last 3 days' period was recognized (r = 0.221; p = 0.027). No correlation between the 6-ISS score and the intensity of itching in the 'entire disease' period, the intensity of pain in the 'last 3 days' period, or the intensity of pain in the 'entire-disease' period was found.

4. Discussion

According to the systematic review of Quaade et al. [39], one of the known risk factors of HE is being of a female sex which may be elucidated by various environmental factors. As a probable consequence, a higher incidence among women is reported. Additionally, a higher prevalence of atopic dermatitis in females is also observed [40] which corresponds with a higher rate of concomitant HE and atopic dermatitis among females. Within the group investigated in this research, the majority was constituted by females (60%), which may confirm the above-mentioned hypothesis. However, a difference regarding the prevalence of atopic predispositions between both sexes was not found.

Sørensen et al. [41] indicated in their study that active tobacco smoking can increase the frequency of hand eczema, especially in high-risk occupations. This was explained by the delayed restoration of the broken skin barrier in smoking HE individuals [41]. Another meta-analysis, comprising 17 studies, revealed low-quality evidence that smoking is associated with a greater incidence of hand eczema (OR, 1.18; 95% CI, 1.09–1.26) [42]. Our study shows no correlation between active smoking or the number of smoked cigarettes and disease severity as well as symptom intensity.

Over one-third of HE cases in the general population are estimated to be moderate to severe [39]. In our study, the mean HESCI score for all participants allowed us to categorize the tested population as moderate HE patients (HECSI score = 35.0 $\pm$ 27.8 points). However, when the comparison between the sexes was taken into account, a difference in disease severity was visible: 29.3 $\pm$ 26.7 points for males, which corresponds to moderate HE, and 38.6 $\pm$ 28.1 points in females, representing severe HE.

HE is described as one of the most frequently occurring diseases in patients suffering from itch [43]. Simultaneously, itch is also reported as one of the most common symptoms among HE patients, being reported by up to 78.1% of them [44–46]. In the study of Meding et al. [44], 50% of patients described the occurrence of itch as "frequent" and another one-third of the studied group reported it to be "occasional". Yet, the data characterizing it are still insufficient. Itch is also defined as a burdensome symptom causing difficulties in daily functioning (touching and gripping objects), sleep disturbances, aesthetic issues, frustration and discomfort [16,45,47]. It is usually associated with disease exacerbation and the occurrence of other symptoms such as erythema, bleeding or scaling [47]. In 2014, Ruppert et al. [46] conducted a cross-sectional analysis evaluating factors associated with the presence and severity of itch among CHE patients. The results of their study demonstrated positive correlations with itch for specific age groups (17–25 and 26–45 years), which contrasted the outcomes of other reports, in which it was revealed thatthe older population was more prone to be affected by itch [48–50]. Furthermore, a correlation between sex and the presence of itch was not found, in contrast to most available data showing that females predominate among patients suffering from itch [51–53]. The results of our study also show the predominance of women in the itch-positive group (regarding itch at 3 days prior to the study and for the entire disease period; p = 0.002 and p = 0.004, respectively). When the entire disease period in the individuals studied in our research was considered, itch correlated positively with disease severity measured with the use of both of the following instruments: IGA-CHE and HESCI. These results are in line with those of Ruppert et al. [46] in which positive a correlation of itch with different CHE severity levels (moderate, severe, and very severe) was also observed [46].

Itch can be one of the various symptoms in patients with other dermatoses such as HS (acne inversa), psoriasis and atopic dermatitis [54–56]. Comparing itch-related data in various inflammatory dermatoses, the lack of research and reports concerning HE itch

pathogenesis is visible. Considering the divisions of itch types, itching associated with HE could be classified into the group of dermatological itch (associated with chronic dermatoses). The hypothesis of pruritus of a mixed etiology, with a neurogenic component also seems plausible (taking into account the similarity to AD). The urgency for itch investigations to be conducted on HE patients is unquestionable.

Another symptom of HE that is as yet not fully characterized is pain. In a study by Dibenedetti et al. [45], the prevalence of pain in patients with severe HE was assessed to be 36.0% ± 28.5%. Among the individuals in our group, 53.0% (n = 53) of patients reported pain within the last 3 days prior to the study (37 females, 61.7%; 16 males, 40.0%). In their research, Weigandt et al. [57] determined the mean value of pain severity (NRS) to be 1.94 ± 2.67 points, which corresponds with our results (Table 4). Data concerning etiology, pathogenesis and mechanisms connected with this topic are still unclear. Although pain at 3 days prior to the study period occurred statistically more frequent in women, our study showed no statistically significant difference in pain severity in a comparison between males and females, regarding that 3 days prior to the study and during the entire disease period. Pain intensity correlated positively with IGA-CHE and HESCI scores. In 2020, Passlov et al. [58] conducted a study assessing the influence of HE on hand strength and dexterity. One of the measured parameters was pain level. Researchers observed a strong correlation between perceived disability to perform activities of daily living and pain. Their results indicated that pain experienced by HE patients may be a major limiting factor, regarding patients' daily life [58]. Depending on typical features of HE such as redness, scaling, edema, vesicles, hyperkeratosis, fissures and erosions, a hypothesis of the nociceptive origin of HE-related pain may be proposed [15]. Nevertheless, the neuropathic pain pathway should also be considered and more research on this topic is urgently required. Pain is a symptom of special significance not only in HE individuals. Patients suffering from HS, psoriasis, and AD report pain as a common symptom of their diseases [59–61].

Quality of life and its improvement are some of the most frequently discussed issues in modern medicine and patient-oriented management. Alongside AD, moderate-to-severe HE is proven to have a stronger impact on QoL compared to most other chronic conditions [62]. A significant impairment in quality of life was observed even in patients with low HECSI scores (low severity of HE) [63]. Our study additionally indicates that the severity of the itch and pain also influences significantly HE patients' QoL. What can positively influence the QoL of HE patients is proper education concerning the course of the disease. In the study of Rönsch et al. [64] special attention was focused on the need to receive appropriate and complete information from a physician. Patients also reported the high value of caregivers who listen to them [64].

Our study has several limitations that should be considered. The extent of the study involved only one center from Wroclaw, Lower Silesia, Poland, which reduces the variability of the population. The small sample size is also worth mentioning. In the future, a multicenter study involving patients from different geographical regions would be of special importance. So far, our group focuses neither on the pathogenesis of itch and pain, nor the pathways responsible for transmitting them, which would be crucial for subsequent investigations. Nevertheless, it should be emphasized that our work extends the current knowledge on subjective symptoms in HE patients.

5. Conclusions

Because of the wide range of etiological factors and clinical pictures, HE remains a disease entity which should constantly be investigated. Being one of the most frequently reported HE complaints, itch influences all aspects of patients' life. Concerning the data suggesting that up to 81.0% of individuals suffer form HE, itch correlates with disease severity and is often associated with HE exacerbations. Our study shows that itch is reported more frequently by females (88.3% vs. 70.0%), concerning that at the '3-days-prior to the study' period. Its prevalence was higher than the incidence of pain within a comparable period (81.0% vs. 53.0%). Pain in HE is a symptom which requires more

attention and is often underestimated. Pain, similarly to itch, dominates among females. Our study demonstrates also that pain intensity correlates positively with the severity of the disease. Both itch and pain are major symptoms associated with HE, impairing patients' well-being. Developing data characterizing them may help both physicians in improving their management and scientists in creating new therapeutic options. Symptom-decreasing or even liberating treatment would definitely have a positive influence on patients' QoL and stigmatization level.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and approved by the Wroclaw Medical University Ethics Committee (consent no. KB-234/2023, 9 March 2023).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets generated and analyzed in the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: J.C.S. has served as an advisor for AbbVie, LEO Pharma, Menlo Therapeutics, Novartis, Pierre Fabre, Sienna Biopharmaceuticals and Trevi; has received speaker honoraria from AbbVie, Eli Lilly, Janssen, LEO Pharma, Novartis, Sanofi-Genzyme, Sun Pharma and Berlin-Chemie Mennarini; has served as an investigator; and has received funding from AbbVie, Amgen, Galapagos, Holm, Incyte Corporation, InflaRX, Janssen, Menlo Therapeutics, Merck, Boehringer Ingelheim, Novartis, Pfizer, Regeneron, Trevi, and UCB. Other authors report no conflicts of interests.

