HIGHLIGHTS

AEDV

en la 6ª edición del SPIN

Skin Inflammation & Psoriasis International Network Congress

PARIS
25-27
abril

DIA 1. OTRAS ENFERMEDADES INFLAMATORIAS

Dr Antonio Martorell

Servicio de Dermatologia
Hospital de Manises, Valencia

antmarto@hotmail.com

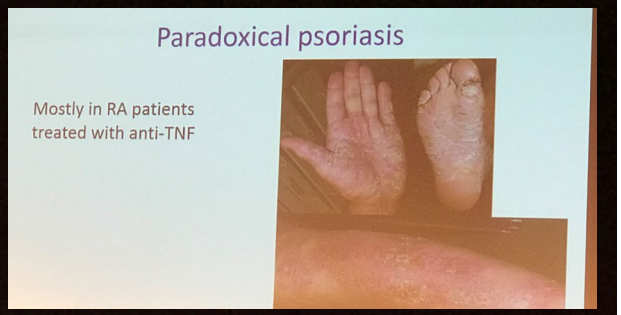
@drmartorell

dr.antoniomartorell

Iniciativa científica de:

Paradoxical reactions to biologics session

Iniciativa científica de:



PARADOXICAL REACTIONS: A DEFINITION

- "The new onset or exacerbation of a symptom/disease, usually improved with the biologic (e-g- TNF Blockers)"

Box 2. The paradoxical effects of anti-TNF agents.

- Psoriasis and psoriasiform lesions
- Uveitis and other eye diseases
- Inflammatory bowel diseases
- Sarcoidosis
- Other granulomatous disorders (rheumatoid nodules)
- Vasculitis
- Miscellaneous auto-immune

REVIEW

Current Opinion **Biologics-induced autoimmune diseases**

Roberto Perez-Alvarez[a], *Marta Pérez-de-Lis*[a], *Manuel Ramos-Casals*[b], *on behalf of the BIOGEAS study group*[*]

Table 1. List of systemic and organ-specific autoimmune processes triggered by biological agents

Systemic autoimmune diseases	Hematological diseases	Neurological diseases	Pulmonary diseases	Ophthalmological diseases	Digestive diseases	Cutaneous diseases	Other processes
Systemic lupus erythematosus	Cytopenia	CNS disease	Interstitial pneumonia	Uveitis	Inflammatory bowel disease	Psoriasis induced by biologics	Orbital myositis
Lupus-like disease	Thrombocytopenia	Optic neuritis	Usual interstitial pneumonia	Scleritis	Autoimmune hepatitis	Palmoplantar pustulosis	Thyroiditis
ANCA+ vasculitis	Neutropenia	Multiple sclerosis	Nonspecific interstitial pneumonia	Endogenous endophthalmitis	Cholestatic hepatitis	Generalized pustular	Inflammatory polyarthritis
Giant cell arteritis	Hemolytic anemia	Demyelinating CNS disease	Organizing pneumonia	Ulcerative keratitis associated with hypereosinophilia	Acute toxic hepatitis	Erythrodermic	Pericarditis
Henoch Schonlein purpura	Thrombotic events	Encephalitis	Diffuse alveolar damage	Retinal vein thrombosis	Granulomatous hepatitis	Plaque psoriasis	Membranous glomerulonephritis
Polyarteritis nodosa	Deep vein thrombosis	Aseptic meningitis	Lymphoid interstitial pneumonia	Retinal arterial thrombosis	Budd-Chiari syndrome	Inverse psoriasis	Scleredema
Antiphospholipid syndrome	Pulmonary embolism	Posterior reversible encephalopathy syndrome	Pulmonary vasculitis			Scalp psoriasis	Reactivation of Langerhan's cell histiocytosis
APS/APS-like disease	Arterial thrombosis of the legs	Peripheral neurological diseases	Antineutrophil cytoplasmic antibody (ANCA) + alveolar hemorrhage			Other cutaneous diseases induced by biologics	
Sarcoidosis	Cutaneous necrosis	Guillain-Barre syndrome	Necrotizing pulmonary nodules			Pyoderma gangrenosum	
Polymyositis	Hypereosinophilic processes induced by biologics	Miller-Fisher syndrome	Pulmonary lymphocytic vasculitis			Pustular folliculitis	
Dermatomyositis	Eosinophilia	Multifocal motor neuropathy with conduction block	Other respiratory processes			Erythema multiforme	
	Pulmonary eosinophilia	Chronic inflammatory demyelinating polyradiculoneuropathy	Rhinitis, sinusitis and self-limited cough			Lichenoid reactions	
	Eosinophilic cellulites	Peripheral neuropathies	Severe bronchospasm			Interface dermatitis	
	Eosinophilic fasciitis	Lewis-Summer syndrome	Hypersensitivity pneumonitis			Granuloma annulare	
	Atopic dermatitis		Acute respiratory distress syndrome			Neutrophilic eccrine hidradenitis	
	Hemophagocytic syndrome					Sweet's syndrome	
						Cutaneous lupus (lupus tumidus, chilblain lupus)	

