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AVANCES EN LA PROFILAXIS ANTIFÚNGICA PRIMARIA EN LA FASE PRECOZ DEL TRASPLANTE ALOGÉNICO

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Para optar al grado de Doctor en Medicina

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INTRODUCCIÓN

El trasplante alogénico de progenitores hematopoyéticos (alo-TPH) constituye un tratamiento potencialmente curativo para una gran variedad de hemopatías malignas y no malignas[1-3]. En las últimas dos décadas se ha incrementado muy significativamente el número de trasplantes alogénicos realizados en Europa, hasta sobrepasar los 15000 anuales en 2012[4]. El continuo incremento de la actividad de trasplante alogénico se ha debido tanto al desarrollo de innovaciones que han permitido ampliar de forma significativa la población potencialmente candidata a trasplante, como los regímenes de acondicionamiento de intensidad reducida[5-10], como a la ampliación de las indicaciones de trasplante y a la mayor disponibilidad y uso de donantes y fuentes alternativas de progenitores hematopoyéticos como los donantes no emparentados o las unidades de sangre de cordón umbilical[2].

En el alo-TPH, las infecciones fúngicas invasivas siguen teniendo un gran impacto sobre la morbi-mortalidad. En particular, la aspergilosis invasiva es la principal causa de mortalidad infecciosa, con tasas de mortalidad atribuibles alrededor del 60-80%[11-16].

La profilaxis, es la única estrategia farmacológica de manejo de las infecciones fúngicas que ha demostrado disminuir la mortalidad global y relacionada con la IFI[17], por lo que las guías internacionales recomiendan la administración de profilaxis antifúngica primaria en pacientes alotrasplantados.

En 2007, tras los resultados de dos ensayos clínicos de registro[18,19], Posaconazol fue posicionado como el antifúngico recomendado como profilaxis primaria por las guías internacionales para los pacientes con neutropenia prolongada tras quimioterapia para leucemia aguda mieloide o síndrome mielodisplásico (LAM/SMD) y para los pacientes alotrasplantados con enfermedad injerto contra huésped (EICH); sin embargo, el potencial beneficio de Posaconazol en la fase neutropénica del alo-TPH y post injerto sin EICH no había sido analizado.

En la presente tesis se presentan los primeros datos de eficacia clínica, seguridad, e interacciones medicamentosas de la profilaxis antifúngica primaria con Posaconazol en la fase precoz del alo-TPH.

1.1. Infección fúngica invasiva en el alo-TPH.

Las infecciones fúngicas invasivas (IFI) son la principal causa de morbi-mortalidad infecciosa en el alo-TPH[13-15,20,21]. En las dos últimas décadas, a pesar de la disminución de las infecciones por *Candida* spp tras la introducción de Fluconazol profiláctico[22-25], la incidencia global de las IFI ha incrementado, sobre todo a expensas de hongos filamentosos, entre los que *Aspergillus* es con diferencia, el más prevalente [13,22,26-28].

La incidencia de las aspergilosis invasivas (AI) en el alo-TPH es de alrededor del 5-25% según las series[12,14,28-30]. Las infecciones por otras especies como *Fusarium* o *Zigomicetos* están mostrando un incremento progresivo con altas tasas de mortalidad; sin embargo la incidencia sigue siendo mucho menor a las descritas para las AI[28].

La mortalidad relacionada con la IFI en general y con la AI en concreto, han sido históricamente muy elevadas en el alo-TPH, de alrededor del 60-80% llegando incluso hasta el 90% en algunas series [11-16,31]. Los resultados de una gran serie italiana sobre más de mil receptores de un alo-TPH reportaron una incidencia de infección por hongos filamentosos de 7.8% con una mortalidad atribuible de AI del 77%[28] y Mikulska et al[32] describieron una incidencia del 15% en el alo-TPH de donante alternativo con un 67% de mortalidad atribuible a AI.

Además, varios estudios han demostrado tras la realización seriada de autopsias que la incidencia de IFI en pacientes hematológicos podría ser mayor de lo estimado con los métodos diagnósticos disponibles. La revisión de 1213 autopsias entre 1989 y 2008 en el MD Anderson Cancer Center mostró una prevalencia de IFI del 31% (principalmente hongos filamentosos), de las que sólo un 16% entre 1989-1993 y 51% entre 2004-2008 habían sido diagnosticadas pre-mortem a pesar del uso de técnicas diagnósticas[33,34]. Aún con la mejoría significativa en el diagnóstico de las IFI en los últimos 5 años del análisis, la mitad de las IFI nunca se diagnosticaron pre-mortem.

Actualmente, las IFI siguen teniendo un gran impacto sobre la morbi-mortalidad en el alo-TPH. En particular, la AI sigue siendo la principal causa de mortalidad infecciosa, por lo que es imprescindible conocer la patogénesis, factores de riesgo, métodos de profilaxis y diagnóstico de las IFI en general y de las AI en particular, en los pacientes alotraspantados.

1.1.1. *Aspergillus* spp. Generalidades y patogénesis.

Aspergillus spp es un hongo saprófito y ubicuo en la naturaleza que crece independientemente de un huésped animal y adaptable a condiciones ambientales extremas. El nombre le vino dado por su semejanza con el aspergillum, un instrumento utilizado en los rituales litúrgicos de las ceremonias católicas románicas (Figura 1).

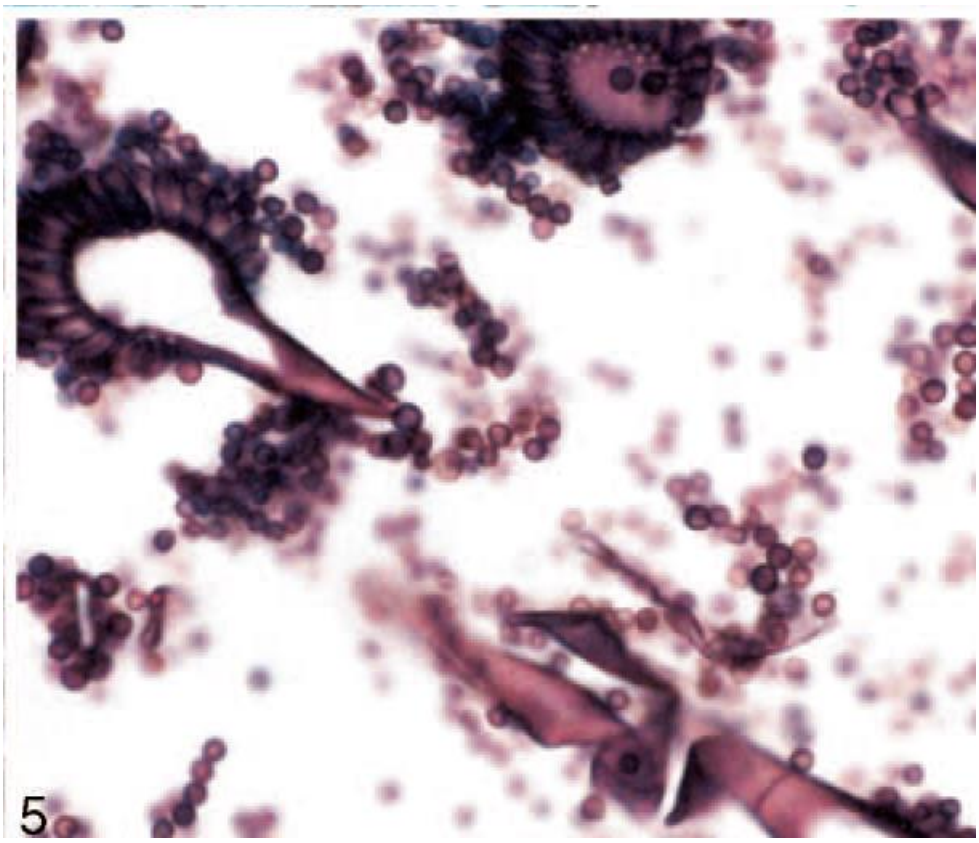

Figura 1. Aspergil (cabeza conidial) de *A fumigatus* con conidias. De Kradin et al[35].

A pesar de estar reconocidas más de 600 especies de *Aspergillus*, sólo alrededor de una decena son responsables de la mayoría de enfermedades severas en humanos. Actualmente, *A. Fumigatus* es la especie que más frecuentemente causa AI, seguida por *A. Flavus, A. niger* y *A. terreus.*

El ciclo de vida infeccioso se inicia con la producción de pequeñas conidias hidrofóbicas (esporas asexuales) que se dispersan fácilmente en el aire. De forma excepcional, la puerta de entrada del hongo puede ser el tracto gastrointestinal o la piel, pero habitualmente, la adquisición del hongo es a través de la inhalación de las conidias. Tal es así, que diariamente los humanos inhalamos varios cientos de esporas de *Aspergillus*, aunque habitualmente son eliminadas sin mayores consecuencias[36].

Las conidias de *A. fumigatus* son suficientemente pequeñas (2-3.5 um de diámetro) como para alcanzar los alveolos, mientras que las conidias de *A niger* y *A flavus* son más grandes y tienden a depositarse en los senos paranasales y vías aéreas superiores causando más frecuentemente, rinosinusitis.

Tras la inhalación, la primera barrera anatómica la forman las células epiteliales respiratorias y el sistema mucociliar. Las conidias que escapan a este sistema de limpieza son fagocitadas por los macrófagos alveolares, que a su vez producen citoquinas y quemoquinas para reclutar neutrófilos, células NK, células dendríticas y monocitos. Sin embargo, los neutrófilos son los principales ejecutores de la respuesta inflamatoria aguda, agregándose alrededor de las conidias y evitando su germinación[37]. Es frecuente la formación de granulomas, donde el hongo queda en estado latente pero con capacidad de generar un espectro amplio de neumopatías, desde el estado de portador asintomático hasta desórdenes de tipo inmunoalérgico[38].

Las conidias que consiguen escapar a esta línea de defensa encuentran en el alveolo un ambiente cálido, húmedo y nutricionalmente rico que les permite germinar y producir hifas multicelulares. Además de la invasión pulmonar, las hifas tienen

capacidad de invadir el torrente sanguíneo y diseminar a otros tejidos produciendo una **aspergilosis invasiva**, donde favorecen la trombosis de pequeños y medianos vasos y necrosis isquémica tisular secundaria[39]. Además, *Aspergillus* es capaz de inhibir la angiogénesis a través de la producción de metabolitos secundarios, favoreciendo todavía más la formación de un ambiente hipóxico[40] en el que el hongo puede seguir creciendo extremadamente bien, pero que prácticamente imposibilita la llegada tanto de efectores inmunes como de los tratamientos antifúngicos.

1.1.2. Factores de riesgo de IFI en el alo-TPH.

En el alo-TPH, las IFI siguen una distribución bimodal que viene determinada por la presencia de diferentes factores de riesgo.

En la ***fase neutropénica*** el principal factor de riesgo es la neutropenia, de mayor relevancia cuanto más profunda (mayor si <100 neutrófilos/uL) y más duradera sea (mayor si >10 días), que condiciona la ausencia de respuesta inflamatoria, favoreciendo la germinación de las conidias, el crecimiento descontrolado de las hifas y la angioinvasión.

Por el contrario, en la ***fase post injerto*** el principal factor de riesgo es la alteración funcional del sistema macrofágico secundario a la inmunodeficiencia, a la EICH y al uso de corticoides para la prevención y tratamiento de ésta que determinan alteraciones en la producción de citoquinas y del reclutamiento celular[14,30,41-43], aunque se mantiene la intensa respuesta inflamatoria por parte de los neutrófilos produciendo necrosis inflamatoria y daño tisular.

Además de estos factores de riesgo muy diferenciados según la fase post trasplante, existen muchos otros factores que pueden aumentar la susceptibilidad a las IFI. Las características de los pacientes entre las que destacan la edad avanzada, la sobrecarga férrica o la presencia de comorbilidades así como ciertas variaciones genéticas podrían aumentar la susceptibilidad a las IFI y modificar la respuesta del huésped a éstas[14,44-49]. Además, la zona geográfica (menor número de conidias en el aire de zonas de gran altitud, lluvia frecuente y clima frío), los periodos estacionales, las obras próximas al centro trasplantador y la colonización de los sistemas de suministros de agua y de ventilación hospitalarios[50-55], así como los factores relacionados con el tipo de trasplante y la fuente de progenitores hematopoyéticos, como el uso de sangre de cordón umbilical, de donantes no emparentados, donantes con diferencias antigénicas o las técnicas de deplección de linfocitos T, pueden incrementar el riesgo de IFI[56-58].

1.1.3 Diagnóstico de las IFI

En 2008 se publicó la revisión de las definiciones de consenso de diagnóstico de las IFI de la EORTC/MSG (European Organization for Research and Treatment of Cancer/Mycoses Study Group), en las que según la presencia de factores del huésped, radiológicos y microbiológicos, se establecen 3 niveles de certeza diagnóstica (probada, probable y posible)[59]. Las principales diferencias respecto a los criterios previos publicados en 2002 radican en la definición de las categorías probable y posible[60].

- La categoría de **IFI probada** precisa evidencia microbiológica o histopatológica de elementos fúngicos en una muestra de una zona estéril.
- Para el diagnóstico de una **IFI probable** se requiere la presencia de un criterio del huésped, un criterio clínico y un criterio microbiológico.
- Los casos que presentan el criterio del huésped y el clínico, pero que no presentan el criterio microbiológico se estratifican como **IFI posibles**, siendo esta categoría, la de menor certeza diagnóstica.

Estos criterios fueron diseñados para estudios clínicos e investigacionales y no para el uso en la práctica clínica diaria[61,62]. Sin embargo, se utilizan para reportar los casos de IFI, por lo que han permitido homogeneizar los diagnósticos y poder comparar los resultados de las diferentes series e instituciones.

TÉCNICAS MICROBIOLÓGICAS

La microbiología es la base del diagnóstico de las IFI ya que los síntomas suelen ser inespecíficos (fiebre, tos seca, dolor pleurítico, etc) y los hallazgos radiológicos aunque sugestivos, no son patognomónicos.

La detección de hongos filamentosos se puede realizar por microscopía o cultivo de muestras. Sin embargo, estos métodos de diagnóstico convencionales tienen limitaciones y las técnicas de detección de anticuerpos no son útiles en los pacientes alotrasplantados con alteraciones del sistema inmune[63]. Por ello, en la revisión de los criterios y en las guías internacionales se incluyeron las técnicas de detección de componentes fúngicos como un criterio de diagnóstico microbiológico.

Galactomanano (GM)

El GM es un componente de la membrana celular de *Aspergillus* que se libera durante el crecimiento del hongo y su detección se realiza mediante una técnica de enzimainmunoanálisis tipo doble sándwich que utiliza un anticuerpo monoclonal murino EBA2 dirigido específicamente contra b(1-5) galactofuronasa (Figura 2)[64,65].

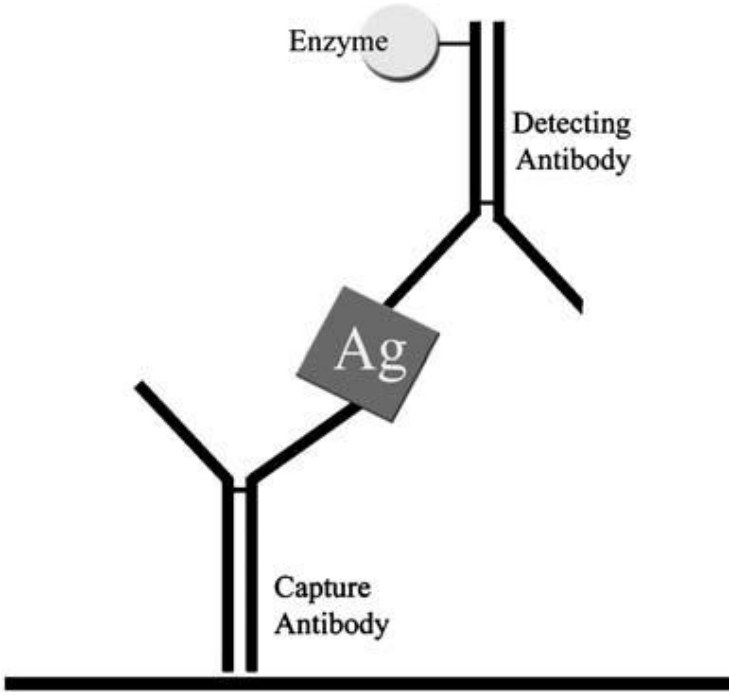

Figura 2. Detección de la antigenemia de Galactomanano por enzimainmunoanálisis de Platelia® Aspergillus. De Wheat et al[65].

El uso del GM se ha incluido en las guías internacionales como una técnica no invasiva de diagnóstico de AI[59,63,66], la determinación se suele realizar de forma anticipada dos veces por semana y se considera positivo en suero 1 test con un índice óptico (IO) >0.7 ó 2 muestras seriadas con índices ópticos >0.5[63]. La determinación puede realizarse también en muestras de lavado broncoalveolar, considerándose positivo un resultado con un IO>1[67] ó >0.5 en líquido cefaloraquídeo[68].

Dos grandes meta-análisis han estimado que la sensibilidad y especificidad medias del test de GM en pacientes hematológicos de alto riesgo es de alrededor del 70% y 90%, respectivamente[69,70]. Sin embargo, numerosos factores pueden alterar los resultados del test, modificando tanto la sensibilidad (uso de antifúngicos[71], grado de neutropenia[72]) como aumentando la tasa de tests falsos positivos (antibióticos betalactámicos, alimentos que contengan GM, suplementos nutricionales, soluciones intravenosas[63,73-75]). A pesar de todo ello, la exactitud diagnóstica del test va a venir determinada fundamentalmente por la incidencia pre-test de la AI en la población a estudio, por lo que para un mayor rendimiento del test, el GM probablemente deba realizarse como técnica diagnóstica en pacientes sintomáticos con alto riesgo de AI[76].

La determinación de **1-3-b-D-glucano**, un componente de la pared celular presente en la mayoría de especies fúngicas también se ha incluido como criterio microbiológico de la EORTC; sin embargo, la experiencia de uso sigue siendo muy limitada y actualmente la mayoría de centros trasplantadores no la utilizan de forma rutinaria[77-80]. Asímismo, la **detección de ácidos nucleicos fúngicos** por técnicas de reacción en cadena de polimerasa está todavía en desarrollo y aunque hay varios estudios en curso, actualmente no está estandarizada, es de acceso limitado para la mayoría de centros trasplantadores y no está incluida como criterio diagnóstico en las guías internacionales[81].

RADIOLOGÍA

El diagnóstico radiológico de la IFI se basa en la tomografía axial computerizada de alta resolución. La EORTC incluye las lesiones densas, bien circunscritas con o sin signo del halo y el signo de la semiluna o *"air-crescent sign"* como signos radiológicos diagnósticos de IFI probable.

El signo del halo y el signo de la semiluna son imágenes muy características y sugestivas de AI aunque no son patognomónicas ya que otros hongos filamentosos angioinvasivos como *Zigomicetos*, *Fusarium* spp y *Scedosporium* spp así como *Pseudomonas* aeruginosa y *Nocardia* spp, pueden mostrar imágenes radiológicas similares[82].

En algunos casos, la evolución radiológica de la AI puede seguir un patrón típico. El **signo del halo** suele ser es el signo radiológico más precoz[83]. Aparece habitualmente durante la fase de neutropenia, aunque también puede observarse en pacientes alotrasplantados con EICH[84,85] y desaparece rápidamente durante los primeros días de la infección. Radiológicamente, se muestra como un anillo en vidrio deslustrado alrededor de un nódulo o masa (Figura 3) y representa una masa de hifas aspergilares con necrosis tisular rodeada por hemorragia alveolar.

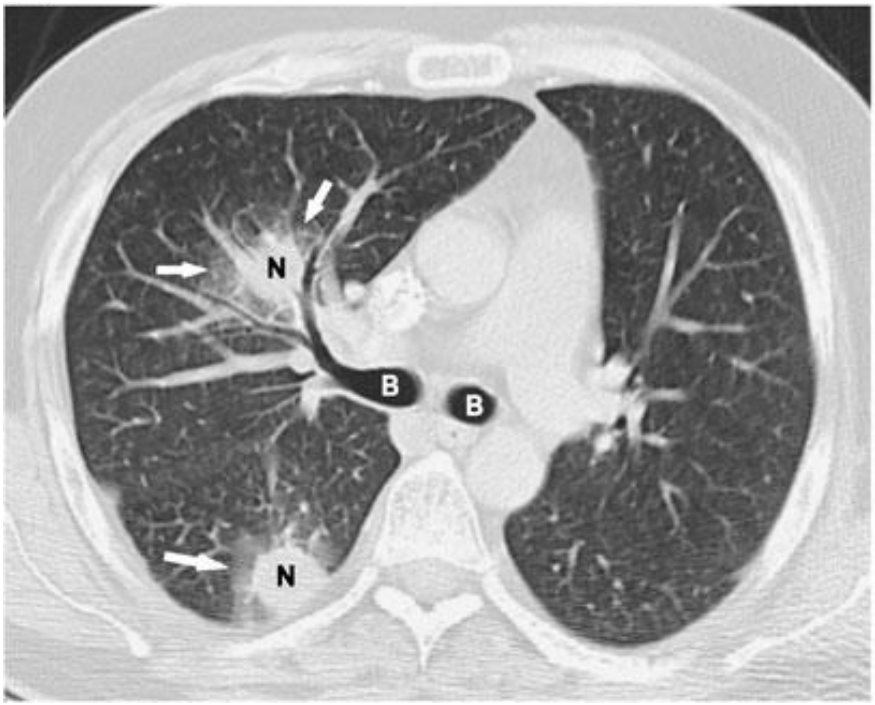

Figura 3. El signo del halo en el que se muestran nódulos pulmonares (N) rodeados por opacidades en vidrio deslustrado. De Georgiadou et al[86].

A los pocos días de la infección, el signo del halo puede dar paso a imágenes radiológicas inespecíficas y posteriormente, con la recuperación e infiltración neutrofílica, puede aparecer **el signo de la semiluna**, una cavitación causada por la retracción del pulmón necrótico adyacente al parénquima viable (Figura 4).

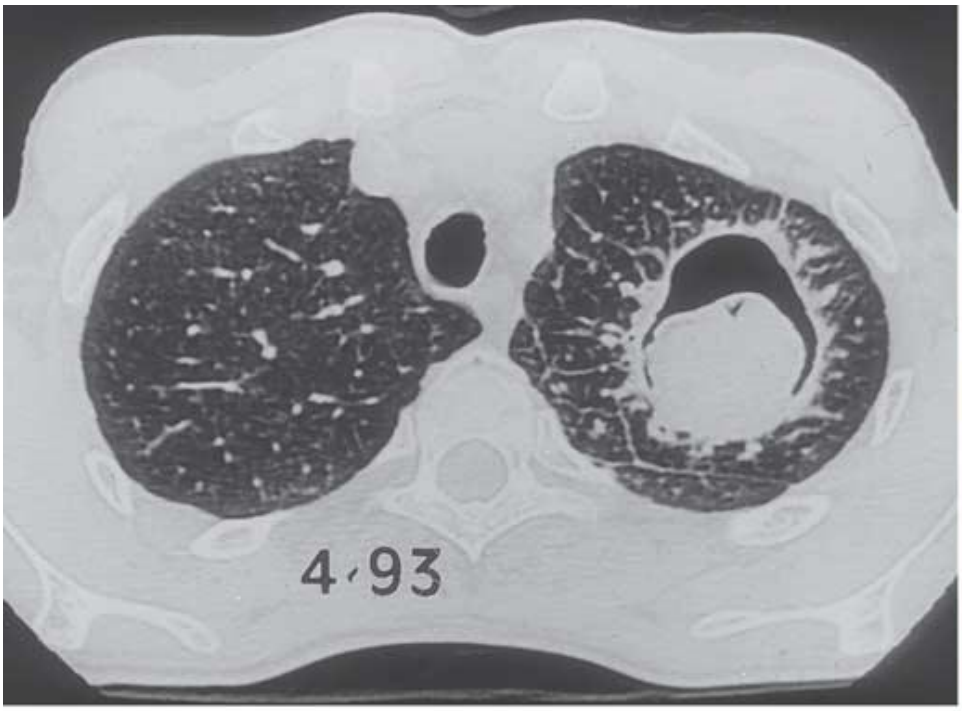

Figura 4. Signo de la semiluna o *"air crecent sign"*. De Franquet et al[87].

A pesar de este patrón típico, más del 50% de los hallazgos radiológicos de las AI en el alo-TPH son inespecíficos. Además, aunque son menos sugestivas, existen otras lesiones radiológicas que pueden estar presentes durante una AI en el paciente alotrasplantado como son los macronódulos sin halo, consolidaciones, cavitaciones, opacidades en *"árbol en gemación"* (*"tree in bud"*), *"wedge-shaped nodules"*, derrame pleural o atelectasias[83,84].

Las zigomicosis sin embargo, pueden presentarse radiológicamente con el **signo del halo inverso,** que se muestra como una opacidad redonda en vidrio deslustrado, rodeada por un anillo de consolidación (Figura 5).

