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Antiviral Drugs

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Abbreviations

3TC	lamivudine (dideoxythiacytidine)
ABC	abacavir
ACV	acyclovir
ADV	adefovir dipivoxil
D4T	stavudine (didehydrodideoxythymidine)
DCV	daclatasvir
DTG	dolutegravir
ETV	entecavir
ETC	emtricitabine
EFV	efavirenz
EVG	elvitegravir
FOS	foscarnet
GCV	ganciclovir
Peg-IFN	peg-interferon-alfa-2a
IM	imiquimod
LAM	lamivudine
LDV	ledipasvir
MVC	maraviroc
RAL	raltegravir
RBV	ribavirin
RPV	rilpivirine
SIM	simeprevir
SOF	sofosbuvir
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
VGV	valganciclovir
ZDV	zidovudine

DRUGS ACTIVE AGAINST CYTOMEGALOVIRUS

Cidofovir [SEDA-35, 503; SEDA-36, 401; SEDA-37, 329; SEDA-38, 261; SEDA-39, 269]

Human Cytomegalovirus (CMV) infection can complicate successful solid organ transplantation in patients. Seven male and two female transplant recipients for the kidney (two recipients), pancreas (two recipients), lung (four recipients), and small bowel (one recipient) received cidofovir for refractory CMV infections. Three recipients were CMV seronegative, but all nine received grafts from CMV-seropositive donors. Five patients were on antithymocyte globulin, four received daclizumab induction, and one suffered from immunodeficiency. Of these treated patients, seven experienced rejection. Eight patients had received prophylactic ganciclovir (GCV), and eight had been treated for CMV infection with one or more drugs (GCV—eight; CMV immunoglobulin—three; foscarnet—three). Four patients had mild nephrotoxicity, and three developed renal failure. Two patients died of uncontrolled infections and concurrent CMV disease, one with invasive aspergillosis and another with nocardiosis. The authors were of the opinion that use of GCV is effective in solid organ transplant patients and adverse events are of low grade (AEs) [1c].

Letermovir [SEDA-38, 261; SEDA-39, 269]

Letermovir acts on the CMV-terminase complex and inhibits viral replication and survival.

Observational Studies

In a Phase 3 double-blinded study in CMV-seropositive transplant recipients, letermovir or placebo was randomly administered orally or intravenously. A total of 565 patients underwent randomization and received letermovir or placebo beginning 9 days after transplantation. Letermovir was administered at a dose of 480 mg per day orally (or 240 mg per day in patients taking cyclosporine). The primary end point for the determination of drug efficiency was the lack of CMV DNA in patients. Among 495 patients with undetectable CMV DNA at the time of

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randomization, fewer patients in the letermovir group than in the placebo group had clinically significant CMV infection (122 of 325 patients vs 103 of 170). The frequency and severity of AEs were similar in the treated and placebo groups. Vomiting was reported in 18.5% of the patients who received letermovir and in 13.5% who received the placebo; edema was reported in 14.5% and 9.4%, and atrial fibrillation or flutter in 4.6% and 1.0%, respectively. The rates of myelotoxic and nephrotoxic events were similar in the letermovir group and the placebo group. The mortality at week 48 after transplantation was 20.9% in letermovir and 25.5% in placebo recipients. Letermovir prophylaxis resulted in a significantly lower risk of CMV infection than placebo. AEs with letermovir were mainly of low grade [2C].

Brincidofovir [SEDA-39, 270]

Brincidofovir (BCV), a lipid conjugated prodrug of cidofovir, is a long-acting, broad-spectrum antiviral that was evaluated for the prevention and treatment of CMV and adenovirus infections in healthy subjects in Phase 1 and in hematopoietic cell transplant (HCT) recipients in Phase 2/3 clinical trials. The most common AEs reported for BCV were mild gastrointestinal events and asymptomatic, transient elevations in serum transaminases.

The kinetics of viremia and toxicity following preemptive treatment with BCV in children and adolescents diagnosed with HCT-related adenoviremia were compared in a multicenter trial. The study included 333 subjects (from January 2015 to May 2016) undergoing allogeneic stem cell transplant from seven pediatric transplant centers. Patients with significant viremia (adenovirus levels $\geq$1000 copies per mL) on two consecutive occasions were treated with cidofovir (5 mg/kg) weekly for 2consecutive weeks, followed by 1 mg/kg, three times weekly. Patients with preexisting renal impairment, those that developed renal impairment on cidofovir, and those that did not respond to 2 weeks of cidofovir were treated with BCV, 2 mg/kg, twice weekly. Adenoviremia was reported in 47 (14.1%) patients and significant viremia requiring antiviral treatment was noted in 27 patients (8.1%). Thirteen patients (80%) treated with BCV cleared viremia compared to eight patients (35%) treated with cidofovir. Two patients treated with cidofovir died of disseminated adenoviral infection. BCV was well tolerated and only one patient required interruption of BCV therapy after 4 weeks, due to severe abdominal cramps and diarrhea. BCV-mediated diarrhea was reported as a frequent side effect in the Phase 3 double-blind placebo-controlled trial for preventing CMV infections. The authors suggested that it is important to distinguish BCV toxicity from gut graft-vs-host disease (GVHD) and virus-associated diarrhea in HCT transplant patients. Nine of 23 patients treated with cidofovir developed mild-to-moderate nephrotoxicity [3C].

