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Development of the Asia Pacific Lupus Collaboration cohort

Running title: APLC cohort

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Abstract

AIM: The aim of this manuscript is to describe the development of the Asia Pacific Lupus Collaboration (APLC) cohort.

METHOD: The APCL cohort is an ongoing, prospective longitudinal cohort. Adult patients who meet either the American College of Rheumatology (ACR) Modified Classification Criteria for SLE, or the Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria, and provide informed consent are recruited into the cohort. Patients are routinely followed up at 3- to 6-monthly intervals. Information on demographics, clinical manifestations, treatment, pathology results, outcomes, and patient reported quality of life (SF36 version 2) are collected using a standardised case report form. Each site is responsible for obtaining local ethics and governance approval, patient recruitment, data collection, and data transfer into a centralised APCL database.

RESULTS: The latest APCL cohort comprises 2160 patients with >12,000 visits from Australia, China, Hong Kong, Indonesia, Japan, Malaysia, Philippines, Singapore, Taiwan and Thailand. The APCL has proposed the Lupus Low Disease Activity State (LLDAS) as a T2T endpoint, and reported several retrospective and cross sectional analyses consistent with the validity of LLDAS. Longitudinal validation of LLDAS as a T2T endpoint is currently underway.

CONCLUSION: The APCL cohort is one of the largest contemporary SLE patient cohorts in the world. It is the only cohort with substantial representation of Asian patients. This cohort represents a unique resource for future clinical research including evaluation of other endpoints and quality of care.

INTRODUCTION

Systemic lupus erythematosus (SLE or lupus) is a heterogeneous, autoimmune disease with a wide spectrum of clinical manifestations caused by autoimmune-mediated inflammation of multiple organs (1). The crude incidence of SLE in the Asia Pacific region ranges from 0.9 – 3.1 per 100, 000 person-years, while the prevalence ranges from 4.3 to 45.3 per 100,000 (2). SLE patients, predominantly young women, suffer from severe morbidity and mortality, and hence have significantly impaired health related quality of life (HRQoL) (3). Tissue inflammation associated with SLE, and the unwanted effects of treatment, result in permanent organ damage in up to 61% of patients within 7 years of lupus diagnosis (4). Patients are generally treated with a combination of glucocorticoids, anti-malarial drugs and non-specific immunosuppressants, and there is no targeted therapeutic regimen effective for all patients (5). Despite combination therapy, significant proportion of patients suffer inadequate disease control, severe toxicity from medications, and inexorably accrue permanent organ damage over time (6). SLE is more prevalent and more severe in Asians (7, 8), and is phenotypically distinct from Caucasian SLE patients with a greater burden of renal disease and cardiovascular complications (9). In Asia, infections, high disease activity, renal disease and cardiovascular events are the leading causes of mortality among SLE patients (10).

For many years, there have been attempts to quantify heterogeneous states of active SLE to assist with patient assessment and trial design (11). However recently, the research momentum has turned towards defining treatment response endpoints or outcome measures (12, 13). This is partly driven from evidence in rheumatoid arthritis (RA), where treat to target (T2T) approaches such as achieving remission or low disease activity (LDA) state have proven to result in improved clinical outcomes (14). A small but significant proportion of RA patients achieve empirically validated definitions of remission, and this has provided powerful motivation to adopt remission as a treatment target in RA clinical practice, with the result that large proportions of patients achieve at least LDA. Unfortunately in SLE, remission is a very difficult target to achieve; existing remission definitions are so stringent only few attain remission (15), and the relapsing/flaring nature of SLE makes remission difficult to sustain (16).

Given the difficulty in attaining remission in SLE, at least with current treatments, targeting a low disease state may be a more achievable and sustainable outcome for T2T approaches. Prior studies in RA have shown that patients who achieved low disease activity (LDA) had favourable outcomes and improved well-being (17). The priority of empirically generating a LDA definition in lupus was recently reported by the SLE T2T International Task

Force (13). This context provided inspiration to form the Asia Pacific Lupus Collaboration (APLC), and consequently to develop the APPLC cohort, in order to conduct a longitudinal, prospective study to objectively define and validate a low disease activity state for lupus. Such a measure has the potential not only as a novel trial endpoint but also as the foundation for a T2T approach to routine patient management.

