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Basophil Activation Test Positivity Decreases With Time in Immediate Allergic Reactions to Proton Pump Inhibitors

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To the Editor,

Omeprazole is a widely prescribed proton pump inhibitor [1], with 1%–3% of adverse reactions being reported. Up to 86% of these reactions are IgE mediated [2] and half of them anaphylaxis [1]. An accurate diagnosis is essential, with skin testing (STs) showing high specificity and positive predictive value (PPV) (100%), but lower sensitivity (60%) and negative predictive value (NPV) (70%–90%) [2]. As stated in a recent position paper of the European Academy of Allergy and Clinical Immunology (EAACI), the basophil activation test (BAT) is a reliable option in the diagnosis of immediate hypersensitivity to proton pump inhibitors [3]. In fact, previous research from our group reported that BAT has a higher sensitivity than STs (73.8%) and similar specificity, PPV (100%) and NPV (66.7%) [1]. Interestingly, the combination of STs and BAT can increase sensitivity up to 85.7%, being BAT positive in 57.1% of patients with negative STs [1].

An important factor influencing the diagnostic sensitivity in these IgE-mediated reactions is the time elapsed between the reaction and the performance of the test, showing a decrease in STs and BAT positivity over time, although highly dependent on the drug and reaction selectivity [4, 5]. This highlights the importance of performing allergology studies close to the reaction. However, no studies have been performed in this regard for omeprazole allergy. We analysed the evolution of BAT over time in 18 patients with confirmed omeprazole allergy and positive BAT results from a previous study published in 2018 [1]. These patients were followed up for three additional years without re-exposure to the drug to determine the interval during which BAT remains reliable. Demographical and clinical characteristics of the patients are shown in Table 1. Besides omeprazole, 8 (44.44%) had a positive BAT to pantoprazole at the beginning of the follow-up study.

BAT was performed on all patients at different time points after reaction occurrence, following the same protocol, and positivity criteria used previously [1]. The mean follow-up was 87.74 months (IQR = 72–116; CI = 73.73–101.8). Similar to betalactams

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Maria Jose Torres and Jose J. Laguna equally contributed to this work and are shared senior authors.

TABLE 1 | Demographic and clinical characteristics of patients included in the study.

Variable		
Gender: N (% women)	12 (66.7%)	
	Mean ± SD	**Median (IQ)**
Age	45.12 ± 10.15	40 (36–55.5)
Interval reaction-study (months)	11.94 ± 15.17	6 (2.5–14)
Interval drug-reaction (min)	67.31 ± 58.27	60 (22.5–90)
Clinical presentation: *N* (%)		
Anaphylactic Shock	5 (27.8%)	
Anaphylaxis	8 (45.5%)	
Urticaria-angioedema	5 (27.8%)	
Administration route: *N* (%)		
Oral	17 (94.4%)	
Parenteral	1 (5.6%)	
Episodes: *N* (%)		
One episode	13 (72.2%)	
Two episodes	5 (27.8%)	
Atopy: *N* (%)		
Yes	10 (55.6%)	
No	6 (33.3%)	
Unknown	2 (11.1%)	
Diagnostic test: *N* (%)		
Omeprazole		
STs	14 (77.7%)	
DPT	3 (16.7%)	
Pantoprazole		
STs	12 (66.7%)	
DPT	1 (5.6%)	
BAT: *N* (%)		
Omeprazole	18 (100%)	
Pantoprazole	8 (44.4%)	

Abbreviations: DPT, drug provocation test; IQ, interquartile range; *N*, number; SD, standard deviation; ST, skin testing.

[5, 6], we observed a progressive decrease in %CD63$^+$ basophils (Figure 1A) and stimulation index (SI) (Figures 1B and S1) for BAT with omeprazole, being significant after 73–108 months ($p = 0.006$ and $p = 0.035$ for %CD63 and SI, respectively). Similar results were found for pantoprazole ($p = 0.046$ for both, %CD63 and SI) (Figure 1C,D). %CD63 values showed a significant negative correlation with the time interval since reaction occurrence for both drugs (omeprazole: $R^2 = 0.2395$ and $p = 0.001$; pantoprazole: $R^2 = 0.1507$ and $p = 0.013$) (Figure 1E,F).

Survival analysis showed that the median time for a negative BAT with omeprazole is 119 months post-reaction, with all patients showing positive BAT results up to 76 months. For pantoprazole, possibly because it was not the reaction trigger, BAT positivity decreased earlier, with a median of 79 months for a negative BAT and a 100% probability of a positive BAT up to 22 months. The difference between both survival curves was statistically significant ($p = 0.044$) (Figure 1G). This decline occurs later compared to amoxicillin or clavulanic acid, which showed 50% negative results around 12 or 24 months, respectively [5, 6]. BAT results and survival analysis using CD203c as an activation marker showed similar results (Figure S2).

