Comparing pregnancy outcomes in patients with criteria and non-criteria autoimmune disease: a systematic review.

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Abstract

Background: Not all patients fulfil criteria for specific Autoimmune Rheumatic Diseases (ARD) and are then defined as having non-criteria (nc)ARD. It is uncertain whether well-recognised associations with adverse pregnancy outcomes in patients with criteria ARD also exist in patients with ncARD or undifferentiated connective tissue disease (UCTD). Therefore, we undertook a systematic review of the prevalence of adverse pregnancy

outcomes in various ncARD and UCTD compared with criteria ARD to identify whether there are increased risks and to examine for any benefits of treatment.

Methods: This study was conducted in accordance with the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard. A systematic literature review was performed using online databases including Medline and PubMed from inception to the beginning of April 2021 using appropriate keywords for various ARD and pregnancy outcomes.

Results: After screening 665 articles, 36 articles were chosen for full text review and 15 selected for final analysis. There were 8 studies of nc Antiphospholipid Syndrome (APS) of more than 7000 pregnancies and 7 studies of UCTD of more than 1000 pregnancies. No studies of any other ncARD in pregnancy were identified. We found that patients with either ncAPS or UCTD seem to have an increased burden of poor pregnancy outcomes compared with the general population. Despite the heterogeneity and poor quality of the studies, we also noted that ncAPS and criteria APS patients may have similar rates of obstetric complications with standard and/or non-standard APS treatment regimens.

Conclusion: Our findings of increased risks of poor pregnancy outcomes in patients with ncAPS or UCTD will be helpful for pre-pregnancy counselling and management of these

patients in pregnancy and support their referral to specialist obstetric-rheumatology and obstetric-haematology clinics.

Introduction

Autoimmune diseases (AD) are comprised of various organ-specific and multisystem conditions that cause significant and chronic morbidity and disability (1). They have an overall prevalence of 4.5% (2), a female predominance and onset typically during reproductive years (3). Consequently, many AD, particularly autoimmune rheumatic diseases (ARD), have been the subject of intense research examining whether women with these diseases have an increased risk of adverse pregnancy outcomes (APO) compared with healthy pregnant women.

Two ARD established to have an increased risk of APO are systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS). These diseases are characterised by immune dysfunction, complement dysregulation, pathogenic autoantibody formation and an increased burden of APO (4,5). Pregnancy in SLE is associated with increased maternal and fetal morbidity, including: preeclampsia, 12 to 35%; preterm birth, 22 to 33%; recurrent pregnancy loss, 4 to 43%; intra-uterine growth restriction (IUGR), 10 to 30%; and small for gestational age (SGA), 13 to 25%; significantly increased compared to the general population (5-7). APS may occur in isolation or in association with other

ARD, commonly SLE, and is characterised by vascular thrombosis and/or obstetric morbidity in the context of persistently positive tests for antiphospholipid antibodies (aPL)(8).

International criteria to classify patients with ARD according to clinical and laboratory manifestations, are widely used in clinical practice to aid diagnosis and management (8-10). Not all patients however, fulfil the relevant classification criteria and are then described as having either incomplete or non-criteria forms of the disease (11-13). In contrast, the term Undifferentiated Connective Tissue Disease (UCTD) is used to describe patients with symptoms suggestive of an ARD lasting for at least one year and persistent positive antinuclear antibodies that does not meet established criteria for any ARD (14-15).

Despite a well-recognised association with APO in patients with criteria SLE and/or APS, there is conflicting evidence as to whether this association also exists in patients with non-criteria (nc)ARD or UCTD. Therefore, uncertainties exist as to how to manage women with ncARD during pregnancy, although given reports of increased risk of APO in ncARD pregnancies these patients are often treated as if they had complete forms of disease. In the absence, however, of an evidence-based consensus of management of ncARD pregnancy it is uncertain whether specific treatment and monitoring by healthcare professionals is required for those ncARD patients.

