ACR REVIEW SANDIEGO

3-8 NOVIEMBRE 2017

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ENFERMEDADES AUTOINMUNES SISTÉMICAS

Dr. J. María Pego Reigosa

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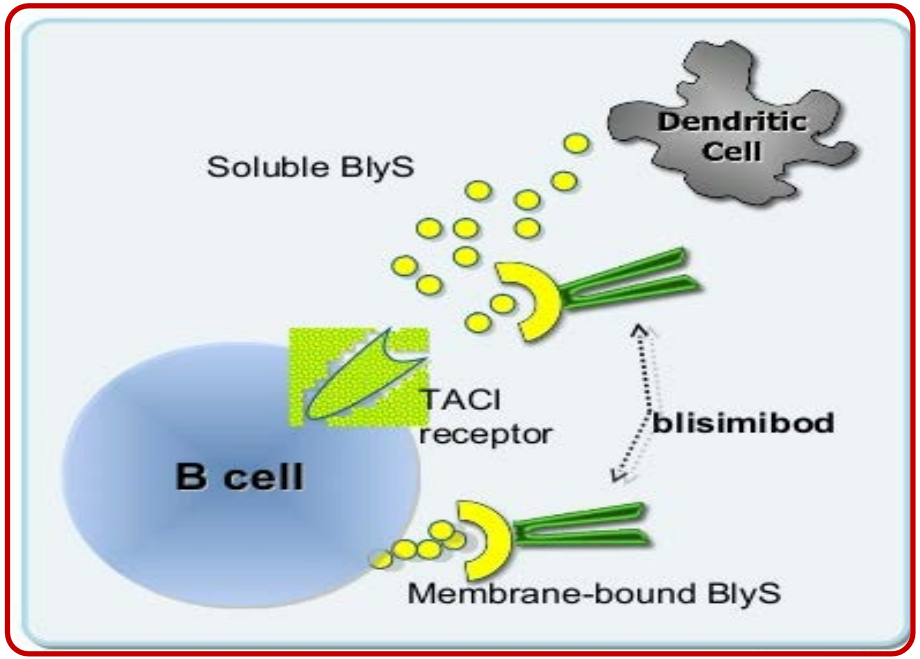
ABSTRACT NUMBER: 888

PHASE 3 TRIAL RESULTS WITH BLISIBIMOD, A SELECTIVE INHIBITOR OF B-CELL ACTIVATING FACTOR, IN SUBJECTS WITH MODERATE-TO-SEVERE SYSTEMIC LUPUS ERYTHEMATOSUS

JOAN T. MERRILL, ET AL.

Purpose

Phase 3 CHABLIS-SC1 trial. To evaluate blisibimod in SLE.



Methods

- Phase 3 randomized, double blind, placebo-control trial.
- SLE patients (ANA and/or a-dsDNA+) + SELENA-SLEDAI ≥10.
- Randomization:
  - weekly s.c. blisibimod (200 mg) vs. placebo (bot + SoC therapies).
- Corticosteroid taper was encouraged (goal: ≤7.5 mg prednisone/day).

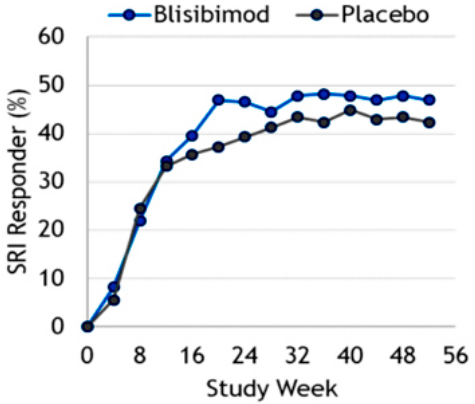
Primary endpoint: SRI-6 at week 52 without new/increased IS or antimalarials.

