2. Helbig G, Wieczorkiewicz A, Dziaczkowska-Suszek J, et al. T-cell abnormalities are present at high frequencies in patients with hypereosinophilic syndrome. Haematologica 2009;94:1236–1241.
3. Ghia P, Prato G, Stella S, et al. Age-dependent accumulation of monoclonal CD4+CD8+ double positive T lymphocytes in the peripheral blood of the elderly. Br J Haematol 2007;139:780–790.
4. Morice WG, Kimlinger T, Katzmann JA, et al. Flow cytometric assessment of TCR-Vbeta expression in the evaluation of peripheral blood involvement by T-cell lymphoproliferative disorders: A comparison with conventional T-cell immunophenotyping and molecular genetic techniques. Am J Clin Pathol 2004; 121:373–383.
5. Helbig G, Wichary R, Razny M, et al. The proportion of CD3- CD4+ T-cell population remained unaffected after corticosteroids treatment for lymphocytic variant hypereosinophilic syndrome (L-HES). Scand J Immunol 2010;72: 372–373.
6. Verstovsek S, Tefferi A, Kantarjian H, et al. Alemtuzumab therapy for hypereosinophilic syndrome and chronic eosinophilic leukemia. Clin Cancer Res 2009;15: 368–373.

More definitions in sickle cell disease: Steady state *v* base line data

Ballas et al. [1] published concise definitions of the complications of sickle cell disease (SCD). There are other definitions that pertain to SCD that are not complications of the disease as such but are associated with establishing the accurate diagnosis, management, and natural history of each complication. Definition of the steady state and of baseline clinical features and lab data are two such examples. These are important in detecting any significant acute change in the clinical picture or any change after the initiation of therapeutic modalities.

The steady state refers to a point in time where the patient in question is not experiencing an acute painful crisis or any changes due to therapy. Typically, a steady state should fulfill the following criteria:

1. No history of an acute painful episode that required treatment in the emergency department or in the hospital for at least four consecutive weeks after a previous painful crisis.

2. No history of admission to the hospital or emergency department 2–3 days after the point in time in question. Previous studies showed that the number of irreversibly sickled cells increases and RBC deformability decreases 2–3 days before admission to the hospital in crisis [2]. This change coincides with the prodromal phase of the acute painful crisis described in children and adults [3,4].

3. No history of blood transfusion during the previous 4 months of the point in time. Alternately, the % of Hb A determined by electrophoresis or by high performance liquid chromatography must be $\leq$10%. The exception would be in patients with sickle-β^+-thalassemia in whom endogenous Hb A could be as high as 30%. In these patients, history of recent blood transfusion could be obtained from the blood bank that usually supports the institution in question. Patients on chronic blood transfusion or exchange transfusion may be exempt from this requirement or their Hb S steady state level could be the average of 3 determinations of the % of Hb S before scheduled transfusion or exchange transfusion.

4. No history of intercurrent illness such as infection, inflammation during the previous 4 weeks.

5. No treatment with medications such as antibiotics that may affect the blood counts during the previous 3 weeks.

6. The steady state values may change with time. It is, therefore, advisable to determine them periodically every 2–3 years.

Knowing the steady state values is extremely important in evaluating patients who present themselves with acute episodes. Comparing data during the acute event with the steady state values often reveals objective changes during crisis.

Baseline values include clinical and lab data determined before the initiation of therapy or other interventions. They do not need to meet the requirement of steady state values. Occasionally, they could be the same as steady-state values especially in patients who have relatively mild disease with infrequent painful episodes. Baseline values are markers of the effect of an intended intervention whereas steady-state values are markers of the disease itself.

