CEPARM: Four decades of dedication to advancing Familial Amyloidotic Polyneuropathy research and patient care

CEPARM: Quatro Décadas de Dedicação ao Avanço da Pesquisa e Cuidados com Pacientes com Polineuropatia Amiloidótica Familiar

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ABSTRACT

This paper delves into the remarkable journey of the Centro de Paramiloidose Antônio Rodrigues de Mello (CEPARM), located at the Hospital Universitário Clementino Fraga Filho (HUCFF) of UFRJ, over the past four decades, from its establishment in 1984 to its emergence as a pioneering institution in the so called field of Familial Amyloidotic Polyneuropathy (FAP). Founded in response to the urgent need for specialized research and treatment of this rare genetic disorder prevalent among individuals of Portuguese descent mainly with expressive Polyneuropathy (Hereditary Transthyretin Amyloidosis with Polyneuropathy - hATTR-PN) or even Cardyomyopathy (Hereditary Transthyretin Amyloidosis with Cardyomyopathy hATTR-CM), CEPARM has played a crucial role in the evolution of this field.

The paper offers a comprehensive overview of the center's development, emphasizing its major achievements, research contributions, and advancements in patient care. It highlights CEPARM's pivotal role in developing innovative treatment protocols, including the introduction of liver transplantation for FAP and groundbreaking therapies such as tafamidis, patisiran, inotersen, vutrisiran, and eplontersen. Additionally, the paper explores CEPARM's efforts to enhance patient quality of life through multidisciplinary care and support programs.

By reflecting on the center's historical milestones, leadership transitions, and ongoing initiatives, this paper underscores CEPARM's unwavering commitment to advancing scientific knowledge and improving patient outcomes mainly in the realm of hATTR-PN.

Keywords: Familial Amyloidotic Polyneuropathy, Hereditary Transthyretin Amyloidosis, Familial Amyloidotic Cardyomyopathy, Patient Care

RESUMO

Este artigo descreve a marcante trajetória do Centro de Paramiloidose Antônio Rodrigues de Mello (CEPARM), localizado no Hospital Universitário Clementino Fraga Filho (HUCFF) da UFRJ, ao longo das últimas quatro décadas, desde sua criação em 1984 até seu surgimento como instituição pioneira no chamado campo da Polineuropatia Amiloidótica Familiar (PAF). Fundado em resposta à necessidade urgente de investigação especializada e tratamento desta doença genética rara prevalente entre indivíduos de ascendência portuguesa, principalmente com Polineuropatia expressiva (Amiloidose Hereditária por Transtirretina com Polineuropatia - hATTR-PN) ou mesmo Cardiomiopatia (Amiloidose Hereditária pot Transtiretina com Cardiomiopatia - hATTR-CM), o CEPARM tem desempenhado um papel crucial na evolução deste campo.

O artigo oferece uma visão abrangente do desenvolvimento do centro, enfatizando suas principais conquistas, contribuições de pesquisa, e avanços no atendimento ao paciente. Destaca o papel fundamental do CEPARM no desenvolvimento de protocolos de tratamento inovadores, incluindo a introdução do transplante de fígado para PAF e terapias inovadoras como tafamidis, patisiran, inotersen, vutrisiran e eplontersen. Além disso, o artigo explora os esforços do CEPARM para melhorar a qualidade de vida dos pacientes através de cuidados multidisciplinares e programas de apoio.

Ao refletir sobre os marcos históricos do centro, as transições de liderança e as iniciativas em curso, este artigo sublinha o compromisso inabalável do CEPARM com o avanço do conhecimento científico e a melhoria dos resultados clínicos dos pacientes, principalmente no domínio da hATTR-PN.

Palavras-chave: Polineuropatia Amiloidótica Familiar, Amiloidose Hereditária por Transtiretina, Cardiomiopatia Amiloidótica Familiar , Cuidados com o paciente.

