Post-Eular 2022

Prof dr TWJ Huizinga, LUMC

Inhoud

- Op weg naar preventie
- Registries
- Guidelines
- SLE

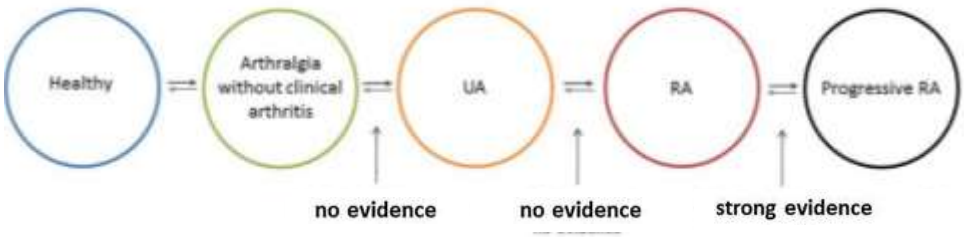
Leiden University Medical Center

Intervention with methotrexate in arthralgia at risk for RA
to reduce the development of persistent arthritis and its disease burden

A double-blind, randomised, placebo-controlled trial

EULAR 2022
Dept. of Rheumatology, LUMC
Speaker: Doortje Krijbolder

The window of opportunity:
A critical period for disease modification



- Bos et al (2x corticoid injection)
- PRAIRI trial (1x rituximab)

Burgers, Raza, Van der Helm–van Mil 2019 RMD Open

Aim

To modify disease in arthralgia-patients with a temporary course of MTX, by reducing:

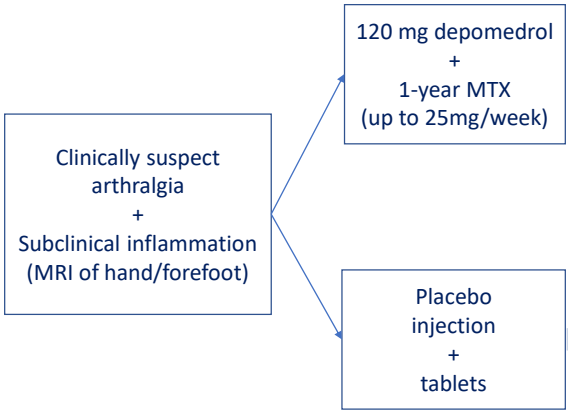
- RA development
- Disease burden
  - ➢ Following the EULAR definition of disease modification
  - ➢ Sustained modification is key

Smolen et al, ARD 2020

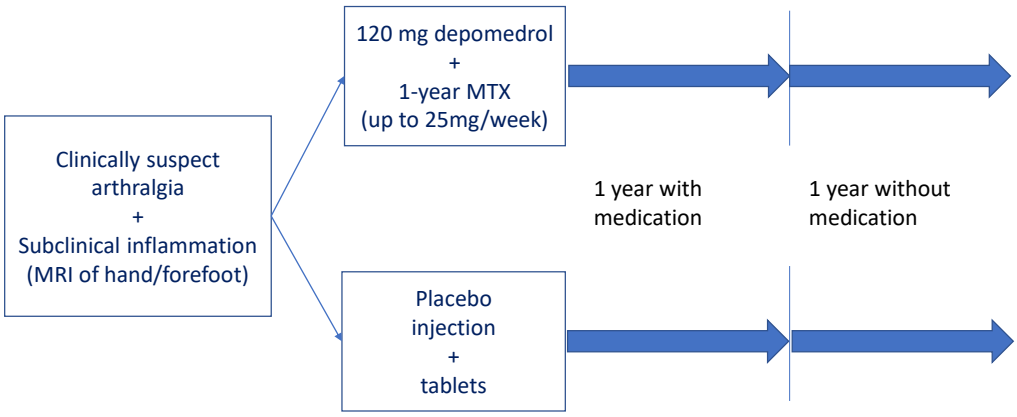
Double-blind randomised design

Clinically suspect
arthralgia
+
Subclinical inflammation
(MRI of hand/forefoot)

Double-blind randomised design



Double-blind randomised design



Outcomes

Primary: Persisting clinical arthritis for ≥2 weeks, fulfilling 2010-criteria or involving ≥2 joints

Secondary: Disease burden
- Functional disability, HAQ
- Pain, morning stiffness
- Workability

