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Cohort profile: The Observational cohort for the study of DOlutegravir in Antiretroviral Combination REgimens (ODOACRE)

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ABSTRACT

Purpose The Observational cohort for the study of DOlutegravir in Antiretroviral Combination REgimens (ODOACRE) cohort was established in Italy in 2016 to evaluate the overall efficacy and tolerability of dolutegravir (DTG)-based antiretroviral (ARV) regimens in clinical practice.

Participants The ODOACRE cohort enrols all adult HIV-1-infected patients, both treatment-naïve and treatment-experienced, starting a DTG-based ARV regimen, in 11 clinical centres in Italy from 2014.

Findings to date In recent years, various works by the ODOACRE cohort have been produced, demonstrating the high efficacy and tolerability of DTG-based ARV regimens in clinical practice, both in ART-naïve (in the setting of acute HIV-1 infection and late presenters patient) and experienced patients. We confirmed the virological efficacy of DTG-based regimens and we evaluated predictors of virological failure. We investigated cause of discontinuation and evaluated tolerability and metabolic profile of the regimens. Within these investigations, we explored particularly the use of DTG in simplification in two-drug regimen with either rilpivirine or lamivudine. We also compared DTG-based regimens with other integrase inhibitors in clinical practice.

Future plans To continue to study long-term efficacy and tolerability of DTG-based regimens is the purpose of the ODOACRE cohort.

Strengths and limitations of this study

- The ODOACRE cohort includes 4139 patients, 481 of which are treatment naïve, who started a dolutegravir (DTG)-based regimen in each of the participating centres, providing a real clinical practice scenario of the use of DTG in Italy.
- Another strength is the cumulative length of follow-up (6937 patient-years of follow-up),which, along with the clinical, laboratory and demographic data of such a large number of patients, allows us to thoroughly define the safety and tolerability of the regimens.
- A predominant feature of our cohort is that it is prevalently composed of highly treatment experienced patients.
- The main weakness of our study is that it only collects routine clinical data and therefore some data could be missing in the analysis.
- Although a yearly update is planned, a delay exists between local data collection and availability of an updated central database.

INTRODUCTION

Since the introduction of combination antiretroviral therapy (cART) in the mid-1990s, the management of HIV infection has dramatically changed along with the natural history and the prognosis of the disease.[1] For decades, the standard of cART has been the association of two nucleos(t)ide reverse transcriptase inhibitors (N(t)RTIs) with an anchor drug, namely, either a ritonavir-boosted protease inhibitor (PI/r) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Such standard three-drug regimen proved to be effective in the vast majority of cases, obtaining and stably maintaining virological suppression and reducing the morbidity and mortality of HIV/AIDS. However, as longer follow-up data became available, clinician's attention shifted towards the toxicity of these aforementioned classes of antiretroviral (ARV) agents, with events such as osteoporosis and dyslipidaemia becoming increasingly evident in clinical practice.[2 3] The marketing of the first-generation integrase inhibitors (INIs) represented a new turning point, which gave clinicians a new class of

