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Short Communication

High dose Folic Acid Plus Vitamins B6 and B12 Added to Adalimumab can Worsen Psoriasis In Patients with Low BMIs and in Others May Cause Unanticipated EKG Effects

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Abstract

This was to be a study of 16 weeks adalimumab then 12 weeks adalimumab plus 5mg. folic acid, B6 and B12 in 10 patients. In the adalimumub-vitamin study four subjects showed psoriasis area and severity index reduction after B vitamin addition by week 28 (one more reported clearing by week 38). The study was stopped after eight subjects because one developed pneumonia before vitamins and, after vitamins were added, one subject who improved developed left axis deviation on vitamins. Two subjects flared. They had the 2 lowest BMIs.

Both were female. Both had baseline vascular endothelial growth factor (VEGF) levels of 140 pg/ml or higher. One male subject did also. One female had elevated H. pylori antibodies.

Five mg folic acid daily promotes creation of anti-inflammatory dimeric endothelial nitric oxide synthase (eNOS) over the inflammatory monomeric eNOSassuming folic acid absorption is not blocked by Helicobacter pylori. Leptin can maintain eNOS function. Lighter patients treated thusly would have less stable pro and anti-eNOS actions withproinflammatoryVEGF less opposed.

ABBREVIATIONS

BMI: body mass index; eNOS: endothelial nitric oxide synthase; pg/ml: picograms per milliliter; iNOS: inducible nitric oxide synthase; IV: intravenous; mcg: micrograms; mg: milligrams; mRNA: mitochondrial ribonucleic acid; NO: nitric oxide; PASI: psoriasis area and severity index; PPD: purified protein derivative tuberculosis skin test; TB: tuberculosis; VEGF: vascular endothelial growth factor; VEGFR-2: vascular endothelial growth factor receptor 2

INTRODUCTION

Homocysteine affects psoriasis by affecting neutrophil function [1,2]. Folic acid with vitamins B6 and B12 lowers homocysteine [3]. Plasma folic acid levels inversely correlate with psoriasis area and severity index (PASI). [4]

Folic acid derivatives reduce oxidative injury by creating anti-inflammatory endothelial NOS (eNOS) dimers [5-6] A published study suggested increased psoriasis risk with low dietary folate equivalent in beer drinkers, however, study median daily folate intake was 976-1000 mcg [7].

Flow –mediated vasodilation is regulated by endothelial nitric oxide (NO) release. Endothelial nitric oxide synthase (eNOS) synthesizes NO. Five mg/day, but not 400 mcg/day, folic acid improves blood vessel cell function measured by flow mediated vasodilation [8]. Low dose folic acid creates uncoupled monomeric eNOS results leading to reduction of net NO synthesis and to pro-inflammatory superoxide generation a change called eNOS uncoupling [9,10]. High dose folates in contrast are anti-inflammatory [9].

Endothelial NOS generally produces low NO levels. Inducible NOS (iNOS) is induced by cytokines and microbial factors and produces high NO levels [1,12]. mRNA expression of iNOS appears to promote inflammation since it is markedly and continuously increased in psoriasis [12]. However, iNOS coupling using tetrahydrobiopterin and L-arginine is anti-inflammatory and there is an anti-inflammatory effect of iNOS-created NO

after exposure to reactive oxygen species [1,12]. Quantitative statistical analysis of two genome wide association studies of psoriasis identified iNOS as one of several susceptibility loci for psoriasis [13]. Etanercept (another TNF-alpha blocking medication)-cleared psoriasis skin has 87% less iNOS [14]. High dose folic acid reduces eNOS [15] and, at least in animal models, iNOS [16].

Two published cases by the authors showed improved of psoriasis at least in part by the addition of 5 mg folic acid, 100 mg vitamin B6 and 100 mcg B12 [17].

MATERIALS AND METHODS

Subjects were non-immunocompromised and ≥18 years old with moderate-to-severe (>10% BSA) plaque psoriasis who are candidates for systemic therapy and adalimumab naive.

There was to be a total of 10 subjects.

