European Review for Medical and Pharmacological Sciences 2018; 22: 4299-4309

Serum calprotectin correlates with risk and disease severity in psoriasis patients and the decrease of calprotectin predicts better response to tumor necrosis factor inhibitors

M. QIAN, N.-J. SONG

Department of Dermatology, Tongren Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Abstract. – OBJECTIVE: This study aimed to investigate the correlation of serum calprotectin expression with risk and severity of psoriasis, as well as its predictive value for clinical response to tumor necrosis factor inhibitors (TNFi) treatment in psoriasis patients.

PATIENTS AND METHODS: 72 psoriasis patients and 70 health controls (HCs) were enrolled. Blood samples were collected, and serum calprotectin was determined by commercial enzyme-linked immuno sorbent assay (E... All patients were treated by TNFi treatment and followed up at 6 months, and the last follow-up date was 2016/11.

RESULTS: Calprotectin level was elevated in psoriasis patients compared to... ($p < 0.001$) and it disclosed a good diagnostic value of psoriasis with area under curve (AUC) 0.8... 95% CI: 0.810-0.935. Calprotectin expression was positively associated with psoriasis area and Severity Index (PASI) score (R = ..., $p < 0.001$), while it was not associated with ... (R = 0.125, $p = 0.297$). 58... patients achieved PASI75 and 43.1% patients achieved PASI90 at M6. Calprotectin was decreased during the 6-month treatment (...0.001). Changes of calprotectin during the first month (calprotectin (M0-M1)) in PASI75 group were ... than that of non-PASI75 group ($p <$ ...). Also, multivariate logistic analysis revealed that Δcalprotectin (M0-M1) ($p = 0.001$) was an independent factor for PASI75 achievement at M6 of TNFi treatment, while pre-systemic biologic treatment ($p = 0.001$) was an independent factor for non-PASI75 achievement.

CONCLUSIONS: Serum calprotectin expression is correlated with risk and severity of psoriasis, and the decrease of calprotectin during the first month could predict better clinical response to TNFi treatment in psoriasis patients.

Key Words:
Serum, Calprotectin, Psoriasis, Tumor necrosis factor inhibitors (TNFi), Response.

Introduction

Psoriasis is a chronic inflammatory skin disease affecting more than 125 million people worldwide, which is considered as a crucial threat imperiling human physical and psychological health due to its major clinical symptoms including sharply demarcated papules, pustules and plaques[1,2]. In recent years, various treatments for psoriasis patients, such as topical therapy, phototherapy, systemic therapy and biologic therapy, have been greatly developed and improved[3,4]. Among these treatments, tumor necrosis factor inhibitors (TNFi), one of the important biological therapy drugs, have been popularly performed in psoriasis patients[5]. However, the effects of TNFi therapy in some psoriasis patients are still far more from satisfaction resulted from individual heterogeneity, drug toxicity, and prolonged delay of diagnosis[6]. Thus, additional biomarkers for evaluating the risk of psoriasis and predicting the responses to TNFi therapy are greatly needed.

Calprotectin, a calcium-zinc binding protein secreted by monocyte and neutrophil, has been found to play a key role in multiple physiological and pathological processes, including regulation of immune response, inhibition of cell proliferation, as well as repression of pathogenic microorganism growth[7,8]. Large amounts of evidences have proven that calprotectin expression is related to the development and progression of various immune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and psoriasis[9-11]. However, few studies about the effects of calprotectin expression in psoriasis patients receiving TNFi therapy have been explored. Hence, the purpose of this study was to investigate the correlation

Corresponding Author: Ning-Jing Song, Ph.D; e-mail: songningjing@126.com

of serum calprotectin expression with risk and severity of psoriasis, as well as its predictive value for clinical response to TNFi treatment in psoriasis patients.

Patients and Methods

Patients

The current study was a prospective cohort study, which consecutively enrolled 72 patients who were diagnosed with plaque psoriasis in moderate to severe degree and receiving TNFi therapy in Department of Dermatology, Tong Ren Hospital, Shanghai Jiao Tong University School of Medicine from June 2014 to May 2016. Inclusion criteria: (1) more than 18 years old; (2) diagnosed by with plaque psoriasis; (3) in a moderate to severe degree which defined as body surface area (BSA) ≥ 10%. Also, Psoriasis Area and Severity Index (PASI) score ≥ 8 points; (4) about to switch to or initiate TNFi therapy. Exclusion criteria: (1) patients with malignant tumor history; (2) patients with severe infection; (3) patients with moderate-severe liver or [illegible] dysfunction (defined as more than three ti[illegible] normal value); (4) women during pregnant o[illegible]-tation period; (5) patients who were not able t[illegible] followed up regularly. In addition, 70 health v[illegible] unteers were recruited as hea[illegible]ls (HC[illegible] from Department of Physic[illegible]xamin[illegible]n in the same duration. The age, [illegible]der and [illegible]dy mass index (BMI) of HCs [illegible]re [illegible] patients. HCs with [illegible]ry of m[illegible]te-severe hepatic or renal d[illegible]tion, autoi[illegible]ne disease, malignancy a[illegible] infection w[illegible] excluded. This study [illegible]as been a[illegible]ved by Ethics Committee o[illegible]g Ren Hospi[illegible] Shanghai Jiao Tong Univ[illegible]y Schol of Medic[illegible] All patients and HC[illegible]ned t[illegible]formed consents.

[illegible]ath[illegible] and [illegible]ow-Ups

[illegible] pati[illegible]ved TNFi treatment (infliximab (IFX) [illegible]g AG, Schaffhausen, Switzerland), etanercept (ETN) (Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany)) according to clinical experience and disease conditions. The common routine of TNFi treatments were as follows: ETN, 50 mg per week[12]; IFX, 5 mg/kg at weeks 0, 2, 6, 14 and 22[13]. Combinations with topical therapy, phototherapy or systemic non-biologic treatments were recorded. The median follow-up duration was 6 months, and the last follow-up date was 2016/11.

