PHARMACOTHERAPY

The Daily Therapy With L-Arginine 2,500 mg and Tadalafil 5 mg in Combination and in Monotherapy for the Treatment of Erectile Dysfunction: A Prospective, Randomized Multicentre Study

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ABSTRACT

Introduction: A synergistic effect of the combination therapy tadalafil plus L-Arginine is conceivable in patients affected by erectile dysfunction (ED).

Aim: To evaluate the effectiveness and tolerability of tadalafil 5 mg and L-Arginine 2.5 grams in monotherapy and combination therapy.

Methods: Recruited patients completed the International Index of Erectile Function — Erectile Function domain (IIEF-EF) and Sexual Encounter Profile diaries completed at baseline and after treatment. The survey was randomized into 3 groups with an equal allocation ratio. Group A received daily L-Arginine 2,500 mg, group B received daily tadalafil 5 mg, and group C received both daily L-Arginine 2,500 mg plus daily tadalafil 5 mg. The duration of therapy in all 3 groups was 12 weeks. Safety was assessed by evaluating all reported treatment-emergent adverse events.

Main Outcome Measure: The main outcome measure was the change in IIEF-EF score and in per-patient percentage of "yes" responses to Sexual Encounter Profile Question 3 from baseline to after treatment.

Results: 300 eligible patients were enrolled, and 100 subjects for each group were allocated. Based on the IIEF-EF score, the participants were divided into 3 categories: severe, moderate, and mild ED. IIEF-EF score increased in group A from 15 ± 7 to 18.1 ± 9.2, in group B from 14.8 ± 6.9 to 20.8 ± 7.3, and in group C from 14.9 ± 7.1 to 22 ± 7.5. In mild ED group, the mean IIEF-EF score increased from 22.1 ± 2.2 to 27.5 ± 2.3 in group A; from 22.1 ± 2.2 to 27.8 ± 2 in group B, and from 22.2 ± 2.2 to 29.3 ± 0.9 in group C. We report a total of 11, 53, and 67 cases of adverse events in group A, B, and C respectively.

Conclusions: Combination therapy was superior to monotherapies. **Gallo L, Pecoraro S, Sarnacchiaro P, et al. The Daily Therapy With L-Arginine 2,500 mg and Tadalafil 5 mg in Combination and in Monotherapy for the Treatment of Erectile Dysfunction: A Prospective, Randomized Multicentre Study. Sex Med 2020;8:178—185.**

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Key Words: Erectile Dysfunction; L-arginine; Tadalafil; Combination Therapy

INTRODUCTION

Erectile dysfunction (ED) is a very common disease affecting millions of individuals worldwide, which is defined as the inability to achieve or maintain an erection sufficient for a satisfactory sexual activity.[1] The prevalence of this condition increases with age affecting the 52% of men aged between 40 and 70 years.[2] Phosphodiesterase type 5 inhibitors (PDE5is) are currently the first-line treatment for any type and etiology of ED.[3] In particular, the PDE5i with a longer duration of action as that of tadalafil has a half-life of >17 hours, and provides greater flexibility, less anxiety, and major spontaneity to sexual activity.[4] Tadalafil provides a continuous PDE5 inhibition levels sufficient for ED treatment in most patients.[5] However, PDE5is are not

