Drug Toxicity of Anti-Rheumatic Therapies

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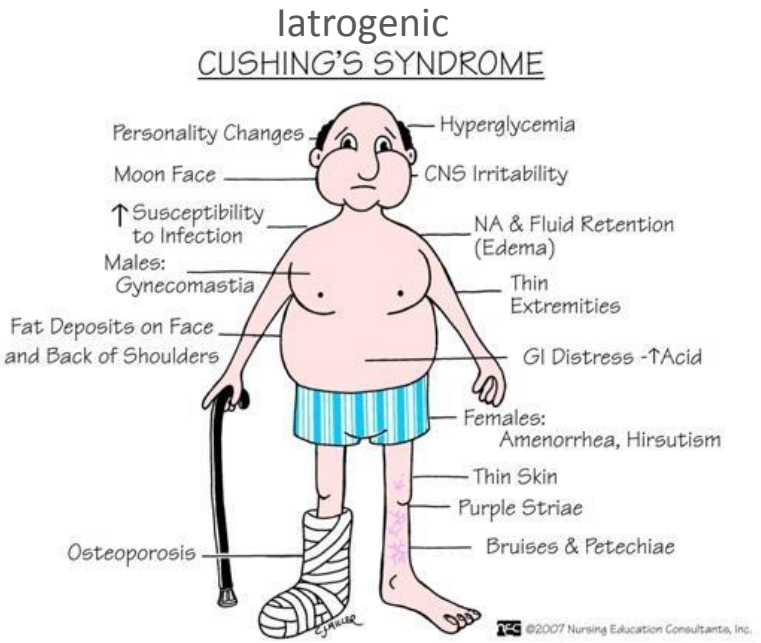
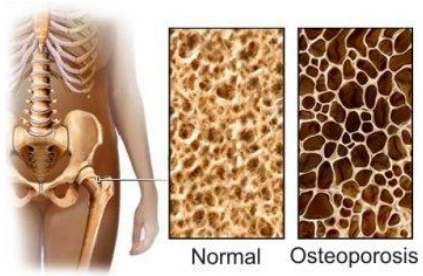
Steroids



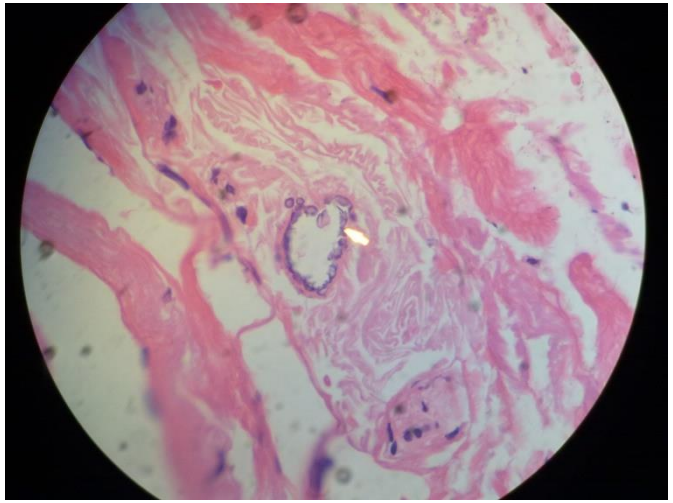


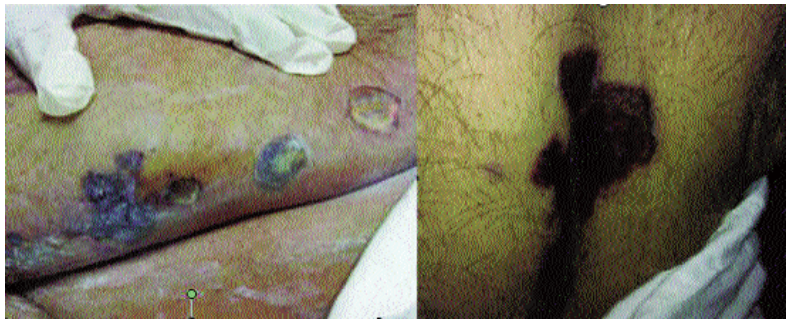
Prednisone 7.5mg
for >3 months

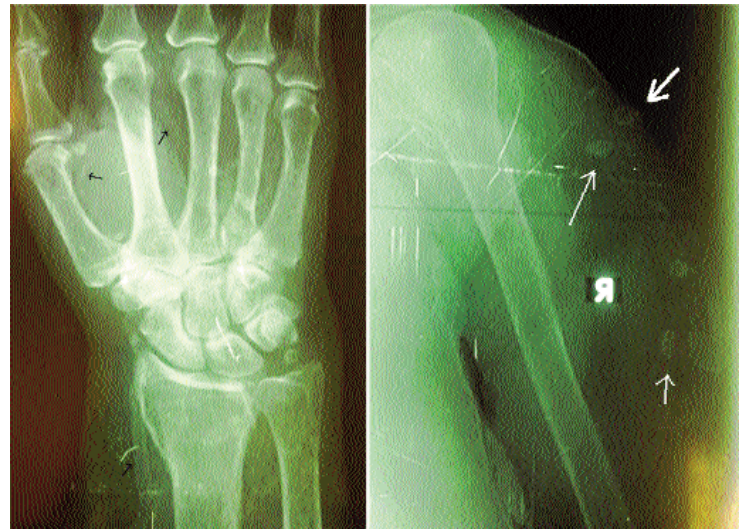
Acute MI (OR=2.15) with Prednisone ≥ 10mg / day