- Secondary: GC reduction, SRI-S + GC reduction

Results

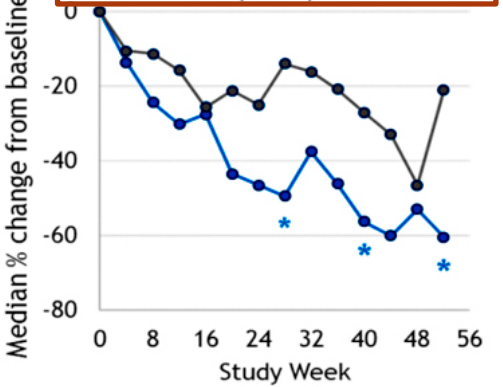
- 442 SLE patients
- The SRI-6 primary endpoint at week 52 was not met.
- Blisibimod > PBO:
  - GC taper to Prednisone ≤ 7.5mg/day during weeks 40-52 and
  - SRI-6 criteria at W52 + GC at W40-52: lower than baseline.
- In subgroup with baseline UPCR ≥0.5mg/mg, at week 52:
  - Significant greater decrease in UPCR.
  - More subjects >50% reduction in UPCR (p=0.006) and/or UPCR <0.5 (p=0.02)

SRI-6 (mITT, N=441)



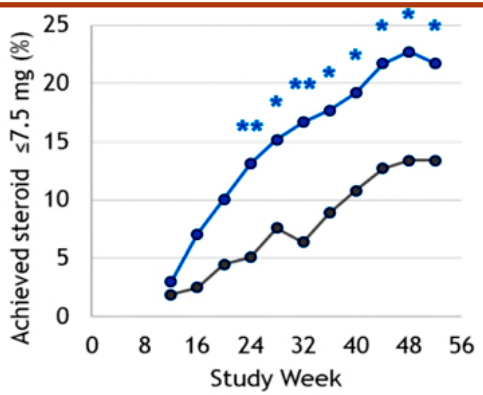
UPCR vs Time

subgroup: baseline UPCR ≥0.5mg/mg (n=135)



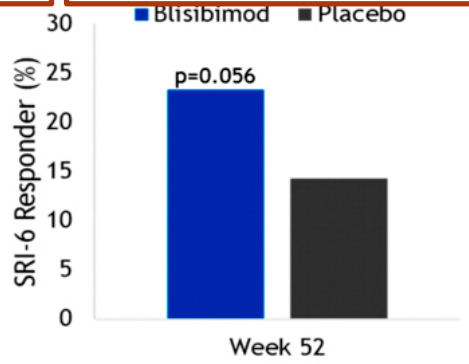
Steroid Taper at Each Visit

Subgroup: baseline steroid >7.5mg, n=355



SRI-6 with Steroid Reduction

Reduction over Week40-52, N=441



*p ≤ 0.05, **p≤0.01

Conclusion

- This study did not meet its primary endpoint
- Blisibimod treatment was associated with successful steroid reduction, decreased UPCR, and biomarker responses.

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ABSTRACT NUMBER: 851

AUTOANTIBODIES PREDICT LONG TERM SURVIVAL IN MYOSITIS ASSOCIATED INTERSTITIAL LUNG DISEASE

SILVIA MARTINEZ, ET AL.

Purpose

- To determine predictors of survival in myositis associated ILD (MA-ILD) and to evaluate differences related to autoantibody subsets.

