Journal of Translational Autoimmunity 4 (2021) 100107

Contents lists available at ScienceDirect

Journal of Translational Autoimmunity

journal homepage: www.sciencedirect.com/journal/journal-of-translational-autoimmunity

Baricitinib and primary biliary cholangitis

Stuart C. Gordon [a,b,*], Sheri Trudeau [c], Arie Regev [d], Jonathan M. Uhas [a], Sujatro Chakladar [d], Ana Pinto-Correia [d], Klaus Gottlieb [d], Doug Schlichting [d]

[a] Division of Gastroenterology and Hepatology, Henry Ford Health System, Detroit, MI, USA
[b] Wayne State University School of Medicine, Detroit, MI, USA
[c] Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, USA
[d] Eli Lilly & Company, Indianapolis, IN, USA

ARTICLE INFO

Keywords:
Liver disease
Jak1/2 inhibitors
Itch
12-Week

ABSTRACT

Background and aims: There is an unmet need for alternative treatments for patients with primary biliary cholangitis (PBC) who do not respond to treatment with ursodeoxycholic acid (UDCA). A proof-of-concept study of baricitinib, an orally administered Janus kinase 1 and 2 inhibitor, was initiated to evaluate its use in PBC patients.

Approach and results: Patients with PBC showing inadequate response or intolerance to UDCA were eligible. This was a randomized, double-blinded placebo-controlled trial. Enrollees were assigned 1:1 to baricitinib (2 mg/day) or placebo. Endpoints included change in alkaline phosphatase (ALP), itch Numeric Rating Score (NRS), and fatigue NRS at 12 weeks post-baseline; exploratory markers included high sensitivity C-reactive protein (hs-CRP) and Enhanced Liver Fibrosis (ELF) score.

Due to low enrollment, the study was terminated early. Two patients were enrolled and completed the trial; 1 was randomized to receive baricitinib and 1 to placebo. Over the treatment period, the baricitinib-treated patient demonstrated a 30% decrease in ALP and a 7-point improvement in the itch NRS, but a 2-point increase in the Fatigue NRS. Markers of inflammation and liver fibrosis (hs-CRP and ELF score) also improved over the study period. In contrast, the placebo-treated patient showed no improvement in primary or secondary endpoints. A single non-serious treatment-emergent adverse event of moderate sinusitis was reported by the baricitinib-treated patient at day 47.

Conclusions: In a 12-week trial, a patient with PBC showing inadequate response to treatment with UDCA demonstrated a dramatic response to treatment with baricitinib.

Financial Support

Financial support by Eli Lilly and Company.

Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic liver disease affecting the small and medium-sized intrahepatic bile ducts. Rate of disease progression varies, but may ultimately result in cholestasis, portal inflammation, fibrosis and cirrhosis [1,2]. Ursodeoxycholic acid (UDCA) was approved in 1997 for the treatment of PBC and remains a first-line treatment for this indication. Although several clinical trials have shown UDCA improves the natural history of PBC, roughly 40% of patients do not respond to treatment, as evidenced by persistently elevated levels of alkaline phosphatase (ALP), which in turn have been associated with reduced transplant-free survival [3–5]. Obeticholic acid was approved in 2016 to be used in combination with UDCA for those patients who have an inadequate response to UDCA or as monotherapy for those patients intolerant to UDCA [6,7]. Other drugs with varied mechanisms of action are currently in development with the goal of expanding treatment options, improving response rates and prolonging survival [8,9].

Given its classic automimmune presentation, a number of immunesuppressive therapies have been trialed for treatment of PBC, including corticosteroids, azathioprine, cyclosporine, methotrexate and mycophenolate mofetil; none has been shown to be effective. Despite the success of emerging biologic immune-based regimens in treating other autoimmune conditions, trials of rituximab, ustekinumab, NI-0801, and

