
Medical University of Gdańsk
Faculty of Medicine

# DOCTORAL THESIS

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## Interleukin-17 genes polymorphisms in the context of safety and danger of novel treatments for atopic dermatitis and psoriasis in cutaneous T-cell lymphoma

Polimorfizmy genów interleukiny-17 w kontekście bezpieczeństwa i zagrożeń wypływających ze stosowania nowych terapii w atopowym zapaleniu skóry i łuszczycy w pierwotnie skórnych chłoniakach T-komórkowych

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I would like to dedicate this thesis to my grandfather
Zenon Kołkowski MSc, PhD

(Pol.) Pracę dedykuję mojemu dziadkowi dr inż. Zenonowi Kołkowskiemu

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# ABBREVATIONS

| | |
|---|---|
| PCL | Primary cutaneous lymphoma |
| CTCL | Cutaneous T-cell lymphoma |
| CBCL | Cutaneous B-cell lymphoma |
| mAb | Monoclonal antibody |
| JAKi | Janus kinase inhibitor |
| JAK | Janus kinase |
| STAT | Signal transducer and activator of transcription |
| IL-4 | Interleukin-4 |
| IL-12 | Interleukin-12 |
| IL-13 | Interleukin-13 |
| IL-17 | Interleukin-17 |
| IL-17A | Interleukin-17A |
| IL-17F | Interleukin-17F |
| IL-22 | Interleukin-22 |
| IL-23 | Interleukin-23 |
| IL-31 | Interleukin-31 |
| TNF- α | Tumor necrosis factor α |
| SNP | Single nucleotide polymorphism |
| MF | Mycosis fungoides |
| SS | Sezary Syndrome |
| NB-UVB | narrowband UVB |


# KEYWORDS

Cutaneous T-cell lymphoma; mycosis fungoides; biologic treatment; psoriasis, atopic dermatitis; interleukin-17; IL-17; TNF-α; Sézary syndrome; cytokine; tumor microenvironment; biologic treatment; small molecule inhibitors; JAK-STAT pathway; interleukins; janus kinase inhibitors.

# LIST OF PAPERS INCLUDED IN THE DOCTORAL THESIS

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# ABSTRACT

## INTRODUCTION

In the era of novel biologic and small molecule inhibitors treatments we are currently managing their adverse effects. In the course of inflammatory skin diseases, the risk of developing primary cutaneous lymphomas (PCLs) has been significantly higher. The microenvironment of PCLs has been proven to be important in their pathogenesis in numerous studies.

## AIM

Our general aim was to elucidate the associations of selected IL-17 single nucleotide polymorphisms (SNPs) with the diagnosis and stages of cutaneous T-cell lymphomas (CTCLs). Furthermore, we have also studied incidence of IL-17 polymorphisms typical for CTCL in patients with psoriasis undergoing biologic therapy (to check the possible risk of lymphoma in the future). Additionally, we have reviewed the possible influence of the novel therapies for atopic dermatitis and psoriasis on the progression and/or induction of PCLs.

## MATERIAL AND METHODS

Using polymerase-chain reaction (PCR) with sequence-specific primers, we have analyzed single-nucleotide polymorphisms in the interleukin-17 genes of 150 patients with CTCL. Next, we have also analyzed 16 patients with psoriasis in the course of treatment with anti-interleukin-17A (anti-IL-17A) antibodies (secukinumab and ixekizumab). The patients have been chosen from the group of 123 patients receiving biologic treatment (tumor necrosis alpha (TNF-a)-inhibitors and TNF-a-receptor inhibitors (e.g. adalimumab, etanercept, infliximab) and interleukin-12 (IL-12) and/or interleukin-23 (IL-23) pathway blockers (e.g. guselkumab, ixekizumab, risankizumab, tildrakizumab, and ustekinumab) for psoriasis in the Department of Dermatology, Venereology and Allergology, Medical University of Gdańsk, Poland.

Furthermore, we have performed a comprehensive search of the literature using the PubMed database, titles and abstracts were screened for the inclusion and exclusion criteria. Based on title and abstract analysis, we included articles concerning the role

of interleukins and janus kinase/signal transducers and activators of transcription (JAK/STAT), and biologic drugs affecting cytokine profiles and JAK inhibitors on PCLs. At this step, we excluded records not related to the topic, non-English manuscripts, personal opinions, and duplicates. The remaining were qualified as eligible for full-text reading. After reading the full manuscripts, some were excluded (not relevant, not original, and not providing information concerning earlier mentioned cytokines, pathways, and new drugs' impact on PCLs). Finally, additional relevant, eligible records identified through a references search were included, in which information on the effect of PCL microenvironmental influence on the specific lymphoma subtypes were included.

## RESULTS

In the first study we have found that GG homozygote rs8193036 A/G of interleukin-17A gene occurred less commonly in the CTCL group, however, patients with this single-nucleotide polymorphism experience significantly more intense pruritus. Next, the rs2397084 AG heterozygote of interleukin-17F has been found to be more common in the lymphoma population. In addition, there were significant differences in the frequencies of interleukin-17 genotypes when comparing early (Ia to IIa) and advanced stages (IIb, III and IV) of these neoplasms.
A similar result in significant differences in the frequencies of interleukin-17 genotypes have been revealed in Sézary syndrome versus Mycosis fungoides.

In CTCL group analyzed in the first study, there were three patients, in whom prior to the lymphoma diagnosis psoriasis was diagnosed both clinically and histopathologically. All of these patients had heterozygotic AG rs2397084 IL-17F polymorphisms, which is significantly more often found in the CTCL group when compared with the general population. Due to this reason, we have decided to test this variant in patients with psoriasis and monitor them for the development of lymphoma in the future.

In the additional study concerning psoriasis (data not published) we have found that patients having homozygotic AA variant of rs8193036 IL-17A have been characterized by a worse clinical response to secukinumab or ixekizumab in comparison to patients having GG and GA variants. Furthermore, we have found that the heterozygotic AG

of rs2397084 A/G IL-17F single nucleotide polymorphism (SNP) patients experienced a substantially lower quality of life compared to patients having GG homozygote of rs2397084 A/G IL-17F SNP before the anti-IL-17A treatment (secukinumab or ixekizumab). AG variant has probably a higher activity of IL-17F (in our group at the beginning patients with this variant had a similar median PASI and higher BSA, despite the fact that three of the patients have been included in the drug program because of the disease occupying the intimate areas and therefore their BSA was very low). The lower quality of life of these patients may also be a result of affecting the intimate areas by the disease, which did not respond to alternative therapies for 6 months prior to the inclusion in the drug program. DLQI, PASI and BSA scores at the first and second control appointment after initiating the therapy, did not differ among studied variants. Patients are currently on different stages of the therapy – there is a tendency to a better response to treatment of patient having the AG rs2397084 SNP, which may support the thesis that IL-17F is important in the pathogenesis and as a therapeutic target of psoriasis. Secukinumab and ixekizumab block IL-17A homodimer and IL-17A/F heterodimer. It is possible, that after initiating therapy with the agents affecting IL-17F homodimer (bimekizumab and sonelokimab) the response in patients having AG IL-17F rs2397084 SNP would have been significantly different than the response of patients having GG variant.

The facts that the severe course of psoriasis increases the risk of developing lymphomas, including PCLs, and the hazard ratio of occurrence of lymphomas in patients with psoriasis equals more than 6 are well known in the literature. Patients with psoriasis, who have the AG rs2397084 IL-17F variant should be strictly observed in the context of developing PCLs.

Lastly, the results of our extensive literature review suggest that most novel treatments (mAbs and small-molecule inhibitors) may have a direct impact on the progression of cutaneous lymphomas. This issue requires further study and meticulous monitoring of patients receiving these drugs to ensure their safety. In the case of the rapid progression of atopic dermatitis/eczema, especially in patients older than 40 years old, there is a necessity to perform a biopsy followed by a very careful pathological examination. Furthermore, in case of uncertain psoriatic lesions, a biopsy followed by

pathologic examination should exclude the possibility of co-existence of a primary cutaneous lymphoma before administration of therapies affecting cytokine profiles.

In the course of atopic dermatitis there also is an increased risk of developing PCLs. However, we did not decide to test the IL-17 variants in this subset of patients, due to the lack of efficacy of IL-17 inhibitors in the treatment of atopic dermatitis. Despite some studies reporting the elevated levels of IL-17 in the skin of patients with atopic dermatitis, it seems to be a result of innate defense mechanisms. Due to the disruption of epidermal barrier in atopic dermatitis, these patients are prone to various types of infections and colonization by several pathogens, which activate the innate defense mechanisms in the skin thereby elevating the level of IL-17 in their skin.

## CONCLUSION

In the first publication and an additional study we have shown significant associations between IL-17 SNPs and stage of CTCLs as well as with decreased of DLQI in psoriasis. Furthermore, our study and a review of the literature contributed to elucidating the pathogenic role of IL-17 in PCLs and supporting the importance of IL-17F in psoriasis pathogenesis, which already has clinical implications.

In our review of the literature, we have described the mAbs and small molecule inhibitors in the context of PCLs. Currently, it seems that their impact on the lymphoma microenvironment is significant and not fully understood and elucidated. Therefore, in case of atypical course of the inflammatory diseases, especially during the treatment with novel therapies there is a necessity to perform additional examinations in order to exclude the possibility of lymphoma coexistence.

# STRESZCZENIE


## WSTĘP

W erze nowoczesnych leków biologicznych I inhibitorów drobnocząsteczkowych mierzymy się z ich działaniami niepożądanymi. W przebiegu dermatoz zapalnych ryzyko względne wystąpienia chłoniaków pierwotnych skóry (PCL z ang. primary cutaneous lymphomas) jest istotnie zwiększone. Mikrośrodowisko w wielu badaniach okazało się istotne w patogenezie PCLs.

## CEL

Celem pracy było wyjaśnienie, w kontekście ryzyka rozwoju chłoniaków pierwotnych skóry w przebiegu dermatoz zapalnych i nowych metod leczenia - czy częstość wybranych pojedynczych polimorfizmów nukleotydowych genów IL-17 jest związana z podatnością na chłoniaki pierwotnie skórne T-komórkowe (CTCL) lub ich progresją. Ponadto przeanalizowaliśmy częstość występowania polimorfizmu typowego dla CTCL u pacjentów z łuszczycą leczonych biologicznie (celem sprawdzenia w przyszłości ryzyka rozwoju chłoniaków u tych pacjentów). Dodatkowym celem naszej pracy było wyjaśnienie wpływu nowoczesnych terapii skierowanych przeciwko atopowemu zapaleniu skóry i łuszczycy na wpływ na potencjalną progresję lub/i indukcję PCL.

## MATERIAŁY I METODY

Używając reakcji łańcuchowej polimerazy (PCR) ze specyficznymi primerami, przeanalizowaliśmy wybrane polimorfizmy genów interleukiny-17 (IL-17) u 150 pacjentów z CTCL. Następnie przeanalizowaliśmy 16 pacjentów z łuszczycą plackowatą leczonych przeciwciałami anty-interleukina-17A (anty-IL-17A) (secukinumabem i ixekizumabem). Pacjenci zostali wybrani z grupy 123 osób otrzymujących biologiczne leczenie przeciw-łuszczycowe (przeciwko czynnikowi martwicy nowotworów a (TNF-a inhibitorom) oraz inihbitorom receptora dla TNF-a (np. adalimumab, etanercept, infliximab), oraz inhibitorów szlaku interleukiny-12 i/lub interleukiny-23 (guselkumab, ixekizumab, risankizumab, tildrakizumab i ustekinumab) w Klinice Dermatologii, Wenerologii i Alergologii Gdańskiego Uniwersytetu Medycznego.

Ponadto, przeprowadziliśmy analizę danych z piśmiennictwa z bazy PubMed. Tytuły i abstrakty zostały przeszukane pod kątem kryteriów włączenia i wyłączenia do badań. Do badań włączyliśmy artykuły dotyczące roli interleukin oraz kinaz janusowych/przekaźników sygnału i aktywatorów transkrypcji (JAK/STAT, ang. janus kinase/signal transducers and activators of transcription) oraz leków biologicznych wpływających na poziomy i profil działania cytokin oraz leków hamujących JAKi. W trakcie tego kroku eliminowaliśmy artykuły niezwiązane z tematem, nieanglojęzyczne, personalne opinie oraz duplikaty. Pozostałe artykuły zostały zakwalifikowane do analizy. Po przeczytaniu pełnych tekstów wybranych w powyższy sposób artykułów niektóre zostały wykluczone (nie związane z tematem, nie oryginalne, nie wnoszące istotnych informacji dotyczących cytokin, szlaków metabolicznych oraz nowoczesnych terapii w kontekście PCLs). Do badania włączono ponadto dodatkowe istotne artykuły, które znaleźliśmy poprzez listę cytowań w zakwalifikowanych wcześniej artykułach, zawierające istotne dla naszej analizy i wnioskowania informacje.

## WYNIKI

W pierwszym badaniu wykazaliśmy, że homozygota GG polimorfizmu rs8193036 A/G interleukiny-17A (IL-17A) wystąpiła istotnie rzadziej w grupie CTCL, ale, pacjenci posiadający ten wariant istotnie częściej odczuwali intensywniejszy świąd. Wariant heterozygotyczny AG rs2397084 interleukiny-17F (IL-17F) okazał się występować częściej w populacji pacjentów z chłoniakiem. Dodatkowo, znaleźliśmy również inne istotne różnice pomiędzy częstością występowania polimorfizmów IL-17A porównując stadia wczesne (Ia-IIa) i zaawansowane ( IIB-IV). Podobne wyniki wykazaliśmy również w odniesieniu do porównania częstości występowania polimorfizmów IL-17A pomiędzy pacjentami z zespołem Sezary'ego oraz z ziarniniakiem grzybiastym.

W grupie pacjentów z chłoniakami skóry, których analizowaliśmy w badaniu pierwszym były trzy przypadki pacjentów, u których wcześniej diagnozowano łuszczycę na podstawie zarówno oceny klinicznej jak i wyniku badania histopatologicznego skóry. Wszyscy Ci pacjenci mieli heterozygotyczny AG rs2397084 IL-17F, który istotnie częściej występuje w chłoniakach pierwotnych skóry w stosunku do populacji ogólnej. Z tego powodu postanowiliśmy zbadać ten polimorfizm u

pacjentów z łuszczycą i obserwować ich pod kątem potencjalnego rozwoju chłoniaków.

W badaniu obejmującym pacjentów z łuszczycą wykazaliśmy wstępnie (dane nie opublikowane), że pacjenci posiadający homozygotyczny polimorfizm AA rs8193036 IL-17A odpowiadają gorzej na terapię secukinumabem lub ixekizumabem w stosunku do pacjentów posiadających warianty GA i GG. Ponadto, wykazaliśmy również, że w grupie posiadającej heterozygotyczny polimorfizm AG rs2397084 IL-17F przed włączeniem nowoczesnej terapii biologicznej przeciwko IL-17A (secukinumab lub ixekizumab) pacjenci odczuwali istotnie niższą jakość życia w porównaniu do pacjentów posiadających polimorfizm GG rs2397084 IL-17F. Wariant AG charakteryzuje się najprawdopodobniej większą aktywnością IL-17F, co może wiązać się z większym nasileniem choroby (w naszej grupie wyjściowo pacjenci z tym wariantem mieli porównywalne mediany PASI i podwyższone BSA, pomimo, iż trzech z nich było włączonych do programu lekowego z powodu zajęcia okolic szczególnych, to znaczy ich BSA było bardzo niskie). Niższa mediana jakości życia może też wynikać z faktu zajęcia w tej grupie pacjentów okolic szczególnych takich jak okolice intymne, nie poddających się standardowym terapiom systemowym przez około 6 miesięcy. Wyniki oceny PASI, BSA i DLQI pochodzące z pierwszej i drugiej wizyty kontrolnej po włączeniu do terapii secukinumab lub ixekizumabu nie wykazały istotnych statystycznie różnic pomiędzy analizowanymi grupami pacjentów. Pacjenci pozostają na różnym etapie leczenia – rysuje się tendencja lepszej odpowiedzi na terapię u pacjentów z polimorfizmem AG co może być przyczynkiem do tezy, iż IL-17F ma wpływ zarówno na przebieg jak i odpowiedź na leczenie łuszczycy. Aby wesprzeć tą tezę konieczne jest badanie na większej grupie chorych. Secukinumab i ixekizumab blokują homodimer IL-17A oraz heterodimer IL-17A/F. Możliwe, iż po wdrożeniu leków blokujących również homodimer IL-17F (bimekizumab lub sonelokimab) odpowiedź u tych pacjentów byłaby istotnie różna w porównaniu z pacjentami charakteryzującymi się wariantem GG.

Wiadomo z danych literaturowych, że ciężki przebieg łuszczycy jest czynnikiem ryzyka rozwoju chłoniaka, w tym pierwotnego skóry, a ryzyko (ang. hazard ratio) wystąpienia chłoniaków pierwotnych skóry w przebiegu łuszczycy wynosi ponad 6. Pacjenci, z

polimorfizmem AG rs2397084 IL-17F powinni być szczególnie wnikliwie obserwowani pod kątem rozwoju chłoniaka skóry.

Dane z przeprowadzonego przeglądu piśmiennictwa sugerują, że w większości przypadków nowoczesnych terapii (leki biologiczne oraz inhibitory drobnocząsteczkowe) mogą mieć bezpośredni wpływ na progresję chłoniaków pierwotnych skóry. To zagadnienie wymaga dalszych badań i bardzo szczegółowego i uważnego monitorowania pacjentów podczas terapii, aby zapewnić im jak najwyższy stopień bezpieczeństwa. W przypadku nagłego pogorszenia objawów atopowego zapalenia skóry/wyprysku, szczególnie u pacjentów powyżej 40 roku życia, istnieje konieczność pobrania wycinka do badania histopatologicznego celem wykluczenia limfoproliferacji. Należy również pobrać wycinek do badania histopatologicznego w przypadku, gdy nie jesteśmy pewni co do diagnozy łuszczycy lub wykazuje ona ciężki przebieg i nie odpowiada na standardowe leczenie. Jest to wskazane celem wykluczenia możliwości współwystępowania chłoniaka pierwotnego skóry przed podażą leków wpływających na omawiane szlaki cytokinowe.

W przebiegu atopowego zapalenia skóry również istotnie częściej występują chłoniaki pierwotne skóry. Nie zdecydowaliśmy się na badanie polimorfizmów IL-17 u pacjentów z atopowym zapaleniem skóry, ze względu na nieskuteczność terapii anty-IL-17 w tej chorobie. Pomimo badań donoszących o zwiększonym poziomie IL-17 w skórze pacjentów z atopowym zapaleniem skóry, wydaje się, że jest to tylko wynik wrodzonych mechanizmów obronnych przeciwko drobnoustrojom. Ze względu na zaburzoną barierę naskórkową u pacjentów w atopowym zapaleniu skóry są oni podatni na wystąpienie różnych infekcji i kolonizację przez drobnoustroje, które pobudzają wrodzone mechanizmy obronne tym samym podnosząc poziom IL-17 w skórze tych pacjentów. Blokując IL-17 ryzykuje się osłabienie mechanizmu obronnego co byłoby niekorzystne

## WNIOSKI

W pierwszej publikacji oraz w badaniu uzupełniającym w grupie pacjentów z łuszczycy (wyniki nie opublikowane) wykazaliśmy istotne związki pomiędzy konkretnymi polimorfizmami IL-17, a stopniem zaawansowania CTCL oraz obniżeniem jakości życia i gorszą odpowiedzią na terapię secukinumabem lub ixekizumabem w łuszczycy.

Ponadto, wyniki naszych badań i analiza danych z piśmiennictwa stanowi przyczynek do wyjaśnienia patogennej roli IL-17 w PCLs oraz do podparcia tezy o istotności IL-17F w patogenezie łuszczycy, co już teraz ma implikacje kliniczne.

W przeglądzie piśmiennictwa opisaliśmy leki biologiczne i inhibitory drobnocząsteczkowe w kontekście PCLs. Aktualnie, wydaje się, że ich wpływ na mikrośrodowisko chłoniaków jest istotny i nie w pełni wyjaśniony. Zatem w przypadku nietypowego przebiegu dermatoz zapalnych, szczególnie podczas leczenia nowoczesnymi terapiami, istnieje konieczność wykonania badań dodatkowych celem wykluczenia możliwości współistnienia lub wystąpienia chłoniaka.

# DISCUSSION OF THE SCIENTIFIC PROBLEM

## INTRODUCTION

Primary cutaneous lymphomas (PCLs) are a group of rare lymphoproliferative disorders characterized by accumulation of malignant T-cells in the epidermis and dermis and no evidence of extracutaneous involvement at the time of diagnosis. [1] Tumorous microenvironment has been continuously shown to be an important factor contributing to the pathogenesis of these rare disorders. [2] However, most of the mechanisms regulating the interaction of PCLs malignant lymphocytes with other cells of different origin are still poorly understood. [2] Concomitantly, a wide variety of new therapies affecting cytokine profiles and actions (biologic monoclonal antibodies (mAbs) and small molecule inhibitors) are brought to the market gaining new therapeutic indications every year. [3,4] Solely in the therapy of atopic dermatitis (AD) and psoriasis around thirty agents are or will be registered soon for the therapy. When considering psoriasis the list consists of: tumor necrosis alpha (TNF-a)-inhibitors and TNF-a-receptor inhibitors (e.g. adalimumab, etanercept, infliximab), interleukin-17 (IL-17) and its receptor pathway blockers (bimekizumab, brodalumab, ixekizumab, secukinumab) and interleukin-12 (IL-12) and/or interleukin-23 (IL-23) pathway blockers (e.g. guselkumab, ixekizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab), whereas for atopic dermatitis the drugs are: dupilumab targeting interleukin-4 (IL-4) and interleukin-13 (IL-13), tralokinumab and lebrikizumab targeting IL-13, six Janus kinase inhibitors (JAKi): upadacitinib, baricitinib, abrocitinib, ruxolitinib, tofacitinib, delgocitinib and agents blocking interleukin-22 (IL-22) and interleukin-31 (IL-31), fezakinumab, and nemolizumab. [3,4]

IL-17 has been theorized to be involved in the pathogenesis of PCLs, for example by promoting the oncogenic pathway by stimulation janus kinase 3 (JAK3), which activates signal transducer and activator 3 (STAT3). [5] A significant number of single nucleotide polymorphisms (SNPs) have been studied before in the context of increased risk or worsening the course of different autoimmune and cancerous disorders. Also, SNPs of interleukin-2, interleukin-6, interleukin-10, IL-13, TNF-a and STAT3 have been studied before in cutaneous T-cell lymphomas (CTCLs). [6,7]

Novel mAbs blocking interleukin-17A (IL-17A) (secukinumab, ixekizumab) and the receptor of IL-17A (brodalumab) are highly effective in the treatment of psoriasis and are characterized by a highly safe profile of action. [8,9] Due to these properties, they will probably be widely used in the future. Interleukin-17F (IL-17F) acts similarly like IL-17A. [10] Studies on sonelokimab, which is a mAb blocking both IL-17A and IL-17F, may point to the important role of IL-17F in the process of relapse of psoriasis after treatment with secukinumab. [10]

HLA-Cw6 allele has been shown to have a significant association with psoriasis. [11] Patients who have the mentioned variant are characterized by an earlier onset and a worse course of the disease. [11] The majority of studies did not show any relationship between having HLA-Cw6 and a clinical response to secukinumab. [12–15] However, in one of the studies patients with several SNPs at the HLA-Cw6 region had a significantly better response to the treatment. [12–15] Moreover, a recent study has shown that the clinical response to the treatment with secukinumab and ixekizumab is not connected to the differences at the level of IL-17A gene expression. [16] Two studies have investigated the clinical response to mAbs treatment in the context of several IL-17F SNPs. [17,18] The first study has shown a positive correlation between the IL-17F rs763780 and a response to infliximab (p=0,02) and a negative correlation between the same SNP and a response to adalimumab (p=0,004) and ustekinumab (p=0,02). [18] In the latter, no relationship between IL-17F rs763780 and a response to adalimumab, secukinumab, infliximab, ustekinumab nor etanercept has been shown. [17]

In patients, who have one of the IL-17F rs2397084 SNP, first symptoms of psoriasis appear significantly sooner and these patients more often have the HLA-Cw6 allele. [19] In another study it has been shown that patients having one of the IL-17F rs2397084 variants (presence of C allele) needed to receive more aggressive and longer lasting narrowband UVB (NB-UVB) phototherapy treatment when compared with (TT) variant. [20]

## AIMS OF THE STUDIES

Our general aim was to elucidate the associations of selected IL-17 single nucleotide polymorphisms (SNPs) with diagnosis and stages of cutaneous T-cell lymphomas

(CTCLs). Furthermore, we have also studied incidence of IL-17 polymorphisms typical for CTCL in patients with psoriasis undergoing biologic therapy (to check the possible risk of lymphoma in the future). Additionally, we have reviewed the possible influence of the novel therapies for atopic dermatitis and psoriasis on the progression and/or induction of PCLs.

