Original Research Article

Role of surface APRIL (A Proliferation Inducing Ligand, CD256) expression in patients with rheumatoid arthritis

Abstract

Background: A Proliferation Inducing Ligand (APRIL) is a member of the tumor necrosis factor (TNF) superfamily and is secreted by monocytes, dendritic cells, macrophages, neutrophils, myelocytes, astrocytes adipocytes and activated T and B cells. The study aimed to assess surface APRIL; CD256 expression on circulating monocytes in rheumatoid arthritis patients and to determine its relationship to disease activity.

Methods: This case control study was carried out on 60 subjects They were divided into two groups: group 1: 20 apparently healthy subjects as a reference group., group 2: 40 patients with rheumatoid arthritis according to DAS28, they were subdivided into two equal subgroups: active rheumatoid arthritis. and inactive rheumatoid arthritis

Results: There was a statistical increase in surface APRIL expression in active group and inactive group when compared to normal controls and there was also statistical increase in surface APRIL expression level in active group when compared to inactive group. There was no significant correlation between surface APRIL expression with RF (p=0.745) Anti CCP (p=0.375), Hb (p= 0.056), PLT (p= 0.980), WBCs (p= 0.252), AMC (p= 0.890).

Conclusions: Surface APRIL expression is elevated on circulating monocyte subsets in rheumatoid arthritis patients where it is highly correlated with disease activity. Monocytes in patients with RA is shifted toward intermediate and non-classical monocytes, populations of monocytes known to produce the inflammatory cytokines TNF-α important in the pathogenesis of RA.

Keywords: Rheumatoid arthritis, Proliferation Inducing Ligand, tumor necrosis factor.

Introduction:

Rheumatoid arthritis (RA) is a systemic B cell-mediated autoimmune disease dominated by autoantibodies that recognize intracellular and extra-cellular antigens [1]. These autoantibodies result in chronic systemic immune responses that target the synovium, cartilage, and bone resulting in joint damage [2].

A Proliferation Inducing Ligand (APRIL) is a member of the tumor necrosis factor (TNF) superfamily and is secreted by monocytes, dendritic cells, macrophages, neutrophils, myelocytes, astrocytes adipocytes and activated T and B cells [3, 4].

The effects of APRIL are dependent on the receptor that it binds. APRIL has 2 receptors: (1) TACI (the transmembrane activator, calcium modulator and cyclophilin ligand interactor receptor) (2) BCMA (the B cell maturation antigen receptor). TACI is expressed in B cells (Chang et al., 2006) while BCMA expression has been reported in plasma cells and on fibroblast-like synoviocytes (FLS) from patients with RA [5]. Binding of APRIL to the TACI or BCMA receptor leads to increased B cell or plasma cell survival, respectively [6].

The binding of APRIL to these receptors activates specific TNF receptor-associated factors (TRAFs), which regulate signal transduction in B cells. The interaction with TRAFs induces the nuclear factor (NF)-κB signaling pathway, which plays a vital role in regulating diverse aspects of immune function, including mediating inflammatory responses and facilitating adaptive immunity [7, 8].

The binding of APRIL to TACI, BCMA, and BAFF-R receptors also triggers the up regulation or down regulation of members of the Bcl-2 family of proteins, which are involved in cell death, proliferation, survival, and cell-cell interactions [9].

Increases in serum levels of soluble APRIL, and in specific myeloid cell populations, have been associated with RA. A novel surface form of APRIL and its expression to myeloid cells and RA have been identified. In addition, surface APRIL has been observed by

microscopy in synovial macrophages from patients with RA [10]. Surface APRIL is expressed at high levels in transformed cell lines, cancers of colon, thyroid, lymphoid tissues, and specifically expressed in monocytes and macrophages [11].

The study aimed to assess surface APRIL; CD256 expression on circulating monocytes in rheumatoid arthritis patients and to determine its relationship to disease activity.

Patients and Methods:

This case control study was carried out on 60 subjects selected from the out-patient's clinic of Physical Medicine, Rheumatology and Rehabilitation Department; Tanta University Hospitals.

The criteria of patients included in this study was patients with rheumatoid arthritis, the patients who are pregnant, with evidence of malignant diseases, with systemic inflammatory conditions including advanced liver diseases and unwilling to participate in the study were excluded.

They were divided into the following groups:

Group (1): Twenty apparently healthy subjects as a reference group.

Group (2): Forty patients with rheumatoid arthritis according to DAS28, they were subdivided into two subgroups: A) Twenty patients with active rheumatoid arthritis. B) Twenty patients with inactive rheumatoid arthritis.

