Schweiz. Gastroenterol. 2024 · 5:59–62
https://doi.org/10.1007/s43472-024-00132-x
Published online: 3 July 2024

Advancing treatment frontiers: elafibranor and seladelpar in the management of primary biliary cholangitis

Yakir Guri · Andreas E. Kremer
Department of Gastroenterology and Hepatology, University Hospital of Zürich, University of Zürich, Zürich, Switzerland

Scan QR code & read article online

Original publication

Kowdley, K.V., C.L. Bowlus, C. Levy, U.S. Akarca, M.R. Alvares-da-Silva, P. Andreone, M. Arrese, C. Corpechot, S.M. Francque, M.A. Heneghan, P. Invernizzi, D. Jones, F.C. Kruger, E. Lawitz, M.J. Mayo, M.L. Shiffman, M.G. Swain, J.M. Valera, V. Vargas, J.M. Vierling, A. Villamil, C. Addy, J. Dietrich, J.M. Germain, S. Mazain, D. Rafailovic, B. Tadde, B. Miller, J.F. Shu, C.O. Zein, and J.M. Schattenberg, Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis. New England Journal of Medicine, 2024. 390(9): p. 795-805.
Hirschfield, G.M., C.L. Bowlus, M.J. Mayo, A.E. Kremer, J.M. Vierling, K.V. Kowdley, C. Levy, A. Villamil, A.L.L.D. Cetina, E. Janczewska, E. Zigmond, S.H. Jeong, Y. Yilmaz, Y. Kallis, C. Corpechot, P. Buggisch, P. Invernizzi, M.C.L. Hurtado, S. Bergheanu, K. Yang, Y.J. Choi, D.B. Crittenden, C.A. McWherter, and R.S. Grp, A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis. New England Journal of Medicine, 2024.

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease characterized by the progressive destruction of the small intrahepatic bile ducts, leading to cholestasis, persistent inflammation, and eventual development of liver fibrosis and cirrhosis. PBC predominantly affects middle-aged women, with a global variation in prevalence and incidence suggesting that both genetic and environmental factors might contribute to its etiology [1, 2].

The pathophysiology of PBC involves immune-mediated damage primarily targeting biliary epithelial cells, a process marked by the presence of anti-mitochondrial antibodies (AMAs) or PBC-specific anti-nuclear antibodies (sp100 or gp210) indicative of the disease. Clinically, PBC presents variably from asymptomatic liver test abnormalities to symptoms of advanced disease, notably fatigue and pruritus [1, 2]. Although ursodeoxycholic acid (UDCA) has been the cornerstone of PBC treatment for decades, improving liver biochemistry and survival [3], its efficacy is limited, with approximately 40% of patients exhibiting an inadequate response and remaining at risk of disease progression [4–6]. Furthermore, after a year of UDCA therapy, even meeting the Paris II criteria (alkaline phosphatase [AP] and glutamate oxalacetate transaminase [GOT] < 1.5 xULN and normal bilirubin) may not suffice, as shown in a comprehensive analysis involving over 1000 PBC patients across multiple centers worldwide. This study revealed that patients with advanced fibrosis, identified by liver stiffness measurements exceeding 10 kPa and/or those under the age of 62 years, faced a notable risk of requiring liver transplantation and/or liver-related mortality [7]. This underscores the ongoing need for alternative therapeutic options beyond the current standard, including the FXR agonist obeticholic acid, which, despite its anti-cholestatic, anti-inflammatory, and anti-fibrotic benefits, presents challenges such as exacerbated pruritus and hepatic decompensation in advanced disease stages in some patients [8]. In addition to these treatments, the off-label use of the panPPAR agonist bezafibrate proved efficacious in PBC management

