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LETTER TO THE EDITOR

PHARMACOKINETICS OF COLCHICINE IN PEDIATRIC AND ADULT PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

Y. BERKUN[1], S. WASON[2], R. BRIK[3], Y. BUTBUL[3], E. BEN-CHETRIT[4], P.J. HASHKES[5], A. LIVNEH[6], S. OZEN[7], H. OZDOGAN[8], R. FAULKNER[2] and M.W. DAVIS[2]

[1]Department of Pediatrics, Hadassah Hebrew University Medical Center, Mount Scopus, Jerusalem, Israel; [2]Mutual Pharmaceutical Company, Inc., now part of Takeda Pharmaceuticals USA Inc. Deerfield, IL, USA; [3]Rambam Medical Centre, Haifa, Israel; [4]Department of Medicine, Hadassah Hebrew University Hospital, Jerusalem, Israel; [5]Shaare Zedek Medical Center, Jerusalem, Israel; [6]Sheba Medical Center, Tel Hashomer, Israel; [7]Department of Pediatrics, Hacettepe University, Ankara, Turkey; [8]Istanbul University, Cerrahpasa Medical Center, Istanbul, Turkey

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This study sought to determine the appropriate starting dose of colchicine in children aged 2 to 4 years with familial Mediterranean fever (FMF) based on steady-state pharmacokinetics in pediatric patients with FMF ≥2 to <16 years and adult patients with FMF ≥16 to ≤65 years. Outpatients received colchicine for 90 days starting with a fixed dose for 14 days (blood sampling days 14 and 15). After starting doses of colchicine (0.6 mg/day [≥2 to <4 years], 0.9 mg/day [≥4 to <6 years], 0.9 mg/day [≥6 to <12 years], 1.2 mg/day [≥12 to <16 years], and 1.2 mg/day [≥16 to ≤65 years]), the observed steady-state pharmacokinetic parameters were comparable across age groups, despite the higher doses of colchicine on a mg/kg/day basis in the younger age groups. An exception occurred with once-daily colchicine, whereby mean C_{max} for colchicine was higher in patients 4 to <6 years (9.4 ng/mL) compared with the younger and older age groups (6.1-6.7 ng/mL). Mean AUC_{0-24h} values in children 2 to <4, 6 to <12, and 12 to <16 years were similar to those in adults. However, mean AUC_{0-24h} values in children 4 to <6 years were 25% higher than those observed in adults. The results show that the recommended starting dose for children 2-4 years and 4-6 years should be 0.6 mg/day (half the US adult dose). Children aged 6 to <12 years should receive 0.9 mg/day (i.e. three-quarters of the US adult dose). The safety of colchicine in children 2 to <4 years was comparable to that in older children and adults.

Familial Mediterranean fever (FMF) is the most common inherited monogenic autoinflammatory disease, characterized by recurrent self-limited attacks of febrile serositis, including peritonitis, pleuritis, and synovitis (1, 2). The most severe complication of FMF is amyloidosis, which can lead to renal failure necessitating dialysis and kidney transplantation (3). FMF usually presents in childhood, with first disease manifestations occurring in two-thirds of patients at <10 years of age and in 80%-90% by 18 years of age (4-7), and affects Sephardic Jews, Armenians, Turks, Arabs, and other ethnic groups living around the Mediterranean basin (8).

Colchicine is considered the drug of choice for

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Mailing address: Suman Wason, MD, MBA,
Executive Director of Clinical Development,
Mutual Pharmaceutical Company, Inc.,
Takeda Pharmaceuticals USA Inc.,
Deerfield, IL, USA
Fax: +1 215 701 4162
e-mail: swason@urlpharma.com

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the treatment of patients with FMF. Continuous prophylactic treatment with colchicine controls FMF attacks and prevents the development of amyloidosis, which is the primary cause of premature death from renal failure (3, 9). The Tel Hashomer clinical criteria for the diagnosis of FMF set forth the pharmacodiagnostic utility of colchicine in conjunction with major and minor manifestations of FMF (10). Therefore, the safe use of colchicine in children may provide an earlier confirmatory diagnostic tool for definite FMF.

The recommended dosage of colchicine in the United States for FMF is 1.2-2.4 mg daily given as a single dose or 2 divided doses in adults. Lower doses are recommended in children as young as 4 years of age. The tablet formulation of colchicine is not approved for use and there are no dose recommendations for children <4 years of age, although colchicine is used in this very young population at nonstandard, inexact doses. Treatment in very young children is usually performed by crushing tablets and administering in a liquid or mixed with soft food. No pharmacokinetic studies of colchicine have been performed in children to date, and there have been only 2 pharmacokinetic studies with Food and Drug Administration (FDA)-unapproved colchicine in low numbers of adult patients with FMF reported in the literature (11, 12).

