

PACIENTE 4. ARTRITIS REUMATOIDE

**TRATAMIENTO CON FÁRMACOS
MODIFICADORES DE LA ENFERMEDAD**

**POLIMORFISMOS DE LOS GENES:
MTHFR, CYP1A2, TNF, TPMT**

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20 de Febrero de 2013



**Hospital General Universitario
Gregorio Marañón**

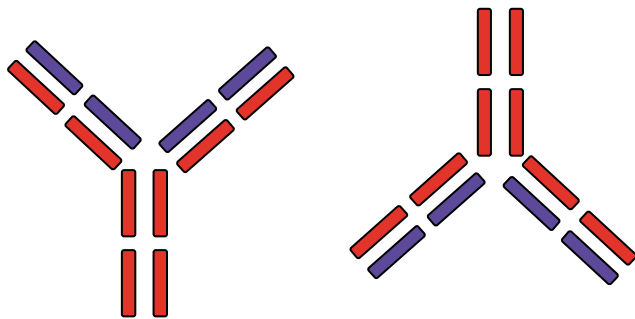
Comunidad de Madrid



**Consejería de Salud
Hospital Universitario
Virgen de la Nieves**

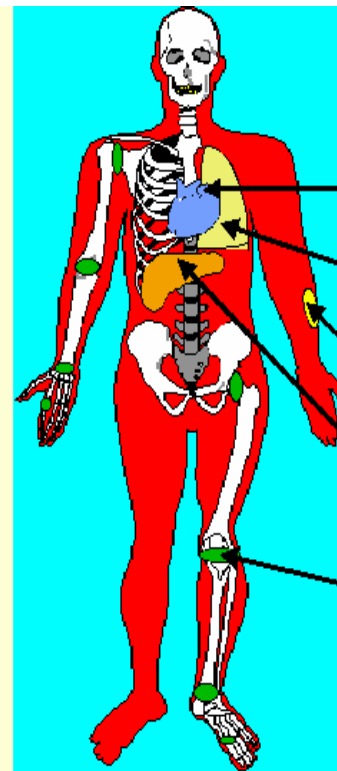
Artritis Reumatoide

1. Predisposición genética
Epítipo compartido/ PTNP22 / DR
Tabaco



2. Formación de AutoAc
FR/ anti-PCC

3. Enfermedad sistémica con diana en la sinovial



Sd. seco

Pericarditis

Fibrosis pulmonar

Nódulos reumatoides

Disfunción hepática

Sinovitis

Estrategia terapéutica: Step-up

"Treat to target"/ Remisión (DAS28, CDAI, SDAI)/ Imagen (Eco)

-Respondedores
-Respondedores parciales
-Pérdidas de respuesta
-No respondedores

PCC+, Rx erosiones

Anti-TNF?
Cambio de diana:
antiCD20
Anti- IL6R/ CTL4Ig

PCC+, Rx erosiones

Anti-TNF

PCC+, Rx erosiones

Corticoides
Mtx
¿Mtx +2º FAME?

Supervivencia fármacos 5 años
Efectos adversos
Progresión Rx
Mantenimiento indefinido de terapias

Estrategia terapéutica

Objetivo

Remisión-Baja actividad

Responsabilidad

Treat to target

ARTHRITIS & RHEUMATISM
Vol. 62, No. 9, September 2010, pp 2569–2581
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Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology
www.arthritisrheum.org and www.interscience.wiley.com

2010 Rheumatoid Arthritis Classification Criteria

An American College of Rheumatology/European League Against Rheumatism
Collaborative Initiative

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Treating rheumatoid arthritis to target: recommendations of an international task force

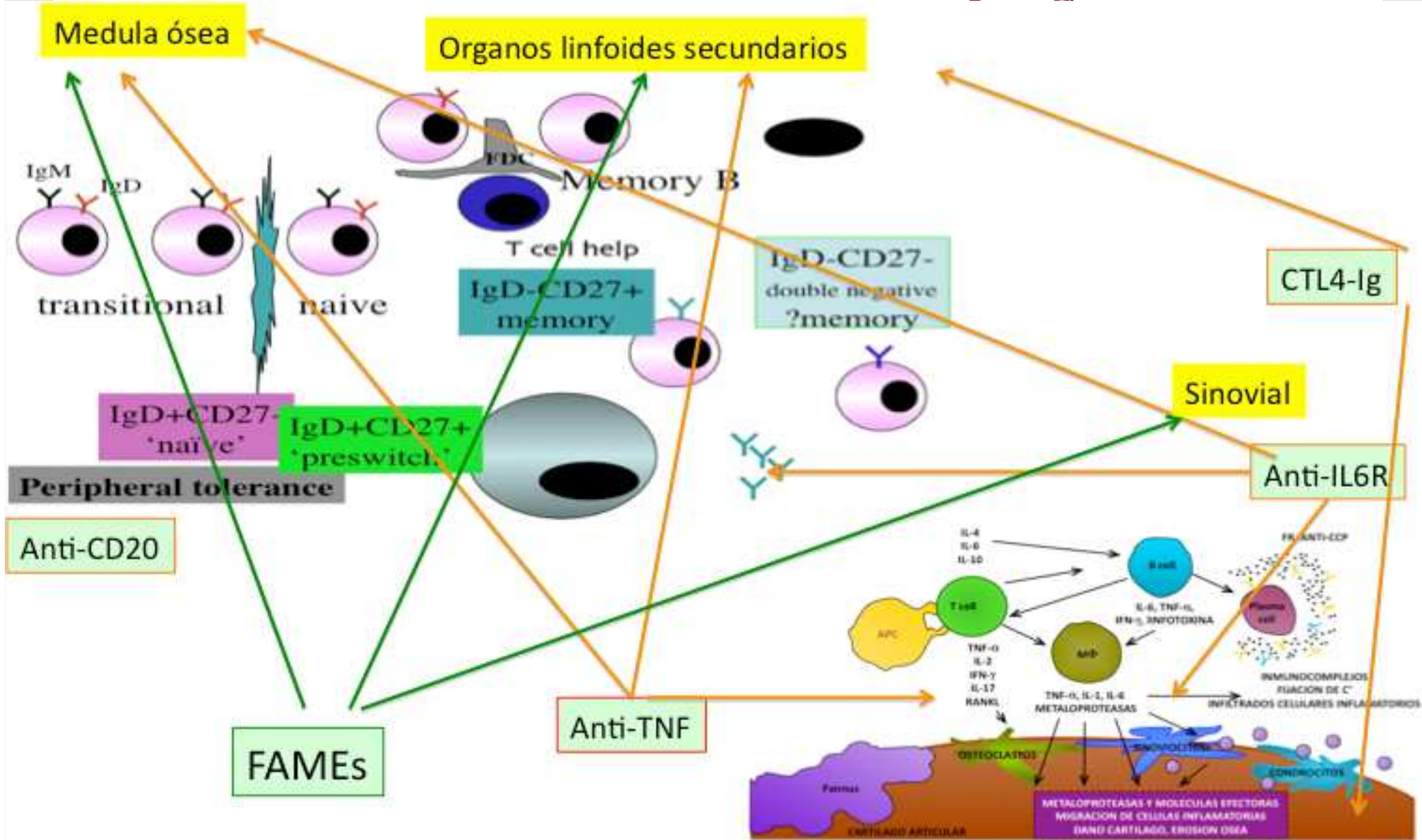
Josef S Smolen,^{1,2} Daniel Aletaha,¹ Johannes W J Bijlsma,³ Ferdinand C Breedveld,⁴
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Desirée van der Heide,⁴ for the T2T Expert Committee

