SARCOIDOSIS

The Relationship Between Serum Angiotensin Converting Enzyme Level and the Decision to Escalate Treatment of Sarcoidosis

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Abstract

Purpose We performed a retrospective analysis of a sarcoidosis cohort who had sACE obtained at their initial clinic visit, but the treating physician was blinded to the results. We examined the relationship between sACE and the treating physician's decision to escalate sarcoidosis treatment.

Methods Treatment was considered escalated if the prednisone dose was increased or if the prednisone dose was not changed but an additional anti-sarcoidosis drug was added or the dose was increased.

Results 561 sarcoidosis patients were analyzed. The most common target organ was the lung (84%). Using a cut-off of > 82 units/L for an elevated sACE, 31/82 (38%) with an elevated sACE had treatment escalation whereas 91/497 (18%) had treatment escalation with a normal sACE ($p < 0.0001$). For the need of treatment escalation, a sACE (cut-off of > 82) had sensitivity 0.25, specificity 0.89, positive predictive value 0.38, negative predictive value 0.81. These results were not appreciably different using other sACE cut-off values such as 70, 80, 90, or 100. A multivariable logistic regression model that included demographics, the target organ, spirometry results estimated that sACE level and lower FVC were significantly associated with the likelihood of treatment escalation. These findings held when sACE > 82 replaced sACE level in the multivariable logistic regression model.

Conclusions Although there was a strong correlation between sACE at the initial sarcoidosis clinic visit and subsequent treatment escalation of sarcoidosis, the predictive power was such that sACE is not adequately reliable to be used in isolation to make this determination.

Keywords Sarcoidosis · Serum angiotensin converting enzyme · Treatment · Prednisone

Introduction

Angiotensin converting enzyme (ACE) is a carboxypeptidase enzyme that converts angiotensin I into angiotensin II [1]. ACE is produced by the epithelioid cell within the sarcoid granuloma [2, 3], and serum ACE levels (sACE) are thought to correlate with the granuloma burden of the disease [3]. Over the past several decades, there has been controversy concerning the clinical usefulness of sACE. The reliability of ACE as a biomarker of active sarcoidosis has been questioned [4], as sACE is neither perfectly sensitive or specific for the disease [4]. Furthermore, sACE is affected by genetic polymorphisms, variation in assays, and the effects of medications including ACE-inhibitors and anti-sarcoidosis drugs [4]. Even if sACE is a reliable measure of sarcoidosis disease activity, such activity does not necessarily mandate sarcoidosis treatment [5]. Nevertheless, the relationship between sACE and the need for sarcoidosis treatment has not been rigorously evaluated. We performed a retrospective analysis of a large cohort of sarcoidosis patients seen for an initial visit at a university medical center sarcoidosis clinic. All patients had sACE obtained on the day of their initial visits, but the treating physician was blinded to the results. We examined the relationship between sACE and the treating physician's decision to escalate sarcoidosis treatment at this initial visit.

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Methods

This study was approved by the Albany Medical Center Institutional Review Board (study number 6272). This is a retrospective analysis of data obtained for clinical purposes. These data were collected in real time in an institution-approved sarcoidosis clinical database. All patients were analyzed who had a diagnosis of sarcoidosis based by established international criteria [6] and had their initial visit at Albany Medical Center for the care of sarcoidosis with one of the authors (MAJ) between February 2013 and September 2021. The following data were collected on all patients for this analysis included: (a) demographics (sex, self-designated race); (b) age at sarcoidosis diagnosis, (c) age at their initial clinic visit; (d) the specific organs that were treated or were being considered for treatment by the clinician described as "the target organ(s)"; (e) anti-sarcoidosis medications currently prescribed at the time of the initial visit. These medications included corticosteroids, antimetabolites, anti-malarials, tumor necrosis factor antagonists, and other systemic immunosuppressive treatments; (f) sACE levels obtained within 24 h of first visit. The sACE levels were not available to the treating physician for at least 48 h after the initial clinic visit, and therefore the clinician was "blinded" to the sACE results when treatment decisions were made; (g) the clinician's decision to escalate or not escalate anti-sarcoidosis treatment. It should be noted that it is routine policy that all sarcoidosis patients initially seen undergo sACE testing; no patients are excluded from testing. Treatment was considered to be escalated if the corticosteroid dose was increased or if the corticosteroid dose was not changed but an additional anti-sarcoidosis drug was added or increased. All other medication changes and no changes in anti-sarcoidosis medications were considered not to be treatment escalations; (h) % predicted forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV1) at the initial clinic visit as determined by Hankinson and colleagues [7]; (i) for those patients who returned for a second visit, the clinician routinely subjectively evaluated change in the target organ in real time using the following qualitative 5-point system—improved, worse, no change, could not reliably assess change, resolved. The serum ACE test was performed through Labcorp (Burlington, North Carolina USA) and is an activity (kinetic) test where the normal range is considered 14 to 82 units/L.