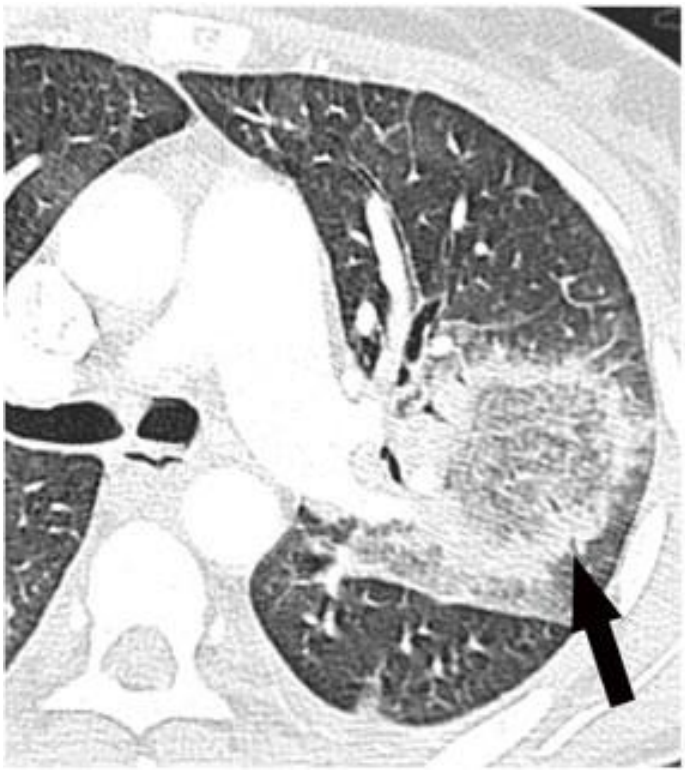

Figura 5. El signo del halo inverso. De Georgiadou et al[86].

1.1.4 Estrategias de prevención de las IFI.

El factor más importante para el desarrollo de infecciones por hongos filamentosos es la exposición a filamentos o esporas del ambiente sobre un sistema inmune dañado[44]. En pacientes hematológicos de alto riesgo, concentraciones de sólo 1 CFU/m3 pueden causar infección[88,89], por lo que es imprescindible la adopción de medidas de prevención.

1.1.4.1 Medidas físicas y ambientales de prevención de las IFI.

Las medidas de protección física y ambiental pretenden reducir la exposición a los hongos que se adquieren principalmente por vía inhalatoria.

Los pacientes alotrasplantados deben seguir una serie de recomendaciones que incluyen evitar el uso de tabaco, cannabis o marihuana[90]. Se debe evitar la aerosolización del agua y realizar controles microbiológicos y limpieza frecuente de las estructuras relacionadas con el agua en los baños de los pacientes[52-54,91,92].

Durante los periodos de mayor riesgo de IFI se recomienda el uso de mascarillas de alta eficiencia (FFP3) para la salida del ambiente protegido y traslado intrahospitalario. A pesar de que el potencial beneficio derivado del uso de filtros HEPA ("*high efficiency particualte arresting filters*") sigue siendo controvertido[93-96], hoy en día las guías tanto nacionales[88] como internacionales[97], así como los estándares de acreditación JACIE *(Joint Accreditation Committee of the ISCT and the EBMT*) recomiendan su uso, y actualmente, es una medida incorporada en la gran mayoría de centros trasplantadores.

Sin embargo, a pesar de la adopción de las estrictas medidas de aislamiento y de protección ambiental, las IFI en el alo-TPH siguen siendo un problema clínico importante con incidencia en aumento y altas tasas de morbi-mortalidad, por lo que los pacientes alotrasplantados requieren medidas de profilaxis de IFI adicionales, que abordaremos a continuación.

1.2. Profilaxis antifúngica en el alo-TPH

Los resultados de una revisión sistemática y meta análisis de 64 estudios randomizados de profilaxis antifúngica mostró que en pacientes alotrasplantados, la profilaxis antifúngica primaria reducía la incidencia de IFI, la mortalidad relacionada con la IFI y la mortalidad global comparada con el uso de placebo, tratamiento tópico o no profilaxis (RR: 0.62; IC 95%: 0.45-0.85)[17]. De hecho, la profilaxis es la única estrategia farmacológica de manejo de las infecciones fúngicas que ha demostrado disminuir la mortalidad global y relacionada con la IFI.

Por todo ello, las guías internacionales recomiendan la administración de profilaxis antifúngica primaria en pacientes alotrasplantados. La duración recomendada de la profilaxis suele ser de alrededor de 75-100 días post-TPH, excepto para los pacientes que desarrollen EICH o que por cualquier otra causa precisen continuar el tratamiento inmunosupresor, y la elección del fármaco a utilizar debe venir determinada por el espectro de actividad antifúngica, seguridad, eficacia, tolerancia, toxicidad, interacciones y coste-efectividad demostrada para cada antifúngico.

1.2.1. Revisión de fármacos.

Las guías internacionales han establecido una gradación de recomendaciones de uso de los diferentes fármacos en profilaxis en el alo-TPH basadas en la calidad de la evidencia de cada antifúngico.

Las **guías ECIL** (*European Conference on Infections in Leukemia*)[98] establecen 3 categorías según la calidad de la evidencia (I-III) y cinco niveles de recomendación (A-E) (Tabla 1).

Tabla 1. Calidad de la evidencia y recomendaciones según el sistema de gradación de la "Infectious Diseases Society of America" (IDSA). Guías de evidencia y consenso de la European Conference on Infections in Leukemia (ECIL). De Maertens et al 2011[98].

Quality of evidence	Strength of recommendations
I- Evidence from at least one well-executed randomized trial.	**A-** Strong evidence for efficacy and substantial clinical benefit: strongly recommended
	B- Strong or moderate evidence for efficacy, but only limited clinical benefit: generally recommended
II- Evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled analytic studies; or dramatic results from uncontrolled experiments.	**C-** Insufficient evidence for efficacy; or efficacy does not outweigh posible adverse consequences (for example, drug toxicity or interactions) or cost of chemoprophylaxis or alternative approaches: optional
	D- Moderate evidence against efficacy or for adverse outcome: generaly not recommended
III- Evidence from opinions of respected authorities base don clinical experience, descriptive studies, or reports from expert committees.	**E-** Strong evidence against efficacy or for adverse outcome: never recommended

Las **guías NCCN** (*National Comprehensive Cancer Network*)[99], sin embargo, establecen 4 categorías de recomendación según la calidad de la evidencia y el consenso de uso del que de ella se deriva (Tabla 2).

Tabla 2. Guías de evidencia y consenso de la National Comprehensive Cancer Network (http://nccn.org)[99].

NCCN Categories of Evidence and Consensus
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Fluconazol fue el primer antifúngico que consiguió disminuir la incidencia de IFI a expensas de la disminución de la infección por *Candida* spp en pacientes hematológicos de alto riesgo[22,24]. Por ello, a pesar de no tener actividad contra hongos filamentosos, la gran mayoría de estudios comparativos de los nuevos antifúngicos en profilaxis se han realizado comparándolos con Fluconazol.

La profilaxis con antifúngicos orales no absorbibles (Amfotericina B, Nistatina y Clotrimazol en solución) no demostraron reducir la incidencia de IFI, por lo que las guías internacionales no recomiendan su uso.

Polienos

Los resultados del uso de Amfotericina B Deoxicolato en profilaxis mostraron elevadas tasas de toxicidad, por lo que las guías internacionales no recomiendan su uso[82,100].

Las formulaciones lipídicas se desarrollaron con la intención de disminuir la toxicidad asociada a la formulación convencional. Sin embargo, tampoco mostraron suficiente evidencia como para recomendar su uso en profilaxis al compararlas con placebo o Fluconazol[101-105]. Asímismo, los estudios que evaluaron diferentes pautas de administración, desde semanales a diarias[106-108] así como un estudio prospectivo, randomizado y abierto en el que se comparó Amfotericina B complejo lipídico con Posaconazol[109] en pacientes trasplantados, mostaron alta incidencia de nefrotoxicidad y en éste último estudio, mayor incidencia de IFI comparado con el azol.

Debido a la elevada toxicidad de la Amfotericina sistémica, varios estudios han analizado la eficacia y seguridad de la formulación **inhalada de Amfotericina B**[110,111]. Aunque las formulaciones inhaladas evitan la toxicidad sistémica, no tienen efecto sobre la prevención de las IFI extrapulmonares y actualmente se requieren más datos para poder evaluar y determinar su eficacia como profilaxis en pacientes alotrasplantados.

Equinocandinas

El uso de **Micafungina** en profilaxis se comparó con Fluconazol en un estudio prospectivo, doble-ciego y randomizado que incluyó a más de 800 pacientes en la fase neutropénica post-TPH. Micafungica mostró superioridad en el “end point” u objetivo

primario (incidencia de IFI posible, probable y probada). Sin embargo, la superioridad de Micafungina se basó sólo en la reducción del uso de tratamiento antifúngico intravenoso para las IFI posibles (15% vs 21%; p=0.024), sin mostrar ningún beneficio sobre la incidencia de IFI probables o probadas (p=0.126), en la mortalidad (4.2% versus 5.7%; p=0.322) o en la supervivencia[112]. La misma comparación se realizó en el estudio de Hiramatsu et al[113], sin observar diferencias significativas en la incidencia de AI probable o probada.

Itraconazol

Itraconazol ha sido ampliamente testado en las diferentes formulaciones; solución oral, cápsulas e intravenosa. La absorción de Itraconazol en solución oral, aunque variable, es mejor que en cápsulas, que es errática e impredecible y llevó a la no recomendación de su uso.

En pacientes neutropénicos tras quimioterapia intensiva por LAM/SMD, Itraconazol resultó efectivo en la prevención de IFI por hongos filamentosos, sin embargo, su uso quedó muy limitado por la baja tolerancia y los efectos adversos, principalmente gastrointestinales, que requirieron la suspensión del fármaco en hasta el 25% de los casos[17,114-116].

En el alo-TPH, se observaron similares resultados. Marr et al[117] compararon Itraconazol *versus* Fluconazol en profilaxis en un estudio monocéntrico, randomizado y doble ciego sobre 304 alo-TPH. A pesar de que Itraconazol mostró menor incidencia de IFI por hongos filamentosos (5% vs 12%; p=0.03), no mejoró la supervivencia global o libre de infección fúngica y un mayor número de pacientes suspendieron el fármaco por intolerancia gastrointestinal (36% vs 16%, p<0.001).

Winston et al[118] mostraron similares resultados en un estudio multicéntrico y randomizado de profilaxis antifúngica durante los 100 primeros días post alo-TPH. Itraconazol mostró una menor incidencia de IFI probadas *versus* Fluconazol (9% vs 25%; p=0.01) aunque con igual incidencia de AI (4% versus 12%; p=n.s), mortalidad global (45 vs 42%; p=n.s), mortalidad relacionada con la infección fúngica (9% vs 18%; p=n.s) y presentó mayor incidencia de toxicidad gastrointestinal (24% vs. 9%; p=0.02).

Tras la revisión de dichos estudios, las guías internacionales (ECIL y NCCN) le otorgaron una recomendación B1 y 2B, respectivamente.

Voriconazol

Wingard et al[119] publicaron en 2010 los resultados de un estudio multicéntrico, randomizado y doble ciego comparando la profilaxis con Voriconazol *versus* Fluconazol en 600 pacientes alotrasplantados. Voriconazol (n=305) resultó similar a Fluconazol (n=295) en cuanto al objetivo primario de supervivencia libre de IFI a los 180 días (78% versus 75%; p=0.49), así como en la incidencia de IFI (posibles, probables y probadas, 7.3% vs 11.2%; p=0.12), incidencia de AI (3% vs 6%; p=0.09) y en la supervivencia global (81% versus 80%; p=0.67). Tampoco hubo diferencias significativas al comparar sólo la incidencia de IFI probables y probadas.

Un segundo estudio multicéntrico, randomizado, prospectivo y abierto comparando Voriconazol con Itraconazol en 489 pacientes alotrasplantados mostró superioridad de Voriconazol en el objetivo primario compuesto que incluía: 1) supervivencia a los 180 días, 2) sin IFI probable o probada y 3) sin discontinuación del

fármaco a estudio durante más de 14 días en el periodo fijado de 100 días (49 versus 34.5%, p=0.0004). Sin embargo, Voriconazol sólo fue más eficaz en la tolerancia y duración de la profilaxis (97 días para Voriconazol versus 68 días para Itraconazol), pero no mejoró la supervivencia a los 180 días (82% versus 81%; p=n.s) y a pesar de que la incidencia de IFI fue muy baja para ambos grupos, tampoco disminuyó la incidencia de IFI probable o probada (1.3% versus 2.1% p=n.s)[120]. Es importante destacar además que en este estudio de diseño abierto en el que el investigador conoce cuál es el fármaco administrado, la objetividad en la decisión de suspender la profilaxis podría ser cuestionable.

Tras los resultados preliminares de los mencionados estudios de Voriconazol en profilaxis, las guías ECIL-3[98], le adjudicaron una evidencia AI preliminar, en espera de los resultados definitivos de los que no se disponían en el momento de la publicación de las guías.

Por el contrario, tras los resultados de los ensayos de registro[18,19] que expondremos en el siguiente apartado, Posaconazol fue posicionado por las guías internacionales como el único antifúngico recomendado para profilaxis primaria en neutropenia prolongada tras quimioterapia intensiva para LAM/SMD y en el alo-TPH con EICH.

1.2.2. Posaconazol.

Posaconazol es un triazol con un amplio espectro antifúngico que incluye *Aspergillus* spp, *Candida* spp, *Zigomicetos* y *Fusarium*[121].

El mecanismo de acción antifúngico de Posaconazol se basa en la inhibición de la biosíntesis de ergosterol, el principal esterol de la membrana fúngica. La inhibición de lanosterol 14α-desmetilasa (CYP51), enzima dependiente del sistema del citocromo P450 fúngico conlleva la disminución de la síntesis de ergosterol, la acumulación de precursores esterólicos metilados, alteraciones en la integridad y funcionalismo de la membrana fúngica e inhibición del crecimiento y replicación del hongo y muerte celular.

Además, Posaconazol a diferencia de otros azoles, dispone de una extensa cadena lateral que le permite incrementar los puntos de contacto con CYP51, enzima diana para su acción antifúngica (Figura 6).

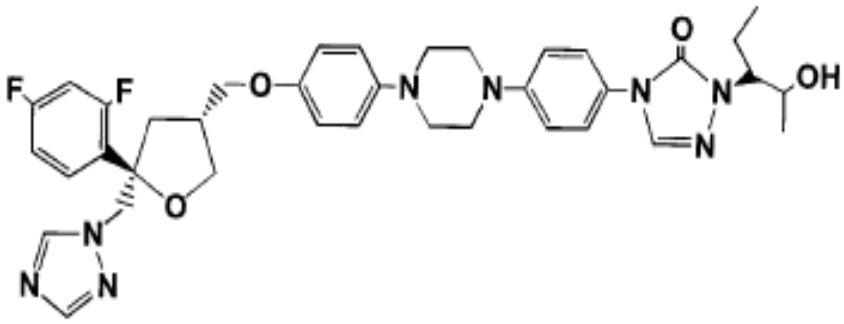

Figura 6. Estructura química de Posaconazol.

Actualmente Posaconazol sólo está disponible en suspensión oral, aunque los estudios farmacocinéticos y de seguridad de la formulación en tabletas sólidas e intravenosa son muy prometedores[122-126].

Posaconazol se administra en una suspensión blanca con sabor a cereza; se tolera bien y presenta baja incidencia de efectos adversos, incluso tras la administración prolongada[127]. Los efectos adversos más frecuentes son las alteraciones gastrointestinales (náuseas, vómitos y diarreas) y de las pruebas de función hepática (hiperbilirrubinemia), que suelen ser reversibles al suspender el tratamiento y en algunos casos se normalizan incluso sin necesidad de interrumpirlo[18,19,128].

Posaconazol es muy lipofílico y para mejorar su biodisponibilidad se recomienda la administración con comida o un suplemento nutricional. Así, en comparación con la administración en ayunas, la exposición aumenta 3.4 veces si el fármaco se administra con comida grasa y 2.6 veces si se administra con comida no grasa o un suplemento alimenticio[129-133]. La exposición de Posaconazol es dosis dependiente (hasta una dosis diaria de 800mg) y es mayor si la dosis total se divide en fracciones, el estado de equilibrio se alcanza a los 7-10 días, y se elimina lentamente, con una semivida media en plasma de 35 horas (20-66 horas)[132,134,135].

Posaconazol se une extensamente a proteínas (>98%), principalmente a albúmina sérica, pero su volumen de distribución es muy alto, lo que sugiere una distribución extravascular y penetración en espacios intracelulares extensa. A pesar de que hay pocos datos sobre su distribución en tejidos, Farowski et al[136] determinaron la concentración intracelular del azol en las diferentes poblaciones sanguíneas celulares,

Conte et al[137] mostraron que la concentración en células alveolares pulmonares es de 31-42 veces mayor de lo correspondiente al plasma y Campoli et al[138] mostraron que los niveles de Posaconazol en la membrana celular eran de 40 a 50 veces mayor respecto a los niveles extracelulares. La intensa lipofilidad de Posaconazol y su amplia distribución tanto intracelular como en las membranas[139] podrían explicar el mayor beneficio de su uso en profilaxis en comparación a otros antifúngicos más hidrofílicos.

1.2.2.1. Metabolismo y farmacocinética

Posaconazol circula mayoritariamente como compuesto parental. Alrededor del 80% de Posaconazol se elimina por las heces, prácticamente sin alterar y sólo alrededor del 20% de la dosis administrada se metaboliza a través del sistema enzimático 1A4 uridin difosfato-glucoronosil transferasa (reacción de fase II o conjugativa)[140,141] para convertirse en metabolitos inactivos que se eliminan vía urinaria.

Determinados factores como el aumento del pH gástrico, la diarrea, el aumento de la motilidad intestinal, mucositis o una mala adherencia al tratamiento pueden disminuir la exposición de Posaconazol[129-131,142-144]. Sin embargo, Posaconazol prácticamente no se metaboliza por la vía del citocromo P450 (metabolismo oxidativo o fase I), por lo que su farmacocinética no se altera por la administración de inhibidores de CYP450[145] y debido a que la oxidación y la eliminación renal son minoritarios, no se requiere ajuste de dosis por insuficiencia hepática o renal[141,146-150].

Sin embargo, debido a la glucoronidación y a que Posaconazol es sustrato de la p-glucoproteína *in vitro*, los inhibidores e inductores de estas vías de aclaramiento pueden aumentar o disminuir respectivamente las concentraciones plasmáticas del azol. Tal es así, que la administración de potentes inductores enzimáticos como Fenitoína o Rifabutina pueden llegar a incrementar el aclaramiento de Posaconazol alrededor de un 90%. Por ello, la administración concomitante de Posaconazol con determinados fármacos está contraindicada (Tabla 3).

Posaconazol es un antifúngico con eficacia demostrada y con un amplio perfil de seguridad, pero para su uso y manejo es imprescindible conocer las interacciones con los inmunosupresores y los múltiples fármacos adicionales que se administran concomitantemente en el paciente alotrasplantado.

1.2.2.2. Interacciones farmacológicas.

Posaconazol es un potente inhibidor del isoenzima 3A4 del citocromo P450, por lo que el aclaramiento de fármacos metabolizados a través de este enzima puede disminuir significativamente y por consiguiente aumentar su concentración al adminsitrarlos conjuntamente con el azol. Es importante destacar sin embargo, que el potencial de interacción farmacológica de Posaconazol es menor que el de otros azoles ya que no inhibe isoformas adicionales del isoenzmia CYP450 como CYP1A2, 2C8/9, 2D6 o 2E1[145].

Debido a las potenciales interacciones farmacológicas con Posaconazol y a las posibles complicaciones derivadas de ellas, se han establecido unas recomendaciones de uso y manejo de fármacos conjuntamente con Posaconazol que se resumen en la tabla 3.

Tabla 3. Interacciones farmacológicas más frecuentes con Posaconazol. Recomendaciones de manejo de tratamientos concomitantes[135,147,151-156].

Uso concomitante contraindicado	
Ergotamina y Dihidroergotamina (ergotismo) Terfenadina, Astemizol, Pimozida, Cisaprida, Quinidina, Halofantrina (alargamiento QT) Inhibidores de la HMG-CsA reductasa (Rabdomiolisis) Sirólimus	
Uso concomitante No recomendado	
Fenitoína	Cimetidina
Rifabutina	Efavirenz
Monitorización* con el uso combinado	
Alcaloides de la Vinca	Fenitoína
Carbamacepina	Irinotecan
corticoides	Bloqueadores del Calcio
Sildenafilo	Sulfonilureas
Digoxina	Rifampicina
Ritonavir	Midazolam y otras BZD
Atazanavir	Amiodarona
Disminuir dosis al inicio del tratamiento combinado	
Ciclosporina (75% de la dosis inicial) Tacrólimus (25% de la dosis inicial)	

* Monitorización, tanto de los efectos adversos como de los niveles plasmáticos de los sustratos enzimáticos. En algunos casos se debe valorar disminuir la dosis al inicio del tratamiento combinado.

1.2.2.2.1. Interacción con inmunosupresores

En el alo-TPH los inmunosupresores juegan un papel crucial para la supervivencia y los buenos resultados del trasplante. La EICH es la principal causa de mortalidad relacionada con el trasplante no infecciosa; está asociada con elevada morbilidad e importantes limitaciones en la calidad de vida, por lo que asegurar una buena profilaxis de EICH es crucial para mejorar el éxito del alo-TPH.

La contraindicación del tratamiento combinado de Posaconazol con **Sirólimus** deriva de un estudio sobre 12 voluntarios sanos en el que la inhibición de Posaconazol sobre el citocromo P450 determinó un incremento de la AUC (área bajo la curva) y de la Cmax (concentración máxima) de Sirólimus de hasta 8.9 y 6.7 veces, respectivamente[157]. Sin embargo, un estudio posterior sobre 15 pacientes alotrasplantados mostró que a pesar de que prácticamente la mitad de ellos presentaron niveles de Sirólimus significativamente altos (>12ng/mL), sólo uno presentó un efecto adverso secundario relacionado, por lo que concluyeron que la administración conjunta de Posaconazol y Sirólimus podría ser segura si se reduce de un 33% a 50% la dosis de Sirólimus antes del inicio del tratamiento combinado y se monitorizan los niveles del inmunosupresor[158].

Los estudios de interacción de Posaconazol sobre la farmacocinética de los inhibidores de la calcineurina han llevado a recomendar la disminución de la dosis del inmunosupresor al inicio del tratamiento combinado.

La interacción con **Tacrólimus** se testó en 36 voluntarios sanos. Tras 14 días de tratamiento con Posaconazol, la AUC y Cmax de Tacrólimus incrementaron un 358% y 121%, respectivamente, por lo que la recomendación es disminuir un 75% la dosis original de Tacrólimus al inicio del tratamiento combinado[159].

La **Ciclosporina A (CsA)** es el inmunosupresor estándar, de elección y más frecuentemente utilizado para la profilaxis de la EICH[160]. La interacción farmacocinética entre Posaconazol y CsA se evaluó sólo en cuatro receptores de un trasplante cardíaco en un estudio abierto y no randomizado en el que tres de los cuatro pacientes requirieron una reducción del 14-29% de la dosis de CsA[159]. Tras estos resultados, la ficha técnica de Posaconazol recomienda disminuir alrededor de un 25% la dosis de CsA al iniciar el tratamiento combinado. Sin embargo, el efecto de Posaconazol sobre los niveles de CsA nunca ha sido estudiada en el post alo-TPH inmediato, en el que la disminución de los niveles de CsA por debajo del rango terapéutico puede tener un impacto muy negativo en la evolución del trasplante.

1.2.2.2.2 Ciclosporina A

La CsA es un péptido cíclico compuesto por 11 aminoácidos producido por el hongo *Tolypocladium inflantum* aislado en 1969 de suelo noruego. Desde que Powles et al[161] reportaron en 1978 los resultados del primer estudio clínico, la CsA ha sido el inmunosupresor por excelencia[162-165] y actualmente, sigue siendo el inmunosupresor estándar y de elección para la profilaxis de EICH[160].

Las **toxicidades** secundarias a la CsA más frecuentes incluyen la insuficiencia renal y la neurotoxicidad (temblores, parestesias, quemazón de pies y manos, etc), habitualmente dosis-dependientes y reversibles con la disminución de dosis. Aunque poco frecuentes, la encefalopatía posterior reversible y el síndrome hemolítico urémico/púrpura trombótica trombocitopénica son las dos toxicidades neurológicas potencialmente más severas asociadas con la CsA. Otros efectos adversos incluyen la hipertensión, hiperbilirrubinemia, hiperglicemia, hiperlipemia, hipomagnesemia, hiperpotasemia, hiperuricemia, cefalea e hirsutismo siendo más rara la aparición de hipertrofia de las encías, debilidad ungueal, acné, pancreatitis, náuseas y vómitos. Durante el tratamiento con CsA, además del control de los efectos adversos, es imprescindible el control de los factores que pueden favorecer la aparición de toxicidades (tabla 4).

Tabla 4. Asociación de factores de riesgo y toxicidades secundarias durante el tratamiento con CsA.

