QUE DEBO CONOCER DEL TRATAMIENTO DE MI PACIENTE CON ENFERMEDAD REUMÁTICA?

EFECTOS ADVERSOS DE LOS DIFERENTES TRATAMIENTOS

MITOS Y EVIDENCIAS

Dr. Farfan Maximiliano Javier
Reumatólogo Pediatra
Hospital Materno Infantil de Salta

Pediatra frente al niño con Enfermedad Reumática

* AINES
* CORTICOIDES
* DMARDs (Drogas Modificadoras de E.R.)
  * METOTREXATE
  * LEFLUNAMIDA
  * HIDROXICLOROQUINA
  * CICLOFOSFAMIDA
  * CICLOSPORINA
  * MOFETIL MICOFENOLATO
* BIOLOGICOS:
  * ADALIMUMAB
  * ETANERCEPT
  * TOCILIZUMAB
  * ABATACEPT
  * CANAKINUMAB
    * RITUXIMAB
    * INFLIXIMAB

Efectos adversos de los diferentes tratamientos Mitos y evidencias

* Los avances en el diagnóstico y tratamiento de las Enfermedades Reumáticas → Mejores resultados

  Traducidos en capacidad funcional, calidad de vida y mayor sobrevida.

* Sin embargo, los EA … *infección*…. principales causas de morbilidad y Mortalidad en estos niños

Planteos de Pediatria, la familia y amigos

* Cuando le sacan la medicación? …
* Porque tantos análisis?....
* Como le va a dar tanto CTC...
* Ese remedio da cancer…
* Con ese remedio nunca va a quedar embarazada…
* No puede vacunarlo…
* No le hará bien el aceite de canavis?...

→ *Las drogas son tan malas como pensamos?....*

Corticoides:
EA solo asociados a dosis altas y uso prolongado?

EFECTOS SECUNDARIOS DE LA TERAPIA CON GLUCOCORTICOIDES	
Inmunológicos	Aumento, susceptibilidad e infecciones Disminución, respuesta inflamatoria Disminución hipersensibilidad retardada Neutrofilia, linfocitopenia
Musculo esqueléticos	Miopatía, osteoporosis, necrosis ósea
Gastrointestinales	Pancreatitis, úlcera péptica
Cardiovasculares	Hipertensión Retención de líquidos Ateroesclerosis acelerada
Dermatológicos	Acné, hirsutismo, estrías Fragilidad piel, equimosis

Retraso del crecimiento: *Bernhar 2003 Textbook Kelley*

* Ocurre con dosis equivalentes a 3 mg/dia de Prednisona *Loeb N. Engl. J. Med 1976*
* Dosis de 5 mg/m^2 por mas de un mes → hay alteración del crecimiento lineal.
* Mayor dosis → Mayor retraso
* *Tto dias alternos tiene un efecto protector*

Corticoides:
EA solo asociados a dosis altas y uso prolongado?

Perdida de masa ósea → depende de dosis y tiempo de tto.

* Dosis 7,5mg/dia generan perdida de masa ósea.
* *Dosis a días alternos NO genera beneficios* *Rueggseger Eur. J. Clin. Pharmacol 1983*
* No todos los ptes expuestos sufren descalcificación

Catarata: *Lubkin Asthma Res 1997*

* Dosis > 9 mg/m^2 → >1 años Catarata no progresivo

Corticoides y riesgo de Infecciones

Alteran la capacidad de respuesta a Infecciones

- Efecto inmunosupresor
- Reducen la resistencia a infecciones virales y bacterianas.

- Efecto antiinflamatorios → enmascara los signos y síntomas de infección
- *La dosis y Tiempo mínimo de tto* ***generar INMUNOSUPRESION*** *en sano* → ***NO definida***

AAP Report of the Committee on Infectious Diseases 1997

Altas dosis y tiempo prolongado → ***Afectan Rta hipersensibilidad retardada***

- ✓ Diversos patógenos intracelulares, virus, hongos, protozoos y parásitos
  - ✓ Tuberculosis
  - ✓ Micosis profundas

Factores potencian la inmunosupresión:

- La Enfermedad de base
- Tto inmunosupresor concurrentes.

CTC e Insuficiencia suprarenal

EA mas grave potencialmente mortal

* Corticoide uso > a 2 semana *Shulman Pediatrics 2007*

→ *Supresión transitoria de producción endógena*

* Tto prolongado →*Supresión eje Hipotalamo - Hipofisiario - Adrenal*

* Dosis y Tiempo TTo: *Inhibir el eje* → *No están bien definidas* *Cunha J. Clin. Endocrinol. Metab 2004*

No reconocer supresión del eje hipotálamo-hipófisis-adrenal

Situación de estrés

Riesgo colapso vascular, crisis suprarrenal y muerte

Graber J. Clin. Endocrinol. Metab. 1965

CTC e Insuficiencia suprarenal

Recomendación:

* Mantenimiento fisiológico

  → Hidrocortisona 6 a 9 mg/m^2 /día (frac c/8hs)

* Enfermedades febriles o enfermedades graves

  → Hidrocortisona 40 mg /m^2/día.

  Shulman , Pediatrics 2007

* Inducción de la anestesia o RCP

  →Hidrocortisona 100 mg/m^2 IV inicial Luego 25 mg /m2 IV cada 6 horas → 24 a 48 hs

* Tto Glucocorticoides → Prednisona dosis ≥ *Hidrocortisona 40 mg/m2/d*

  →***Administrar igual dosis / Tabla conversión***

Corticoides:
EA solo asociados con dosis altas y uso prolongado?

Conclusión:

* EA relacionados a la dosis, tiempo de exposición y frecuencia de administración
* El riesgo de infección aumenta exponencialmente con la dosis
* Dosis y Tiempo Tto capaz de Suprimir el eje Hipotalamo…. → NO definido

Recomendación:

Textbook Rheumat ped. Petty 2015

* Usar dosis mínima aceptable
* Descenso "rapido" y progresivo
* CTC vida media corta / < efecto mineralocorticoide → Prednisona
* Administración matinal
* Monodosis
* Días alternos
* Suplementar tto DMARD (MTX, HCQ, etc…)

Mínimos cambios → reactivar la enfermedad

Metotrexate y Efectos Adversos

Droga Segura, Barata y Eficaz → 1986 (31 años en AIJ) *1º reportes Hafner*

A pesar de ellos Se reportan…

* EA graves: Supresión de medula ósea y hepatotoxicidad

  → Son infrecuentes y transitorios - suspende MTX

* EA en Tto MTX 3984 ptes /año de MTX → 2588 AIJ.
  * Elevacion transitoria de transaminasas 8%
  * Eventos gastrointrestinales 7%
  * Inespecificos 6%
  * Infeciones 3 %
  * Mucositis 3 %
  * Hematologico 1 %
  * Neurologico 1 %
  * ***Eventos serios 0.5%***

Velt, Ped Rheumatol. 2011

Conclusion:

* Riesgo de EA serios 1/200 ptes MTX por año.
* Discontinuacion transitoria o permanente pte MTX/año < 5%

Metotrexate: Efectos adversos son un problema?

