

# 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

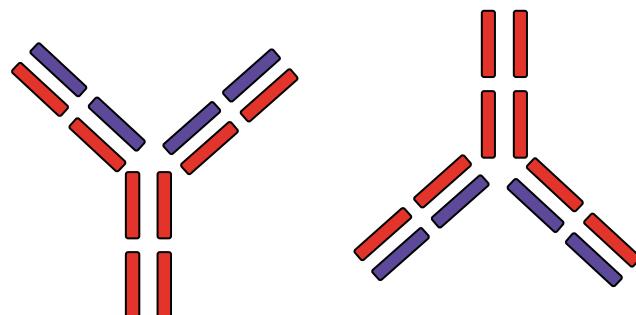
Comunidad de Madrid



Consejería de Salud  
Hospital Universitario  
Virgen de la Nieves

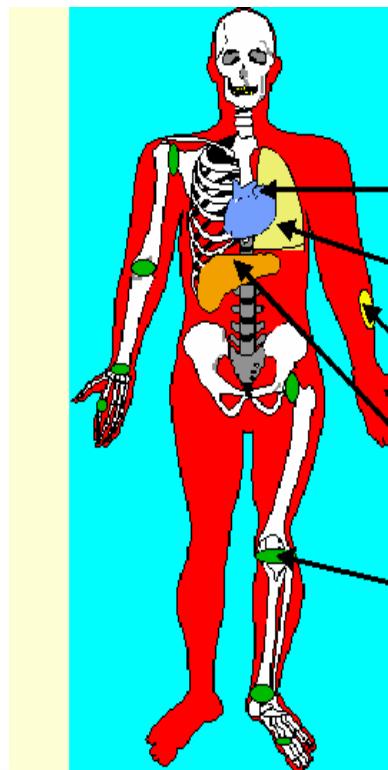
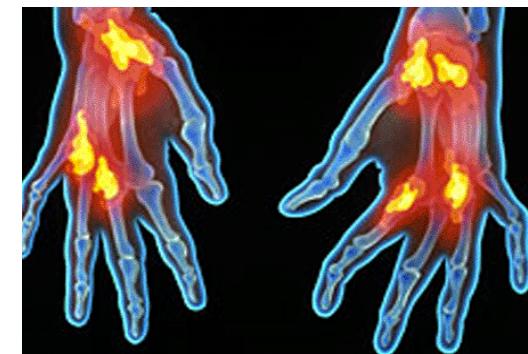
# Artritis Reumatoide

**1. Predisposición genética**  
Epítopo 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 reumatoideos

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

Corticoides

Mtx

¿Mtx +2º FAME?

PCC+, Rx erosiones

Anti-TNF

PCC+, Rx erosiones

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

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  
DOI 10.1002/art.27584  
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## Arthritis & Rheumatism

An Official Journal of the American College of Rheumatology  
[www.arthritisrheum.org](http://www.arthritisrheum.org) and [www.interscience.wiley.com](http://www.interscience.wiley.com)

## 2010 Rheumatoid Arthritis Classification Criteria

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

Daniel Aletaha,<sup>1</sup> Tuhina Neogi,<sup>2</sup> Alan J. Silman,<sup>3</sup> Julia Funovits,<sup>1</sup> David T. Felson,<sup>2</sup>  
Clifton O. Bingham, III,<sup>4</sup> Neal S. Birnbaum,<sup>5</sup> Gerd R. Burmester,<sup>6</sup> Vivian P. Bykerk,<sup>7</sup>  
Marc D. Cohen,<sup>8</sup> Bernard Combe,<sup>9</sup> Karen H. Costenbader,<sup>10</sup> Maxime Dougados,<sup>11</sup>  
Paul Emery,<sup>12</sup> Gianfranco Ferraccioli,<sup>13</sup> Johanna M. W. Hazes,<sup>14</sup> Kathryn Hobbs,<sup>15</sup>  
Tom W. J. Huizinga,<sup>16</sup> Arthur Kavanaugh,<sup>17</sup> Jonathan Kay,<sup>18</sup> Tore K. Kvien,<sup>19</sup> Timothy Laing,<sup>20</sup>  
Philip Mease,<sup>21</sup> Henri A. Ménard,<sup>22</sup> Larry W. Moreland,<sup>23</sup> Raymond L. Naden,<sup>24</sup>  
Theodore Pincus,<sup>25</sup> Josef S. Smolen,<sup>1</sup> Ewa Stanislawska-Biernat,<sup>26</sup> Deborah Symmons,<sup>27</sup>  
Paul P. Tak,<sup>28</sup> Katherine S. Upchurch,<sup>18</sup> Jiří Vencovský,<sup>29</sup>  
Frederick Wolfe,<sup>30</sup> and Gillian Hawker<sup>31</sup>

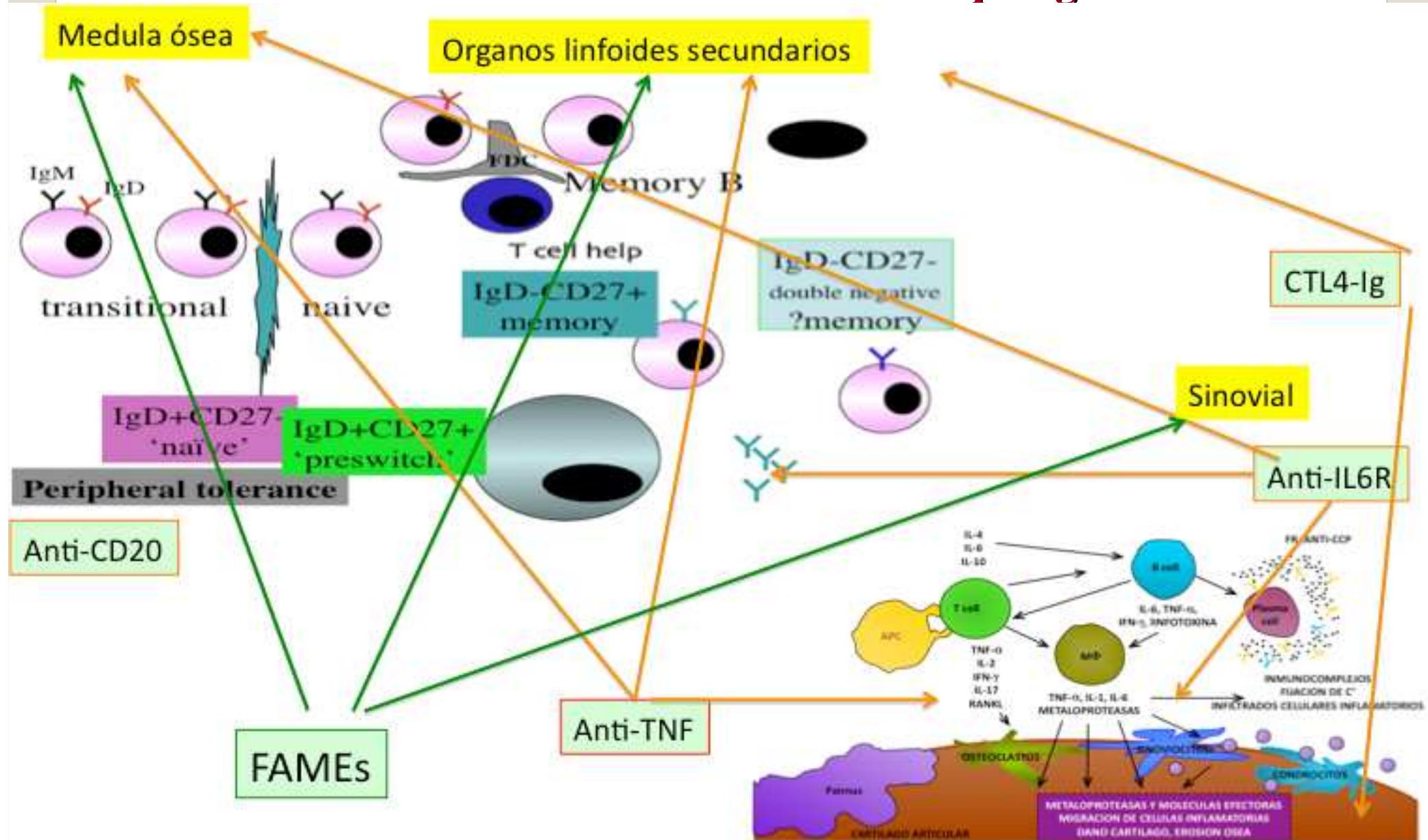
## Treating rheumatoid arthritis to target: recommendations of an international task force