Studied groups were subjected to the following:

Detailed clinical evaluation: including history taking and clinical examination. History taking from the affected person makes a subjective assessment (SA) of disease activity during the preceding 7 days on a scale between 0 and 100, where 0 is "no activity" and 100 is "highest activity possible" according to DAS28 score.

The clinical parameters that were assessed are age, sex and 28 Joints examination. Joints included were (bilaterally): proximal inter phalangeal joints (10 joints), metacarpo phalangeal joints (10), wrists (2), elbows (2), shoulders (2) and knees (2). When looking at these joints, both the number of joints with tenderness upon touching (TEN28) and swelling (SW28) were counted.

Laboratory investigation: Routine laboratory investigation including: Complete blood count (CBC), C reactive protein (CRP), Erythrocyte sedimentation rate (ESR), Rheumatoid factor (RF), Anti citrullinated protein antibodies ACPAs (anti-CCP antibodies)

With these parameters, DAS28 is calculated as: $DAS28 = 0.56\times\sqrt{((TEN\ 28))} + 0.28\times\sqrt{((SW\ 28))} + 0.70\times\ln(ESR) + 0.014\times SA$

Specific laboratory test

Flow Cytometric analysis for peripheral blood monocytes subsets using mono clonal antibodies against CD14 (FITC labeled) (Steensma et al., 2013), CD16 (PE labeled) [12] and surface APRIL detection were done by Flow Cytometer [13].

Blood samples were taken under complete aseptic conditions: two ml of peripheral blood were delivered in to EDTA vacutainer tube for CBC measurement and flow Cytometric analysis. 1.6 ml of peripheral blood were delivered into tube containing 0.4 ml of 3.8% sodium citrate for ESR test. 3ml of blood were collected into sterile tube allowed to be clotted and serum was separated for measurement of RF, CRP& anti-CCP.

Statistical analysis

Statistical analysis was done by SPSS v27 (IBM©, Chicago, IL, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analysed by ANOVA (F) test with post hoc test (Tukey). Quantitative non-parametric data were presented as median and interquartile range (IQR) and were analysed by Kruskal-Wallis test with Mann Whitney-test to compare each group. Qualitative variables were presented as frequency and

percentage (%) and were analysed utilizing the Chi-square test. Spearman coefficient was done to evaluate the degree of correlation between variables. A two tailed P value < 0.05 was considered statistically significant.

Results

There was no statistically significant difference between the two groups according as regard age and sex. There was statistical increase in the disease activity score in active patients when compared to inactive patients. There was no statistically significant difference between the two groups according to duration of the disease [Table 1]

Table 1: Comparison between the studied groups as regard age and sex

	Control (n = 20)		**Active (n = 20)**		**Inactive (n = 20)**		**P**
	No.	**%**	**No.**	**%**	**No.**	**%**	
Sex							0.256
Male	8	40.0%	4	20.0%	4	20.0%	
Female	12	60.0%	16	80.0%	16	80.0	
Age (years)							0.110
Range	50.0–28.0		56.0–32.0		56.0–28.0		
Mean ± SD.	7.06±39.0		7.33±46.0		7.23±44.0		
DAS							<0.001*
Range			6.95–3.34		2.90–0.77		
Mean ± SD.			0.99±4.66		0.78±1.86		
Duration(years)							0.547
Range			2.0 – 12.0		3.0 – 16.0		
Median (IQR)			8.0 (6.0 – 10.0)		8.0 (6.0 – 12.0)		

DAS; Disease activity score

There was no statistically significant difference in Hb level between active group when compared to inactive group. There was no statistically significant difference in Platelets count between the three groups. There was no statistically significant difference in WBCs count between inactive patients when compared to normal controls and no statistically significant difference between active group when compared to inactive group. There was no statistically significant difference in AMC between inactive patients when compared to normal controls and no statistically significant difference between active group when compared to inactive group. There was statistical increase in CRP level in active group and in inactive group when compared to normal controls. There was also statistical increase in CRP level in active group when compared to inactive group. There was also statistical increase in ESR level in active group when compared to inactive group. There was no statistically significant difference in RF level between active group and inactive group. There was statistical increase in Anti CCP level in active group and inactive group when compared to normal controls while There was no statistically significant difference in Anti CCP level between active group and inactive group. Table 2

Table 2: Comparison between the different studied groups as regard CBC, CRB, ESR, RF and anti CCP.

