Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor for 24 Weeks or Longer in People with Cystic Fibrosis and One or More F508del Alleles: Interim Results of an Open-Label Phase 3 Clinical Trial

Rachel Linnemann, *Emory University*
M Griese, *Ludwig Maximilians Univ Munchen*
S Costa, *University of Messina*
MA Mall, *Charite Univ Med Berlin*
EF McKone, *St Vincents Univ Hosp*
D Polineni, *University of Kansas*
BS Quon, *University of British Columbia*
FC Ringshausen, *Hannover Medical School*
JL Taylor-Cousar, *Natl Jewish Hlth*
NJ Withers, *Royal Devon & Exeter NHS Fdn Trust*

Only first 10 authors above; see publication for full author list.

Journal Title: AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE

Volume: Volume 203, Number 3

Publisher: AMER THORACIC SOC | 2021-02-01, Pages 381-385

Type of Work: Article

Publisher DOI: 10.1164/rccm.202008-3176LE

10. Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. *N Engl J Med* 1968;278:1355–1360.

Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor for 24 Weeks or Longer in People with Cystic Fibrosis and One or More *F508del* Alleles: Interim Results of an Open-Label Phase 3 Clinical Trial

To the Editor:

Cystic fibrosis (CF) is caused by mutations in the *CFTR* (CF transmembrane conductance regulator) gene (1). The most common *CFTR* mutation in populations of European descent is *F508del*, with up to 90% of people with CF (pwCF) having one or more *F508del* alleles (2–4).

Two pivotal phase 3 studies of a triple-combination regimen consisting of small-molecule CFTR modulators elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) showed unprecedented clinical efficacy in pwCF 12 years old or older heterozygous for the *F508del-CFTR* mutation and a minimal function mutation (*F*/MF; an MF mutation results in either no CFTR protein or a CFTR protein that does not respond to IVA and TEZ/IVA *in vitro*) or homozygous for *F508del* (*F*/*F*) (5–7). ELX/TEZ/IVA was generally safe and well tolerated in both studies (5, 6).

Eligible participants from both pivotal phase 3 studies could elect to participate in an ongoing, phase 3, open-label extension (OLE) study to evaluate the long-term safety and efficacy of ELX/TEZ/IVA. We report the results of an interim analysis of the OLE performed after the last ongoing participant had completed the Week 24 visit. Final results from this study will be published after study completion. These interim results have been accepted for oral presentation (8).

Methods

Participants who completed the last visit of the 24-week treatment period in the *F*/MF pivotal study (NCT03525444) or of the 4-week treatment period in the *F*/*F* pivotal study (NCT03525548) and who met other eligibility criteria could enroll in the OLE (NCT03525574). In the OLE, all participants receive ELX 200 mg/TEZ 100 mg/IVA 150 mg each morning and IVA 150 mg each evening.

The primary objective of the OLE is to evaluate long-term safety and tolerability of ELX/TEZ/IVA in pwCF with one or more *F508del* mutations. Secondary objectives include evaluating long-term efficacy and pharmacodynamics (PD) of ELX/TEZ/IVA. The primary endpoint is safety as assessed by adverse events (AEs), clinical laboratory values, vital signs, ECGs, and pulse oximetry. Secondary endpoints include absolute change from parent study baseline in FEV_1% predicted ($ppFEV_1$), sweat chloride (SwCl) concentration, body mass index (BMI), and CF Questionnaire-Revised (CFQ-R) respiratory domain (RD) score in addition to the cumulative number of pulmonary exacerbations (PEx).

An interim analysis with prespecified analyses was conducted when the last ongoing participant reached their Week 24 visit (i.e., the data cutoff). Safety and efficacy data sets included all participants who received one or more doses of ELX/TEZ/IVA during the OLE. Safety data include events up to the data cutoff for the OLE interim analysis. Parent study baseline (before ELX/TEZ/IVA treatment) was used as the baseline for the efficacy analyses; for *F*/*F* participants, the baseline in the parent study was assessed after a 4-week run-in period with TEZ/IVA. $ppFEV_1$, SwCl, BMI, and CFQ-R RD data were analyzed using a mixed-effects model for repeated measures with absolute change from baseline as the dependent variable. PEx event rate was calculated starting from each participant's first dose of ELX/TEZ/IVA (whether during the parent study or OLE) using a negative binomial regression model.

