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Management of chronic pulmonary aspergillosis

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Chronic pulmonary aspergillosis (CPA) is a relatively rare, slowly progressive pulmonary syndrome caused by *Aspergillus* spp. The scarcity of clinical evidence for its management is an important issue. Oral azoles are recommended as the primary treatment of CPA; however, the evidence for their effectiveness is insufficient. Azole-resistant *A. fumigatus* is rapidly increasing and becoming a serious concern. Because long-term administration of azoles is the mainstay of CPA, azole resistance may pose a serious threat. Furthermore, prolonged oral administration of azoles may lead to increased azole resistance in CPA patients. Therefore, alternative management strategies for CPA must be considered, and one option may involve the use of intravenous antifungals such as echinocandins and polyens. The utility of these antifungals, however, has not been well evaluated and remains controversial because the drugs are expensive and require patients to be admitted to the hospital for their use. New antifungal drugs with novel mechanisms of action are also needed.

Keywords: chronic pulmonary aspergillosis; azole resistance; azoles; echinocandins; polyens

Chronic pulmonary aspergillosis

The incidence of deep-seated fungal infections, along with increasing numbers of mild-to-severe immunocompromised hosts, is climbing due to advanced medical procedures and treatments. Aspergillosis is particularly important because of its high mortality and morbidity. There are more than 250 *Aspergillus* spp., including the common human pathogens *Aspergillus fumigatus*, *A. flavus*, *A. niger*, *A. terreus,* and *A. versicolor.*[1] Various types of aspergillosis, such as invasive chronic infections and allergic disease, can be caused by *Aspergillus* spp. Chronic pulmonary aspergillosis (CPA) is defined as a slowly progressive pulmonary syndrome. Compared to invasive pulmonary aspergillosis (IPA), the pathophysiology of CPA ranges widely from aspergilloma to chronic necrotizing pulmonary aspergillosis (CNPA), also known as subacute IPA, semi-invasive aspergilloma, symptomatic pulmonary aspergilloma, or *Aspergillus* pseudotuberculosis in the previous literature.[2–5] Recent consensus classification of CPA includes simple aspergilloma, chronic cavitary pulmonary aspergillosis (CCPA), and chronic fibrosing pulmonary aspergillosis (CFPA).[3] Figure 1 shows the summarized classification of pulmonary aspergillosis based on pathological and radiological features, time course, and innate immunity defect.[6–9] However, pathological samples may not be acquired in every CPA case and the time course is arbitrary. These subcategories of CPA may overlap and a clear distinction is difficult to make.

The clinical features of CPA have been characterized in several recent reports. CPA and aspergilloma usually occur in middle-aged to elderly patients with relatively lower body mass index.[10,11] Preexisting or residual cavities following mycobacterial infection are the most common dwelling sites of *Aspergillus*, and these cavitary lesions are mostly located in the upper lobes.[10–13] Other pulmonary diseases that result in cavity formation, such as emphysematous bullae, chronic obstructive pulmonary diseases, bronchiectasis, pulmonary

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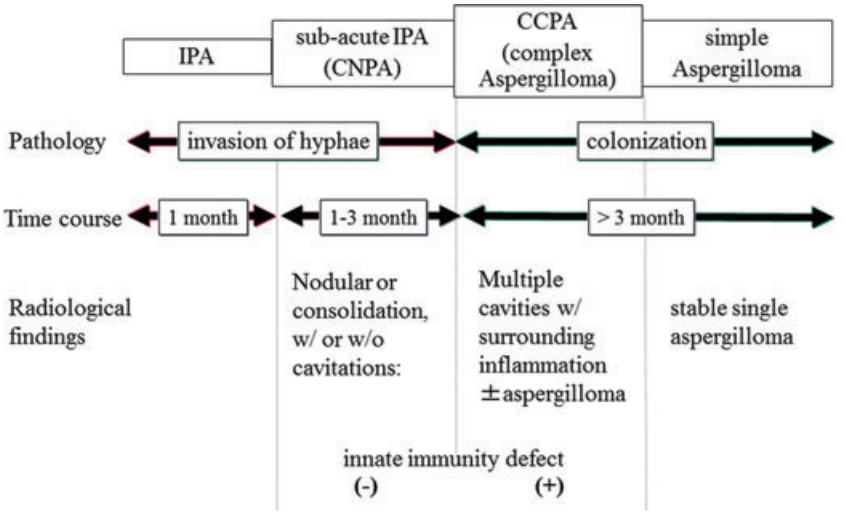