CBC	Control (n = 20)	Active (n = 20)	Inactive (n = 20)	p
Hb (gm/dl)				
Range	15.30–13.5	12.50–8.50	12.80–8.90	<0.001*
Mean ± SD.	0.95±13.84	1.06±10.64	1.15±10.67	
Sig. bet. Grps	$p_1<0.001^*$, $p_2<0.001^*$, $p_3=0.996$			
PLT(x10^9/L)				
Range	368.0–210.0	483.0–142.0	490.0–162.0	0.263
Mean ± SD.	69.72±242.15	89.43±260.90	90.46±285.80	
Sig. bet. Grps	$p_1=0.760$, $p_2=0.234$, $p_3=0.617$			
WBCs(x10^9/L)				
Range	9.80–5.20	11.60–6.20	11.20–4.80	0.040*
Mean ± SD.	1.49±7.30	1.81±8.64	1.89±7.53	
Sig. bet. Grps	$p_1=0.046^*$, $p_2=0.908$, $p_3=0.117$			
AMC (cells/mm3)				0.015*

Range	484.0 –223.0	816.0 –268.0	672.0 –144.0	
Mean ± SD.	75.0 ±315.80	135.80 ±430.60	149.41 ±399.55	
Sig. bet. grps	$p_1=0.014^*$, $p_2=0.093$, $p_3=0.711$			
CRP(mg/L)				$<0.001^*$
Range	1.0 – 5.0	14.0 – 100	7.0 – 26.0	
Median (IQR)	3.0(2.0 – 4.75)	48.0(15.0 – 48.0)	12.0(6.0 – 24.0)	
Sig. bet. Grps	$p_1<0.001^*$, $p_2<0.001^*$, $p_3=0.009^*$			
ESR (mm/1h)				$<0.001^*$
Range	4.0 – 7.0	28.0 – 70.0	15.0 – 25.0	
Median (IQR)	5.50 (5.0 – 6.0)	41.0 (30.0 – 46.0)	17.50 (15.0 – 20.0)	
Sig. bet. grps	$p_1<0.001^*$, $p_2<0.001^*$, $p_3<0.001^*$			
RF(IU/ml)				$<0.001^*$
Range	1.0 – 6.0	8.0 – 512.0	8.0 – 256	
Median (IQR)	3.0 (2.0 – 5.0)	32.0(10.0 – 64.0)	64.0(20.0 – 120.0)	
Sig. bet. Grps	$p_1<0.001^*$, $p_2<0.001^*$, $p_3=0.363$			
Anti CCP(U/ml)				$<0.001^*$
Range	5.0 – 39.0	13.0 – 280.0	10.0 – 250.0	
Median (IQR)	20.0 (10.0 – 32.25)	143.50 (98.75 – 244.25)	128.0 (18.0 – 211.5)	
Sig. bet. Grps	$p_1<0.001^*$, $p_2=0.001^*$, $p_3=0.294$			

p: p value for comparing between the three studied groups, p1: p value for comparing between Control group and Active group, p2: p value for comparing between Control group and Inactive group, p3: p value for comparing between Active group and Inactive group,·: Statistically significant at $p \leq 0.05$

In active group there was strong positive correlation between surface APRIL expression with CRP (r=0.556&p=0.011), ESR(r=0.504&p=0.023) and DAS score (r=0.943&p=0.001) but there was no significant correlation between surface APRIL expression with RF (p=0.745) Anti CCP (p=0.375), Hb (p= 0.056), PLT (p= 0.980), WBCs count(p= 0.252), **Monocytes** (p= 0.890). In inactive group there was strong positive correlation between surface APRIL expression with ESR(r=0.564&p=0.010) and DAS score (r=0.910&p=0.001) but there was no significant correlation between surface APRIL expression with RF (p= 0.671), Anti CCP (p= 0.073), HB (p= 0.094) PLT (p= 0.462), WBCs (p= 0.636), AMC (p= 0.767) and CRP (p= 0.243) [

Table 3**]**

Table 3: Correlation between APRIL expression and different findings in active and inactive groups

	Active (n = 20)		Inactive (n = 20)	
	APRIL expression (%)		APRIL expression (%)	
	r_s	p	r_s	p
RF(IU/ml)	-0.078	0.745	-0.101	0.671
Anti CCP(U/ml)	0.210	0.375	0.410	0.073
Hb(gm/dl)	0.434	0.056	-0.385	0.094
PLT($x10^3$/L)	0.006	0.980	0.174	0.462
WBCs($x10^9$/L)	0.269	0.252	-0.113	0.636
Monocytes(cells/mm^3)	0.033	0.890	0.071	0.767
CRP (mg/L)	0.556	0.011*	0.273	0.243
ESR (mm/1h)	0.504	0.023*	0.564	0.010*
DAS	0.943	0.001*	0.910	0.001*

r_s: Spearman coefficient *: Statistically significant at $p \leq 0.05$

Regarding surface APRIL expression in circulating monocytes.in comparison among the studied groups There was statistical increase in surface APRIL expression in active group and inactive group when compared to normal controls and there was also statistical increase in surface APRIL expression level in active group when compared to inactive group. **[Table 4]**

Table 4: Comparison between the studied groups as regard surface APRIL expression in circulating monocytes.