Subjects must have met pre-study inclusion and exclusion criteria (Tables 1, 2). They must undergo an active washout (discontinue restricted medications) prior to starting the study treatment at Week 0

Adalimumab was given by subcutaneous injection Week 0- 80 mg then Week 1- 40 mg, then 40 mg every other week to completer a 28 weeks study. At week 16 folic acid 5mg, vitamin B6 100 mg and B12 1000 mcg were added daily. All were to be measured at: Week 0 [Baseline], and Week 28.

Table 1: Adalimumab-B-vitamin Study Inclusion Criteria.

Subject
Is a non-immunocompromised male or female\ 18 years of age or older
Has moderate-to-severe (≥10% total body surface area prior to therapy) plaque psoriasis
Has a negative urine pregnancy test within 7 days before the first dose of adalimumab in all women (except those surgically sterile or at least 5 years postmenopausal)
Must sign/date the appropriate written informed consent and HIPAA authorization
If sexually active: subjects of childbearing potential must agree to use medically acceptable form of contraception during screening and throughout the study
Has no evidence of active or latent tuberculosis based on a negative PPD skin test performed at screening, or within one year of starting this study. Patients with documentation of adequately treated tuberculosis may be enrolled. Patients who are PPD positive and CXR negative can be enrolled if they finish appropriate INH prophylaxis prior to enrollment
Is willing and able to self-administer subcutaneous injections or to have a qualified person available to administer subcutaneous injections
Agrees to comply with protocol requirements, attend all regularly study visits and is considered to be a good study subject
Meets concomitant medication washout requirements
Is willing to use only allowed psoriasis medications and treatments (see below entitled “Allowed psoriasis medications/treatment”) and agree not to start any topical, systemic, or phototherapy for psoriasis during the study period
Is adalimumab naïve.

Table 2: Adalimumab B-Vitamin Study Exclusion Criteria.

Subject
Has erythrodermic, pustular, or guttate psoriasis
Has evidence of skin conditions other than psoriasis that would interfere with study-related evaluations of psoriasis
Has a known sensitivity to any component of the study medications
Has evidence of active infections such as fevers, chills, sweats, or history of untreated
Has had Lyme disease and active severe infections within 4 weeks before screening visit, or between the screening and Week 0 visits.
Has a history of listeriosis, untreated TB, persistent or active infections requiring hospitalization or treatment with IV antibiotics, IV antiretrovirals, or IV antifungals within 30
Days of baseline, OR oral antibiotics, antivirals, or antifungals for purpose of treating infection,
Within 14 days of baseline
Has a positive PPD and positive chest x-ray for latent or active tuberculosis
Has positive PPD and negative chest x-ray that have not completed appropriate INH prophylaxis
Has history of immune compromised status [e.g. human immunodeficiency virus (HIV) positive status or other immune suppressing drug] or a congenital or acquired immunodeficiency
Has a poorly controlled medical condition including, but not limited to, unstable cardiovascular disease, poorly controlled diabetes, recent stroke, history of recurrent infections, or any other condition for which, in the opinion of the investigator, participation in the study would place the subject at risk
Has a history of congestive heart failure
Has a history of demyelinating CNS disease
Has a history of malignancy (other than previously treated localized carcinoma in situ of the cervix or previously treated non-melanoma skin cancer)
Has a history of or ongoing drug or alcohol abuse
Has past or present psychiatric morbidity which may compromise the study in the opinion of the investigator
Is a pregnant woman, nursing mother, or woman planning to become pregnant during the study or within 150 days after the last dose of study medication, or male subjects planning a pregnancy with their spouse/partner while in the study are to be excluded
Plans to receive any live vaccines during the study
Has a history of liver disease (e.g. hepatitis, cirrhosis)
Is currently enrolled in another clinical study and/or is on treatment with another experimental drug or approved therapy for experimental use within 30 days prior to Week 0
Has previously been enrolled in this study
Cannot commit to all the assessments required by the protocol
Has any disorder that compromises the ability of the subject to give written informed consent and/or to comply with study procedures
Is considered by the investigator, for any reason, to be an unsuitable candidate for study participation
Cannot or does not wish to comply with the protocol washout requirements
Is on oral folic acid in doses greater than the minimal daily requirements
Is on doses of vitamins greater than the minimal daily requirements (multivitamins are allowed)
Has history of colon polyps or colon cancer
Has a prior history of adalimumab therapy

Height and Weight, PASI scores, Physician Global Assessment of Psoriasis, Static Physician Global Assessment of Psoriasis and Dermatology Life Quality Index, serum magnesium, serum phosphorus, complete blood cell count with differential, homocysteine, serum B6, serum B12, serum folic acid, and VEGF measured at weeks 0, 16 and 28. EKG was to be measured weeks 0, 16 and 28. Helicobacter pylori antibody was to be measured at baseline.