Figure 1. Classification of pulmonary aspergillosis based on pathological and radiological features, time course, and innate immunity defect.

cysts, and others, may be a cause of CPA and aspergilloma.[8,12]

CPA slowly causes lung destruction, for example, progressive cavitation, fibrosis, and pleural thickening, that is reflected in patients' radiological features. Single or multiple fungus balls may be seen in cavitary lesions. CPA patients often present with chronic pulmonary or systemic symptoms (usually for longer than a month), such as weight loss, low grade fever, productive cough, chronic sputum, hemosputum, or hemoptysis.[3,10,11,13] The worldwide prevalence of CPA is estimated at around three million, and its mortality is 50% over 5 years, but no large-scale epidemiological data are available.[11,14]

Serum *Aspergillus* precipitins tests that detect antibodies (IgG) to *Aspergillus* are usually positive[7,10,15,16] in CPA patients, including those with aspergilloma. Although serum *Aspergillus* galactomannan antigen ELISA tests have been approved for the diagnosis of IPA, with a sensitivity of 79% and a specificity of 86% in meta-analysis,[17] they are not considered useful for CPA diagnosis due to a lower positive rate.[10,16] Sputum, bronchoalveolar lavage cultures, and surgical biopsy specimens usually reveal the causative organism in pulmonary infections. However, because *Aspergilli* are ubiquitous in the environment, careful evaluation is required to confirm colonization or infection. Pathological examination by transbronchial, surgical, and computed tomography–guided biopsies are the confirmatory methods of CPA diagnosis. However, they may not be applied in all cases owing to underlying diseases in the patients.

Management of CPA

The latest Infectious Diseases Society of America (IDSA) guidelines for the treatment of aspergillosis recommend oral voriconazole (VRCZ) or itraconazole (ITCZ) as the primary treatment for CNPA and CCPA, and surgical resection is recommended for simple aspergilloma cases.[9,18] Bronchial artery embolization (BAE) to occlude the causative vessels in patients with hemosputum or hemoptysis is another option for the treatment of CPA. However, BAE is only temporarily effective due to the presence of collateral vascular channels at the site of bleeding.

Only one randomized study for the management of CPA has been conducted,[13] and some case series reports are currently available. Additionally, the following issues have not been standardized or even described in the IDSA guidelines: timing of the initiation of treatment, duration of treatment, and timing of the discontinuation of treatment for CPA.

The efficacy of oral azoles for CPA is summarized in Table 1.[3,11,19–29] From the late 1980s to today the reported efficacy of oral ITCZ is somewhat variable, with a range of 30–93% duration administration approximately 4–12 months, and adverse effects in 16–33% of patients. In the last decade, four reports

Table 1. The efficacy of oral antifungals to chronic pulmonary aspergillosis

Antifungals	CPA	Response rate (%)	Route	Study design	Year reported	Reference
Itraconazole	CNPA+aspergilloma	60–66	Oral	Case series	1988	19
Itraconazole	CNPA+aspergilloma	71–93	Oral	Case series	1990	20
Itraconazole	Aspergilloma	30	Oral	Case series	1991	21
Itraconazole	CNPA	67	Oral	Case series	1996	22
Itraconazole	CNPA	67	Oral	Case series	1997	23
Itraconazole	Aspergilloma	63	Oral	Case series	1997	24
Itraconazole	CPA	71	Oral	Case series	2003	3
Itraconazole	CNPA	38	Oral	Case series	2009	11
Voriconazole	CCPA	64	Oral	Case series	2006	25
Voriconazole	CNPA+CCPA	50–80	Oral	Case series	2006	26
Voriconazole	CNPA+CCPA	70	Oral	Case series	2007	27
Voriconazole	CNPA+CCPA	30–43	Oral	Case series	2012	28
Posaconazole	CPA	46–61	Oral	Case series	2010	29

CNPA, chronic necrotizing pulmonary aspergillosis; CPA, chronic pulmonary aspergillosis; CCPA, chronic cavitary pulmonary aspergillosis.