Publication 1 - Interleukin-17 Genes Polymorphisms are Significantly Associated with Cutaneous T-cell Lymphoma Susceptibility

Our aim was to elucidate, if the frequency of selected single nucleotide polymorphisms of interleukin-17 genes (interleukin-17A (rs2275913, rs3819024, rs8193036) and interleukin-17F (rs763780, rs2397084)) are associated with susceptibility to the cutaneous T-cell lymphoma.

Furthermore, after analyzing the results of the study "Interleukin-17 Genes Polymorphisms are Significantly Associated with Cutaneous T-cell Lymphoma Susceptibility" and the literature we aimed to establish the influence of interleukin-17F (IL-17F) rs2397084 A/G SNP on quality of life and response to the treatment with biologic drugs blocking interleukin-17 pathway (secukinumab and ixekizumab) in patients with psoriasis.

Publication 2 - Safety and Danger Considerations of Novel Treatments for Atopic Dermatitis in Context of Primary Cutaneous Lymphomas

Our aim was to elucidate the role of interleukin-4, interleukin-13, interleukin-22, interleukin-31, and the janus kinases/ signal transducers and activators of transcription pathway in primary cutaneous lymphomas in the context of novel treatment of atopic dermatitis.

Publication 3 - Safety and danger of biologic treatments in psoriasis in context of cutaneous T-cell lymphoma (CTCL)

Our aim was to elucidate the role of interleukin-12, interleukin--17, interleukin-23 and tumor necrosis factor a in mycosis fungoides, which sheds the light on the safety of new biologic treatments in psoriasis in context of cutaneous T-cell lymphoma.

## MATERIALS AND METHODS

### Publication 1 - Interleukin-17 Genes Polymorphisms are Significantly Associated with Cutaneous T-cell Lymphoma Susceptibility

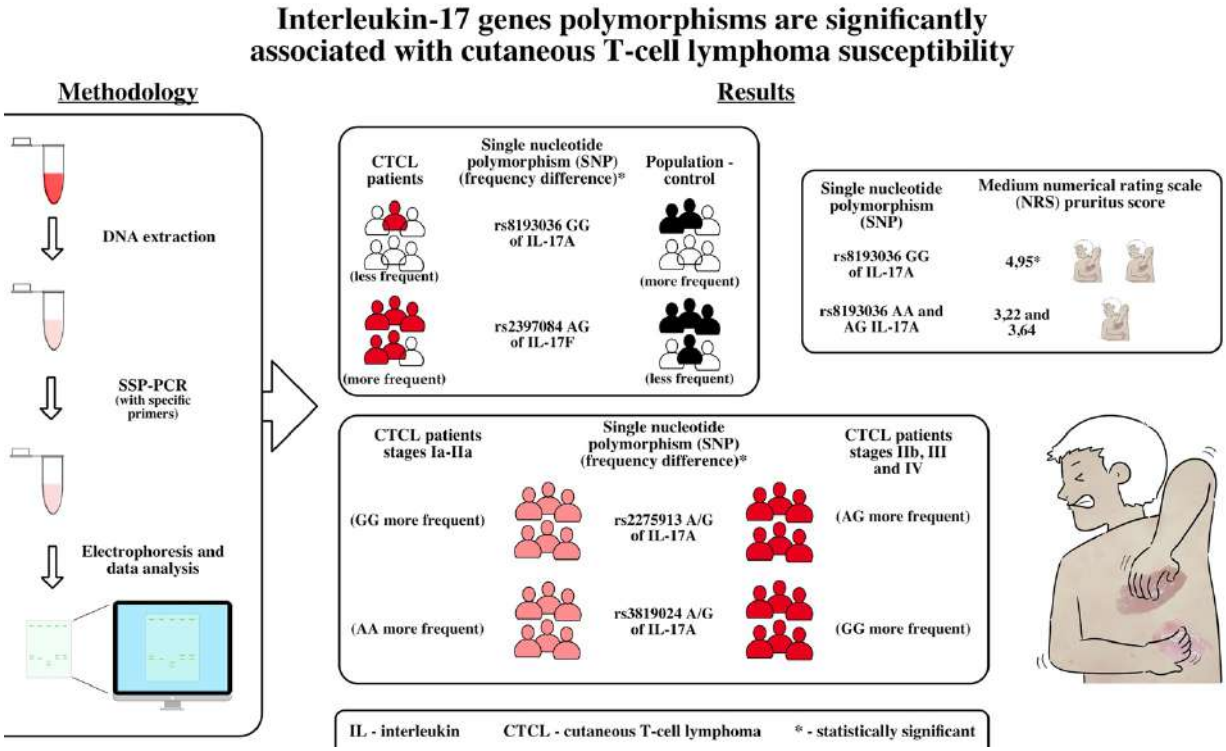
The study was approved by the Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk, Poland (decision number NKBBN/313/2017). A total of 150 blood samples of patients with CTCL: 139 MF in stages IA (44 cases), IB (38 cases), IIA (3 cases), IIB-IV (54 cases), and 11 Sézary syndrome (SS) diagnosed and treated at the Department of Dermatology of the Medical University in Gdańsk and a control non-CTCL group of 196 unrelated healthy individuals within similar age and sex distribution, without personal or family history of chronic skin diseases, without pruritus and without personal history of malignancy were included in the study. Patients had been diagnosed on the basis of clinical, histopathological and immunohistochemical findings, according to the European Organization of Research and Treatment of Cancer (EORTC) criteria. [1] Pruritus intensity was evaluated according to visual analogue scale (VAS) and numeric rating scale (NRS) and correlated with IL-17 gene polymorphisms. The demography of the studied group has been presented in the table below (Table 1).

**Table 1.** Analysis of the demography of the studied group from the publication " Interleukin-17 Genes Polymorphisms are Significantly Associated with Cutaneous T-cell Lymphoma Susceptibility"

| **Variable** | | **n** | **%** |
|---|---|---|---|
| Sex | F | 53 | 35,33% |
| | M | 97 | 64,67% |
| Medium age at the time of diagnosis (years) | F | 64,09 | - |
| | M | 61,9 | - |
| Median age at the time of diagnosis (years) | F | 64 | - |
| | M | 62 | - |
| Minimum age at the time of diagnosis (years) | F | 35 | - |
| | M | 20 | - |
| Maximum age at the time of diagnosis (years) | F | 90 | - |
| | M | 89 | - |

**DNA extraction/genotyping**

Genomic DNA was isolated from all blood samples with the Blood Mini A&A Biotechnology (A&A Biotechnology, Gdansk, Poland) according to the instructions of the manufacturer. Analysis of the polymorphic variants IL-17A (rs2275913, rs3819024, rs8193036) and IL-17F (rs763780, rs2397084) were analyzed by PCR with sequence-specific primers (SSP-PCR). Graphical visualization of this method is shown on the left side of a figure in Appendix S1 of Publication 1.




**Statistical analysis**

Statistical calculations were made with Statistica, version 12.0 (StatSoft, Inc. 2015). Analysis of qualitative features was made with the χ2 test in the Pearson method. Independent variables fulfilling the assumptions for parametric tests were analyzed with the Student's t-test. Independent variables that did not meet the parametric test assumptions were analyzed with non-parametric tests (analysis of variance (ANOVA) equivalents): Mann–Whitney U test (comparison of 2 tests) or Kruskal–Wallis test (comparison of many samples). Odds ratios (ORs) with 95% confidence intervals (95% CI) were determined by a logistic regression. In all tests, $p<0,05$ was considered a significant level of statistical significance.

Publication 2 - Safety and Danger Considerations of Novel Treatments for Atopic Dermatitis in Context of Primary Cutaneous Lymphomas

A comprehensive search of the literature using the PubMed (https://pubmed.ncbi.nlm.nih.gov/) electronic database using the search queries "(IL-4 and cutaneous lymphoma) OR (IL-4 and mycosis fungoides)", "IL-22 and cutaneous lymphoma", and "IL-31 and cutaneous lymphoma" was performed in the second week of August 2021, from the database inception to the 14th of August 2021. Further research using the

queries "(dupilumab and lymphoma)", "(fezakinumab and cutaneous lymphoma) or (fezakinumab and mycosis fungoides)", "(lebrikizumab and cutaneous lymphoma) or (lebrikizumab and mycosis fungoides)", "(tralokinumab and cutaneous lymphoma) or (tralokinumab and mycosis fungoides)", "(baricitinib and cutaneous lymphoma) or (baricitinib and mycosis fungoides)", "(ruxolitinib and cutaneous lymphoma) or (ruxolitinib and mycosis fungoides)", "(upadacitinib and cutaneous lymphoma) or (upadacitinib and mycosis fungoides)", and "(jak inhibitor and cutaneous lymphoma) or (jak inhibitor and mycosis fungoides)" was performed in the third week of August 2021, from the database inception to the 25th of August 2021 and a "((jak) OR (stat)) AND (cutaneous lymphoma)" search was performed in the second week of September 2021, from the database inception to the 11th of September 2021. After the initial search, titles and abstracts were screened for the inclusion and exclusion criteria. Based on title and abstract analysis, we included articles concerning the role of IL-4, IL-13, IL-22, IL-31, JAK/STAT, and biologic drugs affecting cytokine profiles and JAK inhibitors on PCLs. At this step, we excluded records not related to the topic, non-English manuscripts, personal opinions, and duplicates. The remaining were qualified as eligible for full-text reading. After reading the full manuscripts, some were excluded (not relevant, not original, and not providing information concerning earlier mentioned cytokines, pathways, and new drugs' impact on PCLs). Finally, additional relevant, eligible records identified through a references search were included, in which information on the effect of PCL microenvironmental influence on the specific lymphoma subtypes were included. Concentration of cytokines in the biopsies and in the blood of the patients, genetic alterations concerning genes linked to the featured subject, the possible effects of interleukins, pathways, and administration of the agents blocking them in the clone cells were analyzed and summarized.

Publication 3 - Safety and danger of biologic treatments in psoriasis in context of cutaneous T-cell lymphoma (CTCL)

A comprehensive search of the literature using the PubMed (https://pubmed.ncbi.nlm.nih.gov/) electronic database using the search queries "(IL-17 and cutaneous lymphoma) OR (IL-17 and mycosis fungoides)" was performed in the second week of December 2020, from the database inception to the 11th of December 2020. Further research using the queries "(tumor necrosis factor alfa and cutaneous lymphoma)",

"(secukinumab and cutaneous lymphoma)", "(monoclonal antibody and cutaneous lymphoma)", "(biologic treatment and cutaneous lymphoma)", "(interleukin-12 and mycosis fungoides)", "(interleukin-12 and cutaneous lymphoma)" was performed in the second week of February 2021, from the database inception to the 14th of February 2021. After the initial search, titles and abstracts were screened for the inclusion and exclusion criteria. Based on title and abstract analysis, we included articles concerning the role of IL-12, IL-17, IL-23, TNF- a, JAK/STAT, and biologic drugs affecting cytokine profiles on CTCLs. At this step, we excluded records not related to the topic, non-English manuscripts, personal opinions, and duplicates. The remaining were qualified as eligible for full-text reading. After reading the full manuscripts, some were excluded (not relevant, not original, and not providing information concerning earlier mentioned cytokines, pathways, and new drugs' impact on CTCLs). Finally, additional relevant, eligible records identified through a references search were included, in which information on the effect of CTCL microenvironmental influence on the specific T-cell lymphoma subtypes were included. Concentration of cytokines in the biopsies and in the blood of the patients, genetic alterations concerning genes linked to the featured subject, the possible effects of interleukins, pathways, and administration of the agents blocking them in the clone cells were analyzed and summarized.

Analysis of IL-17A (rs2275913, rs8193036) and IL-17F rs2397084 A/G SNPs influence on the quality of life and the response to treatment with biologic drugs blocking interleukin-17 pathway (secukinumab and ixekizumab) in patients with psoriasis (preliminary data, not published yet).

The study was approved by the Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk, Poland (decision number NKBBN/865/2022-2023). A total of 16 blood samples of patients with psoriasis diagnosed and treated at the Department of Dermatology of the Medical University in Gdańsk were included in the study. Patients had been diagnosed on the basis of recommendations of the Polish Dermatological Society and have been chosen from the group of 123 patients receiving biologic treatment (tumor necrosis alpha (TNF-a)-inhibitors and TNF-a-receptor inhibitors (e.g. adalimumab, etanercept, infliximab) and interleukin-12 (IL-12) and/or interleukin-23 (IL-23) pathway blockers (e.g. guselkumab, ixekizumab,

risankizumab, tildrakizumab, and ustekinumab) for psoriasis in the Department of Dermatology, Venereology and Allergology, Medical University of Gdańsk, Poland. Psoriasis area and severity index (PASI), dermatology life quality index (DLQI) and body surface area (BSA) affected by psoriatic lesions have been evaluated by the physicians working at the Department of Dermatology of the Medical University in Gdańsk during the control appointments within the drug programs. Ten patients have been treated with secukinumab and seven patients have received ixekizumab. In fourteen cases patients have been treated in the national drug program for psoriasis, while in the remaining three cases patients have been treated in the national drug program for psoriatic arthritis. The demography of the studied group has been presented in the table below (Table 2).

**Table 2.** Analysis of the demography of the studied group from the "Analysis of IL-17A (rs2275913, rs8193036) and IL-17F rs2397084 A/G SNPs influence on the response to the treatment with biologic drugs blocking interleukin-17 pathway (secukinumab and ixekizumab) in patients with psoriasis"

| **Variable** | | **n** | **%** |
|---|---|---|---|
| Sex | F | 7 | 43,75% |
| | M | 9 | 56,25% |
| Medium age (years) | F | 38,29 | - |
| | M | 33,11 | - |
| Median age (years) | F | 37 | - |
| | M | 32 | - |
| Minimum age at the time of diagnosis (years) | F | 16 | - |
| | M | 4 | - |
| Maximum age at the time of diagnosis (years) | F | 32 | - |
| | M | 32 | - |

**DNA extraction/genotyping**

Genomic DNA was isolated from all blood samples with the Blood Mini A&A Biotechnology (A&A Biotechnology, Gdansk, Poland) according to the instructions of the manufacturer. The polymorphic variants of IL-17A (rs2275913, rs8193036) and IL-17F (rs2397084) were analyzed by PCR with sequence-specific primers (SSP-PCR).

**Statistical analysis**

Statistical calculations were made with Statistica, version 12.0 (StatSoft, Inc. 2015). Analysis of qualitative features was made with the χ2 test in the Pearson method. Independent variables fulfilling the assumptions for parametric tests were analyzed with the Student's t-test. Independent variables that did not meet the parametric test assumptions were analyzed with non-parametric tests (analysis of variance (ANOVA) equivalents): Mann–Whitney U test (comparison of 2 tests) or Kruskal–Wallis test (comparison of many samples). Odds ratios (ORs) with 95% confidence intervals (95% CI) were determined by a logistic regression. In all tests, p<0,05 was considered a significant level of statistical significance.

## RESULTS

### Publication 1 - Interleukin-17 Genes Polymorphisms are Significantly Associated with Cutaneous T-cell Lymphoma Susceptibility

Several SNPs of IL-17 genes have been found to be associated with susceptibility to CTCL. The GG homozygote of rs8193036 A/G of interleukin 17A occurred less often in the CTCL group (Table I Publication I). The rs2397084 AG heterozygote of IL-17F was more common in the CTCL population (Table I Publication I).

**Table I. Polymorphism rs8193036 A/G of interleukin (IL) 17A and rs2397084 A/G of interleukin 17F**

| Genotypes | Cutaneous T-cell lymphoma *n* = 150 *n* (%) | Control group *n* = 196 *n* (%) |
|---|---|---|
| rs8193036 A/G of IL-17A | | |
| AA | 45 (30.00) | 45 (22.96) |
| AG | 84 (56.00) | 98 (50.00) |
| GG | **21 (14.00)** | 53 (27.04) |
| rs2397084 A/G of IL-17F | | |
| AG | **133 (88.67)** | 146 (74.49) |
| GG | 17 (11.33) | 50 (25.51) |

Bold indicates statistical significance $p < 0.05$.

However, patients with the GG homozygote of rs8193036 A/G of interleukin 17A experienced significantly more intensive pruritus (Table II Publication I).

**Table II. Medium numerical rating scale scale score in comparison with rs8193036 A/G of interleukin 17A**

| Genotype | Cutaneous T-cell lymphoma $n = 140$ | Medium nummerical rating scale score | SD |
|---|---|---|---|
| AA | 44 | 3.22 | 3.20 |
| AG | 77 | 3.64 | 3.25 |
| GG | 19 | **4.95** | 2.58 |

SD: standard deviation.
Bold indicates statistical significance $p<0.05$.

Statistically significant differences between rs2275913 A/G and rs3819024 A/G of interleukin 17A have also appeared when comparing early and advanced CTCLs (Table III Publication I).

**Table III. Polymorphism rs2275913 A/G and rs3819024 A/G of interleukin 17A frequency difference between disease stages and subtypes**

| Genotypes | Stages and subtypes | | | |
|---|---|---|---|---|
| rs2275913 A/G of IL-17A | Stage Ia-IIa CTCL $n = 85$ $n$ (%) | Stages IIb-IV CTCL $n = 61$ $n$ (%) | MF $n = 135$ $n$ (%) | SS $n = 11$ $n$ (%) |
| AA | 1 (1.18) | 6 (9.84) | 5 (3.70) | 2 (18.18) |
| AG | 20 (23.53) | **24 (39.34)** | 39 (28.89) | 5 (45.45) |
| GG | **64 (75.29)** | 31 (50.82) | **91 (67.41)** | 4 (36.36) |
| rs3819024 A/G of IL-17A | | | | |
| AA | **49 (57.65)** | 23 (37.70) | | |
| AG | 30 (35.29) | 22 (36.07) | | |
| GG | 6 (7.06) | **16 (26.23)** | | |

CTCL: cutaneous T-cell lymphoma; MF: mycosis fungoides: SS: Sezary syndrome.
Bold indicates statistical significance $p < 0.05$.

GG homozygote in rs2275913 A/G of interleukin 17A has been more common in the group of non-SS patients (Table III Publication I). Most important results have also been summarized on the right side of a figure in Appendix S1 of Publication 1.

Some studies indicated pathogenic role of IL-17 in PCLs, while others reported the opposite. Our analysis together with the literature review has contributed to elucidating the role IL-17 in PCL.

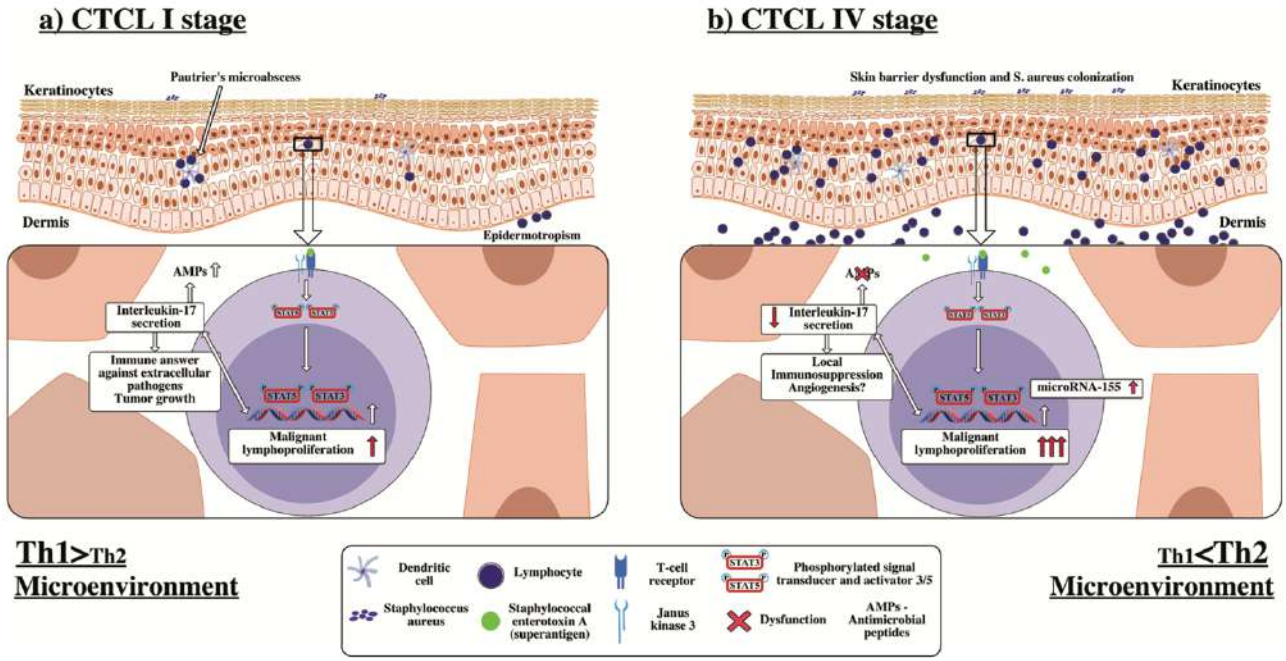



**Figure 1 Publication I: Possible pathogenic role of interleukin-17 (IL-17) in cutaneous T-cell lymphoma (CTCL).** (a) An early stage of a CTCL is shown in the first panel. There is a domination of T helper 1 (Th1) microenvironment with the contribution of IL-17, which plays role in promoting cytotoxic answer against extracellular pathogens (bacteria and fungi). Staphylococcal enterotoxins (superantigens) promote immunological dysregulation by causing benign lymphocytes to stimulate malignant clones. IL-17 has also been shown to promote the oncogenic pathway by stimulation janus kinase 3 (JAK3), which activates signal transducer and activator 3 (STAT3). (b) A late stage of CTCL is presented in the second panel. A clear domination of T helper 2 (Th2) microenvironment has been shown. The secretion of IL-17 may be reduced in that stage leading to local immunosuppression. Also, the antimicrobial peptides (AMPs) have been shown to be reduced and dysfunctional in CTCL. In case of microbiota colonization of the skin, dysfunction of AMPs is one of the crucial elements of impaired skin function. Angiogenesis is signed with a question mark on this figure, because of a possibility, that IL-17 may promote formation of new vessels thorough all stages of the disease. The resistance to anti-VEGF drugs in other lymphomas, lung and colorectal cancer has been previously shown to be promoted by Th-17 subset of cells.

First, through the staphylococcal enterotoxins the oncogenic pathway of JAK3 and STAT3 is activated, which contributes to malignant proliferation of the CTCL lymphocytes. In the latter stages of the lymphoma the secretion of IL-17 decreases, which seems to cause a local immunosuppression state, thereby contributing to the colonization of the skin by Staphylococcus aureus. A recent study has shown that the progression of CTCLs is dependent on the microbiota. The colonization rates by S. aureus of CTCL patients range from 44-76% according to various studies. The infection rates of CTCL patients are significantly higher in the advanced stages of the disease, often contributing to their death. Furthermore, IL-17 may also have pro-angiogenic effects, as IL-17F secreted by malignant T-cell of MyLa2059 cell lines (a Primary cutaneous T-cell non-Hodgkin lymphoma lines) was able to trigger endothelial tube formation, thereby proving stimulation of angiogenesis by IL-17F. The promotion of angiogenesis by Th-17 subset of cells has also been shown in other neoplasms.

Lastly, we have shown that the rs2397084 AG heterozygote of IL-17F was more common in the CTCL population than the control group. Mentioned polymorphism loci is located at the coding region of IL-17F. Patients with the GG variant of SNP rs2397084 of IL-17F at position 7383A/G have been characterized by a change from glutamic acid (GAG) to glycine (GGG) creating a missense molecular consequence. Importantly, it has been theorized that this change may affect the level of expression of IL-17F In patients with GG homozygote of rs2397084 of IL-17F, and those having AG heterozygote are characterized by a normal level and activity of IL-17F. As we have described in the introduction – several SNPs of IL-17F had a significant association with the clinical response to mAbs in psoriatic patients, and therefore we decided to check the influence of this SNP on the response to secukinumab and ixekizumab in these patients.

In cutaneous T-cell lymphoma group analyzed in this study, there have been three cases of patients, in whom prior to the lymphoma diagnosis the psoriasis was diagnosed both clinically and histopathologically. All of these patients had heterozygotic AG rs2397084 IL-17F polymorphisms, which is significantly more often found in the cutaneous T-cell lymphoma group when compared with the general population. Due to this reason, we have decided to test this variant in patients with psoriasis.