The aim of this study was to determine the steady-state pharmacokinetics and safety/tolerability of colchicine after administration of multiple oral doses of a new sprinkle formulation of colchicine in pediatric patients with FMF (≥2 to <16 years of age) compared with adult patients with FMF (≥16 to ≤65 years of age) to provide data to support dosing recommendations in children 2-4 years of age.

MATERIALS AND METHODS

Patients

Patients 2-65 years of age with a diagnosis of FMF based on a set of published criteria formulated for the diagnosis of FMF (10) were eligible for study entry. Exclusion criteria included the following: women who were pregnant based on urine pregnancy test result within 24 hours of the first dose of study medication, lactating, or sexually active and of childbearing potential if not receiving effective birth control; use of any drugs that might affect colchicine absorption or metabolism during the previous 30 days (notably, but not exclusively, P-glycoprotein, CYP3A4 and protease inhibitors, lipid-lowering drugs, and digoxin); any clinically relevant renal or hepatic dysfunction at screening; participation in any other investigational study in the previous 30 days or during the study; any history within the previous 6 months of severe, unstable, or uncontrolled neurologic, cardiovascular, gastrointestinal, hematologic, hepatic, or renal disease; self-reported history or current infection with human immunodeficiency virus (HIV) or hepatitis A, B, or C; and evidence of any disease at screening physical examination that might preclude safe participation in the study or for any other reason in the opinion of the principal investigator.

Study design

The study protocol received local independent ethics committee approval at each participating center. All patients or their parent or legal guardian provided signed written informed consent before participation in the study, which was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and adhered to the ethical principles of the Declaration of Helsinki.

This was a phase 1, multicenter, open-label, nonrandomized, parallel-group, 90-day outpatient pharmacokinetic and safety study of multiple oral doses of a new formulation of colchicine 0.3 mg. The objective was to determine whether there are pharmacokinetic differences of colchicine as a function of age. Because patients with FMF take colchicine from an early age, and continue it throughout their life, this population provided a unique opportunity to study the pharmacokinetics of colchicine across several ages. The target was to recruit 10 patients in each of the following age groups: ≥2 to <4 years, ≥4 to <6 years, ≥6 to <12 years, ≥12 to <16 years, and ≥16 to ≤65 years.

Patients were recruited at a total of 10 sites: Israel (6 sites), Turkey (2 sites), Armenia (1 site), and the United States (1 site). All of the investigators at the study sites received centralized training with respect to the study protocol to ensure homogeneous recording of data.

The study consisted of 4 phases: a 4-week screening period, a 7-day up-titration phase (if previously colchicine naïve), a 14-day fixed-dose phase with pharmacokinetic blood sampling on days 14 and 15 (pharmacokinetic period), and a flexible-dose phase for safety assessment (up to 90 days including the fixed-dose phase) (Fig. 1A). For the pharmacokinetic period, the total daily dosage was targeted at 0.6–1.2 mg/day (regardless of previous dose) according to age as 1 (a.m.) or 2 (a.m. and p.m.) doses. Colchicine-naïve patients had prior 1-week dose up-titration to reach full target dose or be scheduled directly

for baseline/day 1 (if already on colchicine). The dosage of colchicine for the fixed-dose pharmacokinetic period was targeted by patient age and within the range of the currently approved starting dosage as follows: 0.6 mg/day for ≥2 to <4 years, 0.9 mg/day for ≥4 to <6 years, 0.9 mg/day for ≥6 to <12 years, 1.2 mg/day for ≥12 to <16 years, and 1.2 mg/day for ≥16 to ≤65 years (Fig. 1B). The dosage of colchicine was selected as the currently approved starting dosage for the tablet formulation in patients ≥4 years of age and from a consensus recommendation in patients ≤5 years of age (13); the dosages were equivalent to approximately 0.03-0.05 mg/kg in the pediatric population. The dosage of colchicine had to remain fixed throughout the pharmacokinetic period or the patient was discontinued from the study. After the pharmacokinetic period, the daily dosage could be adjusted up or down during the subsequent safety assessment period as needed according to efficacy and tolerability. The required dosage of colchicine was administered using the appropriate amount of the new formulation given orally.