* Corresponding author. Henry Ford Health System, 2799 W. Grand Blvd, K16, Detroit, MI, 48202, USA.
E-mail addresses: sgordon3@hfhs.org (S.C. Gordon), strudea1@hfhs.org (S. Trudeau), regev_arie@lilly.com (A. Regev), juhas1@hfhs.org (J.M. Uhas), chakladar_sujatro@lilly.com (S. Chakladar), pinto_correia_ana_luisa@lilly.com (A. Pinto-Correia), klaus.gottlieb@lilly.com (K. Gottlieb), schlichting_douglas_e@lilly.com (D. Schlichting).

https://doi.org/10.1016/j.jtauto.2021.100107
Received 25 May 2021; Accepted 26 May 2021
Available online 1 June 2021

Abbreviations list

PBC	primary biliary cholangitis
UDCA	ursodeoxycholic acid
ALP	alkaline phosphatase
NRS	Numeric Rating Score
hs-CRP	high sensitivity C-reactive protein
ELF	Enhanced Liver Fibrosis
JAK	Janus kinase
TYK	tyrosine-protein kinase
IL	interleukin
ULN	upper limit of normal
ALT	alanine aminotransferase
AST	aspartate aminotransferase
PIIINP	procollagen III amino terminal peptide
HA	hyaluronic acid
TIMP-1	tissue inhibitor of metalloproteinase 1
AE	adverse events
SAE	serious adverse events
AESI	AEs of special interest
QIDS-SR16	Quick Inventory of Depressive Symptomatology Self Rated–16
IFN	interferon
STAT	signal transducer and activator of transcription

abatacept in treatment of PBC have likewise failed to show promise.

Baricitinib, a novel small molecule approved in 2018 for treatment of moderate to severe rheumatoid arthritis, belongs to the pharmacological class of Janus kinase (JAK) inhibitors [10]. Baricitinib is theorized to inhibit the activity of a number of cytokines implicated in PBC, most notably type I interferon (IFN [JAK1/*tyrosine-protein kinase (*TYK2)]), interleukin (IL)-12 and IL-23 (JAK1/TYK2). Additionally, in Phase III studies of baricitinib treatment for rheumatoid arthritis, ALP decreased in the first 20 weeks and mean values remained within the normal range over the course of treatment. Reductions in fatigue and tiredness were also noted. Studies of baricitinib for treatment of atopic dermatitis and psoriasis reported reductions in itch. These findings, along with the activity profile of baricitinib and its overlap with cytokine pathways involved in the pathogenesis of PBC, support evaluating baricitinib for the treatment of PBC. Herein, we describe the results from 2 patients who completed a Phase II, proof-of-concept, double-blind, randomized, parallel placebo-controlled study of baricitinib in the treatment of PBC.

1. Methods

The study consisted of 3 periods: a 49-day screening period, a 12-week treatment period, and a 4-week post-treatment follow-up. Due to low enrollment, the study was terminated after only 2 patients had been randomized (1 to baricitinib 2 mg/day, and 1 to placebo). Both patients remained on the blinded study drug and completed study procedures per protocol.

Eligibility criteria included: 1) a diagnosis of PBC, defined as the presence of at least 2 of the following 3 factors: ≥6 month history of elevated ALP, positive antimitochondrial antibodies titer, and/or liver biopsy consistent with PBC; 2) ALP ≥1.67 x upper limit of normal (ULN) but ≤6 x ULN; and 3) UDCA intolerance or ≥52 weeks of previous treatment with UDCA with a stable dose for ≥12 weeks without adequate response (as determined by the investigator) or no receipt of UDCA within 12 weeks prior to enrolment.

Exclusion criteria included: 1) alanine aminotransferase (ALT) > 3 x ULN; 2) aspartate aminotransferase (AST) > 3 x ULN; 3) ALP >6 x ULN; 4) or total bilirubin level > ULN; all as defined from tests administered during the screening process. The ULN for the ALP assay used in the study was 104 IU/L (for total ALP) and 94 IU/L (for liver-specific ALP).