APRIL (%)	Control (n = 20)	Active (n = 20)	Inactive (n = 20)	p
Range	27.70 – 77.20	90.80 – 99.80	76.20 – 90.10	<0.001*
Median(IQR)	57.0 (36.30 – 72.85)	96.45 (92.40 – 97.58)	85.05 (80.20 – 86.28)	
Sig. bet. grps	$p_1<0.001^*$, $p_2<0.001^*$, $p_3<0.001^*$			

p: p value for comparing between the three studied groups, p1: p value for comparing between control group and active group, p2: p value for comparing between control group and inactive group, p3: p value for comparing between active group and inactive group, *: Statistically significant at $p \leq 0.05$

There was statistical decrease in classical monocyte in active group and inactive group when compared to normal control and there was also statistical decrease in classical monocyte in active group when compared to inactive group. There was statistical increase in intermediate monocytes in active group and inactive group when compared to normal control. There was also statistical increase in Intermediate monocytes in active group when compared to inactive group. There was statistical increase in non-classical monocytes in active group and in inactive group when compared to normal control. There was also statistical increase in non-classical monocytes in active group when compared to inactive group. In active group there was no significant correlation between surface APRIL expression with RF (p=0.745) Anti CCP (p=0.375), HB (p= 0.252), PLT (p= 0.980), WBCs (p= 0.252), AMC (p= 0.890). In inactive group. There was no significant correlation between surface APRIL expression with RF (p= 0.671), Anti CCP (p= 0.073), HB (p= 0.094) PLT (p= 0.462), WBCs (p= 0.636), AMC (p= 0.767) and CRP (p= 0.243). **[Table 4]**

Table 5: Comparison between the studied groups as regard distribution of monocyte subsets

	Control (n = 20)	Active (n = 20)	Inactive (n = 20)	F	p
Classical (%) (CD14++CD16 -)					
Range	92.20–83.30	72.90–20.20	75.20–36.80	131.12	<0.001
Mean ± SD.	2.64±88.31	10.36±44.11	11.46±54.15		
Sig. bet. Grps	$p_1<0.001^*$, $p_2<0.001^*$, $p_3=0.003^*$				
Intermediate (%) (CD14++CD16 +)					
Range	10.50–4.40	55.80–20.20	51.40–19.20	113.49	<0.001
Mean ± SD.	1.76±7.56	8.79±43.28	10.45±36.30		
Sig. bet. Grps	$p_1<0.001^*$, $p_2<0.001^*$, $p_3=0.020^*$				
Non-classical (%) (CD14+ CD16++)					
Range	6.50–2.20	18.0–5.20	15.0–4.30	44.744	<0.001
Mean ± SD.	1.21±4.13	3.65±12.01	2.65±9.58		
Sig. bet. Grps	$p_1<0.001^*$, $p_2<0.001^*$, $p_3=0.016^*$				

F: F for ANOVA test, Pairwise comparison between each 2 groups was done using post Hoc Test

p: p value for comparing between the three studied groups

p_1: p value for comparing between control group and active group

p_2: p value for comparing between control group and inactive group

p_3: p value for comparing between active group and inactive group

*: Statistically significant at $p \leq 0.05$

Discussion

Since APRIL was discovered, a great amount of evidence has been reported about the involvement of APRIL in autoimmune diseases including RA [14]. APRIL have been shown to play roles in the process of inflammation associated lymphoproliferation and germinal center formation in the rheumatoid synovium [15].

APRIL causes the accumulation of plasma cells in the joint, further increasing, the production of inflammatory cytokines such as TNF, IL1, and IL6; the auto production of APRIL ultimately causes the proliferation of FLSs [16] .

The etiology of RA is unknown, but genetic factors are associated with the condition and its severity. Multiple environmental and lifestyle factors have been shown to be associated with its development [17].

The result of this work showed that there was statistical increase in RF in active and in inactive group. These results were in accordance with **Solbritt et al., (2003)** [18] and **Yang et al., (2015)** [19]. However, there was no statistically significant difference in rheumatoid factor between the active and in active group.

