ORIGINAL ARTICLE

Impact of the COVID-19 pandemic in the lipid control of the patients that start PCSK9 inhibitors

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Abstract

Objectives: MEMOGAL study (NCT04319081) is aimed at evaluating changes in cognitive function in patients treated with PCSK9 inhibitors (PCSK9i). This is the first analysis: (1) discussion about the role of the Hospital Pharmacists during the pandemic, and also the assessment of the impact of COVID-19 in the lipid control; (2) descriptive analysis; (3) effectiveness in LDL cholesterol (LDL-c) reduction of alirocumab and evolocumab; (4) communicate PCSK9i safety.

Material and methods: It is a prospective Real-World Evidence analysis of patients that take PCSK9i for the first time in the usual clinical practice, and they are included after the first dispensation in the public pharmacy consultations of 12 Hospitals in Galicia from May 2020 to April 2021. Baseline values of LDL-c are the previous values before taking PCSK9 and the follow-up values are in 6 months time.

Results: 89 patients were included. 86.5% with cardiovascular disease and 53.9% with statin intolerances. 78.8% of the patients were treated with high intensity statins. Statins most used were rosuvastatin (34.1%) and atorvastatin (20.5%). Baseline value of LDL-c was 148 mg/dl and the follow-up value was 71 mg/dl. The baseline value of patients treated with alirocumab

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(N = 43) was 144 mg/dl and 73 mg/dl in the follow-up. With evolocumab (N = 46) was 151 mg/dl in basaline and 69 mg/dl in follow-up. The LDLc- reduction was 51.21% with evolocumab and 51.05% with alirocumab. 43.1% of the patients showed values >70 mg/dl in six month time; 19.4% between 69 mg/dl and 55 mg/dl and 37.5% <55 mg/dL. 58.3% of the patients achieved a reduction >50% of LDL-c. The adverse events were: injection point reaction (N = 2), myalgias (N = 1), flu-like symptoms (N = 1) and neurocognitive worsening (N = 1).

Conclusions: (1) Despite the number of prescriptions was reduced because of the pandemic, the lipid control was not affected. (2) Half of the patients treated with PSCK9i is due to statins intolerance and the 86% is for secondary prevention. (2) The reduction results were similar to pivotal clinical trials. Despite this, 39% of the total of the patients and 60% of patients with dual teraphy did not reach the goal of ESC/EAS guidelines (< 55 mg/dl and/or reduction > 50%). There were not significant differences between evolocumab and alirocumab: 51.21% vs 51.05% (P = .972). (3) There were not any adverse events of special interest. The possible neurocognitive worsening will be studied as the primary endpoint once the MEMOGAL study has been completed.

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Impacto de la pandemia por COVID-19 en el control lipídico de pacientes que inician inhibidores de la PCSK9

Resumen

Objetivos: El estudio MEMOGAL (NCT04319081) está dirigido a evaluar cambios en la función cognitiva en pacientes tratados con inhibidores de la PCSK9 (iPCSK9). Se realiza primer análisis: 1) discutir el papel de los farmacéuticos hospitalarios durante de la pandemia, así como evaluar el impacto de la misma en el control lipídico; 2) análisis descriptivo; 3) eficacia en reducción de colesterol-LDL (c-LDL) de alirocumab y v; y 4) reportar seguridad de los iPCSK9.

Material y métodos: Se trata de un análisis prospectivo en vida real de pacientes tratados por primera vez con iPCSK9 en la práctica clínica habitual e incluidos en su primera dispensación en las consultas de farmacia de 12 hospitales de Galicia desde mayo de 2020-abril de 2021. Los valores basales de c-LDL son los previos al inicio del tratamiento con iPCSK9 y como seguimiento los valores a los 6 meses.