always the adapted treatment because a selected subgroups of patients, the so called "difficult to treat" populations affected by severe ED, remains refractory to these molecules.[6] Penile erection is determined by a dynamic vascular process involving relaxation of the arterial and trabecular smooth muscle in the corpora cavernosa.[7] The essential mediator required for penile erection is nitric oxide (NO).[8] NO binds to guanylate cyclase inside the cells of vascular smooth muscle generating the cyclic guanosine monophosphate that acts as a second messenger to exert relaxation and vasodilation determining the penile erection.[9] NO is generated by an enzyme named NO synthase, whose only physiological substrate is the semiessential amino acid L-arginine.[10] Because an increased concentration of the substrate leads to a higher amount of NO into account, L-arginine was showed in many studies being an effective treatment for ED, especially for patients affected by mild to moderate ED.[11] In particular, the natural origin of this amino acid, its good bioavailability after oral absorption, and its excellent tolerance allowing long-course therapy has made arginine a widely used supplement by men seeking natural treatment and/or self-medication for ED.[12] Since PDE5i enhance NO activity and require this molecule to exert their action, is conceivable a synergistic therapeutic approach based on the concomitant subscription of these molecules with L-Arginine. However, surprisingly, although both tadalafil and arginine were already evaluated in combination therapy with many others drugs or supplements in several studies, to the best of our knowledge, the synergistic and concomitant subscription of these 2 molecules was never been investigated. The aim of this prospective, randomized, multicenter study was to evaluate the effectiveness and tolerability of tadalafil 5 mg and L-Arginine 2.5 gm in monotherapy and combination therapy in patients affected by various grades of ED.

METHODS

All patients affected by ED who came to our 4 centers specialized in male sexual dysfunction were considered for recruitment in this prospective, randomized, multicenter, three-arm study. The diagnosis of ED at first consultation was based on sexual and medical history, physical examination, and standard laboratory analysis. For all recruited patients, age, marital status, cigarette smoking, full medical history, and current therapy were recorded. At the baseline visit, all patients completed the Italian translation of the 2 questionnaires: the International Index of Erectile Function-erectile function (IIEF-EF) domain (defined as the sum of responses to IIEF questions 1−5 and 15) and Sexual Encounter Profile (SEP) diaries. Both the 2 questionnaires (IIEF-EF and SEP diaries) have been shown to be simple, reliable, and valid tools for the assessment of erectile function in clinical trials research.[13,14] The inclusion criteria of the present study were: age ≥18 years, patients suffering from ED for at least 3 months, an IIEF-EF score totalized at first consultation ≤25 (IIEF-EF score can range from 1, severe ED, to 30, normal erection), and men in a stable relationship desiring

an active heterosexual life. The exclusion criteria were: kidney disease of any type and severity, macroalbuminuria, severe retinopathy, liver failure, coronary heart disease, peripheral or cerebrovascular disease, diabetic or non-diabetic neuropathy, endocrine diseases, pelvic surgery, drug or alcohol abuse, testes hypotrophy, Peyronie's disease, and major psychiatric disorders. The following medications were contraindicated during the trial: nitrates, estrogens, antiandrogens, anxiolytic drugs, LH-RH analogs, and tricyclic antidepressants. The consumption of other drugs that may have affected erectile disorders and may have been prescribed once a patient had entered the trial was restricted. Patients who had previously received one of the trial treatments within 30 days before inclusion into the trial were also excluded. Patients were recruited based on the total score of the IIEF-EF questionnaire and were further divided into 3 categories: severe ED (score 1−10), moderate ED (score 11−17), and mild ED (score 18−25). All patients were asked to sign an informed consent form in conformity with the Declaration of Helsinki. The ethics committees of all participating institutions approved the study. All eligible patients were randomized in 3 groups with an equal allocation ratio (1:1:1). The randomization sequence was generated using a computer by the study coordinating team. Treatment allocation was communicated by the coordinating center to the investigators through a web-based registration system to ensure allocation concealment and minimize bias. Recruited patients were treated as follows: group A received L-arginine 2,500 mg daily, group B received tadalafil 5 mg daily, and group C received both L-arginine 2,500 mg plus tadalafil 5 mg daily. The duration of the therapy in all 3 groups was 12 weeks. At the end of treatment, all the subjects underwent a second visit where they again completed the IIEF-EF questionnaire and the SEP diaries Figure 1). All patients were examined in each center by a certified urologist specialized in male sexual dysfunction who evaluated the adverse events (AEs) and assisted patients to fill the questionnaires at the baseline and at the control visit.

The main outcome measures were the changes from the baseline to after treatment in the IIEF-EF score and in the per-patient percentage of "yes" responses to SEP question 3 (SEP3: "Did your erection last long enough for you to have a successful intercourse?").