The primary goal of these analyses was to explore the relationship between the sarcoidosis patient's sACE level at the initial clinic visit and the treating physician's decision to escalate or not escalate treatment. We used demographic and clinical information in multivariable models as covariates for adjustment.

Statistical Methods

All cases with no sACE value available were excluded from the analysis. Descriptive statistics (means, standard deviation, or proportion) were used to summarize the characteristics of patients. Test of significance was performed in both treatment and no treatment subgroups. Chi-square test was used to examine the relationship between ACE levels (dichotomized using various cutoff values), the need for treatment, and treatment outcomes. Sensitivity, specificity, and positive and negative predictive values were estimated at different ACE cut-off values to determine the predictive power of the sACE level on treatment escalation. Logistic regression models adjusted for age, sex, race, duration of the disease, sACE level, and target organs to predict the probability of escalating or not escalating treatment. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4.

Results

This analysis was performed in 561 consecutive sarcoidosis patients who met the study entry criteria. Table 1 shows the baseline demographics, clinical features and sACE levels of these patients. The patients were predominantly white (83%) and there were slightly more females (55%) than males. Mean spirometric values were in the low-normal range, and the duration of disease was quite scattered with a median of less than 2 years and a mean of 7 years. Table 2 shows the target organs (organs that required treatment). The most common target organ was the lung at nearly 84%, with no other single organ requiring treatment in more than 14% of the patients.

Table 3 compares the corticosteroid doses at the initial clinic visit. Corticosteroids were most common medications used, and all analyses were performed using prednisone dose equivalents. One hundred and forty-four of 561 patients (26%) were receiving corticosteroids. Fifty-seven (10%) were receiving a non-corticosteroid agent for sarcoidosis at their initial clinic visit. In those receiving corticosteroids at their initial visit, the mean daily dose of prednisone was approximately 20 mg.

Table 4 shows the relationship between an elevated ACE level > 82 (units/liter) and the decision to escalate treatment. There was a strong positive association ($p < 0.0001$) between these variables. In terms of the predictive power of a sACE level of > 82 to determine dose escalation, the sensitivity was 25.4%, specificity 88.3%, positive predictive value 37.8%, and negative predictive value 81.0%. In addition, we used alternative cutoff values for sACE of $> 70, > 80, > 90$, and > 100 (Table e1). In terms of the predictive power of

Table 1 Baseline characteristics

Demographics	N	%
Sex (N = 559)		
Male, N, %	249	45
Female, N, %	310	55
Race (N = 559)		
Black, N, %	80	14
White, N, %	464	82
Other, N, %	15	3

	N	Mean ± sd, (median)
Duration of the disease from dx	521	7.0 ± 10.3, (1.9)
FVC % predicted	550	87.1 ± 17.3, (88.0)
FEV1% predicted	550	82.4 ± 19.1, (84.0)
FEV1/FVC	546	0.74 ± 0.11, (0.76)
Serum ACE level	561	53.8 ± 36.1, (47.0)

FVC forced vital capacity, *FEV1* forced expiratory volume in 1 s, *ACE* angiotensin converting enzyme

Table 2 Organs assessed for treatment (target organs)

Target organ	N	%
Lung	467	83.7
Skin	77	13.8
Eye	63	11.3
Heart	49	8.8
Neuro	24	4.3
Other	161	28.9
No target organ	3	0.5

Table 4 Relationship between initial serum ACE level and decision to escalate treatment

Serum ACE level	Treatment escalation	No treatment escalation	Wald chi-square p value
≤ 82	91	388	< 0.0001
> 82	31	51	

Sensitivity: 0.254, specificity: 0.884, positive predictive value: 0.378, negative predictive value: 0.810

ACE angiotensin converting enzyme

Table 3 Sarcoidosis treatment at initial visit (N = 560)

	N	%
No sarcoidosis treatment	385	68.8
Only receiving non-CS agent	31	5.5
Receiving both CS and non-CS agent	57	10.2
Only receiving CS agent	113	20.2
Daily prednisone dose (mg) (N = 144*)		
0 < dose < 5	6	1.1
5	15	2.7
5 < dose ≤ 10	33	5.9
10 < dose < 20	8	1.4
20	39	7.0
> 20	43	7.7

CS corticosteroid

*Number of patients receiving CS

sACE to determine dose escalation at these different cut-offs, the sensitivities were progressively lower and the specificities were progressively higher as the ACE cutoff was raised. At the cutoff of sACE > 100, the sensitivity was 17.2%, specificity 93.2%, positive predictive value 41.2%, and negative predictive value 80.2%. Although a sarcoidosis patient sACE level of > 100 is likely to need treatment escalation, the low sensitivity suggests that this will not occur in many patients.