PARADOXICAL REACTIONS: MECHANISMS

- Still a matter of debate; counter regulation theory
- An imbalance of cytokines, favoring Type 1 INFs, chemokines, IL-2/17 and Tregs are implicated*

  *Inhibition of TNF could activate Tregs
- Type 1 INFs induce chemokines and receptors (CXCL9, CXCR3), leading to increased influx of lymphocytes
- Genetic factors

GENETIC FACTORS

- A relationship with a few SNIPs have been demonstrated
- These SNIPSs impact genes like CARD 14, CARD 15, IL-23R, CTLA4, FBXL19
- Atopic constitution, vitiligo, lupus
- Genetic investigacions in these cases are scarce

SCHEMATIC OVERVIEW

frontiers in Pharmacology

MINI REVIEW
published: 26 March 2019
doi: 10.3389/fphar.2019.00282

Paradoxical Skin Reactions to Biologics in Patients With Rheumatologic Disorders

Simone Garcovich[1], Clara De Simone[1], Giovanni Genovese[2,3], Emilio Berti[2,3], Massimo Cugno[3,4] and Angelo Valerio Marzano[2,3]

[1] Institute of Dermatology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Roma, Italy, [2] UOC Dermatologia, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, [3] Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi di Milano, Milan, Italy, [4] Medicina Interna, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

Targeted immune-modulating treatment with biological agents has revolutionized the management of immune-mediated inflammatory diseases, including rheumatologic conditions. The efficacy and tolerability of biological agents, from the initial tumour necrosis factor (TNF)-α inhibitors to the new anti-cytokine monoclonal antibodies, have dramatically changed the natural history of debilitating conditions such as rheumatoid arthritis and seronegative spondyloarthropathies. The widening use of biologics across several rheumatologic diseases has been associated with a new class of adverse events, the so-called paradoxical reactions. These events are inflammatory immune-mediated tissue reactions, developing paradoxically during treatment of rheumatologic conditions with targeted biologics that are commonly used for treating the idiopathic counterparts of these drug-induced reactions. The skin is frequently involved, and, even if considered rare to uncommon, these cutaneous manifestations are an important cause of biologic agent discontinuation. TNF-α antagonist-induced psoriasis, which can manifest *de novo* or as exacerbation of a pre-existing form, is the prototypic and most frequent paradoxical skin reaction to biologics while other reactions, such as eczematous and lichenoid eruptions, hidradenitis suppurativa, pyoderma gangrenosum, Sweet's syndrome and granulomatous skin diseases, occur much more rarely. Management of these reactions consists of topical or systemic skin-directed therapies, depending on the severity and extension of the cutaneous picture, and it is generally associated with switching over to other disease-modifying regimens for treating the underlying rheumatologic condition. Here, we review in detail the current concepts and controversies on classification, pathogenesis and clinical management of this new class of cutaneous adverse events induced by biologics in rheumatologic patients.

