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Real-World Screening Data for Liver Fibrosis in Psoriasis Patients Treated with Biologics

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) is positively associated with the prevalence and severity of psoriasis. The fibrosis-4 (FIB-4) index was developed to predict significant liver fibrosis. Using the FIB-4 index, the present study evaluated screening data for liver fibrosis, including MASLD, in patients with refractory psoriasis treated with biologics.

Methods: All adult patients with psoriasis who were prescribed biologics at Nippon Medical School from August 2023 to May 2024 were included in this study. The FIB-4 index was classified as high (≥2.67), intermediate (1.30-2.66), and low (<1.30). Patients younger than 65 years were referred to a hepatologist if the FIB-4 index was high. If the score was intermediate, type IV collagen 7S (4COL7S) was checked, and they were referred to a hepatologist if it was ≥4.8 ng/mL. Patients aged ≥65 years were referred to a hepatologist if the FIB-4 index was high. If it was 2.00-2.66, they were referred to a hepatologist if the 4COL7S level was ≥4.8 ng/mL.

Results: Data from 96 patients were analyzed. The FIB-4 index was high in 10 patients, intermediate in 35 patients, and low in 51 patients. Eleven of 96 registered patients were newly referred to a hepatologist. Of these 11 patients, 5 received lifestyle guidance.

Conclusions: For patients with refractory psoriasis, close cooperation between dermatologists and hepatologists is essential to prevent progression of liver fibrosis. (J Nippon Med Sch 2024; 91: 534–540)

Key words: biologics, FIB-4 index, 4COL7S, liver fibrosis, psoriasis

Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disease characterized by hyperproliferation of epidermal keratinocytes[1,2]. Psoriasis is now regarded as a disease accompanied by systemic inflammation, and high prevalences of comorbidities such as hypertension, dyslipidemia, diabetes mellitus, hyperuricemia, cardiovascular disease, and cerebral vascular disorders have been reported in psoriasis patients[3,4]. Metabolic dysfunction-associated steatotic liver disease (MASLD)[5], previously known as nonalcoholic fatty liver disease (NAFLD), is positively associated with the prevalence and severity of psoriasis[6–10].

Biologics have been available for treatment of moderate to severe refractory psoriasis since 2010 and, as of May 2024, twelve biologics were available in Japan[11]: three tumor necrosis factor (TNF) inhibitors (infliximab, adalimumab, and certolizumab pegol), four interleukin (IL)-17 inhibitors (secukinumab, ixekizumab, brodalumab, and bimekizumab), four IL-23 inhibitors (ustekinumab, guselkumab, risankizumab, and tildrakizumab), and one IL-36 inhibitor (spesolimab). The fibrosis-4 (FIB-4) index was developed as a simple, noninvasive index to predict significant liver fibrosis[12] and is

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used as a screening tool in psoriasis patients[3,13,14]. However, there have been few real-world screening studies of liver fibrosis in patients with moderate to severe refractory psoriasis undergoing biological therapy. The present study used the FIB-4 index to evaluate screening data for liver fibrosis, including MASLD, in psoriasis patients treated with biologics.

Methods

Data from all patients with moderate to severe refractory psoriasis who were aged 20 years and older and prescribed biologics at Nippon Medical School from August 2023 to May 2024 were analyzed in this retrospective study. Refractory disease was defined as inadequate response to topical treatment or standard systemic treatment including phototherapy[11]. The psoriasis patients had plaque-type psoriasis (psoriasis vulgaris: PsV), psoriatic arthritis (PsA), or generalized pustular psoriasis (GPP). PsV was diagnosed by the typical clinical feature of scaly erythematous plaques, and PsA and GPP were diagnosed according to the classification criteria for psoriatic arthritis and the diagnostic criteria proposed by the Ministry of Health, Labor and Welfare Study Group for Rare Intractable Skin Diseases in Japan, respectively[15,16]. This study was approved by the ethical committee of the Nippon Medical School (No. 2022-217). Peripheral blood was obtained from each patient, and levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and platelet (PLT) number were measured. The FIB-4 index was calculated as follows: (age [yr] × AST [U/L]) / (PLT [$\times 10^9$/L] × ALT [U/L]$^{1/2}$)[12]. One of eleven biologics—infliximab, adalimumab, certolizumab pegol, secukinumab, ixekizumab, brodalumab, bimekizumab, ustekinumab, guselkumab, risankizumab, or tildrakizumab—was administered to psoriasis patients, in accordance with a protocol described elsewhere[11].