Ann Rheum Dis 2010;**69**:631–637. doi:10.1136/ard.2009.123919

Reto

Medicina Individualizada

**Intervención terapéutica en diferentes puntos
NO EXCLUYENTES dentro del CICLO etiopatogénico de la AR**



CASO CLÍNICO

Antecedentes

- ✓ **Mujer, 32 años. Sin antecedentes de interés**
- ✓ **Madre con AR**
- ✓ **Oligoartritis (4 articulaciones, simétrica y bilateral), 2 semanas de evolución**
- ✓ **FR -, anti-PCC (<25 UI): >3200 UI**
- ✓ **PCR (0-0.5 mg/dl): 0.8 mg/dl, VSG (<10 mM/h): 26 mM/h**
- ✓ **Rx manos y pies: sin alteraciones**
- ✓ **Anemia normocítica-normocrómica**

CASO CLÍNICO

Nuevos criterios diagnósticos de AR: ACR-EULAR 2010 ($\geq 6/10$)

- A. Tipo de articulación (3)
- B. Serología (2)
- C. Reactantes de fase aguda (1)
- D. Duración de los síntomas (0)



ARTRITIS REUMATOIDE

Table 3. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)*	
2) with the synovitis not better explained by another disease†	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of $\geq 6/10$ is needed for classification of a patient as having definite RA)‡	
A. Joint involvement§	
1 large joint¶	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)#	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)**	5
B. Serology (at least 1 test result is needed for classification)††	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms§§	
<6 weeks	0
≥ 6 weeks	1

CASO CLÍNICO

Tratamiento de AR

"Treating rheumatoid arthritis to target: recommendations of an international task force".

Smolen et al, Ann Rheum Dis 2010.

"Recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs".

Smolen et al, Ann Rheum Dis 2010

3 primeros meses: MTX 7.5 mg pasa a 20 mg/semana

DAS28 (4.1 → 2.6), SDAI (14 → 3.0), CDAI (14.8 → 3.3)

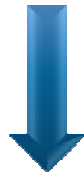
HAQ:0

CASO CLÍNICO

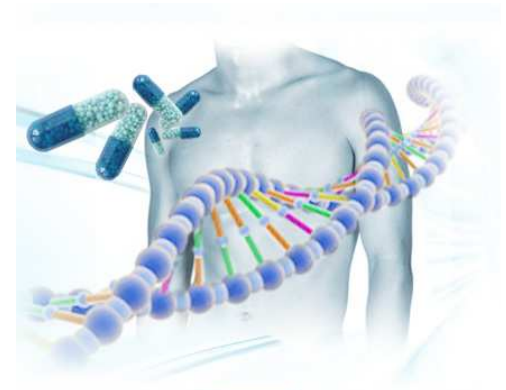
Evolución

A los 6 meses:

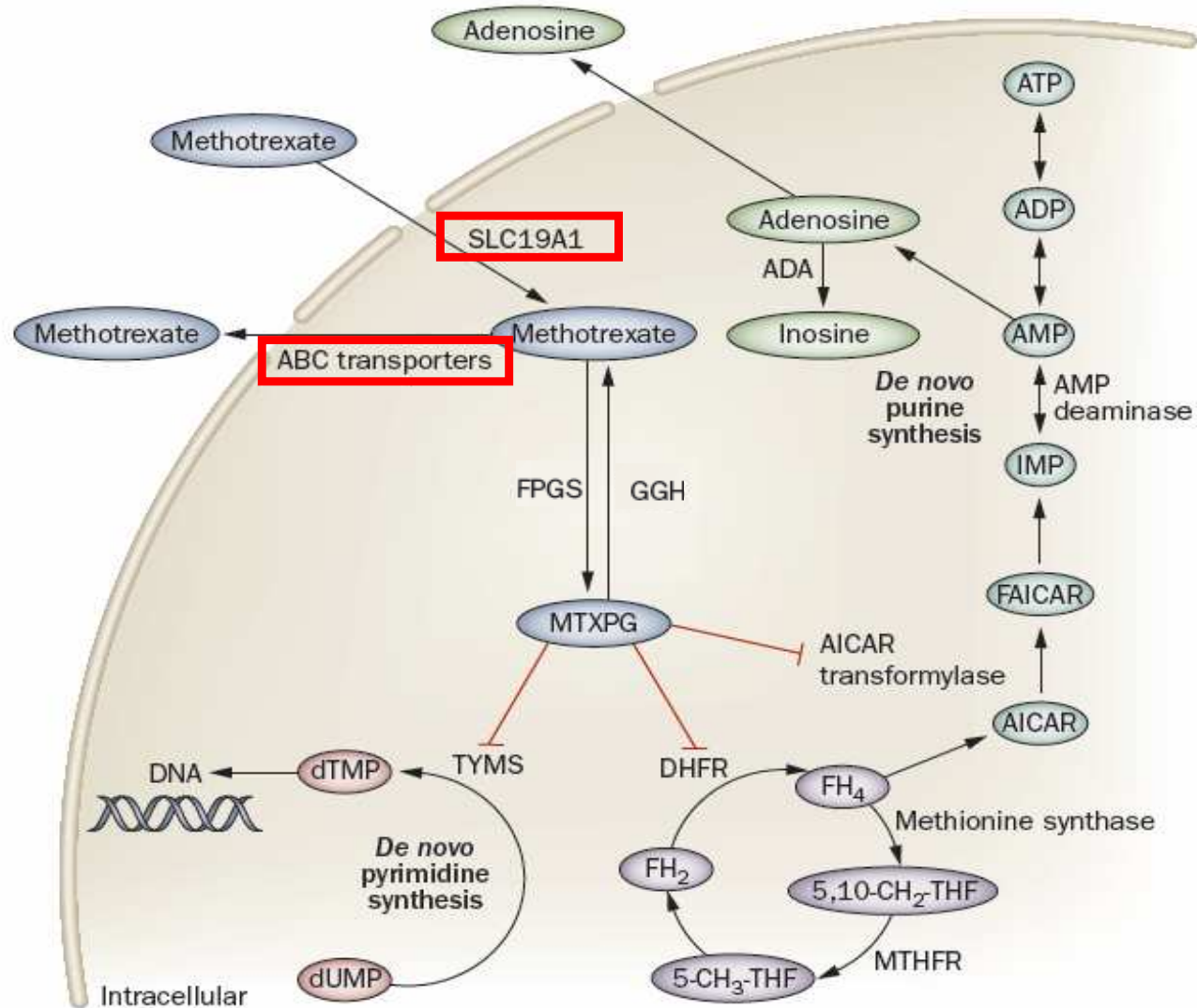
**Presenta molestias gastrointestinales y toxicidad hepática
(AST y ALT >3 veces valor referencia)**



ESTUDIO FARMACOGENÉTICO



Mecanismo de acción del metotrexato



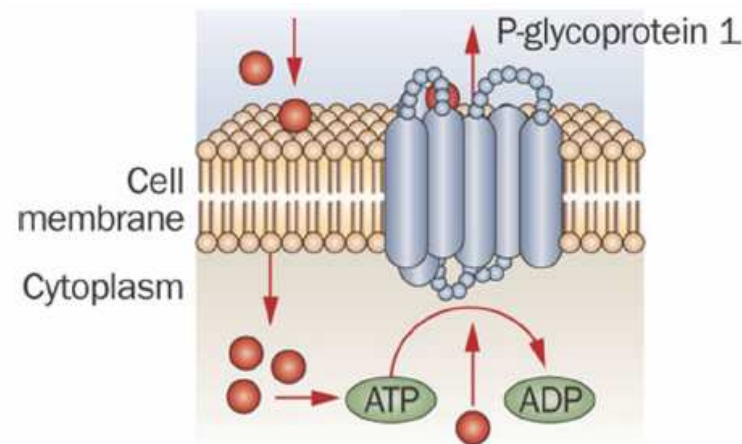
Davila et al. Pharmacogenetics: implications for therapy in rheumatic diseases. Nat Rev Rheumatol. 2011;7(9):537-50

