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ORIGINAL ARTICLE

Evaluation of the convenience of changing the rivastigmine administration route in patients with Alzheimer disease

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KEYWORDS
Alzheimer's disease;
Rivastigmine;
Treatment;
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Administration route

Abstract
Introduction: Rivastigmine transdermal patches for the treatment of Alzheimer's disease (AD) have potential benef ts compared to capsules because of their sustained absorption through the skin, good local tolerability and reduction of gastrointestinal problems.
Purpose: To assess gastrointestinal and skin tolerability and the need for optimal dose titration of rivastigmine transdermal patches in Alzheimer's disease patients previously treated with oral rivastigmine.
Patients and methods: A multicenter, randomized, open-label study including patients with mild to moderate AD (DSM-IV) previously treated with rivastigmine capsules (6-12mg/day) was conducted. P atients were randomized to: continue with capsules for 3 months (n=49) or switch to rivastigmine patch without titration (9.5mg/day for 3 months; n=48), or switch to rivastigmine patch with titration (4.6mg/day for 1 month followed by 9.5mg/day for 2 months, n=43).
Results: Incidence of gastrointestinal adverse events was 6.1% in the group treated orally and 4.2% in the group treated with non-titrated patches (*P*=.908). Skin tolerability was good (n=15, 16.7%) without any serious adverse events registered. P atch treatment was considered very easy to use by 72% of patients compared with 30% in the group with oral treatment (*P*=.0005). 60% of patients were satisf ed with the patch, while only 14% were satisf ed with capsules (*P*<.0001).
Conclusions: Rivastigmine patches have a tolerability pro f le similar to that shown by capsules, but are associated with greater patient satisfaction.

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PALABRAS CLAVE
Enfermedad de Alzheimer;
Rivastigmina;
Tratamiento;
Tolerabilidad;
Satisfacción;
Vía de administración

Evaluación de la conveniencia del cambio de vía de administración de rivastigmina en pacientes con enfermedad de Alzheimer

Resumen
Introducción: Los parches transdérmicos de rivastigmina para el tratamiento de la enfermedad de Alzheimer presentan posibles beneficios respecto a las cápsulas por su absorción sostenida a través de la piel, buena tolerabilidad local y reducción de problemas gastrointestinales.
Objetivo: Evaluar la tolerabilidad gastrointestinal y cutánea y la necesidad de titulación para obtener dosis óptimas de rivastigmina transdérmica en pacientes con Alzheimer previamente tratados oralmente.
Pacientes y métodos: Se llevó a cabo un estudio multicéntrico, aleatorizado y abierto que incluyó a 142 pacientes con Alzheimer de leve a moderado y previamente tratados con rivastigmina oral (6-12 mg/día). La muestra fue aleatorizada a: continuar con tratamiento oral durante 3 meses (n = 49); cambio al parche sin titulación (9,5 mg/día durante 3 meses, n = 47) o cambio al parche con titulación (4,6 mg/día por 1 mes seguido de 9,5 mg/día por 2 meses, n = 43).
Resultados: La incidencia de efectos adversos gastrointestinales fue del 6,1% en el grupo tratado oralmente y del 4,2% en el grupo tratado con parche sin titulación (p = 0,908). La tolerabilidad cutánea fue buena (n = 15, 16,7%), sin observarse acontecimientos adversos graves. El tratamiento con parche fue considerado muy fácil de utilizar por el 72% de pacientes en comparación con el 30% con tratamiento oral (p = 0,0005). El 60% se mostraron satisfechos con el parche, mientras que únicamente un 14% se declaró satisfecho con las cápsulas (p < 0,0001).
Conclusiones: Los parches de rivastigmina presentan un perfil de tolerabilidad similar a las cápsulas y se asocian con una mayor satisfacción de los pacientes.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that manifests itself with cognitive deterioration and loss of memory, a gradual worsening of normal activities in daily life and a group of different neuropsychiatric symptoms and changes in behaviour.[1] As such, AD is considered the most common cause of dementia in the elderly. The cause, generally sporadic (non-hereditary), of AD is unknown although there is a probable heterogenic origin, derived from effects associated with ageing combined with complex interactions between genetic and environmental risk factors.[2]

