Highlights:
Annual European Congress of Rheumatology 2012
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Clinical Highlights

Rheumatoid arthritis
Objectives: MTX+IFX vs. MTX+high dose IV steroid as induction therapy on radiographic progression in pts with DMARD-naïve RA.

Methods:
- A 78 wk RCT of pts with early (3-12 months symptoms), DMARD-naïve RA (DAS>2.4).
- Randomised to: a) IFX (3 mg/kg) +dose adjustment from wk 26, or
  b) IV steroid (IV-MP 250mg at wk 0, then placebo infusions) + from wk 26 DMARDs and/or IV MP 120mg
- Both groups: MTX (20 mg/wk). Other biologics were allowed from wk 26 per NICE guidelines.
- Radiographs of hands & feet done at 0,26,52 & 78 wks were scored

Results:
- MTX+IFX (n=55) or MTX+IV steroid (n=57).
- Remission (DAS<1.6) at wk 50 was achieved in 52% in the IFX and 36% in the IV-steroid grp (p=0.088).
- Proportions of pts with radiographic non-progression (vdH-S <2.0) in the IFX and IV-steroid arms were 88% vs. 84% respectively at 26 wks, 74% vs. 71% at 78 wks (p=0.730).
- No between-grp differences were seen with non-progression defined as change≤0.5: 69% in the IFX and 57% in the IV-steroid grp at 52 wks

Conclusions: In this study of DMARD naïve pts with moderate to severe RA, initial therapy with IFX+MTX and high dose IV steroid+MTX, together with tight disease control prevented radiographic progression in a significant majority of patients.
Background: To study the prolonged effect on disease activity by an early induction therapy with adalimumab (ADA) plus methotrexate (MTX) versus MTX alone in DMARD naïve patients (pts) with early RA

Methods:
- Double-blind RCT. RA pts (disease duration of ≤12 months, ≥6 swollen, ≥6 tender joints, and CRP≥10 mg/l)
- Placebo (PBO) plus s.c. MTX (n=85; 15 mg/w versus MTX 15 mg/w s.c. plus 40 mg ADA s.c. eow over 24w (n=87).
- After w24, both groups were treated only with MTX up to w48.

Results:
- ADA/MTX reduced disease activity to a significantly greater extent than PBO/MTX (Table 1).
- After termination of ADA or PBO and continuation with MTX alone, the differences between groups decreased at w24/48 and did not reach statistical significance at w48.
- Combination therapy significantly reduced radiographic progression when analyzed after w48

<table>
<thead>
<tr>
<th>Table 1. Comparison of clinical parameters at w 24 and w 48</th>
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<td>Variable/Groups</td>
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<tr>
<td>DAS28</td>
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<td>Remission (%)</td>
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<td>ACR50 (%)</td>
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<td>HAQ, mean±SD</td>
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<td>SF36 mental score, mean±SD</td>
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<td>SF36 physical score, mean±SD</td>
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Values are means and standard deviations if not otherwise specified.
Objectives: To evaluate the 1 year clinical outcomes of remission steered therapy in early arthritis, initially with MTX and a tapered high dose of prednisone

Methods:

• IMPROVED multicenter clinical trial in 479 patients with early (<2 years) RA and 131 patients with undifferentiated arthritis (UA) with baseline DAS $\geq$1.6 → MTX 25mg/wk + prednisone 60mg/day tapered in 7 weeks to 7.5 mg/day.

• Patients in early remission (DAS <1.6 at 4 mo) tapered prednisone to zero and when still in remission at t=8 months, also tapered MTX to zero.

• Patients not in early remission: randomized either to:
  – Arm1 = MTX 25 mg/wk + HCQ 400mg/day + SSZ 2g/day + prednisone 7.5 mg/day, or
  – Arm2 = Adalimumab (ADA) 40mg/2weeks + MTX 25mg/wk

Results:

• After 4 months, 61% patients achieved early remission → at 1-year: 68% were in remission (36% drug-free remission)

• N=161 patients were randomized to arm 1 or 2

• At 1 year 21/83 (25%) patients in arm 1 and 32/78 (41%) in arm 2 were in remission (p<0.001).

• At 1 year, 53% of the total study population were in remission: 53% RA patients and 53% UA patient

Conclusions: In patients with early RA or UA, early remission was achieved in 61% after initial treatment with MTX and a tapered high dose of prednisone. For those not in early remission, treatment with adalimumab resulted in more remission than a combination of DMARDs with low dose prednisone.
USE OF ANTI-TNF THERAPY IS ASSOCIATED WITH REDUCED CARDIOVASCULAR EVENT RISK IN RHEUMATOID ARTHRITIS

Objectives: To assess the effects of treatment with anti-TNF therapy, MTX, or other non-biologic DMARDs on CV event risk in RA.