Resultados: Se incluyeron 89 pacientes. El 86,5% con enfermedad cardiovascular y un 53,9% intolerancia a las estatinas. Un 78,8% de los pacientes fueron tratados con estatinas de alta intensidad. Las estatinas más usadas fueron rosuvastatina (34,1%) y atorvastatina (20,5%). El nivel basal de c-LDL fue 148 mg/dl y de 71 mg/dl al seguimiento. Los pacientes tratados con alirocumab (n = 43) presentaban valores basales de 144 mg/dl y de 73 mg/dl al seguimiento y con evolocumab (n = 46) de 151 mg/dl basal y 69 mg/dl al seguimiento. La reducción de c-LDL fue para evolocumab 51,21% y alirocumab 51,05%. El 43,1% presentaba a los 6 meses valores > 70 mg/dl, el 19,4% entre 55 y 69 mg/dl y el 37,5% < 55 mg/dl. Los pacientes que obtuvieron una reducción > 50% de c-LDL fueron el 58,3%. Los eventos adversos presentados fueron: reacción en el lugar de inyección (n = 2), mialgias (n = 1), síntomas pseudogripales (n = 1) y deterioro neurocognitivo (n = 1).

Conclusiones: 1) A pesar de haber disminuido el número de prescripciones de iPCSK9 durante la pandemia, el control lipídico de estos pacientes no se ha visto afectado; 2) la mitad de los pacientes tratados con iPSCK9 se debe a intolerancia a estatinas y el 86% es en prevención secundaria; 3) se presentaron valores de reducción similares a los ensayos clínicos pivotales. A pesar de esto, un 39% del total y un 60% en doble terapia no alcanzaron las recomendaciones de las guías ESC/EAS (< 55 mg/dl y/o reducción > 50%). No hubo diferencias significativas entre evolocumab y alirocumab: 51,21% vs. 51,05% (p = 0,972); y 4) no se observaron eventos de especial interés con el uso de estos fármacos. El posible deterioro cognitivo será analizado como variable principal una vez completado el estudio MEMOGAL.

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Introduction

Low-density lipoprotein or LDL-cholesterol (LDL-C) is associated with atherosclerosis, the leading cause of coronary heart disease.[1] Reducing LDL-C has been strongly associated with a reduction in the incidence of cardiovascular disease, and is considered the primary target for cardiovascular prevention.[2,3]

PCSK9 belongs to the subtilisin family of serine proteases and is mainly expressed in the liver.' PCSK9 is involved in the regulation of the protein levels of the low-density lipoprotein receptor (LDLR). Once secreted into plasma, PCSK9 binds directly to the LDLR and stimulates its lysosomal degradation after internalisation. The increased degradation of the LDLR results in less reduction of LDL-C and therefore higher levels of circulating LDL-C.[3,4]

Two monoclonal antibodies that inhibit PCSK9 (PCSK9i) have been developed: alirocumab and evolocumab. Both have been shown to reduce LDL-C levels by 50%, as well as the risk of myocardial infarction,[5,6] and therefore have been licensed for the treatment of familial hypercholesterolaemia (FH) or cardiovascular atherosclerosis that requires further lowering of LDL-C, despite the use of maximum-dose statins.

The current SARS-CoV-2 pandemic has triggered an enormous worldwide economic, social and, above all, health crisis. The first cases were reported in mid-December 2019, and by the first half of 2021, 180 million cases and more than 4 million deaths had been reported.[7] Cardiovascular diseases are a primary complication in patients hospitalised for COVID-19, giving rise to increased hospitalisations, in-hospital complications, and mortality.[8] Therefore it is essential that these patients be followed up to reduce hospitalisations and complications.

Hospital Pharmacy outpatient clinics play a key role in the management of these patients. One of the objectives of this article is to evaluate the role played by hospital pharmacists during the pandemic, to determine how the pandemic may have influenced the prescription and dispensing of PCSK9i and the management of these patients.

The MEMOGAL study (NCT04319081) is an observational, multicentre, prospective study aimed at assessing changes in cognitive function in patients treated with PCSK9i.[9] This study began in May 2020, in the midst of the pandemic, and we list below a number of points to be analysed in parallel to the study objectives:

1) To discuss the role of hospital pharmacists during the pandemic and assess the impact of the pandemic on lipid control.
2) Indications and frequency of PCSK9i prescription during the COVID-19 pandemic and a descriptive analysis of patients treated with PCSK9i.
3) To assess the efficacy in reducing LDL-C and differences between alirocumab and evolocumab.
4) To report the safety of PCSK9i.