Therefore, we carried out this systematic review of available evidence on pregnancy outcomes in various ncARD and UCTD to identify whether there are increased risks. Specifically, we aimed to answer the following questions: are pregnancy outcomes different between women with complete and ncARD and healthy pregnant women and if so, which ncARD have a higher risk of APO? In addition, we reviewed available evidence to try to answer whether standard or other treatment regimens are

Results

Outcome from systematic search

A total of 665 articles were screened, 36 articles selected for full text review and then 15 original articles selected for inclusion (Fig. 1). Of these studies, there were 11/15 single centre, 4/15 multicentre, 7/15 retrospective, 7/15 prospective and 1/15 mixed retrospective and prospective study. There were 8/15 studies of ncAPS and 7/15 of UCTD with control groups of healthy pregnant women in 4/15 studies and pregnant women fulfilling criteria for an ARD in 10/15 studies. Three studies lacked any control group. We did not find publications in relation to pregnancy outcomes in patients with any other ncARD.

Pregnancy outcomes in treated and untreated ncAPS versus APS and/or HC

We identified 8 (six single, one triple and one multicentre) studies (Table beneficial in ncARD pregnancies.

Methods

This study was conducted in accordance with the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard (16). A systematic literature review was carried on Medline and PubMed (criteria shown in box 1) from its inception to the beginning of April 2021.This systematic review protocol was registered at PROSPERO in October 2020 under the registration number CRD42020212860.

Definitions

APO, disease and treatment definitions/abbreviations are shown in Table 1 and 2.

Inclusion criteria

Relevant articles were those deemed to contain original information about pregnancy outcomes in patients with features of ARD who do not fulfil current classification criteria (8,14). We selected studies with or without controls, of either pregnant women with criteria ARD and/or healthy controls (HC). Rates of APO in articles without a control group were compared with those expected for the general population.

Exclusion criteria

We excluded studies with incomplete reporting of obstetric outcomes; written in a language other than English, Italian (17) or Spanish; and those only published as abstracts. We also excluded articles that examined APO in patients with preclinical (pre)ARD, defined as patients who subsequently developed an ARD years after the APO.

Study selection

Two independent reviewers (CM and KA) screened each title and abstract to identify studies that met inclusion criteria for full text review. A data extraction sheet was designed, piloted using 5 papers, and then revised to optimise data retrieval. The final report included: study design and methodology, number of patients and pregnancies, pregnancy outcomes and a summary of the most relevant findings in each study. In the ncAPS group, we also include details about subgroups of ncAPS patients, titre of aPL and data of the different treatments used. Study limitations were documented. The quality of evidence in each article was assessed using GRADE methodology (18).

3) of pregnancy outcomes in ncAPS with 1/8 ‘moderate’, 6/8 ‘low’ and 1/8 ‘very low’ quality of evidence according to GRADE. They included 6 cohort and 2 case-control studies (11,19-25).

Eight studies compared pregnancy outcomes in (n=1042) ncAPS patients with (n=1396) APS and/or (n=920) HC (11,19-25). The largest (multicentre, mixed retrospective and prospective) study from the European Registry on Obstetric Antiphospholipid Antibody Syndrome (EUROAPS) examined 1640 (n=640 ncAPS and n=1000 APS) patients (11). They reported an increased incidence of obstetric complications in the APS compared with the ncAPS group [spontaneous abortion (25vs7%, p<0.001), stillbirth (23vs6%, p<0.001), IUGR <34 weeks (16vs3%, p<0.001), preterm birth (28vs5%, p<0.001), preeclampsia <34 weeks (18vs3%, p<0.001) and HELLP syndrome (3vs1%, p= 0.001)].

However, similar obstetric outcomes (including live birth) were found in both groups when they received standard APS therapy [381/448 (85%) in the APS group versus 276/308 (90%)] in the ncAPS). Similarly, a triple centre retrospective study (19) of 200 patients with 283 (n=54 ncAPS, n=66 TAPS, n=124 OAPS and n=39 aPL carriers) pregnancies found no statistical differences in incidence of APOs [including: spontaneous abortion (40vs50vs41vs14%); stillbirth (20vs25vs18vs43%) or preterm birth (40vs25vs32vs43%)] treated with LDA +/- prophylactic or therapeutic LMWH. A single centre retrospective study (21) of patients (n=117) with ncAPS and (n=126) with APS (44% received standard and non-standard APS therapy and 56% did not receive any treatment), showed comparable rate of APO