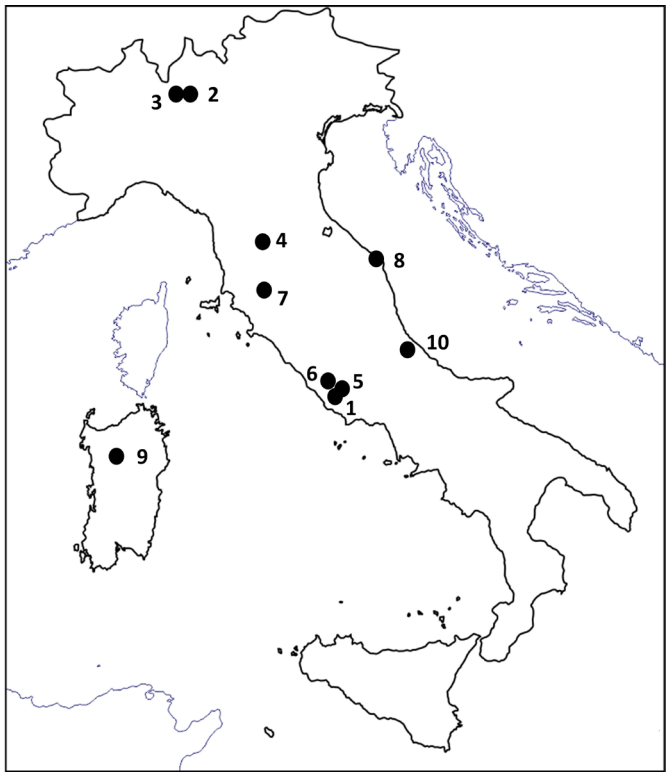

Figure 1 Enrolling centres of the ODOACRE cohort. (1) Infectious Diseases Unit, Catholic University of the Sacred Heart, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome. (2). Infectious Diseases Unit, DIBIC Luigi Sacco, University of Milan, Milan. (3) Division of Infectious Diseases, Department of Infectious Diseases, Luigi Sacco University Hospital, Milan. (4) Division of Tropical and Infectious Diseases, 'Careggi' Hospital, Florence. (5) Infectious Dermatology and Allergology Unit, IFO S. Gallicano Institute (IRCCS), Rome. (6) Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome. (7) University Division of Infectious Diseases, Siena University Hospital, Siena. (8) Clinic of Infectious Diseases, Azienda O.U. Ospedali Riuniti di Ancona, Ancona. (9) Department of Clinical and Experimental Medicine, University of Sassari, Sassari. (10) Infectious Disease Clinic, Department of Medicine and Science of Ageing, 'SS Annunziata' Hospital, Chieti. (11) Clinic of Infectious Diseases, Azienda Ospedaliero-Universitaria Policlinico, Modena.

molecules with a better tolerability profile compared with NNRTIs and PIs. The down sides were a low genetic barrier, the bis-in-die formulation of raltegravir (RAL) and the need for a pharmacological booster for elvitegravir (EVG), which hindered a vast use of these drugs as switch strategies in experienced patients.[4]

Dolutegravir (DTG), a second-generation INI, presented high efficacy in early clinical trials, along with minimal drug–drug interaction risk and overall favourable tolerability profile.[5–7] DTG also presented a higher genetic barrier compared with first-generation INI[8–10] and has become, since its introduction, one of the preferred choices by clinicians for both treatment-naïve and experienced patients.[11 12] However, in recent years, observational studies showed conflicting data on DTG tolerability, with some cohorts reporting high rate of discontinuations of DTG-based regimens due to neuropsychiatric events.[13 14] DTG has also been related to neural-tube defects in newborns of mothers in treatment with this drug.[15] Moreover, concerns have been raised about weight gain[16] and a decline in renal function in patients taking DTG,[17] the latter a problem that could be related to the effect of DTG on organic cation transporter 2 (OCT2).[18] To further investigate DTG tolerability and to assess the efficacy of DTG-based in clinical practice, several Italian clinicians joined their efforts creating a large observational cohort analysing patients starting DTG in real-life scenario.

COHORT DESCRIPTION

The Observational cohort for the study of DOlutegravir in Antiretroviral Combination REgimens (ODOACRE) was established in Italy in 2016 to evaluate the overall efficacy and tolerability of DTG-based regimens in clinical practice. Initially, the cohort was composed of 6 centres but rapidly expanded; currently, the ODOACRE cohort is composed of 11 centres, representing some of the most populated areas of the country (figure 1). In Italy, DTG-based regimens has become one of the first-line regimens both in ARV-naïve patients and in treatment-experienced ones; moreover, DTG-based dual regimens are listed as possible switch strategies for both patients on standard three-drug regimen with a 2 NRTI-backbone, in order to reduce the risk of drug-related toxicity ('NRTI-sparing' approach) and in patients on PI-based or NNRTI-based strategies, in order to improve the metabolic profile and to reduce the risk of drug–drug interactions.[19] The main objectives of the cohort are to assess the virological efficacy of DTG in real clinical practice settings and to assess the overall tolerability of DTG-based regimens. Moreover, the ongoing widespread use of less-drug regimens, following the results from clinical trials, showed promising results of DTG-based two-drug regimen both in treatment-experienced patients and in treatment-naïve subject.[20–23] This fact has lead the ODOACRE cohort to focus on assessing the efficacy, safety and tolerability of DTG-based dual regimens (ie, DTG plus either rilpivirine, RPV, or lamivudine, 3TC) in clinical practice.

