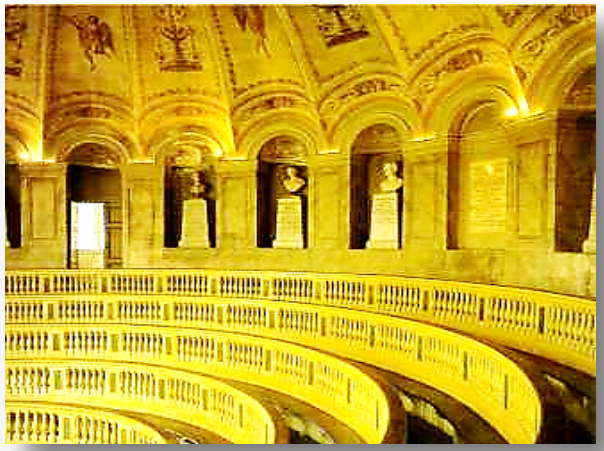
Small molecules for RA: PROS

Roberto Caporali

Early Arthritis Clinic

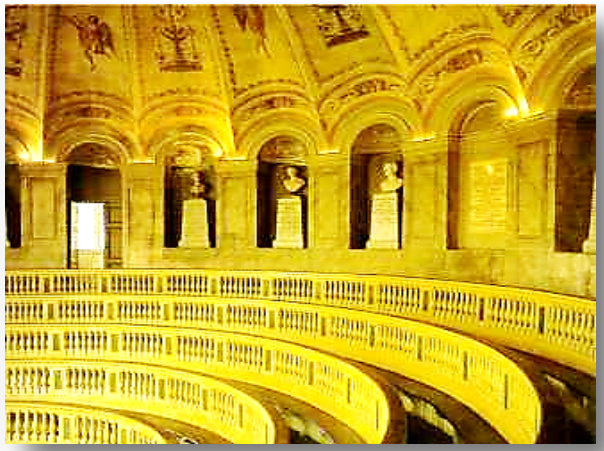
Division of Rheumatology
University of Pavia School of Medicine
IRCCS Policlinico San Matteo Foundation
Pavia, Italy



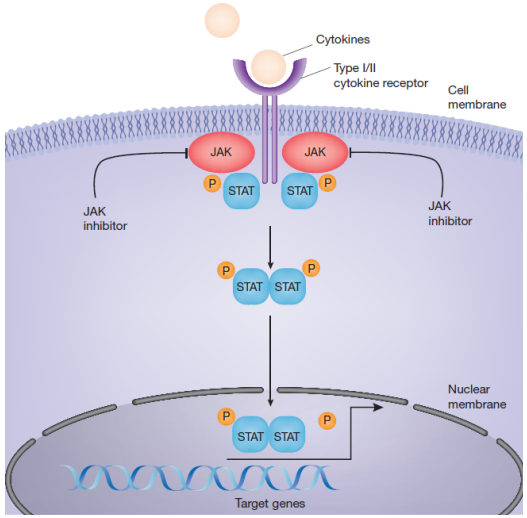
Small molecules for RA: CONS!!

Roberto Caporali

Early Arthritis Clinic
Division of Rheumatology
University of Pavia School of Medicine
IRCCS Policlinico San Matteo Foundation
Pavia, Italy



Small molecules

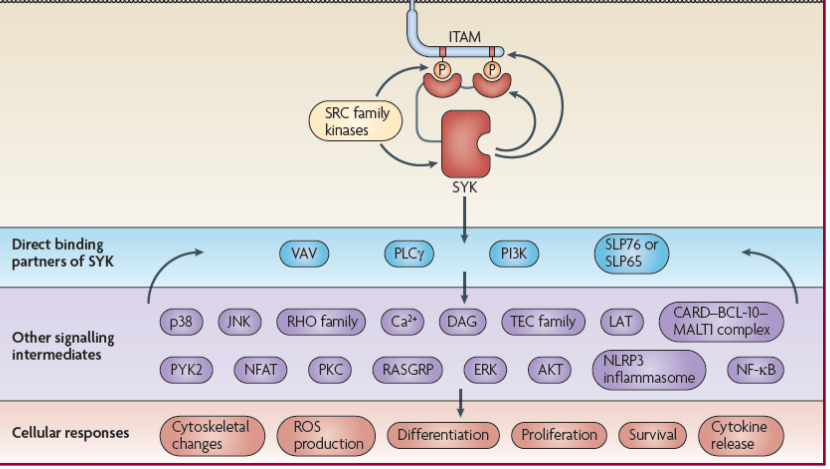


- Chemical compunds able to interfere with intracellular mechanisms able to mediate the effects of different cytokines
- Many molecules in phaseI-III development with different targets
- Two compounds (JAK inhibitors) are under examination by EMA (TOFACITINIB, BARICITINIB)
- One already on the market outside Europe (TOFACITINIB)

© MARK ANDERSON

WWW.ANDERTOONS.COM

"OK, who's ready for a breather."