Efectos Graves

* ***Fibrosis pulmonar, hepática - cirrosis*** *Kremer Arthritis Rheum 1994*

Manifestaciones referidas a pte adultos

* Cirrosis hepática /fibrosis pulmonar. → NO en niños con ER *Best Pract Clin Rheum Wallace 2006*

* Seguimiento con Bx hepática en niños (2,3 a 6 años tto)

→ NO anormalidad.

Metotrexate Intolerancia GI

ARTHRITIS & RHEUMATISM
Vol. 63, No. 7, July 2011, pp 2007–2013
DOI 10.1002/art.30367

High Prevalence of Methotrexate Intolerance in Juvenile Idiopathic Arthritis

Development and Validation of a Methotrexate Intolerance Severity Score

Maja Bulatović,[1] Marloes W. Heijstek,[1] Marleen Verkaaik,[1] E. H. Pieter van Dijkhuizen,[1] Wineke Armbrust,[2] Esther P. A. Hoppenreijs,[3] Sylvia Kamphuis,[4] Wietse Kuis,[1] Toine C. G. Egberts,[1] Gerben Sinnema,[1] Carin M. A. Rademaker,[1] and Nico M. Wulffraat[1]

Score MISS (MTX Intolerante Severity Score)

Art & Rheumatol. Bulatovie 2011

Dolor abdominal, náuseas, vómitos, epigastralgia y síntomas conductuales (0 a 12 puntos)

* Intolerancia GI (23 a 50%) → EA leves
  * Disconfor abdominal 74%
  * Nauseas 91%
  * Vomitos post-MTX 49%
  * Sintomas anticipados o Pre-MTX (cuando se piensa en tomar) 77%.
  * Sintomas conductuales 88% → inquietud, llanto, irritabilidad y rechazo

Intolerancia → *Mas jóvenes, Mas año de consumo, Mas dosis*

Metotrexate Intolerancia GI

Estrategias:

- Terapia conductuales → 80% rta
- Rotar vía de administración
- Antieméticos → 41% continúan con intolerancia
- Ac fólico → 74% rta *Alarcon J Rheumat 1996*
  - NO Rta → *Cambiar Medicación*

35% discontinua Tto

- 27 % decisión medica
- 8 % abandona

Da Silva, Ped Rheumatol 2014

Ped Rheumat. Mulligan 2015

Guidelines for Blood Test Monitoring of Methotrexate Toxicity in Juvenile Idiopathic Arthritis

OLIVA ORTIZ-ALVAREZ, KIMBERLY MORISHITA, GLENDA AVERY, JAYNE GREEN, ROSS E. PETTY, LORI B. TUCKER, PETER N. MALLESON, and DAVID A. CABRAL

Alteración: GOT/GPT > dos valores, HB 2 > puntos, PMN <1500 Linf < 900

(J Rheumatol 2004;31:2501–6)

* 40% anormalidad global – 26% anormal hematológica – 14% alt HPTG

→Alteración hepática: 52% leve → Transitoria → No Suspender Tto

→ *95% infección viral concomitante*

* Estudio de probabilidad → 11% a 3 meses vs 10% por estudios al azar

Recomendación:

* ***Control cada 2 – 3 meses*** → Pte sin otra condición: MTX < 17.5/m2 + Ac. Folico
* ***Control mensual***:
  * Ptes con intercurrencia infecciosa
  * Factores de riesgo: obesidad, DBT, abuso de alcohol
  * Consumo concomitante otras drogas.
  * Dosis > 17,5mgt/m2

Recomendaciones previas:

Trabajo en adultos (ACR) → Probabilidad 90% a 30 días y 17 % a 45 días *Kremer, A Rheumat 1994*

→ control cada 4 a 6 semanas

Diferencias….. NIÑOS: menos exposición alcohol – Coomorbildiad - Mejor metabolismo

Metotrexate y riesgo de Malignidad

AIJ y riesgo de Cancer

Bart, Pediatric Rheumatl 2016

- Inflamación Crónica → ***25% CA asociados***

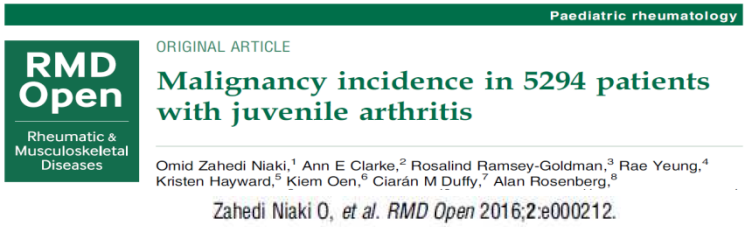
Mantovani 2008

- Exposición radiaciones ionizantes
- Exposición a drogas inmunosupresoras

Mtx cáncer:

Zahedi 2016

5294 pte Canada - 6 series 1978 a 2012



- 9 CA → 3 Hemat. (Hodking /no Hod/ Leucemia) Solidos: Glioma – Ewing - Adeno. Tiroideo y endometrio
- 6/9 expuesto a DMARD y 5/9 a Biológico + DMARD

Conclusión:

- *No riesgo de malignidad* → ***9 CA vs 10,9 Esperado***

Metotrexate – Biologico y Malignidad

2282 Ptes Taiwan → AIJ riesgo de CA

- AIJ → **virgen MTX** → **RR 3,1 (RR1,9-4.9)**
- AIJ → con MTX → RR 2,02 (IC 0,7 – 6)
- AIJ con anti-TNF → RR 2,07 (0,36-11)

Concluye: *El riesgo de CA NO influenciado MTX o anti-TNF*

Kok et al. BMC Cancer 2014, 14:634
http://www.biomedcentral.com/1471-2407/14/634

BMC Cancer

RESEARCH ARTICLE Open Access

Population-based cohort study on the risk of malignancy in East Asian children with Juvenile idiopathic arthritis

Victor C Kok[1,2], Jorng-Tzong Horng[1,3*], Jing-Long Huang[4,5*], Kuo-Wei Yeh[4], Jia-Jing Gau[3], Cheng-Wei Chang[6] and Lai-Zhen Zhuang[3]

Arthritis Rheum. 2012 April ; 64(4): 1263–1271

Estudio Sueco: 9027 AIJ vs 44858 controles 1969 a 2007

Simard A & Rheumat.2010

- No riesgo de CA ptes virgen Biológico RR 1.1 (0,9 -1.5).
- 0,46 vs 0,40/1000 personas año → AIJ vs Población general
- Post-1987 → *Llegada del MTX*
  - Ca gral AIJ RR 2.3 (1.2 – 4.4)
  - Linfoprolif: RR 4,2 (1.7-10)

ARTHRITIS & RHEUMATISM
Vol. 62, No. 12, December 2010, pp 3776–3782
DOI 10.1002/art.27741

Juvenile Idiopathic Arthritis and Risk of Cancer

A Nationwide Cohort Study

J. F. Simard,[1] M. Neovius,[1] S. Hagelberg,[2] and J. Askling[3]

Conclusión:

Hay un claro incremento de malignidad en AIJ luego de 1987 → ***MTX***

Metotrexate - Biologico y malignidad

Cleary: AIJ en Tto MTX *Arch of Dis in Chil 2002*

* Reportes 5 ptes con AIJ y enf Linfoproliferativa → la mayoría asociado a VEB

2008 FDA → Advierte posible riesgo de malignidad con Anti TNF

Published in final edited form as:
Arthritis Rheum. 2012 April ; 64(4): 1263–1271. doi:10.1002/art.34348.