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6. ARTYKUŁ TRZECI:

PSYCHOSOCIAL CONSEQUENCES OF HAND ECZEMA – A PROSPECTIVE CROSS-SECTIONAL STUDY

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Psychosocial Consequences of Hand Eczema—A Prospective Cross-Sectional Study

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Abstract: Background: Hand eczema (HE) is a chronic inflammatory disease with a high prevalence, negatively influencing patients' quality of life (QoL). It may also affect patients' psychological status. The aim of this study was to assess and characterize the psychological burden of HE, its influence on patients' QoL, and the presence and severity of anxiety and depressive disorders in HE patients. Methods: The study group consisted of 100 adult HE individuals. To assess the severity of the disease, two instruments were used: the Investigator Global Assessment for Chronic Hand Eczema (IGA-CHE) scale and the Hand Eczema Severity Index (HECSI). Assessment of patients' quality of life (QoL) was obtained with the use of the DLQI tool. Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) questionnaires were employed to assess depression and anxiety, respectively, as well as a modified version of the Hospital Anxiety and Depression Scale (HADS-M). Results: The mean DLQI value for the whole group reached 11.62 ± 6.35 points (13.27 ± 6.67 points in females and 9.15 ± 4.95 points in males; p = 0.023). A decrease in QoL correlated positively with the severity of the disease and the severity of itch and pain. In 17 patients (17%), a possible diagnosis of depressive disorder was found. Patients scoring higher results on the PHQ-9 and HADS-M depression (D) questionnaires reported greater intensity of the itch (r = 0.363, p < 0.001, and r = 0.237, p = 0.017, respectively) and the pain (r = 0.445, p < 0.001, and r = 0.287, p = 0.004, respectively). The anxiety disorder might possibly be diagnosed in 25% of patients (n = 25). This study revealed a positive correlation between the severity of the anxiety symptoms, measured with the use of both GAD-7 and HADS-M anxiety (A) tools, and the intensity of the pain (r = 0.248, p = 0.013, and r = 0.342, p = 0.001, respectively). The severity of depressive and anxiety symptoms correlated positively with the severity of the disease. Conclusions: The psychosocial burden of HE is an undeniable phenomenon. The disorder influences patients' QoL and may cause mental disturbances such as depression and anxiety disorders.

Keywords: hand eczema; itch; pain; chronic inflammation; inflammatory disease; quality of life; anxiety; depression

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1. Introduction

Hands can be defined as a terminal part of a human's arm, responsible for touching, grabbing, moving, or feeling things. Thanks to their mobility and visibility, they play an important role in not only work or social life but also verbal (writing or sign language) and non-verbal communication. Hand eczema (HE), being a chronic inflammatory disease of high prevalence, depends on various etiological factors [1]. The clinical picture of HE is heterogeneous, and the course of the disease presents a wide spectrum. Itching and pain are described as two of the most burdensome symptoms of HE, correlating with the severity of the disease [2,3]. Also, because of the localization of skin lesions on hands and often challenging treatment, the disorder frequently places a major psychological burden on patients suffering from HE [1,4]. It undeniably negatively influences interpersonal relations and quality of life (QoL), causing embarrassment, stigmatization, and social withdrawal [5,6]. According to data available in the literature, the disease also has a major

financial consequence, causing days lost through illness and the need to use sick leave because of the hands' condition and associated symptoms [5,7]. As a result of all the above-mentioned factors, HE may severely affect patients' psychological status, causing depressive or anxiety disorders, a reduction in self-esteem, or sexual dysfunctions [5,8].

In this study, the authors aimed to assess and characterize the psychosocial burden of HE, the influence of the disease on QoL, and both the presence and severity of anxiety and depressive disorders in HE patients.

2. Materials and Methods

2.1. Studied Group

A cross-sectional, prospective study was performed. The studied population comprised a group of 100 consecutive individuals. All participants were patients of the Department of Dermatology, Venereology, and Allergology in Wroclaw, Poland, where they were either admitted as inpatients to the hospital ward or received treatment as outpatients at the outpatient clinic. The authors of the study (dermatology specialists and dermatology residents) recruited them on the day of admission. A total of 60% of the group were women (n = 60) and 40% were men (n = 40). Population age ranged from 18 to 80 years (mean 46.0 ± 17.23). The diagnosis of HE was made based on clinical manifestation criteria. The mean duration of the disease was determined at 42.5 ± 60.84 months and ranged from 3 to 396 months. Study inclusion criteria were as follows: ≥18 years old (adult age) and a course of the disease lasting over 3 months (chronic HE diagnosis). All subjects with suspicion of CHE but waiting for the final diagnosis to be made were excluded from the study (uncertain biopsy result, unclear clinical picture). Detailed group characteristics may be found in Table 1.

Table 1. Group characteristics.

Characteristics	Whole Population (n = 100)	Females (n = 60)	Males (n = 40)	*p*
Age, years (mean ± SD)	46.0 ± 17.23	46.6 ± 18.27	36.9 ± 13.2	NS
Disease duration, months (mean ± SD)	42.5 ± 60.84	30.85 ± 40.34	27.7 ± 7.1	NS
Previous treatment	71 (71.0%)	47 (78.3%)	24 (60.0%)	0.048
Systemic treatment	28 (28.0%)	17 (28.3%)	11 (27.5%)	NS
History of atopy/allergy	45 (45.0%)	26 (43.3%)	19 (47.5%)	NS
Diagnosed allergic contact background	14 (14.0%)	8 (13.3%)	6 (15.0%)	NS
Previous patch testing	27 (27.0%)	13 (21.7%)	14 (35.0%)	NS
Itch in last 3 days	81 (81.0%)	28 (70.0%)	53 (88.3%)	0.022
Pain in last 3 days	53 (53.0%)	16 (40.0%)	37 (61.7%)	0.033
Lesion location				
Only hands	65 (65.0%)	38 (63.3%)	27 (67.5%)	NS
Hands and feet	23 (23.0%)	15 (25.0%)	8 (20.0%)	NS
Disseminated lesions	12 (12.0%)	7 (11.7%)	(12.5%)	NS

NS—'not significant'.

This study was approved by the local ethics committee (Consent No. KB-234/2023), and written informed consent was obtained from all studied individuals.

2.2. Disease Severity Assessment

To assess the severity of the disease, two instruments were used: the Investigator Global Assessment for Chronic Hand Eczema (IGA-CHE) scale [9] and the Hand Eczema Severity Index (HECSI) [10].

IGA-CHE (Investigators Global Assessment; IGA) classifies the severity of HE into five categories: 'clear' (IGA-CHE 0), 'almost clear' (IGA-CHE 1), 'mild' (IGA-CHE 2), 'moderate' (IGA-CHE 3), and 'severe' (IGA-CHE 4) [9].

Another approach employed for assessing the disease severity in patients with HE included using the HECSI scale. This scale incorporates the intensity, extent, and clinical manifestations of the ailment. The hands of each patient are divided into five distinct regions: fingertips, fingers (excluding the fingertips), palm of the hand, back of the hand, and wrists. Within each of these regions, the intensity of six specific clinical indicators—erythema, induration/papulation, vesicles, fissuring, scaling, and edema—is assessed and graded using the following scale: 0 (indicating no observable skin changes), 1 (indicating mild disease), 2 (indicating moderate disease), and 3 (indicating severe disease). For each individual area, the cumulative affected area is scored between 0 and 4 to indicate the extent of clinical symptoms (0 = 0%, 1 = 1–25%, 2 = 26–50%, 3 = 51–75%, and 4 = 76–100%). The score assigned to the extent of clinical symptoms within each area is then multiplied by the total sum of the intensity levels for each clinical feature and added together. The final HECSI score ranges from 0 to 360 points, with 360 representing the highest level of severity [10]. To classify patients into severity groups, the following cutoff values were applied: clear (0 points; HECSI 0), almost clear (1–16 points; HECSI 1), moderate (17–37 points; HECSI 2), severe (38–116 points; HECSI 3), and very severe (117 points or higher; HECSI 4) [10,11].

2.3. Itch and Pain Assessment

The intensity of itch and pain was assessed using the Numeric Rating Scale (NRS). Study participants were tasked with rating the intensity of the most severe itch and pain experienced in the three days preceding the study, as well as the most intense itch and pain since the disease's onset.

The NRS is a tool designed to evaluate the intensity of specific symptoms like itch or pain. This scale is unidimensional and spans from 0 (indicating no itch/pain) to 10 (representing the most intense itch/pain imaginable). The interpretation of the Itch-NRS scoring is as follows: no itch (0 points), mild itch (1–3 points), moderate itch (4–6 points), severe itch (7–8 points), and very severe itch ($\geq$9 points) [12]. The following cutoffs on the pain-related NRS were implemented for pain assessment: $\leq$5—mild pain; 5–7—moderate pain; and 7–10—indicating severe pain on the 0–10 rating scale [13].