1.1. Efficacy measures

The primary efficacy assessment was change in ALP at Week 12 of treatment. Secondary efficacy assessments included proportion of patients with ALP <1.67 x ULN (and at least 15% decrease from baseline), change from baseline in Itch Numerical Rating Score (NRS) and Fatigue NRS. The Itch NRS is a patient-administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable" [11]. Overall severity of a patient's itching is indicated by selecting the number that describes the worst level of itching in the past 7 days. The Fatigue NRS is a single-item, patient--administered, 11-point horizontal scale anchored at 0 and 10, with 0 representing "no fatigue" and 10 representing "as bad as you can imagine" [12]. Overall severity of a patient's fatigue is indicated by selecting the number that describes the worst level of fatigue during the past 7 days. Exploratory efficacy measures included total bilirubin, high sensitivity C-reactive protein (hs-CRP) and Enhanced Liver Fibrosis (ELF) Score, which uses serum measurements of procollagen III amino terminal peptide (PIIINP), hyaluronic acid (HA) and tissue inhibitor of metalloproteinase 1 (TIMP-1), calculated as ELF score = 2.494 + 0.846 $\ln(C_{HA})$ + 0.735 $\ln(C_{PIIINP})$ + 0.391 ($C_{TIMP\text{-}1}$) [13].

1.2. Safety measures

Patients were monitored for adverse events (AEs), serious AEs (SAEs) (including death) and AEs of special interest (AESI) including infection (including opportunistic infections), malignancies, hepatic events, major adverse cardiovascular events and thrombotic events (deep-vein thrombosis and pulmonary embolism). Monitoring also included Quick Inventory of Depressive Symptomatology Self Rated–16 (QIDS-SR16), a 16-item safety assessment intended to assess the existence and severity of symptoms of depression, with higher scores denoting greater symptom severity [14].

2. Results

Two patients, both white females, were enrolled in the study in 2019; 1 was randomized to baricitinib 2 mg per day, and 1 to placebo. Both patients completed the 12-week treatment study. At baseline, the baricitinib-treated patient was 65 years old and weighed 45 kg. She was diagnosed with PBC in 2005; a recent biopsy and transient elastography were consistent with advanced fibrosis/early cirrhosis. Her medical history included dyslipidemia and hypertension. Concomitant medications included cholecalciferol, ezetimibe, lisinopril, amoxicillin and UDCA. The placebo-treated patient was 51 years old and weighed 75 kg at baseline. She was diagnosed with noncirrhotic PBC in 2015, and her medical history included gastroesophageal reflux disease and hypertension. Concomitant medications included metoprolol, dexlansoprazole, cholecalciferol and UDCA.

As shown in Fig. 1A, the baricitinib-treated patient's ALP ranged from 224 to 240 U/L (>2 x ULN) prior to treatment initiation. After an increase to 253 U/L observed at roughly 4 weeks post-treatment initiation, the patient's ALP levels declined consistently across the rest of the treatment period. This decline continued even when treatment was paused due to the patient experiencing sinusitis. By the end of the 12-week treatment period, the patient's ALP was 157 IU/L, a 30% reduction from baseline and below the target threshold of 173 U/L (1.67 x ULN) used to evaluate efficacy of PBC treatment. Based on these endpoints, the patient was considered to be a responder to baricitinib. Within 4 weeks of treatment discontinuation, the patient's ALP

