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ORIGINAL ARTICLE

Anti-Müllerian hormone serum levels in systemic lupus erythematosus patients: Influence of the disease severity and therapy on the ovarian reserve

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Abstract

Purpose Systemic lupus erythematosus (SLE) mainly affects childbearing age women and pharmacological treatments may negatively influence the ovarian reserve. Anti-Müllerian hormone (AMH) could be a good biomarker for ovarian reserve.

Methods AMH serum levels were assessed in 86 consecutive SLE female patients with regular menstrual cycle compared with 44 aged matched healthy controls. Clinical and demographic characteristics, disease duration, pattern of organ involvement, and previous and current therapies were recorded.

Results AMH levels were comparable between patients and controls (4.2 ± 3.1 ng/ml vs. 5.0 ± 3.1 ng/ml, $p = 0.21$). According to disease severity, AMH levels were lower in SLE patients with major organ involvement than in controls (3.8 ± 2.7 ng/ml vs. 5.0 ± 3.1 ng/ml, $p = 0.08$); no difference was found between SLE patients with mild organ involvement (4.5 ± 3.4 ng/ml) and controls ($p = 0.43$). Grouping patients based on the pharmacological treatments, AMH serum levels did not differ among SLE patients treated with antimalarials only (4.7 ± 3.3 ng/ml), conventional disease-modifying antirheumatic drugs (cDMARDs) only (4.8 ± 3.2 ng/ml), cDMARDs and antimalarials (3.9 ± 2.9 ng/ml) or cyclophosphamide (CYC) only (4.9 ± 3.9 ng/ml), compared to controls, but patients sequentially treated with cDMARDs and CYC, had significantly lower AMH serum levels than controls ($p = 0.01$).

Conclusions SLE patients showed comparable AMH levels than controls, however, a reduction of the ovarian reserve was associated with sequentially therapy with CYC and cDMARDs and with the disease severity. AMH could be a sensitive and specific biomarker of ovarian reserve in SLE and it could be useful for therapeutic strategy and family planning.

Keywords Systemic lupus erythematosus · Anti-Müllerian hormone · Infertility · Therapy

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that predominantly affects women of reproductive age. The prevalence of infertility in SLE patients is similar than the average population rate [1]. However, epidemiological studies reported that among the

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estimated 9% of women suffering from infertility worldwide [2], SLE contributes nearly 10% of infertile patients. Considering that the incidence of SLE is 1:2000 in adult women these data suggest that SLE per se may influence the rate of fertility [3, 4]. In SLE patients, fertility can be affected by disease activity, disease severity, and pharmacological treatments such as the prolonged immunosuppressive therapy [5], generally used in SLE patients with severe and/or refractory clinical manifestations [6, 7]. In particular, autoimmune mechanisms were involved in reducing the ovarian reserve being an important cause of premature ovarian failure (POF) [8, 9] as shown by the detection of anti-ovarian antibodies whose presence was found to be related with early ovarian aging [10]. As previously reported by Carp and colleagues, in SLE patients the ovarian function can be reduced by autoimmune oophoritis resulting in the reduction of specific ovarian reserve's hormones [11].

The ovarian reserve is represented by the quantity and quality of the ovarian follicle pool and declines with the age increase, resulting in the decrease of a woman's reproductive function [12]. There is appreciable individual variation in the age of menopause and in the age of subfertility [13], hence chronological age is not a good predictor of ovarian reserve. To date, there isn't a recognized marker directly related to the ovarian follicle pool. Some biological markers have been assessed to predict the ovarian reserve such as the measurement of serum levels of follicle stimulating hormone (FSH), inhibin B, estradiol, Anti-Mullerian hormone (AMH) and the measurement of the ovarian antral follicle count (AFC) by transvaginal ultrasound examination. These tests have limitations that include the lack of sensitivity and, in some cases, their dependency on cycle stage. Recently, the Practice Committee of the American Society for Reproductive Medicine reported that combined ovarian reserve test models do not consistently improve the predictive ability more than a single ovarian reserve test, and they conclude suggesting the use of AMH as a screening test for poor ovarian response [14].

