Psoriasis: Targets and Therapy

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ORIGINAL RESEARCH

Baseline Pathological Liver Function Tests in Patients With Psoriasis Support the Indication for Systemic Therapy Rather Than Being a Reason Against It: A Real-World Analysis

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Purpose: Modern systemic therapies offer a high probability of significant improvement for psoriasis. However, elevated liver function tests (LFTs) may cause physicians to be reluctant to initiate systemic treatment. Especially considering the already increased risk of liver disease in patients with psoriasis, clinicians are often concerned about potential further liver damage caused by systemic therapies. The aim of this study was to provide real-world evidence to address this issue.

Patients and methods: This study retrospectively analyzed the treatment courses of N = 278 patients with psoriasis who received systemic anti-psoriatic therapy with secukinumab, ixekizumab, adalimumab, or apremilast in clinical routine. The cohort was divided into two subgroups based on normal or elevated LFTs prior to the start of therapy. AST, ALT, and GGT levels as well as Fibrosis-4 score (FIB-4) were measured at baseline, after 3 months, and after 6 months of therapy.

Results: The subgroup of patients with elevated LFTs had a higher mean PASI (Psoriasis Area and Severity Index), were more likely to be male, and had a higher prevalence of metabolic syndrome comorbidities compared to the subgroup with normal LFTs. During the follow-up period, there were no significant changes in LFTs and FIB-4 for the subgroup with normal LFTs at baseline. In the group of patients with initially elevated LFTs, all LFTs decreased significantly over time, whereas FIB-4 scores demonstrated no significant change. Drug survival, discontinuation rates, and PASI-75 response did not significantly differ between subgroups.

Conclusion: This study provides real world evidence that systemic therapy with secukinumab, ixekizumab, adalimumab, or apremilast does not present a general risk, but rather an opportunity for patients with psoriasis with elevated LFTs at baseline.

Keywords: biologics, hepatic dysfunction, real world data, psoriasis, safety

Introduction

Psoriasis is a chronic systemic inflammatory disorder with typical cutaneous manifestations and one of the most frequent dermatological diseases worldwide.[1–4] Next to other known comorbidities, patients with psoriasis have a higher risk of liver disorders such as metabolic dysfunction-associated steatotic liver disease (MASLD, former known as non-alcoholic fatty liver disease (NAFLD)), drug-induced hepatitis and alcoholic liver disease (ALD) than the general population.[5,6] The increased prevalence of MASLD in psoriasis patients is likely related to the high rate of obesity and metabolic syndrome within this patient population.[7,8] Chronic inflammation, mediated by proinflammatory adipokines and skin-derived cytokines, may contribute to steatotic liver disease development by increasing insulin resistance, which in turn enhances hepatic lipid accumulation.[9,10] MASLD and ALD encompass a spectrum of hepatic disorders ranging from steatosis to steatohepatitis, fibrosis and cirrhosis.[11,12] Steatosis is often accompanied by inflammation characterized by

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infiltration and activation of immune cells in the liver also known as metabolic dysfunction-associated steatohepatitis (MASH, former known as non-alcoholic steatohepatitis (NASH)).[6] Persistent activation of immune cells is thought to enhance pro-fibrogenic signaling in hepatic stellate cells leading to fibrosis, and potentially cirrhosis.[12] The increased risk of MASLD and other liver disorders is an important challenge in the treatment of patients with psoriasis as it both impedes the use of potentially hepatotoxic anti-psoriatic systemic therapies such as methotrexate (MTX) and necessitates more careful monitoring of the patients.[13]

In the past 15 years, breakthroughs in the understanding of the pathogenesis of psoriasis have been translated into highly effective targeted therapies. Tumor-necrosis factor (TNF)-α inhibitors (TNFi) are considered the first-generation biologics and have been broadly used for therapy of psoriasis and psoriatic arthritis (PsA) over the last two decades. The substance class is considered safe, however, TNFi have been associated with elevated liver enzymes, drug-induced liver injury, immuno-mediated liver injury (autoimmune hepatitis) and reactivation of hepatitis B virus (HBV) infection.[14–16] In a single RCT of the TNFi etanercept in the treatment of moderate-to-severe alcoholic hepatitis, higher mortality and serious infection rates at six months were detected in the etanercept versus placebo group, giving rise to the recommendation to avoid etanercept and other TNFi in patients with psoriasis with moderate-to-severe ALD.[17,18]

The first biologic to be approved for plaque psoriasis after the TNFis was ustekinumab, a monoclonal antibody directed against interleukin (IL)-12 and IL-23. The clinical efficacy of ustekinumab and the further clarification of its mechanism of action highlighted the crucial role of IL-23 in shaping the Th17 response, which builds the basis for development of drugs targeting the IL-23-exclusive subunit p19 (tildrakizumab, guselkumab, risankizumab). In addition, IL-17 was shown to be the main effector cytokine in psoriatic inflammation. So far, four human monoclonal antibodies targeting IL-17 are available (secukinumab, ixekizumab, brodalumab, and bimekizumab).

The newer biologics targeting IL-(12)/23 and 17, as well as apremilast, a licensed oral phosphodiesterase (PDE)-4 inhibitor, have an excellent safety profile and are considered safe concerning adverse liver effects.[19–22] Potentially, IL-17 blockers could even have positive effects on the liver, as accumulating evidence points towards IL-17 and Th17 cells playing a critical role in different liver diseases, including chronic viral hepatitis, autoimmune liver diseases, ALD, and hepatocellular carcinoma.[23–25]

Regulatory T cells (Tregs) play an important role in regulating inflammatory processes in MASH and because Th17 cells functionally oppose Treg-mediated responses, the role of Th17 was investigated using a MASLD mouse model. Th17 cells and IL-17 were shown to be associated with hepatic steatosis and proinflammatory response in MASLD and to promote the transition from simple steatosis to steatohepatitis.[26] These results imply that strategies designed to alter the Th17/Treg balance and/or to interfere with Th17 migration or differentiation in the liver should be explored in order to prevent progression to advanced liver diseases.[25,26] Thus, it might be worthwhile to take a closer look at the effect of anti-psoriatic treatment with IL-17 blocking agents on patients' liver function.