on the efficacy of oral VRCZ have been published: response rates ranged from 30% to 80% following several months of administration, and the frequency of adverse effects that resulted in the discontinuation of therapy ranged from 9% to 27%.[25–28] The efficacy of ITCZ and VRCZ in most of these studies was assessed by clinical, radiological, and mycological improvement at the end of treatment or at regular intervals, regardless of whether there was a partial or complete response. Figure 2 indicates the radiographs of CPA patient with "good response" to long-term azole treatment. Recent case series reports regarding posaconazole showed a response of 61% at 6 months and 46% at 12 months, which was similar to the data for other oral ITCZ or VRCZ treatments.[29]

Table 2. The efficacy of injectable antifungals to chronic pulmonary aspergillosis

Antifungals	CPA	Response rate (%)	Route	Study design	Year reported	Reference
Micafungin	CNPA+ aspergilloma	55–67	Intravenous	Case series	2004	31
Micafungin	CPA	78	Intravenous	Case series	2007	30
Micafungin versus voriconazole	CPA	60 (micafungin) versus 53 (voriconazole)	Intravenous	Randomized controlled study	2010	10
Micafungin	CPA	68	Intravenous	Case series	2011	13
Caspofungin versus micafungin	CPA	30 (caspofungin) versus 33 (micafungin)	Intravenous	Randomized controlled study	2012	Paper submitted
Liposomal amphotericin B versus voriconazole	CPA	Currently underway (150 cases in trial)	Intravenous	Randomized controlled study		Under analysis

CNPA, chronic necrotizing pulmonary aspergillosis; CPA, chronic pulmonary aspergillosis.

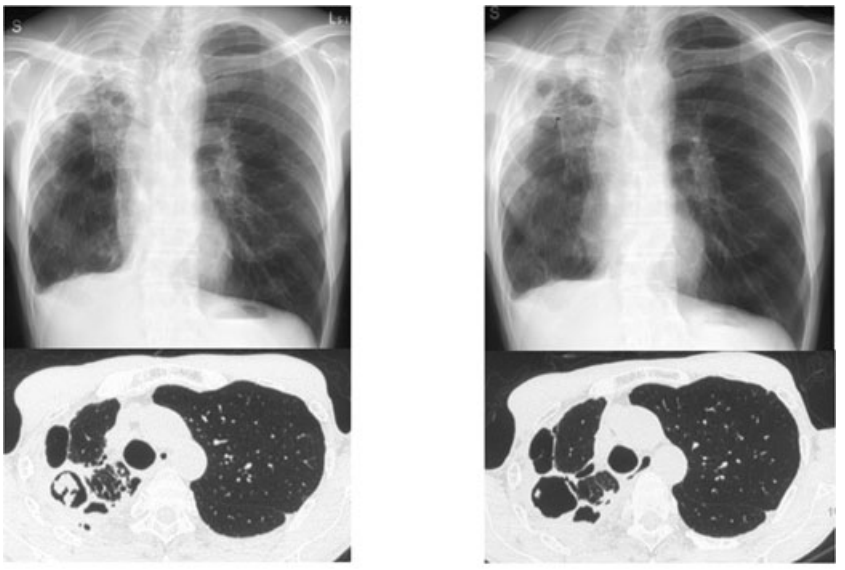

Figure 2. **A patient with chronic pulmonary aspergillosis showed good response to azole. Multiple cavitary lesions with fungus ball and pericavity infiltrations were presented in right upper lung field before treatment. Fungus ball and infiltrations were diminished and improved, respectively, after eight months of azole treatment.**

There are limited published data on the use of injectable antifungal agents such as echinocandins, azoles, and amphotericin B in the treatment of CPA (Table 2). Several series of studies evaluating the efficacy of intravenous micafungin (MCFG) in CPA were exclusively reported by Kohno and Izumikawa. The first two case series, including one clinical trial for marketing approval conducted in Japan, indicated that the success rates of treatment were 12/22 cases (duration of treatment; 11–57 days) and 7/9 cases (duration of treatment; 29–96 days).[30,31] Another prospective observational study to evaluate MCFG was also conducted and the overall clinical efficacy rate was 68.4% (26/38 patients), which is comparable to the results obtained in a previous small study.[31]

A randomized controlled study of CPA therapy comparing intravenous VRCZ and intravenous MCFG reported a favorable response rate with both MCFG (60%) and VRCZ (53%) with no significant difference.[10] However, fewer adverse events occurred in the MCFG than that in the VRCZ group (26.4% vs. 61.1%, $P = 0.0004$) in the safety evaluation. MCFG and VRCZ were equally effective, but MCGF was significantly safer as an initial treatment for CPA patients who required immediate hospital admission.[10] We conducted this series of studies on MCFG in Japan in patients who required immediate treatment. The treatment duration was a maximum of four weeks in almost all studies, and the assessment was performed at the end of treatment. Therefore, outcomes or prognosis a few months or years after the treatment were not assessed.

