Long-term use of pharmacological treatment in Alzheimer's disease: a retrospective cohort study in real-world clinical practice

European Journal of Clinical Pharmacology
https://doi.org/10.1007/s00228-022-03325-y

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Long-term use of pharmacological treatment in Alzheimer's disease: a retrospective cohort study in real-world clinical practice

G Lombardi[1] · N Lombardi[2] · A Bettiol[2] · G Crescioli[2] · C Ferrari[2] · G Lucidi[3] · C Polito[1] · V Berti[4] · V Bessi[5] · S Bagnoli[2] · B Nacmias[1,2] · A Vannacci[2] · S Sorbi[1,2]

Received: 14 June 2021 / Accepted: 18 April 2022

Abstract

Purpose To assess the impact of long-term use of different drugs commonly prescribed in Alzheimer's disease (AD) on its clinical course and to identify clinical and therapeutic factors associated with a delay in AD progression.

Methods We retrospectively enrolled 50 patients visited at the Neurology Unit, Careggi University Hospital (Florence), followed for at least 24 months. AD diagnosis was made according to clinical diagnostic criteria for probable/possible AD dementia, always supported at least by one biomarker. Clinical features, MMSE scores evaluated at diagnosis and every 6 months, and AD drugs used for at least 6 months, were recorded. Cox regression analysis was performed to estimate the hazard ratio (HR) for AD progression, assuming as the "final event," the progression to a more severe disease stage, defined as the achievement of an MMSE score less than 10.

Results At baseline, the median MMSE score was 22. During follow-up (median of 41 months), 56% of patients progressed to a more severe disease stage. The use of memantine, either alone (HR 0.24; 95% CI 0.09–0.60) or combined with acetylcholinesterase inhibitors (HR 0.35; 95% CI 0.14–0.88) and a higher MMSE score at baseline (HR 0.82; 95% CI 0.70–0.96) were associated with a significantly lower risk of AD progression.

Conclusion Nowadays, effective disease-modifying therapy for AD is missing. Nevertheless, when the diagnosis is established, our results support the advantage of long-term use of available pharmacological treatments, especially in combination, in delaying AD progression to its more severe disease stage.

Keywords Alzheimer's disease · Progression · Acetylcholinesterase Inhibitors · Memantine · Dementia

Introduction

Nowadays there is no cure for Alzheimer's disease (AD) dementia and maximizing the effects of the currently available pharmacological treatments could be crucial to slow AD progression. Acetylcholinesterase inhibitors (AChEIs) such as donepezil, rivastigmine and galantamine and the N-methyl-D-aspartate (NMDA) receptor antagonists such as memantine are usually prescribed in AD. Guidelines by the European Federation of Neurological Societies (EFNS) recommend initially AChEIs as the standard of care for the treatment of mild to moderate AD, whereas memantine is recommended for the treatment of moderate to severe AD [1]. At a moderate disease stage, AChEIs can be combined with the memantine to exert a complementary and synergistic action [2]. Recent evidence confirmed the efficacy and safety of these medications in AD dementia [3, 4]. Anyway, conclusions of Cochrane reviews underline a moderate level

Lombardi G and Lombardi N these authors contributed equally to the work.

✉ G Lombardi
gemmalomb@gmail.com; glombardi@dongnocchi.it

1 IRCCS Fondazione Don Carlo Gnocchi, via di Scandicci 269, 50143 Florence, Italy

2 Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, viale Pieraccini 6, 50139 Florence, Italy

3 Neurology Unit, S. Giovanni Di Dio Hospital, Via Torregalli, 3, 50143 Florence, Italy

4 Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", Nuclear Medicine Unit, University of Florence, Largo Brambilla 3, 50134 Florence, Italy

5 Neurology Unit, Azienda Ospedaliera-Universitaria Careggi, Florence, Largo Brambilla 3, 50134 Florence, Italy

Published online: 28 April 2022

of evidence of these results and argue that long-term effects of these medications should be confirmed [5–7]. Controversies on the impact of Selective serotonin reuptake inhibitors (SSRIs) in the clinical course of AD exist [8–11], whereas the use of antipsychotics (APs) and benzodiazepines (BZDs) has been associated with a worse outcome [12–14].

This retrospective cohort study aimed to assess the impact of long-term use of different drugs commonly prescribed in Alzheimer's disease (AD) on its clinical course and to identify clinical and therapeutic factors associated with a delay in the AD progression.

Methods

Study design and population

We conducted a retrospective cohort study on 50 patients affected by AD dementia evaluated for the first time at the Neurology Unit, Careggi University Hospital (Florence) between 2014 and 2016. According to routine clinical practice, all patients received follow-up visits every six months**.**

Clinical diagnosis of probable/possible AD was made according to the McKhann criteria [15]. The study cohort included patients with: 1) diagnosis supported by at least one biomarker; 2) baseline Mini-Mental State Examination (MMSE) score equal or more than 15; 3) follow-up length of 24 months or over; and 4) prescription of specific treatments for cognitive decline (AChEIs and/or memantine). In detail, we enrolled exclusively patients that showed a typical parieto-temporal hypometabolism on 18-fluorodeoxyglucose positron emission tomography (FDG-PET) and/or an amyloid accumulation on Amyloid-PET (Amy-PET) and/or a cerebrospinal fluid (CSF) AD-like pattern. Patients were excluded if a stroke was documented at the onset of the cognitive symptoms or when a high vascular load was detectable on the brain imaging (Fazekas score above 2) [16] and in case of secondary causes of dementia. All procedures performed in the study were in accordance with the Helsinki Declaration, and the study protocol was approved by the local Ethics Committee (reference 17951_oss). Patients or their caregivers gave their informed consent to participate in the study.