Cyclic adenosine monophosphate (cAMP) is a key second messenger molecule that regulates various cellular functions in the liver including lipid metabolism, inflammation, cell differentiation and injury by affecting gene/protein expression and function. The elevation of cAMP was shown to decrease fibroblast proliferation and impede extracellular matrix (ECM) protein synthesis leading to fibrosis.[27] PDE enzymes are suggested to play a major role in fibrogenesis of the liver as they degrade cAMP.[28] Thus, the use of PDE inhibitors is becoming relevant in the treatment and management of liver diseases.[12] Up to now, PDE inhibitors have not undergone rigorous clinical trials, nor have they been approved for liver diseases, but the PDE4-inhibitor apremilast is in use for the treatment of plaque psoriasis, PsA, and Behçet's disease.[21,29]

Despite the fact that the newer cytokine blockers, as well as apremilast are considered safe with regard to adverse liver effects, there is often restraint in initiating biologic therapies in patients with elevated liver function tests (LFTs) and/or known hepatic disease due to fear of worsening of the liver condition in dermatological practice.[19,20,30] Furthermore, conventional systemic therapies that have the potential to be hepatotoxic, such as MTX, are frequently prescribed prior to the costly administration of modern systemic therapies. Consequently, LFTs of these patients might be particularly elevated at the time of transition to modern therapy.[31] Thus, modern and effective anti-psoriatic therapies are sometimes withheld in patients with pre-existing hepatic diseases.

The aim of our study was to provide real-world evidence assessing the potential liver toxicity of systemic treatment in patients with psoriasis. To this end, we analyzed data of patients with psoriasis with normal and elevated LFTs before and under therapy with the IL-17A-blockers secukinumab and ixekizumab, the TNFi adalimumab, and the PDE-4 inhibitor apremilast.

Methods

We conducted a retrospective, observational study of consecutive patients who initiated treatment with secukinumab, ixekizumab, adalimumab, or apremilast at the Department of Dermatology, Venereology, and Allergology, University Hospital Essen, between June 2015 and April 2019. All patients analyzed had moderate-to-severe psoriasis according to the German S3 guideline definitions at that time.[32]

The study was approved by the Ethics committee of the Medical Faculty of the University of Duisburg-Essen (IRB protocol number 19–8684-BO) and followed the principles stated in the Declaration of Helsinki. Patients aged <18 years or whose clinical history lacked valid data (eg missing LFTs or PASI at more than one time point) were excluded. The baseline data recorded included patients' age and sex, presence of PsA, information on common comorbidities, previous liver disease, alcohol consumption, and anti-psoriatic as well as concomitant medication. The diagnosis of MASH was listed according to the treating physician's assessment. Objective as well as subjective scores to grade severity of psoriasis (PASI) and Dermatology Life Quality Index (DLQI), the results of blood samples especially including LFTs in terms of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyl transpeptidase (GGT) were recorded every three months for a period of up to six months after the start of therapy.[33,34] Subgroups were created based on whether AST, ALT, or GGT exceeded the laboratory reference value of 35 U/L in patients' blood at treatment initiation (= defined as "elevated LFTs" throughout the manuscript). To further investigate the extent of liver fibrosis, the Fibrosis-4 (FIB-4) score was calculated in the following way: age (years) × AST (U/L) / platelets (10^9/l) × ALT (U/L)$^{1/2}$).[35] A FIB-4 of less than 1.3 indicates a greater than 90% certainty that there is no significant liver fibrosis.[35,36] Patients with a FIB-4 between 1.3 and 2.67 are considered to have an intermediate risk of advanced liver fibrosis, while patients with a FIB-4 of greater than 2.67 are considered to have a high risk of severe liver fibrosis.[36] The FIB-4, with a cut-off greater than 2.67, has 70.7% sensitivity and 78.9% specificity for predicting severe liver fibrosis.[37]

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics (Statistical Package for the Social Sciences, IBM Inc., Chicago, Illinois, version 27). Variables were assessed for normal distribution using the Kolmogorov–Smirnov test. As the Kolmogorov–Smirnov test indicated that data were not normally distributed, non-parametric tests were used. To detect significant differences in patient characteristics between the subgroups, the Chi-square test was used to analyze categorical data while a Mann–Whitney *U*-test was used to evaluate continuous variables. The Friedman test was used to assess whether there were significant changes in LFT values during the follow-up period. Furthermore, a Bonferroni-corrected post-hoc analysis was conducted to quantify the difference in laboratory symptoms between the baseline and six-month follow-up for the different drugs individually, thereby affording the possibility of comparison between drugs. The Log rank test was used to evaluate differences in drug survival between the subgroups. Drug survival time was defined as the duration from therapy initiation to treatment discontinuation for any reason. To identify the drug with the highest PASI-75 response rate within each subgroup based on elevated or non-elevated LFTs at baseline at three and six months, the chi square test was used. The Chi-square test was also employed to ascertain whether there are differences in the PASI-75 response rate of the same drug classes between the subgroups, after three and six months of therapy and odds ratios were calculated. The alpha level was set at 0.05 for all analyses. Figures were created using Microsoft PowerPoint (Microsoft, Redmond, Washington, US, version 2306) and BioRender (Science Suite Inc., Toronto, Ontario, Canada).

Results

Baseline Characteristics

Altogether, N = 276 psoriasis patients (N = 138 male (55.8%)) were included in the analysis. The mean age was 49 years (range 18–82 years), with a mean PASI of 13.2 (SD = 10.6) and a mean DLQI of 13.7 (SD = 8.4) at the start of therapy.

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A comorbid PsA was present in 42.5% (N = 117) of the patients. At baseline, the most prevalent comorbidities were obesity (36.5%), nicotine abuse (35.5%), and arterial hypertension (35.0%). In addition, 7.2% of the patients had alcohol abuse, 6.5% MASH, and 0.3% ALD.

Slightly more than half of the patients were treated with an IL-17A blocker, thereof 31.8% (N = 88) with secukinumab and 21.3% (N = 59) with ixekizumab. More than one fourth of the patients included (27.5%, N = 76) received a systemic therapy with the TNFi adalimumab and the remainder of the investigated cohort was under therapy with the PDE4-inhibitor apremilast (N = 53, 19.2%). Co-medication with low-dose methotrexate (MTX) was used in 10.8% (N = 30) of the patients.