The FIB-4 index was classified as high (≥2.67), intermediate (1.30-2.66), and low (<1.30)[17]. Patients aged <65 years were observed if the FIB-4 index was low (<1.30) but were referred to a hepatologist if it was high (≥2.67), or if it was intermediate (1.30-2.66) and type IV collagen 7S (4COL7S) level was ≥4.8 ng/mL[18]. Patients aged ≥65 years were observed if the FIB-4 index was <2.00[19,20] but were referred to a hepatologist if it was high (≥2.67), or if it was 2.00-2.66 and the 4COL7S level was ≥4.8 ng/mL. Liver stiffness values were measured by transient elastography with a FibroScan 502 device equipped with an M-probe (Echosens SA, Paris, France).

Non-repeated measures ANOVA was used to compare age, body mass index (BMI), and FIB-4 index among patients treated with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors. If there was a significant difference, Bonferroni correction was used to perform multiple comparisons. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical School)[21]. A two-sided *P*-value of <0.05 was considered statistically significant.

Results

In total, 96 patients (64 men) were included in this study. In 41 of 96 (43.2%) patients, the present biologics were switched from other biologics. The characteristics of the patients are shown in **Table 1**. The median age (years) in the TNF-, IL-17-, and IL-23 inhibitor-treated groups was 54, 64, and 64 years, respectively. Twenty-eight of the 96 patients had PsA, and 22 and 6 of the PsA patients were treated with TNF inhibitors and IL-23 inhibitors, respectively. Eight of the 96 patients had GPP, and 5 and 2 of the GPP patients were treated with TNF inhibitors and IL-23 inhibitors, respectively. The median BMI in the TNF-, IL-17-, and IL-23 inhibitor-treated groups was 22.8, 24.75, and 23.4, respectively. The median FIB-4 index values in the TNF-, IL-17-, and IL-23 inhibitor-treated groups were 1.03, 1.18, and 1.44, respectively. Age significantly differed among the patients treated with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors ($P < 0.05$). Patients treated with TNF inhibitors were significantly younger than those treated with IL-17 inhibitors or IL-23 inhibitors ($P < 0.01$). There was no significant difference in BMI or FIB-4 index among patients treated with TNF inhibitors, IL-17 inhibitors, and IL-23 inhibitors ($P > 0.05$).

In the 96 patients, the FIB-4 index was high in 10 (10.4%), intermediate in 35 (36.5%), and low in 51 (53.1%). As shown in **Table 2**, all 10 patients with high FIB-4 index values were aged 65 years or older. One had already been treated for hepatitis C (Pt. 3), three were already visiting our hospital's hepatology department or a nearby internal medicine department (Pt. 1, 6, 7), and six were referred to our hospital's hepatology department (Pt. 2, 4, 5, 8-10).

Of the 35 patients with an intermediate FIB-4 index value, 24 (68.6%) and 11 (31.4%) patients were aged ≥65 and <65 years, respectively. As shown in **Table 3**, FIB-4 index values were ≥2.00 in 10 of 24 (41.7%) patients aged ≥65 years. 4COL7S levels were checked in 9 of these 10 patients, and 4 with 4COL7S levels of ≥4.8 ng/mL were referred to our hospital's hepatology department (Pt. 12, 14, 15, 18). As shown in **Table 4**, 4COL7S levels were

Table 1 Patient characteristics

Variable		Drug type					
		TNF inhibitors (n=37)		IL-17 inhibitors (n=19)		IL-23 inhibitors (n=40)	
Age (years), median (range)		54 (34-78)		64 (42-88)		64 (27-87)	
Male, no. (%)		23 (62.2)		15 (78.4)		26 (65.0)	
Disease type, no. (%)	PsV	10 (27.0)		18 (94.7)		32 (80.0)	
	PsA	22 (59.5)		0 (0.0)		6 (15.0)	
	GPP	5 (13.5)		1 (5.3)		2 (5.0)	
Drug, no. (%)	IFX	3 (8.1)	SEC	9 (47.4)	UST	5 (12.5)	
	ADA	18 (48.6)	IXE	4 (21.1)	GUS	6 (15.0)	
	CER	16 (43.2)	BRO	5 (26.3)	RIS	26 (65.0)	
			BIM	1 (5.3)	TIL	3 (7.5)	
BMI, median (range)		22.8 (17.6-37.6)		24.75 (18.0-31.7) n=18		23.4 (15.8-42.1) n=39	
AST (U/L), median (range)		22 (13-79)		21 (11-56)		21.5 (10-45)	
ALT (U/L), median (range)		22 (6-120)		18 (11-71)		18.5 (7-82)	
PLT ($\times 10^9$/L), median (range)		242 (139-472)		224 (107-320)		224 (139-411)	
FIB-4 index, median (range)		1.03 (0.45-4.72)		1.18 (0.64-5.41)		1.44 (0.29-3.20)	

