

Invasive Mould Disease – Predictive Risk Factors in Acute Leukemia Patients Receiving Intensive Chemotherapy and its Impact on Survival

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Abstract

Background: Invasive mould disease (IMD) after chemotherapy in patients with acute leukemia has traditionally caused much morbidity and mortality.

Methods: We conducted a retrospective, matched case-control study of IMD in patients with acute leukemia managed in our institution from January 2004 to March 2007 to determine the incidence and clinical outcomes of IMD, including its impact on 1-year survival.

Results: During this period, 172 patients with acute leukemia underwent chemotherapy with curative intent. A probable or proven IMD developed in 19 patients (cases), giving an incidence of 11%. *Aspergillus* was the commonest mould. Cases were more likely than controls to have prolonged neutropenia, fever that did not respond to carbapenems, a bacteremia and a longer length of stay. Three-month survival was 93.3% among both cases and controls, but one-year survival was 46.7% among cases and 93.3% among controls. Having an IMD appears to impart a higher risk of mortality at one year.

Conclusion: The incidence of invasive mould disease in acute leukemia patients receiving chemotherapy is 11%. Absolute neutropenia more than 14 days is a risk factor for IMD. Itraconazole prophylaxis did not reduce the likelihood of an IMD and a change should be considered. Having an IMD appeared to predict mortality at 12 months.

Keywords: Invasive fungal infection; Acute leukemia; Invasive aspergillosis; Survival

Introduction

Invasive mould disease (IMD) after chemotherapy in patients with acute leukemia has traditionally caused much morbidity and mortality. Recent series, however, suggest an improved survival, attributed to the newer anti-fungal agents. Pagano et al noted that the attributable mortality of invasive aspergillosis (IA) in patients with acute myeloid leukemia fell from 48% in the 1987-1998 periods to 38% in the 1999-2003 period [1]. In a more recent survey, the same investigators noted an attributable mortality of only 27% at 120 days [2]. Nivoix et al. in a series of mixed haematology-oncology patients found that survival was only 47% before 2002, but 60% after 2002 [3]. We conducted a retrospective, matched case-control study of IMD in patients with acute leukemia managed in our institution to determine the incidence and clinical outcomes of IMD, including its impact on one-year survival.

Materials and Methods

This was a retrospective, matched case-control study of IMD in patients with acute leukemia managed in our institution from 1st Jan 2004 to 31st Mar 2007. The Department of Haematology, Singapore General Hospital has had a Leukemia Registry from 2000. All patients with acute leukemia treated in our hospital were entered into the registry.

This registry was mined for all patients diagnosed with acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL) and acute biphenotypic leukemia (ABL) within the study period. The following were excluded: patients who never received chemotherapy, and those who received only palliative chemotherapy. The case records (electronic and paper) of included patients were then reviewed-only those with 'proven' or 'probable' IMD were finally entered into our study as 'cases' [4]. Controls were patients with the same type of leukemia (according

to WHO 2008 classification) who fulfilled the following criteria: their leukemia was diagnosed in the same month (± 1 month) as the case, and they were on chemotherapy at about the same time that the index case was diagnosed with IMD. The date of diagnosis of IMD was taken as the day on which an investigation yielded a result fulfilling a criterion for the diagnosis of IMD [e.g., a positive serum galactomannan (GM)]. For calculation of survival after IMD, the date of diagnosis in the control was the same as that in the matched case. The follow-up period for the purpose of the study was one year from the diagnosis of the IMD.

Paper and electronic records of cases and controls were reviewed for demographic, laboratory, and medication data. A diagnosis was captured from the casenotes and verified by the authors themselves. Computerised tomography scans of the thorax, abdomen and pelvis were ordered when chest x-rays (CXRs) were abnormal, when patients had persistent symptoms or signs despite normal CXR or for persistent febrile neutropenia beyond 96 hours of antibiotics treatment. All CT scans and X-rays were reviewed by two of the authors (BHT and GCW). Cut-offs for abnormal liver function tests and the oral bioavailability of itraconazole (ITC) were obtained from literature [5-7]. Neutropenia (unless otherwise specified) refers to an absolute neutrophil count

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(ANC) <500/mm³. Data were entered into a standardized data collection form. Episodes of IMD were counted. A patient with two episodes of IMD will contribute a count of two to the total number of IMD episodes. This study was approved by the hospital's institutional review board (IRB). The setting up and maintenance of the Leukemia Registry were also approved by the hospital's IRB.