Explorative: MRI-detected joint inflammation

Analyses

Intention to treat

Prespecified subgroup analyses: 1) Risk stratification: PVV ≥70%

2) ACPA stratification

Matthijssen et al EULAR 2020

All hospitals in South-West of the Netherlands participated

CSA patients in region, possibly eligible, N=901

MRI screening for subclinical inflammation, N =763

MRI positive, N=384

Consented and randomized, N= 236

119 Treatment

117 Placebo

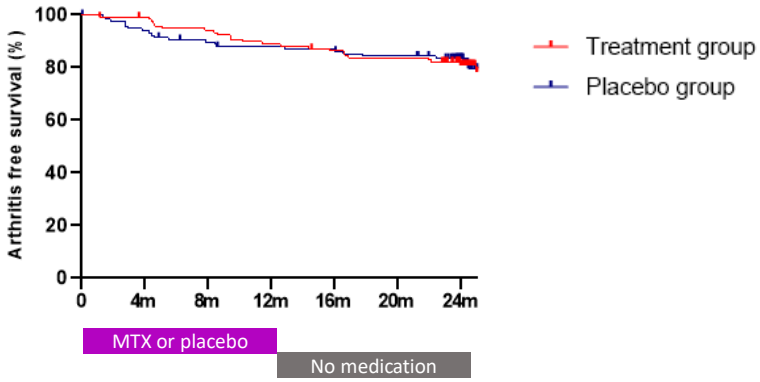
Lost to F up, N=3

Lost to F up, N=5

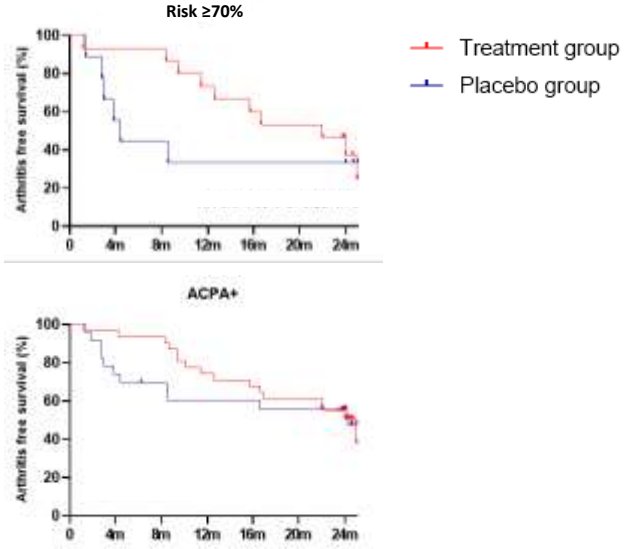
Patient characteristics

	Treatment-group (N=119)	Placebo-group (N=117)
Age (years)	46	47
Female (%)	62	68
Symptom duration (weeks)	28	27
68-TJC	4	3
CRP increased (%)	30	27
RF pos (%)	28	30
ACPA pos (%)	26	20
HAQ score	0.7	0.7

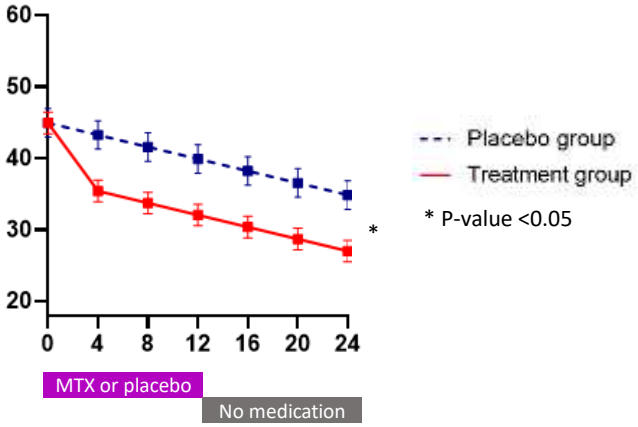
Development of persistent clinical arthritis



Delay of persistent clinical arthritis in subgroups

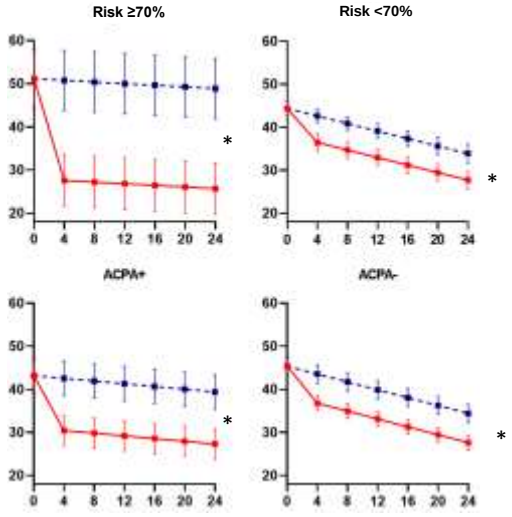


Pain (scale 0-100)

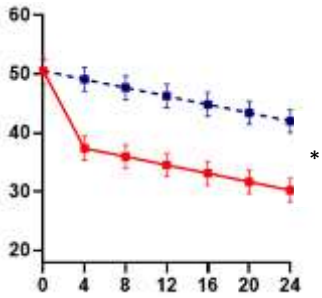


Data from LMM

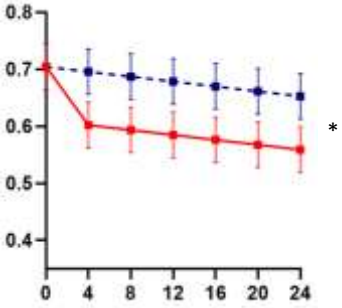
Pain (scale 0-100)



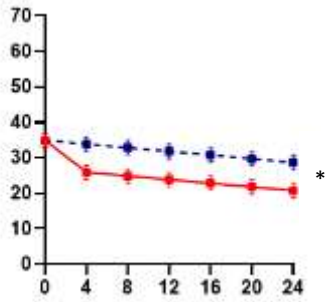
Morning Stiffness
(scale 0-100)



Functional impairment
(HAQ)

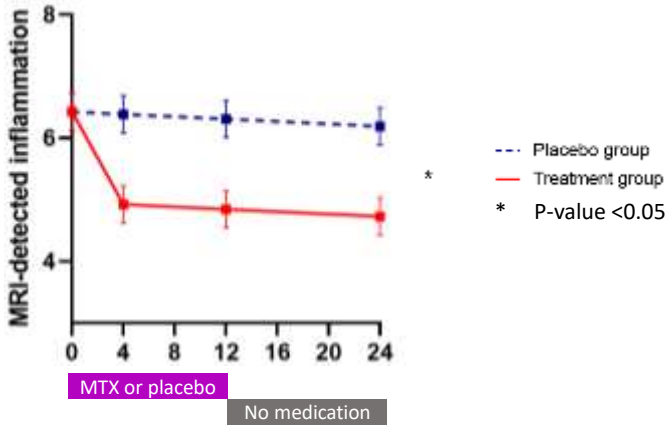


Presenteeism
(scale 0-100)