Methods

This is an observational, multicentre, prospective analysis with a quasi-experimental design using Real-World Evidence of patients treated for the first time with PCSK9i under current funding conditions in the pharmacy outpatient clinics of 12 hospitals of the Public Health System from May 2020 to April 2021.

Patients were included in the study who had been diagnosed with homozygous or heterozygous FH and/or with established cardiovascular disease (ischaemic heart disease, ischaemic cerebrovascular disease, or peripheral artery disease) prescribed evolocumab or alirocumab for the first time in routine clinical practice, not achieving an LDL-C<100 mg/dl after treatment with statins at the maximum tolerated dose, or intolerance to statins, and with correct therapeutic adherence to statins (≥80% per dispensing record).

The participating centres were Hospital Clínico Universitario de Santiago, Hospital Universitario de Ourense, Hospital Álvaro Cunqueiro (Vigo), Hospital Provincial de Pontevedra, Hospital Barco de Valdeorras, Hospital Virxe da Xunqueira (Cee), Hospital Arquitecto Macide de Ferrol, Hospital Universitario de A Coruña, Hospital da Costa (Burela), Hospital Universitario Lucus Au-gusti (Lugo), and Hospital Comacal de Monforte.

LDL-C values prior to starting treatment with PCSK9i once the informed consent form had been signed were taken as baseline, and those at 6 months were taken as follow-up values. The rest of the study variables were taken from the electronic medical records after signing the informed consent form and by direct interview with the patient in hospital pharmacy consultations.

Statistical analysis

Quantitative variables are presented as mean or standard deviation or median and interquartile range, and qualitative variables as frequency and percentage. Differences between LDL-C levels were assessed using the Wilcoxon Sign test. In addition, percent reductions in LDL-C were calculated and the Student's t-test was used to determine differences between the patients taking alirocumab and evolocumab.

Statistical significance was accepted at $p < .05$. All analyses were performed with SPSS 19.0 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

Results

After the first lockdown from March to April 2020, the most critical period in Spain, a total of 89 patients from Galician hospitals were included from May 2020 to April 2021 (mean age 60.44 years; 27% were women).

The inclusion rate was May 2020 5 patients; June 2020 6 patients; July 2020 10 patients; August 2020 7 patients; September 2020 8 patients; September 2020 8 patients; October 2020 7 patients; November 2020 14 patients; December 2020 8 patients; January 2021 5 patients; February 2021 9 patients; March 2021 5 patients; and April 2021 5 patients (Fig. 1).

Table 1 shows the baseline and demographic characteristics of the patients and changes in LDL-C are described in Table 1. The most relevant characteristics are 25.8% had FH, 86.5% had cardiovascular disease and 53.9% were intolerant
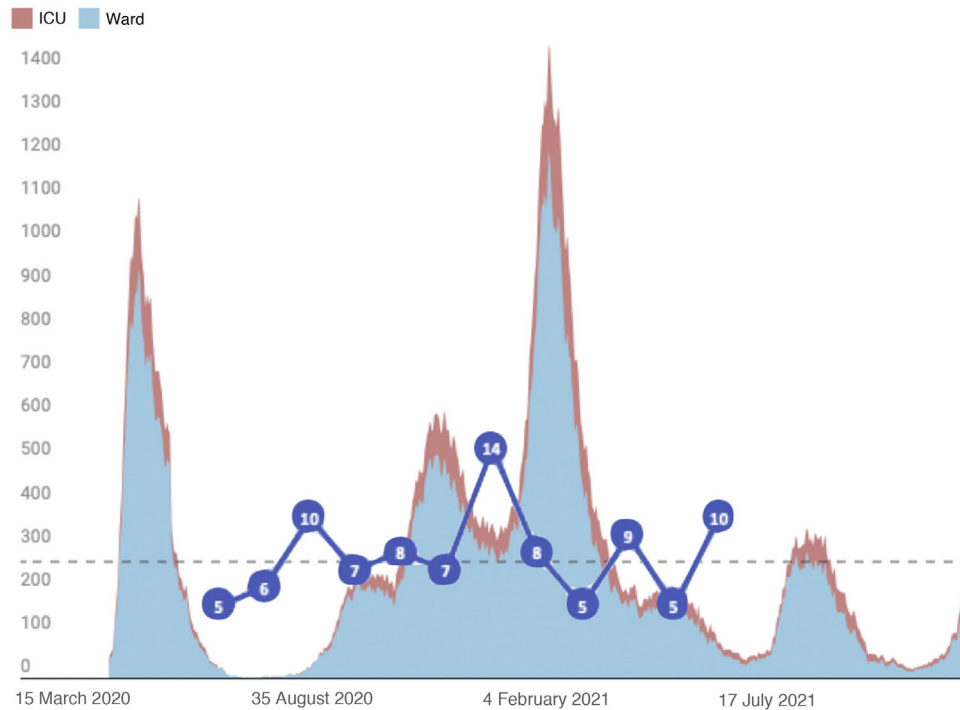
Figure 1 Inclusion of COVID-19 patients and cases in Galician hospitals.

