Ombitasvir, paritaprevir, and ritonavir plus ribavirin for chronic hepatitis C virus genotype 4 infection in Egyptian patients with or without compensated cirrhosis (AGATE-II): a multicentre, phase 3, partly randomised open-label trial

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Summary

Background In Egypt, chronic hepatitis C virus (HCV) infection occurs in around 10% of the population (about 8 million individuals), and is a leading cause of liver cirrhosis, hepatocellular carcinoma, and mortality. Although HCV genotype 4 constitutes about 20% of HCV infections worldwide, the prevalence in Egypt is more than 90%. We assessed the efficacy and safety of the two direct-acting antiviral drugs ombitasvir, an NS5A inhibitor, and paritaprevir, an NS3/4A protease inhibitor dosed with ritonavir, plus ribavirin in treatment of chronic HCV infection in Egypt.

Methods AGATE-II was a phase 3, open-label, partly randomised trial in patients with chronic HCV genotype 4 infection recruited from five academic and hepatology centres in Egypt. Patients were HCV treatment-naive or treatment-experienced with interferon-based regimens. Eligible patients were aged 18 years or older, and had been chronically infected with HCV genotype 4 for at least 6 months with a plasma HCV RNA concentration of more than 1000 IU/mL at screening. Patients without cirrhosis were assigned to receive 12 weeks of 25 mg ombitasvir, 150 mg paritaprevir, and 100 mg ritonavir orally once daily plus weight-based ribavirin. Patients with compensated cirrhosis were randomly assigned (1:1) to receive the same treatment for either 12 weeks or 24 weeks. Randomisation was stratified by previous pegylated interferon and ribavirin treatment experience using a web-based interactive response technology system and computer-generated schedules prepared by personnel from the funder's statistics department. Investigators were masked to randomisation schedules and were informed of each patient's assigned treatment by the interactive response technology system immediately after allocation. The primary endpoint was the proportion of patients with a sustained virological response (HCV RNA <15 IU/mL) 12 weeks after the last dose of study drug (SVR12). All patients who received at least one dose of study drugs were included in the primary and safety analysis. This study is registered with ClinicalTrials.gov, number NCT02247401.

Findings Between Nov 4, 2014, and March 16, 2015, we screened 182 patients with HCV infection, of whom 160 were eligible for inclusion; 100 patients were assessed as not having cirrhosis and were given 12 weeks of treatment, and 60 patients assessed as having cirrhosis were randomly assigned to the 12-week treatment group (n=31) or the 24-week treatment group (n=29). 94 (94%; 95% CI 88–97) of 100 patients in the without cirrhosis group, 30 (97%; 84–99) of 31 patients in the cirrhosis 12-week treatment group, and 27 (93%; 78–98) of 29 patients in the cirrhosis 24-week treatment group achieved SVR12. The most common adverse events in patients without cirrhosis were headache (41 [41%]) and fatigue (35 [35%]). Fatigue occurred in nine (29%) patients in the cirrhosis 12-week treatment group and 11 (38%) patients in the cirrhosis 24-week treatment group, and headache occurred in nine (29%) patients in the cirrhosis 12-week treatment group and in 10 (35%) patients in the cirrhosis 24-week treatment group. Adverse events were predominantly mild or moderate in severity, and laboratory abnormalities were not clinically meaningful. No patients discontinued treatment because of an adverse event. One serious adverse event in the group without cirrhosis was attributed to study drugs by the investigators; the patient had deep venous thrombosis.

Interpretation Ombitasvir, paritaprevir, and ritonavir plus ribavirin for 12 weeks achieved SVR12 in a high proportion of patients and was well tolerated in Egyptian patients with HCV genotype 4 infection with or without compensated cirrhosis. Extension of treatment to 24 weeks in patients with cirrhosis did not improve the proportion of patients achieving SVR12. A shorter duration regimen could be useful to address the significant burden of HCV genotype 4 infection in patients with compensated cirrhosis.

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Research in context

Evidence before this study

We searched PubMed and meeting abstracts from the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) from Jan 1, 2011, to Dec 7, 2015, for clinical studies in Egypt including patients with hepatitis C virus (HCV) genotype 4 infection, using the search terms "HCV" and "Egypt", and "clinical study" or "trial". We excluded studies that included pegylated interferon in combination with a direct-acting antiviral. We identified no clinical or observational studies of direct-acting antiviral therapies in Egyptian patients in PubMed. We identified three conference abstracts with this search: a pooled analysis of sofosbuvir plus ribavirin from US and Egyptian studies, and two studies of sofosbuvir in combination with either simeprevir or ravidasvir in Egypt. 61 (73%) of 83 patients achieved sustained virological response at 12 weeks (SVR12) with 12 weeks of sofosbuvir plus ribavirin and 73 (91%) of 80 achieved SVR12 with 24 weeks of the same treatment. Fewer patients with cirrhosis or with treatment experience achieved SVR12. For patients with genotype 4 infection without cirrhosis receiving simeprevir plus sofosbuvir, 15 (75%) of 20 achieved SVR4 with 8 weeks of treatment and 19 (95%) of 20 achieved SVR4 with 12 weeks of treatment; 23 (100%) of 23 patients with cirrhosis receiving 12 weeks of treatment achieved SVR4. Lastly, 176 (97%) of 182 patients achieved SVR12 with ravidasvir plus sofosbuvir, with all virological failures occurring in patients with cirrhosis.

