Prevention and management of co-morbidities in SLE

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Mortality in systemic lupus erythematosus (SLE) patients has a bimodal pattern with early demise being most commonly from disease activity and infections and later demise from cardiovascular disease [1]. Survival in SLE, though, has not improved since the 1980s [2]. The importance of co-morbidities related to both SLE itself and its treatment has now emerged. These include hypertension, hyperlipidemia, obesity and smoking (all of which contribute to atherosclerosis) as well as osteoporosis and malignancy. In addition, patients with SLE have an increased prevalence of fibromyalgia and fatigue, which interferes with the quality of life.

In this article, we will review the above co-morbidities. We will elucidate strategies to timely identify and aggressively treat them, and where possible, prevent them.

Cardiovascular disease

Magder and Petri found a 2.66-fold increased risk of cardiovascular disease in the Hopkins Lupus Cohort, as compared to Framingham controls [3]. A higher risk, five-fold, in the 35 to 44-year age group was found, confirming an earlier study by Manzi et al. [4]. In the Nurses Health Study, Hak et al. found a more than two-fold increase in cardiovascular disease in women with SLE, as compared to the general population [5]. Esdaile et al. found that the risk could not be explained by traditional risk factors alone [6]. However, Magder and Petri proved that traditional cardiovascular risk factors do independently increase the risk of cardiovascular events in SLE [3].
Smoking

Data
Smoking is an environmental trigger for SLE [7,8], it may increase disease activity in lupus, and it interferes with the action of antimalarial drugs [8–10]. Smokers with SLE have a three-fold increase in the risk of cardiovascular events as compared to non-smokers with SLE [11,12]. In the PROFILE cohort of 1339 SLE patients, cigarette smoking was significantly associated with a shorter time to a cardiovascular event (HR = 2.20, 95% CI 1.40–3.46) [13]. Smoking also contributes to progression of coronary artery calcium in SLE [14].

Targeting smoking
Because nicotine addiction is a product of behavior and psychological dependence on nicotine, counseling and nicotine replacement therapy together are recommended in current guidelines [15,16]. Randomized controlled trials have shown a two-fold increase in quit rates with use of nicotine replacement therapy as compared to placebo, but no data are available comparing different routes of nicotine replacement [15,16]. Nicotine replacement therapy can also be used safely in patients with known cardiovascular disease [17–19]. Other cessation treatments included bupropion with a quit rate of 21–34% [15]. In a recent meta-analysis, varenicline had an odds ratio of 2.88 compared to placebo, 1.57 compared to single forms of nicotine replacement therapy and 1.59 compared to bupropion, in quit rate [20]. No studies of smoking cessation have been done in SLE, however.

Obesity

Data
Obesity is a modifiable risk factor contributing to an increased risk of cardiovascular disease in the general population. Petri et al. proved the association of weight gain in SLE with prednisone. A 10 mg increase in prednisone led to a 5.50 ± 1.23 lb weight gain in 3 months [21]. In Magder and Petri, there was an increasing relative risk of cardiovascular events with increase in body mass index from less than 20 to more than 30, but this did not meet statistical significance (relative risk 1 with body mass index less than 20, to 2.09 for body mass index more than 30 [95% CI 0.83 –5.25]) [3]. Obesity is also associated with subclinical measures of atherosclerosis in SLE. A pediatric SLE study found an increased carotid intima thickness with obesity [22]. Kiani et al. showed an increased association of obesity in adults with both coronary calcium and non-calcified coronary plaque [14,23].

Targeting obesity
The American Heart Association recommends a low calorie diet and aerobic exercise to lose weight. They recommend a deficit of 500 calories daily along with two and a half hours of moderate intensity aerobic exercise every week. This regimen should lead to a one pound weight loss every week [24]. No studies of weight reduction in SLE have been done.

Hypertension

Data
Magder and Petri described a statistically significant rate ratio for cardiovascular events of 1.26 for every 10 mmHg increase in systolic blood pressure above 120 mmHg [3]. Hypertension is also associated with multiple measures of subclinical atherosclerosis in SLE. Hypertension was found to cause progression of carotid intima medial thickness over a period of two years and also poor renal outcomes [14,25]. Maksimowicz-McKinnon et al. showed an increased association of carotid plaque with hypertension (age-adjusted risk 18% vs 8%; P = 0.00010) and with systolic blood pressure more than 140 mmHg (age-adjusted risk 23% vs 13%; P = 0.028) [26]. Hypertension (P = 0.04) was also found to be associated with semi-quantified coronary non-calcified plaque in SLE [23].