Data source

We retrospectively retrieved data related to baseline clinical parameters and examinations, including neuropsychological examination, brain CT scan or conventional MRI. Results related to AD-biomarkers were also collected to assess the inclusion eligibility. For a subgroup of patients, information on Apolipoprotein E (ApoE) genotype was also available. We retrieved information related to comorbidities, in particular, vascular risk factors such as hypertension, glucose intolerance/diabetes, hypercholesterolemia, smoke assessed at baseline. Then, we considered that the presence of 3 or more severe comorbidities, assessed with the modified cumulative illness rating scale [17], might significantly impact the progression of AD. Moreover, information on the assumption of concomitant medications was also collected. We further retrieved data related to the MMSE (range of scores 0–30; higher score indicating a better cognitive level) [18], to the basic activities of daily living (BADL) (range of scores 0–6; higher score indicating a better functional level) [19] and to AD pharmacological treatments, in particular about the start of treatment, discontinuation, switching between medications and adverse drug reactions (ADRs) collected at each follow-up visit with a standard interview. We considered only treatments regularly used for at least 6 months. AD treatments with a duration less than 6 months were not included in our analysis, as their possible impact on AD clinical course was considered negligible.

Outcomes

The impact of AD treatments on the clinical outcome was assessed in terms of AD progression; thus, the primary outcome was defined as the progression to the more severe disease stage, detectable by the achievement of an MMSE score less than 10, as established by the Italian Medicines Agency (AIFA https://www.aifa.gov.it/nota-85). Indeed, in our study the MMSE score was used both to classify the severity of disease and to measure cognitive changes, assuming the progression to the more severe stage of disease as the "final event." Then, the disease stage was defined as follows: mild dementia for MMSE score between 26 and 21; moderate dementia for MMSE score between 20 and 10; severe dementia for MMSE score less than 10. Basing on the progression or not to the more severe disease stage, participants were defined as "*Progressors*" (achievement of MMSE score less than 10 in the follow-up) and "*Non-Progressors*" (missing achievement of this cut-off). For the Progressors group, the follow-up length was defined as the time interval between the baseline visit and the "final event." For the Non-Progressors group, the follow-up length was defined as the time interval between the baseline visit and the last recorded visit.

Statistical analysis

Analyses were carried out using STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). The sample size was calculated on the "disease progression" outcome defined as achieving an MMSE score less than 10. In particular, it was assumed that the proportion of patients who progress in the follow-up to the more severe stage

of the disease is 48% among patients treated pharmacologically with AChEIs/Memantine for at least 6 months and 88% among untreated patients. Based on this estimate, the enrollment of 50 cases is sufficient to guarantee a power of 80%, with an alpha error equal to 0.05. The enrollment of this sample appeared feasible also on the basis of what is expected from clinical data, as at least two factors limit the sample size: a follow-up duration of at least 24 months, the presence of biomarkers as diagnostic support. Characteristics of *Progressors* and *Non-Progressors* were compared with nonparametric tests, using the Fisher test for categorical variables and the Mann–Whitney U test for continuous variables. Univariate Cox regression models were fitted to estimate the hazard ratio (HR) (95% Confidence Interval, CI) of AD progression in relation to age, gender, education, baseline MMSE score, ApoE status, type of AD presentation, vascular risk factors, comorbidities and medications.

Multivariate Cox regression models were also fitted: co-variates were chosen based on univariate analysis; moreover, age, sex, use of AChEIs and SSRIs were also included among co-variates, due to their clinical relevance. For each parameter, the analysis was made only on subjects with available data, without imputing missing data. In order to show the rate of progression to a more severe disease stage over time, different Kaplan–Meier curves were generated in relation to pharmacological treatment. Finally, the correlation between MMSE and BADL scores obtained at the end of follow-up was assessed with the Spearman's rank correlation coefficient.

Results

Characteristics of the study population

Fifty outpatient participants were included in the study (Table 1), 31; (62%) were female, the median age at baseline was 70.3 years (Interquartile Range, IQR 64.6–77.7), and the median years of education was 8 (IQR 5–13). Fifty-seven percent of patients carried at least one ApoE ε4.

The median baseline MMSE score was 22 (IQR 19–25) and was significantly higher in *Non-Progressors* as compared to *Progressors* (24 (22–25) and 21 (19–23), $p = 0.006$, respectively).

Thirty-two participants were affected by mild AD, 18 by moderate AD: cases enrolled as moderate AD at baseline, progressed most frequently at follow-up compared to mild AD cases ($p = 0.036$). All cases were defined as functional independent based on their baseline BADL score, anyway, according to McKhann criteria, a decrease in the ability to function at work or in their usual activities compared to the previous level had been documented at the inclusion.

Clinical presentation of disease was typical in the majority of cases (66%). The atypical presentation was more common in *Progressors* than in *Non-Progressors* (50% vs 14%, $p = 0.008$) and mostly represented by the "logopenic variant" (82%). Dyslipidemia, current or past cigarettes smoking and hypertension were the most frequently observed vascular risk factors, and 38% of patients were affected by 3 or more moderate to severe comorbidities. During a median follow-up of 41 months (IQR 30–56), 28 (56%) patients progressed to a more severe disease stage. Final MMSE and ADL scores were significantly different between *Progressors* and *Non-Progressors* (MMSE = 7 vs MMSE = 18, $p < 0.001$; ADL = 3 vs ADL = 6, $p < 0.001$, respectively).