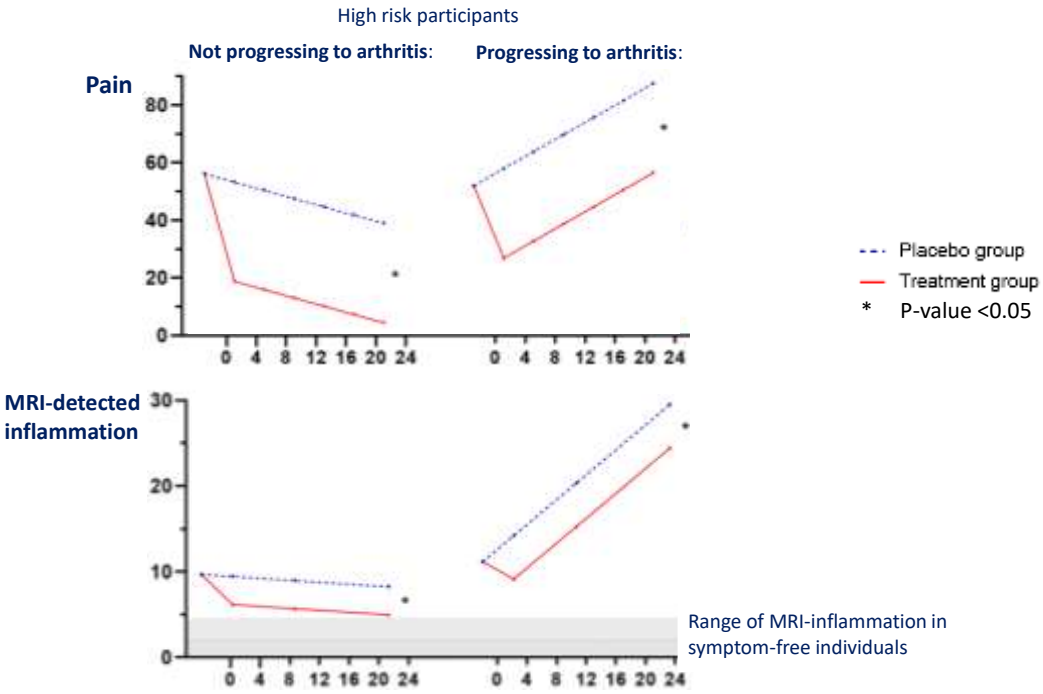


Similar effects in all subgroups

MRI-detected joint inflammation
(RAMRIS units, sum of synovitis, tenosynovitis and osteitis)



Similar effects in all subgroups



Conclusion

Temporary MTX in arthralgia:

- Delays, but not prevents clinical arthritis development
- Induced sustained reduction of disease burden & MRI detected inflammation in all at risk subgroups

First evidence for disease modification when intervening in 'pre-RA'

Poster with abatacept as preventive therapy, similar MRI outcomes

Inhoud

- Op weg naar preventie
- Registries
- Guidelines
- SLE

MORE THAN SIX-FOLD INCREASED MORTALITY RISK IN PATIENTS WITH INCIDENT RHEUMATOID ARTHRITIS AND DEPRESSION IN A LARGE COHORT WITH 10-YEAR FOLLOW-UP
J. K. Pedersen et al

- We used the first filling of antidepressants as proxy for depression with the objective to describe the mortality risk associated with depression in patients with incident RA
- Among 11,071 RA patients followed for 56,993 person-years, 1,095 (10%) filled prescriptions for antidepressants. The median age at diagnosis was 61 years, 66% were female, and 64% diagnosed with seropositive RA

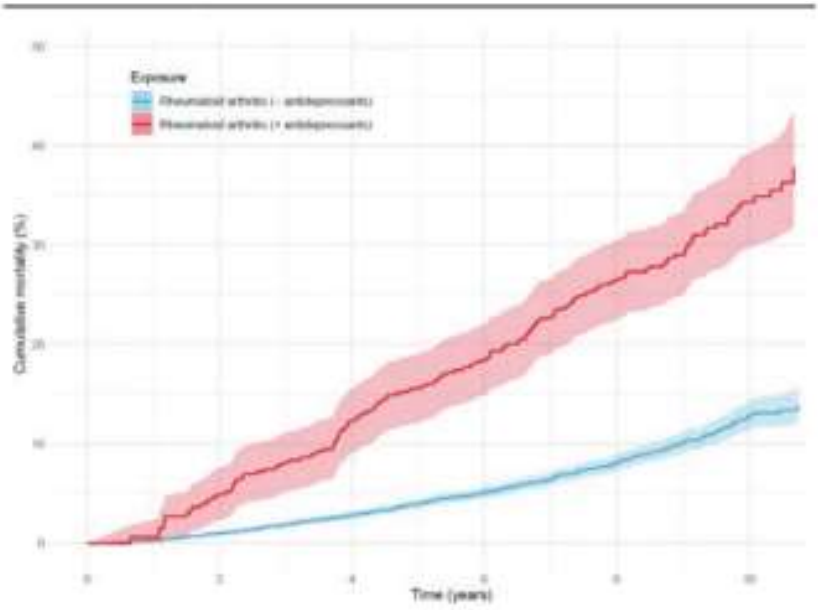


Figure 1.
Conclusion: Depression, defined as first filling of antidepressants, was associated with more than six-fold increased mortality risk in patients with incident RA.

ASSOCIATION BETWEEN LONG-TERM EXPOSURE TO AIR POLLUTION AND IMMUNE-MEDIATED DISEASES: A POPULATION-BASED COHORT STUDY G. Adami et al

81,363 subjects were included in the study. We found a positive association between PM10 and the risk of autoimmune diseases (ρ +0.007, p 0.014). Every 10 µg/m3 increase in PM10 concentration was associated with an incremental 7% risk of having autoimmune disease

Figure 1. A. Prevalence of auto-immune diseases across Italy in the DeFRA database; B. Long-term exposure to particulate matter (PM) of less than 10 µm in Italy (2013-2019 average concentration µg/m3)

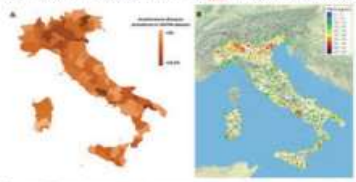


Figure 2. Risk of immune-mediated conditions at chronic exposure to PM10 ≥30 µg/m³