METHODS

Organisation and governance of the APPLC

The APPLC was formed in late 2012, bringing together physicians and researchers in the Asia Pacific region with the common goal of improving outcomes for SLE patients. The APPLC has since grown to constitute 23 sites in 13 countries (Figure 1). Each site has signed a Memorandum of Understanding (MOU) that states the rules under which APPLC operates. In addition, each institute has signed a legally binding collaborative research agreement (CRA) to conduct the LLDAS study. The APPLC has formalised a steering committee to ensure transparency and accountability, oversee resource utilisation, provide research focus and optimise outputs. The APPLC has established policies including a Publication Policy and Data Access Policy to manage a range of contingencies.

Lupus Low Disease Activity State (LLDAS)

The approach to define a low disease activity state for lupus began with the recognition that patients with low disease activity are more homogeneous than patients who have high disease activity, as the heterogeneity of lupus stems from the diverse range of features of active disease that diminishes as patients respond (12). This recognition permitted the development of a definition that avoids the complexity intrinsic to quantification of heterogeneous states of active disease.

The APPLC consensus definition of the Lupus Low Disease Activity State (LLDAS) was defined using Delphi methods and nominal group technique, which support face and content validity, wherein 56 items generated by a panel of experts were reduced to five items forming a definition of LLDAS with high levels of agreement (18). The final list of five items defining LLDAS is depicted in Figure 2. The initial validation of LLDAS was performed retrospectively using data from a single centre, and attainment of LLDAS was found to be associated with improved patient outcomes, including lower disease activity during follow ups, fewer flares, lower prednisolone dose during follow-up, and less new organ damage (18). These findings

provided preliminary evidence for the validity of the APLC definition of LLDAS, and its ability to predict favourable patient outcomes. Several other retrospective studies have since confirmed the association of LLDAS with protection from damage accrual, and it has been evaluated as an endpoint in two clinical trials (19-23). Using the APLC cohort, we are now in the process of executing a study to evaluate the validity of LLDAS prospectively, in a large, international, multi-centre patient population. The hypothesis being tested is that achieving LLDAS is associated with reduction in organ damage and improved quality of life. In addition, the APLC cohort data are, and will be used for many other scientific purposes in the years to come.

Patient recruitment and consent

All patients must meet either the 1997 American College of Rheumatology (ACR) Modified Classification Criteria for SLE (24), with at least 4 of the 11 items; or fulfil the Systemic Lupus International Collaborating Clinics (SLICC) 2012 Classification Criteria (25), with at least 4 of the 17 items or with lupus nephritis in the presence of at least one immunological criteria. Principal Investigators at each site are responsible for identifying eligible patients, who can be either newly diagnosed or pre-existing SLE patients; age must be 18 years or over, and patients must be competent to provide informed consent. Individual centres obtain valid written informed consent in accordance with local authority regarding ethical conduct of human research. Human research ethics approvals have been obtained at each participating site. In addition, Monash University ethics approval has been obtained to store the pooled database, perform analyses and subsequently publish the findings. The first patient was recruited into the APLC cohort in November 2013 in Thailand, and recruitment is still ongoing.

Data collection

APLC investigators at participating sites collect data at patients' 3 to 6-monthly routine visits using a standardised case report form (CRF). Table 1 summarises the data items collected at recruitment (baseline), at subsequent routine follow-ups and at annual visits. In brief, demographics and classification criteria (ACR (24) and SLICC (25)) are collected at baseline visit; variables related to organ damage accrual (SLICC-ACR Damage Index (SDI) (26)) and quality of life (SF36 version 2 (27)) are collected at baseline and annual visits, and data on disease activity (SLEDAI-2k (28)), flare index (29), Physician Global Assessment (PGA 0-3) (30), mortality, pathology and treatment (prednisolone, anti-malarial and immunosuppressant use) are captured at each visit (baseline/annual/routine visits).

Data transfer and data management

Since the commencement of the APLC cohort, de-identified data have been pooled twice into the centralised database. The first data pooling was carried out in August 2015 (baseline visits only) and the next data pooling was carried out in January 2017, which included baseline and all follow-up visits up to December 2016 (Table 2). During the time period between the two data transfers, most sites have recruited additional patients. New centres have recently joined the APLC and have yet to commence patient recruitment (Figure 1). The number of patients included in analyses in such studies is often less than the number of enrolled patients due to data cleaning stringency.