Among the most successful treatment strategies to confront the progress of Alzheimer's, we should highlight the use of acetylcholinesterase inhibitors that act in strengthening the remaining cholinergic neurotransmission by inhibiting the degradation of the acetylcholine released[3]. Following the disclosure of the limitations and potential hepatotoxicity of first-generation acetylcholinesterase (AChE) inhibitors, such as tacrine, various second-generation AChE inhibitors have been introduced, including rivastigmine. These are currently considered a lot more effective and do not have serious adverse effects.[4]

Specifically, Rivastigmine (Exelon®) is a carbamate-type AChE and butyrylcholinesterase (BuChE) inhibitor, designed to ease cholinergic neurotransmission through a process of slowing down degradation of the acetylcholine released by functionally intact cholinergic neurons.[5] Adverse effects of rivastigmine are generally those associated with a second-generation AChE inhibitor: gastrointestinal effects, especially nausea and vomiting.[6] These adverse effects are usually slight or moderate, do not last long and are spontaneously resolved after the dosage is decreased or the treatment is stopped.

The mode of Rivastigmine action and specific metabolism has suggested, from previous studies, that it is improbable that it significantly interacts with other types of drugs.[7] This characteristic is of particular relevance in elderly patients with AD, as the majority of them will very probably be receiving concomitant medication.[8] Another of this population's frequent problems is the lack of adherence to treatment, especially with a chronic disease such as AD. Administration of sustained-release treatments —through their ease of use, tolerability and absorption type— can significantly contribute in reducing non-adherence.[9]

A new rivastigmine formulation has recently been developed in the form of transdermal patches, which provide a stable release over time.[10] It is a safe, well-tolerated system, which at the same time allows good adherence and effective drug penetration via the skin, with good local tolerability, ensuring ease of use together with optimised pharmacokinetics.[11,12]

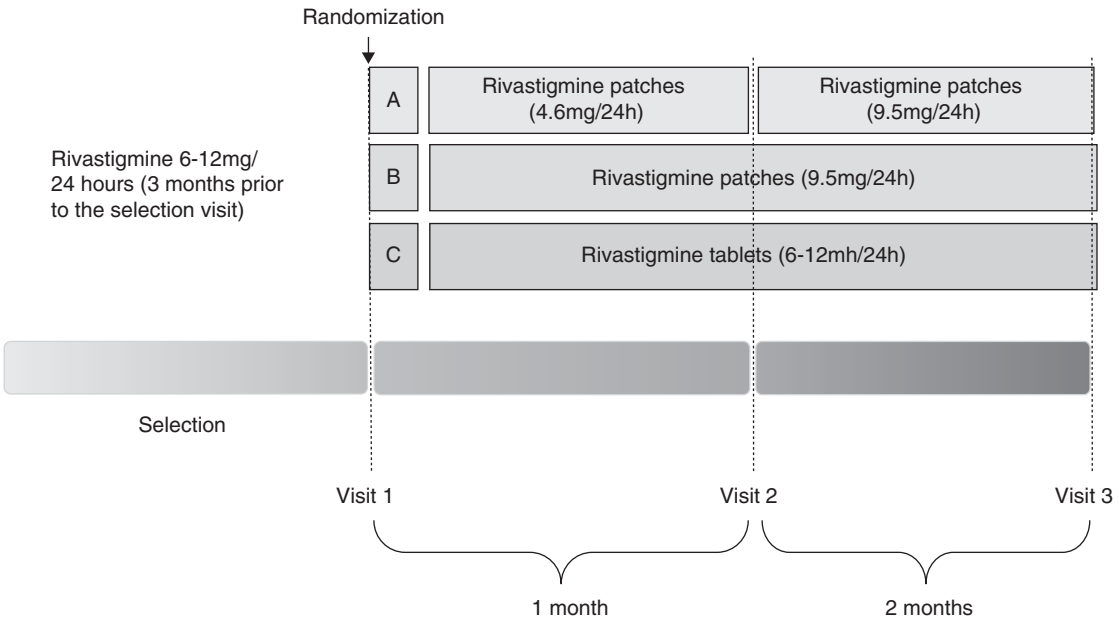

Figure 1 Design of the study and treatment regime.

The main aim of this study was to assess the gastrointestinal tolerability when changing the form of rivastigmine administration from oral to transdermal patches (with or without a titration period), when compared to a group of patients remaining on oral treatment. The secondary objective in the study included assessing the overall systemic tolerability of the two types of treatment considered, cutaneous tolerability in the case of transdermal administration and the level of satisfaction that carers and patients using the different administration methods reported.