Several studies demonstrated a good predictive value in estimating the ovarian reserve by AFC and AMH levels superior to FSH [15–17]. In particular, AMH is a growth and differentiation factor belonging to the transforming growth factor β-family, produced in the granulosa cells of pre-antral and small antral follicles [18]. In women, AMH serum levels are undetectable at birth reaching the maximum level after puberty and then progressively declining during reproductive life until AMH becomes undetectable when in menopause [19]. Moreover, AMH serum levels do not depend on menstrual cycle stage and do not fluctuate during the menstrual cycle [20, 21]. These features make AMH a good predictive biomarker of ovarian reserve overtime.

AMH has been studied in several populations of women exposed to chemotherapic drugs and data from oncology field showed that AMH serum levels decline during and after chemotherapy, suggesting that AMH is an early and sensitive serum marker of ovarian reserve damage [22, 23].

Recently, some studies investigated the significance of AMH as a predictor of ovarian reserve in SLE but they produced conflicting results [24–27].

The aims of our study were to assess AMH serum levels in a cohort of SLE women patients compared to healthy controls and to assess whether the disease per se, the pharmacological treatments and/or the disease severity may affect the ovarian reserve.

Patients and methods

Patients

Consecutive female patients fulfilling the American College of Rheumatology (ACR) classification criteria for SLE [28] were screened and enrolled in the study at the Lupus Clinic of the Division of Rheumatology of the Fondazione Policlinico Universitario "A. Gemelli"—I.R.C.C.S.—Università Cattolica del Sacro Cuore. SLE patients were considered eligible if they fulfilled the following criteria: age between 18–45 years old and regular menstrual cycles without diagnosis of ovarian failure. SLE patients were considered not eligible for the study if they were on treatment with cytotoxic therapy or radiation for cancer diseases, if they had a diagnosis of polycystic ovarian syndrome (PCOS) [29] ovarian surgery and ovarian cyst, or they were using oral contraceptives. Age-matched healthy controls were enrolled in a 2:1 ratio. Clinical and demographic characteristics, gynecological assessment, disease duration, pattern of organ involvement, and previous and current therapies for SLE were collected at the time of peripheral blood drawing.

Each SLE patient was tested for antinucler autoantibodies (ANA), anti-dsDNA, extractable nuclear antigen (ENA) antibodies, antiphospholipid antibodies (aPL), C3 and C4 complement components serum levels. The SLE Activity Index (SLEDAI) was used to evaluate disease activity [30].

Each patients was evaluated for previous and current therapies: prednisone, antimalarials (chloroquine and hydroxychloroquine), conventional disease-modifying antirheumatic drugs (cDMARDs, i.e., methotrexate, azathioprine, mycophenolate mofetil, and cyclosporine) and cyclophosphamide (CYC). For SLE patients treated with CYC, cumulative drug dose was recorded.

SLE patients were divided based on the organ involvement into patients with mild organ involvement (mainly

