Title

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Journal

Dermatology and Therapy, 14(1)

ISSN

2193-8210

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Publication Date

2024

DOI

10.1007/s13555-023-01074-z

Peer reviewed

Dermatol Ther (Heidelb) (2024) 14:15–30
https://doi.org/10.1007/s13555-023-01074-z

REVIEW

Risk of Cutaneous T Cell Lymphoma with Psoriasis Biologic Therapies

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Received: October 6, 2023 / Accepted: November 13, 2023 / Published online: December 3, 2023

ABSTRACT

Background: The risk of developing cutaneous T cell lymphoma (CTCL) in patients using psoriasis biologics has not been well characterized. The goals of this review were to investigate the incidence of CTCL in patients with psoriasis receiving biologic therapy in clinical trials and psoriasis registries, and to review cases of CTCL and biologic use reported in scientific publications.
Methods: The US National Library of Medicine clinical trials database (clinicaltrials.gov) was queried to identify phase 3 and 4 clinical trials of the 12 biologic agents currently FDA approved for psoriatic disease. The incidence of CTCL in these trials was examined and summarized. To examine the incidence of CTCL in psoriasis registries, a Medline search was conducted. Finally, we performed a systematic review of CTCL cases reported in the literature.
Results: Only two cases of CTCL were reported in 35,801 subjects with psoriasis receiving a biologic agent in the active arm of 108 psoriasis phase 3 clinical trials. One of these CTCL cases was determined by the investigator to be CTCL misdiagnosed as psoriasis prior to randomization. No cases of CTCL were reported in 5440 subjects with psoriasis in 34 phase 4 clinical trials. Only one case of CTCL was identified in 34,111 registry subjects. In the literature, tumor necrosis factor (TNF) inhibitors had the highest number of reported cases of CTCL (34 cases), followed by interleukin (IL)-17 inhibitors (7 cases), and IL-12/23 inhibitors (6 cases). No cases of CTCL were found to be reported with IL-23 inhibitors.
Conclusion: Our findings indicate that the development of CTCL is rare in the setting of psoriasis biologic use. Of the limited number of cases of CTCL found, most were in the setting of TNF inhibitor use and no cases of CTCL were reported in the setting of IL-23 inhibitor use.

Keywords: Biologic; Cutaneous T cell lymphoma; CTCL; Interleukin-17 inhibitor;

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13555-023-01074-z.

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Interleukin-23 inhibitor; Interleukin-12/23 inhibitor; Mycosis fungoides; Malignancy; Psoriasis; TNF inhibitor

Key Summary Points

CTCL risk in the setting of biologic therapy in the management of psoriasis has not been well characterized.
In clinical trials, the incidence of CTCL was not significantly increased with the use of biologic therapy relative to placebo.
In psoriasis registries, only a single case of CTCL has been reported.
Of the CTCL cases reported in the literature, most were in the setting of TNF inhibitor use.
No cases of CTCL were reported with the use of IL-23 inhibitors.

INTRODUCTION

Psoriasis is a common, multisystem inflammatory disease characterized by erythematous, scaling patches, and plaques. Psoriasis affects roughly 125 million people worldwide (3% prevalence) and is associated with comorbidities such as psoriatic arthritis, cardiovascular disease, diabetes mellitus, and obesity [1, 2]. The underlying pathogenesis involves dysregulated cutaneous immunity with dysfunction of T1 and T17 cells, dendritic cells, keratinocytes, fibroblasts, and macrophages. This results in keratinocyte hyperproliferation and the production of proinflammatory cytokines such as interleukin (IL)-17, IL-23, tumor necrosis factor-alpha (TNFα), and interferon-gamma (IFNγ) [1, 3, 4].

Our improved understanding of the inflammatory molecular pathways involved in psoriasis has led to the development and US Food and Drug Administration (FDA) approval of multiple biologic therapies. These therapies target the cytokine-mediated pathogenesis of psoriasis and are approved for the treatment of moderate-to-severe psoriasis [5]. The main classes of biologics include TNFα inhibitors, IL-17 inhibitors, IL-23 inhibitors, and IL-12/23 inhibitors.