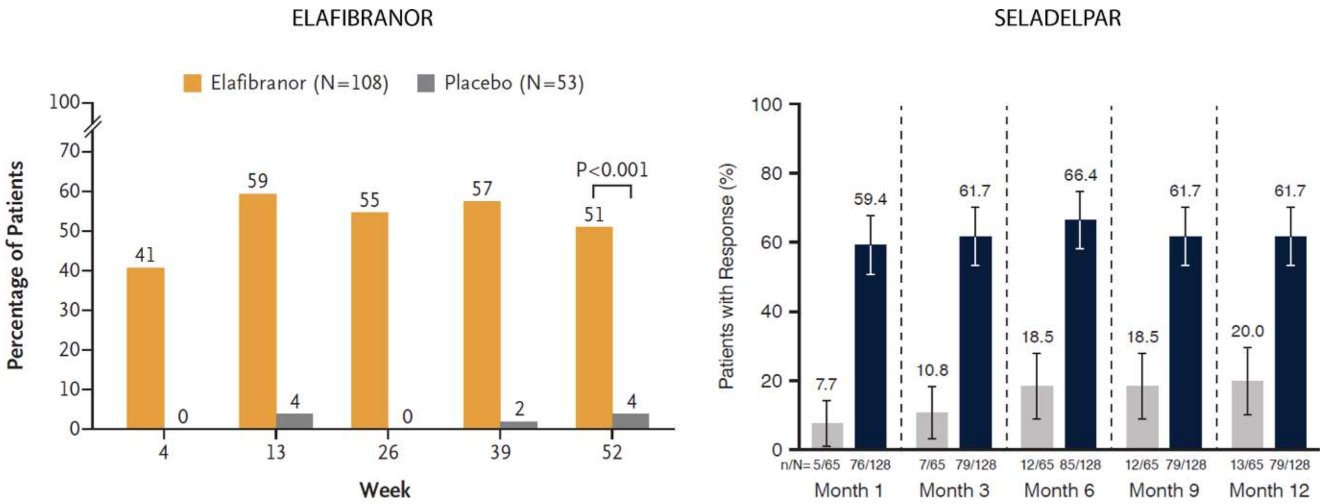

Fig. 1 ▲ Biochemical response according to the primary endpoint (AP < 1.67 xULN, AP reduction > 15% and total bilirubin < 1.0 xULN). Modified from Kowdley et al. and Hirschfield et al. [9, 10]

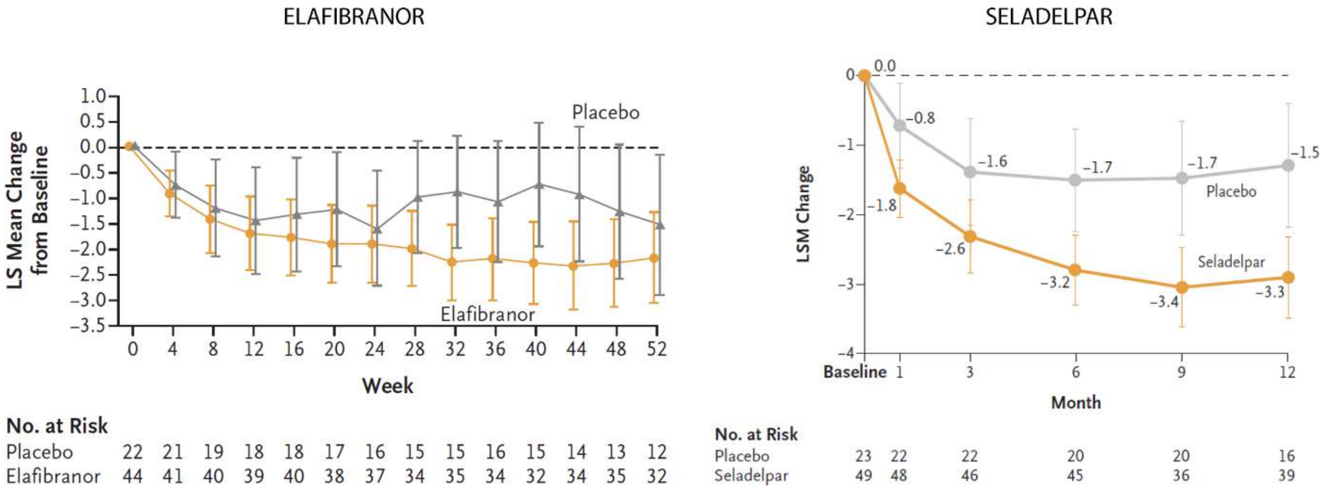

Fig. 2 ▲ Change in worst itch numeric rating scale (WI-NRS) in patients with moderate to severe pruritus as secondary endpoint. Modified from Kowdley et al. and Hirschfield et al. [9, 10]

(as seen in the BEZURSO study). However, its application is limited by significant side effects, including hepatotoxicity, which was observed in up to 6% of patients, occasionally requiring steroid therapy, myopathy, and contraindications in chronic kidney disease patients [7].