Table 5 shows the results of a multivariable logistic regression estimating the association of sACE level and several clinical variables with treatment escalation. Only sACE level and a low FVC % predicted at the initial clinic visit were significantly associated with treatment escalation. In Table 6, a similar multivariable logistic regression was performed where a dichotomous variable was used for the sACE level: > 82 versus ≤ 82. The results of this analysis were very similar to that in Table 5: only the sACE > 82 and a low FVC % predicted were associated with treatment escalation.

Table 7 shows association between treatment escalation at the initial visit and the clinician's assessment of improvement or no improvement at the subsequent visit (506/579, 87.6% had a subsequent clinic visit). There was a strong association (p < 0.001) between these variables.

We performed all of the above analyses in the subgroup of 385 patients who were "treatment naïve" (not receiving any

Table 5 Multivariable logistic regression estimating treatment escalation using serum ACE level as a continuous variable (*N*=561)

Parameter	DF	Estimate	Standard error	Wald chi-square	*p* value
Intercept	1	0.0923	0.9578	0.0093	0.9232
ACE level	**1**	**0.00878**	**0.00324**	**7.3433**	**0.0067**
Sex (female)	1	− 0.0905	0.1143	0.6272	0.4284
Race (black)	1	0.6609	0.4008	2.7192	0.0991
Race (other)	1	− 0.9261	0.7127	1.6884	0.1938
Age	1	− 0.00827	0.00942	0.7715	0.3797
Duration of disease	1	− 0.0249	0.0137	3.3051	0.0691
Lung	1	− 0.2759	0.3062	0.8123	0.3674
Skin	1	0.5669	0.3057	3.4388	0.0637
Neuro	1	0.7383	0.4626	2.5473	0.1105
Eye	1	0.0877	0.3543	0.0613	0.8044
Heart	1	0.3302	0.383	0.7431	0.3887
No target organ	1	− 11.9527	644.1	0.0003	0.9852
FVC, % predicted	**1**	**− 0.0172**	**0.00654**	**6.9276**	**0.0085**

ACE angiotensin converting enzyme, *DF* degrees of freedom, *FVC* forced vital capacity

Parameters in bold are significant

Table 6 Multivariable logistic regression estimating treatment escalation using serum ACE≤82 vs>82 as a dichotomous variable (*N*=561)

Parameter	DF	Estimate	Standard error	Wald chi-square	*p* value
Intercept	1	1.0612	0.9077	1.367	0.2423
ACE level > 82	**1**	**0.4054**	**0.1405**	**8.3219**	**0.0039**
SEX (female)	1	− 0.0785	0.1142	0.4733	0.4915
Race (black)	1	0.6206	0.3988	2.4218	0.1197
Race (other)	1	− 0.8548	0.7092	1.4529	0.2281
Age	1	− 0.0102	0.00933	1.2067	0.272
Duration of disease	1	− 0.0255	0.0137	3.4938	0.0616
Lung	1	− 0.2901	0.3064	0.8964	0.3437
Skin	1	0.5956	0.305	3.8143	0.0508
Neuro	1	0.6578	0.4614	2.0325	0.154
Eye	1	0.0651	0.3546	0.0337	0.8543
Heart	1	0.2667	0.3822	0.4868	0.4853
No target organ	1	− 11.8978	646.5	0.0003	0.9853
FVC, % predicted	**1**	**− 0.0179**	**0.00651**	**7.5472**	**0.006**

Parameters in bold are significant

ACE angiotensin converting enzyme, *DF* degrees of freedom, *FVC* forced vital capacity

Table 7 Relationship between treatment escalation and improved sarcoidosis at the subsequent visit, *N*=505

Variables	Improved subjective outcome	Not improved subjective outcome	Wald chi-square *p* value
Treatment escalation	57	59	<0.0001
No Treatment escalation	41	348	

sarcoidosis treatment at their initial visit, and all the aforementioned results of the entire cohort held with this subgroup, Tables e2–e5). The only additional association found in this subgroup was that the multivariate logistic regressions (both with a dichotomous and continuous sACE level) found an association between the skin as a target organ and the need to escalate treatment.