During this period, patients undergoing chemotherapy were given ciprofloxacin as anti-bacterial prophylaxis. Most patients received oral itraconazole (ITC) for anti-fungal prophylaxis-the syrup formulation was recommended, but patients could receive the capsule formulation if they could not tolerate the syrup. The serum GM assay was not available in our hospital and was done at another laboratory [8]. The antibiotic protocol for the management of febrile neutropenia was amended slightly from the one we had previously published [9]. The recommended first-line antibiotic for febrile neutropenia was cefepime, with or without amikacin. If the patient was still febrile after 48 hours and cultures were negative, second-line antibiotics (imipenem or meropenem) could be started for patients who were unwell, after repeating a septic work-up. Vancomycin could be introduced if there was suspicion of line sepsis. Amphoterin B (amB) was the recommended anti-fungal agent for fever persisting beyond four days. The practice of sending bronchoalveolar lavage (BAL) fluid for GM was not routine then in our institution.

Statistics

Although 19 cases were found, only 15 had matched controls. For global data (baseline demographics and clinical features of IMD), data

	Cases (%) (n=19)	Controls (%) (n=15)
Sex (male:female)	11:8	10:6
Age (median, range)	50.69 (19.0-62.8)	30.37(16.4-65.2)
Type of leukemia		
AML	12 (63.2)	10 (66.7)
ALL	7 (36.8)	5 (33.3)
Chemotherapy in admission in which IMI was diagnosed**		
Induction	15 (78.9)	9 (60.0)
Consolidation	4 (21.1)	5 (33.3)
Mobilisation	0	1 (6.7)
Duration of neutropenia [^]		
>=14d	13 (68.7)	1 (6.7)
<14d	2 (13.3)	14 (93.3)
Duration ANC <100/mm ³ [^]		
>=10d	15 (78.9)	5 (33.3)
<10d	4 (21.1)	10 (66.7)
ANC at diagnosis of leukemia		
>=500/mm ³	8 (42.1)	13 (86.7)
<500/mm ³	11 (57.9)	2(13.3)
Absolute monocyte count **		
<120/mm ³	9 (47.4)	11 (73.3)
>120/mm ³	10 (52.6)	3 (20.0)
No. given FQ prophylaxis	9 (47.4)	9 (60)
No. given ITC prophylaxis	14 (73.7)	12 (80)
No. given syrup ITC	14 (73.7)	14 (93.3)
Anti-fungal prophylaxis >14days	5 (26.3)	8(53.3)
Median LOS (days)	46 (22-88)	23 (9-65)

* for controls, this was the chemotherapy received in the month (± 1 month) in which the IMD in the matched case was diagnosed

[^] refers to admission during which IMD was diagnosed

[^] refers to absolute monocyte count on date of diagnosis of IMD, value not available for 1 control

^α 5 of the cases did not receive ITC

ANC: Absolute Neutrophil Count; LOS: Length of Stay; FQ: Fluoroquinolone; ITC: Itraconazole

Table 1: Baseline Demographics.

Patient No.	Proven/Probable	Criteria* met	Additional comments
1	Proven	Fusarium from skin biopsy	Multiple skin nodules
2	Proven	Fusarium from skin biopsy	
3	Proven	Fusarium from blood culture	A posthumous result -see text
4	Proven	Aspergillus flavus from skin biopsy	CT: Lung nodules with typical halo sign
5	Proven	Blood and BAL fluid culture with Nodulisporium sp	CT: Lung nodules with typical halo sign
6	Proven	Lung biopsy with septate branching fungi	CT: Lung nodules with cavitation
7	Proven	Lung biopsy with septate branching fungi	CT: Lung nodules with typical halo sign
8	Proven	Lung biopsy with hyphae amidst necrotic lung	Lung biopsy sample grew Conidiolobolus; hyphae also seen in microscopy of BAL fluid
9	Proven	Lung biopsy with septate branching fungi, evidence of vessel invasion noted	CT: Lung nodules with typical halo sign
10	Proven	Lung biopsy: infarct with septate hyphae	CT: Lung nodules with typical halo sign
11	Proven	Lung biopsy with septate branching fungi	CT: Lung nodules with typical halo sign
12	Proven	Lung biopsy: infarct with septate hyphae	CT: Lung nodules with typical halo sign
13	Probable	Characteristic CT + serum GM	
14	Probable	Characteristic CT + serum GM	
15	Probable	Characteristic CT + BAL culture with Aspergillus	
16	Probable	Characteristic CT + BAL culture with Aspergillus	
17	Probable	Characteristic CT + BAL microscopy showing hyphae	
18	Probable	Characteristic CT + serum GM	
19	Probable	Characteristic CT + symptoms	