A total of N = 138 patients (50.0%) did not have elevated LFTs at baseline, while N = 138 patients (50.0%) did. Within the subgroup of patients with elevated LFTs at baseline, 28.2% of patients (N = 39) exhibited an isolated increase in GGT, while 72.8% of patients (N = 99) had elevated transaminases. The subgroups based on elevated or non-elevated LFTs at baseline differed significantly in some characteristics. There were more male patients in the group with elevated LFTs at baseline (63.8% vs 47.8%, $Chi^2 = 7.11$, $p = 0.008$) and the mean PASI was higher (14.8 vs 11.6, $r = 0.152$, $p = 0.013$). In addition, patients with elevated LFTs at baseline were more likely to be obese (47.4% vs 23.9%, $Chi^2 = 13.11$, $p < 0.001$) and to suffer from arterial hypertension (45.7% vs 24.4%, $Chi^2 = 8.77$, $p = 0.003$), diabetes mellitus (24.0% vs 8.0%, $Chi^2 = 9.71$, $p = 0.002$), MASH (13.7% vs 1.3%, $Chi^2 = 13.23$, $p < 0.001$), or alcohol abuse (7.2% vs 0%, $Chi^2 = 8.0$, $p < 0.001$), compared to those without elevated LFTs. Furthermore, the median FIB-4 was found to be significantly increased in the elevated LFTs subgroup in comparison to the subgroup with normal LFTs at baseline (1.13 vs 0.84, $r = 0.130$, $p = 0.027$). Table 1 summarizes the baseline characteristics (Table 1).

Table 1 Patient Characteristics at Baseline

Total	All Patients N (%)	Patients without Elevated LFTs at Baseline N (%)	Patients with Elevated LFTs at Baseline N (%)
	276 (100.0)	**138 (100.0)**	**138 (100.0)**
Mean age, years (range)	49 (18–82)	48 (18–82)	50 (22–79)
Sex			
Female	122 (44.2)	72 (52.2)	50 (36.2)
Male	154 (55.8)	66 (47.8)	88 (63.8)
Psoriatic Arthritis			
Yes	117 (42.5)	61 (44.5)	56 (40.6)
No	159 (57.5)	76 (55.5)	83 (59.4)
Comorbidities			
Arterial hypertension	97 (35.1)	33 (23.9)	64 (46.3)
Nicotine abuse	98 (35.5)	45 (32.6)	53 (38.4)
Obesity	101 (36.5)	32 (23.1)	69 (50.0)
Diabetes mellitus	45 (16.3)	11 (7.9)	34 (24.6)
Alcohol abuse	20 (7.2)	0 (0.0)	20 (14.4)
MASH	18 (6.5)	1 (0.7)	17 (12.3)
ALD	1 (0.3)	0 (0)	1 (0.7)

(*Continued*)

Table 1 (Continued).

Total	All Patients N (%)	Patients without Elevated LFTs at Baseline N (%)	Patients with Elevated LFTs at Baseline N (%)
	276 (100.0)	**138 (100.0)**	**138 (100.0)**
Mean PASI (SD)	13.2 (10.6)	11.6 (9.9)	14.8 (11.0)
Mean DLQI (SD)	13.7 (8.4)	13.6 (8.5)	13.8 (8.4)
Medication			
Adalimumab	76 (27.5)	43 (31.1)	33 (23.9)
Secukinumab	88 (31.8)	38 (27.6)	50 (36.2)
Ixekizumab	59 (21.3)	34 (24.6)	25 (18.1)
Apremilast	53 (19.2)	23 (16.7)	30 (21.8)
Comedication with methotrexate			
No	246 (89.2)	119 (86.2)	127 (92.0)
Yes	30 (10.8)	19 (13.8)	11 (8.0)
FIB-4			
Mean (SD)	0.98 (0.89)	0.84 (0.45)	1.13 (1.16)
< 1.3	233 (84.4)	123 (89.1)	110 (79.7)
1.3–2.67	35 (12.7)	15 (10.9)	20 (14.5)
> 2.67	8 (2.9)	0	8 (5.8)

Notes: Baseline characteristics.
Abbreviations: N, number; LFTs, liver function tests; SD, standard deviation; MASH, metabolic dysfunction-associated steatohepatitis; ALD, alcoholic liver disease; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; FIB-4, Fibrosis-4 score for Liver Fibrosis.

Analyses of LFTs and FIB-4 Index Courses

In the subgroup of patients without elevated levels of AST, ALT, or GGT at baseline, there were no statistically significant changes in LFTs from baseline to the end of follow-up at 6 months. The same was true in this subgroup when different drug classes were assessed individually.

A total of N = 28 patients within this subgroup of N = 138 patients (20.2%) showed discrete elevations in LFTs of less than 3 x above the upper limit of normal: N = 6 patients (4.3%) had an increase in AST, sixteen patients (11.6%) exhibited an increase in ALT, and N = 6 patients (4.3%) demonstrated an increase in GGT after three months. After six months, N = 4 patients (2.8%) showed an increase in AST, N = 14 patients (10.1%) had an increase in ALT, and N = 9 patients (6.5%) in GGT. A parallel increase in bilirubin was not observed in any of the patients. The analysis of the mean FIB-4 revealed no statistically significant changes within this subgroup over the follow-up period (mean FIB-4 after 6 months: 0.87, $Chi^2 = 0.80$, $p = 0.670$). At three months, 9.7% and at six months, 11.6% of patients analyzed in the subgroup of patients without elevated LFTs at baseline had a FIB-4 between 1.3 and 2.67, while all other patients had a FIB-4 below 1.3.

In the subgroup of patients with elevated LFTs at baseline, the FIB-4 also showed no significant change during the follow-up period (mean FIB-4 after 6 months: 1.13, $Chi^2 = 3.54$, $p = 0.170$). After three months, 20.3% of patients had a FIB-4 between 1.3 and 2.67, while 4.3% demonstrated a FIB-4 exceeding 2.67. After six months, 12.6% of the subgroup had a FIB-4 between 1.3 and 2.67, while 5.9% had a FIB-4 greater than 2.67.

