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Galactomannan antigen detection as a screening tool for early diagnosis of invasive aspergillosis: Experience of Turkish adult patients

Short title: Galactomannan experience from Turkey

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Abstract

Background: The aim of the present study was to investigate the usefulness of galactomannan (GM) antigen as a screening test for the early diagnosis of invasive aspergillosis (IA) in adult patients in Turkish centers.

Methods: PubMed was searched using the keywords “galactomannan” and “Turkey.” Only studies that used the GM antigen as a screening tool in adult patients were included in the analysis.

Results: Four peer-reviewed articles that matched the inclusion criteria were identified. A total of 314 adult patients with several hematological malignancies and who underwent allogeneic hematopoietic stem cell transplantation were included in the four studies. Patients were followed up for 459 neutropenia episodes. GM antigen testing was performed in 2662 serum samples. The sensitivity, specificity, positive predictive value, and negative predictive value were 23.07%–100%, 5.7%–90.36%, 6.7%–73.07%, and 55.5%–100%, respectively. Early diagnosis of IA by GM screening was found in only one patient in one of the four studies.

Conclusion: The performance of the GM antigen test as a screening tool in Turkish centers was not promising. However, it can be used as a diagnostic test for patients with clinical and radiological findings suggesting invasive fungal disease.

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Keywords: Galactomannan, invasive aspergillosis, diagnosis, Turkey

Introduction

The diagnosis of invasive aspergillosis (IA) is a challenge in patients with hematological malignancies. Although isolation of *Aspergillus* species from culture is the golden standard, several conditions such as severe thrombocytopenia and hypoxemia can limit to obtain deep tissue or bronchoalveolar lavage fluid to perform fungal culture. The low sensivitiy of clinical and radiological signs can cause a significant delay in the accurate diagnosis of IA [1].

Detection of aspergillus galactomannan (GM) antigen in serum by sandwich enzyme immunoassay (EIA) method (Bio-Rad Laboratories, Marne-La-Coquette, France) has been accepted as an important tool for the early diagnosis of IA. Although screening the high risk hematology patients with GM antigen was recommended in several guidelines, the performance of the test can be influenced by several factors such as duration of neutropenia, number of the neutrophils, sampling schedule, incidence of IA, exposure to mold active antifungal drugs, and laboratory experience [1, 2]. The Turkish national expert report for the diagnosis of invasive fungal diseases (IFD) recommended GM antigen as a screening test based on the studies performed at different countries [3]. There was only one paper from Turkey

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regarding GM antigen detection in high risk hematology patients for early diagnosis of IA when this report was written [4]. Therefore, no country specific recommendation could be made in the national expert report [3]. Here, we aimed to review the recently published national literature and evaluate the role of GM screening for the early diagnosis of IA in Turkish centers.

1. Methods

Pubmed was searched with the keywords “galactomannan” and “Turkey”. Only studies that investigated the performance of the GM antigen in adult patients as a screening test were included in the literature analysis.

2. Results

Four peer reviewed articles from Turkey about the diagnostic performance of GM antigen as a screening test for diagnosis of IA were published at the international journals between 2010 and 2018 that included adult patients with different hematological malignancies or hematopoietic stem cell transplantation (HSCT) [4-7]. Twice weekly sampling was performed in all studies. Screening tests were started at the day of an absolute neutrophil count of <500/mm^3 until recovery of neutropenia except Uludag University Hospital where GM

screening started at the first day of hospitalization. To define the probability of IA, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria published in 2002 [8], was used in the study performed at Hacettepe University Hospital [4]. The other studies [5-7], used EORTC/MSG criteria published in 2008 to define IA [9].

A total of 301 adult patients with several hematological malignancies and 13 patients who underwent allogeneic HSCT were included in four studies. Patients were followed for 459 neutropenia episodes. GM antigen testing was performed in 2662 serum samples. Mold active antifungal prophylaxis was administered in two studies [6, 7]. Fluconazole was the choice of antifungal prophylaxis in the other studies [4, 5].

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were as follows; 23.07-100%, 5.7-90.36%, 6.7-73.07%, and 55.5-100% (Table 1). Early diagnosis of IA by GM screening was mentioned for only one patient (positive GM before detection of aspergillus rhinosinusitis) in one of the four studies [4].