Participants enrolling from the *F*/*F* pivotal study entered the OLE earlier and therefore in this interim analysis, had longer follow-up than those entering from the *F*/MF pivotal study. For *F*/*F* participants, the most recent $ppFEV_1$ and BMI were obtained at Week 36, whereas the most recent SwCl concentration and CFQ-R RD score were obtained at Week 24.

Results

A total of 506 participants received ELX/TEZ/IVA in this study ($n = 399$ *F*/MF; $n = 107$ *F*/*F*). Participant demographics were similar to those observed in the pivotal studies (5, 6). A total of 471 (93.1%) participants experienced AEs (Table 1); AE rates in the ELX/TEZ/IVA arm of the larger, longer *F*/MF pivotal study, which was the primary source of phase 3 safety data, are provided for comparison (5, 9). The majority of participants had mild or moderate AEs that were similar to those observed in the pivotal studies (5, 6). The most common AEs included infective PEx of CF (exposure-adjusted rate, 49.6 per 100 participant-years), cough (44.3), and oropharyngeal pain (25.7). A total of 80 (15.8%) participants experienced serious AEs (exposure-adjusted rate, 27.5 per 100 participant-years), with infective PEx of CF, hemoptysis, and distal intestinal obstruction syndrome as the more common events. Seven participants (1.4%) had AEs resulting in treatment

Supported by Vertex Pharmaceuticals Inc., which participated in the design, statistical analysis, and interpretation of the data and provided editorial and writing assistance.

Author Contributions: The study sponsor (Vertex Pharmaceuticals, Inc.) designed the protocol in collaboration with the academic authors. Site investigators collected the data, which were analyzed by the sponsor. All authors contributed to data interpretation, conception, drafting, and/or revisions to the manuscript, and all approved the final version submitted for publication. All authors had full access to the study data, and M.G. had the final responsibility for the decision to submit for publication.

Data sharing statement: Vertex is committed to advancing medical science and improving the health of people with cystic fibrosis. This includes the responsible sharing of clinical trial data with qualified researchers. Proposals for the use of these data will be reviewed by a scientific board. Approvals are at the discretion of Vertex and will be dependent on the nature of the request, the merit of the research proposed, and the intended use of the data. Please contact CTDS@vrtx.com if you would like to submit a proposal or need more information.

Originally Published in Press as DOI: 10.1164/rccm.202008-3176LE on September 24, 2020