Targeting hypertension
Guidelines recommend a target blood pressure of less than 130/80 mmHg for patients with co-morbidities, including diabetes mellitus, chronic kidney disease and congestive heart failure (American Society of Hypertension [2008], American Diabetes Association [2005], National Kidney Foundation [2004] and Joint National Commission 7 [2003]). More recently, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study did not prove any benefit in decreasing cardiovascular events in diabetic patients with a blood pressure target of less than 120 mmHg as compared to more than 130 mmHg [27]. However, in the Hopkins Lupus Cohort, an increase in cardiovascular events was seen with elevation in blood pressure above a level of 120/80 mmHg. We, therefore, recommend a goal of less than 120 mmHg systolic in SLE patients with hypertension [3]. The seventh Joint National Commission recommended thiazide diuretics as the first line of therapy in the general population [28]. However, it is not proven that diuretics should be the first line in SLE. In particular, Ravenell et al. has shown that ACE non-use was associated with increased atherosclerotic plaque area in patients with SLE (likelihood ratio = 9.0, P = 0.02) [29]. We prefer ACE inhibitors as the first line agents in SLE patients, given their safety and additional beneficial role, beyond hypertension, in patients with lupus nephritis [28].

Diabetes mellitus

Data
In a study by Bruce et al., diabetes mellitus was more common in women with SLE as compared to controls [30]. Magder and Petri found a two-fold increase in risk of cardiovascular events in SLE patients with diabetes [3]. In the Hopkins Lupus Cohort, diabetes mellitus had a borderline association with the pre-
sence of carotid plaque (age-adjusted risk 19% vs 13%; \( P = 0.075 \)). Kiani et al. showed that diabetes mellitus was a significant independent predictor of coronary calcium score greater than 100 Agatson units [31].

**Targeting diabetes mellitus**

The American Diabetes Association updated guidelines in 2013 recommend a HbA1c level less than 7% to decrease the microvascular complications associated with diabetes. This goal is also found to be reasonable to decrease the macrovascular complications. A more liberal goal of less than 8% is acceptable for patients with severe hypoglycemia, less than expected life expectancy, or advanced microvascular and macrovascular complications [32].

Metformin is the first line of treatment in the absence of contraindications. In a meta-analysis of 6 studies, metformin was significantly associated with prolonging the onset of diabetes in prediabetes patients in 3 of 6 studies [33]. GLP1 analogues are recommended if noninsulin monotherapy at maximal dose fails to achieve the target A1c for 3 to 6 months. Insulin therapy is recommended at the outset in a newly diagnosed diabetes mellitus with severely symptomatic or uncontrolled blood sugars [32].

Hydroxychloroquine was shown to improve the glycemic control in sulphonylurea refractory type II diabetes mellitus patients [34]. Quatraro et al. showed that the addition of hydroxychloroquine to anti-diabetic therapy in refractory non-insulin dependent diabetes mellitus helped to control hyperglycemia [35]. In the Hopkins Lupus Cohort, patients using hydroxychloroquine had significantly lower levels of fasting blood glucose levels as compared to those not on it. Hydroxychloroquine is also associated with lower mean glucose and lower fasting insulin levels [21]. A healthy lifestyle, with weight loss and nutrition education, avoidance of corticosteroids, and use of steroid sparing agents should be implemented to avoid development and progression of diabetes in SLE.

**Hyperlipidemia**

**Data**

Cholesterol is a known risk factor for cardiovascular disease in SLE [36]. Even a 10 mg increase in prednisone increases total cholesterol [21]. Magder and Petri showed that increasing cholesterol levels were significantly associated with cardiovascular events (relative risk of 8.22, 95% CI 3.10–21.79, \( P < 0.0001 \)) with total cholesterol more than or equal to 250 mg/dL [3].