Long-term pharmacological treatments (over 6 months)

AChEIs, SSRIs and memantine were the most frequently prescribed medications, the percentage of users ranging between 64% (memantine) and 88% (AChEIs) (Table 2). No significant difference in pharmacological treatments was found between *Progressors* and *Non-Progressors*, with the exception of the combination AChEIs with memantine, which was prescribed in 50% of cases and was significantly more used in *Non-Progressors* (68% vs 36%, $p = 0.045$). All patients assumed at least one drug (AChEIs or memantine) or both for 6 months or over, in 98% of cases at full dose (donepezil 10 mg, rivastigmine transdermal patch 9.5 mg/13.3 mg, memantine 20 mg). In 40/44 cases (90%) AChEIs were prescribed as first-line therapy. Regarding AChEIs, donepezil was continuously prescribed in 23 out of 44 cases, transdermal rivastigmine in 20 out of 44 cases and oral rivastigmine in 1 case. The combined therapy was prescribed mostly at a moderate level of cognitive decline (19/25), whereas in 6 cases was prescribed at a mild level of impairment basing on a relevant worsening referred by the caregiver or documented by an MMSE score decrease. Discontinuation before 6 months (for all causes) in medication intake was higher in *Progressors* compared to *Non-Progressors* and the difference was significant for the combined therapy (4/14 vs 0/15, $p = 0.042$, Table 2). The combined therapy was discontinued before 6 months/not prescribed in 50% of cases, mainly due to these reasons: contraindications (n = 6), ADR (n = 5), absence of indications basing on the level of impairment (n = 4), low compliance (n = 1); in 9 cases, the reason for nonprescription was not clearly identifiable. SSRIs were largely used (68%), in association or not, whereas only 14% and 8% of participants received APs and BZDs for at least 6 months, respectively. Concomitant treatments used to control vascular risk factors were continued during the follow-up: antihypertensives (48%), statins (48%), antiplatelets (40%), anticoagulants (10%), antidiabetics (6%). ADRs and switching between AChEIs have been reported and described in Supplementary Table 1.

Table 1 Baseline characteristics of the study cohort, follow-up length, baseline and final MMSE and BADL scores

	Total cohort N (% out of 50)	**Progressors N (% out of 28)**	**Non-Progressors N (% out of 22)**	***p-value****
Gender				
Male	19 (38)	10 (36)	9 (41)	0.770
Female	31 (62)	18 (64)	13 (59)	
Age at baseline				
Median (IQR)	70 (65–78)	71 (64–78)	70 (64–78)	0.740
Years of education				
Median (IQR)	8 (5–13)	8 (5–13)	8 (5–11)	0.380
MMSE at baseline				
Median (IQR)	22 (19–25)	21 (19–23)	24 (22–25)	0.006*
Level of cognitive decline (baseline)				
Mild AD	32 (64)	14 (50)	18 (82)	0.036*
Moderate AD	18 (36)	14 (50)	4 (18)	
BADL at baseline				
Median (IQR)	6 (6–6)	6 (6–6)	6 (6–6)	1
APO E ε4 carriers				
(13 missing data)	21 (57)	11 (52)	10 (63)	0.780
Biomarker availability				
FDG-PET	44 (88)	26 (93)	18 (82)	0.385
Amy-PET	22 (44)	11 (39)	11 (50)	0.568
CSF analysis	17 (34)	9 (32)	8 (36)	0.773
Type of AD presentation				
Typical	33 (66)	14 (50)	19 (86)	
Atypical	17 (34)	14 (50)	3 (14)	0.008*
Vascular risk factors				
Hypertension	23 (46)	10 (36)	13 (59)	0.153
Diabetes/IGT	8 (16)	5 (18)	3 (14)	1.000
Current or past cigarettes smoking (12 missing data)	22 (58)	13 (68)	9 (47)	0.325
Dyslipidemia	33 (66.0)	17 (61)	16 (73)	0.548
Sleep disorders (5 missing data)	13 (29)	6 (25)	7 (33)	0.743
3 or more moderate to severe comorbidities	19 (38.0)	8 (29)	10 (45)	0.250
Follow-up, months				
Median (IQR)	41 (30–56)	38 (28–46)	50 (30–61)	0.085
MMSE at last follow-up				
Median (IQR)	9 (7–17)	7 (5–8)	18 (14–22)	< 0.001*
BADL at last follow-up				
Median (IQR)	4 (3–6)	3 (2–5)	6 (4–6)	< 0.001*

MMSE Mini-Mental State examination, *BADL* basic activities of daily living, *CSF* cerebrospinal fluid, *IGT* impaired glucose tolerance, *IQR* interquartile range

**p*-value comparisons between Progressors and Non-Progressors; *statistically significant for $p < 0.05$.

Risk of progression

Regarding patients' clinical characteristics, a higher level of education and an atypical presentation of AD were significantly associated with AD progression (HR 1.04 (1.02–1.07) and 2.58 (1.21–5.47), respectively), while a higher MMSE score at baseline (HR 0.85 (0.75–0.96)) and the use of memantine, alone (HR 0.34 (0.16–0.72)) or in combination with AChEIs (HR 0.30 (0.14–0.68)) were associated with a lower risk of progression (Table 3). Results from the adjusted analysis confirmed that a higher baseline MMSE (HR 0.82 (0.70–0.96)) and the assumption