Post drug portion of study telephone call: a telephone call day 70 post study.

Table 3 summarizes the results (but after the study was approved, it was found that full adalimumab effect may not occur until week 33) [18].

RESULTS AND DISCUSSION

The study was stopped after 8 subjects were enrolled with only 7 completing the study because one subject was hospitalized for pneumonia before starting the vitamins and was therefore

Table 3: Adalimumab- B Vitamin Study Results.

Subject	Sex	Age	Week	Weight In Pounds	BMI week 0	PASI	DLQI	Folic	H. pylori	Hcy	VEGF	EKG
7	F	23	0	136	23	13.6	16	18.3		7.3	259	normal
			4	136.6		0.4	3					
			16	134.2		0.4	3	18.2	<0.89	6.5	39	normal
			28	134.4		0.8	2					
8	F	65	0	163.6	24.9	8	17	6.4	5.7	24.7	147	normal
			4	159.4		3.2	8					
			16	169		2.6	9	4.3		15.7	68	n/s ST-T
			28	165.8		3.4	9					n/s ST-T
3	M	31	0	202	26.6	12.2	10	7.3	0.39	8.6	144	normal
			4	202.8		1.5	2					
			16	202.4		1.4	0	5.5		8.1	27	normal
			28	206		0.5	1	11.4	0.47	5	37	LAD
10	M	48	0	193.2	27.3	30	11	11.2	0.55	16.8	44	normal
			4	195.8		11	0					
			16	201.6		0.6	0	11.7			19	normal
			28	195.8		0.6	0	>20	0.52	12.7	28	normal
9	M	56	0	171	29.4	15.3	23	9		12.9	19	normal
			2	168		6.3	5					
			16	159.8		0.5	0	6.9		12.5	26	LAD
			28	158.8		0	0	>20	5.07	18	126	normal
2	M	44	0	225	31.4	35.6	11					
			4	226		18.2	2					
			16	228		2.8	4	>20		11	35	brady
			28	218.8		1.5	0	>20	0.22	9.8	22	brady
11	M	62	0	241.9	37.9	36	30	13.3	<0.89	15	68	RBBB
			4	242		15.2	5					
			16	234.5		4.4	2	>20		18	55	RBBB
			28	233.6		3	0	>20		13.4	222	RBBB
1	F	49	0	255.2	44.8	25.9	15	7.4	0.27	11.9		Prolonged QT
			4			30.9	3					
			SAE									

Note: Subjects 4, 5 and 6 failed screening

Abbreviations: BMI: body mass index; **brady:** sinus bradycardia; **DLQI:** Dermatology Life Quality Index; **EKG:** electrocardiogram; **F**:Female ; **Hcy:** serum homocysteine in micromoles per liter; **H. Pylori**: Helicobacter pylori IgG enzyme linked immunosorbent assay; **M:**male; **n/s ST-T**: nonspecific ST segment and T wave electrocardiogram changes; **PASI**: Physician's Area and Severity Index; **RBBB**: right bundle branch block; **SAE**: serious adverse event; **VEGF**: vascular endothelial growth factor in pictograms per milliliter

disqualified from completing the study this was a serious adverse event. second subject developed left axis deviation at week 28 after vitamins were added to adalimumab. One subject developed st-t wave EKG changes not thought to be significantly different from a baseline EKG which was read as normal. A third subject, however, normalized left axis deviation after B vitamins were added. Two subjects' psoriasis worsened after the vitamins were added to the adalimumab. These 2 subjects had the 2 lowest BMIs. Both are women, one was premenopausal and the other post-menopausal. Both had baseline vascular endothelial growth factor levels (VEGF) greater or equal to 140 pg/ml (a third subject with levels this high improved). Helicobacter pylori antibody was elevated prior to B vitamins in one subject who flared and one who improved (Table 3).