In the subgroup of patients with elevated LFTs at baseline, there was a significant decrease in all analyzed liver parameters at follow-up. After 6 months of therapy, AST decreased from an initial median of 27.0 U/L to 24.0 U/L, ALT declined from 39.0 U/L to 34.0 U/L, and GGT dropped from 52.0 U/l to 44.0 U/L. A comparative analysis of the

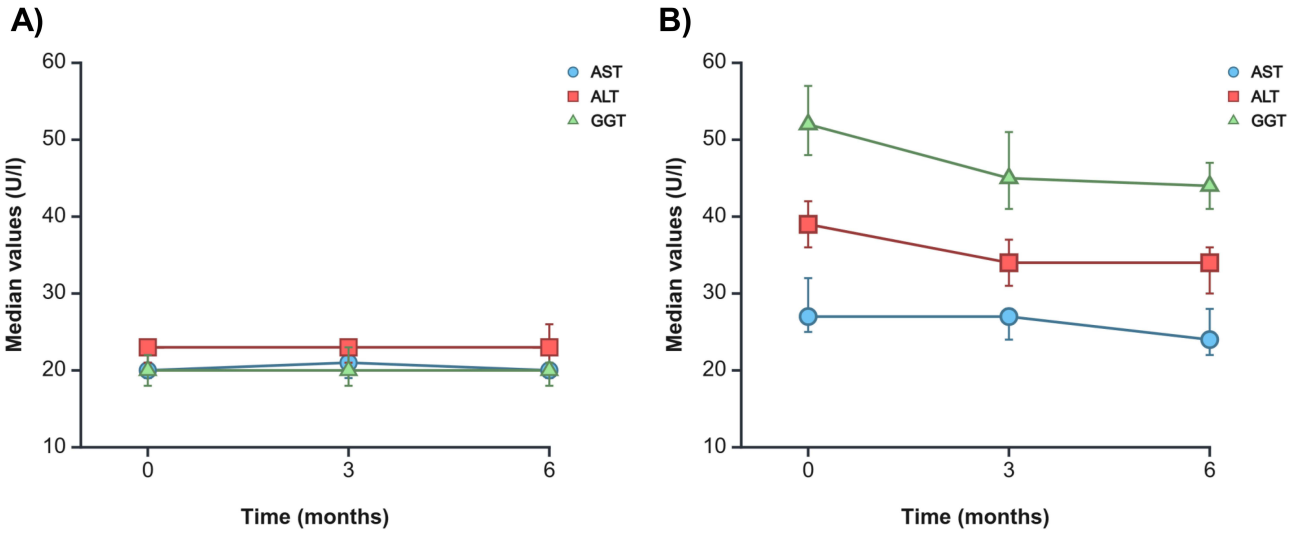

Figure 1 Development of LFTs. (**A**) Illustration of median values of LFTs with 95%-Confidence Interval during follow-up in patients without elevated LFTs at baseline. (**B**) Illustration of median values with 95%-confidence interval of LFTs during follow-up in patients with elevated LFTs at baseline.

different drug classes within this subgroup revealed that ixekizumab was most efficacious in reducing LFTs during the follow-up period, as evidenced by the largest effect size compared to the other drugs.

Figure 1 shows the values of AST, ALT, and GGT over the course of treatment for the subgroups with and without elevated LFTs at baseline, while Table 2 summarizes the statistical analyzes.

Table 2 Comparison of LFTs During Follow-up

	N	Median at Baseline (U/L) (range)	Median after 6 Months (U/L) (range)	Chi^2	p	r Baseline vs. 6 Months
Patients without elevated LFTs at baseline						
All patients						
AST	121	20.0 (10–34)	20.0 (10–52)	1.87	0.391	0.03
ALT	121	23.0 (6–34)	23.0 (9–64)	3.14	0.207	0.09
GGT	121	20.0 (7–34)	20.0 (7–104)	2.41	0.298	0.10
Medication						
Adalimumab						
AST	40	19.5 (10–34)	20.0 (10–34)	1.02	0.599	0.11
ALT	40	21.5 (8–33)	23.0 (9–64)	4.01	0.134	0.26
GGT	40	17.5 (9–34)	18.0 (7–56)	1.31	0.517	0.13
Secukinumab						
AST	34	20.0 (10–34)	21 (10–52)	3.82	0.147	0.04
ALT	34	21.0 (10–34)	23.0 (11–48)	3.98	0.136	0.08
GGT	34	21.5 (10–33)	20.5 (9–99)	0.95	0.621	0.16

(*Continued*)

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Table 2 (Continued).

	N	Median at Baseline (U/L) (range)	Median after 6 Months (U/L) (range)	Chi²	p	r Baseline vs. 6 Months
Ixekizumab						
AST	32	19.5 (10–34)	19.0 (11–32)	0.41	0.812	0.06
ALT	32	24.5 (6–33)	24.5 (9–57)	3.30	0.192	0.22
GGT	32	20.0 (7–34)	21.0 (9–104)	1.37	0.502	0.13
Apremilast						
AST	15	21.0 (12–34)	19.0 (13–32)	3.57	0.167	0.35
ALT	15	27.0 (14–34)	22.0 (10–34)	0.78	0.582	0.11
GGT	15	22.0 (12–33)	19.0 (14–56)	0.55	0.759	0.09
Patients with elevated LFTs at baseline						
All patients						
AST	118	27.0 (9–107)	24.0 (9–114)	11.56	0.003	0.31
ALT	118	39.0 (12–187)	34.0 (12–200)	16.43	<0.001	0.37
GGT	118	52.0 (15–310)	44.0 (10–282)	14.08	<0.001	0.31
Medication						
Adalimumab						
AST	28	32.0 (13–69)	23.0 (11–114)	5.25	0.072	0.43
ALT	28	40.5 (20–94)	34.0 (14–200)	3.87	0.144	0.36
GGT	28	45.0 (15–107)	39.5 (10–282)	3.78	0.151	0.35
Secukinumab						
AST	45	27.0 (9–107)	25.0 (11–92)	0.24	0.887	0.05
ALT	45	36.0 (12–187)	34.0 (11–117)	2.55	0.278	0.24
GGT	45	54.0 (22–256)	47.0 (12–191)	7.80	0.020	0.48
Ixekizumab						
AST	25	26.0 (17–71)	22.0 (9–45)	9.72	0.008	0.44
ALT	25	49.0 (21–99	32.0 (12–91)	15.08	<0.001	0.75
GGT	25	58 (15–126)	42.0 (14–100)	9.31	0.010	0.52
Apremilast						
AST	20	28.0 (11–64)	28.0 (9–76)	1.87	0.392	0.12
ALT	20	38.0 (19–148)	35.5 (15–84)	2.12	0.362	0.15
GGT	20	54.5 (21–310)	58.0 (23–214)	0.93	0.626	0.19

