VOLUME 40 • ISSUE 2 • APRIL - JUNE 2021

Achaiki Iatriki

OFFICIAL PUBLICATION OF THE MEDICAL SOCIETY OF WESTERN GREECE AND PELOPONNESUS

ISSN: 1106-3319
ISSN (ON LINE): 1792-3018

ACHAIKI IATRIKI

OFFICIAL JOURNAL OF THE MEDICAL SOCIETY OF WESTERN GREECE AND PELOPONNESUS (IEDEP)

GENERAL INFORMATION

ISSN Print Edition: 1106-3319

ISSN Electronic Edition: 1792-3018

Journal Homepage: http://www.iedep.gr/

NLM Unique ID: 9802550

Journal citation: *Achaiki Iatriki* is published on behalf of the Journal of the Medical Society of Western Greece and Peloponnesus (IEDEP), representing the Society's official Journal. Please cite articles of the Journal as: Author names. Title of article. Ach Iatriki year;volume:pages.

Aims and scope: The journal publishes original papers on clinical and basic research from all areas of the health sciences including healthcare. *Achaiki Iatriki* is an open access journal. It provides immediate free access to its scientific contents and authors are not charged for submission, processing or publication of the manuscripts.

Abstracting and indexing services: Achaiki Iatriki is abstracted/indexed in the following databases: Mulford Health Science Library, Index Copernicus, Google Scholar, the Greek IATROTEK and National Library of Medicine.

MEDICAL SOCIETY OF WESTERN GREECE AND PELOPONNESUS

42 Votsi Street, Patras 26221, Greece

Tel: +30 2610 279579, Fax: +30 2610 220518

email: iede_pel@yahoo.gr

Publisher

Medical Society of the Western Greece and Peloponnesus

Editor-in-Chief

Christos Triantos

email: achaiki.iatriki@gmail.com

ACHAIKI IATRIKI

OFFICIAL JOURNAL OF THE MEDICAL SOCIETY OF WESTERN GREECE AND PELOPONNESUS (IEDEP)

ACHAIKI IATRIKI

OFFICIAL JOURNAL OF THE MEDICAL SOCIETY OF WESTERN GREECE AND PELOPONNESUS (IEDEP)

ACHAIKI IATRIKI

OFFICIAL JOURNAL OF THE MEDICAL SOCIETY OF WESTERN GREECE AND PELOPONNESUS (IEDEP)

ACHAIKI IATRIKI

Quarterly Official Journal of the
Medical Society of Western Greece And Peloponnesus (IEDEP)

CONTENTS

Letter from the Editor 80

Editorials

Mental Health Consequences of COVID-19 81
Nick Bouras

Laser for stone treatment 84
Angelis Peteinaris, Panagiotis Kallidonis, Evangelos Liatsikos

Original Research Articles

Liver fibrosis regression in patients with β-thalassemia major following hepatitis C treatment with direct-acting antivirals (DAAs) 87
Efthymios P. Tsounis, Alexandra Kourakli, Myrto Christofidou, Vasileios Lazaris, Stavros Kanaloupitis, Paraskevi Katsaouni, Ioanna Aggeletopoulou, Eugenia Verigou, Katerina Karaivazoglou, Vasiliki Labropoulou, Konstantinos Zisimopoulos, Evanthia Tourkochristou, Konstantinos Thomopoulos, Argiris Symeonidis, Christos Triantos

An investigation of dentists' knowledge, attitudes and practices towards infectious diseases in Greece 96
Karolina Akinosoglou, Panagiota Ntolou, Vasilina Dimakopoulou, George Moutousis, Charalambos Gogos

Case Reports

Late spontaneous healing of a severe spontaneous coronary artery dissection causing an acute coronary syndrome 107
Ioannis Vogiatzis, Konstantinos Koutsampasopoulos, Pavlos Roditis

Rupture of a Salmonella-infected iliac aneurysm: A case report 111
Ioannis Ntouvas, Chrysanthi Papageorgopoulou, Konstantinos Nikolakopoulos, Polyzois Tsantrizos, Spyros Papadoulas, Stavros Kakkos

Review

Natalizumab in the treatment of Crohn's disease 115
Angeliki Sapsani, Maria Kalafateli

Dear colleagues,

In the current issue, the editorial by Bouras N, comments on the psychological burden on people's working and social lives due to the rapid worldwide spread of COVID-19 and presents the most common consequences of the virus on mental health based on a rapidly growing literature. The editorial by Peteinaris et al. discusses the development of laser lithotripsy as an option for urinary stone treatment, and its current use for the treatment of urolithiasis of every part of the urinary tract. The original article by Tsounis et al. evaluates the impact of direct-acting antivirals (DAAs) on liver fibrosis in β-Thalassemia major (β-TM) patients with chronic HCV infection with the utilization of transient elastography (TE). Another original study by Akinosoglou et al. investigates dentists' perspectives on infectious diseases and explores their knowledge and practices towards respective patients.

Moreover, this issue includes two case reports. Vogiatzis et al. describes the case of a male patient who presented with spontaneous coronary artery dissection (SCAD) extending in the middle of the left anterior descending (LAD) after coronary angiography and complete angiographic healing in the coronary angiography, 6 months later. Ntouvas et al. presents the rare case of a patient with a rupture of a salmonella infected iliac aneurysm, who was operated successfully with complete excision of the aneurysmal sac, debridement of the surrounding infected tissue and arterial revascularization via femo-femoral bypass.

Lastly, the review article of this issue, by Sapsani et al. summarizes existing data on the efficacy and safety of natalizumab, with a special reference to progressive multifocal leukoencephalopathy (PML), in an attempt to determine which patients are in the highest risk of developing this infection and which patients could possibly benefit from natalizumab treatment.

C. Triantos
Assistant Professor in Internal Medicine
and Gastroenterology Faculty of Medicine,
School of Health Sciences, University of Patras
Editor-in-Chief of the journal "ACHAIKI IATRIKI"

Mental Health Consequences of COVID-19

Nick Bouras

The rapid worldwide spread of COVID-19 has created an enormous psychological burden with serious consequences on people's working and social lives. It is recognized that COVID-19 is associated with severe mental health repercussions mainly due to the sudden drastic change in daily life, fear of illness and death, generalized stress and financial adversities. The effects on mental health can be as severe as the physical symptoms of COVID-19 and are both short-term and long-term [1]. It is plausible to assume that there will be a multitude of mental health problems when the threat of COVID-19 is mitigated or overcome, which will include post-traumatic stress, adjustment disorders, anxiety, fear, depression and even an increase in suicide rates.

This article highlights some of the consequences of COVID-19 on mental health based on a rapidly growing literature. In a large study using data from 69 million individuals, 62 354 of whom had a diagnosis of COVID-19, it was found that COVID-19 patients were at increased risk of mental health problems, including anxiety and depression. There was a range of physical health risk factors for COVID-19, but it is not known if there were also psychiatric risk factors [2].

Sleep disturbances, which is a common consequence of stress, has also been frequently reported during the course of COVID-19 [3]. Social touch plays a silent but powerful role in human life, with important physical and mental health benefits throughout the life span. Touch is central in building the foundations of social interaction and attachment and can have unique, beneficial neurophysiological and epigenetic effects. The health risks of COVID-19 however necessitated unprecedented social distancing policies, including novel conditions of physical distancing [4]. The COVID-19 large periods of confinement may also affect people's sense of time [5]. In addition, the effects of the COVID-19 pandemic and the subsequent restrictive measures on children's and adolescents' mental health have been profound [6]. Unemployment, increased family conflicts and deteriorating parental psychological health, as well as children's previous history of physical illness seem to be significantly associated with negative psychological effects.

The COVID -19 pandemic has put healthcare professionals across the world in an unprecedented situation, having to make impossible decisions and work under extreme pressure including coming into daily and intense contact with people who are losing their lives. These decisions may include how to allocate scant resources to equally needy patients, how to balance their own physical and mental healthcare needs with those of patients, how to align their desire and duty to patients with those to family and friends, and how to provide care for all severely unwell patients with constrained or inadequate resources. This may cause some to experience moral injury or mental health problems [7].

Moral injury is a term that originated from the military and can be defined as the psychological distress that results from actions, or the lack of them, which violate someone's moral or ethical code. Unlike formal mental health problems such as depression or post-traumatic stress disorder, moral injury is not a recognisable mental illness. Healthcare managers need to proactively take steps to protect their staff's mental wellbeing. Managers should be frank about the situations their personnel are likely to face. Staff should be supported by reinforcing teams which would seek regular contact to discuss decisions and check on wellbeing. Once the crisis begins to recede, staff should be actively monitored and supported [7].

King's College London, Institute of Psychiatry, Psychology & Neuroscience, London SE5 8AF

Received: 22 Feb 2021; Accepted: 05 May 2021

Key words: *COVID-19; mental health; prevention; mitigation; ethics*

Global Challenge

The COVID-19 pandemic represents a global challenge to public mental health. To avoid the adverse effects of COVID-19 on population's mental health, there is an urgent need for the effective and wide-scale implementation of public health practices and innovative mental health interventions. The COVID-19 pandemic poses a triple global public mental health challenge: (1) to prevent an associated increase in mental health problems and a reduction in mental wellbeing across populations; (2) to protect people with a mental health problem from COVID-19 and the associated consequences, given their increased vulnerability; and (3) to provide healthcare professionals and carers with appropriate public mental health interventions [8].

It would be helpful to include mental health professionals at national policy and public health decision-making processes. Mental health professionals may have a significant contribution to the development of resilience and optimal coping skills for caregivers and the general population. Advice can be offered on how to manage isolation and quarantine and how to minimise adverse psychological effects such as frustration, loneliness, stress, anxiety, confusion, anger and family problems.

Primary prevention of mental problems addresses risk factors exacerbated by COVID-19, such as socio-economic inequalities, poverty, debt, unemployment, parental mental disorder, work-related stress, poor physical health, physical inactivity, and social isolation. Secondary prevention focuses on early intervention for mental health problems and their related effects to those associated with COVID-19. Tertiary prevention is an intervention for people with a pre-existing mental health problem to prevent the consequences and disability of COVID-19, social isolation, stigma and discrimination.

The promotion of mental well-being is important and includes the value that individuals and societies place on mental health and well-being, and the implementation of interventions to enhance mental well-being. It is inevitable that COVID-19 will change our perceptions and practices regarding social habits. During the pandemic many of our personal encounters have been replaced by remote communications and video calling. These changes in our traditional habits are expected to continue but we do not know what impact they will have on mental health in the future.

Ethics

COVID-19 presents new challenges for mental health services as clinical management, ethical dilemmas and administrative complications need to be addressed. The COVID-19 pandemic also raises a number of bioethical issues concerning medical and nursing staff as well as government policy and care. Some of them are specifically related to mental health practice such as involuntary hospitalizations and the protection of people living in various forms of public facilities e.g., hostels, supported accommodation etc. Self-isolation carries its own risks, including those of loneliness and mental health deterioration, even for people without pre-existing mental health problems. Change or inability to work, financial difficulties, family problems may worsen these problems [9].

Mitigation

Interventions should aim to mitigate the impact of the pandemic on mental health, by improving the well-being of the population and by preventing mental health problems' relapse. Such interventions should proportionately target vulnerable groups with a higher risk of mental health problems and poorer mental well-being compared to the general population.

Despite the existence of effective public mental health interventions, implementation is poor. Globally, only a minority of individuals with a mental health problem receive any treatment or intervention that may prevent the COVID-19-related mental health effects and promote mental wellbeing [10].

The relationship between physical and mental health has never been so important. People with severe mental health problems are three times more likely to suffer from physical health problems than the general population.

To improve personal well-being, various self-help programs with documented actions have been developed and implemented. Among them is «The Five Ways to Wellbeing» which is a simple set of practical actions that can be performed daily under unusual circumstances of self-isolation [11]. These include new knowledge, communication, senses, solidarity & volunteering and physical exercise. Acquiring new knowledge can give a sense of accomplishment and reward. The internet and the majority of lay press contain information that can stimulate learning and provide opportunities for skills development. There is also free tutoring on a range of easily accessible topics, including online libraries and audio books.

Despite the social constraints imposed by COVID-19

which reduce regular contact with others, there is more time to use modern technology, remote communication, telephones, etc. New social networking groups can also be set up between friends, family, colleagues and neighbours to support vulnerable people and manage new isolation guidelines. Gaining experiences from pleasant senses, smells, visual pleasures can positively affect our thoughts and improve enjoyment. Solidarity and voluntarism constitute additional ways of strengthening ties within a community and helping isolated and potentially lonely people.

Exercise and activity has been described as a «miracle cure», with impressive physical and mental health benefits. Reducing sitting or lying time, even if simply standing, is associated with improved physical health outcomes no matter how much exercise people do. A regular routine is important for physical and mental well-being and can help alleviate the impairment caused by the loss of normal daily work and school activities. Findings showed that people in Greece, during the first lockdown, adapted to the stress caused by the pandemic using predominantly positive active strategies [12].

Isolation can represent a new challenge for some by providing the opportunity to change their lifestyle and they could benefit from myriads of new initiatives emerged during these unexampled moments. The above simple suggestions, combined with new opportunities, might be able to improve the well-being of people with or without mental health problems under the adverse conditions of COVID-19.

Conflict of interest disclosure: *None to declare.*

Declaration of funding sources: *None to declare.*

REFERENCES

1. Campion J, Javed A, Sartorius N, Marmot M. Addressing the public mental health challenge of COVID-19 Lancet Psychiatry. 2020;7(8):657-9.
2. Taquet M, Luciano S, Geddes J R, Paul J Harrison P J. Bidirectional associations between COVID-19 and psychiatric disorder: retrospective cohort studies of 62 354 COVID-19 cases in the USA. Lancet Psychiatry. 2021;8(2):130-40.
3. Cheng C, Ebrahimi OV, Lau Y-C. Maladaptive coping with the infodemic and sleep disturbance in the COVID-19 pandemic. J Sleep Res. 2020;e13235.
4. https://www.theguardian.com/lifeandstyle/2021/jan/24/lost-touch-how-a-year-without-hugs-affects-our-mental-health
5. Holman EA, Grisham EL. When time falls apart: The public health implications of distorted time perception in the age of COVID-19. Psychol Trauma. 2020;12(S1):S63-5.
6. Newlove-Delgado T, McManus S, Sadler K, Thandi S, Vizard T, Cartwright C, et al. Child mental health in England before and during the COVID-19 lockdown Lancet Psychiatry. 2021;8(5):353-4.
7. Greenberg N, Docherty M, Gnanapragasam S. Managing mental health challenges faced by healthcare workers during covid-19 pandemic. BMJ 2020;368:m1211.
8. Duan L, Zhu G. Psychological interventions for people affected by the COVID-19 epidemic. Lancet Psychiatry. 2020;7(4):300-2.
9. Ploubidis D. Living with COVID19. Psychiatriki. 2020; 31(3).
10. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet. 2020;395(10227):912-20.
11. Strous R D. and Gold A. Psychiatry and COVID-19: Putting Our Best Foot Forward. Br J Psychiatry. 2020;217(2):410-2.
12. Skapinakis P, Bellos S, Oikonomou A, Dimitriadis G, Gkikas P, Perdikari E, et al. Depression and Its Relationship with Coping Strategies and Illness Perceptions during the COVID-19 Lockdown in Greece: A Cross-Sectional Survey of the Population. Depress Res Treat. 2020;2020:3158954.

Corresponding author:

Nick Bouras, MD, PhD, FRCPsych,
Professor Emeritus, King's College London,
Institute of Psychiatry, Psychology & Neuroscience,
London SE5 8AF
E-mail: nick.bouras@kcl.ac.uk

Laser for stone treatment

Angelis Peteinaris[1], Panagiotis Kallidonis[1], Evangelos Liatsikos[1-4]

Laser lithotripsy is used worldwide and is an increasingly evolving field based on novel and continuous research. It has been almost 35 years since laser was established as an option for urinary stone treatment, and as most technological advancements, laser technology has not ceased to develop. It is currently used for the treatment of urolithiasis of every part of the urinary tract and is one of the most attractive specializing fields for urologists.

Lasers for the management of renal stones are used during two endoscopic procedures. The first one is flexible ureteroscopy /retrograde intrarenal surgery (RIRS) and the second is percutaneous nephrolithotomy (PCNL).

RIRS is the treatment of choice for renal stones with a maximal diameter smaller than 2cm. The patient must be placed into lithotomy position under general anesthesia. With the use of a flexible ureteroscope, the surgeon approaches the stone and a laser fiber is inserted through the working channel of the instrument to fragmentize the stone. The surgeon has the ability to investigate through this flexible instrument the renal pelvis and calyxes for stones and to address any stone in the pelvicalyceal system. Usually, after this type of surgery, a double-j stent is inserted for a few days. The double-j stent provides safety for the removal of fragments and the possible post-surgical edema of the ureter [1].

PCNL is the treatment of choice for renal stones with a maximal diameter larger than 2cm. This technique can be used even for the fragmentation of staghorn stones. These stones occupy more than one branch of the renal collecting system. For this type of surgery, the patient must be placed into prone position under general anesthesia. A percutaneous access to the pelvicalyceal system is established under fluoroscopic and/or ultrasound guidance. A rigid or flexible endoscope (nephroscope) is inserted through the tract and the renal pelvis and calyxes are investigated for stones. A laser is used for stone fragmentation by inserting a laser fiber though the working channel of the nephroscope. Larger stones and a more direct access to the pelvicalyceal system allows for faster stone management with the use of the laser and the removal of large fragments with a grasper or basket. Thus, large renal stones could be more efficiently managed. Compared to RIRS, PCNL has a higher stone free-rate. In addition, PCNL has a longer hospital stay. The operation time and the complication rate are similar between these two types of surgery [2]. After the surgery, a renal drainage with or without a double-j stent is inserted for several days. The indications, contraindications and possible complications of both kind of surgery are presented in Table 1.

Lithotripters

Pulsed lasers, such as the holmium:yttrium–aluminum–garnet (Ho:YAG) are mainly used for lithotripsy. The main reason is that they deliver their energy in pulses, which is more efficient and safer during stone lithotripsy[3]. Ho:YAG lithotripters allow the surgeon to control three parameters: pulse energy, pulse length and pulse frequency. During a short pulse, the energy is delivered during a short period of time (~ 300 μs). In long-pulse mode, the energy is distributed over approximately 600μs or more [4].