Josef S Smolen,<sup>1,2</sup> Daniel Aletaha,<sup>1</sup> Johannes W J Bijlsma,<sup>3</sup> Ferdinand C Breedveld,<sup>4</sup>  
Dimitrios Boumpas,<sup>5</sup> Gerd Burmester,<sup>6</sup> Bernard Combe,<sup>7</sup> Maurizio Cutolo,<sup>8</sup> Maarten  
de Wit,<sup>9</sup> Maxime Dougados,<sup>10</sup> Paul Emery,<sup>11</sup> Alan Gibofsky,<sup>12</sup> Juan Jesus Gomez-  
Reino,<sup>13</sup> Boulos Haraoui,<sup>14</sup> Joachim Kalden,<sup>15</sup> Edward C Keystone,<sup>16</sup> Tore K Kvien,<sup>17</sup>  
Iain McInnes,<sup>18</sup> Emilio Martin-Mola,<sup>19</sup> Carlomaurizio Montecucco,<sup>20</sup> Monika Schoels,<sup>2</sup>  
Desirée van der Heijde,<sup>4</sup> 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)*	0
2) with the synovitis not better explained by another disease†	1
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)‡	2
A. Joint involvement§	3
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)¶¶	0
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)¶¶	0
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms§§	0
<6 weeks	0
$\geq 6$ 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

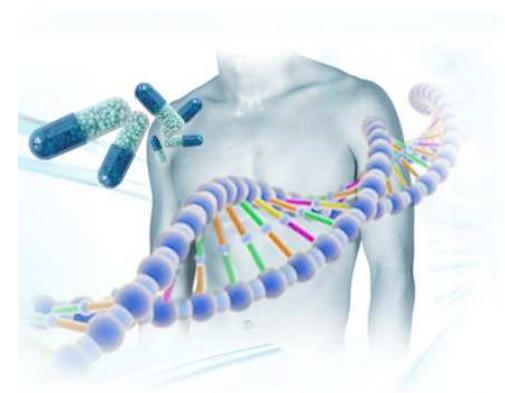
## Evolución

A los 6 meses:

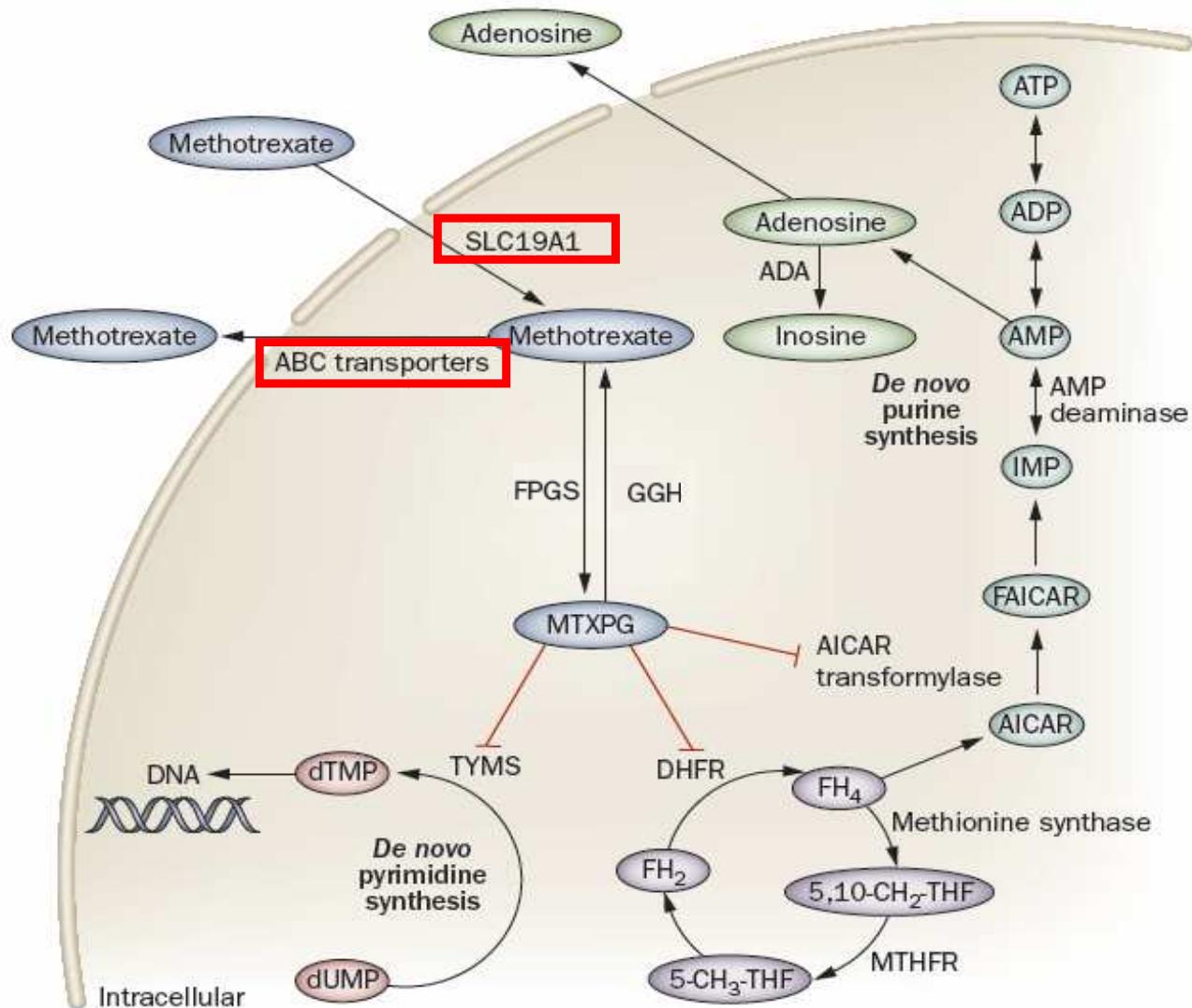
Presenta molestias gastrointestinales y toxicidad hepática  
(AST y ALT >3 veces valor referencia)