Notes: Comparison of LFTs during follow-up. Chi² and p-value of Friedman analysis. Bonferroni-corrected post-hoc analysis with indication of Cohen's r between baseline and after 6 months of treatment as effect size.

Abbreviations: N, number; U/L, units per litre; Chi², chi-square statistic; p, p-value of Friedman analysis; r, Cohen's r; LFTs, liver function tests; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transpeptidase.

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Analyses of Drug Survival, Reasons for Discontinuing Treatment, and Treatment Efficacy

During the follow-up period, N = 37 out of N = 276 patients (13.4%) discontinued their treatment. Of these, N = 20 belonged to the subgroup of patients with elevated LFTs at baseline (N = 138, 14.5%), while N = 17 were in the group with non-elevated initial LFTs (N = 138, 12.3%) (Chi^2 = 0.281, p = 0.596). There was no statistically significant difference in drug survival between the subgroups with elevated (mean drug survival: 5.71 months) or non-elevated (mean drug survival: 5.74 months) LFTs at baseline (p = 0.600). Figure 2 illustrates the drug survival analysis between the subgroups. (Figure 2).

In total, N = 4 patients (1.4%) discontinued treatment due to liver-specific side effects. All of these patients had elevated LFTs at baseline (4/138, 2.9%), whereas none of the patients in the group with initially normal LFTs had to discontinue treatment due to liver-specific side effects. Patients whose systemic therapies were terminated by the treating physicians due to increasing LFTs had previously suffered from MASH. Two patients received apremilast and exhibited a FIB-4 of less than 1.3 prior to initiation of therapy. One patient received adalimumab and demonstrated a FIB-4 between 1.3 and 2.67, while one patient was treated with secukinumab and initially exhibited a FIB-4 of greater than 2.67. None of the patients who discontinued treatment due to liver-specific adverse events were on statin therapy, which can also cause elevated liver enzymes in some cases.[38] At the time of treatment discontinuation, no change was observed

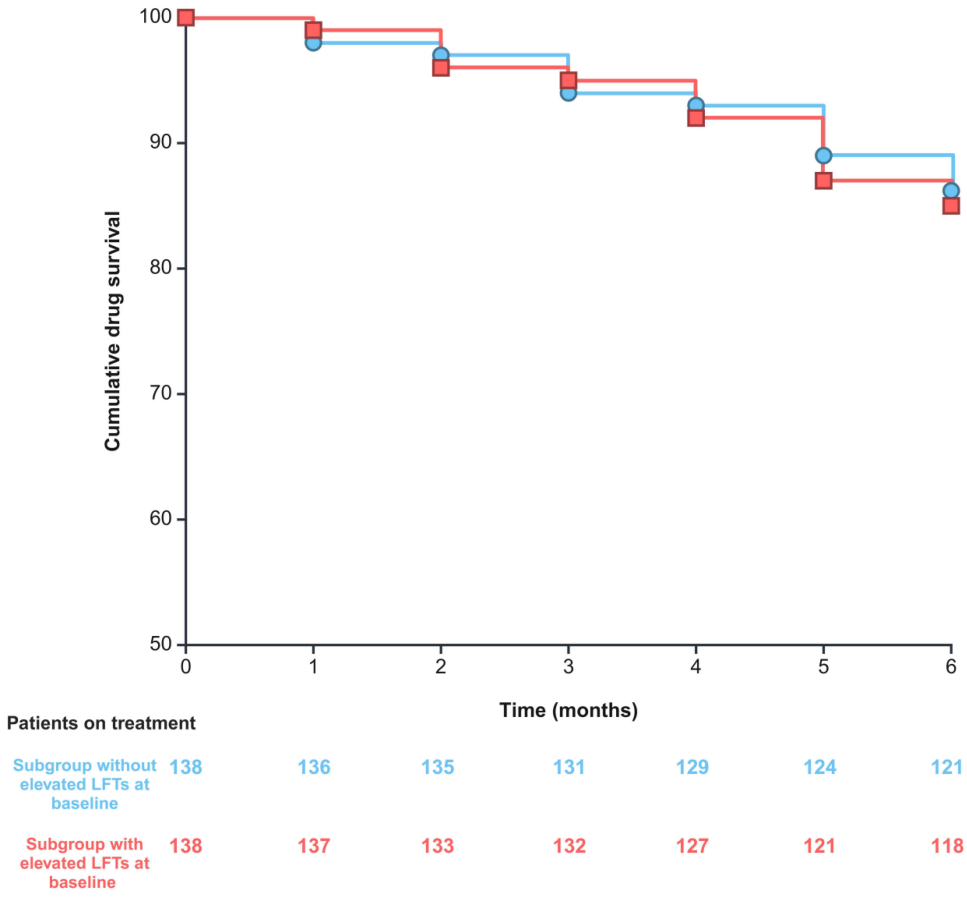

Figure 2 Drug survival analysis. Cumulative drug survival between subgroups over time.

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in the FIB-4 to a new risk level, nor was there a parallel increase in bilirubin, parallel decrease in albumin, or decrease in blood coagulation parameters. All reasons for discontinuation in each group are shown in Figure 3 (Figure 3).