Analysis of IL-17A rs2275913 G/A, rs8193036 A/G and IL-17F rs2397084 A/G SNPs influence on the quality of life and response to the treatment with biologic drugs blocking interleukin-17 pathway (secukinumab and ixekizumab) in patients with psoriasis

In the analysis of IL-17A rs2275913 G/A we have not found significant correlations in PASI, DLQI and BSA before and on the first and second appointment after initiating the secukinumab or ixekizumab in our group. We also did not find statistically significant correlations in PASI, DLQI and BSA between variant in patients among IL-17A rs8193036 A/G before the start of the treatment. However, in the tables below we present the statistically significant (defined as $p<0,05$) differences between AA variant versus AG and GG of IL-17a rs8193036 A/G SNP (Table 1, 2 and 3).

**Table 1. PASI of IL-17A rs8193036 A/G SNPs after first appointment**

| IL-17A A/G rs8193036 | PASI 1 Mean | PASI 1 Patients | PASI 1 Standard deviation | PASI 1 Minimum | PASI 1 Maximum | PASI 1 Q25 | PASI 1 Median | PASI 1 Q75 |
|---|---|---|---|---|---|---|---|---|
| GA | 1,22 | 12 | 1,47 | 0 | 4,3 | 0 | 0,55 | 1,75 |
| GG | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| AA | 8,95 | 2 | 7,14 | 3,9 | 14 | 3,9 | 8,95 | 14 |
| Summary | 2,03 | 16 | 3,53 | 0 | 14 | 0 | 0,550 | 2,8 |

**Table 2. PASI of IL-17A rs8193036 A/G SNPs after second appointment**

| IL-17A A/G rs8193036 | PASI 2 Mean | PASI 2 Patients | PASI 2 Standard deviation | PASI 2 Minimum | PASI 2 Maximum | PASI 2 Q25 | PASI 2 Median | PASI 2 Q75 |
|---|---|---|---|---|---|---|---|---|
| GA | 0,49 | 11 | 0,67 | 0 | 1,8 | 0 | 0 | 1,1 |
| GG | 0,6 | 2 | 0,85 | 0 | 1,2 | 0 | 0,6 | 1,2 |
| AA | 3,55 | 2 | 1,77 | 2,3 | 4,8 | 2,3 | 3,55 | 4,8 |
| Summary | 0,91 | 15 | 1,32 | 0 | 4,8 | 0 | 0,3 | 1,4 |

**Table 3. BSA of IL-17A rs8193036 A/G SNPs after second appointment**

| IL-17A A/G rs8193036 | BSA 2 Mean | BSA 2 Patients | BSA 2 Standard deviation | BSA 2 Minimum | BSA 2 Maximum | BSA 2 Q25 | BSA 2 Median | BSA 2 Q75 |
|---|---|---|---|---|---|---|---|---|
| GA | 0,006 | 11 | 0,007 | 0 | 0,02 | 0 | 0 | 0,01 |
| GG | 0,004 | 2 | 0,005 | 0 | 0,008 | 0 | 0,004 | 0,008 |
| AA | 0,055 | 2 | 0,049 | 0,02 | 0,090 | 0,02 | 0,055 | 0,090 |
| Summary | 0,012 | 15 | 0,023 | 0 | 0,090 | 0 | 0,008 | 0,015 |

PASI on both appointments and BSA at the second appointment after initiation of treatment, in patients with AA homozygote of IL-17A in rs8193036 SNP have been significantly higher in comparison with patients having GA and GG variants. As we have described – before the treatment there have been no statistically significant differences, which means that in our study homozygotic AA patients have responded worse to the anti-IL-17A therapy. Up to date, we have not found any literature reports on the significance of IL-17A rs8193036 A/G SNP.

In our analysis of IL-17F rs2397084 A/G SNP we have been able to mark GG homozygote and AG heterozygote. AA homozygote was not present in our population. The mean PASI of patients before treatment equaled 17 and twelve patients (75%) had PASI over 10, which describes severe chronic plaque psoriasis. The mean DLQI was 19,38, which equals to very large effect on the quality of life. The mean BSA equaled 27,28%. Importantly, three patients characterized by AG heterozygote of IL-17F rs2397084 SNP and one homozygotic patient have been qualified to the drug program due to the psoriasis affecting intimate areas (three patients with AG heterozygote) and due to the nail psoriasis (GG homozygotic patient). Their PASI and BSA have been significantly lower than the rest of the studied group. The lower quality of life of these patients may be also a result of affecting the intimate areas by the disease, which did not respond to alternative therapies for 6 months prior to the inclusion in the drug program.
Furthermore, we have analyzed PASI, DLQI and BSA in each variant both before initiating the treatment and at the first and second recorded appointment. In the tables below we present the statistically significant (defined as $p<0,05$) differences between AG and GG of IL-17F rs2397084 A/G SNP (Table 4).

Table 4. DLQI of IL-17F rs2397084 A/G SNPs before initiating the treatment

| IL17F A/G rs2397084 | DLQI before treatment Mean | DLQI before treatment Patients | DLQI before treatment Standard deviation | DLQI before treatment Minimum | DLQI before treatment Maximum | DLQI before treatment Q25 | DLQI before treatment Median | DLQI before treatment Q75 |
|---|---|---|---|---|---|---|---|---|
| AG | 22,27 | 11 | 5,59 | 11 | 29 | 19 | 24 | 26 |
| GG | 13 | 5 | 8,86 | 1 | 25 | 10 | 12 | 17 |
| Summary | 19,38 | 16 | 7,84 | 1 | 29 | 13 | 22,5 | 25 |

The DLQI appeared to be statistically significantly different among the variants (Table 4). According to the expectations as the AG variant should have a higher IL-17F

activity, the heterozygotic patients experienced a substantially lower quality of life compared to patients having GG homozygote of rs2397084 A/G IL-17F SNP. PASI and BSA did not differ before initiating the treatment. Next, we have evaluated patients after receiving treatment with secukinumab or ixekizumab on their first and second appointment.

**Table 5. PASI of IL-17F rs2397084 A/G SNPs after first appointment**

| IL17F A/G rs2397084 | PASI 1 Mean | PASI 1 Patients | PASI 1 Standard deviation | PASI 1 Minimum | PASI 1 Maximum | PASI 1 Q25 | PASI 1 Median | PASI 1 Q75 |
|---|---|---|---|---|---|---|---|---|
| AG | 1,07 | 11 | 1,48 | 0,00 | 3,9 | 0 | 0,4 | 1,6 |
| GG | 4,14 | 5 | 5,76 | 0,00 | 14 | 0,5 | 1,9 | 4,3 |
| Summary | 2,03 | 16 | 3,54 | 0,00 | 14 | 0 | 0,550 | 2,8 |

**Table 6. PASI of IL-17F rs2397084 A/G SNPs after second appointment**

| IL17F A/G rs2397084 | PASI 2 Mean | PASI 2 Patients | PASI 2 Standard deviation | PASI 2 Minimum | PASI 2 Maximum | PASI 2 Q25 | PASI 2 Median | PASI 2 Q75 |
|---|---|---|---|---|---|---|---|---|
| AG | 0,7 | 11 | 0,84 | 0,00 | 2,3 | 0 | 0,3 | 1,4 |
| GG | 1,5 | 4 | 2,27 | 0,00 | 4,8 | 0 | 0,6 | 3,0 |
| Summary | 0,91 | 15 | 1,32 | 0,00 | 4,8 | 0 | 0,3 | 1,4 |

The DLQI, PASI and BSA did not differ among the variants on both first and second control visits. However, a tendency to a better response to the treatment in patients having rs2397084 AG IL-17F SNP has been noticed (Tables 5 and 6). The results may prove in the future, that there is a subset of patients, in whom the IL-17F signaling contributes to a bigger extent to the psoriasis pathogenesis and significantly decreases their quality of life.

Our preliminary results are supported by the literature. First, as we have described in Publication 3, the IL-17 family consists of IL-17A having the highest activity and other analogues (IL-17B, IL-17C, IL-17D, IL-17F). IL-17E is an antagonizing cytokine having immunomodulatory effect, also known as IL-25 [21]. IL17F has a second highest activity of IL-17 profile among this family. Importantly, IL17A and IL-17F are believed to be co-expressed (both genes have the same locus) and most T17 cells express either IL-17A or IL-17F, with <10% of cells co-expressing both cytokines [21,22]. IL-17A and IL-17F may be secreted either as an IL-17A homodimer, IL-17A/F heterodimer or IL-17F homodimer. Among novel drugs secukinumab and ixekizumab block IL-17A homodimer and IL-17A/F heterodimer, bimekizumab and sonelokimab block IL-17A/F heterodimer and IL-17F homodimer, while brodalumab blocks all the IL-17 signaling [21].

What is important, IL-17F appeared to be more abundant in patients with psoriatic skin than IL-17A [23]. Probably this fact contributes the most to the recent success of sonelokimab and bimekizumab, which block IL-17A homodimer, IL-17A/F heterodimer and IL-17F homodimer [21]. The three-way blockade of IL-17A and IL-17F signaling resulted in successful treatment of patients who failed to respond to selective anti IL17A therapy before [24–26]. IL-17F has also been theorized to have a significant role in a reoccurrence of psoriasis [10].

Our results highlight the importance of IL-17F blocking in the therapy of psoriasis and are in accordance with the literature. Secukinumab and ixekizumab block only IL-17A homodimer and IL-17A/F heterodimer, and this phenomenon is a probable explanation of why patients with AG heterozygote of IL-17F rs2397084 A/G SNP did not respond better to these mAbs despite the initial thoughts. Along with the significant role of blocking IL-17F homodimer in the therapy of psoriasis, especially in patients with AG heterozygote of IL-17F rs2397084, which was 68,75% of our group, should benefit from it.

The facts that the severe course of psoriasis increases the risk of developing lymphomas, including PCLs, and the hazard ratio of occurrence of lymphomas in patients with psoriasis equals more than 6 are well known in the literature. The rs2397084 AG SNP contributes to a substantially lower quality of life of psoriasis patients. Therefore, individuals, who have the AG rs2397084 IL-17F variant should be strictly observed in the context of developing PCLs.

Publication 2 - Safety and Danger Considerations of Novel Treatments for Atopic Dermatitis in Context of Primary Cutaneous Lymphomas

In that paper we have carefully and comprehensively reviewed the similarities and differences between AD and PCLs, the possible impact of new therapies concerning IL-4/IL-13, IL-22, IL-31 and JAK/STAT pathways on the PCLs. Lastly, we evaluated the real-world data summarizing the cases of CTCL patients treated with dupilumab or ruxolitinib.

In the (Table I Publication II) most important similarities between AD and PCLs have been summarized.

**Table 1.** Clinical and immunological similarities between atopic dermatitis (AD) and cutaneous T-cell lymphoma (CTCL).

| Similarities | Atopic Dermatitis | Cutaneous T-Cell Lymphoma |
|---|---|---|
| Eosinophilia | Often present | May be present in the advanced stage |
| Immunoglobulin E (IgE) | Often elevated | May be elevated in the advanced stage |
| Lactate dehydrogenase (LDH) | May be elevated | Severity marker of MF/SS |
| Soluble interleukin receptor 2 (sIL-2R) | May be elevated | Severity marker of MF/SS |
| Th-2 microenvironment activation | Always present | Present in the advanced stage |
| Levels of filaggrin | Significantly lowered | May be significantly lowered |
| Transepidermal water loss (TEWL) | Significantly lowered | May be significantly lowered |
| Levels of antimicrobial peptides (AMPs) | Significantly lowered | Significantly lowered |
| Colonization of *S. aureus* | 80% of patients | 50–60% of patients |

Especially in case of erythroderma it may be difficult to distinguish both diseases. [27] To make this challenge harder in some cases AD and PCL may coexist or PCL may develop as according to cohort studies, the risk of developing NHL with cutaneous manifestation is especially high in AD patients. [28–30]

Basing on the data concerning numerous cytokines effects on the microenvironment of PCLs we have been able to distinguish some theoretical assumptions on the effects of dupilumab, lebrikizumab, tralokinumab, fezakinumab, nemolizumab and JAKi. Decreasing the concentration and/or stopping the secretion of IL-4 and IL-13 could lead to the restoration of the Th-1 microenvironment, which may enhance tumorous toxicity. The reduction in the levels of these interleukins after receiving certain treatments discussed earlier is one of the supporting facts for this theory. Therefore, dupilumab, lebrikizumab, and tralokinumab may appear to be clinically efficient in the treatment of the PCL. Agents blocking IL-22, i.e., fezakinumab, could also stop the lymphomagenesis and additionally reduce the ability of the tumorous cells to metastasize in the advanced stages of the lymphoma. We also show the possible involvement of IL-31 in the pathogenesis of PCLs, which is still elusive. Theoretically, blocking the role in the establishment of the Th-2 microenvironment and in the growth of the tumor might be beneficial for the lymphoma patients after administration of nemolizumab, similar to other lymphomas. Lastly, JAK1 and JAK3 seem to have the pathogenic role by activating the STAT3, STAT5, and STAT6, which contribute significantly to lymphomagenesis. Therefore, blocking them may reduce tumor development. In contrast, JAK2 may also play some role in preventing the growth of lymphomas. Despite the mentioned effects of ruxolitinib on the CTCL cell lines, obstructing this pathway may appear to be harmful for the patients by reducing the Th-1 cytotoxicity directed to the clones.

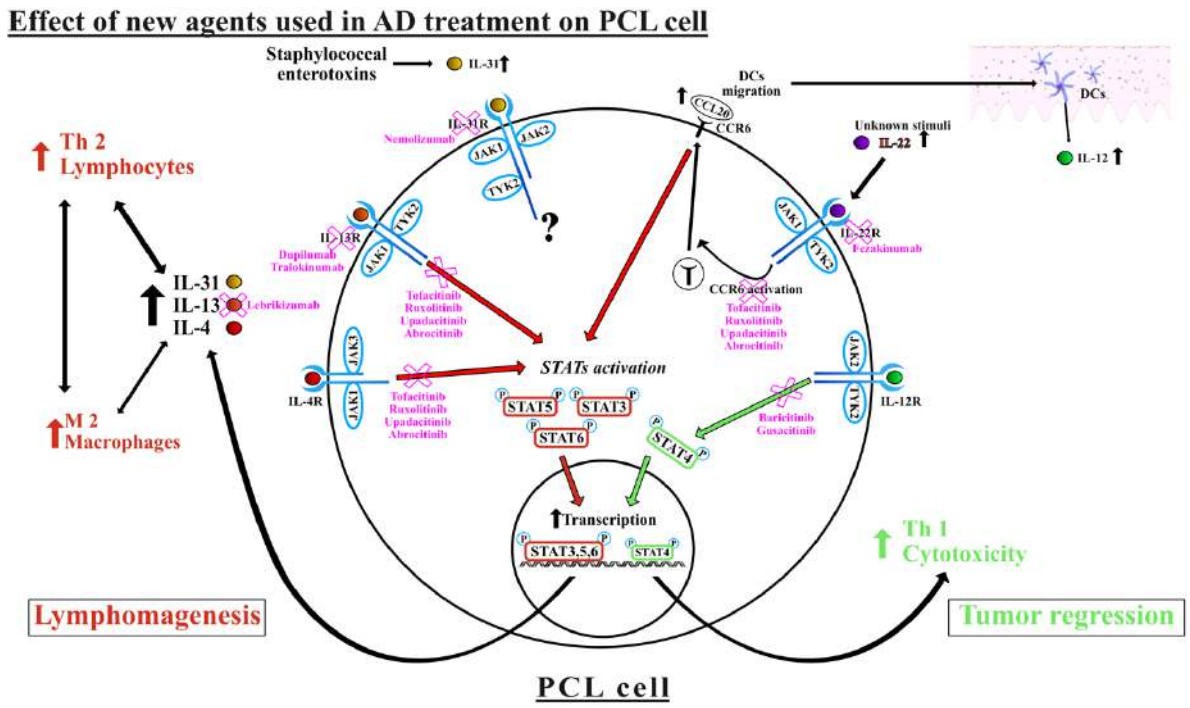



**Figure 1 Publication II:** The influence of agents targeting interleukins (IL) 4, 13, 22, and 31 and JAK/STAT pathways on the primary cutaneous lymphomas (PCLs) cells and tumorous microenvironment. The up and down arrows stand for increase/decrease of the interleukins concentration, cell count or receptor's upregulation. IL-12 promotes phosphorylation of STAT4, thereby stimulating the cytotoxic mediated CD8(+) answer. Concomitantly, IL-4, IL-13, and IL-31 contribute to forming the Th-2 cytokine profile, which results in decreased cytotoxic immunosurveillance and lymphomagenesis. IL-4, IL-13, and IL-22 activate different Janus kinases, which promote the STAT3, STAT5, and STAT6 activation contributing to the transcription of pro-tumorous factors. In the advanced stages of the disease, this phenomenon may be seen more prominently. By blocking several pathways or cytokines, biologic drugs and small molecule inhibitors may affect both the malignant microenvironment and pathways in the PCLs cells.

Figure above summarizes the most important aspects of our assumptions (Figure 1 Publication II).

Our research of Pubmed database has led us to identify a total of 23 cases in which a PCL and use of dupilumab coexisted. A total of 21 people in this group were above 40 years old. What may be surprising in the context of our theoretical assumptions is that the most common event in the mentioned group was the progression of the lymphoma, which led to the death of two patients, who progressed to SS. No clinical

improvement of the CTCL was observed four times, whereas the disease course improved in three cases. In 16 cases, the original diagnosis was AD or eczema while remaining patients were treated for PCL or mogalizumab-associated rash off-label. Interestingly, dupilumab appeared to be effective for the treatment of lichenoid reaction associated with mogalizumab in a patient with CD8+ MF.

Ruxolitinib, which targets JAK1/JAK2 is used in the treatment of psoriatic arthritis, AD, and several lymphoid malignancies, e.g., myelofibrosis and polycythemia vera. [31,32] Moreover, trials on animal models of hemophagocytic lymphohistiocytosis (HLH) prove this JAK inhibitor to be efficient in the treatment of this condition. [33,34] Assuming that JAK inhibitors prove to be effective in the treatment of cutaneous lymphomas, clinicians may feel comfortable administering them if the final diagnosis is difficult to make. [31] These facts led the researchers to administer ruxolitinib to nine patients with PCLs (four MF, three non-specified CTCL, one primary cutaneous anaplastic large cell lymphoma (pcALCL), and one subcutaneous panniculitis-like-T-cell lymphoma (SPTCL)). Some improvement was observed in three cases (one MF, one pcALCL and one STPCL), but the disease course remained stable or worsened in the others.
Despite that five of the seven CTCLs patients have revealed the signs of JAK/STAT activation, only one patient whose tumor showed 20% overactivation of pSTAT3 responded to the treatment.

Data on dupilumab and ruxolitinib administration have been summarized in the table II (Table II Publication II).

**Table 2.** Cutaneous T-cell lymphoma cases treated with dupilumab or ruxolitinib. We have updated the table continuing the results by doctor Sugaya [91].

| Drug | Age (Years) | Sex | Pre-Diagnosis | Final Diagnosis | Response to Treatment | Death | Reference |
|---|---|---|---|---|---|---|---|
| Dupilumab | 58 | M | AD | MF | Progression of MF | No | [199] |
| Dupilumab | 64 | M | AD | SS | Progression of SS | No | [200] |
| Dupilumab | 51 | F | AD | MF | Progression of MF | No | [201] |
| Dupilumab | 64 | M | AD | CTCL-NOS | Progression of erythroderma | No | [202] |
| Dupilumab | 72 | M | AD | MF | Progression of MF | No | [202] |
| Dupilumab | 59 | F | AD | MF and AD | Progression of MF | No | [202] |
| Dupilumab | 40 | F | AD | MF | Progression of MF | No | [202] |
| Dupilumab | 67 | M | MF | SS | Progression of SS | Yes | [202] |
| Dupilumab | 58 | M | MF | SS | Progression of SS | Yes | [202] |
| Dupilumab | 77 | F | MF | SS | Progression of SS | No | [202] |
| Dupilumab | 61 | M | Eczema | MF | Progression of MF | No | [203] |
| Dupilumab | 52 | M | Eczema | MF | No clinical improvement | No | [203] |
| Dupilumab | 60 | F | Eczema | MF | No clinical improvement | No | [203] |
| Dupilumab | 68 | M | SS and AD | SS and AD | Improvement in SS and AD | No | [204] |
| Dupilumab | 37 | F | Eczema | SS | Progression of SS | No | [205] |
| Dupilumab | 55 | M | MF and AD | MF and AD | Improvement of MF and AD | No | [205] |
| Dupilumab | 74 | F | SS | SS | Improvement of SS | No | [206] |
| Dupilumab | 48 | F | AD | SS and AD | No clinical improvement | No | [207] |
| Dupilumab | 40 | F | AD | MF | Progression of MF | No | [208] |
| Dupilumab | 43 | M | AD | MF and AD | Progression of MF | No | [209] |
| Dupilumab | 48 | F | AD | MF | Progression of MF | No | [210] |
| Dupilumab | 55 | M | AD | MF | Progression of MF | No | [210] |
| Dupilumab | 26 | M | MF | MF | No clinical improvement | No | [211] |
| Ruxolitinib | 13 | M | HLH | HLH and SPTCL | Improvement of SPTCL and HLH | No | [212] |
| Ruxolitinib | NS | NS | MF | MF | Progression of MF | No | [213] |
| Ruxolitinib | NS | NS | CTCL | CTCL | No clinical improvement/ Stable disease | No | [213] |
| Ruxolitinib | NS | NS | CTCL | CTCL | Progression of CTCL | No | [213] |
| Ruxolitinib | NS | NS | CTCL | CTCL | Progression of CTCL | No | [213] |
| Ruxolitinib | NS | NS | MF | MF | Progression of MF | No | [213] |
| Ruxolitinib | NS | NS | MF | MF | No clinical improvement/ Stable disease | No | [213] |
| Ruxolitinib | NS | NS | MF | MF | Improvement of MF/ Partial remission | No | [213] |
| Ruxolitinib | NS | NS | pcALCL | pcALCL | Improvement of MF/ Complete response | No | [213] |

**Table 2.** *Cont.*

Abbreviations: NS: not specified; M: male; F: female; MF: mycosis fungoides; AD: atopic dermatitis; CTCL: cutaneous t-cell lymphoma; pcALCL: primary cutaneous anaplastic large-cell lymphoma; SS: Sézary Syndrome; HLH: hemophagocytic lymphohistiocytosis; SPTCL: subcutaneous panniculitis-like T-cell lymphoma; CTCL-NOS: CTCL-not otherwise specified.

Blockage of several mechanisms by which the interleukins act and occur in PCLs should be beneficial in the treatment of the disease. However, dupilumab, in most of patients with lymphoma misdiagnosed as AD or eczema, makes it fully apparent. This

drug does not seem to be beneficial for CTCL patients in most cases. Accordingly, despite the JAK/STAT activation, most of the lymphomas did not respond to ruxolitinib.

Publication 3 - Safety and danger of biologic treatments in psoriasis in context of cutaneous T-cell lymphoma (CTCL)

In the paper "Safety and danger of biologic treatments in psoriasis in context of cutaneous T-cell lymphoma (CTCL)" we have carefully and comprehensively reviewed the role of IL-17, IL-12/IL-23 and TNF-a in mycosis fungoides (MF) – the most common type of CTCL. Main aspects of this analysis have been summed up on the figure presented below (Figure I Publication III).