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Conflicts of Interest: MMG declares no conflicts of interest. MWC has served as an investigator in multiple therapeutic trials related to hATTR-PN, including the FX 005 and 006 tafamidis trials, the ATTR-ACT trial for tafamidis in hATTR-CM, and trials for first and second-generation TTR silencers such as Neuro-TTR, APOLLO, Neuro-TTransform, and HELIOS.
Financial Support: This work has not received any contribution grant or scholarship.
Contributorship statement: MMG and MWC - Conceptualization, Writing, editing and review of the manuscript.

INTRODUCTION

Centro de Paramiloidose Antônio Rodrigues de Mello (CEPARM), established in 1984, is a cornerstone of research and treatment for familial amyloidotic polyneuropathy (FAP), particularly focusing on Hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN).

This rare and debilitating genetic disorder, caused by mutations in the transthyretin (TTR) gene, predominantly affects individuals of Portuguese descent, resulting in severe neuropathic and cardiac symptoms and significantly impairing quality of life. Amyloidosis encompass a diverse group of diseases pathologically characterized by the aggregation of amyloid-fibril proteins, which are deposited extracellularly, leading to a toxic gain of function. TTR is an amyloidogenic protein, and hereditary transthyretin amyloidosis (hATTR) arises from the deposition of variant TTR proteins. The primary ATTR phenotypes include polyneuropathy (hATTR-PN) and cardyomyopathy (hATTR-CM).

The founding of CEPARM represented a groundbreaking response to the urgent need for effective management strategies for this complex condition, employing advanced research, innovative treatments, and holistic patient care.

Known historically as paramyloidosis, hATTR-PN was first identified by Corino Andrade in 1952. It is characterized by the Val30Met (V30M) mutation, which is found in over 90% of cases. Without treatment, the disease can progress rapidly, leading to a median survival of just 12 years post-onset. From its inception, CEPARM has been at the forefront of pioneering research and treatment approaches for this challenging disorder[1].

Development and Establishment of a New Center for hATTR-PN in 1984

The historical journey of CEPARM is marked by significant milestones, showcasing its growth, strategic partnerships, and contributions to medical research. The founding of the CEPARM at Hospital Universitário Clementino Fraga Filho (HUCFF)-UFRJ in 1984 was pivotal, with continual adaptations ensuring the center's enduring success.

Under the leadership of Prof. Marleide da Mota Gomes, CEPARM adopted a multidisciplinary approach to managing hATTR-PN. The center focused on a holistic patient care protocol, addressing not only clinical symptoms but also the psychological and emotional needs of patients, establishing itself as a leading institution in Brazil and beyond.

As CEPARM progressed, it achieved several key milestones, including the introduction of new treatment modalities and the development of a robust research infrastructure. Leadership transitions - from Prof. Gomes to Dr. Charles André and Prof. Sérgio Novis, and later to Dr. Marcia Waddington Cruz - brought significant advancements and innovations. Under Dr. Cruz's guidance, CEPARM expanded its research capabilities and continued to explore new frontiers in treatment and patient care for those affected by hATTR-PN.

CEPARM's original objectives, outlined in its first newsletter in April 1985 and detailed in a 2011 publication in Revista Brasileira de Neurologia[2], focused on a comprehensive patient care protocol. The center emphasized initial diagnosis, routine check-ups, psychological stabilization, and targeted treatment for complications.

The initial team, led by Prof. Marleide da Mota Gomes, included experts from various fields, exemplifying CEPARM's commitment to a multidisciplinary approach. The team comprised specialists in Neurology (Prof. Marleide da Mota Gomes and Dr. Charles André), Genetics (Prof. Dayse Neves Falcão Conceição), Gastroenterology (Prof. Marcus Tulio Haddad), Cardiology (Prof. José Hallake), Ophthalmology (Prof. Eliezer Israel Benchimol), Pathology (Prof. Francisco Duarte), Physiatry (Prof. Isabel Maria Loureiro Maior), Hemotherapy (Dr. José Vitório Estevam Dias), and others who joined later. The center responded to the growing demand for patient care and collaborated with the Portuguese Center for Paramyloidosis Studies in Porto, led by Prof. Paula Coutinho.