3. Discussion

The diagnostic performance of GM was highly variable between centers. The sensitivity of GM antigen was low in the first study from Turkey [4]. This can be associated with the high rate of false GM positivity related to piperacillin-tazobactam (TZP) administration in the same center [10]. The study from Uludag University hospital [5], showed a better performance contrast to Hacettepe study [4] (Table 1), but there were still 65 patients with clinical and radiologic findings concordant with IA (possible cases based on EORTC/MSG criteria) in whom GM antigen was negative despite twice weekly screening [5]. Both centers did not use mold active prophylaxis during the study periods, and false positive GM related to TZP administration was not an issue in Uludag University [11]. The debate on false positive GM related to administration of TZP (orginal brand) seemed to be solved in Turkish centers but false positive GM in patients receiving a generic TZP was reported very recently [12-14]. Obtaining the blood sample for GM antigen test just before the next dose of TZP was shown to be a very effective way for avoiding false positivity [15].

The later studies reported very low sensitivity (23.07.-35.7%) for GM screening that were performed when posaconazole prophylaxis became the standard of care particularly for patients receiving induction chemotherapy for acute myeloid leukemia (AML) [6, 7]. However,

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specificity was higher than 90% that indicates a positive GM result should trigger the diagnostic pathway for early detection of IA [6, 7].

A total of 2972 serum GM tests were performed in a 4-year study with 262 unselected consecutive high-risk episodes who received posaconazole prophylaxis. GM antigen was negative in 96.7% of tests and 83.6% of episodes. There were 30 false positive episodes which mainly occurred in tests performed as preemptive surveillance (26 of these 30 episodes (86.7%). When GM antigen testing was used for screening the PPV was 11.8%, while PPV increased to 89.6 when used a diagnostic test in case of suspicion of IFD. NPV remained as 100% at any scenario [16]. While the sensitivity of GM in serum decreases under mold active prophylaxis, GM antigen can remain positive in bronchoalveolar lavage fluid despite posaconazole prophylaxis [17]

In the study from Erciyes University [7], the serum samples from patients with radiologic evidence of IA and serum samples from patients without IA (1 to 10 ratio) were re-tested by a modified methodology which was previously proven to increase the sensitivity of GM antigen detection [18]. The sensitivity increased from 35.7 to 92.3 % with a slight decrease in the specificity from 99.6 to 97.6 % [7]. The method is based on the concentration

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of GM antigen. It can be suitable for the patients with radiologic findings suggesting IA rather than a screening test due to high workload and extra-cost.

GM antigen screening was supported as an early diagnostic tool for IA since 2001 and recommended by several guidelines as the part of the routine care for patients with prolonged neutropenia [1, 2, 19]. However, there are some studies not concordant with this statement. A previous study showed that GM detection does not precede detection of major lesions by pulmonary CT. The authors reported that only 7 (10%) of 70 patients with pulmonary signs of IA had positive GM test results before detection of the pathologic change by CT [20]. When the results of the randomized controlled study that compared voriconazole and amphotericin B in the treatment of IA were re-evaluated with EORTC/MSG 2008 criteria, possible cases who received voriconazole had better outcomes when compared with patients received amphotericin B. The authors concluded that possible cases diagnosed by radiology without positive GM or Aspergillus isolation were real aspergillosis diagnosed early by radiology [21]. The rate of possible IFD (diagnosed by radiology without any microbiological evidence of IFD) was higher than probable IFD in the recent prospective European audit for invasive mold diseases (PIMDA) that recruited AML and allogeneic HSCT patients. Only centers that have an immediate access to GM antigen testing were allowed to sign patients for this study, and it was surprising that possible cases were more frequent despite serial GM screening in a

prospective study [22]. These findings rise questions about GM antigen screening for early diagnosis of IA. A recent study from Switzerland analyzed the performance of GM antigen as screening tool in hematological cancer patients with a duration neutropenia longer than 14-days. Serum GM was measured twice weekly and mold-active prophylaxis was not routinely part of the care. IA was diagnosed in 30 out of 268 patients and a positive serum GM was the first indicator of IA in 10 (33%) patients. A total of 500 GM antigen tests were required to diagnose one IA case based on GM screening which would cost 15.000 $ in this setting [23]. Cost and logistics are the other important issues to use GM screening as an effective tool for early diagnosis of IA. The time period for reporting the results of GM test was reported as one week from a Turkish university hospital [24].