An important consideration for using biologic agents is their safety profiles. The efficacy of a biologic agent in treating psoriasis must be weighed against potential adverse events [6]. Through clinical trials and post-marketing surveillance, multiple adverse events have been reported. Reported events include injection site reactions, infections, heart failure, and malignancy [7, 8]. The goal of this review is to focus on one particular type of malignancy, which is cutaneous T cell lymphoma (CTCL).

METHODS

Prior to initiating the study, a protocol outlying the study goals, search strategy, and plan for analysis was established. First, the US National Library of Medicine clinical trials database (clinicaltrials.gov) was queried to identify phase 3 and phase 4 clinical trials of the 12 biologic agents currently FDA approved for psoriatic disease. Incident cases of CTCL were recorded. Fisher's exact test was performed to elucidate differences in rates of CTCL between patients receiving biologic medication and patients receiving placebo. A p value less than 0.05 was considered statistically significant.

Next, publications involving psoriasis biologic registry studies were identified via a PubMed (MEDLINE) search. Search criteria included psoriasis AND registr* AND biologic* NOT (clinical trial NOT case series) AND (safety OR malignancy OR cancer OR CTCL OR mycosis fungoides) AND (*name of psoriasis registry). Psoriasis registries examined included Corrona/CorEvitas, BADBIR, BIOBADADERM, BioCAPTURE, PsoReg, PSOLAR, Child-Capture, Psocare, Psonet, DERMBIO, PsoRA, PsoBest, MPR, AMC Psoriasis Registry, Australasian Psoriasis Registry, Swedish National Psoriasis Registry, Swiss Dermatology Network of Targeted Therapies, PsoREP, PsoBioTeq, Clalit Health Service Database, PSODIT, PSOREAL, and SDNB.

The incidence of CTCL was analyzed. References were reviewed to identify potentially omitted studies.

Finally, a systematic review was performed by two individuals (M.S.D. and R.K.S.). This study was conducted in accordance with the Preferred Reporting Items for Systematic Review (PRISMA) guidelines (Supplementary Fig. 1). Articles involving psoriasis biologics and CTCL were identified in PubMed (MEDLINE) and Embase from inception through October 28, 2022 using a combination of terms: psoriasis AND (lymphoma OR mycosis fungoides OR cutaneous T-cell lymphoma OR non-Hodgkin T-cell lymphoma) AND ("tumor necrosis factors" OR "tumor necrosis factor*" OR "tumor necrosis factor alpha" OR guselkumab OR risankizumab OR tildrakizumab OR etanercept OR infliximab OR adalimumab OR golimumab OR certolizumab pegol OR brodalumab OR "anti-IL-17" OR secukinumab OR ixekizumab OR "anti-IL-23" OR ustekinumab OR "anti TNF alpha" OR "anti TNF"). Comprehensive review articles and references were reviewed to identify potentially omitted studies. The search was limited to publications in English and human participants.

Records were then screened by title and abstracts with duplicate records removed. Articles deemed relevant or potentially relevant were selected for full-text review. Disagreement between (M.S.D. and R.K.S.) were resolved through discussion and the resultant conclusions were unanimous. For the systematic review, studies were eligible if they were observational cohort studies, case series, or case reports with a full-text article or conference abstract available. Patients must have been treated with a biologic for psoriasis and a report of adverse events (e.g., CTCL, etc.) must have been included in the publication. We limited our systematic analysis to include all forms of CTCL. Studies that did not specify subtype of malignancy or, more specifically, subtype of lymphoma were excluded. We avoided including the same cases more than once (e.g., multiple articles referencing the same cases of CTCL). For quality assessment, two independent reviewers (R.K.S., M.S.D.) performed initial screening of studies. No filters or limits were utilized during the study selection process. Discrepancies in eligibility criteria were resolved by an additional reviewer (W.L.). Data abstraction was performed by M.S.D., and quality assessment was performed by two independent authors (K.G.E., J.Q.J.). All randomized controlled trials included were manually assessed by two independent authors (R.K.S., J.Q.J.) for risk of bias in six different domains. Bias assessment outcomes were compiled using the Cochrane Review Manager application.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Phase 3 and 4 Trials