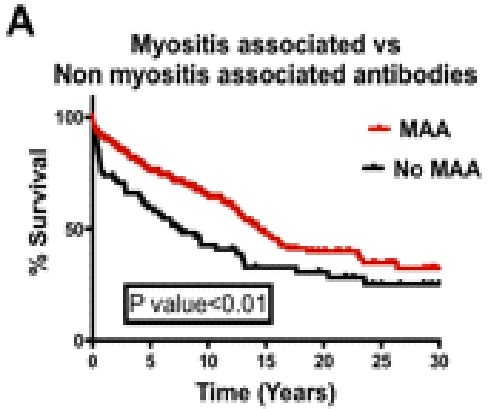
Methods

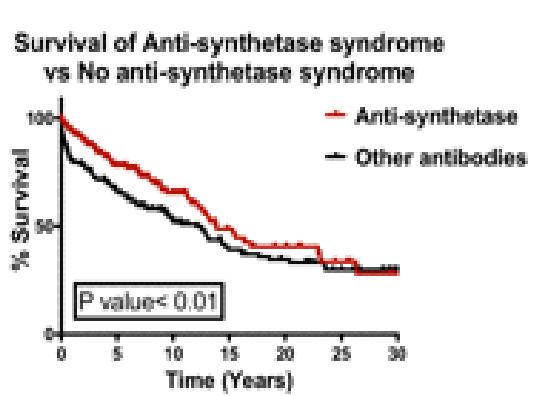
- PM and DM subjects (or with the antisynthetase syndrome) with ILD from the Univ. of Pittsburgh CTD registry (>30y of prospective data + sample repository).
- ILD was radiographically defined (x-ray or HRCT findings).
- Death or transplant: determined from the registry or e-medical record.

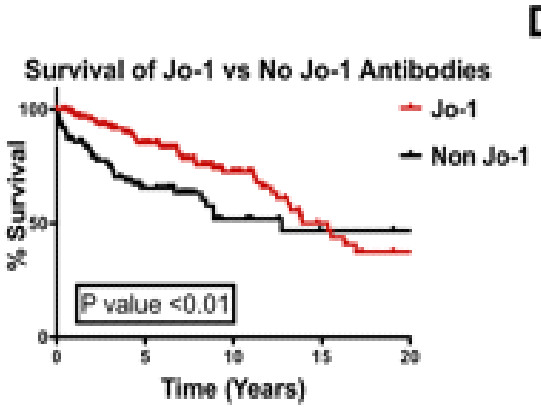
Results

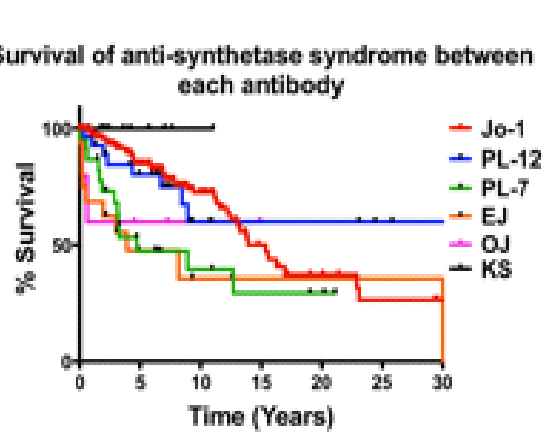
- 369 patients met criteria for MA-ILD.
- 63% (231/369) had MAAs and 54% (198/369) had a positive the a-syn Ab.
- The most common autoAb subset in the autoAb (+) cohort: a-Jo 1 (41%).
- Overall 5 and 10y survival of MA-ILD: 80% at 5 years and 72% at 10 years
- Patients with an MAA: better survival vs. MAA (-) subjects (5 and 10 year survival 80% vs. 72%; 72% vs. 58%, p=0.003).
- Among MAA (+) patients: a-syn + had better survival vs. non-a-syn Abs (5 and 10y survival 80% vs. 73%; 73% vs. 61%, p=0.004).
- Among a-syn + subjects, those with a-Jo1 had better survival vs. patients with 1 of the 7 other a-syn Abs: 5 and 10y survival 86% vs. 72%; 77% vs. 65%, p=0.04

Figure 1


A
Myositis associated vs
Non myositis associated antibodies
MAA
No MAA
% Survival
P value<0.01
Time (Years)


B
Survival of Anti-synthetase syndrome
vs No anti-synthetase syndrome
Anti-synthetase
Other antibodies
% Survival
P value< 0.01
Time (Years)


C
Survival of Jo-1 vs No Jo-1 Antibodies
Jo-1
Non Jo-1
% Survival
P value <0.01
Time (Years)


D
Survival of anti-synthetase syndrome between
each antibody
Jo-1
PL-12
PL-7
EJ
OJ
KS
% Survival
Time (Years)

Conclusion

- Myositis patients with MAA, particularly anti-syn Abs: better survival compared to those without Abs.
- Among a-syn + patients, Jo-1 positivity confers a better survival.

