Patients with a genomic classifier result positive for UIP show a greater decline in lung function when treated with combination immunosuppressive therapy

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BACKGROUND

The Envisia Genomic Classifier (EGC) is a molecular diagnostic test that identifies a genomic Usual Interstitial Pneumonitis (UIP) pattern in tissue samples obtained by transbronchial biopsy.[1] It was designed to be highly specific to minimize false positive results. A recent systematic review and meta-analysis on EGC reported an aggregate specificity of 92% and a sensitivity of 68%.[2] It is used to aid in the diagnosis of Idiopathic Pulmonary Fibrosis (IPF) and other progressive fibrotic lung diseases, obviating the need for surgical lung biopsy (SLB) in patients for whom SLB might be considered, primarily those patients who lack a definite UIP pattern on high resolution CT imaging.[3]

An EGC result can help inform an ILD multidisciplinary discussion regarding both diagnosis and prognosis and can help inform therapy selection.[4] Clarity around the latter is critical in order to avoid possibly inappropriate empiric treatments. In particular, empiric therapy with combination corticosteroids and nonsteroidal immunosuppressants may be considered for some patients. This combined therapy has been shown to be harmful in patients with IPF.[5]

AIMS AND OBJECTIVES

We hypothesized that patients with an EGC (+) result treated with combination therapy (steroids combined with a nonsteroidal immunosuppressant) would show a greater decline in forced vital capacity (FVC) compared to EGC (+) patients not treated with combination therapy.

METHODS

Patients in the BRAVE study who underwent pathological evaluation for an undiagnosed ILD, had an EGC result, and had serial Forced Vital Capacity (FVC) maneuvers performed were identified. Patients were included if they had at least one FVC at least six months after their baseline FVC at study enrollment. In patients with FVC measurements at multiple time points, the one closest to one-year follow-up was used for this analysis. Retrospective analyses of EGC result, change in FVC percent predicted, and treatment for ILD were performed. We compared change in FVC percent predicted in the group of patients that were treated at any point with combination immunosuppressive therapy (steroids combined with a nonsteroidal immunosuppressant) to those not treated with combination therapy, and we further evaluated patients by pathologic diagnosis (pathologic UIP vs. pathologic not UIP vs. pathology nondiagnostic).

RESULTS

The consort diagram for the study population is shown in Figure 1. 135 patients met all inclusion criteria. 73 of 135 (54%) of patients had an EGC (+) result. EGC (+) and EGC (-) groups were demographically similar except for age, with EGC (+) patients being older (66 vs. 61 years, p=0.030). Baseline, follow-up, and absolute change in FVC % predicted are shown in Table 1. EGC (+) patients had a lower baseline FVC (66.9% predicted) compared to the EGC (-) group and had an absolute 1-year decline of 3.7%. 28 patients (21% of the total cohort) received both corticosteroids and a nonsteroidal immunosuppressant, with a similar proportion in both groups (18% vs. 23%, p=0.6) EGC (+) patients exposed to both corticosteroids and a nonsteroidal immunosuppressant showed a 1-year decline of 9.4% compared to a decline of 1.9% in EGC (+) patients not taking both (p=0.01) (Figure 2). EGC (–) patients did not show a significant difference in 1-year FVC change for those taking combination therapy compared to those not treated with both (1.9% decline vs. 0.3% increase, p = 0.4). Findings were similar independent of pathologic result (Table 2 and Figure 3).

FIGURE 1.
Flowchart of diagnostic samples from the BRAVE Study used in this analysis

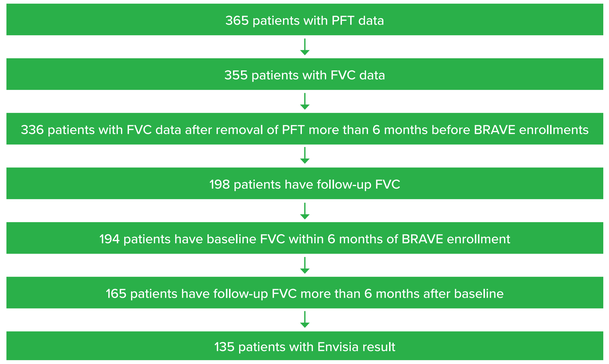

TABLE 1.
Baseline, Follow-up, and Absolute change in FVC % predicted in the subset of patients (n=28) who were treated with combination immunosuppressive therapy (steroids and nonsteroidal immunosuppressant) compared to those not treated with combination therapy) grouped by Envisia result