Data Collection and Efficacy Assessment

Clinical and pathological properties in all psoriasis patients at baseline were collected, including age, gender, BMI, disease duration, BSA, PASI, treatment history and combinations. Besides, PASI score at month 1 (M1), month 3 (M3) and month 6 (M6) in all patients was e[illegible] during 6-month TNFi treatment. As [illegible]patients who lost follow-up, lacked efficacy [illegible]th severe side effects during the study, the mea[illegible]ment of calprotectin at the last follow[illegible] was u[illegible] the value of each later missin[illegible]t, and dise[illegible] sessment (PASI score) a[illegible]t follo[illegible] was as the value at each la[illegible] miss[illegible] visit as well. Achievement of P[illegible]5/9[illegible]ssessed [illegible]each visit, which w[illegible]lined as [illegible]e th[illegible]5% or 90% improv[illegible] PASI sco[illegible] treatment. In the me[illegible]while, [illegible]tors affec[illegible] PASI75/90 achievement at M6 [illegible] TNFi treatment were anal[illegible]

[illegible]od Sample[illegible]llection and C[illegible]rotectin M[illegible]surement

[illegible] periphe[illegible] blood samples were obtained from p[illegible]tients and HCs when enrolled in this study, besides, 4 ml peripheral blood samples [illegible] collected at month 1, 3, 6 after TNF inhibi[illegible]ment in psoriasis patients. Serum samples were extracted from peripheral blood immediately after collection and stored as -80°C for further detection. Expression of serum calprotectin was determined by commercial enzyme-linked immuno sorbent assay (ELISA) kit (R&D, Minneapolis, MN, USA) according to the instructions of manufacturers.

Statistical Analysis

Statistical analysis was carried out using SPSS 22.0 (IBM, Armonk, NY, USA). Data were presented as mean ± standard deviation, median (25^{th}-75^{th}) or count (%). Comparison between two groups was detected by t test, Wilcoxon rank sum test or Chi-square test. Friedman rank sum test was used to analyze difference in calprotectin values among each visit in psoriasis patients during 6-months treatment. Receiver operating characteristic (ROC) curve was performed to evaluate diagnostic value for psoriasis. Univariate logistic regression model was used to evaluate factors affecting PASI75/90 achievement at M6 after TNFi treatment, all factors with a p-value < 0.1 were further analysed by the multivariate logistic regression model. $p < 0.05$ was considered significant.

Results

Study Flow

In the present study, 98 psoriasis patients were invited: 11 cases were not assessed for eligibility, among which 2 patients missed invitation to participate, and 9 patients declined to be invited (Figure 1). In the remaining 87 patients who were screened for eligibility, 15 cases were excluded: 13 patients with the exclusion criteria and 2 disagreed with informed consents, leading to 72 patients included. Ultimately, among these 72 included patients, 5 cases did not complete the whole study: 3 lost follow-up, 1 lacked efficacy and 1 with moderated hepatic dysfunction, thereby 67 patients completed 24-week follow-ups. In the study, the analysis of treatment response (PASI75, PASI90) was based on 72 patients; the measurement of calprotectin and disease assessment (PASI score) at last follow up was used as the value of each later missing visit.

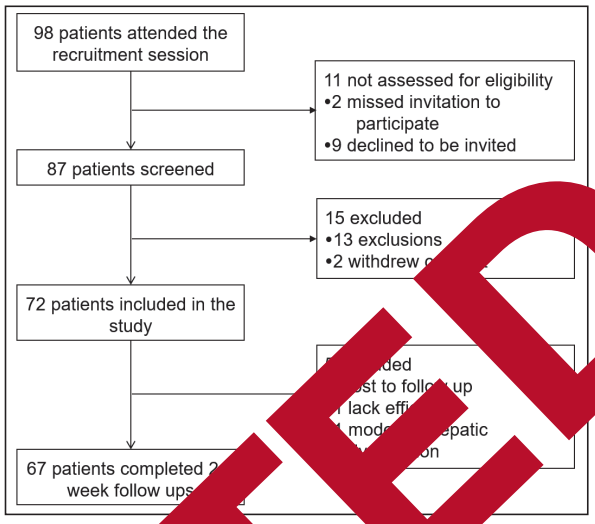

Figure 1. St… flow…

Characteristics of Psoriasis Patients and HCs

The mean age of psoriasis patients and … were 42.25 ± 10.93 and 40.73 ± 7.49, respe… (Table I). Male and female were 52 and … psoriasis group, 46 and 24 in HCs. No di… ence of age (p = 0.334), gender (p = 0.402) a… BMI (p = 0.810) between p… oup an… HCs were observed. As f… soria… patients, th… edian BSA was 26.5… (21.0%-35.0%), and P… score was …66 (10.86-22.44). 58 (80.6%) p… sis patient… ceived ETN treatment, while 14 (…%) pati… received IFX treatment. The numb… nts with previous treatment by topical therapy, phototherapy, systemic non-biologic treatment and pre-systemic biologic treatment were 65 (90.3%), 59 (81.9%), 40 (55.6%) and 10 (13.9%) respectively. Other characteristics of psoriasis patients and HCs were shown in Table I.

Table I. Characteristics … oriasis … at base… and HCs.

	…oriasis patients (N = 72)	HCs (N = 70)	*p*-value
Age (years)	42.25 ± 10.93	40.73 ± 7.49	0.334
Gender (… emale)	52/20	46/24	0.402
BMI (…)	24.55 ± 2.72	24.44 ± 2.81	0.810
Dis… duration… ears)	17.83 ± 10.20	–	–
E… …)	26.5 (21.0-35.0)	–	–
PA… …e	13.66 (10.86-22.44)	–	–
Curre… …ment (n/…		–	–
…TN	58 (80.6)	–	–
…X	14 (19.4)	–	–
…binations …		–	–
…therapy	56 (77.8)	–	–
…py	39 (54.2)	–	–
Systemic non-biologic treatment	34 (47.2)	–	–
Previous treatment (n/%)		–	–
Topical therapy	65 (90.3)	–	–
Phototherapy	59 (81.9)	–	–
Systemic non-biologic treatment	40 (55.6)	–	–
Pre-systemic biologic treatment	10 (13.9)	–	–

Data was presented as mean ± standard deviation, median (25^{th}-75^{th}) or count. Comparison between two groups was detected by t-test, Wilcoxon rank sum test or χ^2 test. $p < 0.05$ was considered significant. HCs, health controls; BMI, body mass index; BSA, body surface area (affected by psoriasis); PASI, psoriasis area and severity index; ETN, etanercept; IFX, Infliximab.