The ODOACRE cohort enrols all adult HIV-1-infected patients, both treatment-naïve and treatment-experienced, starting a DTG-based antiretroviral regimen in one of the enrolling centres. All patients signed informed consent for data collection. Children under 18 years of age and adults incapable of providing informed consent are excluded. At first visit, subjects are required to provide written informed consent to allow the input of their clinical, epidemiological and biological data in the cohort's database. Informed consent covers the use of clinical care data for research purposes, the record linkage of patient data with other databases and permission to collect patient biosamples for cell and pharmacogenomics analysis. The primary outcome

of the cohort is to evaluate the virological efficacy and safety of DTG in both treatment-naïve and treatment-experienced patients. The secondary outcomes include the assessment of tolerability, changes in immunological, metabolic and inflammatory profile. Main statistical analyses are as follows: parametric and non-parametric test, as appropriate, to compare continuous and categorical values, survival analysis (ie, Kaplan-Meier estimator) and regression analyses (Cox regression, linear and logistic, as appropriate). As of 31 December 2018, 4139 patients have been enrolled in the cohort, prevalently male (72.5%), with a median age of 50.4 years (IQR 42.2–55.6). Full patients' characteristics are shown in table 1. Median follow-up time was 19.7 months (IQR 10.7–28.7), with a cumulative time of follow-up of 6937 patient-years of follow-up (PYFU). Almost 90% of the enrolled naïve patients were on an ARV regimen made up of a 2-NRTI backbone plus DTG (39.3% with abacavir (ABC)+3TC and 50.9% with emtricitabine (FTC) plus either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF)); conversely, less than two-thirds of the experienced subjects were on such standard regimens (41.8% with ABC+3TC and 16.9% with FTC plus TDF or TAF), while 16.6% switched to 3TC +DTG, 10.1% switched to a dual therapy with a PI plus DTG and 7.1% to RPV+DTG. Table 2 comprehends all the analysed ARV regimens. Interestingly, there is a small group of 25 treatment -naïve patients on a dual regimen in our cohort; in this group, during 43.7 PYFU we observed just one virological failure (VF, defined as failure to achieve HIV-1 RNA below 50 copies/mL after 6 months since ARV initiation) and four treatment discontinuations (TDs). The single patient who experienced VF was a 38-year-old woman starting DTG plus etravirine, presenting at 6 months an HIV viral load of 280 000 copies/mL; she was then switched to FTC/TDF+DTG+DRV/r, achieving virological suppression. These data are of particular interest since data on safety and tolerability of two-drug regimen in treatment-naïve patients are only recently being published with the 48-week results of the GEMINI trials.[23]

Each patient usually attends one of the centres for a routine check-up every 3–4 months or when a new clinical event occurs, a new treatment is prescribed or a change in biological markers is observed. The overall 3 years probability of maintaining the prescribed regimen was 57.0%. It is to be noted however that we considered as treatment interruption also the change of backbone while maintaining DTG or the optimisation to single tablet regimen (ie, from ABC/3TC+DTG to ABC/3TC/DTG or from FTC/TDF to FTC/TAF). Discontinuation of the prescribed regimen was due to:

- Treatment simplification (41.9%).
- Toxicities (29.7%): gastrointestinal (GI) tract (11.7%), neuropsychiatric (11.0%), renal (2.3%), other toxicities (1.6%), hypersensitivity reaction (3.1%).
- Virological failure (4.3%).
- Treatment intensification (1.2%).
- Drug–drug interaction (1.2%).
- Other reasons (21.6%): concern of cardiovascular disease (2.2%), death (1.4%), unspecified/unknown (18.0%).

There were significant differences in the causes of discontinuation between naïve and experienced patients, with almost two-thirds of naïve patients (64.6%) interrupting for proactive switch compared with the 36.4% of experienced patients. It is to be noted that in the last 2 years, both a single tablet regimen with ABC/3TC/DTG and a coformulation of FTC with TAF (instead of TDF) became widely available in Italy, prompting clinicians to further simplify ARV regimens.