The pooled APLC cohort database is managed by investigators at Monash University on behalf of the APLC, in accordance with the operating principles and technical standards for Australian clinical quality registries published by the Australian Commission on Safety and Quality in Healthcare (31). The pooled database is stored in Monash University's secure file servers, which are backed up nightly, and access is limited to the APLC Data Manager.

Data access and research release

Access to APLC pooled data is subject to the specific access guidelines outlined in the APLC Data Access Policy (provided upon request). We welcome requests for aggregate (summary) data or to perform analyses of new research questions, and such requests can be submitted to the APLC steering committee via Data Manager.

RESULTS

To date, the APLC cohort comprises 2160 patients with >12,000 visits from 14 centres in 10 countries (Table 2). Baseline characteristics of these patients are summarised in Table 3. In brief, 93% of the APLC cohort is female with a median age ([inter-quartile range (IQR)] (range)) of 40 years ([31, 51] (18, 77)). The majority of APLC patients are of Asian ethnicity, predominantly Chinese (49%) followed by Thai (16%). Approximately 8% were of Caucasian ethnicity. About 8% had a family history of lupus, and the majority (45%) had a post-secondary education level. Approximately 78% of patients were on prednisolone, 69% were on anti-malarials and 50% were on immunosuppressants at recruitment. About 45% were in LLDAS at recruitment (Table 3).

Two papers have been published based on the baseline data pooled in 2015, in which we examined the frequency and predictors of LLDAS (32), and its association with HRQoL (33) using cross-sectional analyses (<https://www.asiapacificlupus.com/publications>). In brief, we observed that patients with shorter disease duration, a history of cutaneous and/or renal disease, elevated anti-dsDNA or hypocomplementaemia were less likely to be in LLDAS. When countries were compared, LLDAS was positively associated with higher national social wealth as measured by the Gross Domestic Product per capita, but not with any particular ethnic group(s) (32). We also found that patients who were in LLDAS at baseline had significantly better HRQoL measured in terms of Physical and Mental Component Summary scores (PCS and MCS, both with p-values less than 0.001) and in multiple individual SF-36 domain scores, when compared to those who were not in LLDAS (33).

The current patient cohort has a median length of follow up of two years. Patients from this cohort with multiple visits will be used to conduct the first ever prospective validation of LLDAS.

DISCUSSION

Within a short period, the APLC has established the largest cohort of SLE patients in the Asia Pacific region, and one of the largest contemporary cohorts of SLE patients under study worldwide. Several high-quality lupus cohorts exist, but they are predominantly in Western countries and include historical data going back up to 20 years. The Toronto Lupus Cohort in Canada, and the Hopkins lupus cohort in USA, are two of the longest running single centre cohorts, which have close to 2,000 patients each with a mixture of long-standing and new patients who are being followed up on annual basis (34) (35).. The LUMINA (**L**upus in **M**inorities: **N**ature vs. **N**urture) cohort and the Euro-lupus project are both large multisite multinational cohorts, however both lack significant representation of Asians (36) (37). The SLICC inception cohort has >1700 patients and includes almost 16% patients of Asian ethnicity, with longitudinal collection of data for patients recruited from 2000 to 2011 from 31 centres in 11 countries in North America, Latin America, Europe and Asia (38). However, this cohort has data collected at annual visits only (38), which does not capture the fluctuating natural history of SLE disease activity. The APLC cohort is the only large multicentre cohort with a significant proportion of Asian SLE patients, and which has frequently captured extensive data on disease activity, medication exposure and laboratory results, which makes it one of the most well described SLE cohorts in the world.

Data collected in the course of the APLC LLDAS validation study will represent a unique resource for future research. In the long term, data from the APLC will be used to evaluate other endpoint definitions, such as the DORIS remission definitions (39). It is essential for remission definitions adopted to be clearly distinguished from LLDAS in both attainability and outcome (40). We intend to soon analyse the results of prospective evaluation of LLDAS and its association with damage accrual, as well as a rigorous evaluation of existing and proposed remission definitions in comparison to LLDAS. We also plan to study quality of care by identifying gaps in best practice and benchmarking performance, and to evaluate with considerable power associations of outcome with various clinical manifestations and treatment.