Farmacogenética del metotrexato

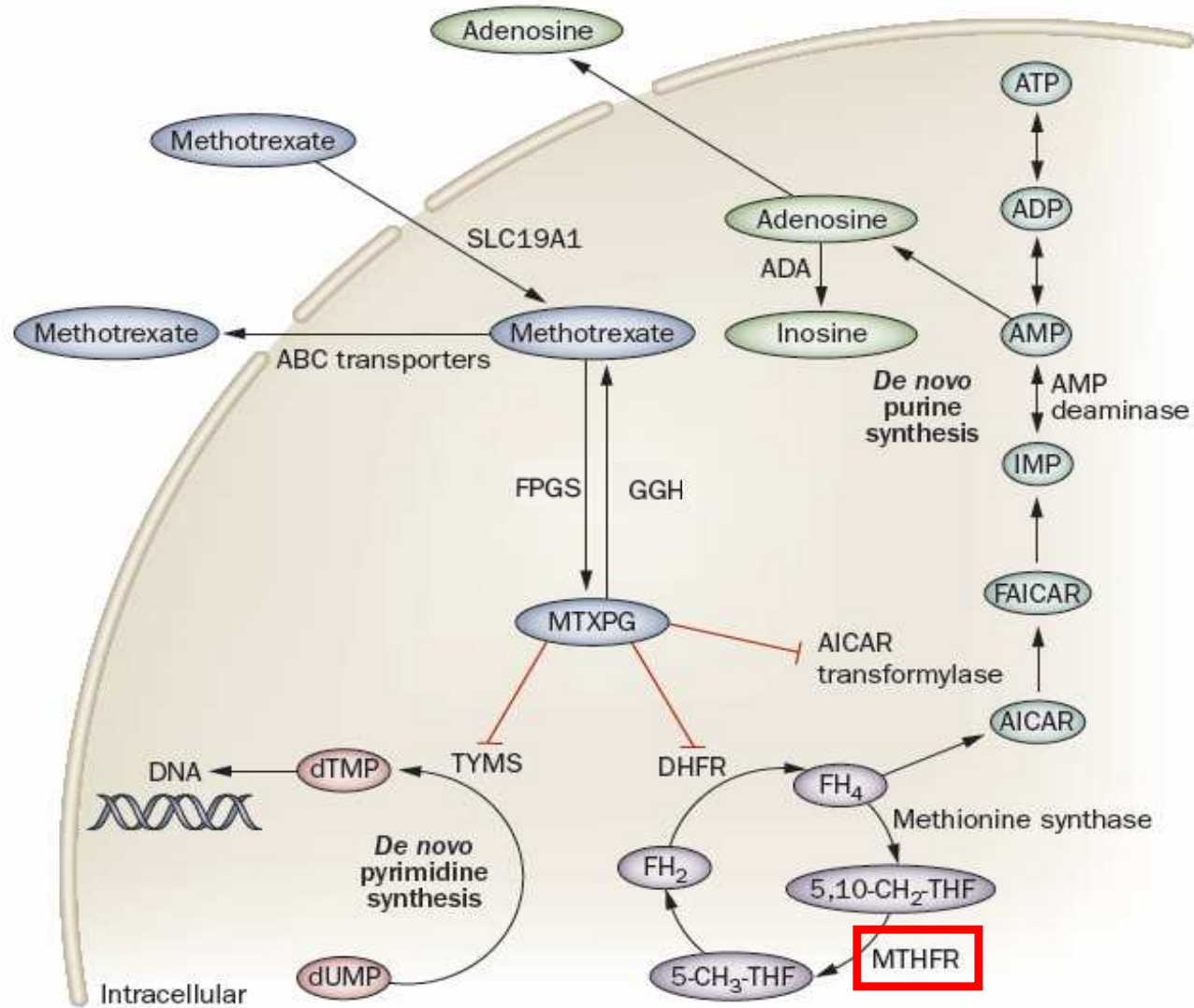
POLIMORFISMOS EN LAS MOLÉCULAS TRANSPORTADORAS

SLC19A1, FOLT, transports folate (and methotrexate) into cell	80G>A	Results in higher intracellular levels of MTXPGs	Takatori (2006), ²⁶ retrospective, n=124; all patients with RA	No effect on efficacy
			Dervieux (2004), ³⁰ cross-sectional, n=108; all patients with RA	Associated with increased efficacy
ABCB1, MDR1, efflux pump	3435C>T	Increases efflux of methotrexate	Takatori et al. (2006), ²⁶ retrospective, n=124; all patients with RA	Associated with decreased efficacy

Davila et al. Pharmacogenetics: implications for therapy in rheumatic diseases. Nat Rev Rheumatol. 2011;7(9):537-50



Mecanismo de acción del metotrexato



Davila et al. Pharmacogenetics: implications for therapy in rheumatic diseases. Nat Rev Rheumatol. 2011;7(9):537-50