Most recently, another randomized controlled study comparing intravenous MCFG and caspofungin (CPFG) was conducted as a part of an approval study of CPFG in Japan. Overall response of CPFG and MCFG in CPA patients was 46.7% (14/30 cases) and 42.4% (14/33), respectively. There was no statistical difference in the safety profile between both groups (paper submitted). Studies assessing the utility of anidulafungin for CPA are not currently available. Another randomized controlled study comparing intravenous liposomal amphotericin B and intravenous VRCZ is currently underway.

Many CPA patients require maintenance treatments of oral azoles. Importantly, comparison of oral azoles during long-term treatment is particularly required. However, due to the complexity of its pathogenesis and the underlying diseases of CPA, conducting studies while establishing good study design and ensuring the efficacy of the assessment

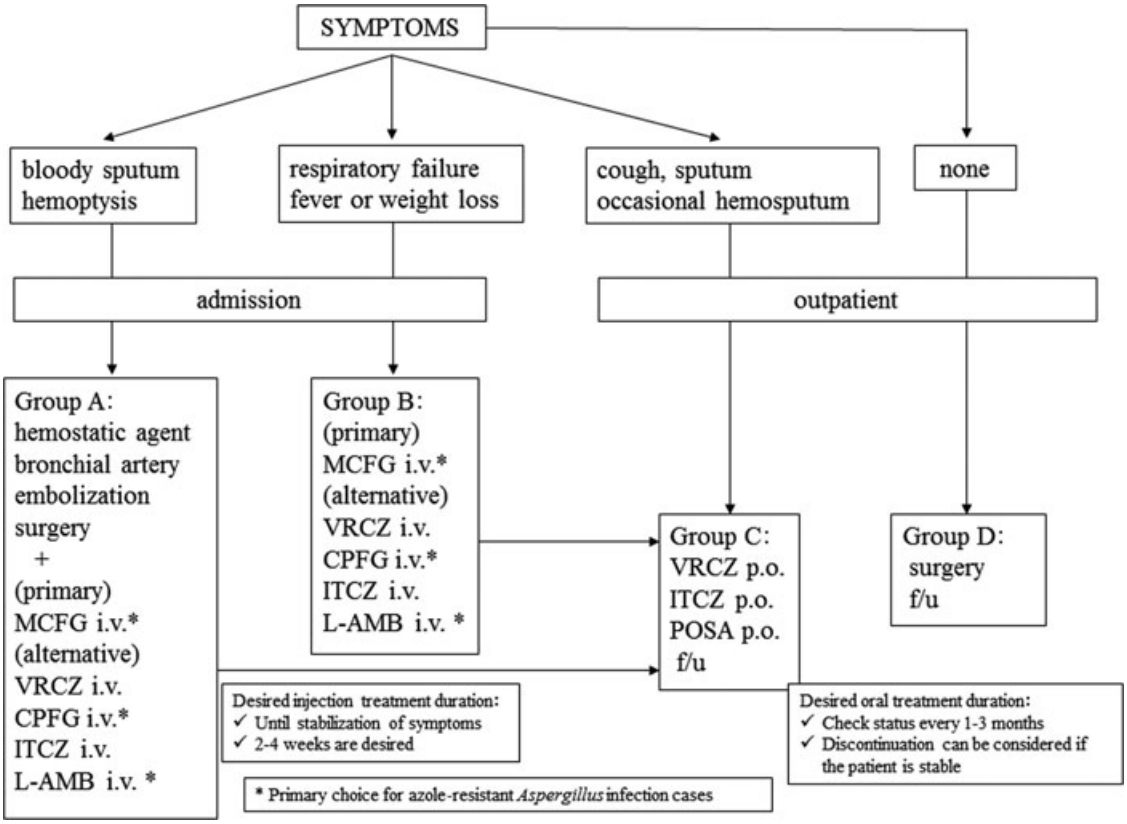

Figure 3. Proposal for the management of CPA in Japan based on the severity of symptoms and status of the patient. The intravenous administration of antifungals may be desired for two to four weeks, followed by oral antifungals. MCFG, micafungin; VRCZ, voriconazole; CPFG, caspofungin; ITCZ, itraconazole; L-AMB, liposomal amphotericin B; f/u, follow-up.

methods for long-term oral azole administration may be difficult.