The Moses effect is designed for a high-power 120-W Ho:YAG lithotripter. This lithotripsy mode releases a modulated laser pulse. The first pulse creates space

[1]Department of Urology, University Hospital of Rion, Patras, Greece
[2]Medical School, University of Patras, Patras, Greece
[3]Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia
[4]Medical University of Vienna, Vienna, Austria

Received: 28 Feb 2021; Accepted: 21 Apr 2021

Key words: *Laser; lithotripsy; endourology*

Table 1. *Possible complications of PCNL and RIRS. Except of the main indication for each category of surgery, the remaining of indications are for active removal of stones and could be considered for both PCNL and RIRS [13-15].*

Surgery	Indications	Contraindications	Complications (%) (based on severity by the modified clavien classification system)
PCNL	Main indication: large renal stones >2.cm in maximal diameter/ Smaller stones which could not be treated by RIRS or SWL Stone growth High Risk patient for stone formation Obstruction Infection Symptoms Stones >1,5cm Stones<1,5cm (if not observation) Patient preference Comorbidity Social situation of the patient Choice of treatment	Anti-coagulant therapy Untreated UTI Tumor in the access tract area Potential malignant kidney tumor Pregnancy	Transient fever >38oC (11) Transient elevation of creatinine (0,7) Pneumonia (0,3) Renal hemorrhage (1,4) Hemothorax (1,1) Pneumothorax (1,1) Collecting system perforation (0,4) Sepsis (0,6)
RIRS	Main indication: Renal stones <2.5cm not appropriate for SWL or after unsuccessful SWL (shock wave lithotripsy) Stone growth High Risk patient for stone formation Obstruction Infection Symptoms Stones >1,5cm Stones<1,5cm (if not observation) Patient preference Comorbidity Social situation of the patient Choice of treatment	Untreated UTI Inability for general anesthesia	Mucosal injury (1,5) Fever (2) Transient elevation of creatinine (1,35) UTI (6) Perforation (2,7) Extravasation ans open conversion (1,35) Myocardial infraction, Pulmonary embolism (1,35) Sepsis (0,7)

between the stone and the fiber tip dividing the water, and the second pulse can hit the stone without obstruction. This can increase efficiency and lower retropulsion [5]. The burst laser lithotripsy is a mode of the Ho:YAG lithotripter. Three rapidly successive pulses constitute a burst. The pulses have increasing lengths and decreasing energy. The novel new mode increases significantly the ablation [6]. Pulsed thulium laser has recently been used in lithotripsy. It appears fast, does not produce much heat and produces less retropulsion than the Ho:YAG lithotripsy [7].

Laser Fibers

The lithotripter is important, but the laser fiber plays also an important role in the lithotripsy procedure. In urology the use of small-diameter fibers is preferred. Larger fibers may decrease the flexibility of surgical instruments and the irrigation fluid's flow through the scope. In addition, they create larger stone fragments and produce more retropulsion. It is also known that thulium lithotripters are compatible with smaller diameter laser fibers, than the fibers used with the Ho:YAG lasers. This fact is an advantage of the thulium laser lithotripsy [8].

There are single-use or reusable fibers. Regardless of the fiber type, the fibers can be damaged during the surgery. It has been proved that higher pulse energy, shorter pulse length and harder stones can create more damage to the fiber. Because of these degradation factors, laser fibers are "renewed" before or during surgery. This means that the plastic fiber coating and the glassy fiber part are cut by special instruments [9].

Laser settings-techniques

It is known that higher pulse energy combined with shorter pulse length are ideal for breaking large stones into smaller. These settings are usually used for kidney and bladder stones that could have a large caliber percutaneous approach. In ureteroscopy the "dusting" technique is preferred [10]. Dusting settings consist of low pulse energy (0.2–0.5 J), higher frequency, and longer pulse length. This may increase the ablation time of stone material, but it reduces extraction-associated complications, as dust is naturally eliminated and reduces operation time as no extraction procedures are needed [11]. In addition, there are two different settings that are used for the non-contact lithotripsy technique. This is usually used in an enclosed and small space (e.g. calix) and the aim is to break stones to smaller fragments that will spontaneously pass. The first one is the "pop-corn" technique. Its settings consist of high pulse energy (≈ 1.5 J), high frequency (20-40 Hz) and long-pulse mode in order to break a stone to clinically insignificant fragments. The second technique is the "popdusting". It is using lower pulse energy (0.5 J) than the pop-corn technique in order to create smaller fragments while partially protecting the fiber tip.

In conclusion, the kind of the lithotripter, the size of the fiber or the settings are important, but the most vital part for this procedure is the experience and the ability of the surgeon to use all these advantages in a wise and efficient way [12].

Conflict of interest disclosure: *None to declare.*

Declaration of funding sources: *None to declare.*

REFERENCES

1. Sarikaya S, Unsal A, Ebiloglu T, Ozbek R, Guvenir G, Senocak C, et al. Is retrograde intrarenal surgery replacing percutaneous nephrolithotomy as surgical treatment of stone disease: Our clinical experience. Arch Esp Urol. 2018;71(5):506-11.
2. Zhu M, Wang X, Shi Z, Ding M, Fan D, Wang X, et al. Comparison between retrograde intrarenal surgery and percutaneous nephrolithotripsy in the management of renal stones: A meta-analysis. Exp Ther Med. 2019;18(2):1366-74.
3. Zörcher T, Hochberger J, Schrott KM, Kühn R, Schafhauser W. In vitro study concerning the efficiency of the frequency-doubled double-pulse Neodymium:YAG laser (FREDDY) for lithotripsy of calculi in the urinary tract. Lasers Surg Med. 1999;25(1):38-42.
4. Kronenberg P, Traxer O. Update on lasers in urology 2014: current assessment on holmium:yttrium-aluminum-garnet (Ho:YAG) laser lithotripter settings and laser fibers. World J Urol. 2015;33(4):463-9.
5. Mullerad M, Aguinaga JRA, Aro T, Kastin A, Goldin O, Kravtsov A, et al. Initial Clinical Experience with a Modulated Holmium Laser Pulse-Moses Technology: Does It Enhance Laser Lithotripsy Efficacy? Rambam Maimonides Med J. 2017;8(4).
6. Lange B, Jocham D, Brinkmann R, Cordes J. Stone/tissue differentiation for Holmium laser lithotripsy using autofluorescence: Clinical proof of concept study. Lasers Surg Med. 2017;49(4):361-5.
7. Kamal W, Kallidonis P, Koukiou G, Amanatides L, Panagopoulos V, Ntasiotis P, et al. Stone Retropulsion with Ho: YAG and Tm: YAG Lasers: A Clinical Practice-Oriented Experimental Study. Journal Endourol. 2016;30(11):1145-9.
8. Pasqui F, Dubosq F, Tchala K, Tligui M, Gattegno B, Thibault P, et al. Impact on active scope deflection and irrigation flow of all endoscopic working tools during flexible ureteroscopy. Eur Urol. 2004;45(1):58-64.
9. Wollin DA, Ackerman A, Yang C, Chen T, Simmons WN, Preminger GM, et al. Variable Pulse Duration From a New Holmium:YAG Laser: The Effect on Stone Comminution, Fiber Tip Degradation, and Retropulsion in a Dusting Model. Urology. 2017;103:47-51.
10. El-Nahas AR, Almousawi S, Alqattan Y, Alqadri IM, Al-Shaiji TF, Al-Terki A. Dusting versus fragmentation for renal stones during flexible ureteroscopy. Arab J Urol. 2019;17(2):138-42.
11. Santiago JE, Hollander AB, Soni SD, Link RE, Mayer WA. To Dust or Not To Dust: a Systematic Review of Ureteroscopic Laser Lithotripsy Techniques. Curr Urol Rep. 2017;18(4):32.
12. Aldoukhi AH, Roberts WW, Hall TL, Ghani KR. Holmium Laser Lithotripsy in the New Stone Age: Dust or Bust? Front Surg. 2017;4:57.
13. Shin TS, Cho HJ, Hong SH, Lee JY, Kim SW, Hwang TK. Complications of Percutaneous Nephrolithotomy Classified by the Modified Clavien Grading System: A Single Center's Experience over 16 Years. Korean J Urol. 2011;52(11):769-75.
14. Ibrahim AK. Reporting ureteroscopy complications using the modified clavien classification system. Urol Ann. 2015;7(1):53-7.
15. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, et al. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol. 2016;69(3):475-82.

Corresponding author:

Evangelos Liatsikos
Medical School, University of Patras, Patras, GR-26500, Greece,
Tel.: +30 2610999385, E-mail: liatsikos@yahoo.com

ORIGINAL RESEARCH ARTICLE ACHAIKI IATRIKI | 2021; 40(2):87–95

Liver fibrosis regression in patients with β-thalassemia major following hepatitis C treatment with direct-acting antivirals (DAAs)

Efthymios P. Tsounis[1], Alexandra Kourakli[2], Myrto Christofidou[3], Vasileios Lazaris[2], Stavros Kanaloupitis[1], Paraskevi Katsaouni[2], Ioanna Aggeletopoulou[1], Eugenia Verigou[2], Katerina Karaivazoglou[1], Vasiliki Labropoulou[2], Konstantinos Zisimopoulos[1], Evanthia Tourkochristou[1], Konstantinos Thomopoulos[1], Argiris Symeonidis[2], Christos Triantos[1]

Abstract

Background: Infection with hepatitis C virus (HCV) and transfusion-induced iron overload are the main causes of liver disease in patients with β-thalassemia major (β-TM). Direct-acting antivirals (DAAs) have improved the management of chronic hepatitis C achieving high rates of sustained virological response (SVR). However, there are limited data concerning the influence of DAAs on fibrosis progression in this setting. The aim of this study was to examine the impact of DAAs treatment on liver fibrosis in patients with chronic hepatitis C (CHC) and β-TM with the utilization of transient elastography (TE).

Methods: Between 1/2015 and 7/2019 [median follow-up: 35 months (IQR range: 24-36.5)] 11 β-TM HCV-infected patients [median age: 46 years (IQR range: 40-57); genotype 1/2/3/4: 9.1/9.1/45.4/36.4%] who received DAA-based treatment were evaluated. All patients were under regular iron chelation treatment. The stage of liver fibrosis was determined using transient elastography (TE).

Results: Overall SVR rate after treatment with DAAs was 100% (11/11). Median liver stiffness at first year of follow-up (range: 6-12 months) was significantly decreased compared to baseline value (6.7 kPa vs 10.3 kPa; p= 0.013). Improvement of liver stiffness measurements (LSMs) in 4 patients corresponded to reversal of cirrhosis according to predefined TE cut-off values. All but two patients attained decreased TE values in their post-SVR examinations. No significant change was observed in 5 patients who were re-assessed at 12-48 months post-treatment (5.6 kPa vs 6.7 kPa; p=0.461).

Conclusion: DAAs treatment is a highly effective therapeutic option in HCV-infected β-TM patients regarding its effect on liver fibrosis.

Key words: *Thalassemia; chronic hepatitis C; liver cirrhosis; elastography; direct-antiviral agents*

[1]Division of Gastroenterology, Department of Internal Medicine, University Hospital of Patras, Patras, Greece
[2]Division of Hematology, Department of Internal Medicine, University of Patras Medical School, University Hospital, Patras, Greece
[3]Department of Microbiology, University Hospital of Patras, Patras, Greece

Received: 09 Nov 2020; Accepted: 08 Jan 2021

INTRODUCTION

β-Thalassemia major or Cooley's disease (β-TM) is an inherited genetic disorder, caused by impaired synthesis of beta chains of the hemoglobin tetramer [1]. A serious consequence of the disease is iron overload, induced by regular transfusions, necessary for the maintenance of normal growth and development, and by the paradoxical suppression of hepcidin production [2,3]. One of the

main target-organs affected by iron toxicity is the liver and hepatic fibrosis has been reported to correlate with transfusion burden and liver iron concentration (LIC) [4].

Hepatitis C virus (HCV) is a prominent transfusion-transmitted infection, affecting approximately 71 million people globally, that causes chronic inflammation with complications, such as liver cirrhosis and hepatocellular carcinoma (HCC) [5]. Notably, the prevalence rate of HCV infection in β-TM patients is recorded to be as high as 40% in our region, varying widely among international studies [6-8]. Apparently, individuals with β-TM and HCV infection represent a special group with two concomitant independent risk factors to develop advanced liver disease [9].

Preceding the introduction of direct-acting antivirals (DAAs), interferon (IFN) based regimens and ribavirin were the standard of care in HCV infection. Patients with β-TM were a population difficult to cure, with poor response to treatment and higher HCV reactivation rates [10-13]. In addition, ribavirin administration induces increased transfusion requirements and elevated body iron accumulation [14,15]. DAAs revolutionized the treatment against HCV, achieving unprecedented rates of sustained virological response (SVR>90%) without significant adverse effects [16,17].

However, the progression of liver fibrosis following treatment with novel agents in patients with β-TM has not yet been thoroughly clarified. Transient elastography (TE) is a non-invasive diagnostic tool, used to assess liver stiffness, and a surrogate marker of fibrosis, through analysis of vibration generated mechanical waves. Markedly, TE measurements are not influenced by liver iron deposition and provide satisfactory accuracy in predicting hepatic fibrosis in HCV-infected patients with β-TM, comparable to liver biopsy [18-21].

The aim of this study was to assess the impact of DAAs on liver fibrosis in β-TM patients with chronic HCV infection with the utilization of TE.

MATERIALS AND METHODS

Study population

In this observational study registering real-world experience, recruitment took place in the University Hospital of Patras in a period from January 2015 up until July 2019. Inclusion criteria were: 1) transfusion-depended, well-established β-TM 2) chronic hepatitis C (CHC) infection, defined by positive HCV RNA test for at least 6 months, and 3) treatment with DAAs. Patients with hepatitis B virus (HBV) or human immunodeficiency virus (HIV) co-infection were excluded. All patients were under regular chelation therapy, according to their individual features. Once the specific population of the study was defined (n=11), analysis of baseline characteristics was performed. Response to treatment was assessed and, subsequently, liver stiffness progression was evaluated using TE.

Ethical considerations

All study participants, or their legal guardian, provided informed written consent prior to study enrollment. The study protocol was reviewed and approved by the Ethics committee of the University Hospital of Patras. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki for medical research involving human subjects.

Patient assessment

Comprehensive medical history, complete blood cell count and blood biochemistry analysis were performed in all patients at baseline. Physical examination and monitoring of adverse effects were carried out at each visit.

HCV RNA was quantified by a highly sensitive viral load assay, the Versant HCVRNA 1.0 Assay (kPCR) - Siemens Healthineers, a real-time kinetic polymerase chain reaction (kPCR). HCV genotype was identified by Versant HCV Genotype 2.0 Assay, Line Probe Assay (LiPA) - Siemens Healthineers, a reverse-hybridization technology designed to identify HCV genotypes 1-6 and HCV subtypes. Quantitative detection of HCV RNA and HCV genotype identification tests were performed in the Microbiology Laboratory of the University Hospital of Patras, as a standard process in the Thalassemia Center patients. SVR was defined as undetectable HCV RNA, with a limit of detection <13 IU/ml in serum sample, 12 weeks after the therapy's cessation and it was used for determining patients' response to treatment [22,23]. Diagnosis of cirrhosis was based on solid clinical, biochemical, radiological or histological findings. T2* Magnetic Resonance Imaging was performed for the estimation of the LIC, applying the formula 0.202+25.4/T2* adapted from Wood et al. [24] Liver fibrosis status was evaluated before the administration of DAAs using TE (Fibroscan®; Echosens, Paris, France). Measurements were performed in the Gastroenterology Department of the hospital. The right hepatic lobe was targeted through an intercostal space access while the patient remained in the dorsal decubitus position with the right arm in maximal abduction. Using the ultrasound guide, the operator located a liver part of an adequate thickness of 6 cm or above without large vessels according to manufacturer's instructions. For all patients medium (M) size probe was used. The ratio between the number of valid

measurements and the total number measurements was used to describe the success rate. Only the examinations with at least 10 validated measurements, success rate of at least 60% and interquartile range (IQR) of less than 30% of the median TE value were considered reliable. The results were expressed in kilopascals (kPa). Cut-off values for diagnosing different stages of hepatic fibrosis were predefined. TE value ≥ 12 kPa was considered indicative of cirrhosis (F4), whereas a limit of 7.9 kPa was used to discriminate mild or no liver fibrosis (F0/F1) from moderate to severe fibrosis (F2/F3) [19,25]. All patients had their liver stiffness re-assessed within 6-12 months after the end of treatment.

Treatment

Treatment regimens were administered, taking into consideration the patient's HCV genotype, the availability of pharmaceutical agents and the Greek national and European guidelines for hepatitis C therapeutic intervention [22,26]. Patients were reimbursed for their treatment in accordance to the Greek national insurance system. Interferons had been the fundamental drug before the breakthrough of DAAs in the last decade and, thus, most of our patients (n=7, 63.6%) had received IFN-based treatment in the past.

In this study, five different regimens using DAAs were administrated: (i) SOF/LDV: A co-formulation of Sofosbuvir (SOF), a nucleotide analogue NS5B polymerase inhibitor, with Ledipasvir (LDV), a NS5A inhibitor; (ii) GRZ/EBR: A co-formulation of Grazoprevir (GRZ), a NS3/4 protease inhibitor, with Elbasvir (EBR), a NS5A inhibitor; (iii) OBV/PTV/r +DSV: A combination of Dasabuvir (DSV), a non-nucleotide analogue NS5B polymerase inhibitor, with a co-formulation of Ombitasvir (OBV), a NS5A inhibitor, with paritaprevir (PTV), a NS3/4 protease inhibitor, boosted by ritonavir (r); (iv) SOF/VEL: A co-formulation of Sofosbuvir (SOF) with Velpatasvir (VEL), a NS5A inhibitor; (v) SOF+DCV: A combination of Sofosbuvir (SOF) plus Daclatasvir (DCV), a NS5A inhibitor.

Deferoxamine was the first line agent of the chelation therapy in the majority of our patients. For patients exhibiting poor compliance, intolerance or side effects an alternative oral compound was used, either deferiprone or deferasirox. Combination of two chelators for undertreated individuals was in the physician's discretion.

Statistical analysis

Continuous variables were presented as medians (interquartile range, IQR). Frequency data were presented as absolute numbers and percentages, while comparison between categorical variables was performed with Pearson's chi-squared test or two-sided Fisher's exact test, when applicable. For non-parametric paired samples Wilcoxon rank sum test was applied. Statistical analysis was performed with the SPSS statistical software package (version 26.0; SPSS, Chicago, IL, USA). The threshold of statistical significance was set at 5% ($p \leq 0.05$).

RESULTS

Patients' characteristics

Fifty-four patients with transfusion depended β-TM and CHC infection, who received anti-HCV treatment, were identified in University Hospital of Patras. Among them, eleven individuals without HIV/HBV co-infection were treated with DAAs and, thus, were enrolled in our study. The main clinical and laboratory findings of these patients are presented in Table 1.

The most prevalent HCV genotype was genotype 3 (n=5, 45.4%), whereas genotype 1 and genotype 2 virus were each identified in one patient. Chelation therapy remained unchanged during the period of DAAs treatment and most of the patients received deferoxamine, as part of their chelation treatment (n=9, 81.8%). Although adherence was reported to be optimal, manifestations of iron deposition in endocrine glands, such as hypogonadism (n=6, 54.5%), diabetes (n=2, 18.2%) and thyroiditis/hypothyroidism (n=5, 45.4%), were observed in remarkable rates. Heart disease, a primary cause of mortality and morbidity in β-TM was recorded in 4 (36.4%) cases, while 4 other (36.4%) patients were diagnosed with liver cirrhosis.

