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AVANAFIL FOR THE TREATMENT OF ERECTILE DYSFUNCTION. AN UPDATED REVIEW

María Alejandra Egui-Rojo[1], Ignacio Moncada-Iribarren[2], Joaquín Carballido-Rodríguez[3] and Juan Ignacio Martínez-Salamanca[4].

[1]Attending Urologist. Urology Departmen. Hospital Universitario de Fuenlabrada. Madrid. Spain.
[2]Chief. Department of Urology. Hospital de la Zarzuela. Madrid. Spain.
[3]Chief. Department of Urology. Hospital Universitario Puerta de Hierro Majadahonda. Madrid. Spain.
[4]Attending Urologist. Urology Department. Hospital Universitario Puerta de Hierro Majadahonda. Madrid. Spain.

Summary.- *OBJECTIVES: Avanafil is a highly selective phosfosdiesterase 5 inhibitor (PDE5 inhibitor), with rapid onset of action, approved by the Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of erectile dysfunction (ED). It had been recently commercialized in Spain. This article presents a detailed review of the available literature, where the safety, tolerability and efficacy of avanafil were evaluated.*

METHODS: A systematic literature search using the Medline database was performed. The search included the terms Avanafil and erectile dysfunction. The pivotal studies of clinical development of the drug, and also those randomized, double-blind, placebo-controlled, well-designed studies were analyzed. We included those studies published in English up to January 2014. Likewise, studies of the pharmacokinetics and pharmacodynamics of the drug were also included.

RESULTS: The avanafil pivotal studies, conducted in general population of patients with ED, patients with Diabetes mellitus type I and II and patients with ED secondary to nerve sparing radical prostatectomy were analyzed. In all these studies, avanafil demonstrated a statistically significant improvement in erectile function /(IIEF), and all the coprimary outcomes (SEP2 and SEP3) compared to placebo. Also, a good tolerance profile and few side effects compared to placebo were evident.

CONCLUSIONS: Avanafil is a selective PDE5 inhibitors, that is rapidly absorbed and that has a short time to peak response. It found to be effective in randomized, double-blind, placebo-controlled trials conducted in men with erectile dysfunction, including in patients with diabetes mellitus and after radical prostatectomy. It was generally well tolerated across trials, with very few patients withdrawing because of adverse effects. Similarly, avanafil had a significantly lower rate of hemodynamic side effects compared with sildenafil.

Keywords: *Avanafil. Erectile dysfunction. Prostatectomy. Phosphodiesterase 5 inhibitors.*

CORRESPONDENCE

Juan Ignacio Martínez-Salamanca
Servicio de Urología
Hospital Puerta de Hierro-Majadahonda
Calle Manuel de Falla, 1
28220 Majadahonda Madrid (Spain)

jims09@me.com

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Resumen.- *OBJETIVO: Avanafilo es un inhibidor de la fosfodiesterasa 5 (IPDE5) altamente selectivo, aprobado por la Food and Drug Administration (FDA) y por la Agencia Europea del medicamento, para el tratamiento de la disfunción eréctil (DE), comercializado recientemente en España. Este artículo presenta una revisión de la literatura, donde se evalúa la seguridad, tolerabilidad y eficacia de avanafilo.*

MÉTODOS: Se realizó una búsqueda sistemática de la literatura utilizando la base de datos Medline, que incluyó los términos Avanafilo y disfunción eréctil. Se analizaron los estudios pivotales del desarrollo clínico del fármaco, así como aquellos ensayos clínicos aleatorizados, doble ciego y controlados con placebo, bien diseñados, publicados en inglés hasta Enero de 2014. Igualmente, se incluyeron estudios acerca de la farmacocinética y farmacodinámica del fármaco.

RESULTADOS: Se analizaron los estudios pivotales de Avanafilo, llevados a cabo en la población general de pacientes con DE, en pacientes con DE y diabetes mellitus tipo I y II y en pacientes con DE secundaria a prostatectomía radical, demostrando una mejoría estadísticamente significativa de la función eréctil (IIEF) y del resto de los objetivos primarios (SEP2 y SEP3), respecto a placebo. De igual manera, avanafilo presentó un buen perfil de tolerancia y escasos efectos adversos.