Spleen tyrosin kinase inhibition

Clinical response rates to Fostamatinib studies

	Weinblatt E et al. *A&R* 2008				Weinblatt E et al. *NEJM* 2010			Genovese MC et al *A&R* 2011	
Study population	MTX inadequate responders				MTX inadequate responders			Biologic non-responders	
Size, *n*	189				457			219	
Previous biologic, %	20				15			100	
Duration, months	3				6			3	
Intervention	Placebo	50 mg bd	100 mg bd	150 mg bd	Placebo	150 mg/ day	100 mg bd	Placebo	100 mg bd
ACR20, %	38	32	65*	72*	35	57*	67*	37	38
ACR50, %	19	17	49*	57*	19	32*	43*	12	22
ACR70, %	4	2	33*	40*	10	14	28*	5	9
DAS28<2.6	8	16	26*	49*	7	21*	31*	10	12

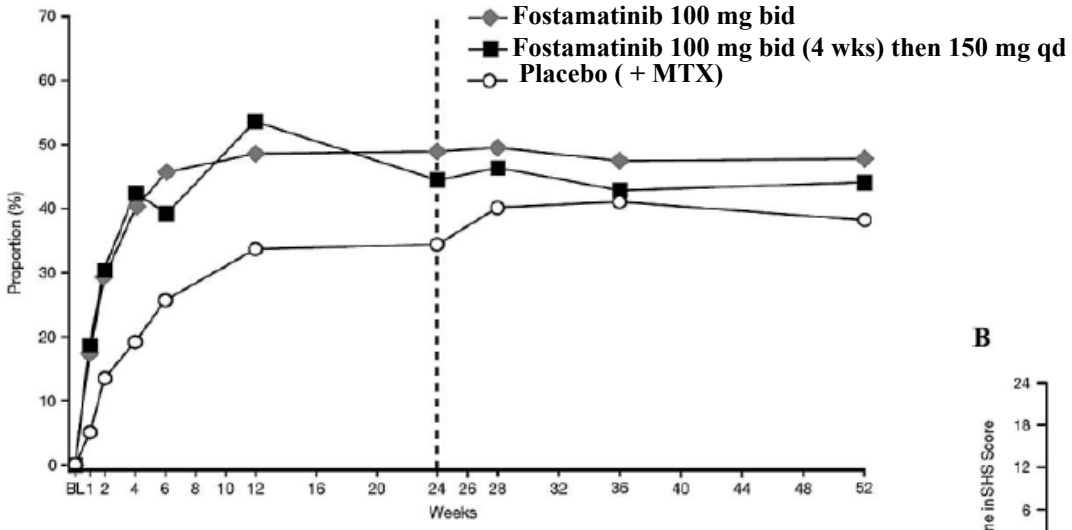
*$P < 0.05$ in comparison with placebo for that study. DAS28: DAS in 28 joints.

Effects of Fostamatinib, an Oral Spleen Tyrosine Kinase Inhibitor, in Rheumatoid Arthritis Patients With an Inadequate Response to Methotrexate

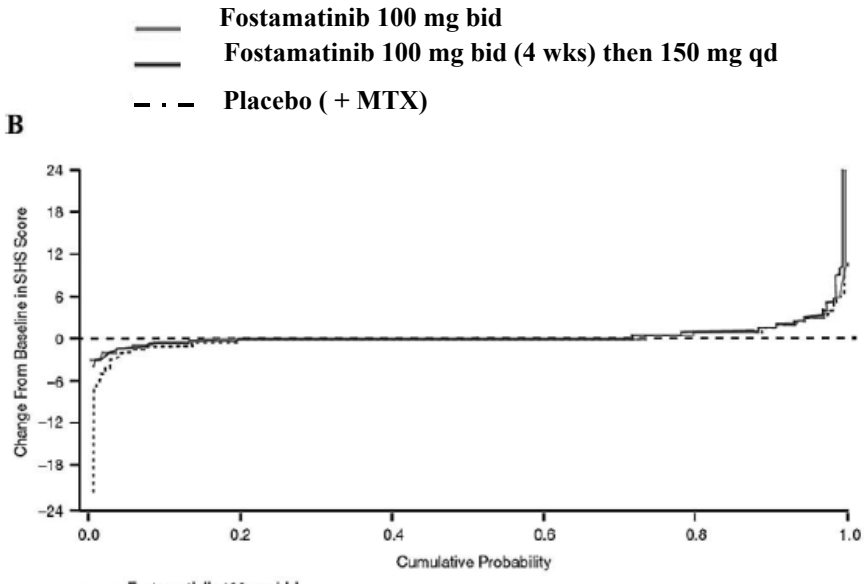
Results From a Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study