	Envisia Negative N = 62[1]	Envisia Positive N = 73[1]	p-value[2]
Baseline FVC %	73.4 (18.4)	66.9 (16.4)	0.034
Follow-up FVC %	73.3 (18.9)	63.2 (17.8)	0.002
Absolute Change FVC %	-0.1 (11.2)	-3.7 (10.8)	0.064
Corticosteroids and/or Nonsteroidal Immunosuppressant			0.6
Both	11 (18%)	17 (23%)	
Nonsteroidal Immunosuppressant Only	4 (6.5%)	2 (2.7%)	
Steroid Only	12 (19%)	17 (23%)	
Neither	35 (56%)	37 (51%)	

1. Mean (SD); n (%)
2. Welch Two Sample t-test; Pearson's Chi-squared test; Fisher's exact test

FIGURE 2.
Absolute change in FVC % predicted in the subset of patients (n=28) who were treated with combination immunosuppressive therapy (steroids and nonsteroidal immunosuppressant) compared to those not treated with combination therapy grouped by Envisia result

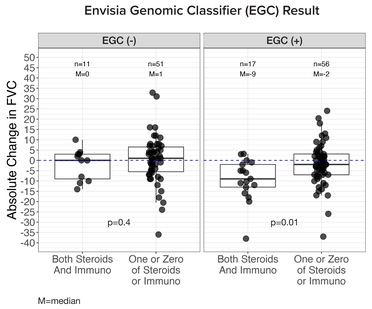

FIGURE 3.
Absolute change in FVC percent predicted in the subset of patients (n=28) who were treated with combination immunosuppressive therapy (steroids and nonsteroidal immunosuppressant) compared to those not treated with combination therapy) grouped by Envisia result and pathologic diagnosis

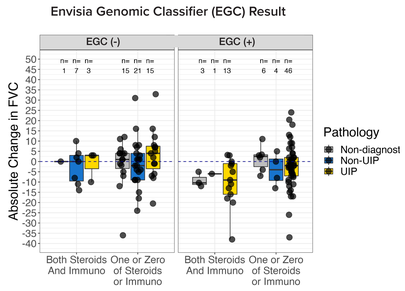

TABLE 2.
Median absolute change in FVC percent predicted in the subset of patients (n=28) who were treated with combination immunosuppressive therapy (steroids and nonsteroidal immunosuppressant) compared to those not treated with combination therapy) grouped by Envisia result

Pathology = UIP		Envisia Result		Median (combined EGC + and -)
		EGC (+)	EGC (-)	
Steroids/Nonsteroidal Immunosuppressants	Both	-9 (n=13)	3 (n = 3)	-7 (n=16)
	One or Neither	-2 (n=46)	4 (n=15)	-1 (n=61)
		-2 (n=59)	3 (n=18)	

Pathology = Non-UIP or Non-diagnostic		Envisia Result		
		EGC (+)	EGC (-)	
Steroids/Nonsteroidal Immunosuppressants	Both	-8.2 (n=4)	0 (n=8)	-5.5 (n=12)
	One or Neither	1 (n=10)	1 (n=36)	1 (n=46)
		-4.5 (n=14)	0.5 (n=44)	

DISCUSSION

The Envisia Genomic Classifier (EGC) is a molecular diagnostic test that identifies a genomic UIP pattern in tissue samples obtained by transbronchial biopsies.[1] It is currently commercially available in the U.S. and is expected soon outside the U.S. The test is intended for those patients with a fibrotic interstitial lung disease in whom a finding of genomic UIP would help inform diagnosis and prognosis but who lack a definite UIP pattern on CT imaging. The classifier was trained on a large cohort of patients with ILD who were undergoing invasive tissue sampling in an attempt to establish a diagnosis. Therapy with steroids combined with nonsteroidal immunosuppressants is not uncommon for patients in whom a diagnosis is uncertain, as evidenced by the fact that more than a fifth of patients in this cohort had received empiric combination therapy at some point prior to their surgery.

These findings show that an EGC (+) result can provide information that goes beyond diagnosis, highlighting those patients for whom combination therapy might, in fact, be harmful. Although this finding is reflected in a decline in lung function rather than the increase in mortality seen in the PANTHER Trial,[5] it stands to reason that the findings support the idea that the EGC (+) patients include a significant fraction of patients with IPF. Had Envisia been used before initiation of treatment, harm might have been avoided in these patients. The fact that the results were similar for patients whose pathologic diagnosis was not UIP, suggests the hypothesis that the genomic signal of UIP may reflect the basic biology of progression independent of pathologic manifestations of disease.

CONCLUSIONS

- An EGC (+) result may help identify patients in whom combination immunosuppressive therapy is harmful.
- These results further support the utility of the Envisia Genomic Classifier, highlighting the potential of a EGC (+) result to inform both diagnosis and treatment decisions, identifying patients in whom antifibrotic therapy may be preferred.

References

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