to statins. A total of 78.8% of the patients were receiving high-intensity statin therapy, 19.2% medium-intensity, and 1.9% low-intensity statin therapy, 62.9% were on statin therapy, 62.9% were on ezetimibe.

The baseline LDL-C level was 148 mg/dl and 71 mg/dl at follow-up (up to 6 months). Forty-six patients were treated with evolocumab (51.7%) and 43 with alirocumab (49.3%). Patients treated with alirocumab had baseline values of 144 mg/dl and 73 mg/dl at follow-up, and those treated with evolocumab had baseline values of 151 mg/dl and 69 mg/dl at follow-up (Fig. 2). The reduction in LDL-C was 51.14%, with evolocumab 51.21% and with alirocumab 51.05% (Fig. 3). At 6 months, 43.1% had values>70 mg/dl, 19.4% had values between 55 and 69 mg/dl, and 37.5% had values<55 mg/dl. Patients achieving a reduction>50% of LDL-C comprised 58.3%.

The adverse events presented were injection site reaction (n = 2), myalgia (n = 1), flu-like symptoms (n = 1), and neurocognitive impairment (n = 1).

Discussion

In the present study we analysed PCSK9i prescription and lipid control in patients treated with these drugs during the COVID-19 pandemic. It is probably the first real-life study of patients treated with PCSK9i over that time. The results show that PCSK9i prescriptions cover a small proportion of patients, which may be due to the fewer face-to-face consultations or the non-implementation

of telemedicine consultations. However, also taking into account that our PCSK9i -treated population is similar to all previous studies,[6,10,12,13,20] the results in terms of efficacy are consistent with those published in pivotal and real-life clinical trials in non-COVID-19 times.[5,6,10,11] These conclusions may be relevant when considering health policies in times of decreasing face-to-face activity so that the results of drugs with proven evidence can be applicable.

Pandemic and PCSK9i prescription

This may be mainly due to the work by healthcare professionals and the home dispensing system,[14] which has resulted in good adherence to all treatments initiated in this period. This shows that applying these healthcare resources is effective in terms of efficacy and safety, and presumably cost-effective.[15,16]