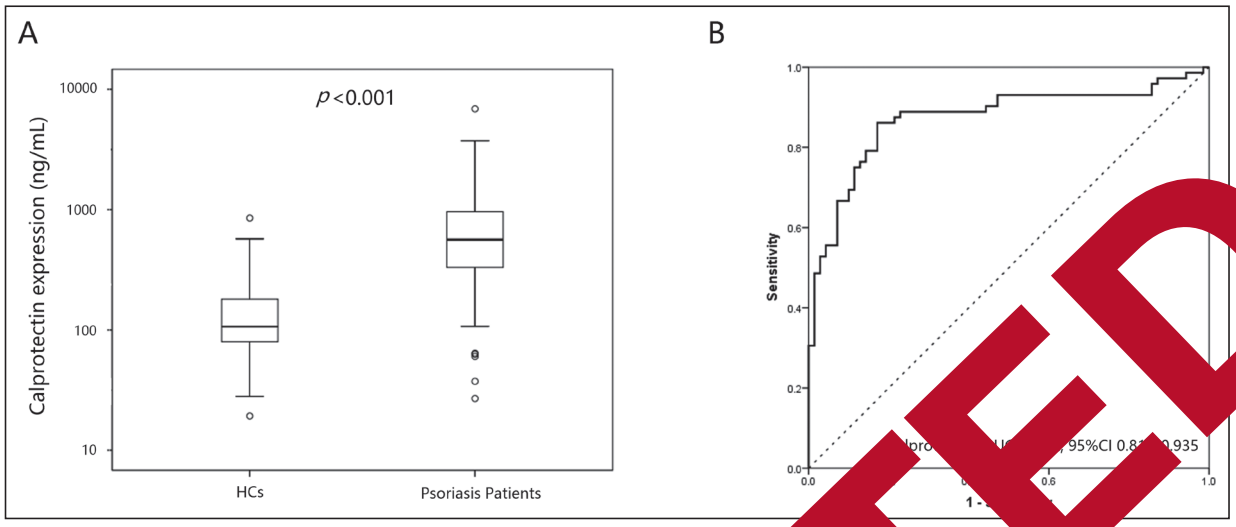

Figure 2. Predictive value of calprotectin in risk of psoriasis. ***A,*** Comparison ween tectin expre ons in psoriasis patients and in HCs. ***B,*** ROC curves of calprotectin for psoriasis. Wilcoxon rank sum test w d to analyze the comparison of calprotectin expressions in psoriasis patients and in HCs. $p < 0.05$ wa ed significa C curve was conducted to evaluate the diagnostic value of calprotectin for psoriasis.

Predictive Value of Calprotectin in Risk of Psoriasis

Predictive value of calprotectin in risk riasis was analyzed in Figure 2. Calpro n level was elevated in psoriasis group (562 (329.923-964.154) ng/mL) com d to H (106.047 (78.939-181.338) ng < 0.00 (Figure 2A). In addition, protec expres- sion disclosed a good va n the nosis of psoriasis with AUC 0. 2, C (Figure 2B).

Ca tectin pression Positively Corr n PASI Score But Not BSA Score in Psoriasis Patients

e association of calprotectin expression A and PASI score in psoriasis patients were evaluated in Figure 3. No correlation of calprotectin expression with BSA was observed (R = 0.125, $p = 0.297$, N = 72) (Figure 3A), while calprotectin expression was positively associated with PASI score (R = 0.452, $p < 0.001$, N = 72) (Figure 3B).

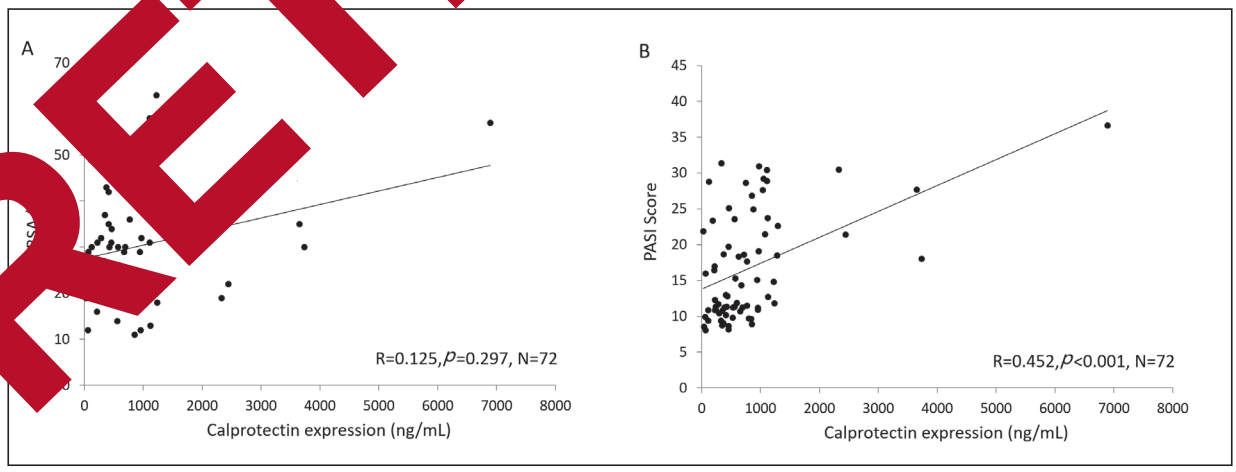

Figure 3. Association of calprotectin expression with BSA and PASI score. ***A,*** Association of calprotectin expression with BSA. ***B,*** Association of calprotectin expression with PASI score. Kaplan-Meier curves were used to evaluate the correlation of calprotectin expression with BSA and PASI score. $p < 0.05$ was considered significant.

PASI75 and PASI90 Achievement

After TNFi treatment, 59.7% patients at M3 and 58.3% patients at M6 with PASI75 achievement were observed, while 43.1% patients with PASI90 achievement at M3 and M6 were found (Figure 4).

Calprotectin Expression After Treatment

Comparisons of calprotectin expression after treatment at M0, M1, M3 and M6 were determined by Friedman rank sum test (Figure 5). Calprotectin expression in psoriasis patients was decreased during the 6-month period after treatment ($p < 0.001$), and calprotectin value was 562 (330-964) at M0, 317 (214-649) at M1, 269 (158-431) at M3, and 199 (137-394) at M6, respectively.