Table 1 Demographic and clinical characteristics of the SLE cohort

Variables	Controls	SLE patients	*p*	SLE patients with major organ involvement	SLE patients with minor organ involvement	*p*
N	44	86		41	45	
Age, years	31.1 ± 4.8	30.4 ± 6.3	*0.62*	30.4 ± 5.5	30.4 ± 7.0	*0.93*
Age at the SLE onset, years	-	22.5 ± 7.3	-	21.8 ± 6.5	23.2 ± 8.0	*0.43*
Disease duration, years	-	7.6 ± 5.9	-	8.5 ± 5.6	6.8 ± 5.9	*0.12*
BMI (Kg/m^2)	21.7 ± 2.7	22.3 ± 3.8	*0.51*	23.1 ± 4.0	21.7 ± 3.6	*0.08*
Smoking, n. (%)	15 (34.1)	27 (31.4)	*0.75*	12 (29.3)	15 (33.3)	*0.82*
APS n. (%)	-	9 (10.5)	-	5 (12.2)	4 (8.9)	*0.62*
aPL positivity, n. (%)	-	36 (42.0)	-	17(41.5)	19(42,2)	*0.91*
anti-dsDNA, n. (%)	-	38 (44.0)	-	23 (56.1)	30 (66.1)	*1.0*
AMH, ng/ml	5.0 ± 3.1	4.2 ± 3.1	0.21	3.8 ± 2.7	4.5 ± 3.4	0.49
C3, mg/dl	-	84.7 ± 24.1	-	85.4 ± 25.2	84.2 ± 23.2	*0.63*
C4, mg/dl	-	14.1 ± 7.4	-	14.6 ± 8.0	13.7 ± 6.8	*0.63*
ESR, mm/1st hour	-	22.0 ± 19.7	-	24.6 ± 21.7	19.8 ± 17.8	*0.19*
CRP, mg/l	-	3.1 ± 6.1	-	2.0 ± 2.2	4.0 ± 8.0	*0.38*
SLEDAI	-	3.2 ± 3.8	-	3.6 ± 4.4	2.9 ± 3.1	*0.80*
Renal involvement, n. (%)	-	34 (39.5)	-	34 (82.9)	-	-
Cutaneous involvement, n. (%)	-	56 (65.1)	-	29 (70.7)	27 (60.0)	*0.30*
Articular involvement, n. (%)	-	77 (89.5)	-	37 (90.2)	40 (88.9)	*0.84*
Hematologic involvement, n. (%)	-	60 (69.8)	-	24 (58.5)	36 (80.0)	*0.03*
Neurologic involvement, n. (%)	-	12 (14.0)	-	12 (29.3)	-	-
Major organ involvement, n. (%)	-	41 (47.7)	-	-	-	-
Minor organ involvement, n. (%)		45 (52.3)	-	-	-	-
Medications (previous or current)						
Antimalarials n. (%)	-	73 (84.9)	-	33 (80.5)	40 (88.9)	*0.28*
Azathioprine, n. (%)	-	28 (32.6)	-	20 (48.8)	8 (17.3)	*0.002*
CYC, n. (%)	-	14 (16.3)	-	13 (31.7)	1 (2.2)	*< 0.001*
MTX, n. (%)	-	16 (18.6)	-	8 (19.5)	8 (17.8)	*0.84*
MMF, n. (%)	-	29 (33.7)	-	24 (58.5)	5 (11.1)	*< 0.001*
Cyclosporine, n. (%)	-	13 (15.1)	-	11 (26.8)	2 (4.4)	*0.004*
Gynecological and obstetric data						
Age at menarche, years	12.2 ± 1.7	12.2 ± 1.2	*0.65*	12.3 ± 1.2	11.8 ± 1.2	*0.34*
Subjects with full-term pregnancy, n. (%)	9/42 (21.4)	19/83 (22.9)	*0.85*	10/40 (25.0)	9/43 (20.9)	*0.66*
Subjects with miscarriage, n. (%)	2/42 (4.8)	12/83 (14.5)	*0.14*	5/40 (12.5)	7/43 (16.3)	*0.63*

Values are mean ± SD unless otherwise indicated

SLE systemic lupus erythematosus, *BMI* body mass index, *APS* antiphospholipid syndrome, *ESR* erythrocyte sedimentation rate, *CRP* creactive protein, *SLEDAI* SLE disease activity index, *CYC* cyclophosphamide, *MTX* methotrexate, *MMF* mycophenolate mofetil, *AMH* Anti-Müllerian hormone

P value <0.05 was considered statistically significant

articular and/or cutaneous) and patients with severe organ involvement (mainly renal and neurological), respectively. Moreover, all participants filled out a questionnaire on lifestyle and obstetric data. Written informed consent was obtained before the inclusion from each study participant.

Determination of ovarian reserve: AMH assay

AMH serum levels were measured in duplicates in SLE patients and controls. Peripheral blood samples of SLE patients and controls were centrifuged at 300 × *g* for 15 min and serum samples were stored at –80 °C until assayed.