Treatment

Seven patients with unsuccessful IFN-based therapy plus 4 patients, who had not received treatment in the past, were assigned to be treated with DAAs [median age: 46 (40-57), median follow-up: 35 months (IQR: 24-36.5)] (figure 1). SOF/LDV was administrated in 1 patient (9.1%), GRZ/EBR in 2 patients (18.2%), OBV/PRT/r+DSV in 1 patient (9.1%), SOF/VEL in 2 patients (18.2%) and SOF+DCV in 5 patients (45.4%). The selection of DAAs between individuals with different HCV genotypes is displayed in figure 2. All patients (n=11) responded to treatment and their serum HCV-RNA turned to be undetectable 12 weeks after the end of treatment (SVR=100%).

Baseline transient elastography

Prior to DAAs administration, liver fibrosis was assessed in all patients with TE and median liver stiffness was found 10.3 kPa (IQR 6.1-14.6). There were no cases of failure in the performance of TE, as 60% success rate and

Table 1. *Baseline characteristics of the patients.*

Age, years	46 (40-57)
Male sex, n (%)	4 (36.4)
Follow-up, months	35 (24-36.5)
BMI, kg/m2	23 (22-25)
HCV genotype, n (%)	
1	1 (9.1)
2	1 (9.1)
3	5 (45.4)
4	4 (36.4)
Chelation agent, n (%)	
Deferoxamine	4 (36.4)
Deferiprone	1 (9.1)
Deferasirox	1 (9.1)
Deferoxamine + Deferiprone	5 (45.4)
Cirrhosis, n (%)	4 (36.4)
Splenectomy, n (%)	8 (72.7)
MRI Liver Iron Concentration a, μg/g dry weight	4.2 (2.6-7.9)
IFN-experienced, n (%)	7 (63.6)
Fibroscan, kPa	10.3 (6.1-14.6)
AST, iu/ml	39 (35-76)
ALT, iu/ml	77 (33-138)
Bilirubin total, mg/dl	1.7 (1.4-2.5)
Albumin, g/l	45 (42-47)
Hemoglobin, g/l	10 (9.5-11.2)
Platelet count, x109/l	435 (258-506)
Diabetes, n (%)	2 (18.2)
Heart Disease, n (%)	4 (36.4)
Osteoporosis, n (%)	5 (45.4)
Hypogonadism, n (%)	6 (54.5)
Thyroidopathy, n (%)	5 (45.4)

Notes: Quantitative values are presented as median (interquartile range). a Data available on 6 patients.

Abbreviations: HCV, hepatitis C virus; BMI, body mass index; IFN, interferon; MRI, magnetic resonance imaging; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

IQR less than 30% of the median TE value were achieved in all patients. Applying the correspondence of TE values to stages of liver fibrosis, patients were classified in the following categories of liver damage: F0-F1/F2-F3/F4: n=4 (36.4%)/n=3(27.3%)/n=4(36.4%). Interestingly, patients previously treated with INF presented significantly higher baseline TE values in comparison with treatment-naïve patients [14.4 kPa (IQR 9.8-14.9) vs 5.75 kPa (IQR 4.45-9.3); p=0.038].

Furthermore, a T2* MRI was performed to quantify LIC in 6 patients and median value was found 4.2 mg/(g dry weight) (IQR: 2.6-7.9). In agreement with previous studies, no correlation was identified between LIC and TE results (r=0.123, p=0.816) [18-20].

Liver fibrosis regression

The effect of DAAs on liver fibrosis was evaluated using TE within the first post-treatment year (range: 6-12 months). Additionally, in 5 individuals liver stiffness was re-assessed during the following years of surveillance (range:12-48 months). Median TE value of the first post-

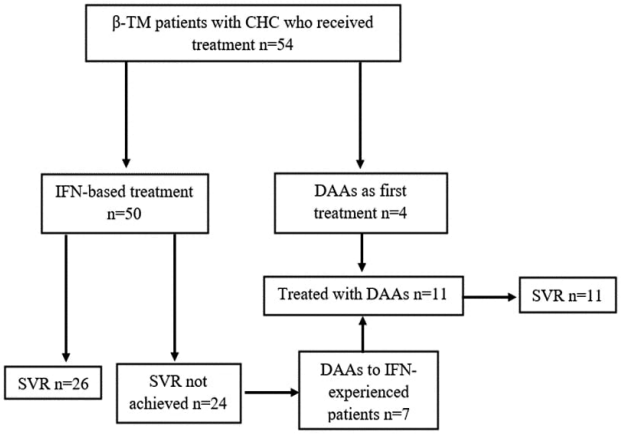

Figure 1. Flowchart of patients. β-TM: beta thalassemia; HCV: hepatitis C virus; CHC: chronic hepatitis C; IFN: Interferon; DAAs: direct-acting antivirals; SVR: sustained virological response.

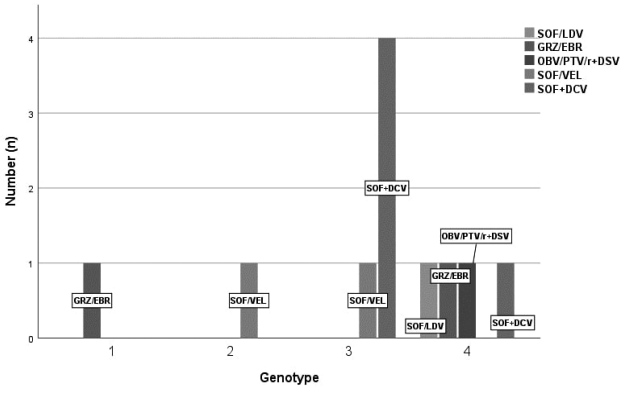

Figure 2. DAAs selection among patients with different HCV genotypes. DAAs: direct-acting antivirals; SOF: Sofosbuvir; LDV: Ledipasvir; VEL: Velpatasvir; DCV: Daclatasvir; GRZ: Grazoprevir; EBR: Elbasvir; OBV: Ombitasvir; PTV: Paritaprevir; r: Ritonavir; DSV: Dasabuvir.

treatment year was significantly decreased compared to baseline measurements [6.7 kPa (IQR: 4.8-8.8) vs 10.3 kPa (IQR 6.1-14.6); p= 0.013]. In patients with repeated post-treatment LSMs median TE remained unaltered during the following years [5.6 kPa (IQR: 5.2-8.3) vs 6.7 kPa (IQR: 4.8-8.8); p=0.461] (figure 3). Moreover, significant improvement of liver fibrosis was observed when the most recent LSMs of the patients [median liver stiffness was 6.7 kPa (IQR: 4.3-8.8)] were compared to their baseline values (p=0.016).

Notably, all but two patients had lower TE value in their most recent assessment, in comparison to their baseline measurement (figure 4). Even though 7 (63.6%) individuals had baseline liver stiffness corresponding to ≥F2 stage of fibrosis (≥7.9kPa), only 3 of them maintained a TE value above 7.9 kPa in post-treatment measurements (figure 5). Importantly all patients, who had pre-treatment LSMs indicative of cirrhosis (n=4), were classified as having an improved stage of liver fibrosis in their post-treatment TE examination (TE<12 kPa) (figure 4, 5).

Safety

All DAA-based treatment regimens were well-tolerated and no major adverse events were reported. Clinically significant drug-drug interactions between DAAs and chelation therapy were not observed. Adherence to treatment was optimal and early discontinuation was not recorded.

During the study follow-up, one 51 years-old male patient, who was diagnosed with hepatocellular carcinoma died.

DISCUSSION

The present study demonstrates that successful treatment with DAAs in β-TM patients with hepatitis C infection contributed to decreased post-treatment liver stiffness measurements (LSMs). DAAs appear to induce regression of hepatic fibrogenesis and even potential reversal of cirrhosis.

Various studies have provided estimates of liver fibrosis regression after DAAs treatment [27-38]. Our analysis focused on a particular subgroup of HCV infected patients, those with underlying β-TM. The key strength of our investigation is that the impact of DAAs was assessed with paired TE measurements in the course of a longer-term follow-up period compared to previous studies [27-38]. Post-treatment LSMs were carried out at least 6 months after the end of treatment (EOT). Besides, in certain cases, we conducted repeated post-treatment TE examinations over a period spanning

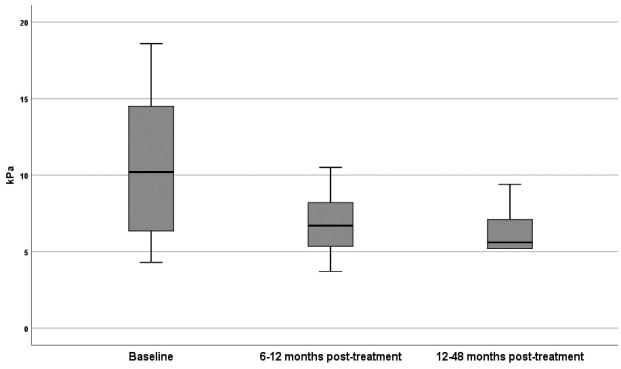

Figure 3. Boxplots of transient elastography measurements in patients: (i) before the administration of direct antiviral agents, (ii) during the first year after treatment, (iii) during the following years of monitoring.

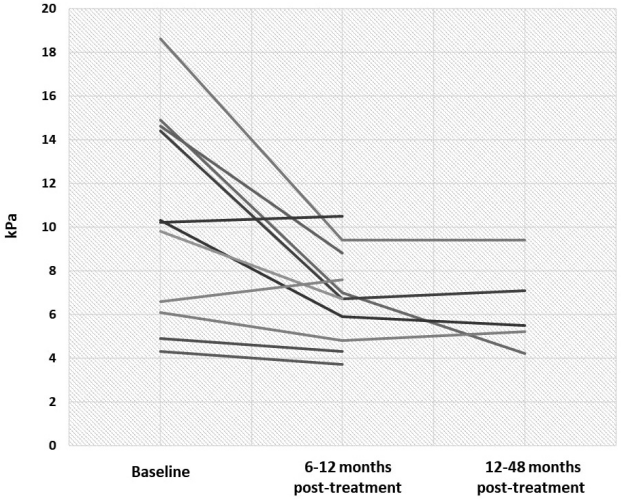

Figure 4. Liver stiffness measurements in patients (i) before the treatment with direct-acting antiviral agents, (ii) during the first year of follow-up, (iii) during the following years of monitoring.

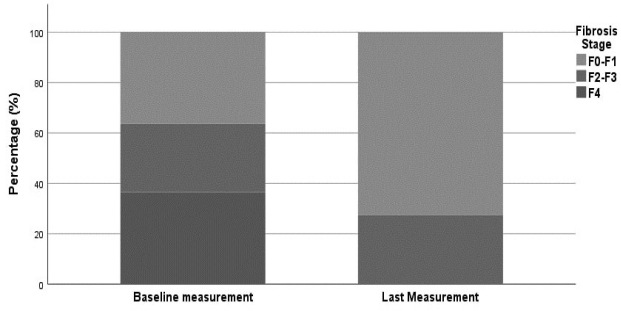

Figure 5. Classification of patients in groups corresponding to different stages of liver fibrosis in accordance with predefined transient elastography cut-off values. In the first column patients are categorized before the administration of direct-acting antivirals, while in the second column patients are categorized based on their most recent post-treatment liver stiffness measurement.

48 months. Hence, the continuing improvement of LSMs was appraised, allowing us to consolidate the assumption of liver fibrosis regression in patients treated with DAAs.

Liver stiffness change has been investigated in different categories of patients undergoing treatment with novel antivirals [27-38]. There is solid evidence that achieving SVR is related with decreased LSMs in accordance to our findings. More accentuated decline has been described in individuals with advanced liver disease [27,31-34,39]. In line with this, as portrayed in figure 4, our patients with baseline TE measurement equivalent to cirrhosis (>12 kPa) demonstrated improved stage of fibrosis in post-treatment LSM. Nevertheless, current data suggest that cirrhosis does not necessarily resolves in patients attaining SVR and might persist in a rate as high as 60%, potentially aggravated by the coexistent iron overload [38,40].

TE is a simple, noninvasive technique with satisfactory inter- and intra-observer reproducibility and has acquired an established role in the assessment of liver fibrosis in CHC by measuring hepatic stiffness [23,41]. D'Ambrosio et al. underlined that TE, although in post-eradication patients has lower sensitivity and, thus, lacks the ability to reliably exclude advanced liver disease, still remains a specific tool with high confirmatory strength in diagnosing cirrhosis. This might be attributable to the fact that, while cirrhosis is characterized by a shift from lobular to nodular architecture followed by annular fibrosis, in some cases nodular organization with trivial fibrous tissue is observed in post-SVR biopsies (bona fide cirrhosis) [40]. Obviously, TE retains its place as a reliable method for monitoring, versus consecutive invasive liver biopsies, which are plagued by sampling error and procedural risk of pain and hemorrhage. One basic factor for unreliable TE examination is obesity and particularly BMI >28 kg/m2. This explains the absence of invalid measurements in our study taking into consideration that our patients had a median BMI of 23 kg/m2 (IQR: 22-25) [42].

Whether lower LSMs mirror a regression of liver fibrosis remains controversial. It has been reported that the reduction of TE value correlates significantly with pre-treatment ALT level, a marker of necro-inflammatory hepatic activity [29,33,43]. In addition, a steeper decline of LSMs is witnessed during treatment rather than during the post-SVR period [29,38,39]. Hence, it has been supported that the observed improvement is mainly driven by suppression of liver inflammation due to viral eradication, rather than reversal of fibrotic histopathology. On the contrary, Chan et al. reported significant LSM decline between EOT and 12 months after, suggesting a combination of improvement in liver fibrosis and continued resolution of inflammation [31]. Moreover, studies comparing paired biopsies before and 6 months after IFN-based treatment indicate that a significant proportion (30-56%) of responders presented improved liver parenchyma histopathology [44,45]. Therefore, regression of fibrosis is possible as early as 6 months after achieving SVR. Our analysis was based on examinations that took place at least 6 months after the EOT and, possibly, depicts a degree of restored liver architecture without overlooking the parallel effect of the deescalated viremia-induced inflammation. However, patients with advanced liver disease in pre-treatment evaluation should be under close surveillance during follow-up because reduced TE values might be overestimated and not necessarily portray sufficient recovery of hepatic damage [46].

Transfusion-dependent β-TM cases with underlying HCV infection represent a challenging patient group for clinicians. Particularly, CHC and high liver iron concentration due to transfusions are two separate but co-existing risk factors for developing advanced fibrosis and, eventually, cirrhosis. The era of DAAs was accompanied with impressive rates of viral clearance even in populations with β-TM. Indeed, the highly effective treatment with DAAs in our patients (SVR=100%) was previously published as part of a large-scale Greek multicenter study [16]. According to the European Association for the Study of Liver (EASL) the IFN-free, ribavirin-free anti-HCV regimens for patients with hemoglobinopathies are recommended to be similar to standard treatment [23]. Besides, close monitoring is indicated after HCV eradication, due to residual danger of developing HCC [47]. There is a growing consensus that all patients with advanced fibrosis, namely F3 or F4 fibrosis before HCV treatment, should continue to be screened twice a year for HCC with a low-risk, noninvasive method such as ultrasound [47,48]. In a large retrospective study including 29,033 patients treated with DAAs, Ioannou et al. have reported that, except from cirrhotics, patients without cirrhosis but with FIB-4 scores ≥3.25 have a high enough risk to merit HCC surveillance, especially if FIB-4 remains ≥3.25 post-SVR [49]. This is crucial in β-TM patients, where underlying liver siderosis plays a pivotal role in fibrogenesis and consists a per se risk factor for end stage liver disease and HCC. In a recent panhellenic survey of neoplastic diseases, occurring among patients

with β-TM and other hemoglobinopathies, HCC was the most common cancer and was mainly attributed to the coexistent CHC infection [50]. Moreover, as reported by Triantos et al. poor adherence to chelation treatment, instead of antiviral therapy, is a predictor of worse prognosis in β-TM with CHC [10]. Therefore, implementation of regular monitoring and strict adherence to chelation treatment should be prioritized even after achieving SVR.

We acknowledge certain limitations of the current study. Firstly, the relatively small sample size reduces its statistical power and does not allow us to test specific parameters, such as cirrhosis, which might influence LSM improvement. However, β-TM constitute a small group between patients with CHC, implicating a demanding recruitment process. Furthermore, patients did not undergo sequential liver biopsies, which remain the benchmark of assessing liver fibrosis, in order to confirm histological alterations at time of LSMs. Nevertheless, the conduction of repeated post-treatment TE examinations during a long-term follow-up lessened the confounding effect of rapid regression of viremia-associated inflammation and confirmed the ongoing improvement of liver fibrosis.

In conclusion, the present study illustrates that treatment with DAAs in patients with β-TM is associated with significant improvement of TE values in line with current knowledge concerning other patient groups with CHC. We assume that this improvement, to a certain extent, accounts for a regression of hepatic parenchyma fibrosis without underestimating the parallel impact of the resolved inflammatory activity. Although reversal of cirrhosis can be hypothesized under circumstances, TE alone lacks the strength to confirm it. Patients with β-TM should be closely monitored after HCV eradication, especially those with advanced liver disease, since residual liver damage leading to the development of eventual hepatic complications is not yet fully elucidated. Longer follow-up period, larger cohort of patients and assessment of liver histology are some of the characteristics of additional studies that are essential in order to comprehensively interpret the long-term impact of novel antiviral therapy on patients with β-TM major.