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ABSTRACT NUMBER: 854

PREDICTIVE MODELING OF MORTALITY IN POLYMYOSITIS / DERMATOMYOSITIS PATIENTS WITH INTERSTITIAL LUNG DISEASE BASED ON COMBINATION OF SERUM MYOSITIS-SPECIFIC AUTOANTIBODIES AND CONVENTIONAL BIOMARKERS

TAKAHISA GONO, ET AL.

Purpose

- The aim of this study is to establish predictive modeling of mortality in patients with PM/DM-associated ILD using a large cohort data.

Methods

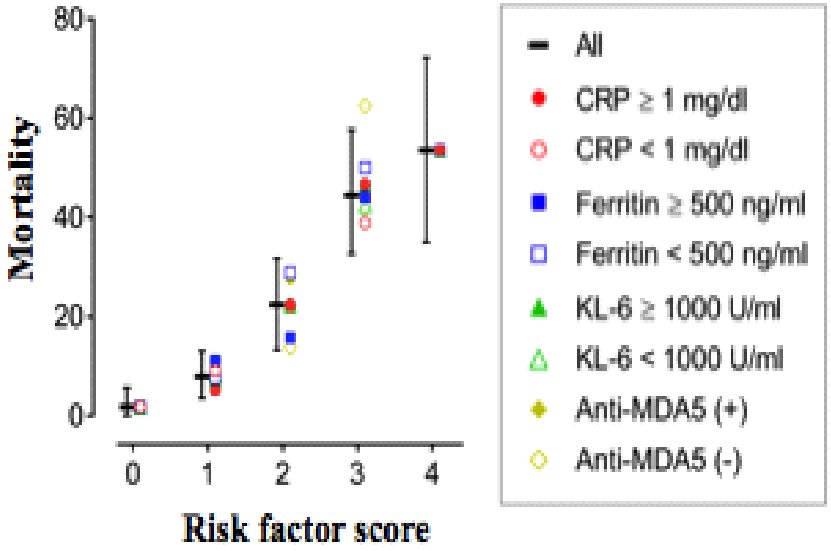
- Database of a multicenter retrospective cohort of patients with PM/DM-ILD (JAMI cohort): 44 institutions across Japan.
- 487 patients with adult-onset PM/DM + ILD confirmed by imaging study.
- Myositis-specific autoantibodies (MSAs). CRP, ferritin, KL-6 and surfactant protein-D (SP-D) were chosen as serum biomarkers for PM/DM-ILD.

Results

- The overall survival rate was 83% at 1 year.
- Survival rate:
- significantly lower in patients anti-MDA5 + than in those without, $p<0.0001$
- The cut-off values of serum biomarkers for predicting mortality:
  - CRP ≥1 mg/dl, ferritin ≥500 ng/ml, KL-6 ≥1000 mg/dl, SP-D <100 ng/ml
- Risk factors for poor prognosis:
  - anti-MDA5 ---------- HR = 3.0, 95% CI = 1.6-5.7
  - CRP ≥1 mg/dl ---------- HR = 2.4, 1.4-4.0
  - KL-6 ≥1000 mg/dl ---------- HR = 2.0, 1.3-3.3
  - ferritin ≥500 ng/ml ---------- HR = 1.8, 1.0-3.2

Figure 1. Association between mortality rate and risk factor score in PM/DM-ILD

Risk factor score for mortality
The score of each factor as below is 1 point.
- ✧CRP ≥1.0 mg/dl
- ✧Ferritin ≥ 500 ng/ml
- ✧KL-6 ≥1000 U/ml
- ✧Anti-MDA5 (+)



Conclusion

- Predictive modeling of mortality in patients with PM/DM-associated ILD using convenient serum biomarkers.
- Model potentially useful in identifying patients with high mortality risk, which apparently require intensive treatment.

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ABSTRACT NUMBER: 891

LONG-TERM EFFICACY AND SAFETY OF TOCILIZUMAB IN PATIENTS WITH REFRACTORY TAKAYASU ARTERITIS TREATED CONTINUOUSLY OVER 52 WEEKS: RESULTS FROM PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL AND OPEN-LABEL EXTENSION IN JAPAN

YOSHIKAZU NAKAOKA, ET AL.