Patients and methods

A selection was made from out-patients who were 60 years old or over, of any race or gender, with probable or possible AD diagnosis (DSM-IV), with a score of mild or moderately severe according to the result assessed by the Folstein Mini-Mental State Examination (MMSE) (MMSE ≥10),[13] who were being treated with oral rivastigmine at a minimum dosage of 6mg/day and a maximum dosage of 12mg/day during the three months prior to entering the study.

Demonstrated hypersensitivity to rivastigmine was considered one of the exclusion criteria, as well as the disease being advanced, serious, progressive or unstable in any way, as this could interfere with assessments of safety and tolerance or put the patient at risk. Patients who presented a neurological disorder, which might not be Alzheimer's and justified the presence of a dementia (Huntingdon's disease, Parkinson's disease, abnormal results in thyroid function, vitamin B12 or folic acid deficiency, post-traumatic conditions or syphilis) were not considered either.

The study was designed as a Phase IIIb/IV multicentre, randomized open-label clinical trial. The group of patients included were randomly assigned to 1 of the 3 following treatment groups: *a)* rivastigmine in a transdermal patch with titration (RPT) (application of 1 daily patch of 4.6mg/day during the first month of treatment and going on to a daily application of 1 patch of 9.5mg/day during the 2 following months); *b)* rivastigmine in a transdermal patch with no titration (RP) (application of a daily patch of 9.5mg/day during the entire treatment period); and *c)* rivastigmine in tablets (oral) (RO) (continuing the previous treatment regime from the start of the study at a steady rate, that is, administration of rivastigmine tablets with a dosage of between 6 and 12mg/day) (fig. 1). The follow-up period was of 3 months and 3 visits were carried out (basal, first month and third month).

The main variable assessed by the study was the percentage of patients who presented gastrointestinal-type adverse events. The following were defined as secondary variables: overall tolerance (percentage of patients with at least one systemic-type adverse event), local tolerance (percentage of patients with some type of cutaneous adverse effect in the treatment groups using patches), level of satisfaction for the patients and/or carers with the treatment (semi-guided interview with 22 items and 4 response options [from easiest to most difficult or from most satisfied to least satisfied], which assessed the ease of use of the treatment, ease in following the regime, interference with daily life and level of satisfaction with the treatment) and cognitive state of the patients (MMSE score).

The safety analysis included the description of the number of patients who presented adverse effects according to the system/organ and preferred term, intensity, relationship with the treatment and response action taken. Patients' weight, vital signs per visit and treatment group, number and percentage of patients with a normal electrocardiogram result, number and percentage of patients with normal results for each category of physical

Table 1 Demographic and basal characteristics of the sample

	Patch 4.6mg/24h 9.5mg/24h (N=43)	Patch 9.5mg/24h (N=47)	Tablets (N=49)	Total (N=139)
Age (years), mean±SD	77.0±4.8	75.3±7.2	77.3±6.6	76.6±6.4
Gender, n (% males)	13 (30.23%)	18 (38.30%)	24 (48.98%)	55 (39.57%)
Weight (kg), mean±SD	67.9±13.7	71.1±10,0	69.6±12,0	69.6±11.9
Height (cm), mean±SD	158.0±9.2	158.7±10.1	160.1±9.4	158.9±9.5
MMSE	18.2±4.5	16.9±4.4	16.8±4.9	

MMSE: Mini-Mental State Examination.

and neurological examination at the basal visit and V isit 3 were also recorded during the programmed visits.

The statistical analysis was carried out according to intention-to-treat (ITT) principles. All the random patients who received at least one dosage of the drug in the study were included in the analysis (security population). The variables were recorded by treatment group and visit. For the categorical variables, the relative percentage with respect to the total in the column and the n totals were recorded. For continuous variables, the following descriptive statistics were calculated: mean, standard deviation, conf dence interval [CI] of 95%, minimum, maximum, media, percentiles, n and number of lost data.

To assess the differences in cognitive state (MMSE) by treatment group during the second visit and f nal visit, we estimated these according to a CI of 95%. A covariance analysis was used to obtain this interval (ANCOV A model), which included the basal visit as the covariable. All analyses were carried out using the SAS programme, version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Study population

There were 149 patients selected and 142 were randomly chosen from 10 centres. Seven patients were excluded, 4 because they withdrew their consent, 2 because they violated protocol and 1 due to an alteration in laboratory values. Figure 2 indicates the distribution of the population in the study and the reasons for being excluded from the analysis.