Decrease of Calprotectin From M0 to M1 (Δcalprotectin (M0-M1)) Correlates with PASI75 Achievement After 6-month TNF Inhibitor Treatment

According to whether psoriasis pat achieved PASI75 or not, patients were d into two groups: PASI75 group and Non-PA 5 group. As listed in Figure 6, the correla of calprotectin and its changes d ng the f month with PASI75 achieve M6 aft TNFi treatment, were asse No d rence o calprotectin expression en PA 5 group and Non-PASI75 grou = (Figure 6A), while uprotec M0-M1) level

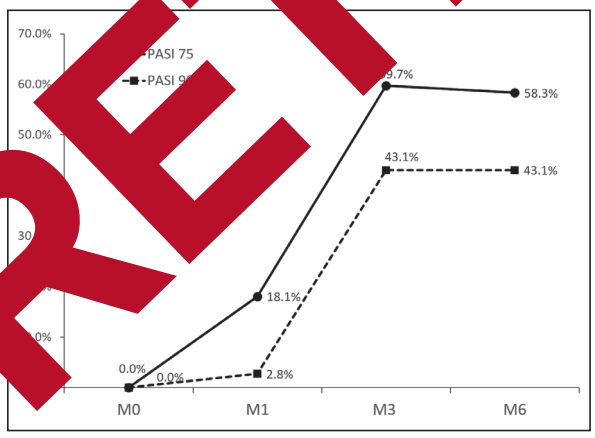

Figure 4. Comparison of PASI75 and PASI90 achievement after TNFi treatment. *t*-test was used to analyze the comparison of PASI75 and PASI90 achievement after TNFi treatment.

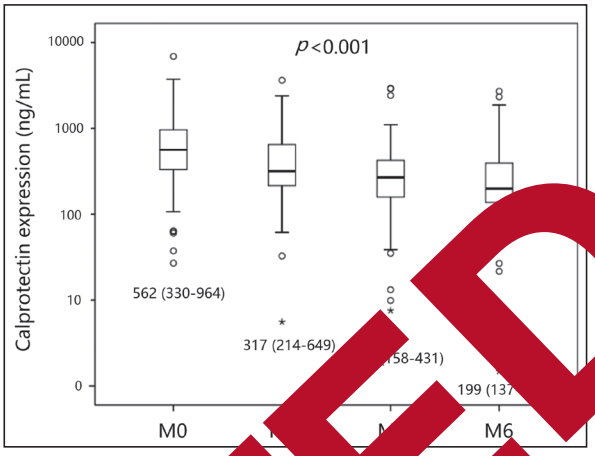

Figure 5. Compa of cal in exp n after treatment at M0 M3 and M ed rank sum test was used the compar calprotectin expression af treatm M0, M1, M nd M6. $p < 0.05$ was considered significa

w ncreased in SI75 group than Non-PASI75 g ($p < 0.001$ igure 6B).

PASI9 o difference in either calprotectin ($p = 0.708$) (Figure 6C) or Δcalprotectin (M0-M1) ($p = 0.096$) (Figure 6D) was between PASI90 group and Non-PASI90

ΔCalprotectin (M0-M1) Could Predict PASI75 Achievement in Psoriasis Patients After TNFi Treatment

Univariate logistic regression model was used to evaluate factors affecting PASI75 achievement at M6 after TNFi treatment, as presented in Table II, which indicated that Δcalprotectin (M0-M1) ($p = 0.001$) was positively associated with PASI75 achievement at M6 after TNFi treatment, while Pre-systemic biologic treatment ($p = 0.008$) was negatively correlated with it. All factors with a p-value < 0.1 were further analyzed by the multivariate logistic regression model. It revealed that Δcalprotectin (M0-M1) ($p = 0.001$) was an independent factor for PASI75 achievement at M6 after TNFi treatment, while Pre-systemic biologic treatment ($p = 0.001$) was an independent factor for non-PASI75 achievement.

Univariate and multivariate logistic analysis were performed to assess the factors affecting PASI90 achievement at M6 after TNFi treatment (Table III). No factors could predict PASI90 achievement at M6 after TNFi treatment independently.