Table 1. Adverse Events

	OLE Study (*N* = 506; *Mean Duration of Exposure: 37.2 wk*)		*F*/MF Pivotal Study* ELX/TEZ/IVA Arm (*n* = 202; *Mean Duration of Exposure: 23.6 wk*)	
	Participants with AEs [*n* (%)]	Event Rate per 100 Participant-Years	Participants with AEs [*n* (%)]	Event Rate per 100 Participant-Years
Any AE	471 (93.1)	739.9	188 (93.1)	1,096.0
AEs by maximum severity				
Mild	180 (35.6)	ND	67 (33.2)	ND
Moderate	238 (47.0)	ND	102 (50.5)	ND
Severe	51 (10.1)	ND	19 (9.4)	ND
Life-threatening†	2 (0.4)	ND	0	ND
AEs leading to treatment discontinuation	7 (1.4)	3.3	2 (1.0)	3.0
AEs leading to treatment interruption	29 (5.7)	13.7	19 (9.4)	26.0
AEs leading to death	0	0	0	0
Most common AEs in the OLE study (occurring in ⩾10% of participants)				
Infective pulmonary exacerbation of CF	127 (25.1)	49.6	44 (21.8)	64.9
Cough	118 (23.3)	44.3	34 (16.8)	38.9
Oropharyngeal pain	74 (14.6)	25.7	20 (9.9)	27.0
Nasopharyngitis	69 (13.6)	21.6	22 (10.9)	30.0
Headache	66 (13.0)	24.9	35 (17.3)	48.9
Sputum increased	63 (12.5)	20.6	40 (19.8)	46.9
Upper respiratory tract infection	60 (11.9)	18.3	24 (11.9)	30.0
Fatigue	51 (10.1)	16.3	9 (4.5)	9.0
SAEs	80 (15.8)	27.5	28 (13.9)	36.9
Most common SAEs (occurring in ⩾1% of participants)				
Infective pulmonary exacerbation of CF	42 (8.3)	12.2	11 (5.4)	12.0
Hemoptysis	5 (1.0)	1.5	2 (1.0)	2.0
Distal intestinal obstruction syndrome	5 (1.0)	1.5	1 (0.5)	1.0
Any rash event	50 (9.9)	15.8	22 (10.9)	30.0
SAEs	1 (0.2)	0.3	3 (1.5)	3.0
Leading to treatment interruption	5 (1.0)	1.3	4 (2.0)	4.0
Leading to treatment discontinuation	1 (0.2)	0.3	1 (0.5)	1.0
ALT or AST increase‡				
>3× to ⩽5× ULN	21 (4.2)	ND	11 (5.4)	ND
>5× to ⩽8× ULN	8 (1.6)	ND	2 (1.0)	ND
>8× ULN	3 (0.6)	ND	3 (1.5)	ND
Elevated transaminase AEs‡				
Any AEs	36 (7.1)	16.5	22 (10.9)	42.9
SAEs	2 (0.4)	1.0	0	0
Leading to treatment interruption	11 (2.2)	5.1	2 (1.0)	3.0
Leading to treatment discontinuation	3 (0.6)	1.5	0	0

Definition of abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CF = cystic fibrosis; ELX = elexacaftor; *F*/MF = heterozygous for the *F508del-CFTR* mutation and a minimal function *CFTR* mutation; IVA = ivacaftor; ND = not determined; OLE = open-label extension; SAE = serious adverse event; TEZ = tezacaftor; ULN = upper limit of normal.

*Some of the data from the *F*/MF pivotal study were previously published (5) but are provided here for comparison.

†The life-threatening AEs were a suicide attempt and a pulmonary hemorrhage.

‡In the placebo arm of the *F*/MF pivotal study, 8 (4.0%) participants had an elevated transaminase AE. Laboratory elevations in ALT or AST of >3× to ⩽5× ULN, >5× to ⩽8× ULN, and >8× ULN were seen in 8 (4.0%), 1 (0.5%), and 2 (1.0%) participants, respectively.

discontinuation; these AEs included liver events ($n = 4$), depression ($n = 1$), rash ($n = 1$), and tinnitus and contusion ($n = 1$ [in the same participant]). AEs of elevated transaminases occurred in 36 (7.1%) participants, and laboratory elevations in alanine aminotransferase or aspartate aminotransferase >3×, >5×, and >8× the upper limit of normal occurred in 32 (6.3%), 11 (2.2%), and 3 (0.6%) participants, respectively.

Key efficacy and PD data from the OLE and parent studies are provided in Figure 1. In *F*/MF participants, the mean absolute changes from baseline (95% confidence interval [CI]) in $ppFEV_1$ at