By 1985, under Prof. Marleide da Mota Gomes's leadership, CEPARM had established it self as a pioneering institution in Brazil. However, due to Prof. Gomes's pursuit of a Master's Degree at McMaster University in Canada and an extended tenure at the Ministry of Health in Brasilia, leadership changes occurred. Dr. Charles André and Prof Sérgio Novis briefly assumed leadership, followed by Dr. Marcia Waddington Cruz, who has led the center for the past 36 years. Under her guidance, CEPARM achieved numerous milestones in the treatment and investigation of hATTR-PN, including clinical trials, conferences, the construction of a new facility, and the supervision of theses and publications on various topics, including epidemiological issues.

The introduction highlights the significance of scientific research in the context of FAP and underscores the crucial role of CEPARM. It also provides a brief historical background on FAP's discovery by Mário Corino da Costa Andrade.

Figure 1 presents the key figures and facilities at HUCFF associated with CEPARM.

Treatment Advancements for hATTR-PN

The treatment landscape for hATTR-PN has seen significant advancements over the years, reflecting our evolving understanding of the disease. From the 1950s to the 1990s, treatment primarily focused on symptomatic management to improve the quality of life for those affected. Symptomatic treatments during this time included

Figure 1. CEPARM key persons and places. HUCFF=Hospital Universitário Clementino Fraga Filho[2].

pain management, physical therapy, and other supportive measures.

Understanding the physiopathology of hATTR-PN involves exploring the mechanisms that lead to the abnormal accumulation of transthyretin (TTR) and its impact on nerve function. The key factor is a mutation that destabilizes the tetrameric structure of the TTR protein. This destabilization causes the protein to disaggregate into monomers, which then misfold and accumulate in tissues as amyloid material, ultimately contributing to the progression of neuropathy.

The 1990s marked a pivotal moment with the introduction of liver transplantation. Recognizing that the liver is the main source of TTR production, the approach aimed to replace a liver genetically determined to produce a variant and unstable TTR, with a healthy donor liver, with the expectation of reducing the production of abnormal TTR. Despite its significance, liver transplantation faced challenges, such as the scarcity of donor organs and its inability to uniformly halt the progression of neuropathy[3].

The early 2010s saw a shift in treatment approaches with the approval of tafamidis, an oral medication designed to stabilize the TTR protein. By preventing misfolding and aggregation, tafamidis aimed to slow down the progression of hATTR-PN.

CEPARM was a pioneer in clinical research in the field of ATTR in Brazil. It was the only center to take part in the multicentric international trial of tafamidis to treat ATR-PN (FX 005 and 006). Tafamidis was the first drug to treat ATTR. After the trial, from 2014 to 2018, the center actively worked with Ministry of Health (CONITEC) to approve PCDT (Protocolo clínico e diretrizes terapêuticas), a guidelines for the diagnosis and treatment of ATTR-PN, including tafamidis for stage 1 ATTR-PN patients. ANVISA approved tafamidis to treat hATTR-PN in 2016, and in the present moment Tafamidis is available by SUS (Brazilian Public Health System) all over Brazil for about 638 patients[4].

CEPARM was also the only center in Brazil to participate in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT), the first trial using tafamidis to treat hATTR-CM, published in the New England Journal of Medicine in 2019. Tafamidis was subsequently approved by the FDA, EMA, and ANVISA for the treatment of hATTR-CM at the dose of 80 mg (or the corresponding 61 mg dose). Tafamidis for hATTR-CM will be available through the Brazilian public health system (SUS) in 2025, benefiting thousands of patients with hereditary and wild-type ATTR (non-hereditary ATTR)[5].

Looking forward, ongoing research is exploring gene silencing technologies, such as antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs). These approaches aim to further reduce the production of abnormal TTR, showcasing the continuous evolution of therapeutic strategies.

Continuing this trend, the approval of patisiran and inotersen in 2018, both RNA-targeted therapies, marked another advancement. Administered via intravenous infusion and subcutaneous (SC) injection, respectively, these therapies reduce the production of abnormal TTR in the liver, offering alternative options for patients.