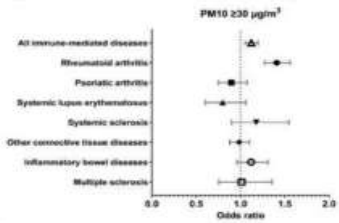
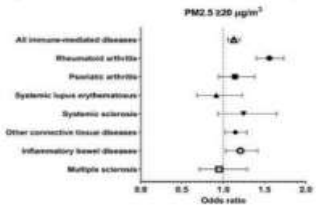


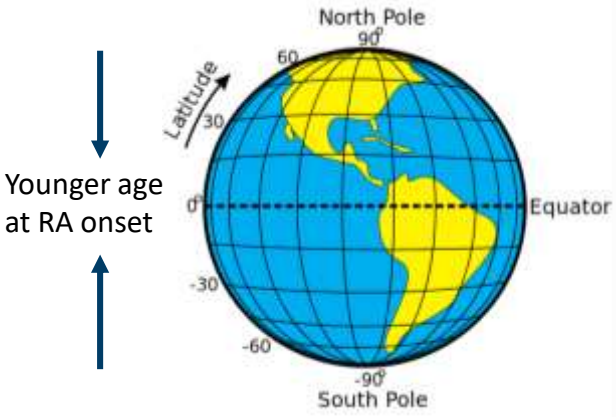
Figure 3. Risk of immune-mediated conditions at chronic exposure to PM2.5 ≥20 µg/m³



Introduction

- Young age at RA onset: higher personal, societal and economic burden, worse prognosis

- Unclear what explains this association
- Latitude may be a proxy for genetic (e.g. ACPA) and environmental (e.g. smoking, wealth) risk factors



Ramos-Remus et al. Clin Rheumatol 2007;26(10):1725-8

METEOR

Aim

To study how age at RA onset varies with latitude worldwide and to what extent patient and country level factors explain this variability.

METEOR

Outcomes and indicators

- Main outcome: patient's age at diagnosis
- Explanatory variable: absolute value of hospital latitude

- Patient factors: gender, rheumatoid factor and ACPA positivity, smoking status, symptom duration (months), year of first visit in the database and BMI
- Country factors: physician density, health expenditure, life expectancy, GDP per capita and gross enrolment in secondary school

METEOR

Included patients

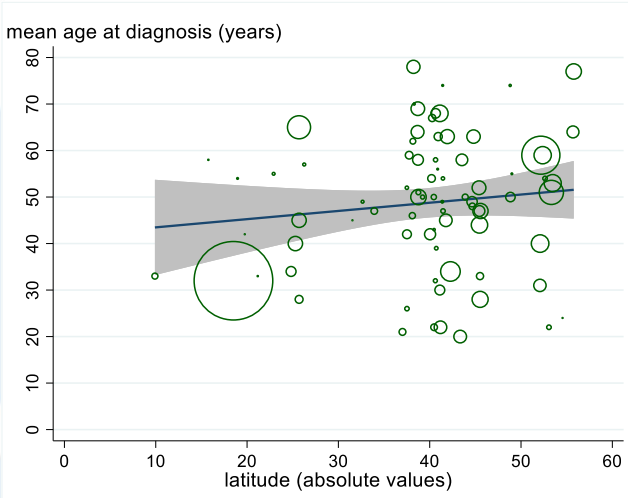
39 782 patients
94 hospitals
17 countries

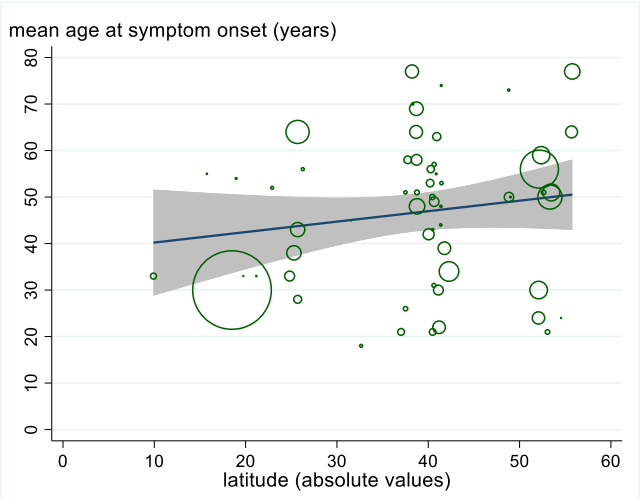
Mean age at diagnosis per country: 39 to 55 years

Brazil, Spain, France, UK, Ireland, India, Iran, Italy, Japan, Mexico, Nigeria, the Netherlands, Pakistan, Portugal, Qatar, USA, South-Africa

METEOR

Mean age at RA onset increases with latitude





METEOR

Conclusion

- Patients living close at the equator indeed get RA far earlier than those living closer to the poles
- Rather than due to variation in patients' characteristics, this latitude gradient seems to be a country level phenomenon
- Which is explained by indicators of countries' socioeconomic status, and not by patient specific genetic or environmental factors.
- This big data analysis in a worldwide prevalence cohort provides a direct link between countries' levels of welfare and the onset of rheumatoid arthritis.