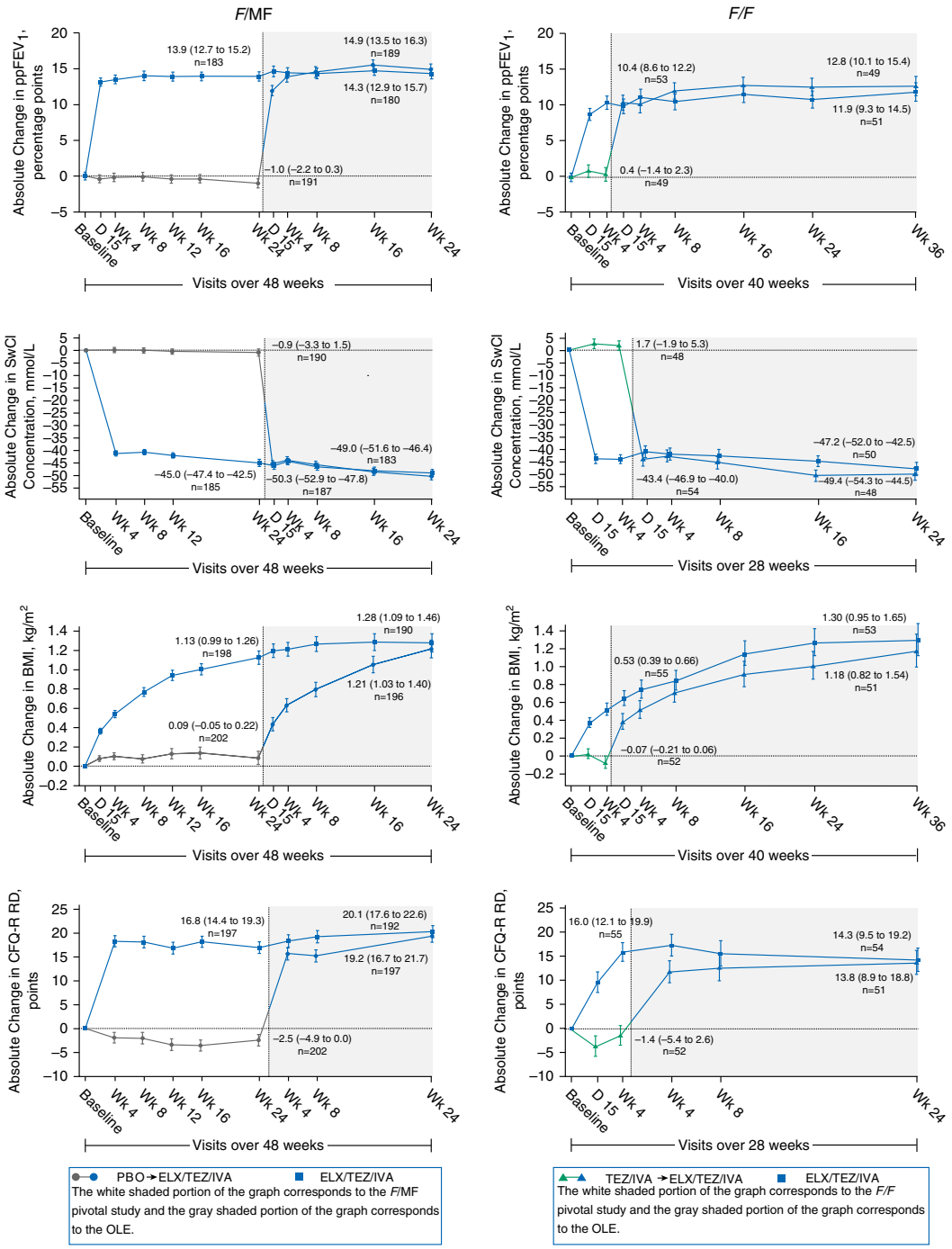

Figure 1. Mixed-effects model for repeated measures analysis of absolute change from baseline in FEV_1% predicted ($ppFEV_1$), sweat chloride (SwCl), body mass index (BMI), and Cystic Fibrosis Questionnaire-Revised respiratory domain (CFQ-R RD) by visit. The graphed data represent the least squares mean (SE) absolute change from parent study baseline by mixed-effects model for repeated measures at each visit. The data labels on each plot represent the least squares mean (95% confidence interval) absolute change from parent study baseline and the number of evaluable participants for that visit. For participants heterozygous for the *F508del-CFTR* mutation and a minimal function *CFTR* mutation (*F*/MF) (5), the data labels correspond with the Week 24 visit of the *F*/MF pivotal study and the Week 24 visit of the open-label extension. For participants homozygous for the *F508del-CFTR* mutation (*F/F*) (6), the data labels correspond with the Week 4 visit of the *F/F* pivotal study and the Week 24 (SwCl and CFQ-R RD) or Week 36 visit ($ppFEV_1$ and BMI) of the open-label extension. Baseline for *F/F* participants occurred after a 4-week run-in with tezacaftor (TEZ)/ivacaftor (IVA). SwCl and CFQ-R RD were assessed through Week 24 in all participants. The $ppFEV_1$ and BMI were assessed through Week 24 in participants with *F*/MF genotypes and through Week 36 in participants with the *F/F* genotype. For participants with *F*/MF genotypes, $n = 203$ for those who received placebo in the 24-week *F*/MF pivotal study and $n = 196$ for those treated with elexacaftor (ELX)/TEZ/IVA. For participants with the *F/F* genotype, $n = 52$ for those treated with TEZ/IVA and $n = 55$ for those treated with ELX/TEZ/IVA in the 4-week *F/F* pivotal study. OLE = open-label extension; PBO = placebo.