**Targeting hyperlipidemia**

SLE is a diabetes equivalent and hence, the goal of treatment can be a LDL less than 100 mg/dL, as per the NCEP ATP III guidelines. NCEP ATP IV recommends the goal of LDL less than 100 mg/dL for diabetes mellitus patients with no other major risk factors for cardiovascular disease, such as smoking, hypertension or history of premature coronary artery disease. The recommended goal for LDL is less than 70 mg/dL for diabetes mellitus patients with one or more major risk factors. NCEP ATP IV does not recommend addition of fibrate or niacin to statins for lowering LDL levels, as they have not been found to reduce cardiovascular events [37]. The same guidelines recommend both therapeutic lifestyle changes and medications for patients with coronary heart disease equivalent conditions. Statins are the first agent of choice in dyslipidemia [37]. However, in the two-year clinical trial in adult SLE patients, atorvastatin did not prevent progression of coronary artery calcium, carotid intima media thickness or carotid plaque [38]. Similar negative results with atorvastatin and progression of carotid intima thickness were replicated in pediatric SLE patients [22]. Even in mice with SLE, statins do not prevent progression of atherosclerosis [39]. However, statins should be used to reach the LDL goal in SLE patients with hyperlipidemia. We do not recommend the use of omega-3 fatty acids, given no proven clinical benefit in preventing cardiovascular events, and the potential for omega-3 fatty acids to increase total and LDL cholesterol [40].

Hydroxychloroquine is known to have a favorable effect on the metabolic profile, including decreasing LDL, triglyceride and cholesterol levels. Petri et al. proved that hydroxychloroquine could balance the deleterious effect of 10 mg of prednisone on total cholesterol [21]. Cairoli et al. also demonstrated a significant decrease in total cholesterol (198 ± 33.7 vs 183 ± 30.3 mg/dL, \( P = 0.023 \)) and LDL levels (117 ± 31.3 vs 101 ± 26.2 mg/dL, \( P = 0.023 \)) with three months of hydroxychloroquine use [41].

**Homocysteine**

**Data**

In the Hopkins Lupus Cohort, elevated homocysteine levels were associated with stroke (2.44 [1.04–5.75], \( P = 0.04 \)) and arterial thrombosis (3.49 [0.97–12.54], \( P = 0.05 \)) [42]. Finjheer et al. found elevated homocysteine levels in patients with SLE and arterial thrombosis as compared to those without thrombotic events (20.6 ± 10.2 vs 13.2 ± 6.8 μmol/L; \( P < 0.001 \)). This was most noticeable in patients with renal failure [43]. Homocysteine was significantly associated with non-calciﬁed plaque in SLE in an univariate analysis by Kiani et al. (\( P = 0.05 \)) [44].

**Targeting homocysteine**

Clinical trials in the general population have not shown any clinical beneﬁt with treatment of hyperhomocysteinemia with folic acid, vitamin B6 and vitamin B12 [45,46]. However, clinical trials in SLE are not available.

**Disease activity**

Magder and Petri showed that disease activity (measured by SELENA-SLEDAI) was associated with an increased risk of
cardiovascular events in SLE [3]. Kiani et al. found that non-calcified plaque was significantly associated with current, three and six month Physician’s Global Assessment of activity [23]. There was no association between disease activity and cardiovascular events in the LUMINA cohort [11].

Corticosteroid use

Data

In a necropsy study of 36 SLE patients, Bulkley and Roberts showed that systemic hypertension, left ventricular hypertrophy, atherosclerotic plaques, congestive heart failure, epicardial and myocardial fat were increased in patients treated with corticosteroids [47]. Corticosteroid use has been shown to increase cardiovascular events by Magder and Petri. Doses of prednisone more than 10 mg per day were associated with a two-fold increased risk and more than 20 mg with a five-fold increased risk. This remained true after adjusting for disease activity [3]. Wei et al. found a 2.56-fold increase in risk of cardiovascular events with a prednisone dose of 7.5 mg or more [48]. In the Hopkins Lupus Cohort, an increase in prednisone dose of 10 mg caused an increase in cholesterol of 7.5 mg/dl, weight change of 5.5 lbs and change in blood pressure of 1.1 mmHg [49].