Data from 116 phase 3 trials of psoriasis biologics were analyzed (Supplementary Table 1 and Supplementary Fig. 2). Out of 35,801 patients with psoriasis who received a psoriasis biologic in the active arm of a phase 3 trial, two were diagnosed with CTCL (Table 1). Out of the 4519 patients who received placebo, none were diagnosed with CTCL. The biologics used in the two cases of CTCL were secukinumab and ustekinumab. These two cases were diagnosed during weeks 0–12 of the study period when the patients were receiving the study drug. The patient treated with secukinumab received 300 mg subcutaneous loading doses weekly for five weeks (weeks 0, 1, 2, 3, 4) and then every four weeks until week 28 (weeks 8, 12, 16, 20, 24, 28) [9]. The CTCL case associated with ustekinumab was retrospectively determined by the investigator to have existed prior to the administration of the biologic, but had been incorrectly diagnosed as psoriasis [10]. The patient treated with ustekinumab received 90 mg subcutaneous doses at weeks 0, 4, and then every 12 weeks until week 52. Depending on PGA evaluation at week 12, this patient may have been given an

Table 1 Cases of CTCL reported in phase 3 clinical trials of psoriasis biologics

	Placebo-controlled trials		Biologic comparator trials[a]	
	# CTCL in active drug arm	# CTCL in placebo arm	# CTCL in active drug arm	# CTCL in active comparator arm
Certolizumab	0/361	0/100	0/332	0/170
Golimumab	–	–	–	–
Adalimumab	0/3991	0/195	–	–
Etanercept	0/2549	0/3	–	–
Infliximab	0/1626	0/45	0/653	0/215
TNFi total	0/8527	0/343	0/985	0/385
Guselkumab	0/1167	0/133	0/1533	0/1096
Risankizumab	0/931	0/838	0/822	0/362
Tildrakizumab	0/617	0/155	0/621	0/313
IL-23i total	0/2715	0/1126	0/2976	0/1771
Ixekizumab	0/2854	0/593	0/1774	0/990
Brodalumab	0/758	0/220	0/2475	0/1475
Secukinumab	1/8584	0/1382	0/1726	0/1355
IL-17i total	1/12,196	0/2195	0/5975	0/3820
Ustekinumab	0/1871	0/855	1/556	0/347
IL-12/23i total	0/1871	0/855	1/556	0/347
Total	1/25,309	0/4519	1/10,492	0/6323

[a]Comparator agents included the 12 biologic agents approved for psoriatic disease, other biologic agents not yet approved for psoriatic disease, biosimilars, apremilast, methotrexate, and fumaric acid esters

extra 90 mg dose at week 12, but it is unknown if this patient received the supplemental dose [11].

Fisher's exact test was performed to assess for any difference between the collective active drug group (all biologics combined) and placebo group. The test showed that there was no significant association between biologic administration and incidence of CTCL ($p > 0.05$).

Data from 34 phase 4 trials of psoriasis biologics were analyzed (Supplementary Table 2). Out of 5440 patients who received a biologic in these trials, 0 cases of CTCL were reported (Table 2).

Review of Psoriasis Registries

Initial search for psoriasis registry studies in the Medline database yielded 68 total articles. Of these articles, 37 were excluded on the basis of title and abstract, leading to the identification of 31 articles for full-text review. Ultimately, 11 publications investigating adverse events reported in registry studies were included after full text-review (Table 3). Safety data was reported on 34,111 patients. Only one case of CTCL (mycosis fungoides subtype) was reported. This case was reported in the PSOLAR Registry study [12]. This registry study included the following biologic medications: adalimumab, infliximab, etanercept, and ustekinumab.

Table 2 Cases of CTCL reported in phase 4 clinical trials of psoriasis biologics

Biologics in phase 4 trials	CTCL cases of total subjects
Certolizumab	0/0
Golimumab	0/0
Adalimumab	0/460
Etanercept	0/2344
Infliximab	0/31
TNFi total	0/2835
Guselkumab	0/0
Risankizumab	0/0
Tildrakizumab	0/0
IL-23i total	0/0
Ixekizumab	0/0
Brodalumab	0/105
Secukinumab	0/1809
IL-17i total	0/2058
Ustekinumab	0/547
IL-12/23i total	0/547
Total	0/5440

However, the identity of the specific biologic associated with this reported case of CTCL was not available and additional clinical details of this case were not reported.