PsV: psoriasis vulgaris, PsA: psoriatic arthritis, GPP: generalized pustular psoriasis, IFX: infliximab, ADA: adalimumab, CER: certolizumab pegol, SEC: secukinumab, IXE: ixekizumab, BRO: brodalumab, BIM: bimekizumab, UST: ustekinumab, GUS: guselkumab, RIS: risankizumab, TIL: tildrakizumab, BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PLT: platelet, FIB-4: Fibrosis-4

Table 2 Patients with a high FIB-4 index

Pt.	Age	Sex	Disease type	Drug used	BMI	AST (U/L)	ALT (U/L)	PLT ($\times 10^9$/L)	FIB-4	Status of consultations to Hepatology Department
1	75	M	PsV	IXE	24.2	37	23	107	5.41	(Already undergoing treatment for liver cirrhosis)
2	67	M	PsV	ADA	21.6	79	43	171	4.72	Referred to our hospital's Hepatology Department
3	77	M	PsV	SEC	21.5	26	21	118	3.70	(Already treated for hepatitis C)
4	75	F	PsA	ADA	35.7	22	13	139	3.29	Referred to our hospital's Hepatology Department
5	81	M	PsV	SEC	20.9	16	11	119	3.28	Referred to our hospital's Hepatology Department
6	69	F	PsV	RIS	22.8	36	26	152	3.20	(Already undergoing treatment for SLD)
7	83	M	PsA	GUS	25.2	21	11	164	3.20	(Already undergoing treatment for DLD)
8	83	F	PsV	GUS	21.5	28	26	151	3.02	Referred to our hospital's Hepatology Department
9	88	M	PsV	SEC	25.2	17	15	129	2.99	Referred to our hospital's Hepatology Department
10	73	M	PsV	SEC	25.4	56	71	175	2.77	Referred to our hospital's Hepatology Department

Pt.: patient, BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PLT: platelet, FIB-4: Fibrosis-4, PsV: psoriasis vulgaris, PsA: psoriatic arthritis, IXE: ixekizumab, ADA: adalimumab, SEC: secukinumab, RIS: risankizumab, GUS: guselkumab, SLD: steatotic liver disease

checked in 10 of 11 patients aged <65 years with an intermediate FIB-4 index, and one patient with a 4COL7S level of ≥4.8 ng/mL was referred to our hospital's hepatology department (Pt. 24).

Liver stiffness, as measured by the FibroScan 502, was 7.5 kPa (normal: 1.5-5) for Pt. 2[22]. He was diagnosed as having alcoholic liver cirrhosis and was instructed to abstain from alcohol. Patient 4 was diagnosed as having liver cirrhosis on the basis of abdominal CT findings. Her BMI was 35.7 and she was instructed to lose weight. The liver stiffness value of Pt. 5 was 2.9 kPa and he did not have chronic liver disease. Patient 8 was diagnosed as having steatotic liver disease (SLD) by abdominal ultrasound examination. The liver stiffness value of Pt. 9 was 3.3 kPa and he did not have chronic liver disease. Patient 10 was diagnosed as having severe SLD by abdominal

Table 3 Patients aged ≥ 65 years with an FIB-4 index ≥2.00

Pt.	Age	Sex	Disease type	Drug used	BMI	AST (U/L)	ALT (U/L)	PLT ($\times 10^9$/L)	FIB-4	4COL7S (ng/mL)	Status of consultations to Hepatology Department
11	80	M	PsV	UST	21.3	24	21	158	2.65	3.3	
12	78	F	PsA	CER	30.3	39	44	179	2.56	4.8	Referred to our hospital's Hepatology Department
13	76	M	PsV	TIL	23.7	19	18	139	2.45	4.7	
14	77	M	PsV	RIS	22.8	27	13	244	2.36	5.6	Referred to our hospital's Hepatology Department
15	76	M	PsV	GUS	21.8	28	22	194	2.34	6.6	Referred to our hospital's Hepatology Department
16	71	M	PsA	CER	22.7	20	13	181	2.18	2.2	
17	87	F	PsV	UST	28.0	25	16	252	2.16	4.0	
18	77	M	PsV	RIS	22.8	17	16	158	2.07	5.4	Referred to our hospital's Hepatology Department
19	75	M	PsV	SEC	26.0	24	26	176	2.01	3.5	
20	65	M	PsA	RIS	32.5	26	31	152	2.00		