Targeting corticosteroid use

The FLOAT trial compared the use of oral tapering methylprednisolone and intramuscular triamcinolone 100 mg in 50 SLE patients with mild to moderate flare. Complete improvement occurred in 37.4% (triamcinolone group) versus 25% (methylprednisolone group) at the end of 4 weeks. There may be a more rapid response to intramuscular triamcinolone 100 mg as compared to methylprednisolone (69.5% vs 41.6% with some improvement at day one). Thus, triamcinolone 100 mg intramuscularly is used at the Hopkins Lupus Center for mild to moderate flares, to avoid long-term commitment to a higher oral prednisone dose [50].

Antiphospholipid antibodies

Data

Gustafsson et al. showed that any antiphospholipid antibody and anti-beta 2 glycoprotein 1 in a medium titer were associated with cardiovascular mortality in the Swedish cohort [51]. In the LUMINA cohort, any antiphospholipid antibody was associated with vascular events [11]. Magder and Petri found that the lupus anticoagulant was associated with higher rates of cardiovascular events in SLE [3]. Kiani et al. reported that anticardiolipin was associated with higher coronary non-calcified plaque in the Hopkins Lupus Cohort [23]. Roman et al. found no statistically significant association of antiphospholipid antibodies and carotid atherosclerotic plaque [52].

Targeting antiphospholipid antibodies

The role of hydroxychloroquine in preventing thrombosis in SLE with and without antiphospholipid antibodies is well documented [53–57]. Hydroxychloroquine is associated with a decrease in the risk of thrombosis and improved survival in SLE patients [55,58]. This effect is thought to be from the action of hydroxychloroquine in inhibiting platelet aggregation and decreasing binding of anti-beta 2 glycoprotein 1 to phospholipid layers [59,60]. Erkan et al. showed a decreased probability of a thrombotic event with the use of hydroxychloroquine or aspirin in a chart review of antiphospholipid syndrome patients [61]. However, two trials of aspirin therapy have failed to show any benefit [62,63].

Vitamin D deficiency

Data

Women with SLE are known to have a higher incidence of vitamin D deficiency [64–66]. SLE patients are at an increased risk of vitamin D deficiency due to photosensitivity leading to avoidance of sun exposure, use of sunscreens, renal disease and medication use (most commonly being glucocorticoids). Kamen et al. found lower levels of vitamin D in recently diagnosed SLE patients as compared to controls. Risk factors for significantly lower vitamin D levels were African American ethnicity, winter months more than summer months, increasing age and increased number of cigarettes smoked. There was a statistically significant association between low vitamin D levels and photosensitivity (OR 12.9, 95% CI 2.2–75.5, P < 0.01) and renal disease (OR 13.3, 95% CI 2.3–76.7, P < 0.01) [67]. There is disagreement on whether low vitamin D is or is not associated with disease activity in SLE [68–73]. Ravenell et al. showed that low vitamin levels were associated with increased total carotid plaque area in atherosclerosis [29].

Targeting Vitamin D

Vitamin D replacement is recommended in all SLE patients who are deficient. The effect of vitamin D supplementation on disease activity was studied by Petri et al., who found a statistically significant decrease in the mean level of the physiologic global assessment score of 0.04 (95% CI –0.08, –0.01) (P = 0.026). There was also a decrease in the mean SELENA-SLEDAI of 0.22 (95% CI –0.41, –0.02) (P = 0.032). In the same study, a decrease in proteinuria was found with a 2% decrease in urine protein:creatinine ratio (95% CI –0.03, –0.01) (P < 0.0001) with a 20 ng/mL increase in vitamin D levels. When this association was adjusted for angiotensin-converting enzyme inhibitors and immunosuppressant medications, a 4% decrease in urine protein:creatinine ratio was found (95% CI 2, 5). Overall, this improvement was clinically modest [74]. A randomized clinical trial by Abou-Raya et al. showed statistically significant impro-
Osteoporosis