Systematic Literature Review

The Medline and Embase search for reported cases of CTCL yielded 294 articles. Of these articles, 31 duplicates were excluded, and 263 publications were screened on the basis of title and abstract. Subsequently, 135 articles were excluded, leading to the identification of 126 articles for full-text review. Ultimately, 28 publications reporting CTCL cases in the setting of psoriasis biologic treatment were included after full text-review (Supplementary Fig. 1). In total, 38 cases of CTCL with 48 distinct biologic exposures were reported (Table 4). Eight patients had been treated with two or more biologics prior to CTCL diagnosis. Mycosis fungoides was specifically listed as the diagnosis in 28 of the cases. The average patient age was 53 years (21 male, 7 female, 10 unspecified gender). The most frequently reported overall CTCL stage at time of diagnosis was stage 1 (10/38). Five cases were diagnosed at stage 2, one case at stage 3, and seven cases at stage 4.

TNF inhibitors were used in the majority of the CTCL cases reported (34/38). Adalimumab was the biologic agent with the greatest number of CTCL cases reported (17). Other biologic exposures with reported CTCL cases include etanercept (11), secukinumab (6), ustekinumab (6), infliximab (6), ixekizumab (1), and an unspecified psoriasis biologic (1). No cases of CTCL were reported with IL-23 inhibitor use. The average duration with a biologic medication prior to CTCL diagnosis was 11 months. The five most frequent therapies utilized in the management of CTCL diagnosed in these patients were acitretin, narrow-band UVB, bexarotene, interferon alpha, and histone deacetylase inhibitors (e.g., romidepsin). Examples of other treatments used include total skin electron beam therapy (TSEBT), PUVA, methotrexate, prednisone, electrophoresis, and various other chemotherapeutic agents (e.g., doxorubicin).

Of the 38 cases reported from all sources, five patients died of their CTCL disease (Table 4). Each of these patients was diagnosed with CTCL after the administration of the biologic medication. In each of these cases, a TNF inhibitor was involved. One of the five patients had also received ustekinumab after a trial of a TNF inhibitor (adalimumab).

DISCUSSION

Psoriasis is a chronic, systemic inflammatory disease associated with comorbidities including psoriatic arthritis, heart failure, multiple sclerosis, mood disorders, and malignancy [13–15]. The greatest concern for malignancy in the setting of biologic use has been with the TNF inhibitor class of biologics. This concern may in

Table 3 CTCL cases identified in psoriasis biologic registries

Author	Year [reference]	Registry	Biologics	Patient number	CTCL cases
Burden	2012 [34]	BADBIR	ETC, ADM, UST	2193	0
Warren	2015 [35]	BADBIR	ETC, INX, ADM, UST	3523	0
Carretero	2015 [36]	BIOBADADERM	ETC, INX, ADM, UST	1030	0
Dauden	2020 [37]	BIOBADADERM	ETC, INX, ADM, UST, SEK	2845	0
Hernandez-Fernandez	2021 [38]	BIOBADADERM	ETC, INX, ADM, UST, SEK, IXK	9728	0
Ter Haar	2022 [39]	BioCAPTURE	ETC, INX, ADM, UST, SEK, IXK, BDL, CEZ, GLK, RSK, TDK	115	0
Fiorentino	2017 [12]	PSOLAR	ETC, INX, ADM, UST	12,090	1
Reich	2015 [40]	PsoBest	ETC, INX, ADM, UST	908	0
Foley	2022 [41]	Australian Psoriasis Registry	SEK	294	0
Garcia-Doval	2017 [42]	BIOBADADERM, Psocare, Clalit Health Service database	ETC, INX, ADM, UST	269	0
Garcia-Doval	2018 [43]	BADBIR, BIOBADADERM, Psocare, Clalit Health Service database	ETC, INX, ADM, UST	1116	0
Total				34,111	1