Factor de riesgo	Toxicidad
Hipomagnesemia	Convulsiones
Hipocolesterolemia, Imipenem/Cilastatina, Metilprednisolona a altas dosis	Neurotoxicidad
Fármacos nefrotóxicos (Trimetoprim-Sulfametoxazol, Aminoglucosidos, Vancomicina, AINE's, etc)	Insuficiencia renal
Diuréticos ahorradores de Potasio	Hiperpotasemia
Estatinas, Fibratos	Miopatía
Nifedipino	Hiperplasia gingival

La CSA se metaboliza extensamente por el sistema enzimático CYP3A4 hepático y se elimina mayoritariamente por vía biliar (95%), con sólo alrededor del 5% del fármaco eliminado vía urinaria. Su biotransformación es amplia ya que se han

identificado alrededor de 15 metabolitos en orina, algunos de los cuales tienen actividad inmunosupresora o nefrotóxica y sólo el 0.1% de la dosis administrada se elimina como droga no modificada.

Debido a que la CsA se metaboliza extensamente por el sistema enzimático del citocromo P450, su aclaramiento puede verse alterado por la coadministración con fármacos que inhiben o inducen esta vía enzimática (Tabla 5).

Tabla 5. Fármacos que modifican los niveles de CsA**.**

Aumentan los niveles de CsA	Disminuyen los niveles de CsA
ANTIFÚNGICOS AZÓLICOS	Barbitúricos
Macrólidos	Carbamazepina
Bloqueadores del Calcio	Oxcarbazepina
Metoclopramida	Fenitoína
Metilprednisolona	Fenobarbital
Alopurinol	Metamizol
Amiodarona	Clindamicina
Inhibidores de la proteasa	Octeótride
Imatinib	Rifampicina
Omeprazol	Rifabutina
Imipenem	Isoniazida
Ciprofloxacino, Levofloxacino	Ticlopidina
Fluoxetina	Sulfinpirazona
Tigeciclina	Sulfadimina
Ticarcilina	Terbinafina
Metronidazol	Trimetoprim
Danazol	*Hypericum perforatum* (hierba de
Acetazolamida	San Juan)

En particular, **Posaconazol** es un potente inhibidor del sistema enzimático CYP3A4, por lo que su administración conjunta, disminuirá el aclaramiento e incrementará los niveles de CsA. Por ello, la ficha técnica de Posaconazol recomienda disminuir la dosis de CsA al inicio del tratamiento combinado[135]. Sin embargo, dicha

recomendación deriva de un estudio realizado en sólo cuatro trasplantes cardíacos y no se han realizado estudios para evaluar el efecto de Posaconazol sobre la cinética de la CsA en el alo-TPH.

1.2.2.2.3 Profilaxis antifúngica con Posaconazol. Posicionamiento en guías internacionales.

En dos grandes estudios randomizados, Posaconazol demostró ser un antifúngico eficaz para la profilaxis de las IFI y tener un excelente perfil de seguridad.

Cornely et al[18] reportaron los resultados de un estudio randomizado y abierto, comparando Posaconazol con Itraconazol y Fluconazol en 602 pacientes neutropénicos tras tratamiento quimioterápico de inducción para LAM/SMD. Los pacientes en profilaxis con Posaconazol presentaron una incidencia significativamente menor de IFI probable o probada (2% versus 8%; <0.001), de AI (1% versus 7%; p<0.001), de mortalidad global (16% versus 22%; p=0.048) y de mortalidad relacionada con la IFI (2% versus 5%; p=0.01) respecto a Itraconazol/Fluconazol. La supervivencia global fue significativamente mejor para el grupo de Posaconazol, y aunque presentaron más efectos adversos severos (6% vs 2%, p=0.01), no comportaron una mayor tasa de discontinuación del fármaco y la distribución de éstos fue comparable entre grupos, siendo la toxicidad gastrointestinal la afectación más frecuente.

La incidencia de IFI probable y probada durante los 100 días tras la randomización también fue significativamente menor para los pacientes en profilaxis con Posaconazol en comparación con Itraconazol/Fluconazol (5% vs 11%, p=0.003), así como el tiempo a IFI (p=0.003), a mortalidad global (p=0.04) y tiempo a IFI o mortalidad (p=0.01) (Figura 7).

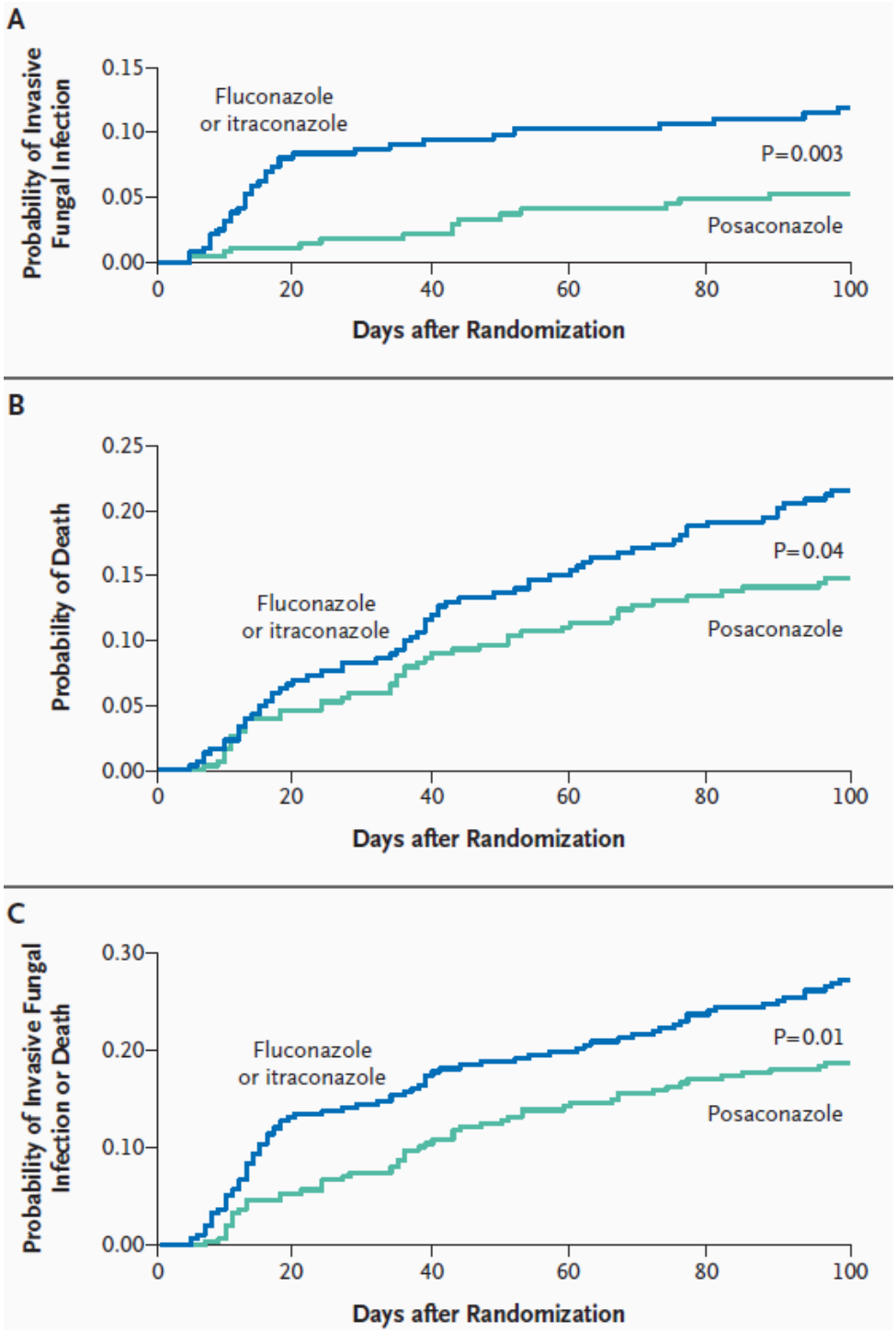

Figura 7. Curvas de Kaplan Meier de tiempo a IFI (A), mortalidad global (B) e IFI o muerte (C) durante los 100 días post randomización. De Cornely et al[18].

Ullmann et al[19] publicaron un estudio randomizado y doble ciego comparando Posaconazol con Fluconazol en 600 pacientes alotrasplantados con EICH. Posaconazol resultó ser comparable a Fluconazol en seguridad y tolerancia. Los pacientes en el grupo de Posaconazol presentaron menor incidencia de IFI de brecha (2.4% versus 7.6%; p=0.004) y de AI de brecha (1% versus 5.9%; p=0.001). La incidencia de IFI durante el periodo fijado de 16 semanas no mostró diferencias estadísticamente significativas (5.3% versus 9%; p=0.07), pero los pacientes en el grupo de Posaconazol presentaron menor incidencia de AI (2.3% versus 7%; p=0.006) y el tiempo a IFI fue mayor (p=0.048) (Figura 8). Es importante destacar que en este estudio de diseño doble ciego, no hubieron diferencias significativas en la incidencia de efectos adversos (36% en Posaconazol versus 38% en Fluconazol) y aunque la mortalidad global fue similar para ambos grupos (25% versus 28%; p=n.s), la mortalidad relacionada con la IFI fue significativamente menor para el grupo de Posaconazol (3% versus 8%; p=0.046).

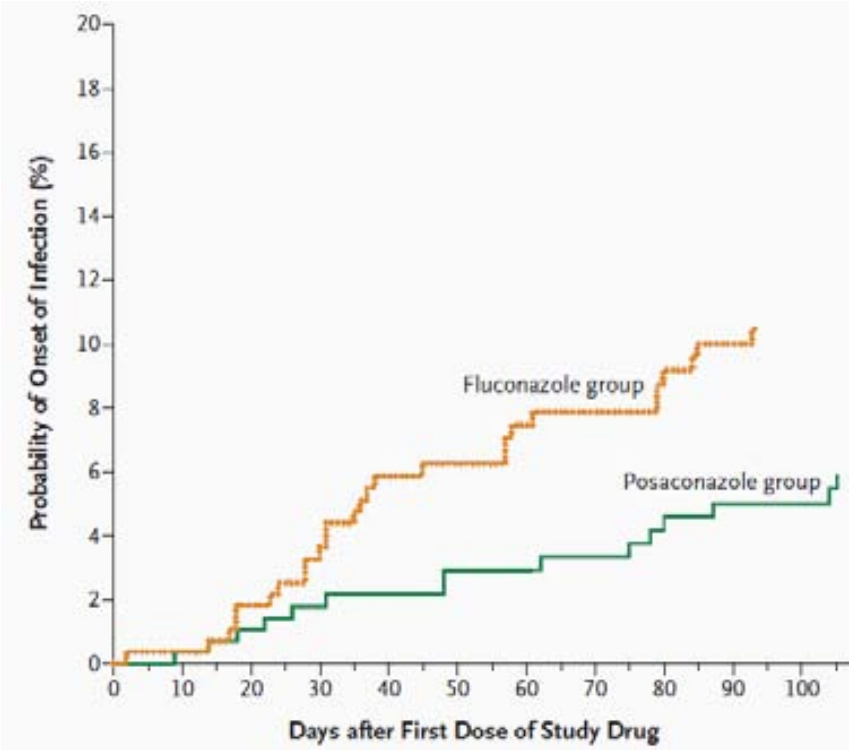

Figura 8. Tiempo a IFI probable o probada. De Ullmann et al[19].

Tras los resultados de estos dos grandes estudios, Posaconazol fue posicionado como el único antifúngico recomendado con evidencia 1 y AI por la NCCN, ECIL-3, IDSA (*Infectious Diseases Society of America*) y otras guías internacionales para la profilaxis en neutropenia prolongada tras quimioterapia para LAM/SMD y en el alo-TPH con EICH[82,98-100] (Tabla 6).

Asísmismo, desde la publicación de los dos grandes ensayos[18,19], numerosos estudios realizados en la práctica clínica real en pacientes hematológicos de alto riesgo en profilaxis con Posaconazol han reportado de forma reproducible datos de eficacia clínica con incidencias de AI de menos del 5%[166-174].

Tabla 6. Calidad y evidencia de las recomendaciones de profilaxis antifúngica primaria en el alo-TPH según ECIL-3 (European Conference on Infections in Leukemia)[98] y NCCN v2.2011 (National Comprehensive Cancer Network)[99].

Antifúngico	Fase neutropénica		EICH	
	ECIL-3	**NCCN**	**ECIL-3**	**NCCN**
Fluconazol (400mg/d)	AI	1	CI	--
Itraconazol[♯]	BI	2B	BI	--
Voriconazol (400mg/d)	AI (provisional)	2B	AI (provisional)	2B
Posaconazol (200mg/8h)	--	2B	**AI**	**1**
Equinocandinas	CI*	1*	--	2B
Polienos (IV)	CI	2B	CI	2B
L-Amb aerosolizado + Fluconazol oral	BII		--	

[♯]400mg/d seguidos de 200mg IV solución oral; *Micafungina 50mg/d.

A pesar del consenso establecido en éstas y otras guías internacionales sobre la eficacia de Posaconazol en neutropenia post quimioterapia intensiva para LAM/SMD y en el alo-TPH con EICH, no hay ensayos ni estudios clínicos en los que se evalúe la eficacia y seguridad de Posaconazol en la fase neutropénica del alo-TPH y post injerto sin EICH, por lo que la ausencia de datos no ha permitido establecer un consenso sobre su uso en esta fase de alto riesgo de IFI.

En la presente tesis presentamos los primeros datos del uso de Posaconazol en la fase precoz del alo-TPH desde un punto de vista tanto clínico como de interacciones medicamentosas.

Ninguno de los estudios de la presente tesis doctoral fue financiado por casas comerciales.

OBJETIVOS

El objetivo de la presente tesis doctoral es evaluar el uso de la profilaxis antifúngica primaria con Posaconazol en la fase precoz del alo-TPH en términos de:

1. Eficacia clínica y seguridad.
2. Interacciones medicamentosas.

ANÁLISIS DE EFICACIA CLÍNICA Y SEGURIDAD (Manuscrito 1)

Realizamos un primer estudio observacional, prospectivo y retrospectivo para evaluar la eficacia clínica y seguridad de la profilaxis antifúngica primaria con Posaconazol *versus* Itraconazol en la fase precoz del alo-TPH.

Los objetivos del estudio fueron:

- Incidencia de IFI probable y probada según los criterios de la EORTC/MSG[59].
- Supervivencia libre de infección fúngica, supervivencia global, incidencia de fiebre, fiebre persistente (>72 horas) a pesar de tratamiento antibiótico de amplio espectro, toxicidad (versión 2.0, Bethesda, 1999) y fallo de profilaxis definido como la discontinuación de la profilaxis antifúngica antes del periodo establecido de 100 días por una decisión clínica o sospecha de falta de eficacia.

ANÁLISIS DE LA INTERACCIÓN FARMACOLÓGICA CON CsA (Manuscrito 2)

Realizamos un estudio prospectivo para analizar el impacto de Posaconazol sobre el manejo de CsA en el post alo-TPH inmediato.

Los objetivos del estudio fueron:

- La determinación de la concentración “valle” de CsA.
- El ajuste de dosis de CsA tras el inicio del tratamiento combinado con Posaconazol.
- La ratio concentración/dosis de CsA.
- La evaluación de las toxicidades secundarias a CsA durante los 30 primeros días del tratamiento combinado.

PACIENTES Y MÉTODOS

ANÁLISIS DE EFICACIA CLÍNICA Y SEGURIDAD (Manuscrito 1)

Definimos la fase precoz del alo-TPH como aquélla que incluye desde el inicio del acondicionamiento hasta día +100, quedando a su vez subdividida en una fase neutropénica inicial que incluye hasta el injerto de neutrófilos (>0.5 neutrófilos/uL) y una segunda fase post-injerto hasta día +100.

La población a estudio incluyó todos los alo-TPH consecutivos realizados en nuestro centro desde Agosto 2005 a Marzo 2009 que recibieron profilaxis antifúngica primaria con Itraconazol (Agosto 2005-Mayo 2007, solución oral 200mg/12h o intravenoso 200mg/12h durante dos días seguido de 200mg/día) o Posaconazol (Junio 2007-Marzo 2009, solución oral 200mg/8h). La profilaxis, independientemente del fármaco utilizado se administró durante un mínimo de 100 días post alo-TPH.

Los criterios de exclusión incluyeron: antecendente de IFI previa, uso de profilaxis antifúngica secundaria o tratamiento activo con antifúngico no tópico hasta cuatro semanas antes del alo-TPH.

Para el análisis estadístico se siguieron las guías de la EBMT[175], se utilizó la versión 13 de SPSS (http://www.spss.com) y R (http://r-project.org) y se calculó la incidencia acumulada de fallo de profilaxis y de IFI probable y probada versus mortalidad como riesgo competitivo, comparadas mediante el test de Gray. Los valores de $p<0.05$ se consideraron como estadísticamente significativos.

ANÁLISIS DE LA INTERACCIÓN FARMACOLÓGICA CON CsA (Manuscrito 2)

En este estudio se incluyeron receptores de un primer alo-TPH de tres centros españoles que recibieron tratamiento combinado con Ciclosporina y Posaconazol durante un mínimo de 30 días post alo-TPH.

La profilaxis con 200mg/8h de suspensión oral de Posaconazol se inició en el día +1 post alo-TPH tras adquirir el estado de equilibrio de CsA administrada vía intravenosa en 120 minutos cada 12 horas.

Debido al elevado riesgo de adquirir niveles subterapéuticos, para este estudio no se disminuyó la dosis de CsA al inicio del tratamiento combinado, sino que se monitorizaron sus niveles al menos tres veces por semana y se ajustó la dosis para mantener niveles terapéuticos en sangre o en caso de toxicidad.

La evaluación de los objetivos, a excepción de la toxicidad que se determinó diariamente, se realizaron al inicio del tratamiento combinado (día 0) y posteriormente un mínimo de 3 veces por semana hasta los 30 días post-TPH, tomando como referencia para los análisis estadísticos las evaluaciones de los días 0, 7, 14 y 30.

Para el análisis estadístico, se utilizó la versión 17 de SPSS y se realizaron compraraciones mediante análisis de varianza (ANOVA) entre los diferentes puntos temporales y test de Student para los datos pareados entre puntos temporales específicos. Los valores de $p<0.05$ se consideraron estadísticamente significativos.

RESULTADOS

ANÁLISIS DE EFICACIA CLÍNICA Y SEGURIDAD (Manuscrito 1)

En este estudio observacional y monocéntrico se incluyeron 49 alo-TPH, 16 de los cuales recibieron profilaxis con Itraconazol y 33 recibieron profilaxis con Posaconazol durante los 100 primeros días post trasplante.

- La incidencia de IFI probable y probada según los criterios revisados de la EORTC/MGS[59] fue significativamente menor en el grupo de Posaconazol en comparación con el grupo de Itraconazol (0% vs 12.5%, p=0.04).

- Los dos casos de IFI diagnosticados durante el periodo de estudio fueron AI probables, ambas en el grupo de Itraconazol a los 12 y 29 días post alo-TPH. Ningún paciente en el grupo de Posaconazol fue diagnosticado de una IFI probable o probada.

- La supervivencia libre de infección fúngica (91 vs 56%; p=0.003) y la supervivencia global (91 vs 63%; p=0.011) también fueron significativamente mejores para el grupo de Posaconazol.

- No hubo diferencias en la incidencia de toxicidad hepática o gastrointestinal entre grupos.

- Tampoco hubo diferencias en la incidencia de fiebre (84%), fiebre persistente de >72 horas a pesar de antibioticoterapia de amplio espectro (27%) o en la duración de ésta (mediana de 4 días, 0-36).

- No hubo diferencias significativas en la incidencia de fallo de profilaxis (31% Itraconazol *vs* 15% Posaconazol, p=0.246) ni en el mantenimiento en profilaxis hasta el inicio de tratamiento empírico para estos pacientes, a pesar de que la media para Posaconazol fue de 31 días (mediana 23.5; 15-54) y de 17.8 días para Itraconazol (mediana: 10; 4-37).

ANÁLISIS DE LA INTERACCIÓN FARMACOLÓGICA CON CsA (Manuscrito 2)

En este estudio se incluyeron 41 receptores de un primer alo-TPH de tres centros españoles que recibieron tratamiento combinado con Ciclosporina y Posaconazol durante los 30 primeros días post trasplante.

- Nuestros resultados confirman que Posaconazol aumenta los niveles de CsA en sangre (p=0.011).

- A pesar de que el aumento de los niveles ya es significativo desde la primera semana del tratamiento combinado (desde 225.8ng/ml a día 0 hasta 293.1ng/ml a día 7; p=0.028), no es necesario reducir la dosis de CsA antes de iniciar Posaconazol (p=0.857), sino hasta pasadas las dos semanas del tratamiento combinado (p<0.001).

- Durante el periodo de estudio, la dosis de CsA se fue ajustando en base a los niveles en sangre y a criterios clínicos. En global, la dosis de CsA se disminuyó un 50% durante los primeros 30 días de tratamiento combinado, desde una dosis media de 3mg/Kg/d antes del inicio de Posaconazol a 1.58mg/Kg/d, tras 30 días de tratamiento combinado ($p=0.028$).

- La magnitud de esta interacción farmacológica quedó evidenciada además por la tendencia ascendente de la ratio de concentración/dosis de CsA durante todo el periodo de estudio (desde 82 a día 0 hasta 172 a día 30; $p<0.001$).

- La estrategia de no disminuir la dosis de CsA al inicio del tratamiento combinado con Posaconazol, resultó segura. No se identificaron casos de toxicidad severa y sólo siete de los 41 pacientes (17%) presentaron toxicidad leve relacionada con la CsA que se resolvió tras el ajuste de dosis.

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ORIGINAL ARTICLE

Clinical efficacy and safety of primary antifungal prophylaxis with posaconazole vs itraconazole in allogeneic blood and marrow transplantation

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Posaconazole has been recently approved for primary antifungal prophylaxis in patients with prolonged neutropenia after AML induction chemotherapy and patients with GVHD. We now present the first experience of the efficacy and safety of posaconazole during the early phase of post-allogeneic BMT ($n=33$; from June 2007), in comparison with itraconazole primary prophylaxis ($n=16$; up to May 2007). More patients receiving posaconazole were T-cell depleted ($P=0.003$). Groups were otherwise comparable in terms of age, sex, disease, neutrophil engraftment, incidence of GVHD, use of unrelated donors and type of conditioning. Safety data as well as the incidence of fever (84%) and persistent fever (27%) during the 100-day treatment period were comparable for both antifungal agents. Patients receiving posaconazole had a lower cumulative incidence of proven or probable invasive fungal disease, as defined by the European Organization for Research and Treatment of Cancer criteria (0 vs 12%; $P=0.04$), which associated with a higher probability of fungal-free survival (91 vs 56%; $P=0.003$) and an improved probability of OS (91 vs 63%; $P=0.011$) compared with patients receiving itraconazole. Our single-centre experience suggests that antifungal prophylaxis with posaconazole may lead to a better outcome than itraconazole for patients in the early high-risk neutropenic period after allogeneic BMT.
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Introduction

Invasive fungal infections (IFIs) in recipients of allogeneic blood and marrow transplantation (allo-BMT) have a higher mortality rate than in other immunocompromised hosts, and are recognized as the leading infectious cause of mortality.[1–5] For this reason, primary antifungal prophylaxis to prevent the occurrence of life-threatening IFI in allo-BMT recipients has been established by professional guidelines and clinical practice as a standard antifungal strategy in this setting.[6–8] Fluconazole has been used for antifungal prophylaxis for more than a decade, improving the outcome of allo-BMT recipients through an effective reduction of the incidence of invasive *Candida* infections.[9–11] For nearly as long, and in the context of a changing epidemiology, the challenge remained to identify antifungal agents with a good safety profile that could successfully prevent mould infections, in particular invasive pulmonary aspergillosis (IPA), and reduce fungal-related mortality.[2,3,12–16]

Posaconazole is a new-generation triazole agent with a favourable toxicity profile and an extended spectrum of antifungal activity that includes species of *Candida*, *Aspergillus*, *Zygomycetes* and *Fusarium*.[17] The results from two large prospective randomized trials have granted posaconazole FDA and EMEA approval in patients with neutropenia after AML-type chemotherapy and GVHD after allo-BMT,[18,19] and have positioned this new triazole as the recommended antifungal prophylactic agent in these clinical settings for a number of professional groups.[6–8] Despite this evidence, a question remains whether these encouraging results would translate onto other populations of patients at high risk of IFI. In particular, no data have been provided so far about the use of primary prophylaxis with posaconazole in allo-BMT, in the absence of GVHD. In this study, we present the first report on the efficacy and safety of posaconazole primary antifungal prophylaxis in allo-BMT recipients during the early neutropenic phase until engraftment and up to 100 days post transplant. Our results suggest that posaconazole antifungal prophylaxis, compared with itraconazole, may reduce the incidence of invasive fungal disease (IFD), and improve IFD-free survival (FFS) and OS in this clinical setting.