Two international, phase 3, double-blind, placebo-controlled trials investigated the efficacy and safety of the novel PPAR agonists elafibranor [9] and seladelpar [10] in PBC patients with an inadequate response to UDCA. The ELAVITE study enrolled 161 patients, whereas the RESPONSE trial included 193, both using a 2:1 randomization favoring treatment over placebo. These studies were aimed at filling the therapeutic gap by evaluating these new agents' ability to improve biochemical markers of PBC and to alleviate symptoms, particularly pruritus, while maintaining a favorable safety profile. Of note, the investigated cohorts in both trials had very similar baseline criteria such as cholestasis parameters, advanced disease stages and a significant number of patients with moderate to severe pruritus as outlined in more detail below.

As mentioned above, both trials focused on adult PBC patients exhibiting inadequate responses to UDCA, categorized by specific biochemical criteria (AP > 1.67 xULN, bilirubin normal or up to 2 xULN) with a high risk for disease progression. Importantly, inclusion criteria did not limit patients to early disease stage but also accepted those with compensated cirrhosis, allowing the assessment of treatment efficacy across a broader spectrum of PBC severity. The primary endpoint for both studies was a biochemical composite endpoint defined by AP < 1.67 xULN with a reduction of at least 15% and normal bilirubin levels that has been used in various previous trials including the POISE Study [11].

In the seladelpar study, cirrhosis was reported in 14% of participants. Conversely, the elafibranor study reported that 39% of participants had either bridging fibrosis or cirrhosis. However, this statistic applies only to the 29% of participants who underwent a baseline liver biopsy, not the entire study cohort. The elafibranor study does not provide an exact count of patients with cirrhosis alone but defines advanced disease as having liver stiffness over 10 kPa, bridging fibrosis, or cirrhosis confirmed by liver histology or stiffness measurement of 16.9 kPa or higher. Following this definition, 34% of the elafibranor group and 38% of the placebo group had advanced disease. Similarly, in the RESPONSE study with seladelpar, 36% of the treatment group and 32% of the placebo group were classified as having advanced disease using the same criteria. These data indicate that there is no significant difference in the representation of patients with advanced liver disease across these studies.

Similar to disease severity, baseline pruritus in the overall population of both studies was comparable quantified on a numerical rating scale (NRS), with 3.0 ± 3.0 for seladelpar and 3.3 ± 2.8 for elafibranor. In addition, the percentage of patients with moderate to severe pruritus was comparable, with 38% in RESPONSE and 41% in ELAVITE. In the pre-specified population with baseline moderate-to-severe itch (NRS $\geq$ 4), the RESPONSE study mean NRS was 6.6 ± 1.2 in the seladelpar arm; the proper comparison is not reported for elafibranor. Differences in the recording of pruritus and statistical plans between studies are recognized; however, a re-analysis of pruritus data for the RESPONSE study using the approach reported by Kowdley et al. found the same highly significant observation for the key secondary endpoint of pruritus between seladelpar-treated participants and those receiving placebo.

Elafibranor exhibited a significant biochemical response in 51% of treated patients versus 4% receiving placebo [9]. Seladelpar demonstrated a comparable efficacy, with 62% of treated patients experiencing a biochemical response compared with 20% in the placebo group (**Fig. 1**; [10]). As an important novel treatment goal, elafibranor resulted in AP normalization in 15% and seladelpar in 25% of all treated patients within 1 year of therapy. Notably, seladelpar achieved a secondary endpoint by substantially reducing itch severity in patients with moderate to severe pruritus, as quantified on an NRS whereas elafibranor only indicated a trend toward improvement (**Fig. 2**). Using other itch scores, such as the 5-D itch scale and the itch domain of the PBC-40 questionnaire, both drugs achieved significant results.

In summarizing the findings from the two large clinical studies on seladelpar and elafibranor for the second-line treatment of PBC, it is evident that both medications offer rapid and strong biochemical improvements. Aside from this benefit on the underlying disease, seladelpar and potentially also elafibranor attenuate pruritus in those patients with a significant symptom burden, a major clinical unmet need in PBC. The introduction of these two medications represents a significant advance in the treatment landscape of PBC, particularly for those inadequately served by existing therapies.