Methods:
• Thomson Reuters MarketScan® database (2003–2010).
• Patients were assessed from index fill date to first inpatient CV diagnosis of myocardial infarction (MI), stroke, unstable angina, or heart failure (HF) to the end of health plan enrollment or to 6 months after the discontinuation of their index drug, whichever came first.

Results:
• N=109,462 patients with 105,920 total patient-years (PYs) of follow-up,
• A total of 1743 patients (1.6%) had a CV event after their index prescription.
• Multivariate regression model: each additional 6 months of anti-TNF therapy reduced the risk for any study CV event (hazard ratio [HR]=0.87, P=.005) and for MI (HR=0.80, P=.013), compared with patients without anti-TNF biologics
• Effects of cumulative use of MTX and other non-biologic DMARDs were not statistically significant.
• Cumulative use of anti-TNF therapy for 1, 2, or 3 years would reduce CV event risks by 24%, 42%, and 56%, respectively, compared to not using anti-TNF therapies during those time periods, adjusting for background use of MTX or other nonbiologic DMARDs.

Conclusions: Use of anti-TNF therapies vs. non-use was associated with significantly lower risks for CV events (ie, inpatient diagnoses for MI, stroke, unstable angina, or HF) in patients with RA, older patients with RA, and patients without prior exposure to MTX, adjusting for use of MTX and other nonbiologic DMARDs.
[LB0003] TOCILIZUMAB (TCZ) MONOTHERAPY IS SUPERIOR TO ADALIMUMAB (ADA) MONOTHERAPY IN REDUCING DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA): 24-WEEK DATA FROM THE PHASE 4 ADECTA TRIAL

Objectives: To evaluate efficacy and safety of TCZ vs adalimumab (ADA), both given as monotherapy, in RA with DAS28 >5.1

Methods:
• ADECTA. Multicentre, randomised, double-blind, 24-wk study (superiority trial) in MTX intolerant/contra-indicated pts
• Assigned (1:1) to TCZ 8 mg/kg IV q4 wks (+ placebo ADA) or ADA 40 mg SC q2 wks (+ placebo TCZ) x24 wks.

Results:
• Mean baseline DAS28 6.72-6.76
• Mean change DAS28 was significantly greater with TCZ (–3.3) than with ADA (–1.8)
• Serious AEs and serious infections also were similar (TCZ: 11.7%, 3.1%; ADA: 9.9%, 3.1%).

Conclusions: Monotherapy with TCZ was superior to monotherapy with ADA in reducing signs and symptoms of RA in MTX-intolerant pts or pts for whom MTX treatment was considered ineffective or inappropriate.
Objectives: To compare the efficacy and safety of SC abatacept (ABA) and adalimumab (ADA) on background MTX in RA.

Methods:
- **AMPLE** trial. Phase IIIb randomized, investigator-blinded study (non-inferiority)
- Biologic-naïve patients with active RA and inadequate response to MTX
- Arms: 125 mg SC ABA (without an IV load) weekly or 40 mg SC ADA bi-weekly, in combination with a stable dose of MTX

Results:
- Of 646 patients who were randomized and treated, 86% ABA and 82% ADA patients completed 12 months.
- ITT analysis (1 year): ACR 20 = 65% in ABA versus 63% in ADA patients; ACR70 = 29% versus 26%.
- Radiographic non-progression rates were comparable and the mean changes in mTSS were 0.58 versus 0.38, for ABA versus ADA.
- Similar rates of AE, SAE, serious infections and malignancies.
- Injection site reactions in 3.8% of ABA versus 9.1% of ADA patients (p=0.006).

Conclusions: This first head-to-head study in RA patients comparing biologic DMARD agents demonstrated that SC ABA is comparable to ADA in efficacy (by non-inferiority analysis) with similar kinetics of response and inhibition of radiographic progression at one year.
Background: GLPG0634 is an orally-available, selective inhibitor of Janus kinase 1 (JAK1).

Objectives: Evaluate the short-term efficacy and safety of GLPG0634 in RA patients with insufficient response to MTX alone.

Methods:
- A double-blind, placebo-controlled proof-of-Concept trial in patients with active RA
- N=24 patients received GLPG0634 200 mg (200 mg q.d. or 100 mg b.i.d.), and n=12 received a matching placebo for a period of four weeks, while continuing to take their stable background therapy of MTX.

Results:
- G0634 was found well tolerated and safe with a rapid onset and high level of efficacy.
- ACR20 responses: 83% of GLPG0634 vs. 33% of placebo (p<0.01).
- GLPG0634 showed improvements in DAS28 (-2.5), CRP (-24.4 mg/L), both significant changes vs. placebo (p<0.0001).
- No treatment-emergent safety signals were reported.
- No severe adverse events; instead of anemia, a modest improvement in hemoglobin was observed. No increases in LDL/cholesterol and no liver effects (ALT/AST) were observed in this trial.