CEPARM was a top recruiter in the main trials for the first generation of TTR silencers, including Neuro-TTR and APOLLO (ASO, inotersen; imRNA, patisiran). These therapies were approved by ANVISA in 2019 and are currently under review by CONITEC[6,7,8] .

From 2019 to the present, CEPARM has also participated in trials for the second generation of TTR silencers, such as Neuro-TTransform (eplontersen, used SC once a month), and HELIOS (vutrisiran, used SC each 3 months). They offer better benefit risk relation and improve quality of life for the patients. This highlights the continuous effort of the center to bring innovative treatment to patients[9,10] .

In addition to these approved treatments, diflunisal, a non-steroidal anti-inflammatory drug (NSAID), has been under investigation for its potential to stabilize TTR and slow disease progression, although it lacks specific FDA and ANVISA approval for hATTR-PN.

It is crucial to acknowledge that the field of hATTR-PN is dynamic, with the potential emergence of new therapies as research progresses. The approval and accessibility of treatments can vary by region, emphasizing the importance of close collaboration between patients, their families, and healthcare providers to stay informed about the latest advancements in managing hATTR-PN.

Main Initiatives for Quality of Life Improvement and Researchers

This section provides an in-depth analysis of specific programs and initiatives launched by CEPARM to improve the quality of life for patients. This includes advancements in treatment, the establishment of support systems, and active community engagement efforts.

The interdisciplinary team developed research based on patient cohorts, with published and ongoing studies. The medical student and resident observership program and the training of professionals from other Brazilian states have contributed to CEPARM's national

leadership.

CEPARM's involvement in research and global collaboration, including the Brazilian guidelines on familial amyloid polyneuropathy, underscores the center's commitment to advancing scientific understanding and developing innovative treatments.

The legacy of CEPARM is not confined to Brazil. The center has established a reputation for contributing to the global understanding of hATTR-PN, participating in international clinical trials, and presenting research findings at prominent conferences. These global collaborations have enabled CEPARM to stay at the forefront of research and treatment, ensuring that Brazilian patients benefit from the latest advancements in care.

In October 2023, Dr. Márcia Waddington received the *Grande Colar do Mérito*, granted by the Federal Audit Court (TCU) for her work at CEPARM. It is intended to reward personalities, national or foreign, who, due to their exceptional merits and relevant contribution to the country, have become worthy of special distinction.

Another important aspect to be mentioned is the savings that the center makes for Ministry of Health Public Health System (SUS), since patients included in the clinical trials will have lifetime access to their respective medicines at no cost. This means savings of hundreds of thousands of Reais per year.

Milestones summary and overall balance

CEPARM was founded in 1984, marking the beginning of a journey dedicated to advancing research and care in ATTR. In 1989, the center further expanded its influence with the founding of the Associação dos Portadores de Paramiloidose no Brasil (APBAR), a critical step in supporting patients and families affected by the condition. The first liver transplant for a patient from Rio de Janeiro was successfully performed in São Paulo in 1993, by Prof. Silvano Raia (FM-USP), and by 1997, the first liver transplant was carried out in Rio de Janeiro, by Prof. Joaquim Ribeiro (FM-UFRJ) underscoring the center's role in pioneering treatment options.

From 2007 to 2020, CEPARM participated in the clinical trial of tafamidis for polyneuropathy, a groundbreaking study that later extended to cardiomyopathy from 2017 to 2020. CEPARM's contribution to the international database THAOS, from 2008 to 2023, was significant, with the center's leadership highlighted by the presidency of the Scientific Committee from 2016 to 2019[11].

These efforts culminated in the approval of tafamidis by ANVISA for peripheral neuropathy in 2016, followed by its inclusion in the Brazilian Clinical Protocol and Therapeutic Guidelines (PCDT) in 2018. By 2024, 638 patients will have gained access to tafamidis, marking a substantial impact on patient care[12].

CEPARM was also at the forefront of trials for the first generation of TTR silencers, including antisense oligonucleotides (ASO) and small interfering RNAs (imRNA), from 2012 to 2023. This led to the approval of these therapies by ANVISA in 2019. Continuing its innovative approach, the center has been involved in trials for second-generation silencers from 2019 to the present.