Added value of this study

Although Egypt is likely to provide approval for other direct-acting antiviral regimens, the combination of ombitasvir, paritaprevir, and ritonavir plus ribavirin is already approved to treat patients infected with HCV genotype 4. This approval was based on extrapolation from data in patients without cirrhosis and in patients with other HCV genotypes. The results of our study corroborate the findings of phase 2 and 3 trials in patients from Europe and North America, and provide further evidence that this HCV regimen achieves high rates of SVR12 in patients with HCV genotype 4 infection with and without cirrhosis, specifically in patients from Egypt. Additionally, the results substantiate that a 12-week treatment duration for patients with compensated cirrhosis is sufficient to yield high rates of SVR12.

Implications of all the available evidence

As of April 29, 2016, three principal organisations provide treatment recommendations for those infected with HCV: WHO, AASLD and Infectious Diseases Society of America (IDSA), and EASL. The WHO guidelines do not list ombitasvir, paritaprevir, and ritonavir plus ribavirin as a treatment option for patients with HCV genotype 4 infection and cirrhosis. The AASLD–IDSA recommendations have used this study to provide a strong evidence rating for 12 weeks of ombitasvir, paritaprevir, and ritonavir plus ribavirin patients with HCV genotype 4 infection with cirrhosis. By contrast, EASL provides a moderate evidence rating for a 24-week treatment with the same regimen. Therefore, data from our study (AGATE-II), together with data from the complementary AGATE-I study, provide additional evidence that can be used in updates to the treatment guidelines and upgrades in evidence quality.

Introduction

Chronic infection with hepatitis C virus (HCV) occurs in roughly 180 million people worldwide, and although genotype 1 accounts for roughly 48% of infections, distribution of the seven genotypes differs geographically.[1] Genotype 4 infections account for 13–20% of all HCV infections worldwide, but make up about 93% of all HCV cases in Egypt.[2,3] HCV is a near epidemic in Egypt since seroprevalence has been reported in more than 10% of Egyptians (8 million individuals), which is substantially higher than in other geographic regions, and an estimated 7–10% of Egyptians are chronically infected.[2,4,5] This high seroprevalence is attributed to a national campaign to treat schistosomiasis from the 1950s to the 1980s, contaminated blood transfusions, medical practices, and needle reuse.[5] In the past three decades, mortality from HCV-associated hepatocellular carcinoma has increased by more than 200% in the Middle East, which is substantially higher than increases observed worldwide.[6] In response, the Egyptian Ministry of Health and Population formed the National Committee for Control of Viral Hepatitis in 2006 to enable education and awareness, and provide treatment free of charge to people with HCV.[7] With the emergence of highly effective HCV direct-acting antiviral therapy options, the Egyptian National Committee for Control of Viral Hepatitis began recruiting patients for treatment in September, 2014, and about 1·1 million Egyptians have subsequently registered for treatment.[8] However, access, cost, and an estimated 100 000–150 000 new infections annually remain substantial obstacles to elimination of HCV in Egypt.[4,8]

New direct-acting antiviral treatment options for HCV have mainly focused on treatment of patients with genotype 1 infection because of the high worldwide prevalence of this genotype and because it has historically been difficult to cure with interferon-based regimens.[9] Some direct-acting antiviral regimens have shown activity against several genotypes,[10,11] and future regimens have the potential to be pangenotypic.[12] However, few dedicated studies with these new regimens have been done in patients with HCV genotype 4 infection, especially in Egyptian patients, who make up 35–45% of the global pool of genotype 4 infection, and in whom subtype 4a predominates.[5,13] The standard of care for

treatment of genotype 4 infection in Egypt before the study was the combination of sofosbuvir plus ribavirin, either with or without pegylated interferon, according to interferon eligibility.

Ombitasvir is a potent NS5A inhibitor with broad antiviral activity against HCV genotypes 1a, 1b, 2a, 2b, 3a, 4a, and 6a.[14] Paritaprevir, an NS3/4A protease inhibitor (with the pharmacokinetic enhancer ritonavir), has similarly broad genotypic activity against HCV genotypes 1a, 1b, 2a, 3a, 4a, and 6a.[15] In-vitro potencies of these two antivirals in genotype 4a replicon assays are similar to those against HCV genotype 1b, in which phase 3 studies of these drugs plus dasabuvir (a non-nucleoside NS5B inhibitor with high potency against only genotype 1) achieved a sustained virological response at 12 weeks (SVR12) in 575 (99%) of 581 patients with or without compensated cirrhosis taking the label-recommended regimen in the USA and Europe.[16] The direct-acting antiviral combination of ombitasvir, paritaprevir, and ritonavir plus ribavirin has achieved SVR12 in all 91 HCV treatment-naive patients or pegylated interferon plus ribavirin treatment-experienced patients with genotype 4 infection, although all patients were enrolled outside Egypt and none had cirrhosis.[11] This regimen achieved SVR12 in 40 (91%) of 44 patients without ribavirin, and in some countries is an approved treatment option for patients unable to tolerate ribavirin.[11] Based on these data, the European approved label, and modelling for patients with cirrhosis, this regimen was approved in Egypt for treatment of patients with genotype 4 infection without cirrhosis (12-week treatment duration) and with compensated cirrhosis (24-week treatment duration).