2.4. QoL Assessment

For the evaluation of patients' quality of life (QoL), the Polish version of the Dermatology Life Quality Index (DLQI) questionnaire was employed [14]. The DLQI is a specialized dermatological tool designed to assess symptoms and emotions, daily activities, leisure, work and school-related aspects, relationships, and treatment side effects over the preceding 7 days. It is composed of 10 items, each assigned a score ranging from 0 to 3 points (0 indicating 'not at all'; 1 indicating 'a little'; 2 indicating 'a lot'; 3 indicating 'very much'). These scores are then summed to obtain a total DLQI score, which ranges from 0 to 30 points. A score of 0–1 point signifies the minimal impact of the disease on QoL; 2–5 points indicate a small impact; 6–10 points represent a moderate impact; 11–20 points suggest a large impact; and 21–30 points indicate an extremely large impact [14–16].

2.5. Depression and Anxiety Assessment

Various questionnaires (Polish versions) were used to screen for depression and anxiety among the studied population, such as the Patient Health Questionnaire-9 (PHQ-9) [17], the 7-item anxiety scale (GAD-7) [18], and the Hospital Anxiety and Depression Scale (HADS-M) [19].

The PHQ-9 is a nine-item tool created to screen for depression in different medical settings. Patients are assessing the incidence of each of nine major depressive disorder diagnosis criteria (based on the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV) occurrences, scoring 0 ('not at all'), 1 ('several days'), 2 ('more than half of the

days'), and 3 ('nearly every day'). Standard cutoff scores were used as 5, 10, 15, and 20, representing cutoff points for mild, moderate, moderately severe, and severe depression, respectively. When screening for a depression diagnosis, a result of 10 points or greater presents 88% of both sensitivity and specificity for the possibility of a major depression diagnosis and is defined as a diagnostic cut-point [17,20,21].

The GAD-7 scale is a self-reported measure screening for the presence of generalized anxiety disorder (GAD) and the level of anxiety and is composed of seven items. Each item is a statement describing general somatic tension or worry and is rated on a 4-point Likert-type scale assessing symptom frequency in the range from 0 ('not at all sure') to 3 ('nearly every day'). The higher the score, the higher the level of GAD symptoms. The sum of 5, 10, and 15 points were implemented as the cutoff values for mild, moderate, and severe anxiety, respectively. A score of 8 or higher is a cut-point for identifying the probable occurrence of generalized anxiety disorder [18,22–24].

HADS-M stands for a modified version of the Hospital Anxiety and Depression Scale (HADS) created by Zigmond et al. [19]. This variant comprises 16 queries, with a potential score of 0 to 3 points for each question. The highest achievable scores are distinct for depression (21 points), anxiety (21 points), and aggression (6 points). The scoring criteria adopted for the anxiety and depression subsections are as follows: no disorders (0–7 points), borderline states (8–10 points), and disorders (11–21 points) [25,26].

2.6. Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics v. 26 (SPSS Inc., Chicago, IL, USA) software. In the beginning, the normality of all data was assessed with the Shapiro–Wilk normality test. Subsequently, minimum, maximum, means, standard deviations, medians, and quartiles were calculated. In order to assess quantitative variables, the Student's *t*-test and Mann–Whitney U test, depending on normality, were implemented. For qualitative data, the Chi2 test was used. For the assessment of differences between more than two groups, ANOVA or Kruskal–Wallis one-way analysis of variance on ranks was used. Post-hoc analysis with Bonferroni corrections was implemented for both tests. The two-sided *p*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Disease Severity Assessment

Out of the examined population of 100 individuals (n = 100), the distribution across IGA-CHE categories was: group IGA-CHE 1 (almost clear) comprised 15.0% (n = 15), group IGA-CHE 2 (mild) included 25.0% (n = 25), group IGA-CHE 3 (moderate) accounted for 37.0% (n = 37), and group IGA-CHE 4 (severe) constituted 23.0% (n = 23). In terms of gender breakdown, the majority of men fell into IGA 1 and 2 groups (n = 11; 27.5% in both groups), while among women, IGA 3 was the predominant category (n = 28; 46.7%). Regarding the HECSI score, the mean value was 35.0 ± 27.8 points (29.3 ± 26.7 points in males and 38.8 ± 28.1 points in females).

3.2. QoL Assessment

The mean DLQI value for the whole group was assessed at 11.62 ± 6.35 points. In most cases, HE had a moderate (33%; n = 33) or very large (39%; n = 39) effect on patients' QoL. In 18% of respondents, the disease's effect on QoL was none or small (2%, n = 2, and 16%, n = 16, respectively), and 10 patients assessed that effect as extremely large. Considering the gender division among females, the mean DLQI value reached 13.27 ± 6.67 points, while the mean DLQI score for males amounted to 9.15 ± 4.95 points; the difference was statistically significant ($p = 0.023$). In 28 (46.7%) females, the influence on QoL was found to be very large, which was the most common result, whereas the most frequent in males was a moderate effect (n = 17; 42.5%). Detailed data are presented in Table 2.

Table 2. Distribution of patients in DLQI groups, considering gender division.

DLQI Group (Effect on Patients QoL)	Total Group Size/ Frequency (n = 100)	Females (n = 60)	Males (n = 40)	*p*
no effect	2 (2.0%)	1 (1.7%)	1 (2.5%)	0.023
small	16 (16.0%)	6 (10.0%)	10 (25.0%)	
moderate	33 (33.0%)	16 (26.7%)	17 (42.5%)	
very large	39 (39.0%)	28 (46.7%)	11 (27.5%)	
extremely large	10 (10.0%)	9 (15.0%)	1 (2.5%)	

Considering the whole studied population, statistically significant differences in QoL were found when comparing different IGA-CHE severity groups ($p < 0.001$). Post hoc analysis revealed that when comparing individual IGA-CHE severity groups, the difference in the decrease in QoL was statistically significant in four cases: 1 (almost clear) vs. 3 (moderate) ($p < 0.001$); 1 (almost clear) vs. 4 (severe) ($p < 0.001$); 2 (mild) vs. 3 (moderate) ($p = 0.009$); 2 (mild) vs. 4 (severe) ($p < 0.001$). In low disease severity groups, a lower decrease in patients' QoL was observed. Outcomes are presented in Figure 1.

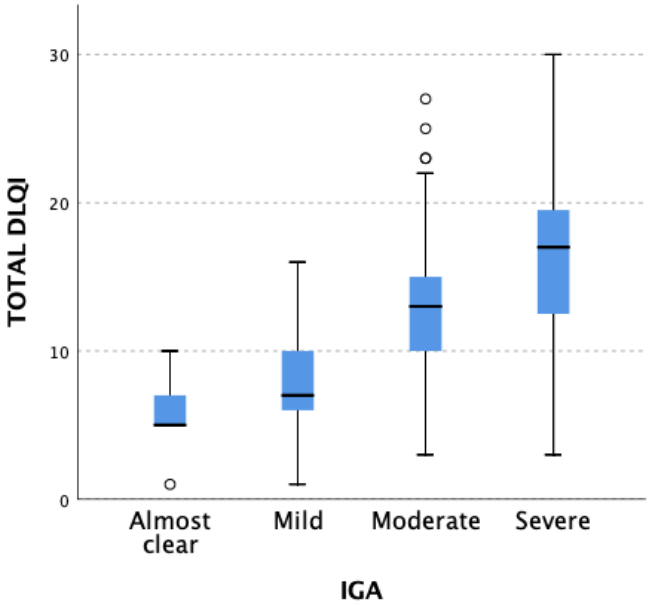

Figure 1. Differences in total DLQI score result in patients from particular IGA-CHE severity groups ($p < 0.001$). The statistically significant difference was observed when comparing the following IGA-CHE groups: 1 (almost clear) vs. 3 (moderate) ($p < 0.001$), 1 (almost clear) vs. 4 (severe) ($p < 0.001$), 2 (mild) vs. 3 (moderate) ($p = 0.009$), and 2 (mild) vs. 4 (severe) ($p < 0.001$). Mild–severity groups present a lower decrease in QoL. White circles correspond to patients with DLQI scores out of range.

Similar observations were made concerning patients from different HECSI groups ($p < 0.001$). Statistically significant differences in reduction in QoL measured in DLQI were also found when comparing patients from the HECSI 1 (almost clear) group vs. the HECSI 2

(moderate) group ($p = 0.023$) and the HECSI 1 (almost clear) group vs. the HECSI 3 (severe) group ($p < 0.001$). Results are presented in Figure 2.