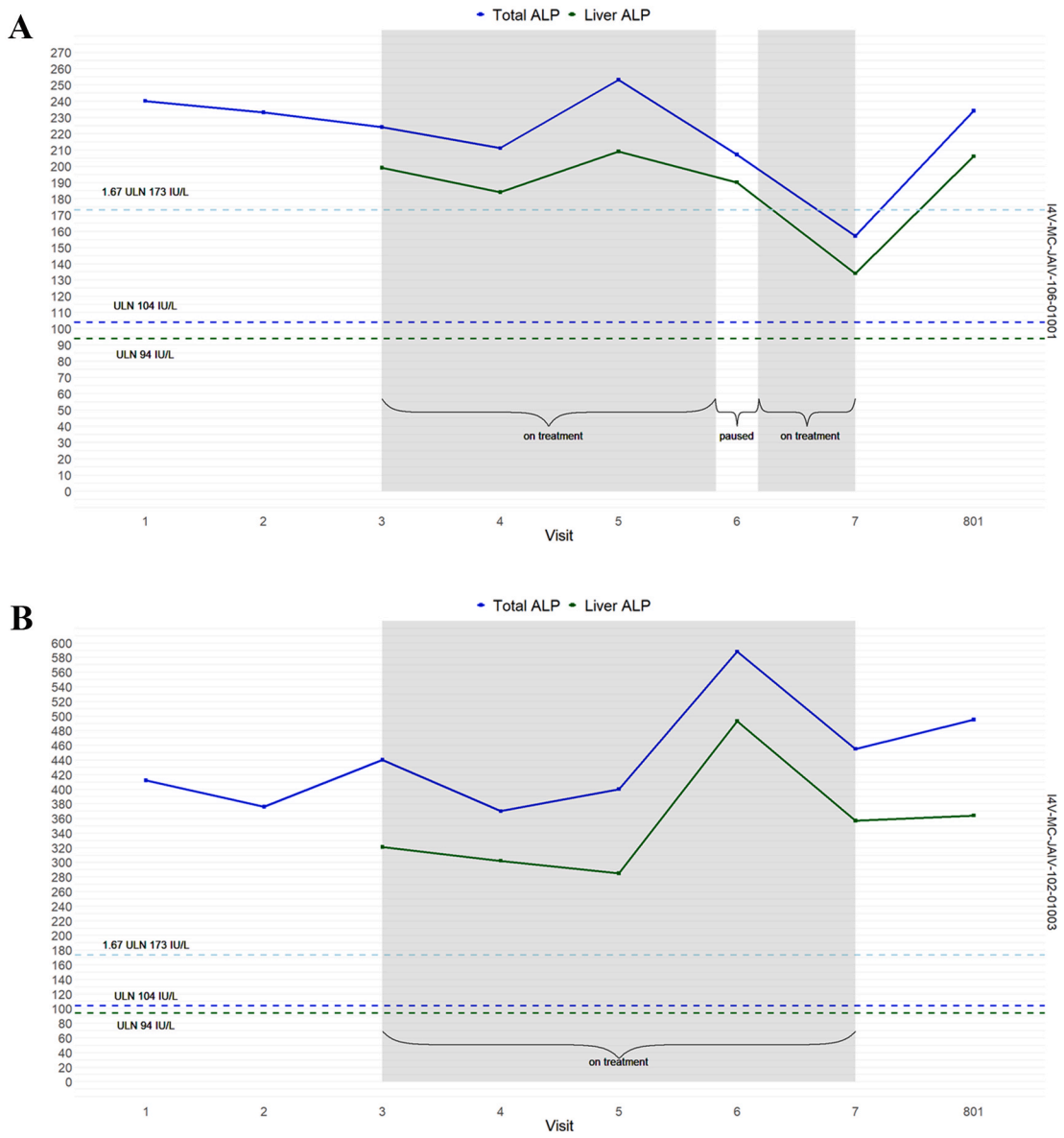

Fig. 1. Serum alkaline phosphatase (blue) and liver-specific alkaline phosphatase (green) for primary biliary cholangitis patients treated with baricitinib (A) and placebo (B). ULN and relevant multiples of the ULN are noted. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

rebounded to pre-treatment levels (234 U/L).

Table 1
Efficacy measures at treatment Weeks 0 and 12 for baricitinib- and placebo-treated patients.

Measure (reference range)	Baricitinib 2 mg		Placebo	
	Week 0	Week 12	Week 0	Week 12
Alkaline phosphatase (<104 U/L)	224	157	440	455
Itch NRS (10 = worst; 0 = none)	9	2	3	0
Fatigue NRS (10 = worst; 0 = none)	8	10	5	7
Total bilirubin (<1.2 mg/dL)	<0.2	0.2	0.9	0.8
hs-CRP (<3.0 mg/L)	3.5	0.6	6.7	8.0
ELF score (6.6–9.3)	9.8	9.4	9.4	9.7
PIIINP (<8 μg/L)	9.2	5.6	8.9	8.5
HA (<54 μg/L)	62.9	61.6	41.0	56.8
TIMP-1 (μg/L)	287.2	234.6	246.8	285.7

ELF, Enhanced Liver Fibrosis; hs-CRP, high-sensitivity C-reactive protein; HA, hyaluronic acid; NRS, Numerical Rating Score; PIIINP, procollagen III amino terminal peptide; TIMP-1, tissue inhibitor of metalloproteinase 1.