The large population of patients with HCV genotype 4 infection, the lack of substantial data with other interferon-free direct-acting antiviral regimens to treat the genetic diversity of genotype 4 (17 confirmed subtypes), and paucity of data in patients with cirrhosis created an opportunity for a large clinical trial to address a major medical need. Therefore, this phase 3 study was designed to assess the efficacy and safety of ombitasvir, paritaprevir, and ritonavir plus ribavirin in patients with HCV genotype 4 infection in Egypt and to identify the appropriate treatment duration in patients with compensated cirrhosis.

Methods

Study design and patients

AGATE-II is a multicentre, phase 3, partly randomised open-label study in which patients were recruited from five academic and hepatology centres in Egypt.

We screened adults aged 18 years or older from each study site's clinical database. Eligible patients were chronically infected with HCV genotype 4 for at least 6 months with a plasma HCV RNA concentration of more than 1000 IU/mL at screening. We included patients who had been previously untreated for HCV or who had documented previous treatment failure with pegylated interferon plus ribavirin. We excluded patients with hepatitis B virus or HIV co-infection, or infection with any HCV genotype other than genotype 4.

For patients without cirrhosis, exclusion criteria were: alanine or aspartate aminotransferase more than five times the upper limit of normal, calculated creatinine clearance less than 60 mL/min, an international normalised ratio more than 1·5, haemoglobin or albumin below the lower limit of normal, and platelet count lower than 100×10^9 per L. Exclusion criteria for patients with cirrhosis were the same as above, except for the following: alanine or aspartate aminotransferase higher than seven times the upper limit of normal, albumin less than 2·8 g/dL, international normalised ratio greater than 2·3, and platelet count less than 50×10^9 per L.

Patients were categorised as not having cirrhosis if there was no evidence of cirrhosis by liver biopsy in the 24 months before screening or during screening, and in the absence of a biopsy, must have had a screening FibroTest score of 0·72 or lower and an aspartate aminotransferase to platelet ratio index of 2 or lower, or a screening transient elastography (eg, FibroScan) result of less than 12·5 kPa. Patients categorised as having compensated cirrhosis had a diagnosis of cirrhosis based on a previous or screening liver biopsy (eg, Metavir Fibrosis Score >3 [including 3/4 or 3–4] or Ishak score >4), FibroScan score 14·6 kPa or greater within 6 months of, or during, screening, or a screening FibroTest score of more than 0·72 and aspartate aminotransferase to platelet ratio of more than 2. A Child-Pugh score of 6 or less was required at screening.

This study was done in accordance with the International Conference of Harmonisation guidelines, applicable regulations, and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. Ethics approval was granted by each study site (appendix). All patients gave written informed consent.

See Online for appendix

Randomisation and masking

Eligible patients assessed as having cirrhosis were assigned to receive study drugs for 12 weeks, whereas patients assessed as having cirrhosis were randomly assigned (1:1) to receive either 12 weeks or 24 weeks of treatment. Randomisation was stratified by treatment experience, and further stratified by type of previous response to therapy: null response, partial response, or relapse (definitions for each type of response are in the appendix p 3). Patients were randomised using a web-based interactive response technology system, and computer-generated schedules were prepared by personnel from AbbVie's statistics department. Investigators were masked to randomisation schedules and were informed of each patient's assigned treatment by the interactive response technology system immediately after the patient's randomisation. Patients were treated and assessed in an unmasked, open-label

manner. The study was unmasked and open label to reduce probability of error in study conduct and risk to patients, and because knowledge of receiving active drug is unlikely to affect the primary efficacy endpoint (suppression of HCV RNA levels).

Procedures

All patients received oral once-daily co-formulated 25 mg ombitasvir, 150 mg paritaprevir, and 100 mg ritonavir plus weight-based ribavirin dosed twice daily (1000 mg daily if bodyweight <75 kg, 1200 mg daily if bodyweight ≥75 kg). Ribavirin dose could be reduced by 200 mg if haemoglobin concentration decreased to less than 10 g/dL, and interrupted if haemoglobin concentration decreased below 8·5 g/dL. Additionally, patients with a history of stable cardiac disease experiencing a decrease in haemoglobin of 2 g/dL or more during any 4-week treatment period were to reduce ribavirin by 200 mg.

Post-treatment follow-up was for 48 weeks for all treatment groups. We took plasma samples at screening and on-treatment study visits on day 1, weeks 1, 2, 4, 6, 8, 10, and 12 (and 16, 20, and 24 in the 24-week treatment group), and on post-treatment weeks 2, 4, 8, and 12. Screening plasma samples were assessed for genotype and subtype using GEN-C 2.0 Reverse Hybridization Strip Assay (Nuclear Laser Medicine, Settala, Italy).

We measured HCV RNA levels with AmpliPrep/COBAS TaqMan HCV Test version 2.0 (Roche, Basel, Switzerland) at a designated laboratory in Egypt with a lower limit of quantification (LLOQ) of 15 IU/mL. We assessed vital signs, and collected samples for chemistry, haematology, and urinalysis at each study visit.

Outcomes

The primary outcome was the proportion of patients with SVR12, defined as HCV RNA less than LLOQ 12 weeks after the last dose of study drug, analysed by treatment group at a designated central laboratory in Egypt. Secondary outcomes were the percentage of patients in each treatment group with on-treatment virological failure and with post-treatment relapse within 12 weeks of the end of treatment.