in ncAPS versus APS patients [recurrent early miscarriage (16vs16%, p=0.91), IUGR (6vs6%, p=0.93), preeclampsia (5vs2%, p=0.3) and HELLP syndrome (2vs0, p=0.1)] Another single centre retrospective study (22) of 740 (n=68 ncAPS and n=672 with unexplained miscarriages) subjects reported that LDA significantly improved the live birth rate in ncAPS pregnancies (84%) compared with untreated ncAPS pregnancies (84vs50%, p=0.004) and untreated patients with unexplained miscarriages (84vs76%, p=0.008). A smaller single centre retrospective study (20) of 57 (n=32 ncAPS, n=25 APS) patients found a similar rate of APO in ncAPS versus APS patients [recurrent early miscarriage (41vs36%), stillbirth (50vs44%), preeclampsia (19vs20%) and IUGR (22vs36%)] between groups before APS treatment. This study also reported a substantial improvement in pregnancy and neonatal outcomes in both groups after standard and non-standard APS treatment [recurrent early miscarriage (0vs0%), stillbirth (6vs0%), preeclampsia (3vs0%) and IUGR (3vs12%)], as well as that the total number of obstetrical events per patient decreased significantly in both groups after treatment to reach an identical median value (from 3 [1–8] to 0 [0–2] in Group 1 ($p < 0.05$) and from 3 [1–6] to 0 [0–2] in Group 2 [$p < 0.05$]). A single centre prospective study (25) of 270 (n=91 ncAPS, n=41 APS and n=135 HC) patients did not show significant difference in APO between groups [stillbirth (2vs4.5vs0%),

preterm birth (7vs14vs8%) and preeclampsia (10vs7vs13%)], except for the rate of IUGR (5.5vs16vs4%, $p < 0.05$) which was higher in both APS and ncAPS than healthy pregnant women. They also found that women with positivity for aPL (including APS and ncAPS patients) who were treated with LDA +/- an unspecified dose of LMWH achieved better pregnancy outcomes. In contrast, two studies (23,24) found an increased rate of APO in APS compared with ncAPS pregnancies. A single centre retrospective study of 19 (n=7 ncAPS and n=12 APS) patients (23), reported that APO were more common in APS compared

to ncAPS pregnancies after anticoagulant therapy [including preterm birth (37vs0%, p=0.02) and preeclampsia (25vs0%, p=0.12)]. In addition, a single centre prospective study (24) of 948 (n=48 ncAPS, n=62 APS; n=53 aPL carriers and n=785 HC) patients with different treatment regimens including standard and non-standard APS treatment (table 3) found that all aPL groups (ncAPS, APS and aPL carriers) had an increased risk of APO compared with HC. The adjusted attributable fraction of adverse pregnancy outcomes was significantly larger among subjects with complete APS compared to ncAPS ($p < 0.001$) or carriers ($p < 0.001$).

In conclusion, 6/8 studies with moderate (11) and low (19-22,25) quality evidence, described similar rates of pregnancy outcomes between ncAPS and APS groups after standard and non-standard APS treatments, whilst other two with very low (23) and

low (24) quality of evidence did not. Less conclusive is the information about the rate of APO in ncAPS and APS patients before APS treatment. While one study (11) reported an increased risk of APO in APS compared with ncAPS patients, another study (20) suggested similar rates of APO between groups. Two studies compared APO in ncAPS and HC with inconclusive results. While one reported a similar rate of APO between groups (24), another study concluded that ncAPS patients had an increased risk of pregnancy complications compared to healthy pregnant women (25). Despite the limited information in terms of APO between ncAPS and HC, the overall rate of APO in both ncAPS and APS groups was higher than expected from the general comparator population of each study (26-28). Overall, these findings identify a comparable risk of APO in ncAPS and APS pregnancy after standard and/or non-standard APS treatment regimens treatments. However, most of this data comes from low quality studies which were not controlled by HC. Therefore, well designed and controlled studies need to be done before any firm conclusion is given. Notably, these studies used different assays and cut-off values to measure aPL positivity, including low titre aPL (table 3).

Pregnancy outcomes in UCTD versus ARD, HC and/or general population

We identified seven (four single-centre prospective, one single-centre retrospective, one multicentre prospective and one multicentre retrospective) studies (Table 4) of APO in UCTD pregnancies of 1/7 moderate and 6/7 low quality evidence. There were four cohort and three case-control studies (15,17, 29-33).

