IgG responses are associated with severe disease and mortality in AIDS-associated talaromycosis

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BACKGROUND

- There is dearth of data on antibody responses to AIDS-associated talaromycosis and how antibody response impacts disease severity and patient outcomes.
- Data from our talaromycosis Itraconazole versus Amphotericin B for Penicilliosis (IVAP) trial (N=440) showed that patients presenting with an acute pulmonary syndrome had higher mortality.
- **Objective**: we tested the hypothesis that acute pulmonary syndrome is associated with a serological pattern of acute infection, and an acute serological pattern is associated with poor clinical outcomes.

METHODS

- Longitudinal IgG antibody responses to talaromycosis were measured in available plasma samples of IVAP patients using a direct anti-Mp1p IgG enzyme immunoassay.
- Patients were classified into three IgG response types: **1) Negative IgG, 2) Increasing IgG, 3) Positive Unchanged IgG** through analysis of longitudinal IgG trend over 24 weeks.
- Univariate and multivariate logistic regression were used to assess **association of IgG type** and **disease severity** (defined as a respiratory rate >22, dyspnea requiring oxygen, and/or respiratory failure diagnosis at presentation) and **24-week mortality**.

Table 1. Comparison of AIDS-associated talaromycosis patient characteristics between IgG response types.

Characteristics	Negative IgG (N = 88)	Increasing IgG (N = 115)	Positive Unchanged (N = 113)	P value
Age (yrs)	35 [29.8, 40.2]	33 [29, 38]	33.0 [29, 36]	0.094
Sex (male)	57 (64.8%)	77 (67.0%)	74 (65.5%)	0.944
IVDU	20 (22.7%)	34 (26.6%)	38 (33.6%)	0.239
CD4 (cells/dL)	8 [4, 15]	12 [7, 25]	11 [6, 23]	0.006
Respiratory rate >22	17 (19.3%)	15 (13.0%)	20 (17.7%)	0.444
Dyspnea/oxygen requirement	9 (10.2%)	6 (5.22%)	10 (8.85%)	0.381
Respiratory failure	9 (10.2%)	8 (6.96%)	6 (5.31%)	0.406
Severe disease*	24 (27.3%)	18 (15.7%)	24 (21.2%)	0.130
IRIS/relapse	8 (9.09%)	6 (5.22%)	13 (11.5%)	0.231
24-week mortality	9 (10.2%)	2 (1.74%)	6 (5.31%)	0.028

- Severe disease = respiratory rate >22 +/- dyspnea +/- respiratory failure)
- IVDU, injection drug use; IRIS, immune reconstitution inflammatory syndrome
- Summary statistics are % for binary and median [IQR] for continuous variables

Talaromycosis patients who do not mount an IgG response have more severe disease and higher mortality suggesting an important role for humoral immunity in pathogenicity

RESULTS

Plasma samples and complete data were available for 423 of 440 IVAP patients. Mean age 34.0 (IQR [30.0; 38.0]) years; mean CD4 count 10.0 (IQR [5.00; 22.5]) cell/mm3. Major findings are:

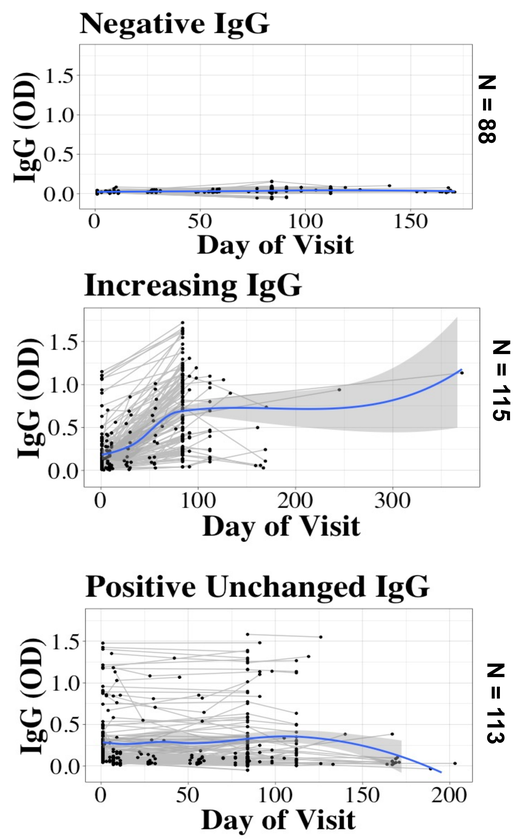
1. Serial samples for classification into three IgG type responses were available for 316 patients: Negative IgG, Increasing IgG, and Positive Unchanged IgG (**Figure 1**).
2. Patient characteristics were similar in each of the three IgG response types (**Table 1**). **The Negative IgG group had the lowest CD4+ count and the highest mortality**.
3. Multivariate models (N=312) (adjusted for age, history of injection drug use, CD4 count, and antifungal treatment arm) demonstrated (**Table 2**):
   - **Negative IgG was associated with higher risk of death** (OR=3.20, 95% CI: 1.18-8.96, P=0.023)
   - **Increasing IgG was protective of death** (OR=0.14, 95% CI: 0.02-0.56, P=0.013).
4. Multivariate models of full population (N=423) (IgG type classified as negative or positive at baseline)
   - **Negative IgG was associated with disease severity** (OR=1.62, 95% CI: 1.02-2.55, P=0.039) and had a **non-statistically significant association with mortality**.
   - **Disease severity was an independent predictor of death** (OR=2.44, 95% CI:1.38–4.34, P=0.002).

Table 2. Independent association of Negative IgG response and 24-week mortality in 312 AIDS-associated talaromycosis patients

Characteristics	All patients (N = 312)	Dead (N = 18)	Alive (N = 294)	Univariate model OR (95% CI)	Multivariate model OR (95% CI)
Age (years)	33.0 [29.0-38.0]	35.5 [31.2-44.8]	33.0 [29.0-37.8]	1.85 (1.05 – 3.17), P = 0.035	1.70 (0.94 – 3.02), P = 0.080
IVDU	91 (29.2%)	5 (27.8%)	86 (29.3%)	0.93 (0.29 – 2.55), P = 0.893	1.38 (0.41 – 4.15), P = 0.581
CD4 (cells/dL)	10.0 [5.0-21.2]	5.0 [2.0-10.8]	11.0 [6.0-22.0]	0.90 (0.63 – 1.08), P = 0.345	0.91 (0.63 – 1.09), P = 0.398
Negative IgG response	88 (28.2%)	10 (55.6%)	78 (26.5%)	3.46 (1.32 – 9.37), P = 0.012	3.20 (1.18 – 8.96), P = 0.023
Treatment (Itraconazole)	164 (52.6%)	12 (66.7%)	152 (51.7%)	1.87 (0.71 – 5.49), P = 0.212	2.12 (0.78 – 6.40), P = 0.1447

- Summary statistics are % for binary and median [IQR] for continuous variables.

Figure 1. Three IgG response types in AIDS-associated talaromycosis



CONCLUSIONS

Although not as hypothesized, the findings that **28% of talaromycosis patients do not mount an IgG response, and these patients have more more severe disease and higher mortality** suggest a **central role of humoral immune response** in talaromycosis pathogenicity. These findings may have important clinical implications in early identification of talaromycosis patients at risk of more severe outcomes and death.

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