CONCLUSIONES: Avanafilo es un IPDE5 de vida media corta e inicio rápido de acción. Su eficacia clínica con respecto a placebo ha sido demostrada en ensayos clínicos aleatorizados, doble ciego, controlados con placebo, en pacientes con DE. Adicionalmente, su eficacia ha sido demostrada en pacientes diabéticos y pacientes sometidos a prostatectomía radical.

Avanafilo, ha demostrado ser un fármaco seguro y bien tolerado. Los efectos adversos registrados fueron de carácter leve o moderado, con una baja tasa de abandono del fármaco debido a éstos. Adicionalmente cuenta con menores tasas de efectos hemodinámicos respecto a sildenafilo.

Palabras clave: *Avanafilo. Disfunción eréctil. Prostatectomia. Inhibidores de la fosfodiesterasa 5 (PDE5).*

INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent inability to achieve or maintain an erection for satisfactory sexual performance (1) affects more than 150 million men worldwide (1). The incidence of ED increases with increasing age, found rates up to 61% in males over 70 years (2).

The European Association of Urology guidelines includes the oral PDE5 inhibitors oral treatment (sildenafil, tadalafil and vardenafil) as a first line therapy for ED with a level of evidence 1a and a grade of recommendation A (3,4). The PDE5 inhibitors have been prescribed for more than a decade, demonstrated clinical efficacy ranging from 52% to 66% at their highest doses (5,6,7).

Although efficacy has been demonstrated with commonly prescribed PDE5I, adverse effects (AEs) have been reported. Most often reported AE´s are headache, flushing, dyspepsia, nasal congestion, visual disturbance and myalgia (5,7,8). These events may be related to a lack of exclusive selectivity for PDE5I with cross-reactivity occurring in the tissues of other PDE isozimes (9). For example, inhibition of PDE6, is responsible for cyanopsia or blue vision (10).

There are 11 types of PDE enzymes, all of which function in the degradation of cyclic adenosine monophosphate to adenosine monophosphate and cGMP to GMP. PDE enzymes are widely distributed throughout the body, with varying activity in different tissues. PDE5 is found in the smooth muscle of the corpus cavernosum, skeletal muscle, vascular and visceral smooth muscle, cerebelar and pancreatic tissue, platelets, kidneys and lungs (10). Other isozimes such as PDE1, were found in the heart, PDE6 in the retina and PDE11 in skeletal muscle (11).

Avanafil (4-[(3-chloro-4-methoxybezil)amino]-2-[2-(hydroxymethyl)-1-pyrrolidinyl]-N-(2-pyrimidinylmethyl)-5-pyrimidinecarboxamide;(S)-2-(2-hydroxymethyl-1-pyrrolidinyl)-4-(3-clhoro-4-methoxybenzylamino)-5-[(2-pyrimidinylmethyl) carbamoyl] pyrimidine , is a a pyrimidine derivative that exist as a single enantiomer with S stereochemistry. Avanafil works in penile tissue to increase the level of cyclic guanosine monophosphate (cGMP). As level of cGMP increase, smooth muscles relax in the penis, increasing local blood flow, wich results in an erection (12).

Avanafil strongly inhibits PDE5 in a competitive manner. The drug is more potent (100 fold) and show higher selectivity (120 fold) for PDE5 and for PDE6 than sildenafil (16 fold) and vardenafil (21 fold); and its selectivity for PDE5 versus PDE1 is greater than 10 000 fold (sildenafil 380 fold and vardenafil 1000 fold). In contrast to tadalafil, considerable inhibition by avanafil of PDE 11 was not registered (13).

Avanafil has been designed to be a fast-acting highly selective PDE5I, approved by de Food and Drug Administration (FDA) on April 2012 (14)

and by the European Medicines Agency in 2013 (15), after reviewing several studies that have shown its efficacy over placebo. It is marketed in Europe under the name of Spedra and is available in doses of 50, 100 and 200 mg.