ADM adalimumab, *BDL* brodalumab, *CEZ* certolizumab, *ETC* etancercept, *GLK* guselkumab, *GOM* golimumab, *INX* infliximab, *IXK* ixekizumab, *SEK* secukinumab, *RSK* risankizumab, *TDK* tildrakizumab, *UST* ustekinumab

part be related to the observation of TNFα's activity against tumors in laboratory models [16]. TNFα is a predominant cytokine in the inflammatory cascade and was initially recognized for its ability to lyse tumors in vitro and in mouse models [16]. TNF appears to be critical in CD8 lymphocyte- and natural killer cell-mediated killing of tumor cells [17]. Introduction of TNFα has been shown to cause thrombosis and necrosis of blood vessels feeding neoplastic cells [18]. However, TNFα has shown both tumor-inhibiting and tumor-promoting effects [19].

The majority of the concern for malignancy now likely stems from clinical trial data, observational studies, and meta-analyses, which report an increased risk of some types of cancer, particularly systemic lymphoma in rheumatoid arthritis and nonmelanoma skin cancer in rheumatoid arthritis and psoriasis in the setting of TNF inhibitor use [17, 18, 20–23]. For example, a relatively small registry study in Sweden demonstrated an increase in lymphoma in patients with rheumatoid arthritis treated with TNF inhibitor therapies [24]. It is important to note, however, that results have varied and that other studies have not been able to confirm an increased risk malignancy in the setting of biologic therapy use (TNF inhibitors included) [8, 17, 21, 22]. Regarding systemic lymphoma specifically, multiple large registry- and population-based studies have not been able to demonstrate an increased risk in the setting of biologic use [19–22, 25–28].

The collective data on CTCL from phase 3 and 4 clinical trials, registry studies, and a systematic review of two biomedical literature

Table 4 Systematic review: CTCL cases

CTCL case [reference]	Age (sex)	Diagnosis (clinical stage at time of diagnosis)	Biologic duration (Months) prior to CTCL diagnosis	Patient disposition at time of publication	Treatment for CTCL	Prior non-biologic therapies
1 [44]	N/A (N/A)	Primary cutaneous anaplastic large cell lymphoma (N/A)	Adalimumab (120)	AWD	N/A	N/A
2 [45]	65 (N/A)	Folliculotropic mycosis fungoides (FMF) (N/A)	Adalimumab (N/A), secukinumab (N/A), ustekinumab (N/A)	AWD	BXT, INF, acitretin	Acitretin
3 [46]	79 (N/A)	MF (N/A)	Secukinumab (3)	AWD	TSEBT	Acitretin, MTX, apremilast, oral PUVA
4 [46]	71 (N/A)	MF (N/A)	Secukinumab (2)	AWD	IFN and extracorporeal photopheresis	NB-UVB, acitretin, MTX, prednisolone
5 [47]	52 (N/A)	MF (N/A)	Etanercept (N/A) and ixekizumab (9)	AWD	NB-UVB	N/A
6 [48]	52 (N/A)	MF (4)	Adalimumab (1.5)	AWD	CHOEP 4 cycles → brentuximab vedotin and TSEBT (18 Gy) → plan for bone marrow transplant	TCS
7 [49]	69 (N/A)	CTCL (N/A) (T3N3M0)	Adalimumab (1)	DOD (last follow-up at 7 months)	HDAC (romidepsin)	MTX, acitretin, MMF, prednisone
8 [49]	63 (N/A)	CTCL (N/A) (T3N3M1)	Adalimumab (1)	AWD	PUVA, methotrexate, gemcitabine, NB-UVB	NB-UVB