As shown in Table 1, the baricitinib-treated patient's self-reported itch score decreased from 9 to 2 (on a 10-point NRS scale) across the study period, but self-reported fatigue increased from 8 to 10. Likewise, total bilirubin remained normal (<1.2 mg/dL) across the study period. ELF Score for the patient declined from 9.8 to 9.4 (reference range for healthy females = 6.6–9.3). PIIINP and TIMP normalized and HA declined over the treatment period.

In contrast, the placebo-treated patient's ALP ranged from roughly 3.5 to 5.5 x ULN for the entire observation period (Fig. 1B), increasing slightly from 440 U/L at Week 0–450 U/L at Week 12. The patient reported a decrease in Itch NRS from 3 to 0 points, and an increase in Fatigue NRS from 5 to 7 points over the study period (Table 1).

2.1. Safety

The treated patient was exposed to baricitinib for 74 days. A single non-serious treatment-emergent AE of sinusitis (moderate) was reported 47 days after treatment initiation. The study drug was temporarily interrupted. The sinusitis was treated with levofloxacin and resolved

after 13 days. Treatment protocol resumed and the event was reported as not related to study procedure or study treatment. No AEs were reported for the placebo patient. No SAEs, AESIs or study discontinuations due to AEs were reported in the study.

The QIDS-SR-16 score for the baricitinib-treated patient decreased from 20 (severe) in Week 0 to 10 (mild) in Week 12. Scores for the placebo-treated patient were unchanged over the study period (Table 2).

The baricitinib-treated patient's ALT and AST remained in the normal range during the course of the study. The placebo patient's ALT and AST were elevated on Day 1 and remained elevated throughout the course of the study (Table 2.)

Table 2
Safety measures throughout treatment for baricitinib- and placebo-treated patients.

Week	Baricitinib, 2 mg			Placebo		
	QIDS-SR16	ALT (U/L)	AST (U/L)	QIDS-SR16	ALT (U/L)	AST (U/L)
Week 0	20	21	23	6	79	70
Week 1	11	23	24	5	67	63
Week 4	6	22	21	5	54	54
Week 8	11	17	21	8	141	130
Week 12	10	17	22	6	82	67

ALT, alanine aminotransferase; AST, aspartate aminotransferase; QIDS-SR16, Quick Inventory of Depressive Symptomatology Self Rated–16 (higher scores indicate worse depression).

3. Discussion

A dramatic decline in ALP, the primary biomarker of PBC severity, was observed in a single female patient during a 12-week course of treatment with baricitinib. The patient also reported a significant reduction in pruritus and depressive symptoms during treatment. ALP rebounded to pre-treatment levels (greater than twice the upper limit of normal) within 4 weeks of treatment withdrawal. Additional measures, including ALT, AST and total bilirubin, remained within normal ranges throughout the study period. Moreover, the baricitinib-treated patient also demonstrated reductions in markers for liver fibrosis (P3NP, HA and TIMP-1) and inflammation (hs-CRP) markers over the course of the study. Similar improvements were not observed in the matched placebo-treated patient.

PBC is a prototypical autoimmune disease. Associations between risk of PBC and presence of common genetic variants at the HLA class II, interleukin (IL)-12A and IL-12RB2 loci have been established and suggest the IL-12 immunoregulatory signaling axis is relevant to the pathophysiology of PBC [15]. More recent data have identified a relationship between the interferon (IFN), IL-12 and IL-23 pathways and the pathogenesis of PBC [16]. However, current PBC treatments do not directly address immune mechanisms; rather, treatment is directed toward the biliary canaliculus and regulation of bile salts. Early trials of immune suppressive treatment included corticosteroids, but detrimental effects on bone precluded this treatment. Cyclosporine, methotrexate, azathioprine and other immune suppressive regimens were either ineffective or deleterious and none showed demonstrable anti-cholestatic or anti-pruritic activity.