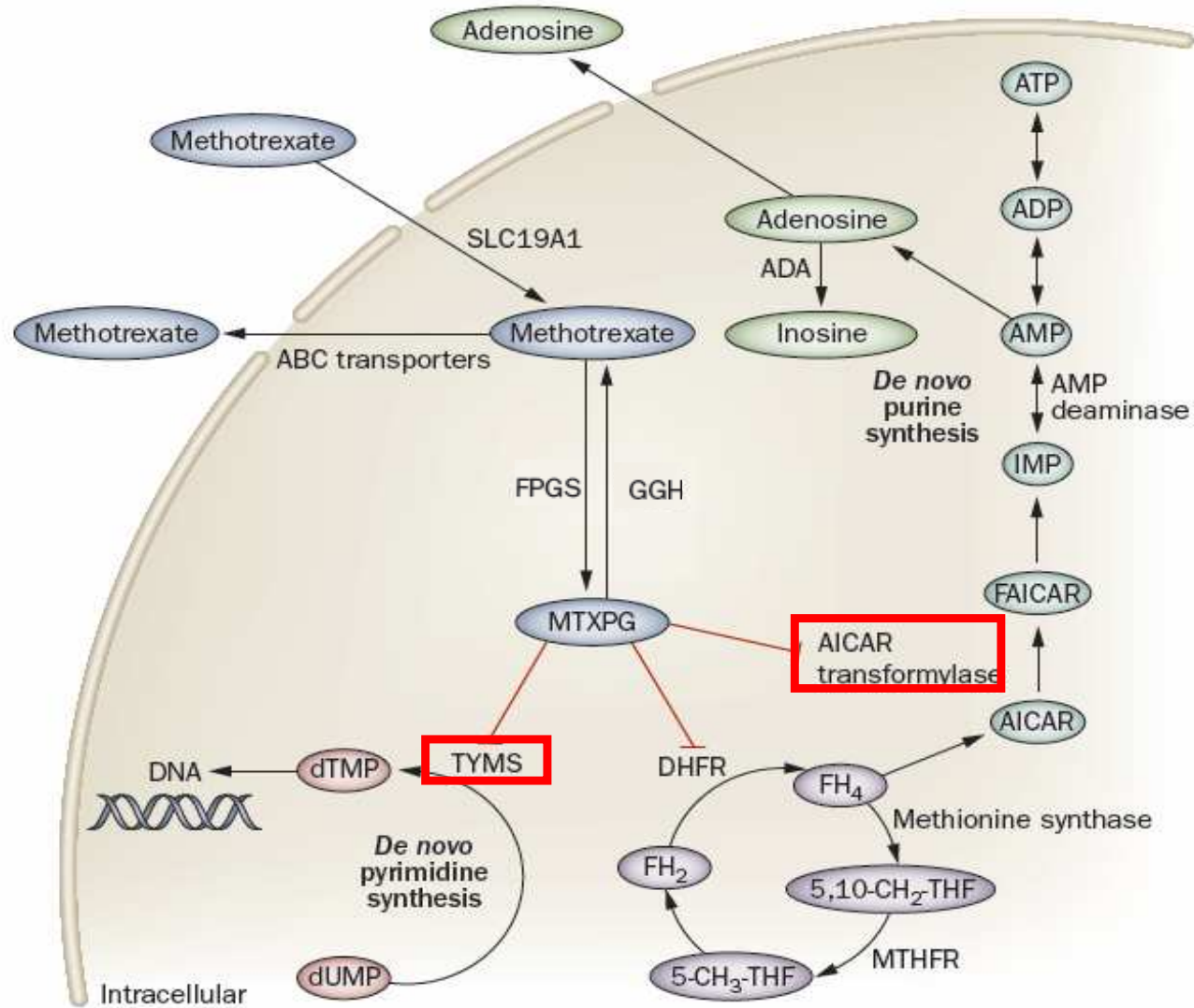
Farmacogenética del metotrexato

POLIMORFISMOS EN EL CICLO DEL FOLATO

MTHFR, MTHFR, generation of 5-methyl tetrahydrofolate	677C>T	Produces a thermolabile MTHFR variant; decreases enzyme levels	Van Ede <i>et al.</i> (2001), ¹³ prospective, <i>n</i> =236; all patients with RA	Associated with discontinuation of methotrexate due to increased toxicity
			Urano <i>et al.</i> (2002), ¹⁵ retrospective, <i>n</i> =106; all patients with RA	Associated with increased toxicity
			Fisher & Cronstein (2009), ¹⁶ meta-analysis, <i>n</i> =1,400	Associated with increased toxicity
			Lee & Song (2010), ¹⁷ meta-analysis, <i>n</i> =1,514	No effect on toxicity or efficacy
			Weisman <i>et al.</i> (2006), ³¹ cross-sectional, <i>n</i> =214; all patients with RA	Associated with increased toxicity
	1298A>C	Decreases MTHFR enzymatic activity	Berkun <i>et al.</i> (2004), ¹⁴ cross-sectional, <i>n</i> =93; all patients with RA	Associated with reduced toxicity
			Urano <i>et al.</i> (2002), ¹⁵ retrospective, <i>n</i> =106; all patients with RA	Associated with increased efficacy
			Fisher & Cronstein (2009), ¹⁶ meta-analysis, <i>n</i> =660	No effect on toxicity
			Lee (2010), ¹⁷ meta-analysis, <i>n</i> =1,514	No effect on toxicity or efficacy
SHMT1, SHMT, generation of 5,10-methylene tetrahydrofolate	1420C>T	Alters enzyme activity	Weisman <i>et al.</i> (2006), ³¹ cross-sectional, <i>n</i> =214; all patients with RA	Associated with increased toxicity

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Mecanismo de acción del metotrexato



Davila et al. Pharmacogenetics: implications for therapy in rheumatic diseases. *Nat Rev Rheumatol.* 2011;7(9):537-50

Farmacogenética del metotrexato

POLIMORFISMOS EN LA SÍNTESIS DE NUCLEÓTIDOS

TYMS, TYMS, conversion of dUMP to dTMP in <i>de novo</i> pyrimidine synthesis (Inhibited by MTXPGs)	5'-UTR repeat element	Triple repeat allele associated with increased TYMS activity	Kumagai et al. (2003), ²⁴ retrospective, <i>n</i> =167; 115 patients with RA treated with methotrexate, 52 controls	Triple repeat allele associated with decreased efficacy
			Dervieux et al. (2004), ³⁰ cross-sectional, <i>n</i> =108; all patients with RA	Triple repeat allele associated with decreased efficacy
	3'-UTR deletion	Decreases mRNA stability and expression	Kumagai et al. (2003), ²⁴ retrospective, <i>n</i> =167; 115 patients with RA treated with methotrexate, 52 controls	Associated with improved efficacy
ATIC, PURH, formylation of AICAR during <i>de novo</i> purine synthesis (Inhibited by MTXPGs)	347C>G	Alters enzyme activity and increases intracellular AICAR levels	Wessels et al. (2006), ²⁵ prospective, <i>n</i> =205; all patients with RA	Associated with improved efficacy and increased toxicity
			Takatori et al. (2006), ²⁶ retrospective, <i>n</i> =124; all patients with RA	No effect on efficacy
			Dervieux et al. (2004), ³⁰ cross-sectional, <i>n</i> =108; all patients with RA	Associated with improved efficacy
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Davila et al. Pharmacogenetics: implications for therapy in rheumatic diseases. Nat Rev Rheumatol. 2011;7(9):537-50

PREGUNTA 1

**¿EL POLIMORFISMO DE QUÉ
GEN SE ASOCIA CON UNA
MAYOR PROBABILIDAD DE
TOXICIDAD?**

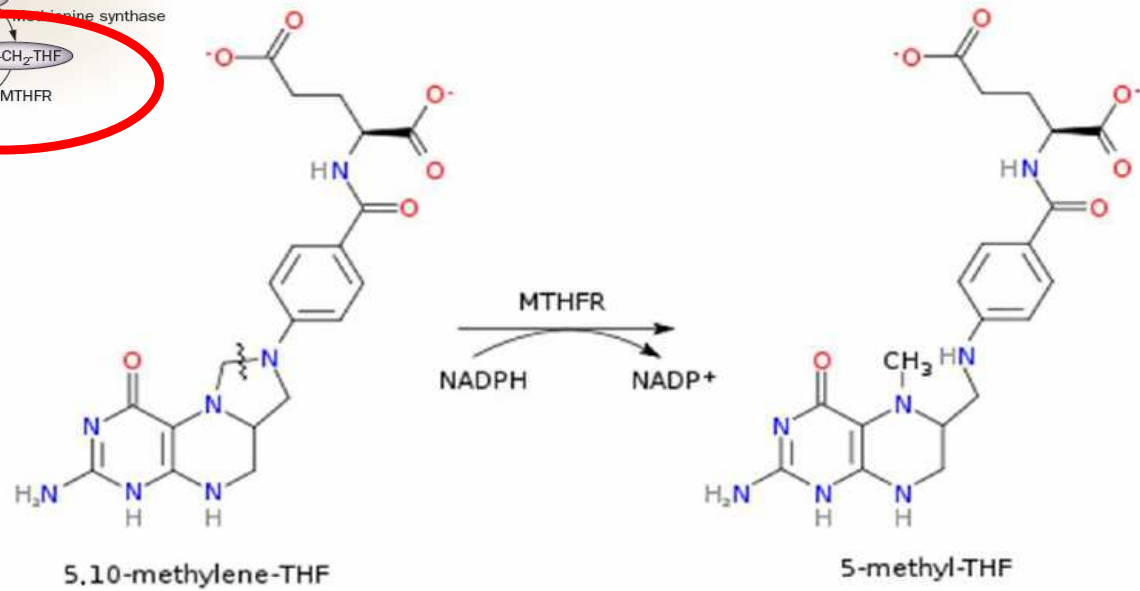
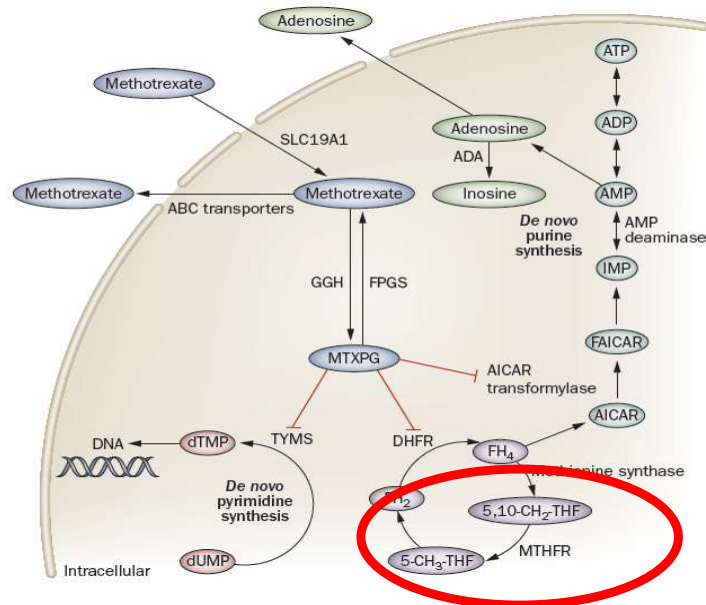
1. Metilentetrahidrofolato reductasa (MTHR)
2. Timidilato sintasa (TYMS)
3. Transpotador SLC19A1
4. Transportador ABCB1