OBJECTIVE

The present work aimed to make a review about, randomized, double-blind, placebo-controlled studies, conducted during the clinical development program of Avanafil.

MATERIALS AND METHODS

A systematic literature search of the Medline database was performed using the MeSH terms avanafil and erectile dysfunction. The pivotal studies of the drug were included: REVIVE (TA-301), REVIVE-Diabetes (TA-302), TA-314. Well designed, randomized clinical trials, with a large number of patients have published in English until January 2014 were also included, as well as phase I trials and relevant information about the pharmacokinetics and pharmacodynamics of avanafil.

RESULTS

The first study is a phase I double-blind, randomized, placebo-controlled, parallel-group, dose escalation study which aim was to determine the tolerability and pharmacokinetics of avanafil (16), enrolled 30 healthy male volunteers randomly assigned to one of three avanafil dose groups: 50 mg, 100 mg and 200 mg respectively (three groups of 8 patients each) administered at 24 hours intervals for 7 days, and six patients who received placebo. Blood samples were collected several times after drug administration to assess the pharmacokinetic characteristics. The mean time of peak plasma concentration was 0.33-0.52 hours and the mean half-life was 5.36-10.66 hours, without differences in this pattern between days 1 and 7. Dose proportionality was observed.

Blood analysis (hematology, biochemistry), urinalysis, vital signs, 12-lead ECG and color discrimination tests were employed to assess the tolerability of avanafil.

Adverse events (AEs) were monitored by self-reporting and specific questioning throughout the study period. AEs were reported by 20 patients in the avanafil group and 5 patients in the placebo group. Both groups reported flushing, headache and dizziness. Additional AEs in the avanafil group included orbital pain, chest discomfort, epigastric heartburn, nasal congestion, abdominal discomfort, and paresthesia, all of them considered mild in intensity and resolved spontaneously. No significant changes in ECG, blood tests, or visual tests were reported.

In conclusion, avanafil proved to be well tolerated and had linear pharmacokinetics properties at daily doses of 50 to 200 mg (16).

Another phase I study, performed by Swearingen and cols. (17), whose objective was to determine the magnitude and duration of the hemodynamic effects of coadimistration of avanafil and Gliceryl trinitrate (GTN), compared with sildenafil and placebo. A double-blind, randomized, crossover study was conducted, where 106 healthy men between 30 and 60 years, who randomly received in separate visits placebo, avanafil 200 mg and sildenafil 100 mg orally, followed by the administration of GTN 0.4 mg 12, 8 , 4, 1 and 0.5 hours post-dose, via sublingual route . Systolic blood pressure (SBP) and heart rate (HR) were measured at defined intervals. Throughout the study (after administration of GTN) , the effects of sildenafil and avanafil on SBP and HR were significantly greatest overall, at the shortest intervals (0.5 hours) compared with placebo. But in the intervals between 8 and 12 hours, no statistically significant diferences were found in the group of avanafil (8 and 12 hours) or sildenafil (12 hours) ($p > 0.05$), compared with placebo (17).

When compared with avanafil, sildenafil has a significantly greater hemodynamic effect, in all time intervals.

The study concludes that avanafil and sildenafil have no effect on SBP and HR in healthy subjects administered within 8 hours (avanafil) and 12 hours (sildenafil) prior to taking a dose of sublingual NTG, but these results may differ in populations with a diagnosed cardiovascular disease and therefore the clinical applicability of these results may be limited.

We will describe the pivotal studies for Avanafil:

The first study is a phase III, prospective, multicenter, randomized, double-blind, placebo controlled trial, to compare the safety and efficacy of avanafil (TA-301) (18), enrolling 646 men 18 years or older with 6 month or longer history of moderate to severe ED (>= 50% failure rate in maintaining erections of sufficient duration to allow for successful intercourse, IIEF (International Index of Erectile Function) ranking 5-25 inclusive, and had made at

least four attempts at sexual intercourse during the initial 4 week run in period).