Conflict of interest disclosure: *None to declare.*

Declaration of funding sources: *None to declare.*

Author contributions: *C.T., A.S. were responsible for study conception and design; E.P.T., M.C., V.L., S.K., P.K., I.A., E.V., K.K., V.L., K.Z., E.T. were responsible for analysis and interpretation of the data; E.P.T. was responsible for drafting the article; C.T., A.K., K.T., A.S. were responsible for critical revision of the article for important intellectual content. All authors read and approved the final manuscript.*

REFERENCES

1. Cao A, Galanello R. Beta-thalassemia. Genet Med 2010; 12:61-76.
2. Gardenghi S, Marongiu M, Ramos P, Guy E, Breda L, Chadburn A, et al. Ineffective erythropoiesis in β-thalassemia is characterized by increased iron absorption mediated by down-regulation of hepcidin and up-regulation of ferroportin. Blood 2007; 109:5027-35.
3. Kohgo Y, Ikuta K, Ohtake T, Torimoto Y, Kato J. Body iron metabolism and pathophysiology of iron overload. Int J Hematol 2008; 88:7-15.
4. Maurer H, Lloyd-Still J, Ingrisano C, Gonzalez-Crussi F, Honig A. Prospective Evaluation of Iron Chelation Therapy in Children With Severe β-Thalassemia. Am J Dis Child 1988; 142:287-92.
5. Jafri SM, Gordon SC. Epidemiology of Hepatitis C. Clin Liver Dis (Hoboken) 2018; 12:140-2.
6. Di Marco V, Capra M, Angelucci E, Borgna-Pignatti C, Telfer P, Harmatz P, et al. Management of chronic viral hepatitis in patients with thalassemia: recommendations from an international panel. Blood 2010; 116:2875-83.
7. Behzadifar M, Gorji H, Bragazzi N. The prevalence of hepatitis C virus infection in thalassemia patients in Iran from 2000 to 2017: a systematic review and meta-analysis. Arch Virol 2018; 163:1131-40.
8. Triantos C, Kourakli A, Kalafateli M, Giannakopoulou D, Koukias N, Thomopoulos K, et al. Hepatitis C in patients with β-thalassemia major. A single-centre experience. Ann Hematol 2013; 92:739-46.
9. Di Marco V, Capra M, Gagliardotto F, Borsellino Z, Cabibi D, Barbaria F, et al. Liver disease in chelated transfusion-dependent thalassemics: the role of iron overload and chronic hepatitis C. Haematologica 2008; 93:1243-6.
10. Harmatz P, Jonas M, Kwiatkowski J, Wright E, Fischer R, Vichinsky E, et al. Safety and efficacy of pegylated interferon -2a and ribavirin for the treatment of hepatitis C in patients with thalassemia. Haematologica 2008; 93:1247-51.
11. Paschos P, Vlachaki E, Pasvanti C, Sinakos E, Kalpaka A, Klonizakis P, et al. Safety and Efficacy of Combination Therapy with Pegylated Interferon Alpha-2a and Ribavirin in Treating Patients with Chronic Hepatitis C and Beta-Thalassaemia Major: A Greek Single-Center Experience. Acta Haematol 2011; 126:231-3.
12. Inati A, Taher A, Ghorra S, Koussa S, Taha M, Aoun E, et al. Efficacy and tolerability of peginterferon alpha-2a with or without ribavirin in thalassaemia major patients with chronic hepatitis C virus infection. Br J Haematol 2005; 130:644-6.

13. Kalafateli M, Kourakli A, Gatselis N, Lambropoulou P, Thomopoulos K, Tsamandas A, et al. Efficacy of Interferon A-2b Monotherapy in B-Thalassemics with Chronic Hepatitis C. J Gastrointestin Liver Dis 2015; 24:189-96.
14. Alavian S, Tabatabaei S. Treatment of chronic hepatitis C in polytransfused thalassaemic patients: a meta-analysis. J Viral Hepat 2010; 17:236-44.
15. Franceschi LD, Fattovich G, Turrini F, Ayi K, Brugnara C, Manzato F, et al. Hemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: Role of membrane oxidative damage. Hepatology 2000; 31:997-1004.
16. Sinakos E, Kountouras D, Koskinas J, Zachou K, Karatapanis S, Triantos C, et al. Treatment of chronic hepatitis C with direct-acting antivirals in patients with β-thalassaemia major and advanced liver disease. Br J Haematol 2017; 178:130-6.
17. Ponti ML, Comitini F, Murgia D, Ganga R, Canu R, Dessì C, et al. Impact of the direct-acting antiviral agents (DAAs) on chronic hepatitis C in Sardinian patients with transfusion-dependent Thalassemia major. Dig Liver Dis 2019; 51:561-7.
18. Marco VD, Bronte F, Cabibi D, Calvaruso V, Alaimo G, Borsellino Z, et al. Noninvasive assessment of liver fibrosis in thalassaemia major patients by transient elastography (TE)- lack of interference by iron deposition. Br J Haematol 2010; 148:476-9.
19. Fraquelli M, Cassinerio E, Roghi A, Rigamonti C, Casazza G, Colombo M, et al. Transient elastography in the assessment of liver fibrosis in adult thalassemia patients. Am J Hematol 2010; 85:564-8.
20. Poustchi H, Eslami M, Ostovaneh MR, Modabbernia A, Saeedian FS, Taslimi S, et al. Transient elastography in hepatitis C virus-infected patients with beta-thalassemia for assessment of fibrosis. Hepatol Res 2013; 43:1276-83.
21. Friedrich–Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al. Performance of Transient Elastography for the Staging of Liver Fibrosis: A Meta-Analysis. Gastroenterology 2008; 134:960-74.
22. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol 2015; 63:199-236.
23. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol 2018; 69:461-511.
24. Wood JC, Enriquez C, Ghugre N, Tyzka JM, Carson S, Nelson MD, et al. MRI R2 and R2* mapping accurately estimates hepatic iron concentration in transfusion-dependent thalassemia and sickle cell disease patients. Blood 2005;106: 1460-5.
25. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015; 63:237-64.
26. Papatheodoridis G, Germanidis G, Dalekos G. Treatment recommendations for patients with hepatitis C virus infection [Online, 10 Oct 2020]. Available from: https://www.eemh.gr/images/files/keelpno-hep c recommendations 12-2015.pdf.
27. Ogasawara N, Kobayashi M, Akuta N, Kominami Y, Fujiyama S, Kawamura Y, et al. Serial changes in liver stiffness and controlled attenuation parameter following direct-acting antiviral therapy against hepatitis C virus genotype 1b. J Med Virol 2017; 90:313-9.
28. Bachofner JA, Valli PV, Kröger A, Bergamin I, Künzler P, Baserga A et al. Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. Liver Int 2016;37: 369-76.
29. Pons M, Santos B, Simón-Talero M, Ventura-Cots M, Riveiro-Barciela M, Esteban R, et al. Rapid liver and spleen stiffness improvement in compensated advanced chronic liver disease patients treated with oral antivirals. Therap Adv Gastroenterol 2017;10:619-29.
30. Dolmazashvili E, Abutidze A, Chkhartishvili N, Karchava M, Sharvadze L, Tsertsvadze T. Regression of liver fibrosis over a 24-week period after completing direct-acting antiviral therapy in patients with chronic hepatitis C receiving care within the national hepatitis C elimination program in Georgia. Eur J Gastroenterol Hepatol 2017;29:1223-30.
31. Chan J, Gogela N, Zheng H, Lammert S, Ajayi T, Fricker Z, et al. Direct-Acting Antiviral Therapy for Chronic HCV Infection Results in Liver Stiffness Regression Over 12 Months Post-treatment. Dig Dis Sci 2017;63:486-92.
32. Fernandes FF, Piedade J, Guimaraes L, Nunes EP, Chaves U, Goldenzon RV, et al. Effectiveness of direct-acting agents for hepatitis C and liver stiffness changing after sustained virological response. J Gastroenterol Hepatol 2019;34: 2187-95.
33. Rout G, Nayak B, Patel AH, Gunjan D, Singh V, Kedia S, et al. Therapy with Oral Directly Acting Agents in Hepatitis C Infection Is Associated with Reduction in Fibrosis and Increase in Hepatic Steatosis on Transient Elastography. J Clin Exp Hepatol 2019;9:207-14.
34. Attia D, Deterding K, Cornberg J, Gebel MJ, Cornberg M, Manns MP, et al. Different kinetics of liver stiffness using shear wave elastography in patients with chronic hepatitis C infection treated with interferon-free regimens. Eur J Gastroenterol Hepatol 2019;31:67-74.
35. Tag-Adeen M, Sabra A, Akazawa Y, Ohnita K, Nakao K. Impact of hepatitis C virus genotype-4 eradication following direct acting antivirals on liver stiffness measurement. Hepat Med 2017;9:45-53.
36. Tada T, Kumada T, Toyoda H, Sone Y, Takeshima K, Ogawa S, et al. Viral eradication reduces both liver stiffness and steatosis in patients with chronic hepatitis C virus infection who received direct-acting anti-viral therapy. Aliment Pharmacol Ther 2018;47:1012-22.
37. Malin J, Boesecke C, Schwarze-Zander C, Wasmuth J, Schlabe S, Trebicka J, et al. Liver stiffness regression after successful Hepatitis C treatment is independent of HIV coinfection. HIV Med 2019;20:230-6.
38. Chekuri S, Nickerson J, Bichoupan K, Sefcik R, Doobay K, Chang S, et al. Liver Stiffness Decreases Rapidly in Response to Successful Hepatitis C Treatment and Then Plateaus. Plos One 2016;11:e0159413.
39. Singh S, Facciorusso A, Loomba R, Falck-Ytter YT. Magnitude

and Kinetics of Decrease in Liver Stiffness After Antiviral Therapy in Patients With Chronic Hepatitis C: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2018; 16:27-38.
40. Tachi Y, Hirai T, Kojima Y, Ishizu Y, Honda T, Kuzuya T, et al. Liver stiffness reduction correlates with histological characteristics of hepatitis C patients with sustained virological response. Liver Int 2017;38:59-67.
41. Fraquelli M, Rigamonti C, Casazza G, Conte D, Donato M, Ronchi G, et al. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. Gut 2007; 56:968-73.
42. Wong GL, Wong VW, Chim AM, Yiu KK, Chu SH, Li MK, et al. Factors associated with unreliable liver stiffness measurement and its failure with transient elastography in the Chinese population. J Gastroenterol Hepatol 2011;26:300-5.
43. D'Ambrosio R, Aghemo A, Fraquelli M, Rumi MG, Donato MF, Paradis V, et al. The diagnostic accuracy of Fibroscan® for cirrhosis is influenced by liver morphometry in HCV patients with a sustained virological response. J Hepatol 2013;59:251-6.
44. Cammà C, Bona DD, Schepis F, Heathcote EJ, Zeuzem S, Pockros PJ, et al. Effect of peginterferon alfa-2a on liver histology in chronic hepatitis C: A meta-analysis of individual patient data. J Hepatol 2004;39:333-42.
45. Maylin S, Martinot–Peignoux M, Moucari R, Boyer N, Ripault MP, Cazals–Hatem D, et al. Eradication of Hepatitis C Virus in Patients Successfully Treated for Chronic Hepatitis C. Gastroenterology 2008;135:821-9.
46. Pockros P, Crissien-Martinez A, Frenette C, Skillin C, Bao F, Du E, et al. Degree of liver fibrosis regression predicted by transient elastography after cure of chronic hepatitis C with direct acting antivirals is overestimated but confirmed by liver biopsy. J Hepatol 2017; 66(Suppl 1): S108.
47. Khan R, Velpari S, Koppe S. All Patients With Advanced Fibrosis Should Continue to Be Screened for Hepatocellular Carcinoma After Sustained Virological Response of Hepatitis C Virus. Clin Liver Dis 2018;12:137-9.
48. Roche B, Coilly A, Duclos-Vallee JC, Samuel D. The impact of treatment of hepatitis C with DAAs on the occurrence of HCC. Liver Int. 2018; 38(Suppl 1):139-45.
49. Ioannou G, Beste L, Green P, Singal A, Tapper E, Waljee A, et al. Increased Risk for Hepatocellular Carcinoma Persists Up to 10 Years After HCV Eradication in Patients With Baseline Cirrhosis or High FIB-4 Scores. Gastroenterology. 2019;157(5):1264-78.e4.
50. Kourakli A, Diamantidis M, Skafidas M-E, Delicou S, Pantelidou D, Fragodimitri C, et al. Hepatitis C Virus Infection, but Not Hepatic Iron Overload Is the Dominant Risk Factor for the Manifestation of Hepatocellular Carcinoma Among Greek Thalassemic Patients. Blood 2018;132(Suppl 1): 2347.

Corresponding author:

Christos Triantos
Division of Gastroenterology, Department of Internal Medicine, University Hospital of Patras, Patras, Greece
D. Stamatopoulou 4, Rio 26504, Greece
E-mail: chtriantos@hotmail.com

ORIGINAL RESEARCH ARTICLE ACHAIKI IATRIKI | 2021; 40(2):96–106

An investigation of dentists' knowledge, attitudes and practices towards infectious diseases in Greece

Karolina Akinosoglou[1], Panagiota Ntolou[2], Vasilina Dimakopoulou[3], George Moutousis[4], Charalambos Gogos[1]

Abstract

Background: A difficulty of patients with infectious diseases to access dental care is still identified worldwide. We aimed to explore dentists' knowledge and attitude towards infectious diseases in Greece, where no data is currently available.

Methods: We performed a survey among dentists of a wide region of Southwestern Greece, via electronic distribution of anonymous questionnaires, within a period of three months.

Results: Of 199 questionnaires that were delivered to dentists, 60 (30%) were finally completed and returned. The majority of participants were males (53.3%) and below 45 years of age (65%). Almost all had studied dentistry in Greece (90%) and practiced dentistry in the private sector (96.7%). Most practised in large urban centres (78.3%), and treated between 5-10 patients in a typical working shift (75%), assisted by other personnel (61.7%). Knowledge upon ID was found to be poor; nonetheless, 56.7% showed confidence of appropriate action post occupational exposure. The majority (81.7%) treat any patient as potentially contagious, however, only 51.7% were willing to treat a patient with ID upon disclosure. Occupational exposure has been common (71.7%), without any major long-term physical or psychological consequences (95.5%) following immediate advice from an ID specialist (32.6%). No correlation was found between any socio-demographic characteristic and knowledge on ID or current practice, although, a trend towards reluctancy (r=-0.247) to treat patients with ID (p=0.05) was detected.

Conclusion: Although, dentists' compliance with universal precaution measures is satisfactory, knowledge on infectious diseases is poor, potentially hampering access to care for these patients

Key words: *Infectious diseases; occupational exposure; dentists; HIV; access to care*

[1]Department of Internal Medicine and Infectious Diseases, University Hospital of Patras, Patras, Greece
[2]Medical School University of Patras, Patras, Greece
[3]Department of Internal Medicine, University of Patras, Patras, Greece
[4]Department of Oral and Maxillofacial Surgery, University Hospital of Patras, Patras, Greece

Received: 31 Oct 2020; Accepted: 25 Nov 2020

INTRODUCTION

Dental care is not free from infectious disease transmission risk [1, 2].Cross-infection during dental practice can occur through infected blood, air droplets, saliva, and instruments contaminated with secretions between patients and healthcare workers [3]. Dental care providers have an ethical and legal obligation to treat patients suffering from infectious diseases [4], in line with respective dental association recommendations worldwide

[5]. Nonetheless, recent observations in Europe [6, 7], suggest lack of preparedness against infectious diseases [8] and persistent undetected discomfort of dental practitioners to treat patients with infectious disease, thus compromising their care [9-11].

Most reports concerning dentists' knowledge and practice towards infectious diseases, patients originate from the era before 2000s, following which, immunization practices and therapeutic developments significantly changed our approach. At the same time, incidents of reported occupational exposure have been rare [12-14]. No respective data has ever been available in Greece as for dentist's attitude and practice towards patients with infectious diseases. Moreover, infection-related occupational diseases are rarely reported among professionals in Greece, similar to other countries [15, 16]. Our study set out to investigate dentists' perspectives on infectious diseases and explore their knowledge and practices towards respective patients.

METHODS

Study population and methodology

We performed a cross-sectional observational survey among dental practitioners-members of the largest Greek Dental Association of Southwestern Greece. To this purpose, an anonymous questionnaire was developed by a dentist, a hygienist, and 2 specialists in infectious diseases and was electronically distributed and reminded twice by phone and e-mail, within the respective dental association. It was previously approved by the respective bioethics research committee Π7Θ9/16-10-2018, and tested for validity by two independent users. The questionnaire was accompanied by an informative letter, describing the purpose of the research, the modalities to fill in the questionnaire and the anonymous procedure of the study. About 10-15 min were needed to fill in the questionnaire. A 3-month period was fixed for data collection, at the end of which the study was considered completed.

Structure of the questionnaire

The questionnaire was composed of three major sections, containing 35 multiple choice questions (Table 1). The aim of the first section was to investigate personal demographic and epidemiological data (i.e., gender; age; area where the professional activity is mainly performed; university degree in dentistry; years in practice; public or private practice). The second section was aimed at investigating the scientific knowledge of hygienists on infectious diseases and associated issues. For each knowledge question, a score of "1" was given for the correct answer and "0" for the incorrect or unknown answers. A total knowledge score was calculated, and it ranged from 0 to 7. Finally, the aim of the third section was to ascertain the precautions normally taken during the practice and the cleaning and/or sterilization procedure, to avoid the spread of infection between dental healthcare workers and patients and among patients, explore relative exposure experience, as well as, investigate the relationship between dental practitioners and infectious patients, to identify the presence of discriminatory behaviour and understand motives.

Statistical analysis

Differences between group proportions were assessed using chi-square test or Fisher's exact test. Two-tailed tests of significance at the $P < 0.05$ level were used to determine statistical significance and Pearson test to explore correlations between knowledge score and socio-demographic parameters and attitudes. Statistical analysis was performed using SPSS (v.22).

RESULTS

In total, 199 questionnaires were e-mailed, followed by respective reminders. Of the 199 questionnaires that were delivered to dentists 30% (60) of them were completed within the prefixed time period. It is important to note that all participants answered all questions as in Table 1, except for questions 25-29 where the denominator was respectively adjusted upon those that replied positively in question 24 (43).

The majority of participants were males (53.3%) and below 45 years of age (65%). Almost all had studied dentistry in Greece (90%) and practiced dentistry in the private sector (96.7%). A big proportion practiced in large urban centres (78.3%), and treated between 5-10 patient in a typical 6-hour working shift (75%), usually assisted by other personnel (61.7%).

Knowledge upon transmittable diseases remains poor to moderate as suggested by correct answers ranging from 0-75% per question. Only 1 dentist scored 4 correct answers (1.7%), 5 provided 3 correct answers (8.3%), while 53 scored 2 or less correct answers (90%) in questions examining knowledge on infectious diseases. Despite that, 56,7% shows confidence and supports good knowledge of appropriate action post occupational exposure.