Future research should focus on long-term outcomes and direct comparisons between these new therapeutic agents to further refine PBC management strategies. It is crucial to evaluate their efficacy in populations with advanced disease stages and to continue innovation in developing tailored treatment strategies to address the complex needs of PBC patients. These developments not only offer new options for disease management but also highlight the importance of ongoing innovation and personalized treatment strategies in addressing the complex needs of PBC patients.

Corresponding address

Prof. Dr. med. Andreas E. Kremer, PhD, MHBA
Department of Gastroenterology and Hepatology, University Hospital of Zürich, University of Zürich
Zürich, Switzerland
Andreas.Kremer@usz.ch

Funding. Open access funding provided by University of Zurich

Conflict of interest. Y. Guri and A. Kremer declare that they have no competing interests.

References

1. Boonstra K, Beuers U, Ponsioen CY (2012) Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: A systematic review. J Hepatol 56(5):1181–1188
2. Kremer AE, Namer B, Bolier R, Fischer MJ, Elferink RPO, Beuers U (2015) Pathogenesis and Management of Pruritus in PBC and PSC. Dig Dis 33:164–175
3. Harms MH, van Buuren HR, Corpechot C, Thorburn D, Janssen HLA, Lindor KD, Hirschfield GM, Pares A, Floreani A, Mayo MJ, Invernizzi P, Battezzati PM, Nevens F, Ponsioen CY, Mason AL, Kowdley KV, Lammers WJ, Hansen BE, van der Meer AJ (2019) Ursodeoxycholic acid therapy and liver transplant-free survival in patients with primary biliary cholangitis. J Hepatol 71(2):357–365
4. Goet JC, Hirschfield GM (2019) Guideline review: British Society of Gastroenterology/UK-PBC Primary Biliary Cholangitis treatment and management guidelines. Frontline Gastroenterol 10(3):316–319
5. Hirschfield GM, Dyson JK, Alexander GJM, Chapman MH, Collier J, Hübscher S, Patanwala I, Pereira SP, Thain C, Thorburn D, Tiniakos D, Walmsley M, Webster G, Jones DEJ (2018) The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. Gut 67(9):1568–1594
6. Corpechot C, Abenavoli L, Rabahi N, Chrétien Y, Andréani T, Johanet C, Chazouilléres O, Poupon R (2008) Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology 48(3):871–877
7. Corpechot, C., S. Lemoinne, P.A. Soret, B. Hansen, G. Hirschfield, A. Gulamhusein, A.J. Montano-Loza, E. Lytvyak, A. Pares, I. Olivas, J.E. Eaton, K.T. Osman, C. Schramm, M. Sebode, A.W. Lohse, G. Dalekos, N. Gatselis, F. Nevens, N. Cazzagon, A. Zago, F.P. Russo, A. Floreani, N. Abbas, P. Trivedi, D. Thorburn, F. Saffioti, L. Barkai, D. Roccarina, V. Calvaruso, A. Fichera, A. Delamarre, N. Sobenko, A.M. Villamil, E. Medina-Morales, A. Bonder, V. Patwardhan, C. Rigamonti, M. Carbone, P. Invernizzi, L. Cristoferi, A. van der Meer, R. de Veer, E. Zigmond, E. Yehezkel, A.E. Kremer, A. Deibel, T. Bruns, K. Grosse, A. Wetten, J.K. Dyson, D. Jones, J. Dumortier, G.P. Pageaux, V. de Ledinghen, O. Chazouilleres, F. Carrat, Global, and E.R.N.R.-L.P.S. Groups, Adequate versus deep response to ursodeoxycholic acid in primary biliary cholangitis: To what extent and under what conditions is normal alkaline phosphatase level associated with complication-free survival gain? Hepatology, 2024. 79(1): p. 39–48.
8. Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, Drenth JPH, Pockros PJ, Regula J, Beuers U, Trauner M, Jones DE, Floreani A, Hohenester S, Luketic V, Shiffman M, van Erpecum KJ, Vargas V, Vincent C, Hirschfield GM, Shah H, Hansen B, Lindor KD, Marschall HU, Kowdley KV, Hooshmand-Rad R, Marmon T,

Sheeron S, Pencek R, MacConell L, Pruzanski M, Shapiro D, Grp PS (2016) A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. N Engl J Med 375(7):631–643