The demographic and basal characteristics of the study population at the time they were included were comparable among the 3 treatment groups considered (table 1). There was a percentage of 28.8% (n=40) of patients who had previously experienced some gastrointestinal disorder. This incidence rate of previous gastrointestinal disorders was similar in the 3 groups treated (P>.05, χ^2 test).

Pharmacokinetics of rivastigmine

A pharmacokinetic follow-up of the plasma concentrations of rivastigmine and its metabolite NAP226-90 was carried out on the treatment groups considered. The pharmacokinetic prof le of rivastigmine after its administration in tablets was appropriately described from a behavioural model with f rst-order kinetics of absorption and elimination. When rivastigmine was administered by patch, the absorption followed a zero-order process. The f uctuations in the plasma levels of rivastigmine were less after transdermal administration than with oral administration. The patches also showed a lower maximum concentration peak and maintained sustained concentrations over time.

The pharmacokinetics of rivastigmine after transdermal administration could be modelled as a continuous infusion of 18-23hrs duration. The AUC relationship between the metabolite and rivastigmine was smaller with transdermal administration, showing the lesser effect of the f rst step (metabolic) with the use of a patch. A f rst-order process was assumed from the plasma concentrations of rivastigmine and the distribution was better adjusted through a compartment model with f rst-order elimination. The internal validation of the model showed a good prediction model.

Gastrointestinal tolerability

The percentage of patients with at least one gastrointestinal-type adverse effect (AE) (diarrhoea, nausea and/or vomiting) was less than 5% in groups treated with transdermal rivastigmine patches (4.7% in RPT and 4.3% in RP). In the group treated with tablets, the percentage of patients with gastrointestinal AE rose to 6.1% (table 2). The differences were not signi f cant (χ^2, P=.8667). We counted up a total number of 11 cases with gastrointestinal AE: 2 in RPT patients, 6 in RP patients and 3 in the RO group (χ^2; P=.3067).

The majority of gastrointestinal AEs were classi f ed as mild or moderate. Five gastrointestinal AEs were considered related to the study medication: 2 of them were produced in patients in the RP group (nausea), 1 in a patient in RPT (nausea) and 2 more in patients treated with tablets (diarrhoea and nausea).

Local tolerability

When examining skin tolerance, 5 patients (11.6%) of the RPT group presented some AE in the skin or subcutaneous