Patients and methods

Patients and study design

An observational study on adult patients receiving antifungal prophylaxis for a first allo-BMT between August 2005 and March 2009 was conducted at the Catalan Institute of Oncology, Barcelona, Spain. Up to May 2007, prophylaxis consisted of itraconazole administered either as an oral solution (200 mg twice daily) or intravenously (200 mg twice daily for 2 days followed by 200 mg once daily) depending on patient tolerance. From June 2007 onwards, and on the basis of the new evidence available,[18,19] our local antifungal policy committee, with representatives from the Hospital Pharmacy and the Departments of Haematology and Infectious Diseases, decided to change antifungal prophylaxis to posaconazole oral solution (200 mg three times daily). In addition to prolonged neutropenia and GVHD, posaconazole was adopted into our clinical protocol during allo-BMT in the absence of GVHD, with a commitment to prospectively auditing this experience and to compare it with our previous experience with itraconazole in this particular clinical setting. Allo-BMT antifungal prophylaxis in our centre was administered, regardless of the antifungal agent used, to cover both the post transplant neutropenic phase and the early post-engraftment phase, up to 100 days post transplantation, and discontinued at this point in the absence of GVHD. Patients with a previous history of IFI, on secondary antifungal prophylaxis or active treatment with other non-topical antifungal drugs up to 4 weeks before allo-BMT, were excluded from the study. Participants were all adults (>18 years) and had signed informed consents for treatment and data collection. The study was approved by our local clinical research ethics committee (CEIC Bellvitge; EPA 008/08).

The standards of protective environment, including single rooms with laminar flow or HEPA filters, recommendations for hand, skin and oral hygiene and low microbial content diet did not significantly change throughout the study period. No antibacterial prophylaxis was administered to our allo-BMT recipients. Management of febrile neutropenia included chest X-ray, urine and blood cultures and empiric antibiotic treatment on the first day of neutropenic fever. High-resolution computed tomography of the thorax was performed when unexplained fever persisted over 72 h, despite empirical antibiotic therapy or when any clinical signs or symptoms developed. In the case of radiological chest abnormalities and no other microbiological evidence elsewhere, bronchoscopy with bronchoalveolar lavage was performed whenever possible for microbiological testing, including galactomannan detection. Galactomannan test was performed in peripheral blood samples twice weekly, and defined positive as an optical index $\geqslant 0.5$ in two consecutive blood samples or a single bronchoalveolar lavage fluid sample (Platelia *Aspergillus* enzyme-linked immunosorbent assay; Bio-Rad Laboratories, Madrid, Spain). Additional blood, sputum or other relevant samples were cultured from possible infected sites when clinically indicated.

Primary end point of our analysis was the incidence of probable or proven breakthrough IFD as defined according to the 2008 criteria of the European Organization for Research and Treatment of Cancer (EORTC).[20] Other efficacy end points were the probabilities of FFS and OS, incidence of fever, persistent fever unresponsive to broad-spectrum antibiotic treatment for $\geqslant 72$ h, antifungal drug toxicity, classified according to the Common Toxicity Criteria grading system of the NCI (version 2.0, Bethesda, 1999), and prophylaxis failure, defined as an early discontinuation of prophylaxis before the fixed 100-day treatment period for a clinical decision of suspected lack of efficacy. As opposed to the definition of IFD for end-point analysis, which follows EORTC criteria, real-life clinical decisions to replace primary prophylaxis with i.v. antifungal therapy relied in all cases on an individualized clinical judgement (for example, patient general condition, signs and symptoms, test results and treatment compliance), rather than on the fulfilment of EORTC IFD criteria, which were not developed to fit this daily clinical practice purpose.[20–22] Persistent fever was considered too unspecific to trigger a change in antifungal treatment on its own.[23] Neither itraconazole nor posaconazole drug level monitoring were available during this study to guide clinical decisions. Short-term bridging with i.v. antifungals for oral intolerance to posaconazole was not planned upfront in this observational audit. The occurrence and reasons for early discontinuation of prophylaxis were recorded in all cases. Data on demographic and baseline characteristics, clinical features and follow-up, diagnostic tests and changes in antimicrobial treatments were recorded in a specific database. Clinical outcomes were evaluated for a fixed prophylaxis period of 100 days post transplant.

Statistical analysis

Software packages SPSS (version 13; http://www.spss.com) and R (http://www.r-project.org) were used for statistical analysis, which followed the guidelines established in 2003 by the EBMT, including the analysis of cumulative incidence of prophylaxis failure and probable or proven IFD vs death as a competing risk, compared with Gray test.[24] The probability of FFS is an EFS curve, in which the events of interest are death and proven or probable IFD, so that the FFS curve shows the decreasing probability of being alive and without IFD (fungal-free) during the fixed treatment period. All reported *P*-values are two-sided and were accepted as statistically significant if <0.05.

Results

A total of 49 consecutive adult recipients of a first allo-BMT with no previous history of IFI or other antifungal treatments who received primary antifungal prophylaxis were included in this study. Sixteen cases transplanted between August 2005 and May 2007 received oral and i.v. itraconazole prophylaxis, and 33 cases from June 2007 onwards received oral posaconazole. Patient demographics for the whole series and by antifungal group are summarized in Table 1. *In vivo* T-cell depletion with either alemtuzumab for reduced-intensity allo-BMT (100 mg i.v. divided into 5 doses, days −8 to −4) or ATG for

Table 1 Patient demographics and transplant characteristics

	Itraconazole (n = *16*)	*Posaconazole* (n = *33*)	*All patients* (n = *49*)
Date of Allo-BMT, range	08/2005–05/2007	06/2007–03/2009	08/2005–03/2009
Age, median (range)	46 (20–67)	48 (23–68)	48 (20–68)
Sex, n (%)			
Male	9 (56)	21 (64)	30 (61)
Female	7 (44)	12 (36)	19 (39)
Underlying disease, n (%)			
AML-MDS	8 (50)	27 (82)	35 (71.4)
ALL	3 (19)	—	3 (6.1)
CML	4 (25)	—	4 (8.2)
CLPD	1 (6)	6 (18)	7 (14.3)
T-cell depletion, *n* (%)	—	13 (39)	13 (26.5)
Conditioning regimen, n (%)			
Myeloablative	10 (62.5)	11 (33)	21 (43)
Reduced intensity	6 (37.5)	22 (67)	28 (57)
Donor type, n (%)			
Related	14 (87.5)	20 (61)	34 (69)
Unrelated	2 (12.5)	13 (39)	15 (31)

Abbreviations: Allo-BMT = Allogeneic BMT; CLPD = chronic lymphoproliferative disorders; MDS = myelodysplastic syndromes.

myeloablative allo-BMT (7.5 mg/kg i.v. divided into 3 doses, days −3 to −1) was more frequent for patients in the posaconazole group (39 vs 0%; $P = 0.003$). There were no other statistically significant differences in patient and transplant characteristics.

Three patients in the posaconazole group had primary engraftment failure, defined as ANC not reaching $\geqslant 500/\mu L$ by day +28. They all had AML in first CR at allo-BMT. The first patient was a 23-year-old woman who received a single umbilical cord blood unit allo-BMT (HLA match 5/6; 1.52×10^5/kg CD34+ cells and 2.2×10^7/kg nucleated cells) following the Spanish Pethema protocol.[25] Post-thawing cell viability (CD34+ and total nucleated cells) was low (40%), and BM chimerism on day +15 showed only 16% donor cells. Temporary CYA discontinuation improved cord chimerism, the patient engrafted neutrophils on day +49, and reached full donor chimera in the marrow and in peripheral blood lymphoid and myeloid subsets on day +62. The second case was a 50-year-old man receiving a reduced-intensity allo-BMT from his HLA-identical sister, who mobilized suboptimally, providing a total dose of 3.1×10^6/kg CD34+ cells after four apheresis procedures. This patient had only a minor delay in neutrophil engraftment to day +33. Finally, the third case was a 58-year-old woman who received a reduced-intensity allo-BMT with cryopreserved peripheral blood progenitors from an older HLA-identical sister. Post-thawing colony-forming units growth were poor, and the patient required a second infusion from the same donor with a total of 8×10^6/kg CD34+ cells after ATG and CYA. She engrafted on day +53, 11 days after the second stem cell infusion. These patients stayed on posaconazole prophylaxis for the whole duration of neutropenia, had no IFD, and remained alive and in maintained CR at the end of the observation period (day +100), and also at their most recent follow-ups, more than 18 months post transplant in all three cases. Other than these cases with graft failure, time to engraftment was virtually identical between posaconazole and itraconazole groups (16.5 ± 3.1 vs 16.1 ± 2.7, respectively; $P = 0.647$). In addition, the incidence of acute GVHD grade II–IV was comparable between groups (33% for all cases; 44% in itraconazole vs 27% in posaconazole; $P = 0.249$).

Itraconazole administration started as an oral suspension in all patients, with a low threshold to change onto i.v. route based on patient tolerance. In fact, all patients on itraconazole received i.v. drug for the majority of their in-patient admission for allo-BMT and resumed oral suspension at discharge. Retrospective analysis of this cohort does not allow to clearly dissecting real intolerance to oral itraconazole from patient's or physician's preference. In the case of posaconazole, two patients had the drug discontinued for liver function test abnormalities (grade 3 bilirubin and transaminases) that normalized 1 and 2 weeks after stopping the drug, which could be subsequently restarted without toxicity recurrence. Laboratory safety details during the observation period were comparable for both antifungal agents (Figure 1 and Supplementary data). Only one patient had to stop posaconazole prophylaxis for grade 3 gastrointestinal symptoms (that is, diarrhoea). Five additional posaconazole cases had grade $\geqslant 3$ oral mucositis. In keeping with the recommendations from our nutrition support team, these patients started enteral nutrition through a nasogastric tube, and continued to receive oral suspension posaconazole three times daily immediately after the enteral feeding through the nasogastric tube, which has been examined as a feasible alternative to standard oral administration in healthy volunteers.[26] Other minor side effects reported, such as nausea or vomiting and headaches, were more difficult to attribute to posaconazole and resolved with no need for drug discontinuation.

A total of 41 patients (84%) presented at least one episode of fever during the study period. Thirteen of these

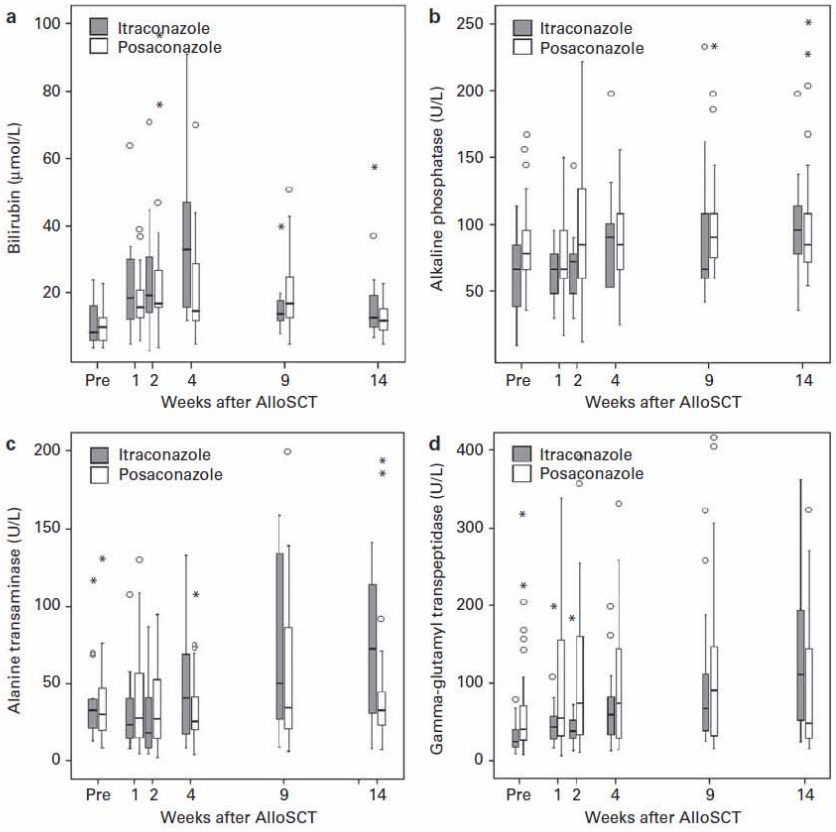

Figure 1 Laboratory safety data during the 100-day fixed prophylaxis period. (**a**) Bilirubin; (**b**) alkaline phosphatase; (**c**) alanine transaminase; and (**d**) γ-glutamyl transpeptidase laboratory results during the 100-day fixed prophylaxis period for patients with itraconazole (dark boxes) and posaconazole (open boxes). Graphics show the median, quartiles 1–3 in central bars, 95% results range and individual, both mild (○) and extreme (*), outliers. Results are all expressed in IS units. Time points are before the start of prophylaxis (PRE) and at various weeks (± 1 day) after allo-BMT.

41 patients (27% of all cases) had persistent fever for longer than 72 h (five itraconazole cases and eight posaconazole cases). The median duration of fever was 4 days (mean 6.8 days; range 0–36). The commonest microbiological isolates were coagulase-negative *Staphylococcus* (52%), *Klebsiella* (12%), *Escherichia coli* (12%), *Staphylococcus aureus* (8%) and other Gram-negative bacteria (16%). The commonest sources of bacterial infection were central venous catheters and lower respiratory tract infections. Twenty-one patients (43%) did not have any microbiological isolates in relation with their febrile episodes. There were no statistical differences between itraconazole and posaconazole groups in terms of the incidence of fever, persistent fever and fever total duration (Table 2).

Five patients on itraconazole (31%) and five on posaconazole (15%) discontinued prophylaxis and started i.v. antifungal treatment as a clinical decision in the context of persistent fever unresponsive to broad-spectrum antibiotic treatment for $\geqslant$72 h (defined as prophylaxis failure; no difference between groups, $P=0.246$). Time of exposure to antifungals for all patients and time on oral prophylaxis to first use of empirical antifungal therapy in these 10 patients (Table 2) showed no statistical differences between patients receiving itraconazole and posaconazole. Only two patients, both on itraconazole prophylaxis had an EORTC diagnosis of probable or proven IFD, both cases of IPA. Cumulative incidence of breakthrough proven or probable IFD during the 100-day study period was significantly lower in patients receiving posaconazole prophylaxis than in their itraconazole counterparts (0 vs 12%; $P=0.04$; Figure 2). These two IPA cases were both male, aged 42 and 48 years old, with diagnoses of AML and CML. They had both received an HLA-identical sibling myeloablative allo-BMT. The first case had a dense well-circumscribed single nodule without a clear halo-sign on a first chest computed tomography scan, which additionally cavitated

Table 2 Febrile episodes and exposure to prophylactic antifungals

	Itraconazole (n = 16)	*Posaconazole* (n = 33)	*All patients* (n = 49)
Fever[a], *n* (%)	14 (87)	27 (82)	41 (84)
Persistent fever[b], *n* (%)	5 (31)	8 (24)	13 (27)
Duration of fever (days), mean, median (range)	6.7, 4 (0–36)	6.9, 3.5 (0–35)	6.8, 4 (0–36)
Exposure to prophylactic antifungals[c] (days), mean, median (range)			
Exposure time in all cases	66.3, 95 (4–100)	84.5, 100 (15–100)	78.6, 100 (4–100)
Exposure time to first use of antifungal empirical therapy	*n* = 5 (31%) 17.8, 10 (4–37)	*n* = 5 (15%) 31.0, 23.5 (15–54)	*n* = 10 (20%) 25.0, 21 (4–54)

[a]Temperature ⩾38.5 °C once, or ⩾38 °C twice consecutively in the same episode.
[b]Persistent fever longer than 72 h.
[c]From the start of prophylaxis to discontinuation for toxicity or start of empirical treatment, or end of prophylaxis period (day +100).

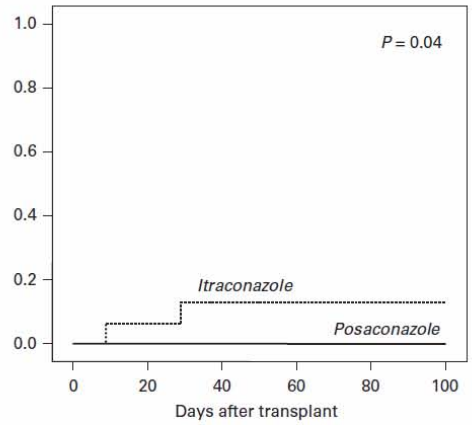

Figure 2 Time to invasive fungal disease during the 100-day fixed prophylaxis period. Cumulative incidence of invasive fungal disease for the whole group was 4%, 12.5% in the itraconazole group and 0% in the posaconazole group ($P = 0.04$; Gray test).

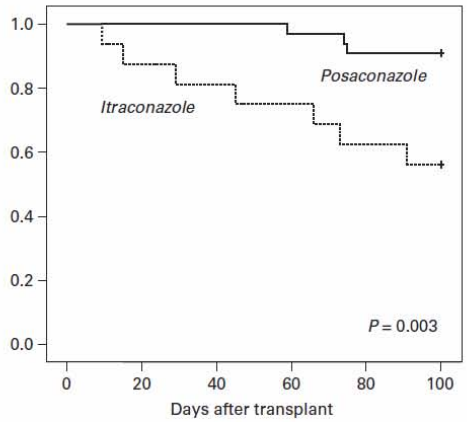

Figure 3 Invasive fungal disease-free survival during the 100-day fixed prophylaxis period. The invasive fungal disease-free survival for the whole group was 80%, 56% in the itraconazole group and 91% in the posaconazole group ($P = 0.003$; log rank). Data were censored on day +100 post transplant.

on follow-up images and positive galactomannan test in peripheral blood (consecutive index 0.72 and 1.3) for a probable IPA during the early neutropenic phase post-allo-BMT, starting voriconazole treatment on day +12. The second case was diagnosed with probable IPA on day +29, 11 days after neutrophil engraftment, based on radiological findings (initial computed tomography scan with unspecific lung infiltrates including several small nodules, and subsequent air-crescent sign in the same episode) and positive galactomannan test in serum (index 0.63) and the bronchoalveolar lavage (index 1.1) in the context of persistent fever refractory to wide-spectrum antibiotics and removal of the central catheter, and was also treated with voriconazole. Eight additional cases received either caspofungin ($n = 4$) or lipid formulations of amphotericin B ($n = 4$) as empiric treatment based on clinical decision, and for whom probable or proven IFD was not subsequently confirmed. Finally, patients on posaconazole antifungal prophylaxis had a significantly higher FFS (91 vs 56%; $P = 0.003$; Figure 3) and OS (91 vs 63%; $P = 0.011$; Figure 4) than patients who received itraconazole prophylaxis.

Discussion

As a general antifungal strategy, primary prophylaxis reduces all-cause mortality, IFI-related mortality and documented IFI in allo-BMT, and should be used for all allo-BMT recipients according to a recent systematic review and meta-analysis of 64 randomized controlled trials.[27] Despite the encouraging results of primary antifungal prophylaxis with posaconazole for AML and GVHD patients, there are currently no data on whether this experience would translate onto the use of posaconazole for antifungal prophylaxis in the early phase of allo-BMT in the absence of GVHD. Here, we present the first study analysing primary antifungal prophylaxis with posaconazole in the early phase of allo-BMT, and comparing it to itraconazole prophylaxis. This is an observational study, a prospective and retrospective audit of our experience in this setting at the Catalan Institute of Oncology in Barcelona, Spain. The study includes all consecutive patients complying with inclusion and exclusion criteria. As for any other

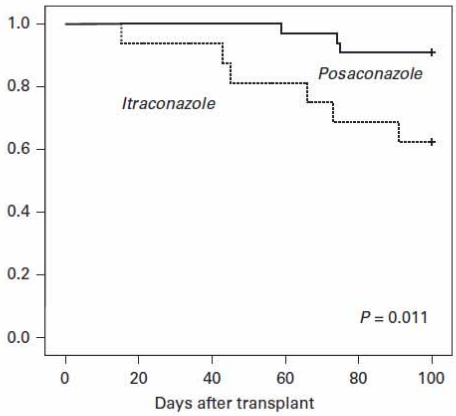

Figure 4 OS during the 100-day fixed prophylaxis period. The OS for the whole group was 82%, 63% in the itraconazole group and 91% in the posaconazole group ($P = 0.011$; log rank). Data were censored on day +100 post transplant.

observational single-centre non-randomized sample, the study population is somewhat heterogeneous and changes over time along with clinical practice. Even so, the standards of protective isolation and the availability of diagnostic tests did not change during the study period, and there were no differences between groups in terms of engraftment or incidence of acute GVHD.

Patients on posaconazole had a reduced cumulative incidence of IFD, and an increased FFS and OS during the study period, compared with their itraconazole counterparts. As expected, there were no differences between groups in terms of incidence of fever, persistent fever, fever duration, bacterial isolates or infection source. Reassuringly, none of the patients with persistent fever in the posaconazole group who remained on prophylaxis rather than starting treatment (three out of eight) ended up developing an IFD. Posaconazole was overall well tolerated, included a few patients with mucositis who received it after enteral feeding through nasogastric tubes. Toxicity profiles for both azoles have been reported at length and analysed in larger patient populations. Our results reproduce that most posaconazole side effects were minor and not different from those with itraconazole.

In summary, our results show that in addition to prolonged neutropenia and GVHD, antifungal prophylaxis with posaconazole, as compared with itraconazole, may reduce the incidence of IFD and improve the outcome of patients after allo-BMT. Undoubtedly, the evidence from an observational non-randomized single-centre study, such as our own, has caveats. In addition, local characteristics, such as fungal epidemiology, incidence of IFD and cost-effectiveness, to mention only a few, must be reviewed and incorporated into the algorithms to manage IFI in allo-BMT recipients in individual centres. Nevertheless, and in the absence of randomized trials with posaconazole in this indication, our single-centre study provides the first direct supporting evidence to explore its use in this important clinical setting.

Conflict of interest

Drs Arnan, Duarte, Fernández de Sevilla, Gudiol and Parody have received consultation and/or speaker fees from Esteve, Gilead Science, Merck Sharp and Dohme, Pfizer and/or Schering-Plough during the study period. Other authors declare no conflict of interest.

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References

1 Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis* 2001; **32**: 358–366.
2 Marr KA, Carter RA, Boeckh M, Martin P, Corey L. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. *Blood* 2002; **100**: 4358–4366.
3 Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2002; **34**: 909–917.
4 Post MJ, Lass-Floerl C, Gastl G, Nachbaur D. Invasive fungal infections in allogeneic and autologous stem cell transplant recipients: a single-center study of 166 transplanted patients. *Transpl Infect Dis* 2007; **9**: 189–195.
5 Gratwohl A, Brand R, Frassoni F, Rocha V, Niederwieser D, Reusser P *et al*. Cause of death after allogeneic haematopoietic stem cell transplantation (HSCT) in early leukaemias: an EBMT analysis of lethal infectious complications and changes over calendar time. *Bone Marrow Transplant* 2005; **36**: 757–769.
6 Walsh TJ, Anaissie EJ, Denning DW, Herbrecht R, Kontoyiannis DP, Marr KA *et al*. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2008; **46**: 327–360.
7 Meunier F, Lukan C. The First European Conference on Infections in Leukaemia—ECIL1: a current perspective. *Eur J Cancer* 2008; **44**: 2112–2117.
8 Cornely OA, Bohme A, Buchheidt D, Einsele H, Heinz WJ, Karthaus M *et al*. Primary prophylaxis of invasive fungal infections in patients with hematologic malignancies. Recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. *Haematologica* 2009; **94**: 113–122.
9 Goodman JL, Winston DJ, Greenfield RA, Chandrasekar PH, Fox B, Kaizer H *et al*. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med* 1992; **326**: 845–851.
10 Marr KA, Seidel K, Slavin MA, Bowden RA, Schoch HG, Flowers ME *et al*. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. *Blood* 2000; **96**: 2055–2061.

11 Slavin MA, Osborne B, Adams R, Levenstein MJ, Schoch HG, Feldman AR *et al.* Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation—a prospective, randomized, double-blind study. *J Infect Dis* 1995; **171**: 1545–1552.
12 Baddley JW, Stroud TP, Salzman D, Pappas PG. Invasive mold infections in allogeneic bone marrow transplant recipients. *Clin Infect Dis* 2001; **32**: 1319–1324.
13 Upton A, Marr KA. Emergence of opportunistic mould infections in the hematopoietic stem cell transplant patient. *Curr Infect Dis Rep* 2006; **8**: 434–441.
14 Richardson M, Lass-Florl C. Changing epidemiology of systemic fungal infections. *Clin Microbiol Infect* 2008; **14**(Suppl 4): 5–24.
15 Ullmann AJ, Cornely OA. Antifungal prophylaxis for invasive mycoses in high risk patients. *Curr Opin Infect Dis* 2006; **19**: 571–576.
16 Bow EJ, Laverdiere M, Lussier N, Rotstein C, Cheang MS, Ioannou S. Antifungal prophylaxis for severely neutropenic chemotherapy recipients: a meta analysis of randomized-controlled clinical trials. *Cancer* 2002; **94**: 3230–3246.
17 Frampton JE, Scott LJ. Posaconazole: a review of its use in the prophylaxis of invasive fungal infections. *Drugs* 2008; **68**: 993–1016.
18 Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ *et al.* Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007; **356**: 348–359.
19 Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR *et al.* Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. *N Engl J Med* 2007; **356**: 335–347.
20 De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T *et al.* Revised definitions of invasive fungal disease from the 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) Consensus Group. *Clin Infect Dis* 2008; **46**: 1813–1821.
21 Subirá M, Martino R, Rovira M, Vázquez L, Serrano D, De la Cámara R. Clinical applicability of the new EORTC/MSG classification for invasive pulmonary aspergillosis in patients with hematological malignancies and autopsy-confirmed invasive aspergillosis. *Ann Hematol* 2003; **82**: 80–82.
22 Borlenghi E, Cattaneo C, Capucci MA, Pan A, Quaresmini G, Franco F *et al.* Usefulness of the MSG/IFICG/EORTC diagnostic criteria of invasive pulmonary aspergillosis in the clinical management of patients with acute leukemia developing pulmonary infiltrates. *Ann Hematol* 2007; **86**: 205–210.
23 Segal BH, Almyroudis NG, Battiwalla M, Herbrecht R, Perfect JR, Walsh TJ *et al.* Prevention and early treatment of invasive fungal infection in patients with cancer and neutropenia and in stem cell transplant recipients in the era of newer broad-spectrum antifungal agents and diagnostic adjuncts. *Clin Infect Dis* 2007; **44**: 402–409.
24 Labopin M, Iacobelli S. Statistical Guidelines for EBMT. 2003, pp 1–24.
25 Sanz GF, Saavedra S, Planelles D, Senent L, Cervera J, Barragan E *et al.* Standardized, unrelated donor cord blood transplantation in adults with hematologic malignancies. *Blood* 2001; **98**: 2332–2338.
26 Dodds Ashley ES, Varkey JB, Krishna G, Vickery D, Ma L, Yu X *et al.* Pharmacokinetics of posaconazole administered orally or by nasogastric tube in healthy volunteers. *Antimicrob Agents Chemother* 2009; **53**: 2960–2964.
27 Robenshtok E, Gafter-Gvili A, Goldberg E, Weinberger M, Yeshurun M, Leibovici L *et al.* Antifungal prophylaxis in cancer patients after chemotherapy or hematopoietic stem-cell transplantation: systematic review and meta-analysis. *J Clin Oncol* 2007; **25**: 5471–5489.