However, it is worth noting that the number of inclusions per month in the study suggests that during the periods with more health restrictions, specifically the period of greater hospitalisation, the number of PCSK9i prescriptions decreased. The infection and inclusion curves are completely opposite in both graphs (Figs. 1 and 2). This may be because face-to-face medical consultations had been discontinued or decreased and/or teleconsultation was not implemented as efficiently in the different healthcare areas when prescribing these drugs[17,30] (Fig. 1).
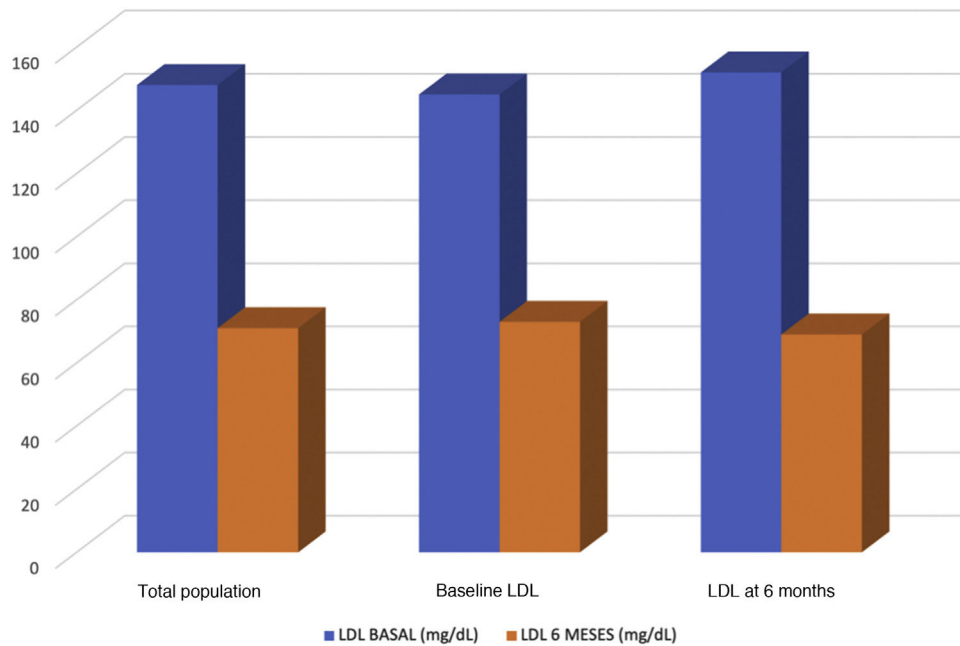
Figure 2 LDL level at baseline and at follow-up.

PCSK9i results

In the present study, more than half the patients were intolerant to statins and 86% were prescribed PCSK9i in secondary prevention, which highlights the large number of patients with cardiovascular disease and the importance of these drugs in this disease,[1–3,5,6] for which only .89% of patients in Spain are currently prescribed them 12 months after an acute coronary syndrome.[18] Moreover, the use of statins in monotherapy has been shown in many cases to be insufficient to achieve objectives in this group of patients.[19–21]

iPCSKs9 effectively and safely reduce LDL-C by around 50%.[5,6,10,11] Evolocumab has been shown to be effective in homozygous FH.[23] Alirocumab reduces the need for LDL-C apheresis in this type of patient, one of the few effective therapies for LDL-C control in FH.[25] Other studies such as OSLER[26] and ODYSSEY Long-term[27] also demonstrated the efficacy of evolocumab and alirocumab in reducing LDL-C and major adverse cardiovascular events (MACE). Evolocumab and alirocumab show similar effects in reducing LDL-C at equipotent doses.[5,6] Our results are coincide with these pivotal trials[5,6] and show that there is no significant difference in mean percentage reduction in LDL-C between evolocumab and alirocumab: 51.21% vs. 51.05% (p = .972).

The new European lipid guidelines (ESC guidelines)[21] recommend that patients with FH or cardiovascular disease should reduce baseline LDL-C by 50% or target LDL-C by 50%. Furthermore, in cardiovascular disease after ACS the lipid profile should be reassessed at 4–6 weeks, and if targets have not been met PCSK9i (level of evidence I, class B) should be initiated.[21]

In the present analysis, statin-treated patients had 78% high intensity, 20% medium intensity and 2% low intensity, a percentage similar to the population studied in previous studies of statin monotherapy in secondary prevention, which concluded that 70% of patients did not reach targets below 70 mg/dl LDL-C and only 11% did not reach the target of 50 mg/dl LDL-C.[22,23]

Our results of PCSK9i use, both in monotherapy and in double or triple therapy (statins and/or ezetimibe) were that 43.1% of patients had LDL-C values above 70 mg/dl at follow-up; 19.4% of patients between 55 mg/dl and 69 mg/dl, and 37.5% of all patients had values below 55 mg/dl, therefore we have gone from 30% (in previous studies[22,23]) of patients below 70 mg/dl to 60%, and also from 11% of patients below 55 mg/dl (in previous studies[22,23]) to 37% in this study population.

In conclusion, we can see how the addition of PCSK9i improves the targets set by the guidelines, but nevertheless there are still around 40% of patients who do not reach the target of a 50% reduction in LDL-C or <55 mg/dl.[21] This happens essentially in triple therapy treatment (statins + ezetimibe + PCSK9i), however in patients totally intolerant to statins we see how the number of subjects who do not reach these targets increases to 60%, from which we can conclude and highlight the importance of maintaining statins as far as is possible.