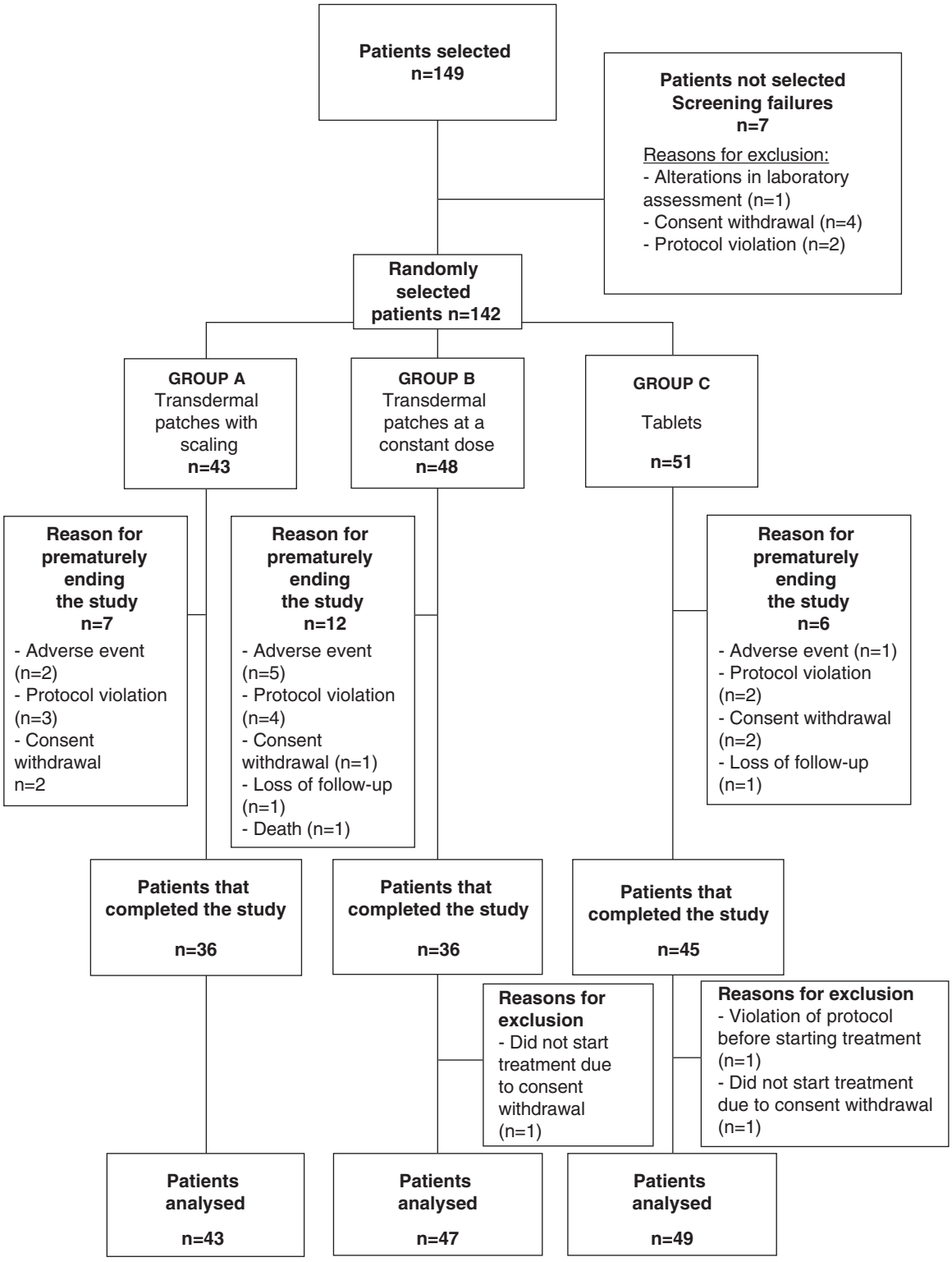

Figure 2 Disposition of study patients and reasons for exclusion or prematurely ending the study.

tissue during the study period (table 3). In the RP group, this percentage was greater, reaching 17% of patients with some skin AE (n=8), but with no signi f cant differences detected among the groups (χ^2; *P*=.4055). The total number of related cutaneous AEs was 15 cases: 5 in the RPT group and 10 in RP (χ^2; *P*=.1967).

All the AEs relating to skin or subcutaneous tissue during the study were reported as slight or moderate intensityThe

Table 2 Number of gastrointestinal adverse events related to rivastigmine treatment during the study. Safety population

	Patch 4.6mg/24h 9.5mg/24h (N=43)	Patch 9.5mg/24h (N=47)	Tablets (N=49)	Total (N=139)	*P**
Number of GI AE	2	6	3	11	0.3067
Patients with some GI AE	2 (4.65%)	2 (4.26%)	3 (6.12%)	7 (5.04%)	0.8667
Diarrhoea	0 (0.00%)	1 (2.13%)	2 (4.08%)	3 (2.16%)	0.3679
Nausea	1 (2.33%)	1 (2.13%)	1 (2.04%)	3 (2.16%)	1.0000
Vomiting	1 (2.33%)	2 (4.26%)	0 (0.00%)	3 (2.16%)	0.3679

AE: adverse effects; GI: gastrointestinal.
*χ^2 test.

majority of these AEs concerned the application process of the patches (13 out of the 15 AEs of the skin and subcutaneous tissue belonged to this subgroup). Only 2 patients (2.2% of the total) had their medication withdrawn as a result of the local adverse events (skin).

Overall tolerability

The overall tolerance of the different treatment groups was similar, with no significant differences (χ^2; *P*=0.8239). The total percentage of patients with some adverse effect detected during the study was 48.8% (n=21) in RPT patients, 55.3% (n=26) in RP patients and 53.1% (n=26) in RO patients (χ^2; *P*=.7099). Amongst the most frequently observed AEs during the study and after treatment was applied we must point out psychiatric disorders (n=7 in RPT, n=6 in RP and n=8 in RO; *P*=.8667), nervous system disorders (n=6 in RPT, n=9 in RP and n=3 in RO; *P*=.2231) and general disorders in the application site (n=5 in RPT and n=10 in RP; *P*=.1967).