Four articles of moderate (29) and low (30-32) quality evidence, compared rates of APO in UCTD, ARD patients, HC and/or general population. Two different studies from the same group found increased rates of APO in UCTD compared with HC pregnancies (29,31). An initial study (31) of 123 (n=41 UCTD and n= 82 HC) pregnancies found patients with UCTD experienced more pregnancy complications (39vs13%) than HC (adjusted OR 3.98; 95% CI, 1.59-9.49). A later study of 796 (n=131 UCTD, n=68 ARD and n=597 HC) patients found an increased risk of developing APO in UCTD and ARD (n= 19 rheumatoid arthritis; n=16 SS, n=14 APS, n=13 SLE, n=1 SSc, n=1 granulomatosis with polyangiitis; n=1 mixed connective tissue disease and n=1 monoarticular arthritis) pregnancies compared with HC [including IUGR (16vs26vs4%, p<0.001), SGA (17vs26vs8%, p<0.001) and preeclampsia (14vs22vs3%, p<0.001)]. Although, the risk for APO was even higher for ARD patients, the burden of pregnancy complications was similar between UCTD and ARD groups (29). In addition, a study of 244 pregnancies in 133 patients with UCTD reported an increased risk of APO in UCTD compared to the

general population, especially preterm birth (17%) and SGA (12%) (32). In contrast, a study of 100 pregnancies in 81 UCTD patients reported similar rates of APO [spontaneous abortion (11%), preterm birth (9%) and SGA (10%)] between UCTD patients with stable disease at conception and the expected rate for the general population (30). Another study of 25 pregnancies in 20 patients with UCTD found a live birth rate of 88% (15).

Two studies with moderate (29) and low (31) grade evidence also examined maternal outcomes in UCTD, ARD and HC pregnancies. They reported an increased risk of developing preeclampsia in UCTD and criteria ARD compared with HC (29,31), with the risk of preeclampsia greatest in ARD pregnancies ($p<0.001$) (29). Only one study evaluated the incidence of disease flares in 20 patients with UCTD according to physician's assessment compared to a cohort of 70 non-pregnant UCTD patients, followed for one year and found a higher incidence of disease flare during pregnancy or puerperium (24%) compared with those non-pregnant UCTD patients (7%) (15).

Overall, most (3/4) articles with moderate (29) and low (31-32) quality evidence, found an increased rate of adverse materno-fetal outcomes in UCTD pregnancy compared with HC or general population, whilst one study with low quality evidence (30) reported similar outcomes in UCTD (with stable disease at conception) and HC pregnancy. These studies identify an increased risk of APO in pregnancy that warrants

close monitoring of these pregnancies for adverse outcomes and to ensure low disease activity.

Role of the immunological profile in terms of flare and APO in UCTD versus ARD patients, HC and/or general population

Four (one single-centre prospective, one single-centre retrospective, one multicentre prospective and one multicentre retrospective) studies examined the impact of different autoantibodies on UCTD pregnancy outcomes (17,30,32-33). A single centre retrospective study (30) concluded that in patients with UCTD and active disease and/or the presence of any positive titre of anti-dsDNA antibodies at conception significantly increased the risk of flare in UCTD pregnancies ($p<0.01$). A multicentre study of 244 pregnancies in 133 patients with UCTD (32) found an increased risk of miscarriages and stillbirth in patients positive for aPL and/or anti-ENA antibodies (anti-Ro/SSA, anti-La/SSB, anti-RNP, anti-U1RNP, anti-Sm and anti-Jo1) before conception ($p<0.05$). A multicentre prospective study (33) of 118 pregnancies in 100 (n=19 UCTD; n=25 SS; n=53 SLE; n=1 APS; n=1 SSc) patients with positive anti-Ro/SSA antibodies found an increased

incidence of Congenital Heart Block (CHB) in UCTD and SS compared with SLE patients. Similarly, a single centre prospective study (17) study of 46 pregnancies in 41 (n=25 UCTD and n=16 SS) patients found that UCTD and SS patients with positive anti-Ro/SSA

antibodies, had a higher incidence of CHB than patients with SLE (33-34).