Week 24 were 14.9 (13.5–16.3) and 14.3 (12.9–15.7) percentage points in those who had been in the respective placebo ($n = 189$) or ELX/TEZ/IVA ($n = 180$) groups in the *F*/MF pivotal study. Among *F*/MF participants, the estimated PEx event rate per 48 weeks (95% CI) was 0.30 (0.24–0.39) ($n = 403$). In *F*/*F* participants, the mean absolute changes from baseline (95% CI) in $ppFEV_1$ at Week 36 were 12.8 (10.1–15.4) and 11.9 (9.3–14.5) percentage points in those who had been in the TEZ/IVA ($n = 49$) or ELX/TEZ/IVA ($n = 51$) groups, respectively, in the *F*/*F* pivotal study. Among *F*/*F* participants, the estimated PEx event rate per 48 weeks (95% CI) was 0.30 (0.20–0.45) ($n = 107$). Efficacy in these and all other secondary endpoints tested was comparable with and maintained from parent studies.

Discussion

Safety results from this interim analysis were consistent with the initial 24-week placebo-controlled *F*/MF pivotal study, with similar or lower exposure-adjusted event rates observed in the OLE (Table 1) (5). ELX/TEZ/IVA was generally safe and well tolerated. Most AEs were consistent with common manifestations of CF and were not treatment limiting (3, 10). In participants who received ELX/TEZ/IVA in parent studies, improvements in efficacy and PD measures, including $ppFEV_1$, SwCl concentration, BMI, CFQ-R RD score, and PEx event rate, were maintained or continued to improve further over 24 weeks (*F*/MF genotypes) or 36 weeks (*F*/*F* genotype) of additional treatment. These results validate the durability of ELX/TEZ/IVA efficacy responses, with no emerging safety concerns. Among participants who had received placebo or TEZ/IVA in the respective parent studies, initiation of ELX/TEZ/IVA rapidly led to marked improvements in these efficacy measures that were consistent with the results seen in the ELX/TEZ/IVA arms of those parent studies. Thus, the results of this combined-group interim analysis demonstrate the safety and sustained efficacy of long-term ELX/TEZ/IVA treatment in pwCF 12 years old or older with one or more *F508del* alleles. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Acknowledgment: Editorial coordination and support were provided by Morgan Deng, Pharm.D., who is an employee of Vertex Pharmaceuticals, Inc., and may own stock or stock options in that company. Medical writing and editorial support were provided by Samantha Keller, Ph.D., and Karen Kaluza Smith, Ph.D., C.M.P.P., of ArticulateScience LLC, and were funded by Vertex Pharmaceuticals, Inc.

Matthias Griese, M.D.*
Ludwig Maximilians University
Munich, Germany
and
German Center for Lung Research
Munich, Germany

Stefano Costa, M.D.
University of Messina
Messina, Italy

Rachel W. Linnemann, M.D.
Emory University
Atlanta, Georgia

Marcus A. Mall, M.D.
Charité–Universitätsmedizin Berlin
Berlin, Germany
and
German Center for Lung Research
Berlin, Germany

Edward F. McKone, M.D.
St. Vincent's University Hospital
Dublin, Ireland

Deepika Polineni, M.D.
University of Kansas Medical Center
Kansas City, Kansas

Bradley S. Quon, M.D.
University of British Columbia
Vancouver, British Columbia, Canada
and
St. Paul's Hospital
Vancouver, British Columbia, Canada

Felix C. Ringshausen, M.D.
Hannover Medical School
Hannover, Germany
and
German Center for Lung Research
Hannover, Germany