**ESTUDIO FARMACOGENÉTICO**



# Mecanismo de acción del metotrexato



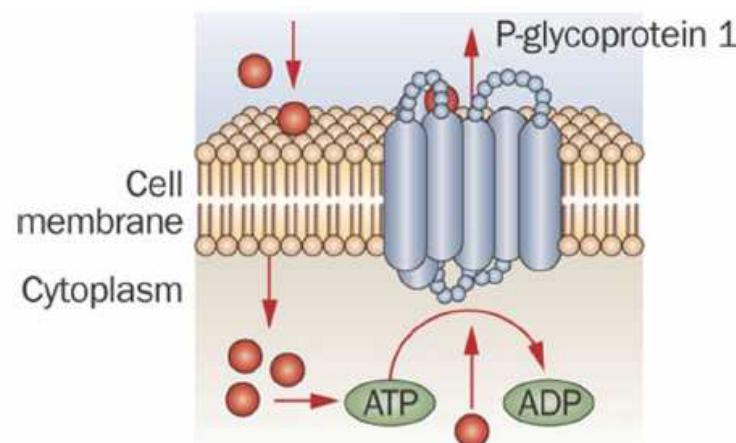
Davila et al. Pharmacogenetics: implications for therapy in rheumatic diseases. *Nat Rev Rheumatol*. 2011;7(9):537-50