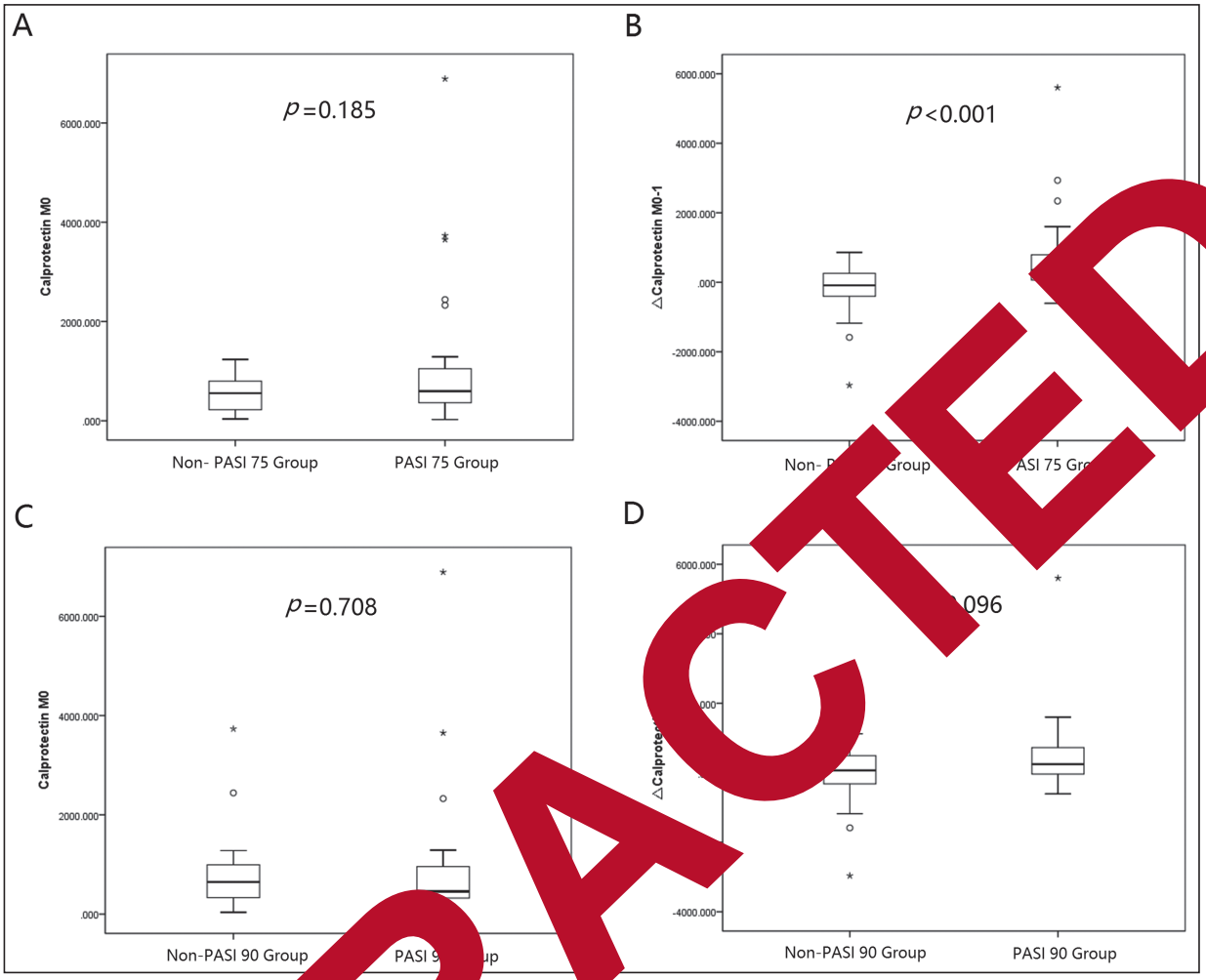

Figure 6. Correlation of [illegible] during the first month with PASI75/90 achievement at M6 after TNFi treatment. ***A,*** Com[illegible]pressions in non-PASI75 and in PASI75. ***B,*** Comparison between Δcalprotectin (M0-M1) [illegible] PASI75. ***C,*** Comparison between calprotectin expressions in non-PASI90 and in PASI90. ***D,*** Compa[illegible] (M0-M1) in non-PASI90 and in PASI90. Wilcoxon rank sum test was used to analyze the corr[illegible] anges during the first month with PASI75/90 achievement at M6 after TNFi treatment. $p < 0.0$[illegible] was co[illegible] significant.

Discussion

The [illegible]s in th[illegible]tudy showed that: (1) the le[illegible] of c[illegible]t[illegible] was elevated in psoriasis pa[illegible]ts com[illegible]d to HCs, and it disclosed a [illegible]gnostic value for psoriasis. Additionally, [illegible]protectin expression was positively associated with PASI score. (2) After TNFi treatment, [illegible]% patients at M3 and 58.3% patients at M6 a[illegible]eved PASI75, while 43.1% patients realized PASI90 at M3 and M6 respectively. In the meanwhile, calprotectin expression in psoriasis patients was decreased during the 6-month period after treatment. (3) Δcalprotectin (M0-M1) level was increased in PASI75 group than Non-PASI75 group, and Δcalprotectin (M0-M1) was an independent factor of PASI75 achievement at M6 after TNFi treatment, while Pre-systemic biologic treatment was an independent factor of Non-PASI75 achievement. Psoriasis, a recurrent systemic disease with inflammation regulated by T lymphocyte, is characterized by excessive infiltration of inflammatory cell, hyper proliferation of epidermal keratinocytes and abnormal angiogenesis[14, 15]. Although psoriasis etiology is still confused, many risk factors including genetic predisposition, immune-mediated disorder and environmental change contribute to its development[16].

Calprotectin, consisting of SI00A8 and SI00A9 heterodimer, is considered as an inflammation-re-

Table II. Analysis of factors affecting PASI 75 achievement after 6-month TNFi treatment.

	Univariate model				Multivariate model			
			95% CI				95% CI	
	p-value	OR	Lower	Higher	*p*-value	OR	Lower	Higher
Calprotectin at M0	0.126	1.001	1.000	1.002	–	–	–	
ΔCalprotectin (M0-M1)	**0.001**	1.002	1.001	1.003	**0.001**	1.004	1.002	
Age (years)	0.503	0.985	0.944	1.029	–	–	–	–
Gender (male)	0.722	1.208	0.427	3.419	–	–	–	–
BMI (kg/m^2)	0.208	0.891	0.746	1.066	–	–	–	–
Disease duration (years)	0.906	0.997	0.952	1.044	–	–	–	
BSA at baseline (%)	0.211	1.027	0.985	1.070	–	–	–	
PASI Score at baseline	0.488	1.023	0.959	1.091	–	–	–	
TNFi agent (ETN *vs.* IFX)	0.098	0.313	0.079	1.241	0.053	[illegible]57	0	1.02
Combinations								
Topical therapy	0.341	0.564	0.173	1.836			–	
Phototherapy	0.549	1.333	0.520	3.417		–	–	–
Systemic non-biologic treatment	0.132	2.091	0.801	5.458		–		–
Previous treatment								
Topical therapy	0.389	2.000	0.413	9.681	–	–	–	–
Phototherapy	0.717	1.250	0.374	[illegible]	–	[illegible]	–	–
Systemic non-biologic treatment	0.873	0.926	0.360	[illegible]	–	[illegible]	–	–
Pre-systemic biologic treatment	**0.008**	0.057	0.007	0.480	**0.001**	[illegible]6	0.000	0.114

Factors affecting PASI 75 achievement at M6 were analyzed by u[illegible]riate logistic [illegible]ession model, and all factors with $p < 0.1$ were further detected by multivariate logistic regression [illegible] $p < 0.05$ [illegible] considered significant. BMI, body mass index; BSA, body surface area (affected by psoriasis); PASI, [illegible]d severity index; ETN, etanercept; IFX, Infliximab.

Table III. Analysis of factors affecting [illegible] achieven[illegible]er 6-month TNFi treatment.