Treatment adherence

When examining treatment adherence, the greater percentages of patients who adhered to treatment after the first month of random testing was reached in the RO group (95.7%), although the adherence was not significantly different in the rest of the groups (92.5% in RP and 90.7% in RPT). However, in contrast, 3 months after the treatment was started, the medium- and long-term adherence became minimum in the RO group (83.3%), maximum for RP (88.4%) and intermediate in RPT (84.6%).

Level of satisfaction for patients/carers with the treatment

The satisfaction expressed not only by the carers but also by the Alzheimer patients was assessed with regards to the use of the rivastigmine patch and patients' previous experience with the oral version of the treatment. For all questions carried out on the level of satisfaction, the significance obtained was clearly more noteworthy when comparing the RP assessment against RO than when comparing RO with RPT (*P*<.0001 in the 4 categories on satisfaction for the first case vs *P*<.0001 in a sole category for the second case, Mann-Whitney-Wilcoxon test) (table 4).

Rivastigmine treatment by patch without titration (RP) was defined as very easy to use by 72% of patients, while RO was considered very easy to use by only 30% of patients treated with tablets (*P*=.0005). In RP patients, 67% considered the treatment regime as very easy to follow, compared with 19% of RO patients (*P*<.0001). Finally, 72% of

Table 3 Number of skin and subcutaneous tissue adverse events related to the transdermal treatment of rivastigmine gathered during the study. Safety population

	Patch 4.6mg/24h 9.5 mg/24h (N=43)	Patch 9.5 mg/24h (N=47)	*P**
Number of cutaneous AE	5	10	0.1967
Patients with some cutaneous AE	5 (11.63%)	8 (17.02%)	0.4055
Erythema at the application site	3 (6.98%)	6 (12.77%)	0.3173
Itching at the application site	0 (0.00%)	3 (6.38%)	0.0833
Hives at the application site	1 (2.33%)	1 (2.13%)	1.0000
Pigmentation disorder	1 (2.33%)	0 (0.00%)	0.3173

AE: adverse effect.
*χ^2 test.

Table 4 Level of satisfaction of patients/carers with the treatment (according to semi-guided interview)

		Patch 4.6 mg/24 h-9.5 mg/24 h		Patch 9.5 mg/24h	
		Assessment of the patches	Assessment of the tablets	Assessment of the patches	Assessment of the tablets
Ease of use of treatment	NA	1 (2.56%)	1 (2.56%)	0 (0.00%)	1 (2.33%)
	Very easy	22 (56.41%)	18 (46.15%)	31 (72.09%)	13 (30.23%)
	Easy	14 (35.90%)	14 (35.90%)	9 (20.93%)	25 (58.14%)
	Diff cult	2 (5.13%)	6 (15.38%)	2 (4.65%)	3 (6.98%)
	Very diff cult	0 (0.00%)	0 (0.00%)	1 (2.33%)	1 (2.33%)
	P *		0.2302		0.0005
Ease of following treatment schedule	NA	1 (2.56%)	1 (2.56%)	0 (0.00%)	1 (2.33%)
	Very easy	31 (79.49%)	7 (17.95%)	29 (67.44%)	8 (18.60%)
	Easy	6 (15.38%)	25 (64.10%)	12 (27.91%)	29 (67.44%)
	Diff cult	1 (2.56%)	6 (15.38%)	1 (2.33%)	4 (9.30%)
	Very diff cult	0 (0.00%)	0 (0.00%)	1 (2.33%)	1 (2.33%)
	P *		< 0.0001		< 0.0001
Treatment interference with their daily lives	NA	1 (2.56%)	1 (2.56%)	0 (0.00%)	1 (2.33%)
	Always	2 (5.13%)	1 (2.56%)	2 (4.65%)	1 (2.33%)
	The majority	3 (7.69%)	1 (2.56%)	2 (4.65%)	2 (4.65%)
	of times	1 (2.56%)	13 (33.33%)	2 (4.65%)	14 (32.56%)
	Sometimes	10 (25.64%)	8 (20.51%)	6 (13.95%)	7 (16.28%)
	Rarely	22 (56.41%)	15 (38.46%)	31 (72.09%)	18 (41.86%)
	Never		0.0885		0.0085
	P *				
Overall satisfaction with the treatment	NA	1 (2.56%)	2 (5.13%)	0 (0.00%)	2 (4.65%)
	Very satisf ed	23 (58.97%)	9 (23.08%)	26 (60.47%)	6 (13.95%)
	Satisf ed	10 (25.64%)	23 (58.97%)	13 (30.23%)	28 (65.12%)
	Unsatisf ed	4 (10.26%)	5 (12.82%)	2 (4.65%)	6 (13.95%)
	Very unsatisf ed	1 (2.56%)	0 (0.00%)	2 (4.65%)	1 (2.33%)
	P *		0.0111		< 0.0001

*Mann-Whitney-Wilcoxon test. NA: not available.