We defined on-treatment virological failure as a confirmed increase from nadir in HCV RNA (defined as two consecutive HCV RNA measurements >1 $\log_{10}$ IU/mL above nadir) at any point during treatment; failure to achieve an HCV RNA concentration lower than LLOQ by week 6; or confirmed HCV RNA at LLOQ or higher in two consecutive measurements at any point during treatment after HCV RNA concentration decreased below LLOQ. We defined post-treatment relapse as two consecutive post-treatment HCV RNA measurements at LLOQ or higher within 12 weeks of completion of treatment with HCV RNA concentration below LLOQ. If a patient did not have data in the SVR12 visit window, but had an HCV RNA value less than LLOQ at the following visit, then we imputed the SVR12 value as lower than LLOQ. We counted patients still missing an SVR12 value after this backward imputation as non-responders in the analysis to obtain a conservative estimate of the proportion of patients achieving SVR12.

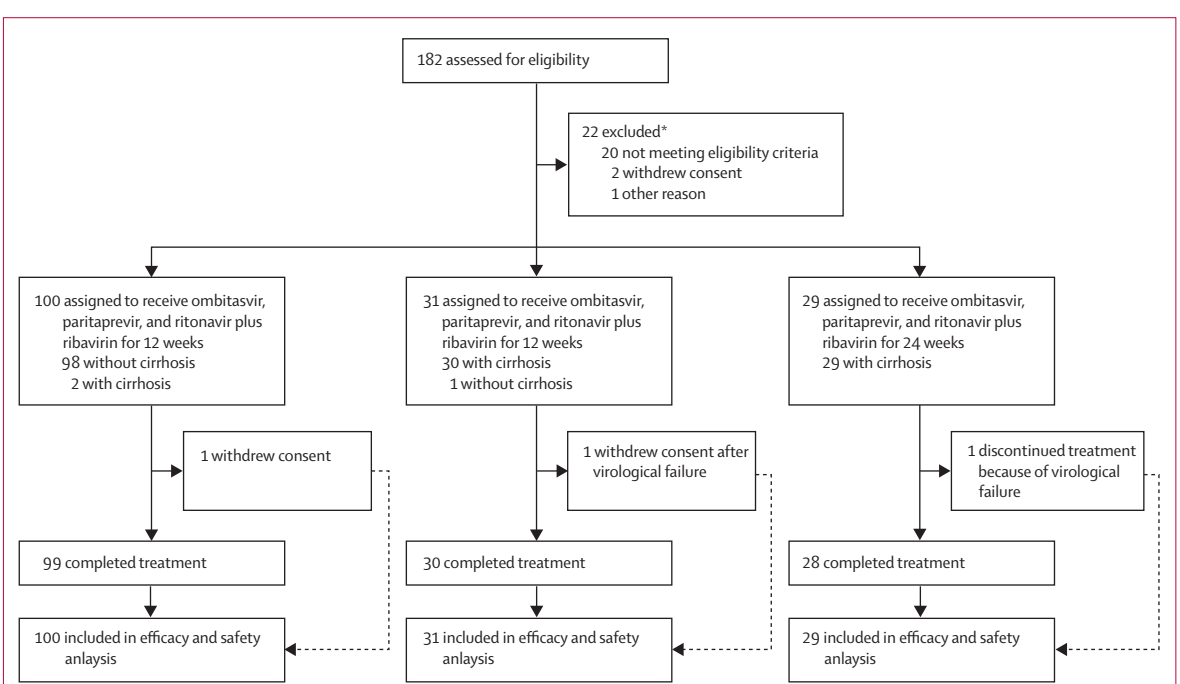

Figure: **Trial profile**

*Exclusion from the study could be for more than one reason. One patient did not meet eligibility criteria but also listed one other unspecified reason.

We monitored adverse events in all patients who received at least one dose of study drugs and categorised adverse events using the Medical Dictionary for Regulatory Activities coding dictionary version 18.1. We defined treatment-emergent adverse events as any event occurring after the first dose of study drugs until 30 days after the last dose; serious adverse events were collected throughout the study. The severity and relation of adverse events to study drugs were assessed by the investigator.

Statistical analysis

We planned to enrol roughly 100 patients without cirrhosis and 60 patients with cirrhosis to gain experience in Egyptian patients with and without compensated cirrhosis. Assuming that 90% of the patients in each treatment group achieved SVR12, the two-sided 95% Wilson score CI for binomial proportion would be 82·6–94·5 with a width of 11·9% in patients without cirrhosis and 74·4–96·5 with a width of 22·1% in patients with cirrhosis.

We analysed efficacy and safety in all patients who received at least one dose of study drugs, and summarised by the assigned treatment group.

We did two prespecified sensitivity analyses of the primary endpoint: one excluding patients with non-virological failure (ie, lost to follow-up or missing SVR12 data); and one grouping the patients assigned to one of the 12-week treatment groups by their baseline cirrhosis stage (≤F3 *vs* F4).

The results reported here are from the planned primary analysis completed when all patients had reached post-treatment week 12 or prematurely discontinued the study. Patients are to be followed for 48 weeks after their last dose of study drugs to assess durability of response and improvements in hepatic function. All statistical tests and all CIs were two-sided with a significance level of 0·05. We estimated CIs for efficacy endpoints using the Wilson score method. We used SAS version 9.3 for the UNIX operating system for all analyses.