Patients were randomized to received avanafil 50 mg, 100 mg, 200 mg or placebo (1:1:1:1 ratio) throughout a 12 weeks treatment period, during which randomized subjects were instructed to administer the drug approximately 30 minutes prior to initiation of sexual activity: subjects were allowed to take up to two doses in a 24 hours period, separated by at least 12 hours.

The co-primary efficacy end points were: the change in percentage of sexual attempts in which subjects were able to insert the penis into the partners vagina between the run in period and the end of the treatment period (SEP2); the change in percentage of sexual attempts in which subjects were able to maintain an erection of sufficient duration to have successful intercourse between the run-un period and the end of the 12 week treatment period (SEP3), and the change from baseline to the end of the treatment in the IIEF-EF (International Index of Erectile function) domain score.

Avanafil demonstrated significant improvements with doses of 50 mg, 100 mg and 200 mg ($p < 0.001$), for all comparisons over placebo. The 50 mg dose was inferior to the 100 mg dose ($p=0.0064$) and 200 mg ($p<0.0004$), however, there was no significant difference between the avanafil 100 mg and 200 mg doses ($p=0.4221$) (Table I) (18).

Similarly, avanafil demonstrated a significant improvement respect to placebo in SEP3, at the end of the treatment, experienced a 41 % mean change with 50 mg dose and 57% mean change with the 100 mg and 200 mg doses. Significant differences were also found between avanafil 100 mg and 50 mg ($p<0.0001$), and between avanafil 200mg and 50 mg ($p<0.0001$) doses. The difference between 100 mg and 200 mg doses was not significant. Also, the three treatment groups showed significant improvements in the IIEF-EF domain score compared with placebo (Table I) (18).

An analysis to determine the number of sexual attempts at different periods after administration of the dose was performed. Between 64% and 71% of patients treated with avanafil, were able to maintain a successful sexual intercourse, compared with 27% of patients in the placebo group, of a total of 300 sexual attempts. Similarly, the percentage of successful intercourse attempts at 15-30 minutes, 30-45 minutes, 2-4 hours, 4-6 hours and > 6 hours after ingestion of the dose, were higher in the avanafil group, compared to placebo.

With regard to secondary endpoints, avanafil enabled significant improvements compared with placebo regarding the other four IIEF domains (orgasmic function, sexual desire, intercourse satisfaction, overall satisfaction). Reported AE´s included headache (4.4%- 9.3%), flushing (3.8%-6.2%), nasal, congestion (0.6%- 4,3%), back pain (1.9-2.5%), nasopharyngitis (0.6%-3.7%), and bronchitis 0.6- 2.5%).

The study concludes that avanafil is effective and well tolerated treatment for mild to severe ED. Treatment responses were reported as early as 15 minutes followed a dose and maintain up to 6 hours.

The second study is the REVIVE-Diabetes (TA-302) (19), focused on patients with diabetes (DM) and ED published in 2012, to assess the safety and effectiveness of avanafil to treat ED in men with diabetes mellitus. The design was a 12 week, multicenter, double-blind, placebo controlled study randomized 390 men with ED and DM 1:1:1 to receive avanafil 100 mg (n= 129), avanafil 200 mg (n= 131) or placebo (n= 130). Coprimary endpoints were to assess the change in SEP 3, SEP 2 and IIEF EF respect to the baseline. With regard to demographic characteristics, most of the patients had type 2 diabetes (89.5%), and presented moderate or severe ED (78.2%), patients had been diagnosis as having diabetes for approximately 11.3 years.

Up to 61% of patients were taking concomitant medication to control blood pressure or alfa blockers, 57.4% had dyslipidemia at baseline. Seventy five percent of patients reported previous oral ED therapies. Results demonstrated significant improvements in all the coprimary endpoints respect to baseline. SEP 3 improved statistically significant with both doses ($p<0.001$) versus placebo, with 34.4 and 40% of successful sexual attempts versus 20.5% in placebo group. Te difference observed between 100 mg and 200 mg of avanafil doses was not significant (Table I) (19).