RP patients conf rmed that the treatment never interfered with their daily lives, compared to 42% of the RO group (*P*=.0085). In the overall satisfaction category , the differences were even clearer, with 60% of RP patients very satisf ed, compared to 14% in the RO group (*P*<.0001).

Cognitive state

The patient's cognitive state was assessed by applying the MMSE questionnaire, by their assessment score during the study and according to the treatment group. There were no signif cant overall differences among the 3 treatment groups considered for the total MMSE score in Visit 2 (1 month after treatment started) and on Visit 3 (3 months after treatment commencement) (*P*=.2432 and *P*=.4126, ANCOV A, respectively).

The adjusted MMSE score measurements on Visit 2 for the different treatment groups were 18.3 points in RPT patients, 17.3 points in RP patients and 17.7 points in RO patients. During Visit 3, the adjusted means for the MMSE scores were 17.8 points in RPT, 17.1 points in RP and 16.4 points in RO (f g. 3).

Discussion

The difference among the ways of administering AD treatment can have notable repercussions in its ef f ciency and stability in the medium to long term. This is especially true when considering the discouraging factors in treatment adherence and satisfaction with the treatment, as would be the case in adverse effects, low medication tolerability complexity of the associated administration regime and interaction with concomitant medication.[14-16]

Likewise, with respect to rivastigmine tolerability , AEs are generally those expected for a cholinesterase inhibitor The adverse effects are usually slight or moderate, of short duration and are spontaneously resolved after the dosage is decreased or the treatment is stopped. [6] Their nature is most commonly gastrointestinal, speci f cally nausea and vomiting, which is related to the cholinomimetic effects of rivastigmine. A study on cholinesterase inhibitors indicates that AE incidence depends on the level and duration of enzyme inhibition and duration of the daily f uctuations in enzyme activity .[17] This is why that it has been postulated that the reduction of daily f uctuations in the pharmacokinetic pattern of rivastigmine leads to a

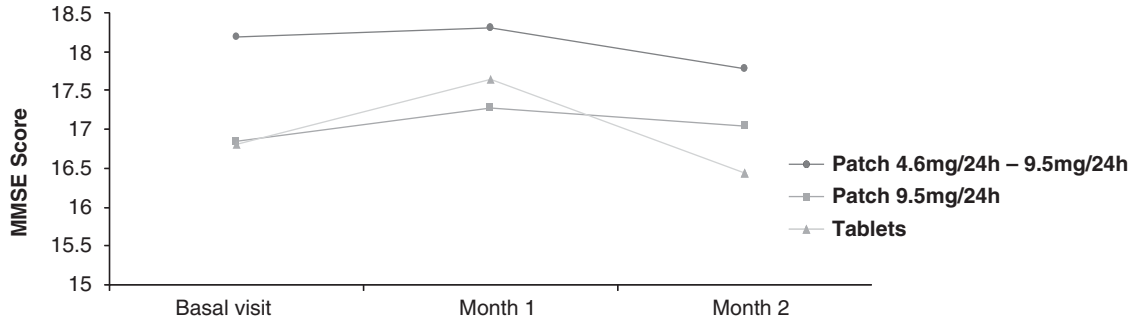

Figure 3 Total Mini-Mental State Examination (MMSE) scale score on the different visits by treatment group.

reduction in the fluctuations of cholinesterase enzyme inhibition, increasing the overall tolerance and maintaining efficiency throughout the day.[18]

Transdermal rivastigmine patches have been developed recently to achieve this pharmacokinetic pattern. The transdermal patches offer noteworthy advantages over the ways of orally administering rivastigmine, as they continuously release the drug, reducing absorption peaks and producing stable, prolonged drug levels in the blood.[11,12] Theoretically, these advantages can improve the tolerability pattern of rivastigmine, especially when referring to gastrointestinal tolerance, allowing easier access to better therapeutic doses. Additionally, the application of rivastigmine in transdermal patches could offer a clear advantage in AD treatment by increasing treatment adherence because it is easier to use the patches.