Rates of Malignancy Associated with Juvenile Idiopathic Arthritis and Its Treatment

Abstract

Objective—To determine relative rates of incident malignancy among children with juvenile idiopathic arthritis (JIA) with respect to treatment compared to children without JIA

Methods—Using national U.S. Medicaid data from 2000 through 2005, we identified cohorts of children with JIA and without JIA using physician diagnosis codes and dispensed medication prescriptions. Study follow-up began after a 6 month lag period to exclude prevalent and misdiagnosed malignancies. Treatment with methotrexate and TNF inhibitors was categorized as ever or never exposed. Malignancy outcomes were identified using an adapted version of a previously validated algorithm. Incident malignancies were categorized as possible, probable, or highly probable based on a comprehensive review of all claims. Malignancy rates were standardized to the age, sex, and race distribution of the overall JIA cohort. Standardized incidence ratios (SIR) were calculated using children without JIA (N=321,821) as the referent group.

Results—The JIA cohort included 7,812 children with a total follow-up time of 12,614 person-years, of whom 1,484 children contributed 2,922 person-years of TNF inhibitor exposure. For all children with JIA versus children without JIA, the SIR was 4.4 (1.8–9.0) for probable and highly probable malignancies. For methotrexate users without TNF inhibitor use, the SIR was 3.9 (0.4–14). Following any use of TNF inhibitors, no probable or highly probable malignancies were identified (SIR 0 (0–9.7)).

Conclusions—Children with JIA appeared to have an increased rate of incident malignancy compared to children without JIA. JIA treatment, including TNF inhibitors, did not appear significantly associated with the development of malignancy.

7812 ptes 12614 pers/años - AIJ vs DAH y Asmas

- AIJ vs No AIJ ***SIR 4,4*** ***(2 – 9)***
- AIJ con MTX ***SIR 3,9*** ***(0.4 – 14)***
- AIJ con TNF ***SIR 0*** ***(0 -9,7)***

SIR: tasa de Incidencia estandarizada

Los ptes con AIJ parecen tener un incremento de tasa de malignidad vs niños s/AIJ.
Tto incluidos Anti-TNF **no** están significativamente asociados a malignidad

Metotrexate - Biologico y malignidad

RHEUMATOLOGY

Rheumatology 2014;53:968-974
doi:10.1093/rheumatology/ket318
Advance Access publication 31 October 2013

Review

Juvenile idiopathic arthritis and malignancy

Nicolino Ruperto[1] and Alberto Martini[1,2]

Abstract

Biologic agents represent a major advance in the treatment of JIA. In 2008 a US Food and Drug Administration (FDA) warning raised the hypothesis that anti-TNF therapies may be associated with an increased incidence of malignancies in children. More recent data seem to suggest that JIA itself, as in the case of RA, is associated with an increased risk of malignancy and that this risk is not further increased with anti-TNF treatment. However, only long-term prospective data on a very large number of patients will provide a definite answer. This article summarizes the current evidence in order to help health professionals properly advise patients and their families about the possible risk of malignancies in JIA treated with biologic agents.

Key words: juvenile idiopathic arthritis, anti-TNF therapy, etanercept, abatacept, infliximab, malignancy, lymphoma, adverse events.

REVIEW

Introduction

The introduction of the so-called biologic agents has profoundly changed the treatment of JIA [1, 2]. The efficacy profile of these drugs is remarkable and has led to the approval of several of them by regulatory authorities [3, 4] and to the first recommendation for the treatment of JIA issued by the ACR [5]. Currently available treatments include anti-TNF agents [6–8] and other targeted therapies such as anti-T-cell co-stimulation [9] for polyarticular JIA and anti-IL-1 [10–12] or anti-IL-6 for systemic JIA [13, 14]. Even if these treatments show disease-modifying potential in adults (limited information in children [15]), they are still considered symptomatic drugs unable to cure the underlying disease, therefore the need for long-term treatment is compelling, as disease flares are common if the drugs are discontinued [16].

The safety information in children with JIA is still limited; the number of treated patients is relatively small and the long-term follow-up is relatively short. Current safety information is coming primarily from randomized phase III clinical trials, including medium-term follow-up, from national registries and from experience in adult patients with RA. Most of the information concerns anti-TNF therapies (especially etanercept, which was the first to be introduced), and the overall safety profile appears satisfactory, especially in relation to the marked efficacy. The paediatric rheumatology community was therefore surprised and very worried in 2008 when the US Food and Drug Administration (FDA) issued a 'black box warning' [17] about the possible association between the use of anti-TNF agents in children and the development of malignancy.

This article summarizes the available evidence in order to help health professionals to properly advise patients and their families about the possible risk of malignancies in JIA treated with biologic agents.

Study design and types of adverse event

For ethical reasons, most of the phase III clinical trials in a chronic disease like JIA employed a randomized, double-blind, placebo-controlled withdrawal design. With this design, eligible children are treated in an open-label fashion with the experimental therapy for a few months, then JIA ACR30 responders [18] are randomized in a double-blind fashion either to continue the experimental therapy or to switch to placebo [19]. In this segment of the study, called the double-blind withdrawal phase, patients who demonstrate a pre-defined definition of JIA disease worsening (e.g. flare) [20] are withdrawn and, if on placebo, are re-treated with the experimental therapy in an open-label fashion [6, 8, 9, 12–14, 21]. The remaining trials employed the classic parallel study design with placebo comparison [7, 12, 14]. However, the limited duration of the placebo phase and the relatively small sample sizes from phase III clinical trials with both study designs usually hampered a statistically powerful comparison of the safety of biologic agents with placebo.

[1]Pediatria II, Reumatologia, Istituto Giannina Gaslini and [2]Department of Paediatrics, University of Genoa, Genoa, Italy.