# Farmacogenética del metotrexato

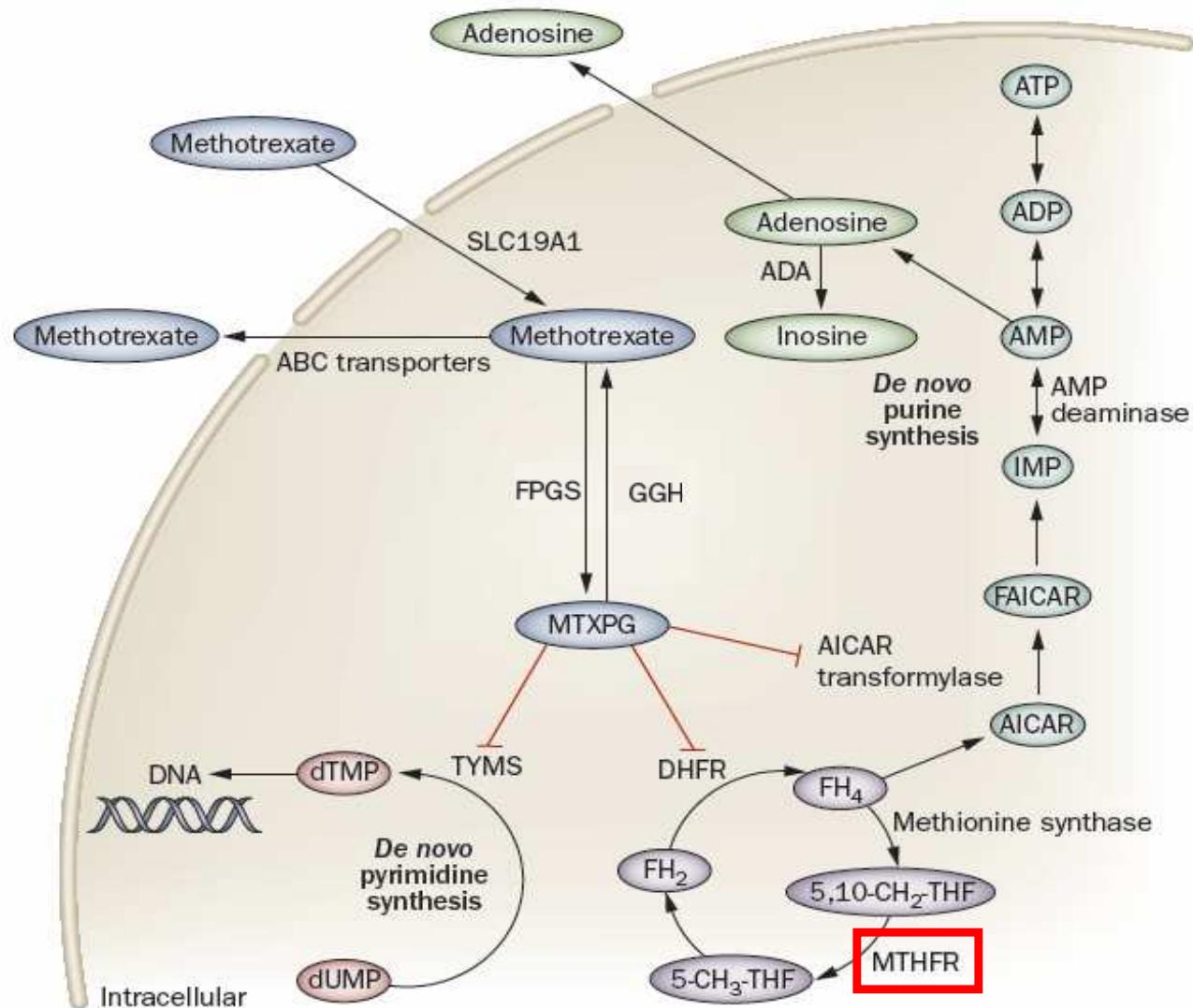
## POLIMORFISMOS EN LAS MOLÉCULAS TRANSPORTADORAS

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



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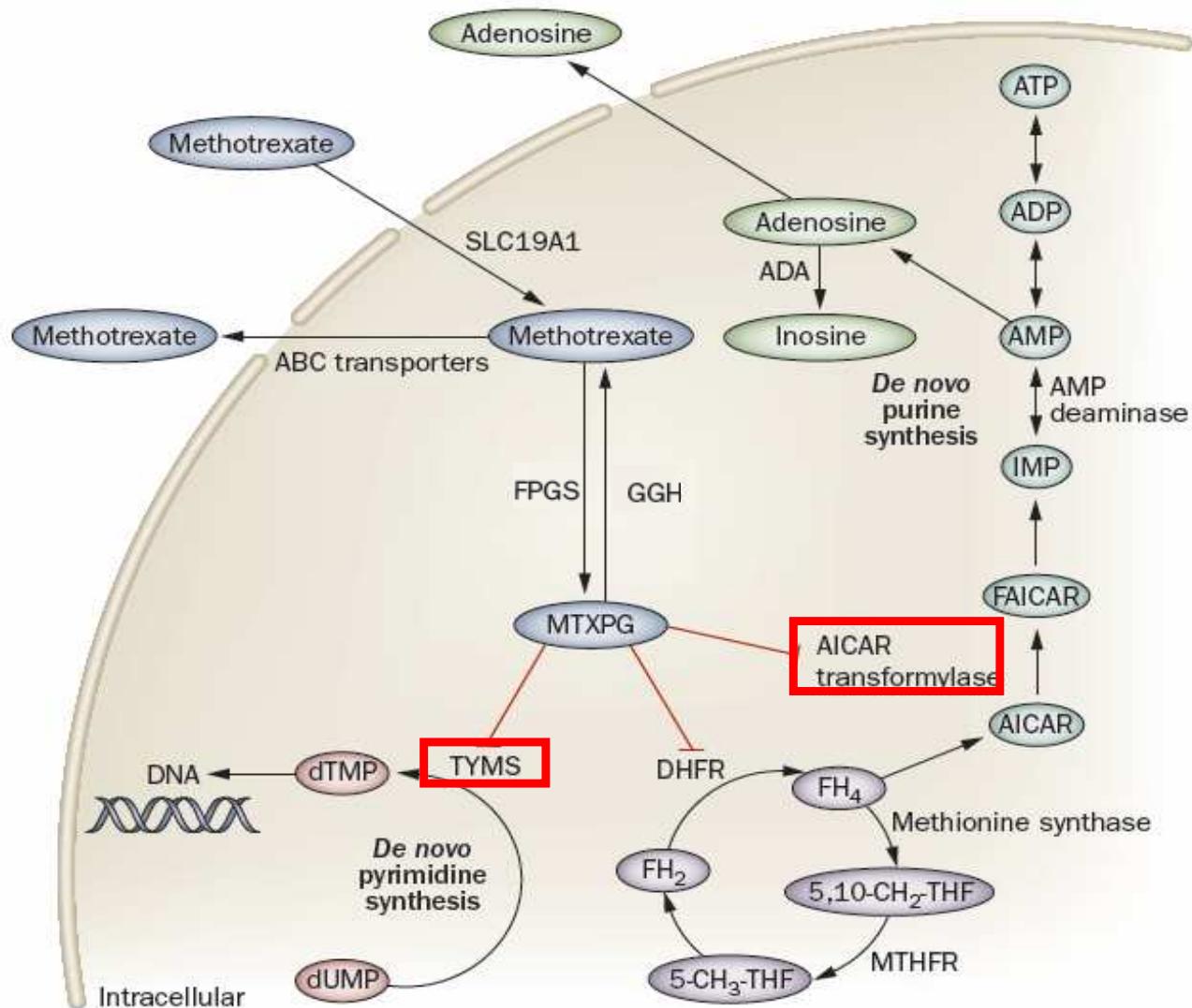
# *Farmacogenética del metotrexato*

## **POLIMORFISMOS EN EL CICLO DEL FOLATO**

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

# 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), <sup>24</sup> retrospective, n=167; 115 patients with RA treated with methotrexate, 52 controls	Triple repeat allele associated with decreased efficacy
			Dervieux et al. (2004), <sup>30</sup> cross-sectional, n=108; all patients with RA	Triple repeat allele associated with decreased efficacy
	3'-UTR deletion	Decreases mRNA stability and expression	Kumagai et al. (2003), <sup>24</sup> retrospective, n=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), <sup>25</sup> prospective, n=205; all patients with RA	Associated with improved efficacy and increased toxicity
			Takatori et al. (2006), <sup>26</sup> retrospective, n=124; all patients with RA	No effect on efficacy
			Dervieux et al. (2004), <sup>30</sup> cross-sectional, n=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. Transportador SLC19A1
4. Transportador ABCB1