This study is registered with ClinicalTrials.gov, number NCT02247401.

Role of the funding source

AbbVie funded the study and contributed to study design and conduct, data management, analysis, and interpretation, and the preparation and approval of this report. All authors had access to all the data in the study, reviewed and approved the final report, and take full responsibility for the accuracy of the data and statistical analysis. The corresponding author had full access to all data in the study and had the final responsibility for the decision to submit for publication.

Results

We recruited patients between Nov 4, 2014, and March 16, 2015. Of 182 patients screened, 160 were eligible for inclusion. 100 enrolled patients were assessed as not having cirrhosis and were assigned to receive ombitasvir, paritaprevir, and ritonavir plus ribavirin for 12 weeks. 60 patients were assessed as having cirrhosis, 31 of whom were randomly assigned to receive 12 weeks of treatment and 29 of whom were randomly assigned to receive 24 weeks of treatment (figure). Of the 22 patients who did not meet eligibility criteria, the most common reason was an exclusionary laboratory value. Two patients with cirrhosis (baseline fibrosis stage F4) were miscategorised during enrolment as not having cirrhosis and assigned to the group of patients without cirrhosis, and one patient without cirrhosis (baseline fibrosis

	Patients without cirrhosis, 12 weeks (N=100)	Patients with cirrhosis, 12 weeks (N=31)	Patients with cirrhosis, 24 weeks (N=29)
Sex			
Male	70 (70%)	29 (94%)	22 (76%)
Female	30 (30%)	2 (6%)	7 (24%)
Ethnicity			
White	98 (98%)	29 (94%)	28 (97%)
Black	2 (2%)	2 (6%)	1 (3%)
Age (years)	48·6 (13·1)	57·3 (6·5)	55·8 (8·0)
Age ≥55 years	39 (39%)	20 (65%)	16 (55%)
BMI (kg/m²)	29·1 (4·5)	29·3 (4·4)	31·0 (4·7)
BMI ≥30	36 (36%)	13 (42%)	16 (55%)
Interferon experienced*	51 (51%)	16 (52%)	14 (48%)
Null responder	33 (65%)	9 (56%)	7 (50%)
Relapser	10 (20%)	5 (31%)	5 (36%)
Partial responder	8 (16%)	2 (13%)	2 (14%)
HCV RNA (log_{10} IU/mL)	6·01 (0·61)	6·02 (0·62)	5·97 (0·69)
Metavir fibrosis stage			
F0–1	68 (68%)	0	0
F2	11 (11%)	0	0
F3	19 (19%)	1 (3%)†	0
F4	2 (2%)‡	30 (97%)	29 (100%)
HCV genotype 4 subtype§			
Subtype could not be identified	11 (11%)	4 (13%)	6 (21%)
4a	44 (44%)	13 (42%)	10 (34%)
4c or 4d	40 (40%)	13 (42%)	11 (38%)
4f	1 (1%)	0	0
4h	4 (4%)	1 (3%)	2 (7%)
Platelet count (×10⁹/L)	229 (61)	156 (81)	138 (57)
Serum albumin (g/dL)	4·5 (0·3)	4·2 (0·4)	4·0 (0·5)

Values are n (%) or mean (SD). *Definitions for treatment experience are in the appendix p 3. †One patient without cirrhosis was miscategorised as having cirrhosis. ‡Two patients with compensated cirrhosis were miscategorised as not having cirrhosis. §Screening samples were genotyped using GEN-C 2.0 Reverse Hybridization Strip Assay. Assay cannot distinguish genotypes 4c and 4d, so these genotypes are grouped together.

Table 1: **Baseline patient demographics and disease characteristics**

	Patients without cirrhosis, 12 weeks treatment	Patients with cirrhosis, 12 weeks treatment	Patients with cirrhosis, 24 weeks treatment
SVR12	94/100 (94%)	30/31 (97%)	27/29 (93%)
SVR12 excluding non-virological failures*	94/98 (96%)	30/31 (97%)	27/28 (96%)
SVR12 correcting for baseline cirrhosis status†	94/99 (95%)	30/32 (94%)	NA
Reasons for not achieving SVR12			
On-treatment breakthrough	1/100 (1%)	1/31 (3%)	1/29 (3%)
Relapse	3/98 (3%)	0	0
Missing SVR12 data	1/100 (1%)	0	1/29 (3%)
Premature discontinuation	1/100 (1%)	0	0

Values are n/N (%). NA=not applicable. SVR12=sustained virological response at 12 weeks after last dose of study drugs. *Sensitivity analysis excludes patients with non-virological failure. †Sensitivity analysis groups the patients assigned to the 12-week treatment groups by their baseline cirrhosis stage (≤F3 *vs* F4) because two patients with F4 fibrosis were enrolled into the group of patients without cirrhosis, and one patient with F3 fibrosis at baseline was enrolled into the cirrhosis 12-week treatment group.