Table 2 Comparison of pharmacological treatments between *Progressors* and *Non-Progressors*. In each row: above the use of the drug for at least 1 month, below the use of the drug for at least 6 months

	Total cohort N (% out of 50)	**Progressors N (% out of 28)**	**Non-Progressors N (% out of 22)**	***p-value****
AChEIs				
•For at least 1 month	46 (92)	26 (93)	20 (91)	1.000
•For at least 6 months	44 (88)	24 (86)	20 (91)	0.683
Memantine				
•For at least 1 month	35 (70)	18 (64)	17 (77)	0.367
•For at least 6 months	32 (64)	15 (54)	17 (77)	0.137
AChEIs and memantine				
•For at least 1 month	29 (58)	14 (50)	15 (68)	0.253
•For at least 6 months	25 (50)	10 (36)	15 (68)	0.045*
SSRIs				
•For at least 1 month	37 (74)	21 (75)	16 (73)	1.000
•For at least 6 months	34 (68)	18 (64)	16 (73)	0.559
APs				
•For at least 1 month	9 (18)	6 (21)	3 (14)	0.713
•For at least 6 months	7 (14)	5 (18)	2 (9)	0.444
BZDs	4 (8)	3 (11)	1 (5)	0.621
•For at least 1 month	4 (8)	3 (11)	1 (5)	0.621
•For at least 6 months	4 (8)	3 (11)	1 (5)	0.621
Antiepileptics	4 (8)	3 (11	1 (5)	0.621
•For at least 1 month	4 (8)	3 (11	1 (5)	0.621
•For at least 6 months	3 (6)	2 (7.1)	1 (5)	1.000
Levodopa	3 (6)	0	3 (14)	-
•For at least 1 month	3 (6)	0	3 (14)	-
•For at least 6 months	3 (6)	0	3 (14)	-
Other drugs for at least 6 months				
Antihypertensives	24 (48)	11 (39)	13 (59)	0.254
Statins	24 (48)	12 (43)	12 (55)	0.569
Antiplatelets	20 (40)	13 (46)	7 (32)	0.387
Anticoagulants	5 (10)	3 (11)	2 (9)	1.000
Antidiabetic drugs	3 (6)	1 (3.6)	2 (9)	0.576

AChEIs Acetylcholinesterase inhibitors, *SSRIs* Selective serotonin reuptake inhibitors, *APSs* Antipsychotics, *BZDs* Benzodiazepines

**p-value* comparisons between *Progressors* and *Non-Progressors*; *statistically significant for $p < 0.05$

of memantine alone (HR 0.24 (0.09–0.60)) or in combination with AChEIs (HR 0.35 (0.14–0.88)) were associated with a significantly lower risk of AD progression (Table 3 and Fig. 1). No impact of statins on AD progression was found. A statistically significant correlation was found between the MMSE and BADL scores obtained at the end of follow-up ($p < 0.0001$, Spearman' rank correlation coefficient 0.641, 95% CI 0.44–0.780).

Discussion

This retrospective study aimed to assess the impact of long-term use of different drugs commonly prescribed in AD dementia on its clinical course and to identify clinical and therapeutic factors associated with the progression of AD. Baseline characteristics of *Progressors* and *Non-Progressors* significantly differed in the median MMSE score and in the type of AD presentation. The use of the combined therapy during the follow-up was also significantly different between the two groups. The median MMSE score was higher in *Non-Progressors*, indicating a less severe disease stage in this group at baseline. In this regard, the severity of dementia is one of the main factors associated with faster clinical deterioration [20–22]. In our sample, atypical AD presentation, mostly represented by the logopenic variant (82%), was more frequent among *Progressors* (50%). Compared to AD typical cases, language impairment, characteristic of logopenic patients, could have had a significant impact on MMSE score, resulting in detection of a faster decline. In this regard, previous studies reported the "hippocampal sparing"

Table 3 Risk of Alzheimer's disease progression (MMSE score < 10) according to clinical and therapeutic features

	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Gender Female (Male Ref.)	1.22 (0.56 – 2.65)	0.616	1.09 (0.46 – 2.63)	0.841
Age at baseline	0.98 (0.93 – 1.04)	0.472	0.98 (0.92 – 1.04)	0.508
Years of education	1.04 (1.02 – 1.07)	0.001*	1.03 (1.00 – 1.06)	0.098
MMSE at baseline	0.85 (0.75 – 0.96)	0.011*	0.82 (0.70 – 0.96)	0.014*
APO E	0.56 (0.23 – 1.34)	0.195	-	
Atypical presentation of AD (Typical presentation Ref.)	2.58 (1.21 – 5.47)	0.014*	1.71 (0.71 – 4.09)	0.228
Risk factors for AD				
Hypertension	0.56 (0.25 – 1.22)	0.142	–	
Diabetes/ITG	0.77 (0.29 – 2.06)	0.607	–	
Smoke (current or past)	1.43 (0.54 – 3.77)	0.472	–	
Dyslipidemia	0.59 (0.27 – 1.26)	0.172	–	
Overweight/Obesity	0.15 (0.02 – 1.15)	0.067	–	
Sleep disorders	0.74 (0.29 – 1.85)	0.514	–	
Three or more serious comorbidities	0.63 (0.28 – 1.44)	0.275	–	
AChEIs use	0.77 (0.26 – 2.26)	0.631	0.58 (0.14 – 2.46)	0.461
Memantine use	0.34 (0.16 – 0.72)	0.005*	0.24 (0.09 – 0.60)	0.002*
Combination of AChEIs and memantine use	0.30 (0.14 – 0.68)	0.004*	0.35 (0.14–0.88)	0.017*
SSRIs	0.58 (0.26 – 1.27)	0.172	0.75 (0.27 – 2.05)	0.573
APs	0.74 (0.28 – 1.97)	0.550	–	
BZDs	1.32 (0.39 – 4.45)	0.650	–	
Statins	0.76 (0.35 – 1.64)	0.483	–	