Michael E. Weinblatt,[1] Mark C. Genovese,[2] Meilien Ho,[3] Sally Hollis,[3] Krystyna Rosiak-Jedrychowicz,[4] Arthur Kavanaugh,[5] David S. Millson,[3] Gustavo Leon,[6] Millie Wang,[3] and Désirée van der Heijde[7]

ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 12, December 2014, pp 3255–3264



918 randomized patients



..statistically significant but not clinically significant improvements in the ACR20 repsonse over placebo at 24 weeks..

Randomized trials

Real-life studies

Ann Rheum Dis. 2016 Apr 25. . doi: 10.1136/annrheumdis-2016-209131. [Epub ahead of print]

Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis.

Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL

METHODS:

Using health plan data from 2010 to 2014, patients with RA initiating tofacitinib or biologics with no history of HZ or HSV were identified, as were incident cases of HZ or HSV. Crude incidence rates were calculated by drug exposure. Cox proportional hazards models evaluated the adjusted association between tofacitinib and HZ, and a composite outcome of HZ or HSV.

RESULTS:

A total of 2526 patients initiating tofacitinib were compared with initiations of other biologics: anti-tumour necrosis factor (TNF) (n=42 850), abatacept (n=12 305), rituximab (n=5078) and tocilizumab (n=6967). Patients receiving tofacitinib were somewhat younger (mean age 55 years) versus those on other biologics, and somewhat less likely to use concomitant methotrexate (MTX) (39% vs 43%-56%, depending on drug). Crude incidence of HZ associated with tofacitinib was 3.87/100 patient-years (py). After multivariable adjustment, HZ risk was significantly elevated, HR 2.01 (95% CI 1.40 to 2.88) compared with abatacept. Rates and adjusted HRs for all other RA biologics were comparable with each other and abatacept. Older age, female sex, prednisone >7.5 mg/day, prior outpatient infection and greater number of hospitalisations were also associated with increased HZ risk

CONCLUSIONS:

The rate of zoster associated with tofacitinib was approximately double that observed in patients using biologics

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 July 2013
EMA/460814/2013
EMEA/H/C/002542

Questions and answers

Refusal of the marketing authorisation for Xeljanz (tofacitinib)

What were the CHMP's main concerns that led to the refusal?

The CHMP had major concerns about the overall safety profile of Xeljanz. There were significant and unresolved concerns about the risk and type of serious infections seen with tofacitinib, which are related to the immunosuppressant action of the medicine.

These safety concerns also included a risk of other severe side effects including certain cancers, gastro-intestinal perforations (holes in the wall of the gut), liver damage and problems with increased lipid (fat) levels in the blood. It was not clear that these risks could be managed successfully in medical practice.

In April 2013, the Committee considered that, taken together, the data from the five main studies showed that treatment with Xeljanz resulted in an improvement in the signs and symptoms of rheumatoid arthritis and the physical function of patients. However, the studies were not sufficient to show a consistent reduction in disease activity and structural damage to joints, particularly at the lower 5-mg dose of Xeljanz and in the target population of patients in whom treatment with at least two other DMARDs has been unsuccessful. At re-examination in July 2013 the company proposed to remove claims of an effect on structural damage from the indication. However, the lack of robust evidence on prevention of structural damage with Xeljanz in the proposed dose and population still contributed to the Committee's view that the benefits of treatment did not outweigh significant and unresolved concerns about safety.

Therefore, in April 2013 the CHMP was of the opinion that the benefits of Xeljanz did not outweigh its risks and recommended that it be refused marketing authorisation. The CHMP refusal was confirmed after re-examination.