Conclusions: An extended GLPG0634 dose-range finding trial is now being conducted to further define the optimal doses for efficacy and safety for longer term studies.
Background: Once remission in RA is achieved, rheumatologists face the challenge of maintaining it while considering means to limit dosages and duration of treatments.

Objectives: To assess characteristics that may predict loss of remission in pts with moderately active RA who continued:

– etanercept (ETN) 50 mg QW + MTX (E50/M),
– reduced ETN from 50 mg to 25 mg QW + MTX (E25/M), or
– replaced ETN with placebo+MTX (P/M) over 52 wks after induction of initial response

Methods:

• Pts with moderately active RA (36 wks of open-label E50/M (Period 1 [P1]) were randomized to double-blind treatment with E50/M, E25/M, or P/M for 52 wks (Period 2 [P2]).

Results:

• Failing to achieve a sustained remission in P1 was the strongest predictor of loss of remission in P2 (HRs 1.7-2.5)
• In all treatment groups, pts who achieved DAS28 remission only at wks 28 and 36 or only at wk 36, vs at wks 12, 20, 28, and 36, were significantly more likely to lose DAS28 remission through wk 88.
• At wk 88, 29%, 34%, and 65% in the E50/M, E25/M, and P/M groups lost DAS28 remission (LOCF).

Conclusions: Failure to achieve sustained remission over wks 12-36 of P1 was consistently associated with loss of remission through wk 88 with all treatment regimens. Loss of remission occurred at wk 88 in approximately one-third of patients in the full- and reduced-dose etanercept-MTX groups and two-thirds in the MTX-only group.
Seronegative SpA
Conclusion: The studies failed to demonstrate the efficacy of anti-IL6R over placebo for the treatment of symptoms of AS, irrespective of baseline CRP level.
Objectives: To assess efficacy and safety of UST (anti-IL12/IL23) in reducing signs and symptoms of active PsA

Methods:
- Multicenter, double-blind, placebo (PBO)-controlled, Ph3 trial. Active PsA despite DMARD and/or NSAIDs
- Groups: UST45mg, 90mg, or PBO at wks 0, 4, and q12wks, thereafter. At wk16, pts w/ <5% improvement in TJC & SJC entered blinded early escape (PBO→ UST45mg; UST45mg→90mg; 90mg→90mg).
- Stable concomitant MTX use was permitted but not mandated.

Results:

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<th>Table: Efficacy Results at Wk 24</th>
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<td>ACR20, %</td>
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<td>ACR50, %</td>
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<td>ACR70, %</td>
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<td>DAS28-CRP response, %</td>
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<td>Median HAQ-DI change from BL</td>
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<td>Pts w/ ≥0.3 reduction, %</td>
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<td>PASI75*, %</td>
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<td>Median % change in enthesitis score*</td>
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<td>Median % change in dactylitis score*</td>
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• Among pts affected w/ enthesitis (n=425) or dactylitis (n=286), sig greater improvements in enthesitis and dactylitis were observed at wk24 in the UST grp than PBO.
• No difference in AEs

Conclusions: In pts w/ active PsA, UST reduced the signs and symptoms of arthritis, improved physical function, enthesitis and dactylitis and improved plaque psoriasis vs PBO-treated pts at wk24
Osteoarthritis
[OP0129] EFFECT OF LOW DOSE ORAL PREDNISOLONE ON SYMPTOMS AND SYSTEMIC INFLAMMATION IN OLDER ADULTS WITH MODERATE TO SEVERE KNEE OSTEOARTHRITIS: A RANDOMIZED PLACEBO-CONTROLLED TRIAL

**Background:** In osteoarthritis (OA), pain is the leading symptom and is often chronic in nature.

**Objectives:** A randomized double-blind placebo-controlled trial to assess whether low dose oral prednisolone would improve pain, mobility and systemic low-grade inflammation in older adults with moderate to severe knee OA.

**Methods:**
- 125 community-dwelling older adults aged ≥65 years with knee OA (documented by radiography)
- Symptomatic OA: need for daily NSAIDs and high algofunctional score
- Randomized: 7.5 mg/day prednisolone or placebo together with their usual therapy for 6 weeks.

**Results:**
- Significant reduction in knee pain in the intervention group compared to the placebo group, p<0.001 at 6 & 12 weeks
- Improvement in physical function and 6MWD
- Reductions in the serum levels of IL-1, IL-6, TNF-alpha and hsCRP at 6 weeks and at 12 weeks
- NSAID use was significantly less in the intervention group compared to the placebo group, p<0.05.