Our study aim was focused on assessing tolerance to rivastigmine in patients who had changed their usual administration route from oral to transdermal by using the newly available patches, compared to patients who maintained administration by tablets. This study also hoped to empirically establish the needs for a period of titration to proceed to a safe change in the administration method until achieving the optimum dose. The tolerability of rivastigmine application was assessed at a gastrointestinal level, overall systemic level for both routes of administration and specifically at cutaneous level for the transdermal route. Finally, we proposed an assessment of the levels of satisfaction of patients and carers with the procedure of applying the rivastigmine patch.

The study did not demonstrate significant differences in gastrointestinal tolerability by one or another administration route, although it showed a certain reduced tendency with applying rivastigmine patches. In any case, we should point out the low incidence rate of gastrointestinal adverse effects in patients treated with rivastigmine tablets compared to the incidences indicated in previous studies.[19-21] Probably, this relatively reduced percentage of gastrointestinal adverse effects, not only in groups treated with patch rivastigmine but orally, when compared to the data available from previous work[12] could be easily explained by the nature of the study population comprising our study: these were patients who had received treatment with oral rivastigmine before being included in our study and were consequently already used to considerable doses of rivastigmine.[14]

Given that transdermal application implies an additional risk of adverse effects associated to the administration route, we also assessed the local tolerability (cutaneous) of applying the patches in this study. We did not detect significant differences in the percentage of patients with cutaneous AE between the two treatment groups with patches, which showed a lack of effect in titration on the determination and the appearance of these types of adverse effects. These percentages were similar[22,23] or inferior[24] to those reported in previous studies available.

Following the arguments referring to the overall tolerance of the rivastigmine patch —not only gastrointestinal but cutaneous— this was found to be comparable between the two groups of patients treated with transdermal patches (with and without titration). Overall, this result seems to suggest that patients could benefit from passing from oral to transdermal administration (patches of 9.5mg/24h of rivastigmine), with no need of previous dosage scaling. It also confirms previous observations by Aguera et al,[25] who did not find favourable arguments in better efficiency and tolerability of transdermal treatments based on scaling the doses. Additionally, this result backs the research conclusions that confirm the need to reach maximum tolerated dosage as soon as possible so as to get maximum correlations between the MMSE measurement and final rivastigmine dosage.[26]

When examining the nature of the most common AEs in the treatment groups using a transdermal rivastigmine patch, the most frequent categories reported were psychiatric disorders, nervous system disorders and general disorders on the administration site. However, the low numbers of these incidences agree with the results that highlight the better overall tolerability associated to this type of treatment in patients with AD.[23]

When considering satisfaction of the carers/patients in the different treatment groups, the patients treated with transdermal rivastigmine patches at a constant dose found the treatment easier with patches than with tablets. Similarly, patients treated with patches considered that their application regime and use was easier to follow, probably as a consequence of the treatment interfering less with their daily lives. Finally, when dealing with overall satisfaction of treatment, the two groups of patients treated with transdermal patches confirmed a higher satisfaction than that shown with previous oral treatment, especially as a consequence of their greater ease of use and less

interference with their daily lives. These values coincide with the general patterns obtained in studies where they valued the satisfaction of carers exclusively.[27] Likewise, the patches are associated to an overall greater satisfaction with the treatment by carers and patients than the oral route, a result that con f rms preferences related to the inherent advantages of pharmacokinetics that are more rational and constant when associated with transdermal administration.[18-28]

Focusing on the patients' cognitive states throughout the study period, there seems to be a certain sustained tendency against deterioration in state for patients treated with transdermal patches. Although the differences were not statistically signi f cant, oral treatment showed a greater cognitive worsening from the third visit. This result could be related to a tendency of a lesser therapeutic adherence in the long term with this type of administration and with a greater interference of the oral administration regimes in the patient's daily life.[29]

To conclude, the change in the way of administering rivastigmine (from tablets to transdermal patches) can be undertaken with good overall gastrointestinal and cutaneous tolerability. We have also seen that patients could bene f t from going on to higher rivastigmine doses, which are therefore more effective, without the need of scaling the dosage and with the purpose of attaining appropriate therapeutic doses as soon as possible with maximum drug eff ciency.[30,31]

Conf ict of interest

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Anex

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