CI confidence interval, *IGT* impaired glucose tolerance, *AChEIs* Acetylcholinesterase inhibitors, *SSRIs* Selective serotonin reuptake inhibitors, *APs* Antipsychotics, *BZDs* Benzodiazepines

*p-value related to unadjusted analysis (third column) and to adjusted analysis (fifth column) statistically significant for $p < 0.05$. HR: hazard ratio

presentation (non-amnestic) of disease as more aggressive in comparison with the typical one [23]. *Non-Progressors* generally discontinued less their treatments and more frequently assumed AChEIs and memantine in combination, suggesting a beneficial effect of these concomitantly administered drugs. According to their indications [24], AChEIs and memantine were widely prescribed in our clinic and administered to patients mainly for at least 6 months. For AChEIs, the same prescription rate was observed in a previous study that involved 88 Italian Alzheimer Evaluation Units [25]. Pharmacological treatments have been prescribed following recommendations and/or international guidelines, which recommend starting the therapy with a dose up-titration regimen of AChEIs and, eventually, applying a switch between AChEIs in case of ADRs.

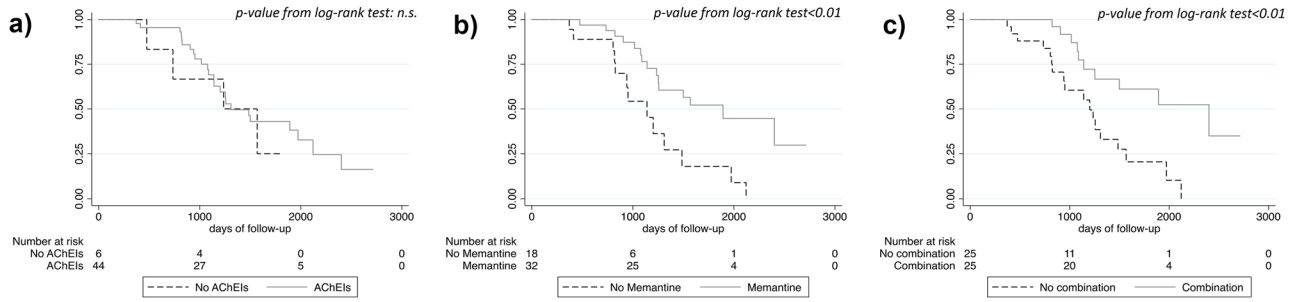

Fig. 1 Kaplan–Meier curves of time to disease progression (MMSE < 10) according to **a**) treatment with AChEIs, **b**) treatment with memantine and **c**) use AChEIs + memantine in combination; results from log-rank test on the top of the curves

AChEIs and memantine have been combined in moderate to severe dementia or in cases of worsening. In our sample, the reason for the nonprescription of the combined therapy was not always retrospectively identifiable, and it was possibly due to the variability in patient management by neurologists. Indeed, a different predisposition in detecting an ongoing or imminent worsening may have influenced the timeline of drugs' prescription or treatment with a single drug may have been preferred, at a single-subject level, to avoid pharmacological interactions. Of note, the EFNS guidelines on the recommendation for using the combined therapy in moderate to severe AD [2] are relatively recent and they were not in use before 2015. Regression analysis showed that some clinical factors such as education, baseline MMSE score, presentation of disease and use of specific treatments influenced the clinical course of AD. In agreement with the cognitive reserve theory [26], higher education was associated with a faster decline. Also, an atypical presentation of disease was associated with a faster decline, as reported by some Authors [23]. ApoE genotype, gender, age at onset, vascular risk factors, other comorbidities and sleep disturbances did not influence the clinical course. In this regard, the impact of the ApoE ε4 genotype has not always been associated with a faster decline [21, 27, 28]. Moreover, the effect of the above-mentioned variables on AD progression is still contradictory [29], and the role of ApoE genotype, together with that of vascular risk factors and sleep disorders, could be more significant in relation to the AD onset, instead of AD progression. In our sample, a higher MMSE score at baseline and the assumption of memantine alone or in combination with AChEIs were associated with a slower progression. Usually, due to their different indications based on disease stage and their different mechanism of action, AChEIs and memantine cannot be directly compared in terms of effectiveness. Moreover, some patient- or drug-related factors could affect treatment response. In this regard, response to AChEIs can be influenced by genetic polymorphism or concomitant vascular load/hippocampal atrophy of patients and by specific drug pharmacological properties [24, 30, 31]. On the contrary, the response to memantine could be less dependent on these factors [32]. Despite recommendations on AChEIs use, some evidence suggests the opportunity to continue AChEIs for a long period [33] [34] even in the absence of an initial clinical improvement because a long-term response is frequent in the initial "non-responders." The efficacy of memantine alone or in combination with AChEIs on cognitive symptoms has been confirmed in moderate to severe stages of disease [2, 4, 7]. Anyway, long-duration trials are needed to establish whether the benefit persists beyond 6 months, as suggested by some Authors [35] and to determine whether starting memantine earlier would be beneficial [7]. SSRIs, APs and BZDs did not impact the AD course in our study. Literature data on the effect of SSRIs on AD course are controversial. SSRIs have been associated with a delayed AD conversion in Mild Cognitive Impairment cases previously affected by depression [8]. However, SSRIs use has been associated with an increased risk of dementia in older adults [9]. Thus, the possible impact on the clinical course of AD is debated [10, 11] and the controversy may depend on the presence of depression as a possible confounding factor. Differently, the use of APs has been associated with mortality in older persons with AD [12, 13] and the use of BZDs with further cognitive impairment and serious ADRs [14]. In our study, the absence of a negative effect of these medications on the clinical outcome could depend on their low prescription rate. Additionally, the impact of statins on AD progression was also evaluated and, according to recent reports, no relation with slowing progression was found [36, 37]. At the study end, cognition and functionality were highly correlated, as expected [38, 39], implying that patients with the lowest MMSE score were also those with greater functional impairment and, in consequence, with higher family burden.