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Correspondence to: Alberto Martini, Pediatria II, Reumatologia, Istituto Giannina Gaslini, Via Gerolamo Gaslini 5, 16147 Genoa, Italy.
E-mail: albertomartini@ospedale-gaslini.ge.it

Los datos recienten sugieren que la AIJ y AR por si misma tiene un riesgo incrementado de Malignidad, Este riesgo no se incrementa con el uso de anti-TNF

Ruperto, Rheumatology 2014

Recomendación generales

- Control de la actividad inflamatoria
- Monitoreo Clínico y bioquímico
  - → Buscar activamente signos de C.A.
- Atentos a Linfoproliferativos

ETC y Fertilidad

MTX: Fertilidad y Teratogenicidad

* Pte AIJ: 126 ptes

Noruega -Ostense J. Rheumatol 2000

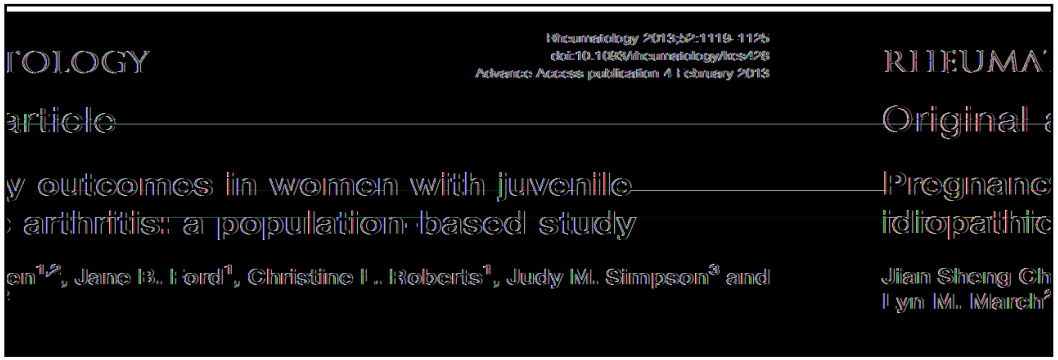
  * Fertilidad similar a controles.
  * Fecundidad significativamente reducida
  * Tasa de abortos aumentadas.

Wallenius 75 mujeres AIJ

Fertility in women with chronic arthritides, Rheumatol 2011

  * 43% historia de embarazo vs 59% controles.
  * Tasa de embarazo reducida en 16%

ETC y Fertilidad



Chen 78 embarazos AIJ vs controles

- Mayor riesgo de preeclamsia
- Mayor tasa de cesárea – hemorragia postparto.

RN: Mayor riesgo de parto prematuro y Retardo de crecimiento.

Feldman 1680 AIJ

Feldman , J Rheumatol 2016 43;804-9

- Alta tasa de prematurez y PEG
- Mayor proporción de malformaciones congeniticas

→ defecto del tubo neural RR 6,5 (5,5-8,3)

ETC y Fertilidad

* **Viktil 2012**
  * El riesgo de anomalía congénita no aumento en M/F
    * Suspenden IS 3 meses antes del embarazo

J Rheumatol 2012;41:196–201.

Recomendación:

* No embarazo durante el tto
* Suspender inmunosupresion 3 meses previos a la concepción.

Infección y ETC

* **Lo ptes con ETC tiene mayor riesgo de Infección.**
    * Disregulación del Sistema inmune.
    * Inflamación no controlada → Factor Riesgo independiente para infección
    * Tratamiento inmunosupresor: CTC, DMARD – Biologicos, etc
* La tasa de infección:
    * Pte **AIJ Sin Inmunosup.** → ***2,8 -100/ pers/año*** vs NO AIJ (TDAH) → ***1 x 100 per a.***
* Niños con JIA sin Tto actual (CTC/MTX/Inh-TNF)

    Doble Riesgo → Internación Infección Bacteriana vs No AIJ

Rates of hospitalized bacterial infection associated with juvenile idiopathic arthritis and its treatment
Beukelman, Arthritis Rheum 2012

Infeccion y ETC

Arthritis Care res 2017 Apr;69(4):552-560.

Risk of Serious Infection in Juvenile Idiopathic Arthritis Patients Associated With Tumor Necrosis Factor Inhibitors and Disease Activity in the German Biologics in Pediatric heumatology Registry

Becker, Horneff G.

Abstract

OBJECTIVE:
To examine the effects of tumor necrosis factor inhibitors on the risk for serious infections and other influencing factors in a registry.

METHODS:
Patients exposed for the first time to etanercept, adalimumab, or methotrexate and serious infections were identified in the German Biologic Registry for Pediatric Rheumatology (BIKER) registry. Serious infection rates per 1,000 observation-years and relative risks were calculated. Cox regression identified risk factors and provided hazard ratios (HRs) for occurrence of infections.

RESULTS:
A total of 3,350 patients with 5,919 observation-years fulfilled the inclusion criteria for the study. The first biologic agents were etanercept (1,720 cases) and adalimumab (177 cases). A total of 1,453 patients were treated with methotrexate and no biologic agent. In total, 28 serious infections were reported in 26 patients (4.7 per 1,000 patient-years), 5 with methotrexate (1.6 per 1,000 patient-years), 21 with etanercept (8.1 per 1,000 patient-years), and 2 with adalimumab (9.7 per 1,000 patient-years). Significant univariate risk factors for infection were therapy with biologic agents, disease duration before therapy start, corticosteroid medication, nonbiologic premedications, higher clinical Juvenile Arthritis Disease Activity Score including maximal 10 joints (cJADAS10) at therapy start, and higher mean cJADAS10 during therapy. In multivariate Cox regression, only biologic therapy and cJADAS10 at therapy start remained significant. Risk for infection was increased by etanercept (univariate HR 6.0 [95% confidence interval (95% CI) 2.0-17.5]) or adalimumab (HR 7.3 [95% CI 1.3-40.0]) compared to methotrexate as well as by an elevated cJADAS10 at therapy start (HR 1.1 [95% CI 1.0-1.2] per unit increase).

CONCLUSION:
The total rate of serious infections reported in the BIKER registry seems low. Treatment with etanercept or adalimumab increases the risk for serious infection slightly, compared to methotrexate. Disease activity expressed by cJADAS10 appears to be an independent risk factor.

3350 AIJ – Registro Alemán 2017

Biológicos:

* Etanercept (1.720 casos) - Adalimumab (177 casos) - MTX (1.453 casos)

Infección grave: 28 en 26 ptes

→ ***4,7 por 1.000 ptes/año***

Distribucion

* 5 MTX → 1,6 por 1.000 pte/año
* 21 ETN → 8,1 -1.000 pte /año
* 2 ADA → 9,7 -1.000…

Fact de riesgo (Univariado)

* Tto Biologico
* CTC asociado.
* JADAS10 elevado –Enf activa durante el tto.

Infeccion y ETC

Multivariado:

* tto Biologico y cJADAS10 al inicio del tto.