Table 2: **Sustained virological response and reasons for non-response**

	Patients without cirrhosis, 12 weeks treatment (N=100)	Patients with cirrhosis, 12 weeks treatment (N=31)	Patients with cirrhosis, 24 weeks treatment (N=29)
Any adverse event	80 (80%)	26 (84%)	25 (86%)
Adverse events occurring in ≥10% of patients			
Headache	41 (41%)	9 (29%)	10 (35%)
Fatigue	35 (35%)	9 (29%)	11 (38%
Pruritus	23 (23%)	4 (13%)	9 (31%)
Dyspepsia	17 (17%)	4 (13%)	4 (14%)
Upper abdominal pain	19 (19%)	2 (6%)	3 (10%)
Cough	6 (6%)	4 (13%)	9 (31%)
Insomnia	9 (9%)	2 (6%)	5 (17%)
Serious adverse event	2 (2%)	0	2 (7%)
Death	1 (1%)	0	0
Ribavirin dose reduction due to haemoglobin decline	11 (11%)	4 (13%)	6 (21%)
Haemoglobin*			
Grade 2 (8–10 g/dL)	7 (7%)	2 (6%)	4 (14%)
Total bilirubin			
Grade 2 (>1·5–3 × ULN)	17 (17%)	13 (42%)	13 (45%)
Grade ≥3 (>3 × ULN)	2 (2%)	2 (6%)	4 (14%)

Treatment-emergent adverse events were defined as any event occurring after the first dose of study drug until 30 days after the last dose; serious adverse events were collected throughout the study. No adverse events led to study drug discontinuation. *No patients had grade 3 haemoglobin abnormalities. ULN=upper limit of normal. No patient experienced an aminotransferase or alkaline phosphatase value >3 × ULN (grade 2) during treatment.

Table 3: **Treatment-emergent adverse events and laboratory abnormalities**

stage F3) was miscategorised during enrolment as having cirrhosis and randomised to the 12-week treatment group of patients with cirrhosis. All patients assigned to treatment received at least one dose of study drugs. One patient in each group discontinued treatment prematurely.

Enrolled patients were predominantly men (76%; table 1). Patients who had previously been treated with pegylated interferon and ribavirin made up 51 (51%) of 100 patients in the cirrhosis group, 16 (52%) of 31 patients in the cirrhosis 12-week treatment group, and 14 (48%) of 29 patients in the cirrhosis 24-week treatment group (table 1). HCV genotype 4 subtypes based on LiPA analysis of screening samples were mainly 4a (67 [42%]), or 4c or d (64 [40%]). Patients with cirrhosis were older and had lower mean platelet counts and serum albumin concentrations than patients without cirrhosis, indicative of more advanced liver disease.

SVR12 was achieved in 94 (94%; 95% CI 88–97) of 100 patients in the group without cirrhosis (table 2). Four patients in this group experienced virological failure (one on-treatment rebound and three relapses), one patient discontinued treatment prematurely (withdrawn consent), and one patient died on post-treatment day 17 for reasons deemed unrelated to study drugs. One of the patients who experienced relapse in the without cirrhosis group had F4 compensated cirrhosis at baseline.

In the cirrhosis 12-week treatment group, 30 (97%; 95% CI 84–99) of 31 achieved SVR12; one patient did not suppress HCV RNA to less than the LLOQ by treatment week 6 and discontinued treatment. In the cirrhosis 24-week treatment group, SVR12 was achieved in 27 (93%; 78–98) of 29 patients; one patient had on-treatment virological breakthrough and one patient was lost to follow-up after achieving an SVR at post-treatment week 4.

In the sensitivity analysis excluding non-virological failures, SVR12 was achieved in 94 (96%; 95% CI 90–98) of 98 patients in the without cirrhosis group, 30 (97%; 84–99) of 31 patients in the cirrhosis 12-week treatment group, and 27 (96%; 82–99) of 28 in the cirrhosis 24-week treatment group (table 2). In the sensitivity analysis grouping patients assigned to a 12-week treatment group by baseline fibrosis stage, SVR12 was achieved in 94 (95%; 89–98) of 99 patients without cirrhosis, and 30 (94%; 80–98) of 32 patients with compensated cirrhosis. Baseline characteristics for patients who did not achieve SVR12 are presented in the appendix (p 4).

Adverse events were reported by 80 (80%) of 100 patients in the without cirrhosis group, 26 (84%) of 31 patients in the cirrhosis 12-week treatment group, and 25 (86%) of 29 patients in the cirrhosis 24-week treatment group (table 3). Most adverse events were mild or moderate in intensity. The most common adverse events (≥10% of overall patients) were headache, fatigue, pruritus, dyspepsia, upper abdominal pain, cough, and insomnia. Serious adverse events were reported in four patients. One patient in the without cirrhosis group experienced a serious adverse event of deep venous thrombosis on treatment day 69, which was considered by the investigator to have a reasonable possibility of being related to study

drugs, and one patient experienced a serious event of succinylcholine-induced apnoea leading to cardiac arrest and death on post-treatment day 17. This patient self-administered succinylcholine to treat pain associated with cramping of a leg muscle, and the events leading to death were not considered to be related to study drugs. Two patients in the 24-week treatment group experienced single serious adverse events assessed as not related to study drugs: one patient experienced variceal bleeding (post-treatment day 19) and a patient who had previously diagnosed gallstones experienced acute cholecystitis requiring cholecystectomy (treatment day 137). No patients in the cirrhosis 12-week treatment group experienced any serious adverse events, and treatment was not interrupted or discontinued in any patient because of adverse events.