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Effect of Posaconazole on Cyclosporine Blood Levels and Dose Adjustment in Allogeneic Blood and Marrow Transplant Recipients

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The posaconazole prescribing information recommends an upfront cyclosporine dose reduction upon initiation of posaconazole prophylaxis. We examined this recommendation in the early phase of allogeneic transplantation, where cyclosporine levels potentially becoming subtherapeutic following upfront dose reduction would be deleterious to transplant outcome. Our data show that while posaconazole leads to an increase in cyclosporine levels, subsequent cyclosporine dose reduction can be safely guided by therapeutic drug monitoring and is not required upfront. Therefore, the current recommendation may be modified.

Posaconazole is a novel triazole with broad-spectrum antifungal activity and a favorable toxicity profile (4, 7) that is currently approved for primary antifungal prophylaxis in allogeneic blood and marrow transplantation (allo-BMT) recipients with graft-versus-host disease (GVHD) (18). Posaconazole prophylaxis in allo-BMT recipients is normally administered in combination with immunosuppressive drugs for GVHD prophylaxis and/or treatment, most commonly cyclosporine (CsA). On the basis of its CYP3A4-inhibitory activity, posaconazole increases the exposure to CsA, warranting a recommendation for close monitoring of blood CsA levels and subsequent CsA dose adjustment, as required. It is noteworthy that the posaconazole prescribing information also includes a recommendation for upfront reduction of the dose of CsA upon initiation of combined treatment (17), which emerged from a very small study of cardiac transplantation (16) and has never been analyzed in allo-BMT recipients. In these patients, the potential occurrence of subtherapeutic blood CsA levels, even transiently, has a strong negative impact on GVHD and on the outcome of allo-BMT (5, 6, 11, 12, 14, 19). The clinical need for such an upfront CsA dose reduction in patients starting posaconazole in this clinical setting ought to be studied.

We have recently reported on the clinical efficacy and safety of primary antifungal prophylaxis with posaconazole during the early phase of allo-BMT (15). Here we present an analysis of the impact of posaconazole prophylaxis on CsA management in this clinical setting. Since potential subtherapeutic blood CsA levels pose the highest risk during the early posttransplant period, for this study we prospectively decided not to reduce the dose of CsA at the start of combined treatment with posaconazole. Instead, blood CsA levels were monitored at least three times weekly and the dose was adjusted as required to maintain trough CsA levels within the therapeutic range (125 to 300 ng/ml) or if CsA-related toxicity occurred. Other than this, all patients received posaconazole in keeping with the recommendations for administration in the product prescribing information. A total of 41 recipients of a first allo-BMT were included in this study (Table 1), with institutional approval by the clinical research ethics committee (CEIC Bellvitge; EPA 008/08). Patients were on steady-state CsA twice daily as a 2-h intravenous infusion for GVHD prophylaxis and started receiving 200 mg of an oral posaconazole suspension three times daily the day following transplantation. The primary endpoints included the trough CsA concentration, CsA dose adjustment, the CsA concentration-to-dose ratio, and clinical toxicity. Endpoints were assessed on days 0 (at initiation of combined

TABLE 1 Patient demographics and transplant characteristics

Parameter	Value
No. of patients	41
Median age in yr (range)	51 (18–68)
No. (%) of:	
Males	25 (61)
Females	16 (39)
Median wt in kg (range)	71.3 (48–104)
No. (%) with underlying disease	
AML/MDS[a]	29 (71)
CLPD[b]	9 (22)
Other	3 (7)
No. (%) with donor type	
Related	25 (61)
Unrelated	16 (39)
Matched	33 (80)
Mismatched	8 (20)
No. (%) with conditioning regimen	
Myeloablative	12 (29)
Reduced intensity	29 (71)

[a] AML/MDS, acute myeloid leukemia/myelodysplastic syndrome.
[b] CLPD, chronic lymphoproliferative disease.

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TABLE 2 Impact of antifungal prophylaxis with posaconazole on the blood CsA level, dose adjustment, and concentration-to-dose ratio in allogeneic BMT recipients[a]

Time point	Blood CsA level (ng/ml)	*P* value	CsA dose (mg/kg/day)	*P* value	CsA level/dose ratio	*P* value
Day 0	225.8 ± 119.3 200 (85–598)	0.028[b]	3.09 ± 1.01 3.01 (1.32–5.17)	0.857[b]	82.1 ± 72.2 64.5 (26.6–449.6)	0.108[b]
Day 7	293.1 ± 150.9 256.0 (92–873)	0.478[c]	3.06 ± 1.10 3.01 (0.63–5.63)	0.082[c]	113.1 ± 90.5 83.5 (21.1–525.4)	0.158[c]
Day 14	304.9 ± 132.9 284.5 (72–719)	0.009[d]	2.61 ± 1.15 2.63 (0.63–5.63)	<0.001[d]	138.0 ± 80.3 114.7 (26.1–424.5)	0.072[d]
Day 30	245.8 ± 121.8 221.0 (89–702)	0.011[e]	1.58 ± 0.82 1.34 (0.53–4.50)	0.028[e]	172.6 ± 76.2 171.3 (64.5–375.4)	<0.001[e]

[a] Data are expressed in all cases as the mean ± standard deviation, median, and range. *P* values for changes across the study period were measured by one-way ANOVA, and those for comparisons between specific time points were measured with the Student *t* test for paired data.
[b] *P* value for the comparisons between days 0 and 7.
[c] *P* value for the comparisons between days 7 and 14.
[d] *P* value for the comparisons between days 14 and 30.
[e] *P* value for changes across the study period.

treatment), 7, 14, and 30 and at least three times weekly, except for clinical toxicity, which was evaluated daily. Whole-blood trough CsA levels were measured by an enzyme multiplied immunoassay technique (EMIT 2000 TDM; Siemens Healthcare Diagnostics) immediately before the morning dose. Comparisons used one-way analysis of variance (ANOVA) across multiple time points and the Student *t* test for paired data between specific target time points, with statistical significance accepted for $P < 0.05$. Statistical analysis was performed using SPSS software packages (version 17; IBM).

Our results confirm that posaconazole increases blood CsA levels in allo-BMT recipients ($P = 0.011$; Table 2) and also show that a significant effect can already be detected within the first week of combined treatment ($P = 0.028$). In keeping with this effect on blood CsA levels and on the basis of clinical criteria, the daily dose of CsA was adjusted during combined treatment from 3.09 ± 1.01 mg/kg at the baseline down to 1.58 ± 0.82 mg/kg on day 30 ($P = 0.028$), which represents an approximately 50% dose reduction. However, this CsA dose reduction was not clinically required upfront during the first week (3.06 ± 1.1 on day 7; $P = 0.857$) because it occurred normally by day 14 ($P = 0.082$) and most frequently in the last 2 weeks of combined treatment ($P < 0.001$). The clinical magnitude of this drug-drug interaction is best described by the CsA concentration-to-dose ratio (2), which shows a significant steady increase with time ($P < 0.001$). The blood posaconazole levels in this study are not available, and an association between blood posaconazole and CsA levels could not be analyzed. Our strategy was safe and well tolerated from a clinical perspective (Table 3). Only seven patients (17%) had CsA-related toxicities, including renal dysfunction ($n = 4$), hypertension ($n = 1$), essential tremor ($n = 1$), and mild thrombotic microangiopathy ($n = 1$), all of which resolved with dose adjustment, as planned.

Interactions among azoles and immunosuppressive drugs are important in the clinical management of transplant recipients. Since the approval of posaconazole in allo-BMT, increasing evidence has emerged on the effect of CsA and other drugs and factors on posaconazole pharmacokinetics (8, 20), as well as on the effect of posaconazole on the management of immunosuppressive drugs such as tacrolimus (2) and sirolimus (9, 13). However, very little is known about the impact of posaconazole on CsA. The original prescribing information recommendation to reduce the dose of CsA upon the initiation of combined treatment with posaconazole (17) results from a study of only four cardiac transplant recipients, three of whom required a CsA dose reduction because of important decreases in its clearance (16). The only report on the impact of posaconazole on CsA in allo-BMT comes in abstract format in a subset of 19 patients from the registration trial whose blood CsA level data were available, showing an increase in the CsA concentration-to-dose ratio after the start of posaconazole (10). Unfortunately, levels were assessed only twice, at the baseline and 2 weeks from the start of combined treatment, and neither earlier time points nor the need for upfront dose adjustment was analyzed. From 1988, when Yee et al. first reported a significant association between low trough CsA concentrations and the risk of developing acute GVHD the following week (19), it is well established that subtherapeutic CsA levels after allo-BMT have a negative impact on transplant outcome (5, 6, 11, 12, 14). In order to avoid such subtherapeutic CsA levels, even transiently, general practice developed to widely accept that in the absence of toxicity, high blood CsA levels up to twice the upper limit of the therapeutic range would not require a dose reduction (1). While CsA dose reduction might have less of an impact in patients with GVHD, who are concomitantly receiving high-dose steroids and other immunosuppressive drugs, in the early phase of allo-BMT, the achievement and maintenance of therapeutic blood CsA levels is critical to prevent GVHD.

To the best of our knowledge, this is the first study that analyzed the impact of posaconazole on the management of CsA in the early phase of allo-BMT. Our results confirm that posacona-

TABLE 3 Laboratory safety data on combined CsA and posaconazole treatment of allogeneic BMT recipients[a]

Time point	Bilirubin	ALT	AST	Creatinine
Day 0	1 (2.4); 16.7 ± 12.9, 12 (3–62)	2 (4.8); 0.85 ± 0.89, 0.48 (0.14–3.74)	1 (2.4); 0.64 ± 0.72, 0.43 (0.13–4.63)	0; 72 ± 20.5, 68 (42–124)
Day 7	0; 19.7 ± 10.8, 17 (3–41)	2 (4.8); 0.75 ± 0.79, 0.45 (0.11–3.77)	0; 0.45 ± 0.44, 0.34 (0.02–2.92)	0; 76 ± 30.7, 68 (41–202)
Day 14	3 (7.3); 22.4 ± 16.9, 17 (3–77)	1 (2.4); 0.85 ± 1.63, 0.47 (0.03–10.42)	0; 0.56 ± 0.53, 0.4 (0.04–2.85)	0; 82.5 ± 36.4, 79 (40–188)
Day 30	1 (2.4); 19.9 ± 12.0, 17 (5–56)	1 (2.4); 0.78 ± 0.81, 0.47 (0.09–4.69)	0; 0.56 ± 0.38, 0.43 (0.06–2.17)	0; 89.4 ± 27.5, 86 (44–180)

[a] Data are expressed both as the number (percentage) of cases with grade III to IV toxicity (CTCAE v3.0) and as the mean bilirubin (μmol/liter), alanine transaminase (ALT; μkat/liter), aspartate transaminase (AST; μkat/liter), or creatinine (μmol/liter) level ± the standard deviation and median (range) in all cases.

zole treatment leads to an increase in blood CsA levels and an overall 50% reduction in the dose of CsA over the course of a few weeks. While the potential risk derived from subtherapeutic CsA levels following an upfront reduction of the CsA dose may depend on the type of allo-BMT, the timing of the reduction, or the concomitant use of other immunosuppressive drugs, our data clearly show that an upfront CsA dose reduction is not required to manage these patients despite the significant increase in levels from the first week of combined treatment. In addition, since it is difficult to isolate and predict the independent effect on CsA levels of posaconazole from that of other drugs and factors in such complex patients, it would also appear more cautious not to automatically reduce the CsA dose in all cases upfront but rather let changes be guided by therapeutic drug monitoring. Our recommendation is to maintain CsA at the initiation of combined treatment with posaconazole and to subsequently adjust the CsA dose on the basis of individualized patient results of close monitoring of blood CsA levels a minimum of three times weekly and clinical toxicity. In our study, this strategy has been shown to be safe and effective in the early phase of allo-BMT.

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REFERENCES

1. Applebaum FR, Forman SJ, Negrin RS, Blume KG. 2009. Pharmacologic prevention of acute graft-versus-host disease, p 1257–1274. *In* Applebaum FR, Forman SJ, Negrin RS, Blume KG (ed), Thomas' hematopoietic cell transplantation, 4th ed. Blackwell Publishing, Ltd., Oxford, United Kingdom.
2. Berge M, et al. 2009. Safe management of tacrolimus together with posaconazole in lung transplant patients with cystic fibrosis. Ther. Drug Monit. 31:396–399.
3. Reference deleted.
4. Farowski F, Vehreschild JJ, Cornely OA. 2007. Posaconazole: a next-generation triazole antifungal. Future Microbiol. 2:231–243.
5. Ghalie R, Fitzsimmons WE, Weinstein A, Manson S, Kaizer H. 1994. Cyclosporine monitoring improves graft-versus-host disease prophylaxis after bone marrow transplantation. Ann. Pharmacother. 28:379–383.
6. Kanda Y, et al. 2006. Effect of blood cyclosporine concentration on the outcome of hematopoietic stem cell transplantation from an HLA-matched sibling donor. Am. J. Hematol. 81:838–844.
7. Keating GM. 2005. Posaconazole. Drugs 65:1553–1567.
8. Kohl V, et al. 2010. Factors influencing pharmacokinetics of prophylactic posaconazole in patients undergoing allogeneic stem cell transplantation. Antimicrob. Agents Chemother. 54:207–212.
9. Kubiak DW, et al. 2012. Safety of posaconazole and sirolimus coadministration in allogeneic hematopoietic stem cell transplants. Biol. Blood Marrow Transplant. 18:1462–1465.
10. Langston A, Lipton JH, Brundage T, Patinmo H, Ullmann AJ. 2007. Impact of posaconazole vs fluconazole on cyclosporine and tacrolimus dosing in hematopoietic stem cell transplant recipients with graft-versus-host disease. Biol. Blood Marrow Transplant. 13(Suppl. 2):76.
11. Malard F, et al. 2010. Impact of cyclosporine-A concentration on the incidence of severe acute graft-versus-host disease after allogeneic stem cell transplantation. Biol. Blood Marrow Transplant. 16:28–34.
12. Martin P, et al. 2003. Relationship between CsA trough blood concentration and severity of acute graft-versus-host disease after paediatric stem cell transplantation from matched-sibling or unrelated donors. Bone Marrow Transplant. 32:777–784.
13. Moton A, et al. 2009. Effects of oral posaconazole on the pharmacokinetics of sirolimus. Curr. Med. Res. Opin. 25:701–707.
14. Przepiorka D, et al. 1991. Cyclosporine and methylprednisolone after allogeneic marrow transplantation: association between low cyclosporine concentration and risk of acute graft-versus-host disease. Bone Marrow Transplant. 7:461–465.
15. Sánchez-Ortega I, et al. 2011. Clinical efficacy and safety of primary antifungal prophylaxis with posaconazole vs itraconazole in allogeneic blood and marrow transplantation. Bone Marrow Transplant. 46:733–739.
16. Sansone-Parsons A, et al. 2007. Effect of oral posaconazole on the pharmacokinetics of cyclosporine and tacrolimus. Pharmacotherapy 27:825–834.
17. Schering Corporation. 2008. Prescribing information for Noxafil (posaconazole) oral suspension. Schering Corporation, Kenilworth, NJ.
18. Ullmann AJ, et al. 2007. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N. Engl. J. Med. 356:335–347.
19. Yee GC, et al. 1988. Serum cyclosporine concentration and risk of acute graft-versus-host disease after allogeneic marrow transplantation. N. Engl. J. Med. 319:65–70.
20. Zhuang D, et al. 2008. Effect of calcineurin inhibitors on posaconazole blood levels as measured by the MVista microbiological assay. Antimicrob. Agents Chemother. 52:730–731.

DISCUSIÓN

La presente tesis se compone de dos manuscritos que evalúan el uso de Posaconazol como profilaxis antifúngica primaria en la fase precoz del alo-TPH, desde desde el punto de vista tanto de eficacia clínica y seguridad, como de manejo de la interacción con la CsA.

En el mansucrito 1 se describen los resultados del estudio clínico de eficacia y seguridad del uso de la profilaxis antifúngica con Posaconazol comparado con Itraconazol en la fase precoz del alo-TPH.

Desde Agosto de 2005 a Marzo de 2009 incluimos un total de 49 pacientes consecutivos receptores de un primer alo-TPH. A pesar de ser un estudio observacional, monocéntrico y no randomizado en el que los pacientes se incluyeron en dos grupos consecutivos en el tiempo (Agosto 2005-Mayo 2007 para Itraconazol y Junio 2007-Marzo 2009 para Posaconazol), las medidas de protección ambiental y aislamiento, así como la disponibilidad y frecuencia de exploraciones complementarias diagnósticas de IFI fueron similares para los dos periodos. Del mismo modo, a excepción del mayor uso de técnicas de depleción de células T en el grupo de Posaconazol (39% vs 0%; p=0.003), las características demográficas de los pacientes y del tipo de trasplante, fueron similares entre grupos.

En consistencia con los favorables resultados de los estudios de Posaconazol en profilaxis en pacientes hematológicos de alto riesgo, nuestros resultados muestran una menor incidencia de IFI (0% vs 12.5%) con mayor supervivencia libre de IFI (91%

vs 56%) y supervivencia global (91% vs 63%) en el grupo de Posaconazol en comparación con Itraconazol durante la fase precoz del alo-TPH. Como era esperable, no hubieron diferencias significativas en la incidencia de fiebre, fiebre persistente, duración de la fiebre, infecciones bacterianas o foco de infección. Asímismo, la incidencia de fallo de profilaxis, mantenimiento en profilaxis hasta el inicio de tratamiento empírico para estos pacientes y tiempo de exposición al antifúngico para todos los pacientes, fue similar para ambos grupos.

Itraconazol ha sido ampliamente testado, tanto en pacientes con neutropenia prolongada secundaria a quimioterapia intensiva como en el alo-TPH. A pesar de haber demostrado ser más efectivo que Fluconazol en la reducción de la incidencia y mortalidad por IFI, la persistente alta tasa de efectos secundarios, especialmente gastrointestinales, ha limitado su uso[114,117,118,176]. De forma similar, nuestros resultados muestran que a pesar de que el espectro de toxicidad global fue comparable entre grupos, y similar a los publicados en las grandes series, todos los pacientes de nuestro estudio en profilaxis con Itraconazol presentaron intolerancia a la administración en solución, precisando paso a administración intravenosa durante prácticamente todo el periodo de ingreso. Por el contrario, Posaconazol fue muy bien tolerado, con sólo un paciente requiriendo la suspensión de la profilaxis por toxicidad gastrointestinal en forma de diarreas.

La ausencia de una formulación intravenosa de Posaconazol ha sido motivo de preocupación a la hora de recomendar la administración del azol a pacientes con potencial toxicidad gastrointestinal secundaria a tratamiento quimioterápico o EICH. Sin embargo, la administración de Posaconazol a través de una sonda nasogástrica después de un suplemento nutricional ha demostrado ser una alternativa a la administración oral en voluntarios sanos[177] y en nuestro estudio pudo realizarse de

forma segura y con muy buena tolerancia en cinco pacientes que desarrollaron mucositis oral severa.

Desde la aprobación de Posaconazol, varios estudios han analizado el efecto de la CsA y otros factores sobre la farmacocinética del azol[142,178], así como el efecto de éste sobre el manejo de inmunosupresores como Tacrólimus[179] y Sirólimus[157,158]. Sin embargo, prácticamente no disponíamos de datos del impacto de Posaconazol sobre la CsA.

El efecto de Posaconazol sobre los niveles de CsA se analizó en un pequeño estudio de sólo cuatro trasplantes cardíacos en el que tres de ellos requirieron una reducción de un 14-29% de la dosis de CsA por disminución significativa de su aclaramiento[159]. Estos resultados determinaron que la ficha técnica de Posaconazol incluyera una recomendación de disminución de un 25% de la dosis total de CsA al inicio del tratamiento combinado[135]. Posteriormente, sólo una comunicación en forma de abstract analizó la interacción de Posaconazol sobre CsA en 19 receptores de un alo-TPH. A pesar de que observaron un incremento de la ratio de concentración/dosis de CsA tras el inicio del tratamiento combinado, los niveles de CsA sólo se determinaron al inicio y a los 14 días después de iniciar el tratamiento con Posaconazol, por lo que la falta de datos adicionales no permite analizar el grado de interacción ni la necesidad del ajuste de dosis de CsA antes del tratamiento combinado.

En el manuscrito 2 presentamos el primer estudio analizando el impacto de Posaconazol sobre el manejo de la CsA en el primer mes post alo-TPH. Nuestros resultados confirman que el tratamiento con Posaconazol conlleva un incremento de

los niveles de CsA en sangre y a una reducción global del 50% de la dosis de CsA tras 30 días de tratamiento combinado. Sin embargo, la reducción de la dosis de CsA no es necesaria al inicio del tratamiento combinado, sino hasta pasadas las dos primeras semanas.

En 1988, Yee et al[180] describieron por primera vez la asociación entre los niveles infraterapéuticos de CsA y el riesgo de desarrollo de EICH una semana después. Desde entonces, varios estudios han demostrado que la ocurrencia de niveles subterapéuticos de CsA, aunque sólo sea transitoriamente, tiene un impacto negativo en la incidencia y severidad de la EICH y de la evolución post-trasplante[181-185]. Por todo ello, el acuerdo general en la práctica clínica determina que en ausencia de toxicidad, niveles de CsA hasta dos veces por encima del limite terapéutico no deben conducir a una disminución de la dosis[186].

Además, los pacientes alotrasplantados con EICH habitualmente reciben tratamiento con CsA junto a altas dosis de corticoides y/o algún otro inmunosupresor, por lo que la potencial disminución de los niveles de CsA no tiene tanta trascendencia como en el post alo-TPH inmediato, donde la adquisición y mantenimiento de los niveles es imprescindible para una buena profilaxis de EICH y por lo tanto para el pronóstico y evolución del trasplante.

Los riesgos derivados del infratratamiento con CsA, tras la reducción de la dosis antes del inicio del tratamiento combinado con Posaconazol pueden depender del tipo de trasplante, del *timing* de la reducción o del uso concomitante de otros inmunosupresores. Sin embargo, nuestros datos muestran que a pesar del incremento significativo de sus niveles desde la primera semana del tratamiento combinado, no es necesario reducir la dosis de CsA antes de iniciar el tratamiento con Posaconazol.

Además, en la complejidad del paciente post trasplantado, es difícil separar y predecir el efecto que va a tener sobre la CsA, concretamente Posaconazol u otro factor o fármaco utilizado concomitantemente. Por ello, sería más prudente no reducir automáticamente la dosis de CsA en todos los pacientes, sino hacer los cambios guiados por la monitorización clínica y farmacológica. Nuestra recomendación es mantener la dosis de CsA al inicio del tratamiento combinado con Posaconazol y ajustarla posteriormente en función de una estricta monitorización de la toxicidad clínica y de los niveles en sangre. En nuestro estudio esta estrategia resultó segura y eficaz.

CONCLUSIONES

ANÁLISIS DE EFICACIA Y SEGURIDAD (Manuscrito 1)

- La profilaxis con Posaconazol reduce la incidencia de IFI y se asocia a una mejor supervivencia global y libre de infección fúngica en la fase precoz del alo-TPH en comparación con Itraconazol.

- Posaconazol se tolera bien y los efectos secundarios son mayoritariamente leves y similares a los descritos en los grandes ensayos clínicos y otras pequeñas series.

- A pesar de las limitaciones de un estudio observacional, no randomizado y monocéntrico, nuestros resultados determinan que además de para las dos indicaciones ya establecidas, Posaconazol puede ser eficaz y seguro en la fase precoz del trasplante alogénico.

ANÁLISIS DE LA INTERACCIÓN FARMACOLÓGICA CON CsA (Manuscrito 2)

- La dosis de CsA no debe disminuirse al inicio del tratamiento combinado con Posaconazol, sino que debe ajustarse en función de la monitorización de sus niveles y de la toxicidad.

- En el post trasplante inmediato esta estrategia ha demostrado ser eficaz y segura.

