

RECOMENDACIÓN 4

BÚSQUEDA Y SÍNTESIS DE EVIDENCIA DE EFECTOS DESEABLES E INDESEABLES Guía de Práctica Clínica Influenza - 2018

A. PREGUNTA CLÍNICA

En personas adultas con sospecha o diagnóstico de influenza hospitalizado ¿Se debe usar oseltamivir en comparación a no usar?

Análisis y definición de los componentes de la pregunta en formato PICO

Población: Personas adultas con sospecha o diagnóstico de influenza hospitalizado.

Intervención: Oseltamivir.

Comparación: No usar.

Desenlace (outcome): Mortalidad, neumonía, náuseas y vómitos.

B. BÚSQUEDA DE EVIDENCIA

Se realizó una búsqueda general de revisiones sistemáticas asociadas al tema de “Influenza”. Las bases de datos utilizadas fueron: Cochrane database of systematic reviews (CDSR); Database of Abstracts of Reviews of Effectiveness (DARE); HTA Database; PubMed; LILACS; CINAHL; PsycINFO; EMBASE; EPPI-Centre Evidence Library; 3ie Systematic Reviews and Policy Briefs Campbell Library; Clinical Evidence; SUPPORT Summaries; WHO institutional Repository for information Sharing; NICE public health guidelines and systematic reviews; ACP Journal Club; Evidencias en Pediatría; y The JBI Database of Systematic Reviews and implementation Reports. No se aplicaron restricciones en base al idioma o estado de publicación. Dos revisores de manera independiente realizaron la selección de los títulos y los resúmenes, la evaluación del texto completo y la extracción de datos. Un investigador experimentado resolvió cualquier discrepancia entre los distintos revisores. En caso de considerarse necesario, se integraron estudios primarios.¹

Seleccionadas las revisiones sistemáticas o estudios primarios asociados a la temática, se clasificaron en función de las potenciales preguntas a las que daban respuesta. Al momento de definir la pregunta, la evidencia ya se encontraba previamente clasificada según intervenciones comparadas. Los resultados se encuentran alojados en la plataforma Living Overview of the Evidence (L·OVE), sistema que permite la actualización periódica de la evidencia.

¹ Para revisar la metodología, las estrategias y los resultados de la búsqueda, favor revisar el informe “Búsqueda sistemática de evidencia de los efectos deseables e indeseables” en la sección de método de la Guía de Práctica Clínica respectiva.

C. SÍNTESIS DE EVIDENCIA

Resumen de la evidencia identificada

Se identificaron 33 revisiones sistemáticas que incluyeron 376 estudios primarios, de los cuales 85 corresponden a ensayos aleatorizados. Para más detalle ver “*Matriz de evidencia*”², en el siguiente enlace: [Inhibidores de neuraminidasa para influenza](#).

Tabla 1: Resumen de la evidencia seleccionada

Revisión Sistemática	33 [1-33].
Estudios primarios	85 ensayos aleatorizados [34-118], 291 observacionales [119-409].

Estimador del efecto

Se realizó un análisis de la matriz de evidencia, sin identificar revisiones que hayan analizado la población de interés (hospitalizados), ya sea de manera directa o a través de análisis de subgrupo. Con el fin de informar la decisión de manera indirecta (evidencia de tratamiento en cualquier contexto, no solo hospitalizados), se seleccionó una revisión sistemática que incluye la mayor proporción del total de estudios pertinentes identificados en la matriz [18]. De los ensayos que esta revisión no incluye, la gran mayoría no son relevantes para la pregunta, por las siguientes razones:

- Se administró el inhibidor de neuraminidasa en conjunto con otras intervenciones [33, 112].
- Comparan un inhibidor de neuraminidasa contra otro [34, 37, 49, 50, 51, 87, 108, 109, 111].
- Comparan biterapia con dos inhibidores de neuraminidasa versus monoterapia [40].
- Comparan diferentes dosis del mismo inhibidor de neuraminidasa [36, 52, 57].
- Compara inhibidor de neuraminidasa con ribavirina [107].
- No corresponden a ensayos sobre tratamiento [53, 84, 105].
- Modelo experimental de influenza en voluntarios sanos [41, 48, 110].
- Niños de 1 a 3 años [39].
- Por último, se excluyó un ensayo de peramivir versus placebo en hospitalizados, que si bien se trata del único ensayo evaluando inhibidores de neuraminidasa versus placebo en la población exacta de interés [35], se consideró que se trata de una intervención no representativa de la intervención de interés para este informe (oseltamivir).