Farmacogenética del metotrexato

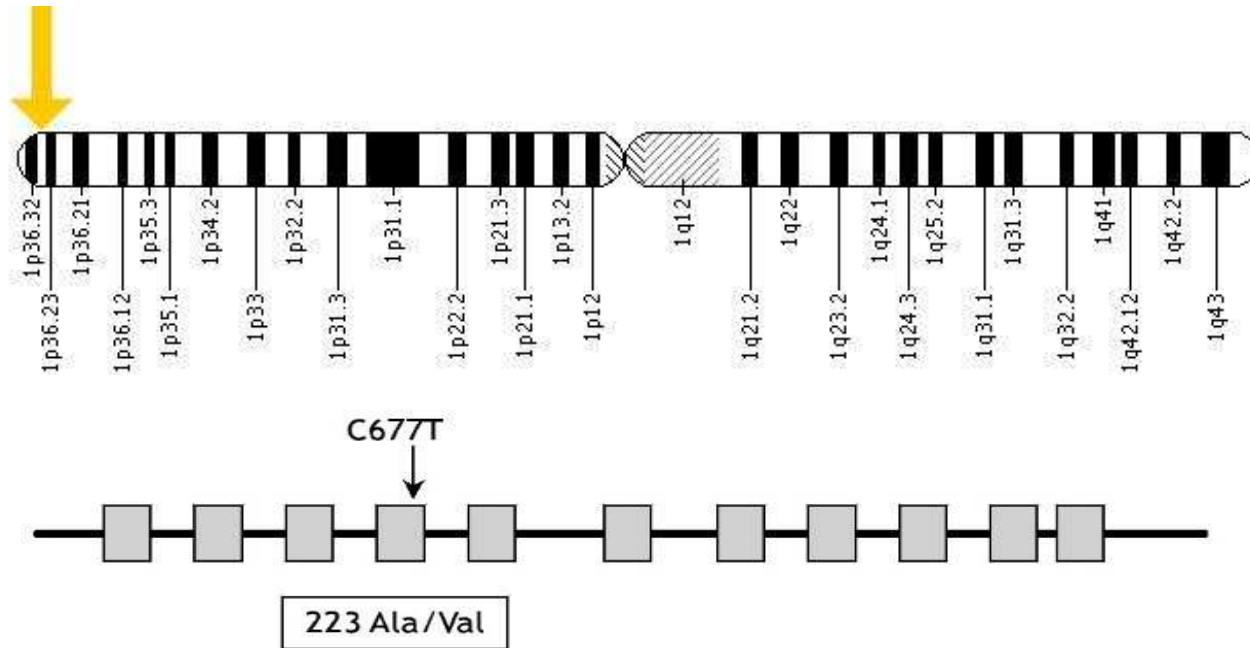
POLIMORFISMOS EN EL CICLO DEL FOLATO

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SHMT1, SHMT, generation of 5,10-methylene tetrahydrofolate	1420C>T	Alters enzyme activity	Weisman et al. (2006), ³¹ cross-sectional, n=214; all patients with RA	Associated with increased toxicity

Metilentetrahidrofolato reductasa (MTFHR)



Metilentetrahidrofolato reductasa (MTFHR)



- ✓ Prevalencia variable → 35% CC, 50% CT, 15% TT (caucásicos).
- ✓ Enzima termolábil → Reducción 50% actividad.
- ✓ Genotipo TT/CT → Mayor toxicidad (elevación enzimas hepáticas).

CASO CLÍNICO

RESULTADO FARMACOGENÉTICO

Presenta el **gentotipo TT** para el polimorfismo **C677T** de la **MTHFR**

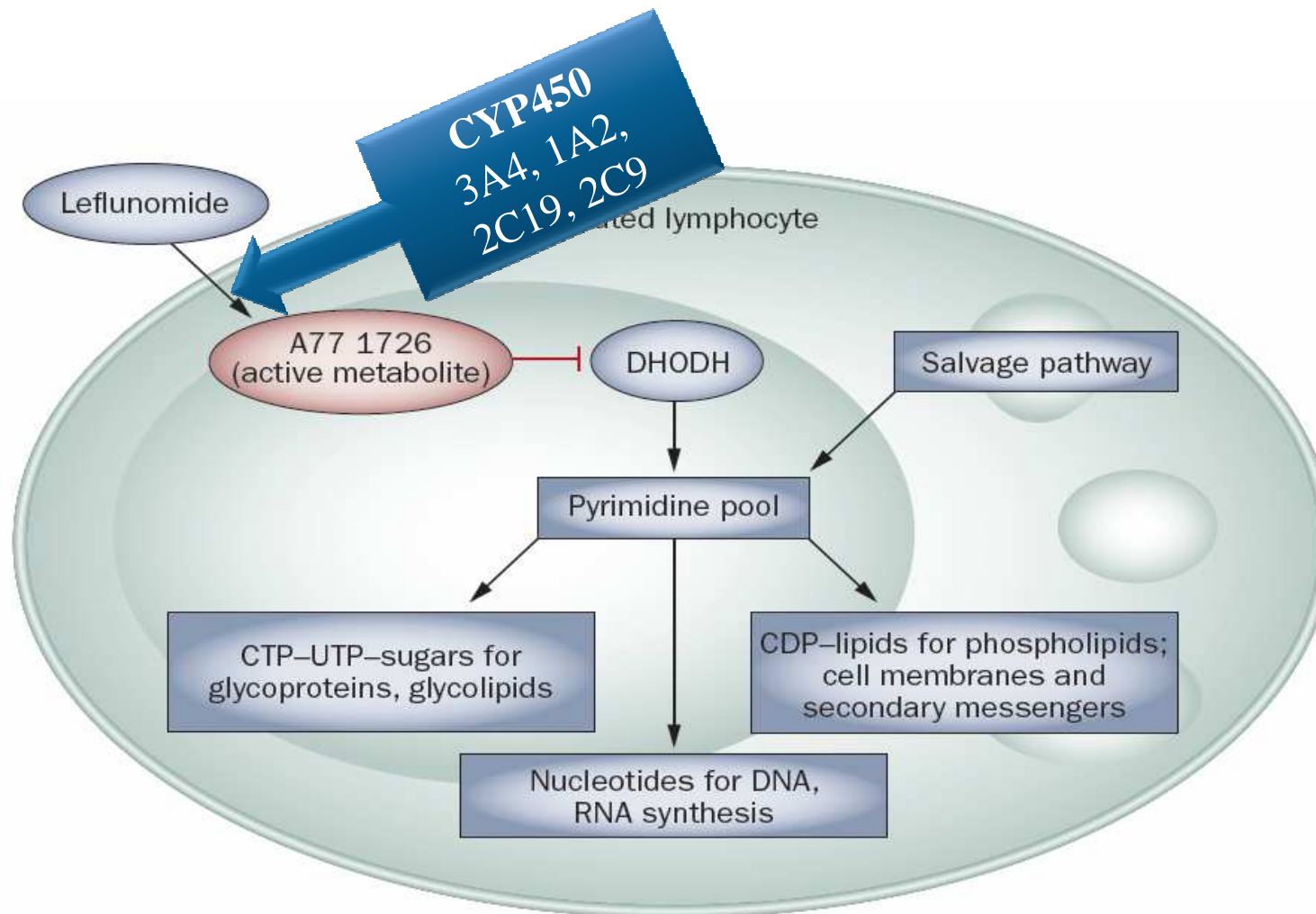
- ✓ Se suspende la escalada de metotrexato: 7.5 mg/semana
- ✓ Factores de mal pronóstico (PCR, anti-PCC+) → añadir un segundo FAME
Leflunomida