El riesgo de infección:

* Etanercept (HR 6 (2 -17) → Adalimumab HR 7 (1,3 - 40)
* MTX HR 1 (1-1,2)

Concluye.

* El Tto ETN / ADA aumenta el riesgo de infección grave vs MTX
* La act. enfermedad (JADAS10) → *Factor de Riesgo independiente*.

Infeccion y ETC

Beukelman, Art. & Rheum 2013

* Riesgo Infección triplica con CTC altas dosis → NO así con MTX.

Conclusión:

* *La drogas usadas y la enfermedad per se*

  → Predisponen al riesgo de infecciones

* ***Conducta medica similar a ptes Oncologicos***

CFM: *mito o realidad?*

La ciclofosfamida → Terapia para manifestaciones severas

* Nefritis lúpica III-IV –RP
* LES Neuropsiquiatrico.
* Vasculitis sistémica….
* HAD, Insterticiopatia pulmonar
* Anemia hemolítica refractaria…..

Buena tasa de respuesta → efectos tóxicos considerables…..

* Insuficiencia ovárica …
* Susceptibilidad a la infección.
* Supresión de la médula ósea.
* Alopecia
* Cistitis hemorrágica.
* Malignidad

CFM: *Disfunción ovárica*

CFM y disfunción ovárica: → Irregularidad, amenorrea e infertilidad

El riesgo depende del grado de maduración sexual y la dosis acumulada

La amenorrea persistente difícil evitar >32 años incluso con tto cortos.

* < 30 años → 14%
* > 40 años → 50%
* Dosis acumulada: < 10gr 4% .→ > 30gr 70% → *Promedio LESp 15 gr*

* Mujeres pre púberes menor efecto toxico → > Reserva ovarica

Katsifis 2004 – Shaham 2003

CFM: *Disfuncion ovarica*

pISSN 1598-2998, eISSN 2005-9256

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Original Article

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Gonadal and Sexual Dysfunction in Childhood Cancer Survivors

Ju Young Yoon, MD[1,a]
Hyeon Jin Park, MD, PhD[1]
Hee Young Ju, MD[1]
Jong Hyung Yoon, MD[1,b]
Jin Soo Chung, MD, PhD[2]
Sang Hyun Hwang, MD, PhD[3,c]
Dong Ock Lee, MD[4]
Hye Young Shim, PhD[5]
Byung-Kiu Park, MD, PhD[1]

[1]*Center for Pediatric Cancer, National Cancer Center, Goyang,* [2]*Center for Prostate Cancer, National Cancer Center, Goyang,* [3]*Department of Laboratory Medicine, National Cancer Center, Goyang,* [4]*Center for Uterine Cancer, National Cancer Center, Goyang,* [5]*Division of Cancer Management Policy, National Cancer Center, Goyang, Korea*

Purpose
Few studies have addressed gonadal and sexual dysfunctions in childhood cancer survivors. We evaluated the prevalence rates and risk factors for gonadal failure among adolescent/young adult childhood cancer survivors and their sexual function.

Materials and Methods
Subjects were childhood cancer survivors aged 15-29 years who had completed therapy more than 2 years ago. Demographic and medical characteristics were obtained from the patients' medical records. In addition, hormonal evaluation and semen analysis were performed and sexual function was evaluated via questionnaire.

Results
The study included 105 survivors (57 males, 48 females), of which 61 were adults (age > 19 years) and 44 were adolescents. In both males and females, the proportion of survivors with low sex hormone levels did not differ among age groups or follow-up period. Thirteen female subjects (27.1%) needed sex hormone replacement, while five males subjects (8.8%) were suspected of having hypogonadism, but none were receiving sex hormone replacement. Of 27 semen samples, 14 showed azospermia or oligospermia. The proportion of normospermia was lower in the high cyclophosphamide equivalent dose (CED) group (CED ≥ 8,000 mg/m^2) than the low CED group (27.3% vs. 62.5%, p=0.047). Among adults, none were married and only 10 men (35.7%) and eight women (34.3%) were in a romantic relationship. Though a significant proportion (12.0% of males and 5.3% of females) of adolescent survivors had experienced sexual activity, 13.6% had not experienced sex education.

Conclusion
The childhood cancer survivors in this study showed a high prevalence of gonadal/sexual dysfunction; accordingly, proper strategies are needed to manage these complications.

Key words
Gonads, Sexual dysfunction, Survivors, Child, Neoplasms

Correspondence: Hyeon Jin Park, MD, PhD
Center for Pediatric Cancer, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang 10408, Korea
Tel: 82-31-920-1654
Fax: 82-31-920-1244
E-mail: hjpark@ncc.re.kr

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[a]Present address: Department of Pediatrics, Gyeongsang National University Changwon Hospital, Changwon, Korea
[b]Present address: Department of Pediatrics, Hallym University College of Medicine, Chuncheon, Korea
[c]Present address: Department of Laboratory Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Sobrevivientes de CA pediátrico

Tto CFM 105 ptes dosis > 8 gr/m2

* 27% mujeres necesitaban tto remplazo hormonal
* 9% hombres datos hipogonadismo
* 50% hombres presentaba azo u oligoespermia.
* Normoespermia *CFM alta vs Baja* 27 % vs 62%

Conclusión:

- Ptes sobrevivientes CA tto CFM → Alta tasa de disfunción gonadal

Yoon, Cancer Rest Treat, 2017

CFM: *es la única causa?*

Disfunción ovárica en Lupus.

Ozgur 2015

- Estado inflamatorio crónico → afecta el eje hipotalamo-hipofiso-ovarico. *Labarbera 1988*
- Actividad lupica se asocia → Hiperprolactinemia, descenso de progesterona *Blanco 1999*
- Lesión ovárica autoinmune → ooforitis autoinmune *Silva 2011*
- FSH > en LES vs Controles *Shabanova 2008*
- Hormona anti Mulleriana (marcador de reserva ovarica)
  - LES vs controles → HAM niveles bajos → ***LES efecto directo reserva y función ovárica***

Recomendaciones:

- Esquemas de tratamiento cortos
- Pulsos ev → Menos dosis acumulada a lo largo plazo
- El co-tratamiento agonistas de la hormona liberadora de gonadotrofina
  → Preserva la fertilidad futura y la función ovárica mujeres jóvenes → resultados dipares
- Ovopreservacion?

CFM *supresión medular malignidad*

Supresión de medula ósea → *Efecto adverso > frecuente*

* ***Leucopenia***, trombocitopenia *y anemia*
* Máxima toxicidad → ***Nadir 7 a 14 dias***
    * Rápida recuperación 20 a 25 dias.