AE Overview (Baricitinib)

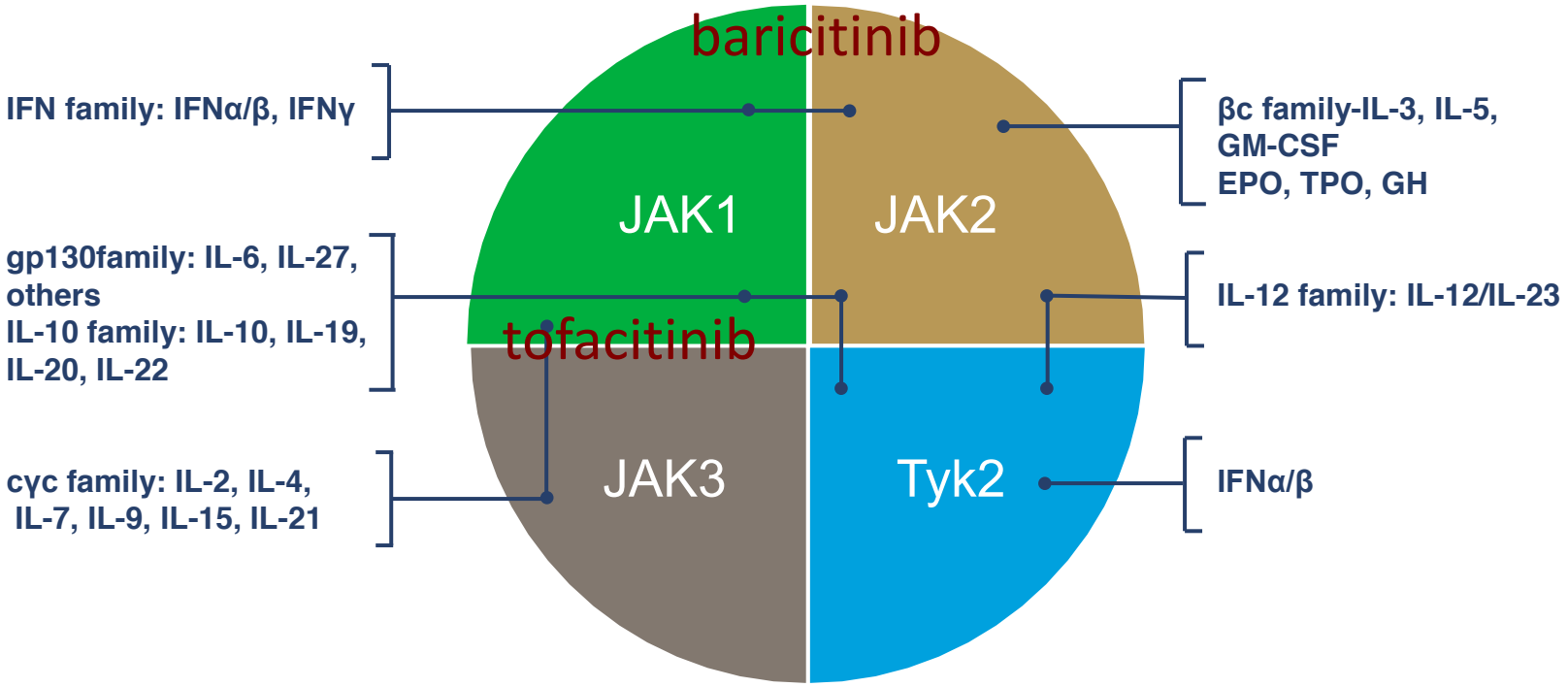
	Weeks 0-12			Weeks 0-24		
	Placebo (N=176)	Bari 2 mg (N=174)	Bari 4 mg (N=177)	Placebo (N=176)	Bari 2 mg (N=174)	Bari 4 mg (N=177)
SAEs						
ICH-defined	7 (4.0)	3 (1.7)	11 (6.2)	13 (7.4)	7 (4.0)	18 (10.2)
Protocol-defined	1 (0.6)	5 (2.9)	4 (2.3)	2 (1.1)	5 (2.9)	5 (2.8)
TEAEs	96 (54.5)	107 (61.5)	119 (67.2)	112 (63.6)	123 (70.7)	137 (77.4)
TEAEs rated as severe	14 (8.0)	8 (4.6)	16 (9.0)	16 (9.1)	14 (8.0)	21 (11.9)
TEAEs leading to interruption	10 (5.7)	19 (10.9)	22 (12.4)	12 (6.8)	26 (14.9)	27 (15.3)
Infections	35 (19.9)	61 (35.1)	48 (27.1)	55 (31.3)	76 (43.7)	70 (39.5)
Serious infections	3 (1.7)	3 (1.7)	3 (1.7)	5 (2.8)	4 (2.3)	6 (3.4)
Severe infections	2 (1.1)	2 (1.1)	3 (1.7)	2 (1.1)	6 (3.4)	6 (3.4)
Herpes zoster	1 (0.6)	2 (1.1)	4 (2.3)	2 (1.1)	2 (1.1)	7 (4.0)
Malignancies	0	0	0	0	0	2 (1.1)
NMSC	0	0	0	0	0	2 (1.1)
MACE	0	0	1 (0.6)	0	0	2 (1.1)

Data displayed are n (%) patients, up to the time of rescue. Any AE or lab abnormality that led to permanent discontinuation was required to be reported as an SAE ("protocol-defined"). No opportunistic infection, TB, lymphoma, or GI perforation was observed. MACE was defined as CV death, MI or stroke positively adjudicated by the independent CV evaluation committee.