ESTUDIO FARMACOGENÉTICO



Mecanismo de acción de la leflunomida



Farmacogenética de la leflunomida

DHODH, DHODH, key enzyme of <i>de novo</i> pyrimidine synthesis	19 C>A	Alters N-terminal region of DHODH, affecting insertion into mitochondrial membrane	Pawlik (2009), ⁶² prospective, n=147; all patients with RA	Associated with increased efficacy
			Grabar (2009), ⁶³ retrospective, n=105; all patients with RA	Associated with increased toxicity
ESR1, estrogen receptor, interferes with downmodulation of cytokines	rs9340799 AA rs2234693 TT	Alters estrogen receptor expression	Dziedziejko (2010), ⁶⁴ prospective, n=115; all women with RA	Associated with increased efficacy
CYP1A2, CYP enzyme, involved in activation of leflunomide	CYP1A2*1F CC	Increases activation, leading to higher drug levels	Grabar (2008), ⁶⁸ prospective, n=106; all patients with RA	Associated with increased toxicity

Davila et al. Pharmacogenetics: implications for therapy in rheumatic diseases. Nat Rev Rheumatol. 2011;7(9):537-50

PREGUNTA 2

**¿CUÁL DE LAS SIGUIENTES
AFIRMACIONES ES
VERDADERA?**

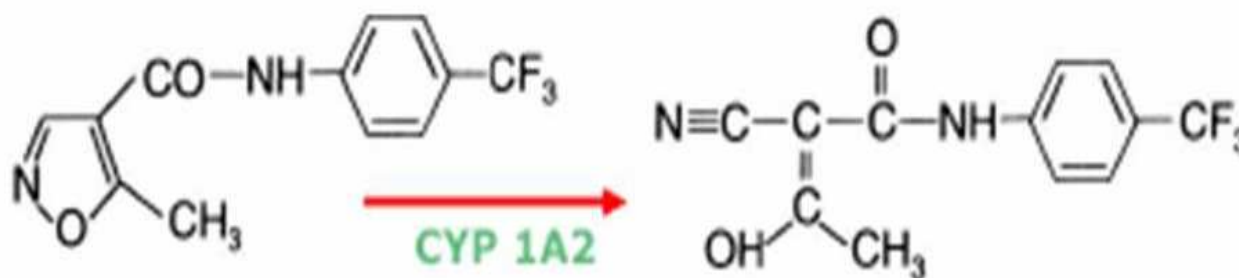
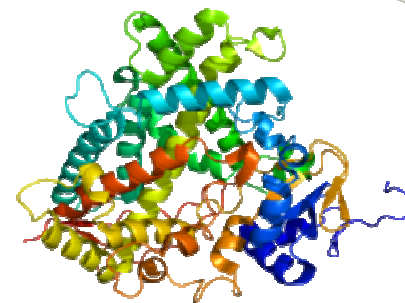
1. El CYP3A4 metaboliza la leflunomida y por tanto reduce su efectividad
2. No se ha encontrado ningún polimorfismo asociado a la efectividad de la leflunomida
3. El polimorfismo 19C de la DHODH se asocia con la efectividad y no con la toxicidad de la leflunomida
4. El alelo CYP1A2*1F se asocia con un aumento de la toxicidad de la leflunomida

Farmacogenética de la leflunomida

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CYP1A2



Leflunomida

A77 1726 (metabolito activo)

- ✓ Sustitución de una citosina por una adenosina en la posición 163 (rs762551).
- ✓ Presenta mayor capacidad de inducción.
- ✓ Genotipo CC presenta mayor probabilidad de toxicidad.

CASO CLÍNICO

RESULTADO FARMACOGENÉTICO

Presenta el **genotipo CC** del polimorfismo **CYP1A2*1F**

- ✓ Aumento de actividad de la enfermedad
- ✓ DAS28 (4.1), SDAI (14.3), CDAI (15.3)
- ✓ Factores de mal pronóstico

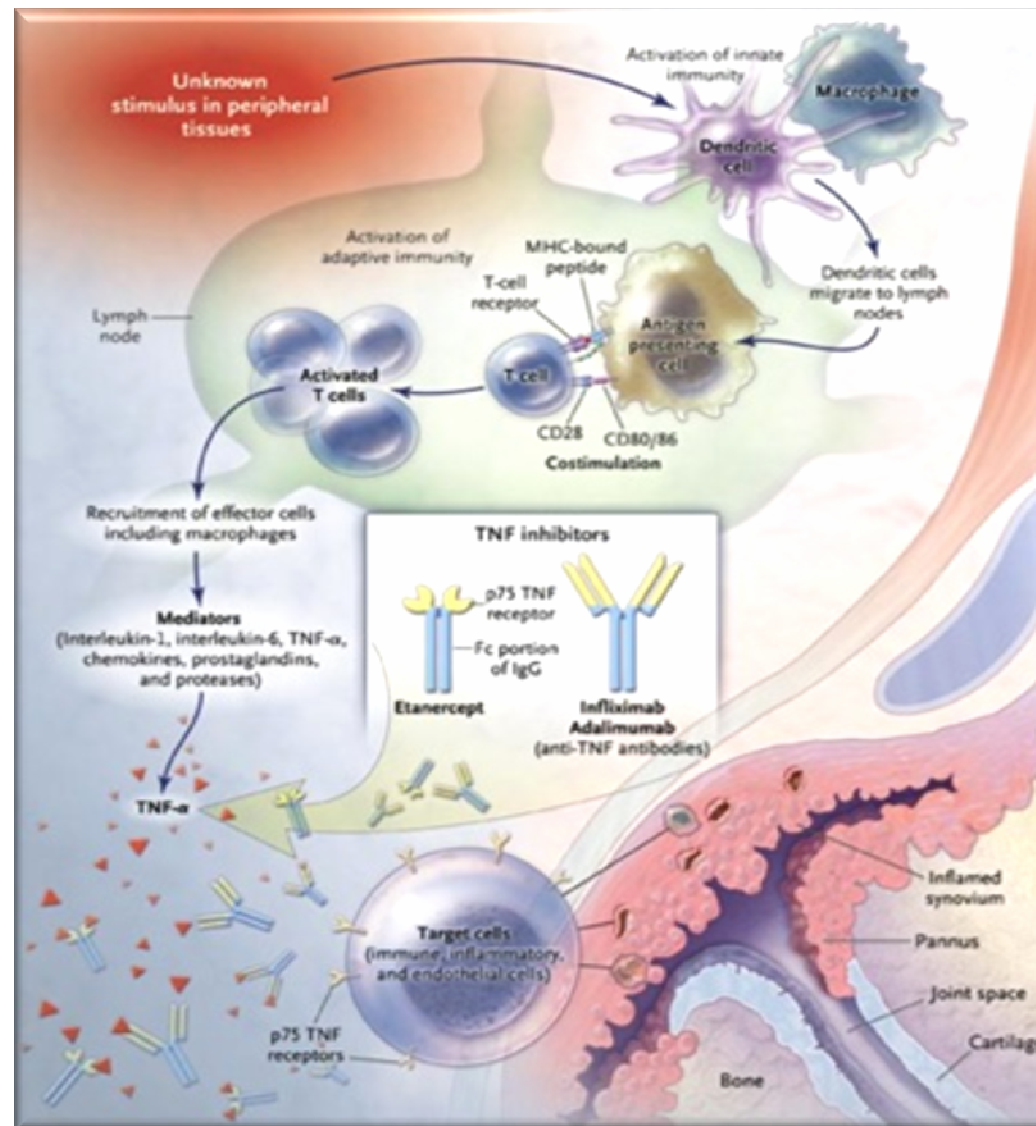
Se decide iniciar anti-TNF



ESTUDIO FARMACOGENÉTICO



Mecanismo de acción de los anti-TNF α



Scott DL et al. Tumor Necrosis Factor Inhibitors for Rheumatoid Arthritis. *N Engl J Med* 2006;355:704-12