Also, significant improvements in SEP2 respect to baseline were reported. Patients taken avanafil 100 mg and 200 mg doses experienced a 21.5% and 25.9% mean increase in sexual attempts with successful vaginal penetration, respect to 7.5% in the placebo group ($p<0.001$ for both doses). However, placebo arm shows also significant results ($p=0.09$). No significant differences were observed between 100 and 200 mg doses (19).

At the end of the treatment, the mean change of IIEF EF domain score were 13.2, 15.8 and 17.3 for placebo, avanafil 100 mg and avanafil 200 mg

Table I. Effectiveness of on demand treatment with Avanafil in patients with mild to severe erectile dysfunction, in multicenter, randomized, double-blind, placebo-controlled 12-week studies

STUDY	AVANAFIL DOSE (mg)	Nº PATIENTS	IIEF-EF			SEP2			SEP3		
			12 week	Baseline	Avanafil/ PBO	12 week	Baseline	Avanafil/ PBO	12 week	Baseline	Avanafil/ PBO
Goldstein et al[1]	50	152-154	18.1	12.6	2.6*	64.3	45.4	11.1 **	41.3	13.5	13.8 **
	100	156	20.9	12.6	5.5 ***++	73.9	46.6	20.1 ***+	57.1	13.9	29.3 ***+++
	200	155	22.2	12.8	6.7 ***++	77.3	48.3	22.7 ***+	57	12.4	30.2 ***+++
	PBO	155	15.3	12.4	-	53.8	46.7	-	27	12.6	
Goldstein et al[2]	100	125	15.8 *	11.2		54 **	32.5		34.4**	8.2	
	200	125	17.3 **	12.0		63.5 **	41.5		40.0 **	8.0	
	PBO	125	13.2	11.4		42.0	36.0		20.5	10.0	
Mulhall et al[3]	100	94	13 *	9		33 *	18		23 *	5	
	200	96	16 *	10		42 *	20		27 *	5	
	PBO	96	9	9		19	20		9	4	

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*∑ p<0.01, **p<0.001, *** p<0.0001, vs Placebo + p<0.001, ++p< 0.0005, +++ p< 0.0001 vs avanafilo 50 mg*

Modified from: Sanford M. Avanafil: A Review of its use in patients with Erectile Dysfunction. Drugs Aging (2013) 30: 853-862.

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respectively, with significantly greater improvement compared to placebo (p=0.002 and p=0.001 for avanafil 100 and 200 mg respectively).

Moreover, a numerically higher proportion of patients in the avanafil group normalized the IIEF EF domain scores (>= 26). As the other coprimary endpoints, no significant changes were observed between both avanafil doses (Table I) (19).

Also, significant improvements in the secondary endpoints were observed with both doses of avanafil, including the orgasmic domain (p=0.003 and p=0.002), intercourse satisfaction (p=0.02 and p=0.001) and overall satisfaction (p=0.001 and p<0.001), at doses of 100 mg and 200mg, respectively (19).

The third phase III studies mentioned, is that performed by Belkoff and cols (TA-314) (20), whose main objective was to evaluate the efficacy and long-term safety of avanafil, with patients who had completed the pivotal studies: TA 301 (18), which excluded patients with diabetes mellitus and TA 302 (REVIVE) (19), where the activity of the drug in patients with diabetes mellitus was evaluated and discussed below. Inclusion criteria were successfully been completed the protocol of previous trials in which they had participated and have at least 4 attempts of intercourse per month throughout the study period. Similarly, the use of any additional treatment for erectile dysfunction was prohibited during the course of the study. These is a randomized, placebo-controlled, 52 -week study, with an open label 12-

week period, which included a total of 712 patients (20).