Even though, 81.7% of practitioners treat any patient

Table 1. *Questionnaire on dentist's knowledge, attitude and practice towards infectious diseases: Dentist Responses.*

	Sample Size N=60(%)
PART A. SOCIO-DEMOGRAPHIC INFORMATION	
Question 1. Gender	
Men	32 (53.3)
Female	28 (46.6)
Question 2. Age (in years)	
25-35	21 (35)
36-45	18 (30)
46-55	15 (25)
56-67	6 (10)
Question 3. How many years in practice?	
Up to 5 years	18 (30)
5-10 years	6 (10)
10-15 years	9 (15)
Over 15 years	27 (45)
Question 4. You studied dentistry	
In Greece	54 (90)
Abroad	6 (10)
Question 5. You work in	
Public practice	2 (3.3)
Private practice	58 (96.7)
Question 6. What amount of population does the area you work in have?	
Up to 10.000	2 (3.3)
10-50.000	11 (18.3)
50-100.000	9 (15)
Over 100.000	38 (63.3)
Question 7. How many patients do you normally examine in a typical 6-hour shift?	
5-10	45 (75)
10-20	13 (21.6)
20-30	1 (1.7)
>30	1 (1.7)
Question 8: Do you have a medical or paramedical assistant at your service?	
Yes	37 (61.7)
No	23 (38.3)

Table 1. *Questionnaire on dentist's knowledge, attitude and practice towards infectious diseases: Dentist Responses (continued).*

	Sample Size N=60(%)
PART B. PRESENT KNOWLEDGE	
Question 9. Which of the following do you believe are blood or air-borne transmittable diseases?	
HBV	51
HCV	43
HPV	29
Measles	32
Influenza	56
HIV	58
Tuberculosis	54
Correct response	11 (18.3)
Question 10: Against which of the following transmittable disease, there is a vaccine available?	
HBV	50
HCV	18
HPV	44
Measles	52
Influenza	56
HIV	3
Tuberculosis	51
Correct response	18 (30)
Question 11. For which of the following do you think post-exposure prophylaxis is available?	
HBV	26
HCV	21
HPV	6
Measles	10
Influenza	17
HIV	30
Tuberculosis	34
Correct response	0 (0)
Question 12. Are you familiar with actions to take in the case of occupational exposure?	
Yes, I am confident what actions to take	34
No, I will immediately ask for advice	26
Correct response	34 (56.7)
Question 13. For which of the following do you think we should regularly test for antibody existence / titres?	
HBV	53
HCV	28
HPV	7

Table 1. *Questionnaire on dentist's knowledge, attitude and practice towards infectious diseases: Dentist Responses (continued).*

	Sample Size N=60(%)
Measles	4
Influenza	13
HIV	16
Tuberculosis	10
Correct response	0 (0)
Question 14. The risk of blood transmission after accidental needlestick injury is higher for	
HAV	7
HBV	45
HCV	25
HIV	20
Correct response	45 (75)
Question 15. Which of the following pathogens do you think survives more than a couple of minutes on surfaces?	
Influenza virus	12
M.tuberculosis	11
HBV	33
HCV	26
HIV	16
Measles	3
Correct response	3 (5)
PART C: ATTITUDES AND EXPERIENCE	
Question 16. Would you be willing to treat an HIV-positive patient or a patient with another transmittable disease?	
Yes	31 (51.7)
No	4 (6.7)
Depends on severity of disease	25 (41.6)
Question 17. Do you use protective measures and disinfectant solutions during your surgeries?	
Yes, in every patient	60 (100)
It depends upon known medical history	0 (0)
Question 18. What kind of protective measures do you usually use?	
Only Mask	0 (0)
Only Gloves	1 (1.7)
Only Protective gown	0 (0)
All of the above	59 (98.3)
Question 19. Do you cap your needle after every use?	
Yes	60 (100)
No	0 (0)

Table 1. *Questionnaire on dentist's knowledge, attitude and practice towards infectious diseases: Dentist Responses (continued).*

	Sample Size N=60(%)
Question 20. Do you wash your hands before and after each patient, despite of changing gloves?	
Yes	43 (71.7)
Not always	17 (28.3)
Question 21. Do you use protective membranes on your work area, as well as, the light handle?	
Yes, always	41 (68.3)
Yes, most of the times	12 (20)
Rarely	7 (11.7)
Question 22. Do you disinfect your work area after every patient?	
Yes, always	51 (85)
Yes, most of the times	8 (13.3)
Rarely	1 (1.7)
Question 23. What kind of decontamination measures do you use at your surgery?	
Dry - Heat	12 (20)
Steam	56 (93.4)
Unsaturated Chemical Vapor	1 (1.7)
Microwave / Ultrasonic Vibrations	1 (1.7)
Radiation	1 (1.7)
At least any two of the above	10 (16.7)
Question 24. Have you ever experienced an incident of occupational exposure at your surgery (e.g needlestick injury etc)?	
Yes, once	13 (21.7)
Yes, more than once	30 (50)
No	17 (28.3)
Question 25. In case of occupational exposure at your surgery, how many times did this occur during a period of one year?	
Once	36 (83.7)
Twice	5 (11.6)
More than twice	2 (7.7)
Question 26. In case of occupational exposure at your surgery, what did you do?	
Rinse with soap and water	35 (81.4)
Use of chlorhexidine solution	32 (74.4)
Ask an ID specialist for advice, receive post-exposure prophylaxis and follow-up with antibody titre measurements	14(32.6)
Ask a colleague dentist for any advice	6 (14)
Question 27. In case of occupational exposure did that finally have any physical consequences on you or your beloved?	
Yes	0 (0)
No, but I took some action	31(72.1)

Table 1. *Questionnaire on dentist's knowledge, attitude and practice towards infectious diseases: Dentist Responses (continued).*

	Sample Size N=60(%)
No, without taking any particular measures	12 (27.9)
Question 28. In case of occupational exposure did that finally have any psychological consequences on you or your beloved?	
Yes	2 (4.7)
Yes, but only until I found out I did not get infected	23 (53.5)
No, it happens all the time and represents an occupational risk after all	18 (42)
Question 29. Following an incident of exposure, did you modify anything in your everyday practice?	
Yes	21 (48.8)
No	22 (51.2)
Question 30. Do you have a standard operation procedure in place, in case of occupational exposure?	
Yes	27 (45)
No	33 (55)
Question 31. Do you follow the chemical disinfection procedure required to clean the water tank at the end of every day?	
Yes	27 (45)
No	17 (28.3)
At the end of every week	16 (26.7)
Question 32. Against which of the following have you been ever vaccinated?	
HAV	17 (28.3)
HBV	56 (93.3)
HCV	12 (20)
Tuberculosis	35 (58.5)
Influenza	34 (56.7)
Question 33. For which diseases do you regularly test for antibody titres?	
HAV	5 (8.3)
HBV	54 (90)
HCV	24 (40)
All three	8 (13.3)
Question 34. If so, how often do you check for antibodies?	
Every 6 months	1 (1.7)
Annually	10 (16.7)
Every 2- 3 years	22 (36.7)
Rarely	27 (45)
Question 35. Do you treat any patient as potentially contagious?	
Yes, always	49 (81.7)
No, this would make my work more difficult	4 (6.7)
It depends, I always ask the patient and check his/her prescription log	7 (11.7)

as potentially contagious and take necessary precautions in terms of protective and disinfection/decontamination measures, only 51.7% would be willing to treat a patient with communicable disease upon disclosure. Occupational exposure has been common in 71.7% of cases, half of which more than once, without any major long-term physical or psychological consequences (95.5%) following immediate advice from an infectious diseases' specialist (32.6%). Despite exposure, only half modified their every practice or set a standard operating procedure in place, following incident. Immunization against HBV is almost universal among dentists (93.3%) who check for their serostatus (90%), however, yearly vaccination against influenza remains poor (56.7%), even though higher than average among other healthcare practitioners.

No correlation was found between any socio-demographic characteristic and knowledge on infectious diseases or current attitudes and practice, although a mild trend towards reluctancy (r=-0.247) to treat patients with communicable diseases despite good knowledge was observed (p=0.057).

DISCUSSION

This has been the first study to explore dentists' knowledge, attitude and practice towards infectious diseases in Greece. Our pilot survey highlights efficient protective and decontamination practices, that - do not justify by any means, but - seem to counter – balance poor knowledge of dental practitioners of infectious diseases and result in few, or no incidents of cross-infection, as per available national data. Nonetheless, reluctancy to treat this population remains high, and if occupational exposure takes place, validity of adopted individual practices is controversial. Our study represents a pilot survey and bears limitations further discussed, nonetheless, it significantly reflects dentists' attitudes towards infectious diseases, in Greece; a population never examined before, while global data remain scarce and relatively old.

Poor or blurry knowledge of infectious diseases by dentists is a common observation in many studies and various settings [17-25]. In our study, only 10% reached 43% (3 points) of maximum knowledge score. Knowledge was not associated with age, neither years in practice as one would expect and observed in other studies [26]. Nonetheless, most dentists (56.7%) confidently replied, that are well aware of procedures to be followed post-exposure, similar to other studies, where false perception of adequacy of scientific knowledge appears disproportionate to findings following direct questions [27]. These observations can be worrying, since any further educational effort can be hampered, and underlying discomfort or even malpractice go undetected. Encouragingly, respective findings of poor knowledge in Croatia and Romania did highlight the need and wish on behalf of dental practitioners to acquire more in-depth education on infectious diseases [28, 29]

In our study, we found no correlation between dentist knowledge and behaviour towards infectious diseases. Previous studies in both the UK [30, 31] and US [32-34] have also examined dentists' knowledge, attitudes and behaviours in order to assess which factors may be influential in affecting dentists' willingness to treat patients with infectious disease like HIV/AIDS. The proportion of dentists that would treat a patient with HIV, HBV or HCV without hesitation ranges from 20-50% similar to our findings [31]. It seems, that even though, admittance of right to equal dental care for these patients does exist, most dentists are reluctant to be involved themselves to it and refer patients to someone else [35, 36]. It has been suggested that dentists' behaviour towards patients with infectious diseases is inversely related to their current knowledge [5, 9, 37, 38] in terms of willingness to treat, but also sense of ethical responsibility [31]. Age, type and years of practice, as well as, type of procedure to be performed, have also been reported to be implicated in the decision to treat this population [26, 27, 31, 39, 40], however, this was not detected in our study.

Compliance with protective and good hygiene measures in this study was high, similar or even higher to previous reports [31, 41]. Interestingly however, previous authors have reported the belief that, protective measures may not be adequate in all cases [42] and infectious patients should be treated in a specially adapted dental office (64.2%) [26, 43]. Only one study did not find changes in the behaviour of dentists, despite their awareness that the patient was infected [44], in line with the notion that, every patient should be treated as potentially infected [23, 26]. The majority (71%) complied with washing hands and other infection control measures, [23] showing improvement to previously described practices [45-47]. Immunization against HBV among dentists was high according to international guidelines and other reports in other countries [46, 48-52], although in developing regions only 39.3% completed all three doses [53]. Even though,

the majority checks for their serostatus in our survey, use of repeated performance remains controversial following initial seroconversion [54].

Occupational exposure has been common in 71.7% of cases, a percentage significantly higher than reports from South Wales (56%) [55], Netherlands (32%) [52], Italy (>40%) [56] or Jordan; in these studies the authors further looked into accidents among dental staff (27%) and nurses (35%) [46]. In our study, dentists did ask for advice from an expert following an incident at a percentage of 32.6%, in accordance to a retrospective report in Netherlands [52]. Worryingly though, no change in every day practice was noticed following accidental exposure, while even though our survey was not designed to detect for incident reporting, it appears that occupational exposure in dental settings can go undetected [57].

Limitations

Our study bears significant limitations including a convenience sample, a low response rate and a fixed time during which it was carried out, in the context of a pilot survey that can be further improved, for safer conclusions to be drawn. Electronic distribution, may limit responses to professionals of younger age and urban centres that are familiar with worldwide web, whereas personal on site contact could further enhance response and overcome such obstacles [58]. Our study also came from a specific geographical part of Greece, hence, results cannot be extrapolated to other areas that different socio-demographic conditions may apply, even though, our centre remains a reference centre of infectious diseases for Southwestern Greece.

CONCLUSION

Following this pilot survey, the design of a larger nationwide study to capture knowledge and attitudes of dentists towards infectious diseases is pivotal. A careful description and a full understanding of the numerous delicate interpersonal problems arising between dentists and patients with infectious diseases are both essential to avoid discrimination and offer patients the best possible dental health care.

ACKNOWLEDGEMENTS

The authors would like to thank members of Dental Association of Achaia.

Conflict of interest disclosure: *None to declare.*

Declaration of funding sources: *None to declare.*

Author contributions: *All authors have made substantial contributions to conception and design of the study and have given final approval of the version to be published. PN and GM have been involved in data collection. KA, VD and CG have been involved in data interpretation and data analysis. KA drafted the manuscript, and CG critically corrected it.*

REFERENCES

1. McCarthy GM, Britton JE. A survey of final-year dental, medical and nursing students: Occupational injuries and infection control. J Can Dent Assoc. 2000;66(10):561.
2. Laheij AM, Kistler JO, Belibasakis GN, Valimaa H, de Soet JJ, European Oral Microbiology W. Healthcare-associated viral and bacterial infections in dentistry. J Oral Microbiol. 2012;4.
3. Baseer MA, Rahman G, Yassin MA. Infection control practices in dental school: A patient perspective from Saudi Arabia. Dent Res J (Isfahan). 2013;10(1):25-30.
4. Shaw D. Dentistry and the ethics of infection. J Med Ethics. 2008 Mar;34(3):184-7.
5. Quartey JB. Impact of HIV on the practice of dentistry in Houston, Texas. Tex Dent J. 1998;115(11):45-56.
6. Giuliani M, Lajolo C, Rezza G, Arici C, Babudieri S, Grima P, et al. Dental care and HIV-infected individuals: Are they equally treated? Community Dent Oral Epidemiol. 2005;33(6):447-53.
7. Giuliani M, Lajolo C, Sartorio A, Lacaita MG, Capodiferro S, Cauda R, et al. Attitudes and practices of dentists treating patients infected with human immunodeficiency virus in the era of highly active antiretroviral therapy. Medical Science Monitor. 2009;15(6):PH49-PH56.
8. Ghai S. Are dental schools adequately preparing dental students to face outbreaks of infectious diseases such as COVID-19? J Dent Educ. 2020;84(6):631-3.
9. McCarthy GM, Koval JJ, MacDonald JK. Factors associated with refusal to treat HIV-infected patients: The results of a national survey of dentists in Canada. Am J Public Health. 1999;89(4):541-5.
10. Nostlinger C, Rojas Castro D, Platteau T, Dias S, Le Gall J. HIV-Related discrimination in European health care settings. AIDS Patient Care STDS. 2014;28(3):155-61.
11. Douay C, Toullier A, Benayoun S, Castro DR, Chauvin P. Refusal to provide health care to people with HIV in France. Lancet. 2016;387(10027):1508-9.
12. Cleveland JL, Gray SK, Harte JA, Robison VA, Moorman AC, Gooch BF. Transmission of blood-borne pathogens in US dental health care settings: 2016 update. J Am Dent Assoc. 2016;147(9):729-38.
13. Merte JL, Kroll CM, Collins AS, Melnick AL. An epidemiologic investigation of occupational transmission of Mycobacterium tuberculosis infection to dental health care personnel: infection prevention and control implications. J Am Dent

Assoc. 2014;145(5):464-71.
14. Ricci ML, Fontana S, Pinci F, Fiumana E, Pedna MF, Farolfi P, et al. Pneumonia associated with a dental unit waterline. Lancet. 2012;379(9816):684.
15. Alexopoulos CG, Rachiotis G, Valassi M, Drivas S, Behrakis P. Under-registration of occupational diseases: the Greek case. Occup Med (Lond). 2005;55(1):64-5.
16. Szeszenia-Dabrowska N, Wilczynska U. [Occurrence of occupational diseases in Poland, 2014]. Med Pr. 2016;67(3):327-35.
17. Kitaura H, Adachi N, Kobayashi K, Yamada T. Knowledge and attitudes of Japanese dental health care workers towards HIV-related disease. J Dent. 1997;25(3-4):279-83.
18. Gachigo JN, Naidoo S. HIV/AIDS: the knowledge, attitudes and behaviour of dentists in Nairobi, Kenya. SADJ. 2001;56(12):587-91.
19. Zhu H, Duan K, Lei Y, He H, Huang A. The intervention research on understanding of the AIDS prevention and occupational safety of the dentist in Kunming and west part of Yunnan. Zhonghua Kou Qiang Yi Xue Za Zhi. 2002;37(5):395-7.
20. Maupome G, Borges-Yanez SA, Diez-De-Bonilla FJ, Irigoyen-Camacho ME. Attitudes toward HIV-infected individuals and infection control practices among a group of dentists in Mexico City--a 1999 update of the 1992 survey. Am J Infect Control. 2002;30(1):8-14.
21. Chan R, Khoo L, Goh CL, Lam MS. A knowledge, attitudes, beliefs and practices (KABP) survey on HIV infection and AIDS among doctors and dental surgeons in Singapore. Ann Acad Med Singapore. 1997;26(5):581-7.
22. Khosravanifard B, Rakhshan V, Ghasemi M, Pakdel A, Baradaran-Eghbal S, Sheikholeslami R, et al. Tehran dentists' self-reported knowledge and attitudes towards HIV/AIDS and observed willingness to treat simulated HIV-positive patients. East Mediterr Health J. 2012;18(9):928-34.
23. Askarian M, Mirzaei K, Cookson B. Knowledge, attitudes, and practice of Iranian dentists with regard to HIV-related disease. Infect Control Hosp Epidemiol. 2007;28(1):83-7.
24. Shaghaghian S, Pardis S, Mansoori Z. Knowledge, attitude and practice of dentists towards prophylaxis after exposure to blood and body fluids. Int J Occup Environ Med. 2014;5(3):146-54.
25. Batool A, Ul Islam, M., Sherwani, K., Bano, K. and Aasim, M. Knowledge, Attitude and Practices of Dentists about Hepatitis B and C Infection in Lahore. Pak J Med Res. 2012;51(3):91-6.
26. Rostamzadeh M, Afkhamzadeh A, Afrooz S, Mohamadi K, Rasouli MA. Dentists' knowledge, attitudes and practices regarding Hepatitis B and C and HIV/AIDS in Sanandaj, Iran. BMC Oral Health. 2018;18(1):220.
27. Giuliani M, Tumbarello M, Marino M, Capodiferro S, Scivetti M, Rezza G, et al. Dental hygienists behaviour towards HIV-positive patients in highly active antiretroviral therapy era: a pilot survey. Int J Dent Hyg. 2011;9(3):204-10.
28. Brailo V, Pelivan I, Skaricic J, Vuletic M, Dulcic N, Cerjan-Letica G. Treating patients with HIV and Hepatitis B and C infections: Croatian dental students' knowledge, attitudes, and risk perceptions. J Dent Educ. 2011;75(8):1115-26.
29. Barlean L, Danila I, Saveanu I, Balcos C. Occupational health problems among dentists in Moldavian Region of Romania. Rev Med Chir Soc Med Nat Iasi. 2013;117(3):784-8.
30. Craven RC, O'Brien KD, Bennett EM. Impact on English dentists of the threat of HIV infection. Community Dent Oral Epidemiol. 1996;24(3):228-9.
31. Crossley ML. An investigation of dentists' knowledge, attitudes and practices towards HIV+ and patients with other blood-borne viruses in South Cheshire, UK. Br Dent J. 2004;196(12):749-54, quiz 80.
32. Gerbert B. AIDS and infection control in dental practice: dentists' attitudes, knowledge, and behavior. J Am Dent Assoc. 1987;114(3):311-4.
33. Kunzel C, Sadowsky D. Comparing dentists' attitudes and knowledge concerning AIDS: differences and similarities by locale. J J Am Dent Assoc. 1991;122(3):55-61.
34. Kunzel C, Sadowsky D. Assessing HIV-related attitudes and orientations of male and female general dentists. J Am Dent Assoc. 1995;126(7):862-71.
35. Gerbert B. The impact of AIDS on dental practice: update 1989. J Dent Educ. 1989;53(9):529-30.
36. Garus-Pakowska A, Gorajski M, Szatko F. Knowledge and Attitudes of Dentists with Respect to the Risks of Blood-Borne Pathogens-A Cross-Sectional Study in Poland. Int J Environ Res Public Health. 2017;14(1).
37. Seacat JD, Litt MD, Daniels AS. Dental students treating patients living with HIV/AIDS: the influence of attitudes and HIV knowledge. J Dent Educ. 2009;73(4):437-44.
38. Mubaraki MG, Alamir SA, Qohal MM, Alamir OH, Quadri MF. Relation between Knowledge, Attitude and Practice of Hepatitis B among Dental Undergraduates in the Kingdom of Saudi Arabia. J Contemp Dent Pract. 2019;20(12):1447-55.
39. Daniel SJ, Silberman SL, Bryant EM, Meydrech EF. Infection control knowledge, practice, and attitudes of Mississippi dental hygienists. J Dent Hyg. 1996;70(1):22-34.
40. Ebrahimi M, Ajami BM, Rezaeian AR. Longer Years of Practice and Higher Education Levels Promote Infection Control in Iranian Dental Practitioners. Iran Red Crescent Med J. 2012;14(7):422-9.
41. Burke FJ, Wilson NH, Cheung SW. Trends in glove use by dentists in England and Wales: 1989-1992. Int Dent J. 1994;44(3):195-201.
42. Hardie J. The attitudes and concerns of Canadian dental health care workers toward infection control and the treatment of AIDS patients. J Can Dent Assoc. 1992;58(2):131-8.
43. Scheutz F. Dental care of HIV-infected patients: attitudes and behavior among Danish dentists. Community Dent Oral Epidemiol. 1989;17(3):117-9.
44. Arenas MD, Sánchez-Payá J, Barril G, García-Valdecasas J, Gorriz JL, Soriano A, et al. A multicentric survey of the practice of hand hygiene in haemodialysis units: Factors affecting compliance. Nephrol Dial Transplant. 2005;20:1164-71.
45. Scully C, Porter SR, Epstein J. Compliance with infection control procedures in a dental hospital clinic. Br Dent J. 1992 Jul 11;173(1):20-3.
46. Qudeimat MA, Farrah, R. Y., & Owais, A. I. Infection control knowledge and practices among dentists and dental nurses