ANEXO 1

Presentamos un estudio como anexo o parte no fundamental de la presente tesis doctoral.

ANÁLISIS DE COSTE-EFECTIVIDAD (Anexo 1).

El presente estudio analiza el coste de la profilaxis con Posaconazol *versus* Itraconazol en la fase precoz del alo-TPH desde una perspectiva hospitalaria.

Los objetivos del estudio fueron :

- El análisis del coste global del alo-TPH hasta día +100 así como los subanálisis de costes de profilaxis antifúngica, uso de antifúngicos alternativos y uso de recursos hospitalarios.
- La ratio incremental de coste-efectividad (ICER) por IFI evitada y por año de vida ganado.

La población a estudio y los datos clínicos y de seguridad se obtuvieron del estudio clínico presentado previamente (manuscrito 1). El estudio incluyó costes totales de todos los pacientes desde una perspectiva hospitalaria[187], desde el ingreso inicial para el trasplante hasta el día +100 post alo-TPH, tanto en fase de ingreso hospitalario como de control ambulatorio. Los costes recogidos para cada paciente incluyeron el coste de día de hospitalización (según unidad de hospitalización), costes de visita en consultas, costes diagnósticos y de todas las pruebas complementarias (microbiológicas, radiológicas, laboratorio general, hematología especial,

interconsultas de especialistas, etc), costes de procedimientos especializados (broncoscopias, angioradiología, etc) y costes de medicación y tratamientos, con especial interés en el coste del tratamiento antifúngico, pero incluyendo también los costes de los productos sanguíneos transfundidos, acondicionamientos del trasplante, antimicrobianos, inmunosupresores, tratamientos sintomáticos, etc.

Es importante resaltar que este estudio no incluyó costes de seguimiento y manejo de los pacientes más allá del día +100 post alo-TPH y tampoco los costes derivados de la donación, colección y/o procesamiento de los progenitores hematopoyéticos para los donantes familiares, ni los correspondientes a la búsqueda y obtención de progenitores de donantes no emparentados o unidades de sangre de cordón umbilical.

El precio de las distintas unidades de coste se obtuvieron de la farmacia del centro y de otros servicios, de la base de datos del Consejo General del Colegio Oficial de Farmacia (www.portalfarma.com) y de la base de datos Soikos (Barcelona) y están todos expresados en Euros 2008.

En este estudio analizamos los costes del alo-TPH desde el ingreso para el trasplante y hasta día +100 sobre la población de pacientes del estudio clínico (manuscrito 1; 49 alo-TPH; 16 en profilaxis con Itraconazol y 33 en profilaxis con Posaconazol) y se obtuvieron lo siguientes **resultados:**

- El coste total del alo-TPH durante los primeros 100 días del procedimiento ascendió hasta una media de 46562.10 € para los pacientes que recibieron profilaxis con Posaconazol y 45079.80 € para los pacientes que recibieron profilaxis con Itraconazol.

- Los costes derivados de la hospitalización, tests de laboratorio y costes diagnósticos por paciente sobrepasaron los 30000 € en ambos grupos, pero fueron mayores para el grupo de Itraconazol (32690 € versus 31272 €).

- Los costes derivados del uso de antifúngicos alternativos también fueron mayores para el grupo de Itraconazol (7445 € vs 5914 €).

- El coste medio de la profilaxis antifúngica (Posaconazol o Itraconazol) por paciente fue mayor en el grupo de Posaconazol que en el de Itraconazol (9376 € vs 4944 €).

- La diferencia global en la media de costes del alo-TPH a día +100 fue de 1482 € mayor para el grupo de Posaconazol. Sin embargo, los pacientes en profilaxis con Posaconazol presentaron una incidencia de IFI significativamente menor (0 vs 12.5%) (manuscrito 1) que determinó una ratio de coste-efectividad por IFI evitada de 11856 € en favor de Posaconazol.

- Los pacientes en profilaxis con Posaconazol presentaron una mayor supervivencia global durante el periodo de estudio de 100 días post-TPH (63% versus 91%) (manuscrito 1), resultando en una ratio de coste-efectividad por año de vida ganado de 6534 € con el uso de Posaconazol.

Las IFI en el alo-TPH conllevan, además de altas tasas de mortalidad, un incremento en la duración del ingreso hospitalario y de los costes globales[188-190]. Por ello, tras analizar la eficacia clínica y seguridad de Posaconazol en la fase precoz del alo-TPH (manuscrito 1), realizamos un análisis de coste-efectividad del uso de profilaxis antifúngica primaria con Posaconazol *versus* Itraconazol en los 100 primeros días post alo-TPH.

Para poder analizar la contribución de la IFI sobre el coste global del procedimiento y determinar si el cambio en la estrategia de profilaxis desde Itraconazol a Posaconazol era coste-efectiva, incluimos en el análisis, no sólo los costes directamente relacionados con la profilaxis, diagnóstico y tratamiento de la IFI, sino también todos los posibles costes adicionales desde una perspectiva hospitalaria.

El coste farmacológico de la profilaxis con Posaconazol fue superior al de Itraconazol. Para el grupo de Itraconazol, el factor que influyó de manera más significativa en el aumento del coste de la profilaxis fue la necesidad de administrar el tratamiento vía intravenosa por intolerancia a la formulación oral. Sin embargo, para el grupo de Posaconazol, el factor que más incrementó el coste fue la buena tolerancia y eficacia clínica, que conllevó a una menor tasa de discontinuidad de la profilaxis y necesidad de tratamiento intravenoso.

Asímismo, los costes de hospitalización para el grupo de Itraconazol fueron mayores que para el grupo de Posaconazol, debido a que, a pesar de que el tiempo medio de hospitalización fue similar para ambos grupos, el uso, la duración y el coste total de la administración de tratamientos antifúngicos alternativos fue mayor para los pacientes en el grupo de Itraconazol.

La mayor incidencia de IFI en el grupo de Itraconazol (12.5% versus 0%) (manuscrito 1) determinó un incremento significativo en los costes derivados de los tratamientos antifúngicos alternativos y de hospitalización, tests diagnósticos y de laboratorio. Por todo ello, a pesar del menor coste farmacológico de Itraconazol, el mayor uso de recursos y tratamientos antifúngicos determinó que el uso de Itraconazol fuera globalmente sólo 1482 € menor a Posaconazol.

Los estudios realizados en diferentes países muestran que tanto en neutropenia prolongada tras quimioterapia intensiva para LAM/SMD como en el alo-TPH con EICH, el uso de Posaconazol en profilaxis es coste-efectivo comparado con Fluconazol e Itraconazol[191-196].

Los datos de nuestra serie muestran que el coste del trasplante alogénico a día +100 es comparable entre los pacientes que reciben profilaxis antifúngica con Posaconazol (46562 €) y con Itraconazol (45079 €). Sin embargo, la reducción en la incidencia de la IFI con Posaconazol y la mejor supervivencia de este grupo comparado con el grupo de Itraconazol, da lugar a un ratio incremental de coste-efectividad de 11856 € por IFI evitada. Debido a que este valor está por debajo del umbral de la recomendación para una estrategia de salud en España (30000 €), el uso de la profilaxis con Posaconazol en la fase precoz del alo-TPH resultó coste-efectiva.

Por todo ello, de nuestro estudio se conluye que:

- El uso de Posaconazol como profilaxis antifúngica primaria en la fase precoz del alo-TPH, incluyendo tanto la fase neutropénica como post-injerto y hasta día +100 es coste-efectiva, comparado con Itraconazol.

- A pesar de que el coste farmacológico de Posaconazol es mayor que el de Itraconazol, la mejoría en la eficacia y el menor uso de recursos tanto de exploraciones complementarias como de fármacos alternativos, conlleva que la ratio de coste-efectividad por IFI evitada sea favorable a Posaconazol.

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Brief report

Cost-effectiveness of primary antifungal prophylaxis with posaconazole versus itraconazole in allogeneic hematopoietic stem cell transplantation

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Abstract

Purpose:
To evaluate the cost-effectiveness of posaconazole vs itraconazole in the prevention of invasive fungal infections (IFIs) in recipients of allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Methods:
Total hospital-based costs from initial admission for allo-HSCT until day 100 after transplantation were evaluated for 49 patients in whom the clinical efficacy of antifungal prophylaxis with posaconazole vs itraconazole had been previously analyzed and reported. Clinical and economic data were used to determine the incremental costs per IFI avoided and per life-year gained for posaconazole compared with itraconazole. Confidence intervals for the incremental cost-effectiveness ratio (ICER) and a cost-effectiveness acceptability curve were estimated through bootstrapping with the bias-corrected percentile method.

Results:
According to our analysis, the total cost of allo-HSCT per patient during the 100-day fixed-treatment period was €46,562 in the posaconazole group ($n=33$) and €45,080 in the itraconazole group ($n=16$). However, the reduction in the incidence of IFI and the improved outcome with posaconazole resulted in a favorable ICER of €11,856 per IFI avoided and €5218 per life-year gained. With the outcomes of the bootstrap procedure, the cost-effectiveness acceptability curve was constructed. Assuming a threshold of €30,000 per life-year gained, the ICER based on life-years gained is acceptable with 75% certainty.

Limitations:
This evaluation is based on data from a single-center, non-randomized study. Preference weights or utilities were not available to calculate quality-adjusted life-years. Extra-mural costs were only partially evaluated from a hospital perspective. Indirect costs and economic consequences are not included.

Conclusions:
This economic evaluation compared direct medical costs associated with posaconazole or itraconazole treatment; the data suggest that posaconazole may be cost-effective as antifungal prophylaxis during the early high-risk neutropenic period and up to 100 days after allo-HSCT.

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Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has become a common procedure for patients with malignant and non-malignant hematologic disorders, causing a profound patient immune compromise and leading to a considerable risk and incidence of invasive fungal infection (IFI) in allo-HSCT recipients[1]. Early diagnosis of IFI is often difficult, and delays in diagnosis and treatment are associated with a mortality rate of 30–90%[2]. Furthermore, antifungal treatment of established IFI has a high failure rate (60–70%) among allo-HSCT recipients[3] and is associated with high healthcare costs (including antifungal therapy costs, costs of treating adverse events, and hospital resources)[4]. For these reasons, current guidelines recommend primary antifungal prophylaxis as a management strategy in high-risk patients with hematologic disorders[5].

Posaconazole is an oral, extended-spectrum triazole effective against *Candida* spp and moulds (including *Aspergillus* spp, the Zygomycetes, and *Fusarium*)[6]. In two large, prospective, randomized trials, primary prophylaxis with posaconazole was associated with fewer IFIs compared with standard azole therapy (fluconazole or itraconazole) in patients with neutropenia undergoing remission or induction chemotherapy for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) and in patients with graft-vs-host disease (GVHD) following allo-HSCT[7,8]. The clinical data reported on the former trials have been extensively used to perform several modeled cost-effectiveness analyses in different countries; the outcomes of these economic analyses suggest that prophylaxis with posaconazole is a dominant or cost-effective option compared with standard azole therapy in the approved indications, including GVHD after allo-HSCT[9–14]. Beyond GVHD, antifungal prophylaxis is also recommended during the early high-risk neutropenic phase and up to 100 days after allo-HSCT. Our group has recently published the first study suggesting that posaconazole antifungal prophylaxis, compared with itraconazole in the latter allo-HSCT clinical setting, might also reduce the incidence of IFI and improve IFI-free survival and overall survival[15]. Using clinical and safety data from this previous work, this study applied direct medical costs from a hospital perspective in Spain to conduct an economic evaluation to compare posaconazole with itraconazole as antifungal prophylaxis in allo-HSCT recipients.

Patients and methods

Patients

We conducted an observational study of adult patients (>18 years old) receiving antifungal prophylaxis for a first allo-HSCT between August 2005 and March 2009, at the Catalan Institute of Oncology, Hospital Duran i Reynals, Barcelona, Spain[15]. Until the end of May 2007, prophylaxis consisted of itraconazole administered either as an oral solution (200 mg twice daily) or intravenously (200 mg twice daily for 2 days, followed by 200 mg once daily), depending on patient tolerance. From June 2007 onwards, and based on new evidence available[7,8], our local antifungal policy committee, with representatives from the Hospital Pharmacy and the Departments of Haematology and Infectious Diseases, changed the recommended antifungal prophylaxis to posaconazole oral solution 200 mg 3-times daily. In addition to prolonged neutropenia and GVHD, posaconazole was adopted into our protocol for primary antifungal prophylaxis during the early phase of allo-HSCT in the absence of GVHD, with a commitment to prospectively audit this experience and to

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compare it with our previous experience with itraconazole in this particular clinical setting. Allo-HSCT antifungal prophylaxis in our center was administered, regardless of the antifungal agent used, to cover both the post-transplantation neutropenic phase and the early post-engraftment phase, up to 100 days after transplantation, and discontinued at this point in the absence of GVHD. This study included all consecutive adult recipients of a first allo-HSCT with no previous history of IFI who received primary antifungal prophylaxis during the study period. Both treatment groups had the same management algorithms[15].

Thirty-three allo-HSCT recipients (27 AML; 21 men; median age 48 [23–68]; 22 reduced intensity conditioning; 13 unrelated donor transplants with *in vivo* T-cell depletion) receiving posaconazole prophylaxis were compared with 16 itraconazole counterparts (eight AML; nine men; median age 46 [20–67]; six reduced intensity conditioning; two unrelated donor transplants). More patients receiving posaconazole were T-cell depleted (39% vs 0%; $p = 0.003$). Groups were otherwise comparable, in terms of patient and transplant characteristics and post-transplant complications including incidence of acute GVHD and cytomegalovirus reactivations (data not shown).

Clinical outcomes data

The clinical data required for the cost-effectiveness analysis, which consisted of the IFIs avoided and overall survival while patients received active prophylaxis, were obtained from our former observational study. The results of this study showed that patients receiving posaconazole had a reduced cumulative incidence of probable or proven IFI and an increased IFI-free survival and overall survival during the 100-day fixed prophylaxis period, compared with patients receiving itraconazole[15].

Resource use and costs

Data on total costs of in-patient and out-patient medical resource use from a hospital perspective were recorded[16]. The cost analysis does not include the cost derived from managing allogeneic donors and/or stem cell procurement or processing. All hospital-based costs were evaluated for every patient, starting from patient initial admission for allo-HSCT until day 100 after transplantation. Cost of hospital stay was included, taking into consideration whether the stay was in the general ward, the hematology transplant unit, or other special units such as the intensive care unit. Management of febrile neutropenia included chest radiography, urine and blood cultures, and combined empiric antibiotic treatment—namely, cefepime and amikacin—on the first day of neutropenic fever. Galactomannan enzyme immunoassay (Platelia® *Aspergillus* enzyme-linked immunosorbent assay; Bio-Rad Laboratories, Redmond, WA) was performed in peripheral blood samples twice weekly. High-resolution computed tomography (CT) of the thorax was performed when unexplained fever persisted for >72 h despite empiric antibiotic therapy or when any clinical signs or symptoms developed. In the case of radiologic chest abnormalities and no other microbiologic evidence, bronchoscopy with bronchoalveolar lavage (BAL) was performed whenever possible for microbiologic testing, including galactomannan detection. Additional blood, sputum, and other relevant samples were collected for culture from possibly infected sites when clinically indicated. Change of antifungal treatment in this real-life experience relied on clinical judgment individualized for each patient, taking into consideration signs and symptoms, diagnostic test results, and patient drug tolerance and adherence. Diagnostic costs included microbiology tests (BAL, galactomannan detection in serum or BAL, cytomegalovirus antigenemia, polymerase chain reaction, urine and blood cultures, and staining and culture of sputum), radiology tests (chest radiographs, high-resolution CT scans), general laboratory tests (complete blood count, biochemistry, coagulation screenings, cyclosporine level detection), and other diagnostic consultations and procedures (bronchoscopy, CT-guided biopsies, skin biopsies, other medical or surgical consultations). Treatment costs included all blood product transfusions; antibiotic, antiviral, and antifungal drug use; transplant conditioning regimens; other general drugs for symptom control; and other therapeutic surgical or medical procedures. Unit costs, expressed in 2008 euros, were obtained from the hospital pharmacy, the drug database of the General Council of the Official College of Pharmacists[17], and the Spanish Health Costs database[18]. Discounting does not apply to this study, given the short follow-up of patient management (maximum, 100 days after transplantation).

Economic and statistical analyses

In the original study, cumulative incidence of probable or proven IFI were compared between treatment groups using a Gray test[15]. Clinical and economic data were then used to determine the incremental costs per IFI avoided and per life-year gained with posaconazole compared with those associated with itraconazole. Confidence intervals (CIs) for the incremental costs per life-year gained were calculated using a bootstrap procedure with a bias-corrected percentile method[19]. In such a procedure, a random sample with replacement is taken from the original sample of patients, for both groups, with a size equal to the original sample size (i.e., 16 patients in the itraconazole group and 33 patients in the posaconazole group).

For such a bootstrap sample, the mean costs, effects, and incremental cost-effectiveness ratio (ICER) were calculated. This procedure was repeated 1000 times to assess the uncertainty surrounding the ICER. We chose to use the simple bias-corrected percentile method to adjust for any bias in the bootstrap distribution from which the CI limits would be taken. The bootstrapped ICERs and the CIs obtained with the bias-corrected percentile method were graphically represented on the cost-effectiveness plane.

With the outcomes of the bootstrap procedure, an acceptability curve was constructed. This curve shows for every threshold value the probability that the ICER is below that limit. Variations in cost or survival were included in the bootstrap estimates of the ICER. No sensitivity analysis was conducted.

Results

Clinical data

Table 1 presents clinical data from the study. There were no significant differences between groups in the incidence of fever or of persistent fever (>72 h) or in the percentage of patients maintaining their antifungal prophylaxis for the 100-day fixed period. The incidence of IFI was significantly higher in patients taking itraconazole than in those taking posaconazole (12.5% vs 0; $p=0.04$). Furthermore, IFI-free survival and overall survival were significantly greater for patients taking posaconazole than for those taking itraconazole (90.9% vs 56.3%, $p=0.003$; and 90.9% vs 62.5%, $p=0.011$, respectively).

Table 2 presents the incidence of grade III or IV antifungal drug toxicities, according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0[21]. Grade III or IV elevations in alkaline phosphatase, alanine transaminase, and bilirubin were similar between groups. There were more grade III or IV elevations in gamma-glutamyltransferase in the posaconazole group (e.g., 33.3% vs 12.5% at week 4). However, 21.2% of posaconazole patients had grade III or IV elevations in gamma-glutamyltransferase before antifungal treatment began, compared with 0 itraconazole patients. This may be related to a higher percentage of patients undergoing in vivo T-cell depletion with alemtuzumab or thymoglobulin for unrelated donor transplantation in the posaconazole group (39% vs 0; $p=0.003$)[15].

Cost of allogeneic HSCT per patient from a hospital perspective

Unit costs of healthcare resources considered in the cost-effectiveness analysis are shown in Table 3 in 2008 euros. Mean total cost of allo-HSCT per patient up to day 100 was €46,562.10 in the posaconazole group and €45,079.80 in the itraconazole group (Figure 1). Allo-HSCT hospitalization costs (including hospital stay, laboratory tests, and diagnostic tests) exceeded €30,000.

Table 1. Clinical data from observational study[15].

	Posaconazole ($n=33$)	Itraconazole ($n=16$)	p-value
Fever, n (%)	27 (81.8)	14 (87.5)	NS
Persistent fever (≥72 h), n (%)	8 (24.2)	5 (31.3)	NS
Prophylaxis maintenance for fixed 100-day period, n (%)	27 (81.8)	11 (68.8)	NS
Time, in days, to empiric therapy initiation, median (range)	23.5 (15–54)	10 (4–37)	NS
Incidence of proven/probable IFI,[a] n (%)	0 (0)	2 (12.5)	0.04
IFI-free survival, 100 days, n (%)	30 (90.9)	9 (56.3)	0.003
Overall survival, 100 days, n (%)	30 (90.9)	10 (62.5)	0.011

IFI, invasive fungal infection; NS, not significant.
[a]According to the 2008 criteria of the European Organization for Research and Treatment of Cancer (EORTC)[20].

Table 2. Incidence of grade III or IV[a] antifungal drug toxicities, n (%), from observational study[15].

Week	Posaconazole ($n=33$)				Itraconazole ($n=16$)			
	Bili	ALT	Alk Phos	GGT	Bili	ALT	Alk Phos	GGT
0	0	1 (3.0)	0	7 (21.2)	1 (6.1)	0	0	0
1	0	0	0	10 (30.3)	1 (6.1)	0	0	1 (6.1)
2	2 (6.1)	0	0	9 (27.3)	1 (6.1)	0	0	1 (6.1)
4	1 (3.0)	1 (3.0)	1 (3.0)	11 (33.3)	4 (25.0)	2 (12.5)	0	2 (12.5)
9	1 (3.0)	1 (3.0)	0	10 (30.3)	1 (6.1)	2 (12.5)	0	3 (18.8)
14	0	0	0	7 (21.2)	1 (6.1)	2 (12.5)	0	5 (31.3)

Alk Phos, alkaline phosphatase; ALT, alanine transaminase; Bili, bilirubin; GGT, gamma-glutamyltransferase.
[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0[21].

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The mean cost per patient associated with posaconazole and itraconazole as initial medication was higher for posaconazole (€9376 vs €4944). However, hospitalization costs per patient (including laboratory tests and diagnostic costs) were higher for itraconazole than for posaconazole (€32,690 vs €31,272), and the costs of other drugs were also higher for the itraconazole group than for the posaconazole group (€7445 vs €5914).

Table 3. Costs of healthcare resources considered in the cost-effectiveness analysis.

Healthcare resource	Cost, €[a]
Stay/day	
Hematology unit	456.37
Intensive care unit	1270.80
Imaging procedures	
X-ray examination	20.65
Ultrasonography	69.24
Computed tomography	174.22
Testing	
Biochemistry	14.73
Hemogram	13.42
Cerebrospinal fluid biochemistry	36.40
Fungus identification methods	
Blood culture	24.77
Sputum microculture	22.13
Stool culture	19.17
Urine culture	17.99
Galactomannan antigen detection (ELISA)	17.51
Other	
Blood smear from a central venous catheter	17.72
Bronchial aspiration	20.73
Cytomegalovirus detection	79.33
Packed red blood cell transfusion	97.46
Platelet transfusion	238.19

ELISA, enzyme-linked immunosorbent assay.
[a]2008 euro value.

Cost-effectiveness analysis

The difference in mean costs between the treatment arms was €1482 higher in the posaconazole group than in the itraconazole group because of the higher drug acquisition cost of posaconazole vs itraconazole. Nonetheless, posaconazole patients had a lower incidence of IFI than itraconazole patients (0 vs 12.5%)[15], which resulted in a cost-effectiveness ratio per IFI avoided with posaconazole of €11,856. Furthermore, patients receiving posaconazole had a higher overall survival during the 100-day fixed prophylaxis period than those receiving itraconazole (90% vs 62.5%)[15], resulting in a favorable cost-effectiveness ratio per life-year gained with posaconazole of €5218.

Figure 2 presents a cost-effectiveness acceptability curve; point estimates for ICERs, with the bias-corrected 95% CIs graphically presented on the cost-effectiveness plane with health effect expressed in life-years gained. Assuming a threshold of €30,000 per life-year gained, the ICER based on life-years gained is acceptable, with 75% certainty (Figure 2). The results of the bootstrap analysis are presented in Figure 3.

Discussion

Several studies have reported the cost-effectiveness of posaconazole in different patient populations using economic decision-analytic models with data derived from clinical trials[9–14]. One economic model developed to assess the cost-effectiveness of posaconazole vs standard azole therapy to prevent IFI was adapted by at least 11 countries[9]. The model showed that posaconazole was cost-saving or cost-effective vs fluconazole/itraconazole, with increases in life-years saved ranging from 0.016–0.1 years[9]. Our economic analysis explores a different clinical setting during the neutropenic period after allo-HSCT and

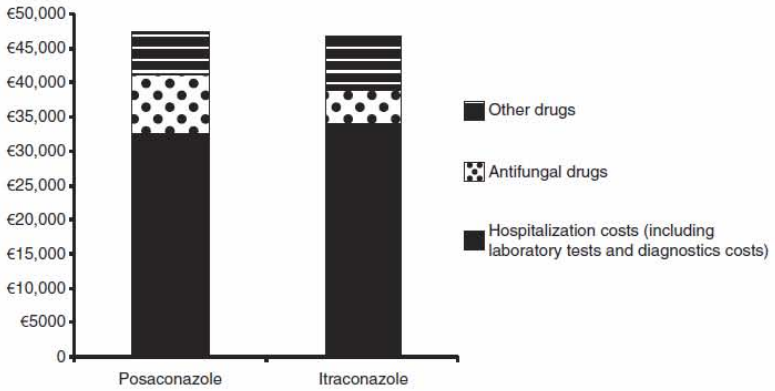

Figure 1. Total treatment costs (€) per patient up to 100 days after transplantation.