Variables collected at patient enrolment include ages, gender, country of origin, mode of HIV transmission, date of primary infection if available and first positive HIV test. At baseline and at each follow-up visit, the following information are collected: body weight, viroimmunological markers of HIV infection such as CD4+ cell count, CD4/CD8 ratio and plasma HIV-1 RNA level, complete blood cell counts, lipid and liver enzymes; creatinine value and estimated glomerular filtration rate, antiretroviral drug start and stop dates, and the reasons for changing drug regimens, prophylaxis of opportunistic infections and comedications, serological and virological data on coinfection with hepatitis C virus and hepatitis V virus; date and type of AIDS and non-AIDS events (including cardiovascular events, cancers, neuropsychiatric events, bacterial infections and so on), changes in bone mineral density (dual-energy X-ray absorptiometry (DEXA) scan), date and cause of death (if applicable). In this regard, we recently published a work analysing trends of hospitalisation in HIV-infected patients.[24] During 6937 PYFU, we observed 363 virological failures (described as two-consecutive HIV-1 RNA determination >50 copies/mL or a single HIV-1 RNA >1000 copies/mL in patients who previously achieved virological suppression or as failure to achieve HIV-1 RNA below 50 copies/mL after 6 months since ARV initiation in treatment-naïve patients), with an overall incidence of 5.2 VF per 100 PYFU.

Currently, the ODOACRE cohort aims at collaborating with other European cohorts and databases, collecting data on HIV resistance mutations in order to further investigate DTG sensibility and efficacy in the context of resistance-associated mutations (RAMs). Preliminary collaboration with the 'Euresist cohort' led to a recent work showing that genotypic susceptibility score was a predictor of virological failure in INI-based regimens.[25] Future projects also included the collection of biological samples to study HIV-DNA, inflammation markers (such as sCD14, interleukin 6, annexins and so on).

Patient and public involvement

The patients had no role in the design, recruitment and conduct of the study.

Table 1 Patients' characteristics at last available update (31 December 2018)

Variables	Overall n=4139 (%)	Treatment-experienced n=3658 (%)	Naive n=481 (%)	P values
Male, n (%)	2979 (72.5)	2609 (71.7)	370 (78.7)	0.001
Age (years), median (IQR)	50.4 (42.2–55.6)	51.0 (43.8–56.0)	41.3 (33.2–50.4)	<0.001
Risk factor, n (%)				<0.001
MSM	1540 (37.9)	1310 (36.4)	230 (50.1)	
Eterosexual	1572 (38.7)	1416 (39.3)	156 (34.0)	
IDU	753 (18.5)	712 (19.8)	41 (9.0)	
Other/Unknown	196 (4.9)	164 (4.6)	32 (6.9)	
HCV[c] Ab positive, n (%)	833 (21.2)	804 (22.8)	29 (7.3)	<0.001
HBsAg positive, n (%)	107 (2.7)	96 (2.7)	11 (2.7)	ns
CDC stage C, n (%)	837 (26.9)	774 (28.0)	63 (17.8)	<0.001
Years from HIV diagnosis, median (IQR)		14.0 (5.4–23.1)	/	/
Zenith HIV-RNA (log_{10} copies/mL), median (IQR)	4.82 (4.29–5.37)	4.82 (4.29–5.36)	5.05 (4.57–5.56)	<0.001
Nadir CD4+ (cells/mmc), median (IQR)	194.0 (61.0–324.0)	191.0 (58.0–312.0)	272.0 (94.5–488.5)	<0.001
BL CD4+ (cell/mmc), median (IQR)	583 (365-810)	601 (400-823)	330 (110-560)	<0.001
Years on cART, median (IQR)		10.6 (4.0–18.5)	/	/
Time on virological suppression (months), median (IQR)		43.9 (8.4–97.0)	/	/
Virologically suppressed patients at baseline, n (%)		2222 (80.4)	/	/
Previous virological failure, n (%)		1183 (44.9)	/	/
Therapies before switch, n (%)				/
2NRTI+PI		944 (25.9)		
2NRTI+INI		835 (22.9)		
2NRTI+NNRTI		702 (19.2)	/	
Mono/Dual		763 (20.9)		
Others		405 (11.1)		
Reasons for previous treatment discontinuation, n (%)				/
Virological failure		209 (5.7)		
Treatment Intensification		106 (2.9)		
Dyslipidaemia		247 (6.8)	/	
Proactive switch/Simplification		1773 (48.5)		
GI toxicity		170 (4.6)		
Renal toxicity		113 (3.1)		
Neurological toxicity		34 (0.9)		
Osteopoenia/Osteoporisis		61 (1.7)		
Other toxicity		44 (1.2)		
Hypersensitivity		20 (0.5)		
Drug–drug interactions		155 (4.2)		
Other/Unknown		723 (19.8)		