Bempedoic acid, which at the time of publication of these data was in the process of approval in Spain, plays a key role in these patients. Several clinical trials[28,29] have been published evaluating the reduction in LDL-C at 12 weeks. A reduction of 18% was observed when associated with statins and a reduction of 25% when used in monotherapy. The combination of bempedoic acid plus ezetimibe achieved a 38% reduction. For all these reasons, we believe it could be a very effective alternative in this type of patient who cannot tolerate any dose of statin and who do not meet the recommendations of the dyslipidaemia guidelines.

Table 1 Baseline and demographic characteristics of patients and changes in LDL-C.

Variables	Patients included, n = 89
Sociodemographic characteristics	
Age (years)[a]	60.44 ± 9.973
Sex (female), n(%)	24 (27.0)
BMI (kg/m²)[a]	28.47 (±4.531)
Previous medical history, n (%)	
Familiar hypercholesterolaemia	23 (25.8)
Cardiovascular disease	77 (86.5)
Diabetes mellitus	18 (20.2)
Hypertension	52 (58.4)
Intolerant to statins	48 (53.9)
Type of statins, n (%)	
Atorvastatin	18 (20.5)
Rosuvastatin	30 (34.1)
Rosuvastatin	1 (1.1)
Pitavastatin	4 (4.5)
No statin	35 (39.8)
Potency	
High potency	41 (78.8)
Medium potency	10 (19.2)
Low potency	1 (1.9)
Ezetimibe	56 (62.9)
PCSK9i (n,%)	
Evolocumab 140 mg	46 (51.7)
Alirocumab 75 mg	33 (37.1)
Alirocumab 150 mg	10 (11.2)
LDL levels (mg/dl)	
LDL at baseline (mg/dl)[a]	148 ± 53
LDL at follow-up (mg/dl)[a]	71 ± 4
Reduction in LDL (%)	51 ± 20
Alirocumab	
LDL at baseline (mg/dl)[a]	145 ± 43
LDL at follow-up (mg/dl)[a]	73 ± 36
Reduction in LDL (%)	51 ± 15
Evolocumab	
LDL at baseline (mg/dl)[a]	152 ± 62
LDL at follow-up (mg/dl)[a]	69 ± 34
Reduction in LDL (%)	51 ± 234
LDL controls at follow-up, n (%)	
>70 mg/dl	31 (43.1)
55–69 mg/dl	14 (19.4)
<55 mg/dl	27 (37.5)
Reduction >50% baseline	42 (58.3)
Patients with LDL targets, n (%)	44 (61.1)
EST + EZE + PCSK9i	26 (59.1)
EZE + PCSK9i	18 (40.9)

[a] Mean ± SD are the descriptive data used.

Safety

Regarding the safety of these drugs, excessive reduction of LDL-C has been related to the hypothesis of possible changes in cognitive function.

There is currently no evidence of this potential cognitive impairment as reported to date in only one publication: the EBBINGHAUS substudy.[27] The adverse events reported in our study were injection site reaction (n = 2), myalgia (n = 1), flu-like symptoms (n = 1), and neurocognitive impairment (n = 1). Possible cognitive impairment is being studied as a main variable in the MEMOGAL study.[9]

Limitations include a small sample size as the analysis was conducted during the pandemic, when there may have been fewer PCSK9i prescriptions, therefore we believe that our results will provide important information on the current status of these drugs during the pandemic.

Conclusions

1) The COVID-19 pandemic has had a direct impact on PCSK9i prescription, which has decreased in the Galician population. Nevertheless, the results in terms of efficacy and safety are similar to previous studies, probably due to the work of healthcare professionals.
2) More than half the patients were prescribed iPSCK9 due to statin intolerance, and 86% are in secondary prevention.
3) These patients have similar reduction values to pivotal clinical trials. However, 39% of all patients on triple therapy and 60% of patients on dual therapy did not meet ESC/EAS guideline recommendations. There was no significant difference in the mean percentage reduction in LDL-C between evolocumab and alirocumab: 51.21% vs. 51.05% (p = .972).
4) No events of special interest were observed with the use of these drugs.