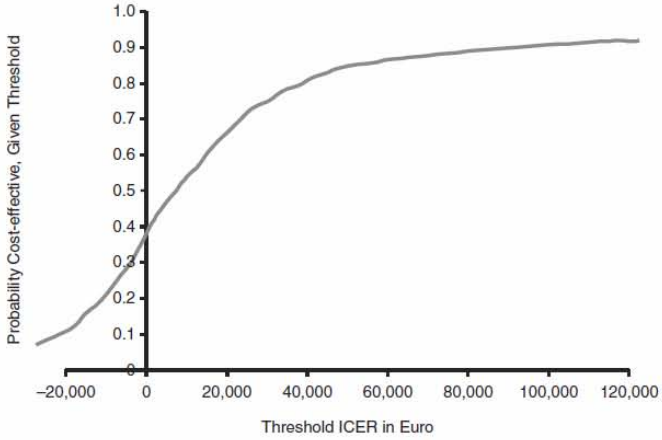

Figure 2. Acceptability curve presenting, for each possible threshold on the ICER, the probability that the ICER is acceptable. ICER indicates incremental cost-effectiveness ratio. Assuming a threshold of €30,000 per life-year gained, the ICER based on life-years gained is acceptable, with 75% certainty.

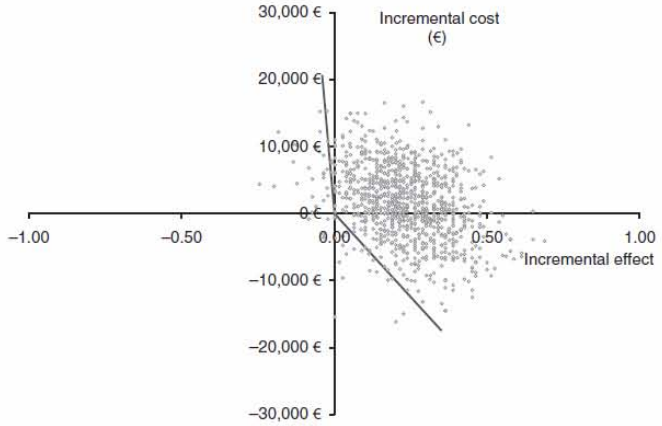

Figure 3. Representation of the uncertainty in differential mean costs and effectiveness showing 1000 bootstrap replications, with 95% bias-corrected confidence intervals.

the early post-engraftment phase up to 100 days after allo-HSCT, and for this it relies on a comprehensive direct data collection of total hospital costs from inpatient and outpatient medical resource use. It is well known that IFI increases the duration of the hospital stay and the overall cost[22,23]. For this reason, we included not only costs directly related to IFI prophylaxis, diagnosis, and treatment but also every possible additional cost from a hospital perspective in order to have an idea of the relative contribution of IFI to the overall cost of the procedure and whether the change in strategy makes the whole procedure cost-effective. It should be noted that our analysis did not include donor and allo-HSCT-derived costs.

The cost per patient associated with initial prophylaxis was higher for posaconazole than for itraconazole. For itraconazole, intolerance to the oral formulation was the major clinical outcome that most influenced therapeutic cost; for posaconazole, the major clinical outcome affecting cost was the rate of success among patients who did not discontinue because of prophylaxis failure or intolerance.

The total cost of alternative drugs was higher with itraconazole than with posaconazole. However,

hospitalization costs associated with the itraconazole group were higher than those associated with the posaconazole group because, although overall average durations of hospital stay in the posaconazole and itraconazole groups were similar, the duration of administration of high-cost alternative medication was longer in the itraconazole group than in the posaconazole group. Despite the lower treatment cost of itraconazole compared with posaconazole, the higher use of hospitalization resources and alternative drugs in the itraconazole group makes this alternative only €1482 less expensive per patient than the use of posaconazole as antifungal prophylaxis. In this study, posaconazole resulted in a favorable ICER of €11,856 per IFI avoided and €5218 per life-year gained. In previous cost-effectiveness analyses, prophylaxis with posaconazole was found to be cost-saving in most countries[9]. In Belgium and Germany, however, the cost per life-year saved was reported as €1173 and €6820, respectively[9]; as in this study, the incremental cost was well below the pre-determined cost-effectiveness thresholds for these countries.

From a clinical standpoint, initial therapy with posaconazole demonstrated longer overall survival, and reduction in IFI incidence. Reduction in IFI incidence has been previously reported with posaconazole prophylaxis. In two large, prospective, randomized trials of primary prophylaxis vs standard azole therapy (fluconazole or itraconazole), breakthrough IFI incidence was lower with posaconazole treatment in neutropenic patients undergoing remission or induction chemotherapy for AML or MDS (2.3% vs 8.4%; $p<0.001$)[7] and in patients with GVHD following allo-HSCT (2.4% vs 7.6%, $p=0.004$)[8].

Study limitations

This economic evaluation is based on data from a single-center, non-randomized study, and an ideal evaluation would be based on data from double-blinded randomized clinical trials, from which the most robust evidence of efficacy could be drawn. Nonetheless, such robust data from randomized clinical trials are not available for the early phase after allo-HSCT. Thus, the use of study data from Sánchez-Ortega *et al.*[15], despite it being on historical cohorts from a single center study with a small number of cases of IFI, reflects valuable real-life clinical practice. In addition to the small number of subjects, the treatment groups were unbalanced, with 33 patients in the posaconazole group vs 16 patients in the itraconazole group.

Ideally, the ICER is expressed as costs per quality-adjusted life-years (QALYs) gained. At the time of this study, however, no preference weights or utilities were available to calculate QALYs; therefore, we were not able to express the health effect in terms of QALYs gained.

Extra-mural costs were only partially evaluated from a hospital perspective, in terms of radiology CT scans and antifungal treatment provided by the hospital. Furthermore, this analysis leaves out indirect costs and economic consequences, such as productivity losses.

Costs were calculated in 2008 euros giving an ICER of €11,856 per IFI avoided and €5218 per life-year gained. However, when the costs were multiplied by the Spanish inflation index from 2008–2013[24] (~14%), the 2013 values would be €16,598 per IFI avoided and €9148 per life-year gained, which is still within the threshold of €30,000 per life-year gained.

Conclusions

Our single center observational study confirms the results of published modeled economic evaluations and offers additional data regarding the costs of the procedure and the cost-effectiveness of posaconazole. While our study had a very low number of breakthrough IFIs, our data suggest that posaconazole may be cost-effective as antifungal prophylaxis during the early high-risk neutropenic period and up to 100 days after allo-HSCT.

Transparency

Declaration of funding
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R.F.D. has received a grant from Schering-Plough; is a board member of Genzyme, Merck, Sanofi Oncology, and Schering-Plough; and has received payment for lectures/speaker bureaus from Amgen, Bristol Myers-Squibb, Celgene, Esteve, Genzyme, Gilead Sciences, Merck, Novartis, Pfizer, and Schering-Plough. The other authors declare no conflicts of interest.

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References

1. Richardson MD. Changing patterns and trends in systemic fungal infections. J Antimicrob Chemother 2005;56:i5–i11
2. Fukuda T, Boeckh M, Carter RA, et al. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. Blood 2003;102:827–33
3. Caggiano V, Weiss RV, Rickert TS, et al. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. Cancer 2005;103:1916–24

4. Jansen JP, Meis JF, Blijlevens NM, et al. Economic evaluation of voriconazole in the treatment of invasive aspergillosis in the Netherlands. Curr Med Res Opin 2005;21:1535–46
5. Maertens J, Marchetti O, Herbrecht R, et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3-2009 update. Bone Marrow Transplant 2011;46:709–18.
6. Keating GM. Posaconazole. Drugs 2005;65:1553–67
7. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007;356:348–59
8. Ullmann AJ, Lipton JH, Vesole DH, et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 2007;356:335–47
9. Papadopoulos G, Hunt S, Prasad M. Adapting a global cost-effectiveness model to local country requirements: posaconazole case study. J Med Econ 2013;16:374–80
10. Stam WB, O'Sullivan AK, Rijnders B, et al. Economic evaluation of posaconazole versus standard azole prophylaxis in high risk neutropenic patients in the Netherlands. Eur J Haematol 2008;81:467–74
11. Collins CD, Ellis JJ, Kaul DR. Comparative cost-effectiveness of posaconazole versus fluconazole or itraconazole prophylaxis in patients with prolonged neutropenia. Am J Health Syst Pharm 2008;65:2237–43
12. De la Camara R, Jarque I, Sanz MA, et al. Economic evaluation of posaconazole vs fluconazole in the prevention of invasive fungal infections in patients with GVHD following haematopoietic SCT. Bone Marrow Transplant 2010;45:925–32
13. Michallet M, Gangneux JP, Lafuma A, et al. Cost effectiveness of posaconazole in the prophylaxis of invasive fungal infections in acute leukaemia patients for the French healthcare system. J Med Econ 2011;14:28–35
14. Lyseng-Williamson KA. Posaconazole: a pharmacoeconomic review of its use in the prophylaxis of invasive fungal disease in immunocompromised hosts. PharmacoEconomics 2011;29:251–68
15. Sanchez-Ortega I, Patino B, Aman M, et al. Clinical efficacy and safety of primary antifungal prophylaxis with posaconazole vs itraconazole in allogeneic blood and marrow transplantation. Bone Marrow Transplant 2011;46:733–9
16. Drummond MF, O'Brien B, Stoddart GL, et al. Methods for the Economic Evaluation of Health Care Programmes, 2nd edn. New York, NY: Oxford University Press, 1997
17. Spanish General Council of Pharmacists (Consejo General de Colegios Oficiales de Farmaceuticos). Database of medicines. https://botplusweb.portalfarma.com/botplus.asp. Accessed July 27, 2011
18. Spanish Health Costs (CD-ROM database). Barcelona: Centre d'Estudis en Economia de la Salut de la Politica Socia, 2005. SOIKOS version 2.2
19. Campbell MK, Torgerson DJ. Bootstrapping: estimating confidence intervals for cost-effectiveness ratios. QJM 1999;92:177–82
20. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the 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) Consensus Group. Clin Infect Dis 2008;46:1813–21
21. National Cancer Institute. Common terminology criteria for adverse events (CTCAE), v3.0. 2006. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_30. Accessed
22. Menzin J, Meyers JL, Friedman M, et al. Mortality, length of hospitalization, and costs associated with invasive fungal infections in high-risk patients. Am J Health Syst Pharm 2009;66:1711–7
23. van Gool R. The cost of treating systemic fungal infections. Drugs 2001;61:49–56
24. Worldwide inflation data. http://www.inflation.eu/inflation-rates/spain/historic-inflation. Accessed March 7, 2013

BIBLIOGRAFÍA

1. Passweg JR, Baldomero H, Bregni M et al. Hematopoietic SCT in Europe: data and trends in 2011. Bone Marrow Transplant 2013; 48: 1161-7.

2. Passweg JR, Baldomero H, Gratwohl A, et al. The EBMT activity survey: 1990-2010. Bone Marrow Transplant 2012; 47: 906-23.

3. Yoshimi A, Suzuki R, Atsuta Y et al. Hematopoietic SCT activity in Asia: a report from the Asia-Pacific Blood and Marrow Transplantation Group. Bone Marrow Transplant 2010; 45: 1682-91.

4. Passweg JR, Baldomero H, Peters C et al. Hematopoietic SCT in Europe: data and trends in 2012 with special consideration of pediatric transplantation. Bone Marrow Transplant 2014. Mar 17. [Epub ahead of print]

5. Bacigalupo A, Ballen K, Rizzo D et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant 2009; 15: 1628-33

6. Sureda A, Robinson S, Canals C et al. Reduced-intensity conditioning compared with conventional allogeneic stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma: an analysis from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol 2008; 26: 455-62.

7. Valcárcel D, Martino R, Caballero D et al. Sustained remissions of high-risk acute myeloid leukemia and myelodysplastic syndrome after reduced-intensity conditioning allogeneic hematopoietic transplantation: chronic graft-versus-host disease is the strongest factor improving survival. J Clin Oncol 2008; 26: 577-84.

8. Bacigalupo A, Sormani MP, Lamparelli T et al. Reducing transplant-related mortality after allogeneic hematopoietic stem cell transplantation. Haematologica 2004; 89: 1238-47.

9. Barrett AJ, Savani BN. Stem cell transplantation with reduced-intensity conditioning regimens: a review of ten years experience with new transplant concepts and new therapeutic agents. Leukemia 2006; 20: 1661-72

10. Gratwohl A, Baldomero H, Passweg J et al. Increasing use of reduced intensity conditioning transplants: report of the 2001 EBMT activity survey. Bone Marrow Transplant 2002; 30: 813-31.

11. Upton A., Kirby KA, Carpenter P et al. Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality. Clin Infect Dis 2007; 44: 531-40.

12. Cordonnier C., Ribaud P, Herbrecht R, et al., Prognostic factors for death due to invasive aspergillosis after hematopoietic stem cell transplantation: a 1-year retrospective study of consecutive patients at French transplantation centers. Clin Infect Dis 2006; 42: 955-63

13. Marr, K.A., Carter, R.A., Crippa, F et al. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis 2002; 34: 909–1117.

14. Marr KA, Carter RA, Boeckh M et al. Invasive aspergillosis in allogeneic stem cell transplant recipients: changes in epidemiology and risk factors. Blood 2002; 100: 4358–66.

15. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatalit rate: systematic review of the literature. Clin Infect Dis 2001; 32: 358–66.

16. Ribaud P, Chastang C, Latgé JP et al. Survival and prognostic factors of invasive aspergillosis after allogeneic bone marrow transplantation. Clin Infect Dis 1999; 28: 322-30.

17. Robenshtok E, Gafter-Gvili A, Goldberg E et al. Antifungal prophylaxis in cancer patients after chemotherapy or hematopoietic stem cell transplantation: systematic review and meta-analysis. J Clin Oncol 2007; 25: 5471–89.

18. Cornely OA, Maertens J, Winston DJ et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007; 356: 348-59

19. Ullmann AJ, Lipton JH, Vesole DH et al. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 2007; 356: 335-47.

20. Gratwohl A, Brand R, Frassoni F et al. Cause of death after allogeneic haematopoietic stem cell transplantation (HSCT) in early leukaemias: an EBMT analysis of lethal infectious complications and changes over calendar time. Bone Marrow Transplant 2005; 36: 757-69.

21. Post MJ, Lass-Floerl C, Gastl G, Nachbaur D. Invasive fungal infections in allogeneic and autologous stem cell transplant recipients: a single center study of 166 transplanted patients. Transpl Infect Dis 2007; 9: 189–95.

22. Marr KA, Seidel K, Slavin MA et al. Prolonged fluconazole prophylaxis is associated with persistent protection against candidiasis-related death in allogeneic marrow transplant recipients: long-term follow-up of a randomized, placebo-controlled trial. Blood 2000; 96: 2055–61.

23. Marr KA, Seidel K, White TC et al. Candidemia in allogeneic blood and marrow transplant recipients: evolution of risk factors after the adoption of prophylactic fluconazole. J Infect Dis 2000; 181: 309–16.

24. Slavin MA, Osborne B, Adams R et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation – a prospective, randomized, double-blind study. J Infect Dis 1995; 171: 1545–52.

25. Goodman JL, Winston DJ, Greenfield RA et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N Engl J Med 1992; 326: 845–51

26. Kontoyiannis DP, Marr KA, Park BJ et al. Prospective surveillance for invasive fungal infections in hematopoietic stem cell transplant recipients, 2001-2006: overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database. Clin Infect Dis 2010; 50: 1091-100.

27. Neofytos D, Horn D, Anaissie E et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. Clin Infect Dis 2009; 48: 265-73.

28. Pagano L, Caira M, Nosari A et al. Fungal infections in recipients of hematopoietic stem cell transplants: results of the SEIFEM B-2004 study--Sorveglianza Epidemiologica Infezioni Fungine Nelle Emopatie Maligne. Clin Infect Dis 2007; 45: 1161-70.

29. Fukuda T, Boeckh M, Carter RA, et al. Risks and outcomes of invasive fungal infections in recipients of allogeneic hematopoietic stem cell transplants after nonmyeloablative conditioning. Blood 2003; 102: 827-33.

30. Martino R, Subirà M, Rovira M et al. Invasive fungal infections after allogeneic peripheral blood stem cell transplantation: incidence and risk factors in 395 patients. Br J Haematol 2002; 116: 475-82.

31. Parody R, Martino R, Sánchez F et al. Predicting survival in adults with invasive aspergillosis during therapy for hematological malignancies or after hematopoietic stem cell transplantation: single center analysis and validation of the Seattle, French and Strasbourg prognostic indexes. Am J Hematol 2009; 84: 571-8

32. Mikulska M, Raiola AM, Bruno B et al. Risk factors for invasive aspergillosis and related mortality in recipients of allogeneic SCT from alternative donors: an analysis of 306 patients. Bone Marrow Transplant 2009; 44: 361-70.

33. Lewis RE, Cahyame-Zuniga L, Leventakos K et al. Epidemiology and sites of involvement of invasive fungal infections in patients with haematological malignancies: a 20-year autopsy study. Mycoses 2013; 56: 638-45

34. Chamilos G, Luna M, Lewis RE et al. Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989-2003). Haematologica 2006; 91: 986-9.

35. Kradin RL, Mark EJ. The patology of pulmonary disorders due to *Aspergilllus* spp. Arch Pathol Lab Med 2008; 132: 606-14.

36. Hope WW, Walsh TJ, Denning DW. Laboratory diagnosis of invasive aspergillosis. Lancet Infect Dis 2005; 5: 609–22.

37. McCormick A, Loeffler J, Ebel F. Aspergillus fumigatus: contours of an opportunistic human pathogen. Cell Microbiol 2010; 12: 1535-43.

38. Mircescu MM., Lipuma L, van Rooijen N et al. Essential role for neutrophils but not alveolar macrophages at early time points following Aspergillus fumigatus infection. J Infect Dis 2009; 200: 647-56.

39. Shibuya K, Ando T, Hasegawa C, et al. Pathophysiology of pulmonary aspergillosis. J Infect Chemother 2004; 10: 138-45.

40. Ben-Ami R, Lewis RE, Kontoyiannis DP. Enemy of the (immunosuppressed) state: an update on the pathogenesis of Aspergillus fumigatus infection. Br J Haematol 2010; 150: 406-17.

41. Dagenais T.R. Keller NP. Pathogenesis of Aspergillus fumigatus in Invasive Aspergillosis. Clin Microbiol Rev 2009. 22:447-65.

42. Thursky K, Byrnes G, Grigg A et al. Risk factors for post-engraftment invasive aspergillosis in allogeneic stem cell transplantation. Bone Marrow Transplant 2004; 34: 115-21.

43. Lionakis, M. S. and D. A. Kontoyiannis. Glucocorticoids and invasive fungal infections. Lancet 2003; 362: 1828–38.

44. Pagano L, Akova M, Dimopoulos G et al. Risk assessment and prognostic for mould-related diseases in immunocompromised patients. J Antimicrob Chemother 2011; 66: Suppl 1 i5-14.

45. Kanda J, Kawabata H, Chao NJ. Iron overload and allogeneic hematopoietic stem-cell transplantation. Expert Rev Hematol 2011; 4: 71-80.

46. Mezger M, Einsele H, Loeffler J. Genetic susceptibility to infections with Aspergillus fumigatus. Crit Rev Microbiol 2010; 36: 168–77.

47. Sainz J., Hassan L., Perez E et al. Interleukin-10 promoter polymorphism as risk factor to develop invasive pulmonary aspergillosis. Immunology Letters 2007; 109: 76–82.

48. Altés A, Remacha AF, Sarda P et al. Frequent severe liver iron overload after stem cell transplantation and its possible association with invasive aspergillosis. Bone Marrow Transplant 2004; 34: 505–9

49. Bochud PY, Chien JW, Marr KA, et al. Toll-like receptor polymorphisms and aspergillosis in stem cell transplantation. N Engl J Med 2008; 359: 1766–77

50. Panackal AA, Li H, Kontoyiannis DP et al. Geoclimatic influences on invasive aspergillosis after hematopoietic stem cell transplantation. Clin Infect Dis 2010; 50: 1588–97.

51. Brenier-Pinchart MP, Lebeau B, Quesada JL et al. Influence of internal and outdoor factors on filamentous fungal flora in hematology wards. Am J Infect Control 2009; 37: 631–7.

52. Anaissie EJ, Stratton SL, Dignani MC et al. Pathogenic Aspergillus species recovered from a hospital water system:a 3-year prospective study. Clin Infect Dis 2002; 34: 780–9

53. Anaissie EJ, Stratton SL, Dignani MC, et al. Cleaning patient shower facilities: a novel approach to reducing patient exposure to aerosolized Aspergillus species and other opportunistic molds. Clin Infect Dis 2002; 35: E86–8.

54. Anaissie EJ, Stratton SL, Dignani MC, et al. Pathogenic molds (including Aspergillus species) in hospital water distribution systems: a 3-year prospective study and clinical implications for patients with hematologic malignancies. Blood 2003; 101: 2542–6.

55. Perfect JR, Cox GM, Lee JY et al. The impact of culture isolation of Aspergillus species: a hospital-based survey of aspergillosis. Clin Infect Dis 2001; 33: 1824–33.

56. Camps IR. Risk factors for invasive fungal infections in haematopoietic stem cell transplantation. Int J Antimicrob Agents 2008; 32 Suppl 2: S119-23.

57. Parody R, Martino R, Rovira M et al. Severe infections after unrelated donor allogeneic hematopoietic stem cell transplantation in adults: comparison of cord blood transplantation with peripheral blood and bone marrow transplantation. Biol Blood Marrow Transplant 2006; 12: 734–48.

58. Van Burik JA, Carter SL, Freifeld AG et al. Higher risk of cytomegalovirus and aspergillus infections in recipients of T cell-depleted unrelated bone marrow: analysis of infectious complications in patients treated with T cell depletion

versus immunosuppressive therapy to prevent graft-versus-host disease. Biol Blood Marrow Transplant 2007; 13: 1487-98

59. De Pauw B, Walsh TJ, Donnelly JP et al. Revised definitions of invasive fungal disease from the 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) Consensus Group. Clin Infect Dis 2008; 46: 1813–21.

60. Ascioglu S., Rex JH, de Paw B. et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002. 34: 7-14.

61. Borlenghi E, Cattaneo C, Capucci MA et al. Usefulness of the MSG/IFICG/EORTC diagnostic criteria of invasive pulmonary aspergillosis in the clinical management of patients with acute leukemia develop- ing pulmonary infiltrates. Ann Hematol 2007; 86: 205–10.

62. Subirà M, Martino R, Rovira M, Vázquez L, Serrano D, De la Cámara R. Clinical applicability of the new EORTC/MSG classification for invasive pulmonary aspergillosis in patients with hematological malignancies and autopsy-confirmed invasive aspergillosis. Ann Hematol 2003; 82: 80–2.

63. Cuenca-Estrella M, Bassetti M, Lass-Flörl C et al. Detection and investigation of invasive mould disease. J Antimicrob Chemother 2011; 66 Suppl 1: i15-24.

64. Platelia® Aspergillus EIA [prescribing information]. Hercules, CA: Bio-Rad Laboratories, 2006.

65. Wheat LJ, Walsh TJ. Diagnosis of invasive aspergillosis by galactomannan antigenemia detection using an enzyme immunoassay. Eur J Clin Microbiol Infect Dis 2008; 27: 245-51.

66. Marchetti O, Lamoth F, Mikulska M et al. ECIL recommendations for the use of biological markers for the diagnosis of invasive fungal diseases in leukemic patients and hematopoietic SCT recipients. Bone Marrow Transplant 2012; 47: 846-54.

67. Maertens J, Maertens V, Theunissen K et al. Bronchoalveolar lavage fluid galactomannan for the diagnosis of invasive pulmonary aspergillosis in patients with hematologic diseases. Clin Infect Dis 2009; 49: 1688–93.

68. Viscoli C, Machetti M, Gazzola P et al. Aspergillus galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. J Clin Microbiol 2002; 40: 1496–9.

69. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis 2006; 42: 1417–27.

70. Leeflang MM, Debets-Ossenkopp YJ, Visser CE, et al. Galactomannan detection for invasive aspergillosis in immunocompromized patients. Cochrane Database Syst Rev 2008: CD007394.

71. Marr KA, Laverdiere M, Gugel A et al. Antifungal therapy decreases sensitivity of the Aspergillus galactomannan enzyme immunoassay. Clin Infect Dis 2005; 40: 1762–9.

72. Cordonnier C, Botterel F, Ben Amor R et al. Correlation between galactomannan antigen levels in serum and neutrophil counts in haematological patients with invasive aspergillosis. Clin Microbiol Infect 2009; 15: 81–6.

73. Racil Z, Kocmanova I, Lengerova M et al. Intravenous Plasma-Lyte as a major cause of false-positive results of platelia Aspergillus test for galactomannan detection in serum. J Clin Microbiol 2007; 45: 3141–2

74. Aquino VR, Goldani LZ, Pasqualotto AC. Update on the contribution of galactomannan for the diagnosis of invasive aspergillosis. Mycopathologia 2007; 163: 191–202.

75. Mennink-Kersten MA, Klont RR, Warris A et al. Bifidobacterium lipoteichoic acid and false ELISA reactivity in aspergillus antigen detection. Lancet 2004; 363: 325–7.

76. Sánchez-Ortega I, Cuesta I, Patiño B et al. A prospective validation of the use of the serum galactomannan assay as part of a diagnostic strategy for high-risk hematology patients on posaconazole primary prophylaxis. 24th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID). Poster presentation. Barcelona, Spain, 10 – 13 May 2014.

77. Glucan Assay for (1,3)-b-d-Glucan in Serum: Fungitell®–Instructions for Use [prescribing information]. East Falmouth, MA: Associates of Cape Cod Incorporated, 2004.