Risk present in even the first month of use.

Varas-Lorenzo et al. Atherosclerosis. 2007. PMID: 16787647.

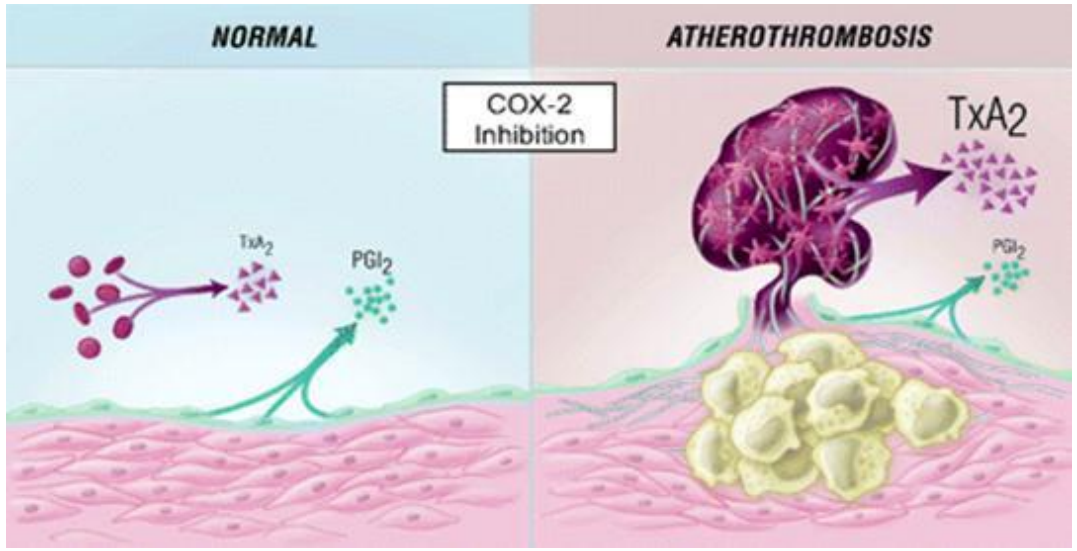


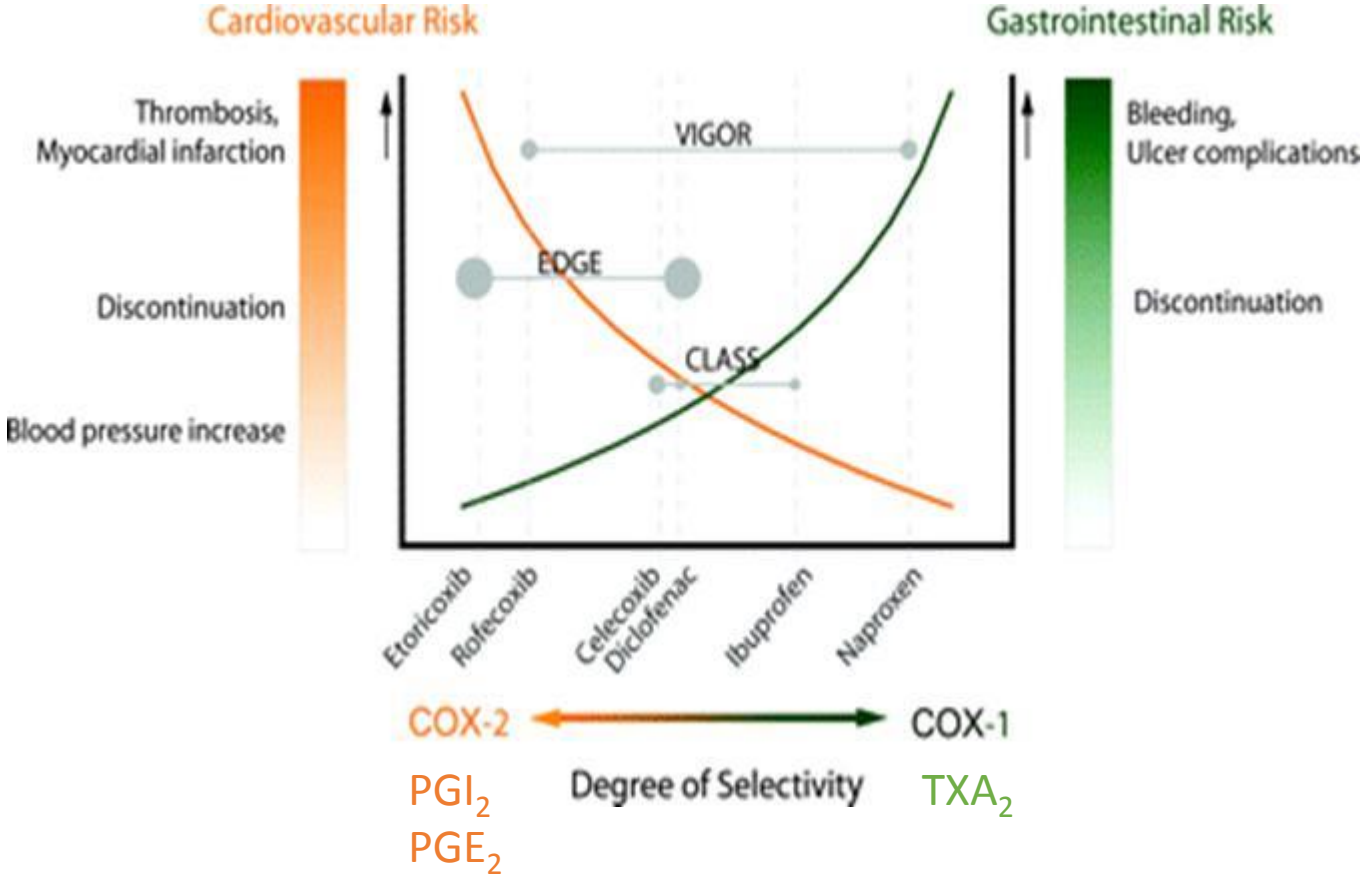




Nazir L, Saeed M. The calcium invasion: Calciphylaxis in Lupus. J Pak Med Assoc. 2015 Apr;65(4):427-8. PubMed PMID: 25976582.

NSAIDs





~ 2 fold increased risk for MI and ischemic stroke risk with Aceclofenac (COX2 selective inhibitor).

de Abajo et al. Pharmacoepidemiol Drug Saf. 2014;23(11):1128-38. PMID: 24692325.

García-Poza et al. J Thromb Haemost. 2015;13(5):708-18. PMID: 25611553.

Hydroxychloroquine & Sulfasalazine

Safe in Pregnancy.

Gerosa et al. Expert Opin Pharmacother. 2016;17(11):1539-47. PMID: 27283340.

Kaplanet al. Br J Clin Pharmacol. 2016;81(5):835-48. PMID: 26700396

PLAQUENIL has been shown to cause **severe hypoglycemia** including loss of consciousness that could be life threatening in patients treated with and without antidiabetic medications. Patients treated with PLAQUENIL should be warned about the risk of hypoglycemia and the associated clinical signs and symptoms.

Product Monograph of PLAQUENIL
http://products.sanofi.ca/en/plaquenil.pdf

Lower fasting glucose levels:
Penn et al. J Rheumatol. 2010;37(6):1136-42. PMID: 20436082.

Hydroxychloroquine

Retinal toxicity is dose dependent
6.5 mg/kg ideal (lean) body weight

Skin darkening and patches
(Bahloul et al. Lupus. 2017 :961203317700486. PMID: 28355984.)

Cardiomyopathy and inclusion myositis
(Prevalence 6.7% - Casado et al. Ann Rheum Dis. 2006;65(3):385-90. PMID: 16096334)

SSZ

Hypersensitivity ~ 9%
(Cildag & Senturk. J Clin Rheumatol. 2017;23(2):77-79. PMID: 28121807.)

Lamenting the limited availability of Sulfasalazine . . .