Discussion

In this retrospective analysis of 561 sarcoidosis patients seen for an initial visit at a university sarcoidosis clinic, there was a strong association between an elevated sACE level and the clinician's decision to escalate sarcoidosis treatment. Despite this strong association, the sensitivity (25.4%), specificity (88.3%), positive and negative predictive value (37.8% and 81%) were inadequate for an elevated sACE level to be used in isolation to make treatment decisions. Similar findings were observed when this analysis was restricted to patients who were not receiving any anti-sarcoidosis treatment initially. In a multivariable logistic regression, demographic characteristics, duration of disease, and target organ did not significantly affect these results. Similar findings were also observed when the cutoff value for an elevated sACE level was raised to > 100, where although the specificity of the association between sACE and treatment escalation increased to 93.1%, the positive predictive value was only 41.2%. These data suggest that although an elevated serum ACE is supportive evidence that treatment of sarcoidosis should be escalated, such decision needs to be augmented by other clinical data. In the multivariable logistic regression analysis, a low FVC % predicted was associated with treatment escalation. As the lung was the overwhelmingly most common target organ for treatment, we suspect that the low FVC % predicted was an indicator of active pulmonary sarcoidosis that warranted treatment. These results were not significantly affected by whether the patient was treatment naive at the time that a sACE level was obtained.

The use of sACE as a measure of sarcoidosis activity and the need for treatment is controversial. The sACE level has been shown to correlate with the overall disease activity, total body granuloma burden, and total number of extrapulmonary organs involved [8–11]. Serial sACE measurements have been suggested to be useful to assess the clinical course of disease [12–14]. However, others have found that the sACE level does not correlate with the severity of alveolitis in pulmonary sarcoidosis [15], the initial sACE level does not reliably predict progression of pulmonary sarcoidosis [5, 16] and sACE is not a reliable predictor of corticosteroid responsiveness for pulmonary sarcoidosis [17–20]. The recent European Respiratory Society clinical practice guidelines on the treatment of sarcoidosis did not mention the use of sACE or any other serum biomarker as useful in making treatment decisions. [21]

This analysis has several limitations. First and foremost, the decision to escalate treatment was not determined by protocol but by the subjective determination of a single clinician (MAJ). Although this individual is experienced in the treatment of sarcoidosis, his approach may not be optimal and might be prone to personal subjective assumptions. To account for the subjective nature of the decision to treat these patients, all patients who returned for a follow-up clinic visit were assessed for improvement or lack of improvement of their condition. This analysis showed a strong correlation between treatment escalation and improvement in the target organ, suggesting that treatment was indicated. This method of assessment is routine in this clinic and was not performed for study purposes. However, it is possible that the clinician's assessment of improvement was influenced by his previous decision to escalate treatment. Clearly, the limitation of a single clinician determining the need for treatment escalation could only be resolved by duplicating this study with the participation of multiple clinicians. A second limitation was that this analysis was performed on sarcoidosis patients in one medical center, and the results may not reliably extend universally. However, our cohort was demographically diverse, and in a multivariate logistic analysis, there was no significant effect of demographics upon the study results. Thirdly, sACE is affected by many factors including the use of angiotensin converting enzyme inhibitor drugs, the specific sACE assay, and the status of the patient's ACE gene deletion/insertion polymorphism genotype [4]. Although we used the same sACE assay for these patients, we did not control for these other factors. Finally, the patients were also diverse in terms of their clinical course of sarcoidosis, with some patients having their initial clinic visit soon after diagnosis whereas others had chronic disease and had an initial clinic visit several years after diagnosis. However, in the multivariate logistic regression analysis, the duration of disease did not affect the relationship between sACE level and treatment escalation.

In conclusion, our retrospective analysis of patients with an initial visit in one university sarcoidosis clinic found a strong correlation between the sACE level and the clinician's decision to escalate therapy. The clinician was blinded to the sACE result when the treatment decision was made. However, despite this strong association, the predictive power of the sACE level to determine the need for treatment escalation was inadequate to be used in isolation. The sACE level may possibly be useful as adjunctive data that could be used in combination with other clinical information to make treatment decisions. It is also possible that other promising serum biomarkers such as serum IL2-receptor [22], chitotriosidase [23], or Krebs von den Lungen-6 (KL-6) [24] may be helpful in determining the need to treat sarcoidosis.

Declarations

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