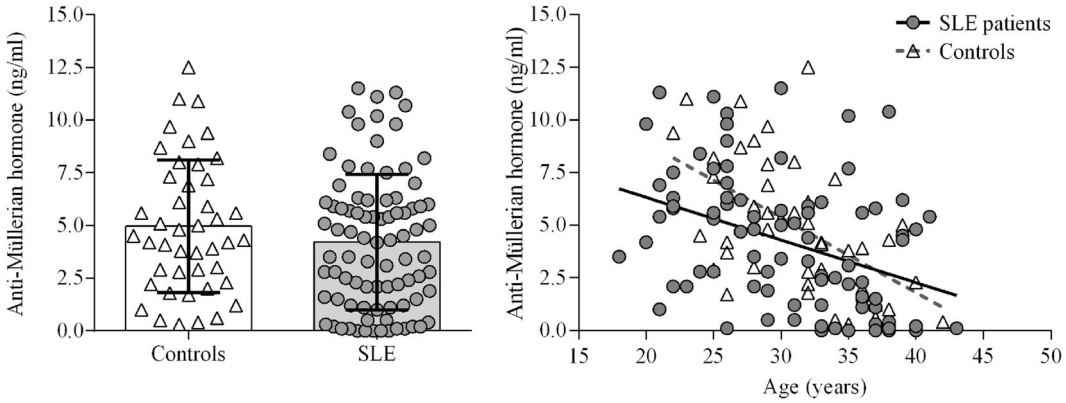

Fig. 1 **a**, **b** Serum levels of Anti-Müllerian hormone (AMH) in SLE patients. **a** AMH serum levels in 86 consecutive SLE patients and 44 healthy controls matched by age enrolled in the study. **b** Inverse correlation between current age and AMH serum concentration in the group of controls ($r = –0.56$; $p < 0.001$) and in the whole group of SLE patients ($r = –0.43$; $p < 0.001$, respectively)

Serum AMH levels were assayed according to a 2-stage enzyme-linked immunosorbent assay technique using a commercially kit (AMH Gen II ELISA, Beckman Coulter, Inc, Brea, CA, USA) according to the manufacturer's revised protocol [31]. The intra-assay CV (coefficient of variation) was 3.7% (at 3.8 ng/ml) and 3.4% (at 16.4 ng/ml). The inter-assay CV was 4.4% (at 3.8 ng/ml) and 3.4% (at 16.4 ng/ml). The assay range was 0.4–21 ng/ml and the sensitivity 0.08 ng/ml.

Statistical analysis

Data were analyzed using SPSS Statistics 22.0 (IBM, Armonk, NY, USA) and Prism software 5.0 (Graph-Pad, San Diego; CA 92121-USA). Categorical and quantitative variables were recorded as frequencies, percentage, mean ± standard deviation (SD). The non-parametric Mann–Whitney *U*-test was used to compare the continuous variables. Categorical variables were analyzed using χ^2 test or the Fisher's exact test. The Spearman rank correlation was used to evaluate the relationship between AMH serum levels and inflammatory and clinical parameters.

A multivariate logistic regression analysis, in which "AMH serum levels" were the dependent variables to be explained, was performed and results were expressed as Beta coefficient (standard error). *P*-values < 0.05 were considered statistically significant.

Results

Relationship between AMH levels and demographic and clinical parameters in a cohort of female SLE patients

Eighty-six consecutive SLE female patients and 44 female age-matched healthy controls were recruited. Table 1 summarizes the study population characteristics. The average age of SLE patients at the study entry was 30.4 ± 6.3 years, comparable with healthy controls (31.1 ± 4.8 years, $p = 0.62$). The mean age of SLE onset was 22.5 ± 7.3 years and the mean disease duration at the time of AMH assessment was 7.6 ± 5.9 years. The mean SLEDAI was 3.2 ± 3.8. Concerning the drugs used for SLE treatment overtime, 30 patients (34.9%) were taking low dose of prednisone (<7.5 mg per day), 14 patients (16.3%) had been exposed to CYC, 44 (51.2%) were treated with one or more conventional disease-modifying antirheumatic drugs (cDMARDs, i.e., methotrexate, azathioprine, mycophenolate mofetil and cyclosporine) [30 (68.2%) patients were exposed, during the course of the disease, to one cDMARDs, 10 (10%) to 2 cDMARDs and 4 (9%) were treated with to 3 cDMARDs over the years of the disease; none of the patients was treated with a combination of two cDMARDs] and 32 (37.2%) with antimalarials only, respectively. The mean cumulative dose of CYC was 8.3 ± 5.4g and none of the patients had received ovarian protection measures while assuming CYC therapy. Considering the reproductive background, there were no differences between SLE patients and controls: mean age at menarche was 12.2 ± 1.2 years for SLE patients and 12.2 ± 1.7 years for healthy controls ($p = 0.65$). A full-term pregnancy was conducted in 23% of SLE patients and in 21.4% of controls. Moreover, SLE patients experienced miscarriage in 14.5% of cases compared to 4.8% of controls ($p = 0.14$) (Table 1).