All patients received a dose of 100 mg of avanafil. Once in the open phase of the study could increase the dose to improve the effectiveness, or otherwise reduce the dose in order to improve tolerance to the drug. The primary endpoints of the study included the percentage of positive responses to SEP2, SEP3 respect to baseline, and the percentage change in IIEF -EF from baseline. The results shows an improvement in all the primary endpoints, during the treatment with 100 mg avanafil; the SEP2 increase from 44.1 % to 83.3 % respect to baseline during the treatment period and from 43% to 79.4 % during the open period. SEP3 increased by 5 times during the treatment phase, compared to baseline and during the open phase, over 65 % of patients was reported successful intercourse. IIEF -EF improved from 13.6 at baseline to 22.2 during the treatment phase and from 11.9 to 22.7 during the open phase of the study. The overall normalization of the IIEF (> = 26), at the end of the treatment, was achieved in 64%, 55.1 % and 36 % of patients with mild, moderate and severe erectile dysfunction respectively (20). Avanafil was effective in 83% of patients within 15 minutes after taking the drug and for more than 6 hours after taking the dose (74%). The 65% of non-responders to avanafil 100 mg (112/172), responded with a dose of 200 mg (20).

The sub-analysis of the results showed that the effect of avanafil was higher in the group taking 100-200 mg of the drug, compared to the group that only received the 100 mg dose. Regarding sub-analysis performed in diabetic patients, the increasing percentage of SEP2, SEP3 was higher with 200mg dose (20).

Adverse effects were similar to those described in previous studies, including headache (5.6%), flushing (3.5%), nasopharyngitis (3.4%), nasal congestion (2.1%) and back pain (1.5%); leading to discontinuation of therapy in <3 % of patients. This study concluded that the long-term tolerability of avanafil, the improved sexual function and the rapid onset of drug action, make of avanafil, a reliable choice indicated for the on demand treatment of erectile dysfunction (20).

Two further trials have to be mentioned. The first trial is a phase III, placebo controlled study to determine the safety and efficacy of avanafil for the treatment of ED after nerve sparing radical prostatectomy (NSRP) enrolling 298 men18 to 70 years with history of ED of 6 month or more after bilateral NSRP for prostate cancer pT2c stage or less and Gleason score (4+3) or less (21).

Patients with prior radiotherapy, chemotherapy, androgen deprivation therapy, cryotherapy, nonnerve sparing radical prostatectomy and bladder or penile surgery were excluded. The use of penile rehabilitation was not allowed before beginning the 4-week run in period.

Patients were randomized to receive 100 or 200 mg avanafil or placebo, taking 30 minutes before sexual activity in a 12 week period. Primary endpoints included SEP 2 and SEP 3 question and change on IIEF EF score from baseline. Secondary end points included the changes in response to individual questions and for other domains of IIEF questionnaire between baseline and weeks 4, 8 and 12; responses to secondary subject diary questions and the response to GAQ (global assesment questions), and future use question at week 12. Two hundred and fifty two patients (84.6%) completed the study. A higher percentage of patients in the placebo group (24%) discontinued the study compared with the 100 mg group (14.1%) and 200 mg group (8.1%). At baseline, mean overall IIEF score were 9.2 and mean SEP3 success rate was less than 5%. The majority of patients (80.5%) had robotic surgical technique for NSRP.

After 12 weeks of treatment avanafil 100 and 200 mg resulted in a significantly greater increase in SEP2, SEP3 and change in mean IIEF-EF domain score in 3.6 (40%) for 100 mg dose and 5.2 (55%) for 200 mg dose respectively, compared with placebo (1%) ($p<0.01$). Following dosing with avanafil, 36.4% of sexual attempts (SEP3) at 15 minutes or less were successful compared with 4.5% in the placebo group ($p<0.01$) despite the surgical technique employed (21).

Respect to secondary endpoints, avanafil 100 mg and 200 mg doses was associated with significant improvements in the IIEF orgasmic function domain ($p<0.05$), intercourse satisfaction ($p=0.01$ and $p<0.01$) respectively and overall satisfaction score ($p<0.05$ and $p<0.01$) respectively, compared with placebo. Moreover, subject diary responses and GAQ ($p<0.01$) were significantly greater for the avanafil group. In conclusion, avanafil 100 mg and 200 mg doses was effective and well tolerated in improving EF after NSRP, with rapid onset of action and sustained duration of effect with all 3 primary endpoints being achieved at both dose levels (Table I) (21).