Realidad conocida → pero ignorada

Recomendacion:

* ***Control HMG 10 a 14 dias***

Malignidad

* Adultos incremento del riesgo → linfoproliferativa *Rosental 1996*
    * Otras CA piel y vejiga.
* ***Niños no evidencia de malignidad*** *Petty 2015*

CFM *toxicidad vesical*

Toxicidad vesical: → *Cistitis Hemorragica , fibrosis, CA celulas Trancicional*

Cistitis hemorrágica: Incidencia del 6% en transplantados con CFM

* Contacto prolongado

→ Metabolito CFM (Acroleína) → Epitelio transicional vesical.

Recomendaciones:

* Micciones frecuentes cada 2 hs.
* Abundante liquido.
* No administrar por las noches.
* Profilaxis ***Mesna*** → quelante de Acroleina

Antimalaricos: Hidroxicloroquina

En dosis adecuada → Drogas mas seguras

Runge Am J Med 1983

Efectos adversos:

* Intolerancia GI 10%
* Hiperpigmentación cutánea - Debilidad muscular
* SNC → cefalea, mareo, insomnio y ansiedad

→ ***Revierten con reducción de dosis.***

Toxicidad retiniana

* Causa ceguera irreversible

Rynes Arthritis Rheum 1979

* La HCQ [altas] : Hígado, pulmón, riñón y Células pigmentarias de la retina

→ persisten > 5 años luego de suspendida.

* Toxicidad dosis dependiente:

Easterbrook Ophthalmol 1998 – Berstein Am J Med 1983

  * ***No dosis < 6 mg/kg/dia***

Antimalaricos: Hidroxicloroquina

Manifestaciones clinica:

- Alteración visión de colores, campo visual.
- ***0.5 a 10% asintomáticos*** → Dx exámenes oftalmologicos *Berstein Am J Med 1983*
- Si hay clínica → sinónimo de daño irreversible.

Recomendación.

- Evaluación periódica .
  - Inicio → 6 meses → 12 meses …. *Marmor Ophthalmology 2011*
- Examen:
  - ***Agudeza visual - Campo visual - Visión colores y retinoscopia***
  - Tomografía de coherencia óptica > sensibilidad que el campo visual
  - ***Niños menores de 6 años uso limitado (falta de colaboración)***
- Anomalías de la retina o interferencia visual

→ Indicación absoluta de suspender HCQ

Biológicos

Llegaron cambiar la historia ptes Enf Reumáticas…..

Sin embargo, No están libres de efectos adversos…

* Infecciones
* Malignidad.
* Otras enfermedades inflamatorias. Uveítis , EII.
* Enfermedad desmielinizante
* Eventos cardiovasculares
* Alteraciones hematológicas.

ARD Online First, published on April 29, 2015 as 10.1136/annrheumdis-annrheumdis-2014-206747

EXTENDED REPORT

Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA)

Jens Klotsche,[1,2] Martina Niewerth,[1] Johannes-Peter Haas,[3] Hans-Iko Huppertz,[4] Angela Zink,[1,5] Gerd Horneff,[6] Kirsten Minden[1,7]

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ETA = 1414, ADA = 320, MTX =1455

Table 2 Incidence of serious adverse events and infections in children, adolescents and young adults treated with methotrexate, etanercept or adalimumab (3-month at-risk window approach)

	MTX		ETA		ADA		ETA versus MTX	ADA versus MTX	ETA versus ADA
	n	rate per 100 EY (95% CI)	n	rate per 100 EY (95% CI)	n	rate per 100 EY (95% CI)	RR (95% CI); p value	RR (95% CI); p value	RR (95% CI); p value
Serious adverse events	75	2.58 (2.03 to 3.23)	199	4.46 (3.86 to 5.13)	23	4.67 (2.96 to 7.00)	2.18 (1.56 to 3.06); <0.001	2.17 (1.25 to 3.77); 0.006	1.00 (0.60 to 1.65); 0.988
All infections	160	5.50 (4.68 to 6.43)	255	5.72 (5.04 to 6.46)	56	11.36 (8.58 to 14.75)	1.37 (1.06 to 1.77); 0.015	2.24 (1.51 to 3.33); <0.001	1.63 (1.12 to 2.38); 0.010
Bacterial	9	0.31 (0.14 to 0.59)	14	0.31 (0.17 to 0.53)	6	1.22 (0.45 to 2.65)	1.17 (0.47 to 2.87); 0.739	4.27 (1.38 to 13.26); 0.012	3.67 (1.30 to 10.31); 0.014
Viral	35	1.20 (0.84 to 1.67)	67	1.50 (1.16 to 1.91)	5	1.01 (0.33 to 2.37)	1.44 (0.90 to 2.31); 0.128	0.86 (0.31 to 2.36); 0.773	0.60 (0.23 to 1.58); 0.298
Epstein–Barr virus infection	4	0.14 (0.04 to 0.35)	4	0.09 (0.02 to 0.23)	0	–	0.68 (0.17 to 2.70); 0.580	–	–
Varicella zoster infection	8	0.28 (0.12 to 0.54)	24	0.54 (0.34 to 0.80)	2	0.41 (0.05 to 1.47)	2.07 (0.88 to 4.87); 0.096	1.44 (0.28 to 7.37); 0.659	0.70 (0.15 to 3.17); 0.641
Chickenpox	6	0.21 (0.08 to 0.45)	8	0.18 (0.08 to 0.35)	2	0.41 (0.05 to 1.47)	0.89 (0.27 to 2.92); 0.849	1.70 (0.27 to 10.57); 0.570	1.90 (0.34 to 10.79); 0.466
Herpes zoster	2	0.07 (0.01 to 0.25)	16	0.36 (0.21 to 0.58)	0	–	5.48 (1.23 to 24.44); 0.026	–	–
Human papillomavirus infection	2	0.07 (0.01 to 0.25)	0	–	0	–	–	–	–
MII infections	15	0.52 (0.29 to 0.85)	41	0.92 (0.66 to 1.25)	2	0.41 (0.05 to 1.47)	2.12 (1.08 to 4.17); 0.030	0.88 (0.18 to 4.28); 0.872	0.41 (0.09 to 1.90); 0.257
Sepsis	1	0.03 (0.00 to 0.19)	3	0.07 (0.01 to 0.20)	0	–	2.03 (0.21 to 19.51); 0.540	–	–
Epstein–Barr virus infection	1	0.03 (0.00 to 0.19)	2	0.04 (0.01 to 0.16)	0	–	1.35 (0.12 to 14.92); 0.805	–	–
Varicella zoster infection	2	0.07 (0.01 to 0.25)	8	0.18 (0.08 to 0.35)	0	–	2.77 (0.50 to 15.27); 0.243	–	–
Chickenpox	2	0.07 (0.01 to 0.25)	4	0.09 (0.02 to 0.23)	0	–	1.11 (0.12 to 10.08); 0.921	–	–
Herpes zoster	0	–	4	0.09 (0.02 to 0.23)	0	–	–	–	–
Human papillomavirus infection	1	0.03 (0.00 to 0.19)	0	–	0	–	–	–	–

Years of drug exposure: MTX 2907; ETA 4461; ADA 493.ADA, adalimumab; AE, adverse event; ETA, etanercept; EY, years of drug exposure; MII, medically important infections; MTX, methotrexate; RR, relative risk.