During the 4-week screening period (days -28 to -1), medical history within the previous year, physical examination, vital signs, routine clinical laboratory tests, virologic tests for HIV and hepatitis, and urine pregnancy test were performed. Clinic visits were scheduled at the start of the 1-week dose-titration period for those who were initially colchicine naïve (day -7), during the pharmacokinetic period (days 1, 7, 14, and 15), and during the continued dosing safety period (days 30, 60, and 90). Physical examination (including height/weight measurement for patients ≥2 to <16 years of age to monitor pediatric growth), vital signs, and urine pregnancy tests were performed at clinic visits, and clinical laboratory tests were repeated at the end of the study (day 90). Pharmacokinetic sampling was performed on days 14 and 15 (see the following text). All treatment-emergent adverse events (AEs) were coded using the MedDRA Version 13.1 adverse event dictionary and were graded by intensity (mild, moderate, or severe) and relationship to the study drug (unrelated, unlikely, possibly, or probably) by the investigator.

Pharmacokinetic measurements

Venous blood samples (1 mL in KK3 EDTA 3-EDTA tubes) were taken by direct venipuncture at 0 (predose on day 14), 0.25-0.5, 1.5-2.5, 3-5, 7-9, and 24 (predose on day 15) hours. After centrifugation, plasma samples were stored at -20°C for 24 h at the study sites and shipped to a central analytical laboratory (Frontage Laboratories Inc., Malvern, PA, USA), where they were stored at -70°C before analysis. Plasma concentrations were determined using a validated high-performance liquid chromatography method with tandem mass spectrometry detection. The assay had lower limits of quantitation of 0.020 ng/mL for colchicine and 0.05 ng/mL for 2-DMC and 3-DMC. The method has been shown to be linear over the range of 0.020-20 ng/mL. Intraday precision (%CV) and accuracy (% nominal) for colchicine were measured on 3 days; overall, the values ranged from 1.1% to 4.8% and 99.1% to 110.0%, respectively. Interday precision and accuracy were 1.8% to 4.7% and 100.1% to 106.7%, respectively.

Statistical and Pharmacokinetic Analyses

Determination of timing intervals for blood sampling

Given both practical and ethical limitations in the amount of blood that can be collected from young children, a sparse sampling approach was used. The windows for blood sampling for pharmacokinetic analysis were selected on the basis of optimal blood sampling strategy techniques. Specifically, the expectation of the Fisher information matrix determinant was optimized

A

Phase 1: Screening	Phase 2: 7-Day Up-titration	Phase 3: 14-Day Fixed Dose	Phase 4: Flexible Dose
4 weeks	If previously colchicine naïve	Pharmacokinetic blood sampling on days 14 and 15	Safety assessment (up to 90 days including phase 3)

B

Age (y)	2 to <4	4 to <6	6 to <12	12 to <16	16 to ≤65
Daily dose (mg)	0.6	0.9	0.9	1.2	1.2

Fig. 1. *A) Study design. B) Study dosing of colchicine.*

within each age cohort using E-D optimal design, WinPOPT® (WinPOPT, Dunedin, New Zealand). This method took into account between-patient variability of pharmacokinetic parameters as well as residual variability derived from a population pharmacokinetic model, assuming once- or twice-daily dosing of colchicine as well as flexible time windows. One of the time points (1.5-2.5 hours postdose) includes the expected time of maximum plasma concentration (C_{max}), one time point precedes this to better characterize absorption, and there are 2 or 3 subsequent postabsorption time points (depending on whether colchicine was administered once or twice daily) to characterize postabsorption elimination.

Descriptive statistics

Descriptive statistics were used for each group to summarize the observed steady-state pharmacokinetic data for plasma colchicine and its metabolites, including C_{max}, minimum drug concentration (C_{min}), area under the plasma concentration-time curve from time zero to 24 hours postdose (AUC_{0-24h}), and time to reach C_{max} (T_{max}).

Sample size determination

The sample size was initially determined from population pharmacokinetic analysis of plasma colchicine data obtained from phase 1 studies conducted in healthy adult subjects who received multiple doses of the immediate-release tablet formulation of colchicine. A post hoc Bayesian analysis was conducted to minimize the number of patients while maximizing the precision of the apparent total body clearance (CL/F) of colchicine in pediatric patients using the aforementioned sampling windows. Using a sample size of 10 patients within each cohort, the sampling windows were expected to result in a robust assessment of population CL/F, with standard error values ranging from 3.79% to 3.82%. Based on this sample size analysis, it was originally planned to enroll up to 50 patients (up to 10 patients/age group). Ultimately, the final number of patients to enroll was to be determined based on obtaining a precision of ≤20% in the standard error on CL/F during interim analysis of sample size. An earlier interim population pharmacokinetic analysis conducted in December 2010 analyzed 31 patients who had completed the pharmacokinetic phase of the study and found that the CL/F and V_c/F obtained a precision of ≤20%. In light of the difficulties experienced in recruitment of certain groups of pediatric patients and scientifically robust data, the current interim report analyzes 53 patients with adequate pharmacokinetic data.