Samir K. Ballas
Department of Medicine
Cardeza Foundation for Hematologic Research
Jefferson Medical College
Philadelphia, Pennsylvania
Conflict of interest: Nothing to report.
Published online 23 November 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/ajh.22259

References

1. Ballas SK, Lieff S, Benjamin LJ, et al. Definitions of the phenotypic manifestations of sickle cell disease. Am J Hematol 2010;85:6–13.
2. Ballas SK, Smith ED. Red cell changes during the evolution of the sickle cell painful crisis. Blood 1992;79:2154–2163.
3. Jacob E, Beyer JE, Miaskowski C, et al. Are there phases to the vaso-occlusive painful episode in sickle cell disease? J Pain Symptom Manage 2005;29: 392–400
4. Ballas SK. The sickle cell painful crisis in adults: phases and objective signs. Hemoglobin 1995;19:323–333.

Drug interaction between lenalidomide and itraconazole

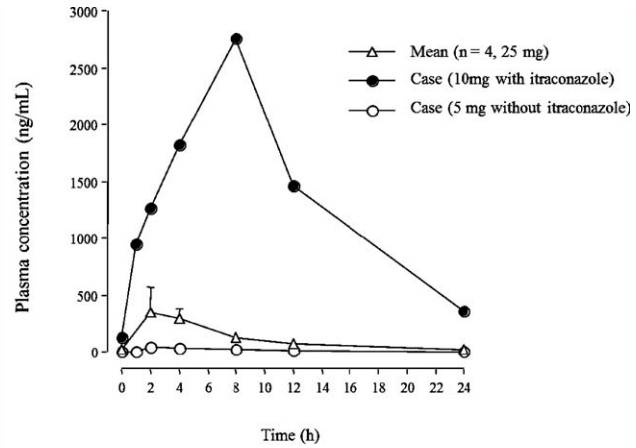
To the Editor: In July 2010, a 53-year-old woman was diagnosed with multiple myeloma, IgG-lambda stage 2, and was initially administered chemotherapy with melphalan and prednisone. Because of continued disease progression, however, in October 2010 she was administered lenalidomide 25 mg plus low-dose dexamethasone (Rd). Although she achieved partial response after one course of Rd (IgG declined from 6,977 to 1,200 mg/dL), she began suffering from febrile neutropenia, which persisted for 10 days. Following the recommendation of Dimopoulos et al. [1], in November 2010, we reduced the patient's lenalidomide dosage to 15 mg and added 100 mg/day itraconazole and 400 mg/day–80 mg/day sulfamethoxazole–trimethoprim for infection prophylaxis. Nevertheless, she suffered repeated infections associated with neutropenia, even after further reducing her lenalidomide to 10 mg. We therefore began monitoring the patient's plasma lenalidomide concentrations using high-performance liquid chromatography (Fig. 1, closed circles). Lenalidomide was separated using a mobile phase of 0.5% KH_2PO_4 (pH 2.5)–acetonitrile (87.5:12.5, v/v) on a Capcell Pak C_{18} MG II column at a flow rate of 0.5 mL/min and UV absorbance at 220 nm. The lenalidomide and itraconazole were then stopped because the AUC_{0-24} and maximum plasma lenalidomide concentration (C_{max}) after intake of 10 mg with prophylaxis using itraconazole were 33,249 ng hr/mL and 2,757 ng/mL, respectively. After 10 days, lenalidomide was restarted at a dosage of 5 mg, without itraconazole, and its plasma concentrations were monitored (Fig. 1, open circles). The AUC_{0-24} and lenalidomide C_{max} after intake of 5 mg were 283 ng hr/mL and 38 ng/mL, respectively; however, there was no difference in the terminal elimination half-life ($t_{1/2}$) of lenalidomide, with or without itraconazole (5.5 hr vs. 5.6 hr). By comparison, the mean (±SD) AUC_{0-24}, C_{max}, and elimination $t_{1/2}$ in four other myeloma patients taking 25 mg of lenalidomide were 2,763 ± 917 ng hr/mL, 400 ± 172 ng/mL and 6.7 ± 1.3 hr, respectively (Fig. 1).