Pt.: patient, BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PLT: platelet, FIB-4: Fibrosis-4, PsV: psoriasis vulgaris, PsA: psoriatic arthritis, UST: ustekinumab, CER: certolizumab pegol, TIL: tildrakizumab, RIS: risankizumab, GUS: guselkumab, SEC: secukinumab

Table 4 Patients aged <65 years with an intermediate FIB-4 index

Pt.	Age	Sex	Disease type	Drug used	BMI	AST (U/L)	ALT (U/L)	PLT ($\times 10^9$/L)	FIB-4	4COL7S (ng/mL)	Status of consultations to Hepatology Department
21	64	M	PsV	IXE	25.6	16	11	121	2.55		
22	54	F	PsV	RIS	21.3	28	21	169	1.95	3.9	
23	53	M	PsV	RIS	22.5	33	16	224	1.95	3.7	
24	52	M	PsV	RIS	23.6	45	64	160	1.83	5.1	Referred to our hospital's Hepatology Department
25	59	F	PsV	ADA	21.2	21	15	211	1.52	4.7	
26	62	F	GPP	CER	30.8	21	19	199	1.50	4.4	
27	63	F	PsA	ADA	18.4	19	13	229	1.45	2.7	
28	53	F	PsV	RIS	21.4	22	23	172	1.41	3.2	
29	64	F	GPP	ADA	36.5	28	33	223	1.40	4.3	
30	55	F	PsA	GUS	20.0	23	17	224	1.37	3.3	
31	55	F	PsV	IXE	18.0	22	16	224	1.35	2.9	

Pt.: patient, BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PLT: platelet, FIB-4: Fibrosis-4, PsV: psoriasis vulgaris, GPP: generalized pustular psoriasis, PsA: psoriatic arthritis, IXE: ixekizumab, RIS: risankizumab, ADA: adalimumab, CER: certolizumab pegol, GUS: guselkumab

ultrasound examination and was instructed to abstain from alcohol. The liver stiffness value of Pt. 12 was 6.6 kPa and MASLD was diagnosed. Because her BMI was 30.3, she was instructed to lose weight. The liver stiffness value of Pt. 14 was 6.1 kPa and severe SLD was diagnosed. The liver stiffness value of Pt. 15 was 6.6 kPa. The 4COL7S of Pt. 18 was measured again and was within the normal range (3.9 ng/mL). SLD was diagnosed. Patient 24 was diagnosed as having alcoholic liver disease (ALD) and was instructed to decrease alcohol consumption.

Discussion

This study is one of the few to carefully evaluate screening data on liver fibrosis, including the FIB-4 index, in patients who were using biologics for moderate to severe refractory psoriasis[3,13,14]. FIB-4 index values were high in 10 patients (10.4%), intermediate in 35 (36.5%), and low in 51 (53.1%). Because we did not check the FIB-4 index in age-matched healthy controls, we cannot determine whether the FIB-4 index of these psoriasis patients was higher than that of healthy individuals. Akuta[17] reported that in 4,895 individuals with SLD (fatty liver) diagnosed by abdominal ultrasound examination at Toranomon Hospital Health Management Center, the FIB-4 index values were high in 1.0% of patients, intermediate in 20.4%, and low in 78.4%. Although a direct comparison is not possible, a review of the data from Akuta[17] suggests that

the proportion of patients with a high FIB-4 index is higher among the present psoriasis patients than among those with SLD diagnosed at Toranomon Hospital Health Management Center.

In this study, patients using TNF inhibitors were significantly younger than those using IL-17 or IL-23 inhibitors. TNF inhibitors are less frequently used in older patients because of their greater difficulty of use, as compared with IL-17 and IL-23 inhibitors, in patients with a history of tuberculosis[11]. In contrast, although the FIB-4 index was lower in patients using TNF inhibitors, it did not significantly differ among patients receiving these biologics. The FIB-4 index tended to be higher in older individuals; thus, use of TNF inhibitors might suppress liver fibrosis. Macía-Villa et al.[14] reported that liver fibrosis estimated by FIB-4 index was suppressed in patients with psoriatic arthritis who had used biologics, 80.8% of whom had used TNF inhibitors. Seitz et al.[23] disclosed that administering TNF inhibitors to patients with psoriatic arthritis treated with methotrexate acted protected against liver fibrosis, as determined by transient elastography (FibroScan). Takamura et al.[24] reported that MASLD (NAFLD) fibrosis score and FIB-4 index were lower in psoriasis patients after 6 months of IL-17 inhibitor treatment. However, Takeshima et al.[25] found that IL-23 inhibitors but not IL-17 inhibitors decreased FIB-4 index in psoriasis patients with an elevated FIB-4 index. Because of the small number of present patients and lack of data on change in FIB-4 index after the use of biologics, it is unclear whether biologics, including TNF inhibitors, protect against liver fibrosis. Thus, future studies with a larger number of patients are necessary to investigate whether use of biologics suppresses liver fibrosis in Japanese patients.