In 2015, CEPARM established its own dedicated facility, solidifying its position as a leading center for Amyloidosis research and treatment. The center also hosted the IX International Symposium on FAP and the VII International Symposium on Liver Transplantation in FAP in Rio de Janeiro from November 10-13, 2013, further demonstrating its global engagement and commitment to advancing knowledge in the field.

Many of these milestones are presented on the figure 2.

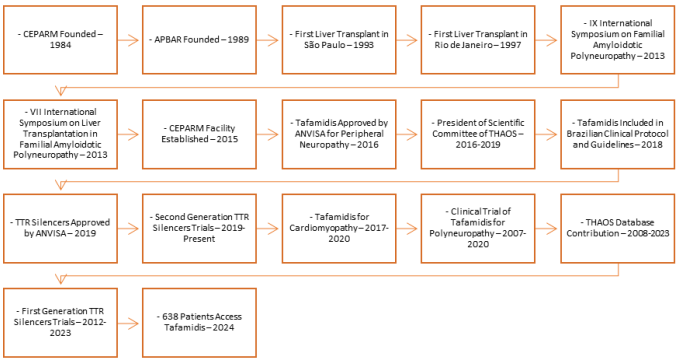

Figure 2. Milestones in CEPARM's Journey: Advancements in Paramiloidosis Research and Treatment. CEPARM=Centro de Paramiloidose Antônio Rodrigues de Mello; APBAR=Associação Brasileira de Paramiloidose; ANVISA=Agência Nacional de Vigilância Sanitária;THAOS=Transthyretin Amyloidosis Outcomes Survey; TTR Silencers=Therapeutic agents for TTR[3,4,5,6,7,8,9,10,11,12,13,14].

CEPARM, founded in 1984, has made significant strides in the field of amyloidosis research and patient care. As of now, the center has managed 406 patients. Between 2008 and 2021, CEPARM conducted 787 multidisciplinary consultations, involving an average of 341 patients with FAP (ATTR) or asymptomatic TTR gene mutation carriers..Prior to 2008, records were not digital, but over 98 patients were followed for several years. These consultations involve a range of specialists, ensuring comprehensive evaluations and often resulting in fewer total visits compared to more general services[13-16] . The specialties included Neurology, Ophthalmology, Gastroenterology, Cardiology, Nephrology, Psychiatry, Palliative Care, Psychology, Dentistry, Nursery, and Nutrition.

The center has invested in a variety of medical equipment, including electroretinograph, electromyograph, echocardiograph with strain technique, quantitative sensory test, sudoscan, electrocardiograph and holter, as well as in furniture and IT infrastructure. The facility includes a reception area with an adapted bathroom, three consultation rooms, a kitchenette, and a coordination room.

In terms of research, CEPARM has conducted 15 trials plus four post access studies (PSDS) and has published 106 papers internationally and 62 in Brazil. The center has delivered 179 lectures on ATTR both in Brazil and abroad

and has actively participated in several international committees including THAOS : The Transthyretin Amyloidosis Outcomes Survey.

CEPARM has received notable awards, including the Brazilian Academy of Neurology Award for best dissertation (1999-2000), the European Federation of Neurological Societies Investigator Award (2011) for research on baseline nutritional status in THAOS, and the Top Ten Clinical Research Achievement Award (2019) for tafamidis in transthyretin cardiac amyloidosis. The center was also honored by Pfizer for its outstanding contribution to THAOS and for chairing the Scientific Board from 2016 to 2019.

The center has supported several dissertations and has hired 30 or more staff with self-funding.

Current collaborators include Prof. Débora Foguel from the Instituto de Bioquímica Médica at UFRJ, Prof. Roberto Coury Pedrosa from Cardiology at HUCFF, UFRJ, Prof. Carlos Perez Gomes, Dr. Moises Dias, and Dra. Renata Gervais de Santa Rosa from Nephrology at HUCFF, UFRJ, Dra. Glória Regina Bandeira from Psychiatry at HUCFF, UFRJ, Dr. Luiz Felipe Pinto from CEPARM, Dr. Marcus Vinícius Pinto from Mayo Clinic in Rochester, USA, and nurses and coordinators Joyce Dias, Maria Alice Penetra, and Aline Abreu.