Overall, four studies with low (17,30,32-33) quality of evidence, examined the impact of different antibodies on UCTD pregnancy outcomes and observed that positivity for anti-dsDNA, aPL or anti-ENA and/or the presence of disease activity at conception were associated with an increased risk of developing APO and/or UCTD flare during pregnancy.

Discussion

Overall, we found an increased incidence of adverse materno-fetal pregnancy outcomes in UCTD compared with HC and/or general population. Despite a similar comparison of ncAPS and HC pregnancies being lacking and marked study heterogeneity, a similar rate of APO was found when ncAPS patients were compared to those patients with a full diagnosis of APS after standard and non-standard APS therapy.

No publications were found reporting on pregnancy outcomes in patients with any other ncARD. Positivity for anti-dsDNA, aPL or anti-ENA antibodies and/or the presence of disease activity at conception in patients with UCTD was associated with an increased risk of developing APO and/or flare during pregnancy.

The concept, description and management of incomplete forms of ARD are a matter of

great debate. In general, ncARD are identified in patients with incomplete clinical or laboratory criteria according to current classification criteria of the suspected ARD (8-10). Current European guidelines recommend the use of LDA+LMWH as standard treatment for APS (35). Despite a general European consensus to treat pregnant aPL carriers with aspirin (35), therapeutic guidelines for the management of ncARD patients are not currently available. Therefore, controversy exists whether patients with incomplete forms of ARD require exposure to standard treatment regimens and toxicities used in patients with criteria ARD (36) to avoid adverse materno-fetal consequences. The benefits of this standard regime may be largely attributable to LDA since it has been shown to improve gestational complications when used alone in women at risk of pre-eclampsia without ARD, with a reduction in preeclampsia in 53% of cases, IUGR in 56% and preterm birth in 78% of cases (37). Furthermore, a recent randomized trial by Llurba et al (38) found that LMWH in women at high risk of pre-eclampsia without thrombophilia did not reduce placental insufficiency compared with no intervention.

Few of the studies that we identified have examined whether patients with ncARD who received standard therapy had similar APO compared to those with criteria ARD (11). Therefore, it is hardly surprising that data relating to outcomes of ncARD pregnancies has provided lack of consensus on optimal management in pregnancy. Consequently,

many physicians assume that ncARD have comparable risks and thus requirement for standard ARD treatment regimens in pregnancy (11,12); whilst other healthcare professionals do not recognise ncARD as a potential hazard in terms of APO. It is important to clarify whether patients with ncARD have similar rates of APO to ARD and to validate an evidence-based management guideline for ncARD pregnancies to inform counselling and treatment of ncARD pregnancy and thus improve maternal and fetal pregnancy outcomes.

One difficulty of studying ncARD relates to nomenclature. Although we identified publications examining a large (n=915) number of patients with ncAPS and >7000 pregnancy outcomes, the term ncAPS remains controversial (12,13). Despite definitions of (Table 1) being defined (12), it is not accepted by all physicians experienced in managing patients with APS. For instance, some authors have proposed that ncAPS is a variant of APS and could be classified as such with the inclusion of non-criteria aPL (such as antiphosphatidylethanolamine, anti-annexin V or antiphosphatidylserine/prothrombin antibodies) in current classification criteria and/or improving the detection of the conventional antibodies using new methodological approaches different from the traditional assays (38,39). The availability and utility however, of these non-criteria aPL assays remains limited (40) and none of the studies we identified (11,19-25) used them to define patients with ncAPS.

Overall, we found discrepant results regarding rates of APO in ncAPS and APS groups and/or HC before receiving APS treatment. The largest study (11) reported an increased risk of APO in (n=1000) APS compared with (n=640) ncAPS pregnancies, whilst another smaller study (20) suggested similar rates of APO between (n=25) APS and (n=32) ncAPS groups. Of the other studies two found no difference (19,21), one other (23) found reduced LB in ncAPS compared with APS and the other (22) lacked an APS group. Overall, the rate of APO in APS and ncAPS groups in all studies was increased compared with that expected in the general population (26-28). A potential benefit of standard and non-standard APS treatment on pregnancy in n=896 patients with ncAPS was suggested by authors in 6/8 studies (11,19-25) with comparable rate of APO in ncAPS and APS patients following standard and non-standard APS therapy. However, the lack of HC group in most studies and the low overall quality of evidence are limitations**.** Therefore, these findings must be confirmed with well-designed prospective studies with strict clinical and laboratorial criteria compared to healthy controls.