METEOR

Inhoud

Op weg naar preventie
Registries
Guidelines
SLE

METEOR

Recommendations for management of RA

- Prednisone tapered as soon as possible and should be discontinued
- Never longer than 6 months
- bDMARD after failing conventional DMARDs
- tsDMARD only to be considered after taking into account risk factors

Leiden University Medical Center

Prednisone use and the incidence of hyperglycemia and diabetes in patients with rheumatoid arthritis

A 10-year sub-analysis of the BeSt study

J.A. van der Pol, S.A. Bergstra, T.W.J. Huizinga, C.F. Allaart

BeSt
Treatment Strategies in Rheumatoid Arthritis

Leiden University Medical Center

BACKGROUND

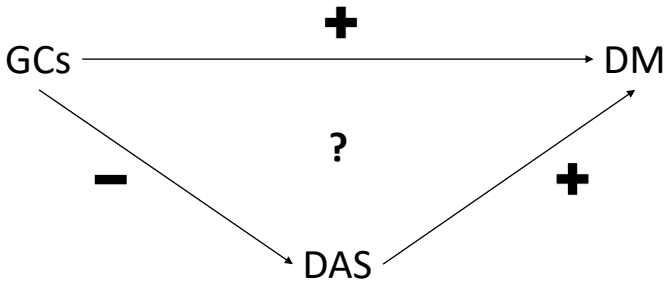
GCs cornerstone in RA treatment[1]
Faster than csDMARDS and prevention of joint damage[2]

Disadvantages: side effects[3]
- Osteoporosis, peptic ulcer, weight gain
- Insulin resistance: hyperglycemia/diabetes mellitus (DM)

Inflammation (CRP/IL-6/TNF-alpha): insulin resistance, hazard of DM development[4,5,6]
- Treatment MTX/bDMARDs: increased insulin sensitivity

1. Fardet L, Petersen I, Nazareth I. Rheumatology, 2011 Nov;50(11):1982-90.
2. Kirwan JR. N Engl J Med. 1995;333(3):142-6.
3. Da Silva JA, Kirwan JR, Boers M et al. Ann Rheum Dis. 2006 Mar;65(3):285-93
4. Dessein PH, Joffe BI. Arthritis and rheumatism. 2006;54(9):2765-75.
5. A. Dregan, J. Charlton, P. Chowienczyk and M.C. Gulliford. Circulation, 2014 Sep 2;130(10):837-44.
6. Chung CP et al. 2008;58(7):2105-12.

OBJECTIVE

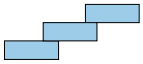


METHODS - BeSt study

- Randomized, single-blind multicenter trial
- 508 patients with DMARD-naive, early RA (1987 criteria)

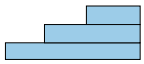
- 3-monthly visits, 10 years FU
- DAS ≤ 2.4 steered trial, including medication tapering

METHODS - Prednisone in treatment steps



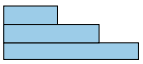
SEQUENTIAL MONOTHERAPY

MTX
↓
SSA
↓
Leflunomide
↓
MTX + IFX
↓
Gold + 3 x MPS 120mg i.m.
↓
MTX + CSA + **pred 7.5mg/day**
↓
AZA + **pred 7.5mg/day**



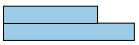
STEP-UP THERAPY

MTX
↓
MTX + SSA
↓
MTX + SSA + HCQ
↓
MTX + SSA + HCQ + **pred 7.5mg/day**
↓
MTX + IFX
↓
MTX + CSA + **pred 7.5mg/day**
↓
leflunomide



INITIAL COMBINATION THERAPY

MTX + SSA + **pred 60 - 7.5mg/day**
↓
MTX + CSA + **pred 7.5mg/day**
↓
MTX + IFX
↓
leflunomide
↓
Gold + 3 x MPS 120mg i.m.
↓
AZA + **pred 7.5mg/day**
↓
Other



ANTI-TNFα

MTX + IFX
↓
SSA
↓
leflunomide
↓
MTX + CSA + **pred 7.5mg/day**
↓
Gold + 3 x MPS 120mg i.m.
↓
AZA + **pred 7.5mg/day**
↓
Other

RESULTS - Baseline

	No prednisone n=264	Ever prednisone n=240	p
Age	54.6 (13.6)	54.1 (13.9)	0.71
Male	91 (34.5)	72 (30.0)	0.28
Smoking	93 (35.6)	84 (35.1)	0.91
BMI	26.1 (4.3)	26.0 (4.0)	0.80
RF-positive	160 (60.0)	168 (70.0)	**0.03**
ACPA-positive	154 (61.6)	145 (62.8)	0.79
DAS	4.4 (0.9)	4.5 (0.9)	0.21
HAQ	1.3 (0.9 - 1.8)	1.4 (1 - 2)	**0.003**
tSHS	2 (0 - 5.5)	1.5 (0 - 5.25)	0.70
Symptom duration (days)	23.5 (13.4 -52.5)	23.6 (14.3 - 53)	0.89

RESULTS – hyperglycemia ≥ 7.8

	Complete analyses		Sensitivity analyses	
	OR	95% CI	OR	95% CI
Current pred dose [1]	1.013	0.989 ; 1.038	**1.033**	**1.003 ; 1.062**
Cum. pred dose [1]	1.013	0.994 ; 1.034	0.988	0.967 ; 1.009
Any prev. pred use [1]	1.220	0.952 ; 1.565	0.888	0.689 ; 1.143
Max. prev. pred dose [1]	1.007	0.995 ; 1.020	0.997	0.985 ; 1.010
Prev. time on pred [1]	1.004	0.996 ; 1.013	0.992	0.982 ; 1.002
Current DAS [2]	1.044	0.960 ; 1.135	**1.290**	**1.170 ; 1.418**

1. adjusted for disease activity over time, effect over time, BMI and age
2. adjusted for prednisone dose, effect over time, BMI, age and gender

RESULTS – diabetes

	Complete analyses		Sensitivity analyses	
	HR	95% CI	HR	95% CI
Current pred dose [1]	1.066	0.995 ; 1.142	1.070	1.000 ; 1.145
Cum. pred dose [1]	0.961	0.897 ; 1.031	0.966	0.903 ; 1.033
Any prev. pred use [1]	0.721	0.334 ; 1.556	0.722	0.333 ; 1.561
Max. prev. pred dose [1]	0.996	0.962 ; 1.031	0.997	0.962 ; 1.033
Prev. time on pred [1]	0.967	0.927 ; 1.009	0.967	0.927 ; 1.009
Current DAS [2]	**1.802**	**1.284 ; 2.529**	**1.797**	**1.276 ; 2.529**

1. adjusted for disease activity over time, effect over time, BMI and age
2. adjusted for prednisone dose, effect over time, BMI, age and gender

SUMMARY

- **Prednisone use in RA:**
  - No effects of prednisone (any definition) on glucose values, hyperglycemia or development of diabetes.
  - Only increased risk of recurrence of hyperglycemia
- **DAS:**
  - Increases glucose values, risk of hyperglycemia and diabetes (regardless of prednisone use) in susceptible patients and risk of diabetes in all patients.