GI, gastrointestinal; INI, integrase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor ; NRTI, nucleoside reverse transcriptase inhibitor ; PI, protease inhibitor.

Table 2 ARV regimens in the cohort

ARV regimen	Overall	Treatment-experienced patients	Naïve patients
DTG+ABC/3TC	1718 (41.5)	1529 (41.8)	189 (39.3)
DTG+FTC/Tenofovir (either TDF or TAF)	863 (20.9)	618 (16.9)	245 (50.9)
DTG+3TC	616 (14.9)	608 (16.6)	8 (1.7)
DTG+RPV	263 (6.4)	259 (7.1)	4 (0.8)
DTG+PI (boosted or unboosted)	380 (9.2)	370 (10.1)	10 (2.1)
DTG monotherapy	8 (0.2)	8 (0.2)	0
Other DTG-based dual regimen	22 (0.5)	19 (0.5)	3 (0.6)
Other DTG-based regimen (three or more drugs)	269 (6.5)	247 (6.8)	22 (4.6)

ARV, antiretroviral; DTG, dolutegravir; PI, protease inhibitor; RPV, rilpivirine; TAF, tenofovir alafenamide ; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate.

Findings to date

In recent years, various works by the ODOACRE cohort have been produced and published in full paper articles. The cohort's production has been mainly focused on the study of the effectiveness and tolerability of DTG-based ARV regimens. In 2017, we published a work on the safety of a switch strategy with DTG plus a dual-NRTI backbone,[26] following reports of high rates of discontinuations of DTG-based regimens due to neuropsychiatric symptoms. In our work, we observed no virological failures during 1090 patient-months of follow-up and a 9.2% rate of TD, with a median time to TD of 81 days.

Baldin *et al*[27] compared a switch regimen with FTC/TDF plus DTG with a single tablet regimen with EVG and found that the 48-week estimated probability of continuing treatment was 74.5% for patients in the DTG group and 84.7% for those in the EVG group, and the difference was not statistically significant. Most recent works, meanwhile, mainly focus on the efficacy and safety of less drug regimens as switch strategies in virologically suppressed HIV-1-positive patients, since clinician's attention has shifted towards the analysis of risk/benefit ratio of dual therapies. Capetti *et al*[28] have described the effectiveness and tolerability of a dual therapy with RPV and DTG, with a median follow-up time of 101 weeks; in this study, the probability of maintaining virological suppression was 96.3% at week 96 while also observing a significant reduction of the low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio. Similarly, a work by Borghetti *et al*[29] showed the results of our experience with a switch regimen of 3TC plus DTG in clinical practice; in this study, over 216.5 PYFU, we observed five virological failures with a probability of maintaining suppression of 95.1% at week 96. Finally, a comparison between the switch regimens of RPV+DTG and 3TC+DTG was published in 2018[30]; in this work, we observed no differences in the rate of virological failure between the two groups with no mutations to INI and with just one patient who developed a resistance mutation to NNRTIs at failure in the RPV group.

Rescue regimen in highly treatment-experienced patients

Our experience with highly treatment-experienced patients was well described in a work by Capetti *et al*,[31] showing the results of a rescue regimen of boosted darunavir plus DTG on 130 patients; about 90% of them had documented resistance to one to five ARV classes. After 48 weeks of follow-up, we observed a decrease in the proportion of patients harbouring active HIV replication from 40% at baseline to 6.1%. Patients starting boosted DRV+DTG with HIV-RNA over 50 copies/mL presented a success rate of 88.5%; meanwhile, 97.4% of those who started this regimen with HIV-RNA below 50 copies/mL maintained virological suppression.