**Conclusions:** The findings of the present study provide evidence that low dose oral glucocorticoids have both a short term and a longer sustained effect resulting in less knee pain, better physical function, and attenuation of systemic inflammation in older patients with knee osteoarthritis.
BACKGROUND: The first double-blind placebo controlled RCT (EudraCT) studied the efficacy and safety of adalimumab (ADA) in patients with erosive osteoarthritis of the interphalangeal finger joints (EOA) during 52 weeks. Inflamed IP joints (with palpable swelling) were found to be at risk to develop further destructive/erosive stages.

OBJECTIVES: To study the 1-year radiographic progression of an open-label extension study with ADA (40mg, eow, sc).

METHODS:
- Hand X-rays were taken after 6 and 12 months (progression was scored by the GUSS and anatomical phase scoring system).

RESULTS:
- One of 49 (2.0%) inflamed (upon palpation) interphalangeal joints at baseline and 6 of 228 (2.6%) non-inflamed joints became erosive under treatment with adalimumab (p = NS).
- The evolution in 148 of the initial 188 target joints (the RCT study phase) was analysed. Two joints became erosive (1.4%). Six joints showed extreme signs of remodellation ("F" phase, ankylosis) (4.1%). The mean GUSS mean change after one year in OLE was +22.2 (SD 35) (p<0.03), indicating overall remodellation.
- The mean GUSS change after 12 months between patients initially treated with adalimumab in RCT did not differ from patients initially treated with placebo (22.1 vs. 22.3, p=0.96).

CONCLUSIONS: Follow-up radiographic data confirm the potency of adalimumab to delay the radiographic progression in EOA.
Osteoporosis - Gout
**Objectives**: To study the number and prevalence of hospitalizations for osteoporotic hip fractures in the elderly (65-79 years, E) and extreme elderly (≥80 years, EE) in the US over 16 years (1993-2008).

**Methods**:
- The Nationwide Inpatient Sample (NIS) is a stratified random sample of all US community hospitals
- Hospitalizations in NIS from 1993 to 2008 with diagnoses of non-traumatic (osteoporotic) hip fractures in E and EE cohorts.
- Patients were excluded if there was major trauma, open fractures, or femoral tumors.

**Results**:
- 4.3 million osteoporotic hip fracture hospitalizations in 565.4 million person-years in individuals ≥65 years from 1993 to 2008.
- **Hip fracture hospitalizations in E decreased** from 96,928 in 1993 (386 per 1,000 person-years) to 80,987 in 2008 (294 per 1,000 person-years) (p<0.001), perhaps reflecting increasing awareness, screening and treatment for osteoporosis.
- However, **in the EE group, osteoporotic hip fracture hospitalizations increased** from 172,209 in 1993 to 180,428 in 2008, even as the hip fracture prevalence decreased from 2,236 per 1,000 person-years in 1993 to 1,600 per 1,000 person-years in 2008 (p<0.001).

**Conclusions**: Osteoporotic hip fractures pose a growing problem in the EE, more so than older adults, increasing their risk for hospitalization, morbidity and mortality greatly. This calls for more aggressive measures towards recognition, prevention and therapy of osteoporosis during the medical care of EE, both ambulatory and in assisted living facilities, where preventive care is not routinely considered or provided.
Background: AMG 785 is a sclerostin antibody (Scl-Ab) that blocks sclerostin from inhibiting osteoblast maturation and function and has been shown to stimulate bone formation.

Objectives: Evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and safety of multiple doses of Scl-Ab in healthy men and postmenopausal women with low bone mass.

Methods:
- Double-blind, placebo-controlled, randomized, ascending multiple dose study
- Healthy men and postmenopausal women aged 45-80 years with a lumbar spine or total hip DXA T-score ≤ –1.0 and ≥ –2.5
- Subjects were enrolled into 1 of 6 groups and were then randomized 3:1 to Scl-Ab or placebo.

Results:
- Scl-Ab treatment significantly increased lumbar spine BMD from baseline, reaching a maximum of 7.2% at 18 weeks (Figure).
- Adverse event rates were balanced between groups and no significant safety findings were observed.

Conclusions: Multiple doses of Scl-Ab significantly increased the bone formation marker PINP, decreased the bone resorption marker sCTX, increased lumbar spine BMD, and were well tolerated in healthy men and postmenopausal women with low bone mass.
Background: It is unclear whether the association between serum uric acid (SUA), inflammatory cytokines and risk of atherosclerosis is causal or an epiphenomenon.

Objectives: To investigate the independent prognostic relationship of SUA and inflammatory markers with adverse cardiovascular outcomes in a patient population with stable CHD at baseline under special consideration of gout.