Contribution to the scientific literature

This paper aims to contribute to the scientific literature with novel data and information on the current situation of patients treated with PCSK9i during the COVID-19 pandemic, in particular patients starting on PCSK9i for the first time. We seek to provide an overview of the current situation in terms of prescriptions, adherence to treatment in the context of health restrictions and different states of alarm and, above all, its effect in terms of efficacy and safety, and how these results conform to the current dyslipidaemia guidelines.

We would also like to highlight the multicentre, multidisciplinary, and prospective nature of the study.

Conflict of interests

The authors have no conflict of interests to declare.[24]

Acknowledgments

Appendix A. MEMOGAL investigators

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References

1. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38:2459–72, http://dx.doi.org/10.1093/eurheartj/ehx144.

2. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73:e285–350, http://dx.doi.org/10.1016/j.jacc.2018.11.003.

3. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J. 2020;41:111–88, http://dx.doi.org/10.1093/eurheartj/ehz455.

4. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD Jr, DePalma SM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol. 2017;70:1785–822, http://dx.doi.org/10.1016/j.jacc.2017.07.745.

5. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1500–9, http://dx.doi.org/10.1056/NEJMoa1500858.

6. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1489–99, http://dx.doi.org/10.1056/NEJMoa1501031.

7. World Health Organization. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020.

8. Choudry FA, Hamshere SM, Rathod K, Akhtar MM, Archbold AR, et al. High thrombus burden in patients with COVID-19 presenting with ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2020;76:1168–76, http://dx.doi.org/10.1016/j.jacc.2020.07.022.

9. Seijas-Amigo J, Rodríguez-Penas D, Estany-Gestal A, Suárez-Artime P, Santamaría-Cadavid M, et al. Observational multicentre prospective study to assess changes in cognitive function in patients treated with PCSK9i. Study protocol. Farm Hosp. 2021;45:150–4, http://dx.doi.org/10.7399/fh.11569.

10. Robinson JG, Colhoun HM, Bays HE, Jones PH, Du Y, Hanotin C, et al. Efficacy and safety of alirocumab as add-on therapy in high cardiovascular-risk patients with hypercholesterolemia not adequately controlled with atorvastatin (20 or 40 mg) or rosuvastatin (10 or 20 mg): design and rationale of the ODYSSEY OPTIONS Studies. Clin Cardiol. 2014;37:597–604, http://dx.doi.org/10.1002/clc.22327.

11. Rodriguez-Escobedo R, Gonzalez-Martinez S, Díaz-Naya L, Suarez-Gutierrez L, Fernández-Morera J, et al. Real-life efficacy and safety of PCSK9 inhibitors treatment: experience in three hospital in Asturias. Semergen. 2021;47:369–75, http://dx.doi.org/10.1016/j.semerg.2021.03.008.

12. Kastelein JJ, Hovingh GK, Langslet G, Baccara-Dinet MT, Gipe DA, Chaudhari U, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 monoclonal antibody alirocumab vs placebo in patients with heterozygous familial hypercholesterolemia. J Clin Lipidol. 2017;11:195–203, http://dx.doi.org/10.1016/j.jacl.2016.12.004, e4.

13. Gitt AK, Lautsch D, Ferrieres J, De Ferrari GM, Vyas A, Baxter CA, et al. Cholesterol target value attainment and lipid-lowering therapy in patients with stable or acute coronary heart disease: results from the Dyslipidemia International Study II. Atherosclerosis. 2017;266:158–66, http://dx.doi.org/10.1016/j.atherosclerosis.2017.08.013.

14. Ley 3/2019, de 2 de julio, de ordenación farmacéutica de Galicia. Available from: https://www.boe.es/buscar/doc.php?id=BOE-A-2019-13517.

15. Ollendorf JDA, Pearson SD, Tice JA, Guzman D, Bibbins-Domingo K. Cost-effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. JAMA. 2016;316:743–53, http://dx.doi.org/10.1001/jama.2016.11004.