	Univari[illegible]model				Multivariate model			
	[illegible]ue	OR	95% CI Lower	95% CI Higher	*p*-value	OR	95% CI Lower	95% CI Higher
Calprotectin at M[illegible]	[illegible]	1.000	1.000	1.001	–	–	–	–
ΔCalprotectin ([illegible]M1)	0.1[illegible]	1.000	1.000	1.001	–	–	–	–
Age (years)	0.454	1.017	0.974	1.062	–	–	–	–
Gender ([illegible])	0.394	1.592	0.547	4.634	–	–	–	–
BMI ([illegible])	0.860	0.985	0.828	1.170	–	–	–	–
Dis[illegible]duration[illegible]rs)	0.830	1.005	0.960	1.052	–	–	–	–
BS[illegible]seli[illegible])	0.195	1.027	0.987	1.068	–	–	–	–
PASI [illegible]seline	0.805	1.008	0.947	1.073	–	–	–	–
[illegible]Fi ag[illegible]TN *vs.* [illegible]	0.560	0.706	0.219	2.276	–	–	–	–
[illegible]inatio[illegible]								
[illegible]ical ther[illegible]	0.231	0.503	0.164	1.549	–	–	–	–
[illegible]otherapy	0.705	0.835	0.327	2.129	–	–	–	–
[illegible]-biologic treatment	0.517	1.363	0.534	3.476	–	–	–	–
[illegible]revious t[illegible]tment								
Topical therapy	0.991	1.009	0.209	4.876	–	–	–	–
[illegible]hototherapy	0.712	1.261	0.369	4.312	–	–	–	–
[illegible]ystemic non-biologic treatment	0.915	0.950	0.372	2.429	–	–	–	–
Pre-systemic biologic treatment	–	–	–	–	–	–	–	–

Factors affecting PASI 90 achievement at M6 were analyzed by univariate logistic regression model, and all factors with $p < 0.1$ were further detected by multivariate logistic regression model. $p < 0.05$ was considered significant. Pre-systemic biologic treatment was not analyzed due to lack of effective events. HCs, health controls; BMI, body mass index; BSA, body surface area (affected by psoriasis); PASI, psoriasis area and severity index; ETN, etanercept; IFX, Infliximab.

lated protein that is involved in the development of various diseases resulted from excessive inflammation and immune disorder[9-11,17]. Accumulating evidence indicates that high expression of calprotectin is observed in RA, SLE and inflammatory bowel disease (IBD); also, it could be served as a convincing diagnostic biomarker in these diseases[10,18,19]. In accordance with these studies, increase of calprotectin was found in psoriasis patients compared with HCs in this study, and it disclosed a good diagnostic value of psoriasis. The possible reason is that calprotectin is secreted by monocytes and neutrophils, and their concentrations reflect inflammation disorder in psoriasis patients directly[20]. The main significance of increased levels of calprotectin is related to inflammation, while it is not the only one. According to previous studies, increased level of calprotectin is also correlated with immune responses through controlling some medically relevant bacteria and fungi including *S. aureus, Candida albicans*, and *Aspergillus fumigates*[21,22]. Further study about detailed mechanisms of calprotectin in psoriasis is greatly needed.

In addition, we also found that calprot[illegible] expression was positively associated with [illegible] score, while no correlation between calpro[illegible]n expression and BSA was revealed in our w[illegible]. The possible explanation might [illegible] that PA[illegible] score is a comprehensive ass[illegible] of disea[illegible] severity considering BSA, [illegible]nema[illegible]a, infil[illegible]trated degree and desqua[illegible]n deg[illegible] which is greatly influenced by i[illegible]dan[illegible]io[illegible]. [illegible] has been demonstr[illegible] to be a[illegible] nflammation protein; its upre[illegible]n in psoria[illegible]atients correlates with b[illegible] i[illegible]mation, w[illegible] may result in the [illegible]ere comp[illegible]sive disease severity. As to B[illegible] it's just an i[illegible] of disease severity inste[illegible] a co[illegible]prehensive [illegible]easurement, thus the [illegible]ence [illegible]SA by inflammation associated with [illegible]n was [illegible]ser[20,23-25].

TNF, [illegible]reat [illegible]y consisted of TNF-α, [illegible]β an[illegible] have been established their va[illegible] on no[illegible]y repressing cell growth, re[illegible]fection, but also participating in in[illegible] and improving cell proliferation nd differentiation[26-29]. As to psoriasis patients, [illegible]F, particularly in TNF-α (occupying 70-95% o[illegible] TNF family), could induce the production of inflammation medium, such as interleukin-1 (IL-1), IL-8 and prostaglandin E2 (PGE2), promoting inflammation. Also, it could increase mitogen proliferation and Ig secretion, causing excessive keratinocytes proliferation and differentiation[30-34]. Therefore, TNFi treatment focus on inhibiting TNF expression, decreasing inflammatory cytokines activation and suppressing keratinocytes proliferation, thereby blocking inflammation and contributing on remission of skin lesions in psoriasis patients[6,35-37]. These could be used to explain the findings i[illegible] study; after TNFi treatment, high[illegible]cts o[illegible] PASI75 of 58.3% and PASI90 of [illegible]% at M6 were observed. Furthermore, we als[illegible]nd that calprotectin expression show[illegible]apidly [illegible]ease from M0 to M6. The pos[illegible]cause is th[illegible] Fi treatment controlls i[illegible]mmatio[illegible] decrea[illegible] activation of inflamma[illegible]me[illegible]ors, resulting in the reduction o[illegible]pro[illegible]xpressi[illegible][39].

As to predi[illegible] value, [illegible]otec[illegible] expression has bee[illegible]ed as a po[illegible] biomarker to predict [illegible]eatm[illegible] response [illegible] several diseases, including RA[illegible] inflammatory bowel dise[illegible]. Among t[illegible] decreased level of se[illegible] calprotectin was [illegible]und in RA patients c[illegible]pared with H[illegible]s, and a rapid reduction of serum calprotectin levels predicted the early clinical response to biological treatments[40]. Lower fecal [illegible] expression was also observed in patients with ulcerative colitis than that of [illegible] and its decrease could predict remission [illegible]se[42]. Partially in line with these results, our study revealed that decrease of calprotectin during the first month in PASI75 group was higher than that of Non-PASI75 group, and it could independently predict PASI75 achievement after 6-month TNFi treatment. Hence, the early changes of calprotectin expression might have potential effects on prediction of TNFi treatment response. There are two possible reasons: one reason is that a rapid change in calprotectin expression could reflect a sharp decrease of inflammation cytokines and reduction of inflammation severity in psoriasis patients, resulting in the sustaining remission of skin lesion in psoriasis patients, thereby decreasing PASI score[39,43]. Another is that fast decrease of calprotectin could regulate several immune cells, including T-helper (Th) 1, Th2 as well as Th17 cells, and so on, which contributes to improvement of skin lesion, decreasing PASI score[24,44,45]. Several limitations still existed in the current study: (1) the follow-up duration of 6 months was relatively short, hence, our study did not explore the long-term response; (2) correlations of calprotectin expression with inflammation cytokines, keratinocytes and angiogenesis were not assessed; (3) sample size was relatively small;

(4) detailed mechanism of calprotectin in psoriasis was not explored. Further investigations with longer follow-up duration and larger sample size need to be carried out in the future.