Of seven studies on 450 patients with UCTD in more than 1000 pregnancies, four compared APO in patients with UCTD and HC pregnancies or the expected rate for the general population. Three of these studies (29,31,32) found an increased rate of APO in (n=305) patients with UCTD compared with (n=679) HC or general population and

one reported similar pregnancy outcomes between (n=81) UCTD patients who were stable at conception and the rate expected for the general population (30). An increased risk of APO was also described in patients with UCTD with either active disease at conception or positivity for specific autoantibodies (anti-DNA, aPL and other anti-ENA) (17,30,32-33). This finding underlines the importance of pre-pregnancy counselling to ensure adequate disease control pre-conception and measurement of the described immunological profile to evaluate risk of obstetric complications.

Epidemiological data support an association between ncARD and APO in several ways. First, 25% of patients with UCTD have been shown to subsequently develop a full-blown criteria-ARD over a five-year period, most frequently SLE, with all associated features (41). Second, women destined to have a well-defined ARD often have a poor antecedent obstetric history, thus indicating that the interference of an ARD on pregnancy outcome may begin well before the clinical manifestations of the disease or that they share a common origin (42,43). The study of preclinical ARD (before symptom onset) in pregnancy however, was an exclusion criteria and thus beyond the scope of this systematic review.

The pathogenic mechanisms of pregnancy complications in ncARD are likely to be similar to those identified in ARD including, defects in various immunoregulatory pathways leading to activation of inflammatory mediators and endothelial damage at

the maternal-fetal interface causing placental insufficiency (44,45). Autoantibodies, particularly aPL, have emerged as triggers of innate immune inflammatory pathways that activate many different white blood/vascular/obstetric-cell types causing placental dysfunction (46). Given that patients with ncAPS and UCTD are also characterised by the presence of circulating autoantibodies, increased inflammatory mediators and endothelial damage (12,47), it is plausible to assume that a similar biological mechanism of APO occurs in patients with ncARD.

Limitations of the literature

Our findings are limited by the high heterogeneity in methodology of the different studies we identified including factors such as: the small number of patients and pregnancies in some studies; the lack of either a healthy pregnancy and/or ARD control group; the inability to separate serological ncAPS subgroups considering all of them as a single ncAPS group; the different titration of aPL included**,** the heterogeneity in ncARD/UCTD definitions and the lack of information in terms of treatment regimes in some studies. In addition, the retrospective nature of most of the studies often meant there was missing data, such as incomplete information on the different possible complications during pregnancy or lack of information on their comorbidities, which limited the ability to identify associations with APO. Therefore, the overall quality of

evidence is low/very low and limits our conclusions accordingly. Another limitation found particularly in the ncAPS group was that some publications contained mixed APS populations with thrombotic and obstetric manifestations. Therefore, their results are more difficult to interpret and potentially less relevant since outcome data was not stratified by APS sub-groups**.** Due to the heterogeneity and the size sample, a sub-analysis of comparable inclusion criteria ncAPS studies was not possible. Finally, it was difficult to draw conclusions as to whether the use of standard treatment of patients with ncARD is beneficial in pregnancy. In particular, some studies did not report complete information about the treatment and those that did, used treatment regimens based on the physician's judgement instead of standardised protocols.

Conclusion

Overall, published studies support that patients with ncAPS and UCTD may have an increased burden of APO compared with healthy pregnant women and the general population. A similar rate of obstetric complications found in ncAPS and APS patients after receiving different APS treatment regimes, supports the use if these regimens in ncARD pregnancies. However, well designed and controlled studies, with strict clinical and laboratorial criteria compared to healthy controls, are needed to confirm these findings.

Therefore, we believe there is sufficient evidence of increased obstetric risk in ncAPS and UCTD pregnancies to support referral of these patients to specialist obstetric-rheumatology or obstetric-haematology clinics for multi-specialist input for individualised planning and management of pregnancy, explaining to patients the uncertainties and risk versus potential benefit.

Declaration of competing interest

The authors do not report any conflicts of interest.

Funding

CM received support from Alfonso Martin Escudero Foundation, Spain.

CM received support from Lupus UK.

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