Table 3 Rates of malignancies and mortality in the study cohort (at-risk window: ever exposed)

	Ever exposed				
	PY	n	rate per 100 PY (95% CI)	RR (95% CI); p value	Cause of death, type of malignancy*
Malignancies					
MTX	2751	2	0.07 (0.01 to 0.26)	Referent	2×acute lymphoblastic leukaemias
ETA	6619	6	0.09 (0.04 to 0.20)	1.03 (0.13 to 6.61); 0.948	Thyroid gland carcinoma, yolk sac carcinoma, non-Hodgkin's lymphoma, 2×Hodgkin's lymphoma, oligodendroglioma
ADA†	745	2	0.27 (0.03 to 0.97)	1.92 (0.15 to 24.1); 0.612	Non-Hodgkin lymphoma, oligodendroglioma
ADA versus ETA				2.05 (0.31 to 13.45); 0.453	
Mortality					
MTX	2751	1	0.04 (0.01 to 0.21)	Referent	Leukaemia
ETA	6619	4	0.05 (0.01 to 0.13)	1.28 (0.13 to 12.28); 0.831	2×sepsis, macrophage activation syndrome, carditis
ADA	745	0	–	–	–

At-risk period for MTX: start of treatment to (i) the end of follow-up in case of not switching to a biologic and (ii) the date of switching to a biological drug in case of switching to a biologic; at-risk period for ETA and ADA: start of treatment to the end of follow-up.
*Multiple entries possible.
†These two patients are also included in ETA by the ever-exposed approach.
ADA, adalimumab; ETA, etanercept; MTX, methotrexate; PY, person-years; RR, relative risk.

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Clinical and epidemiological research

EXTENDED REPORT

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ETA = 1414, ADA = 320, MTX =1455

Eventos adverso:

SAE:→ ***ETA: 4,5 - ADA: 4,7*** *per/100 años vs* ***MTX 2,90*** *per/100años*

Neoplasia: No ≠ significativas

→ *ETA - ADA – MTX → 0,09, 0,27 y 0,07 / 100 personas-años.*

EII - Uveitis:

* ETN mono: > **frec EII y uveitis** → *0,5 y 0,8 / 100 años*
* ETN + MTX → *0,1 y 0,2 / 100 años*
* MTX → *0,03 y 0,1 / 100 años*

Conclusion.

* Tolerancia a largo plazo aceptable → ETN y ADA.
* ETN y (EII – Uveitis) → efecto paradójico? o respuesta inadecuada?

EII – UVEITIS → ETANERCEPT

Prince FHM, Twilt M, ten Cate R, *et al*. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. *Ann Rheum Dis* 2009;68:635–41.

Ruemmele FM, Prieur A-M, Talbotec C, *et al*. Development of Crohn disease during anti-TNF-alpha therapy in a child with juvenile idiopathic arthritis. *J Pediatr Gastroenterol Nutr* 2004;39:203–6.

Van Dijken TD, Vastert SJ, Gerloni VM, *et al*. Development of inflammatory bowel disease in patients with juvenile idiopathic arthritis treated with etanercept. *J Rheumatol* 2011;38:1441–6.

Sunseri W, Hyams JS, Lerer T, *et al*. Retrospective cohort study of methotrexate use in the treatment of pediatric Crohn's disease. *Inflamm Bowel Dis* 2014;20:1341–5.

Dallocchio A, Canioni D, Ruemmele F, *et al*. Occurrence of inflammatory bowel disease during treatment of juvenile idiopathic arthritis with etanercept: a French retrospective study. *Rheumatol Oxf Engl* 2010;49:1694–8.

Kotaniemi K, Kautiainen H, Karma A, *et al*. Occurrence of uveitis in recently diagnosed juvenile chronic arthritis: a prospective study. *Ophthalmology* 2001;108:2071–5.

Schmeling H, Horneff G. Etanercept and uveitis in patients with juvenile idiopathic arthritis. *Rheumatol Oxf Engl* 2005;44:1008–11.

Saurenmann RK, Levin AV, Feldman BM, *et al*. Risk of new-onset uveitis in patients with juvenile idiopathic arthritis treated with anti-TNFalpha agents. *J Pediatr* 2006;149:833–6.

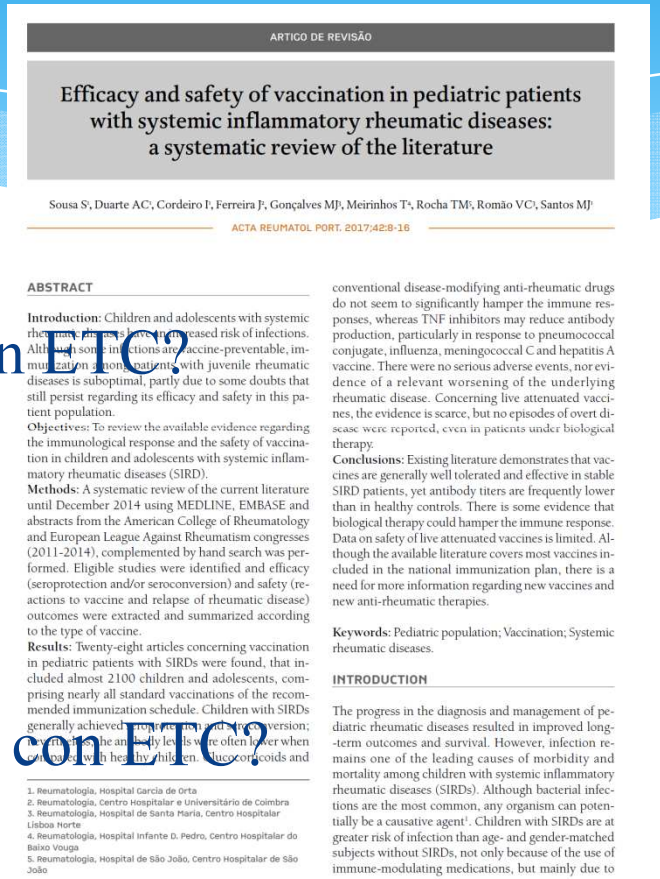
Algunas Conclusiones

* Predomina en mono terapia
* Efecto protector del MTX
* Hacen falta mas estudios para poder afirmar que es causa directa.

Vacunas en niños con Enf. Reumáticas.

Cuales serian las preguntas?

* Las vacunas **son seguras** en niños con ETC?
* Que **grado de respuesta** tienen?
* Podrían **reactivar la enfermedad**?
* Diferencia de Rta entre sanos y niños con ETC?