One of the drawbacks of the APLC is that it is still a young cohort with a relatively short follow up period. Since protection against organ damage accrual is the main outcome measure in the LLDAS validation study, it is preferable to have longer follow up. The APLC cohort is now in the process of extension (continuing data collection of existing patients) and expansion (recruiting new patients). Additionally, the accessibility of health care by SLE patients varies greatly across countries and this could also be a limitation of studies of the APLC cohort, but such is the case with any international cohort. The national wealth of each country has been used as a surrogate variable to account for broad differences in socioeconomic status. The APLC cohort also provides a platform to formally identify how outcomes differ among countries with different health systems. Comorbidities are not captured in the current data collection, but the APLC intends to incorporate this data capture in the near future using an online database for global data capture.

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CONFLICT OF INTEREST

None

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Table 1 – Data items collected in the APLC cohort

Measures	Baseline (recruitment)	Routine Follow ups	Annual Visits
Visit date	✓	✓	✓
<u>Demographics</u>	✓		
Date of Birth			
Gender			
Ethnicity			
Year of SLE onset			
Year of Diagnosis			
Smoking at recruitment			
Family History of SLE			
Educational Level			
<u>Diagnosis Criteria</u>	✓		
ACR criteria			
SLICC Classification criteria			
<u>Pathology Data</u>	✓	✓	✓
Creatinine			
eGFR			
Albumin			
CRP			
C3			
C4			
Urine Protein/creatinine ratio			
Haemoglobin			
White Cell Count (WCC)			
Platelet			
Neutrophils			
Lymphocytes			

ESR			
Anti-dsDNA			
Urine WBC			
Urine RBC			
<u>Medication types and doses</u>	✓	✓	✓
Prednisolone			
Hydroxychloroquine/Chloroquine			
Methotrexate			
Azathioprine			
Mycophenolate mofetil			
Mycophenolic acid			
Leflunomide			
Cyclosporin			
Tacrolimus			
Mizoribine			
Cyclophosphamide			
Rituximab			
Belimumab			
Physician Global Assessment (PGA)	✓	✓	✓
SLE Disease Activity Index – 2k (SLEDAI – 2k)	✓	✓	✓
Mild/Moderate Flare Index	✓	✓	✓
Severe Flare Index	✓	✓	✓
SLICC Damage Index	✓		✓
SF-36v2 (Health Related Quality of Life survey)	✓		✓
Death	✓	✓	✓

Table 2 – Number of patients and visits in 2015 and 2017 APLC cohort databases

	2015 Dataset	2017 Dataset	
	No. of patients & visits	No. of Patients	Visits
Royal Adelaide H./Flinders Medical Centre, SA, Australia	33	44	170
Monash H./Uni., VIC, Australia	169	189	1,576
Liverpool H., NSW, Australia	38	40	190
St. Vincent's H., VIC, Australia	0	58	176
Peking Uni. Health Science Center, Beijing, China	235	235	235†
The University of Hong Kong, Hong Kong	190	190	190†
Padjadjaran Uni., Indonesia	98	107	905
Tokyo Women's Medical Uni., Japan	0	97	461
Uni. Malaya, Malaysia	193	184	919
	124		
Uni. Santo Tomas H., Philippines		124	571
National University H., Singapore	179	201	1,570
	42		
Tan Tock Seng H., Singapore		54	387
	295		
Chang-Gung Memorial Hospital, Taiwan		300	2,373
Chiang Mai Uni., Thailand	250	337	3,419
Total	1846	2160	12762

†Baseline visits only

Table 3 – APLC participant characteristics reported at recruitment (2017 dataset)