Algunas revisiones mencionan ensayos no incluidos en la revisión Cochrane 2014 [18], la gran mayoría realizados en China o Japón, y no fue posible determinar si efectivamente constituyen ensayos diferentes u otras publicaciones de los ensayos incluidos en la revisión Cochrane [32, 38, 54, 58, 59, 86, 88, 113, 114, 115]. Considerando que se trata de ensayos pequeños, es improbable que su inclusión lleve a diferencias sustantivas en las conclusiones de este informe.

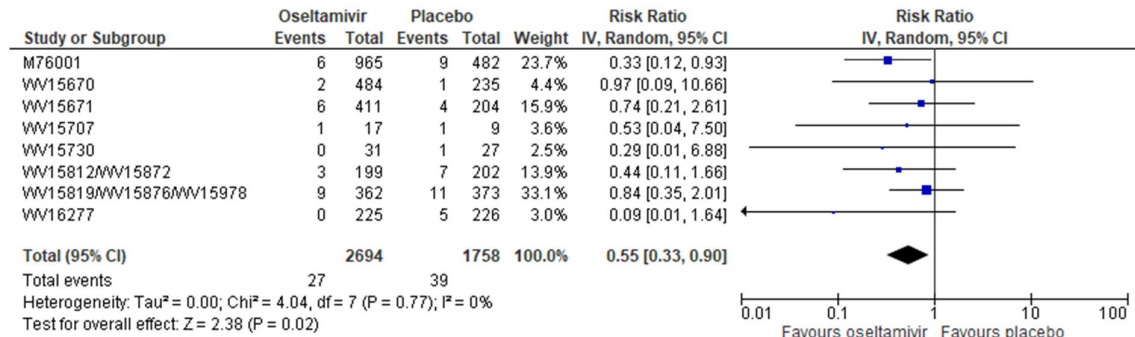
² **Matriz de Evidencia**, tabla dinámica que grafica el conjunto de evidencia existente para una pregunta (en este caso, la pregunta del presente informe). Las filas representan las revisiones sistemáticas y las columnas los estudios primarios que estas revisiones han identificado. Los recuadros en verde corresponden a los estudios incluidos en cada revisión. La matriz se actualiza periódicamente, incorporando nuevas revisiones sistemáticas pertinentes y los respectivos estudios primarios.

En vista de lo anterior, se decidió utilizar los metanálisis de la revisión Cochrane [18] para construir la tabla de resumen de resultados.

También se identificó una revisión analizando estudios observacionales de pacientes hospitalizados durante la epidemia de influenza A/H1N1 durante 2009-2010 [25]. Debido a que esta evidencia también podría informar de manera indirecta la decisión clínica pertinente a este informe, se decidió agregar también el estimador del efecto obtenido por esta revisión en la tabla de resumen de resultados.

Metanálisis

Neumonía



Náuseas y vómitos

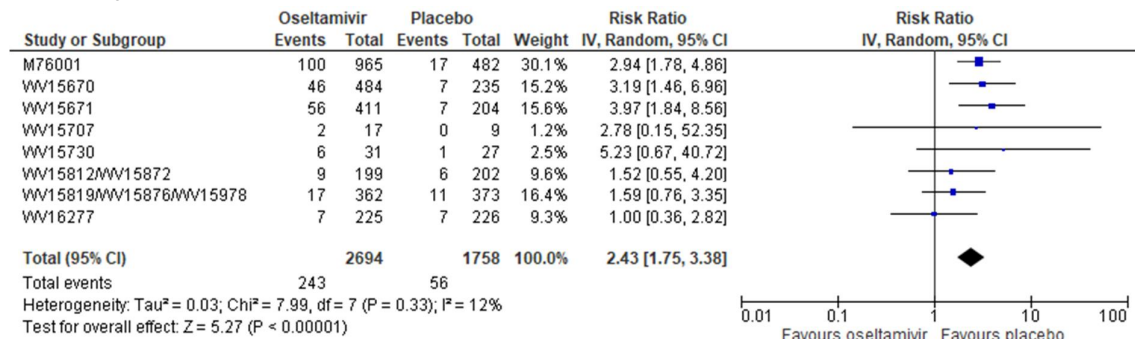


Tabla de Resumen de Resultados (Summary of Findings)