We postulate the JAK/signal transducer and activator of transcription (STAT), pathway may contribute to the mechanisms by which PBC initiates a cytokine cascade. JAKs are a family of protein tyrosine kinases (JAK1, JAK2, JAK3 and tyrosine kinase 2 [TYK2]) that play an important role in cytokine signal transduction. Baricitinib is a JAK1/2 inhibitor that demonstrates selectivity for and inhibition of JAK1 and JAK2 with lower potency towards inhibition of JAK3 or TYK2 [17]. JAKs also transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors involved in hematopoiesis, inflammation and immune function [18]. Within the intracellular signaling pathway, JAKs phosphorylate and activate STATs, which activate gene expression within the cell. Baricitinib modulates these signaling pathways by partially inhibiting JAK1/2 enzymatic activity, then reducing the phosphorylation and activation of STATs and thereby reducing inflammation, cellular activation and proliferation of key immune cells [19,20].

The decline in serum ALP observed in the baricitinib-treated patient was more rapid than that generally observed with UDCA. In a study of 375 PBC patients, Poupon et al. [21] found mean ALP values roughly 2.5 x ULN prior to initiation of UDCA. ALP in these patients declined <10% in the first 12 weeks and <20% in the first year of UDCA treatment. In contrast, similar pre-treatment levels of ALP declined by roughly 30% in the 12 weeks of baricitinib treatment. This is similar to declines in ALP observed among rheumatoid arthritis patients treated with baricitinib (unpublished data). Moreover, similar to results among patients with atopic dermatitis treated with baricitinib, the treated patient experienced a dramatic and prompt resolution of pruritus. There are currently no treatments that effectively address this serious and distressing symptom of PBC. Likewise, although the patient reported some increase in fatigue, self-reported depression scores decreased dramatically across the study period.

Despite an early end due to low enrollment, we believe this study provides a proof-of-concept for the role of baricitinib in the treatment of PBC. The treated patient demonstrated a rapid and significant decline in ALP, markers of inflammation, pruritus and self-reported depression. This constellation of both objective and subjective measures of response represent an important phenomenon that provides both insights into disease mechanisms and avenues for future investigation.

Author contributions

All authors have contributed to drafting and revising the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests. Stuart C Gordon reports financial support was provided by Eli Lilly and Company. Stuart C. Gordon, grant/research support: AbbVie Pharmaceuticals, Brigham and Women's Hospital, CymaBay, DURECT, Eiger, Genfit, Gilead Sciences, GlaxoSmithKline, Intercept, Pilant, Shire, Merck, Viking; advisory Board: CymaBay; royalties: UptoDate. Sheri Trudeau and Jonathan Uhas have no conflict of interest to report. Sujatro Chakladar, Ana Pinto-Correia, Klaus Gottlieb, Arie Regev, and Doug Schlichting are employees of Eli Lilly and Company and may own stock or stock options in Eli Lilly and Company.

Acknowledgments

The authors thank Dana Schamberger of Syneos Health for assisting with manuscript preparation and process support. This study was funded by Eli Lilly and Company.

References

[1] M.M. Kaplan, M.E. Gershwin, Primary biliary cirrhosis, N. Engl. J. Med. 353 (2005) 1261–1273.
[2] K.D. Lindor, M.E. Gershwin, R. Poupon, M. Kaplan, N.V. Bergasa, E.J. Heathcote, Primary biliary cirrhosis, Hepatology 50 (2009) 291–308.
[3] E.M.M. Kuiper, B.E. Hansen, R.A. de Vries, J.W. den Ouden-Muller, can Ditzhuijsen Tjm, E.B. Haagsma, et al., Improved prognosis of patients with primary biliary cirrhosis that have a biochemical response to ursodeoxycholic acid, Gastroenterology 136 (2009) 1281–1287.
[4] A. Pares, L. Caballeria, J. Rodes, Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic Acid, Gastroenterology 130 (2006) 715–720.
[5] C. Corpechot, L. Abenavoli, N. Rabahi, Y. Chrétien, T. Andréani, C. Johanet, et al., Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis, Hepatology 48 (2008) 871–877.