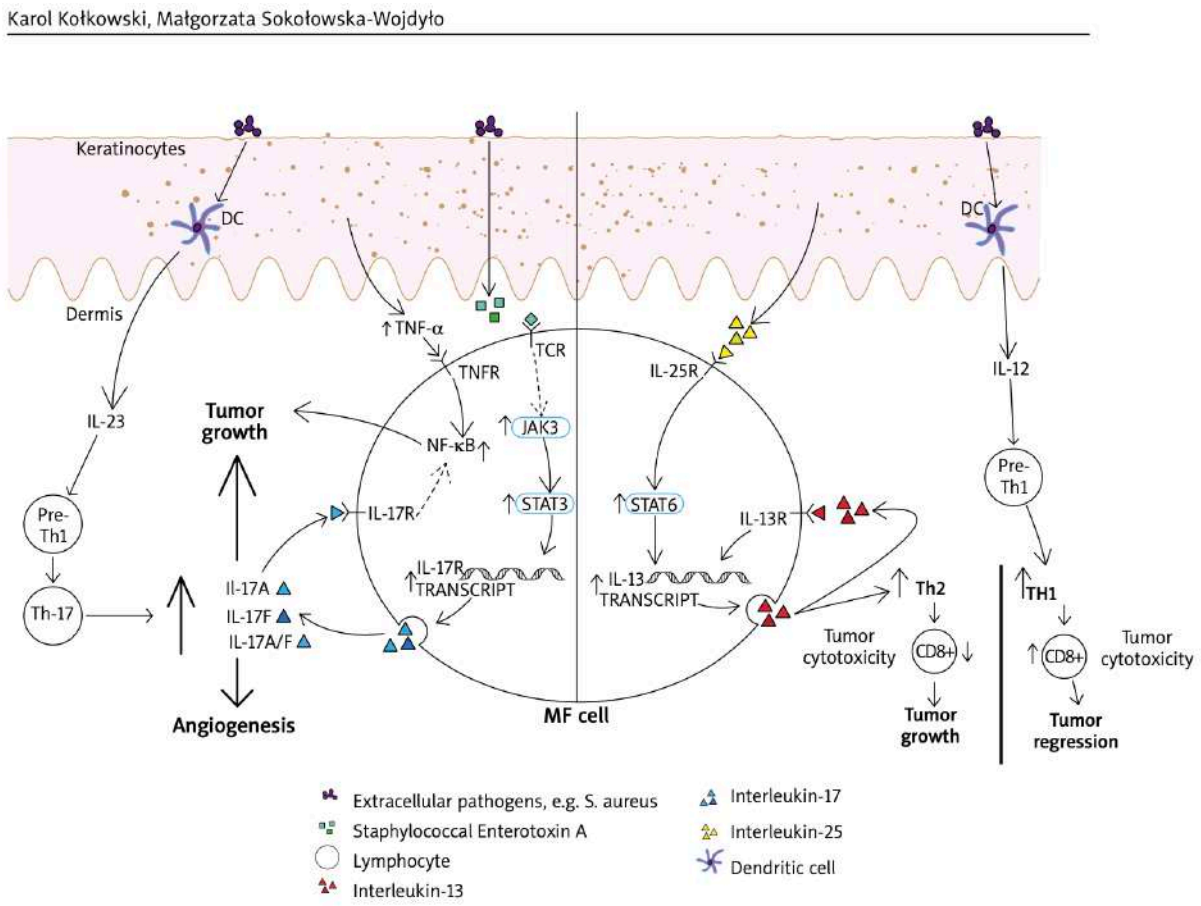



**Figure I Publication III:** Figure 1. The contribution of interleukins (IL) 12, 17, 23 and tumor necrosis factor a (TNF-a) to the tumor microenvironment in mycosis fungoides (MF). IL-12 has been indirectly restoring the cytotoxic mediated CD8(+) answer and promoting tumor regression by stimulating the differentiation of pre-T-helper 1 lymphocytes. IL-23 can stimulate pre-T-helper 1 lymphocytes, followed by creating T-helper 17 cells subset and increased secretion of IL-17 proinflammatory cytokines. MF cell is also able to secrete IL-

17A, IL-17F and IL-17A/IL-17F heterodimers. It is reinforced by upregulated JAK3/STAT3 pathway, which has been shown to be promoted by activated T-cell receptor (TCR), which is necessary for malignant transformation in MF to occur. One of the possible ways of activating TCR is related to Staphylococcal enterotoxin A. NF-kB upregulation, with its anti-apoptotic effect on lymphoma cells, seems to be important and relevant in the pathogenesis of CTCL. It has been promoted by TNF-a as well as proinflammatory IL-17 cytokines. IL-25 (IL-17E) is promoting STAT6 pathway. Those interactions result in increased IL-13 secretion (also in autocrine manner). Especially in the advanced stage of the disease it contributes to forming Th-2 cytokine profile, what results in decreased cytotoxic immunosurveillance and tumor growth.

Furthermore, we have evaluated the possible effects of new therapies for psoriasis on CTCL, which have been later conflicted with the real-world data on patients receiving them. The current knowledge on the role of IL-17 has been in detail described in the chapter discussing results from Publication 1 and further research. Therefore, here I will describe only clinical data on administering treatments for psoriasis to cutaneous lymphoma patients.

We have identified 7 patients described in clinical case studies and 90 cases from retrospective studies reporting CTCL after TNF-a-inhibitor treatment. Eighty-two out of these 97 patients presented with CTCLs, 66 of which were classified as MF and 5 as Sezary Syndrome (SS). Dequidt et al. reported that in each of the 5 cases of large cell transformation in MF, the diagnosis of psoriasis was the reason to treat with biologic drugs and after discontinuing anti-TNF-a, the evolution of the lymphoma was aggressive. Another study has revealed that the majority of MF were misdiagnosed, predominantly as psoriasis, and biologic drugs made the lymphoma fully apparent. During follow-up, 7 patients died because of the CTCL that appeared after the anti-TNF-a administration, all of them in the advanced stage of the disease. On the other hand, most cases of MF have appeared indolent after anti-TNF-a drugs were discontinued, in some cases the topical treatment led to partial or complete response. Moreover, majority of the patients had either a stable disease or a complete response after receiving a stage-suited therapy.

Most of the MF patients may progress after receiving IL-17A, IL-17RA or IL-12/23 inhibitors. [35–39] In fact, one case report has shown significant clinical improvements

after discontinuing of these drugs. [36] Nevertheless, the biggest study on that matter has shown that in 8 of 11 cases, a worsening of the disease was noticed and in the short follow-up of thirteen months 5 patients died, 4 of MF and one of stroke. [38] In contrast to these reports, our assumptions highlighted the possible aggravating role of IL-17 in MF, therefore blocking it would be beneficial. The explanation to these conflicting data may be the aspect of Th17/Treg imbalance leading to immunosuppression and other, not yet known mechanisms. [39]

In the course of atopic dermatitis there also is an increased risk of developing PCLs. However, we did not decide to test the IL-17 variants in this subset of patients, due to the lack of efficacy of IL-17 inhibitors in the treatment of atopic dermatitis. [40] Despite some studies reporting the elevated levels of IL-17 in the skin of patients with atopic dermatitis, it seems to be a result of innate defense mechanisms. [41,42] Due to the disruption of epidermal barrier in atopic dermatitis, these patients are prone to various types of infections and colonization by several pathogens, which activate the innate defense mechanisms in the skin thereby elevating the level of IL-17 in their skin. [41,42]

## CONCLUSIONS

In the first publication and an additional study we have shown significant associations between IL-17 SNPs and stage of CTCLs as well as with decreased of DLQI in psoriasis. Furthermore, our study and a review of the literature contributed to elucidating the pathogenic role of IL-17 in PCLs and supporting the importance of IL-17F in psoriasis pathogenesis, which already has clinical implications.

In additional preliminary study on the IL-17A rs2275913 G/A, rs8193036 A/G and IL-17F rs2397084 A/G SNP influence on the quality of life and response to the treatment with biologic drugs blocking IL-17A pathway (secukinumab and ixekizumab) in patients with psoriasis. we have shown that IL-17A rs2275913 G/A does not have significant correlations affecting anti-IL-17A therapy in our group. However, patients having AA homozygote of rs8193036 IL-17A responded worse to this biologic treatment. Lastly, Patients with AG heterozygote of Il-17F rs2397084 had a worse quality of life prior to the beginning of the biologic therapy. Our results supported by the literature and confirm the importance of IL-17F in the pathogenesis of psoriasis. Blocking both IL-17A and IL-17F seems to be the future of the psoriasis treatment, especially in cases relapsing or

without sufficient clinical benefit from the anti-IL-17A (secukinumab and ixekizumab) treatment.

With the second publication, we would like to raise awareness to the issue of a development or a misdiagnosis of a cutaneous lymphoma in patients with AD. Especially for patients that are 40 years old or above, the chronic and severe course of AD and the sudden worsening of the symptoms should be considered "red flags" to exclude the potential oncologic risk by taking and carefully verifying the biopsy.

The most important conclusion in the third publication is a necessity of psoriatic patients to be carefully examined and in case of any oncological suspicion, take biopsies in order to exclude a potential misdiagnosis.

Despite the initial belief of the safety of the mAbs and small molecule inhibitors in the context of PCLs, now it seems that their impact on the lymphoma microenvironment is significant and not fully understood and elucidated. Therefore, in case of atypical course of the inflammatory diseases, especially during the treatment with novel therapies there is a necessity to stay aware and careful. In case of sudden worsening the symptoms our results suggest discontinuing novel drugs until excluding the possibility of lymphoma coexistence with additional medical tests, especially histopathological examination.

## PUBLICATIONS

The publications constituting to this doctoral thesis have been attached below. Please consider that these publications and supplementary materials are attached in an as-published form, hence the formatting differs across the documents.

ORIGINAL ARTICLE

# Interleukin-17 Genes Polymorphisms are Significantly Associated with Cutaneous T-cell Lymphoma Susceptibility

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PUBLICATION 1

**Tumour microenvironment has an important effect on the progression of cutaneous T-cell lymphomas. Using PCR with sequence-specific primers, this study analysed single-nucleotide polymorphisms in the interleukin-17 genes of 150 patients with cutaneous T-cell lymphoma. GG homozygote rs8193036 A/G of interleukin-17A gene occurred less commonly in the cutaneous T-cell lymphoma group; however, patients with this single-nucleotide polymorphism experience significantly intense pruritus. Conversely, the rs2397084 AG heterozygote of interleukin-17F is more common in the lymphoma population. In addition, there were significant differences in the frequencies of interleukin-17 genotypes when comparing early (Ia to IIa) and advanced stages (IIb, III and IV) of this neoplasms. A similar result has been shown in comparison between Sézary syndrome and mycosis fungoides. The current data may serve as a possible explanation for the increased bacterial infection rates in the course of cutaneous T-cell lymphoma, especially caused by *Staphylococcus aureus*. In summary, specific single-nucleotide polymorphisms occur with different frequencies between cutaneous T-cell lymphoma and healthy patients. Moreover, genetic predisposition of several interleukin-17 single-nucleotide polymorphisms may be a factor causing impaired immune defence in cutaneous lymphomas.**

*Key words:* cutaneous lymphoma; mycosis fungoides; Sézary syndrome; cytokine; interleukin-17; lymphoma pathogenesis; single-nucleotide polymorphism.

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## SIGNIFICANCE

Cutaneous T-cell lymphomas are a rare entity of lymphoproliferative disorders. This study presents genetic predisposition of some single-nucleotide polymorphic variants in the context of developing cutaneous T-cell lymphomas. Moreover, the results show some single-nucleotide polymorphisms of interleukin-17A and interleukin-17F to be significantly associated with pruritus intensity. These results may explain the increased susceptibility and rates of skin infections in the course of cutaneous T-cell lymphomas. Analysis of the current data and the literature may lead to improved care and management of patients with cutaneous T-cell lymphomas.

Cutaneous T-cell lymphomas (CTCLs) belong to a group of rare, lymphoproliferative disorders, which have their origin in skin (1). Interleukin (IL)-17 has been implicated in the pathogenesis of these tumours, but the exact mechanism remains unclear (2–4). Various single-nucleotide polymorphisms (SNPs) of IL-17 genes have previously been associated with increased risk and worse course of autoimmune and neoplastic diseases (5–12). Other cytokines have been studied in this context in CTCL (13, 14). The aim of this study was to elucidate whether the frequency of selected SNPs of IL-17 genes are associated with susceptibility to the CTCL.

## MATERIALS AND METHODS

The study was approved by the Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk, Poland. A total of 150 blood samples of patients with CTCL: 139 MF in stages IA (44 cases), IB (38 cases), IIA (3 cases), IIB-IV (54 cases), and 11 Sézary syndrome (SS) diagnosed and treated at the Department of Dermatology of the Medical University in Gdansk and a control non-CTCL group of 196 unrelated healthy individuals within similar age and sex distribution, without personal or family history of chronic skin diseases, without pruritus and without personal history of malignancy were included in the study. Patients had been diagnosed on the basis of clinical, histopathological and immunohistochemical findings, according to the European Organization of Research and Treatment of Cancer (EORTC) criteria (1). Pruritus intensity was evaluated according to visual analogue scale (VAS) and numeric rating scale (NRS) and correlated with IL-17 gene polymorphisms.

### *DNA extraction/genotyping*

Genomic DNA was isolated from all blood samples with the Blood Mini A&A Biotechnology (A&A Biotechnology, Gdansk, Poland) according to the instructions of the manufacturer. Analysis of the polymorphic variants IL-17A (rs2275913, rs3819024, rs8193036) and IL-17F (rs763780, rs2397084) were analysed by PCR with sequence-specific primers (SSP-PCR). Graphical visualization of this method is shown in Appendix S1.

**Table I. Polymorphism rs8193036 A/G of interleukin (IL) 17A and rs2397084 A/G of interleukin 17F**

| Genotypes | Cutaneous T-cell lymphoma $n=150$ $n$ (%) | Control group $n=196$ $n$ (%) |
|---|---|---|
| rs8193036 A/G of IL-17A | | |
| AA | 45 (30.00) | 45 (22.96) |
| AG | 84 (56.00) | 98 (50.00) |
| GG | **21 (14.00)** | 53 (27.04) |
| rs2397084 A/G of IL-17F | | |
| AG | **133 (88.67)** | 146 (74.49) |
| GG | 17 (11.33) | 50 (25.51) |

Bold indicates statistical significance $p<0.05$.

*Statistical analysis*

Statistical calculations were made with Statistica, version 12.0 (StatSoft, Inc. 2015, Tulsa, Oklahoma, USA). Analysis of qualitative features was made with the $\chi^2$ test in the Pearson method. Independent variables fulfilling the assumptions for parametric tests were analysed with the Student's t-test. Independent variables that did not meet the parametric test assumptions were analysed with non-parametric tests (analysis of variance (ANOVA) equivalents): Mann–Whitney $U$ test (comparison of 2 tests) or Kruskal–Wallis test (comparison of many samples). Odds ratios (ORs) with 95% confidence intervals (95% CI) were determined by a logistic regression. In all tests, $p<0.05$ was considered a significant level of statistical significance.

## RESULTS

Genotype distribution of the studied SNPs (AA, AG, and GG) of IL-17A and IL-17F in which significant differences between studied groups in the distribution of alleles were found are shown in **Tables I–III**.

*Interleukin-17A gene polymorphisms*

Of the 3 studied loci, the only polymorphism which occurred significantly different in comparison with healthy controls was rs8193036 A/G of interleukin 17A. The presence of the IL-17A GG genotype has been found to be less frequent in the current CTCL population (odds ratio (OR) 0.4392, 95% CI 0.2512–0.7679 and $p=0.0039$) (Table I). The pruritus intensity regarding our group has also been studied. Medium NRS in IL-17A rs8193036 polymorphism appeared to be significantly higher when the GG homozygote was present, in comparison with other genotypes ($p=0.03$) (Table II). Moreover, the distinction between pruritus level GG and other polymorphisms has also been discovered to be significant ($p=0.005$) (Appendix S1).

*IL-17F gene polymorphisms*

Of the 2 studied loci of the IL-17F gene, the only polymorphism that occurred significantly more commonly in comparison with the control group was rs2397084 AG (OR 2.6793, 95% CI 1.4729–4.8739 and $p=0.0009$) (Table I). As before, it is also the only polymorphism of IL-17F in the current study, in which the visual analogue scale (VAS) pruritus levels have differed significantly between AG and GG ($p=0.01$) (Appendix S1).

**Table II. Medium numerical rating scale scale score in comparison with rs8193036 A/G of interleukin 17A**

| Genotype | Cutaneous T-cell lymphoma $n=140$ | Medium nummerical rating scale score | SD |
|---|---|---|---|
| AA | 44 | 3.22 | 3.20 |
| AG | 77 | 3.64 | 3.25 |
| GG | 19 | **4.95** | 2.58 |

SD: standard deviation.
Bold indicates statistical significance $p<0.05$.

*Stage of a lymphoma and IL-17 polymorphisms*

Several distinctions were found between the distribution of certain genotypes in the various stages of the CTCL. The distribution of polymorphisms in the early stage (Ia to IIa) and advanced (IIb and higher) stages of lymphomas were analysed. Presence of IL-17A AG and GG genotypes of the rs2275913 polymorphism were respectively more (OR 2.1081, 95% CI 1.0285–4.3210 and $p=0.0417$) and less (OR 0.3391, 95% CI 0.1678–0.6852 and $p=0.0026$) frequent in IIb, III and IV stage CTCL compared with early stages (Table III). The analysis was significant, although not reliable due to the small group size with the AA genotype. Similar observations have been made concerning rs3819024 A/G polymorphism of interleukin 17A. The AA genotype was less frequent in advanced CTCL (OR 0.4447, 95% CI 0.2268–0.8718 and $p=0.0183$), while the GG homozygote was more common in the mentioned group (OR 4.6815, 95% CI 1.7099–12.817 and $p=0.0027$) (Table III). Significant differences were found in the frequency of polymorphism rs2275913 A/G of interleukin 17A genotypes when comparing patients with SS with those with mycosis fungoides (MF). The GG homozygote was found more often in MF than in SS (OR 0.2763, 95% CI 0.0768–0.9939 and $p=0.0489$) (Table III). No significant distinctions were found when analysing other polymorphisms in that manner (Appendix S1).

**Table III. Polymorphism rs2275913 A/G and rs3819024 A/G of interleukin 17A frequency difference between disease stages and subtypes**

| Genotypes | Stages and subtypes | | | |
|---|---|---|---|---|
| rs2275913 A/G of IL-17A | Stage Ia-IIa CTCL $n=85$ $n$ (%) | Stages IIb-IV CTCL $n=61$ $n$ (%) | MF $n=135$ $n$ (%) | SS $n=11$ $n$ (%) |
| AA | 1 (1.18) | 6 (9.84) | 5 (3.70) | 2 (18.18) |
| AG | 20 (23.53) | **24 (39.34)** | 39 (28.89) | 5 (45.45) |
| GG | **64 (75.29)** | 31 (50.82) | **91 (67.41)** | 4 (36.36) |
| rs3819024 A/G of IL-17A | | | | |
| AA | **49 (57.65)** | 23 (37.70) | | |
| AG | 30 (35.29) | 22 (36.07) | | |
| GG | 6 (7.06) | **16 (26.23)** | | |

CTCL: cutaneous T-cell lymphoma; MF: mycosis fungoides: SS: Sezary syndrome.
Bold indicates statistical significance $p<0.05$.

## DISCUSSION

To our knowledge this is the first study of IL-17 SNPs in primary CTCL. Several SNPs of IL-17 genes were associated with susceptibility to CTCL. The GG homozygote of rs8193036 A/G of interleukin 17A occurred less often in the CTCL group (Table I); however, patients with this polymorphism experienced significant pruritus (Table II). The rs2397084 AG heterozygote of IL-17F was more common in the CTCL population (Table I). Moreover, statistically significant differences between rs2275913 A/G and rs3819024 A/G of interleukin 17A have also appeared when comparing early and advanced CTCLs (Table III). That result may explain the more rapid progression to advanced stages of CTCLs in some patients. It is well known that several patients present stable disease for years. GG homozygote in rs2275913 A/G of interleukin 17A has been more common in the group of non-SS patients (Table III). It may suggest that this genotype has a lower predisposition to develop this aggressive, fast-spreading, leukaemic cutaneous lymphoma.

The role of IL-17 in CTCL is complex and not fully understood. It has been reviewed recently in the context of introducing new agents, such as bimekizumab, brodalumab, ixekizumab and secukinumab, in the treatment of psoriasis (15). IL-17A and IL-17F belong to the IL-17 family and are thought to have pro-inflammatory activity (16). They have been important in promoting the answer against extracellular bacteria and fungi (16). The IL-17A and IL-17F SNPs have been previously proven to increase the risk of asthma and rheumatoid arthritis (9–11). Similar correlation has been found in the Spanish cohort of psoriatic patients, but not in the Polish population (8, 12). SNP may play a role as a prognostic factor (6). Moreover, a link between IL-17 functions and carcinogenesis has been implicated in several different neoplasms; for example, in colorectal cancer, but also in the non-melanoma skin cancers (17, 18). Furthermore, several SNPs of IL-17A and IL-17F have been shown to be significantly associated with higher risk of gastric, lung and cervical cancer (5, 7, 19). SNPs have been studied in the context of cutaneous lymphomas, showing that some variants of IL-2 and IL-13 could be estimated as a risk factor, while IL-10 and tumour necrosis factor alpha (TNF-α) have a protective effect against developing CTCL (13).

The exact pathogenesis of CTCL is unknown despite extensive previous research (20). Interestingly, recent studies of the mouse model have shown that T-cell receptor engagement is an important factor of malignant transformation in CTCL (20). Moreover, progression of the disease also appeared to be dependent on microbiota (20, 21). In addition, *Staphylococcus aureus* is known as the most common aetiological factor in infections in patients with CTCL, who are colonized by this bacteria in 44% up to 76% (22). *S. aureus* superantigens may exacerbate and/or perpetuate the clonal expansion of the lymphoma concomitantly with spreading cutaneous inflammation (21, 23). In addition, staphylococcal enterotoxin A isolates have been shown to induce signal transducer and activator 3 (STAT3) activation and expression of IL-17, which pathway has been hypothesized as one of the oncogenic factors in CTCL (3, 24). Recently, another link between staphylococcal enterotoxins and progression of the lymphoma has been noted: they have been shown to induce STAT5 and microRNA-155 (miR-155) (25). STAT3, STAT5 and miR-155 have been previously associated with CTCL pathogenesis (14). Cobomarsen, an inhibitor of miR-155 expression, is thought to be one of the promising novel therapies in CTCL, currently undergoing phase first-in-human clinical studies (26). The constant responses of both malignant and benign lymphocytes to the *S. aureus* inflammation may contribute to carcinogenesis, which would explain why transient, aggressive antibiotic therapy may slow the tumour progression in some cases (22, 27). S. aureus eradication may be a novel treatment for advanced MF/SS in the future (21, 28).

The disturbances in skin barrier also related to extensive inflammation in patients with lymphoma have been described previously (29, 30). Dysfunction of antimicrobial peptides secretion, which is induced by proinflammatory IL-17 cytokines, has been also observed (29, 30). The impaired skin function in case of infection can promote strong immune system defence. Despite elevated IL-17 levels in CTCL in several cases, such a state may lead to local immunosuppression caused by described mechanisms (2, 4, 24, 28, 31). We have summarized data on the possible pathogenic role of IL-17 in CTCL (**Fig. 1**). The results may provide a possible explanation for this phenomenon, as this study has revealed statistically significant differences in IL-17A rs8193036 GG and IL-17F rs2397084 AG SNPs in CTCL (Table I). In the case of IL-17A rs8193036 GG, more severe pruritus has been observed (Table II). Severe pruritus correlates with lower quality of life and both have been observed in advanced stages of MF and in SS (32). The statistical differences between early and advanced CTCL stages may also be an explanation of the fact that the pace of progression of the CTCL is individual. Bearing in mind that IL-17 belongs to a group of proinflammatory cytokines, and that Th2 profile is specific for advanced MF and SS, the rs2275913 A/G of interleukin 17A may protect switching from Th1 to Th2 profile in the CTCL microenvironment (Table III).