Keywords: paradoxical skin reactions, biologics, rheumatological disorders, psoriasis, TNF-α-inhibitors

OPEN ACCESS

Edited by:
Per-Johan Jakobsson,
Karolinska Institutet (KI), Sweden

Reviewed by:
Claudio Feliciani,
Università degli Studi G. d'Annunzio Chieti e Pescara, Italy
Haroon Khan,
Abdul Wali Khan University Mardan, Pakistan

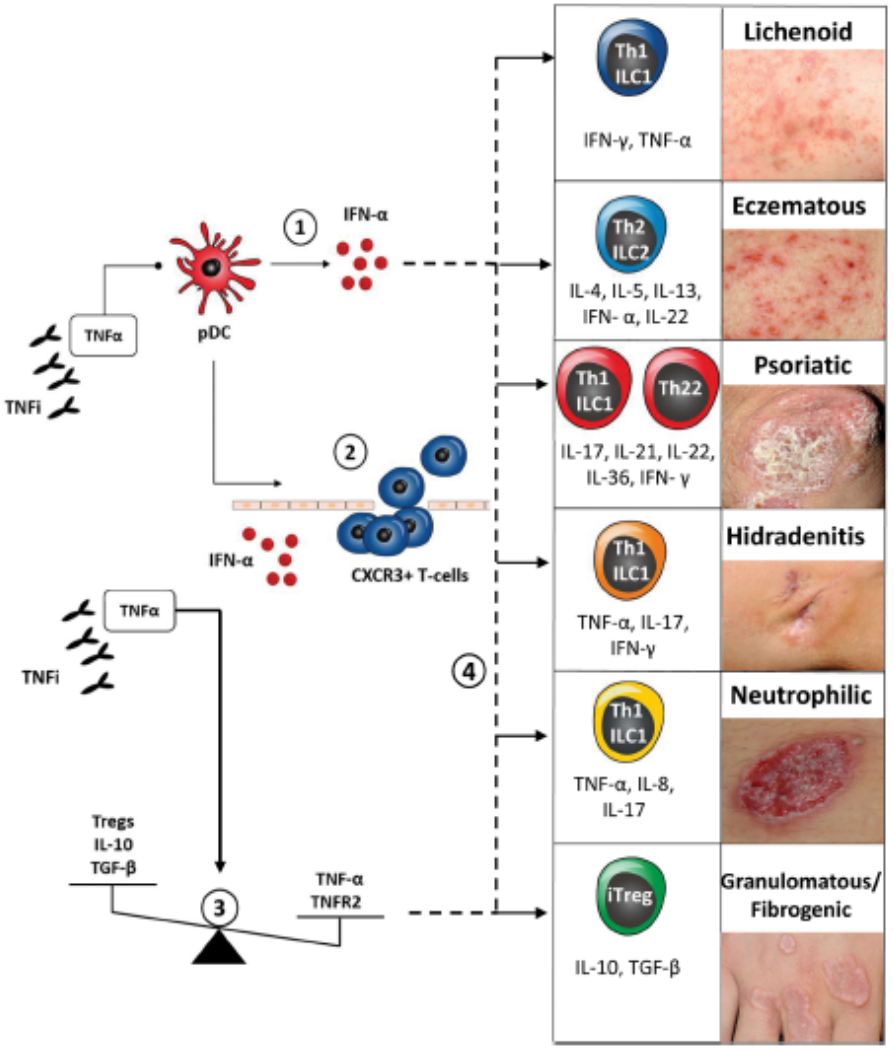
****Correspondence:***
Angelo Valerio Marzano
angelo.marzano@unimi.it

Specialty section:
This article was submitted to Inflammation Pharmacology, a section of the journal Frontiers in Pharmacology

Received: *14 December 2018*
Accepted: *06 March 2019*
Published: *26 March 2019*

Citation:
Garcovich S, De Simone C, Genovese G, Berti E, Cugno M and Marzano AV (2019) Paradoxical Skin Reactions to Biologics in Patients With Rheumatologic Disorders. Front. Pharmacol. 10:282. doi: 10.3389/fphar.2019.00282

Abbreviations: IFN, Interferon; IFN type-1, interferon-type 1; IL, interleukin; IL-10, interleukin 10; ILC, innate lymphoid cell; iTreg, induced regulatory T-cells; NDs, neutrophilic dermatoses; TGF-β, transforming growth factor-beta; Th, T helper cell; TNF-α, tumor necrosis factor-alpha; TNFR2, tumor necrosis factor receptor 2; Tregs, regulatory T-cells.