Data

SLE patients are at risk of osteoporosis and subsequent fractures from the disease itself and its treatment with glucocorticoids. Osteopenia is seen in 25–75% patients with SLE [77,78], with osteoporosis in 1.4 to 68% [79,80]. Tang et al. recently showed that disease activity in SLE was associated with deterioration in bone structure, cortical microstructure and bone strength [81]. Risk factors for bone loss in SLE are traditional and SLE-related. The traditional risk factors include age, low body weight, low body mass index and postmenopausal status [82,83]. SLE-related risk factors include chronic inflammation, as demonstrated by increased levels of TNF-alpha and RANK L, which can affect osteoclast maturation and activity [84]. In 107 SLE patients, Bultink et al. reported vertebral fractures in male patients with intravenous methylprednisolone use [85]. In the Hopkins Lupus Cohort, low C4 was associated with low spine bone mineral density [86]. Smoking, not found to be a risk factor for osteoporotic fractures in some studies, was associated in the Hopkins Lupus Cohort [82,85,86]. Renal failure, lupus anticoagulant and Raynaud’s phenomenon are other potential risk factors [86]. Secondary osteoporosis in SLE most commonly occurs with glucocorticoid use. LoCascio et al. showed that in patients (not SLE) receiving glucocorticoids, bone loss was most prominent in the first year of use (6–12%) as compared to 3% every year after that. It occurred predominantly in the lumbar spine and proximal femur [87]. Van Staa et al. found that the daily dose of glucocorticoids, not the cumulative dose, was associated with an increased risk of vertebral fractures [88]. Among studies in SLE patients, Zonana-Nacach et al. found that for every 36.5 mg of glucocorticoids, the risk of osteoporosis increased 1.9-fold [89].

Targeting osteoporosis

In the general population, the American Association of Clinical Endocrinologists recommends both non-pharmacologic and pharmacologic treatment for osteoporosis. The non-pharmacologic treatment includes adequate calcium and vitamin D supplementation, avoiding alcohol intake more than 2 drinks per day, limiting caffeine intake, avoid/stop smoking, weight bearing exercise for at least 30 minutes daily, adequate protein intake, use of hip protectors in patients at risk of falls and physical/occupational therapy to reduce risk of falling. Pharmacologic therapy is recommended in those with a history of fracture of hip/spine, those with a T-score of −2.5 or below and history of fractures and those with T-score between −1.0 and −2.5, if the FRAX major probability is more than 20%. They recommend alendronate, risedronate, zoledronic acid and denosumab as the first line therapy for treatment of osteoporosis. Ibandonate is recommended as a second line, while raloxifene is a second/third line agent. Calcitonin is recommended as the last line of therapy. Teriparatide is recommended in patients with very high fracture risk, in whom bisphosphonate therapy has failed.

For patients on bisphosphonates, the association recommends a drug holiday after 4 to 5 years in cases of mild osteoporosis. If fracture risk is high, a drug holiday of 1 to 2 years after 10 years of treatment is recommended. They also recommend re-initiating therapy during the drug holiday if bone mineral density worsens or fracture occurs [90].

For glucocorticoid-induced osteoporosis, along with the non-pharmacologic measures, the American College of Rheumatology recommends treatment with bisphosphonates in patients receiving prednisone equivalent doses of 7.5 mg/day or more for at least three months. They also take into consideration the FRAX algorithm to decide bone mineral density threshold [91]. However, because most women with SLE are pre-menopausal, bisphosphonates should not be used if a future pregnancy is planned. Hormone replacement therapy should be avoided in postmenopausal women with SLE, as it is associated with an increase in mild to moderate lupus flares of 20% [92]. Hormone therapy and SERMS would also be avoided in women with SLE and antiphospholipid antibodies.

Malignancy

Data

Studies have shown an increase in risk of overall malignancy in SLE as compared to the general population. This is most distinctly seen with hematological malignancies. Bernatsky et al. showed an increased risk of non-Hodgkin’s lymphoma in SLE. In the most updated study, the standardized incidence ratio was 3.02 [93]. Diffuse large B-cell lymphoma was the most common subtype seen in SLE [94–98]. The association of cancer development in SLE after immuno-suppressive use was studied by the Systemic Lupus International Collaborating Clinics group. They reported an adjusted drug specific hazard ratio after cyclophosphamide of 3.55 (95% CI 0.94–13.3), after azathioprine of 1.02 (95% CI 0.34–3.03) and after methotrexate of 2.57 (95% CI 0.80–8.27). These elevations in risk estimates were not statistically significant. There was an observed increase in non-Hodgkin’s lymphoma with greater exposure to cyclophosphamide (adjusted HR 2.80, 95% CI 0.87–8.98) and cumulative corticosteroids (adjusted HR 2.57, 95% CI 0.94–7.04) in a recent updated study by the same group, but none of these point estimates met statistical significance [93].
There may also be an increase in association of lung cancer, hepatocellular cancer, and genital cancer in SLE, as shown by various observational studies [99–102]. For Tam et al., SLE led to a six-fold increase in the prevalence of squamous intraepithelial lesions as compared to the general population. Women with SLE also had an impaired clearance of human papilloma virus [103,104]. An increase in human papilloma virus associated cancers (anai, vaginal, vulva and carcinoma in situ of cervix) was reported by Dreyer et al. [105]. An increased risk of cervical dysplasia was found from increased use of immuno-suppressive drugs in SLE by Bernatsky et al. This might be explained by impaired eradication of human papilloma virus in women with SLE [104].