Table 2: Proven and probable cases of invasive mould disease [4].

from all 19 cases are presented. Simple descriptive analyses were used for such purpose. For comparison data, only data from the 15 cases that had matched controls are presented. McNemar's test and paired T-test for comparison of proportion and continuous variables were used for analysis of the 15 matched case-control pairs respectively. Survival analysis was carried out using Kaplan Meier test. Multivariate analysis for predictors of death was performed using Cox regression. A p-value of ≤ 0.05 was considered statistically significant.

Results

During this period, 19 cases of IMD were diagnosed. The demographics of cases and controls are shown in Table 1. The incidence of IMD in patients who received curative chemotherapy was 19/172 (11%); the incidence in patients receiving the first cycle of chemotherapy was 15/172 (8.7%).

12 cases were 'proven' and 7 cases were "probable". These are tabulated in Table 2. All cases underwent a diagnostic procedure, though the procedure was not yielding in all cases. A biopsy of suspicious skin lesions provided the diagnosis in 3 cases, a trans-bronchial biopsy in three, a trans-thoracic needle biopsy in four, a wedge resection of the lung in one, and a BAL in another. In nine of these cases, the procedure was performed after the platelet had risen above 80,000/mm³.

	Cases (n=19)
Clinical	
Fever not responding to 2 nd -line antibiotics	16 (84.7%)
Cough	8 (42.1%)
Pleuritic chest pain	4 (21.1%)
Breathlessness	5 (26.3%)
Hemoptysis	4 (21.1%)
Abnormal CXR without fever	1 (5.3%)
Hypotension	3 (15.8%)*
Asymptomatic- just a rising GM	1 (5.3%)*
Sinusitis	1 (5.3%)
Pleural effusion on CXR or CT	10 (52.6%)
MRI brain	
Normal	7 (36.8%)
Abnormal [#]	3 (15.8%)
Not done	9 (74.4%)
Use of AmB or LAmB	
Not given	3 (15.8%)
Started as part of febrile neutropenia protocol	13 (68.4%)
Started when IMD considered	3 (15.8%)
Anti-fungal started when IMD considered[@]	
AmB or Lamb	3 (15.8%)
Voriconazole	4 (21.1%)
Caspofungin	3 (15.8%)
Combination	1 (5.2%)
Further cycles of chemotherapy after IMD	
0 [^]	2 (10.5%)
0 [√]	3 (15.8%)
1	1 (5.3%)
2	2 (10.5%)
3	6 (31.6%)
>3	5 (26.3%)
Delay in chemotherapy	
No delay	8 (42.1%)
Delayed 2-4 weeks	3 (15.8%)
Delayed >4 weeks	6 (31.6%)
Eventual HSCT	
Yes, autologous	4 (21.1%)
Yes, allogeneic	4 (21.1%)

all MRI brain abnormalities were minor, none had infarct, mass, or abscess

* 4 (21.1) did not have a rising GM; 14(73.7) were not monitored

@in 8, amB or LAmB started as part of febrile neutropenia protocol was continued

[^] not because of death but because the patients declined

[√] includes the 2 who died in index admission (see text) and 1 who died at 3-month mark after discharge

Table 3: Clinical features of IMD in patients with acute leukemia.

The clinical features and treatment outcomes of patients with IMD are shown in Table 3. Treatment consisted of conventional amB or a lipid formulation started as part of a febrile neutropenia protocol in 13 case patients. When aspergillosis was considered, four case patients were given (voriconazole) VRC and three caspofungin (CAS). In six case patients (31.6%), defervescence was related to a rise in ANC to above 500/mm³. In two case patients (10.5%), defervescence was related to the introduction of VRC. In one patient (5.3%) it was related to the introduction of CAS and in another one (5.3%) it was related to control of bacterial infection. In seven patients (36.8%), defervescence was related to a combination of these factors.