16. Fonarow GC, Keech AC, Pedersen TR, Giugliano RP, Sever PS, Lindgren P, et al. Cost-effectiveness of Evolocumab therapy for reducing cardiovascular events in patients with atherosclerotic cardiovascular disease. JAMA Cardiol. 2017;2:1069–78, http://dx.doi.org/10.1001/jamacardio.2017.2762.

17. Ruiz-Romero V, Martinez Pillado M, Torres-Domínguez Y, Acón-Royo D, De Toro-Salas, et al. Evaluación de la satisfacción del paciente en la teleconsulta durante la pandemia por COVID-19. Rev Esp Salud Pública. 2021;95:e1–11.

18. Anguita Sánchez MB, Gómez Doblas JJ, Barrios Alonso V. Grado de control del cLDL tras un síndrome coronario agudo en España. ¿Se utilizan adecuadamente los recursos terapéuticos existentes? Rev Esp Cardiol. 2020;74:194–6, http://dx.doi.org/10.1016/j.recesp.2020.06.011.

19. Galve E, Cordero A, Cequier A, Ruiz E, Gonzalez-Juanatey JR. Grado de control lipídico en pacientes coronarios y medidas adoptadas por los médicos. Estudio REPAR. Rev Esp Cardiol. 2016;69:931–8, http://dx.doi.org/10.1016/j.recesp.2016.02.013.

20. Reiner Z, De Backer G, Fras Z, Kotseva K, Tokgözoglu L, Wood D, et al. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries — findings from the EUROASPIRE IV survey. Atherosclerosis. 2016;246:243–50, http://dx.doi.org/10.1016/j.atherosclerosis.2016.01.018.

21. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J. 2020;41:111–88, http://dx.doi.org/10.1093/eurheartj/ehz455.

22. Seijas Amigo J, Rodríguez-Mañero M, Cordero A, Ibarrondo O, Itziar Oyagüez JM, et al. Análisis restrospectivo del grado de control lipídico y eventos coronarios en prevención secundaria en pacientes en vida real. Rev Esp Cardiol. 2020;73 Supl 1:189. Available from: https://www.revespcardiol.org/es-congresos-sec-2020-el-e-congreso-110-sesion-series-largas-cardiologia-la-importancia-5963-analisis-retrospectivo-del-grado-de-71388-pdf

23. Kotseva K, de Backer G, de Bacquer D, Arno Hoes LR, et al. Eur J Prev Cardiol. 2019. Int J Cardiol. 2018;258:1–6, http://dx.doi.org/10.1177/2047487318825350.

24. Stein EA, Honarpour N, Wasserman SM, Xu F, Scott R, Raal FJ. Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. Circulation. 2013;128:2113–20, http://dx.doi.org/10.1161/CIRCULATIONAHA.113.004678.

25. Moriarty PM, Parhofer KG, Babirak SP, Cornier MA, Duell PB, et al. Alirocumab in patients with heterozygous familial hypercholesterolaemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial. Eur Heart J. 2016;37:3588–95, http://dx.doi.org/10.1093/eurheartj/ehw388.

26. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1500–9, http://dx.doi.org/10.1056/NEJMoa1500858.

27. Giugliano RP, Mach F, Zavitz K, Kurtz C, Im K, et al. Cognitive function in a randomized trial of evolocumab. N Engl J Med. 2017;377:633–43, http://dx.doi.org/10.1056/NEJMoa1701131.

28. Ray KK, et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol. CLEAR Harmony Trial. N Engl J Med. 2019;380:1022–103.

29. Goldberg AC, Leiter LA, Erik SG, Stroes MD, et al. Effect of bempedoic acid vs placebo added to maximally tolerated statins on low-density lipoprotein cholesterol in patients at high risk for cardiovascular disease: the CLEAR Wisdom Randomized Clinical Trial. JAMA. 2019;322:1780–8, http://dx.doi.org/10.1001/jama.2019.16585.

30. González-Juanatey JR, Rey-Aldana D, Cinza-Sanjurjo S, Portela-Romero M, López-Barreiro JL, et al. Programa de consulta electrónica universal (e-consulta) de un servicio de cardiología. Resultados a largo plazo. Rev Esp Cardiol. 2020, http://dx.doi.org/10.1016/j.recesp.2020.11.007.