Pharmacokinetic modeling

A population pharmacokinetic modeling approach was chosen as the primary statistical means of estimating the pharmacokinetic parameters. Nonlinear mixed-effects models were constructed to fit rich plasma concentrations of colchicine in 13 healthy adult subjects participating in a multiple oral dose study of the immediate-release tablet formulation. The modeling was performed using Phoenix NLME 1.1 (Pharsight Corp., Montreal, Canada). The first-order conditional estimation method with interaction was used for all model runs.

Various linear pharmacokinetic models (1, 2, and 3 compartments with zero- or first-order absorption, with or without a lag) were tested. For each, the quality of fit was evaluated using a standard model discrimination process that included statistical criteria (e.g., AIC, OBJ) as well as pertinent graphical representations of goodness of fit. Overall, plasma colchicine concentrations were best modeled using a 3-compartment model with a zero-order rate of absorption (K_0) and linear elimination. The CL/F and total apparent volume of distribution at steady state (V_{ss}/F) of colchicine in healthy adults derived with the population pharmacokinetic model were 30.2 L/h and 713.1 L, respectively. Covariate analysis was performed by integrating an allometric model on the population pharmacokinetic parameters of colchicine using theoretical and empirical approaches, with the latter approach resulting in the best quality of fit.

Data from the present study were then added to the model. The pharmacokinetic modeling was performed using Phoenix NLME 1.2 (Pharsight). Data set preparation as well as exploration and visualization of the data were performed using S-PLUS® Version 8.1 (Tibco, Seattle, WA) and R® Version 2-12.0. Pharmacokinetic parameters were assumed to follow a log-normal distribution, and the residual variability in plasma concentrations was fitted using a proportional and additive error model in the structural model buildup. Covariates were screened graphically to identify any that might affect pharmacokinetic parameters. Age, body weight, height, gender, and body surface area calculated by the Du Bois formula (14) were formally evaluated sequentially within the NLME software. The covariate analysis was limited to CL/F and V_c/F. First, a stepwise forward additive approach was used, including potential parameter-covariate relationship one by one, such that the model with the lowest *chi*-squared random variable value [minimum objective function (MOF)] was retained. This was continued until no covariate could be declared statistically significant (P>0.05, corresponding to changes in the MOF of 3.84 for one degree of freedom) or could significantly decrease the between-subject variability of pharmacokinetic parameters. This was followed by a backward elimination step, in which parameters from the "full model" were eliminated one by one and the MOFs compared. The parameter-covariate relationship for which the increase in MOF was least was removed from the

model. This was repeated until an increase of MOF ≥6.83 for one degree of freedom (i.e., *chi*-squared distribution *P* value = 0.01) was obtained for all covariates included in the model.

RESULTS

Study population

A total of 71 patients entered the study between September 14, 2010, and June 30, 2011 (the latter being the cutoff for this interim analysis). The safety population included 70 patients, because one patient was excluded before receiving study medication. A total of 14 patients (20%) prematurely discontinued study medication for the following reasons: withdrawal of consent (n=9), AE (n=1), physician decision (n=1), and other (n=3). Five of these patients discontinued before pharmacokinetic analysis. An additional 10 adult subjects aged ≥16 years were also excluded from all pharmacokinetic analyses because of incorrect labeling of sample tubes. The pharmacokinetics population therefore comprised 55 patients. An additional 2 patients did not have dose-time data and were excluded from the population subjected to pharmacokinetic analysis, which therefore comprised a total of 53 patients. With the exception of the 10 aforementioned patients at the Armenian center who were excluded, there were no major protocol deviations.

The demographic and clinical characteristics of the patients included in the safety and pharmacokinetic analysis are summarized in Table I. Approximately two-thirds of patients were male and one-third female. All patients were white and predominantly Jewish (~50%). Five patients were colchicine naïve, of whom 4 patients were newly diagnosed with FMF and one patient had an established diagnosis of FMF (~1 year). The majority of patients (~75%) received a once-daily and the rest a twice-daily schedule for colchicine administration.

Compliance with dosing was high. Of the 55 patients completing the pharmacokinetic period, 53 (96%) were >90% compliant, of whom 42 (76%) were 100% compliant. The remaining 2 patients were >85% compliant.