Two case patients (10.5%) died in the index admission - both of these deaths were attributed to the IMD. One patient had *Fusarium* spp isolated from blood cultures posthumously. The other was receiving salvage chemotherapy when she developed pulmonary infiltrates. She died a few days after from massive pulmonary hemorrhage - histology (from a bronchoscopy performed a few days before death) revealed hyphae in the midst of necrotic debris.

Two patients (10.5%) did not have any outpatient antifungals for IMD-these were the 2 who died. Although 3 patients (15.8%) received oral VRC for entire duration of treatment, most of the others had

VRC, CAS or amB followed by oral ITC. Oral ITC was continued for long periods (up to a year). One patient with disseminated fusariosis complicating ALL had oral POS as an outpatient, with Lamb whenever she was admitted for chemotherapy.

When cases were compared with controls, neutropenia was a statistically significant risk factor for IMD (Table 4). In addition, no case patient had neutropenia of less than 10 days' duration, and no control had neutropenia of more than 28 days' duration. In fact, 14 of 15 controls had neutropenia <14 days' duration. A bacteremia preceded the diagnosis of IMD more often in cases than in controls, but more cases than controls did not respond to broad-spectrum antibiotics.

The one-year survival curves of cases and controls are shown in Figure 1. Because of the stark difference in mortality at 12 months (log-rank *p* value=0.007), we performed a Cox regression analysis to identify possible independent risk factors for mortality. On univariate analysis, factors that predicted death at 12 months included older age at diagnosis of leukemia, being a case (i.e. the presence of an IMD),

	Cases (n=15)	Controls (n=15)	P-value
Age (Median)	50.69	30.37	0.14
ANC (/mm ³)*			
<500	9 (60%)	2 (13.3%)	0.05
≥ 500	6 (40%)	13 (86.7%)	
Neutropenia duration [^]			0.003
≤14 days	2 (13.3%)	14 (93.3%)	
>14 days	13 (86.7%)	1 (6.7%)	
Absolute monocyte count [#] (/mm ³)			0.22
<120	7 (46.7%)	11 (73.3%)	
≥120	8 (53.3%)	4 (26.7%)	
Steroid use in the year prior to the diagnosis of leukemia			1.00
Yes	0	1 (6.7%)	
No	15	14 (93.3%)	
DM			1.00
Yes	2 (13.3%)	1 (6.7%)	
No	13 (86.7%)	14 (93.3%)	
ITC prophylaxis [^]			1.00
Yes	11 (73.3%)	12 (86.7%)	
No	4 (26.7%)	3 (13.3%)	
ITC bioavailable daily dose [^]			0.25
≤200mg/day	11 ^a	14 ^a	
>200mg/day	0	0	
Bacteremia prior to diagnosis of IMI [^]			0.05
Yes	8 (53.3%)	1 (6.7%)	
No	7 (46.7%)	14 (93.3%)	
Fever unresponsive to 2 nd line antibiotics			0.02
Yes	13 (86.7%)	4 (26.7%)	
No	2 (13.3%)	11 (73.3%)	
Cough			1.00
Yes	5 (33.3%)	4 (26.7%)	
No	10 (67.7%)	11 (73.3%)	
Length of stay			0.01
Mean, days	51.8	27.2	
Range, days	29-88	9-65	
Survival			0.007
At 3 months	14 (93.3%)	14 (93.3%)	
At 12 months	7 (46.7%)	14 (93.3%)	