The SLE cohort had similar AMH serum levels compared to controls (4.2 ± 3.1 ng/ml vs. 5.0 ± 3.1 ng/ml, respectively $p = 0.21$) (Fig. 1a). Moreover, AMH serum levels inversely correlated with age both in SLE patients ($r = -0.43$; $p < 0.001$) and in controls ($r = -0.56$; $p < 0.001$, respectively) (Fig. 1b). Finally, an inverse correlation was observed between AMH serum levels at the study entry and the age at the disease onset in SLE cohort ($r = –0.21$; $p = 0.05$), correlation that was not significant after age

correction ($p = 0.54$). Finally, no correlation was observed between AMH serum levels and disease duration in the SLE cohort ($p = 0.20$).

Considering the SLE cohort, no association was found between AMH serum levels and autoantibody positivity, nor with SLEDAI even if a direct correlation was found between AMH serum levels and complement component C4 ($r = 0.26$; $p = 0.03$).

AMH serum levels and organ involvement in SLE patients

Considering the whole SLE cohort, 41 (47.7%) patients were identified as having a major organ involvement (mainly renal and/or neurological) and 45 (52.3%) patients as a mild organ involvement, mainly an articular and/or cutaneous (Table 1). Based on the disease severity, SLE patients with severe organ involvement had lower AMH serum levels (3.8 ± 2.7 ng/ml) than control subjects ($p = 0.08$), while comparable AMH levels were found between SLE patients with minor organ involvement (4.5 ± 3.4 ng/ml) and control subjects ($p = 0.33$). Finally, AMH serum levels did not differ between SLE patients with major and minor organ involvement ($p = 0.49$).

AMH serum levels and medications in SLE patients

Based on pharmacological treatments used for SLE, we did not find any significant difference in AMH serum levels among SLE patients treated with antimalarials only (4.7 ± 3.3 ng/ml), cDMARDs only with and without MTX (4.8 ± 3.2 ng/ml and 4.3 ± 2.8 ng/ml, p = ns; respectively), cDMARDs and antimalarials (3.9 ± 2.9 ng/ml) or CYC only (4.9 ± 3.9 ng/ml), compared to controls (Fig. 2).

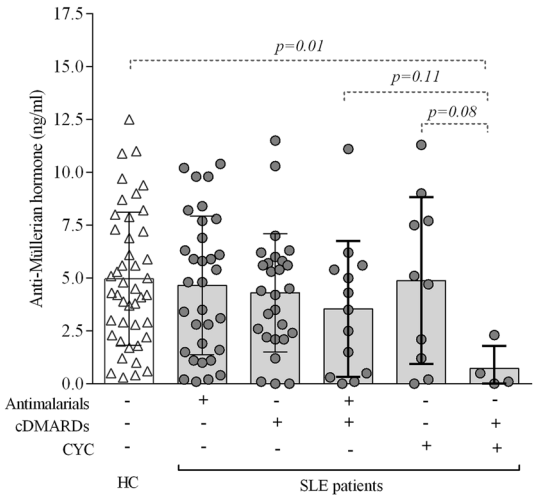

Fig. 2 Serum levels of Anti-Müllerian hormone (AMH) in SLE patients stratified by pharmacological treatments. Grouping patients based on the pharmacological treatments, AMH serum levels did not differ among SLE patients treated with antimalarials only, conventional disease-modifying antirheumatic drugs (cDMARDs) only, cDMARDs and antimalarials or cyclophosphamide (CYC) only, compared to controls, but patients sequentially treated with cDMARDs and CYC, had lower AMH serum levels than controls ($p = 0.01$)

Conversely, SLE patients sequentially treated with cDMARDs and CYC had lower AMH serum levels than controls ($p = 0.01$) (Fig. 2). In the group of SLE patients treated with CYC, those exposed to sequentially therapy with CYC and cDMARDs showed lower AMH serum levels than SLE patients treated with CYC only ($p = 0.08$) or SLE patients treated with cDMARDs only ($p = 0.11$) (Fig. 2). Similar age and age at disease onset were observed comparing SLE patients treated with different drugs. Moreover, age was similar between controls and the different subgroup of SLE patients. (Supplementary Table 1). Finally, the logistic regression analysis confirmed that the previous exposure to CYC with or without cDMARDs was independently associated with AMH serum levels ($p = 0.04$), together with age at AMH serum levels assessment ($p < 0.001$) (Supplementary Table 2).