	Descriptive Statistics
	Total = 2160
Demographics	n (%)
Age at enrolment (years), <i>median [IQR](range)</i>	40 [31, 51] (18, 77)
Age at diagnosis (years), <i>median [IQR](range)</i>	29 [21, 39] (1, 74)
Female	2007 (93%)
Family history of SLE ¹	143 (8%)
Current smoker at baseline ²	91 (5%)
country	
Australia	331 (15%)
China	235 (11%)
Hong Kong	190 (9%)
Indonesia	107 (5%)
Japan	97 (4%)
Malaysia	184 (8%)
Philippines	124 (6%)
Singapore	255 (12%)
Taiwan	300 (14%)
Thailand	337 (16%)
Ethnicity	
Caucasian	178 (8%)
Chinese	1051 (49%)
Filipino	136 (6%)
Indonesian	111 (5%)
Japanese	97 (4%)
Malay	101 (5%)
Other	40 (2%)
South Asians	70 (3%)
Thai	345 (16%)
Vietnamese/Cambodian	31 (1%)

Education level ³	
Primary	308 (16%)
Secondary	750 (39%)
Tertiary	881 (45%)
Diagnosis Criteria	
ACR criteria fulfilled	2024 (94%)
SLICC Classification criteria fulfilled ⁴	1947 (99%)
Medications at baseline	
Prednisolone	1687 (78%)
Prednisolone dose (mg), <i>median [IQR](range)</i>	5 [2, 10] (0, 200)
Anti-malarials ⁵	1493 (69%)
Immunosuppressants ⁶	1072 (50%)
Clinical indications at baseline	
PGA, <i>median [IQR](range)</i>	0.5 [0.3, 1] (0, 3)
SLEDAI-2k, <i>median [IQR](range)</i>	4 [2, 6] (0, 40)
SLICC SDI score, <i>median [IQR](range)</i>	0 [0, 1] (0, 13)
Mild/moderate/severe flare	293 (14%)
Active disease (SLEDAI-2k>4)	677 (31%)
Active disease without serology (SLEDAI-2k>4 no serology)	330 (15%)
Organ damage (SLICC SDI>0)	837 (39%)
in Lupus Low Disease Activity State (LLDAS)	962 (45%)
SF-36 survey ⁷	
Physical Component Score, <i>median [IQR](range)</i>	50 [42, 55] (15, 69)
Mental Component Score, <i>median [IQR](range)</i>	49 [41, 54] (7, 71)

Data missing for ¹161, ²378, ³221, ⁴190 and ⁷443 patients.

⁵Anti-malarials include hydroxychloroquine and chloroquine

⁶Immunosuppressants include methotrexate, azathioprine, mycophenolate, mycophenolic acid, leflunomide, cyclosporine, tacrolimus, mizoribine, rituximab & belimumab

IQR = inter-quartile range

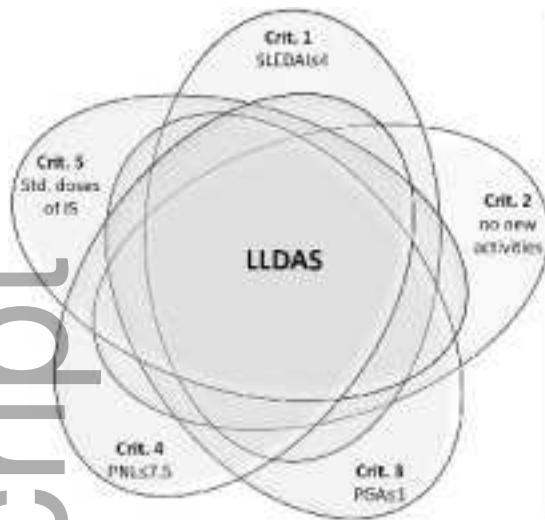
Figure Legends

Figure 1 – Asia Pacific Lupus Collaboration Sites; new sites are in *italic*

Figure 2 – Consensus Definition of Lupus Low Disease Activity State (LLDAS)



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LLDAS Criteria

Criterion 1: SLE Disease Activity Index (SLEDAI-2K) ≤ 4, with no SLEDAI activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, hemolytic anaemia, fever) and no gastrointestinal activity

Criterion 2: No new features of lupus disease activity compared to the previous assessment

Criterion 3: A Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) - SLEDAI Physician Global Assessment (PGA, scale 0-3) ≤ 1

Criterion 4: Current prednisolone (or equivalent) dose ≤ 7.5 mg daily

Criterion 5: Well-tolerated standard maintenance doses of immunosuppressive drugs (IS) and/or approved biologic agents, excluding investigational drugs

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