RF is the most common laboratory serologic marker for the diagnosis of RA however the specificity of RF is relatively low because there is a 50% positive rate of RF in patients with other connective tissue diseases, such as systemic lupus erythematosus, primary Sjögren's syndrome and dermatomyositis, with some infections and in elderly healthy persons, which limits its diagnostic value [20].

This study showed that there was statistical increase in Anti CCP level in active group and inactive group when compared to normal controls while there was no statistically significant difference in Anti CCP level between active group and inactive group. This result is in agreement with the study of **Shen et al., (2015)**[20] that showed significant differences in concentration of anti CCP antibodies between RA patients and control group.

This study showed that there was statistical decrease in classical monocyte (CD14++CD16−) in RA patients when compared to normal control. Both non-classical (CD14+ CD16++) and intermediate (CD14++CD16+) monocyte subsets were statistically increased in patients with RA when compared to normal control. Although these subsets make up less than 20% of the circulating monocyte population in healthy donors, in patients with RA, they represent the majority of circulating monocytes.

This result is in agreement with the study of **Weldon et al., (2015)**[21] which provide that the pool of monocytes in patients with RA is shifted toward intermediate and non-classical monocytes, populations of monocytes known to produce the inflammatory cytokines TNF-α and/or IL-1β, cytokines important in the pathogenesis of RA.

Kawanaka et al., (2002)[22] reported higher frequency of CD16+ monocytes in the peripheral blood of RA patients but without distinguishing between subpopulations of CD16+ monocytes. The CD14 low (non-classical) monocyte subset has previously been the major focus of attention in RA due to reports of increased numbers in inflammatory diseases. **Rossol et al., (2012)**[23] showed that the frequency of non-classical monocytes was higher in patients with RA.

Yoon et al., (2014)[24] demonstrate that proinflammatory intermediate (CD14+CD16+), but not non-classical, monocytes are moderately expanded in peripheral blood and prominently in synovial fluid of RA patients compared to healthy controls. Intermediate monocytes are believed to represent a subset of monocytes that are able to rapidly mature and differentiate into tissue macrophages because of their expression of CD16.

Ruiz-Limon et al., (2019)[25] provide, in a large cohort of RA patients, that monocyte subset distribution is skewed to a more “pro-inflammatory” profile, with elevated frequency

of intermediate monocytes (CD14++CD16+), which were related to the autoimmune and inflammatory profile.

As regard surface APRIL expression on monocytes the result of the present work showed that there was statistical increase in surface APRIL expression in RA patients when compared to normal controls and there was also statistical increase in surface APRIL expression level in active group when compared to inactive group. This study showed strong positive correlation between surface APRIL expression with CRP, ESR and DAS score.

In agreement of these results **Gaugler et al., (2013)**[26]found that high serum APRIL levels have been described in patients with RA or very early RA. **Weldon et al., (2015)**[21]showed that in patients with RA, all myeloid cells indicate the surface expression of the APRIL, which is associated with the plasma level of and the APRIL activity of the disease as indicated by DAS28 score.

Boghdadi et al., (2015)[27] also found that serum APRIL showed elevated levels that correlated significantly with RA disease activity indicated by DAS28. They found significant correlation considering APRIL/CRP and APRIL/ESR levels. They also found that serum APRIL had a good prediction performance to evaluate the joint injury status and therapeutic effect in patients with RA.

Rodríguez-Carrio et al., (2019)[28]found that sAPRIL and serum levels identify a subset of patients with a more severe disease and increased prevalence of autoantibodies, probably linked to a B-cell over-activation and immune-stimulatory status.

APRIL is strong regulators of B cell that play an important role in the development and survival of these cells. This cytokine maintains the activation of B cells and enhance autoimmune diseases [29].

APRIL causes the accumulation of plasma cells in the joint, further increasing, the production of inflammatory cytokines such as TNF, IL1, and IL6; the autoproduction of APRIL ultimately causes the proliferation of FLSs [16].

In the study of **Weldon et al., (2015)**[21] APRIL have been shown to be particularly elevated in very early RA, suggesting that atacicept may prove beneficial in patients with newly diagnosed RA.

Targeting APRIL employing monoclonal antibodies can neutralize the effects of this cytokine in some patients. APRIL inhibition has clear therapeutic effects in autoimmunity such as RA. Also, APRIL inhibition improved the symptoms of RA and delayed the progression of the disease in a certain number of clinical trials [29].

Conclusions:

Surface APRIL expression is elevated on circulating monocyte subsets in rheumatoid arthritis patients where it is highly correlated with disease activity. Monocytes in patients with RA is shifted toward intermediate and non-classical monocytes, populations of monocytes known to produce the inflammatory cytokines TNF-α important in the pathogenesis of RA.

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