**Targeting malignancy**

It is imperative that women with SLE remain up to date with Papanicolou smears. Routine screening for cancer would follow existing guidelines. For cervical cancer, screening should begin at age 21 followed by a Papanicolou test every three years until age 29. Women between the age of 30 to 65 should undergo “co-testing”, consisting of the Papanicolou test and human papilloma virus test every 5 years. After 65 years of age, no testing is recommended if the regular Papanicolou tests were normal. A woman vaccinated against human papilloma virus should still follow screening recommendations for her age [106].

**Fibromyalgia**

**Data**

Fibromyalgia is a chronic pain sensitization syndrome. Staud et al. found abnormalities in central nociceptive processing in fibromyalgia [107]. Functional brain MRI studies found an increase in regional central blood flow in the contralateral caudate and bilateral thalamus [108]. Jolly et al. reported that health related quality of life in SLE was statistically significantly worse in all eight domains as compared to the general population [109]. Patients with SLE consistently reported lower scores on SF-36 as compared to the general population [110]. In a meta-analysis by McElhone et al., health related quality of life was found to be inferior in patients with SLE, irrespective of the instrument used, as compared to the general population. Various studies have shown either no association or a weak association of SLE disease activity and health related quality of life [111]. Kuriya et al. showed that fibromyalgia, but not steroids, disease activity or damage, affected the SF-36 in 146 SLE patients followed over 1047 visits [112]. Kiani et al. concluded that fibromyalgia and not disease activity was associated with poorer health related quality of life in many domains of the SF-36 [110].

**Targeting fibromyalgia**

Duloxetine, pregabalin and milnacipran are approved by the United States Food and Drug Administration for the treatment of fibromyalgia. Both initial randomized control trials and extension studies have demonstrated long-term efficacy and tolerability of these medications. Amitriptyline also has benefited for fibromyalgia. A meta-analysis by Hauser et al. concluded that amitriptyline in a dose of 10–50 mg/d was superior to duloxetine or milnacipran in helping sleep, fatigue, pain and quality of life associated with fibromyalgia [113]. Wasserman et al. showed that patients taking opioids with a centralized pain syndrome reported severe pain while on opioids (P = 0.001). Interestingly, in this study of 582 patients, only 3.2% were given a diagnosis of fibromyalgia by their primary physician, while 40.8% met the American College of Rheumatology survey criteria [114]. In a meta-analysis by Wiffen et al., lamotrigine 200–400 mg daily was not found to be effective in treating fibromyalgia [115]. Kim et al. found that low to moderate alcohol consumption was associated with better quality of life and lower fibromyalgia symptoms. These patients were found to have a higher education, lower unemployment, lower body mass index and lower opioid use [116]. In 188 patients with fibromyalgia, patients receiving sodium oxybate reported improvement in pain visual assessment scores; Jenkins Sleep Scale outcome measures, fatigue and stiffness [117]. Wang et al. reported statistically significant improvement with Tai Chi stretching in the Fibromyalgia Impact Questionnaire score and quality of life in fibromyalgia patients as compared to controls [118]. In a randomized double blind, placebo-controlled trial of naltrexone in 31 women with fibromyalgia, there was a significant reduction in pain (28.8% reduction with naltrexone; P = 0.016), improved general satisfaction with life (P = 0.045) and improved mood (P = 0.039). There was no improvement in fatigue or sleep [119].

**Conclusion**

With better survival of SLE patients, attention has now turned to better management of the co-morbidities associated with SLE itself and with its treatment. Although usually not thought of as “co-morbidity”, quality of life issues related to fatigue and fibromyalgia also need to be addressed with new and better therapeutic options.

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References


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