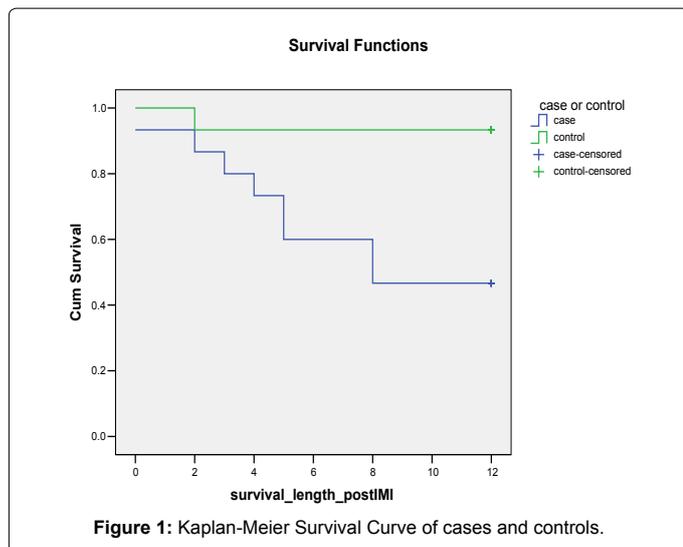
* at diagnosis of leukemia

[^] in admission in which IMD was diagnosed; for controls, value taken is that during admission for chemotherapy in the month ± 1 in which the IMI in the matched case was diagnosed

[#] at diagnosis of IMD

^a the rest did not receive ITC

Table 4: Comparison between cases and controls.



Independent Risk Factors	Mortality at 12 Months		P-value
	Death=9 (%)	Alive=21 (%)	
Age (yr)	53.6 ± 13.7	38.6 ± 15.0	0.02
Gender Male	5 (56)	15 (71)	0.43
Presence of at least one co-morbidity*	3 (33)	3 (14)	0.33
Neutropenia duration ≥28 days	5 (56)	3 (14)	0.03
Development of new renal failure	0 (0)	2 (10)	1.00
Steroid use in the year prior to the diagnosis of leukemia	0 (0)	1(5)	1.00
steroids use > 3 wks in previous 60days	1 (11)	0 (0)	0.30
Any bacteremic episode	5 (56)	7 (33)	0.42
ICU stay	2 (22)	1 (5)	0.21
Relapse disease	4 (44)	5 (24)	0.082
Received HSCT	1	11	0.05
IMD diagnosis	8 (89)	7 (33)	0.01

*Diabetes Mellitus, Ishaemic Heart Disease, Hypertension, renal disease, chronic pulmonary disease, other malignancy, chronic heart disease, chronic liver disease

Table 5: Risk factors for death at 12 months (univariate analysis).

prolonged neutropenia of ≥ 28 days, and the lack of an HSCT following the diagnosis of an IMD (Table 5). However Cox regression failed to identify variables that independently accounted for this difference in survival.

Discussion

This study allowed us to better understand the clinical characteristics and outcomes of IMD in patients undergoing chemotherapy for acute leukemia in our hospital.

We adopted the matched case-control approach because we had not, at that time, standardized our antifungal prophylaxis. In addition, we recognized that there were no definitive guidelines for anti-fungal therapy in febrile neutropenic patients then. Although we did not match for age, the difference in age between cases and controls was not statistically significant. Despite a seemingly difference in the ages of cases and controls in (Table 1), this table merely shows a pooled median age. The insignificant p value in Table 4 indicates that, on a matched basis (case vs. control) the age difference was not statistically significant. This study had 31 March 2007 as the end-date because a

consensus on antifungal prophylaxis was reached in the department in the first quarter of 2007. For classification of proven and probable cases, we used the older EORTC/MSG guide as it was the prevailing guideline then; the newer guide was only published in 2008 (after the period covered by the study) [10].

We did not limit the infections studied to IA for several reasons. There were then increasing reports of non-Aspergillus moulds causing invasive disease in immune compromised persons [11-13]. Anecdotally, we knew that non-Aspergillus moulds surfaced time and again. This series validates our suspicions - of the proven cases, only one was culture positive for Aspergillus. On the other hand, if any microbiologic manifestation (serum GM, BAL cultures etc) was taken as evidence of IA, which is in line with guidelines, then 8 of the 19 cases were cases of IA [4,10]. This makes IA the commonest IMD in this series, a finding consistent with that of other series.

The clinical features of the cases point out several manifestations of IMD that may be diagnostically helpful. Only four cases had pleuritic chest pain, but no control had this symptom. Prolonged fever, not responding to carbapenems, was the commonest manifestation. In an era in which most experts advise restraint with antibiotic use, this point is worthy of re-emphasis because, in the absence of an outbreak of drug-resistant bacteria, it may be more prudent to search for a fungal infection than initiate a change of antibiotics. Prolonged neutropenia was a risk factor for the development of an IMD, as is well-known. Eight of the cases had neutropenia in excess of 28 days, and no control had neutropenia of this duration. A bacteremia preceded the diagnosis of an IMD more often in cases than controls. The best explanation for this is not known, but recent data suggest that there might be a genetic susceptibility to infection [14].