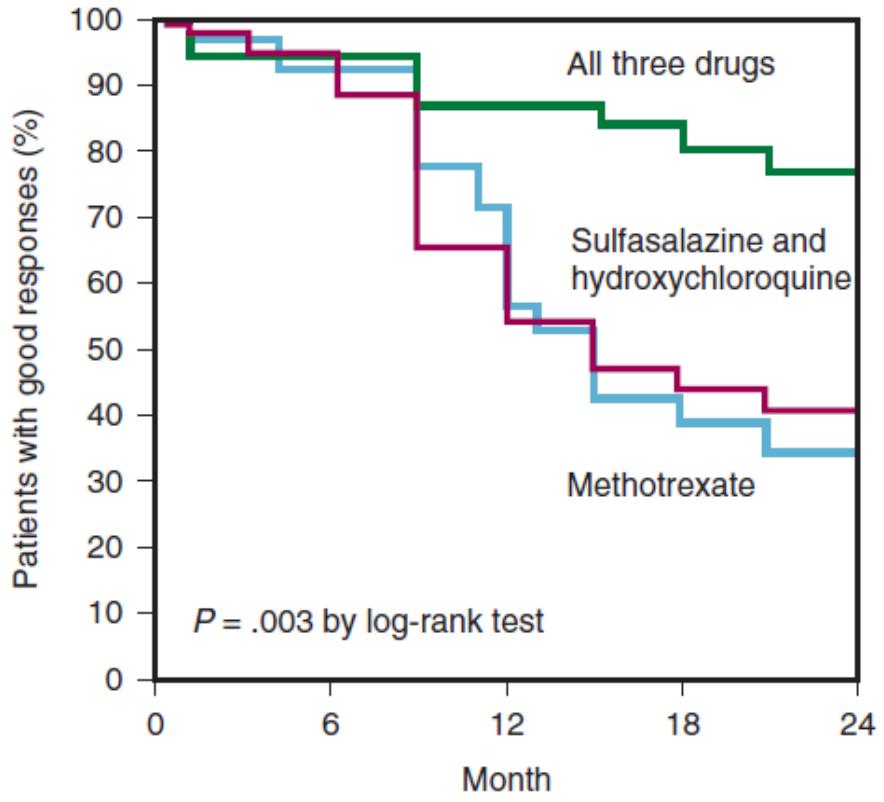
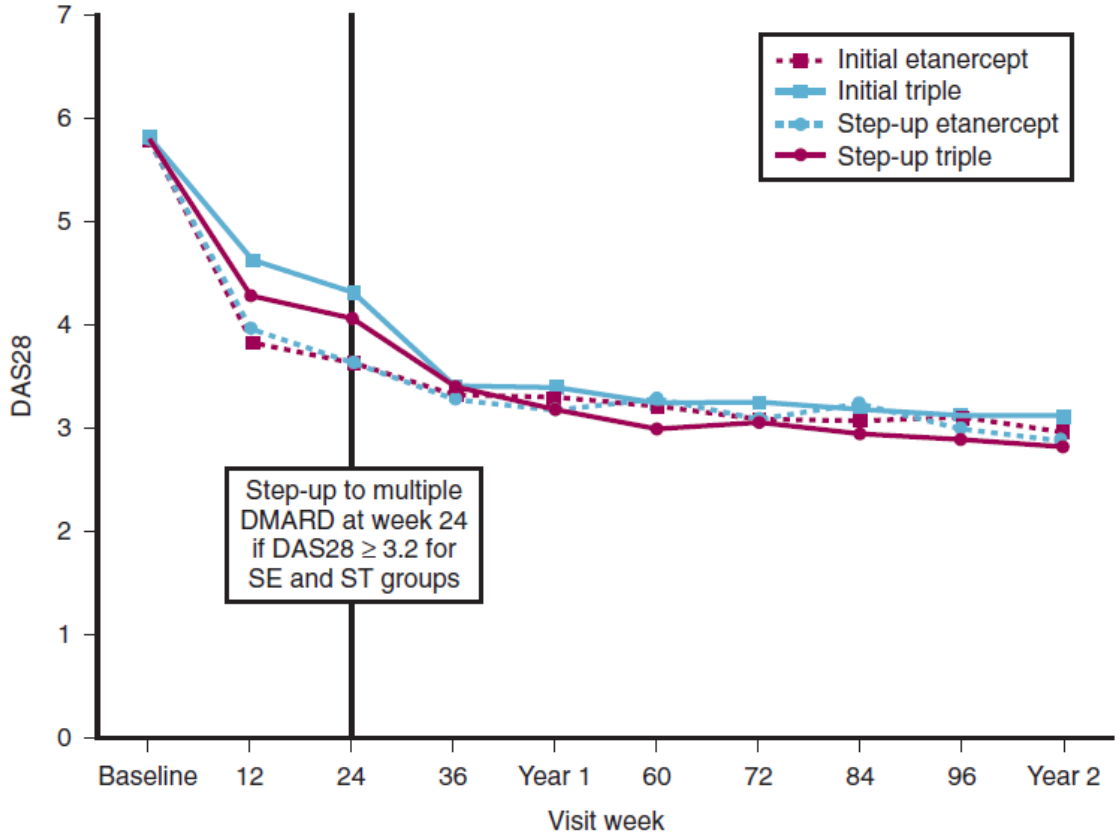


Figure 71-5 Benefits of combination methotrexate/hydroxychloroquine/sulfasalazine (triple) therapy over monotherapy with methotrexate or combination hydroxychloroquine/sulfasalazine. *(Adapted from O'Dell J, Haire C, Erikson N, et al: Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications,* N Engl J Med *334:1287–1291, 1996.)*