Observed pharmacokinetic data

The observed steady-state pharmacokinetic parameters for colchicine (C_{max}, C_{min}, and T_{max}) and 3-DMC (C_{max}) are summarized separately in Table II for patients who received colchicine once or twice daily.

Despite the higher doses of colchicine on a mg/kg/day basis in the younger age groups, the observed steady-state pharmacokinetic parameters in the 2- to 4-year-old age group were comparable to those observed in the group >6 years of age. Children aged 4-6 years received the highest mg/kg dose, which resulted in higher C_{max} of colchicine and 3-DMC than other groups. With once-daily colchicine, mean C_{max} for colchicine and 3-DMC appeared higher in patients ages 4 to <6 years (9.4 and 0.60 ng/mL, respectively) as compared with the younger and older age groups (6.1-6.7 and 0.22-0.32 ng/mL, respectively). 3-DMC metabolite exposure (measured as a percent of parent drug comparing mean C_{max} values) was generally low across the age groups. Plasma 2-DMC metabolite concentrations were not consistently quantifiable (data not shown).

Safety

Study-emergent AEs for the entire cohort and the different age subgroups, collected over the 90-day period of the study, are summarized in Table III. AEs were experienced by 76% of patients in the entire cohort. There were 3 serious AEs, 2 of which were unrelated to study drug (benign pituitary tumor and acute FMF flare, respectively) and one unlikely related to study drug (acute FMF flare). One patient was discontinued because of an AE (mild diarrhea/vomiting) probably related to study drug. Study-emergent AEs were graded as mild (48 patients, 69%), moderate (10 patients, 14%), or severe (2 patients, 3%). The severe AEs were considered unrelated to treatment and did result in study drug interruption; one patient had severe abdominal pain that resolved spontaneously in one day and a separate incident of severe ankle pain that resolved with symptomatic treatment in one day, whereas the other patient had severe stomach pain and high fever lasting 1-2 days that resolved with symptomatic treatment. The study investigators believed that these AEs were most likely due to partial FMF flares. The most common study-emergent AEs regardless of relationship to study medication were acute FMF flares or attacks (22 patients, 31%), abdominal pain

Table I. *Baseline demographic and clinical characteristics of the safety and noncompartmental pharmacokinetic populations*

Characteristic	Safety population				
	≥2 to <4 y (n = 11)	≥4 to <6 y (n = 8)	≥6 to <12 y (n = 21)	≥12 to <16 y (n = 10)	≥16 to ≤65 y (n = 20)
Gender, n (%)					
Male	6 (55)	6 (75)	12 (57)	7 (70)	11 (55)
Female	5 (45)	2 (25)	9 (43)	3 (30)	9 (45)
Mean ± SD age, y (range)	2.8 ± 0.4 (2–3)	4.1 ± 0.4 (4–5)	7.8 ± 1.7 (6–11)	13.6 ± 1.2 (12–15)	34.4 ± 14.5 (16–60)
Mean body mass index, kg/m^2 (range)	15.6 ± 1.2 (13.6–17.6)	15.7 ± 1.4 (13.6–17.7)	16.0 ± 2.5 (12.7–23.1)	19.3 ± 3.1 (14.7–23.4)	25.1 (17.6–36.5)[a]
Ethnicity, n (%)					
Arab	2 (18)	1 (13)	7 (33)	2 (20)	2 (10)
Armenian	0	0	0	0	10 (50)
Jewish	7 (64)	7 (88)	10 (48)	8 (80)	6 (30)
Turkish	2 (18)	0	3 (14)	0	0
Other	0	0	1 (5)[b]	0	2 (10)[c]
	Pharmacokinetic population				
	≥2 to <4 y (n = 10)	≥4 to <6 y (n = 8)	≥6 to <12 y (n = 18)[d]	≥12 to <16 y (n = 10)	≥16 to ≤65 y (n = 9)[d]
Gender, n (%)					
Male	6 (60)	6 (75)	11 (61)	7 (70)	6 (67)
Female	4 (40)	2 (25)	7 (39)	3 (30)	3 (33)
Mean ± SD age, y (range)	2.8 ± 0.4 (2–3)	4.1 ± 0.3 (4–5)	8.0 ± 1.7 (6–11)	13.6 ± 1.2 (12–15)	33.7 ± 15.7 (16–52)
Mean ± SD weight, kg	13.7 (1.41)	17.8 (2.09)	25.8 (8.87)	46.8 (9.31)	62.8 (18.90)[e]
Ethnicity, n (%)					
Arab	2 (18)	1 (13)	7 (33)	2 (20)	2 (10)
Jewish	7 (64)	7 (88)	10 (48)	8 (80)	6 (30)
Turkish	2 (18)	0	3 (14)	0	0
Other	0	0	1 (5)[b]	0	2 (10)[f]