at a Jordanian university teaching center. Am J Infect Control 2006;34(4):218-22.
47. Dagher J, Sfeir C, Abdallah A, Majzoub Z. Infection Control Measures in Private Dental Clinics in Lebanon. Int J Dent. 2017;2017:5057248.
48. McCarthy GM, MacDonald JK. A comparison of infection control practices of different groups of oral specialists and general dental practitioners. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;85(1):47-54.
49. Resende VL, Abreu MH, Paiva SM, Teixeira R, Pordeus IA. Concerns regarding hepatitis B vaccination and post-vaccination test among Brazilian dentists. Virol J. 2010;7:154.
50. Nagao Y, Matsuoka H, Kawaguchi T, Ide T, Sata M. HBV and HCV infection in Japanese dental care workers. Int J Mol Med. 2008;21(6):791-9.
51. Di Giuseppe G, Nobile CG, Marinelli P, Angelillo IF. A survey of knowledge, attitudes, and behavior of Italian dentists toward immunization. Vaccine. 2007;25(9):1669-75.
52. van Wijk PT, Meiberg AE, Bruers JJ, Groenewold MH, van Raalten AL, Dam BA, et al. The risk of blood exposure incidents in dental practices in the Netherlands. Community Dent Oral Epidemiol. 2012;40(6):567-73.
53. Al-Hazmi AH. Knowledge, attitudes and practice of dentists concerning the occupational risks of hepatitis B virus in Al Jouf Province, Saudi Arabia. Niger J Clin Pract. 2015;18(2):276-81.
54. John M. Hepatitis B immunization and postimmunization serology. J Can Dent Assoc. 2000;66(10):551-2.
55. Stevenson AR, Higgins TJ. Infection control in general dental practice. Results of a postal survey of 600 registered dental practitioners in New South Wales. Aust Dent J. 1989;34(2):106-14.
56. Vitale F, Di Benedetto MA, Casuccio A, Firenze A, Calandra G, Ballaro F, et al. [The influence of professional degree on the knowledge of HIV, HBV and HCV infections in dentistry practice]. Ann Ig. 2005;17(3):185-96.
57. Pervaiz M, Gilbert R, Ali N. The Prevalence and Under-reporting of Needlestick Injuries among Dental Healthcare Workers in Pakistan: A Systematic Review. Int J Dent. 2018;2018:9609038.
58. Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. Int J Qual Health Care. 2003;15(3):261-6.

Corresponding author:

Assist. Professor Karolina Akinosoglou
Specialist in Internal Medicine and Infectious Diseases,
Dept of Internal Medicine and Infectious Diseases
University Hospital of Patras, 26500, Rio GR
Tel.: +30 6977 762897
E-mail: akin@upatras.gr

Late spontaneous healing of a severe spontaneous coronary artery dissection causing an acute coronary syndrome

Ioannis Vogiatzis, Konstantinos Koutsampasopoulos, Pavlos Roditis

Abstract

Spontaneous coronary artery dissection is an uncommon cause of myocardial infarction. Young healthy women are most frequently affected. Dissection of the left main coronary artery is even less common; only 18 cases have been reported. We describe the case of a 45-year-old male who presented in our hospital in a stable condition with Spontaneous coronary artery dissection (SCAD) extending in the middle of the Left Anterior Descending (LAD) after coronary angiography. Coronary angiography performed 6 months later, showed complete angiographic healing. The indicated therapeutic approach to hemodynamically stable patients is conservative with spontaneous angiographic healing. SCAD is a potential diagnosis in patients, especially females, presenting with symptoms of acute coronary syndromes.

Key words: *Spontaneous; coronary artery dissection; healing*

INTRODUCTION

Spontaneous coronary artery dissection (SCAD) is a rare, non-atherosclerotic cause of acute coronary syndromes (ACS) (1.7-4% in recent series) [1]. SCAD is caused by the sudden disruption of the coronary artery wall, resulting in separation of the inner intimal lining from the outer vessel wall [2]. Advances in imaging techniques and better recognition of SCAD have led to several new insights into this understudied condition [3]. The treatment is interventional [Percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)] or conservative, depending on the occurrence of extensive ischemia, heart failure or potentially life-threatening ventricular arrhythmias. A variety of stressors (emotional or physical) trigger-mechanisms are responsible for the dissection, as they weaken the arterial wall [4].

We describe the case of a forty-five-year-old male with severe SCAD which resolved spontaneously after six months without any further interventional treatment.

CASE DESCRIPTION

A 45-year-old man was admitted to our hospital for coronary angiography (CA) and possible PCI after 48 hours of ACS. He was stable with a heart rate of 72beats/min, blood pressure of 145/95mmHg and oxygen saturation of 99% in room air. He was asymptomatic, without any sign of ischemia in the ECG. Furthermore, the ECG showed ST-segment elevation in leads V3-V5 (Figure 1), hs-troponin blood level was 4.1ng/ml at admission (this was the peak troponin value) and chest X-ray (CxR) was clear. He reported that he was an athlete of isometric exercises (weight-lifting). However, the event was not associated with any sport activity.

[1]Department of Cardiology, General Hospital of Veroia, Veroia, Greece

Received: 04 Jan 2021; Accepted: 26 Feb 2021

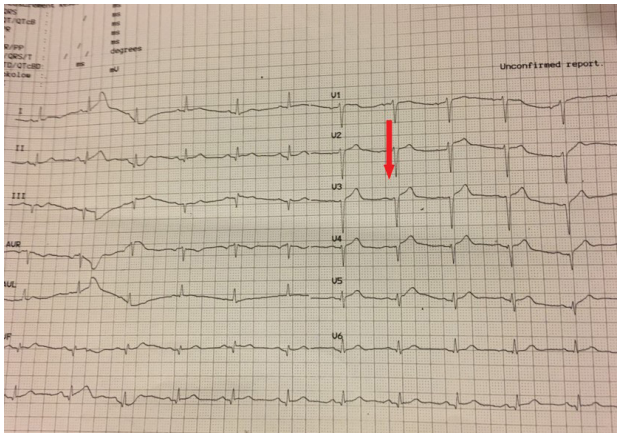

Figure 1. ECG showed an ST-elevation at V3, V4, V5 leads (Arrow).

He had no past medical history or any medication history. The patient's clinical picture pertains to the time he was transferred to our hospital for coronary angiography, 48 hours after the initial administration.

CA was performed showing a type I dissection extending in the middle of the left anterior descending (LAD) (Figure 2A, 2B). No other coronary stenoses or abnormalities were observed. Given that he was clinically stable without any symptoms, we decided to abandon any further coronary intervention and to perform a simple follow up. The following day, the patient was discharged on aspirin, clopidogrel, atorvastatin and metoprolol.

The patient discontinued exercise and after 3 months a new CA was performed with precisely the same results. (Figure 2C).

However, after 6 months from the first episode, the followed CA finally showed complete spontaneous healing, without any sign of dissection (Figure 2D).

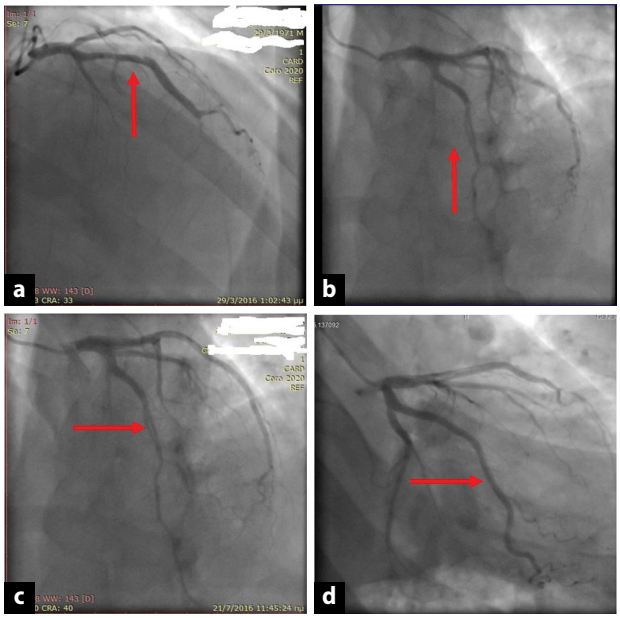

Figure 2. Coronary Arteriography (CA) in successive time intervals showing the spontaneous dissection and the spontaneous late healing. A: 48 hours after the presentation (29/3/2016). The arrow points to dissection in the middle portion of the Left Anterior Descending (LAD) Artery. B: Image from the same CA showing the true and the false lumens. C: Image 4 months after the initial. The arrow shows the LAD artery with the same dissection. D: Image from a repeated CA 6 months after the initial presentation (30/9/2016). The arrow points to the region with the previous dissection which spontaneously had healed with the restoration of normal coronary flow.

DISCUSSION

In the present case, even this severe SCAD healed spontaneously without any interventional treatment. We followed up the case with repeated CA every 3 months to check the condition and to decide follow-up therapy. The dissection was spontaneously healed after six months and this proves that any aggressive interventional treatment strategy should be reconsidered since it induces more complications than benefits in stable patients with SCAD.

Conservative management in stable SCAD patients without evidence of ongoing ischemia features a good overall prognosis with the majority showing spontaneous healing of the dissection on follow-up angiography, which is concordant with our patient. When a spontaneous coronary dissection is presented, with no sign of ischemia, it is recommended a follow-up with a conservative strategy [5]. It is scientifically proven that in most cases, probable revascularization is associated with significantly increased failure rates and complications [2]. Revascularization is restricted to patients with hemodynamic instability or ongoing ischemia.

SCAD is estimated to be responsible for 0.1 to 0.4% of all ACS cases. It is an important cause of ACS in young women, responsible for up to 25% of all ACS cases in women <50 years of age and up to 25% of cases diagnosed during the peripartum period [6]. Forty-five percent of all cases had no cause identified, highlighting that many cases of SCAD remain unexplained [4]. The commonest identified predisposing factors were postpartum, fibromuscular dysplasia (FMD), connective tissue disease and hormonal therapy [4]. Potential stressors include vigorous physical exertion particularly in young male patients, as it was the patient in our case, intense emotional stress, sympathomimetic drugs (such

as cocaine, amphetamines), child-birth and Valsalva-like activities (such as coughing, retching, vomiting) [7]. Triggers for SCAD are thought to increase shear stress on the coronary artery wall, often mediated by elevated catecholamine levels and intra-abdominal pressure [8]. It is routinely advised to these patients to avoid intense isometric exercise (weight lifting as the patient in our case), competitive sports and emotional stress [9].

Type I dissection, which our patient had in the presented case, is the classic description of a longitudinal filling defect, representing the radiolucent intimal flap. There is often contrast staining of the arterial wall with a presentation of a double lumen [10].

Prognosis is favorable since our patient was stable. The risk for future events is minor, therefore patients should be advised of the risk of SCAD relapse. There is no effective treatment for prevention. An interesting observation is that in future relapses the affected vessels are different from them in the initial incident [11].

The time of achieving spontaneous healing varies according to different series where repeated CA was performed. It has been shown [4] that healing occurred >20 days after the dissection, a finding consistent with our case where spontaneous healing was late and was achieved after 6 months. Coronary CTA is a reasonable method to diagnose and follow cases with coronary dissections. However, it presents some limitations as it is rather unsuitable for type II or III dissections [12]. In addition, we had decided to perform an interventional method to follow the patient in order to diagnose exactly the time he could be healed.

Conservative management is preferred in stable patients with SCAD as most dissected segments will heal spontaneously [5]. Medical therapy is based upon opinion, with no randomized clinical trials in this area. Initial treatment is similar to standard ACS patients with the use of dual antiplatelet agents, heparin and beta-blockers to preserve the patency of the true lumen and prevent thrombotic occlusion. The duration of pharmacologic treatment is life-long, except for antiplatelet regimen since that clopidogrel could be discontinued at the end of one year. Many authors recommend this regimen, independently of the use of a coronary stent [12]. Glycoprotein IIb/IIIa inhibitors have also been used without complications. However, these agents could potentially delay the healing of the intramural hematoma and lead to dissection extension. Thrombolytic agents should not be used due to an increased risk of bleeding and extension of intramural hematoma [13]. It is known that statins are not routinely recommended in all cases with SCAD with the exception of specific indications [14]. However, the patient had hyperlipidemia. Besides, the finding of a single study that statin use was associated with higher risks of SCAD recurrence was not replicated in larger studies [12].

CONCLUSION

SCAD should be considered among the differential diagnosis in patients presenting with ACS, especially in particular situations (women, peripartum period, physical and emotional stress). When a spontaneous coronary dissection is observed, without any sign of ischemia, a follow-up is recommended with a conservative strategy to spontaneous healing. Studies or intensive observations are needed to establish a diagnosis and management strategy. Nature takes care of the rest.

Conflict of interest disclosure: *None to declare.*

Declaration of funding sources: *None to declare.*

Author contributions: *Ioannis Vogiatzis: design, analysis and interpretation, drafting the article, final approval of the version; Konstantinos Koutsambasopoulos: conception and design, drafting the article; Pavlos Roditis: interventions, acquisition of data, images.*

REFERENCES

1. Rashid HN, Wong DT, Wijesekera H, Gutman SJ, Shanmugam VB, Gulati R, et al. Incidence and characterization of spontaneous coronary artery dissection as a cause of acute coronary syndrome. A single-centre Australian experience. Int J Cardiol. 2016;202:336-8.
2. Saw J, Mancini GBJ, Humphries KH. Contemporary Review on Spontaneous Coronary Artery Dissection. J Am Coll Cardiol. 2016;68(3):297-312.
3. Poon K, Bell B, Raffel OC, Walters DL, Jang IK. Spontaneous coronary artery dissection: utility of intravascular ultrasound and optical coherence tomography during percutaneous coronary intervention. Circ Cardiovasc Interv. 2011;4(2):e5-e7.
4. Saw J, Aymong E, Sedlak T, Buller CE, Starovoytov A, Ricci D, et al. Spontaneous coronary artery dissection: association with predisposing arteriopathies and precipitating stressors and cardiovascular outcomes. Circ Cardiovasc Interv. 2014;7(5): 645-55.
5. Yamauchi A, Nakagawa N, Shibayama K, Hirai T, Suzuki T, Kitaoka T, et al. Complete healing of spontaneous coronary artery dissection extending from the left main trunk to the left anterior descending and the left circumflex artery. J Cardiol Cases. 2018;18(3):103-5.

6. Garcia NA, Khan AN, Boppana RC, Smith HL. Spontaneous coronary artery dissection: a case series and literature review. J Community Hosp Intern Med Perspect. 2014; 4(4).
7. Nienaber CA, Powell JT. Management of acute aortic syndromes. Eur Heart J. 2012;33(1):26-35b.
8. Erbel R, Aboyans V, Boileau C, Bossone E, Di Bartolomeo R, Eggebrecht H, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases. Eur Heart J 2014;35(41):2873-926.
9. Chou AY, Prakash R, Rajala J, Birnie T, Isserow S, Taylor CM, et al. The First Dedicated Cardiac Rehabilitation Program for Patients with Spontaneous Coronary Artery Dissection: Description and Initial Results. Can J Cardiol. 2016;32(4):554-60.
10. Alfonso F, Bastante T, Cuesta J, Rodríguez D, Benedicto A, Rivero F. Spontaneous coronary artery dissection: novel insights on diagnosis and management. Cardiovasc Diagn Ther. 2015;5(2):133-40.
11. Saw J, Humphries K, Aymong E, Sedlak T, Prakash R, Starovoytov A, et al. Spontaneous Coronary Artery Dissection: Clinical Outcomes and Risk of Recurrence. J Am Coll Cardiol. 2017;70(9):1148-58.
12. Ingrassia J, Diver D, Vashist A. Update in Spontaneous Coronary Artery Dissection. J Clin Med. 2018;7(9):228.
13. Buccheri D, Piraino D, Cortese B. Spontaneous coronary artery dissection: A hint into its diagnosis and therapy. Int J Cardiol. 2016;215:545-7.
14. Tweet MS, Hayes SN, Pitta SR, Simari RD, Lerman A, Lennon RJ, et al. Clinical features, management, and prognosis of spontaneous coronary artery dissection. Circulation 2012; 126(5): 579-88.

Corresponding author:

Dr Ioannis Vogiatzis,
Director of Department of Cardiology
General Hospital of Veroia, 59100 Veroia
Tel/Fax: +30 2331359253 +30 6944 276230
E-mail: ivogia@hotmail.gr

Rupture of a Salmonella-infected iliac aneurysm: A case report

Ioannis Ntouvas[1], Chrysanthi Papageorgopoulou[2], Konstantinos Nikolakopoulos[2], Polyzois Tsantrizos[2], Spyros Papadoulas[2], Stavros Kakkos[2]

Abstract

Infected aneurysms of the abdominal aorta and iliac arteries, are a rare entity with high morbidity and mortality due to sepsis and the possibility of rupture. Salmonella is one of the most common causes of these aneurysms. Although some cases of endovascular treatment have been reported, open repair remains the gold standard treatment. Antibiotics have a complementary but significant role in the treatment of infected aneurysms. We present the rare case of a 62-year-old man with a rupture of a Salmonella infected iliac aneurysm. The patient, was operated successfully with complete excision of aneurysmal sac, debridement of the surrounding infected tissue and arterial revascularization via femo-femoral bypass.