Purpose

- To assess efficacy and safety of TCZ treatment over 52 weeks in the double-blind (DB) period and open-label extension (OLE) of the ongoing TAKT Study.

Methods

- Patients ≥12 years old with TAK
- Relapse while receiving oral GC (≥0.2mg/kg/day PRDL) within the prior 12 weeks
- Randomization 1:1, after remission with oral GC:
  - weekly s.c. TCZ 162mg or
  - weekly s.c. placebo
- In the DB period, GC tapered from Wk 4 to a minimum of 0.1 mg/kg/day.
- Patients relapsing during the DB period enter the OLE period to receive TCZ.
- DB period ended when relapse occurred and all pts moved on to the OLE period. During the OLE period, GC were adjusted at the investigator's discretion.

End-points:

- reduction of GC and relapse of TAK in long-term treatment of TCZ.

Results

- 36 patients randomized:
- 18 TCZ vs. 18 PBO in the DB period. All patients entered the OLE period.
- The median total duration of TCZ treatment: 70.4 weeks.
- 31 patients were treated with TCZ over 52 wks.
- Median GC dose decreased from 0.22 mg/kg/day at relapse before participation in the study to 0.13 mg/kg/day at week 52 (Figure).
- 12/31 patients achieved ≥50% reduction of GC and
- 2 pts were off GC at week 52.
- relapse in 8 patients during the OLE period.

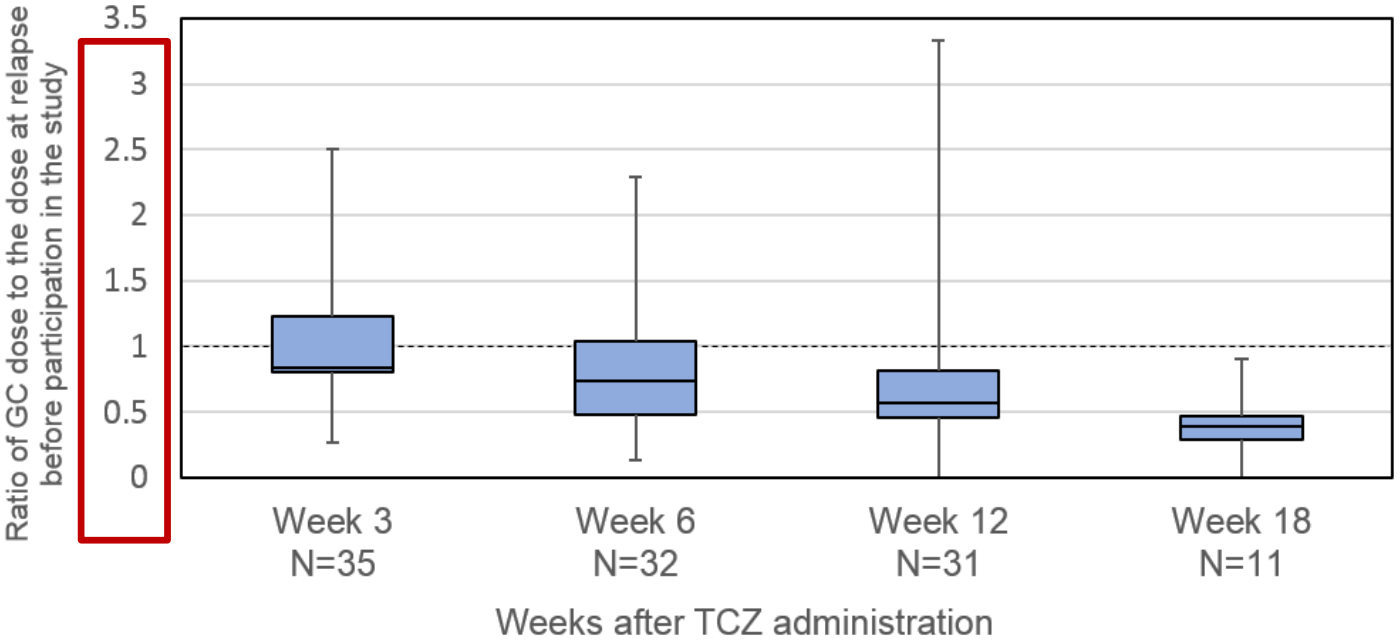

Figure Box plot of the ratio of GC dose after initiation of tocilizumab therapy compared with that at relapse before participation in the study

Conclusion

- Over 52 weeks, TCZ has sustained, clinically meaningful, steroid-sparing effects in patients with refractory TAK.