Discussion

In this study, we assessed the serum levels of AMH, a biomarker of ovarian reserve, in a cohort of SLE patients compared with age-matched healthy controls to investigate whether the disease per se and/or the drugs exposure could interfere with the ovarian reserve. AMH serum level seems to be a good surrogate to estimate the ovarian reserve, but recently data about AMH has produced conflicting results regarding the reduction in ovarian reserve in SLE patients [24–26, 30]. Some authors have found opposite results about AMH serum levels in SLE patients than healthy controls, even regarding to drugs exposure. In our SLE cohort, we found an inverse correlation between AMH serum levels and age both in SLE patients and controls, but we found no differences in AMH serum levels between SLE patients and age-matched healthy controls. In contrast to our results, Lawrenz and co-authors found a significant lower ovarian reserve in a German cohort of SLE patients than controls concluding that disease itself might have a negative influence on the ovarian reserve [25]. Considering the organ involvement, our cohort of SLE patients, mainly with renal and neurological involvement, showed lower AMH serum concentration than controls. Moreover, focusing on the administered drugs, we did not find any significant difference in AMH serum levels among SLE patients treated with antimalarials only, cDMARDs only, cDMARDs and antimalarials combination, or CYC only, compared to controls. However, our study highlights that the use of sequentially therapy with cDMARDs and CYC in SLE patients leads to a significant decrease of AMH serum levels compared to

age-matched controls and to other SLE patients stratified based on the therapy, irrespective to the severity of the disease. These results may suggest that the exposure to CYC and MTX may have a significant impact on the ovarian reserve in SLE patients.

To date, there are several reports producing conflicting results about AMH serum levels in patients exposed to CYC, but no data are available about the effect of sequential exposure to cDMARDs (in particular MTX and CYC) on AMH serum levels in SLE patients. Our study shows that AMH serum levels in SLE patients treated with cDMARDs and CYC therapy, were significantly lower than controls when compared with SLE patients exposed to CYC only and to other immunosuppressant drugs. In contrast with the results reported by Morel et al. [32] and Mok et al. [26] we didn't find any significant correlation between the cumulative dose of CYC and AMH serum levels, mainly because of a small number of patients treated with CYC in our cohort. Moreover, the lower cumulative dose of CYC used by SLE patients included in the present study (mean cumulative dose <9 g), already considered not to definitely influence the ovarian reserve, may justify such difference, suggesting that lower AMH levels are due to a more severe SLE disease.

To date there are no data about the effects of sequentially therapy with cDMARDs as MTX and CYC on the ovarian reserve. It has been studied that in Balb/c mice treated with MTX (5 g/m^2), the MTX could induce destruction of primordial follicles [33] and Araujo et al. [34] reported that also in adult patients with childhood-onset SLE, high cumulative dose of MTX could be a relevant effect on the ovarian reserve.

Our findings should be interpreted in the light of some considerations. A limit of the study could be the use of a single parameter of ovarian reserve but it is known that AMH serum levels correlate with AFC and it has a good predictive value in estimating the ovarian reserve superior to FSH [14–16]. In addition, this is a cross-sectional study without data on the AMH serum levels available before the exposure to drugs administered during SLE.

In conclusion, our data confirm the role of AMH as a sensitive ad specific biomarker of the ovarian reserve in SLE patients, highlighting that the reduction of the ovarian reserve is associated not only with the concomitant pharmacological treatment, in particular with the subsequent use of cyclophosphamide and cDMARDs, but also with the disease severity. Therefore, AMH serum levels assay in SLE patients of childbearing age could be useful in the therapeutic decisions and may help guiding the choice to assess strategies for ovarian preservation in SLE patients who have pregnancy wish.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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