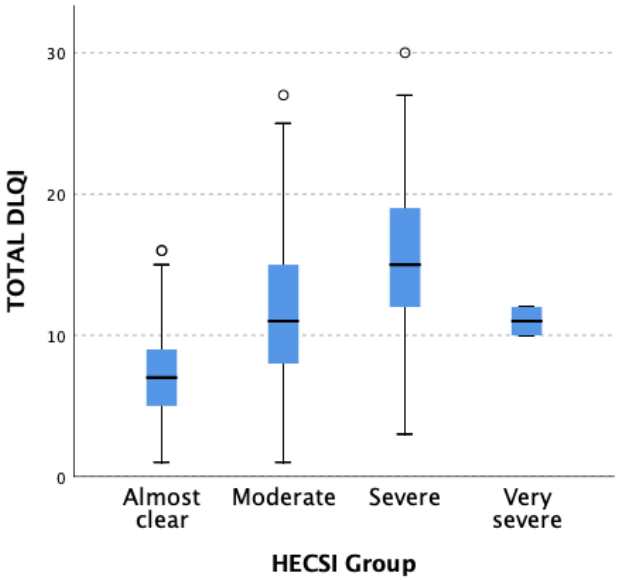

Figure 2. Differences in total DLQI score result in patients from particular HESCI groups ($p < 0.001$). The statistically significant difference was observed when comparing the following HECSI groups: 1 (almost clear) vs. 2 (moderate) ($p = 0.023$) and 1 (almost clear) vs. 3 (severe) ($p < 0.001$). White circles correspond to patients with DLQI scores out of range.

A decrease in QoL correlated positively with the severity of the disease measured in IGA-CHE (r = 0.617; $p < 0.001$) and in HECSI (r = 0.579; $p < 0.001$).

The total DLQI score correlated positively with the severity of both assessed symptoms, itch and pain, in the 3 days prior to the study period (r = 0.436, $p < 0.001$, and r = 0.305, $p = 0.002$, respectively). No correlation between the DLQI score and the duration of the disease was found ($p > 0.05$).

3.3. Depression Assessment (PHQ-9 and HADS-M (D))

3.3.1. PHQ-9

Based on the PHQ-9 cut-point score (≥10 points), among the whole studied population, in 17 patients (17%), a possible diagnosis of depressive disorder was documented. It was more common among females (n = 13; 21.7%) than males (n = 4, 10%), yet the difference between both groups was statistically insignificant.

In relation to the whole group, the mean PHQ-9 score was 6.3 ± 4.9 points. The mean value in females was 7.12 ± 5.14 points and 5.08 ± 4.14 points in males. The difference was statistically insignificant. Table 3 demonstrates the distribution of patients in depression severity groups according to the PHQ-9 score.

Differences in total PHQ-9 score results in patients from particular IGA-CHE severity groups were found and are presented in Figure 3. When comparing IGA-CHE 4 (severe) group patients with IGA-CHE 2 (mild) group patients, significantly higher results of PHQ-9 ($p = 0.028$) were observed. In other IGA-CHE groups (1 (almost clear) vs. 2 (mild), 1 (almost clear) vs. 3 (moderate), and 3 (moderate) vs. 4 (severe)), results were numerically higher but did not achieve statistical significance.

Table 3. Distribution of patients in depression severity groups according to PHQ-9 score, considering gender division.

Depression Severity Group (According to PHQ-9)	Total Group Size/ Frequency (n = 100)	Females (n = 60)	Males (n = 40)	*p*
mild	43 (43.0%)	24 (40.0%)	19 (47.5%)	NS
moderate	35 (35.0%)	19 (31.7%)	16 (40.0%)	
moderately severe	13 (13.0%)	10 (16.7%)	3 (7.5%)	
severe	9 (9.0%)	7 (11.7%)	2 (5.0%)	

NS—'not significant'.

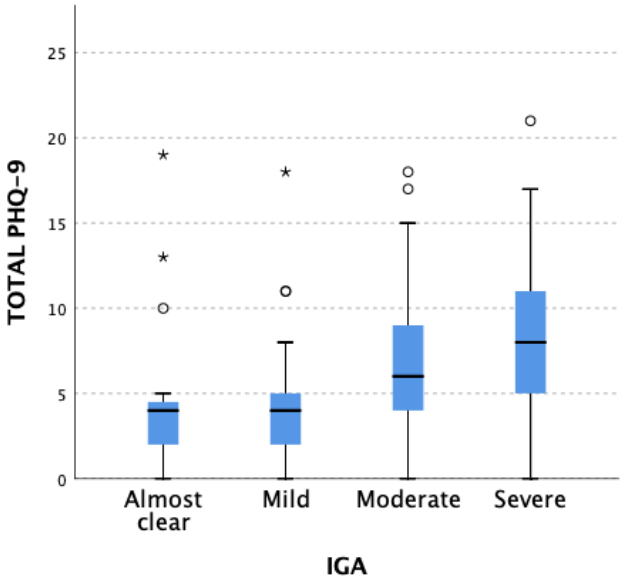

Figure 3. Differences in total PHQ-9 scores result in patients from particular IGA-CHE severity groups. Patients representing the IGA-CHE 4 (severe) group compared with the IGA-CHE 2 (mild) group showed significantly higher results of PHQ-9 ($p = 0.028$). When comparing other groups (1 (almost clear) vs. 2 (mild), 1 (almost clear) vs. 3 (moderate), and 3 (moderate) vs. 4 (severe)), results were numerically higher but did not achieve statistical significance. White circles and asterisks correspond to patients with PHQ-9 scores out of range.

The correlation between the intensity of depressive symptoms and the severity of HE was detected for both HECSI (r = 0.264; $p = 0.008$) and IGA-CHE scores (r = 0.329; $p = 0.001$). Patients scoring higher on the PHQ-9 questionnaire reported greater intensity of the itch (r = 0.363; $p < 0.001$) and pain (r = 0.445; $p < 0.001$) in the last 3 days prior to the study. PHQ-9 scores also correlated with the decrease in QoL (r = 0.537; $p < 0.001$). Moreover, a positive correlation was found between PHQ-9 scores and other scales assessing not only depression (HADS-D: r = 0.664; $p < 0.001$) but also anxiety: GAD-7 (r = 0.617; $p < 0.001$) and HADS-A (r = 0.690; $p < 0.001$).

3.3.2. HADS-M: Depression (D)

The distribution of patients in depressive disorder severity groups, considering gender division, is presented in Table 4.

Table 4. Distribution of patients in depressive disorder severity groups (according to HADS-M), considering gender division.

Depressive Disorder Severity Group (According to HADS-M)	Total Group Size/ Frequency (n = 100)	Females (n = 60)	Males (n = 40)	*p*
no disorders	80 (80.0%)	44 (73.3%)	36 (90.0%)	NS
borderline states	14 (14.0%)	11 (18.3%)	3 (7.5%)	
disorders	6 (6.0%)	5 (8.3%)	1 (2.5%)	

NS—'not significant'.

For the whole group, the mean value of HADS-M (D) was 4.7 ± 3.1 points. Among females, it was assessed at 5.22 ± 3.29 points, whereas in males, it amounted to 3.83 ± 2.74 points. The difference was statistically significant ($p = 0.029$).

The intensity of depressive symptoms measured in HADS-M correlated positively with the severity of the disease (for IGA-CHE: r = 0.283; $p = 0.004$, and HESCI: r = 0.228; $p = 0.004$, respectively), as well as with the intensity of the itch (r = 0.237; $p = 0.017$) and the pain (r = 0.287; $p = 0.004$). No correlation with the duration of the disease was found.

3.4. Anxiety Assessment (GAD-7 and HADS-M (A))

3.4.1. GAD-7

In accordance with GAD-7 anxiety diagnostic criteria (a cut-point of 8 points or higher), anxiety disorder might be diagnosed in 25% of the whole group (n = 25): 17 females (28.3%) and 8 males (20%). The difference did not reach statistical significance.

The mean GAD-7 score for the whole studied population was assessed at 5.8 ± 4.0 points. It reached 6.17 ± 4.13 points in females and 5.23 ± 3.75 points in males, with no significant difference between sexes. Detailed data concerning GAD-7-score-dependent anxiety severity groups are shown in Table 5.

Table 5. Distribution of patients in anxiety disorder severity groups (according to GAD-7), considering gender division.

Anxiety Severity Group (According to GAD-7)	Total Group Size/ Frequency (n = 100)	Females (n = 60)	Males (n = 40)	*p*
mild	43 (43.0%)	22 (36.7%)	21 (52.5%)	NS
moderate	39 (39.0%)	26 (43.3%)	13 (32.5%)	
severe	18 (18.0%)	12 (20.0%)	6 (15.0%)	

NS—'not significant'.