Moreland et al. Arthritis Rheum. 2012 ;64(9):2824-35. PMID 22508468

Triple regimen use in Pak ~ 8% only
Rais et al. JPMA 64: 1430; 2014

Traditional Cytotoxic DMARDs

Drug	Liver	Renal	Heme	Malignancy	ILD	Alopecia	Others
MTX	++	+	++		++	+	
LFN	+	++	+		+	++	HTN
AZA	+	+	+				
MMF	+	+	+				Headache
CsA	+	++	+				HTN
Cyc	++	++	+++	TCC, Lym		++	

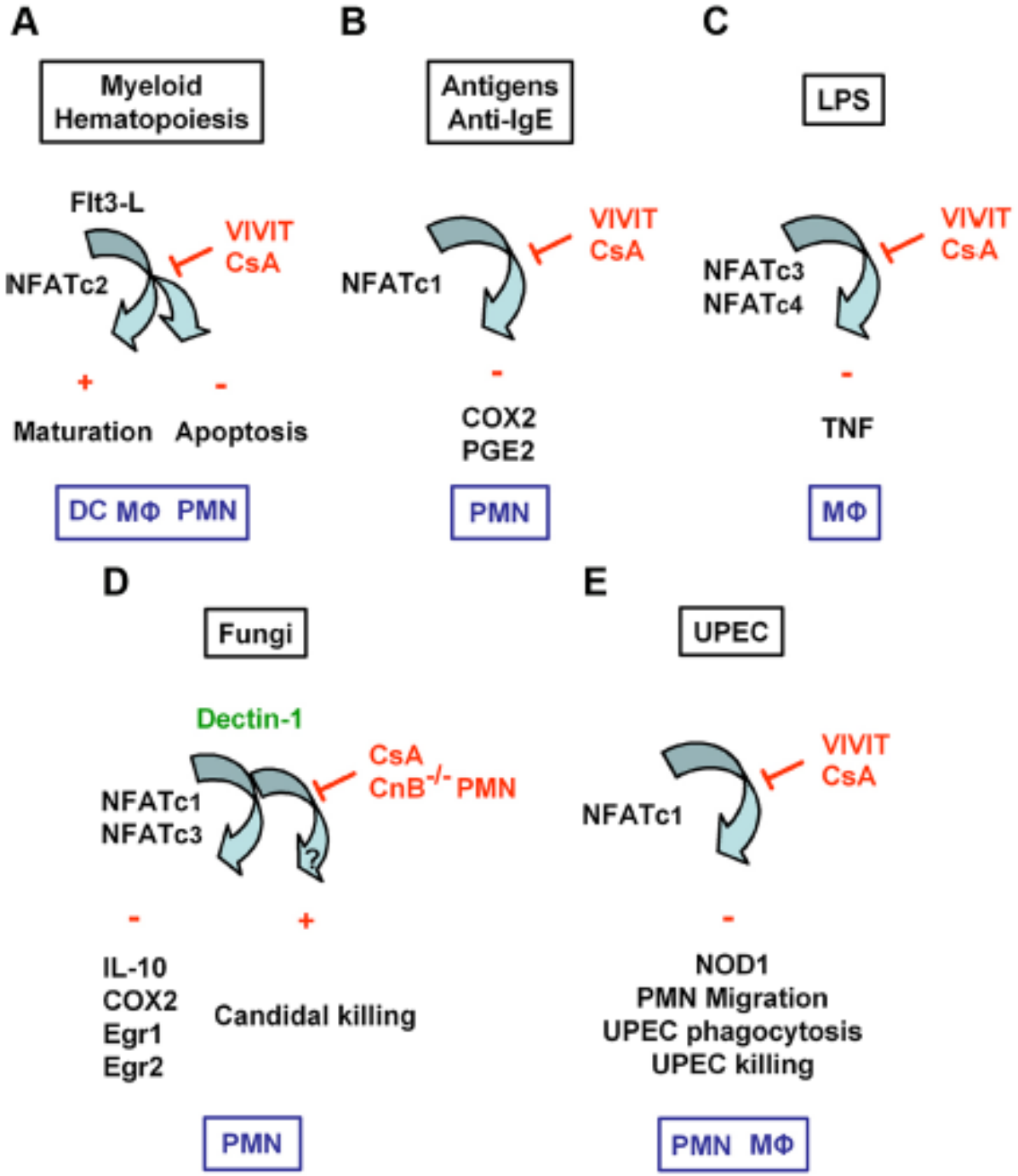
* All DMARDs predispose to infections

CsA Mechanism and ADRs

NFATs (Nuclear Factor of Activated T cells) are modulated by calcineurin, a calcium, calmodulin dependent serine/threonine phosphatase.

Calcineurin inhibitors inhibit the phosphatase activity of calcineurin and the nuclear translocation of NFATs for DNA-binding.