Key words: *Infected aneurysm; rupture femo-femoral by-pass; Salmonella*

INTRODUCTION

Infected abdominal aneurysm is a rare entity with high mortality. It is caused by degeneration of arterial wall of either bacterial or fungal infection. Its incidence is 0,65%-2% of all aortic aneurysms [1]. Salmonella is one of the most common and well-recognized organisms that is implicated in this serious condition. Additionally, Salmonella is the only organism that causes infected aneurysm from a food-born source. In this article, we report the case of a patient that was operated due to the rupture of a Salmonella infected iliac aneurysm.

Case

A 62-year-old man heavy smoker, with a history of insulin dependent diabetes mellitus, hypertension and a coronary angioplasty 8 months ago, was referred to the Emergency Department of our hospital on hypovolemic shock. On physical examination, he was tachycardic and hypotensive with blood pressure 80/40 mmHg and approximately 110 - 120bpm. He also suffered from a sudden-onset profound paralysis on his left lower extremity. Blood tests revealed the following: Hemoglobin 9,1 gr/dl, WBC 26.000 /mm3, CRP 27mg/L. After resuscitation and stabilization, the patient underwent a Computed Tomography (CT) scan. A left iliac aneurysm rupture was detected (fig.1). It is remarkable that ten days ago the patient had visited a general practitioner, due to a back pain combined with fever, and was prescribed a medication for urinary tract infection.

The patient was immediately taken to the operating room. A middle line laparatomy was performed and a large retroperitoneal hematoma at the left side of the abdomen was revealed. After the aorta, right common iliac and left external iliac artery clamping, the hematoma was evacuated. The cause of the hematoma was the rupture of a pseudo-aneurysm at the left common iliac artery near the bifurcation. The sac of the aneurysm and part of the common,

[1]General Hospital of Patras "St. Andrew", Patras, Greece
[2]Department of Vascular Surgery, University of Patras Medical School, Patras, Greece

Received: 18 Sep 2020; Accepted: 06 May 2021

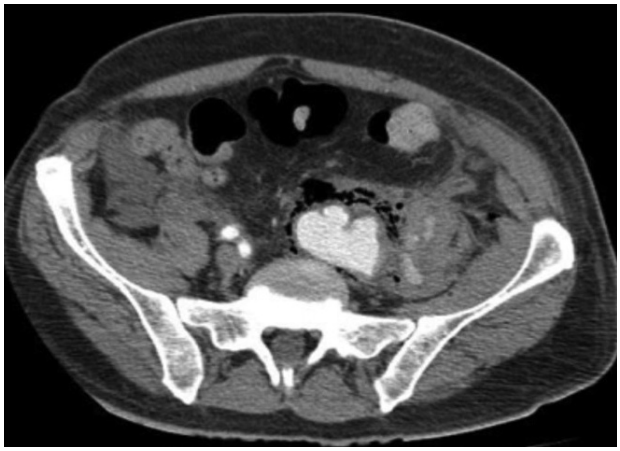

Figure 1. Left iliac aneurysm rupture.

external and internal iliac artery were resected following debridement of the surrounding tissue and ligature of these arteries. After closing the abdomen, we proceeded to a femo-femoral bypass with a PTFE graft (fig 2). Specimens were sent for histopathology and culture-sensitivity. At the end of the operation, the patient had pulses on both legs and he was admitted to the Intensive Care Unit. Postoperative recovery was complicated by an iliac femoral vein thrombosis. Paralysis of the left leg remained, probably due to chronic ischemia of the sciatic nerve by the pressure of the hematoma. Magnetic resonance imaging (MRI) on the 10th postoperative day detected osteomyelitis of the ilium. Specimens culture yielded Salmonella that was multi-sensitive. During hospitalization, the patient received ciprofloxacin and clindamycin. He was discharged on the 22th postoperative day, receiving ciprofloxacin and amoxicillin-clavulanic acid twice daily for 6 months based on cultures' results. Six months post-operatively, the patient has no laboratory sign of infection according to either biological tests or MRI findings with a significant improvement at the mobility of his left lower extremity.

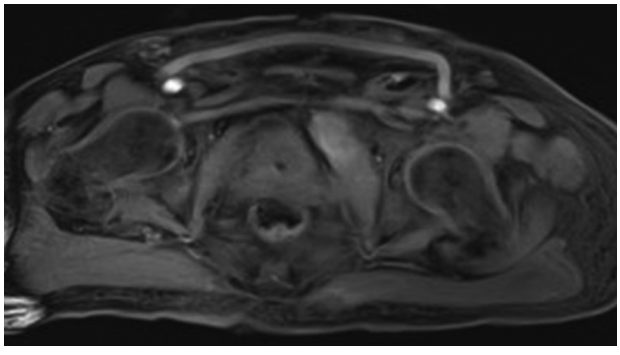

Figure 2. MRI, Femo-femoral by Pass with PTFE.

DISCUSSION

The term mycotic was coined by Osler and was used in his Gulstonian lectures in 1885 to describe multiple aortic aneurysms laden with fungal vegetations in a patient with bacterial endocarditis. Currently, the bibliography term has changed to "infected". The most common cause of infected aneurysms is Staphylococcus aureus, followed by Salmonella [2] which is a genus of rod-shaped (bacillus) gram -negative bacteria of the Enterobacteriaceae family. Gastroenteritis is the dominant clinical manifestation of this infection. However, approximately 5% of Salmonella infected patients develop bacteremia [3]. Salmonella has the ability to invade normal arterial intima and cause endothelial infection in the presence of atherosclerosis [4]. As a consequence, the arterial wall is digested and a pseudo aneurysm is formed. The arteries of diabetic patients (especially the aorta and iliac arteries) are likely to be affected by Salmonella because of the increased incidence of atherosclerosis and intimal damage as well as the reduced immune response. The clinical picture of aortitis consists of fever, back pain, and/or abdominal pain. In one study, that includes patients with Salmonella bacteremia, 25% of those that were older than 50 years-old, developed an endothelial infection [5]. Salmonella-related aneurysms are known to have a fast disease progression with the risk of early rupture [6]. The recurrence of Salmonella infection is possible due to intracellular survival [7].

CT scan with contrast enhancement is considered to be the method of choice to diagnose mycotic aneurysms. Early changes of aortitis, preceding aneurysm formation, include: an irregular arterial wall, periaortic edema, a periaortic soft-tissue mass, and periaortic gas. Periaortic edema can appear as fat stranding or a hypoattenuating concentric rim at CT [8].

The gold standard treatment of infected aneurysm according to the recent guidelines of ESVS (European Society of Vascular Surgery) remains open surgery with surgical resection of the infected artery and surrounding tissues followed by either an extra-anatomic bypass (EABG) or in situ interposition graft (ISB) and a long-term antibiotic therapy [9]. An alternative option either as a permanent or as a bridge therapy is the EVAR (EndoVascular Aneurysm Repair). Patients'

mortality treated non-surgically is about 70–90% [10]. In a published review including 57 cases during the last ten years, for Salmonella mycotic aneurysms only, mortality rates were 21.43% and 7.14 % for open and endovascular treatment, with recurrence rates of infection 0% and 17.85%, respectively. There is no mention for the long-term mortality in this study. In the majority of studies, the short-term rates of mortality in open surgery were 20% - 40% [11]. In a German single-center study, the 5-year survival rate was 35% [12]. Generally, reports on long-term outcome after open repair are scarce. Additionally, there is a debate over the use of in situ interposition graft (ISB) instead of extra-anatomic bypass (EABG). Some authors report similar results between the two methods [13]. In contrary, there are a lot of studies with higher infection rates in ISB. Certainly, EVAR is another option that recently gains a lot of ground. In a European multicenter retrospective study [14] that included only aortic infected aneurysms, the 1-month survival rate was 91% and the 120-month survival was 41%; however, only 19% of deaths, according to the study were due to infection. The recurrence or persistence of infection remains a big issue for EVAR treatment despite the promising results. Hence, it is suggested only for patients with co-morbidities. On the other hand, there is no consensus on the length of antibiotic therapy. According to some authors, there is a tendency to prescribe antibiotic therapy for at least 6 weeks. However, because of the possibility of recurrence during the first 6 to 12 months, a long-term antibiotic therapy for 6 months to 1 year or even lifelong is under consideration [15].

CONCLUSIONS

Infected aneurysms due to Salmonella infections constitute a therapeutic challenge with extremely high morbidity and mortality. Excision of the aneurysmatic sac and surrounding infected tissues followed by revascularization remains the treatment of choice. The alternative option, only for patients with co-morbidities, is endovascular treatment. Antibiotic therapy should be continued for a long time, probably for six months to one year due to the tendency of recurrence.

Conflict of interest disclosure: *None to declare.*

Declaration of funding sources: *None to declare.*

Author contributions: *I. Ntouvas and C. Papageorgopoulou wrote the manuscript; K. Nikolakopoulos, P. Tsantrizos, S. Papadoulas and S. Kakkos were involved in patient management.*

REFERENCES

1. Reddy DJ, Shepard AD, Evans JR, Wright DJ, Smith RF, Ernst CB. Management of infected aortoiliac aneurysms. Arch Surg. 1991;126(7):873-8.
2. Pirvu A, Bouchet C, Garibotti FM, Haupert S, Sessa C. Mycotic aneurysm of the internal carotid artery. Ann Vasc Surg. 2013; 27(6):826-30.
3. Fernandez GM, Aguado JM, Arribas A, Lumbreras C, de Gorgolas M. The spectrum of cardiovascular infections due to Salmonella enterica: a review of clinical features and factors determining outcome. Medicine (Baltimore). 2004;83(2):123-38.
4. Meerkin D, Yinnon AM, Munter RG, Shemesh C, Hiller N, Abraham AS. Salmonella mycotic aneurysm of the aortic arch: case report and review. Clin Infect Dis. 1995;21(3):523-8.
5. Cohen SS, O'Brien TF, Schoenbaum S, Medeiros AA. The risk of endothelial infection in adults with Salmonella bacteremia. Ann Intern Med. 1978;89(6):931-2.
6. Hsu RB, Chen RJ, Wang SS, Chu SH. Infected aortic aneurysms: clinical outcome and risk factor analysis. J Vasc Surg. 2004;40(1):30-5.
7. Chen PL, Tsai LM, Kan CD, Ko WC. Is 2 weeks of antibiotic therapy enough to treat elderly patients with nontyphoid Salmonella bacteremia? A case report of fatal endovascular infection. J Microbiol Immunol Infect. 2014;47(4): 350-3.
8. MacedoTA, Stanson AW, Oderich GS, Johnson CM, Panneton JM, Tie ML. Infected aortic aneurysms: imaging findings. Radiology. 2004;231(1):250-7.
9. Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, et al. Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms. Eur J Vasc Endovasc Surg. 2019;57(1): 8-93.
10. Knouse MC, Madeira RG, Celani VJ. Pseudomonas aeruginosa causing a right carotid artery mycotic aneurysm after a dental extraction procedure. Mayo Clin Proc. 2002;77(10): 1125-30.
11. Yiqun Guo, Yu Bai, Chunxia Yang, Peng Wang and Li Gu. Mycotic aneurysm due to Salmonella species: clinical experiences and review of the literature. Braz J Med Biol Res. 2018 Jun 25;51(9):e6864.
12. Müller BT, Wegener OR, Grabitz K, Pillny M, Thomas L, Sandmann W. Mycotic aneurysms of the thoracic and abdominal aorta and iliac arteries: experience with anatomic and extra-anatomic repair in 33 cases. J Vasc Surg. 2001;33(1):106-13.
13. Lee CH, Hsieh HC, Ko PJ. In situ versus extra-anatomical reconstruction for primary infected infra-renal abdominal aortic aneurysms. J Vasc Surg. 2011;54(1): 64-70.
14. Sorelius K, Mani K, Bjorck M, Sedivy P, Wahlgren CM, Taylor P, et al. Endovascular treatment of mycotic aortic aneurysms:

a European multicenter study. Circulation. 2014;130(24): 2136-42.
15. Clough RE, Black SA, Lyons OT, Zayed HA, Bell RE, Carrell T, et al. Is endovascular repair of mycotic aortic aneurysms a durable treatment option? Eur J Vasc Endovasc Surg. 2009;37(4):407-12.

Corresponding author:

Ioannis Ntouvas
D. Gounari 187, Patras, 26331
Tel: +30 26936188344
E-mail: ntouvas@gmail.com

Natalizumab in the treatment of Crohn's disease

Angeliki Sapsani[1], Maria Kalafateli[2]

Abstract

Natalizumab is a humanized IgG4 antibody against a4 integrin, which blocks the a4b7-mediated homing of lymphocytes to the gut. The efficacy of natalizumab for the induction of remission and clinical response in patients with moderate to severe Crohn's disease has been supported by several studies. However, its association with progressive multifocal leukoencephalopathy (PML), a potentially fatal infection of the central nervous system, resulted in withdrawal and then re-approvement of the drug only under a highly restrictive monitoring program, in order to minimize this risk. This review aims to summarize existing data on the efficacy and safety of natalizumab, with a special reference to PML, in an attempt to determine which patients are in the highest risk of developing this infection and which patients could possibly benefit from natalizumab treatment.

Key words: *Crohn's Disease; natalizumab; progressive multifocal leukoencephalopathy*

INTRODUCTION

Natalizumab (Tysabri; Elan pharmaceuticals and Biogen Idec) is a humanized IgG4 monoclonal antibody against a4 integrin which binds to either b7 or b1 integrin to form a4b7 and a4b1 integrins, respectively. As a result, natalizumab blocks both a4b7 – mucosal addressin cell adhesion molecule 1 (MadCAM-1) interaction that mediates leukocyte homing to the gut, as well as a4b1 – vascular cell adhesion molecule 1(VCAM1) interaction, which is important for the migration of lymphocytes to the central nervous system (CNS) [1,2].

Natalizumab, was first approved by FDA in November 2004, as a quite promising drug for the treatment of relapsing – remitting Multiple Sclerosis (MS). However, its manufacturers withdrew the drug from the market and ceased ongoing clinical trials only 3 months later, as 2 patients with MS and 1 patient with Crohn's disease (CD) developed progressive multifocal leukoencephalopathy (PML), a potentially fatal opportunistic infection of the central nervous system (CNS) caused by John Cunningham polyomavirus (JCV), resulting in two deaths (including the CD patient) [1-3]. Natalizumab was re-approved in 2006 by the FDA as a second line treatment for relapsing remitting MS, under a highly restrictive monitoring program to better assess and minimize patients' PML risk, called TOUCH (Tysabri Outreach: Unified Commitment to Health). Later in 2006, natalizumab was also approved for MS by the European Medicines Evaluation Agency (EMEA), although without a similar monitoring program. In 2008, natalizumab was re-approved for the treatment of moderate to severe CD again under the safety monitoring program TOUCH [1,3-5].

EFFICACY OF NATALIZUMAB IN CD

In a systematic review, Nelson et al [3] analyzed data from five randomized controlled trials (RCT) [6-10] in order to determine the efficacy and safety of natalizumab

[1]Faculty of Medicine, School of Health Sciences, University of Patras, Patras, Greece
[2]Department of Gastroenterology, General Hospital of Patras, Patras, Greece

Received: 05 Jan 2021; Accepted: 02 Mar 2021

for induction of remission in CD. Four out of five RCTs [6-9] compared one, two or three natalizumab infusions (3mg/kg, 6mg/kg, 300mg, respectively) with placebo while one study [10] compared three natalizumab plus infliximab infusions with infliximab plus placebo. The authors concluded that natalizumab was effective for the induction of remission and clinical response in some patients with moderate to severe active disease. More specifically, one infusion of natalizumab was significantly superior to placebo for the induction of remission at 2 and 4 weeks, as 85% and 76% of patients in the natalizumab group compared to 90% (RR 0.94, 95% CI 0.89 to 0.98) and 83% (RR 0.91, 95% CI 0.86 to 0.96) of patients in the placebo group, respectively, failed to enter remission. Furthermore, one infusion was significantly superior to placebo for the induction of clinical response at 4 weeks (49% vs 61%; RR: 0.78, 95% CI: 0.66-0.92). Two infusions were significantly superior for the induction of remission at 6 and 8 weeks (66% vs 76%; RR: 0.85, 95% CI: 0.78-0.93 and 66% vs 77%; RR: 0.85,95% CI: 0.76-0.95, respectively).Three infusions were also significantly superior to placebo for the induction of remission and clinical response at 12 weeks (61% vs 73%; RR: 0.85, 95% CI: 0.78-0.98 and 39% vs 53%; RR: 0.76, 95% CI: 0.67-0.86, respectively). Thus, it seems that the benefit tends to increase with additional infusions of natalizumab. In addition, post hoc subgroup analysis demonstrated significantly greater response in patients with objectively confirmed active inflammation (such as high CRP) or chronically active disease despite the use of conventional therapies (immunosuppressants and anti-TNF agents). In the study which compared combination therapy of natalizumab and infliximab with placebo and infliximab [10], there was no statistically significant difference in remission rates at 10 weeks. However, post hoc subgroup analysis suggested that patients with higher CPR levels achieved higher rates of remission with combination therapy [3]. In a retrospective study, Bellaguarda et al [11] confirmed natalizumab's efficacy in CD. They reported decreased risk of a subsequent surgery in patients treated with natalizumab compared with patients that did not receive natalizumab, while history of CD, fistulizing disease and perianal disease were associated with an increased risk of surgery in Cox regression analysis.

ADVERSE EFFECTS

As far as adverse effects are concerned [3], natalizumab was generally well tolerated with consequent results in all five aforementioned studies [6-10]. Adverse effects occurred infrequently and there was no statistically significant difference in the proportion of patients who experienced adverse effects or discontinued treatment between the natalizumab group treated with one, two or three infusions (300mg or 3mg/kg or 6mg/kg) and the placebo group. Similarly, there was no significant difference in the rates of serious adverse effects among studies. Common adverse effects included headache, abdominal pain, arthralgia, colitis, nausea, vomiting, pharyngitis, influenza syndrome, hypersensitivity-like reactions and development of antibodies against natalizumab, while serious adverse events included exacerbation of CD and complications of CD such as intestinal obstruction. The anti-natalizumab antibodies were associated with infusion and hypersensitivity-like reactions as well as loss of efficacy. One of the studies [8] suggested that concomitant use of immunosuppressive drugs and corticosteroids might be protective against antibody formation. However, one patient under combined 6-mercaptopurine and natalizumab therapy was diagnosed with B-cell lymphoma. None of the included studies reported tuberculosis or opportunistic infections, but two patients developed a malignancy (basal cell carcinoma and B-cell lymphoma, respectively). The study that compared combination therapy of natalizumab and infliximab with infliximab and placebo [10] demonstrated similar rates of side effects, drug discontinuation and serious side effects across groups at 10 weeks. Common adverse events in this study [10] included headache, worsening of CD, nausea, and nasopharyngitis.