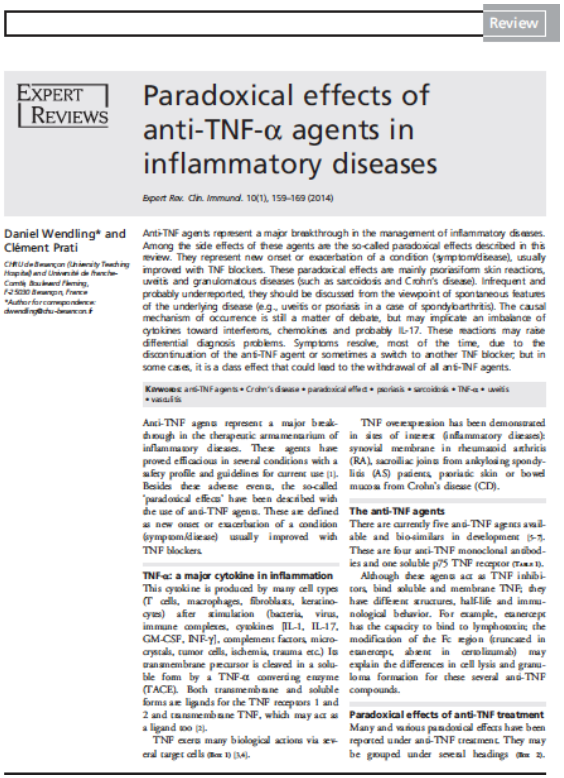
Gargovich et al. 2019

Joint Inflammation

Paradoxal joint inflammation occurs in patients with IBD during anti TNF-alfa therapy

Especially peripheral arthritis in up to 11% of cases, and less frequent as SpA

INDUCED IBD AND UVEITIS



Review

EXPERT REVIEWS

Paradoxical effects of anti-TNF-α agents in inflammatory diseases

Expert Rev. Clin. Immunol. 10(1), 159–169 (2014)

Daniel Wendling* and Clément Prati

CHRU de Besançon (University Teaching Hospital) and Université de Franche-Comté, Boulevard Fleming, F-25030 Besançon, France
**Author for correspondence: dwendling@chu-besancon.fr*

Anti-TNF agents represent a major breakthrough in the management of inflammatory diseases. Among the side effects of these agents are the so-called paradoxical effects described in this review. They represent new onset or exacerbation of a condition (symptom/disease), usually improved with TNF blockers. These paradoxical effects are mainly psoriasiform skin reactions, uveitis and granulomatous diseases (such as sarcoidosis and Crohn's disease). Infrequent and probably underreported, they should be discussed from the viewpoint of spontaneous features of the underlying disease (e.g., uveitis or psoriasis in a case of spondyloarthritis). The causal mechanism of occurrence is still a matter of debate, but may implicate an imbalance of cytokines toward interferons, chemokines and probably IL-17. These reactions may raise differential diagnosis problems. Symptoms resolve, most of the time, due to the discontinuation of the anti-TNF agent or sometimes a switch to another TNF blocker, but in some cases, it is a class effect that could lead to the withdrawal of all anti-TNF agents.

Keywords: anti-TNF agents • Crohn's disease • paradoxical effect • psoriasis • sarcoidosis • TNF-α • uveitis • vasculitis

Anti-TNF agents represent a major breakthrough in the therapeutic armamentarium of inflammatory diseases. These agents have proved efficacious in several conditions with a safety profile and guidelines for current use [1]. Besides these adverse events, the so-called 'paradoxical effects' have been described with the use of anti-TNF agents. These are defined as new onset or exacerbation of a condition (symptom/disease) usually improved with TNF blockers.

TNF-α: a major cytokine in inflammation

This cytokine is produced by many cell types (T cells, macrophages, fibroblasts, keratinocytes) after stimulation (bacteria, virus, immune complexes, cytokines [IL-1, IL-17, GM-CSF, INF-γ], complement factors, microcrystals, tumor cells, ischemia, trauma etc.) Its transmembrane precursor is cleaved in a soluble form by a TNF-α converting enzyme (TACE). Both transmembrane and soluble forms are ligands for the TNF receptors 1 and 2 and transmembrane TNF, which may act as a ligand too [2].

TNF exerts many biological actions via several target cells (Box 1) [3,4].

TNF overexpression has been demonstrated in sites of interest (inflammatory diseases): synovial membrane in rheumatoid arthritis (RA), sacroiliac joints from ankylosing spondylitis (AS) patients, psoriatic skin or bowel mucosa from Crohn's disease (CD).