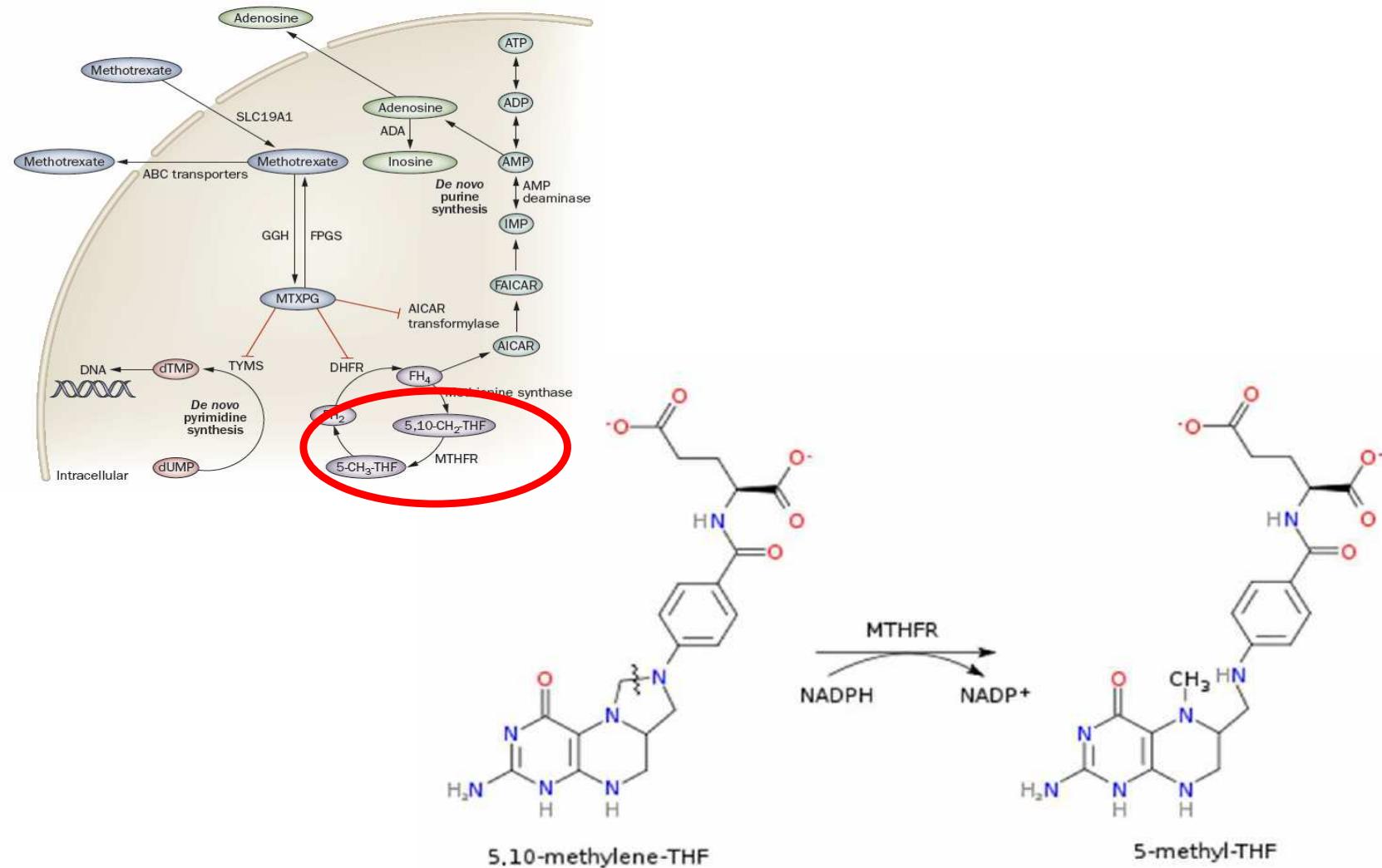
# Farmacogenética del metotrexato

## POLIMORFISMOS EN EL CICLO DEL FOLATO

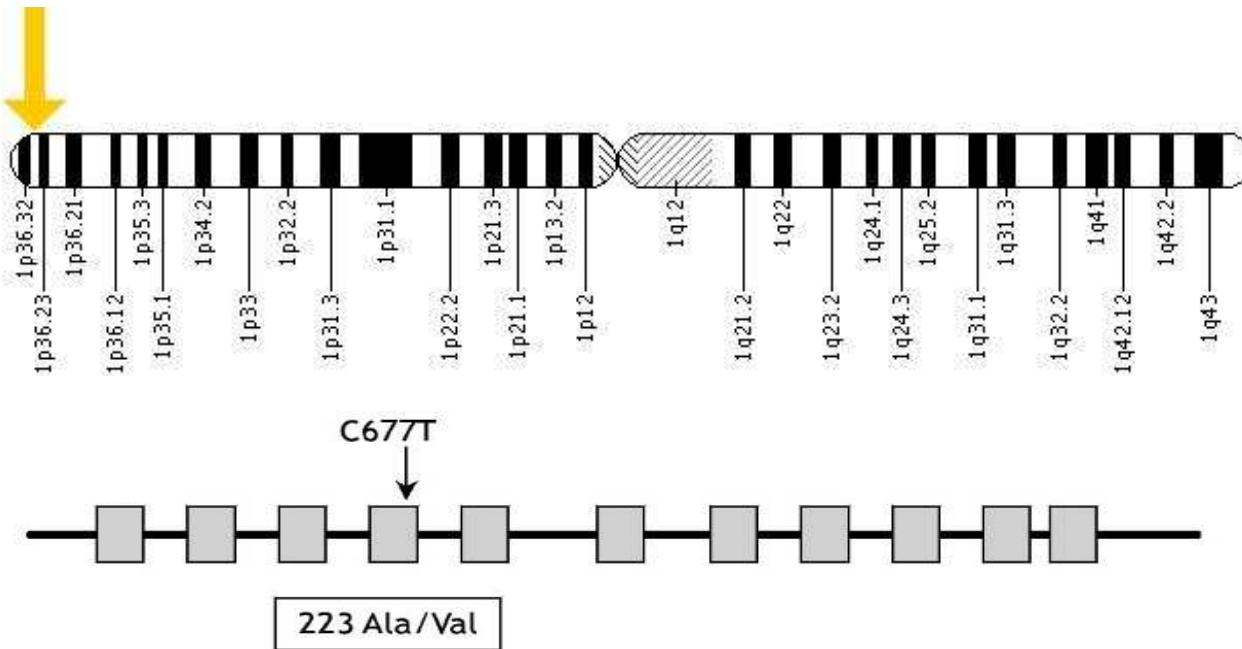
MTHFR, MTHFR, generation of 5-methyl tetrahydrofolate	<u>677C&gt;T</u>	Produces a thermolabile MTHFR variant; decreases enzyme levels	Van Ede et al. (2001), <sup>13</sup> prospective, n=236; all patients with RA  Urano et al. (2002), <sup>15</sup> retrospective, n=106; all patients with RA  Fisher & Cronstein (2009), <sup>16</sup> meta-analysis, n=1,400  Lee & Song (2010), <sup>17</sup> meta-analysis, n=1,514  Weisman et al. (2006), <sup>31</sup> cross-sectional, n=214; all patients with RA	Associated with discontinuation of methotrexate due to increased toxicity  Associated with increased toxicity  Associated with increased toxicity  No effect on toxicity or efficacy  Associated with increased toxicity
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# Metilentetrahidrofolato reductasa (MTHFR)