Comparison of demographic and clinical characteristics between patients with positive ($n = 8$; 44.4%) vs. negative BAT to omeprazole at the end of the study (Table S1) showed a

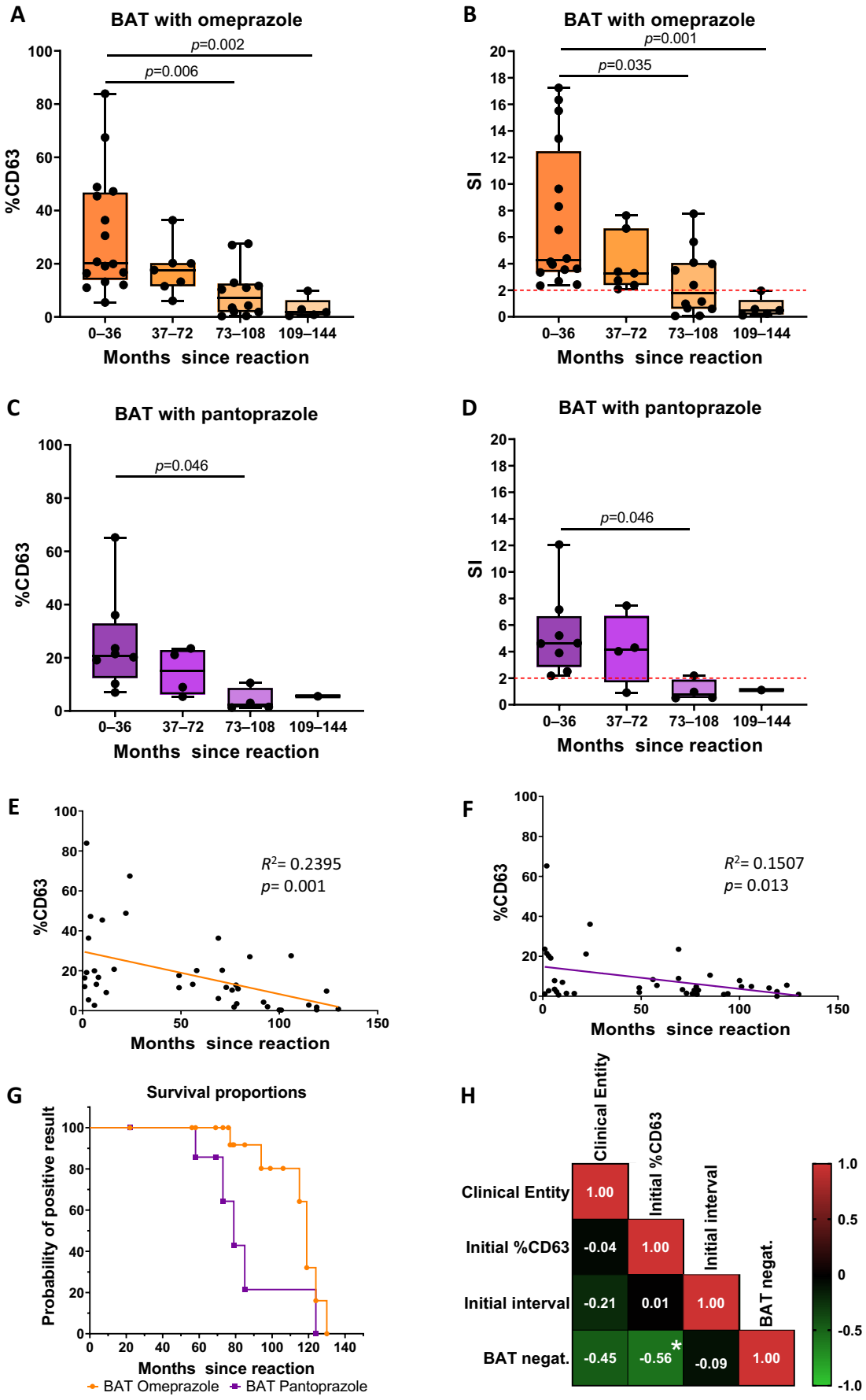

FIGURE 1 | Legend on next page.

FIGURE 1 | BAT analysis using CD63 as activation marker. BAT results with omeprazole performed at different time points after index reaction expressed as %CD63 positive basophils (A) and SI (B). BAT results with pantoprazole performed at different time points after index reaction expressed as %CD63 positive basophils (C) and SI (D). Correlation between % of CD63 positive basophils and time interval since index reaction after BAT with omeprazole (E) and pantoprazole (F). Survival curves show the probability of having a positive BAT with omeprazole or pantoprazole depending on the time interval since the last reaction (G). Multivariant analysis showing Spearman *r* between a negative BAT at the end of the study and the clinical entity, the %CD63 in the first BAT and the time interval between the index reaction and first BAT (H); red = positive correlation; green = negative correlation; $*p < 0.05$.

significantly lower time interval between the reaction and the last BAT performed in patients with a positive test (67.43 ± 26.32 vs 105.7 ± 18.65 months; $p = 0.004$). Multivariant analysis showed that patients with initially higher %CD63 kept positive results longer ($p = 0.016$). However, this cannot be predicted before BAT performance. There was also a correlation with reaction severity, with more severe reactions in patients with positive BAT, although not significant maybe due to the small sample size (Figure 1H).

In summary, BAT remains a reliable diagnostic tool even several years post-reaction for evaluating immediate reactions to omeprazole, particularly in severe cases. However, the duration of BAT positivity is significantly influenced by the activation levels after the reaction.

Author Contributions

M.J.T., J.J.L. and T.D.F. designed the study and coordinated the work of the rest of the authors. M.S., M.A.J., M.R.G.-M., M.L.S. and C.B. recruited the study individuals, managed the clinical procedures and obtained clinical data. R.F.-S. and A.A. performed the in vitro experiments. J.J.L. and T.D.F. analysed the experimental results. T.D.F., C.M., M.S. and R.F.-S. wrote the manuscript and figures, which were reviewed by the rest of the authors.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.