Table 4 continued

CTCL case [reference]	Age (sex)	Diagnosis (clinical stage at time of diagnosis)	Biologic duration (Months) prior to CTCL diagnosis	Patient disposition at time of publication	Treatment for CTCL	Prior non-biologic therapies
9 [49]	29 (N/A)	FMF (2b)	Adalimumab (N/A), ustekinumab (N/A)*	AWD	IFN, PUVA, BXT, HDAC, pralatexate, NM, TSEBT, FM, AHSCT	MTX
10 [49]	76 (N/A)	FMF (2b)	Etanercept (6)	DOD (last follow-up at 31 months)	MTX, GM, BXT	N/A
11 [49]	63 (M)	FMF (LCT) (2b)	Etanercept (2)	AWD	Unspecified radiation therapy, NB-UVB, acitretin, INF, BXT	MTX
12 [49]	21 (M)	FMF (1A)	Adalimumab (20)	AWD	NB-UVB, acitretin	N/A
13 [49]	58 (M)	FMF (4A2)	Adalimumab (4)	AWD @ 6 months	XRT, PUVA, HDAC, NM	N/A
14 [49]	49 (M)	MF (1B)	Adalimumab (24)	AWOD @ 20 months	CHOEP, HDAC, BM, PTX, MTX	N/A
15 [49]	27 (M)	Primary cutaneous aggressive epidermotropic cytotoxic T cell lymphoma (PCAEC-TCL) (N/A) (T3N0MX)	Adalimumab (N/A), ustekinumab (4)*	DOD (last follow-up at 13 months)	NBUVB, MTX, EPOCH, GM, HDAC, brentuximab	CSA, MTX
16 [49]	64 (M)	SS (4A)	Adalimumab (N/A), ustekinumab (24)*	AWD	ECP, BXT, IFN	N/A
17 [49]	40 (M)	SS (4A)	Adalimumab (N/A)	AWD	Acitretin, INF	MTX, CSA
18 [50]	43 (M)	CTCL (N/A)	Etanercept (3), secukinumab (1)	AWD	Chemotherapy	TCS, MTX, CSA, UV therapy (unspecified)

Table 4 continued

CTCL case [reference]	Age (sex)	Diagnosis (clinical stage at time of diagnosis)	Biologic duration (Months) prior to CTCL diagnosis	Patient disposition at time of publication	Treatment for CTCL	Prior non-biologic therapies
19 [51]	35 (F)	PCAEC-TCL (N/A)	Adalimumab (2)	DOD	N/A	Prednisone
20 [52]	60 (F)	MF (2b)	Infliximab (1)	AWD @ 12 months	Topical corticosteroids and UV therapy, etoposide 50 mg/day po	TCS, etretinate, UV therapy (unspecified), CSA
21 [53]	36 (M)	Cutaneous pleomorphic T cell lymphoma (4a)	Etanercept (3)	DOD @ approx. 13 months	Pegylated liposomal doxorubicin Caelyx® at a dose of 40 mg/m^2, administered intravenously once every 4 weeks	Acitretin, MTX
22 [54]	47 (M)	MF (N/A)	Etanercept (3)	AWD @ 24 months	NB-UVB, interferon alfa-2b, and bexarotene therapy	MTX, NB-UVB, PUVA,
23 [55]	79 (F)	MF (1b)	Secukinumab (3)	N/A	N/A	UV therapy (unspecified), 3 "systemics" (unspecified)
24 [55]	71 (M)	MF (3a)	Secukinumab (2)	N/A	N/A	UV therapy (unspecified), 3 "systemics" (unspecified)
25 [56]	47 (M)	Cutaneous CD30$^+$ T cell lymphoma (N/A)	Infliximab (2)	AWOD @ 5 months	N/A	PUVA, acitretin, MTX, CSA, MMF
26 [57]	36 (F)	MF (N/A)	Ustekinumab (N/A)	N/A	Acitretin, methotrexate, phototherapy, bexarotene	Acitretin, MTX, UV therapy (unspecified), bexarotene
27 [57]	64 (M)	MF (N/A)	Ustekinumab (< 1)	N/A	N/A	Acitretin, MTX, UV therapy (unspecified)