There have been several reports on low and high FIB-4 index cut-off values to predict significant fibrosis[12,26,27]. Sterling et al.[12] reported that using 1.45 as the low cut-off value and 3.25 as the high cut-off value yielded a negative predictive value of 90% and a positive predictive value of 65%. McPherson et al.[26] showed that using 1.30 as the low cut-off value and 3.25 as the high cut-off value yielded a negative predictive value of 95% and a positive predictive value of 75%. Sumida et al.[27] found that using 1.45 as the low cut-off value and 3.25 as the high cut-off value yielded a negative predictive value of 98% and a positive predictive value of 53%. Because age is included in the FIB-4 calculation formula, the FIB-4 index tends to be higher in older individuals[19]. McPherson et al.[20] reported that using 2.0 as the low cut-off value improved specificity to 70% without adversely affecting sensitivity (77%) in adults aged ≥65 years. Ishiba et al.[28] showed that using 1.88 and 1.95 as low cut-off values for adults aged 60-69 and ≥70 years improved the accuracy of advanced fibrosis diagnosis, as compared with the conventional cut-off point. On the basis of these findings, Nakajima et al.[19] suggested that a low cut-off value of 2.0 is appropriate for adults aged ≥65 years. Therefore, in the present study, a low cut-off value of 2.0 was set for those aged ≥65 years, and a low cut-off value of 1.3 was set for those aged <65 years.

Because of the low positive predictive value when using a low cut-off value in the FIB-4 index, a two-step selection system has been proposed[18]. If the FIB-4 index is ≥1.3, 4COL7S level is measured, and a hepatologist is consulted if it is ≥4.8 ng/mL[18]. In this study, if the FIB-4 index was ≥2.0 in those aged ≥65 years and ≥1.3 in those aged <65 years, 4COL7S was measured. If 4COL7S was ≥4.8 ng/mL, a hepatologist was consulted. Furthermore, if the FIB-4 index was ≥2.67, a hepatologist was consulted, regardless of age.

In this study, 11 of 96 registered patients (11.5%) were newly referred to the hepatology department of our hospital. In 6 of these 11 patients, the liver stiffness values were measured with the FibroScan 502, and 4 patients had values above the normal upper limit (7.5, 6.6, 6.6, 6.1) and 2 had values within the normal range (3.3, 2.9). Three of the 11 patients were diagnosed with ALD and were instructed to abstain from or reduce alcohol consumption. Two of the 11 patients were diagnosed with obesity and were instructed to lose weight. Thus, 5 of the 11 patients (45.5%) received lifestyle guidance from a hepatologist. In addition, 2 of the 11 patients had no apparent chronic liver disease.

Psoriasis is now considered a disease involving systemic inflammation, not just the skin. Patients treated with biologics for severe refractory psoriasis should undergo a comprehensive examination, including assessment of liver fibrosis. FIB-4 index and 4COL7S values are easily measured by blood testing and are useful for screening for liver fibrosis. Since FIB-4 index values are higher in older individuals, adjusting the low-cut off values for those older and younger than 65 years, as in this study, is practical for screening purposes and helps limit cases requiring hepatologist consultations.

This study has several limitations. The number of patients examined was small, and the study did not include healthy controls. MASLD and alcoholic liver disease were analyzed together. Differences in FIB-4 index before and

after the use of biologics were not examined. The study was performed retrospectively. Therefore, future studies of psoriasis patients should prospectively investigate a larger number of patients and healthy controls. The analysis should focus on MASLD and change in FIB-4 index after the use of biologics.

In summary, we conducted a liver fibrosis screening survey focusing on FIB-4 index in 96 patients with moderate to severe refractory psoriasis treated with biologics. Of the 96 patients, 11 (11.5%) were newly referred to the hepatology department of our hospital. Of these 11 patients, 5 (45.5%) received lifestyle guidance from a hepatologist. Patients with refractory psoriasis require close cooperation between dermatologists and hepatologists to prevent progression of liver fibrosis.

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