Safety was assessed by evaluating all reported treatment-emergent AEs and standard safety laboratory assessments for all randomized patients. Treatment-emergent AEs were defined as any AE that first occurred or worsened after randomization and were mapped with the Medical Dictionary for Regulatory Activities.

At the beginning of the study, the one-way analysis of variance (ANOVA) was performed at the baseline to verify the homogeneity of the 3 groups related to all the parameters evaluated. Subsequently, to check the efficacy of all the 3 therapeutic protocols evaluated in the present study, the mean IIEF-EF scores before and after treatment were compared by Student's t-test,

whereas the per-patient percentage of "yes" responses to SEP 3 before and after treatment was analyzed by a z test (hypothesis tested for means and proportions, respectively.) In the first case, the hypothesis of homogeneity of variances was preliminarily verified. This verification concerned both the overall sample and the 3 ED severity class subgroups (mild, moderate, and severe).

To test the superiority of a protocol with respect to the others (A vs B, A vs C, and B vs C), once the homogeneity of the 3 groups was verified at the baseline, we compared the improvements in the IIEF-EF score obtained by the 3 treatments considering both the overall population and the 3 ED severity categories. This analysis was executed using the one-way ANOVA considering the differences as variables in the mean IIEF-EF score before and after the treatment. If the null hypothesis was rejected, each pair of the mean IIEF-EF score was compared through 3 different statistical tests: LSD, Bonferroni, and Scheffè. For each pair of IIEF-EF scores (before and after treatment), the null hypothesis was that the difference of the 2 values was zero, whereas the alternative was that they differed significantly between them. A chi-square test was performed to evaluate the total incidence of AEs in the 3 groups. The data analysis was performed using the IBM SPSS Statistics v.22 by a professional statistician.

RESULTS

A total of 300 eligible patients satisfying the inclusion/exclusion criteria were enrolled, and 100 subjects were allocated for each group. The 3 groups were homogenous at the baseline because there were no significant differences for the following features: mean age, prevalence of diabetes, prevalence of cardiovascular risk factors (including at least 1 of the following: hypertension, hyperlipidemia, obesity, and smoking), mean IIEF-EF score, category of ED severity distribution, and percentage of "yes" responses to SEP question 3 (Table 1). All patients completed the treatment except one included in group B who was affected by severe ED. The overall IIEF-EF score increased at the follow-up visit after the completion of therapy in

all the 3 groups: in group A (L-arginine), the mean IIEF-EF score increased from 15 ± 7 to 18.1 ± 9.2 ($P = .089$); in group B (tadalafil), from 14.8 ± 6.9 to 20.8 ± 7.3 ($P < .001$); and in group C (L-arginine + tadalafil), from 14.9 ± 7.1 to 22 ± 7.5 ($P < .001$). The increase in the mean IIEF score after treatment was of 3.1, 6, and 7.1 points in group A, B, and C, respectively. The increase in the mean IIEF score was statistically significant in Student's t-test for all the 3 groups after therapy. The percentage of "yes" responses to SEP question 3 increased from 43% to 54% in group A ($P = .007$), from 41% to 62.6% in group B ($P < .001$), and from 42% to 63% in group C ($P < .001$). The benefits of the 3 different therapeutic protocols tested in the present study were further analyzed according to category of ED severity. In the mild-ED population, the mean IIEF-EF score increased from 22.1 ± 2.2 to 27.5 ± 2.3 in group A ($P < .001$), from 22.1 ± 2.2 to 27.8 ± 2 in group B ($P < .001$), and from 22.2 ± 2.2 to 29.3 ± 0.9 in group C ($P < .001$). The increase in the mean IIEF score was of 5.4, 5.7, and 7.1 points in group A, B, and C, respectively. The percentages of "yes" responses to SEP question 3 at the baseline and after treatment were 82.9% and 97.5% in group A ($P = .124$), 84.2% and 100% in group B ($P = .122$), and 85% and 100% in group C ($P = .123$). With regard to patients affected by moderate ED, we report an increase in the mean IIEF-EF score from 13.5 ± 1.9 to $16 \pm 3.1(+2.5)$ in group A ($P = .001$), from 13.8 ± 2 to 20.5 ± 2.2 ($+6.7$) in group B ($P < .001$), and from 13.7 ± 2 to $20.9 \pm 3.3(+7.2)$ in group C ($P < .001$) and a variation of the percentage of "yes" responses to SEP question 3 from 25.7% to 40% ($P = .23$), from 24.3% to 56.7% ($P < .001$), and from 22.9% to 60% ($P < .001$) in the 3 groups, respectively. Considering the severe-ED population, we assisted a variation in the mean IIEF-EF score before and after therapy from 5.1 ± 2.2 to 5.2 ± 2.3 ($+0.1$) in the L-arginine group ($P = .4966$), from 5.3 ± 2.4 to 10.2 ± 4.2 ($+4.9$) in the tadalafil 5 mg group ($P < .001$), and from 5.2 ± 2.3 to 11.8 ± 3.8 ($+6.6$) in the combination therapy group ($P < .001$). In the same ED severity category, the percentage of "yes" responses to SEP3 question was 0% at both the baseline and after therapy in group A, 0% and 12.5% in