Table 4 continued

CTCL case [reference]	Age (sex)	Diagnosis (clinical stage at time of diagnosis)	Biologic duration (Months) prior to CTCL diagnosis	Patient disposition at time of publication	Treatment for CTCL	Prior non-biologic therapies
28 [58]	43 (F)	MF (N/A)	Etanercept (2)	N/A	CHOEP-21	N/A
29 [59]	43 (M)	MF (N/A)	Adalimumab (12)	N/A	Acitretin 25 mg po daily and NB-UVB phototherapy was initiated	N/A
30 [60]	70 (M)	FMF → (N/A)	Etanercept (36)	AWOD→pt developed nodular sclerosing Hodgkin lymphoma	6 cycles of ABVD	NB-UVB, TCS
31 [61]	51 (M)	MF (2b)	Etanercept (24), infliximab (52)	AWOD	MTX 15 mg per week led to complete resolution of the tumor MF in partial remission after 12 months' follow-up	N/A
32 [61]	71 (M)	MF (1A)	Infliximab (2)	AWOD	CSA and MTX	Acitretin, CSA, MTX
33 [61]	67 (M)	MF (1B)	Infliximab (3)	AWD	N/A	CS
34 [61]	73 (M)	MF (1A)	Adalimumab (4)	AWOD	MTX	NB-UVB, CSA
35 [61]	27 (F)	MF (1B)	Etanercept (12)	AWOD	PUVA and acitretin	MTX
36 [61]	68 (M)	MF (1B)	Adalimumab (15)	N/A	CSA, MTX, PUVA	MTX, CSA
37 [61]	73 (M)	MF (1B)	Infliximab (5)	AWOD	Acitretin 25 QD	PUVA, acitretin, CSA

Table 4 continued

CTCL case [reference]	Age (sex)	Diagnosis (clinical stage at time of diagnosis)	Biologic duration (Months) prior to CTCL diagnosis	Patient disposition at time of publication	Treatment for CTCL	Prior non-biologic therapies
38 [61]	44 (F)	MF (1A)	Adalimumab (12), etanercept (12)	AWD	N/A	N/A

ABVD doxorubicin (brand name Adriamycin), bleomycin, vinblastine, and dacarbazine, *AWD* alive with *CTCL* disease, *AWOD* alive without CTCL disease, *AHSCT* allogeneic hematopoietic stem cell transplant, *BXT* bexarotene, *CHOEP* cyclophosphamide, liposomal doxorubicin, vincristine, etoposide, and prednisone, *CSA* cyclosporine, *DOD* died of CTCL disease, *ECP* electrophoresis, *EPOCH* etoposide, prednisone, vincristine, and doxorubicin, *FM* fludarabine/melphalan, *GM* gemcitabine, *HDAC* histone deacetylase inhibitor, *IFN* interferon alpha, *MTX* methotrexate, *MMF* mycofenolate mophetil, *NB-UVB* narrowband ultraviolet B therapy, *NM* nitrogen mustard, *PUVA* psoralen and UVA, *TCS* topical corticosteroids, *TSEBT* total skin electron beam therapy

*Information regarding the timing of biologic treatment in relation to CTCL diagnosis is unavailable

databases provide additional insight into the risk of CTCL in the setting of biologic therapy use for psoriasis. Our study suggests that the risk of incident CTCL in the setting of biologic use is low. Only two cases of CTCL, one of which may have been CTCL misdiagnosed as psoriasis, were reported in phase 3 and phase 4 clinical trials and only one case of CTCL was reported in a psoriasis biologic registry publication. This is significant as over 25,000 patients in the phase 3 clinical trials and over 5000 patients in the phase 4 clinical trials received a biologic.

Nonetheless, 38 cases of CTCL from case reports and case series were found in our systematic review. Eight of these cases were associated with exposure to two or more biologics. Most of the cases of CTCL occurred in the setting of TNF inhibitor use (34/38). The single agent with the highest number of cases was adalimumab with 17 reported. It is important to note that adalimumab, infliximab, and etanercept were approved for treatment of plaque psoriasis prior to biologics in the IL-17, IL-12/23, and IL-23 inhibitor classes. Therefore, we have had more time to observe patient outcomes with the TNF inhibitor class.