[a]Data available for 16 patients, of whom 4 had a body mass index >30 kg/m^2.
[b]Ethnicity is Druze; [c]Ethnicity is Georgian or Egyptian/Iraqi; [d]One patient in each group was excluded from population pharmacokinetic analysis due to missing dose-time data; [e]Data missing for 2 patients: a 40-year-old man and a 20-year-old woman. One 42-year-old woman was obese, as defined by a body mass index >30 kg/m^2; [f]Ethnicity is Georgian.

(23 patients, 33%), pyrexia (12 patients, 17%), diarrhea (9 patients, 13%), headache (9 patients, 13%), and vomiting (7 patients, 10%).

The relationship of AEs to study drug was considered unrelated (44 patients, 63%), unlikely (12 patients, 17%), possibly (13 patients, 19%), and probably (7 patients, 10%). Treatment-related (possible/probable) AEs were experienced by 19 patients (27%), and the most common treatment-related AEs were abdominal pain (5 patients, 7%),

Table II. *Steady-state colchicine pharmacokinetic parameters by age group and dose interval using observed, noncompartmental data*

Parameter	Once-daily dosing				
	≥2 to <4 y (n = 8)	≥4 to <6 y (n = 4)[a]	≥6 to <12 y (n = 13)	≥12 to <16 y (n = 9)[b]	≥16 to ≤65 y (n = 7)
Colchicine					
Dose, mg/day	0.6	0.9	0.9	1.2	1.2
Mean ± SD dose, mg/kg/day	0.045 ± 0.005	0.052 ± 0.009	0.039 ± 0.009	0.026 ± 0.005	0.023 ± 0.008
Mean ± SD C_{max}, ng/mL (range)	6.1 ± 1.71	9.4 ± 1.87	6.7 ± 2.81	6.1 ± 2.87	6.5 ± 2.79
	(4.0–9.2)	(7.1–11.3)	(3.3–11.4)	(3.1–12.1)	(3.1–12.0)
Mean ± SD C_{min}, ng/mL (range)	0.7 ± 0.29	1.0 ± 0.23	0.8 ± 0.31	0.9 ± 0.30	1.0 ± 0.60
	(0.3–1.2)	(0.7–1.2)	(0.5–1.3)	(0.5–1.5)	(0.4–2.2)
Mean ± SD T_{max}, h (range)	1.3 ± 0.87	1.6 ± 0.16	1.5 ± 0.52	1.9 ± 0.53	1.6 ± 0.09
	(0.3–2.6)	(1.5–1.8)	(0.3–2.0)	(1.5–3.1)	(1.5–1.8)
3-*O*-Desmethylcolchicine					
Mean ± SD C_{max}, ng/mL (range)	0.23 ± 0.07	0.60 ± 0.20	0.32 ± 0.18	0.24 ± 0.15	0.22 ± 0.12
	(0.13–0.34)	(0.37–0.86)	(0.11–0.75)	(0.07–0.50)	(0.10–0.47)
Percent of parent ± SD (range)	4.0 ± 1.48	6.3 ± 1.18	4.9 ± 1.69	3.8 ± 1.24	3.5 ± 1.71
	(2.4–6.2)	(5.3–7.6)	(2.3–8.0)	(2.3–6.0)	(1.5–7.0)

	Twice-daily dosing				
	≥2 to <4 y (n = 2)	≥4 to <6 y (n = 2)[a]	≥6 to <12 y (n = 5)	≥12 to <16 y (n = 0)	≥16 to ≤65 y (n = 2)[b]
Colchicine					
AM/PM dose, mg	0.3/0.3	0.6/0.3	0.6/0.3	0.6/0.6	0.6/0.6
Dose, mg/kg/day (range)	–	–	–	–	–
	(0.039–0.046)	(0.046–0.053)	(0.017–0.044)		(0.014–0.015)
Mean ± SD C_{max}, ng/mL (range)	–	–	4.9 ± 2.04	–	–
	(2.1–4.1)	(2.8–9.3)	(1.4–6.4)		(2.1–2.4)
Mean ± SD C_{min}, ng/mL (range)	–	–	0.8 ± 0.11[c]	–	–
	(0.9)	(0.5–1.1)	(0.7–0.9)		(1.0–1.5)
Mean ± SD T_{max}, h (range)	–	–	1.0 ± 0.67	–	–
	(2.0–2.5)[d]	(1.5–2.0)	(0.2–1.8)		(1.5–1.8)
3-*O*-Desmethylcolchicine					
Mean ± SD C_{max}, ng/mL (range)	–	–	0.22 ± 0.16	–	–
	(0.08–0.22)	(0.07–0.26)	(0–0.46)		(0–0.05)
Percent of parent ± SD (range)	–	–	3.7 ± 2.61	–	–
	(3.7–5.5)	(2.3–2.8)	(0–7.2)		(0–2.1)