# *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**

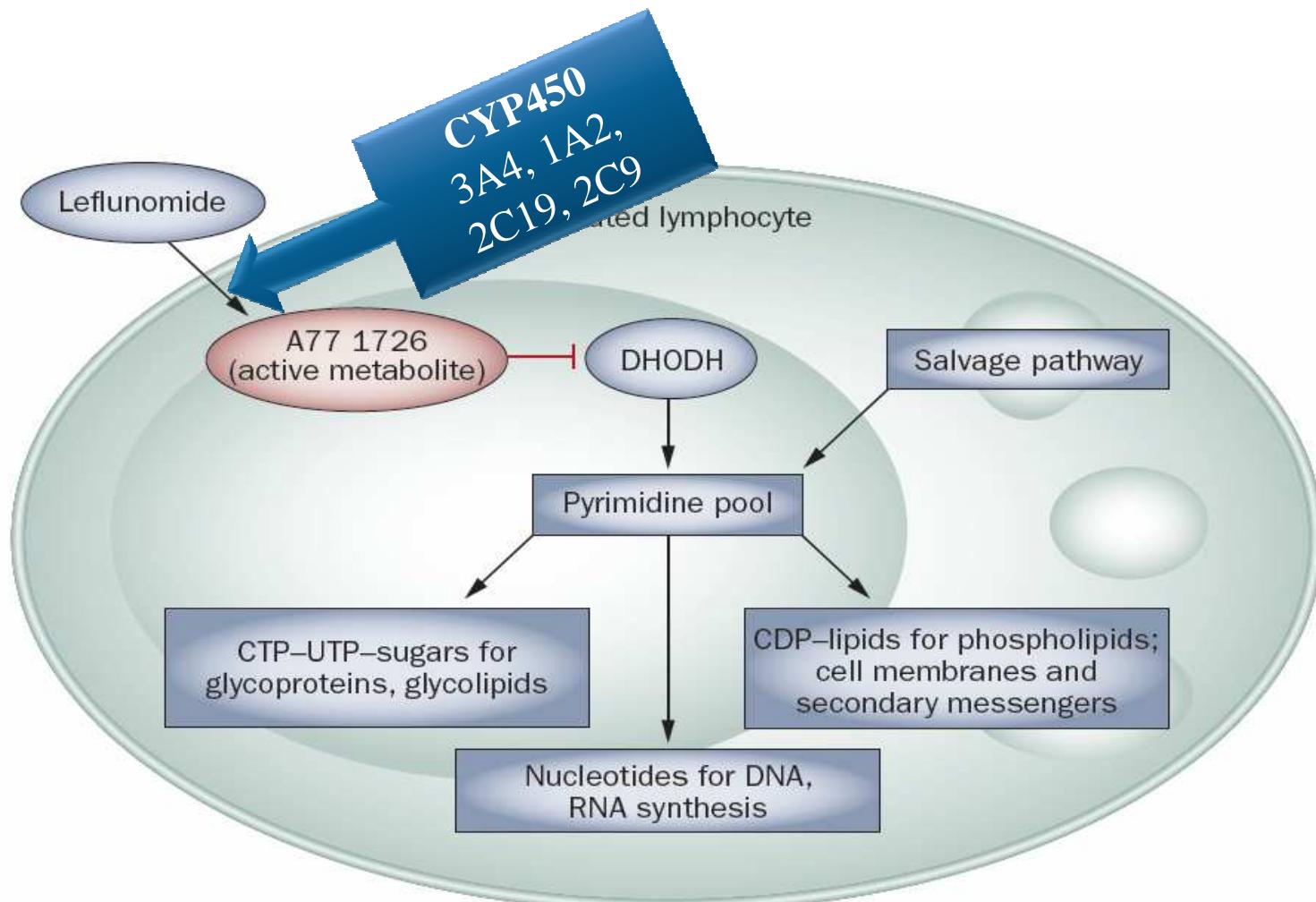
- ✓ Se suspende la escalada de metotrexato: 7.5 mg/semana
- ✓ Factores de mal pronóstico (PCR, anti-PCC+) → añadir un segundo FAME  
**Leflunomida**



## ESTUDIO FARMACOGENÉTICO



# *Mecanismo de acción de la leflunomida*



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## *Farmacogenética de la leflunomida*

DHODH, DHODH, key enzyme of de novo pyrimidine synthesis	19 C>A	Alters N-terminal region of DHODH, affecting insertion into mitochondrial membrane	Pawlik (2009), <sup>62</sup> prospective, <i>n</i> =147; all patients with RA	Associated with increased efficacy
			Grabar (2009), <sup>63</sup> retrospective, <i>n</i> =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), <sup>64</sup> prospective, <i>n</i> =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), <sup>68</sup> prospective, <i>n</i> =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?**

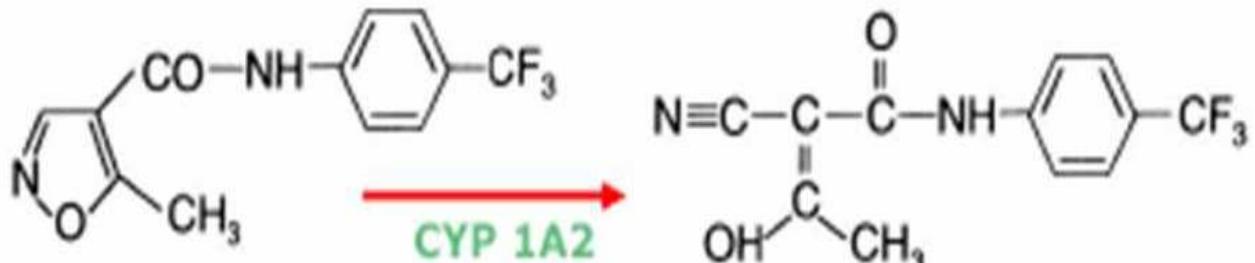
1. El CYP3A4 metaboliza la leflunomida y por tanto reduce su efectividad
2. No se ha encontrado ningún polimorfismo asociado a la efectividad de la leflunomida
3. El polimorfismo 19C de la DHODH se asocia con la efectividad y no con la toxicidad de la leflunomida
4. El alelo CYP1A2\*1F se asocia con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

## *Farmacogenética de la leflunomida*

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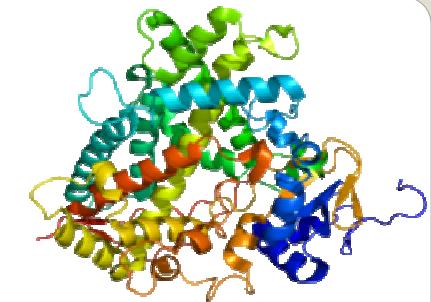
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# *CYP1A2*



**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

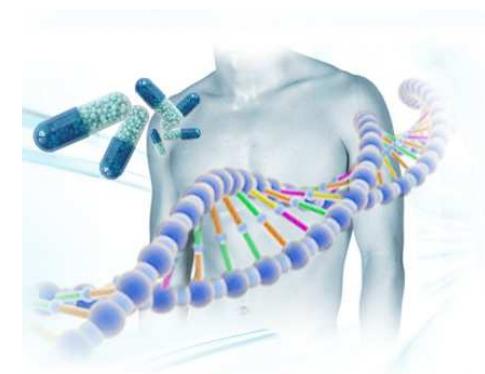
Presenta el **genotipo CC** del polimorfismo **CYP1A2\*1F**