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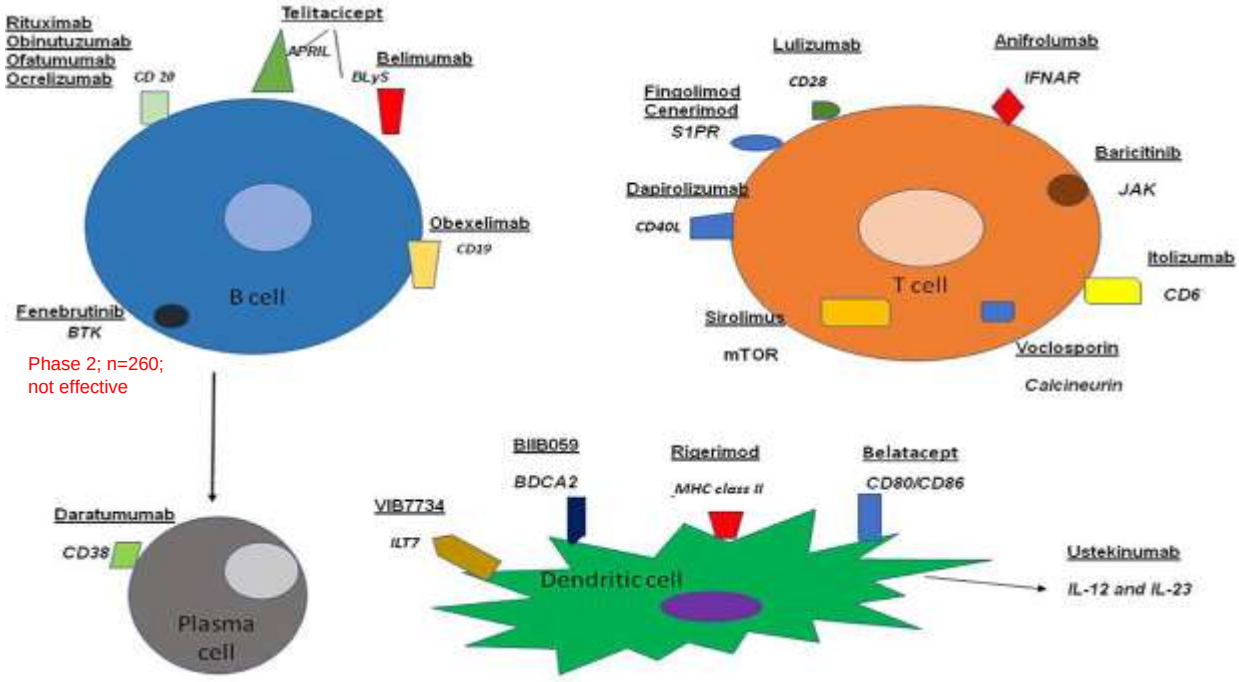


•A Human Recombinant Fusion Protein Targeting B Lymphocyte Stimulator (BlyS) and a Proliferation-Inducing Ligand (APRIL), Telitacicept (RC18), in Systemic Lupus Erythematosus (SLE): Results of a Phase 2b Study

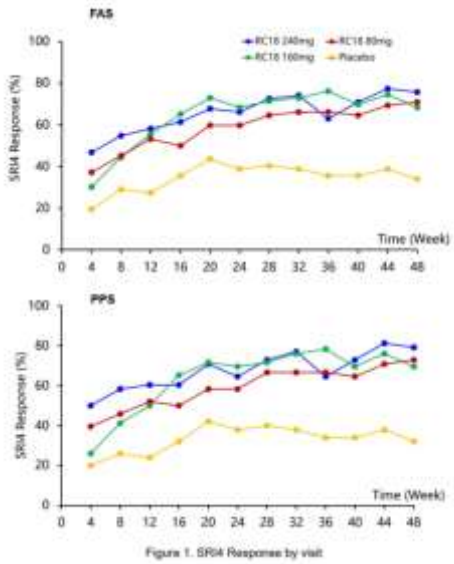
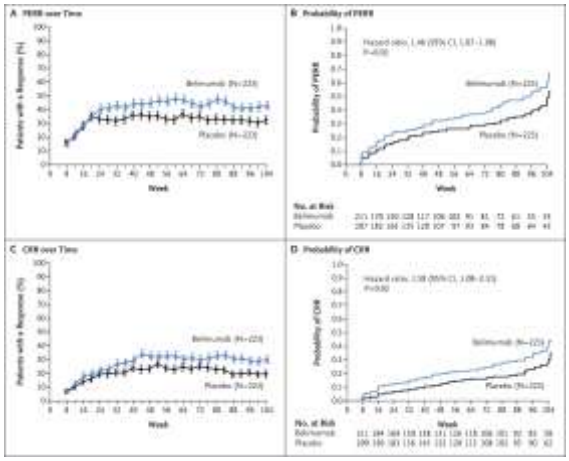