[6] G.M. Hirschfield, A. Mason, V. Luketic, K. Lindor, S.C. Gordon, M. Mayo, et al., Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid, Gastroenterology 148 (2015) 751–761.e8.
[7] U.S. Food & Drug Administration (FDA), Ocaliva Package Insert, 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/207999s000lbl.pdf. (Accessed 16 May 2020).
[8] J.K. Dyson, N. Wilson, L. Jopson, G. Mells, A. Bathgate, M.A. Heneghan, et al., The inter-relationship of symptom severity and quality of life in 2055 patients with primary biliary cholangitis, Aliment. Pharmacol. Ther. 44 (2016) 1039–1050.
[9] C.D. Fuchs, E. Halilbasic, M. Trauner, Novel treatments targeting metabolic and signaling mechanisms in primary biliary cholangitis, Clin. Liver Dis. 9 (2017) 43–47.
[10] K.A. Papp, M.A. Menter, M. Raman, D. Disch, D.E. Schlichting, C. Gaich, et al., A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis, Br. J. Dermatol. 174 (2016) 1266–1276.
[11] Christine Blome, Fleur Fritz, Joachim Gerss, Reich Adam, Toshiya Ebata, Matthias Augustin, Jacek C. Szepietowski, Sonja Stände, Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus, Acta Derm. Venereol. 92 (5) (2012 Sep) 502–507. PMID: 2217009.
[12] G.B. Neuberge, Measures of fatigue: the fatigue questionnaire, fatigue severity scale, multidimensional assessment of fatigue scale, and short form-36 vitality (Energy/Fatigue) subscale of the short form Health survey, Arthritis Rheum. 49 (2003) S175–S183.
[13] N.Q. Phan, C. Blome, F. Fritz, J. Gerss, A. Reich, T. Ebata, et al., Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus, Acta Derm. Venereol. 92 (2012) 502–507.
[14] R. Lichtinghagen, D. Pietsch, H. Bantel, M.P. Manns, K. Brand, M.J. Bahr, The Enhanced Liver Fibrosis (ELF) score: normal values, influence factors and proposed cut-off values, J. Hepatol. 59 (2013) 236–342.
[15] A.J. Rush, M.H. Trivedi, H.M. Ibrahim, T.J. Carmody, B. Arnow, D.N. Klein, et al., The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression, Biol. Psychiatr. 54 (2003) 573–583.
[16] G.M. Hirschfield, X. Liu, C. Xu, Y. Lu, G. Xie, Y. Lu, et al., Primary biliary cirrhosis associated with HLA, IL12A, and IL12RB2 variants, N. Engl. J. Med. 360 (2009) 2544–2555.
[17] K. Kawata, M. Tsuda, G.X. Yang, W. Zhang, H. Tanaka, K. Tsuneyama, et al., Identification of potential cytokine pathways for therapeutic intervention in murine primary biliary cirrhosis, PloS One 8 (2013), e74225.
[18] J.S. Fridman, P.A. Scherle, R. Collins, T.C. Burn, Y. Li, J. Li, et al., Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050, J. Immunol. 184 (2010) 5298–5307.
[19] J.J. O'Shea, D.M. Schwartz, A.V. Villarino, M. Gadina, I.B. McInnes, A. Laurence, The JAK-STAT pathway: impact on human disease and therapeutic intervention, Annu. Rev. Med. 66 (2015) 311–328.
[20] J.J. O'Shea, A. Kontzias, K. Yamaoka, Y. Tanaka, A. Laurence, Janus kinase inhibitors in autoimmune diseases, Ann. Rheum. Dis. 72 (2013) ii111–ii115.
[21] R.E. Poupon, Primary biliary cirrhosis, in: third ed., in: D. Zakim, T.D. Boyer (Eds.), Hepatology. A Textbook of Liver Disease, W.B. Saunders Company, Philadelphia, London, Toronto, Montreal, Sydney, Tokyo, 1996, pp. 1329–1365.