Regarding treatment efficacy, there was no significant difference in PASI-75 response rates between patients with elevated LFTs at baseline and those with non-elevated initial LFTs after 3 months ($Chi^2 = 3.12$, $p = 0.077$) and after 6 months ($Chi^2 = 0.72$, $p = 0.402$). When comparing the PASI-75 response of all treated patients by drug used, patients who received ixekizumab had the highest PASI-75 response rate and apremilast had the lowest (3 months: $Chi^2 = 32.65$, $p < 0.001$; 6 months: $Chi^2 = 16.40$, $p < 0.001$). The same was true within the subgroups based on elevated or non-elevated LFTs at baseline (subgroup with non-elevated LFTs at baseline at 3 months: $Chi^2 = 22.43$, $p < 0.001$; at 6 months: $Chi^2 = 10.83$, $p = 0.013$; subgroup with elevated LFTs at baseline at 3 months: $Chi^2 = 12.45$, $p = 0.006$; at 6 months: $Chi^2 = 11.06$, $p = 0.011$).

Comparisons of each agent with regard to the subgroups based on elevated versus non-elevated LFTs at baseline revealed a significantly better PASI-75 response rate in the secukinumab group for patients without elevated LFTs at baseline (65.7% vs 42.2% at 3 months, $Chi^2 = 4.35$, $p = 0.037$, OR = 1.51; 60.6% vs 36.7% at 6 months, $Chi^2 = 4.51$, $p = 0.034$, OR = 1.48). In addition, the secukinumab-treated group with elevated LFTs at baseline had a significantly higher prevalence of obesity (60.0% vs 31.5%, $Chi^2 = 6.99$, $p = 0.008$), diabetes mellitus (22.0% vs 5.2%, $Chi^2 = 4.80$, $p = 0.028$), and arterial hypertension (54.0% vs 23.6%, $Chi^2 = 8.20$, $p = 0.004$) compared to the group receiving secukinumab with normal LFTs at baseline.

Table 3 provides a summary of the aforementioned results, while Figure 4 illustrates the PASI-75 response by drug in all patients. Furthermore, a comparison of the PASI-75 response between the subgroups and a comparison of the PASI-75 response within the subgroups by drug is presented (Table 3 and Figure 4).

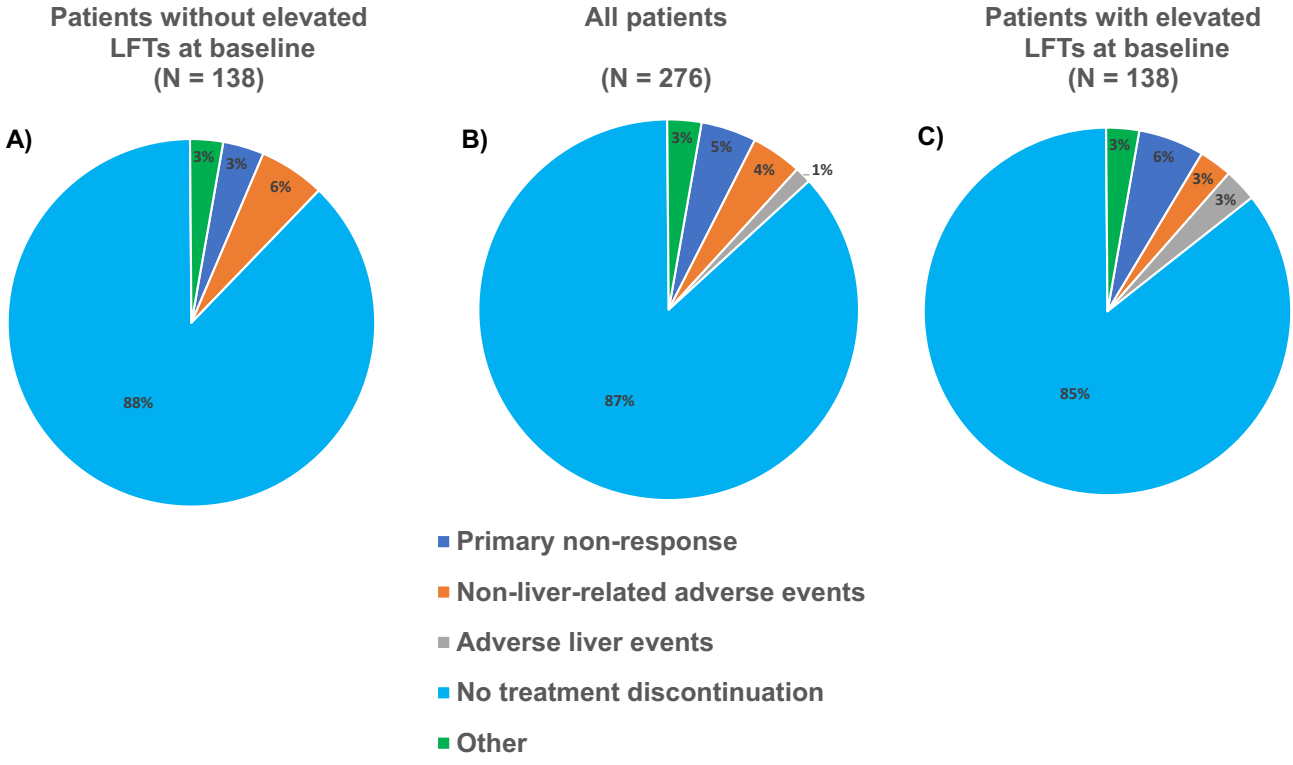

Figure 3 Reasons for discontinuation of treatment. (**A**) Illustration of reasons for discontinuation of treatment of patients without elevated LFTs at baseline. (**B**) Illustration of reasons for discontinuation of treatment of all patients. (**C**) Illustration of reasons for discontinuation of treatment of patients with elevated LFTs at baseline.