In this study, ITC did not protect our patients against IMD, even though ITC, in a meta-analysis, did reduce mortality from invasive fungal infections and the rate of IA, in patients treated for haematologic malignancies [7]. This could be due to the fact that none of our patients received a bioavailable daily dose in excess of 200 mg/day, a level found by investigators to be protective [7]. An Italian review of IA in patients with haematologic malignancies (prior to the availability of POS) similarly found that IA developed in two-thirds of patients given anti-Aspergillus prophylaxis [2]. ITC therapeutic drug monitoring is not available at our centre - its future availability may allow dose adjustments that may improve its efficacy. As a result of ward layout, very few patients were nursed in HEPA-filtered rooms. The provision of HEPA-filtered air has been recognized as an important measure in the prevention of IA in haematological patients [15,16].

Like other authors, we suspect that the low 12-week mortality in our series was related to the improved efficacy and tolerability of CAS and VRC. We based this on the fact that our patients who died did not receive either of these drugs. However, a bigger cohort of patients may help to elucidate this better. In an Austrian survey of IA, crude 12-week mortality was 34%. The authors noted that recipients of VRC had improved survival [17]. Pagano et al. similarly attributed lower mortality rates in more recent series to improved diagnostics and a better treatment armamentarium [2].

Although the 12-week survival among patients with IMD was quite good, this review shows that getting an IMD was associated with some degree of morbidity. Cases tended to have fever that did not respond to second-line antibiotics, required invasive procedures, stayed longer

during the index admission, and required long periods of anti-fungal agents. A good proportion of patients had their chemotherapy delayed. These suggest that preventing an IMD, or detecting it early, will have benefits.

Despite the impressive 12-week survival, one-year survival was much poorer in cases than controls. To understand this, we analyzed a large variety of variables as predictors of death at 12 months. As mentioned, only older age at diagnosis of leukemia, prolonged neutropenia (≥ 28 days), the presence of an IMD, and the lack of an HSCT predicted death in the univariate analysis. None of these reached statistical significance as independent predictors of death on Cox regression but being a case trended towards a higher mortality risk. The small numbers in this series likely prevented a truly significant association to be found. We hypothesize that prolonged neutropenia contributed to IMD, which, by way of its difficult (and perhaps stormy) clinical course, may have led patients and their physicians to delay or even shy away from further intensive chemotherapy and HSCT. This could have contributed to the significance of 'relapsed disease' and 'lack of HSCT' in the univariate analysis.

The data suggest that most deaths caused by IA occur in the early weeks after diagnosis [18]. Although a three-month follow-up may be appropriate for evaluating the efficacy of an anti-fungal agent, a longer follow-up may be needed to understand the true impact of IMD on long-term outcomes in patients with acute leukemia. In this series, only two deaths were directly attributable to an IMD and both occurred early. This is consistent with the literature. What is of concern is the finding that patients with an IMD did poorly when followed up for one year. We are unable to tease out the factors contributing to this dismal one-year outcome. If indeed an IMD per se is contributory, then efforts to prevent an IMD become paramount in the management of patients with acute leukemia.

One limitation of this study is that mutations, with their well-known implications on survival in AML, were not factored into the survival analysis [19,20]. The reason that we were unable to include them is that they became available in our hospital at different times in the years covered by the study, hence they were not available for all patients. The full significance of the impact of these mutations on survival may be said to have been elucidated fairly recently. Given the small size of our study, it is doubtful if a statistically significant association could have been drawn between any of the mutations and survival.

While recognizing this non-inclusion of mutations in the survival analysis, we note that the studies of Shen et al. and Schlenk et al. did not consider the possible impact of an IMD on survival [19,20].

In summary, this review of IMD in patients with acute leukemia has shown that prolonged neutropenia is a risk factor for IMD and that *Aspergillus* was the commonest cause of an IMD in our patients. Although three-month survival in patients with an IMD was good, an IMD appeared to predict mortality at 12 months. A bigger study to understand the reasons for the observed poor outcome at 12 months is needed.

Conflicts of Interest

BH Tan has spoken at symposia organized by Pfizer and MSD. The others report no conflicts of interest.

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