Interestingly, an association between the severity of pain and the presence of an anxiety diagnosis was observed. The mean pain severity in patients with diagnosed anxiety was 3.48 ± 3.31 points, whereas the mean value in patients without anxiety amounted to 2.24 ± 2.93 points, both measured on the NRS scale. The difference was statistically significant ($p = 0.034$). No such dependency was observed for the itch ($p > 0.05$).

The severity of the anxiety disorder diagnosis among the studied population correlated positively with the severity of the disease measured in IGA-CHE (r = 0.223; $p = 0.026$). There was no such correlation found for the HECSI score. The intensity of anxiety symptoms also correlated with the intensity of the pain (r = 0.248; $p = 0.013$). No such relationship was documented between anxiety scores and itch intensity ($p > 0.05$). No correlation between the severity of the anxiety and the duration of the disease was observed ($p > 0.05$). GAD-7 outcomes also correlated with results obtained with the HADS-M (A) questionnaire (r = 0.712; $p < 0.001$).

3.4.2. HADS-M: Anxiety (A)

The mean value of HADS-M (A) was 5.3 ± 3.0 points when considering the whole research population. The mean result of the evaluation in females was 5.87 ± 3.36 points and 4.40 ± 2.12 points in males. The difference was statistically significant (p = 0.001). Table 6 shows detailed data concerning the severity of anxiety disorders.

Table 6. Distribution of patients in anxiety disorder severity groups (according to HADS-M), considering gender division.

Anxiety Disorder Severity Groups (According to HADS-M)	Total Group Size/ Frequency (n = 100)	Females (n = 60)	Males (n = 40)	p
no disorders	80 (80.0%)	41 (68.3%)	39 (97.5%)	0.001
borderline states	14 (14.0%)	15 (25.0%)	0 (0.0%)	
disorders	6 (6.0%)	4 (6.7%)	1 (2.5%)	

A positive correlation was observed between the intensity of anxiety symptoms and the severity of the disease, but solely for the IGA-CHE score (r = 0.230; p = 0.022). Similarly to the GAD-7 assessment, the results of HADS-M (A) correlated with the intensity of pain (r = 0.342; p = 0.001). However, no such association was found for the itch. Intriguingly, the intensity of anxiety symptoms exhibited a negative correlation with the disease's duration (r = −0.215; p = 0.032).

4. Discussion

The impact of HE on patients' QoL is significant. In the paper published by Cazzaniga et al. [7] concerning 199 individuals suffering from HE, most patients reported a moderate (33.7%) or large (39.4%) effect of the disease on their QoL. The mean DLQI score amounted to 9.7 ± 5.8 points [7]. The impact of HE on DLQI was significantly higher among females, which was also observed in other studies [27,28]. The results of our research stay in line with these findings. Our study shows additionally that the severity of HE among women is higher, which can potentially result in a higher QoL decline. Mollerup et al. (2014) [29] created an analysis of gender differences in patients with hand eczema. They concluded that the higher decrease in QoL in females may be associated with the severity of the disease and the quantity of exacerbating factors (such as contact with detergents, hygiene products, handling of food, or handwashing). Also, a significant role of work-related and everyday exposures or routines in treatment and prevention was underlined [29]. Visual and practical aspects associated with the need to apply protection measures and the presence of skin lesions were underlined [7]. Additionally, the authors distinguished factors having a strong impact on DLQI, such as lesions localized on the back of the hands, the presence of the itch, or the necessity to wear gloves. Moreover, HE influenced patients' ability to work: 37% of participants used sick leave, and 15% of them left or changed jobs because of the disease [7]. Data were comparable to the results of different studies [30].

More importantly, the process of sickness and being sick, as well as all their consequences, generate a cost for patients and the whole healthcare system. Loss of productivity, followed by hospitalization and travel expenses, were recognized as the most cost-consuming contributors [31].

Our study shows that several HE symptoms (itch, pain) may also be considered factors whose intensity interferes with the impairment of QoL. A correlation between itch severity and the increase in DLQI scoring was also demonstrated by Wang et al. [32]. On the contrary, in the study of Ruppert et al. [33], itch in severe and very severe forms of HE was observed to be correlated with small or moderate impairments in QoL. More studies in this area need to be carried out.

Apart from the severity of the itch, a positive correlation between pain severity and loss of QoL was observed among the group of our patients. Torisu-Itakura et al. [34], in the study concerning the impact of itch and skin pain on QoL in adult patients with atopic

dermatitis in Japan, revealed that the coexistence of itch and skin pain may cause sleep disturbances or may impair work-related activities. Moreover, patients experiencing both itch and pain were more likely to complain and be bothered by their symptoms ($p = 0.034$). That same group of patients was more likely to be dissatisfied with the lack of improvement and inconveniences of the treatment [34]. Moberg et al. [35] also noticed that pain may be a symptom impairing HE patients' QoL. In a population of young men and women (18–34 years), pain was described as a factor significantly influencing QoL [35].

Multiple studies show anatomical, physiological, functional, and ontogenetic connections between the skin and the nervous system. Various dermatoses have a major impact on patients' psychological status, which may be confirmed by the comorbidity of certain chronic inflammatory skin diseases (such as psoriasis, atopic dermatitis (AD), or hidradenitis suppurativa (HS)) and several mental symptoms or syndromes. It has been estimated that in over 30% of patients suffering from dermatological disorders, psychiatric comorbidity is diagnosed [36]. Markers of inflammation were reported to be elevated in both skin and mental diseases [34,35,37,38].

The idea of an active inflammatory process taking place in the human system is becoming more and more significant among biological theories explaining probable causes of depression. Inflammation indicators that are considered to lead to a deficit in serotonin and melatonin (one of the major reasons for depressive disorder) are as follows: inflammatory enzymes (manganese superoxide dismutase (MnSOD), myeloperoxidase (MPO)), pro- and anti-inflammatory cytokines, and oxidative stress [39]. In some populations, a dysregulated immunological response has been linked to the onset of depression [40].

Systemic inflammation seems to be mainly correlated with depressive symptoms. However, anxiety disorders are also considered to be linked with increased inflammation, primarily because of the activation of the stress response and stimulation of immunological cells to release cytokines [41,42].

Patients suffering from chronic dermatoses such as HS are considered to be more likely to develop depressive symptoms. Studies available in the literature also suggest an association between HS and an elevated risk of anxiety [43,44]. The research of Rymaszewska et al. [37] seems to confirm these findings, showing a high prevalence of mental disorders among that particular group of patients.

Also, up to 90% of patients with psoriasis were reported to have psychological comorbidity [45], with the predominance of anxiety disorders [46,47]. Exacerbation of psoriatic lesions is associated with increased production of inflammatory mediators, which may contribute to neurotransmitter imbalance and cause or intensify existing symptoms of depression and anxiety [48]. Despite the high prevalence of mood disturbances among patients with psoriasis, the common lack or delay of their diagnosis is underlined by some experts, potentially resulting in clinical consequences [49].

A systemic review by Rønnstad et al. [50] demonstrated an increased risk of the coexistence of AD with depression and anxiety in adults. Another study found that 20.1% of AD patients were diagnosed with depressive disorder, compared with 14.8% in the non-AD control group [51]. The pathophysiological and clinical importance of the IL-4/IL-13 axis in AD has been proven [52]. A reduction in depressive and anxiety symptoms (measured with HADS) was presented in two randomized placebo-controlled studies on dupilumab (a monoclonal antibody binding to IL-4/IL-13 receptors), which may link inflammation and mood disorders in the AD patient population [53,54].

In a 15-year follow-up study on HE, as many as 96% of patients reported that the disease influenced their psychosocial functions [55]. In 2018, Marron et al. [6] constructed a large European multicenter study to identify the psychological, social, and clinical characteristics of patients with HE. Statistically significant differences were found between female patients and female controls regarding anxiety and depression measured with HADS—symptoms of both disorders were more severe in HE individuals. Also, the severity of both anxiety and depression differed when comparing females and males (7.00 vs. 5.00 for anxiety, respectively; 4.00 vs. 3.00 for depression, respectively; both mea-

sured with HADS). A similar dependency was also observed in our study. Importantly, based on their results, a relationship between high suicidal ideation, low socioeconomic status, being widowed or divorced, and the possibility of an anxiety diagnosis was found (OR > 1; $p = 0.038$, $p < 0.001$, and $p < 0.001$, respectively). A comparable association was detected for low socioeconomic status ($p = 0.007$), being widowed or divorced ($p = 0.001$), and the potential diagnosis of a depressive disorder. Moreover, the threat of losing their job in patients with severe occupational hand eczema increased levels of anxiety and depression [56].