The anti-TNF agents

There are currently five anti-TNF agents available and bio-similars in development [5–7]. These are four anti-TNF monoclonal antibodies and one soluble p75 TNF receptor (Table 1).

Although these agents act as TNF inhibitors, bind soluble and membrane TNF; they have different structures, half-life and immunological behavior. For example, etanercept has the capacity to bind to lymphotoxin; the modification of the Fc region (truncated in etanercept, absent in certolizumab) may explain the differences in cell lysis and granuloma formation for these several anti-TNF compounds.

Paradoxical effects of anti-TNF treatment

Many and various paradoxical effects have been reported under anti-TNF treatment. They may be grouped under several headings (Box 2).

Table 4. New onset of inflammatory bowel diseases occurring under anti-TNF treatment.

Study, subjects (n)	Disease treated with anti-TNF	Type of anti-TNF	Duration of anti-TNF exposition (months)	Type of IBD	Outcome
French national survey, 16	AS: 12 RA: 1 PsA: 1 JIA: 2	ETA: 14 IFX: 2	29 ± 20	CD: 8 CD like: 6 UC: 1 Indeterminate: 1	Anti-TNF discontinuation and switch to another anti-TNF Mab Favorable outcome, no flare
Literature review, 20	AS: 7 RA: 0 PsA: 2 JIA: 11	ETA: 18 IFX: 2	6–78	CD	Maintenance of same anti-TNF + mesalazine [2] Discontinuation of ETA and switch [17] NA [1]

AS: Ankylosing spondylitis; CD: Crohn's disease; ETA: Etanercept; IBD: Inflammatory bowel diseases IFX: Infliximab; Mab: Monoclonal antibody; NA: Not available; RA: Rheumatoid arthritis; PsA: Psoriatic arthritis; JIA: Juvenile idiopathic arthritis; UC: Ulcerative colitis.
Data taken from [36].

Table 3. Cases of new onset of uveitis in the French national survey and from the literature review.

New-onset uveitis under anti-TNF	AS	RA	PsA	JIA	Etanercept	Infliximab	Adalimumab
French national survey (n = 31; %)	61	19	12	6	74	16	10
Literature review (n = 121; %)	72	10	6	11	84.3	12.4	3.3

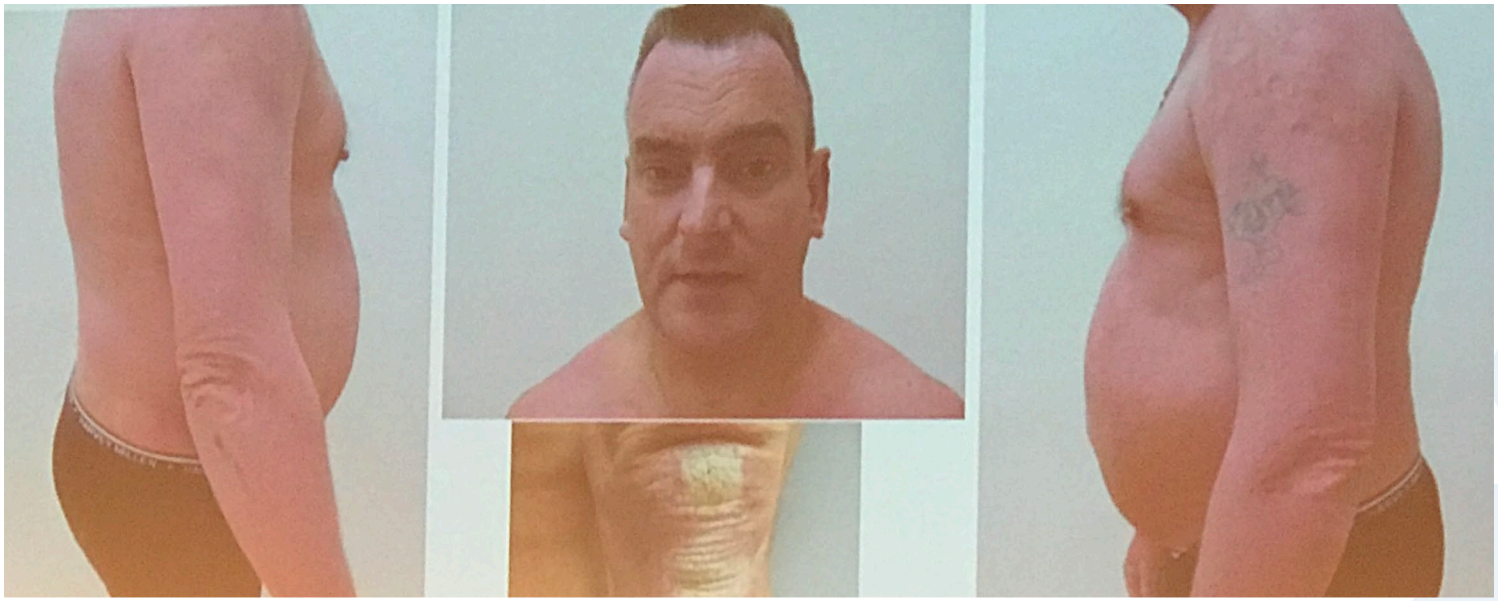
AS: Ankylosing spondylitis; JIA: Juvenile idiopathic arthritis; RA: Rheumatoid arthritis; PsA: Psoriatic arthritis.
Data taken from [31].