Conclusions

We showed that serum calprotectin expression is correlated with risk and severity of psoriasis. The decrease of calprotectin during the first month could predict better clinical response to TNFi treatment in psoriasis patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, Gelfand JM. Psoriasis and comorbid diseases: epidemiology. J Am Acad Dermatol 2017; 76: 377-390.
2) Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet 2007; 370: 263[illegible].
3) Cather JC, Young M, Bergman MJ. Psoriasis psoriatic arthritis. J Clin Aesth[illegible]matol 20[illegible] 10: S16-S25.
4) Farahnik B, Sharma D, Alp[illegible] Sivaman[illegible]. Topical botanical agents for th[illegible]tment [illegible]oriasis: a systematic review. [illegible] J [illegible] De[illegible] 451-468.
5) Wu JJ, Rowan[illegible] Bebchuk JD, [illegible]ony MS. Association b[illegible]nor necrosi[illegible]or inhibitor (TNFi) the[illegible]y and[illegible]nges in C-re[illegible]tive protein (CRP)[illegible]od pressu[illegible]d alanine aminotransfera[illegible]LT) among pa[illegible] with psoriasis, psori[illegible]arthritis or rheumat[illegible]thritis. J Am Acad [illegible]matol 2[illegible]72: 917-919.
6) [illegible]C[illegible]Dobao P. Tumor necrosis factor inhibitor[illegible]nuclear [illegible]odies, and autoimmunity in patie[illegible]ith p[illegible]sis. Actas Dermosifiliogr 2017; [illegible]08: 39[illegible]
7) [illegible]alprotect[illegible]zinc, and abscesses. Lancet 1991; [illegible]55-856.
8) Carr[illegible]D, Corfield A, Spicer R, Cairns P. Faecal calprotectin concentrations and diagnosis of necrotising enterocolitis. Lancet 2003; 361: 310-311.
9) Hurnakova J, Hulejova H, Zavada J, Komarc M, Hanova P, Klein M, Mann H, Sleglova O, Olejarova M, Forejtova S, Ruzickova O, Vencovsky J, Pavelka K, Senolt L. Serum calprotectin discriminates subclinical disease activity from ultrasound-defined remission in patients with rheumatoid arthritis in clinical remission. PLoS One 2016; 11: e0165498.
10) Haga HJ, Brun JG, Berntzen HB, Cervera R, Khamashta M, Hughes GR. Calprotectin in patients with systemic lupus erythematosus: relation to clinical and laboratory parameters of disease activity. Lupus 1993; 2: 47-50.
11) Madsen P, Rasmussen HH, Leffers H, Honore B, Celis JE. Molecular cloning and expression of a novel keratinocyte protein (psoriasis-associ[illegible]ty acid-binding protein [PA-FABP]) th[illegible]high[illegible]ly up-regulated in psoriatic skin a[illegible]at shares similarity to fatty acid-binding pr[illegible] J Invest Dermatol 1992; 99: 299-305.
12) Griffiths CE, Reich K, Lebwo[illegible], van de [illegible]f P, Paul C, Menter A, Camero[illegible], Erickson J, Z[illegible] Secrest RJ, Ball S, Bra[illegible]K, Osu[illegible]un OO, Fernan MP, Nickoloff[illegible]Papp K[illegible]cover, investigators U-. Comp[illegible]on[illegible]nab with etanercept or plac[illegible]n mo[illegible]-to-sev[illegible]psoriasis (UNCO[illegible]2 and UNC[illegible]P-3)[illegible]ults from two pha[illegible]mised trials[illegible]2015; 386: 541-55[illegible]
13) Bar[illegible]J, Hoffmann[illegible]Vozel G, Ortonne JP, Zheng [illegible]oogstraten H[illegible]K. Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1). J Dermatol 2011; 165: 1109-1117.
14) [illegible]IT, Br[illegible]T, Gudjonsson JE, Johnston A, Stuart[illegible]T, Voorhees JJ, Abecasis GR, Nair RP. Molecular dissection of psoriasis: integrating genetics and biology. J Invest Dermatol 2010; 130: [illegible]1226.
15) Malecic N, Young HS. Excessive angiogenesis associated with psoriasis as a cause for cardiovascular ischaemia. Exp Dermatol 2017; 26: 299-304.
16) Rodriguez A, Griffiths-Jones S, Ashurst JL, Bradley A. Identification of mammalian microRNA host genes and transcription units. Genome Res 2004; 14: 1902-1910.
17) Pellegrini L, Milano E, Franceschi F, Belcaro G, Gizzi G, Feragalli B, Dugall M, Luzzi R, Togni S, Eggenhoffner R, Giacomelli L. Managing ulcerative colitis in remission phase: usefulness of Casperome(R), an innovative lecithin-based delivery system of Boswellia serrata extract. Eur Rev Med Pharmacol Sci 2016; 20: 2695-2700.
18) van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. BMJ 2010; 341: c3369.
19) Grossi V, Infantino M, Manfredi M, Meacci F, Bellio E, Bellio V, Gobbi FL, Ugolini S, Catani S, Sarzi-Puttini P, Atzeni F, Benucci M. A proposed serum calprotectin IgG cut-off level for diagnosing inflammatory arthritis. Curr Rheumatol Rev 2017; 13: 93-97.
20) Hagg D, Sundstrom A, Eriksson M, Schmitt-Egenolf M. Severity of psoriasis differs between men and women: a study of the clinical outcome measure Psoriasis Area and Severity Index (PASI) in 5438 Swedish register patients. Am J Clin Dermatol 2017; 18: 583-590.

21) Damo SM, Kehl-Fie TE, Sugitani N, Holt ME, Rathi S, Murphy WJ, Zhang Y, Betz C, Hench L, Fritz G, Skaar EP, Chazin WJ. Molecular basis for manganese sequestration by calprotectin and roles in the innate immune response to invading bacterial pathogens. Proc Natl Acad Sci U S A 2013; 110: 3841-3846.

22) Wakeman CA, Moore JL, Noto MJ, Zhang Y, Singleton MD, Prentice BM, Gilston BA, Doster RS, Gaddy JA, Chazin WJ, Caprioli RM, Skaar EP. The innate immune protein calprotectin promotes Pseudomonas aeruginosa and Staphylococcus aureus interaction. Nat Commun 2016; 7: 11951.