Our results have some points of strengths, in particular diagnosis of dementia was supported by at least one biomarker, increasing the diagnostic accuracy and confidence toward AD etiology. Differently from other studies, we evaluated the potential impact of different drugs on the clinical course of AD, considering the effect of each drug only if its use was superior to 6 months, focusing the attention on long-term effects and assuming as the final event the

progression to a more severe cognitive decline (MMSE < 10) that is characterized also by significant functional impairment. Moreover, the impact of combined therapies was also assessed. As a consequence of including cases with at least one diagnostic biomarker and with long follow-up, the major limitation of the study was the small sample size. In agreement with this decision, we could not stratify our analysis by each AChEI. Unfortunately, as reported in Table 1, there are 13 missing data for ApoE polymorphism; this could have reduced the accuracy in the estimation of ApoE genotype impact on the clinical course. Moreover, intercurrent acute health issues (such as bone fracture, surgical intervention, infectious diseases) have not been taken into account as potential factors capable of modifying the rate of AD progression. However, the frequency of the aforementioned acute health issues was similar between *Progressors* and *Non-Progressors* ($p = 0.108$).

In conclusion, our results support the usefulness of long-term use of currently available pharmacological treatments, especially in combination, in delaying AD progression to the more severe disease stage. Further research is needed to understand whether early combined treatments may offer additional benefits in routine clinical practice. We recommend verification and replication of our findings in larger studies with a prospective design, including a control group in order to confirm a causal relationship between drug assumption and a better course of the disease.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00228-022-03325-y.

Author's statement All authors participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing or revision of the manuscript. Gemma Lombardi, Niccolò Lombardi, Alessandra Bettiol, Giada Crescioli, Sandro Sorbi and Alfredo Vannacci conceived or designed study. Gemma Lombardi, Cristina Polito, Giulia Lucidi, Camilla Ferrari, Valentina Bessi and Valentina Berti performed the research. Alessandra Bettiol and Gemma Lombardi analyzed the data. Alessandra Bettiol, Benedetta Nacmias, Silvia Bagnoli, Cristina Polito, Valentina Berti and Giulia Lucidi contributed to new methods or models. Gemma Lombardi, Niccolò Lombardi, Giada Crescioli, Alfredo Vannacci, Sandro Sorbi, Benedetta Nacmias, Silvia Bagnoli, Valentina Bessi and Camilla Ferrari wrote the paper.

Funding Not applicable (the study was not financially supported).

The data that support the findings of the study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval All procedures performed in the study were in accordance with the Helsinki declaration and the study protocol was approved by the local Ethics Committee (reference 17951_oss).

Consent to participate Patients or their caregivers gave their informed consent to participate in the study.

Consent for publication As reported in the study protocol "A final report will be prepared following the study end and it will be proposed as a possible publication in an international journal".

Conflicts of interest/Competing interests The authors have no conflict of interest to report.

