Adrenal Insufficiency is Not a Barrier to OCS Elimination in the PONENTE Study

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Rationale: Oral corticosteroid (OCS) dependence is prevalent in severe asthma and causes adverse effects, including adrenal insufficiency (AI). Benralizumab may reduce or eliminate the need for long-term OCS for adults with severe asthma. AI may be perceived as a barrier to OCS reduction, and limited data are available to guide the extent to which OCS can be tapered in the presence of AI.

Methods: An analysis of patients in the multicenter, open-label phase IIIb PONENTE trial was conducted to demonstrate benralizumab's ability to eliminate or reduce the daily OCS dosage according to adrenal function status. Hypothalamic-pituitary-adrenal (HPA) axis integrity was evaluated after patients reached a daily OCS dosage of 5 mg for 4 weeks. A morning cortisol level was obtained to determine if patients had normal adrenal function (>350 nmol/L) or complete AI (<100 nmol/L). Patients with indeterminate results (100–350 nmol/L) underwent an ACTH stimulation test. According to this result, patients were classified as having normal cortisol levels (>450 nmol/L), complete AI (<250 nmol/L), or partial AI (250–450 nmol/L). Adrenal status determined whether the OCS down-titration was continued (and the rate of OCS down-titration) or suspended (due to complete AI), and was re-evaluated 2–3 months later to guide further reductions; patients with a finding of complete AI at the second test were not

allowed any further dosage reductions. Endpoints included OCS elimination and achieving a daily OCS dosage ≤5 mg.

Results: A total of 530 of 598 eligible patients completed the initial HPA axis assessment. At first testing, 40% of patients had normal cortisol levels, 33% had partial AI, and 27% had complete AI. Overall, more than one-third of patients with initial complete or partial AI recovered their adrenal function 2 to 3 months later (36.2% from partial AI to normal levels and 31.9% from complete AI to partial AI or normal levels). More than 90% of patients with normal adrenal function or who improved from partial AI to normal levels and more than 60% of patients who improved from complete AI to partial AI or normal levels eliminated OCS use. Nearly all patients eliminated OCS or achieved a dosage ≤5 mg, regardless of initial AI status (**Table**).

Conclusions: Most patients with normal adrenal function eliminated OCS or achieved a daily OCS dosage ≤5 mg, and a substantial percentage of patients with initially impaired adrenal function were able to reduce or eliminate OCS with careful management.

Table. Endpoints according to initial adrenal status

	Patients eliminating OCS, n (%)	Patients achieving daily OCS dosage ≤5 mg if AI was the cause of stopping the taper, n (%)	Patients achieving daily OCS dosage ≤5 mg regardless of the cause of stopping the taper, n (%)
Adrenal function status at initial HPA axis testing (N=530)			
Normal (40.0%; N=212)	196 (92.5)	197 (92.9)	209 (98.6)
Partial AI (33.0%; N=175)	132 (75.4)	151 (86.3)	171 (97.7)
Complete AI (27.0%; N=143)	30 (21.0)	120 (83.9)	135 (94.4)
Patients with improvements in adrenal function status from initial to final HPA axis testing (N=260*; subset of patients with partial or complete AI at initial testing)			
Any improvement in adrenal function status at second HPA testing (34.2%; n/N=89/260)	70 (78.7)	71 (79.8)	86 (96.6)
Improvement from partial AI to normal levels (36.2%; n/N=51/141)	47 (92.2)	47 (92.2)	50 (98.0)
Improvement from complete AI to partial AI/normal levels (31.9%; n/N=38/119)	23 (60.5)	24 (63.2)	36 (94.7)
Patients with compromised adrenal function status at initial and final HPA axis testing (N=472*)			
Complete AI throughout (17.2%; n/N=81/472)	1 (1.2)	79 (97.5)	80 (98.8)
Partial AI throughout (14.4%; n/N=68/472)	56 (82.4)	57 (83.8)	67 (98.5)

AI=adrenal insufficiency; HPA=hypothalamic-pituitary-adrenal axis; OCS=oral corticosteroids.

*58 patients with partial or complete AI (34 and 24 patients, respectively) at initial testing did not have adrenal function status completed at final HPA testing, leading to 141 patients with partial AI and 119 with complete AI being tested for adrenal function status at final HPA axis testing. 58 patients did not have adrenal function status at final HPA axis testing.