Methods:
• CHD patients aged 30-70 were enrolled (January 1999 - May 2000) and followed up for 8 years.
• Self-reported gout diagnosis was ascertained at baseline.
• Subsequent CVD (fatal or non-fatal MI or stroke) was assessed

Results:
• 1,056 patients were included, of whom 229 reported at baseline a diagnosis of gout.
• Overall, 151 patients out of 1,056 (incidence 21.1 per 1000 patient-years) experienced subsequent fatal or non-fatal CVD.
• After adjustment for age, gender and hospital site the hazard ratio (HR) for SUA increased from 1.53 to 1.74 and 2.80 in the second, third, and top quartile, when compared to the bottom one (p for trend <0.0001). The presence of clinical diagnosis of gout did not enhance this association.

Conclusions: The data suggest that, irrespective of the presence of gout, SUA (in contrast to CRP) predicts future CVD risk in patients with stable CHD with a risk increase even at levels considered normal, and therefore may contribute independently to the pathophysiology of CVD events.
Connective tissue diseases
Background: About half of adult SLE patients tend to have stable, high expression levels of genes in the IFN signaling pathways.

Objectives: To determine how gene expression changes with disease flare in SLE patients with high versus low expression of IFN pathway genes.

Methods:
- BOLD study: patients with active disease who are withdrawn from background immunosuppressive therapy and given brief intramuscular depomedrol to induce improvement (Improving Visit), and followed until flare (Flare Visit).
- Expression levels of 272 genes (selected based on reported associations with lupus and/or inflammation) were compared between Improving Visit and Flare Visit.

Results: Striking expression differences between Improving Visit and Flare Visit were observed for some genes, predominantly associated with the IFN High Group.

Conclusions: Several pathways might be tested as sensitive indicators to guide patient selection and dosing in the development of treatments which affect the TLR/IFN pathway, and to optimize the eventual use of these agents in clinic. Could help differentiate between patients who are or are not intrinsically good candidates for targeting of IFN signaling pathways.
Background: There is evidence for a critical role of B cells in the pathogenesis of pSS. Both open labelled and small controlled studies suggested the efficacy of Rituximab (RTX) in specific subgroups of pSS.

Objectives: Multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of RTX in active pSS.

Methods:
- 122 patients assigned to either RTX infusions (1g) or placebo (P) at weeks 0 and 2 → followed up for 24 weeks.
- Patients had an active disease as assessed by mean values of the 2 highest visual analog scales (VAS) ≥50 evaluating dryness, pain, fatigue and global disease activity, and had either a recent (<10 years since first clinical sign) and a biologically active pSS [Auto antibodies (SSA or RF) or cryoglobulinaemia, or hypergammaglobulinaemia, or high level of beta 2-microglobulinemia or hypo-complementaemia] or at least one extra-glandular manifestation.
- Primary end point = improvement of ≥30 mm on 2 of 4 VAS between weeks 0 and 24.

Results:
- 20% had a recent pSS without systemic symptoms, 55% had a recent pSS with systemic signs, 25% had a chronic systemic pSS, 28% had pulmonary involvement, 53% articular involvement, 29% parotidomegaly.
- 21% patients receiving P and 22% treated with RTX had a favourable overall response (P=0.9).
- No significant difference in any of the secondary outcome measures
- The two groups did not differ in term of salivary unstimulated flow rate improvement in both recent and chronic pSS.

Conclusions: This randomized, double blind, placebo controlled study suggest that the efficacy of RTX is not sufficient enough to allow its prescription in a large population of pSS. Further studies are needed to select which subgroups may justify this treatment.
Background: ASTIS-trial (Autologous Stem cell Transplantation International Scleroderma trial): prospective, controlled, randomized trial to compare safety and efficacy of HSCT versus iv CY in dcSSc patients

Objectives: To evaluate whether HSCT is superior over iv pulse CY in terms of safety and efficacy in dcSSc.

Methods:
• Patients with early progressive dcSSc ± major organ involvement were eligible.
• Transplant arm = mobilization with CY + G-CSF, conditioning with CY, rbATG → reinfusion of CD34+ autologous HSCT
• Control arm = treated with 12x monthly IV-CY 750 mg/m². Crossing over was allowed after 2 years.
• Event-free survival (EFS) = survival until death or development of major organ failure at 2 yrs.

Results:
• HSCT (n=79) or pulse CY (n=77). Median follow ups are 33.0 and 27.0 months in the transplant / control groups respectively.
• Forty patients have died: 16 in the transplant group, 24 in the control group.
• Eight deaths in the transplant group were deemed treatment-related = 100d treatment-related mortality 10% (8/79).
• In the control group, none died from treatment-related causes and most deaths were due to progressive disease.
• Seven patients in the control arm received rescue transplant treatment, None of the transplant patients were crossed over to the control arm.

Conclusions: Initial results show fewer deaths in the transplant arm despite 100d TRM of 10%. HSCT should be considered as treatment option for patients with poor prognosis dcSSc. Further studies are needed to optimise the transplant regimen and patient selection.
Background: Various clinical manifestations, including aphthous ulcers are treated with limited success. Rebamipide is an anti-ulcer, gastro-protective drug, that increases mucous and stimulates endogenous prostaglandin biosynthesis.