HE is also described as causing embarrassment and a loss of self-consciousness [5,57]. A study investigating the physical and aesthetic effects of HE conducted on a group of over 1000 participants revealed that 74% of the studied group reported the disease influencing the way they grab objects or touch people. In 70% of cases, patients admitted to wearing gloves or hiding their hands in their pockets because they were ashamed of their skin condition. HE also impacted relationships with partners, families, and friends. The disease kept study participants from taking part in some particular everyday situations [5].

Among others, obsessive–compulsive tendencies appeared to be noticed in HE patients. Kouris et al. [58] linked those behaviors with high anxiety levels. In their research, a significant difference in the Leyton Trait Scale (LTS, an instrument assessing obsessive–compulsive personality traits) was found between HE individuals and healthy controls. Furthermore, a positive correlation was observed between LTS, DLQI, HADS-A, and age. They implied that HE skin lesions might be self-induced in some cases, being triggered by compulsive actions or tendencies such as compulsive hand washing, scratching, rubbing, or skin picking. Yet, the exact cause-and-effect sequence is difficult to estimate [58].

An individual's reaction to stress can be associated with hand dermatoses' coping mechanisms. A study by Niemeier et al. [59] concerning different hand dermatoses (e.g., HE) distinguished a specific subgroup of patients who coped worse with their disease. High-stress responders (patients who identified stress as a factor influencing the disease) with negative results of patch tests were recognized as having a greater need for psychosocial therapy. It was explained by the disappointment caused by negative test results without clarifying the causes of the disease. Not only a psychological consultation but also long-term psychotherapy need to be considered in such cases [59].

Our study has some limitations worth mentioning. Conclusions drawn in our research, especially those related to depressive and anxiety disorder diagnoses, should be confirmed and followed by a detailed psychiatric examination and expertise. Nevertheless, our group proved the urgency of screening HE patients in terms of their mental status using simple, easily accessible screening tools. It would clearly help to distinguish patients belonging to high-risk groups for mental disorders. This study was also conducted on a limited and geographically undifferentiated population (all 100 participants were recruited from the Lower Silesia region in Poland). Future studies incorporating patients from other regions need to be considered. Although some correlations between disease severity, itch and pain intensity, and depressive and anxiety symptoms were found, the exact cause of mood disorders in HE patients remains unclear.

5. Conclusions

This study proves the psychosocial burden of HE. It emphasizes the substantial role of a multidisciplinary approach for patients suffering from HE. Understanding the way the disease affects patients' lives may provide useful advice on treatment regimens or skincare, with adequate compliance. Exploring this part of the knowledge may help medical practitioners improve their management and early suspicion or diagnosis of depressive and anxiety disorders. Finally, such awareness could contribute to the prevention of mood disturbances and all their possible repercussions in HE patients.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the Wroclaw Medical University Ethics Committee (consent No. KB-234/2023, 9 March 2023).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The datasets generated and analyzed in the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest: J.C.S. has served as an advisor for AbbVie, LEO Pharma, Menlo Therapeutics, Novartis, Pierre Fabre, Sienna Biopharmaceuticals, and Trevi; has received speaker honoraria from AbbVie, Eli Lilly, Janssen, LEO Pharma, Novartis, Sanofi-Genzyme, Sun Pharma, and Berlin-Chemie Mennarini; has served as an investigator; and has received funding from AbbVie, Amgen, Galapagos, Holm, Incyte Corporation, InflaRX, Janssen, Menlo Therapeutics, Merck, Boehringer Ingelheim, Novartis, Pfizer, Regeneron, Trevi, and UCB. Other authors report no conflict of interest.

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7. STRESZCZENIE W JĘZYKU POLSKIM

Na rozprawę doktorską składa się cykl 3, monotematycznych artykułów opublikowanych w międzynarodowych czasopismach naukowych indeksowanych w bazie MEDLINE i uwzględnionych na liście Journal Citation Reports by Web of Science oraz znajdujących się w wykazie czasopism naukowych Ministerstwa Edukacji i Nauki (MEiN). Łączny współczynnik wpływu (impact factor – IF) artykułów wchodzących w skład rozprawy doktorskiej wynosi 12,2, a punktacja MEiN 380 punktów. We wszystkich artykułach jestem pierwszym i wiodącym autorem.

Pierwszą pracą wchodzącą w skład cyklu jest przegląd piśmiennictwa dotyczący zastosowania inhibitorów kinaz Janusowych (JAK) w leczeniu przewlekłego wyprysku rąk. Publikacja jest podsumowaniem obecnego stanu wiedzy na temat wykorzystania tej grupy farmaceutyków, efektywności klinicznej terapii, a także aspektów związanych z jej bezpieczeństwem w grupie pacjentów cierpiących na przewlekły wyprysk rąk. Dokonano w niej także podsumowania zakończonych oraz obecnie trwających badań klinicznych związanych z tym zagadnieniem. Przegląd wykonano w grudniu 2022 r.

Następnie, w badaniach będących podstawą drugiej i trzeciej publikacji cyklu stworzono charakterystykę populacji chorującej na przewlekły wyprysk rąk, ze szczególnym uwzględnieniem objawów o charakterze świądu i bólu oraz aspektów psychospołecznych choroby. Badanie prowadzono od 1 lutego 2022 r. do 31 stycznia 2023 r. Do badań włączono grupę liczącą 100 pacjentów z rozpoznanym klinicznie przewlekłym wypryskiem rąk. Do oceny stopnia nasilenia choroby wykorzystano dwa narzędzia diagnostyczne: skalę globalnej oceny badacza dla tej choroby (IGA-CHE) oraz wskaźnika nasilenia wyprysku rąk (HECSI). Od wszystkich pacjentów zostały zebrane dane demograficzne oraz kliniczne. Nasilenie świądu oraz bólu (największe nasilenie obu objawów w ciągu ostatnich trzech dni oraz w ciągu całego okresu choroby) oceniano z użyciem skali numerycznej (ang. Numerical Rating Scale, NRS). Ponadto, pacjenci byli również proszeni o wypełnienie kwestionariuszy: DLQI, oceniającego jakość życia pacjentów z chorobami dermatologicznymi, 6-ISS, związanego z zagadnieniem stygmatyzacji, PHQ-9 oraz GAD-7, służącym do przesiewowego wykrywania oraz badania nasilenia zaburzeń, odpowiednio: depresyjnych i lękowych. Kolejnym narzędziem wykorzystanym w badaniach, który pomaga w ocenie powyższych zaburzeń był kwestionariusz HADS-M. Na podstawie wyników analiz zebranych danych stworzono dwie prace oryginalne.

Celem drugiej pracy było scharakteryzowanie populacji osób cierpiących na przewlekły wyprysk rąk oraz analizę towarzyszących temu schorzeniu świądu i bólu. W badanej populacji przeważały kobiety (60%), wiek uczestników wahał się od 18 do 80 lat. Średni czas trwania choroby wynosił 42,5 miesiąca, a średnia liczba zaostrzeń w ciągu ostatnich 12 miesięcy wynosiła 4,7. Predyspozycje atopowe stwierdzono u 45% pacjentów, większość badanej populacji było wcześniej leczona z powodu choroby. W wyniku analizy stwierdzono, że większość pacjentów należała do grupy 3 IGA-CHE, a średnie nasilenie choroby oceniono jako umiarkowane. Wśród badanych pacjentów 81% zgłaszało świąd, a 53% odczuwało ból, przy czym kobiety częściej doświadczały tych objawów. Świąd był oceniany jako łagodny w ostatnich 3 dniach przed badaniem, natomiast umiarkowany w całym okresie choroby. Nasilenie bólu określono jako łagodne. Analiza wykazała korelację pomiędzy nasileniem świądu i bólu a stopniem nasilenia choroby. Dodatkowo, nasilenie tych objawów korelowało z obniżoną jakością życia mierzoną za pomocą DLQI. Stwierdzono także związek pomiędzy poziomem stygmatyzacji a nasileniem świądu.

W ostatniej z włączonych do dysertacji prac ocenione zostały psychospołeczne konsekwencje przewlekłego wyprysku rąk. Większość badanych zgłosiła umiarkowany lub bardzo duży wpływ choroby na ich jakość życia. Spadek jakości życia korelował z ciężkością choroby. Interpretacja wyników kwestionariusza PHQ-9 wykazała, że u 17% pacjentów istniała możliwość rozpoznania zaburzeń depresyjnych, a średni wynik w skali PHQ-9 wskazywał na łagodną ich postać. Korelacja pomiędzy nasileniem objawów depresyjnych a nasileniem CHE została potwierdzona. Zaburzenia lękowe występowały u 25% badanej grupy, a nasilenie bólu korelowało z obecnością rozpoznania zaburzeń lękowych. Obserwowano również korelację pomiędzy nasileniem objawów lękowych a ciężkością choroby oraz czasem trwania choroby.