The study is limited by its design to test the specific SNPs instead of using new methods, such as next gene sequencing combined with the use of neural networks, which are currently shown in similar papers. It was not possible to perform them. However, the results of the current study seem to be important, especially in light of the

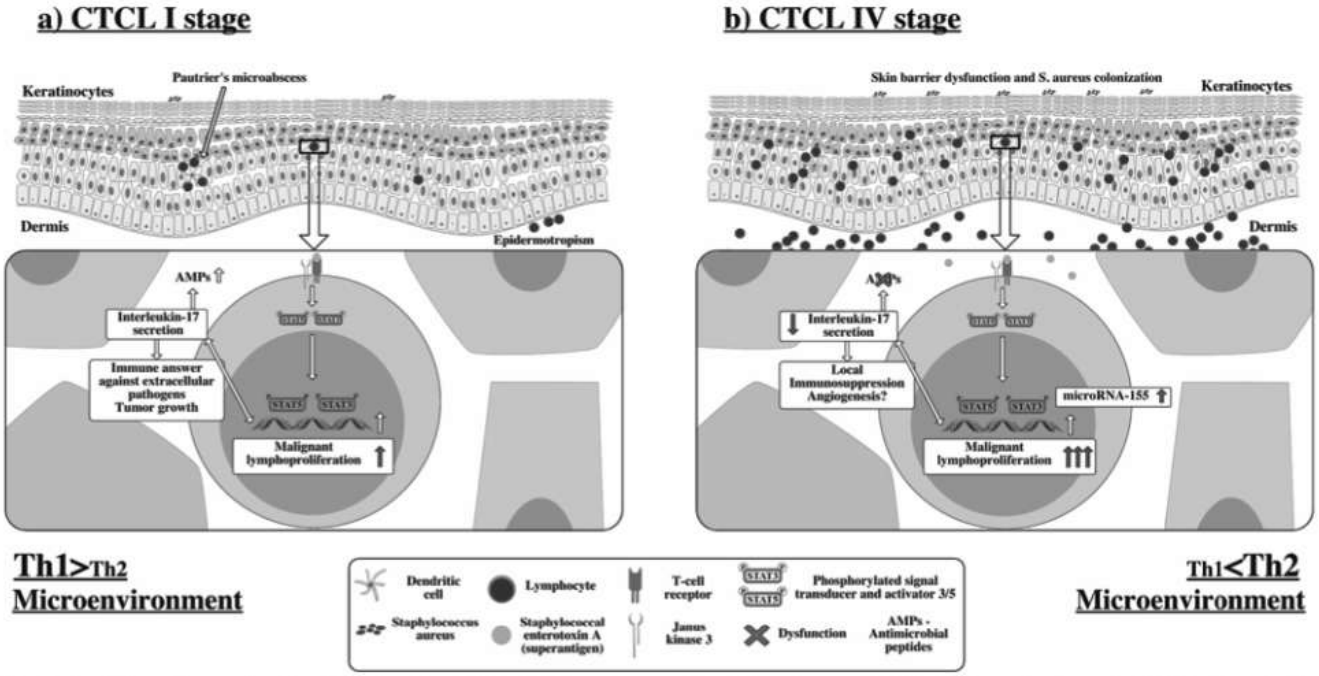


**Fig. 1. Possible pathogenic role of interleukin-17 (IL-17) in cutaneous T-cell lymphoma (CTCL).** (a) An early stage of a CTCL is shown in the first panel. There is a domination of T helper 1 (Th1) microenvironment with the contribution of IL-17, which plays role in promoting cytotoxic answer against extracellular pathogens (bacteria and fungi). Staphylococcal enterotoxins (superantigens) promote immunological dysregulation by causing benign lymphocytes to stimulate malignant clones. IL-17 has also been shown to promote the oncogenic pathway by stimulation janus kinase 3 (JAK3), which activates signal transducer and activator 3 (STAT3). (b) A late stage of CTCL is presented in the second panel. A clear domination of T helper 2 (Th2) microenvironment has been shown. The secretion of IL-17 may be reduced in that stage leading to local immunosuppression. Also, the antimicrobial peptides (AMPs) have been shown to be reduced and dysfunctional in CTCL. In case of microbiota colonization of the skin, dysfunction of AMPs is one of the crucial elements of impaired skin function. Angiogenesis is signed with a question mark on this figure, because of a possibility, that IL-17 may promote formation of new vessels thorough all stages of the disease. The resistance to anti-VEGF drugs in other lymphomas, lung and colorectal cancer has been previously shown to be promoted by Th-17 subset of cells.

pathogenetic influence of S. aureus in CTCL. As shown previously, blocking IL-17 by numerous new biologic drugs used in the therapy of, for example, psoriasis, may cause a progression and/or unmasking of the disease (15).

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The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk (decision number NKBBN/313/2017)

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

The data presented in this study are available in Appendix S1.

*The authors have no conflicts of interest to declare.*

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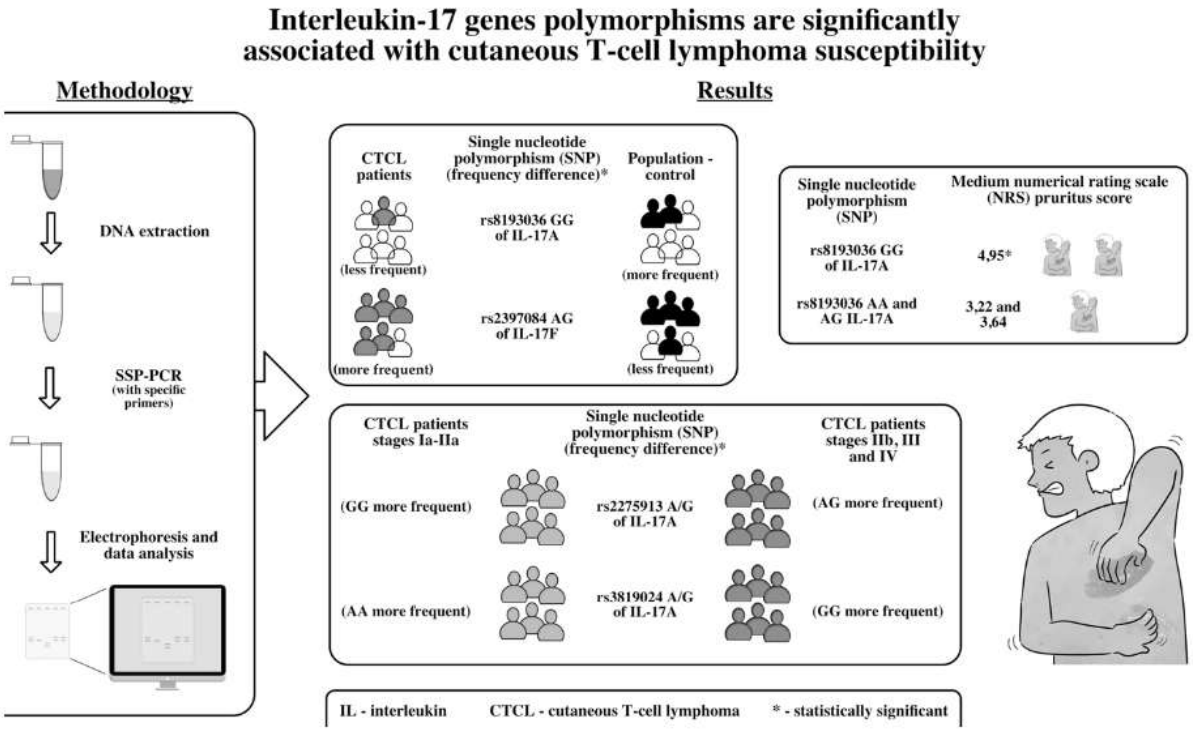
## Appendix S1.

This extensive Appendix has not been edited by ActaDV.

**APPENDIX S1**

## Graphic abstract presenting methods and most important results




Legend:

Asterix (*) – Statistically significant

IL – Interleukin

CTCL – Cutaneous T-cell lymphoma

SSP-PCR – polymerase chain reaction with specific primers

SNP – single nucleotide polymorphism

Red text – indicates statistical significance

| Group | IL-17a/rs2275913 GA | IL-17a/rs2275913 GG | IL-17a/rs2275913 AA | Overall |
|---|---|---|---|---|
| Lymphoma | 46 | 97 | 7 | 150 |
| | 30,67% | 64,67% | 4,67% | |
| Control | 62 | 119 | 15 | 196 |
| | 31,63% | 60,71% | 7,65% | |
| Overall | 108 | 216 | 22 | 346 |

P=0,49

GG p=0,45; GA p=0,85; AA p=0,26

| ALLELE | G | A | p |
|---|---|---|---|
| Lymphoma | 240 | 60 | 0,27 |
| Control | 300 | 92 | |

| Group | IL17a/rs3819024 AA | IL17a/rs3819024 AG | IL17a/rs3819024 GG | Overall |
|---|---|---|---|---|
| Lymphoma | 75 | 52 | 23 | 150 |
| | 50,00% | 34,67% | 15,33% | |
| control | 88 | 85 | 23 | 196 |
| | 44,90% | 43,37% | 11,73% | |
| Overall | 163 | 137 | 46 | 346 |

P=0,23

GG p=0,33; AG p=0,10; AA p=0,35

| ALLELE | G | A | p |
|---|---|---|---|
| Lymphoma | 98 | 202 | 0,84 |
| Control | 131 | 261 | |

| Group | IL17a/rs8193036 AA | IL17a/rs8193036 GA | IL17a/rs8193036 GG | Overall |
|---|---|---|---|---|
| Lymphoma | 45 | 84 | 21 | 150 |
| | 30,00% | 56,00% | 14,00% | |
| Control | 45 | 98 | 53 | 196 |
| | 22,96% | 50,00% | 27,04% | |
| Overall | 90 | 182 | 74 | 346 |

P=0,011

**GG p=0,003**; GA p=0,27; AA p=0,14

| | |
|---|---|
| **Odds ratio GG** | 0.4392 |
| **95 % CI:** | 0.2512 to 0.7679 |
| **Significance level** | P = 0.0039 |

| ALLELE | G | A | p |
|---|---|---|---|
| Lymphoma | 126 | 174 | 0,81 |
| Control | 204 | 272 | |

| Group | IL17F/rs763780 AG | IL17F/rs763780 GG | IL17F/rs763780 AA | Overall |
|---|---|---|---|---|
| Lymphoma | 112 | 7 | 31 | 150 |
| | 74,67% | 4,67% | 20,67% | |
| Control | 136 | 16 | 44 | 196 |
| | 69,39% | 8,16% | 22,45% | |
| Overall | 248 | 23 | 75 | 346 |

P=0,36

GG p=0,20; AG p=0,28; AA p=0,69

| ALLELE | G | A | p |
|---|---|---|---|
| Lymphoma | 126 | 174 | 0,82 |
| Control | 168 | 224 | |

| Group | IL17F/rs2397084 AG | IL17F/rs2397084 GG | Overall |
|---|---|---|---|
| Lymphoma | 133 | 17 | 150 |
| | 88,67% | 11,33% | |
| Control | 146 | 50 | 196 |
| | 74,49% | 25,51% | |
| Overall | 279 | 67 | 346 |

**P=0.0009**

| | |
|---|---|
| **Odds ratio** | 2.6793 |
| **95 % CI:** | 1.4729 to 4.8739 |
| **Significance level** | P = 0.0012 |

| ALLELE | G | A | p |
|---|---|---|---|
| Lymphoma | 167 | 133 | 0,60 |
| Control | 246 | 146 | |

## Stadium VS Genotype

### Early (1a-2a) vs Advanced (2a and higher)

| Group | IL-17a/rs2275913 GA | IL-17a/rs2275913 GG | IL-17a/rs2275913 AA | Overall |
|---|---|---|---|---|
| Advanced (2a and higher) | 24 | 31 | 6 | 61 |
| | 39,34% | 50,82% | 9,84% | |
| Early (1a-2a) | 20 | 64 | 1 | 85 |
| | 23,53% | 75,29% | 1,18% | |
| Overall | 44 | 95 | 7 | 146 |

P=0,003

GG p=0,002; GA p=0,04; AA p=0,043

| | |
|---|---|
| **Odds ratio GG** | 0.3391 |
| **95 % CI:** | 0.1678 to 0.6852 |
| **Significance level** | P = 0.0026 |

| | |
|---|---|
| **Odds ratio GA** | 2.1081 |
| **95 % CI:** | 1.0285 to 4.3210 |
| **Significance level** | P = 0.0417 |

| | |
|---|---|
| **Odds ratio AA** | 9.1636 |
| **95 % CI:** | 1.0737 to 78.2109 |
| **Significance level** | P = 0.0429 |

| ALLELE | G | A | p |
|---|---|---|---|
| Advanced (2a and higher) | 86 | 36 | 0,0005 |
| Early (1a-2a) | 148 | 22 | |

| | |
|---|---|
| **Odds ratio** | 0.3551 |
| **95 % CI:** | 0.1962 to 0.6427 |
| **Significance level** | P = 0.0006 |

| Group | IL17a/rs3819024 AA | IL17a/rs3819024 AG | IL17a/rs3819024 GG | Overall |
|---|---|---|---|---|
| Advanced (2a and higher) | 23 | 22 | 16 | 61 |
| | 37,70% | 36,07% | 26,23% | |
| Early (1a-2a) | 49 | 30 | 6 | 85 |
| | 57,65% | 35,29% | 7,06% | |
| Overall | 72 | 52 | 22 | 146 |

P=0,003

GG p=0,001; AG p ns; AA p=0,017

| | |
|---|---|
| **Odds ratio GG** | 4.6815 |
| **95 % CI:** | 1.7099 to 12.8170 |
| **Significance level** | P = 0.0027 |

| | |
|---|---|
| **Odds ratio AA** | 0.4447 |
| **95 % CI:** | 0.2268 to 0.8718 |
| **Significance level** | P = 0.0183 |

| ALLELE | G | A | p |
|---|---|---|---|
| Advanced (2a and higher) | 54 | 68 | **0,0005** |
| Early (1a-2a) | 42 | 128 | |

| | |
|---|---|
| **Odds ratio** | 2.4202 |
| **95 % CI:** | 1.4692 to 3.9866 |
| **Significance level** | P = 0.0005 |

| Group | IL17a/rs8193036 AA | IL17a/rs8193036 GA | IL17a/rs8193036 GG | Overall |
|---|---|---|---|---|
| Advanced (2a and higher) | 23 | 30 | 8 | 61 |
| | 37,70% | 49,18% | 13,11% | |
| Early (1a-2a) | 21 | 52 | 12 | 85 |
| | 24,71% | 61,18% | 14,12% | |
| Overall | 44 | 82 | 20 | 146 |

P=0,23

GG p ns; GA p ns; AA p ns

| ALLELE | G | A | p |
|---|---|---|---|
| Advanced (2a and higher) | 46 | 76 | 0,23 |
| Early (1a-2a) | 76 | 94 | |

| Group | IL17F/rs763780 AG | IL17F/rs763780 GG | IL17F/rs763780 AA | Overall |
|---|---|---|---|---|
| Advanced (2a and higher) | 43 | 5 | 13 | 61 |
| | 70,49% | 8,20% | 21,31% | |
| Early (1a-2a) | 66 | 2 | 17 | 85 |
| | 77,65% | 2,35% | 20,00% | |
| Overall | 109 | 7 | 30 | 146 |

P=0,25

GG p ns; AG p ns; AA p ns

| ALLELE | G | A | p |
|---|---|---|---|
| Advanced (2a and higher) | 53 | 69 | 0,70 |
| Early (1a-2a) | 70 | 100 | |

| Group | IL17F/rs2397084 AG | IL17F/rs2397084 GG | Overall |
|---|---|---|---|
| 0 | 55 | 6 | 61 |
| | 90,16% | 9,84% | |
| 1 | 74 | 11 | 85 |
| | 87,06% | 12,94% | |
| Overall | 129 | 17 | 146 |

P=0,56

| ALLELE | G | A | p |
|---|---|---|---|
| Advanced (2a and higher) | 67 | 55 | 0,79 |
| Early (1a-2a) | 96 | 74 | |

## SS vs other stages

| ss vs other stages | IL-17a/rs2275913 GA | IL-17a/rs2275913 GG | IL-17a/rs2275913 AA | Overall |
|---|---|---|---|---|
| other stages | 39 | 91 | 5 | 135 |
| | 28,89% | 67,41% | 3,70% | |
| ss | 5 | 4 | 2 | 11 |
| | 45,45% | 36,36% | 18,18% | |
| Overall | 44 | 95 | 7 | 146 |

P=0,032

GG p=0,04; GA p ns; AA p=0,05

| | |
|---|---|
| **Odds ratio GG** | 0.2763 |
| **95 % CI:** | 0.0768 to 0.9939 |
| **Significance level** | P = 0.0489 |

| | |
|---|---|
| **Odds ratio AA** | 5.7778 |
| **95 % CI:** | 0.9806 to 34.0415 |
| **Significance level** | P = 0.0526 |

| ALLELE | G | A | p |
|---|---|---|---|
| other stages | 221 | 49 | 0,01 |
| ss | 13 | 9 | |

| | |
|---|---|
| **Odds ratio** | 3.1224 |
| **95 % CI:** | 1.2638 to 7.7147 |
| **Significance level** | P = 0.0136 |

| ss vs other stages | IL17a/rs3819024 AA | IL17a/rs3819024 AG | IL17a/rs3819024 GG | Overall |
|---|---|---|---|---|
| other stages | 68 | 49 | 18 | 135 |
| | 50,37% | 36,30% | 13,33% | |
| ss | 4 | 3 | 4 | 11 |
| | 36,36% | 27,27% | 36,36% | |

| | | | | |
|---|---|---|---|---|
| Overall | 72 | 52 | 22 | 146 |

P=0,12

GG p=0,05; AG p ns; AA p ns

| | |
|---|---|
| **Odds ratio** | 3.7143 |
| **95 % CI:** | 0.9873 to 13.9729 |
| **Significance level** | P = 0.0522 |

| ALLELE | G | A | p |
|---|---|---|---|
| other stages | 85 | 185 | 0,08 |
| ss | 11 | 11 | |

| ss vs other stages | IL17a/rs8193036 AA | IL17a/rs8193036 GA | IL17a/rs8193036 GG | Overall |
|---|---|---|---|---|
| other stages | 40 | 76 | 19 | 135 |
| | 29,63% | 56,30% | 14,07% | |
| ss | 4 | 6 | 1 | 11 |
| | 36,36% | 54,55% | 9,09% | |
| Overall | 44 | 82 | 20 | 146 |

P=0,84

GG p ns; GAp ns; AA p ns

| ALLELE | G | A | p |
|---|---|---|---|
| other stages | 114 | 156 | 0,59 |
| ss | 8 | 14 | |

| ss vs other stages | IL17F/rs763780 AG | IL17F/rs763780 GG | IL17F/rs763780 AA | Overall |
|---|---|---|---|---|
| other stages | 102 | 6 | 27 | 135 |
| | 75,56% | 4,44% | 20,00% | |
| ss | 7 | 1 | 3 | 11 |
| | 63,64% | 9,09% | 27,27% | |
| Overall | 109 | 7 | 30 | 146 |

P=0,63

GG p ns; AG p ns; AA p ns

| ALLELE | G | A | p |
|---|---|---|---|
| other stages | 114 | 156 | 0,90 |
| ss | 9 | 13 | |

| ss vs other stages | IL17F/rs2397084 AG | IL17F/rs2397084 GG | Overall |
|---|---|---|---|
| other stages | 119 | 16 | 135 |
| | 88,15% | 11,85% | |
| ss | 10 | 1 | 11 |
| | 90,91% | 9,09% | |
| Overall | 129 | 17 | 146 |

P=0,78

GG p ns; AG p ns; AA p ns

| ALLELE | G | A | p |
|---|---|---|---|
| other stages | 151 | 119 | 0,90 |
| ss | 12 | 10 | |

## Early (1a, 1b) vs advanced

| Early (1a, 1b) vs advanced | IL-17a/rs2275913 GA | IL-17a/rs2275913 GG | IL-17a/rs2275913 AA | Overall |
|---|---|---|---|---|
| Advanced | 25 | 33 | 6 | 64 |
| | 39,06% | 51,56% | 9,38% | |
| Early (1a, 1b) | 19 | 62 | 1 | 82 |
| | 23,17% | 75,61% | 1,22% | |
| Overall | 44 | 95 | 7 | 146 |

P=0,004

GG p=0,002; GA p=0,04; AA p=0,05

| | |
|---|---|
| **Odds ratio GG** | 0.3434 |
| **95 % CI:** | 0.1700 to 0.6937 |
| **Significance level** | P = 0.0029 |

| | |
|---|---|
| **Odds ratio GA** | 2.1255 |
| **95 % CI:** | 1.0368 to 4.3574 |
| **Significance level** | P = 0.0395 |

| | |
|---|---|
| **Odds ratio AA** | 8.3793 |
| **95 % CI:** | 0.9822 to 71.4847 |
| **Significance level** | P = 0.0519 |

| **ALLELE** | **G** | **A** | **p** |
|---|---|---|---|
| Advanced | 91 | 37 | **0,0006** |
| Early (1a, 1b) | 143 | 21 | |

| | |
|---|---|
| **Odds ratio** | 0.3612 |
| **95 % CI:** | 0.1989 to 0.6558 |
| **Significance level** | P = 0.0008 |

| **Early (1a, 1b) vs advanced** | **IL17a/rs3819024 AA** | **IL17a/rs3819024 AG** | **IL17a/rs3819024 GG** | Overall |
|---|---|---|---|---|
| Advanced | 23 | 25 | 16 | 64 |
| | 35,94% | 39,06% | 25,00% | |
| Early (1a, 1b) | 49 | 27 | 6 | 82 |
| | 59,76% | 32,93% | 7,32% | |
| Overall | 72 | 52 | 22 | 146 |

P=0,0025

GG p=0,003; AG p ns; AA p=0,004

| | |
|---|---|
| **Odds ratio GG** | 4.2222 |
| **95 % CI:** | 1.5448 to 11.5400 |
| **Significance level** | P = 0.0050 |

| | |
|---|---|
| **Odds ratio AA** | 0.3778 |
| **95 % CI:** | 0.1924 to 0.7420 |
| **Significance level** | P = 0.0047 |

| ALLELE | G | A | p |
|---|---|---|---|
| Advanced | 57 | 71 | 0,0002 |
| Early (1a, 1b) | 39 | 125 | |

| | |
|---|---|
| **Odds ratio** | 2.5731 |
| **95 % CI:** | 1.5595 to 4.2455 |
| **Significance level** | P = 0.0002 |

| Early (1a, 1b) vs advanced | IL17a/rs8193036 AA | IL17a/rs8193036 GA | IL17a/rs8193036 GG | Overall |
|---|---|---|---|---|
| Advanced | 23 | 33 | 8 | 64 |
| | 35,94% | 51,56% | 12,50% | |
| Early (1a, 1b) | 21 | 49 | 12 | 82 |
| | 25,61% | 59,76% | 14,63% | |
| Overall | 44 | 82 | 20 | 146 |

P=0,40

GG p ns; GA p ns; AA p ns

| ALLELE | G | A | p |
|---|---|---|---|
| Advanced | 49 | 79 | 0,28 |
| Early (1a, 1b) | 73 | 91 | |

| Early (1a, 1b) vs advanced | IL17F/rs763780 AG | IL17F/rs763780 GG | IL17F/rs763780 AA | Overall |
|---|---|---|---|---|
| Advanced | 46 | 5 | 13 | 64 |
| | 71,88% | 7,81% | 20,31% | |
| Early (1a, 1b) | 63 | 2 | 17 | 82 |
| | 76,83% | 2,44% | 20,73% | |
| Overall | 109 | 7 | 30 | 146 |

P=0,32

GG p ns; AG p ns; AA p ns

| ALLELE | G | A | p |
|---|---|---|---|
| Advanced | 56 | 72 | 0,62 |

| | | | |
|---|---|---|---|
| Early (1a, 1b) | 67 | 97 | |

| Early (1a, 1b) vs advanced | IL17F/rs2397084 AG | IL17F/rs2397084 GG | Overall |
|---|---|---|---|
| Advanced | 58 | 6 | 64 |
| | 90,63% | 9,38% | |
| Early (1a, 1b) | 71 | 11 | 82 |
| | 86,59% | 13,41% | |
| Overall | 129 | 17 | 146 |

P=0,45

GG p ns; AG p ns

| ALLELE | G | A | p |
|---|---|---|---|
| Advanced | 70 | 58 | 0,73 |
| Early (1a, 1b) | 93 | 71 | |

## Medium VAS scale score of patients according to different genotypes

| IL-17a/rs2275913 | VAS Medium | VAS Valid | VAS Stand.Dev | VAS Minimum | VAS Maximum | VAS Q25 | VAS Median | VAS Q75 |
|---|---|---|---|---|---|---|---|---|
| GA | 3,832051 | 39 | 3,264089 | 0,000000 | 10,00000 | 1,400000 | 2,800000 | 6,600000 |
| GG | 3,273494 | 83 | 3,170100 | 0,000000 | 10,00000 | 0,000000 | 2,500000 | 5,500000 |
| AA | 4,240000 | 5 | 2,540276 | 1,000000 | 7,50000 | 3,300000 | 3,400000 | 6,000000 |
| Overall | 3,483071 | 127 | 3,169793 | 0,000000 | 10,00000 | 0,000000 | 3,000000 | 6,000000 |

P=0,31

| IL17a/rs3819024 | VAS Medium | VAS Valid | VAS Stand.Dev | VAS Minimum | VAS Maximum | VAS Q25 | VAS Median | VAS Q75 |
|---|---|---|---|---|---|---|---|---|
| AA | 3,545238 | 63 | 3,093707 | 0,00 | 10,00000 | 0,400000 | 3,000000 | 5,500000 |
| AG | 2,936364 | 44 | 2,901090 | 0,00 | 10,00000 | 0,100000 | 2,000000 | 5,150000 |
| GG | 4,490000 | 20 | 3,818363 | 0,00 | 10,00000 | 0,000000 | 4,700000 | 7,750000 |
| Overall | 3,483071 | 127 | 3,169793 | 0,00 | 10,00000 | 0,000000 | 3,000000 | 6,000000 |

P=0,53

| IL17a/rs8193036 | VAS Medium | VAS Valid | VAS Stand.Dev | VAS Minimum | VAS Maximum | VAS Q25 | VAS Median | VAS Q75 |
|---|---|---|---|---|---|---|---|---|
| AA | 3,266667 | 42 | 3,257387 | 0,000000 | 10,00000 | 0,000000 | 2,200000 | 6,000000 |
| GA | 3,346324 | 68 | 3,202323 | 0,000000 | 10,00000 | 0,000000 | 2,650000 | 5,450000 |
| GG | 4,564706 | 17 | 2,747258 | 1,000000 | 9,50000 | 2,300000 | 3,900000 | 6,100000 |
| Overall | 3,483071 | 127 | 3,169793 | 0,000000 | 10,00000 | 0,000000 | 3,000000 | 6,000000 |