Objectives: To assess the efficacy of rebamipide in the therapy of recurrent oral aphthous ulcers in BD patients.

Methods:
- N=54 BD patients with oral ulcers within 4 weeks prior to recruitment. All had recurrent oral aphthous ulcers despite tx
- Double-blind placebo controlled study: rebamipide 100mg x 3/day OR placebo in addition to their standard therapy x16w

Results:
- Improvement in oral ulcer count in 29% of the placebo group and 70% rebamipide group respectively, p=0.006.
- No new ulcers were recorded in the rebamipide group whereas 29% of the placebo group showed new ulcers.
- Patient-recorded pain scores decreased significantly in the rebamipide group

Conclusions: Rebamipide showed improvement in oral aphthae count and pain scores in BD patients compared to placebo. The findings of the present study indicate that rebamipide, a gastro-protective drug, displayed an anti-inflammatory action. Rebamipide may thus be a useful addition in the therapeutic armamentarium of recurrent oral ulcers in BD.
Background: Recent lupus nephritis (LN) trials have used various primary endpoints, but it is not yet known which endpoint is most sensitive to detecting differences between groups.

Objectives: The present analysis from the abatacept trial in LN was designed to determine whether CR is the most discriminatory outcome measure or whether alternative measures may be more discriminatory between groups in this data set.

Methods:
- 298 pts randomized 1:1:1 to: ABA 30 mg/kg on Days 1, 15, 28, 57, and then 10 mg/kg through Week 52 (30/10); ABA 10 mg/kg on Days 1, 15, 28, and then every 28 days (10/10); or placebo. All pts received MMF and glucocorticoids (GC).
- We used the following outcome measures: (i) CR at Weeks 24 and 52; (ii) CR + PR; (iii) major clinical response (MCR): pts who met CR and pts who were nephrotic at baseline but achieved UPCR<1.0; (iv) ≥75% reduction in UPCR; (v) ≥25% increase in eGFR; and (vi) frequency of treatment failure (=persistent nephrotic proteinuria; failure of UPCR to improve by at least 25%; eGFR below normal and reduced by ≥25% relative to baseline; failure to taper GC to ≤10 mg/day; or withdrawal due to worsening LN, infection, or drug toxicity).

Results:
- MCR and CR discriminated best → group sizes of 50 pts would have been sufficient to demonstrate a statistically significant difference based on the observed response rates.
- Approximate number of pts that would have been required to show statistical significance, was: CR at Week 24 (~90/group), treatment failure (~90/group), UPCR reduced by ≥75% at Week 52 (~90/group), total response at Week 52 (CR+PR) (~100/group), total response at Week 24 (~250/group), and eGFR increased by ≥25% at Week 52 (>500/group).

Conclusions: The choice among possible outcome measures dramatically influences the likelihood of demonstrating a significant difference between groups.
EULAR-ERA 2012 LN recommendations in a nutshell

• **Acceptable Goals:**
  - **short term (3-4 months):** improvement any reduction in proteinuria
  - **medium term (6-12 months):** partial response (50% reduction in proteinuria to subnephrotic levels). In long standing disease this is a good as someone could go
  - **Long term (1-2 years):** complete response: less than 0.5 gm protein

• **Why MMF and low-dose IV-CY?** MMF or low dose IV-CY based on ease of administration/gonadal toxicity.

• **Refractory patients:** switch to the other drug or directly to rituximab
  Why? Expert opinion

• **Maintenance:** MMF or AZA. If starting with MMF continue with MMF unless pregnancy is contemplated

• **Risk stratification:** for severe LN may use IV-MP with IV-CY or MMF

• **Pediatric lupus:** No significant differences

Bertsias et al ARD 2012 (Accepted with revisions)
Translational Highlights
• ACPA antibodies in animals directly stimulate the osteoclasts and promote bone erosions and bone loss. Link between immune system and the bone.

• Gene signatures (IFN-a activity) and low-B cell presence in peripheral blood predict rheumatoid arthritis above and beyond anti-CCP and RF (only 20-40% positive predictive value in patients with arthralgias)
Gut-Joints Axis.
- P. gingivalis and P. nigrescens strongly induced Th17 differentiation in a co-culture of antigen-presenting cells (APCs) with CD4+ T cells
- Th17 induction was found to depend on TLR2 expression on APCs
- In addition, P. nigrescens markedly suppressed the anti-inflammatory Th2/IL-4 phenotype in vivo, whereas P. gingivalis was the main inducer of local IL-1b, TNFa and Cathepsin K in synovium.
- Conclusions: These data reveal a substantial effect of periodontal pathogens, irrespective of the capability to induce ACPA, on T cell phenotype in the context of arthritis