Table 1. Patient demographics and baseline disease severity

	Group A	Group B	Group C	P value
Sample size	100	100	100	
Age (y), mean ± SD	55.6 ± 10	56.2 ± 9.8	56.7 ± 9.9	.764
Concomitant condition, n (%)				
Diabetes mellitus	21	23	22	.931
Cardiovascular risk factors*	67	68	66	.969
Baseline ED severity, n (%)				
Mild ED (IIEF-EF score 18−25)	41	38	40	.696
Moderate ED (IIEF-EF score 11−17)	35	37	35	.772
Severe ED (IIEF-EF score 0−10)	24	25	25	.881
Baseline IIEF-EF score, mean ± SD	15 ± 7	14.8 ± 6.9	14.9 ± 7.1	.995
SEP question 3 (% yes)	43	41	42	.974

ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function-erectile function; SD = standard deviation; SEP = Sexual Encounter Profile.
*including at least 1 of the following: hypertension, hyperlipidemia, obesity, and smoking

Table 2. Summary of results

	IIEF-EF baseline (mean ± SD)	IIEF-EF after treatment (mean ± SD)	Mean IIEF-EF variation after treatment	P value (Student's t-test)	SEP3 (% yes) baseline	SEP3 (% yes) after treatment	P value (test z)
Overall							
Group A (L-arginine)	15 ± 7	18.1 ± 9.2	+3.1	.0089	43 (43/100)	54 (54/100)	.0007
Group B (tadalafil)	14.8 ± 6.9	20.8 ± 7.3	+6	<.0001	41 (41/100)	62.6 (62/99)	<.0001
Group C (L arginine + tadalafil)	14.9 ± 7.1	22 ± 7.5	+7.1	<.0001	42 (42/100)	63 (63/100)	<.0001
Mild ED (IIEF-EF score 18—25)							
Group A (L-arginine)	22.1 ± 2.2	27.5 ± 2.3	+5.4	<.0001	82.9 (34/41)	97.5 (40/41)	.0124
Group B (tadalafil)	22.1 ± 2.2	27.8 ± 2	+5.7	<.0001	84.2 (32/38)	100 (38/38)	.0122
Group C (L arginine + tadalafil)	22.2 ± 2.2	29.3 ± 0.9	+7.1	<.0001	85 (34/40)	100 (40/40)	.0123
Moderate ED (IIEF-EF score 11—17)							
Group A (L-arginine)	13.5 ± 1.9	16 ± 3.1	+2.5	.0001	25.7 (9/35)	40 (14/35)	.023
Group B (tadalafil)	13.8 ± 2	20.5 ± 2.2	+6.7	<.0001	24.3 (9/37)	56.7 (21/37)	<.0001
Group C (L arginine + tadalafil)	13.7 ± 2	20.9 ± 3.3	+7.2	<.0001	22.9 (8/35)	60 (21/35)	<.0001
Severe ED (IIEF-EF score 0—10)							
Group A (L-arginine)	5.1 ± 2.2	5.2 ± 2.3	+0.1	.4966	0 (0/24)	0 (0/24)	ND
Group B (tadalafil)	5.3 ± 2.4	10.2 ± 4.2	+4.9	<.0001	0 (0/25)	12.5 (3/24)	.0829
Group C (L arginine + tadalafil)	5.2 ± 2.3	11.8 ± 3.8	+6.6	<.0001	0 (0/25)	8 (2/25)	.1614