Although evidence regarding the treatment of CPA is limited, the accumulation of data to date highlights the need for more detailed recommendations for CPA management. The IDSA guidelines indicate oral azoles as a primary treatment and other injectable antifungals as alternative treatments, but it is apparent that some patients require hospital admission and immediate intravenous administration of antifungals. Figure 3 shows a proposal for the management of CPA in Japan based on a classification of the severity of symptoms and status. Since the healthcare system varies in each country, our proposal may not be adaptable in other countries. The intravenous administration of antifungals may be desired for two to four weeks, followed by oral antifungals. There are, however, issues such as the costs of antifungals and admission, tolerance of long-term administration, and scarcity of evidence. Most importantly, the presence of azole-resistant *Aspergillus* is becoming a major threat to CPA management. Because oral azole is the mainstay of CPA treatment, particularly maintenance treatment, azole resistance may eliminate the candidates for long-term administration of antifungals. Additionally, very few new antifungals in both injectable and oral formulations are currently being developed, which is a serious issue not only for the management of CPA but also for all other *Aspergillus* infections.

Impact of azole-resistant *Aspergillus* infection and relation to CPA

Drug resistance in *A. fumigatus* has not been a major research focus in the last decade, with only a few studies performed after the first report by Denning *et al*. of itraconazole resistance among CPA patients in 1997.[32] Recent advances in standardizing susceptibility testing by the Clinical and Laboratory

Table 3. Major epidemiological studies of azole resistance in *A. fumigatus* after 2008

Reported by	Year reported	Number of tested isolates	Number of azole resistant isolates (azole tested in each study)	Rate of azole resistant strains (%)	Region	Reference
Guinea *et al.*	2008	374	0 (voriconazole)	0.0	Spain	39
Snelders *et al.*	2008	1912	32 (itraconazole)	1.7	the Netherlands	37
Rodriguez-Tudela *et al.*	2008	393	32 (itraconazole)	8.1	Spain, the Netherlands, UK, France	35
Espinel-Ingroff *et al.*	2008	292	1 (voriconazole)	0.3	North America	40
Howard *et al.*	2009	519	34 (itraconazole)	0.6	UK	38
Pfaller *et al.*	2009	637	43 (itraconazole)	6.8	Worldwide	41
Baddley *et al.*	2009	181	1 (itraconazole)	0.6	North America	1
Amorium *et al.*	2010	159	1 (posaconazole)	0.6	Portugal	42
Bueid *et al.*	2010	230	62 (itraconazole)	27.0	UK	43
Lockhart *et al.*	2011	497	29 (itraconazole)	5.8	Worldwide*	44
Chowdhary *et al.*	2012	103	2 (itraconazole)	1.9	India	45
Tashiro *et al.*	2012	196	14 (itraconazole)	7.1	Japan	46

*Itraconazole-resistant strains were detected mainly from China.

Standards Institute (M38-A2) and the European Committee on Antimicrobial Susceptibility Testing,[33,34] together with the establishment of interpretative cutoffs[35] and breakpoints,[36] have greatly enhanced clinical and basic research. Two major epidemiological studies from the Netherlands and the United Kingdom were published in 2008 and 2009, respectively.[37,38] Extensive epidemiological data have accumulated in the last few years highlighting that azole-resistant *A. fumigatus* isolates have been recognized in many countries.[1,35,37–46] Table 3 indicates the results of recent epidemiological studies on azole resistance in *A. fumigatus* since 2008. The prevalence of azole resistance is between approximately 0.3 and 28%. However, the definition of resistance varies in each study listed in Table 3, and caution is required when interpreting the data.