CEPARM collaborates with various UFRJ departments and the federal government. This includes the Laboratory of Protein Aggregation and Amyloidosis (LAPA) led by Prof. Débora Foguel, the SONDA Laboratory for genetic and biomarker studies led by the past Prof. Franklim Runjanek, and the Signal Processing Laboratory led by Prof. José Manoel de Seixas at COPPE, UFRJ. The center also engages in research on artificial neural networks for assessing amyloidosis progression and contributed to the development of clinical protocols and guidelines for FAP, published in November 2018, with Márcia Waddington as the first author.

Looking to the Future

With an unwavering commitment to innovation and comprehensive care, CEPARM continues to improve the lives of those living with hATTR-PN while advancing the broader understanding and treatment of this rare genetic disorder. Future efforts will emphasize enhancing patient support and fostering research collaborations to develop more effective treatment options.

As CEPARM forges ahead, the center is set to build on its remarkable legacy. Ongoing research into new therapies, including gene-editing technologies like CRISPR, offers hope for more effective treatments for hATTR. Additionally, the center is dedicated to expanding its outreach, ensuring that more patients across Brazil have access to CEPARM's specialized care.

Looking back on its journey, CEPARM exemplifies what can be achieved through dedication, teamwork, and a relentless pursuit of excellence in neurology, despite challenges such as staff shortages. As the center advances, its impact on patients and the wider medical community is set to continue.

CONCLUSION

Over the past four decades, CEPARM has exemplified the transformative power of dedicated research and patient-centered care in the field of FAP. The center's unwavering commitment to advancing scientific knowledge and improving treatment options has significantly enhanced the quality of life for those affected by hATTR-PN. From its early pioneering research to its current status as a national reference center, CEPARM has consistently demonstrated excellence in both clinical care and scientific innovation.

The introduction of groundbreaking therapies such as tafamidis, patisiran, inotersen, vutrisiran, and eplontersen reflects CEPARM's proactive approach to integrating cutting-edge treatments into patient care. Furthermore, the center's comprehensive support programs and multidisciplinary consultations highlight its dedication to addressing the complex needs of patients.

Looking ahead, CEPARM is poised to continue its legacy of excellence by embracing emerging technologies and expanding its research initiatives. The center's ongoing efforts to improve patient outcomes and advance the field of hATTR-PN will undoubtedly shape the future of care and treatment for this rare genetic disorder. As CEPARM enters its fifth decade, its legacy of innovation, dedication, and impact stands as a testament to its vital role in the global fight against FAP.

Acronyms and related meanings: ANVISA (Agência Nacional de Vigilância Sanitária), APBAR (Associação dos Portadores de Paramiloidose no Brasil), ASO (Antisense Oligonucleotides), ATTR (Amyloid Transthyretin), CEPARM (Centro de Paramiloidose Antônio Rodrigues de Mello), CONITEC (Comissão Nacional de Incorporação de Tecnologias no SUS), diflunisal (Non-Steroidal Anti-Inflammatory Drug), EMA (European Medicines Agency), FAP (Familial Amyloidotic Polyneuropathy), FDA (Food and Drug Administration), hATTR-PN (Hereditary Transthyretin Amyloidosis with Polyneuropathy), hATTR-CM (Hereditary Transthyretin Amyloidosis–Cardiomyopathy), HUCFF (Hospital Universitário Clementino Fraga Filho), imRNA (Interference Messenger RNA), NSAID (Non-Steroidal Anti-Inflammatory Drug), PCDT (Protocolo Clínico e Diretrizes Terapêuticas), RNA (Ribonucleic Acid), SUS (Sistema Único de Saúde), TTR (Transthyretin), THAOS (Transthyretin Amyloidosis Outcomes Survey), V30M (Val30Met Mutation).