		Scheffè			LSD			Bonferroni		
	Test F − P value	A vs B	A vs C	B vs C	A vs B	A vs C	B vs C	A vs B	A vs C	B vs C
Overall	<.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Mild	<.0001	*0.706	<0.0001	<0.0001	*0.4051	<0.0001	<0.0001	*NS	<0.0001	<0.0001
Moderate	<.0001	<0.0001	<0.0001	*0.4941	<0.0001	<0.0001	*0.2361	<0.0001	<0.0001	*0.7082
Severe	<.0001	<0.0001	<0.0001	0.0031	<0.0001	<0.0001	0.0011	<0.0001	<0.0001	0.0021

ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function-erectile function; SD = standard deviation; SEP = Sexual Encounter Profile.
*There was not significant statistical difference between group A and group B in the mild-ED population and between group B and group C in the moderate ED

Table 3. Treatment-emergent adverese events (TEAEs)

TEAE (MedDRA preferred term)	Group A (L-Arginine)	Group B (tadalafil)	Group C (L arginine + tadalafil)	P value (chi-square test)
Headache	2	8	11	
Nasal congestion	0	5	6	
Back pain	0	7	6	
Dyspepsia	2	11	14	
Influenza	0	2	1	
Myalgia	0	8	9	
Upper respiratory tract infection	0	1	0	
Sinusitis	0	1	0	
Bronchitis	0	1	0	
Cough	0	1	2	
Insomnia	5	0	7	
flushing	2	5	7	
Dizziness	0	3	4	
TOTAL OF ADVERSE EVENTS REPORTED	11	53	67	<.0001

MedDRA = Medical Dictionary for Regulatory Activities.

group B, and 0% and 8% in group C, respectively. Regarding the evaluation of the superiority of a protocol with respect to the others, there was no significant statistical difference between group A and group B in the mild-ED population and between group B and group C in the moderate-ED population. Results are shown in Table 2.

The type and the incidence of AEs are illustrated in Table 3. Overall, we report a total of 11, 53, and 67 cases of AEs in group A, B, and C, respectively. The most common AEs were insomnia in the arginine group with a rate of 5% and dyspepsia in both group B and C reported in the 11% and in the 14% of the survey, respectively.

DISCUSSION

The objective of the present prospective, randomized, multi-center study was to evaluate the effectiveness and tolerability of tadalafil 5 mg and L-arginine 2.5 gm in monotherapy and combination therapy in patients affected by various grades of ED. Although in the official medical literature are present several papers concerning those 2 molecules, to the best of our knowledge, this is the first study investigating their conceivable synergistic effects in a concomitant subscription protocol. Furthermore, this is the first study that compared head to head, directly, and prospectively the effectiveness of L-arginine, tadalafil, and a combination of both substances. This is moreover the first clinical trial evaluating the efficacy of L-arginine in monotherapy in relation to ED severity, including patients affected by severe ED.