TNFAIP3 (A20)
- A20 is a potent anti-inflammatory protein that inhibits NF-κB activation in response to multiple cytokine and pattern recognition receptors.
- A20 also negatively regulates TNF-induced cell death.
- Polymorphisms in the A20 genomic locus have been associated with multiple inflammatory and autoimmune disorders, including systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease and psoriasis.
- Tissue specific A20 knockout mice. Specific ablation of A20 in myeloid cells results in spontaneous development of a severe destructive polyarthritis with many features of rheumatoid arthritis.
- Despite higher circulating TNF levels, arthritis development in the myeloid specific A20 deficient mice was TNF-independent.
- Lessons learned from the phenotype of these mice and a number of other cell type specific A20 deficient mice that we generated will be presented.
Miscellaneous scientific abstracts

- Turesson (OP0084); Brink (OP0086): ACPA specificities precede disease onset
- Trenkmann OP0017: mir-18a enhance NF-kb in RA
- Andrew Filer and colleagues: enhanced adhesion of fibroblasts in RA
VASCULITIDES
To study the outcome of HSP

- Retrospective study from Spain (n= 340, 84 adults)

- Precipitating events: 41%

- Rx regimens: NSAIDs =11%, corticosteroids=33%, cytotoxic agents (AZA/CTX/MTX)=5%

- Mean follow-up= 12 months (median)

  - Relapses= 28%

  - **Complete recovery= 84%**

  - Mild renal insufficiency= 1% (n=4)

- The study confirms that HSP is a relatively benign syndrome with favorable outcome
- To study the effect of Tocilizumab in patients with Takayasu's arteritis (TA)

- Case series of 4 pts
  Case 1: 30 yr ♀ refractory to steroids, AZA, CsA, IFX.
  Case 2: 14 yr ♀ refractory to steroids, MTX.
  Case 3: 32 yr ♀ refractory to conventional treatment
  Case 4: 32 yr ♀ refractory to steroids, AZA.

- All showed favorable response to TCZ

- TCZ is a promising agent in pts with TA resistant to steroids, immunosuppressives (± anti-TNF agents)
- Information about repeated RTX therapy in GPA is limited.
- Retrospective study of 11 GPA pts who had received maintenance RTX
- Previous Rx: mean = 5.6 different immunosuppressants
  (CTX/mean cumulative dose=50 gm, steroids)
- Pre-Rx Relapses: n=3
- n of RTX infusions= 4 (2-11) q 6mo,
- Median follow-up = 18 months
- No relapses during Rx, BVAS= 9 (range 15-4) \(\rightarrow\) 0 (range 2-0)
- Remission rate = 64% (7/11)
- n=3 (27%), D/C all immunosuppressants
- Adverse events:
  - Infusion reactions: 3/11-All continued Rx
  - Infections: Common (?)
    One case of Pneumocystis jiroveci (?) prophylaxis)

- Rituximab is an efficacious Rx as maintenance in relapsing GPA but increased vigilance for infections is needed
[THU0091] COMPARISON OF THE CLINICAL UTILITY OF ANTI-IL-6 RECEPTOR ANTIBODY THERAPY AND ANTI-TNF THERAPY IN AA AMYLOIDOSIS IN RHEUMATIC DISEASE

Y. Okuda, et al Japan

- No data comparing TNF inhibitors to IL-6 inhibitors in AA amyloidosis

- Retrospective study of 22 patients Rx with TCZ and 32 Rx with anti-TNF (20 ETN/10 INFIL/2 ADA).

<table>
<thead>
<tr>
<th></th>
<th>TCZ (n=22)</th>
<th>anti-TNF (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 yr retention rate</td>
<td>90%</td>
<td>69%</td>
</tr>
<tr>
<td>5 yr retention rate</td>
<td>90%</td>
<td>34%</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>AE</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Non-response</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>13→3</td>
<td>3→2</td>
</tr>
</tbody>
</table>

- TCZ is probably more efficacious that anti-TNF in AA amyloidosis
SERUM ANGIOPOIETIN-2 LEVEL STRONGLY REFLECTS THE DISEASE ACTIVITY AND RENAL FUNCTION IN ANCA-ASSOCIATED VASCULITIS

Y. Wada, et al, Japan

- **Angiopoietin-2 (Ang-2)** binding to its receptor (Tie-2 in endothelial cells promotes endothelial inflammation, competing with Ang-1 for the same receptor. Ang-2 levels are elevated in RA, SLE and ANCA-associated vasculitis (AAV).

- Ang-2 levels were measured in MPA (n=27), GPA (n=15) and EGPA (Churg-Strauss syndrome, n=14), and compared between pts with active disease (n=45) and disease in remission (n=14).