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ABSTRACT NUMBER: 893

EFFICACY AND SAFETY OF BELIMUMAB IN COMBINATION WITH AZATHIOPRINE FOR REMISSION MAINTENANCE IN GRANULOMATOSIS WITH POLYANGIITIS AND MICROSCOPIC POLYANGIITIS: A MULTICENTER RANDOMIZED, PLACEBO-CONTROLLED STUDY

DAVID JAYNE, ET AL.

Purpose

- To investigate efficacy and safety of belimumab + SoC, for the maintenance of remission in GPA (Wegener's) and MPA after a standard induction regimen.

Methods

- Multicenter, randomized double-blind study.
- Patients (≥18 years) with GPA or MPA in remission + PRDL ≤10 mg/day after induction with CYC or RTX.
- F-U: 12 months.
- Randomization 1:1
  - AZA 2mg/kg/day and oral GC + i.v. BEL 10 mg/kg or
  - AZA 2mg/kg/day and oral GC + placebo until study completion
- Primary endpoint.
  - Time to first relapse (≥1 major BVAS item, total BVAS score ≥6, or receipt of prohibited medications resulting in treatment failure).

Table 1. Baseline demographics and disease characteristics

		Belimumab (n=53)	Placebo (n=52)
Age, years	Mean (SD)	56.2 (13.59)	53.5 (13.56)
Sex: female	n (%)	26 (49)	25 (48)
Disease duration, years	Median (range)	1.3 (0.01–20.6)	2.3 (0.3–14.9)
Disease stage pre-induction	n (%)		
Initial diagnosis		19 (36)	24 (46)
Relapsing disease		34 (64)	28 (54)
GPA	n (%)	42 (79)	41 (79)
MPA	n (%)	11 (21)	11 (21)
ANCA type (historical diagnosis)	n (%)		
Anti-PR3		41 (77)	40 (77)
Anti-MPO		12 (23)	12 (23)
Induction regimen	n (%)		
Intravenous CYC		21 (40)	24 (46)
Oral CYC		18 (34)	15 (29)
Rituximab		14 (26)	13 (25)

ANCA, anti-neutrophil cytoplasm antibodies; CYC, cyclophosphamide; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; RTX, rituximab

Results

- No significant difference in time to first relapse between treatment groups:
- adjusted HR (95% CI): 1.07 (0.44, 2.59); p=0.884
- For patients induced with RTX: 0/1 relapses classified as vasculitis related in the BEL group vs 3/4 in the PBO group.
- AEs in 49 (93%) BEL and 43 (83%) PBO patients post baseline.
- The most common AE category: infection (BEL, 30 [57%]; PBO, 30 [58%]).
- Serious AEs: 18 (34%) BEL and 16 (31%) PBO patients; the most common category: infection (BEL, 4 [8%]; PBO, 4 [8%]).

Conclusion

- In patients with AAV who were in remission, the addition of BEL to maintenance therapy with AZA and oral GC did not reduce risk of relapse.
- RTX-induced patients exhibited numerically fewer relapses of vasculitis with treatment with BEL vs. placebo, warranting further investigation.

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ABSTRACT NUMBER: 783 POSTER

EULAR Recommendations for the Use of Imaging in Large Vessel Vasculitis in Clinical Practice

Christian Dejaco, et al.

Background and Purpose

- US, MRI, CT and 18F-FDG PET/CT: increasingly used in primary large vessel vasculitis (LVV) including giant cell arteritis (GCA) and Takayasu arteritis (TAK).
- Significant controversy and uncertainty about:
  - When to use which imaging technique?
  - Might imaging be helpful during F-U to assess disease activity and damage?
- Aim. To develop EULAR recommendations for the use of imaging modalities in LVV in clinical practice.