References

1. Hort J, O'Brien JT, Gainotti G, Pirttila T, Popescu BO, Rektorova I, Sorbi S, Scheltens P, EFNS Scientist Panel on Dementia (2010) EFNS guidelines for the diagnosis and management of Alzheimer's disease. Eur J Neurol 17:1236–1248. https://doi.org/10.1111/j.1468-1331.2010.03040.x
2. Schmidt R, Hofer E, Bouwman FH, Buerger K, Cordonnier C, Fladby T, Galimberti D, Georges J, Heneka MT, Hort J, Laczó J, Molinuevo JL, O'Brien JT, Religa D, Scheltens P, Schott JM, Sorbi S (2015) EFNS-ENS/EAN Guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer's disease. Eur J Neurol 22:889–898. https://doi.org/10.1111/ene.12707
3. Tricco AC, Ashoor HM, Soobiah C, Rios P, Veroniki AA, Hamid JS, Ivory JD, Khan PA, Yazdi F, Ghassemi M, Blondal E, Ho JM, Ng CH, Hemmelgarn B, Majumdar SR, Perrier L, Straus SE (2018) Comparative Effectiveness and Safety of Cognitive Enhancers for Treating Alzheimer's Disease: Systematic Review and Network Metaanalysis. J Am Geriatr Soc 66:170–178. https://doi.org/10.1111/jgs.15069
4. Dou KX, Tan MS, Tan CC, Cao XP, Hou XH, Guo QH, Tan L, Mok V, Yu JT (2018) Comparative safety and effectiveness of cholinesterase inhibitors and memantine for Alzheimer's disease: a network meta-analysis of 41 randomized controlled trials. Alzheimers Res Ther 10:126. https://doi.org/10.1186/s13195-018-0457-9
5. Birks JS, Grimley Evans J (2015) Rivastigmine for Alzheimer's disease. Cochrane Database Syst Rev 4:CD001191. https://doi.org/10.1002/14651858.CD001191.pub3
6. Birks JS, Harvey RJ (2018) Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev 6(6):CD001190. https://doi.org/10.1002/14651858.CD001190.pub3. PMID: 29923184; PMCID: PMC6513124
7. McShane R, Westby MJ, Roberts E, Minakaran N, Schneider L, Farrimond LE, Maayan N, Ware J, Debarros J (2019) Memantine for dementia. Cochrane Database Syst Rev 3:CD003154. https://doi.org/10.1002/14651858.CD003154.pub6
8. Bartels C, Wagner M, Wolfsgruber S, Ehrenreich H, Schneider A (2018) Alzheimer's Disease Neuroimaging Initiative. Impact of SSRI therapy on risk of conversion from mild cognitive impairment to Alzheimer's dementia in individuals with previous depression. Am J Psychiatry 75:232–241. https://doi.org/10.1176/appi.ajp.2017.17040404
9. Wang YC, Tai PA, Poly TN, Islam MM, Yang HC, Wu CC, Li YJ (2018) Increased risk of dementia in patients with antidepressants: a meta-analysis of observational studies. Behav Neurol. https://doi.org/10.1155/2018/5315098
10. Brendel M, Sauerbeck J, Greven S, Kotz S, Scheiwein F, Blautzik J, Delker A, Pogarell O, Ishii K, Bartenstein P, Rominger A, Alzheimer's Disease Neuroimaging Initiative, (2018) Serotonin selective reuptake inhibitor treatment improves cognition and grey matter atrophy but not amyloid burden during two-year follow-up in mild cognitive impairment and Alzheimer's disease patients with depressive symptoms. J Alzheimers Dis 65:793–806. https://doi.org/10.3233/JAD-170387