No patient experienced an aminotransferase or alkaline phosphatase value more than three times the upper limit of normal (grade 2) during treatment. The most frequent laboratory abnormality was total bilirubin elevation, which was more prevalent in patients with cirrhosis (table 3). Eight patients had grade 3 total bilirubin elevations (>3×the upper limit of normal), seven of which occurred during the first week of treatment, and seven of which lasted for no more than two study visits and resolved with continued study drug dosing. Total bilirubin elevations were not associated with aminotransferase elevations; Hy's law criteria (aminotransferase elevation >3×the upper limit of normal with coincident total bilirubin elevation >2×the upper limit of normal) were not met in any patient.

Ribavirin dose was reduced in 22 patients because of adverse events (11 [11%] patients in the without cirrhosis group, four [13%] patients in the cirrhosis 12-week treatment group, and seven [24%] patients in the cirrhosis 24-week treatment group). All patients with a ribavirin dose modification achieved SVR12. Decreases in haemoglobin concentration led to ribavirin dose reductions in 21 (13%) patients, decreases below 10 g/dL were reported in 13 (8%) patients, and no patients experienced a haemoglobin concentration of less than 8 g/dL (grade 3). More patients in the 24-week treatment group had decreases in haemoglobin concentration to less than 10 g/dL than in the corresponding 12-week treatment group, although all haemoglobin decreases in this group were reported within the first 12 weeks of treatment.

Normalisation of liver aminotransferases in patients with a level above the normal limit at baseline was reported in 89 (99%) of 90 patients by the end of treatment. Patients included in the cirrhosis groups had a mean change from baseline in albumin concentrations at post-treatment week 12 of 0·21 g/dL in the 12-week treatment group and 0·19 g/dL in the 24-week treatment group (data not shown).

Discussion

The results from this phase 3 trial (AGATE-II) of ombitasvir, paritaprevir, and ritonavir plus ribavirin show high proportions of patients in Egypt with HCV genotype 4 infection achieving SVR12, including those with treatment experience and those with and without compensated cirrhosis. 94% of patients who received at least one dose of study drugs achieved SVR12, and 96% achieved SVR12 excluding non-virological failures. Similar proportions of patients receiving 12 weeks of treatment (with or without cirrhosis) achieved SVR12 to those reported for patients without cirrhosis previously,[11] and the results are further supported by the companion AGATE-I study[17] in which SVR12 was achieved in 57 (97%) of 59 patients with compensated cirrhosis receiving 12 weeks of treatment and in 60 (98%) of 61 patients with compensated cirrhosis receiving 16 weeks of treatment with ombitasvir, paritaprevir, and ritonavir plus ribavirin. Additionally, similar proportions of patients with compensated cirrhosis achieved SVR12 with 12 weeks and with 24 weeks of treatment, with one patient in each group experiencing virological failure; thus, 12 weeks of treatment might be sufficient in patients with genotype 4 infection and compensated cirrhosis. Two patients experienced virological failure on treatment: one patient failed to suppress by treatment week 6, and one patient had virological breakthrough on treatment week 8. These early virological failures might have been the result of pharmacokinetics, adherence, or drug potency. On-treatment virological failure does not provide support for a longer treatment duration that aims to reduce the rate of relapse. Only one patient with cirrhosis relapsed.

The study was designed to qualitatively assess the risks and benefits associated with 12-week and 24-week treatment regimens in Egyptian patients with compensated cirrhosis. Although Egypt has the highest prevalence of HCV infection worldwide, large trials of interferon-free regimens in this population are rare. These results are relevant to other countries in the Middle East and sub-Saharan Africa, where 85% of the global prevalence of genotype 4 infection exists,[1,3] and are of interest to parts of southern Europe where the prevalence of genotype 4 is increasing because of injection drug use and immigration from Egypt and the Middle East.[18–22]

The rapidly developing era of direct-acting antiviral regimens for more than one HCV genotype has brought hope to patients and health-care providers that the increasing burden of disease can be eased. Egypt has made a commitment to provide HCV treatment with cure rates around 90% to all Egyptians who are infected in order to reduce the epidemiological, social, and economic toll on its population.[7,8,23] Ombitasvir, paritaprevir, and ritonavir plus ribavirin was approved for use in Egypt in October, 2015, the first multi-direct-acting antiviral regimen to be approved without the use of interferon in Egypt. This approval was based on the phase 2 study results from the PEARL-I study[11] in which all 91 treatment-naive and treatment-experienced patients without

cirrhosis receiving ombitasvir, paritaprevir, and ritonavir plus ribavirin achieved SVR12.

Data with other all-oral regimens—notably daclatasvir plus sofosbuvir, ledipasvir plus sofosbuvir, and elbasvir plus grazoprevir—have been reported in smaller numbers of patients than ombitasvir, paritaprevir, and ritonavir plus ribavirin, with few patients with cirrhosis. The previous interferon-free standard of care for genotype 4 in Egypt was sofosbuvir plus ribavirin, which achieved SVR12 in 73–77% of patients when given for 12 weeks, and 90–91% when given for 24 weeks.[24,25] Rates of response with 12 weeks of sofosbuvir plus ribavirin were lower in patients with cirrhosis (53–63%) than in those without cirrhosis, and in patients with treatment experience (64–66%) than in treatment-naive patients. Ledipasvir plus sofosbuvir for 12 weeks resulted in an SVR12 in 41 (93%) of 44 European patients with genotype 4 infection, only ten of whom had cirrhosis.[26] A pooled analysis of elbasvir plus grazoprevir with or without ribavirin for 12 weeks or 16 weeks achieved SVR12 in 96 (93%) of 103 European patients with genotype 4 infection.[27] For this regimen, notably fewer patients with cirrhosis (19 [83%] of 23) and treatment-experienced patients (32 [86%] of 37) achieved SVR12. In treatment-experienced patients, the addition of ribavirin to elbasvir plus grazoprevir increased the number of patients achieving SVR12 to 14 (93%) of 15, and treatment extension to 16 weeks with this regimen increased the number of patients achieving SVR12 to eight (100%) of eight. Lastly, daclatasvir plus sofosbuvir has been assessed in even fewer patients with genotype 4.[28,29]