L-arginine has been prescribed for ED by uroandrologists worldwide for at least 25 years, since the first article appeared in the far 1994.[15] Recently, the interest about this semiessential amino acid increased significantly for the publication of the first systematic review and meta-analysis on its efficacy and safety in

monotherapy or combined to other supplements.[11] This review led by Chang Rhim et al[11] concluded that L-arginine, compared with placebo or no treatment, improves ED of mild to moderate severity and that its subscription for ED is logical because it represents the only physiological substance for NOS.[16] Arginine was demonstrated to be an attractive alternative for patients with mild to moderate ED for several reasons. First, arginine is more psychologically accepted because it is perceived as a nutrient rather than a drug. Moreover, arginine was found to exert synergistic effects when administered concomitantly with other supplements such as pycnogenol, yohimbine, adenosine, propionyl-L-carnitine, and niacin.[17–20] The minimal dosage of arginine that was showed to be effective was 2.5 grams, since Klotz et al[21] failed to demonstrate significant benefits provided by this supplement administering it at a dose of 500 mg 3 times per day. When arginine was prescribed concomitantly with other substances, the combination worked synergistically determining even greater improvements. However, surprisingly, L-arginine was never investigated in combination with PDE5is, although this class of drugs represents the official first-line therapy for ED. Shirai et al[22] reported encouraging results with the combination therapy of citrulline, a precursor of arginine, administered together with PDE5is in a population of patients with ED complaining of unsatisfied efficacy from on-demand use of PDE5is alone. However, this study had some limitations: it did not include patients with ED taking tadalafil once daily (the oral therapy used in the present study), did not include L-citrulline in monotherapy, had a duration of treatment of only 1 month, and the sample size was small. The unique study found in literature in which arginine and tadalafil were evaluated in combination treatment was a Turkish study reporting protective effect of this therapy against ischemia/reperfusion injury for both the testes after unilateral testis torsion in rats.[23] Another fundamental
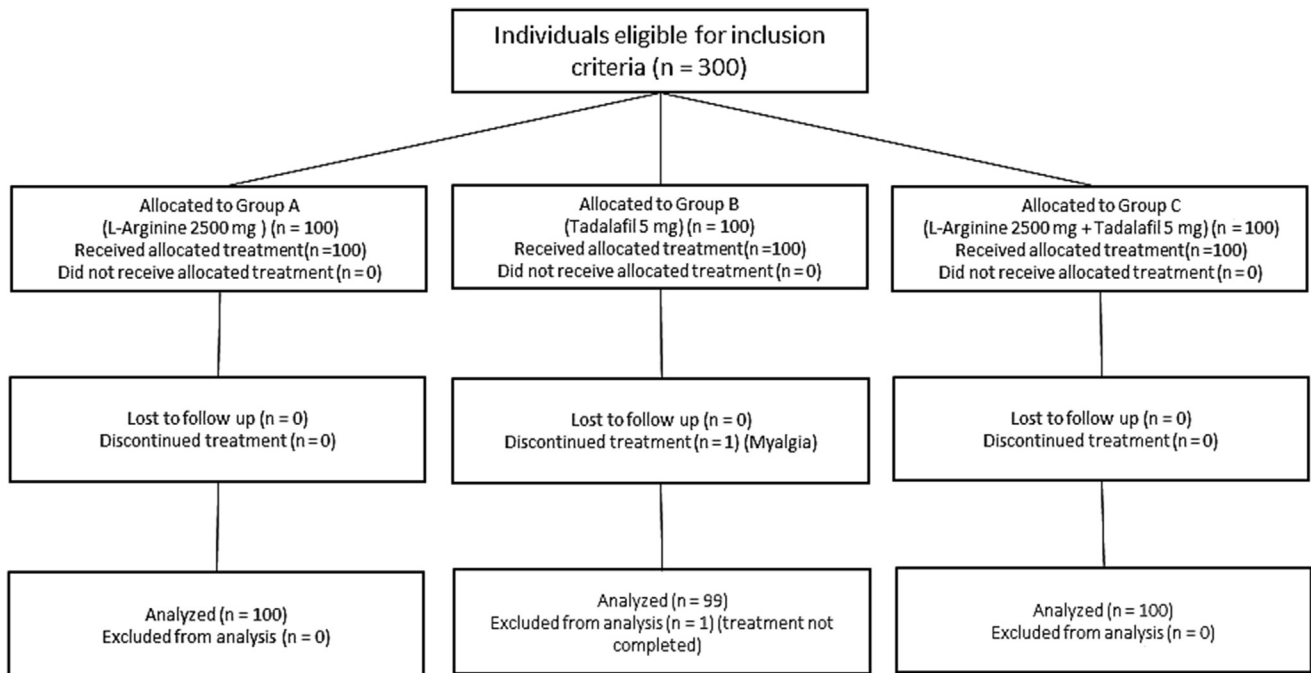
Figure 1. Study flow diagram.