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Table 3 Comparison of PASI-75 Response Rate Between Subgroups Within the Same Drug

	Patients without Elevated LFTs at Baseline	Patients with Elevated LFTs at Baseline
Medication		
Adalimumab		
PASI-75 response at 3 months (%)	38.1	31.3
Chi^2	0.37	
p	0.541	
OR (95%-CI)	1.19 (0.67–2.11)	
PASI-75 response at 6 months	38.5	53.1
Chi^2	1.52	
p	0.217	
OR (95%-CI)	0.72 (0.43–1.21)	
Secukinumab		
PASI-75 response at 3 months	65.7	42.2
Chi^2	4.35	
p	0.037	
OR (95%-CI)	1.51 (1.01–2.24)	
PASI-75 response at 6 months	60.6	36.7
Chi^2	4.51	
p	0.034	
OR (95%-CI)	1.48 (1.01–2.18)	
Ixekizumab		
PASI-75 response at 3 months	67.7	63.6
Chi^2	0.09	
p	0.756	
OR (95%-CI)	1.11 (0.57–2.14)	
PASI-75 response at 6 months	71.4	72.7
Chi^2	0.01	
p	0.919	
OR (95%-CI)	0.96 (0.47–1.95)	
Apremilast		
PASI-75 response at 3 months	10.0	17.2
Chi^2	0.50	
p	0.476	
OR (95%-CI)	0.80 (0.46–1.36)	

(*Continued*)

Table 3 (Continued).

	Patients without Elevated LFTs at Baseline	Patients with Elevated LFTs at Baseline
PASI-75 response at 6 months	31.3	27.8
Chi^2	0.04	
p	0.824	
OR (95%-CI)	1.08 (0.52–2.22)	

Notes: Chi-squared test and odds ratio as effect size to compare PASI-75 response between subgroups within the same drug.
Abbreviations: LFTs, liver function tests; PASI, Psoriasis Area and Severity Index; Chi^2, chi-square statistic; p, p-value of chi-square test; OR, odds ratio; 95%-CI, 95%-confidence interval.

Discussion

Our study aimed to investigate whether it is necessary for clinicians to be reluctant to initiate systemic treatments in patients with psoriasis and abnormal LFTs at baseline. We analyzed treatment courses of N = 276 patients from real-life care. Patients were divided into two subgroups based on the presence or absence of elevated LFTs at the start of treatment. In the subgroup with elevated LFTs at baseline, patients were significantly more severely affected by psoriasis and were more likely to suffer from arterial hypertension, obesity, and diabetes mellitus. This is not unexpected given that liver diseases such as MASLD are often associated with obesity, arterial hypertension, and diabetes mellitus.[39–44] Furthermore, arterial hypertension, obesity, diabetes mellitus, and liver diseases are common comorbidities of psoriasis.[5,10,45–51] Obesity and diabetes mellitus are even known to be aggravating factors in psoriasis, possibly accounting for the higher PASI scores in this subgroup.[48]

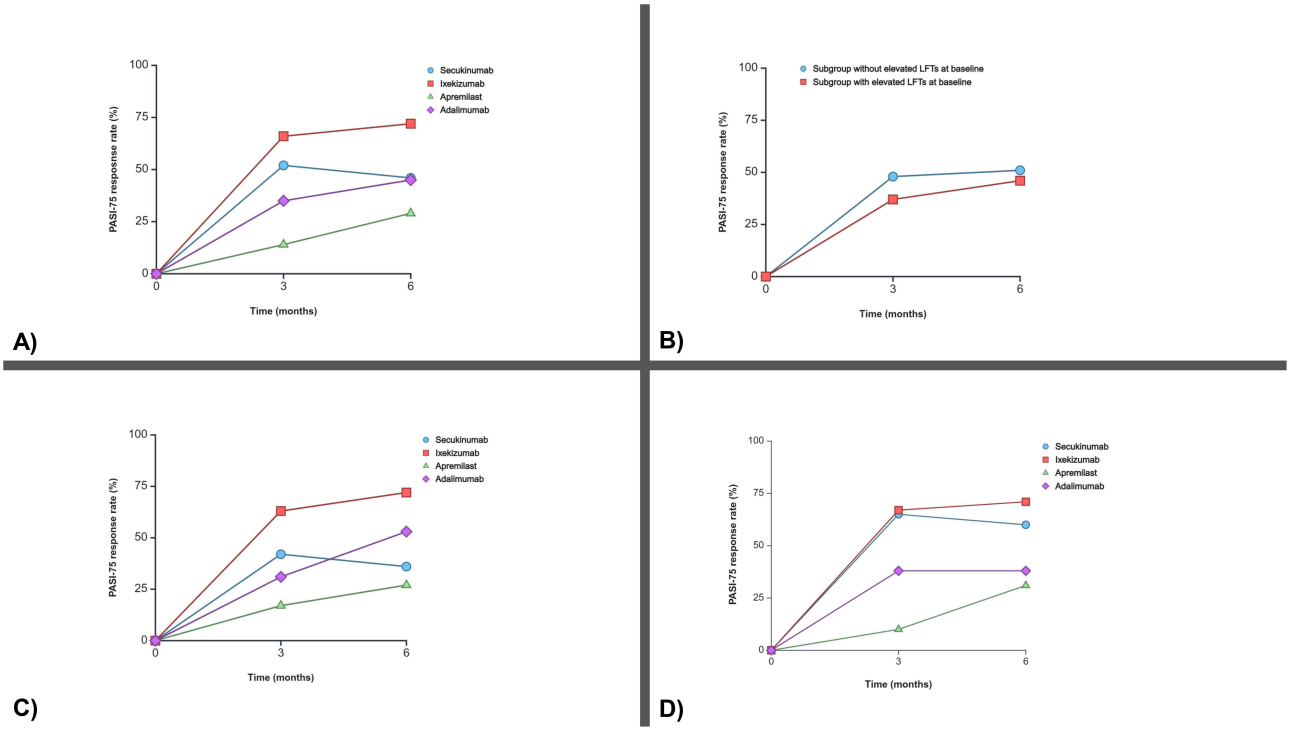

Figure 4 Efficacy analysis. (**A**) PASI-75 response rate by drugs in all patients. (**B**) PASI-75 response rate between the subgroups based on patients with elevated or non-elevated LFTs at baseline. (**C**) PASI-75 response rate by drugs within the subgroup of patients with elevated LFTs at baseline. (**D**) PASI-75 response rate by drugs within the subgroup of patients with non-elevated LFTs at baseline.