[a]One patient excluded because 0.6 mg/day was administered; [b]One patient excluded because 0.9 mg/day was administered. [c]One patient excluded because predose (24-hour) sample was missing on day 15; [d]One patient excluded because sample in the 0.25- to 0.5-hour sampling window was missing. C_{max}: maximum plasma concentration; C_{min}: minimum plasma concentration; T_{max}: time to reach C_{max}.

Table III. *Summary of study-emergent AEs.*

	No. of patients (%)					
	≥2 to <4 y (n = 11)	≥4 to <6 y (n = 8)	≥6 to <12 y (n = 21)	≥12 to <16 y (n = 10)	≥16 to 65 y (n = 20)	Total (N = 70)
Any AE	9 (82)	7 (88)	16 (76)	9 (90)	12 (60)	53 (76)
Treatment-related AEs[a]	0	5 (63)	6 (29)	2 (20)	6 (30)	19 (27)
Severe AEs	2 (18)	0	0	0	0	2 (3)
Serious AEs[b]	0	1 (13)	0	1 (10)	1 (5)	3 (4)
AEs resulting in discontinuation[c]	0	1 (17)	0	0	0	1 (2)
Most common AEs regardless of treatment relationship by preferred[d] MedDRA term						
FMF (flare or attack)	3 (27)	3 (37)	9 (43)	6 (60)	1 (5)	22 (31)
Abdominal pain	3 (27)	4 (50)	5 (23)	4 (40)	7 (35)	23 (32)
Abdominal pain upper	2 (18)	0	1 (5)	0	1 (5)	4 (6)
Diarrhea	3 (27)	3 (37)	0	1 (10)	2 (10)	9 (13)
Vomiting	2 (18)	2 (25)	2 (9)	1 (10)	0	7 (10)
Fatigue	0	2 (25)	0	0	1 (5)	3 (4)
Chest pain (noncardiac)	1 (9)	0	2 (9)	0	2 (10)	5 (7)
Pyrexia	5 (45)	3 (37)	1 (5)	2 (20)	1 (5)	12 (17)
Influenza	0	1 (12)	0	0	2 (10)	3 (4)
Upper respiratory tract infection	3 (27)	0	0	0	1 (5)	4 (6)
Viral infection	0	2 (25)	0	1 (10)	1 (5)	4 (6)
Alanine aminotransferase increased	0	0	0	0	2 (10)	2 (3)
Arthralgia	2 (18)	0	0	2 (20)	1 (5)	5 (7)
Pain in extremity	3 (27)	1 (12)	3 (14)	1 (10)	2 (10)	10 (14)
Headache	0	1 (12)	4 (19)	1 (10)	3 (15)	9 (13)
Asthma	2 (18)	0	0	0	0	2 (3)
Cough	2 (18)	0	0	0	0	2 (3)
Oropharyngeal pain	0	0	2 (9)	2 (20)	0	4 (6)
Rash	1 (9)	0	3 (14)	0	0	4 (6)
Treatment-related AEs[a] by preferred MedDRA term						
FMF (flare or attack)	0	1 (12)	2 (9)	1 (10)	0	4 (6)
Abdominal pain	0	2 (25)	2 (9)	0	1 (5)	5 (7)
Diarrhea	0	3 (37)	0	1 (10)	1 (5)	5 (7)
Frequent bowel movements	0	1 (12)	0	0	0	1 (1)
Nausea	0	0	0	0	1 (5)	1 (1)
Stomatitis	0	0	1 (5)	0	0	1 (1)
Vomiting	0	1 (12)	1 (5)	0	0	2 (3)
Fatigue	0	1 (12)	0	0	1 (5)	2 (3)
Malaise	0	0	0	0	1 (5)	1 (1)
Alanine aminotransferase increased	0	0	0	0	1 (5)	1 (1)
Headache	0	0	0	0	1 (5)	1 (1)

[a]Assessed as possibly or probably treatment-related by the investigator. [b]Three serious AEs were reported, all of which were considered unrelated to study treatment. [c]One patient discontinued (day 37) due to mild diarrhea/vomiting (probably related to study drug). [d]Occurring in ≥2 patients in any age group category. AE: adverse event; FMF: familial Mediterranean fever.

diarrhea (5 patients, 7%), and FMF flares or attacks, vomiting, and fatigue (each in 2 patients, 3%). There were no clear differences in AEs across the age groups. There were no consistent (shift) changes during the study with respect to routine laboratory values and vital signs, and only one patient reported a study-emergent AE in relation to these parameters (mild increase in alanine aminotransferase level), which was deemed by the investigator to be possibly related to study medication.