Podsumowując, pacjenci z przewlekłym wypryskiem rąk doświadczają różnorodnych objawów, a schorzenie znacząco wpływa na ich jakość życia, stan psychiczny oraz dolegliwości fizyczne. Warto zauważyć, że wyniki badań wskazują na potrzebę holistycznego podejścia do tej grupy chorych, podkreślając znaczenie poprawy jakości życia jako jednego z punktów końcowych postępowania. Niezbędne jest również prowadzenie dalszych badań ukierunkowanych na poznawanie nie tylko patomechanizmu choroby, lecz także procesów doświadczania choroby przez pacjentów.

8. STRESZCZENIE W JĘZYKU ANGIELSKIM

The doctoral dissertation consists of a series of 3, monothematic articles published in international scientific journals indexed in MEDLINE database and included in the list of Journal Citation Reports by Web of Science and included in the list of scientific journals of the Ministry of Education and Science (MEiN). The total impact factor (IF) of the articles included in the dissertation is 12.2, and the MEiN score is 380 points. In all articles, I am the first and lead author.

The first paper included in the series is a narrative literature review on the use of Janus kinase (JAK) inhibitors in the treatment of chronic hand eczema. The publication summarizes the current state of knowledge on the use of this group of pharmaceuticals, the clinical effectiveness of the therapy, as well as aspects related to its safety in a group of patients suffering from chronic hand eczema. It also summarizes completed and currently ongoing clinical trials related to this issue. The review was conducted in December 2022.

Subsequently, the studies being the basis of the second and third publications of the series characterized the population suffering from chronic hand eczema, with a focus on pruritic and painful symptoms and psychosocial aspects of the disease. The study was conducted from February 1, 2022 to January 31, 2023. A group of 100 patients with clinically diagnosed chronic hand eczema were included in the study. Two diagnostic tools were used to assess the severity of the disease: the Investigator Global Assessment Scale for the disease (IGA-CHE) and the Hand Eczema Severity Index (HECSI). Demographic and clinical data were collected from all patients. The severity of pruritus and pain (the highest severity of both symptoms in the last three days and throughout the course of the disease) were assessed using the Numerical Rating Scale (NRS). In addition, patients were also asked to complete questionnaires: DLQI, assessing the quality of life of patients with dermatological diseases, 6-ISS, related to the issue of stigma, PHQ-9 and GAD-7, used for screening and examining the severity of depressive and anxiety disorders, respectively. Another tool used in the study to help assess the above-mentioned disorders was the HADS-M questionnaire. Based on the results of the analyses of the collected data, two original papers were created.

The aim of the second study was to characterize the population of people suffering from chronic hand eczema and analyze the pruritus and pain that accompany the condition. The study population was predominantly female (60%), the age of the participants ranged from 18 to 80 years. The average duration of the disease was 42.5 months, and the average number of exacerbations in the last 12 months was 4.7. Atopic predisposition was found in

45% of patients, and most of the study population had been previously treated for the disease. The analysis found that the majority of patients belonged to IGA-CHE group 3, and the average severity of the disease was assessed as moderate. Among the studied patients, 81% reported pruritus and 53% experienced pain, with women more likely to experience these symptoms. Pruritus was rated as mild in the last 3 days before the study, while moderate throughout the disease. The severity of pain was rated as mild. The analysis showed a correlation between the severity of pruritus and pain and the severity of the disease. In addition, the severity of these symptoms correlated with reduced quality of life measured with the DLQI. An association was also found between the level of stigmatization and the severity of pruritus.

The last paper included in the dissertation assessed the psychosocial consequences of chronic hand eczema. The majority of subjects reported a moderate to very high impact of the disease on their quality of life. Decreased quality of life correlated with disease severity. Interpretation of the PHQ-9 questionnaire results showed that 17% of patients had a possible diagnosis of depressive disorder, and the average PHQ-9 score indicated a mild form of it. The correlation between the severity of depressive symptoms and the severity of CHE was confirmed. Anxiety disorders were present in 25% of the study group, and the severity of pain correlated with the presence of an anxiety disorder diagnosis. A correlation was also observed between the severity of anxiety symptoms and the severity of the disease and the duration of the disease.

In conclusion, patients with chronic hand eczema experience a variety of symptoms, and the condition significantly affects their quality of life, psychological state and may cause physical complaints. It is worth noting that the results of the study indicate the need for a holistic approach to this group of patients, emphasizing the importance of improving quality of life as one of the management endpoints. It is also necessary to conduct further research aimed at learning not only about the pathomechanism of the disease, but also about the patients' processes of experiencing the disease.

9. OPINIA KOMISJI BIOETYCZNEJ

KOMISJA BIOETYCZNA
przy
Uniwersytecie Medycznym
we Wrocławiu

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 234/2023

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 278/XVI R/2020 z dnia 21 grudnia 2020 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 514 z 2020 r.) w składzie:

dr Joanna Birecka (psychiatria)
dr Beata Freier (onkologia)
dr hab. Tomasz Fuchs (ginekologia, położnictwo)
prof. dr hab. Dariusz Janczak (chirurgia naczyniowa, transplantologia)
prof. dr hab. Krzysztof Kaliszewski (chirurgia endokrynologiczna)
dr prawa Andrzej Malicki (prawo)
dr hab. Marcin Mączyński, prof. UMW (farmacja)
Urszula Olechowska (pielęgniarstwo)
prof. dr hab. Leszek Szenborn (pediatria, choroby zakaźne)
prof. dr hab. Andrzej Szuba (choroby wewnętrzne, angiologia
ks. prof. Andrzej Tomko (duchowny)
prof. dr hab. Mieszko Więckiewicz (stomatologia)
dr hab. Andrzej Wojnar, prof. nadzw. (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)
dr hab. Jacek Zieliński (filozofia)

pod przewodnictwem
prof. dr hab. Jerzego Rudnickiego (chirurgia, proktologia)

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej po zapoznaniu się z projektem badawczym pt.

„Holistyczne spojrzenie na przewlekłe choroby skóry"

zgłoszonym przez **prof. dr hab. Jacek Szepietowski** zatrudniony w Katedrze i Klinice Dermatologii, Wenerologii i Alergologii Uniwersytetu Medycznego we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badań w Katedrze i Klinice Dermatologii, Wenerologii i Alergologii Uniwersytetu Medycznego we Wrocławiu, **pod warunkiem zachowania anonimowości zgromadzonych danych.**

UWAGA: Jeśli projekt/badanie wymaga ubezpieczenia na podstawie Rozporządzenia Ministra Finansów, Funduszy i Polityki Regionalnej z dnia 23.12.2020r. w sprawie obowiązkowego ubezpieczenia odpowiedzialności cywilnej podmiotu przeprowadzającego eksperyment medyczny, Wnioskodawca zobowiązany jest do złożenia wniosku o zawarcie umowy ubezpieczenia odpowiedzialności cywilnej zgodnie z procedurą przyjętą w Uniwersytecie Medycznym we Wrocławiu. W takim przypadku pozytywna opinia Komisji Bioetycznej ma charakter warunkowy i będzie uprawniała do prowadzenia Badania pod warunkiem zawarcia przez Uniwersytet umowy ubezpieczenia OC zgodnie z Rozporządzeniem wskazanym w zdaniu poprzednim.

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej UM we Wrocławiu.