P=0.74

| IL17F/rs763780 | VAS Medium | VAS Valid | VAS Stand.Dev | VAS Minimum | VAS Maximum | VAS Q25 | VAS Median | VAS Q75 |
|---|---|---|---|---|---|---|---|---|
| AG | 3,380319 | 94 | 3,198380 | 0,00 | 10,00000 | 0,000000 | 2,600000 | 5,700000 |
| GG | 2,300000 | 6 | 2,093800 | 0,00 | 6,10000 | 1,400000 | 1,650000 | 3,000000 |
| AA | 4,103704 | 27 | 3,239953 | 0,00 | 10,00000 | 1,000000 | 4,200000 | 6,000000 |
| Overall | 3,483071 | 127 | 3,169793 | 0,00 | 10,00000 | 0,000000 | 3,000000 | 6,000000 |

P=0,22

| IL17F/rs2397084 | VAS Medium | VAS Valid | VAS Stand.Dev | VAS Minimum | VAS Maximum | VAS Q25 | VAS Median | VAS Q75 |
|---|---|---|---|---|---|---|---|---|
| AG | 3,309292 | 113 | 3,102106 | 0,000000 | 10,00000 | 0,000000 | 2,400000 | 5,700000 |
| GG | 4,885714 | 14 | 3,478032 | 1,000000 | 10,00000 | 1,500000 | 3,850000 | 9,500000 |
| Overall | 3,483071 | 127 | 3,169793 | 0,000000 | 10,00000 | 0,000000 | 3,000000 | 6,000000 |

P=0,43

**VAS pruritus level differences not statistically significant for other genotypes except IL17F/rs2397084 (p=0,01)**

| | VAS mild pruritus (1-3) | VAS moderate pruritus (4-6) | VAS very severe pruritus (10) | VAS severe pruritus (7-9) | Overall |
|---|---|---|---|---|---|
| AG | 61 | 33 | 6 | 13 | 113 |
| | 53,98% | 29,20% | 5,31% | 11,50% | |
| GG | 6 | 4 | 4 | 0 | 14 |
| | 42,86% | 28,57% | 28,57% | 0,00% | |
| Overall | 67 | 37 | 10 | 13 | 127 |

## Medium NRS scale score of patients according to genotypes

| IL-17a/rs2275913 | NRS Medium | NRS Valid | NRS Stand.Dev | NRS Minimum | NRS Maximum | NRS Q25 | NRS Median | NRS Q75 |
|---|---|---|---|---|---|---|---|---|
| GA | 4,040476 | 42 | 3,265568 | 0,00 | 10,00000 | 2,000000 | 3,000000 | 7,000000 |
| GG | 3,497802 | 91 | 3,177245 | 0,00 | 10,00000 | 0,000000 | 3,000000 | 5,000000 |
| AA | 4,000000 | 7 | 2,886751 | 0,00 | 8,00000 | 1,000000 | 4,000000 | 6,000000 |
| Overall | 3,685714 | 140 | 3,179240 | 0,00 | 10,00000 | 1,000000 | 3,000000 | 6,000000 |

P=0,81

| IL17a/rs3819024 | NRS Medium | NRS Valid | NRS Stand.Dev | NRS Minimum | NRS Maximum | NRS Q25 | NRS Median | NRS Q75 |
|---|---|---|---|---|---|---|---|---|
| AA | 3,750725 | 69 | 3,150519 | 0,00 | 10,00000 | 1,000000 | 3,300000 | 6,000000 |
| AG | 3,354000 | 50 | 3,085265 | 0,00 | 10,00000 | 1,000000 | 2,500000 | 5,000000 |
| GG | 4,261905 | 21 | 3,541253 | 0,00 | 10,00000 | 0,000000 | 4,000000 | 7,500000 |
| Overall | 3,685714 | 140 | 3,179240 | 0,00 | 10,00000 | 1,000000 | 3,000000 | 6,000000 |

P=0,45

| IL17a/rs8193036 | NRS Medium | NRS Valid | NRS Stand.Dev | NRS Minimum | NRS Maximum | NRS Q25 | NRS Median | NRS Q75 |
|---|---|---|---|---|---|---|---|---|
| AA | 3,222727 | 44 | 3,203041 | 0,000000 | 10,00000 | 0,000000 | 2,500000 | 5,000000 |
| GA | 3,638961 | 77 | 3,251524 | 0,000000 | 10,00000 | 0,000000 | 3,000000 | 6,000000 |
| GG | 4,947368 | 19 | 2,586797 | 1,000000 | 9,00000 | 3,000000 | 5,000000 | 8,000000 |
| Overall | 3,685714 | 140 | 3,179240 | 0,000000 | 10,00000 | 1,000000 | 3,000000 | 6,000000 |

P=0,26

GG=0,03

| IL17F/rs763780 | NRS Medium | NRS Valid | NRS Stand.Dev | NRS Minimum | NRS Maximum | NRS Q25 | NRS Median | NRS Q75 |
|---|---|---|---|---|---|---|---|---|
| AG | 3,639423 | 104 | 3,233634 | 0,00 | 10,00000 | 0,000000 | 3,000000 | 6,250000 |
| GG | 2,857143 | 7 | 2,794553 | 0,00 | 8,00000 | 1,000000 | 2,000000 | 5,000000 |
| AA | 4,051724 | 29 | 3,117763 | 0,00 | 10,00000 | 2,000000 | 4,000000 | 5,000000 |
| Overall | 3,685714 | 140 | 3,179240 | 0,00 | 10,00000 | 1,000000 | 3,000000 | 6,000000 |

P=0,44

| IL17F/rs2397084 | NRS Medium | NRS Valid | NRS Stand.Dev | NRS Minimum | NRS Maximum | NRS Q25 | NRS Median | NRS Q75 |
|---|---|---|---|---|---|---|---|---|
| AG | 3,560484 | 124 | 3,172002 | 0,000000 | 10,00000 | 0,000000 | 3,000000 | 6,000000 |
| GG | 4,656250 | 16 | 3,166064 | 1,000000 | 10,00000 | 2,500000 | 4,000000 | 6,250000 |
| Overall | 3,685714 | 140 | 3,179240 | 0,000000 | 10,00000 | 1,000000 | 3,000000 | 6,000000 |

P=0,51

**NRS pruritus level differences not statistically significant for other genotypes except IL17a/rs8193036 (p=0,005)**

| GG | NRS mild pruritus (1-3) | NRS moderate pruritus (4-6) | NRS very severe pruritus (10) | NRS severe pruritus (7-9) | Overall |
|---|---|---|---|---|---|
| no | 65 | 38 | 10 | 8 | 121 |
| | 53,72% | 31,40% | 8,26% | 6,61% | |
| yes | 7 | 6 | 0 | 6 | 19 |
| | 36,84% | 31,58% | 0,00% | 31,58% | |
| Overall | 72 | 44 | 10 | 14 | 140 |

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*Review*

# Safety and Danger Considerations of Novel Treatments for Atopic Dermatitis in Context of Primary Cutaneous Lymphomas

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**Abstract:** The impact of new and emerging therapies on the microenvironment of primary cutaneous lymphomas (PCLs) has been recently raised in the literature. Concomitantly, novel treatments are already used or registered (dupilumab, upadacitinib) and others seem to be added to the armamentarium against atopic dermatitis. Our aim was to review the literature on interleukins 4, 13, 22, and 31, and JAK/STAT pathways in PCLs to elucidate the safety of using biologics (dupilumab, tralokinumab, fezakinumab, nemolizumab) and small molecule inhibitors (upadacitinib, baricitinib, abrocitinib, ruxolitinib, tofacitinib) in the treatment of atopic dermatitis. We summarized the current state of knowledge on this topic based on the search of the PubMed database and related references published before 21 October 2021. Our analysis suggests that some of the mentioned agents (dupilumab, ruxolitinib) and others may have a direct impact on the progression of cutaneous lymphomas. This issue requires further study and meticulous monitoring of patients receiving these drugs to ensure their safety, especially in light of the FDA warning on tofacitinib. In conclusion, in the case of the rapid progression of atopic dermatitis/eczema, especially in patients older than 40 years old, there is a necessity to perform a biopsy followed by a very careful pathological examination.

**Keywords:** cutaneous lymphoma; mycosis fungoides; Sézary syndrome; cytokine; atopic dermatitis; tumor microenvironment; biologic treatment; small molecule inhibitors; JAK-STAT pathway; interleukins



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## 1. Introduction

Primary cutaneous lymphomas (PCLs) are a rare entity of lymphoproliferative disorders that have no evidence of extracutaneous involvement at the time of diagnosis [1]. An important impact of the tumor microenvironment on the progression of the disease has been raised in literature [2]. Currently, a variety of drugs affecting the cytokines and pathways are essential in the pathogenesis of atopic dermatitis (AD) and are in the clinical trials phase, whereas dupilumab targeting interleukin-4 (IL-4) and interleukin-13 (IL-13), tralokinumab targeting IL-13 and two Janus kinase inhibitors (JAKi): upadacitinib (JAK1 inhibitor) and baricitinib (JAK1/JAK2 inhibitor), are already registered in the EU [3,4]. Agents blocking interleukin-22 (IL-22) and interleukin-31 (IL-31), fezakinumab, and nemolizumab, as well as lebrikizumab will be available for patients soon [3]. There is a controversy regarding a potential of increased risk of lymphoma in patients with atopic dermatitis (AD). Our aim is to elucidate the role of IL-4, IL-13, IL-22, IL-31, and the JAK/STAT pathway in PCLs in the context of novel treatment of AD.

## 2. Discussion

AD is a chronic, inflammatory skin disease characterized by strong pruritus that less commonly affects adults [5]. This condition is associated with a poorer quality of life in comparison with the general population and causes sleep disturbances and coexisting

comorbidities [6]. As reported by the epidemiological studies, the prevalence of the childhood AD is between 12% and 20% in the United States, Europe, and Eastern Asia, whereas in the elderly population it ranges from 2% to 5% [7–12]. Moreover, the secular trends tend to show an increase in the number of AD patients in both children and adults [9,10]. Unfortunately, a significant number of these patients present moderate to severe AD. Despite the scale of the problem, the arsenal of drugs with a safe profile of action, characterized by a low risk of serious side effects, and appropriate for long-term use is scarce [13]. Therefore, doctors and patients hope for the end of "the draught", which may happen thanks to biologic drugs, e.g., monoclonal antibodies (mAb) like dupilumab/tralokinumab or small molecule inhibitors, e.g., upadacitinib/baricitinib, which are proven to be effective and are registered in the EU [13]. In fact, a few of these medications are already approved for topical and systemic treatment of AD. However, despite the unquestionable potential these drugs hold for AD patients in relieving their burden, we believe that some important issues must be raised.

Among PCLs, heterogenous groups of B-, T- and NK-Cell lymphomas have been differentiated [1]. Mycosis fungoides (MF) belongs to cutaneous T-cell lymphoma (CTCL) and its classical variant is the most common PCL [1]. Our review focuses on the CTCLs; however, when PCLs are mentioned, we refer to the entire spectrum of primary cutaneous lymphomas. Major meta-analysis has shown a relative risk ratio (RR) of developing a lymphoma of 1.43 (95% CI, 1.12–1.81) in patients with AD [14]. The risk of lymphoma is higher in cases where highly potent TCSs are used and in a severe course of the disease [14]. In a recent study, the hazard ratios of developing Non-Hodgkin's lymphoma (NHL) increase with the severity of the eczema [15]. This was the only epidemiological study in which we could find any biologic drug taken into consideration. Dupilumab has been analyzed in the Danish cohort together with the influence of other immunosuppressive drugs, including cyclosporine, azathioprine, mycophenolate and methotrexate [15]. According to some studies, the risk of developing NHL with cutaneous manifestation is especially high, but we have to bear in mind the possible misdiagnosis bias [14–16]. We were not able to find any other studies that describe the incidence of lymphomas in patients treated with biologics or small molecule inhibitors referring to AD except clinical trials and case reports. Incidence of lymphomas in the mentioned studies will now become a baseline for the further analysis of the effects of new immunosuppressives brought to the market.

It may be difficult to clinically differentiate AD and PCL, especially in the case of erythroderma. If a patient develops adult-onset AD, erythrodermic CTCL, and Sézary syndrome (SS), they should always be excluded, as these diseases require distinct treatment and have drastically varying prognoses [17]. Similarities concerning both diseases, which are crucial in their pathogenesis, are illustrated in the Table 1 [17–28].

**Table 1.** Clinical and immunological similarities between atopic dermatitis (AD) and cutaneous T-cell lymphoma (CTCL).

| Similarities | Atopic Dermatitis | Cutaneous T-Cell Lymphoma |
|---|---|---|
| Eosinophilia | Often present | May be present in the advanced stage |
| Immunoglobulin E (IgE) | Often elevated | May be elevated in the advanced stage |
| Lactate dehydrogenase (LDH) | May be elevated | Severity marker of MF/SS |
| Soluble interleukin receptor 2 (sIL-2R) | May be elevated | Severity marker of MF/SS |
| Th-2 microenvironment activation | Always present | Present in the advanced stage |
| Levels of filaggrin | Significantly lowered | May be significantly lowered |
| Transepidermal water loss (TEWL) | Significantly lowered | May be significantly lowered |
| Levels of antimicrobial peptides (AMPs) | Significantly lowered | Significantly lowered |
| Colonization of *S. aureus* | 80% of patients | 50–60% of patients |

Some authors indicate that, due to the significant quantity of similarities, both diseases may require the same treatment at certain stages [29]. However, in our opinion, the safety of emerging drugs used in AD treatment, in the context of a PCL coexistence/induction risk, should be raised. We decided to analyze theoretical and clinical data regarding interleukins

and JAK-STAT pathways, which recently have been proven to be attractive targets in the treatment of AD. On that basis, we excluded IL-5, IL-17, and IL-33 from the analysis, as the trials of drugs targeting them are either terminated, are of unknown status, or they did not meet the primary endpoints [30–35]. In this review, we also omit the IL-12/IL-23 axis affected by ustekinumab for two reasons. Firstly, a recent review on the effectiveness of this agent concluded that the IL-12/IL-23 pathway is not an attractive target for the treatment of AD [36]. Furthermore, the largest cohort of patients receiving ustekinumab has shown that more novel and effective treatments are available for the therapy of this atopic disease [36]. Second, IL-12 has been shown to be one of the possible treatments, despite the fact that it is not currently clinically developed [37]. Therefore, blocking it should be a factor facilitating the lymphoma progression by down-regulating the Th-1 cytotoxicity against malignant clones.

### 2.1. New Medications in AD

AD is thought to be the hallmark of Th-2 microenvironment diseases. Th-2 profile cytokines, such as IL-4, IL-5 and IL-13, play a significant role in the pathogenesis of the disease by switching the immunoglobulin class to IgE and stimulating afferent neurons via IL-4Rα, thereby promoting pruritus [38]. Therefore, drugs blocking these pathways should be clinically effective in reducing the symptoms of this eczematous disease, as they act against the inflammation [39].

One of them is dupilumab—a fully human monoclonal antibody that blocks IL-4Rα, a shared receptor unit for IL-4 and IL-13, actively participating in the decrease of Th-2 mediated immunological response [3]. It is already used in America, Europe, and in several other countries on children, adolescents, and adults. The analysis of four phase-three trials has revealed that patients treated with this monoclonal antibody achieve a significantly higher percentage reduction from the baseline in the most important AD management scales—Eczema Area and Severity Index (EASI), SCORing Atopic Dermatitis (SCORAD), Dermatology Life Quality Index (DLQI), and Patient-Oriented Eczema Measure (POEM) versus control [40]. Notably, these superior effects have been achieved in monotherapy without topical corticosteroids, regardless of previous use of systemic non-steroidal immunosuppressants, e.g., methotrexate or cyclosporine [40].

Other drugs targeting the IL-13 are lebrikizumab and tralokinumab. IL-13 binds and neutralizes the activity of the mentioned cytokine with high affinity [41]. In phase IIb of several randomized clinical trials, it showed promising results [42,43]. Even though adverse effects of this drug were reported in the significant group of patients, they were mostly mild to moderate [42,43]. Phase III clinical trials on patients who suffer from moderate to severe AD are currently ongoing [44–50]. Another promising emerging drug is tralokinumab—a fully human, monoclonal anti-IL-13 IgG4 antibody that binds to two subunits of IL-13R (IL-13Rα1 and IL-13Rα2), thus neutralizing the cytokine from the interaction [3,51]. Recently, three phase III clinical trials (ECZTRA1, ECZTRA2, and ECZTRA3) were completed for this drug [52,53]. Tralokinumab, in combination with topical corticosteroids, is not only effective in reducing the pruritus and improving sleep quality, but it is also well tolerated for up to 52 weeks of treatment, which brings a promising perspective we mentioned earlier [52]. Moreover, this medicament is safe and well tolerated in combination with topical corticosteroids [53]. Interestingly, a long-term extension trial for patients who were participants in the previous studies is currently ongoing and the estimated completion date is in 2024 [54].

IL-22 and IL-31 are also the targets of new drugs, which have been or currently still are under investigation in phases IIa and III of clinical trials [55–57]. Fezakinumab, an anti-IL-22 antibody, has been shown in the IIa randomized, double-blind clinical trial on adults with moderate to severe AD to be well tolerated and to have sustainable improvements after the last dose [55]. Despite the small sample size and common adverse effects, which were upper respiratory tract infections, improvements in SCOring AD (SCORAD) were significant in patients with severe disease [3,55]. Thus, this drug is thought to be

suitable for patients with severe AD, but no further clinical trials are currently ongoing [3]. Another interesting medication, especially for managing the pruritus in patients with AD is nemolizumab, a human monoclonal IL-31 receptor α (IL-31Rα) antagonist [3,57,58]. This drug targets small-diameter neurons and it is thought that the relieving effect of nemolizumab is due to action on cutaneous sensory neurons [3,58]. In the phase III trial, the patients who could not achieve proper control of pruritus by solely using topical treatment were recruited and enrolled [56]. Not only were the primary end points of the study achieved with a significant decrease in pruritus measured in the VAS scale, but also a series of secondary endpoints including EASI, DLQI or Insomnia Severity Index were met [56]. Other phase III trials are currently ongoing [59].

Various systemic and topical JAK inhibitors are about to be widely used in the treatment of AD [4]. The data on the double blind control trials evaluating the efficacy of these drugs in the treatment of AD are promising [60,61]. Baricitinib, abrocitinib, and upadacitinib belong to the group of oral drugs, while ruxolitinib is known as a topical agent considered in the therapy of AD [60].

Baricitinib is known as the first-generation JAK1/2 selective inhibitor [60,62,63]. The efficacy of the drug in monotherapy and combined with topical corticosteroids has been evaluated and the dose of 4 mg appears to significantly improve symptoms [64–66]. In the pooled safety analysis of baricitinib in adults, which contained previously mentioned studies, there were four major cardiovascular-adverse events and one death, however, no malignancies were reported [67].

Abrocitinib is an oral selective JAK1 inhibitor that achieved satisfying results in the phase III trial, proving that it is effective and well tolerated in monotherapy [64,68]. Patients from these studies have been enrolled in the extended trial (NCT03422822) and in the 48th week of this trial, it has been shown, that between 24 and 36 weeks, the proportion of patients meeting primary endpoints increased and was stable thereafter [60]. Comparing abrocitinib, dupilumab, and the placebo in clinical trial, both drugs significantly more reduced AD symptoms; however, a 200 mg dose of abrocitinib was superior to dupilumab in limiting itchiness [69].

The next oral selective JAK1 inhibitor is upadacitinib [60]. It safe and efficient in the monotherapy of moderate to severe AD in three phase III trials [70,71]. Moreover, in comparison with dupilumab it was superior, showing significantly higher proportion of patients who achieved the primary and secondary endpoints of the study [72]. Extension of the mentioned trials and also new ones with pediatric patients are ongoing [73,74].

Ruxolitinib (JAK1/2 inhibitor) and delgocitinib (pan-JAK inhibitor) have proved to be effective topical drugs in AD [60,61]. In the two phase III trials, ruxolitinib has shown anti-inflammatory and anti-pruritic effects superior to the vehicle cream [75]. Adverse effects were infrequent and clinically insignificant [75]. Clinical trials with atopic children are underway [76]. Delgocitinib also seems to be satisfactory, since in the phase III trial it was effective and well tolerated in Japanese patients for up to 28 weeks [77]. Currently, two phase III trials on moderate to severe chronic hand eczema are ongoing [78,79].

### 2.2. Role of Interleukin-4 and Interleukin-13 in PCL

Interleukin-4 (IL-4) and interleukin-13 (IL-13) are the characteristic molecules that induce, drive, and prolong the Th-2 answer both in AD and in advanced stages of CTCL [21–23,38]. Along with the progression of CTCL, Th-2 cytokines are most commonly overproduced, skewing the Th1/Th2 axis towards the latter side, a well-known phenomenon [80–82]. Certain genetic markers are associated with the predisposition to develop the progressive MF. One of them has an increased expression of IL-4 relative to CD3 expression levels, which are significantly associated with lymphoma progression [83]. Each of the discussed cytokines are elevated in the biopsies of MF and SS lesions [84–87]. IL-4 levels are raised in sera of patients; however, it does not always concern the cases of low-grade lymphoma [18,21,81,82,84,88]. The elevated concentrations of these cytokines

are related to the ability of neoplastic cells to secrete IL-4 and IL-13 as well as in the skin and in the blood in vivo [81,82,85].

Also, IL-4 is a potent factor that polarizes tumor-associated macrophages into type 2 cells (M2 Macrophages) [89]. The ability to produce several Th-2 cytokines is characteristic for these phagocytes, thereby affecting the formation of CTCL by stromal factors [86,89]. Furthermore, IL-4 and IL-13 are important growth factors for PCLs and IL-13 acts in an autocrine manner on the neoplastic lymphocytes [81,87]. IL-4 and IL-33 are also found to induce the secretion of IL-31, which is one of the elements alongside with the discussed interleukins, causing pruritus in AD and in CTCL—but the data are ambivalent concerning lymphomas [3,90]. These properties contribute to driving the Th-2 type inflammatory answer propelled in a vicious circle, leading to the depletion of the Th-1 microenvironment. The arrest of the IL-4/IL-13 pathway by neutralizing IL-4 and IL-13 cytokines leads to inhibition of tumor-cell proliferation [81]. Interestingly, blocking certain types of IL-13 receptors (IL-13Rα2) revealed an even stronger inhibition effect. However, this receptor binds with IL-13 stronger than the first IL-13 receptor (IL-13Rα1) and is thought to be a decoy in the normal tissues [81,91]. Recent studies have shown that the tumoral microenvironment created by the malignant lymphocytes in leukemic CTCL is a global bias, which refers also to benign T cells [82]. Thus, in comparison to the normal lymphocytes in healthy individuals, non-tumorous cells are strongly Th-2 biased [82]. Such drastic reduction of the cytotoxic environment is thought to be one of major factors leading to infections which is the most common reason of death in this group of patients [1,92,93].

It is also proven that cytoplasmic IL-4 concentration is the predictor of the advanced stage of MF and SS [94]. Moreover, increased IL-4 concentration is observed frequently in advanced stages of CTCL; it correlates with T-cell immunophenotype differences found in advanced lymphoma stages and is associated with clonality of MF and SS cells [94]. Some available methods of treatment used in clinical practice can reduce the Th-2 polarization in advanced stages of CTCLs. One study revealed that extracorporeal photopheresis (ECP) effectively restores the imbalance in Th1/Th2 microenvironments of peripheral blood mononuclear cells (PBMC) [95]. After one year of such therapy, the concentrations of IL-4, interferon gamma (IFNγ), and IL-12 did not differ from the healthy controls [95]. Also, after administration of the T-cell depleting antibody directed against CD52, alemtuzumab (Campath), which is used to treat refractory leukemic CTCL (L-CTCL), skin T cells have been shown to secrete less IL-4 and more interferon gamma (IFNγ) than before the treatment [96]. Finally, Guenova et al. suggested that inhibiting the Th-2 microenvironment and restoration of Th-1 cytotoxicity should enhance both anti-tumorous and antibacterial responses [82].

Concluding this section, the listed Th-2 cytokines play an essential role in the pathogenesis of PCLs. It is especially prominent in advanced stages of the disease. Therefore, blocking these pathways may be beneficial and may result at least in the stabilization of the lymphoma.