Genovese M, et al. New Engl J Med 2016

Different cytokines use different JAKs

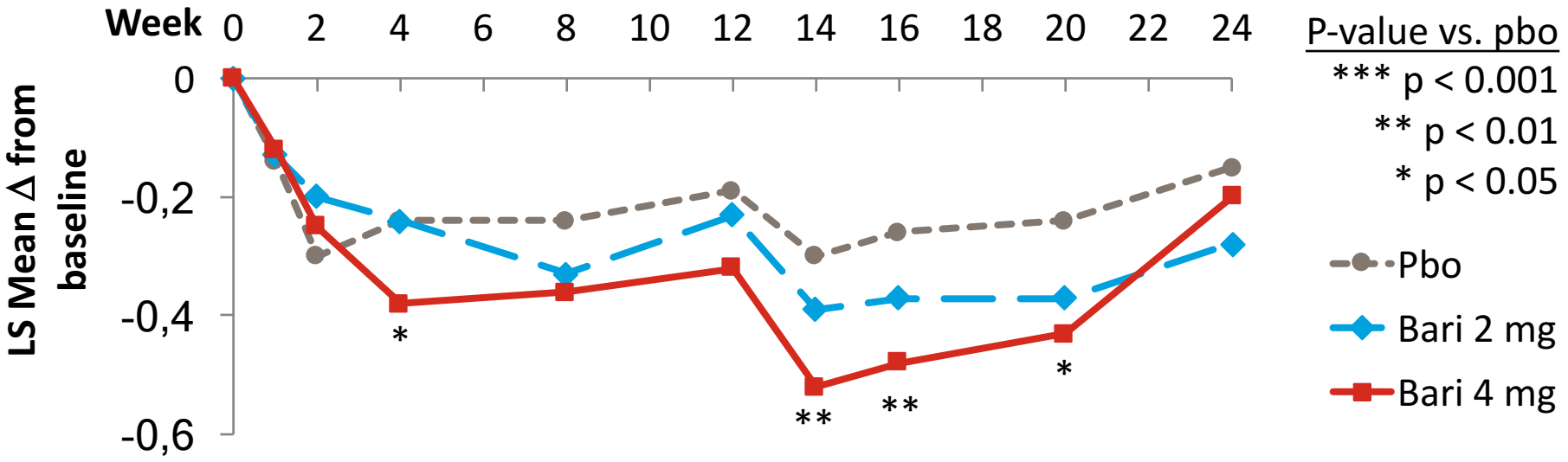
- There are 4 JAK family members: JAK1, JAK2, JAK3, and Tyk2



EPO=erythropoietin; GH=growth hormone; GM-CSF=granulocyte macrophage colony-stimulating factor; gp130=glycoprotein 130; IFN=interferon; IL=interleukin; JAK=Janus kinase; TPO=thyroid peroxidase.

O'Shea et al. *Nat Rev Rheumatol* 2013;9(3):173-82. doi:10.1038/nrrheum.2013.7.

Hemoglobin (g/dL)



	Weeks 0-12			Weeks 0-24		
CTCAE grade	**Placebo (N=176)**	**Bari 2 mg (N=174)**	**Bari 4 mg (N=177)**	**Placebo (N=176)**	**Bari 2 mg (N=174)**	**Bari 4 mg (N=177)**
Grade 1: ≥ 10 g/dL to < LLN	30 (17.0)	33 (19.0)	36 (20.3)	39 (22.2)	45 (25.9)	45 (25.4)
Grade 2: ≥ 8.0 to < 10 g/dL	6 (3.4)	14 (8.0)	9 (5.1)	8 (4.5)	14 (8.0)	12 (6.8)
Grade 3: ≥ 6.5 to < 8.0 g/dL	0	1 (0.6)	0	0	1 (0.6)	0
Grade 4: < 6.5 g/dL	1 (0.6)	0	0	1 (0.6)	0	0

Data in table are n (%) patients, and indicate the worst CTCAE grade in patients who experienced a treatment-emergent increase in grade at any time during the treatment period, up to the time of rescue. One patient with fecal occult blood test +ve and a history of gastric antral vascular ectasia discontinued due to anemia (Bari 2 mg). LLN = 12 g/dL for females and 13.5 g/dL for males. N= number of patients in the analysis.

"To me it's a no-brainer."