11. Sepehry AA, Lee PE, Hsiung GY, Beattie BL, Jacova C (2012) Effect of selective serotonin reuptake inhibitors in Alzheimer's disease with comorbid depression: a meta-analysis of depression and cognitive outcomes. Drugs Aging 29:793–806. https://doi.org/10.1007/s40266-012-0012-5
12. Musicco M, Palmer K, Russo A, Caltagirone C, Adorni F, Pettenati C, Bisanti L (2011) Association between prescription of conventional or atypical antipsychotic drugs and mortality in older persons with Alzheimer's disease. Dement Geriatr Cogn Disord 31:218–224. https://doi.org/10.1159/000326213
13. Zhai Y, Yin S, Zhang D (2016) Association between antipsychotic drugs and mortality in older persons with Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis 52:631–639. https://doi.org/10.3233/JAD-151207
14. Rochon PA, Vozoris N, Gill SS (2017) The harms of benzodiazepines for patients with dementia. CMAJ 189:E517–E518. https://doi.org/10.1503/cmaj.170193
15. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, ManlyJJ MR, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7:263–269. https://doi.org/10.1016/j.jalz.2011.03.005
16. Fazekas F, Chawluk JB, Alavi A, Hurtung HI, Zimmerman RA (1987) MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. Am J Roentgenol 149:351–356. https://doi.org/10.2214/ajr.149.2.351
17. Miller MD, Paradis CF, Houck PR, Mazumdar S, Stack JA, Rifai AH, Mulsant B, Reynolds CF 3rd (1992) Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. Psychiatry Res 41:237–248. https://doi.org/10.1016/0165-1781(92)90005-n
18. Magni E, Binetti G, Bianchetti A, Rozzini R, Trabucchi M (1996) Mini-Mental State Examination: a normative study in Italian elderly population. Eur J Neurol 3:198–202. https://doi.org/10.1111/j.1468-1331.1996.tb00423.x
19. Katz S, Downs TD, Cash HR, Grotz RC (1970) Progress in development of the index of ADL. Gerontologist Spring 10:20–30. https://doi.org/10.1093/geront/10.1_part_1.20
20. Eldholm RS, Barca ML, Persson K, Knapskog AB, Kersten H, Engedal K, Selbæk G, Brækhus A, Skovlund E, Saltvedt I (2018) Progression of Alzheimer's Disease: A Longitudinal Study in Norwegian Memory Clinics. J Alzheimers Dis 61:1221–1232. https://doi.org/10.3233/JAD-170436
21. Yang YH, Wu MN, Chou PS, Su HC, Lin SH, Sung PS (2018) Longitudinal neuropsychological outcome in Taiwanese Alzheimer's disease patients treated with medication. Curr Alzheimer Res 15:474–481. https://doi.org/10.2174/1567205014666171010112518
22. Tchalla AE, Clément JP, Saulnier I, Beaumatin B, Lachal F, Gayot C, Bosetti A, Desormais I, Perrochon A, Preux PM, Couratier P, Dantoine T (2018) Predictors of rapid cognitive decline in patients with mild-to-moderate Alzheimer disease: a prospective cohort study with 12-month follow-up performed in memory clinics. Dement Geriatr Cogn Disord 45:56–65. https://doi.org/10.1159/000487938
23. Ferreira D, Nordberg A, Westman, (2020) Biological subtypes of Alzheimer disease: A systematic review and meta-analysis. Neurology 94:436–448. https://doi.org/10.1212/WNL.0000000000009058
24. Blesa R, Toriyama K, Ueda K, Knox S, Grossberg G (2018) Strategies for continued successful treatment in patients with Alzheimer's disease: an overview of switching between pharmacological agents. Curr Alzheimer Res 15:964–974. https://doi.org/10.2174/1567205015666180613112040
25. Frisoni GB, Canu E, Geroldi C, Brignoli B, Anglani L, Galluzzi S, Zacchi V, Zanetti O (2007) Prescription patterns and efficacy of drugs for patients with dementia: physicians' perspective in Italy. Aging Clin Exp Res 19:349–355. https://doi.org/10.1007/BF03324714
26. Stern Y (2009) Cognitive reserve. Neuropsychologia 47:2015–2028. https://doi.org/10.1016/j.neuropsychologia.2009.03.004
27. Ferrari C, Lombardi G, Polito C, Lucidi G, Bagnoli S, Piaceri I, Nacmias B, Berti V, Rizzuto D, Fratiglioni L, Sorbi S (2018) Alzheimer's disease progression: factors influencing cognitive decline. J Alzheimers Dis 61:785–791. https://doi.org/10.3233/JAD-170665
28. Suzuki K, Hirakawa A, Ihara R, Iwata A, Ishii K, Ikeuchi T, Sun CK, Donohue M, Iwatsubo T, Initiative ADN, Initiative JADN (2020) Effect of apolipoprotein E ε4 allele on the progression of cognitive decline in the early stage of Alzheimer's disease. Alzheimers Dement (N Y) 6:e12007. https://doi.org/10.1002/trc2.12007
29. Barocco F, Spallazzi M, Concari L, Gardini S, Pelosi A, Caffarra P (2017) The progression of Alzheimer's disease: Are fast decliners really fast?. A four-year follow-up. J Alzheimers Dis 57:775–786. https://doi.org/10.3233/JAD-161264
30. Wu MN, Kao YH, Chou PS, Lin TC, Kao LL, Yang YH (2018) Location of white matter changes and response to donepezil in patients with Alzheimer's disease: A retrospective and observational study. Geriatr Gerontol Int 18:123–129. https://doi.org/10.1111/ggi.13153
31. Connelly PJ, Prentice NP, Fowler KG (2005) Predicting the outcome of cholinesterase inhibitor treatment in Alzheimer's disease. J Neurol Neurosurg Psychiatry 76:320–324. https://doi.org/10.1136/jnnp.2004.043539
32. Noetzli M, Eap CB (2013) Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer's disease. Clin Pharmacokinet 52:225–241. https://doi.org/10.1007/s40262-013-0038-9
33. Boccardi V, Baroni M, Smirne N, Clodomiro A, Ercolani S, Longo A, Ruggiero C, Bruni AC, Mecocci P (2016) Short-term response is not predictive of long-term response to acetylcholinesterase inhibitors in old age subjects with Alzheimer's disease: a "Real World" study. J Alzheimers Dis 56:239–248. https://doi.org/10.3233/JAD-160904
34. O'Brien JT, Holmes C, Jones M, Jones R, Livingston G, McKeith I, Mittler P, Passmore P, Ritchie C, Robinson L, Sampson EL, Taylor JP, Thomas A, Burns A (2017) Clinical practice with anti-dementia drugs: A revised (third) consensus statement from the British Association for Psychopharmacology. J Psychopharmacol 31:147–168. https://doi.org/10.1177/0269881116680924
35. Lopez OL, Becker JT, Wahed AS, Saxton J, Sweet RA, Wolk DA, Klunk W, Dekosky ST (2009) Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease. J Neurol Neurosurg Psychiatry 80:600–607. https://doi.org/10.1136/jnnp.2008.158964
36. Mejías-Trueba M, Pérez-Moreno MA, Fernández-Arche MÁ (2018) Systematic review of the efficacy of statins for the treatment of Alzheimer's disease. Clin Med (Lond) 18:54–61. https://doi.org/10.7861/clinmedicine.18-1-54
37. McGuinness B, Craig D, Bullock R, Malouf R, Passmore P (2014) Statins for the treatment of dementia. Cochrane Database Syst Rev 7:CD007514. https://doi.org/10.1002/14651858.CD007514.pub3
38. Lee G (2020) Impaired cognitive function is associated with motor function and activities of daily living in mild to moderate Alzheimer's Dementia. Curr Alzheimer Res 17:680–686. https://doi.org/10.2174/1567205017666200818193916
39. Wajman JR, Oliveira FF, Marin SM, Schultz RR, Bertolucci PH (2014) Is there correlation between cognition and functionality in severe dementia? the value of a performance-based ecological assessment for Alzheimer's disease. Arq Neuropsiquiatr 72:845–850. https://doi.org/10.1590/0004-282x20140145