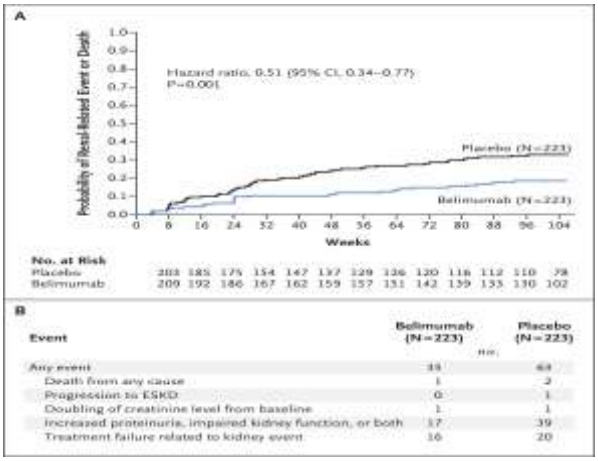
Figure 1. SRI4 Response by visit

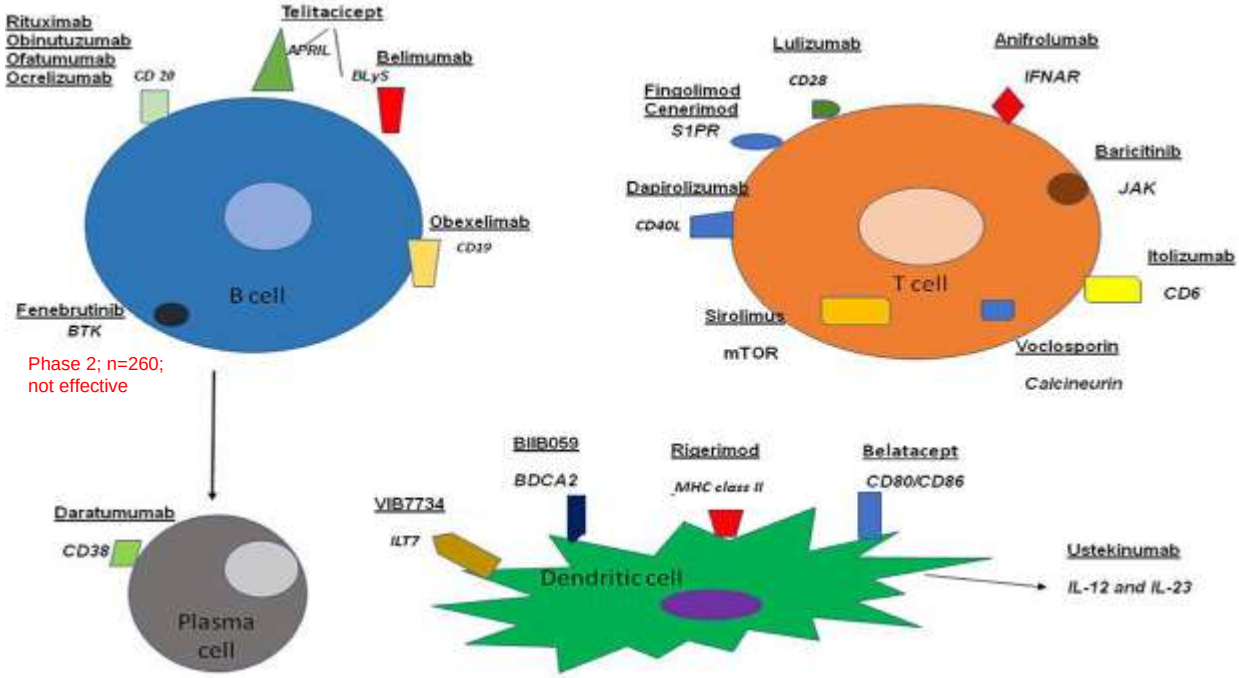
•Two-year RCT of Belimumab in Lupus nefritis Furie et al. New Eng J Med, 2020: 383: 1117-1118

•Patients were randomly assigned in a 1:1 ratio to receive intravenous belimumab (at a dose of 10 mg per kilogram of body weight) or matching placebo

•Standard induction therapy intravenous cyclophosphamide or mycophenolate mofetil (target dose, 3 g per day. At the investigator's discretion, high-dose glucocorticoids (1 to 3 intravenous pulses of methylprednisolone [500 to 1000 mg each]) could be administered during induction,







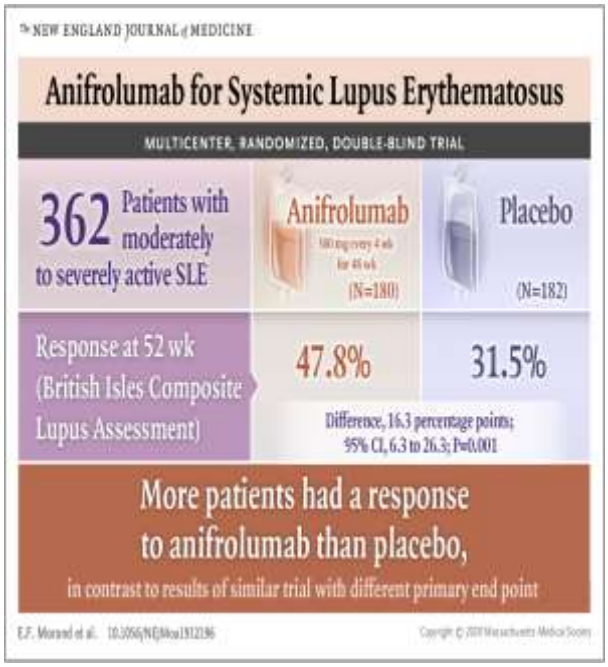
Anifrolumab, a human monoclonal antibody to type I interferon receptor subunit 1

Secondary end points with respect to the glucocorticoid dose and the severity of skin disease, but not counts of swollen and tender joints and the annualized flare rate, also showed a significant benefit with anifrolumab. Herpes zoster and bronchitis occurred in 7.2% and 12.2% of the patients

Eular: meta-analysis, positive effects on swollen joints

Three year follow-up: sustained responses

Chatham et all. Long-Term Safety and Efficacy of Anifrolumab in Adults With Systemic Lupus Erythematosus: Results of a Phase II Open-Label Extension Study. A&R, 2021:73:816-825