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

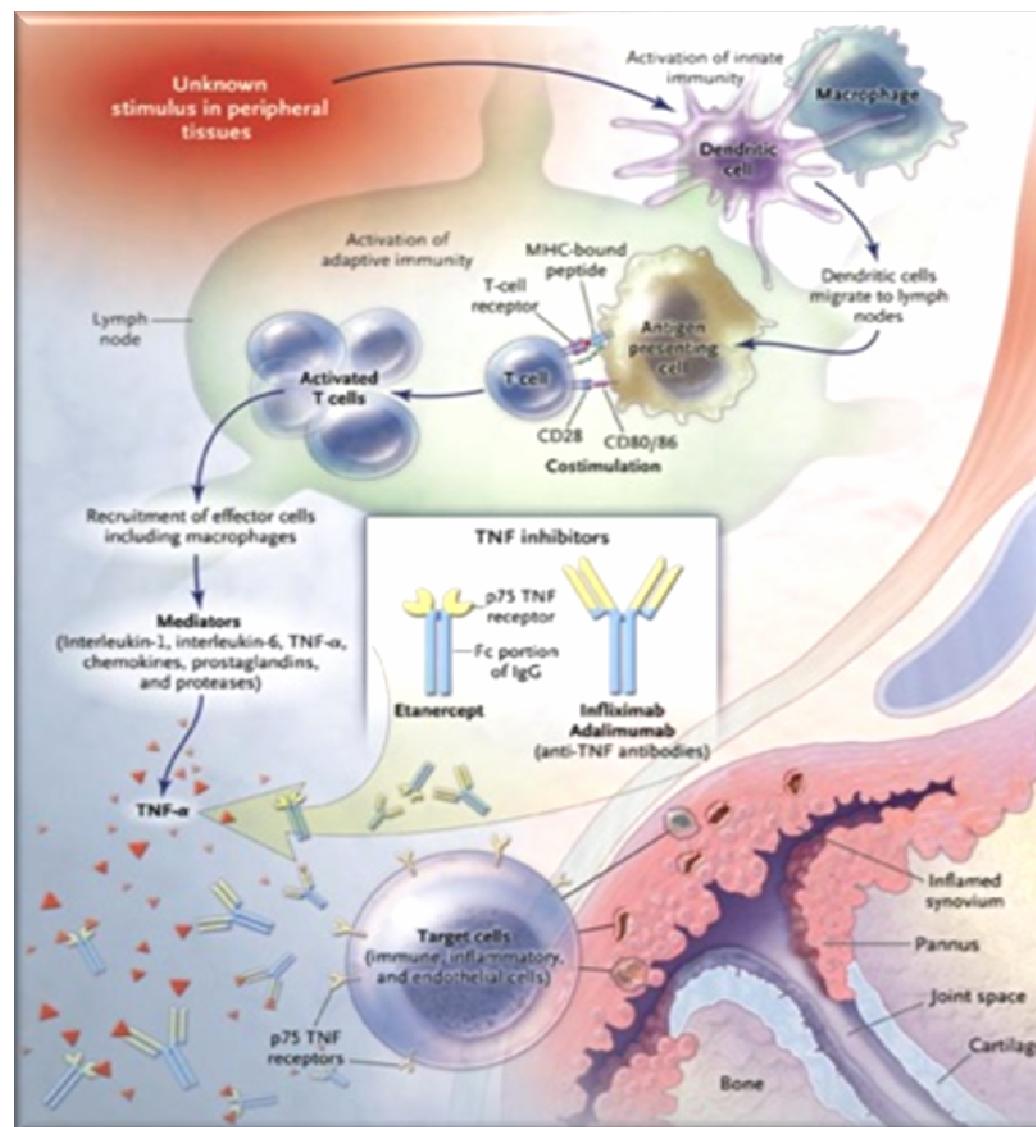
**Se decide iniciar anti-TNF**



**ESTUDIO FARMACOGENÉTICO**



# Mecanismo de acción de los anti-TNF $\alpha$



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

## *Farmacogenética de los anti-TNF $\alpha$*

FCGR genes, Fc $\gamma$ R, receptors for IgG	Fc $\gamma$ R IIIA Val158Phe	Influences Fc $\gamma$ R affinity for IgG1; affects ADCC	Kastbom (2007), <sup>90</sup> 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), <sup>98</sup> 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), <sup>102</sup> prospective, n=1,102; all patients with RA	Associated with increased efficacy of infliximab and adalimumab, but not etanercept

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

# Farmacogenética de los anti-TNF $\alpha$

## TNF blockers

TNF locus, TNF and its receptors	-308 G>A	Influences TNF production	Seitz (2007), <sup>91</sup> prospective, n=86; 54 patients with RA, 10 with PsA, 22 with AS	Associated with increased efficacy
			Cuchacovich (2006), <sup>92</sup> prospective, n=81; all patients with RA	Associated with increased efficacy
	-238A>G	Influences TNF production	Lee (2010), <sup>93</sup> meta-analysis (13 studies), 1,817 patients with RA	Associated with increased efficacy
	<i>TNFRSF1B</i> 196 T>G	Influences receptor shedding and ligand binding; might increase IL-6 production	Fabris (2002), <sup>94</sup> retrospective, n=175; all patients with RA	Associated with decreased efficacy
			Potter (2010), <sup>95</sup> retrospective, n=602, all patients with RA	No effect on efficacy
	TNF microsatellites a-e	Affect DNA folding and conformation	Martinez (2004), <sup>96</sup> prospective, n=420; 78 patients with RA, 342 healthy controls	No effect on efficacy with individual microsatellites; <i>TNFA11;b4</i> haplotype more frequent in responders to infliximab
			Criswell (2004), <sup>97</sup> prospective, n=457; all patients with RA	No effect on efficacy

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## 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. Fc $\gamma$ R III A Val 158 Phe