Types of HSR reactions to biologics

Local
- Angioedema
- injection site reactions

Systemic
- Immediate type / anaphylactic (Type I and IgE mediated)
- Angioedema
- Serum sickness-like (Type III immune complex mediated)
- Vasculitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis .....

Erytroderma, fever, arthralgia & severe itch



Biological agent	Adverse effect
Anti-TNF Infliximab Adalimumab	Acute HSR (local and systemic) Delayed HSR (serum sickness disease)
Certolizumab	Infection Paradoxical adverse effects: vasculitis, colitis, psoriasis-like eruption, etc.... Autoimmunity: lupus, hepatitis, thyroiditis, etc.. Heart failure
Anti- alpha-4 integrin Natalizumab	Acute HSR (local and systemic) Delayed HSR (serum sickness disease) Infection: progressive multifocal leukoencephalopathy Autoimmunity: hepatitis, thyroiditis
Anti-IL12/ anti-IL23 Ustekinumab	Delayed HSR (serum sickness disease) Infection

Table 2. Biological Drugs. Concentrations Used for Prick Tests and Intradermal Tests

Drug	Prick Test	Intradermal Test	Reference
Abciximab	0.2-2 mg/mL	0.2-2 mg/mL	17
Basiliximab	4 mg/mL	0.4-400 µg/mL	18
Cetuximab	500 µg/mL	5-50-500 µg/mL	24
Anakinra	As is		45
Filgrastim	300 µg/mL	As is	98, 112
Lenograstim		As is	98
Sargramostim	100-250 µg/mL		112

Incidence of injection / infusion site reactions and HSR

Drug	Target	Overall injection / infusion reactions	HSR
Infliximab (Remicade)	TNF-a	18%	1%
Etanercept (Enbrel)	TNF-a	15% to 37%	<2%
Adalimumab (Humira)	TNF-a	20%	1%
Golimumab (Simponi)	TNF-a	4% to 20%	n/r
Certolizumab (Cimzia)	TNF-a	0.8% to 4.5%	n/r

From Aubin et al. 2013 and M Corominas, et al. 2014

Diagnostics of HSR to biologics

In Vitro Tests (most are not standardized)

- *Detection of IgG antibodies:* blocking the effect of the biologics or by participating in the HSR reactions
- *Detection of IgE antibodies:* IgE using enzyme immunoassay or ImmunoCAP
- *Basophil activation test:* has been used in a few cases

In Vivo Tests

- Skin prick tests, intradermal tests, and patch tests are used for diagnosis

c

Desensitization:

- successful desensitization protocols have been established

TAKE AT HOME MESSAGES

- Most paradoxal reactions, caused by TNF alfa blockers
- **Cases caused by anti IL12/23: anti IL17s are increasing**
- Most clear upon discontinuation or by switching
- Sometimes, additional therapies required
- **Mechanisms require further research, especially genetic research to identify patients at risk**

Thank you

Dr Antonio Martorell
Hospital de Manises
Valencia (Spain)

Iniciativa científica de:

antmarto@hotmail.com
@drmartorell
dr.antoniomartorell