OSELTAMIVIR PARA INFLUENZA EN HOSPITALIZADOS						
Pacientes	Personas adultas con sospecha o diagnóstico de influenza hospitalizado.					
Intervención	Oseltamivir.					
Comparación	No usar.					
Desenlaces	Efecto relativo (IC 95%)	Efecto absoluto estimado*			Certeza de la evidencia (GRADE)	Mensajes clave en términos sencillos
	-- Estudios/pacientes	SIN oseltamivir	CON oseltamivir	Diferencia (IC 95%)		
Mortalidad A partir de NO hospitalizados	Los ensayos de oseltamivir no detectaron muertes por influenza, reflejando la naturaleza benigna de la influenza en la población. Los ensayos de zanamivir detectaron 8 muertes, de las cuales 2 se relacionan con influenza, ambas en el grupo intervención. La mortalidad en Japón durante el brote de A/H1N1 en el 2009 fue 198 en 20 millones de pacientes (1 de cada 100.000) [18].				--	--
Mortalidad A partir de estudios en influenza A(H1N1)	OR 0,72 (0,51 a 1,01) -- 20 estudios [121, 142, 152, 175, 179, 183, 186, 218, 219, 276, 299, 307, 325, 338, 345, 347, 395, 396, 398, 403]	54 por 1000	39 por 1000	Diferencia: 15 menos (26 menos a 1 más)	Muy baja	Oseltamivir podría disminuir la mortalidad. Sin embargo, existe considerable incertidumbre dado que la certeza de la evidencia es muy baja.
Neumonía	RR 0,55 (0,33 a 0,90) -- 8 ensayos / 4452 pacientes [58, 92, 93, 96, 98, 102, 103, 109]	22 por 1000	12 por 1000	Diferencia: 10 menos (2 a 15 menos)	Muy baja	Oseltamivir podría disminuir el riesgo de neumonía. Sin embargo, existe considerable incertidumbre dado que la certeza de la evidencia es muy baja.
Náuseas y vómitos	RR 2,43 (1,75 a 3,38) -- 8 ensayos / 4452 pacientes [58, 92, 93, 96, 98, 102, 103, 109]	32 por 1000	77 por 1000	Diferencia: 45 más (24 a 76 más)	Moderada	Oseltamivir probablemente aumenta el riesgo de náuseas y vómitos.

IC 95%: Intervalo de confianza del 95%.

RR: Riesgo relativo.

GRADE: Grados de evidencia Grading of Recommendations Assessment, Development and Evaluation.

* El **riesgo SIN oseltamivir** está basado en el riesgo del grupo control en los estudios, excepto para el desenlace mortalidad a partir de estudios en influenza A(H1N1), en que el riesgo se estimó de una revisión sistemática evaluando específicamente este riesgo a nivel global [410]. El **riesgo CON oseltamivir** (y su intervalo de confianza) está calculado a partir del efecto relativo (y su intervalo de confianza).

¹ Diseño observacional.

² Se disminuyó un nivel de certeza de evidencia por sospecha de sesgo de publicación identificado por la revisión sistemática cochrane.

³ Se decidió disminuir por riesgo de sesgo, ya que solo 2 estudios ajustaron por variables confundentes.

⁴ Se disminuyó un nivel de certeza de evidencia por inconsistencia (12 49%).

⁵ Se disminuyó un nivel de certeza de evidencia por imprecisión, ya que cada extremo del intervalo de confianza conlleva a una decisión diferente.

⁶ Se disminuyó un nivel de certeza de evidencia por riesgo de sesgo por limitaciones importantes en la mayoría de los ensayos en diversos aspectos (generación de secuencia, ocultamiento, seguimiento, ciego, reporte selectivo).

⁷ Se disminuyó un nivel de certeza de evidencia por indirecto, ya que la evidencia proviene de pacientes no hospitalizados. En el caso de náuseas y vómitos se decidió no disminuir ya que probablemente mantenga el mismo sentido, pero la magnitud sea mayor.

Fecha de elaboración de la tabla: Octubre, 2018.

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