Vandewalle et al. Cell Communication and Signaling 2014, 12:8



Rituximab

Table 2. SIE rates before and after treatment with biologics, including TNF inhibitors. Multiple occurrences of the same event in 1 individual are counted multiple times. DMARD received after the first day of study RTX dose are the DMARD of interest. N is the number of patients receiving treatment with a DMARD post-RTX.

Variables	All Patients Receiving Any Biologic Following RTX Treatment, n = 353		Subset of Patients Receiving a TNF Inhibitor Following RTX Treatment, n = 280	
	Before Other Biologic, During RTX Treatment	After Other Biologic, After RTX Treatment	Before TNF Inhibitor, During RTX Treatment	After Other TNF Inhibitor, After RTX Treatment
Total exposure, PY	727.48	491.61	514.45	387.30
Serious infections, n	32	20	22	14
Serious infections/100 PY	4.40	4.07	4.28	3.61
95% CI	3.11–6.22	2.62–6.31	2.82–6.49	2.14–6.10

SIE: serious infection events; TNF: tumor necrosis factor; DMARD: disease-modifying antirheumatic drugs; RTX: rituximab; PY: patient-years.

~ 3600 patients followed for 11-years and received an average of 4 courses of RTX (i.e 8g). Range was up to 20 courses.

Max rate of AE during first 6 months after the first RTX dose

Infusion-related reactions predominantly occurred with the first infusion of the first course.

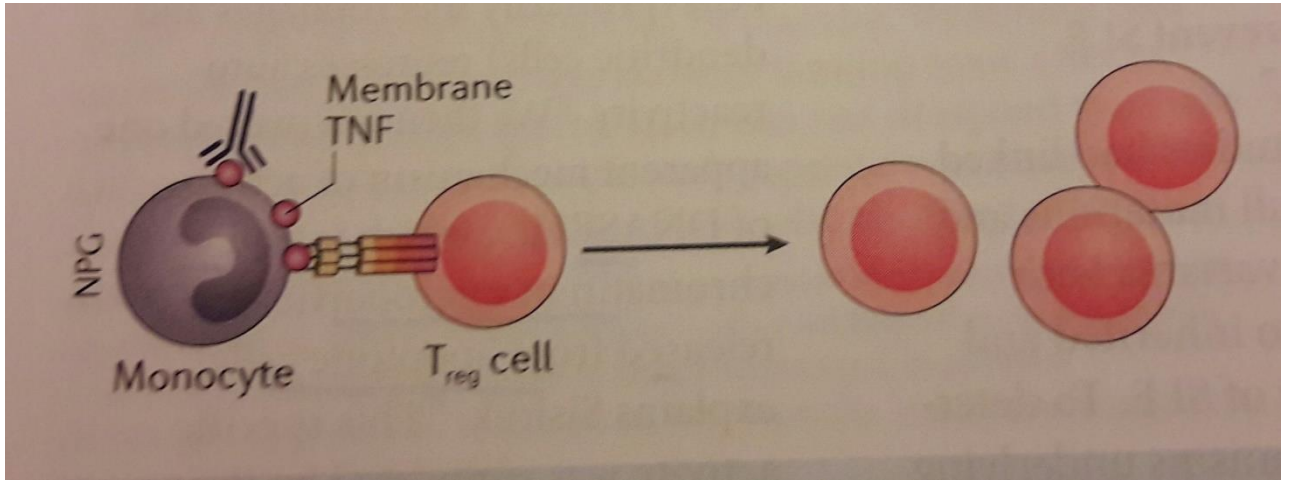
Serious infection event < 4%

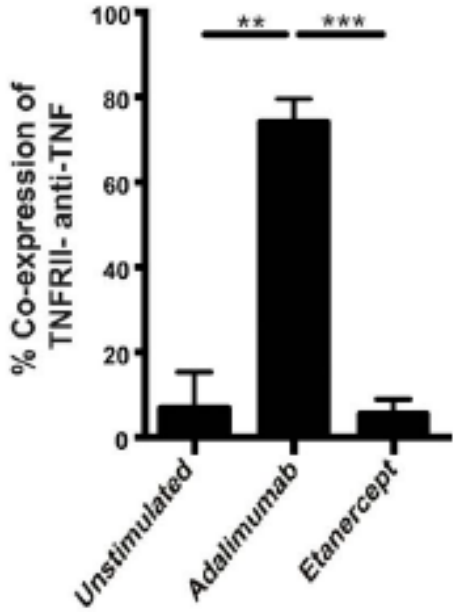
No increased risk for MI or malignancy

van Vollenhoven et al. Longterm Safety of Rituximab: Final Report of the Rheumatoid Arthritis Global Clinical Trial Program over 11 Years. J Rheumatol. 2015;42(10):1761-6. PMID: 26276965.