This is the first report showing a drug interaction between lenalidomide and itraconazole, which is a potent inhibitor of CYP3A4 and P-glycoprotein activity [2]. Hofmeister et al. recently reported an in vitro study indicating that P-glycoprotein is involved in the lenalidomide pharmacokinetics, and drug-interactions via P-glycoprotein between lenalidomide and CCI-779 (temsirolimus) as substrates of P-glycoprotein [3]. Because lenalidomide is scarcely metabolized by cytochrome P450s (CYP), the activity of drug-transporters such as P-glycoprotein may be a key determinant of lenalidomide pharmacokinetics. In the present case, the AUC_{0-24} and C_{max} for lenalidomide were markedly increased by itraconazole, though its elimination $t_{1/2}$ was unaffected. This suggests that the drug interaction between lenalidomide and itraconazole occurs via P-glycoprotein during absorption from the small intestine.

This patient exhibited neutropenia when administered a combination of 10 mg of lenalidomide plus itraconazole, and gave a dose-adjusted AUC_{0-24} for lenalidomide of 3,324.9 ng hr/mL/mg, which is much higher than in four other patients who did not show drug toxicity. This suggests that lenalidomide exposure could contribute to its toxicity [4], and careful monitoring of lenalidomide as well as creatinine clearance may be appropriate to avoid the risk of toxicity.

Naoto Takahashi[1]*
Masatomo Miura[2]
Yoshihiro Kameoka[1]
Maiko Abumiya[2]
Kenichi Sawada[1]

[1]Department of Hematology, Nephrology, and Rheumatology, Akita University Graduate School of Medicine, Akita, Japan; [2]Department of Pharmacy, Akita University Hospital, Akita, Japan
**E-mail: naotot@doc.med.akita-u.ac.jp*
Conflict of interest: Nothing to report.
Published online 23 Novmber 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/ajh.22260



		4 Patients			This case	
Parameters		mean	SD		with ITCZ	without ITCZ
Dose	mg	25			10	5
s-Cre	mg/dL	0.89	0.34		0.63	0.66
CLcr	mL/min	62.1	6.85		72.1	68.8
Elimination $t_{1/2}$	h	6.7	1.3		5.5	5.6
T_{max}	h	3.0	1.2		8.0	2.0
C_{max}	ng/mL	400	172		2757	38
AUC_{0-24}	ng·h/mL	2763	917		33249	283
CL/F	L/h	9.7	2.8		0.3	14.0

s-Cre, serum creatinine; CLcr, creatinine clearance; Elimination $t_{1/2}$, terminal elimination half-life;
T_{max}, observed time to reach the maximum plasma concentration; Cmax, maximum plasma concentration
AUC_{0-24}, area under the plasma concentration-time curve from 0 to 24 h; CL/F, clearance;
SD, standard deviation; ITCZ, itraconazole.

Fig. 1. Plasma concentration-time profiles after administration of 10 mg of lenalidomide with itraconazole (closed circles), 5 mg of lenalidomide without itraconazole (open circles), and 25 mg of lenalidomide without itraconazole (mean values from four patients, open triangles). Pharmacokinetic analysis of lenalidomide was done using the standard non-compartmental method with WinNonlin software (Pharsight Co., Mountain View, CA, version 4.0.1). An estimated creatinine clearance for each patient was calculated using Cockcroft and Gault formulas from the initially analyzed serum creatinine concentration.

References

1. Dimopoulos MA, Palumbo A, Attal M, et al. Optimizing the use of lenalidomide in relapsed or refractory multiple myeloma: Consensus statement. Leukemia 2011;25:749–760.
2. Saad AH, DePestel DD, Carver PL. Factors influencing the magnitude and clinical significance of drug interactions between azole antifungals and select immunosuppressants. Pharmacotherapy 2006;26:1730–1744.
3. Hofmeister CC, Yang X, Pichiorri F, et al. Phase I trial of lenalidomide and CCI-779 in patients with relapsed multiple myeloma: Evidence for lenalidomide-CCI-779 interaction via P-glycoprotein. J Clin Oncol 2011;29:3427–3234.
4. Bonkowski J, Vermeulen LC, Kolesar JM. The clinical utility of lenalidomide in multiple myeloma and myelodysplastic syndromes. J Oncol Pharm Pract 2010; 16:223–232.