Methods

- The EULAR Standardised Operating Procedures have been followed.
- A systematic literature review to retrieve data on the role of imaging in LVV.
- Based on evidence and expert opinion, the task force consisting of 20 EULAR experts developed recommendations, with consensus obtained through informal voting. The final level of agreement was voted anonymously.

Statement	LoE	LoA
1. In patients with suspected GCA, an early imaging test is recommended to complement the clinical criteria for diagnosing GCA, assuming high expertise and prompt availability of the imaging technique. Imaging should not delay initiation of treatment.	1	9.2 (2.1) 90% ≥8
2. In patients in whom there is a high clinical suspicion of GCA and a positive imaging test, the diagnosis of GCA may be made without an additional test (biopsy or further imaging). In patients with a low clinical probability and a negative imaging result, the diagnosis of GCA can be considered unlikely. In all other situations, additional efforts towards a diagnosis are necessary.	2	9.4 (1.0) 90% ≥8
3. US of temporal±axillary arteries is recommended as the 1st imaging modality in patients with suspected predominantly cranial GCA*. A non-compressible 'halo' sign is the US finding most suggestive of GCA.	1	9.7 (0.6) 100% ≥8
4. High resolution MRI of cranial arteries‡ to investigate mural inflammation may be used as an alternative for GCA diagnosis if US is not available or inconclusive.	2	9.2 (1.1) 90% ≥8
5. CT and PET are not recommended for the assessment of inflammation of cranial arteries.	5	9.5 (1.2) 95% ≥8
6. US, PET, MRI and/or CT may be used for detection of mural inflammation and/or luminal changes in extracranial arteries to support the diagnosis of LV-GCA. US is of limited value for assessment of aortitis.	3 (PET, CT) -5 (US, MRI)	9.8 (0.6) 100% ≥8
7. In patients with suspected TAK, MRI to investigate mural inflammation / luminal changes should be used as the 1st imaging test to make a diagnosis of TAK, assuming high expertise and prompt availability of the technique.	3	9.1 (1.4) 90% ≥8
8. PET, CT and/or US may be used as alternative imaging modalities in patients with suspected TAK. US is of limited value for assessment of the thoracic aorta.	3 (CT) –5 (PET, US)	9.4 (0.8) 100% ≥8
9. Conventional angiography is not recommended for the diagnosis of GCA or TAK as it has been superseded by the previously mentioned imaging modalities.	5	9.8 (0.6) 100% ≥8
10. In patients with LVV (GCA or TAK) in whom a flare is suspected, imaging might be helpful to confirm or exclude it. Imaging is not routinely recommended for patients in clinical and biochemical remission.	5	9.4 (0.8) 100% ≥8
11. In patients with LVV (GCA or TAK), MRA, CTA and/or US may be used for long-term monitoring of structural damage, particularly to detect stenosis, occlusion, dilatation and/or aneurysms. The frequency of screening as well as the imaging method applied should be decided on an individual basis.	5	9.3 (1.2) 95% ≥8
12. Imaging examination should be done by a trained specialist using appropriate equipment, operational procedures and settings. The reliability of imaging, which has often been a concern, can be improved by specific training. Suggestions for technical and operational parameters are depicted in Box 1.	5	9.8 (0.6) 100% ≥8

Conclusion

- First EULAR recommendations providing up-to-date guidance on the role of imaging in the diagnosis and monitoring of patients with suspected LVV.

Results

In patients with suspected Large Vessel Vasculitis:

- It is recommended an early imaging test, assuming high expertise and prompt availability of the imaging technique.
- **US: first choice imaging modality in GCA** (good performance, easy access, absence of radiation and other procedural risks, and low resource use).
- MRI, and in case of predominant LV-GCA, PET and CT: alternatives to US.
- For TAK, MRI: preferred imaging modality (absence of radiation and possibility to assess simultaneously the vessel wall and luminal changes of the aorta and its proximal branches). PET, CT and US: alternatives.
- In patients with a suspected flare of LVV, imaging might be helpful to assess disease activity. The frequency and choice of imaging modalities for long-term monitoring of structural damage remains an individual based decision.