### *2.3. Role of Interleukin-22 in PCL*

Interleukin-22 (IL-22) is secreted mainly by the subpopulation of Th22 lymphocytes, but also by other immune cell subsets and is involved in the modification of tissue responses at the inflammation [97]. In two studies and one case report, levels of this cytokine were significantly elevated in both skin lesions and sera of CTCL patients [18,98,99]. Other researchers found that cultured CTCL cells overexpress IL-22 receptor subunit alpha1 (IL22Rα1) and overproduce IL-22 as well as chemokine ligand 20 (CCL20) [100]. Cytokine induces the expression of CCL20 and signal transducer and activator of transcription 3 (STAT3), the latter of plays a role in the pathogenesis of CTCL [98,101]. Moreover, the Sézary cells of one patient who developed sepsis stained positive for CD8 and produced IL-22 [98]. Genetic analysis of SS patients and SS cell lines (SaEx) showed the disruption in the IL-22 receptor subunit alpha2 (IL22Rα2) gene twice [102]. Subsequently, a fusion of several genes occurred and one of them was the CCDC28A-IL22Rα2, which was transcribed

on the messenger RNA level [102]. CCL20 and IL-22 serum levels correlate with the LDH and sIL-2R and thus they correlate with CTCL severity [18]. Their activity seems significant in the pathogenesis of the disease.

Enhanced CCL20 activity may induce epidermal hyperplasia as well as the migration of chemokine receptor 6 (CCR6) positive Langerhans/Dendritic cells to the skin, which are crucial in the evolution of lymphoma cells as the activation of T-cell receptors is crucial for the malignant transformation of MF [18,103]. CCL20 is a ligand of CCR6 [100]. Activation of IL-22 has also been shown to lead to chronic CCR6-CCL20 interaction with CTCL cells [100]. Furthermore, the continuous upregulation of CCR6 was discovered, which results in the continuous activation of CCR6-CCL20, leading the lymphoma cells to metastasize to internal organs [100]. These important findings are supported by recent studies, showing that triggering a STAT3/CCL20/CCR6 cascade that blocks CCR6-CCL20 interaction, may be crucial in stopping lymphomagenesis [104]. Today, it is considered one of the promising strategies in the treatment of advanced CTCL [104].

### *2.4. Role of Interleukin-31 in PCL*

The role of Interleukin-31 (IL-31) in PCL is difficult to establish despite numerous studies covering this topic. Importantly in other lymphomas, such as follicular lymphoma, IL-31 promotes the growth of tumors in an autocrine and paracrine manner [90]. Certainly, this cytokine seems to be involved in the pathogenesis of PCLs [105]. It is typically secreted by Th-2 cells [106]. Signal transducers and activators of transcription 6 (STAT6) and NF-κB induced by IL-4 are main players in mediating the production of IL-31 [106]. Both STAT6 and NF-κB play some role in the pathogenesis of CTCL [101,107]. IL-31 is elevated in both lesions and sera of patients in the majority of studies (five); however, one study found no differences in comparison to control groups [54,105,108–111]. Malignant T-cells may secrete IL-31 [109]. Researchers did not establish with certainty whether IL-31 concentration is correlated with CTCL progression or/and pruritus [54,105,108–111]. Despite the proven central role of this cytokine in mediating pruritus in AD patients and the assumptions to have the same role in CTCL, it is rather not the case here based on our results [58,105,110]. The postulated patomechanism seems to be specific to AD [110].

IL-31, a chemokine ligand expressed by monocytes and dendritic cells, is also correlated with CCL18 and may be associated with the development of CTCL [84]. Both of these cells are important in the pathogenesis of PCL [89,103]. Moreover, exposition of Staphylococcal enterotoxin B, a potent superantigen, to patients with AD rapidly elevates the IL-31 levels secreted by T cells [112]. In cultured patients' tumor cell samples, IL-2 acted as the previously mentioned superantigen, resulting in the expression of IL-31 in 9 of 11 cases [113]. Both illustrated mechanisms could give a reasonable explanation to the observed elevation of IL-31 levels in patients with PCL. Moreover, it may explain why, in some studies, the concentrations were higher in advanced stages of the disease.

### *2.5. Role of JAK-STAT Pathways in PCL*

As of today, four types of Janus kinases (JAKs) (JAK1, JAK2, JAK3 and TYK2) and seven different signal transducers and activators (STATs) (STAT1, STAT2, STAT3, STAT4, STAT5a and STAT5b, STAT6) have been identified [114,115]. These molecules have important roles in the transmission of the cytokine signal in various human cells in vivo [114]. They are abundantly expressed in the healthy human epidermis [115]. Numerous studies have shown the impact of different JAK/STAT pathways on the pathogenesis of PCLs [90,101,103,116–181].

Strong evidence has been collected on genetic abnormalities of JAKs and STATs in cutaneous lymphoma cells, both on the cell lines and PBMCs from patients [103,125,129,137,139,143,144,149,153,157,162,170]. Studies highlight the activating mutations of JAK3, which occurred in 3.3–10.8% of patients with PCL according to different study groups [125,137,139]. Suppressors of cytokine signaling 1 (SOCS-1), a potent CTCL suppressor, regulates the JAK3/STAT5 signaling [119,143,153]. Moreover,

mutations of SOCS-1 that abolished its binding to JAK3 reinforced the aggressive course of the lymphoma [143]. Other researchers found that SOCS-1 deletion was one of the most common events in the group they studied and happened especially in the early stages of MF [153]. Interestingly, JAK3 is activated by the IL-2 and is in its pathway, which may be clinically relevant especially in more aggressive types of the disease [139]. JAK3 is expressed in the nuclei of CTCL cells, both from cell lines and PBMCs, and may also play a novel role in malignant clones [167]. Interestingly, tofacitinib (JAK1 and JAK3 selective inhibitor) could not block the kinase activity inside the nucleus, in contrast to the normal blockage of the IL-2/JAK3 pathway [167,177].

Other genetic studies regarding PCL found the pathological variants in JAK1 and JAK2 genes only in individual cases, and concerning common JAK2 alterations detected in other lymphoid malignancies are worth noticing [129,137,162,170,176]. Interestingly, JAK2 may play a role in keeping the Th-1 cytotoxic answer against the tumor present by mediating the IL-12 signaling and thereby phosphorylating STAT4 [135]. STAT4 and STAT6 genes are inversely regulated in CTCL and the loss of expression of the former may play a role in switching to Th-2 answer in the advanced lymphoma stages [131]. In contrast, JAK2 inhibition resulted in a decreased viability of SaEx, suggesting that it may be important for tumorous survival [164]. Concomitantly, with these results acquired from cell lines, the PBMC isolates showed that JAK inhibition potentiates the cytotoxicity of other agents (e.g., histone deacetylase inhibitors (HDACi)) and allows us to achieve a more generalized lethal effect against the malignant clones [165]. Other studies seem to be consistent with these results by showing the results of combinative cytotoxic effect of ruxolitinib (selective JAK1 and JAK2 inhibitor) and reminostat (HDACi) on the CTCL cell lines [168]. Moreover, another study showed the synergistic role of JAK/STAT inhibition on the in vivo SS model, in which romidepsin (HDACi) and mechloretamine were successfully used in the treatment [173]. A blockage of the malignant cell growth mechanisms in CTCL after the administration of increasing doses of ruxolitinib has also been suggested [137]. Further use of JAK inhibitors in the treatment of SS may be due to their ability to stop the constitutive activation of the activated kinases [176]. In advanced stages of a lymphoma, STAT3 and STAT5 are completely dependent on the constitutively activated JAK1 and JAK3 [135]. However, one study showed that apoptosis in CTCL lines may be augmented via the JAK1 pathway and this activity was blocked by ruxolitinib [145].

The further parts of the JAK/STAT pathway, especially STAT3, STAT5, and STAT6 also play the established role of mediators in the PCLs oncogenesis [101,157,173,175]. These proteins act upon the regulation of several gene transcriptions after being phosphorylated by JAKs. One study demonstrated the constitutive activation of STAT5 in CTCL; however, in most cases, after blocking the specific Janus kinase, these molecules should not be able to maintain their function in regulating different gene transcriptions [134,135]. Currently, there are no ongoing and upcoming trials concerning AD and STATs inhibition. Therefore, the STATs role in PCLs is beyond the scope of this review.

### *2.6. Safety and Danger Concerns of Administering the New Drugs in the Context of PCLs*

AD and psoriasis are distinct medical conditions. However, we have to think about the possible interactions between drugs modifying immune responses in AD and pathogenesis of PCL (followed by Dequidt et al.), especially because of the higher risk of lymphoma in severe cases of AD as well as the problem of differentiation between AD and PCL in some cases [182]. Also, in our opinion, it is crucial to first deduce whether the biologic and small molecule treatments in AD may induce lymphoma and second, in case of an overlap or misdiagnosis between those two diseases, a PCL may progress after administration of these agents.

We would like to shortly summarize the above theoretical assumptions. Decreasing the concentration and/or stopping the secretion of IL-4 and IL-13 could lead to the restoration of the Th-1 microenvironment, which may enhance tumorous toxicity. The reduction in the levels of these interleukins after receiving certain treatments discussed earlier is one of

the supporting facts for this theory. Therefore, dupilumab, lebrikizumab, and tralokinumab may appear to be clinically efficient in the treatment of the PCL. Agents blocking IL-22, i.e., fezakinumab, could also stop the lymphomagenesis and additionally reduce the ability of the tumorous cells to metastasize in the advanced stages of the lymphoma. We also show the possible involvement of IL-31 in the pathogenesis of PCLs, which is still elusive. Theoretically, blocking the role in the establishment of the Th-2 microenvironment and in the growth of the tumor might be beneficial for the lymphoma patients after administration of nemolizumab, similar to other lymphomas. Lastly, we described the current state of knowledge on the influence of JAKs on PCLs. JAK1 and JAK3 seem to have the pathogenic role by activating the STAT3, STAT5, and STAT6, which contribute significantly to lymphomagenesis. Therefore, blocking them may reduce tumor development. In contrast, JAK2 may also play some role in preventing the growth of lymphomas. Despite the mentioned effects of ruxolitinib on the CTCL cell lines, obstructing this pathway may appear to be harmful for the patients by reducing the Th-1 cytotoxicity directed to the clones. Figure 1 summarizes the most important aspects of the above assumptions.

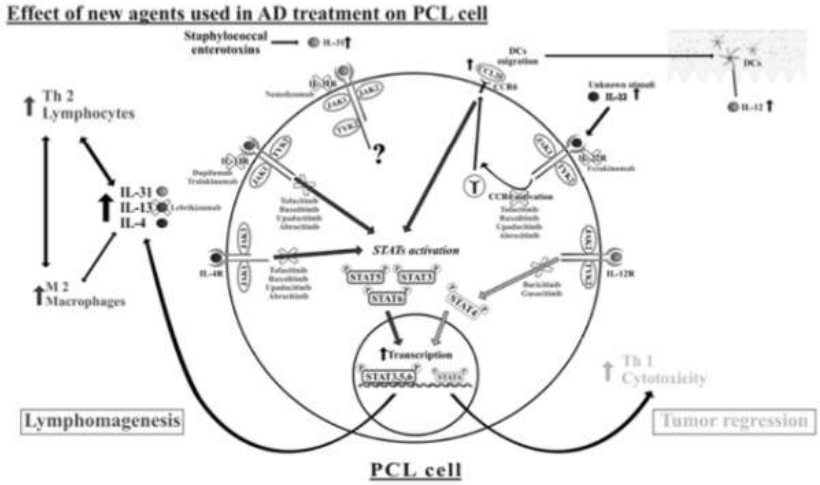


**Figure 1.** The influence of agents targeting interleukins (IL) 4, 13, 22, and 31 and JAK/STAT pathways on the primary cutaneous lymphomas (PCLs) cells and tumorous microenvironment. The up and down arrows stand for increase/decrease of the interleukins concentration, cell count or receptor's upregulation. IL-12 promotes phosphorylation of STAT4, thereby stimulating the cytotoxic mediated CD8(+) answer. Concomitantly, IL-4, IL-13, and IL-31 contribute to forming the Th-2 cytokine profile, which results in decreased cytotoxic immunosurveillance and lymphomagenesis. IL-4, IL-13, and IL-22 activate different Janus kinases, which promote the STAT3, STAT5, and STAT6 activation contributing to the transcription of pro-tumorous factors. In the advanced stages of the disease, this phenomenon may be seen more prominently. By blocking several pathways or cytokines, biologic drugs and small molecule inhibitors may affect both the malignant microenvironment and pathways in the PCLs cells.

However, despite the theoretical expectations of stopping the progression of the disease, after administering the immunomodulating agents, PCL may progress or be induced for reasons currently unknown [183]. Dirk Elston, in his letter discussing the role of dupilumab in CTCL, agrees with our findings. He points out that if a cytokine is upregulated, it does not mean we must down regulate it, contrary to the saying "If it's wet, dry it. If it's dry, wet it" [184]. Concerning the theory we have previously described, we will now discuss what researchers and medical agencies have found when the aforementioned drugs have been used clinically. We were unable to find any reports on the impact of lebrikizumab, tralokinumab, fezakinumab, and nemolizumab on PCLs in PubMed. Also, we performed the search in the "Drug Safety-related Labeling Changes (SrLC)"—the Federal Drug Agency (FDA) database—and could not find any records on these biologic agents [185]. When searching the European Medicines Agency (EMA) website, found

information on tralokinumab (Adtralza), which is authorized for use in the European Union in the treatment of moderate to severe AD [186]. We also found an agreement on the investigation plan for pediatric use of lebrikizumab [187].

Despite a multitude of evidence on potential benefits of using JAKi in the treatment of other lymphoid malignancies, the only JAK inhibitor with reported effects on patients with PCLs is ruxolitinib [188]. Baricitinib, upadacitinib, tofacitinib, and ruxolitinib are authorized for use in the European Union [189–192]. Abrocitinib was recently positively opinioned for marketing authorization [193]. Prior to 22 October 2021, the only JAK inhibitor registered for AD treatment in the EU is baricitinib (Olumiant) [192]. Interestingly, according to the U.S. Food and Drug Administration Database, baricitinib (Olumiant) and tofacitinib (Xeljanz) may increase risk of developing lymphomas, including those of the skin [194,195]. This warning especially raises the problem of potential increased risk of serious adverse events, including cardiovascular and malignant complication in the treatment of chronic inflammatory conditions [195]. Ruxolitinib and upadacitinib do not have such warnings or precautions in their records because they are not used for treatment of arthritis or other inflammatory conditions [195–197]. However, the issue of JAK inhibitor safety in the treatment of AD is raised, since they share the same mechanisms of action [198]. Moreover, currently the only JAK inhibitor that has been studied in a big, four-year surveillance study is tofacitinib [198].

Only dupilumab and ruxolitinib will be discussed in the subsequent paragraph, because to the best of our knowledge, only these drugs are reported to have been administered in the treatment of CTCL misdiagnosed as AD or eczema, CTCL itself, and AD followed by CTCL. These cases are recorded in Table 2.

**Table 2.** Cutaneous T-cell lymphoma cases treated with dupilumab or ruxolitinib. We have updated the table continuing the results by doctor Sugaya [91].

| Drug | Age (Years) | Sex | Pre-Diagnosis | Final Diagnosis | Response to Treatment | Death | Reference |
|---|---|---|---|---|---|---|---|
| Dupilumab | 58 | M | AD | MF | Progression of MF | No | [199] |
| Dupilumab | 64 | M | AD | SS | Progression of SS | No | [200] |
| Dupilumab | 51 | F | AD | MF | Progression of MF | No | [201] |
| Dupilumab | 64 | M | AD | CTCL-NOS | Progression of erythroderma | No | [202] |
| Dupilumab | 72 | M | AD | MF | Progression of MF | No | [202] |
| Dupilumab | 59 | F | AD | MF and AD | Progression of MF | No | [202] |
| Dupilumab | 40 | F | AD | MF | Progression of MF | No | [202] |
| Dupilumab | 67 | M | MF | SS | Progression of SS | Yes | [202] |
| Dupilumab | 58 | M | MF | SS | Progression of SS | Yes | [202] |
| Dupilumab | 77 | F | MF | SS | Progression of SS | No | [202] |
| Dupilumab | 61 | M | Eczema | MF | Progression of MF | No | [203] |
| Dupilumab | 52 | M | Eczema | MF | No clinical improvement | No | [203] |
| Dupilumab | 60 | F | Eczema | MF | No clinical improvement | No | [203] |
| Dupilumab | 68 | M | SS and AD | SS and AD | Improvement in SS and AD | No | [204] |
| Dupilumab | 37 | F | Eczema | SS | Progression of SS | No | [205] |
| Dupilumab | 55 | M | MF and AD | MF and AD | Improvement of MF and AD | No | [205] |
| Dupilumab | 74 | F | SS | SS | Improvement of SS | No | [206] |
| Dupilumab | 48 | F | AD | SS and AD | No clinical improvement | No | [207] |
| Dupilumab | 40 | F | AD | MF | Progression of MF | No | [208] |
| Dupilumab | 43 | M | AD | MF and AD | Progression of MF | No | [209] |
| Dupilumab | 48 | F | AD | MF | Progression of MF | No | [210] |

**Table 2.** *Cont.*

| Drug | Age (Years) | Sex | Pre-Diagnosis | Final Diagnosis | Response to Treatment | Death | Reference |
|---|---|---|---|---|---|---|---|
| Dupilumab | 55 | M | AD | MF | Progression of MF | No | [210] |
| Dupilumab | 26 | M | MF | MF | No clinical improvement | No | [211] |
| Ruxolitinib | 13 | M | HLH | HLH and SPTCL | Improvement of SPTCL and HLH | No | [212] |
| Ruxolitinib | NS | NS | MF | MF | Progression of MF | No | [213] |
| Ruxolitinib | NS | NS | CTCL | CTCL | No clinical improvement/ Stable disease | No | [213] |
| Ruxolitinib | NS | NS | CTCL | CTCL | Progression of CTCL | No | [213] |
| Ruxolitinib | NS | NS | CTCL | CTCL | Progression of CTCL | No | [213] |
| Ruxolitinib | NS | NS | MF | MF | Progression of MF | No | [213] |
| Ruxolitinib | NS | NS | MF | MF | No clinical improvement/ Stable disease | No | [213] |
| Ruxolitinib | NS | NS | MF | MF | Improvement of MF/ Partial remission | No | [213] |
| Ruxolitinib | NS | NS | pcALCL | pcALCL | Improvement of MF/ Complete response | No | [213] |

Abbreviations: NS: not specified; M: male; F: female; MF: mycosis fungoides; AD: atopic dermatitis; CTCL: cutaneous t-cell lymphoma; pcALCL: primary cutaneous anaplastic large-cell lymphoma; SS: Sézary Syndrome; HLH: hemophagocytic lymphohistiocytosis; SPTCL: subcutaneous panniculitis-like T-cell lymphoma; CTCL-NOS: CTCL-not otherwise specified.

An expert opinion on the safety of dupilumab shows that it is a safe, well-tolerated drug in AD [214]. Noticeably, CTCLs which occur during treatment with this drug may be unrelated, but a long-term follow-up performed with a large cohort of patients is needed to elucidate this subject [214]. Another opinion describes the cases of MF or SS identified in patients treated with dupilumab and concludes that in a limited subset of patients, this drug might appear to be beneficial [91]. However, generally it should be avoided and in some cases contraindicated for CTCL treatment [91,215]. Our research of the Pubmed database has led us to identify a total of 23 cases in which a PCL and use of dupilumab coexisted [199–211]. A total of 21 people in this group were above 40 years old [199–207,209–211]. What may be surprising in the context of our theoretical assumptions is that the most common event in the mentioned group was the progression of the lymphoma, which led to the death of two patients, who progressed to SS [199–207,209–211]. No clinical improvement of the CTCL was observed four times, whereas the disease course improved in three cases [199,203,206,207,211]. In 16 cases, the original diagnosis was AD or eczema while remaining patients were treated for PCL or mogalizumab-associated rash off-label [199–207,209–211]. Interestingly, dupilumab appeared to be effective for the treatment of lichenoid reaction associated with mogalizumab in a patient with CD8+ MF [211].

Ruxolitinib, which targets JAK1/JAK2 is used in the treatment of psoriatic arthritis, AD, and several lymphoid malignancies, e.g., myelofibrosis and polycythemia vera [215,216]. Moreover, trials on animal models of hemophagocytic lymphohistiocytosis (HLH) prove this JAK inhibitor to be efficient in the treatment of this condition [217,218]. The genetic abnormalities in the JAK/STAT pathway have been the rationale for therapeutic uses that we discussed earlier. Assuming that JAK inhibitors prove to be effective in the treatment of cutaneous lymphomas, clinicians may feel comfortable administering them if the final diagnosis is difficult to make [215]. These facts led the researchers to administer ruxolitinib to nine patients with PCLs (four MF, three non-specified CTCL, one primary cutaneous anaplastic large cell lymphoma (pcALCL), and one subcutaneous panniculitis-like-T-cell lymphoma (SPTCL)) [212,213]. Some was observed in three cases (one MF, one pcALCL and one STPCL), but the disease course remained stable or worsened in the others [212,213].

Interestingly, despite that five of the seven CTCLs showed the signs of JAK/STAT activation, only one patient whose tumor showed 20% overactivation of pSTAT3 responded to the treatment [213].

The conflicting data revealed in this article seems to be in line with our previous considerations on the safety and danger of the use of biologics in the treatment of psoriasis. Blockage of several mechanisms by which the interleukins act and occur in PCLs should be beneficial in the treatment of the disease. However, dupilumab, in most of patients with lymphoma misdiagnosed as AD or eczema, makes it fully apparent. This drug does not seem to be beneficial for CTCL patients in most cases. Accordingly, despite the JAK/STAT activation, most of the lymphomas did not respond to ruxolitinib. With this paper, we would like to raise awareness to the issue of a development or a misdiagnosis of a cutaneous lymphoma in patients with AD. Especially for patients that are 40 years old or above, the chronic and severe course of AD and the sudden worsening of the symptoms should be considered "red flags" to exclude the potential oncologic risk by taking and carefully verifying the biopsy.

## 3. Materials and Methods

A comprehensive search of the literature using the PubMed (https://pubmed.ncbi.nlm.nih.gov/) electronic database using the search queries "(IL-4 and cutaneous lymphoma) OR (IL-4 and mycosis fungoides)", "IL-22 and cutaneous lymphoma", and "IL-31 and cutaneous lymphoma" was performed in the second week of August 2021, from the database inception to the 14th of August 2021. Further research using the queries "(dupilumab and lymphoma)", "(fezakinumab and cutaneous lymphoma) or (fezakinumab and mycosis fungoides)", "(lebrikizumab and cutaneous lymphoma) or (lebrikizumab and mycosis fungoides)", "(tralokinumab and cutaneous lymphoma) or (tralokinumab and mycosis fungoides)", "(baricitinib and cutaneous lymphoma) or (baricitinib and mycosis fungoides)", "(ruxolitinib and cutaneous lymphoma) or (ruxolitinib and mycosis fungoides)", "(upadacitinib and cutaneous lymphoma) or (upadacitinib and mycosis fungoides)", and "(jak inhibitor and cutaneous lymphoma) or (jak inhibitor and mycosis fungoides)" was performed in the third week of August 2021, from the database inception to the 25th of August 2021 and a "((jak) OR (stat)) AND (cutaneous lymphoma)" search was performed in the second week of September 2021, from the database inception to the 11th of September 2021. After the initial search, titles and abstracts were screened for the inclusion and exclusion criteria. Based on title and abstract analysis, we included articles concerning the role of IL-4, IL-13, IL-22, IL-31, JAK/STAT, and biologic drugs affecting cytokine profiles and JAK inhibitors on PCLs. At this step, we excluded records not related to the topic, non-English manuscripts, personal opinions, and duplicates. The remaining were qualified as eligible for full-text reading. After reading the full manuscripts, some were excluded (not relevant, not original, and not providing information concerning earlier mentioned cytokines, pathways, and new drugs' impact on PCLs). Finally, additional relevant, eligible records identified through a references search were included, in which information on the effect of PCL microenvironmental influence on the specific lymphoma subtypes were included. Concentration of cytokines in the biopsies and in the blood of the patients, genetic alterations concerning genes linked to the featured subject, the possible effects of interleukins, pathways, and administration of the agents blocking them in the clone cells were analyzed and summarized.