VEGF fell after just adalimumab was added in 4 of 5 subjects where it was measured but after vitamins were added levels 4 of 5 subjects' VEGF rose including 3 of the 4 subjects who improved and one subject whose PASI did not change after the vitamins were added (Table 3) (though he reported clearing when contacted day 70 after the week 28 study visit). Homocysteine levels fell in 4 subjects who improved or did not worsen and rose in 1 after B vitamins were added (Table 3). One subject whose homocysteine (and all 3 B vitamin levels) rose also had his VEGF rise after vitamins. He was the subject whose left axis deviation left after B vitamins were added to his adalimumab (Table 3).

Psoriasis worsened in the two subjects with the lowest BMI. It has been shown that VEGF levels Therefore it was unfortunate that leptin was not measured in this study. Endothelial nitric oxide synthase (eNOS) is maintained when blood vessels are incubated with leptin. [19] Patients with psoriasis have increased leptin. [20] Lower BMI patients generally have less leptin [21]. TNF alpha reduces eNOS mRNA [22]. Adalimumab, by inhibiting TNF-alpha, could increase eNOS mRNA. High folic acid promotes anti-inflammatory dimeric eNOS. Therefore, it seems that obese people would have better maintained dimeric eNOS activity than thinner people. However, on lower folic acid doses the obese have more and better maintained proinflammatory monomeric eNOS.

Female sex cannot be eliminated as relevant to a subject flaring after vitamins are added to adalimumab. Both subjects who flared were women, one pre- and the other post-menopausal, We, however have published an erythrodermic psoriasis patient who responded well to 5 mg folic acid plus B12 and B6 [19]. A study has shown that serum leptin levels in male and female psoriasis patients are similar [21]. Others have found no differences in VEGF blood concentrations in men and women [23]. In our study, however, baseline VEGF was above or equal to 140 pg/ml in both women while such baselines levels were found in only one of four men so studied.

Elevated Helicobacter pylori IgG is not 100% predictive of H. pylori infection [24]. If present it may inhibit folic acid absorption raising homocysteine [25] or, when high doses are given, creating pro-inflammatory monomeric eNOS instead of anti-inflammatory dimeric eNOS [9-12]. Both situations can cause psoriasis to flare.

Psoriasis is a disorder with elevated VEGF [26]. Adalimumab lowers VEGF [27]. The addition of B vitamins may increase VEGF flaring psoriasis [28]. In animals [29,30] and in human bone marrow stem cells [31] Hcy also reduces expression of VEGF-A, VEGF and VEGFR-2. Reducing Hcy with B vitamins therefore might sometimes increase VEGF.

TNF-alpha can enhance iNOS mRNA and NO in mice [32]. Blocking TNF-alpha therefore might reduce NO. In mice, up regulation of iNOSmRNA appears to lead to increased NOS and increased superoxide generation which might cause cardiac ischemia and secondary enlargement [33]. Blocking TNF-alpha therefore should have been cardio –protective, but in one one subject left axis deviation appeared on adalimumab alone and in a second it appeared after high dose folic acid, B6 and B12 were added to the adalimumab.

CONCLUSION

Five mg daily folic acid plus B6 and B12 and adalimumab worsens psoriasis in our subjects with low BMIs. EKG changes may be an impediment for use in patient with higher BMIs. Addition of these vitamins may not improve psoriasis over the effects of adalimumab alone. The combination of adalimumab and high dose folic acid cannot for now be recommended.

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Conflict of Interest

Aronson Peter J: Investigator initiated Study: A single center open-label study to Assess the effects of the addition of modulators of homocysteine to adalimumab in the treatment of moderate to severe plaque psoriasis. Abbott Pharmaceuticals, HUM 07-035. clinicaltrials.gov NCT10704599. OBSERVE 5: 5 year safety study of etanercept for moderate to severe plaque Psoriasis.Amgen. Clinicaltrials.gov. NCT00322439. (sinceetanercept is functionally similar to adalimnumab and effects of this drug are mentioned in the text of this article).

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Dr. Aronson personally has psoriasis and it has flared on 1-2 mg folic acid but has cleared twice on 5-7 mg folic acid without biologicals.(why is may be conflict of interest: www.news.harvard.edu/gazette/2004/04.29/11-selfexperiment.htm).

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