78. Koo S, Bryar JM, Page JH et al. Diagnostic performance of the(1-3)-b-D-glucan assay for invasive fungal disease. Clin Infect Dis 2009; 49: 1650–9.

79. Senn L, Robinson JO, Schmidt S et al. 1,3-Beta-D-glucan antigenemia for early diagnosis of invasive fungal infections in neutropenic patients with acute leukemia. Clinical Infectious Diseases 2008; 46, 878–85.

80. Pickering JW, Sant HW, Bowles CA, Roberts WL, Woods GL. Evaluation of a (1—13)-beta-D-glucan assay for diagnosis of invasive fungal infections. J Clin Microbiol 2005; 43: 5957–62.

81. Donnelly JP. Polymerase chain reaction for diagnosing invasive aspergillosis: getting closer but still a ways to go. Clin Infect Dis 2006; 42: 487–9.

82. Walsh TJ, Anaissie EJ, Denning DW et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2008; 46: 327-60.

83. Greene RE, Schlamm HT, Oestmann JW et al. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. Clin Infect Dis 2007; 44: 373–9.

84. Gasparetto EL, Souza CA, Tazoniero P et al. Angioinvasive pulmonary aspergillosis after allogeneic bone marrow transplantation: clinical and high-resolution computed tomography findings in 12 cases. Braz J Infect Dis 2007; 11: 110–3.

85. Kojima R, Tateishi U, Kami M, et al. Chest computed tomography of late invasive aspergillosis after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 2005; 11: 506–11.

86. Georgiadou SP, Sipsas NV, Marom EM et al. The diagnostic value of halo and reversed halo signs for invasive mold infections in compromised hosts. Clin Infect Dis 2011; 52: 1144-55.

87. Franquet T, Müller NL, Giménez A et al. Spectrum of pulmonary aspergillosis: histologic, clinical and radiologic findings. Radiographics 2001; 21: 825-37

88. Ruiz-Camps I, Aguado JM, Almirante B et al. Guidelines for the prevention of invasive mould diseases caused by filamentous fungi by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). Clin Microbiol Infect 2011 Apr; 17 Suppl 2: 1-24.

89. Vonberg RP, Gastmeier P. Nosocomial aspergillosis in outbreak settings. J Hosp Infect 2006; 63: 246-54.

90. Hamadeh R, Ardehali A, Locksley RM et al. Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient. Chest 1988; 94: 432-3.

91. Anaissie EJ, Penzak SR, Dignani MC. The hospital water supply as a source of nosocomial infections: a plea for action. Arch Intern Med 2002; 162: 1483-92.

92. Warris A, Voss A, Abrahamsen TG et al. Contamination of hospital water with Aspergillus fumigatus and other molds. Clin Infect Dis 2002; 34: 1159–60.

93. Passweg JR, Rowlings PA, Atkinson KA et al. Influence of protective isolation on outcome of allogeneic bone marrow transplantation for leukemia. Bone Marrow Transplant 1998; 21: 1231-8.

94. Kumar R, Naithani R, Mishra P et al. Allogeneic hematopoietic SCT performed in non-HEPA filter rooms: initial experience from a single center in India. Bone Marrow Transplant 2009; 43: 115-9.

95. Eckmanns T, Rüden H, Gastmeier P. The influence of high-efficiency particulate air filtration on mortality and fungal infection among highly immunosuppressed patients: a systematic review. J Infect Dis 2006; 193: 1408–18.

96. Russell JA, Chaudhry A, Booth K et al. Early outcomes after allogeneic stem cell transplantation for leukemia and myelodysplasia without protective isolation: a 10-year experience. Biol Blood Marrow Transplant 2000; 6: 109-14.

97. Tablan OC, Anderson LJ, Besser R et al. Healthcare Infection Control Practices Advisory Committee. Guidelines for preventing health-care-associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR Recomm Rep 2004; 53: 1–36.

98. Maertens J, Marchetti O, Herbrecht R et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3--2009 update. Bone Marrow Transplant 2011; 46: 709-18.

99. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Cancer-Related Infections. V.2.2009. National Comprehensive Cancer Network Web site. Available at: http://www.nccn.org. Accessed January 26, 2010.

100. Cornely OA, Böhme A, Buchheidt D et al. Primary prophylaxis of invasive fungal infections in patients with hematologic malignancies. Recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. Haematologica 2009; 94: 113-22.

101. Penack O, Schwartz S, Martus P et al. Low-dose liposomal amphotericin B in the prevention of invasive fungal infections in patients with prolonged neutropenia: results from a randomized, single center trial. Ann Oncol 2006; 17: 1306–12.

102. Koh LP, Kurup A, Goh YT et al. Randomized trial of fluconazole versus low-dose amphotericin B in prophylaxis against fungal infections in patients undergoing hematopoietic stem cell transplantation. Am J Hematol 2002; 71: 260-7.

103. Wolff SN, Fay J, Stevens D, et al: Fluconazole vs low-dose amphotericin B for the prevention of fungal infections in patients undergoing bone marrow transplantation: A study of the North American Marrow Transplant Group. Bone Marrow Transplant 2000; 25: 853-9.

104. Kelsey SM, Goldman JM, McCann S et al. Liposomal amphotericin (Ambisome) in the prophylaxis of fungal infections in neutropenic patients: a randomised, double-blind, placebo-controlled study. Bone Marrow Transplant 1999; 23: 163–8.

105. Tollemar J, Ringden O, Andersson S et al. Randomized double-blind study of liposomal amphotericin B (Ambisome) prophylaxis of invasive fungal infections in bone marrow transplant recipients. Bone Marrow Transplant 1993; 12: 577–82.

106. Gubbins PO, Amsden JR, McConnell SA, et al. Pharmacokinetics and buccal mucosal concentrations of a 15 milligram per kilogram of bodyweight total dose of liposomal amphotericin B administered as a single dose (15 mg/kg), weekly dose (7.5 mg/kg), or daily dose (1 mg/kg) in peripheral stem cell transplant patients. Antimicrob Agents Chemother 2009; 53: 3664-74.

107. Cordonnier C, Mohty M, Faucher C et al. Safety of a weekly high dose of liposomal amphotericin B for pro- phylaxis of invasive fungal infection in immunocompromised patients: PROPHYSOME Study. Int J Antimicrob Agents 2008; 31: 135-41.

108. El-Cheikh J, Faucher C, Furst S, et al. High-dose weekly liposomal amphotericin B antifungal prophylaxis following reduced-intensity conditioning allogeneic stem cell transplantation. Bone Marrow Transplant 2007; 39: 301-6

109. Chaftari AM, Hachem RY, Ramos E et al. Comparison of posaconazole versus weekly amphotericin B lipid complex for the prevention of invasive fungal infections in hematopoietic stem-cell transplantation. Transplantation 2012; 94: 302-8.

110. Schwartz S, Behre G, Heinemann V, et al. Aerosolized amphotericin B inhalations as prophylaxis of invasive *Aspergillus* infections during prolonged neutropenia: results of a prospective randomized multicenter trial. Blood 1999; 93: 3654-61

111. Rijnders BJ, Cornelissen JJ, Slobbe L, et al. Aerosolized liposomal amphotericin B for the prevention of invasive pulmonary aspergillosis during prolonged neutropenia: a randomized, placebo-controlled trial. Clin Infect Dis 2008; 46: 1401-8.

112. Van Burik JA, Ratanatharathorn V, Stepan DE et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. Clin Infect Dis 2004; 39: 1407-16.

113. Hiramatsu, Y., Maeda, Y., Fujii, N et al. Use of micafungin versus fluconazole for antifungal prophylaxis in neutropenic patients receiving hematopoietic stem cell transplantation. Int J Hematol 2008 Dec; 88: 588-95.

114. Wang J, Zhan P, Zhou R et al. Prophylaxis with itraconazole is more effective than prophylaxis with fluconazole in neutropenic patients with hamatological malignancies: a meta-analysis of randomized-controlled trials. Med Oncol 2010; 27: 1082–8.

115. Glasmacher A, Cornely O, Ullmann AJ et al. An open-label randomized trial comparing itraconazole oral solution with fluconazole oral solution for primary prophylaxis of fungal infections in patients with haematological malignancy and profound neutropenia. J Antimicrob Chemother 2006; 57: 317-25.

116. Vardakas KZ, Michalopoulos A, Falagas ME. Fluconazole versus itraconazole for antifungal prophylaxis in neutropenic patients with haematological malignancies: a meta-analysis of randomised-controlled trials. Br J Haematol 2005; 131: 22-28.

117. Marr KA, Crippa F, Leisenring W, et al. Itraconazole versus fluconazol for prevention of fungal infections in patients receiving allogeneic stem cell transplants. Blood 2004; 103: 1527-33.

118. Winston DJ, Maziarz RT, Chandrasekar PH, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients. A multicenter, randomized trial. Ann Intern Med 2003; 138: 705-13.

119. Wingard JR, Carter SL, Walsh TJ et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. Blood 2010; 116: 5111-8.

120. Marks DI, Pagliuca A, Kibbler CC et al. Voriconazole versus itraconazole for antifungal prophylaxis following allogeneic haematopoietic stem cell transplantation. Br J Haematol 2011; 155: 318-27.

121. Frampton JE, Scott LJ. Posaconazole: a review of its use in the prophylaxis of invasive fungal infections. Drugs 2008; 68: 993–1016.

122. Duarte RF, López Jiménez J, Cornely OA et al. Phase 1B study of the pharmacokinetics and safety of Posaconazole Solid oral tablet in patients at risk for invasive fungal infections. 52nd ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy) Poster A1934. September 9-12, 2012.

123. Maertens J et al. Phase 1B study of the pharmacokinetics and safety of Posaconazole IV in patients at risk for invasive fungal infections. 52nd ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy) Poster A 1946a. September 9-12, 2012.

124. Krishna G, Ma L, Martinho M et al. A new solid oral tablet formulation of posaconazole: a randomized clinical trial to investigate rising single and multiple dose pharmacokinetics and safety in healthy volunteers. J Antimicrob Chemother 2012; 67: 2725-30

125. Krishna G, Ma L, Martinho M et al. Single-dose phase I study to evaluate the pharmacokinetics of posaconazole in new tablet and capsule formulations relative to oral suspension. Antimicrob Agents Chemother 2012; 56: 4196-201

126. Cornely OA, Duarte RF, Haider S et al. Phase 3 Pharmacokinetics (PK) and safety study of posaconazole (POS) tablet in oatients at risk for invasive fungal infection. 23rd ECCMID from the European society of clinical microbiology and infectious diseases. Poster presentation. Berlin, Germany 28 april 2013.

127. Raad II, Graybill JR, Bustamante AB et al. Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections. Clin Infect Dis 2006; 42: 1726–34

128. Courtney R, Pai S, Laughlin M, et al. Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults. Antimicrob Agents Chemother 2003; 47: 2788–95.

129. Courtney R, Radwanski E, Lim J et al. Pharmacokinetics of posaconazole coadministered with antacid in fasting or non fasting healthy men. Antimicrob Agents Chemother 2004; 48: 804–8.

130. Courtney R, Wexler D, Radwanski E, et al. Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults. Br J Clin Pharmacol 2004; 57: 218–22.

131. Krishna G, Moton A, Ma L et al. Pharmacokinetics and absorption of posaconazole oral suspension under various gastric conditions in healthy volunteers. Antimicrob Agents Chemother 2009; 53: 958-66.

132. Ezzet F, Wexler D, Courtney R et al. Oral bioavailability of posaconazole in fasted healthy subjects: comparison between three regimens and basis for clinical dosage recommendations. Clin Pharmacokinet 2005; 44: 211-20.

133. Sansone-Parsons A, Krishna G, Calzetta A, et al. Effect of a nutritional supplement on posaconazole pharmacokinetics following oral administration to healthy volunteers. Antimicrob Agents Chemother 2006; 50: 1881–3.

134. Li Y, Theuretzbacher U, Clancy et al. Pharmacokinetic/pharmacodynamic profile of posaconazole. Clin Pharmacokinet 2010; 49: 379-96.

135. Schering Corporation. 2008. Prescribing information for Noxafil (posaconazole) oral suspension. Schering Corporation, Kenilworth, NJ.

136. Farowski F, Cornely OA, Vehreschild JJ et al. Intracellular concentrations of posaconazole in different compartments of peripheral blood. Antimicrob Agents Chemother 2010; 54: 2928-31.

137. Conte JE, Jr, Golden JA, Krishna G et al. Intrapulmonary pharmacokinetics and pharmacodynamics of posaconazole at steady state in healthy subjects. Antimicrob Agents Chemother 2008; 53: 703–7.

138. Campoli P, Al Abdallah Q, Robitaille R et al. Concentration of antifungal agents within host cell membranes: a new paradigm governing the efficacy of prophylaxis. Antimicrob Agents Chemother 2011; 55: 5732-9.

139. Sheppard DC, Campoli P, Duarte RF. Understanding antifungal prophylaxis with posaconazole in hematology patients: an evolving bedside to bench story. Haematologica 2014; 99(4).

140. Ghosal A, Hapangama N, Yuan Y, et al. Identification of human UDP glucuronosyltransferase enzyme(s) responsible for the glucuronidation of posaconazole (Noxafil). Drug Metab Dispos 2004; 32: 267–71.

141. Krieter P, Flannery B, Musick T et al. Disposition of posaconazole following single-dose oral administration in healthy subjects. Antimicrob Agents Chemother 2004; 48: 3543–51.

142. Kohl V, Müller C, Cornely OA et al. Factors influencing pharmacokinetics of prophylactic posaconazole in patients undergoing allogeneic stem cell transplantation. Antimicrob Agents Chemother 2010; 54: 207-12.

143. Alffenaar JW, van Assen S, van der Werf TS et al. Omeprazole significantly reduces posaconazole serum trough level. Clin Infect Dis 2009; 48: 839.

144. Krishna G, Martinho M, Chandrasekar P et al. Pharmacokinetics of oral posaconazole in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease. Pharmacotherapy 2007; 27: 1627–36.

145. Wexler D, Courtney R, Richards W et al. Effect of posaconazole on cytochrome P450 enzymes: a randomized, open-label, two-way crossover study. Eur J Pharm Sci 2004; 21: 645-53.

146. Schiller DS, Fung HB. Posaconazole: an extended-spectrum triazole antifungal agent. Clin Ther 2007; 29: 1862–86.

147. Lass-Flörl C. Triazole antifungal agents in invasive fungal infections: a comparative review. Drugs 2011; 71: 2405-19.

148. Moton A, Krishna G, Ma L et al. Pharmacokinetics of a single dose of the antifungal posaconazole as oral suspension in subjects with hepatic impairment. Curr Med Res Opin 2010; 26: 1-7.

149. Hachem RY, Langston AA, Graybill JR et al. Posaconazole as salvage treatment of invasive fungal infections in patients with underlying renal impairment. J Antimicrob Chemother 2008; 62: 1386-91

150. Courtney R, Sansone A, Smith W et al. Posaconazole pharmacokinetics, safety, and tolerability in subjects with varying degrees of chronic renal disease. J Clin Pharmacol 2005; 45: 185-92.

151. Sandherr M, Maschmeyer G. Pharmacology and metabolism of voriconazole and Posaconazole in the treatment of invasive aspergillosis: review of the literature. Eur J Med Res 2011; 16: 139-44.

152. Neofytos D, Avdic E, Magiorakos AP. Clinical safety and tolerability issues in use of triazole derivatives in management of fungal infections. Drug Healthc Patient Saf 2010; 2: 27-38.

153. Krishna G, Sansone-Parsons A, Kantesaria B. Drug interaction assessment following concomitant administration of posaconazole and phenytoin in healthy men. Curr Med Res Opin 2007; 23: 1415–22.

154. Krishna G, Parsons A, Kantesaria B, Mant T. Evaluation of the pharmacokinetics of posaconazole and rifabutin following co-administration to healthy men. Curr Med Res Opin 2007; 23: 545–52.

155. Krishna G, Moton A, Ma L, Savant I et al. Effects of oral posaconazole on the pharmacokinetic properties of oral and intravenous midazolam: a phase I, randomized, open-label, crossover study in healthy volunteers. Clin Ther 2009; 31: 286–98

156. Krishna G, Ma L, Prasad P et al. Effect of posaconazole on the pharmacokinetics of simvastatin and midazolam in healthy volunteers. Expert Opin Drug Metab Toxicol 2012; 8: 1-10.

157. Moton A, Ma L, Krishna G, Martinho M et al. Effects of oral posaconazole on the pharmacokinetics of sirolimus. Curr Med Res Opin 2009; 25: 701–7.

158. Kubiak DW, Koo S, Hammond SP et al. Safety of posaconazole and sirolimus coadministration in allogeneic hematopoietic stem cell transplants. Biol Blood Marrow Transplant 2012; 18: 1462-5.

159. Sansone-Parsons A, Krishna G, Martinho M et al. Effect of oral posaconazole on the pharmacokinetics of cyclosporine and tacrolimus. Pharmacotherapy 2007; 27: 825–34.

160. Ruutu T, Gratwohl A, de Witte T et al. Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standarized practice. Bone Marrow Transplant 2014; 49: 168-73.

161. Powles RL, Barrett AJ, Clink H et al. Cyclosporin A for the treatment of graft-versus-host disease in man. Lancet 1978; 2: 1327–31.

162. Storb R, Deeg HJ, Whitehead J, et al. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft versus host disease after marrow transplantation for leukemia. N Engl J Med 1986; 314: 729–35.

163. Storb R, Deeg HJ, Farewell V et al. Marrow transplantation for severe aplastic anemia: methotrexate alone compared with a combination of methotrexate and cyclosporine for prevention of acute graft- versus-host disease. Blood 1986; 68: 119–25.

164. Sorror ML, Leisenring W, Deeg HJ et al. Twenty-year follow-up of a controlled trial comparing a combination of methotrexate plus cyclosporine with cyclosporine alone for prophylaxis of graft-versus-host disease in patients administered HLA-identical marrow grafts for leukemia. Biology Blood Marrow Transplant 2005; 11: 814-5.

165. Sorror ML, Leisenring W, Deeg HJ et al. Re: Twenty-year follow-up in patients with aplastic anemia given marrow grafts from HLA-identical siblings and randomized to receive methotrexate/cyclosporine or methotrexate alone for prevention of graft-versus-host disease. Biol Blood Marrow Transplant 2005; 11: 567–8.

166. Pagano L, Caira M, Cuenca-Estrella M. The management of febrile neutropenia in the posaconazole era: a new challenge? Haematologica 2012; 97: 963-5

167. Michallet M, Sobh M, Morisset S, Kraghel S, Nicolini FE, Thomas X, Bienvenu AL, Picot S, Nicolle MC, Vanhems P. Risk factors for invasive aspergillosis in acute myeloid leukemia patients prophylactically treated with posaconazole. Med Mycol 2011; 49: 681-7.

168. Candoni A, Simeone E, Caira Mm, Mazzuzzo M, Fanin R, Pagano L. Prophylaxis of invasive fungal diseases with posaconazole in acute myeloid leukemia. A real life experience. Abstract O804 at 16th EHA (European Hematology Association) Congress, June 11, 2011.

169. Lerolle N, Lafaurie M, Touratier S et al. Breakthrough invasive fungal infections in patients with haematological cancers receiving posaconazole prophylaxis: a four-year study. Abstract M-1521 ICAAC, Chicago, Sept 2011.

170. Egerer G, Geist MJ. Posaconazole prophylaxis in patients with acute myelogenous leukaemia--results from an observational study. Mycoses 2011; 54 Suppl 1: 7-11.

171. Vehreschild JJ, Rüping MJ, Wisplinghoff H et al. Clinical effectiveness of posaconazole prophylaxis in patients with acute myelogenous leukaemia (AML): a 6 year experience of the Cologne AML cohort. J Antimicrob Chemother 2010; 65: 1466-71.

172. Hahn J, Stifel F, Reichle A, Holler E, Andreesen R. Clinical experience with posaconazole prophylaxis--a retrospective analysis in a haematological unit. Mycoses 2011; 54 Suppl 1: 12-6.

173. Busca A, Frairia C, Marmont F et al. Posaconazole vs standard azoles for prevention of invasive fungal infections in patients with acute myeloid leukemia. Poster 088 at 5th TIMM (Trends in Medical Micology) Congress, Valencia, Oct 2-5, 2011.

174. Ananda-Rajah MR, Grigg A, Downey MT et al. Comparative clinical effectiveness of prophylactic voriconazole / posaconazole to fluconazole / itraconazole in patients with acute myeloid leukemia/myelodysplastic syndrome undergoing cytotoxic chemotherapy over a 12-year period. Haematologica 2012; 97: 459-63.

175. Labopin M, Iacobelli S. Statistical Guidelines for EBMT. 2003, pp 1–24.

176. Glasmacher A, Prentice A, Gorschluter M et al. Itraconazole prevents invasive fungal infections in neutropenic patients treated for hematologic malignancies: evidence from a meta-analysis of 3,597 patients. J Clin Oncol 2003; 21: 4615–26.

177. Dodds Ashley ES, Varkey JB, Krishna G et al. Pharmacokinetics of posaconazole administered orally or by nasogastric tube in healthy volunteers. Antimicrob Agents Chemother 2009; 53: 2960–4.

178. Zhuang D, Smedema M, Lemonte A et al. Effect of calcineurin inhibitors on posaconazole blood levels as measured by the MVista microbiological assay. Antimicrob Agents Chemother 2008; 52: 730-1.

179. Berge M, Chevalier P, Benammar M et al. Safe management of tacrolimus together with posaconazole in lung transplant patients with cystic fibrosis. Ther Drug Monit 2009; 31: 396-9.

180. Yee GC, Self SG, McGuire TR et al. Serum cyclosporine concentration and risk of acute graft-versus-host disease after allogeneic marrow transplantation. N Engl J Med 1988; 319: 65–70.

181. Ghalie R, Fitzsimmons WE, Weinstein A et al. Cyclosporine monitoring improves graft-versus-host disease prophylaxis after bone marrow transplantation. Ann Pharmacother 1994; 28: 379-83.

182. Kanda Y, Hyo R, Yamashita T et al. Effect of blood cyclosporine concentration on the outcome of hematopoietic stem cell transplantation from an HLA-matched sibling donor. Am J Hematol 2006; 81: 838-44.

183. Malard F, Szydlo RM, Brissot E et al. Impact of cyclosporine-A concentration on the incidence of severe acute graft-versus-host disease after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2010; 16: 28-34.

184. Martin P, Bleyzac N, Souillet G et al. Relationship between CsA trough blood concentration and severity of acute graft-versus-host disease after paediatric stem cell transplantation from matched sibling or unrelated donors. Bone Marrow Transplant 2003; 32: 777-84.

185. Przepiorka D, Shapiro S, Schwinghammer TL et al. Cyclosporine and methylprednisolone after allogeneic marrow transplantation: association between low cyclosporine concentration and risk of acute graft-versus-host disease. Bone Marrow Transplant 1991; 7: 461-5.

186. Appelbaum FR, Forman SJ, Negrin RS, et al. Pharmacologic prevention of acute graft-versus-host disease, 2009; 1257-74. In Applebaum FR, Forman SJ, Negrin RS, Blume KG (ed), Thomas' Hematopoietic Cell Transplantation, 4th ed, Blackwell Publishing.

187. Drummond MF, O'Brien B, Stoddart GL, et al. Methods for the Economic Evaluation of Health Care Programmes, 2nd edn. New York, NY: Oxford University Press, 1997

188. Menzin J, Meyers JL, Friedman M, et al. Mortality, length of hospitalization, and costs associated with invasive fungal infections in high-risk patients. Am J Health Syst Pharm 2009; 66: 1711-7

189. Van Gool R. The cost of treating systemic fungal infections. Drugs 2001; 61: 49-56

190. Jansen JP, Meis JF, Blijlevens NM et al. Economic evaluation of voriconazole in the treatment of invasive aspergillosis in the Netherlands. Curr Med Res Opin 2005; 21: 1535-46

191. Jansen JP, O'Sullivan AK, Lugtenburg E, et al. Economic evaluation of posaconazole versus fluconazole prophylaxis in patients with graft-versus-host disease (GVHD) in the Netherlands. Ann Hematol 2010; 89: 919-26

192. Stam WB, O'Sullivan AK, Rijnders B, et al. Economic evaluation of posaconazole versus standard azole prophylaxis in high risk neutropenic patients in the Netherlands. Eur J Haematol 2008; 81: 467-74

193. Collins CD, Ellis JJ, Kaul DR. Comparative cost-effectiveness of posaconazole versus fluconazole or itraconazole prophylaxis in patients with prolonged neutropenia. Am J Health Syst Pharm 2008; 65: 2237-43

194. De la Camara R, Jarque I, Sanz MA, et al. Economic evaluation of posaconazole vs fluconazole in the prevention of invasive fungal infections in patients with GVHD following haematopoietic SCT. Bone Marrow Transplant 2010; 45: 925-32

195. Michallet M, Gangneux JP, Lafuma A, et al. Cost effectiveness of posaconazole in the prophylaxis of invasive fungal infections in acute leukaemia patients for the French healthcare system. J Med Econ 2011; 14: 28-35

196. Lyseng-Williamson KA. Posaconazole: a pharmacoeconomic review of its use in the prophylaxis of invasive fungal disease in immunocompromised hosts. Pharmaco Economics 2011; 29: 251-68