Although, these studies demonstrated quite encouraging results regarding the safety profile of natalizumab, they were not designed to detect serious and rare adverse effects as the maximum duration of follow-up was 12 weeks [3]. As already mentioned, two patients with MS and one patient with CD treated with natalizumab developed PML [1-3, 5]. The CD patient that participated in the ENACT-1 trial [8] and was diagnosed with PML, received 3 doses of natalizumab every 4 weeks during the study period (starting from March 2002) followed by 5 further doses of open label natalizumab every 4 weeks (starting from February 2003). Since the diagnosis of CD, the patient had received multiple immunosuppressive treatments including infliximab and azathioprine, the last doses of which were given 20 and 8 months before admission, respectively. The patient was admitted with severe confusion and disorientation in July 2003, one month after the last dose of natalizumab, following a total of 8 doses of the drug. The patient was falsely

diagnosed with astrocytoma and was finally reclassified with the diagnosis of PML in 2005. As frozen serum analysis demonstrated, JCV DNA appeared in serum 3 months after the initiation of open-label natalizumab or 2 months before admission. In conclusion, this patient manifested symptoms of PML after 17 months of intermittent treatment with natalizumab, (i.e., 8 doses of natalizumab), a time interval beyond the observational period of studies conducted at the time of natalizumab's FDA approval [12].

PML RISK

Since PML is the most concerning adverse event and the major reason for which natalizumab does not constitute an appealing option among the available inflammatory bowel disease regimens, an attempt is made in the next section to analyse its pathogenesis and the subgroup of patients with the higher risk to develop PML, in order to assist the prevention of this outcome.

PML is caused by JCV, a polyomavirus that affects almost exclusively severely immunocompromised patients with mainly cell-mediated immune response defects such as HIV infected patients, patients with hematologic malignancies and organ-transplanted patients. JCV is usually acquired during childhood, while seropositivity in the general population ranges from 39% to 91% [5,13,14]. Once the virus enters the host, it can infect the kidneys, the lymphoid tissue and the bone marrow (CD34+, CD19+, CD20+ lymphoid cells) and establish either a persistent or a latent infection. Natalizumab, unlike other immunosuppressive drugs, has two unique features that increase the risk of PML. Firstly, natalizumab forces CD34+ cells, which can differentiate to B – cells, to migrate from the bone marrow to the peripheral circulation. Some of these cells then differentiate to B-cells. Secondly, natalizumab upregulates transcription factors found in CD19+ and CD20+ cells. These transcription factors also bind to JCV DNA transcription sites and promote its replication in latently infected cells. Although some of these cells might be detected by the immune system, JCV infected circulating B-cells as well as free virions, can reach and enter the brain, where JCV causes lytic infection of oligodendrocytes resulting in demyelination foci [13]. Symptoms vary depending on the brain areas involved, ranging from focal neurological deficits to cognitive impairment, often leaving patients with severe and permanent disabilities [13], while mortality rates approach 25% [5].

Following these incidents, the manufacturers in association with the National Institutes of Health (NIH), conducted a retrospective investigation to assess the risk of PML in patients treated with natalizumab. Data from 3116 patients who participated in clinical trials of natalizumab for the treatment of MS (n=1869), CD and rheumatoid arthritis (both n=1247) were evaluated [15]. Clinical history, physical examination and MRI were used to rule out PML. Patients with any abnormal finding consistent with PML were referred to an independent adjudication committee for further evaluation with cerebrospinal fluid testing, and those fulfilling all these criteria, received the diagnosis of PML. Finally, the investigation didn't reveal any new cases of PML and suggested that the incidence of PML in patients exposed to natalizumab was 1 case per 1000 patients in the population that received a mean of 17.9 monthly doses of natalizumab. However, the exact duration of treatment exposure needed to increase the odds of PML development remains unknown. The median exposure in patients with CD was 7 infusions [15]. So far, three factors are known to increase the risk of PML in natalizumab treated patients: longer duration of treatment, prior use of immunosuppressants and the presence of anti-JCV antibodies [14,16].

More recently, Bloomgren et al analysis [16] on MS patients provided an algorithm based on the three risk factors mentioned above, which could help minimize the risk of PML. What is worth mentioning is that the risk increases with longer duration of treatment with the greatest increase occurring after 2 years of therapy. In addition, no seronegative patient developed PML at the time of the analysis, since no seropositive patient had been tested negative before being diagnosed with PML and the incidence of 0.09 cases per 1000 patients was calculated after a sensitivity analysis was performed, taking into consideration the false negative rate of anti-JCV antibody assay [16]. Today, the introduction of anti-JCV antibody index provides another useful tool, that allows more accurate risk stratification of PML via improving detection of low anti-JCV positive responses, thus minimizing intermittent positivity and false negative results [17]. Ho et al [18] calculated the PML risk in seropositive patients treated with natalizumab, depending on yearly exposure to natalizumab and prior immunosuppressant use and further stratified it with the anti-JCV antibody index. PML risk is considered to be low at anti-JCV antibody index values of 0.9 or less and increases at values of 1.5 or more. For patients with anti-JCV antibody index less than 0.9, the cumulative risk is estimated to reach 1.6 per 1000 patients for a period of 6 years or 72 infusions of natalizumab and

remains less than 1 per 1000 patients for a period of 4 years or 48 infusions (0.6 per 1000). For patients with an index more than 0.9 but less than 1.5, the cumulative risk is 8.5 per 1000 patients for a period of 6 years (72 infusions) and remains less than 1 per 1000 patients (0.3 per 1000) for a period of 2 years (24 infusions). As for patients with an index more than 1.5, the cumulative risk for a period of 6 years is 28 per 1000 patients and remains less than 1 per 1000 (0.2 per 1000) only for a period of 1 year of exposure (12 infusions). However, the numerically largest increase in risk is observed after 3 years of exposure in all three index categories. More specifically, for patients with an index less than 0.9, the risk rises from 0.2 for a 3-year exposure period to 0.6 per 1000 patients for a 4-year exposure period. For patients with an index more than 0.9 but less than 1.5 the risk rises from 1.1 to 3.1 per 1000 and for patients with an index more than 1.5 the risk rises from 3.7 to 10.4 per 1000 patients [18]. Thus, the greatest increase in PML risk in this study was observed after 3 years of treatment [18] in contrast to the study by Bloomgren at al [16] where the greatest risk was observed after the first 2 years.

While all data of JCV seroprevalence are derived from MS patients, Bellaguarda et al [11] were the first to assess the prevalence of JCV seropositivity among 191 patients with CD, the effects of natalizumab treatment and the seroconversion rate during treatment. JCV seroprevalence was 67.5%, which is in consistence with the rates reported in the general population and in the large MS populations as well. Among the 22 patients who were seronegative, only 1 patient became seropositive after 22 months of treatment. Prior use of thiopurines was identified as a risk factor for a positive JC serology. In addition, the use of natalizumab was associated with a significantly reduced risk of surgery in both seronegative and seropositive patients, demonstrating its benefit in refractory CD [11]. Applying these results to all CD patients (assuming that they are representative), approximately one third of patients is seronegative and, thus, an appropriate candidate for natalizumab therapy. Taking into consideration the reported incidence of 0.09 cases per 1000 patients by Bloomgren et al [16] and the fact that no patient actually developed PML as well as the fact that seroconversion rates in MS are 2-3% [5], it could be assumed that natalizumab is actually a safe option for seronegative patients. Regarding the seropositive patients with CD, the risk of 1.6 per 1000 after 1 year and 11.1 per 1000 after 2 years of therapy could be deemed low and acceptable for patients suffering from refractory disease. Besides, natalizumab treatment could be discontinued if patients show no response within 3 months, making it extremely unlikely to develop PML [5]. Based on data from MS patients, a proposed algorithm for patients' selection for natalizumab treatment in CD is presented in Figure 1.

As abovementioned, since 2006 for MS and 2008 for CD, natalizumab is prescribed after enrolment in the TOUCH program. The TOUCH program ensures that patients and health care professionals are informed about the risk of PML associated with natalizumab treatment. Only prescribers, infusion centres and pharmacies associated with infusion centres enrolled in the program are allowed to prescribe natalizumab. Risk stratification includes the three factors known to increase risk of PML and already mentioned: prior immunosuppression therapy, number of infusions and duration of treatment, as well as positive JCV serostatus. However, although JCV serostatus is suggested to be checked every 6 months throughout treatment, it's not mandatory. Thus, this recommendation is not always applied in practice, which could compromise patients' safety, especially when no symptom is present (13.3% are asymptomatic as reported from Biogen Database by August 2016 [19]). In addition, TOUCH provides information about concurrent use of antineoplastic, immunosuppressant and immunomodulatory drugs and suggests monitoring of patients for other opportunistic infections [4].

As of June 2017, 731 cases of PML were reported, 24% of which were fatal with an incidence of 4.21 per 1000 patients. The majority of cases are associated with prior immunosuppression, as it is shown from Biogen data collection by February 2017 [20].

FOLLOW-UP OF PATIENTS UNDER TREATMENT WITH NATALIZUMAB

Despite the careful selection of candidates for natalizumab treatment, the risk of PML cannot be eliminated and, thus, natalizumab users should be under close monitoring. This includes regular anti- JCV antibody and neurological examination, as well as MRI screening [21].

More specifically, all seronegative patients receiving natalizumab should be re-tested for anti-JCV antibodies every 6 months [21, 22] considering that seroconversion of previously negative patients can occur as treatment duration increases (approximately 2% per year) [23].

Subsequently, a neurological examination should be performed every 3 months or if new symptoms appear [22]. PML progresses over days to weeks and is presented with cortical symptoms and signs, behav-

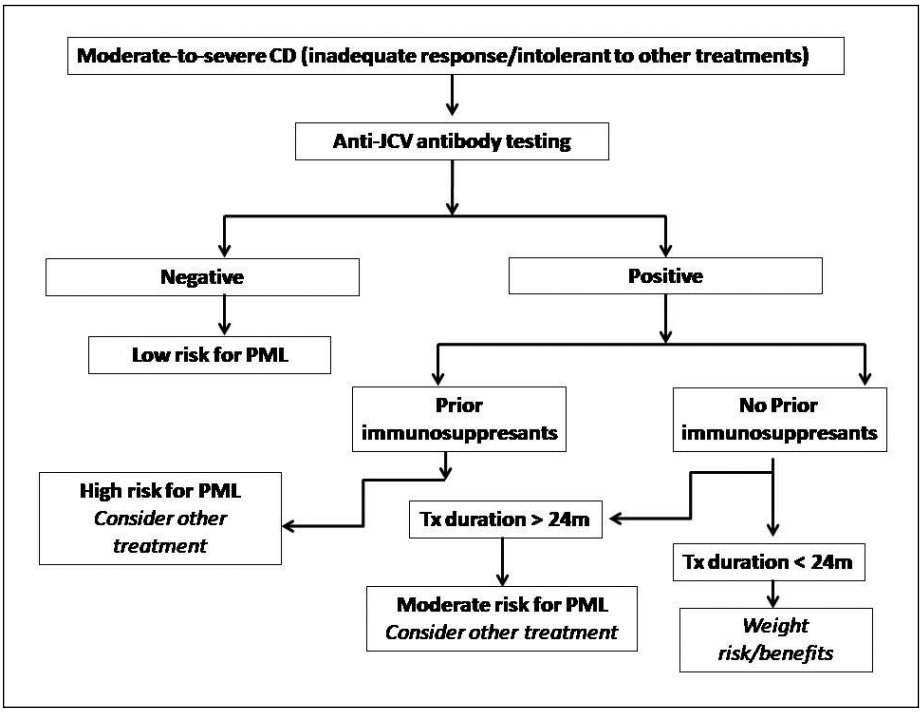

Figure 1. Proposed algorithm for patients' selection for natalizumab treatment in Crohn's disease (CD) depending on the number and type of risk factors for progressive multifocal encephalopathy (PML) development.
JCV, John Cunningham virus; Tx, treatment.

ioral and neuropsychological alteration, retrochiasmal visual deficits, seizures or hemiparesis. High awareness and proper education of physicians, patients and their families, is needed to early identify these features [23].

Furthermore, all patients should have a baseline brain MRI scan before treatment initiation as screening test. Then, MRI imaging should be repeated at regular intervals depending on the evaluated individual risk for PML development [21, 22]. Yearly screening is acceptable for low-risk patients (patients without any risk factor); however, patients in higher risk should be screened on a 3-to-6-month basis, including patients with three risk factors, or seropositive patients with high anti JCV antibody index (≥1.5), without prior immunosuppressant use but treatment duration longer than 2 years [21,22]. MRI should also be performed whenever a patient presents with new-onset neurological symptoms [22]. PML on MRI is depicted as multifocal, asymmetric, subcortical white matter lesions, with little surrounding edema or mass effect [23]. Hyperintense signals in subcortical white matter on FLAIR (fluid-attenuated inversion recovery) sequence has higher sensitivity for detection of PML [23, 24].

If PML is suspected based on clinical and MRI findings, a lumbar puncture with evaluation of cerebrospinal fluid (CSF) for the detection of JCV DNA should be undertaken to confirm the diagnosis. The therapeutic drug monitoring department at Biogen Idec should be informed and the CSF sample should be sent in a certified laboratory for JCV DNA testing [22]. The drug should be discontinued immediately when PML is suspected. Clinicians should be aware that there is no currently FDA-approved treatment for PML [24].

CONCLUSION

To summarise, even though current therapies for CD have achieved revolutionary rates of induction of remission in moderate to severe CD, there are still many patients that fail to enter remission or just don't tolerate first-line and second-line treatments. Thus, there is an increasing need for further options with safe and effective drugs. Natalizumab is an effective drug for some patients with moderate to severe CD. However, its association with PML and the introduction of vedolizumab, a drug with similar mechanism of action but without PML risk, prevents its further use in inflammatory bowel disease. Nevertheless, natalizumab should not be excluded as an option given the relatively high rates of loss of response to anti-TNF agents and the

formation of antibodies against these regimens [5]. In addition to that, if we compare RCTs assessing the efficacy of vedolizumab with those assessing the efficacy of natalizumab, always considering the challenges and errors coming up from such an attempt, natalizumab appears to have higher response rates than vedolizumab which could be either due to trials premature end-points or to the lack of systemic activity of vedolizumab which limits its efficacy [5]. In conclusion, natalizumab should be prescribed in selected patients following a careful consideration of the PML risk. Although natalizumab doesn't consist an appealing option nowadays, it should not be precluded from our list yet, given its high rates of efficacy in patients with refractory disease.

Conflict of interest disclosure: *None to declare.*

Declaration of funding sources: *None to declare.*

Author contributions: *Sapsani A: collection, analysis and interpretation of data, drafting the manuscript; Kalafateli M: design of the study, interpretation of data, drafting and revising the manuscript.*

REFERENCES

1. Guagnozzi D, Caprilli R. Natalizumab in the treatment of Crohn's Disease. Biologics. 2008;2(2):275-84.
2. Lamb CA, O'Byrne S, Keir ME et al. Gut-Selective Integrin-Targeted Therapies for Inflammatory Bowel Disease. J Crohns Colitis. 2018;12(2):S653-68.
3. Nelson SM, Nguyen TM, McDonald JW. Natalizumab for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2018;2018(8):CD006097.
4. Avasarala J. The TOUCH program and natalizumab: Fundamental flaw in patient protection. F1000Res. 2015;4:1450.
5. Scott F, Osterman M. Natalizumab for Crohn's Disease: Down but Not out. Clin GastroenterolHepatol. 2015;13(11):1926-8.
6. Gordon FH, Clement WYL, Hamilton MI, et al. A randomized placebo-controlled trial of a humanized monoclonal antibody to alpha4 integrin in active Crohn's disease. Gastroenterology. 2001;121:268-74.
7. Gosh S, Goldin E, Gordon FH, et al. Natalizumab for active Crohn's disease. N Eng J Med. 2003;348:24-32.
8. Sandborn WJ, Colombel JF, Enns R, et al. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med. 2005;353(18):1912-25.
9. Targan SR, Feagan BG, Fedorak RN, et al. Natalizumab for the treatment of active Crohn's disease:results of the ENCORE trial. Gastroenterology. 2007;132(5):1672-83.
10. Sands BE, Kozarek R, Spainhour J et al. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. Inflamm Bowel Dis. 2007;13(1):2-11.
11. Bellaguarda E, Keyashian K, Pekow J et al. Prevalence of Antibodies Against JC Virus in Serum of Patients With Refractory Crohn's Disease and Effects of Natalizumab Therapy. ClinGastroenterolHepatol. 2015;13(11):1919-25.
12. Van Assche G, Van Ranst M, Sciot R et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's Disease. N Engl J Med. 2005;353:362-8.
13. Major EO, Yoursy TA, Clifford DB. Pathogenesis of progressive multifocal leukoencephalopathy and risks associated with treatments for multiple sclerosis: a decade of lessons learned. Lancet Neurol. 2018;17(5):467-80.
14. Saruta M, Papadakis K. Lymphocyte Homing Antagonists in the Treatment of Inflammatory Bowel Diseases. Gastroenterol Clin N Am. 2014;43:581-601.
15. Yoursy TA, Major EO, Ryschkewitsch C et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl Med 2006;354(9):924-33.
16. Bloomgren G, Richman S, Hotermans C et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012;366:1870-80.
17. Biogen. Medical information website, https://medinfo.biogen.com/medinfo (March 2020).
18. Ho PR, Koendgen H, Campbell N et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. Lancet Neurol. 2017;16(11):925-33.
19. Mason L, Carrillo-Infante C, Richman S. Outcomes of asymptomatic progressive multifocal leukoencephalopathy (PML) in natalizumab-treated multiple sclerosis (MS) patients. Presented at: 4th Congress of the European Academy of Neurology (EAN). Jun 16th – 19th; Lisbon, Portugal. EPR3110.
20. Biogen. Medical information website, https://medinfo.biogen.com/medinfo (Release Date: February 11, 2019).
21. European Medicines Agency. Tysabri: European Public Assessment Report - Product Information (18/06/2009). Available from: https://www.ema.europa.eu/
22. Fernández O, García-Merino J, Arroyo R et al. Spanish consensus on the use of natalizumab (Tysabri®)-2013. Neurología. 2015;30(5):302-14
23. Fernández O.Best practice in the use of natalizumab in multiple sclerosis. Ther Adv Neurol Disord. 2013 Mar; 6(2): 69-79.
24. Biogen – Touch Prescribing Program. Helpful information for evaluation of new neurological symptoms in patients receiving TYSABRI. (Release Date: 07/2020). Available from: https://www.touchprogram.com/TTP/

Corresponding author:

Maria Kalafateli,
Kerineias 12, 26441, Patras, Greece
Tel.: +30 6930 720455
E-mail: mariakalaf@hotmail.com

Achaiki Iatriki