Twenty-three patients missed a dose of study medication, of whom 10 also had a study-emergent AE coincident with missing ≥1 dose of study medication, including 6 patients who missed their doses for consecutive days. There were no trends in the ages of these patients. The events around the time of missed doses appeared likely to be consistent with an underlying illness rather than with study medication.

DISCUSSION

Colcrys® is the only US-approved treatment for FMF. Its use should be initiated as soon as possible following diagnosis of FMF and continued for life (13). The current US-approved formulation of colchicine is the 0.6-mg oral tablet for use in adults and children ≥4 years of age with FMF.

The recommended dosage of the tablet formulation in the United States is 0.3-1.8 mg/day in children ages 4 to <6 years, 0.9-1.8 mg/day in children ages 6 to <12 years, and 1.2-2.4 mg/day in adolescents ages ≥12 years and adults, which can be administered once daily or in a divided dose twice daily. Administration should be started at the lower end of the dose range and titrated up as needed by 0.3-mg/day increments to control FMF disease flares and attacks to the maximum dose and with similar downward titration should intolerable AEs develop (15). These dose recommendations for children and adolescents are in line with a consensus statement (13) and are primarily derived from clinical observation. Outside of the United States, some FMF centers started colchicine and attempted to increase the dose to a minimum of 1 mg at the age of 2 years (7).

Because the current US-approved tablet formulation must be divided and/or crushed for administration with fluids or food at the lower doses required by young children, a new 0.3-mg formulation of colchicine has been developed to be more suitable, convenient, and accurate for administration to young children ages ≥2 to <6 years. The current tablet formulation is not approved for use in children ages 2 to <4 years, and there are no dosing recommendations for this age group.

Population pharmacokinetic modeling showed that a 3-compartment model with zero-order absorption and linear elimination described the pharmacokinetic parameters of CL/F and V_c/F robustly with RSEs of <8% and ≤13%, respectively, when adjusted for body weight (median) and body surface (BSA) by age group. These values were below the 20% required by FDA criteria. Mean AUC_{0-24h} values in children ages ≥2 to <4, ≥6 to <12, and ≥12 to <16 years were similar to those in adults ages ≥16 to ≤65 years. However, the mean AUC_{0-24h} value in children ages 4 to <6 years was 26% higher than that in adults. It is therefore recommended that the starting dosage in this age group should be lowered to 0.6 mg/day instead of the 0.9 mg/day that they received in this study and increased if patients continue to experience FMF attacks.

This study had to accommodate a number of constraints in its design. FMF is rarely diagnosed in children <2 years of age, so this was set as the lower age limit for inclusion. A sparse blood sampling approach (1 mL per sample) with a limited number of time windows (n=6) had to be used for the determination of observed steady-state pharmacokinetics given both practical and ethical limitations in the amount of blood that can be collected from young children and the fact that blood samples also had to be taken at regular intervals for clinical laboratory testing. A population pharmacokinetic modeling approach was therefore chosen as the primary statistical means of estimating steady-state pharmacokinetic parameters. It was planned to include at least 10 patients in each age group for final analysis to provide sufficient statistical robustness, which necessitated a multicenter design incorporating geographic sites that would ensure adequate recruitment given the incidence of FMF.

Colchicine was safe and well tolerated at the doses administered in the different age groups. The safety profile in children as young as 2 years of age was comparable to that seen in older children and adults.

In conclusion, the dosage of the new formulation of colchicine in pediatric patients with FMF ages 2 to <6 years, the intended target population, is 0.6 mg/day administered either once daily or in divided doses twice daily. Children ages ≥6 years should receive the approved tablet formation of colchicine according to current dose recommendations. This is the first study to define the pharmacokinetics of colchicine in patients with FMF and to define dosing recommendations and safety in pediatric patients as young as 2 years of age. This extends evidence-based support for the treatment of children ≥2 years of age with FMF and the recommendation to start lifelong colchicine therapy as soon as possible after diagnosis by providing appropriate dosing guidelines of colchicine for children ages ≥2 to <6 years.

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