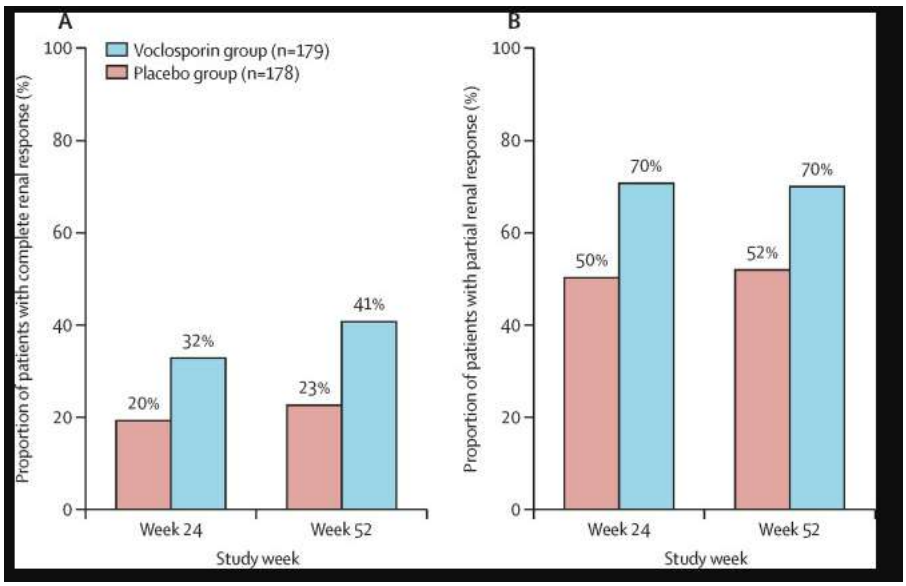
Rovin, Teng et al.

Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet, 2021, 397, 2070-2080

SLE with biopsy proven nefitis III,IV or V

Patients were randomly assigned (1:1) to oral voclosporin (23·7 mg twice daily) or placebo, on a background of mycophenolate mofetil (1 g twice daily) and rapidly tapered low-dose oral steroids

The primary endpoint was complete renal response at 52 weeks defined as a composite of urine protein creatinine ratio of 0·5 mg/mg or less, stable renal function



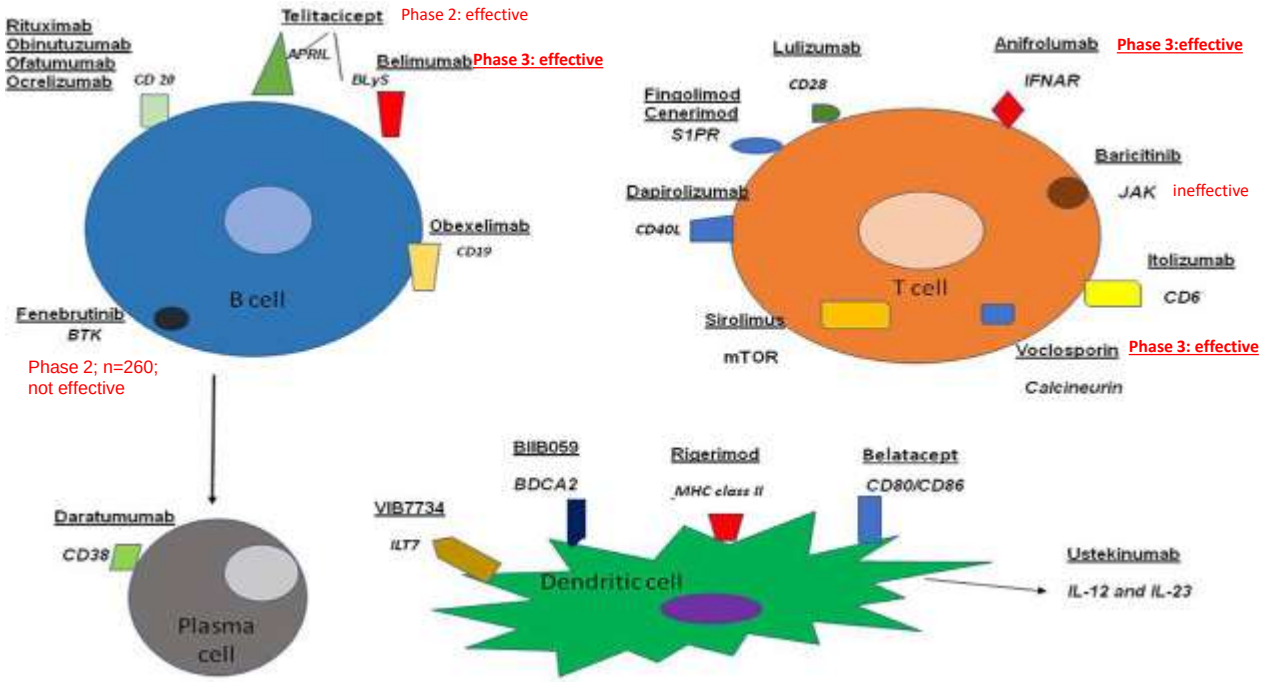
Lilly press release January 28, 2022

Lupus program update:

Based on top-line efficacy results from two pivotal Phase 3 trials (SLE-BRAVE-I and II), Lilly has decided to discontinue the Phase 3 development program for OLUMIANT in lupus.

In SLE-BRAVE-I, the baricitinib 4-mg oral dose met the primary endpoint, demonstrating a statistically significant reduction in disease activity as measured by the proportion of adults with active lupus who achieved an SRI-4 response (a composite measurement of overall disease activity) at Week 52 compared to placebo.

The SLE-BRAVE-II study, which also studied adults with active lupus, did not meet the primary endpoint of SRI-4 response. Key secondary endpoints were not met in either study. Safety findings from both lupus studies were consistent with previously published OLUMIANT data and did not impact our decision to discontinue the program.



Janssen website:

SPRING HOUSE, PENNSYLVANIA, June 26, 2020 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today its decision to discontinue the Phase 3 LOTUS study of STELARA® (ustekinumab) in Systemic Lupus Erythematosus (SLE) due to lack of efficacy in SLE.

The decision is based on data from a pre-planned interim efficacy analysis. Interim safety findings were consistent with the known safety profile of STELARA, and no new safety signals were identified.