There were also two pediatric studies investigating the role of GM for the diagnosis of IA. The first study was from Ege University which included 141 patients with acute lymphoblastic leukemia followed between 2006 and 2015. GM antigen was tested in 3264 serum samples. The authors did not calculate the sensitivity or specificity of GM antigen but investigated the role of GM screening for the management of the neutropenic patients in detail. There were 5 patients with proven or probable IA. Of the 3264 serum samples, 179 (5.5%) from 76 patients were positive at the cut-off as > 0.5. Of the 76 patients, 21.7% were true positive and 52.1% were false positive. Thorax computed tomography (CT) revealed

findings concordant with IA in 12 (15.8%) of the 76 patients with positive GM antigenemia. The 35 out of 76 patients with positive GM were already on mold active antifungal therapy. The positive GM results changed the antifungal treatment in only 13 (17.1%) patients [25]. The second study included 47 hematological patients under 18-years who had at least one GM antigen test result. A total of 158 blood samples were tested for GM antigen and yielded a sensitivity of 36% and a specificity of 90.9% at the cut-off 0.7. Decreasing the cut-off for GM antigen to 0.5 increased the sensitivity to 68% but decreased the specificity 77.2% [26].

Conclusion

In Turkey, access to GM antigen test is available in most of centers treating high risk hematology patients [27], but publication of the experience in the international literature is limited [4-7, 25, 26]. Only one center reported GM as a useful marker for the diagnosis of IA where mold active prophylaxis was not used [5]. After posaconazole prophylaxis was introduced in the clinical practice, the sensitivity of GM was low and the antifungal therapy was mainly triggered by radiological investigation [7]. The benefit of GM screening was extremely limited in pediatric patients, also [25, 26].

As a conclusion, the performance of GM antigen test as a screening tool is poor in Turkish centers based on the findings of the limited number of publications. However,

retaining GM antigen in the laboratory inventory as a diagnostic test for patients with clinical and radiological findings suggesting IA will be helpful to achieve microbiological clues about the etiology of suspected IFD.

Conflict of interests: None related to this study

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Table 1. Characteristics of the studies and diagnostic performance of galactomannan antigen

Study center Time period	Number of the patients	Number of the patients with IA Diagnostic criteria	Number of the serum samples	Antifungal prophylaxis	Cut-off	Sensitivity (%)	Spe
Hacettepe University 2001-2003	58 neutropenia episodes in 45 patients	1 proven 4 probable 20 possible EORTC/MSG 2002	545	None	Single positive results ODI ≥ 0.5 Two consecutive positive results ODI ≥ 0.5	100 60	
Uludag University	165 neutropenia episodes in	4 proven 11 probable	1385	Antifungal administration	Single positive results ODI ≥	100	

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2003-2004	106 patients	65 possible EORTC/MSG 2008		in 111 episodes, types of antifungal drugs were not stated	0.5 Two consecutive positive results ODI ≥ 0.5	86.7	
Osmangazi University 2008-2011	161 neutropenia episodes in 99 patients	1 proven 17 probable 60 possible EORTC/MSG 2008	358 from high risk patients and 20 from non-neutropenic patients without fever	Antifungal administration in 106 episodes, mold active drugs but exact types were not stated	Single positive results ODI ≥ 0.5	23.07	9
Erciyes University 2012-	75 neutropenia episodes in	12 probable 1 possible	354	Posaconazole in 31 episodes Fluconazole in	Single positive results ODI ≥ 0.7	35.7	

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2013	64 patients	EORTC/MSG 2008		42 episodes Voriconazole in 2 episodes			

IA; invasive aspergillosis, EORTC/MSG; European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group, PPV; positive predictive value, NPV; negative predictive value, ODI; optical densitiy index

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