AEs were reported in 23%, 38% and 45% of patients treated with placebo, avanafil 100 mg and avanafil 200 mg doses respectively. No significant changes were recorded in the safety profile of the

drug between 100 and 200 mg doses. Overall, the drug was well tolerated, registering a rate of treatment discontinuation of 2% relative to EAs. The most frequent AEs were headache (7%), flushing (5%), nasopharyngitis (2.7%) and back pain (2%). The other AEs, occurred less than 2% of patients relative to the dose used (21).

The second study is a phase III, multicenter, randomize, double blind, placebo-control trial conducted in Korea, evaluated the safety and efficacy of avanafil for the treatment of ED in 200 males (22).

Inclusion criteria were men with ED of at least 6 month of duration, > 20 years of age, in a stable heterosexual relationship for at least 6 months and who had made at least four attempts at sexual intercourse during the 4 week run in period, of which at least 50% of attempts were unsuccessful.

Duration of the study was 16 weeks, consisted of an initial 4 weeks run in period, followed by a 12 week treatment period. Follow up by telephone call was scheduled every 6-7 days to ensure safety.

The subjects were treated with placebo or avanafil (100 mg and 200 mg) for 12 weeks. Primary endpoint was the change from baseline for IIEF EF domain. Secondary endpoints were SEP2 and SEP3 questions and Global assessment questionnaire (GAQ).

Analysis of the results concluded both avanafil groups have statistically significant increase of the IIEF EF, with an average increase of 8.5 and 8.8 points for 100 mg and 200 mg, as compared to 3, 5 points in the placebo group ($p < 0.001$). No significant differences between 100 mg and 200 mg doses were observed.

Comparison of rates of responses to SEP, the proportion of "yes" responses to the GAQ, and the percentage of patients achieving normal IIEF domain scores (>26), showed that all patients in avanafil group experienced a significant difference, while the placebo group did not. The frequency of AEs were low, indicating that avanafil is safe and well tolerated. Based upon these data, they concluded that avanafil seems to be another reliable treatment option for ED patients (22).

DISCUSSION

Avanafil is a PDE5 inhibitor approved in USA, Europe and South Korea, for the treatment of erectile dysfunction, recently marketed in Spain.

Its clinical efficacy in all available doses (50, 100 and 200 mg) has been demonstrated in several well-designed, randomized, double-blind, placebo-controlled trials, in general population with ED, patients with type I and II diabetes, and in patients undergoing NSRP, with a safety profile comparable to other PDE5 inhibitors.

In patients with DM, avanafil in doses of 100 and 200 mg, was significantly superior to placebo in the evaluation of the 3 coprimary endpoints (IIEF, SEP 2 and SEP3). These results suggest that avanafil might represent an effective treatment option in patients with DM and ED (19).

Similarly, in patients with ED secondary to NSRP, avanafil in doses of 100 and 200 mg was effective and well tolerated. While patients with ED secondary to radical prostatectomy have a less "robust" response to treatment with PDE5 inhibitors, avanafil offers a choice of oral therapy that demonstrated clinical efficacy (21).

The role of avanafil in the treatment of ED and its advantages over other PDE5 inhibitors can only be inferred theoretically, because there are no comparative studies about its effectiveness and safety profile with respect to the other PDE5 inhibitors available in the market.

Its high potency and selectivity for PDE5, likely associated with a lower rate of adverse effects. Future comparative studies may clarify if this is the first second-generation of PDE5 inhibitors.

CONCLUSIONS

Avanafil is a PDE5 inhibitor that is rapidly absorbed, with a short onset of action that allows the patient to maintain satisfactory sexual intercourse within 15 minutes after administration of the drug.

Its clinical efficacy compared to placebo has been demonstrated in several randomized, double-blind, placebo-controlled trials, in patients with ED. Additionally, their effectiveness has been studied in populations with erectile dysfunction difficult to manage, including diabetic patients and patients undergoing radical prostatectomy, with encouraging results.

Avanafil, has proven to be a safe and well-tolerated drug. During clinical trials, adverse effects recorded were mostly mild to moderate, with a low rate of drug discontinuation due to these.

Also has lower rates of hemodynamic side effects and shorter duration of interaction when combined with "nitric oxide releasing" drugs, compared to sildenafil.

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