Jennifer L. Taylor-Cousar, M.D.
National Jewish Health
Denver, Colorado

Nicholas J. Withers, M.D.
Royal Devon and Exeter NHS Foundation Trust
Exeter, United Kingdom

Samuel M. Moskowitz, M.D.
Vertex Pharmaceuticals Incorporated
Boston, Massachusetts

Cori L. Daines, M.D.
University of Arizona
Tucson, Arizona

ORCID IDs: 0000-0003-0113-912X (M.G.); 0000-0002-4057-2199 (M.A.M.); 0000-0001-9084-4968 (F.C.R.); 0000-0002-5436-9722 (J.L.T.-C.); 0000-0002-5326-0258 (N.J.W.).

*Corresponding author (e-mail: matthias.griese@med.uni-muenchen.de).

References

1. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, *et al*. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* 1989;245:1066–1073.
2. Mall MA, Mayer-Hamblett N, Rowe SM. Cystic fibrosis: emergence of highly effective targeted therapeutics and potential clinical implications. *Am J Respir Crit Care Med* 2020;201:1193–1208.
3. Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, *et al*. The future of cystic fibrosis care: a global perspective. *Lancet Respir Med* 2020;8:65–124.
4. Cystic Fibrosis Trust. UK Cystic Fibrosis Registry 2018 Annual Data Report. London, United Kingdom: Cystic Fibrosis Trust; 2019 [accessed 2020 Dec 10]. Available from: https://www.cysticfibrosis.org.uk/the-work-we-do/uk-cf-registry/reporting-and-resources.

5. Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, *et al*.; VX17-445-102 Study Group. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single *Phe508del* allele. *N Engl J Med* 2019;381: 1809–1819.
6. Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, *et al*.; VX17-445-103 Trial Group. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the *F508del* mutation: a double-blind, randomised, phase 3 trial. *Lancet* 2019;394: 1940–1948.
7. Keating D, Marigowda G, Burr L, Daines C, Mall MA, McKone EF, *et al*.; VX16-445-001 Study Group. VX-445-tezacaftor-ivacaftor in patients with cystic fibrosis and one or two *Phe508del* alleles. *N Engl J Med* 2018;379:1612–1620.
8. Griese M, Costa S, Linnemann RW, Mall MA, McKone EF, Polineni D, *et al*. A phase 3, open-label extension study of elexacaftor/ tezacaftor/ivacaftor: interim analysis of safety and efficacy in people with cystic fibrosis and *F508del*/minimal function (*F*/MF) or *F508del*/*F508del* (*F*/*F*) genotypes. Presentation at the 43rd Annual European Cystic Fibrosis Conference Virtual; September 24–25, 2020.
9. Taylor-Cousar JL, Mall MA, Ramsey BW, McKone EF, Tullis E, Marigowda G, *et al*. Clinical development of triple-combination CFTR modulators for cystic fibrosis patients with one or two *F508del* alleles. *ERJ Open Res* 2019;5:00082-2019.
10. Elborn JS. Cystic fibrosis. *Lancet* 2016;388:2519–2531.

Pulmonary Arterial Hypertension Caused by AhR Signal Activation Protecting against Colitis

To the Editor:

Accumulating evidence indicates that AhR (aryl hydrocarbon receptor) ligands are crucial mediators of host health and disease. The Chinese herbal medicine Qing-Dai contains high levels of AhR ligands and has been shown to induce remission of ulcerative colitis (UC) (1). A recent nationwide randomized placebo-controlled trial demonstrated that 8 weeks of Qing-Dai (0.5–2.0 g/d) intake showed effectiveness as treatment for UC (2). However, Qing-Dai has been associated with pulmonary arterial hypertension (PAH) as a potentially serious side effect (3). A Japanese nationwide survey demonstrated that Qing-Dai was used in 877 (1.8%) out of 49,320 patients with UC, and 11 patients with PAH who had a history of regularly taking Qing-Dai were reported (4). Despite the clinical importance of Qing-Dai in the field of UC, the cause-and-effect association between AhR signal activation by Qing-Dai and the development of PAH has not been fully elucidated. Therefore, we conducted a reverse translational study (from bedside back to the bench) to investigate whether Qing-Dai induces PAH experimentally. Importantly, if Qing-Dai is critically involved in the pathogenesis of PAH, it could be possible to establish a novel animal model of PAH, which might be generally used as an AhR ligand-inducing model of PAH.