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No significant changes in mean liver values were observed during therapy in the cohort of patients with normal LFTs at baseline. Although there were slight increases in liver enzymes in 20.2% (N = 28/138) of patients, there was no significant evidence of drug-induced toxic liver damage, as the increase in liver enzymes was, according to Hy's law, not associated with a parallel increase in bilirubin.[52,53] The unchanged FIB-4 scores, together with this finding, suggest that in patients with normal LFTs at baseline, the systemic therapies analyzed do not appear to be a significant risk factor for increasing LFTs.[8,54,55]

More importantly, according to our data, there seems to be no need for concern in patients with elevated LFTs at the time of starting therapy either. Our analysis revealed a statistically significant decrease in all measured LFTs during follow-up. This suggests that a systemic therapy with apremilast, secukinumab, ixekizumab, or adalimumab does not represent a general risk but rather an opportunity for patients with psoriasis and elevated LFTs.

The improved liver function might result from a reduction in systemic inflammation due to the systemic anti-psoriatic therapy also leading to dampened inflammatory reactions in the liver.[56–60]

To gain more insight into whether systemic therapies pose a problem for patients with psoriasis and elevated LFTs at the beginning of treatment, we analyzed drug survival and reasons for treatment discontinuation among subgroups. No statistically significant differences between groups were found, indicating that in patients with elevated LFTs, therapy does not need to be discontinued more frequently. The high rates of drug survival reported in our study are consistent with the existant literature. For example, Gargiulo et al reported a real-world drug survival of over 90% for secukinumab and ixekizumab after six months of therapy. After a four-year observation period, the drug survival for secukinumab was 74.7% and for ixekizumab 82.6% in over 1000 cases analyzed for each drug.[61] In addition, the proportion of patients in the group with elevated LFTs at baseline who had to stop their therapy due to liver-specific side effects was only 2.9% (4/138), supporting the notion that patients with elevated LFTs at the start of therapy are only rarely at risk of further liver injury due to the systemic therapy used. Given the lack of a parallel increase in bilirubin and the absence of a decrease in serum albumin or blood coagulation parameters, it remains debatable whether the therapies of these patients had to be discontinued because Hy's law was not met.[52,53]

The efficacy analysis demonstrated that although patients with elevated LFTs were significantly more severely affected by psoriasis at baseline, there was no significant difference in overall response to the therapies as measured by PASI-75 response. This suggests that patients with elevated LFTs benefit from modern systemic therapy to the same extent as patients with non-elevated LFTs at baseline, providing a further argument in favor of initiating modern systemic therapies in this patient group.

When comparing the efficacy of the different drugs, ixekizumab showed the greatest efficacy across all groups, as evidenced by the highest PASI-75 response rate. These findings align with those of previous efficacy comparisons in the literature, which similarly indicated a higher response rate for ixekizumab compared to adalimumab and apremilast and a similar to slightly better response rate in case of secukinumab.[22,62]

The improvement of skin symptoms of patients with psoriasis has a significant impact on the lives of those affected, leading to a noticeable enhancement in quality of life with a potentially increased physical activity as a result of a reduction in the stigmatization associated with the condition.[63–66] This mechanism may provide an additional explanation for the decrease in LFTs during therapy, as physical activity and weight loss are known to have a positive effect on liver function.[67,68] In accordance with this hypothesis, ixekizumab was the most efficacious drug in improving the skin condition and at the same time reducing elevated LFTs during treatment. Nevertheless, it remains unclear whether the reduction in LFT levels associated with ixekizumab is attributable to a reduction in systemic inflammation, particularly given the evidence that IL-17 inhibition may exert a beneficial effect on steatohepatitis, or whether the reduction is due to a change in the patient's lifestyle, the action of other mechanisms, or a combination of these factors.[69] Another notable finding within the analysis of treatment efficacy was the fact that secukinumab showed a significantly lower treatment response in the subgroup of patients with initially elevated LFTs compared to the subgroup of patients without initially increased LFTs. The explanation for this finding might be less related to the initial elevation in LFTs per se and more related to the high prevalence of obese patients in the secukinumab cohort who had elevated LFTs at baseline, as secukinumab is known to be less effective in obese patients and all analyzed patients received the same dosage of 300 mg every 4 weeks after completion of the induction phase.[70,71]

This analysis is not without limitations due to its retrospective, monocentric design. The design does not allow for control for variation over time, ie spontaneous remission, or indirect effects, eg from lifestyle changes, and calls for future studies using implementing a prospective, randomized, controlled trial design. As patients under the age of 18 were excluded from our analysis, we cannot provide evidence for children and adolescents with psoriasis, who are also known to have an increased risk of liver disease.[72,73] In addition, our approach does also not allow for a clear interpretation of the mechanisms underlying the observed improvements in LFTs. The analysis did not include evaluations of IL-23 inhibitors, which are also frequently utilized in contemporary practice, thus constituting a further limitation of our study. Brodalumab was not included in the study due to the fact that the number of cases in our clinic was very small. Bimekizumab could not be considered because its approval in Germany was obtained after the analysis period. The relatively short observation period of the study of 6 months was chosen to ensure an analysis with a high number of cases with robust data sets, as a longer observation period would have been associated with a significant reduction in the number of cases with valid data.

Nevertheless, the relatively large number of patients included in the analysis is a definite strength of the study.

Taken together, the data help to answer a clinically highly relevant question, which, to our knowledge, has been explicitly investigated for the first time in the context of this work. The results suggest that increased LFTs at the start of systemic therapy do not represent a general risk with regard to a further increase in liver values under the systemic agents investigated. Modern systemic therapies even seem to have the potential to improve not only skin symptoms but also liver function. Thus, our data provide further support for the initiation of one of the systemic therapies analyzed, and possibly other substances not yet studied, in patients with normal but also elevated LFTs at baseline. Our findings may inform further prospective studies, necessary to improve the level of evidence and to further disentangle the underlying mechanisms underlying our observations.

Statement of Ethics

Study approval statement: The study was approved by the Ethics committee of the Medical Faculty of the University Duisburg-Essen (IRB protocol number 19-8684-BO) and followed the principles stated in the Declaration of Helsinki.

Consent to participate statement: According to the Ethics committee of the Medical Faculty of the University Duisburg-Essen (IRB protocol number 19-8684-BO) written informed consent was not required since data was collected in the context of the clinical routine and analyzed anonymously (retrospective data analysis).

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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