Eternacept & Adalumimab

Mechanism





Adalimumab binds membrane TNF on Monocytes which interacts with TNF-R2 on Tregs leading to their clonal expansion. This effect is not shown by Etanercept.

Nat Rev Rheum 2016; 12(8): 438.

J. Exp. Med. 2016 Vol. 213 No. 7 1241–1253

Eternacept & Adalumimab

Malignancy? No!

Table 3 Relative risk* of cancer overall in TNFi-treated patients with SpA from ARTIS and DANBIO (n=8703)† versus Swedish TNFi-naïve SpA patients (n=28 164)† and Swedish general population comparator subjects (n=131 687)† overall and in AS, PsA and SpA undifferentiated (UNS) separately 2001 to 2011

	TNFi (DANBIO and ARTIS)-treated patients with SpA versus TNFi-naïve		TNFi-treated (DANBIO and ARTIS) patients with SpA versus general population		TNFi-naïve patients with SpA versus the general population	
	N cancers TNFi-treated/TNFi-naïve	RR (95% CI)	N cancers TNFi-treated/general population	RR (95% CI)	N cancers TNFi naïve/general population	RR (95% CI)
All SpA	147/1188	0.8 (0.7 to 1.0)	147/5153	0.9 (0.7 to 1.0)	1188/5153	1.1 (1.0 to 1.2)
AS	53/310	0.8 (0.6 to 1.1)	53/1296	0.9 (0.7 to 1.2)	310/1296	1.1 (1.0 to 1.3)
PsA	71/722	0.9 (0.7 to 1.1)	71/3227	0.9 (0.7 to 1.1)	722/3227	1.0 (0.9 to 1.1)
SpA UNS	23/200	0.9 (0.6 to 1.3)	23/979	0.8 (0.6 to 1.3)	202/979	1.0 (0.8 to 1.2)

*Age-standardised and sex-standardised incidence ratio (RR) with 95% CIs.
†DANBIO and ARTIS=TNFi-treated SpA, persons-years=33 908, Swedish TNFi-naïve patients with SpA, person-years=182 136, Swedish general population comparator subjects, person-years=862 380.
ARTIS, Anti-Rheumatic Therapy in Sweden; AS, ankylosing spondylitis; DANBIO, Danish biologics register; PsA, psoriatic arthritis; RR, relative risk; SpA, spondyloarthritis; TNFi, tumour necrosis factor inhibitor.

Hellgren et al.
Ann Rheum Dis. 2017; 76(1):105-111.
PMID: 27147709

ILD from biologics? Yes, but low frequency

Curtis *et al. Arthritis Research & Therapy* (2015) 17:319
DOI 10.1186/s13075-015-0835-7

arthritis research&therapy

RESEARCH ARTICLE Open Access

Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor α agents, a retrospective cohort study

Jeffrey R. Curtis[1*], Khaled Sarsour[2], Pavel Napalkov[2], Laurie A. Costa[3] and Kathy L. Schulman[3]

Results: ~ 14K episodes of biologic exposure in >11K patients for ~ 6 months.

Unadjusted ILD incidence rates ranged from 4.0 (1.6–8.2, abatacept) to 12.2 (5.6–23.2, infliximab) per 1000 person-years.

There were no significant differences by biologic class.

Table 3 ILD incidence rate per 1000 PY, unadjusted

Cohort	Specific definition Events (total PY) Rate (95 % CI)	Sensitive definition Events (total PY) Rate (95 % CI)
All eligible	16 (9107) 1.8 (1.0–2.9)	59 (9154) 6.4 (4.9–8.3)
Anti-TNFα agents	9 (5473) 1.6 (0.8–3.1)	39 (5527) 7.1 (5.0–9.6)
Etanercept	0 (1012) 0.0 (0.0–3.0)	6 (1015) 5.9 (2.2-12.9)
Adalimumab	3 (1674) 1.8 (0.4-5.2)	12 (1692) 7.1 (3.7–12.4)
Infliximab	3 (735) 4.1 (0.8–12.0)	9 (738) 12.2 (5.6–23.2)
Certolizumab pegol	3 (948) 3.2 (0.7–9.3)	7 (962) 7.3 (2.9–15.0)
Golimumab	0 (1104) 0.0 (0.0–2.7)	5 (1119) 4.5 (1.5–10.4)
Tocilizumab	1 (1008) 1.0 (0.0-5.5)	5 (1030) 4.9 (1.6–11.3)
Rituximab	4 (851) 4.7 (1.3–12.1)	8 (830) 9.6 (4.2–19.0)
Abatacept	2 (1775) 1.1 (0.1–4.1)	7 (1767) 4.0 (1.6–8.2)

ILD interstitial lung disease, *PY* person-year, *CI* confidence interval, *TNFα* tumor necrosis factor alpha

Biologic specific ADRs

Rituximab

Hypogammaglobinemia

Low B-cell count in babies post delivery

Blood. 2011;117(5):1499-506. (PMID: 21098742)

Belimumab

URI, N/V, Diarrhea

Bacterial infections,
Leukopenia

Rosman et al. BMC Medicine 2013, 11:88

Ocrelizumab and biosimilars

>70% had infection and
~ 30% serious infection

Serious opportunistic infection 3.2% vs 0.8% for placebo

Trial in LN terminated

Arthritis & Rheumatism. 2013; 65(9):2368–2379.