Farmacogenética de los anti-TNF α

FCGR genes, Fc γ R, receptors for IgG	Fc γ R IIIA Val158Phe	Influences Fc γ R affinity for IgG1; affects ADCC	Kastbom (2007), ⁹⁰ prospective, n=282; all patients with RA	No effect on efficacy
PTPRC, receptor-type tyrosine-protein phosphatase C (CD45), regulates BCR and TCR signaling, and secretion of TNF by monocytes	rs10919563	Influences the secretion of cytokines including TNF	Cui (2010), ⁹⁸ prospective, n=1,283; all patients with RA	Associated with increased efficacy
MAPK14, MAPK 14, signaling molecule involved in production of proinflammatory cytokines and MMPs	SNPs in MAPK14 and in genes encoding proteins upstream and downstream in signaling pathway	Influence MAPK signaling pathway, production of cytokines and MMPs	Coulthard (2011), ¹⁰² prospective, n=1,102; all patients with RA	Associated with increased efficacy of infliximab and adalimumab, but not etanercept

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Farmacogenética de los anti-TNF α

<i>TNF blockers</i>				
TNF locus, TNF and its receptors	-308 G>A	Influences TNF production	Seitz (2007), ⁹¹ prospective, <i>n</i> =86; 54 patients with RA, 10 with PsA, 22 with AS	Associated with increased efficacy
			Cuchacovich (2006), ⁹² prospective, <i>n</i> =81; all patients with RA	Associated with increased efficacy
	-238A>G	Influences TNF production	Lee (2010), ⁹³ meta-analysis (13 studies), 1,817 patients with RA	Associated with increased efficacy
	TNFRSF1B 196 T>G	Influences receptor shedding and ligand binding; might increase IL-6 production	Fabris (2002), ⁹⁴ retrospective, <i>n</i> =175; all patients with RA	Associated with decreased efficacy
			Potter (2010), ⁹⁵ retrospective, <i>n</i> =602, all patients with RA	No effect on efficacy
	TNF microsatellites a-e	Affect DNA folding and conformation	Martinez (2004), ⁹⁶ prospective, <i>n</i> =420; 78 patients with RA, 342 healthy controls	No effect on efficacy with individual microsatellites; TNFa11;b4 haplotype more frequent in responders to infliximab
			Criswell (2004), ⁹⁷ prospective, <i>n</i> =457; all patients with RA	No effect on efficacy

Davila et al. Pharmacogenetics: implications for therapy in rheumatic diseases. Nat Rev Rheumatol. 2011;7(9):537-50

PREGUNTA 4

**¿QUÉ POLIMORFISMO SE
ASOCIA CON UN INCREMENTO
EN LA EFICACIA DE LOS ANTI-
TNF?**

1. TNFRSF1B 196 T>G

2. G308A del locus del TNF

3. A208G del locus del TNF

4. FcγR III A Val 158 Phe

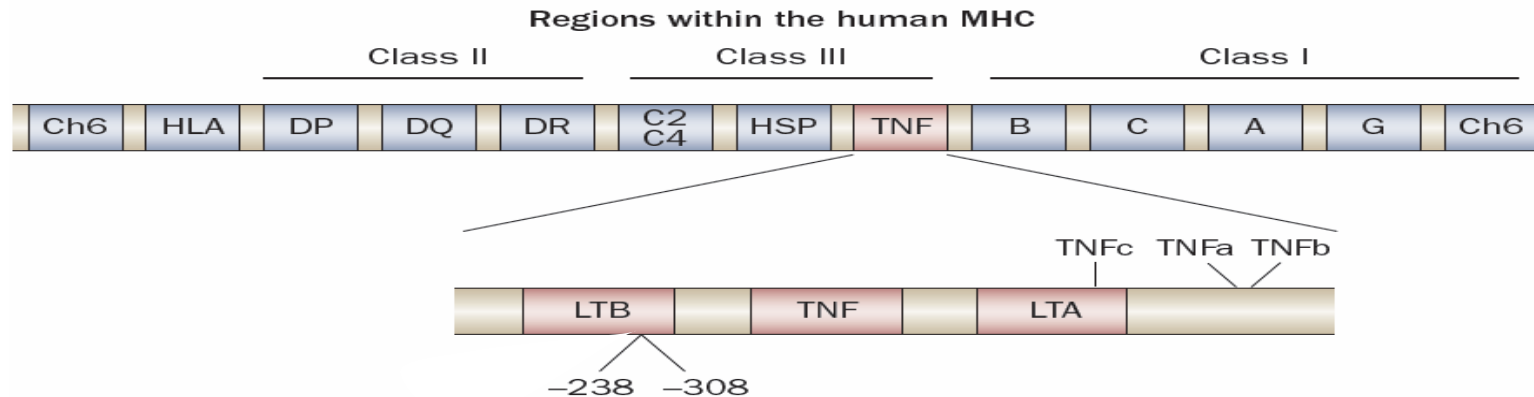
Farmacogenética de los anti-TNF α

TNF blockers

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Polimorfismo G308A del TNF α



Davila et al. Pharmacogenetics: implications for therapy in rheumatic diseases. Nat Rev Rheumatol. 2011;7(9):537-50

- ✓ Sustitución de guanósina por adenósina en la posición 308.
- ✓ G308A influye en los niveles circulantes de TNF- α .
- ✓ Genotipo GG está asociado con una mayor tasa de respuesta a los anti-TNF.

CASO CLÍNICO

RESULTADO FARMACOGENÉTICO

Presenta el **genotipo GG** del polimorfismo **G308A**

Inicia tto. con **INFLIXIMAB:**

3mg/kg/8 semanas+MTX 7.5 mg/semana

- ✓ DAS28, SDAI, CDAI: en remisión.
- ✓ HAQ: 0.
- ✓ Rx manos y pies: sin progresión.