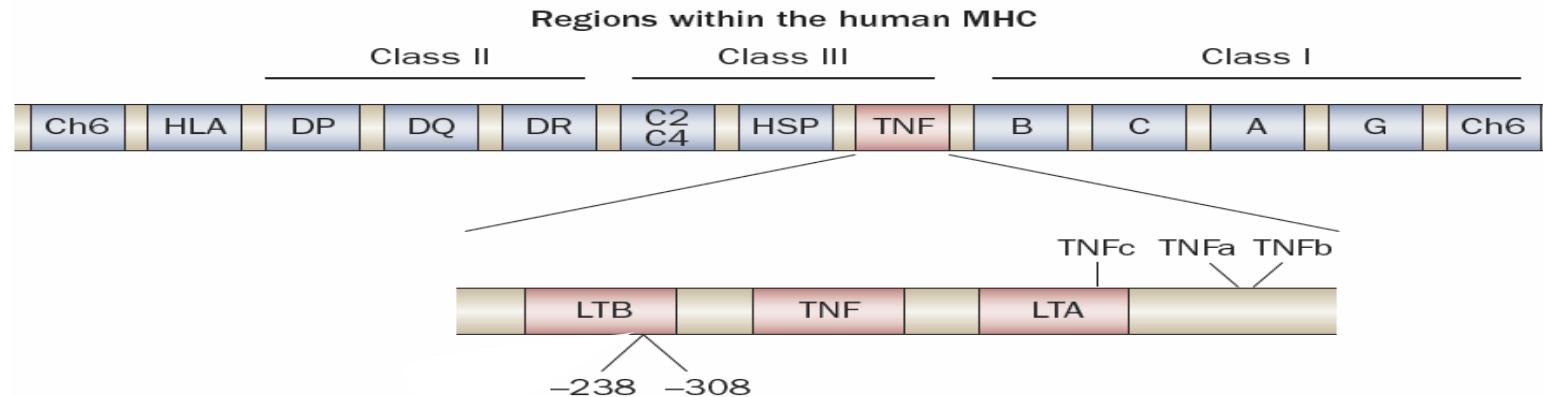
# Farmacogenética de los anti-TNFα

## TNF blockers

TNF locus, TNF and its receptors	<u>-308 G&gt;A</u>	Influences TNF production	Seitz (2007), <sup>91</sup> prospective, n=86; 54 patients with RA, 10 with PsA, 22 with AS  Cuchacovich (2006), <sup>92</sup> prospective, n=81; all patients with RA	Associated with increased efficacy  Associated with increased efficacy
	-238A>G	Influences TNF production	Lee (2010), <sup>93</sup> meta-analysis (13 studies), 1,817 patients with RA	Associated with increased efficacy
<i>TNFRSF1B</i> 196 T>G		Influences receptor shedding and ligand binding; might increase IL-6 production	Fabris (2002), <sup>94</sup> retrospective, n=175; all patients with RA	Associated with decreased efficacy
			Potter (2010), <sup>95</sup> retrospective, n=602, all patients with RA	No effect on efficacy
TNF microsatellites a-e		Affect DNA folding and conformation	Martinez (2004), <sup>96</sup> prospective, n=420; 78 patients with RA, 342 healthy controls	No effect on efficacy with individual microsatellites; <i>TNFA11;b4</i> haplotype more frequent in responders to infliximab
			Criswell (2004), <sup>97</sup> prospective, n=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

# *Polimorfismo G308A del TNF $\alpha$*



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- ✓ Sustitución de guanosina por adenosina en la posición 308.
- ✓ G308A influye en los niveles circulantes de TNF- $\alpha$ .
- ✓ 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)

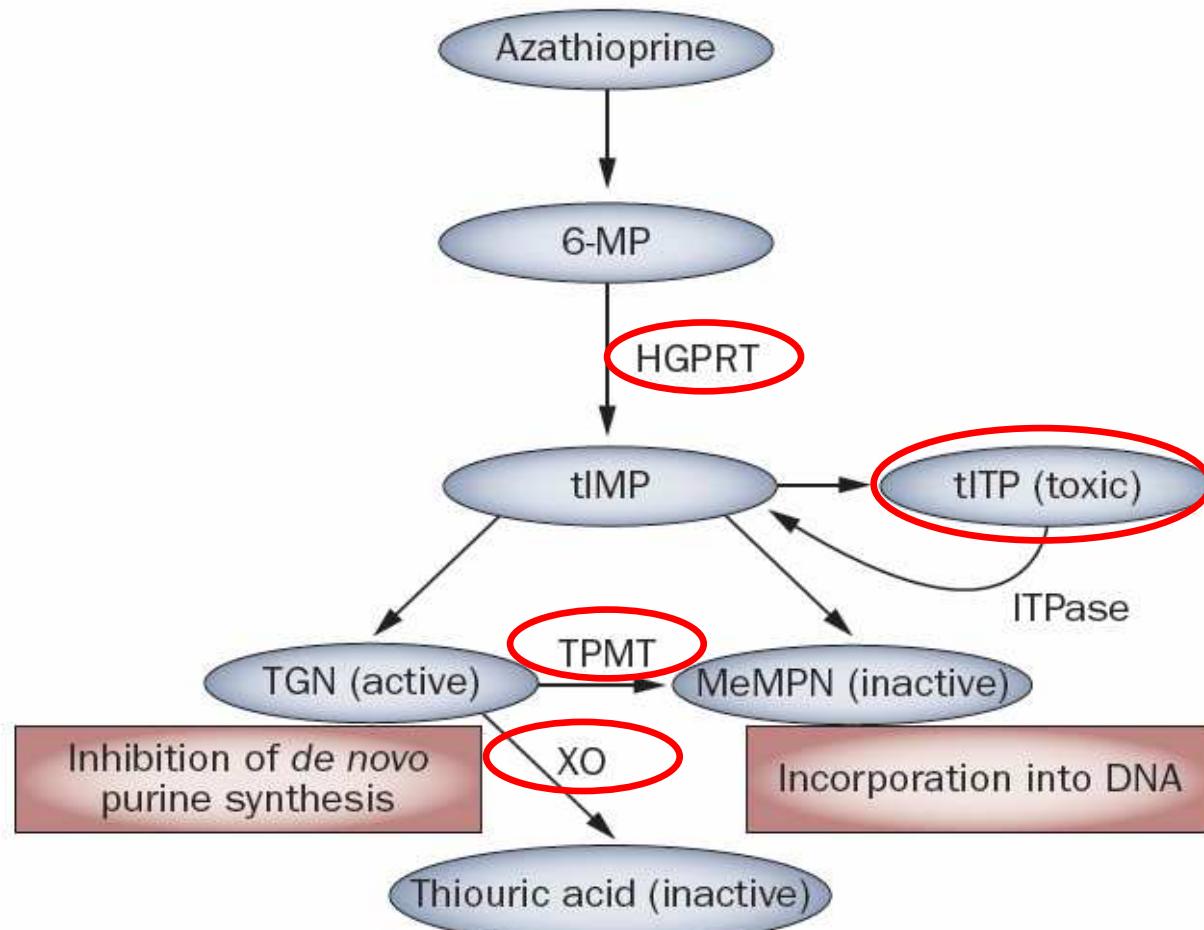
Se decide iniciar Azatioprina



ESTUDIO FARMACOGENÉTICO



# Mecanismo de acción de la azatioprina



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## *Farmacogenética de la azatioprina*

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

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## **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 <sup>HH</sup>	Alta	88.6%	2-3 mg/kg/día
TPMT <sup>HL</sup>	Media	11.1%	1-1.5 mg/kg/día (reducción 50%)
TPMT <sup>LL</sup>	Baja o nula	0.3%	No administrar / reducir dosis al 10%

- ✓ TPMT<sup>LL</sup> 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 (G<sup>460</sup>\*A y A<sup>719</sup>\*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 $\alpha$  -G308A (infliximab)

# CONCLUSIONES

## ***Limitaciones***

- *Muchos mecanismos celulares y gran cantidad de genes implicados en la AR (etología 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- $\alpha$ , IL-6, Fc...).*

## *Otras moléculas...*

- *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)*

Fc $\gamma$ R IIIA Val158Phe

(*Hospital Universitario Santiago de Compostela*)





*Muchas gracias*

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