DTG in naïve patient

Following the results from the GEMINI trials,[23] the use of a dual therapy with 3TC plus DTG in treatment-naïve patients will become more common in clinical practice and we expect to describe the feasibility of this strategy in our centres in the short future. With these data obviously still months away, our experience in naïve patients is represented by two recent studies: Rossetti *et al*[32] described the efficacy of DTG-based regimens (vs non-DTG-containing regimens) in achieving virological suppression in advanced HIV-infected naïve patients. Thirty-six per cent of patients in the DTG group achieved HIV-RNA below 50 copies/mL after 1 month of therapy (vs 17% of the non-DTG group) and 91% of them achieving suppression at 24 months (vs 89%), while the frequency of IRIS was similar between groups. Another study by Lagi *et al*[33] compared the tolerability and viroimmunologic efficacy of DTG-based regimens versus other regimens in naïve patients with acute HIV infection, with both groups showing significant increase in CD4+ cell count and CD4+/CD8+ ratio at 3, 6, 12, 24 and 36 months without significant differences between them.

Further study plans

Given the large data set available, the ODOACRE cohort aims at continuing its observational activity on DTG-based regimens, highlighting rates and reasons of DTG

discontinuation for both standard three-drug regimen and dual regimen, with a focus also on ARV-naïve patients. The already published data, confirming the favourable metabolic profile of DTG, will be implemented with the assessment of inflammation and immunological status. Moreover, given the expanding interest in weight gain during INI-based regimens,[16 34] the cohort will attempt to thoroughly study this matter in its large population. The collaboration with other cohorts, mainly collecting data on HIV genotypic test, will lead to investigate the role of RAMs on the virological outcome of DTG-containing regimens, also considering not only HIV-RNA but also HIV-DNA. Additional assessments will also be conducted on the adverse events reported during therapy with DTG in order to examine possible predictors of these events (ie, neuropsychiatric events).

Strengths and limitations

The main strength of the ODOACRE cohort is that it enrols all the patients starting a DTG-based regimen in each of the participating centres, with a grand total of 4139 patients as of December 2018, providing a real clinical practice scenario of the use of DTG in Italy. Another strength is the cumulative length of follow-up (6937 PYFU), which, along with the clinical, laboratory and demographic data of such a large number of patients, allows us to thoroughly define the safety and tolerability of the regimens. Our observational data on the dual therapy with RPV and DTG have anticipated the results of the SWORD trials; similarly, while the TANGO trials on the efficacy and tolerability of 3TC+DTG are still under way,[35] our group has already described in multiple works the real-life feasibility of the said regimen.

A predominant feature of our cohort is that it is prevalently composed of highly treatment-experienced patients, with an overall median time from HIV diagnosis of 15.6 years (IQR 7.2–23.9), a median time on ARV of 11.4 years (IQR 5.0–18.7) and a median time of virological suppression of 3.9 years (IQR 0.8–8.2). Moreover, 44.9% of the patients experienced at least one virological failure in their clinical history and 21.2% of them switched to DTG coming from a dual/mono regimen.

The main weakness of our study is that it only collects routine clinical data and therefore some data could be missing in the analysis. The observational nature of the study is prone to bias due to unmeasured confounders that may impact on the study endpoints. Inaccurate or incomplete reporting on non-AIDS-related events, concomitant medications and reasons for DTG discontinuation cannot be excluded. Furthermore, as in several other observational studies, patients who refused to give their consent to data collection may differ systematically on some of the baseline characteristics from patients who participated.

Moreover, although a yearly update is planned, a delay exists between local data collection and availability of an updated central database.

COLLABORATION

Data can be obtained on reasonable request. We encourage other clinical centres, even from other countries, to collaborate with our cohort. In particular, we aim to further investigate DTG-based regimens in several clinical contests and we would like to evaluate these regimens in comparison with other INIs and other ARV drugs in order to try to answer the many questions that still come from clinical practice.

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Contributors ACic, GB, LC, FV, BR, AD, MVC, SRes, WG, FL, AG, MC, LB and AB managed patients and collected data. ACic and GB collaborated with the other clinical centers and wrote the manuscript. ACap, VB, GS, AL, GM, CM and SRus critically revised the manuscript. SDG conceived the work and revised the manuscript. All authors approved the submitted version of this manuscript.

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