23) Alpsoy E, Polat M, FettahlioGlu-Karaman B, Karadag AS, Kartal-Durmazlar P, YalCin B, Emre S, Didar-Balci D, Bilgic-Temel A, Arca E, Koca R, Gunduz K, Borlu M, Ergun T, Dogruk-Kacar S, Cordan-Yazici A, Dursun P, Bilgi CO, Gunes-Bilgili S, Sendur N, Baysal O, Halil-Yavuz I, Yagcioglu G, Yilmaz E, Kavuzlu U, Senol Y. Internalized stigma in psoriasis: a multicenter study. J Dermatol 2017; 44: 885-891.

24) Carlesimo M, Garelli V, Fortuna MC, De Vita G, Sorriso-Valvo L, Buccolini F, Melini A, Di Nunno D, Pranteda G, Rossi A. Vascular Psoriasis Area Severity Index: A dermoscopic standard technique for assessing severity psoriasis and therapeutic management. J Dermatol Sci 2017; 6: 249-251.

25) Shrivastava VK, Londhe ND, Sonawane RS, S S. Exploring the color feature power for psor risk stratification and classification: a data m ing paradigm. Comput Biol M 15; 65: 5 68.

26) Watts TH. TNF/TNFR fa nembe costim- ulation of T cell respo Annu mmunol 2005; 23: 23-68.

27) Atretkhany KS, N o MA, va VS, Zvartsev RV, Qin Z, Ne v SA, Drut S. TNF neutralization he delay o splantable tumor gro and ed MDSC cumulation. Front unol 2016;

28) Jia Jiang R, Zhu X, X, Zhan Z. Genip- hibits T F-alpha-indu d vascular smooth cle c oliferation and migration via induc- f . PLoS ne 2013; 8: e74826.

Biss te R, H F, Krueger JG, Guertin MC, Thabo n, Gonzalez J, Maari C, Delo- me I, L v, Tardif JC. TNF-alpha antago- ist and v cular inflammation in patients with vulgaris: a randomized placebo-con- trol tudy. J Invest Dermatol 2017; 137: 1638-1645.

Blauvelt A. IL-6 Differs from TNF-alpha: unpredicted clinical effects caused by IL-6 blockade in psoriasis. J Invest Dermatol 2017; 137: 541-542.

31) Langkilde A, Olsen LC, Saetrom P, Drablos F, Besenbacher S, Raaby L,Johansen C, Iversen L. Pathway analysis of skin from psoriasis patients after adalimumab treatment reveals new early events in the anti-inflammatory mechanism of anti-TNF-alpha. PLoS One 2016; 11: e0167437.

32) Kimura Y, Shimada-Omori R, Takahashi T, Tsuchiyama K, Kusakari Y, Yamasaki K, Nishikawa R, Nishigori C, Aiba S. Therapeutic drug monitoring of patients with psoriasis during tumour necrosis factor (TNF)-alpha antagonist treatment using a novel interleukin-8 reporter cell line. Br J Derma 175: 979-987.

33) Lontz W, Sirsjo A, Liu W, Lindberg ollman O, Torma H. Increased mRNA expres manganese superoxide dismutase psori in lesions and in cultured hu keratino ex- posed to IL-1 beta and T lpha. Free R ol Med 1995; 18: 349

34) Colagiovanni A, Di Re Sar schiavino D, De Lorenzo A. Rol TN polymor m in patients with el allerg marker uscep- tibility to c polysensiti Rev Med Pharma 6: 20: 2663

35) Krueger , Calli otential of tumor necrosis fa hibitors in p sis and psoriatic arthri- Dermatol 20 0: 218-225.

36 u JJ. Tumor necrosis factor inhibitors and myocardial infarc in psoriasis. JAMA 2013; 310: 075-1076.

37) el FA, St BE. Tumor necrosis factor inhibis: an update. Semin Cutan Med Surg 3: S31-36.

Ferreiro-Iglesias R, Barreiro-de Acosta M, Lorenzo-Gonzalez A, Dominguez-Munoz JE. Accuracy of consecutive fecal calprotectin measurements to predict relapse in inflammatory bowel disease patients under maintenance with anti-TNF Therapy: a prospective longitudinal cohort study. J Clin Gastroenterol 2016 Dec 14. [Epub ahead of print]

39) Boschetti G, Garnero P, Moussata D, Cuerq C, Preaudat C, Duclaux-Loras R, Mialon A, Drai J, Flourie B, Nancey S. Accuracies of serum and fecal S100 proteins (calprotectin and calgranulin C) to predict the response to TNF antagonists in patients with Crohn's disease. Inflamm Bowel Dis 2015; 21: 331-336.

40) Choi IY, Gerlag DM, Herenius MJ, Thurlings RM, Wijbrandts CA, Foell D, Vogl T, Roth J, Tak PP, Holzinger D. MRP8/14 serum levels as a strong predictor of response to biological treatments in patients with rheumatoid arthritis. Ann Rheum Dis 2015; 74: 499-505.

41) Patro PS, Singh A, Misra R, Aggarwal A. Myeloid-related protein 8/14 levels in rheumatoid arthritis: marker of disease activity and response to methotrexate. J Rheumatol 2016; 43: 731-737.

42) De Vos M, Dewit O, D'Haens G, Baert F, Fontaine F, Vermeire S, Franchimont D, Moreels T, Staessen D, Terriere L, Vander Cruyssen B, Louis E, behalf of B. Fast and sharp decrease in calprotectin predicts remission by infliximab in anti-TNF naive patients with ulcerative colitis. J Crohns Colitis 2012; 6: 557-562.

43) Sipponen T, Savilahti E, Karkkainen P, Kolho KL, Nuutinen H, Turunen U, Farkkila M. Fecal calprotectin, lactoferrin, and endoscopic disease activity in monitoring anti-TNF-alpha therapy for Crohn's disease. Inflamm Bowel Dis 2008; 14: 1392-1398.

44) Wang K, Xuan XM, Tong L, Huang Q, Zhu LM, Ruan HL. [The role of Treg/Thl7 and calprotectin in ulcerative colitis rat model]. Sichuan Da Xue Xue Bao Yi Xue Ban 2014; 45: 946-949.

45) Wang K, Xuan X, Wang L, Tong L, Huang Q, Zhu L, Ruan H. [Expression and correlation analysis between inflammatory cytokines and calprotectin in the rat model of ulcerative colitis]. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 2014; 30: 278-280, 283.