9. Kowdley KV, Bowlus CL, Levy C, Akarca US, Alvares-da-Silva MR, Andreone P, Arrese M, Corpechot C, Francque SM, Heneghan MA, Invernizzi P, Jones D, Kruger FC, Lawitz E, Mayo MJ, Shiffman ML, Swain MG, Valera JM, Vargas V, Vierling JM, Villamil A, Addy C, Dietrich J, Germain JM, Mazain S, Rafailovic D, Tadde B, Miller B, Shu JF, Zein CO, Schattenberg JM (2024) Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis. N Engl J Med 390(9):795–805
10. Hirschfield GM, Bowlus CL, Mayo MJ, Kremer AE, Vierling JM, Kowdley KV, Levy C, Villamil A, Cetina ALLD, Janczewska E, Zigmond E, Jeong SH, Yilmaz Y, Kallis Y, Corpechot C, Buggisch P, Invernizzi P, Hurtado MCL, Bergheanu S, Yang K, Choi YJ, Crittenden DB, McWherter CA, Grp RS (2024) A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis. N Engl J Med
11. Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, Drenth JP, Pockros PJ, Regula J, Beuers U, Trauner M, Jones DE, Floreani A, Hohenester S, Luketic V, Shiffman M, van Erpecum KJ, Vargas V, Vincent C, Hirschfield GM, Shah H, Hansen B, Lindor KD, Marschall HU, Kowdley KV, Hooshmand-Rad R, Marmon T, Sheeron S, Pencek R, MacConell L, Pruzanski M, Shapiro D, A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. N Engl J Med (2016) 375(7), pp 631–643

Buchbesprechung

Alexandra Köhler, Mirko Gründer

Online-Marketing für die erfolgreiche Arztpraxis

Website, SEO, Social Media, Werberecht

Berlin Heidelberg: Springer 2023, 3. Auflage, 199 S., 22 Abb., (ISBN: *978-3-662-67917-3 (Softcover), 978-3-662-67918-0 (eBook)*), 49,99 EUR

Das 200 Seiten starke Fachbuch „Online-Marketing für die erfolgreiche Arztpraxis" aus der Reihe „Erfolgskonzepte Praxis- & Krankenhaus-Management" informiert umfassend über die wichtigsten Aspekte des digitalen Auftritts von Arztpraxen. Von der Praxiswebsite über Suchmaschinenmarketing bis hin zu den verschiedenen Social-Media-Kanälen ist alles in dem Ratgeber enthalten, der Ende 2023 in 3. Auflage im Springer Verlag erschienen ist. Auch rechtliche Grundlagen wie das Heilmittelwerbegesetz und die Datenschutzgrundverordnung werden mit aktuellen Gerichtsurteilen untermauert und erläutert.

Das 1. Buch über Online-Marketing und Internetpräsenz für die Arztpraxis! ♦ Vorstellung neuer Trends wie Twitter, Blog und Apps ♦ Mit Checklisten, viel Praxis-Know-how und Experteninterviews (link.springer.com)

„Praxisnah" ist für mich auch das wichtigste Stichwort, wenn ich das Fachbuch beschreiben soll. Die Autoren Alexandra Köhler und Mirko Gründer wissen, wie es in den Praxen aussieht, dass weder wir Ärzte noch unsere Medizinischen Fachangestellten viel Zeit haben. Deshalb raten sie, ausgewählte Kommunikationsmaßnahmen, die zur jeweiligen Praxis passen, so umzusetzen, wie es der Zeitplan zulässt.

Viele Zwischenüberschriften und Praxistipps machen es leicht, die Inhalte zu erfassen und das für sich Relevante herauszufiltern. Am Ende jedes Kapitels, insgesamt acht an der Zahl, gibt ein Experte in einem kurzen Interview seine Sicht von außen wieder. Zu Wort kommen IT- und Marketingspezialisten, Rechtsanwälte und bloggende Ärztinnen.

„Online-Marketing für die erfolgreiche Arztpraxis" kann ich jeder Ärzt*in mit eigener Praxis empfehlen. Denn – auch wenn wir am liebsten am Patienten arbeiten – ohne digitale Präsenz geht es nicht mehr. Das Fachbuch ist eine sehr gute Orientierungshilfe für die praktische Umsetzung einer Praxiswebsite mit einer Liste von Ärzteverzeichnissen, in die man sich eintragen lassen kann, und vielen fundierten Tipps für E-Mail-, Online- und Social Media-Marketing.

Dr. Annett Kleinschmidt, Berlin