All animal studies were performed in strict accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals of the NIH. Fischer 344 male rats weighing 90–110 g (CLEA Japan) were used in our experiments. Rats were allocated to eight groups according to a CE-2 diet or a diet containing 4% Qing-Dai (Fujian Province) (600 mg/kg body weight, corresponding to the 10-fold amount of therapeutic dose for patients with UC), single subcutaneous injection of 20 mg/kg Sugen 5416 (SU5416) (Abcam), and gavage of 8 mg/kg/d AhR antagonist CH223191 (Selleck). Rats were housed in a normoxic environment for 8 weeks. A gavage of CH223191 was performed every day for the final 2 weeks. Real-time quantitative PCR was performed to evaluate the relative expression of cytochrome P450 1A1 (*CYP1A1*), which is activated by AhR signaling (5). The primers and PCR protocol were described previously (6). The expression of CYP1A1 and CD31 were assessed by lung immunohistochemistry. Rabbit anti-rat CYP1A1 polyclonal antibody (1:200; Abcam) and mouse anti-rat CD31 monoclonal antibody (1:20; Elabscience) were used as the primary antibodies. Comparisons between two groups were performed by Mann-Whitney *U* test, and comparisons among multiple groups by Kruskal-Wallis test followed by Holm's method (*post hoc* analysis). A value of $P < 0.05$ was considered statistically significant.

Right ventricular systolic pressure was significantly higher in rats with the Qing-Dai diet with SU5416 compared with the normal diet group, which was ameliorated by the addition of CH223191 gavage (Figure 1A). Furthermore, the ratio of right ventricular weight to left ventricle plus septum weight as a parameter for right ventricular hypertrophy was highest in the Qing-Dai diet with SU5416 group and was significantly improved by CH223191 gavage (Figure 1B). The medial wall thickness was also increased in the Qing-Dai diet, SU5416, and Qing-Dai diet with SU5416 groups and was ameliorated by CH223191 gavage (Figures 1C and 1D). Quantitative PCR analysis revealed that the relative lung levels of *CYP1A1* mRNA were significantly elevated in the Qing-Dai diet, SU5416, and Qing-Dai diet with SU5416 groups, and these elevated levels were significantly reduced by the addition of CH223191 gavage (Figure 1E). Immunostaining of lung specimens demonstrated that CYP1A1 was expressed in CD31-positive pulmonary arterial endothelial cells in rats fed with a Qing-Dai diet. Notably, rats in the Qing-Dai diet and SU5416 injection group showed higher expression of CYP1A1 compared with the other groups (Figure 1F).

The results in this study demonstrated that the combination of subcutaneous injection of SU5416 followed by Qing-Dai intake had synergistic or additive effects on the development of PAH in rats, and that these effects were suppressed by AhR signal inhibition. In addition, the expression of CYP1A1 in rat lungs demonstrated that these effects were mediated by activation of AhR signaling in pulmonary arterial endothelial cells. It has been reported that CYP1A1 was highly induced in the lungs of SU5416-treated and hypoxia-induced PAH rats (7). These findings suggest that

Supported by research grants from the Ministry of Health, Labor and Welfare of Japan (201706009A) and the Advanced Research and Development Programs for Medical Innovation (18lk1403023h0001 and Advanced Research and Development Programs for Medical Innovation-Core Research for Evolutional Science and Technology; 16 gm1010003h0001).

Author Contributions: T.H. and T.T. performed the experiments, collected data, and performed the analyses. Y.Y., M.N., and K.F. supervised the analyses. S.U., Y.S., and M.M. supported the animal studies and collected data. E.K. and Y.H. supervised the animal studies. T.K. conceived the study and supervised the analyses. M.K. designed the experiments and supervised the research. T.H., T.T., T.K., and M.K. wrote the paper with contributions from all coauthors.

Originally Published in Press as DOI: 10.1164/rccm.202009-3385LE on October 14, 2020