Secukinumab

Candidiasis ~ 1%
IL-17 plays a major role

NEJM. 2015;373:2534-48. PMID: 26699169.

Tociluzimab

IL-6 plays in bacterial infection

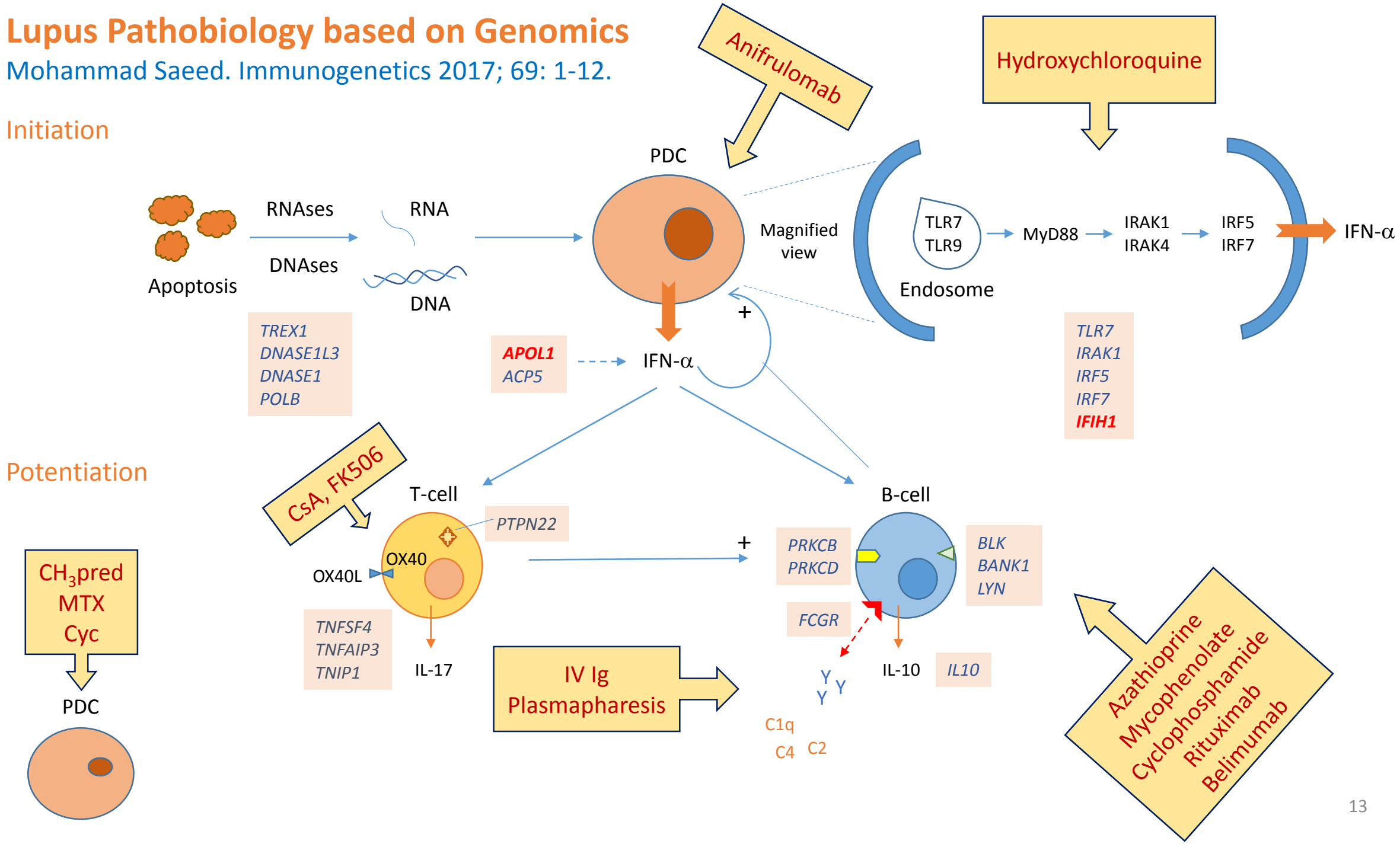
URI, Pneumonia, GE, UTI

[Temporary neutropenia
Elevated transaminases]

Rosman et al. BMC Medicine 2013, 11:88

Lupus Pathobiology based on Genomics

Mohammad Saeed. Immunogenetics 2017; 69: 1-12.



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Thank you

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