aspect to underline, reported in the same review performed by Chang Rhim,[11] is that arginine was reported to have a very high safety profile because only 2% of patients treated with this supplement experienced AEs, none of them severe. The safety of arginine was demonstrated even at the highest dosage of 8 grams, as reported by Neuzillet et al.[18] The tolerability of arginine is in stark contrast with AEs determined by PDE5is because nearly half of the men treated with sildenafil reported at least one adverse reaction.[24] The rational for the use of arginine in patients with ED was demonstrated by Barassi et al,[25] who showed that a significant proportion of patients affected by ED, especially of arteriogenic etiology, have a low arginine or citrulline level. Those authors suggested that arginine or other amino acids (citrulline, ornithine) that can increase the serum arginine level can improve ED. Therefore, for all the reasons explained, arginine has been proposed as an alternative for patients who had already experienced AEs with PDEis. In the present study, L-arginine was administered daily in monotherapy at the minimal effective dosage of 2.5 grams in the remarkable survey of 100 men affected by ED of various grade of severity. Arginine was confirmed to be an effective therapy for individuals affected by mild and moderate ED determining a statistic significant improvement ($P \leq .001$) in the mean IIEF-EF score of 5.4 and 2.5 points, respectively. Moreover, the safety profile of arginine was confirmed even in our study because all 100 patients treated with this supplement concluded the therapy reporting none or insignificant adverse reactions. It is noteworthy to underline that in the mild-ED population, Arginine had effects comparable with tadalafil 5 mg because no significant differences were found between the 2 substances in terms of the IIEF-EF score. Furthermore, individuals treated with L-arginine reported a

lower incidence of AEs than men who received tadalafil 5 mg and/or combination therapy (Table 3). Based on those data, we suggest prescribing L-arginine as an equally effective, cheaper, and safer alternative to tadalafil 5 mg in patients affected by mild ED. On the other hand, in this study, arginine failed to show benefits in the severe-ED population.

In a review of 6 randomized multicenter trial including 1913 men with ED, tadalafil 5 mg once daily was showed to be effective in a variety of relevant patient subpopulations.[5] In particular, tadalafil 5 mg once daily was effective in almost all causes of ED, independent of severity (mild, moderate, and/or severe) and etiology. Tadalafil 5 mg once daily presents an ideal pharmacokinetic profile for chronic dosing because it is has a long half-life of 17.5 hours, and its steady-state blood concentrations are achieved within 5 days permitting an exposure to about 1.6 times higher than after a single dose.[26] The steady-state drug serum concentrations obtained through a daily tadalafil 5 mg regimen are constant and free from wide fluctuations. Thanks to its favorable pharmokinetic features, tadalafil 5 mg is currently the unique PDE5i, officially approved for daily therapy of ED. Several studies concerning patient preference for PDE5is have remarked the importance that men give to the possibility to obtain a satisfying erection several hours after pill intake: long half-life of PDE5i such as tadalafil was preferred to sildenafil by most patients.[4] The longer half-life of tadalafil is a quite crucial pharmacologic feature in order to restore the spontaneity and to free patients from the slavery to be forced to plan their sexual life. Moreover, there are strong data demonstrating that a daily assumption of PDE5is can be potentially effective in improving organic ED acting at the level of vascular endothelium by increasing cyclic guanosine monophosphate concentrations.[4] Thus, based on its specific pharmacokinetic features,