CASO CLÍNICO

Evolución

A los 12 meses:

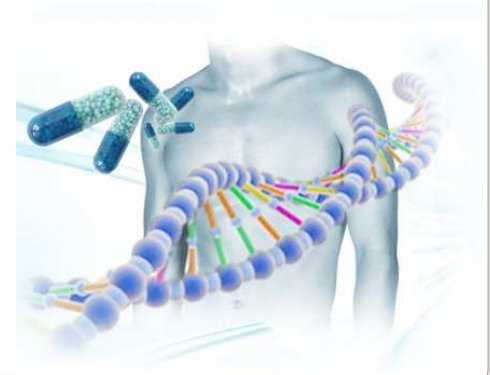
- ✓ Raynaud
- ✓ Lesiones cutáneas
- ✓ Proteinuria en rango nefrótico
- ✓ ANA +. anti-DNA-

→ **Lupus inducido** (<1%, *Katz et al. Autoimmun Rev. 2010*)

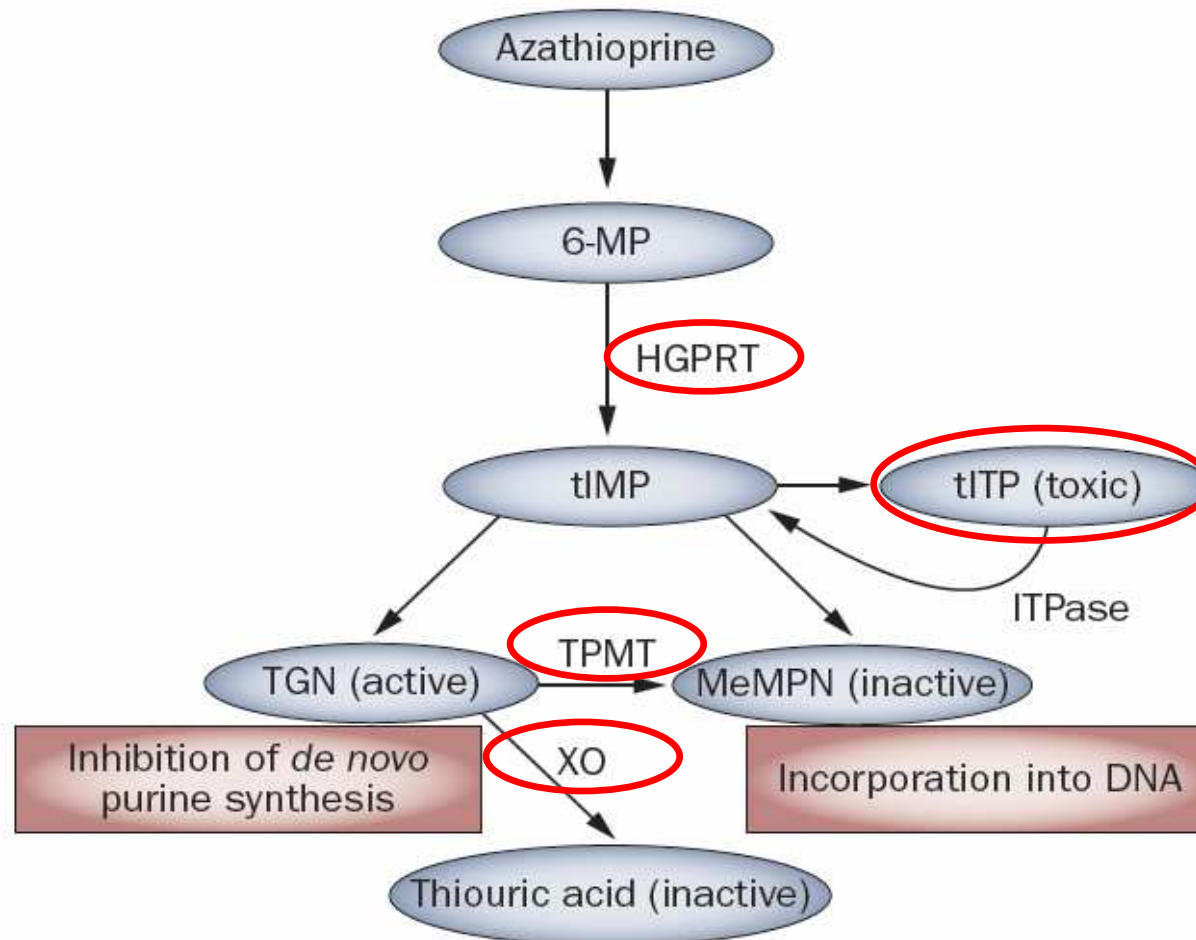
Se decide iniciar **Azatioprina**



ESTUDIO FARMACOGENÉTICO



Mecanismo de acción de la azatioprina



Farmacogenética de la azatioprina

TPMT, TPMT, inactivates thioguanine nucleotides	TPMT*2	Each variant allele results in decreased enzyme activity	Kerstens et al. (1995), ⁴⁰ cross-sectional, n=3; all patients with RA	Associated with increased toxicity
	TPMT*3A			
	TPMT*3C			
			Stolk et al. (1998), ⁴¹ prospective, n=99; 33 patients with established RA, 24 with early RA, 42 healthy controls	Associated with increased toxicity
			Higgs et al. (2010), ⁴³ meta-analysis of 67 studies	Associated with increased toxicity

Davila et al. Pharmacogenetics: implications for therapy in rheumatic diseases. Nat Rev Rheumatol. 2011;7(9):537-50

PREGUNTA 4

**¿QUÉ ACTITUD DEBEMOS
TOMAR SI EL PACIENTE
PRESENTA EL ALELO
TPMT*3A?**

1. Reducir la dosis de azatioprina al 50%
2. Aumentar la dosis de azatioprina
3. Reducir la dosis de azatioprina al 10%
4. No modificar la dosis, ya que TPMT*3A representa una alta actividad enzimática

Tiopurina metiltransferasa (TPMT)

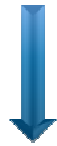
TPMT	Actividad	Prevalencia	Dosis
TPMT ^{HH}	Alta	88.6%	2-3 mg/kg/día
TPMT ^{HL}	Media	11.1%	1-1.5 mg/kg/día (reducción 50%)
TPMT ^{LL}	Baja o nula	0.3%	No administrar / reducir dosis al 10%

- ✓ TPMT^{LL} se asocia con mielosupresión y alteraciones gastrointestinales.
- ✓ Tres alelos identificados: TPMT*2, TPMT*3A, TPMT*3C.
- ✓ TPMT*3A es el más común, resultado de dos cambios de nucleótidos (G⁴⁶⁰*A y A⁷¹⁹*G).

CASO CLÍNICO

RESULTADO FARMACOGENÉTICO

Presenta el **TPMT de alta actividad**



AZT a dosis plenas (2-3 mg/kg/día): 150-200 mg/24 horas

A los 6 meses la paciente presenta una actividad baja (DAS28= 3.4)

PREGUNTA 5

**DE LOS POLIMOSFISMOS
CITADOS, ¿CUÁL ES EL MÁS
UTILIZADO EN LA PRÁCTICA
CLÍNICA?**

1. CYP1A2*1F (leflunomida)

2. TMPT*3A (azatioprina)

3. MTHFR -C677T (metotrexato)

4. TNF α -G308A (infliximab)

CONCLUSIONES

Limitaciones

- *Muchos mecanismos celulares y gran cantidad de genes implicados en la AR (etiología no bien conocida)*
- *Sesgo de selección (factores de confusión, ej. etnia)*
- *Baja significación y baja potencia estadística (tamaño muestral pequeño)*

CONCLUSIONES

PRESENTE

Medir la TPMT antes de iniciar el tratamiento con azatioprina.

Existen polimorfismos asociados a eficacia y toxicidad de FAMEs (metotrexato, leflunomida, anti-TNF...), que pueden ser un dato más en la toma de decisiones.

FUTURO

Confirmación de datos actuales.

Analizar el coste-efectividad de estas técnicas.

Búsqueda de polimorfismos en terapias biológicas (TNF- α , IL-6, Fc...).

Otras moléculas...



*Menos evidencia y
más controversia*

- *Anti-IL6R:*

Polimorfismos: rs8192284 (A > C)

(Hospital Clínico San Carlos, Madrid)

- *Anti-CD20:*

Genes candidatos: ARG1, TRAF1, TLR4

Polimorfismos: IIIA Val158

(Hospital Clinic, Barcelona)

- *Cualquier anticuerpo monoclonal terapéutico (IgG1)*

FcγR IIIA Val158Phe

(Hospital Universitario Santiago de Compostela)



Muchas gracias

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