REFERENCES

1. Adams D, Sekijima Y, Conceição I, Waddington-Cruz M, Polydefkis M, Echaniz-Laguna A, Reilly MM. Hereditary transthyretin amyloid neuropathies: advances in pathophysiology, biomarkers, and treatment. Lancet Neurol. 2023;22(11):1061-1074.
2. Da Mota Gomes M. Amiloidose familiar por transtirretina TTR Val30Met e os primórdios do Centro de Estudos de Paramiloidose. Rev Bras Neurol. 2011;47(2):7-21.
3. Ericzon BG, Wilczek HE, Larsson M, Wijayatunga P, Stangou A, Pena JR et al. Liver Transplantation for Hereditary Transthyretin Amyloidosis: After 20 Years Still the Best Therapeutic Alternative? Transplantation. 2015;99(9):1847-1854.

4. Coelho T, Maia LF, Martins da Silva A, Waddington Cruz M, Planté-Bordeneuve V, Lozeron P et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. Neurology. 2012;79(8):785-792.
5. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M et al. ATTR-ACT Study Investigators. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018;379(11):1007-1016.
6. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018;379(1):22-31.
7. Dias M, Pinto LF, Pinto MV, Gervais R, Accioli P, Amorim G, Guedes M, Gomes CP, Pedrosa RC, Waddington-Cruz M. Real-life experience with inotersen at CEPARM, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro. Arq Neuropsiquiatr. 2024 Apr;82(4):1-7.
8. Adams D, Polydefkis M, González-Duarte A, Wixner J, Kristen AV, Schmidt HH et al. Patisiran Global OLE study group. Long-term safety and efficacy of patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study. Lancet Neurol. 2021;20(1):49-59.
9. Coelho T, Marques W Jr, Dasgupta NR, Chao CC, Parman Y, França MC Jr, et. NEURO-TTRansform Investigators. Eplontersen for Hereditary Transthyretin Amyloidosis With Polyneuropathy. JAMA. 2023;330(15):1448-1458.
10. Adams D, Tournev IL, Taylor MS, Coelho T, Planté-Bordeneuve V, Berk JLet al. Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial. Amyloid. 2023;30(1):1-9.
11. Gentile L, Coelho T, Dispenzieri A, Conceição I, Waddington-Cruz M, Kristen A et al. A 15-year consolidated overview of data in over 6000 patients from the Transthyretin Amyloidosis Outcomes Survey (THAOS). Orphanet J Rare Dis. 2023;18(1):350.
12. Pinto MV, França MC Jr, Gonçalves MVM, Machado-Costa MC, Freitas MRG, Gondim FAA et al. Brazilian consensus for diagnosis, management and treatment of hereditary transthyretin amyloidosis with peripheral neuropathy: second edition. Arq Neuropsiquiatr. 2023;81(3):308-321.
13. Waddington-Cruz M, Pinto MV, Foguel D. Geographic distribution of ATTR cases from CEPARM across the Brazilian territory and their clinical aspects, demographics, ethnical and family background. Amyloid. 2019;26(sup1):53-54.
14. Sequeira VCC, Penetra MA, Duarte L, Azevedo FR, Sayegh RSR, Pedrosa RC, Cruz MW. Hereditary transthyretin-mediated amyloidosis with polyneuropathy: baseline anthropometric, demographic and disease characteristics of patients from a erence center. Arq Neuropsiquiatr. 2022;80(3):262-269.
15. Cruz MW, Pinto MV, Pinto LF, Gervais R, Dias M, Perez C et al. Baseline disease characteristics in Brazilian patients enrolled in Transthyretin Amyloidosis Outcome Survey (THAOS). Arq Neuropsiquiatr. 2019;77(2):96-100.
16. Pinto MV, Pinto LF, Dias M, Rosa RS, Mundayat R, Pedrosa RC, Waddington-Cruz M. Late-onset hereditary ATTR V30M amyloidosis with polyneuropathy: Characterization of Brazilian subjects from the THAOS registry. J Neurol Sci. 2019;403:1-6.