we considered tadalafil 5 mg once daily the ideal PDE5i protocol to be tested in combination with L-arginine in a daily therapeutic regimen to exert synergistic effects. In our study, when administered in monotherapy, daily Tadalafil 5 mg was confirmed to be a safe and effective treatment in all types of ED severity, providing a statistic significant amelioration in the mean IIEF-EF score of 6 points in overall population and of 5.7, 6.7, and 4.9 points in mild, moderate, and severe-ED population, respectively (Table 2). Daily tadalafil 5 mg monotherapy was safe and free from important adverse reactions because all patients except one included in the group B accomplished treatment. Considering the most important issue evaluated in the present study, we demonstrated that the combination therapy with both tadalafil 5 mg and arginine 2.5 grams once a day was superior to monotherapies alone in overall population and in the mild and severe ED. In the moderate ED group, the combination therapy exerted a small but not significant increase of 0.5 points in the mean IIEF-EF score. Our initial hypothesis was confirmed in our prospective, randomized, multicenter study including 300 patients: combination therapy with tadalafil plus L-arginine worked synergistically determining greater improvements than monotherapy in the IIEF-EF score (Table 2). The greater efficacy of combination therapy is probably determined by the enhancement of NO synthase activity caused by the chronic administration of tadalafil 5 mg in the presence of a greater concentration of a NO source for the concomitant administration of a sufficient dosage of L-arginine. The synergistic effects of the combination therapy are demonstrated even by the greater incidence of AEs in the group C. However, it is remarkable that even if the safety profile was lower than in the other 2 groups, all 100 patients included in the combination group completed the treatment. We believe that the findings of the present study provide a further demonstration for the importance of "tailored therapy" in ED: in patients affected by mild ED can be prescribed the only arginine, tadalafil monotherapy that can be sufficient for moderate ED, whereas in cases of severe ED, combination therapy is the most suitable option.

In our opinion, this study could open very promising scenarios for future researches. First of all, L-arginine can be administered even with other PDE5is such as sildenafil, vardenafil, and avanafil. In particular, we suggest studies evaluating stronger PDEis such as sildenafil or vardenafil in combination with L-arginine. Those synergistic treatments could be effective in the severe ED, but they could determine a greater incidence of adverse reactions, especially if a high drug dosage is prescribed (eg, sildenafil 100 mg or vardenafil 20 mg). Our study presents the limitation of a short follow-up because the duration of the protocol was just 3 months. It is conceivable that longer courses of this combination therapy could exert even greater improvements. We contemplate that a long-course chronic PDE5 inhibition in the presence of a greater arginine blood concentration could potentially provide more enduring improvements of endothelial dysfunctions responsible for ED. The vascular effects exerted by this chronic combination therapy might be responsible for a definitive improvement in erectile function and return to spontaneous erections as suggested by other studies evaluating chronic tadalafil alone.[27,28] This new therapeutic approach is in our opinion very promising and could lead to scenarios beyond the palliation of ED. It is conceivable that, in a not quite remote future, this very common disease affecting millions of men worldwide will be curable. Under this point of view, appears rational to use the daily combination therapy tadalafil 5 mg plus L-arginine 2.5 grams in more comprehensive recovery program of erectile function. In particular, we suggest future researches in which this treatment could be prescribed concomitantly with low-intensity extracorporeal shock wave therapy, platelet-rich plasma injections, and/or vacuum erection devices in the effort to maximize the neoangiogenis and revascularization process.

We admit that our finding can be limited by the absence of a placebo group. Unfortunately, the medications prescribed in the present study are available in different formulations: tadalafil in pills, whereas L-arginine in powder for oral suspension. For this reason, it was not possible to include a placebo arm or to provide blinding to the study. We encourage randomized, placebo-controlled studies to confirm our results.

CONCLUSIONS

In the mild-ED population, arginine had effects comparable with tadalafil 5 mg with a lower incidence of AEs. Arginine failed to show benefits in severe ED but was effective in moderate ED. Combination therapy with both tadalafil 5 mg and arginine 2.5 grams once a day was superior to monotherapies alone in overall population and in mild and severe ED.

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Category 3

(a) Final Approval of the Completed Article
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