A total of seven cases of CTCL were reported with use of IL-17 inhibitors (secukinumab, ixekizumab) and six cases were reported with IL-12/23 inhibitor (ustekinumab) use. Interestingly, no cases of CTCL were reported with IL-23 inhibitor use in patients with plaque psoriasis. Other studies on IL-23 safety data are consistent with our findings [29–31]

Several obstacles are present for establishing the true malignancy risk for biologics and other therapies. First, analyses of malignancy risk will often reference SIR, comparing the risk of malignancy in a psoriasis cohort compared to a reference cohort. These unfortunately do not differentiate between malignancy risk associated with biologic therapy and the malignancy risk associated with psoriasis. This is particularly pertinent as psoriasis has been associated with an increased risk of malignancy when compared with the general population in studies of large healthcare databases [32, 33].

Another specific challenge is the assessment of cancer risk in patients with a history of cancer. Patients with cancer are often excluded from participating in clinical trials because of concern about an intervention potentially causing a new malignancy, instigating a recurrence, or exacerbating an existing malignancy. As a result, clinicians treating patients with cancer and concurrent psoriasis are often

unable to make confident, evidence-based recommendations for these patients.

CONCLUSION

Overall, it is important to recognize that biologic agents are associated with various adverse effects, some of which are potentially serious. However, it is also important to assess these risks in the context of the potential benefits of biologics, as well as in the context of potential comorbidities associated with uncontrolled disease. This study demonstrates that the risk of CTCL is extremely low in the setting of biologic use for psoriasis, with no CTCL yet reported with IL-23 inhibitor use. When considering a biologic, clinicians need to factor in the extent of psoriatic disease and all of the associated risks for each individual patient.

Limitations

This analysis is limited by the relatively short exposure to trial drug and placebo per clinical trial protocols. As phase 3 and 4 studies are limited in duration, certain outcomes like CTCL may take a longer period of time to develop. Next, registries oftentimes only include patients with psoriasis and do not include a placebo group for comparison. Reporting bias may also affect the results.

Additionally, we found eight cases in which patients were exposed to multiple biologic agents (Table 4). In three of these cases, information regarding the timing of the biologic treatments in relation to the diagnosis of CTCL was unavailable. These cases are marked with an asterisk in Table 4.

Future Directions

While this study focused on incident CTCL with biologic use, clinicians may face the question of whether to use biologics in patients with psoriasis and a known diagnosis of CTCL. A similar concern may exist when treating patients with malignancy in remission. Therefore, it would be useful to identify studies in the future with patients who had CTCL prior to administration of a biologic to see if biologics therapy could be safely used in this specific population.

ACKNOWLEDGEMENTS

Medical Writing/Editorial Assistance No medical writing/editorial assistance was received for this study.

Author Contributions. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. All named authors contributed to the final paper as follows: Mitchell Davis and Wilson Liao contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mitchell Davis, Riley Spencer, Chandler Johnson, Kareem Elhage, and Joy Jin. The first draft of the manuscript was written by Mitchell Davis and all authors participated in manuscript edits and revision. All authors read and approved the final manuscript.

Funding. No funding or sponsorship was received for this study or publication of this article.

Data Availability. The datasets generated during and/or analyzed during the current study are available in the clinicaltrials.gov repository, https://clinicaltrials.gov.

Declarations

Conflict of Interest. Tina Bhutani is a principal investigator for trials sponsored by Abbvie, Castle, CorEvitas, Dermavant, Galderma, Mindera, and Pfizer. She has served as an advisor for Abbvie, Arcutis, Boehringer-Ingelheim, Bristol Myers Squibb, Janssen, Leo, Lilly, Novartis, Pfizer, Sun, and UCB. Wilson Liao has received research grant funding from Abbvie, Amgen, Janssen, Leo, Novartis, Pfizer,

Regeneron, and TRex Bio. Mitchell Davis, Riley Spencer, Kareem Elhage, Chandler Johnson, and Marwa Hakimi declare that they have no competing interests. Joy Jin has received research grant funding from the National Psoriasis Foundation and institutional funding from the University of California, San Francisco. Tina Bhutani has received research grant funding from Novartis and Regeneron. Wilson Liao has received research grant funding from Abbvie, Amgen, Janssen, Leo, Novartis, Pfizer, Regeneron, and TRex Bio. No funding sources are relevant to this manuscript Mitchell Davis, Riley Spencer, Kareem Elhage, Chandler Johnson, and Marwa Hakimi have nothing to disclose.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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