Resistance mechanisms against antifungal drugs, including azoles, are described elsewhere.[47] In *A. fumigatus*, modification and overexpression of target enzymes due to mutations and activation of drug efflux pumps are major resistance mechanisms. The primary azole resistance mechanism is mutation of the target protein 14 alpha-demethylase encoded by *cyp51*A, and numerous mutation hotspots have been confirmed.[38] Two possible hypotheses for the evolution of azole resistance have been proposed to date.

Several molecular epidemiological analyses have indicated that azole resistance is acquired in infecting strains within the human lung, rather than by inhalation of strains that acquired resistance in the environment before infection.[48,49] Importantly, many azole-resistant strains were isolated from CPA patients with aspergilloma, many of whom had been exposed to azoles for an extended duration (1–30 months).[48,50] We have also recently described a detailed relationship between azole usage (mainly ITCZ) and azole MICs for *A. fumigatus* isolated in our facility. Briefly, we confirmed the presence of acquired resistance to ITCZ and POSA in a patient with CPA after consecutive oral ITCZ therapy in Japan.[51] Our data also supported the hypothesis on resistance stated above, and although long-term administration of oral azoles is the mainstay of treatment of CPA, it may potentially induce resistance.

In contrast, Verweij *et al.* suggested the possibility that environmental fungicides used for agricultural purpose may induce mutations in *cyp51*A, and these environmental strains become a source of *Aspergillus* infection in humans.[52,53] This hypothesis

Table 4. Summary of drug resistance issues of azoles and other antifungals

Antifungals	Administration route	Existence of treatment failure by drug resistance	Possibility of acquired resistance by treatment
Itraconazole	Oral or injection	Reported[38]	Reported[51]
Voriconazole	Oral or injection	Reported[38]	Reported[55,56]
Posaconazole	Oral only	Reported[54]	Reported[51]
Micafungin	Injection only	Not reported	Not reported
Caspofungin	Injection only	Not reported	Not reported
Amphotericin B	Injection only	Not reported	Not reported

is supported by the fact that a single resistance mechanism (TR/L98H; tandem repeat of promoter region and mutation of L98H in *cyp51*A) is predominant in both clinical and environment isolates in the Netherlands, where extremely high amounts of sterol demethylation inhibitor fungicides are used.[53] Interestingly, these sterol demethylation inhibitor fungicides cause cross-resistance to medical azoles, and seven of approximately 30 agricultural fungicides showed cross-resistance with medical azoles.[14]

Although the increase in azole-resistant *A. fumigatus* has become an important topic in the field, the evidence that azole resistant isolates are associated with poorer outcome compared to susceptible strains is very limited to date. Only a few case series and case reports are available, and Table 4 summarizes the drug resistance issues of azoles and other antifungals.[38,51,54–56] Hence, the impact of azole-resistant *A. fumigatus* in CPA cases remains controversial. However, it is apparent that the only other potent antifungals for CPA are intravenous antifungals such as echinocandins and polyens (Fig. 3).

Future direction of management of CPA with azole-resistant *A. fumigatus*

It is obvious that further understanding of how *A. fumigatus* acquires drug resistance is required; in addition, a global network system to monitor the epidemiology data and seek novel drug-resistant mechanisms needs to be established. New antifungal drugs in either oral or intravenous forms with novel mechanisms of action are also certainly required. Other studies to optimize azole regimen pharmacokinetics and pharmacodynamics and therapeutic drug monitoring data to prevent mutation of *cyp51A* and to acquire maximum efficacy are also needed.

Conclusions

Studies regarding CPA management remain limited. A new detailed management scheme based on the severity of CPA is proposed, and the application of injectable and oral antifungals may be considered in each case. The emergence of azole-resistant *Aspergillus* is becoming a major issue in the treatment of aspergillosis. CPA may have its origin in the production of azole-resistant strains during treatment, which has limited the options for antifungal selection. It is therefore necessary to eliminate the continued development of drug-resistance that leads to an increasingly poor prognosis. Further investigations are required to understand the evolution of azole resistance in *A. fumigatus*.

Conflicts of interest

K.I. has received honoraria from Pfizer Japan, Inc., Astellas Pharma Inc., Dainippon Sumitomo Pharma Co., Ltd., and Merck & Co., Inc. S.K. has received research grants and honoraria from Pfizer Japan, Inc., Astellas Pharma Inc., Dainippon Sumitomo Pharma Co., Ltd., and Merck & Co., Inc.

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