Opinia powyższa dotyczy projektu badawczego realizowanego w ramach działalności statutowej Uczelni SUBZ.C260.23.041

Przewodniczący Komisji Bioetycznej
przy Uniwersytecie Medycznym

prof. dr hab. Jerzy Rudnicki

Wrocław, dnia

09 03 2023

10. CURRICULUM VITAE

CURRICULUM VITAE

Adam Zalewski

Adres: ul. Ignacego Daszyńskiego 55/11, 50-310 Wrocław
E-mail: zalewski.adam.med@gmail.com
Telefon: +48 726 331 090
Data i miejsce urodzenia: 02.12.1993 r., Kraśnik

Edukacja:

10/2012 – 06/2018 - *Kraków*

Uniwersytet Jagielloński - Collegium Medicum; *Kierunek Lekarski, Wydział Lekarski*

Doświadczenie:

- **Zawodowe:**

01/10/2023 – obecnie - *Wrocław*

Asystent - *Katedra Dermatologii, Wenerologii i Alergologii, Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu*

01/03/2020 – obecnie - *Wrocław*

Lekarz rezydent (w trakcie specjalizacji) - *Klinika Dermatologii, Wenerologii i Alergologii, Uniwersytecki Szpital Kliniczny im. Mikulicza Radeckiego we Wrocławiu*

01/10/2018 - 29/10/2019 - *Kraków*

Lekarz stażysta – *Szpital Specjalistyczny im. J. Dietla w Krakowie*

- **Naukowe:**

Publikacje:

- 15 pełnotekstowych artykułów opublikowanych w krajowych i międzynarodowych czasopismach, w tym indeksowanych w bazie PubMed, z czego 4 jako pierwszy autor
- Całkowity współczynnik wpływu (Impact Factor) opublikowanych prac = 19,922

Członkostwo w towarzystwach naukowych:

- Polskie Towarzystwo Dermatologiczne
- International Society of Dermatology
- European Academy of Dermatology and Venerology
- International Dermoscopy Society
- Polska Grupa Dermatoskopowa

11. DOROBEK NAUKOWY

(z wyłączeniem prac stanowiących cykl publikacji do Rozprawy Doktorskiej)

11.1. Publikacje w czasopismach z IF

1. Jaworek Andrzej Kazimierz, Szafraniec Krystyna, Jaworek Magdalena, Doniec Zbigniew, **Zalewski Adam,** Kurzawa Ryszard, Wojas-Pelc Anna, Pokorski Mieczysław. Cat Allergy as a source Intensification of Atopic Dermatitis in Adult Patients. Advances in Experimental Medicine and Biology 2020: Vol. 1251, s. 39-47

   IF = 2,622; Punkty MEiN = 20
2. **Zalewski Adam**, Goldust Mohamad, Szepietowski Jacek C.: Tinea gladiatorum: epidemiology, clinical aspects, and management, Journal of Clinical Medicine, 2022, vol. 11, nr 14, art.4066 [14 s.], DOI:10.3390/jcm11144066

   IF = 3,9; Punkty MEiN = 140
3. Dev Eda, Adamska Patrycja, Wolnik Jan, Oleksy Aleksandra, Piętowska Zuzanna, **Zalewski Adam**, Maj Jonna, Dulak Józef, Biniecka Monika: Generation of two induced pluripotent stem cel lines from psoriatic patient with cardiovascular comorbidity, Stem Cell Research, 2023, vol. 73, 103251 [5 s.], DOI:10.1016/j.scr.2023.103251

   IF = 1,2; Punkty MEiN = 70

11.2. Publikacje w czasopismach bez IF

1. Jaworek Andrzej Kazimierz, Jaworek Magdalena, Szafraniec Krystyna, **Zalewski Adam**, Kurzawa Ryszard, Wojas-Pelc Anna. Problem „sterydofobii" wśród pacjentów chorujących na atopowe zapalenie skóry – przegląd zagadnień. (Problem of „corticoteroid phobia" among the patients suffering from atopic dermatitis – review.) Alergia Astma Immunologia 2018: T. 23, nr 3, s. 143-149

   Punkty MEiN = 9
2. Jaworek Andrzej Kazimierz, **Zalewski Adam**, Wojas-Pelc Anna. Znaczenie miejscowych glikokortykosteroidów we współczesnym lecznictwie dermatologicznym. Część 2. (The importance od local glucocorticosteroids in the modern dermatological treatment. Part 2.) Farmacja Współczesna 2018: T. 11, nr 4, s. 220-230

   Punkty MEiN = 5

3. Jaworek Andrzej Kazimierz, Dudek Dominika, Szafraniec Krystyna, Jaworek Magdalena, Sułowicz Joanna, **Zalewski Adam**, Wojas-Pelc Anna. Depresja jako istotny problem kliniczny wśród pacjentów chorujących na atopowe zapalenie skóry – przegląd najnowszych doniesień. (Depression as an important clinical issue among atopic dermatitis patients – an overview of most current reports.) Przegląd Lekarski 2018: T. 75, nr 10, s. 515-519

   Punkty MEiN = 10

4. Jaworek Andrzej Kazimierz, Maciejowska-Podosek Judyta, Malinowska Anna, **Zalewski Adam**, Brzewski Paweł, Dyduch Grzegorz, Wojas-Pelc Anna. Wyrośle kostne podpaznokciowe – trudności diagnostyczne. Opis przypadku klinicznego. (Subungal exostosis – diagnostic difficulties. Case report.) Chirurgia Plastyczna i Oparzenia Plastic Surgery & Byrns: T. 7, z. 3, s. 101-108

   Punkty MEiN = 5

5. Jaworek Andrzej Kazimierz, **Zalewski Adam**, Wojas-Pelc Anna. Wybrane aspekty immunologii aparatu paznokciowego. Dermatologia po Dyplomie 2019: T. 10, nr 5, s. 24-31

   Punkty MEiN = 5

6. Jaworek Andrzej Kazimierz, Szafraniec Krystyna, Pastuszczak Maciej, **Zalewski Adam**, Wojas-Pelc Anna. The knowledge of issues associated with topical corticosteroids using in patients with atopic dermatitis. Polski Merkuriusz Lekarski: T. 46, nr 276, s. 243-247

   Punkty MEiN = 20

7. Jaworek Andrzej Kazimierz, Englert Karolina, Spałowska Magdalena, Dyduch Grzegorz, **Zalewski Adam**, Wojas-Pelc Anna. Atypical presentation of Schamberg's disease – diagnostic challenges. Nietypowy obraz choroby Schamberga – trudności diagnostyczne. Przegląd Dermatologiczny Dermatology Review 2019: T. 106, nr 1, s. 34-45

   Punkty MEiN = 20

8. Jaworek Andrzej Kazimierz, **Zalewski Adam**, Maciejowska-Podosek Judyta, Englert Karolina, Sarek Magdalena, Kozicka Karolina, Wojas-Pelc Anna. Współczesne metody terapii brodawek wirusowych zlokalizowanych w obrębie aparatu paznokciowego. Terapia 2019: R. 27, nr 12, s. 49-55

   Punkty MEiN = 5

9. Jaworek Andrzej Kazimierz, Jaworek Magdalena, **Zalewski Adam**, Mazgaj Magdalena, Kurzawa Ryszard, Wojas-Pelc Anna. Przegląd przydatnych dla lekarzy (także niedermatologów) praktycznych zagadnień związanych ze schorzeniami aparatu paznokciowego. (A review of practical issues related to the doseases of the nail unit useful for doctors (including non-dermatologists).) Pediatria I Medycyna Rodzinna 2020: Vol. 16, nr 1, s. 62-69
   Punkty MEiN = 20

Sumaryczny Impact Factor: 19,922

Punktacja ministerialna: 709,0

12. OŚWIADCZENIA WSPÓŁAUTORÓW

UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

Wydział Lekarski
Katedra i Klinika Dermatologii, Wenerologii i Alergologii
Kierownik : Prof.dr hab. n.med. Jacek Szepietowski
Ul. Chałubińskiego 1, 50-368 Wrocław
Tel. +4871/327-09-41 Fax. +4871/327-09-42
e-mail: dermwen@umw.edu.pl http://www.derm.umed.wroc.pl

Wrocław, 2023-11-27

Oświadczam, że w pracy:

Zalewski A, Szepietowski JC. Topical and systemic JAK inhibitors in hand eczema - a narrative review. Expert Rev Clin Immunol. 2023 Apr;19(4):365-373.

mój udział polegał na współtworzeniu koncepcji badań, nadzorze naukowym oraz pomocy w tworzeniu finalnej wersji manuskryptu.

Uniwersytet Medyczny we Wrocławiu
KATEDRA I KLINIKA
DERMATOLOGII, WENEROLOGII I ALERGOLOGII
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Wrocław, 2023-11-27

Oświadczam, że w pracy:

Zalewski A, Krajewski PK, Szepietowski JC. Prevalence and Characteristics of Itch and Pain in Patients Suffering from Chronic Hand Eczema. J Clin Med. 2023 Jun 21;12(13):4198

mój udział polegał na współtworzeniu koncepcji badań, nadzorze naukowym oraz pomocy w tworzeniu finalnej wersji manuskryptu.

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Wrocław, 2023-11-27

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Zalewski A, Krajewski PK, Szepietowski JC. Psychosocial Consequences of Hand Eczema-A Prospective Cross-Sectional Study. J Clin Med. 2023 Sep 3;12(17):5741.

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mój udział polegał na wykonaniu analizy statystycznej wyników badań.

Dr n. med. Piotr Krajewski
lekarz
3558016

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