## 4. Conclusions

IL-4, IL-13, IL-22, and IL-31 are detectable in the lesions and sera of patients suffering from PCL. The JAK-STAT pathway has an established role in the oncogenesis of this tumor. We summarized the effects of these cytokines in the course of cutaneous lymphomas. We have shown that IL-4, IL-13, and activation of certain JAKs and STATs to be crucial in the development of the tumoral microenvironment as well as in the progression of the disease. IL-22 and IL-31, however, are not as important in the pathogenesis of PCL as they are

in AD. Based on the publications, we have also described the effect of dupilumab and ruxolitinib in the PCL patients misdiagnosed as AD, in PCL itself or AD itself and with PCL in follow up during treatment (coexistence of two diseases). The progression of the lymphoma was observed in most of cases. Thus, we would like to highlight, that in case of severe AD or eczema, especially in a case of rapid evolution of the symptoms in an older individual, it is necessary to perform a biopsy from the skin lesion. Subsequently, a close pathological examination to exclude the possibility of PCL misdiagnosis/evolution should be performed. However, as the authors, we would like to mention that we should not avoid dupilumab in severe AD, especially concerning the portfolio of other systemic drugs used in AD, such as cyclosporine A, methotrexate, and azathioprine, all with known immunosuppressive potential. We realize the necessity of further research concerning the role of IL-22 and IL-31 in PCL. Furthermore, the new biologic and small molecule drugs should be used carefully in the treatment of AD in order not to worsen the course of the cutaneous lymphomas.

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Review paper

PUBLICATION 3

# Safety and danger of biologic treatments in psoriasis in context of cutaneous T-cell lymphoma (CTCL)

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**Abstract**

Microenvironment has a significant impact on the pathogenesis of cutaneous T-cell lymphoma (CTCL), especially in the context of new emerging biologic therapies. Our aim was to review the literature on interleukins 12, 17, 23 and TNF-α in mycosis fungoides in order to clarify the safety of using biologics in the treatment of psoriasis. Our analysis suggests that these drugs may have an impact on the progression of CTCL. Concluding, in case of uncertain psoriatic lesions, a biopsy followed by pathologic examination should exclude the possibility of co-existence of a primary cutaneous lymphoma before administration of therapies affecting cytokine profiles.

**Key words:** cutaneous T-cell lymphoma, mycosis fungoides, biologic treatment, psoriasis, IL-12, IL-17, TNF-α.

## Introduction

Mycosis fungoides (MF), a rare lymphoproliferative disorder characterized by accumulation of malignant T-cells in the skin, is the most common cutaneous T-cell lymphoma (CTCL) [1]. Pathophysiological mechanisms causing the progression of this disease have not been fully understood. A possible impact of tumour microenvironment on the development of the disease has been shown in some recent studies suggesting the impact of interleukin-17 (IL-17) in that matter [2]. A variety of therapies affecting cytokine profiles have been introduced, including tumour necrosis factor α (TNF-α)-inhibitors and TNF-α-receptor inhibitors (e.g. adalimumab, etanercept, infliximab), IL-17 and its receptor pathway blockers (bimekizumab, brodalumab, ixekizumab, secukinumab) and IL-12 and/or IL-23 pathway blockers (e.g. guselkumab, ixekizumab, risankizumab, secukinumab, tildrakizumab, and ustekinumab). They have been used more often in the clinical practice for the last decade.

Our aim in this review is to elucidate the role of IL-12, IL-17, IL-23 and TNF-α in MF, which sheds the light on the safety of new biologic treatments in psoriasis in context of CTCL.

## Involvement of IL-17 in MF

The IL-17 family currently consists of six cytokines (named IL-17A to IL-17F) and five receptors (IL-17RA to IL-17RE) [3]. IL-17A, IL-17C and IL-17F are identified as pro-inflammatory, whereas IL-17E, also termed IL-25, is considered as anti-inflammatory [4]. IL-17A and IL-17F have 50% homology, therefore IL-17F signalling is 10–30-fold weaker [5]. IL-17A/17F heterodimer may also be secreted, and its signalling strength is intermediate [5].

IL-17A and IL-17F are secreted by many cells including Th17 cells, mast cells, macrophages, neutrophils and CD8+ lymphocytes [6]. The IL-17 cytokines are crucial in the answer against extracellular bacteria and fungi. When not strictly controlled, they can also contribute to development of pathogenic response causing autoimmune disorders such as psoriasis [7]. Possible involvement of IL-17 in the pathogenesis of MF has been reported by researchers [8–18].

In 2004 Cirée *et al.* were the first to reveal that tumour cells may express IL-17. The cells derived from patients diagnosed with MF or Sezary Syndrome (SS) expressed IL-17 mRNA and secreted this cytokine *in vitro* [9]. Since then, several studies have reported conflicting

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results. We have found five studies, which have shown the elevated levels of IL-17 in biopsies from MF skin lesions [8, 11–13, 18]. IL-17F cytokine is known to induce gene expression of antimicrobial peptides (AMPs), other proinflammatory cytokines and matrix metalloproteinases (MMPs) [19] by activating numerous pathways such as NF-κB, MAPKs and C/EBPs [19]. Furthermore, IL-17F expression was associated with progressive CTCL [13]. Studies have also revealed that malignant lymphocytes in MF may present a Th-17 phenotype [11] which has been shown to express not only IL-17, but also IL-21, IL-22 and CCL20 [20, 21]. Two other studies have shown the results with normal levels of IL-17 in MF [10, 14]. One of them is suggesting that IL-22 rather than IL-17 is crucial in establishing the tumour microenvironment [10].

It is well known that activation of STAT3/JAK3 pathway plays a significant role in MF pathogenesis [11]. Krejsgaard et al. have found that malignant T-cells in CTCL not only can express IL-17, but also that expression is promoted by the JAK3/STAT3 pathway [11]. The-IL-17 pathway is important in innate defence mechanisms, promoting secretion of anti-microbial peptides (AMPs) or neutrophil-recruiting cytokines, thereby improving response against extracellular pathogens, e.g. Staphylococcus aureus [22]. Recently, it has been proven that T-cell receptor (TCR) engagement is necessary for malignant transformation in MF and that the progression of the disease is dependent also on microbiota [23]. The aetiology of MF is still elusive, nevertheless some bacterial agents are suspected to play an etiologic role. S. aureus has been one of them – reported to colonize 44–76% of CTCL patients [24–26] and to be the most common infection in CTCL [27]. Staphylococcal enterotoxin A (SEA) has been shown to stimulate activation of STAT3 and upregulate IL-17 production in primary patient-derived malignant and non-malignant T cells [16]. Researchers demonstrated the interesting cross-talk between malignant T-cells expressing SEA-nonresponsive TCR variable region β chain and non-malignant T-cell with SEA-responsive TCR, what may suggest that SEA-producing bacteria can promote the STAT3/JAK3 oncogenic pathway [16]. Furthermore, this may be the possible mechanism of the MF progression.

Despite those possible mechanisms and the elevated levels of IL-17 observed in MF patients [8, 11–13, 18], secretion of anti-microbial peptides is significantly lower in CTCL patients than in psoriatic skin. It may resemble what is seen in atopic dermatitis (AD) [14, 28], thereby suggesting the dysfunction in the induction of gene expression of antimicrobial peptides by IL-17, which is its role in healthy skin. Furthermore, studies seem to suggest the Th-2 cytokines to be the main players in advanced stages of MF and SS [29–31]. One study concerning IL-17E, called IL-25 here, showed that IL-25 levels are elevated in MF lesions and in sera of advance-stage patients, which also correlates with lactate dehydrogenase levels [18] known to reflect the CTCL activity [32]. What they concluded using MyLa cell lines (MF cell lines) was that IL-25 is secreted by epidermal keratinocytes in MF and may directly induce IL-13 secretion by tumour cells, which may contribute to formation of Th-2 microenvironment [18]. This mechanism seems to be relevant in the pathogenesis of MF and SS and may be clinically important since Geskin *et al.* established IL-13 to be an autocrine factor of CTCL, blocking of which may be the potential therapeutic target for clinical interventions [33].

## Possible cancerogenic role of IL-17 in MF

Many studies have shown the link between IL-17 mediated answer and cancerogenesis, e.g. in colorectal cancer [34–38], lung cancer [39] and in squamous cell carcinoma (SCC) [40, 41].

A role of IL-17 in CTCL carcinogenesis has been still elusive to the best of our knowledge. Nevertheless, the pro-angiogenic role of IL-17 has been postulated in a few studies, therefore suggesting an indirect pro-carcinogenetic role. Along with the worsening survival rates as the stages of CTCL progress [1], some studies show that in the plaque and tumour stages, the value of the mean microvessel area is significantly higher [42, 43]. The promotion of angiogenesis is contributed to many factors and vascular endothelial growth factor (VEGF) has been one of them, a potent angiogenic protein, which is strongly induced by hypoxia [44]. The resistance of lymphomas, colorectal and lung cancer tumour models to treatment with anti-VEGF drugs, was promoted by Th17 subset cells [45]. VEGF has been present in CTCL lesions [46, 47] and its production is associated with constitutive activity of Janus kinase 3 (Jak3) and the c-Jun N-terminal kinases (JNKs) [46]. Moreover, Lauenborg *et al.* have shown that IL-17F secreted by malignant T-cell of MyLa2059 cell lines was able to trigger endothelial tube formation, thereby proving stimulation of angiogenesis by IL-17F [48]. Accordingly, when applying anti-cancer treatment, e.g. CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone) chemotherapy, IL-17 pathways may be indirectly promoted shifting to Th17 phenotype [17]. Similarly, promotion of Th17 pro-inflammatory cytokines has been noticed in colorectal carcinoma after administration of tamoxifen [49]. Moreover, IL-17RA blocking may be used to potentiate the response to such treatment [49]. Nevertheless, chemotherapy is not recommended as a first-line treatment for CTCL [50]. Mono- and polychemotherapy show elevated risks of death, no chemotherapy regimen has been shown to improve patients survival rates and remissions are significantly short [50]. In summary, IL-17 may have an impact on the promotion of carcinogenesis in MF and a possible aggravating role during chemotherapy. Despite some evidence of positive effects of blocking Th17 pathway during chemotherapy, for now, it is rather not a possible treatment in CTCL [50].

## Role of IL-12/IL-23 in MF

Considering the impact of new biologic therapies on CTCL, it is important to mention the role of IL-12 and IL-23. Both cytokines, which share the same common subunit p40, are known to have pro-inflammatory effects [51]. Interestingly, despite having many similar functions, pre-Th-1 cells differentiate into Th-1 lymphocytes in the presence of IL-12, when IL-23 is present, they rather show Th-17 profile [52]. Though it is important to remember that Th-17 cells are easily interconvertible and they can be turned into Th-1 or Th-2 cells, when a suitable microenvironment occurs, but not vice versa [53]. Therefore recombinant IL-12, strongly inducing Th-1 microenvironment and with its ability to suppress Th-2 cytokines in SS, was considered as one of the emerging therapies for MF [54–56]. The main rationale for use of this cytokine in CTCL treatment was to enhance cell-mediated cytotoxicity and to restore interferon γ (IFN-γ) production [57], which expression has been shown to gradually decrease in the course of lymphoma progression [58]. IFN-γ has been used in MF treatment [59]. Phase II open-label study of recombinant human IL-12 in SS, which was administered in two subcutaneous injections per week in doses ranging from 100 ng/kg escalating up to 300 ng/kg, has shown some antitumor activity [60]. Another aspect is that IL-12 may be used as an early MF marker. Immunohistochemical staining of IL-12p35 has been shown to be useful as the diagnostic tool in patch-stage MF [61] along with exhibition of Th-1 dominant microenvironment in early stages of the disease [31]. The literature on IL-23 in MF is scarce. Due to the fact that IL-23 may induce pre-Th-1 cells to convert to Th-17, there is a possibility that this cytokine activates the secretion of IL-17A and IL-17F, thereby promoting the possible pathogenic effects of IL-17A and IL-17F. Doherty *et al.* have shown that there was an increased expression of IL-23 in keratinocytes and in dermal lymphocytes in all stages of MF, and that atypical lymphocytes infiltrating the tumour in IVB stage patients may demonstrate a weaker staining of IL-23 [62]. This finding shows that IL-23 may play a role in the pathogenesis of MF/SS, but further research is necessary.

## Role of TNF-α in MF

TNF-α, the hallmark of pro-inflammatory cytokines, has also been shown to have an impact on MF. Studies seem to be consistent with the fact that TNF-α levels are elevated in the MF skin lesions [58, 63, 64]. Moreover, an increase in the cytokine concentration concomitant with the progression of the disease has been noticed [64] but not in all of cases [58]. What is also worth mentioning, serum concentrations of TNF-α in patients during treatment of CTCLs with extracorporeal photophoresis (ECP), have significantly increased from baseline during six months' therapy, but no correlation with clinical response has been found [65]. Genetic studies suggest that patch-stage of MF is not determined by TNF-α genotype polymorphism [66]; however, Tracey *et al.* have found an association between tumorigenesis in MF and alteration in TNF receptor signalling [67]. They show the possibility of activating antiapoptotic pathways through first and second TNF receptors (TNFR1 and TNFR2) caused by deregulation of multiple genes, leading the lymphoma cells to avoid apoptosis, predominantly because of NF-κB upregulation [67]. Strong expression of these transcription factors may be one of the characteristic features presented by some MF cell lines [68]. Other researchers have shown that constitutive activation of NF-κB, pathway promoted by TNF-α, can cause the resistance to apoptosis in lymphoma HuT-78 cells [69]. TNF-a, alongside with IFN-γ, has been suspected to be one of the factors causing the epidermotropism in CTCL by inducing Interferon-Inducible Protein (IP-10) [58, 63]. Some of these latter reports were the basis to assess the treatment of a relapsed CTCL with soluble TNF receptor, etanercept [70]. Before the administration of the biologic drug, patients were heavily pretreated (median number of prior regimens was seven) [70]. This therapy was not effective in case of patients in the advanced stage of the disease: all of them did not respond and progressed [70]. Only two patients in the early stage of CTCL (both in IB), had some benefit from the therapy, one with partial response and the other with minor response [70], nevertheless this group is too small to make any reasonable conclusions.

## MF, psoriasis and biological treatment implications

A significant pathogenetic role of IL-23, IL-17 and TNF-α in psoriasis is widely accepted and has important clinical implications in biological treatments of the disease. Anti-TNF-α drugs such as infliximab [71] and agents blocking IL-23, IL-17 pathway e.g. ustekinumab [72], ixekizumab [73] and secukinumab [74, 75] are more commonly used to treat chronic plaque psoriasis, often with superior therapeutic effects and increased quality of life [76, 77]. However, many studies have reported an increased risk of CTCL in patients with psoriasis both in Caucasian and Asian populations [78–80], especially in severe psoriasis [78, 80]. A major review on that topic also concluded that an association between MF and psoriasis is plausible, but prevalence and incidence have not been found yet [81]. Therefore, a question about the effect of these biologic therapies on the course of MF is raised. We believe that the most important issues here have been similar to those considered by Dequidt *et al.* [82]. First, if the biologic treatments in psoriasis may induce MF and second, in case of an overlap or misdiagnosis between those two diseases, if lymphoma may progress after administration of biologic drugs. Solely basing on the above assumptions, blocking IL-17RA (brodalumab), IL-17A (secukinumab, ixekizumab) and IL-17A-F (bime-

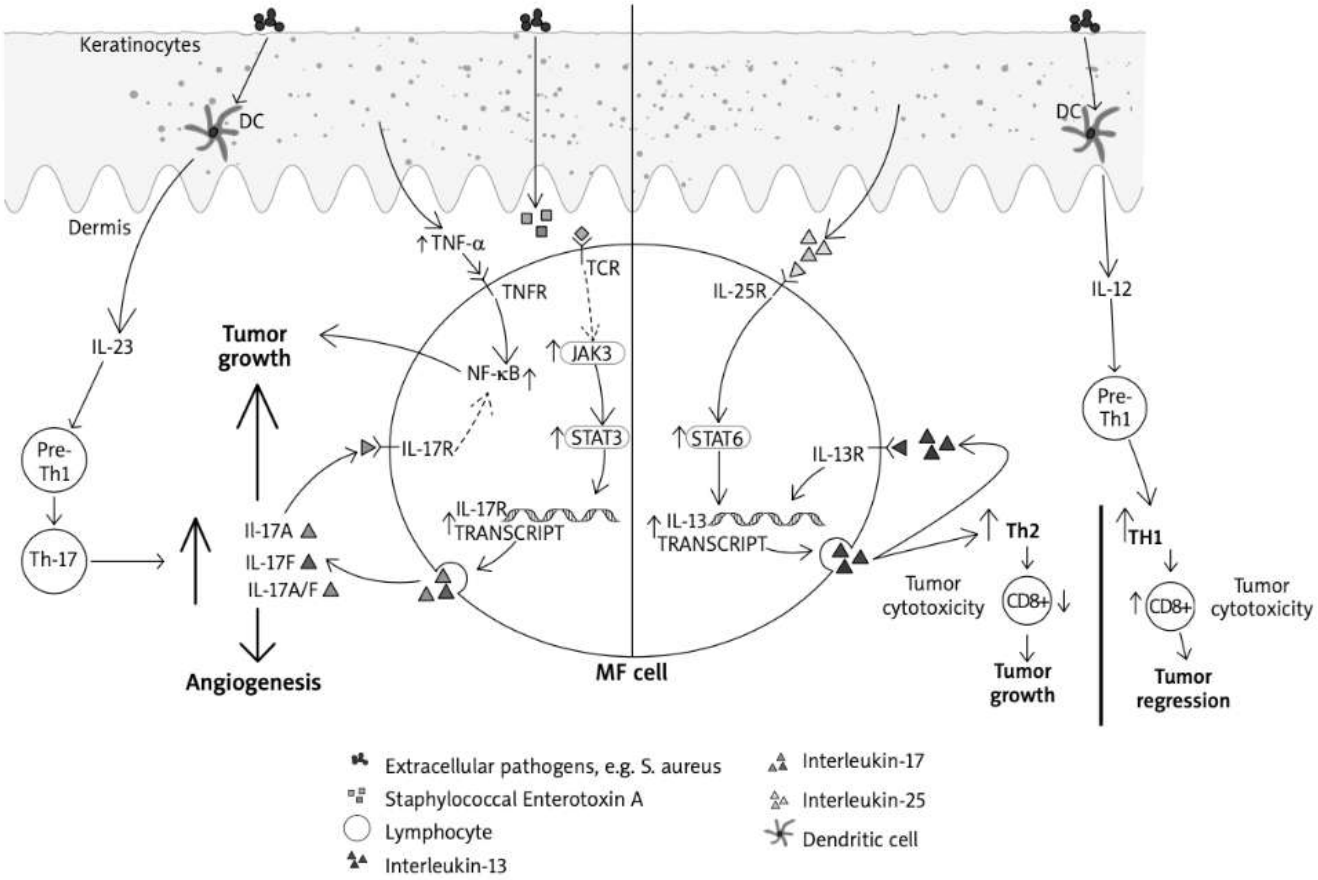


**Figure 1.** The contribution of interleukins (IL) 12, 17, 23 and tumour necrosis factor α (TNF-α) to the tumour microenvironment in mycosis fungoides (MF). IL-12 has been indirectly restoring the cytotoxic mediated CD8(+) answer and promoting tumour regression by stimulating the differentiation of pre-T-helper 1 lymphocytes. IL-23 can stimulate pre-T-helper 1 lymphocytes, followed by creating T-helper 17 cells subset and increased secretion of IL-17 proinflammatory cytokines. MF cell is also able to secrete IL-17A, IL-17F and IL-17A/IL-17F heterodimers. It is reinforced by upregulated JAK3/STAT3 pathway, which has been shown to be promoted by activated T-cell receptor (TCR), which is necessary for malignant transformation in MF to occur. One of the possible ways of activating TCR is related to Staphylococcal enterotoxin A. NF-kB upregulation, with its anti-apoptotic effect on lymphoma cells, seems to be important and relevant in the pathogenesis of CTCL. It has been promoted by TNF-α as well as proinflammatory IL-17 cytokines. IL-25 (IL-17E) is promoting STAT6 pathway. Those interactions result in increased IL-13 secretion (also in autocrine manner). Especially in the advanced stage of the disease it contributes to forming Th-2 cytokine profile, what results in decreased cytotoxic immunosurveillance and tumour growth

kizumab) may be beneficial in stopping progression of MF as we have shown the possible role of proinflammatory IL-17 cytokines. IL-17A and IL-17F may be included in progression of the disease by promoting the JAK3/STAT3 oncogenic pathway and by stimulation of angiogenesis. Furthermore, the anti-inflammatory cytokine, IL-17E, may contribute to creating a Th-2 dependent tumour microenvironment by inducing IL-13 secretion and brodalumab should be able to block this interaction. On the other hand, ustekinumab (blocker of p40 common subunit) and TNF-α inhibitors should not be recommended in the treatment of psoriasis if there is any risk of an overlap with CTCL as they are known to inhibit Th-1 microenvironment. Moreover, as it was shown, etanercept did not appear to be an effective drug in the treatment of CTCL, possibly causing the progression in some patients. Considering all the theoretical background, we have to focus on what researchers have found and published. Studies on the impact of anti-TNF-α drugs on the course of CTCL are much more abundant in contrast to the literature on other biologic therapies. We have identified 7 patients described in clinical case studies [83–87] and 90 cases from retrospective studies [82, 88–91] reporting CTCL after TNF-a-inhibitor treatment. Eighty-two out of these 97 patients presented with CTCLs, 66 of which were classified as MF and 5 as SS [82–91]. Dequidt *et al.* reported that in each of the 5 cases of large cell transformation in MF, the diagnosis of psoriasis was the reason to treat

with biologic drugs and after discontinuing anti-TNF-α, the evolution of the lymphoma was aggressive [82]. Another study has revealed that the majority of MF were misdiagnosed, predominantly as psoriasis, and biologic drugs made the lymphoma fully apparent [89]. During follow-up, 7 patients died because of the CTCL that appeared after the anti-TNF-α administration, all of them in the advanced stage of the disease [88, 90, 91]. On the other hand, most cases of MF have appeared indolent after anti-TNF-α drugs were discontinued, in some cases the topical treatment led to partial or complete response [82, 91]. Moreover, majority of the patients had either a stable disease or a complete response after receiving a stage-suited therapy [82–91]. These results seem to be consistent with our previous considerations.

What may be surprising in terms of our IL-17 findings is what studies show. Most of the MF patients may progress after receiving IL-17A, IL-17RA or IL-12/23 inhibitors [82–84, 91, 92]. In fact, some case report has shown significant clinical improvements after discontinuing of these drugs [83]. Nevertheless, the biggest study on that matter has shown that in 8 of 11 cases, a worsening of the disease was noticed and in the short follow-up of thirteen months 5 patients died, 4 of MF and one of stroke [91]. In contrast to these reports, our assumptions highlighted the possible aggravating role of IL-17 in MF, therefore blocking it would be beneficial. The explanation to these conflicting data may be the aspect of Th17/Treg imbalance leading to immunosuppression [92] and other, not yet known mechanisms. Admittedly, despite the fact that the literature is scarce on the effects of these newest biologic therapies on MF, it seems to be ethically questionable to make further intentional research elucidating these aspects. Also, many authors emphasized what may be done in order to minimize the risk of a lymphoma progression after receiving biological drugs. The most important conclusion is to carefully examine patients and in case of any oncological suspicion, take biopsies in order to exclude a potential misdiagnosis [82, 84–88, 91, 92].

The main limitation of the study in the aspect of biologic therapies is based on the retrospective studies and case reports. The disturbing role of some other medicaments, like cyclosporine, also cannot be excluded, since most patients with psoriasis have undergone at least one non-biological systemic therapy before receiving biologic drugs.

## Conclusions

Interleukin-17 is detectable in MF lesions, sometimes with the elevated level, but it does not seem to be the main player of MF. We show it not to be as important in the pathogenesis of CTCLs as it is in the pathogenesis of psoriasis, nevertheless using IL-17 or IL-17RA blockers (bimekizumab, brodalumab, ixekizumab, secukinumab) may cause a progression of MF in case of an overlap or a misdiagnosis of the mentioned autoimmune disease. Based on the literature, we have also described the beneficial effects of IL-12 on MF, therefore the agents blocking both IL-12/IL-23 pathway (ustekinumab) should be avoided in patients, who have a suspicion or a diagnosed MF. Lastly, the overall contribution of TNF-α to creating cell mediated cytotoxic Th1 microenvironment seems to outweigh the negative effects of TNF-a on the lymphoma, which was reported. TNF-α-inhibitors and TNF-α-receptor inhibitors (e.g. adalimumab, etanercept, infliximab) should not be used if CTCL cannot be ruled out. Before introducing the biological treatment, in case of advanced to severe psoriasis, we recommend performing a biopsy from the skin lesion followed up by a close pathological examination to exclude the possibility of MF misdiagnosis. We believe that further research is necessary to clarify the role of IL-17, IL-23 and TNF-α in MF and new immunosuppressive drugs should be used carefully in order not to aggravate the plausible lymphoma.

## Conflict of interest

The authors declare no conflict of interest.

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