Overall, ombitasvir, paritaprevir, and ritonavir plus ribavirin was well tolerated, with no study drug interruptions or discontinuations due to an adverse event. These results were consistent with the findings from the phase 2 PEARL-I study.[11] Indirect hyperbilirubinaemia was the most frequently observed laboratory abnormality, probably stemming from ribavirin-induced haemolysis and known inhibition of the organic anion transporting polypeptide 1B1 bilirubin transporter by protease inhibitors.[30] Other laboratory abnormalities were rare. Ribavirin dose modification due to adverse events or decreases in haemoglobin concentration had no effect on SVR12. Recent changes in the label for ombitasvir, paritaprevir, and ritonavir either contraindicated or do not recommend the use of this regimen in patients with decompensated cirrhosis (Child-Pugh classes B and C). However, our study population included only patients with Child-Pugh class A compensated cirrhosis. No cases of serious liver injury occurred, further supporting the safety of this regimen for patients with compensated cirrhosis.

We did not do pharmacokinetic analyses, precluding assessment of whether drug exposures might have played a part in virological breakthrough, although patients who experienced on-treatment breakthrough were reportedly adherent to their regimen. Another limitation of this study was the absence of baseline and virological failure sequencing to assess the role of resistance-associated variants in achievement of SVR12.

Strengths of this study include the direct comparison of treatment durations for patients with cirrhosis, large sample size, and the exclusive enrolment of patients in Egypt, who have unique subgenotypic epidemiology and might have demographic characteristics not addressed by studies of patients with genotype 4 infection in Europe or other parts of the world. Conclusions cannot be extrapolated to patients with more advanced liver disease, such as patients with decompensated cirrhosis, who were excluded from this study.

The substantial burden of HCV infection in Egypt requires a disease control strategy to reduce future hardships. This plan includes education about safe injection practices, awareness through HCV screening, and treatment plans to reduce viraemia. Models using interferon-based treatment regimens forecast HCV viraemia to decline for the next decade, whereas incidence of compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and liver-related deaths are projected to continue to increase.[31] Increasing access to therapies, as is being done in Egypt, and the substantially improved efficacy of direct-acting antiviral regimens are expected to reduce the HCV disease burden. The results presented here show that the 12-week, interferon-free, direct-acting antiviral regimen of ombitasvir, paritaprevir, and ritonavir plus ribavirin achieved high SVR12 rates in patients with and without compensated cirrhosis, irrespective of treatment experience. Extension of treatment to 24 weeks in patients with cirrhosis did not have an SVR advantage. In conclusion, this regimen can be applied to the treatment strategy for elimination of HCV in Egypt and potentially in other resource-limited countries where HCV genotype 4 is prevalent.

Contributors

IW, GS, GE, AY, MH, RS, MAM, NA, NZ, and WD undertook the study, including selection, treatment, and follow-up of patients, data interpretation, and preparation and critical review of the report. TA participated in the conception and study design, data interpretation, and preparation and critical review of the report. RBQ and NM participated in the conception and study design, collection, assembly, and analysis of data, interpretation of the data, and preparation and critical review of the report. RR participated in the conception and study design, analysis and interpretation of data, and preparation and critical review of the report. CH participated in the collection, assembly, analysis, and interpretation of data, and preparation and critical review of the report.

Declaration of interests

IW has been speaker for Hoffman–La Roche, Merck, Bristol-Myers Squibb, Gilead Sciences, and Janssen, is an adviser for Janssen, Hoffman–La Roche, Merck, and Abbott, and has been a study investigator for Hoffman–La Roche, Bristol-Myers Squibb, Gilead, Janssen, Pharco, and AbbVie. GS, RS, and WD have been study investigators for AbbVie. NZ has been a study investigator for AbbVie and Marcyrl Pharmaceutical Industries. GE has been an adviser for Merck Sharp & Dohme, Gilead, and Bristol-Myers Squibb, has been a speaker for Bristol-Myers Squibb, Roche, Merck Sharp & Dohme, and GlaxoSmithKline, and has received grant and research support from Gilead, Roche, Merck Sharp & Dohme, GlaxoSmithKline, Bristol-Myers Squibb, AbbVie, and Janssen. AY has been a speaker for AbbVie, Gilead, Merck Sharp & Dohme, Roche, and Janssen, and a study investigator for

AbbVie. MH has been a study investigator for AbbVie, Janssen, and Gilead. MAM has been a study investigator for AbbVie, Gilead, and Bristol-Myers Squibb. NA has been a study investigator for AbbVie, Bristol-Myers Squibb, and Pharco companies. TA has been a clinical investigator, speaker, and consultant for AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen Pharmaceuticals, Merck Sharp & Dohme, and Roche. RBQ, CH, RR, and NM are employees of AbbVie, and own AbbVie stock.

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