- Serum Ang-2 level correlated with **BVAS** (r=0.62, p<0.0001), **CRP** (r=0.47, p=0.0003), serum **creatinine** (r=0.38, p=0.005), and **urinary protein excretion** (r=0.55, p<0.0001), and negatively correlated with **estimated glomerular filtration rate** (r=-0.37, p=0.005).

- Ang-2 may be involved in endothelial injury in AAV and may serve as a marker for disease activity in AAV.
[OP0186] ETIOLOGICAL THERAPY IN HCV-RELATED MIXED CRYOGLOBULINEMIA SYNDROME: THE ROLE OF IL28B GENOTYPE AS PREDICTOR OF RESPONSE

T. Urraro, et al Italy

- In hepatitis C, genetic variations in the **IL28B gene** (coding for IFN-λ3) are strongly associated with the response to anti-HCV therapy

- To evaluate the role of IL28B genotype in predicting response to IFN-based treatment in **HCV-related mixed cryoglobulinemia syndrome (MCS)**

- IL28B polymorphisms (rs12979860/rs8099917) were investigated in 267 pts with MCS *(n=123 completed Rx)*

- In patients with HCV-related MCS (genotypes 1 and 4), IL28B genotype was a strong independent predictor of Rx response *(OR= 6.11)*

- IL28B genotype is a useful predictor of IFN-response in HCV-MCS similar to what has been observed in HCV pts without cryos
[FRI0209] INTRAVITREAL INFlixIMAB FOR SIGHT-THREATENING ACUTE UVEITIS ATTACKS IN BEHCET'S DISEASE: A PILOT STUDY IN 15 PATIENTS

N. Markomicheklakis et al, Greece

- IV infliximab is beneficial in BD-related uveitis.

- To assess the efficacy and safety of a single intravitreal injection of INFL for sight-threatening uveitis in BD.

- Prospective, non-comparative, interventional study of 15 pts with acute unilateral posterior uveitis given intravitreal INFL (1mg/0.05mL)

- Infliximab administration resulted in:
  - Significant improvement of visual acuity
  - Decrease in anterior chamber, vitreous cells
  - Improvement of retinal vasculitis, retinitis and total inflammation
  - No ocular or extra-ocular side effects were noted.

- Intravitreal infliximab appears efficacious and should be considered when systemic administration is not feasible or contraindicated
[FRI0237] OUTCOME OF AORTIC INVOLVEMENT IN GIANT CELL ARTERITIS (GCA) AFTER 1-YEAR FOLLOW-UP: PROSPECTIVE STUDY USING COMPUTED TOMOGRAPHY ANGIOGRAPHY (CTA)

S. Prieto-González et al Spain

- A recent prospective study with newly diagnosed, bx-proven GCA showed aortitis in 65% and aortic dilation in 15% by CTA
- To prospectively evaluate the outcome of aortic involvement after 1 year of treatment (data were available from 25 pts)
- Aortitis was still present in 10 (62,5% )
- A significant reduction in mean wall thickening was detected in all but one of the aortic segments
- No new lesions/aortic dilation or increase in aortic dilation was noted
- Longer follow-up is necessary to determine the clinical significance of these inflammatory findings and their possible relationship with dilation.
Large vessel vasculitides (LVV)
Medium vessel vasculitides (MVV)
Small vessel vasculitides (SVV)
Variable vessel vasculitides (VVV)
Single organ vasculitis (SOV)
Vasculitis associated with probable etiology
Vasculitis associated with Systemic Disease
Large vessel Vasculitides (LVV)
- Giant cell arteritis (GCA)
- Takayasu arteritis (TAK)

Medium vessel vasculitides (MVV)
- Polyarteritis nodosa (PAN)
- Kawasaki disease (KD)
Small vessel vasculitides (SVV)

ANCA-associated vasculitis (AAV)
- Microscopic polyangiitis (MPA)
- Granulomatosis with polyangiitis (GPA-WG)
- Eosinophilic granulomatosis with polyangiitis (EGPA-CSS)

Immune-complex SVV
- Anti-GBM
- Cryoglobulinemic
- IgA vasculitis
- Anti-C1q vasculitis
Variable vessel vasculitides (VVV)

- Behcet disease
- Cogan’s syndrome

Single organ vasculitis (SOV)

- Cutaneous leucocytoclastic angiitis
- Cutaneous arteritis
- Primary CNS vasculitis
- Isolated aortitis
Vasculitis associated with probable etiology

- HCV-associated cryoglobulinemic vasculitis
- HBV-associated vasculitis
- Syphilis associated aortitis
- Serum sickness associated IC vasculitis
- Drug-associated IC vasculitis
- Drug-associated ANCA-associated vasculitis
- Cancer associated vasculitis
Vasculitis associated with Systemic Disease

- Lupus vasculitis
- Rheumatoid vasculitis
- Sarcoid vasculitis