ARTIGO DE REVISÃO

Efficacy and safety of vaccination in pediatric patients with systemic inflammatory rheumatic diseases: a systematic review of the literature

Sousa S[1], Duarte AC[2], Cordeiro I[3], Ferreira J[3], Gonçalves MJ[3], Meirinhos T[4], Rocha TM[5], Romão VC[3], Santos MJ[3]

ACTA REUMATOL PORT. 2017;42:8-16

ABSTRACT

Introduction: Children and adolescents with systemic rheumatic diseases have increased risk of infections. Although some infections are vaccine-preventable, immunization options for patients with juvenile rheumatic diseases is suboptimal, partly due to some doubts that still persist regarding its efficacy and safety in this patient population.

Objectives: To review the available evidence regarding the immunological response and the safety of vaccination in children and adolescents with systemic inflammatory rheumatic diseases (SIRD).

Methods: A systematic review of the current literature until December 2014 using MEDLINE, EMBASE and abstracts from the American College of Rheumatology and European League Against Rheumatism congresses (2011-2014), complemented by hand search was performed. Eligible studies were identified and efficacy (seroprotection and/or seroconversion) and safety (reactions to vaccine and relapse of rheumatic disease) outcomes were extracted and summarized according to the type of vaccine.

Results: Twenty-eight articles concerning vaccination in pediatric patients with SIRDs were found, that included almost 2100 children and adolescents, comprising nearly all standard vaccinations of the recommended immunization schedule. Children with SIRDs generally achieved [illegible] and seroconversion; however, the antibody levels were often lower when compared with healthy children. Glucocorticoids and conventional disease-modifying anti-rheumatic drugs do not seem to significantly hamper the immune responses, whereas TNF inhibitors may reduce antibody production, particularly in response to pneumococcal conjugate, influenza, meningococcal C and hepatitis A vaccine. There were no serious adverse events, nor evidence of a relevant worsening of the underlying rheumatic disease. Concerning live attenuated vaccines, the evidence is scarce, but no episodes of overt disease were reported, even in patients under biological therapy.

Conclusions: Existing literature demonstrates that vaccines are generally well tolerated and effective in stable SIRD patients, yet antibody titers are frequently lower than in healthy controls. There is some evidence that biological therapy could hamper the immune response. Data on safety of live attenuated vaccines is limited. Although the available literature covers most vaccines included in the national immunization plan, there is a need for more information regarding new vaccines and new anti-rheumatic therapies.

Keywords: Pediatric population; Vaccination; Systemic rheumatic diseases.

INTRODUCTION

The progress in the diagnosis and management of pediatric rheumatic diseases resulted in improved long-term outcomes and survival. However, infection remains one of the leading causes of morbidity and mortality among children with systemic inflammatory rheumatic diseases (SIRDs). Although bacterial infections are the most common, any organism can potentially be a causative agent[1]. Children with SIRDs are at greater risk of infection than age- and gender-matched subjects without SIRDs, not only because of the use of immune-modulating medications, but mainly due to

1. Reumatologia, Hospital Garcia de Orta
2. Reumatologia, Centro Hospitalar e Universitário de Coimbra
3. Reumatologia, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte
4. Reumatologia, Hospital Infante D. Pedro, Centro Hospitalar do Baixo Vouga
5. Reumatologia, Hospital de São João, Centro Hospitalar de São João

Sousa S, Duarte A Acta Reumatol Port. 2017;42:8-16

Vacuna Antigripal *600 ptes*

Eficacia

Sousa, Acta Reumatol Port 2017

* Seroconversión 82%
* Respuesta: niveles de Atc bajos → **Adecuada**.
* *Baja tasa de respuesta en pte con **CTC >20mg/dia –CTC + MTX**.*

Seguridad:

* Similar a controles sanos.
* Reportes escasos reactivación debajo grado.

Ogima C, Tanaka R, Saitoh A, Oh-ishi T. Immunogenicity of Influenza Vaccine in Children With Pediatric Rheumatic Diseases Receiving Immunosuppressive Agents. The Pediatric Infectious Disease Journal 2011; 30(3):208-211.

Vacuna Anti-Hepatitis B 128 ptes

Eficacia

* Seroconversión 80% vs sano 95%.
* Tto inmunuspresor **LESp y AIJ** → No modifican respuesta
* Titulos AC > 10mUI/ml → mas bajos que sanos

Seguridad.

* No efectos adversos ni reactivación

Kasapçopur -. Ann Rheum Dis 2004; 63: 1128-1130.
Maritsi D, Clin and Exp Rheumat 2013; 31: 969-973.

Vacuna Anti-Hepatitis A 47 ptes

- Respuesta adecuada
  - 4 pte con AIJ sistemica Activa /anti-TNF → No rta

Erguven M J Chinese Med Association 2011; 74:205-208

Vacuna Anti-HPV 89 **AIJ** – 6 **LES**- 6 **DMJ**

- Seroconversión 100%
- Títulos bajos vs controles
- Sin eventos adversos

Heijstek M, The J Rheu 2013; 40(9):1626-27.
Heijstek M Ann Rheum Dis 2014; 73:1500–07.
Esposito S, Expert Rev Vaccines 2014; 13(11):1387-93

Vacuna Anti-Meningococo C

- Rta adecuada, Títulos bajos vs controles.

Seguridad:

- Sin efectos adversos

Zonneveld, Art & Rheu 2007; 56:639–646.
Stoof S, Ann Rheum Dis 2014; 73:728–734.

Vacunas a virus vivos

Vacuna Triple viral

Eficacia

* 131 pte **AIJ** MTX- ETN → Rta adecuada

Seguridad:

* No Enfermedad veccinal.
* Reacciones: ***artritis transitoria, artralgia***

Heijstek M JAMA 2013; 309(23):2449-2456.

Anti- Varicela

79 niños **AIJ- LES** (CTC 3 a 20mg -MTX- otros DMARD)

* Seroconversion 52 vs 72%

Seguridad:

* No episodio de enfermedad post vaccinal.
* No reactivación

Pileggi G, Art Care & Res 2010; 62:1034–1039
Barbosa C, Clin and Exp Rheu 2012; 30: 791-798

Vacunas en niños con Enf. Reumáticas.

Conclusiones:

- *Buena eficacia y perfil de seguridad*
- *Respuesta con Bajos titulo AC → Suficientes*

Recomendación

- ***Vacunar a pte con ETC***
- No virus vivos → *Aunque los escaso trabajos refieren seguridad.*

Conclusiones

* La enfermedad no controlada ***responsable*** de muchos EA
* Baja incidencia EA en ***dosis adecuada***
* Efectos adversos ***graves son raros*** en Pediatria
* Monitoreo ***clínico y bioquímico*** en pte con tratamiento IS
* Toda Infeccion deben ser asumidas como ***Urgencia Infectologica***

Muchas Gracias