Foscarnet [SEDA-35, 504; SEDA-36, 403; SEDA-37, 329; SEDA-38, 262; SEDA-39, 270]

Observational Study

A 4-month-old infant had severe combined immunodeficiency disease (SCID), with undetectable levels of immunoglobulins and severe lymphopenia (476 cells/mL). The patient also was diagnosed with CMV viremia. Further analysis showed CD19 (341 cells/mL) and CD56 (250 cells/mL) expressing cells with no cells expressing CD3, which is the basic diagnosis of T − B + NK + SCID. DNA sequence analysis revealed a G615T homozygous stop codon mutation in the IL-7 Ra gene. Treatment was initiated with ganciclovir (GCV), and within 3 weeks CMV copies increased (5.8×10^6). First course of foscarnet (FOS) was initiated (180 mg/kg/day). During this time, total serum calcium was 10.6 mg/dL. Concurrent medications given were: piperacillin–tazobactam, prophylactic trimethoprim/sulfamethoxazole, rifampicin, isoniazid, and fluconazole. After 2 weeks of treatment, the CMV copies doubled and FOS was discontinued. This regimen followed Cidofovir administration 5 mg/kg once weekly. There was no decrease in CMV copies and FOS (180 mg/kg/day) was reintroduced combined with GCV (10 mg/kg/day). A CMV point mutation was detected suggesting that the virus was drug resistant. At initiation of the combined treatment, serum creatinine and urea levels were within the normal range. However, after 30 days of FOS treatment the calcium level reached 15.8 mg/dL, although the patient did not have any symptoms of hypercalcemia. CMV levels were reduced in the patient over time and FOS was withdrawn from the treatment regimen. The patient's treatment was again supplemented with FOS at a lower dose along with GCV to reduce the CMV count. This patient underwent a bone marrow transplant and was administered the same dose of FOS and GCV, but the patient died due to respiratory failure. The authors suggested that FOS binds to the inorganic bone matrix creating hypercalcemia, and calcium levels should be monitored closely during the treatment with FOS [4C].

The clinical safety and efficacy of FOS prophylaxis and pre-emptive therapy for CMV infection in allogeneic hematopoietic stem cell transplantation (HSCT) have also been reported. Ninety-six patients undergoing HSCT were included in this study. FOS was given at 60 and 120 mg/kg/day in a prevention and a preemptive study, respectively. The side effects of FOS prophylaxis were mild without any hematologic toxicities [5c].

Ganciclovir and Valganciclovir [SEDA-35, 504; SEDA-36, 404; SEDA-37, 330; SEDA-38, 262; SEDA-39, 270]

Observational Study

A renal transplant patient showed delayed graft and renal impairment leading to resistance to valganciclovir (VGC) [6A]. In another case study, a 71-year-old CMV-seronegative Caucasian man having end-stage renal disease had a renal transplantation from a CMV-seropositive donor. He was on hemodialysis and received 2 doses of thymoglobulin (1.5 mg/kg) and methylprednisolone (500 mg) and tacrolimus, mycophenolate mofetil 1000 mg (twice a day), and prednisone during the first month of post-transplantation. The patient was on sulfamethoxazole–trimethoprim and VGC 900 (mg each), daily, at the time of transplantation. Four months after transplantation, the recipient developed CMV viremia and acute thrombocytopenia. VGC was replaced with GCV 5 mg/kg twice daily and mycophenolate mofetil was lowered to 500 mg, twice daily. During the first 3 weeks of treatment, the patient's viral load progressively reduced, but after 27 days, the viral load doubled. GCV dosage was then increased to 10 mg/kg, twice daily. Further analysis showed a UL97-resistant mutation, and the patient was administered with FOS. Seven weeks after FOS treatment, the viral load increased and resistant strains to FOS, cidofovir, and GCV were detected in the patient's serum. CMV immunoglobulin was administered three times per week to overcome the mutant strains and that resulted in complete viral clearance. No side effects were reported from these treatments [6A].

Combination Study

A 61-year-old man with a 6-year history of diarrhea was admitted for weight loss. He had chronic sinusitis and continuous cough, and his sputum cultures showed positive for *Haemophilus influenzae* and β-haemolytic *Streptococcus*. The patient was subsequently diagnosed with oesophageal candidiasis, CMV disease, and a bacterial chest infection. The patient's CMV infection was treated with intravenous (IV) FOS (60 mg/kg, three times daily) for 3 weeks, followed by VGC (900 mg, once daily). Three months after treatment, the patient became negative for blood CMV DNA, and VGC was removed from the treatment regimen. He subsequently relapsed with CMV viremia and diarrhea due to CMV colitis and was again retreated with VGC (900 mg, twice daily) for the next 3 weeks, followed by long-term VGC prophylaxis (900 mg, once daily). A VGC resistance mutation (UL97 mutation H520Q) was detected in CMV isolated from the patient's blood. Cidofovir (5 mg/kg daily) was administered to reduce the CMV mutants. Oral Leflunomide (20 mg, once daily) was added to his treatment regimen. This study demonstrated viral resistance to VGC and severe side effects from FOS, emphasizing the difficulties in long-term suppression of CMV in patients with persistent immunodeficiency [7A].

Valaciclovir

A 43-year-old diabetic patient reported having partial vision and was on oral steroids and anti-viral therapy. The right eye of the patient showed inferior and had temporal retinal thinning. The right eye also had pigmentation and periarterial whitish focal Kyrieleis' plaques. The patient's left eye had mild vitritis, optic disc pallor, arteriolar attenuation, and whitening of the retina. Serology for human immunodeficiency virus (HIV), herpes simplex virus (HSV), and CMV was all negative, but IgM positive for varicella zoster virus. Valaciclovir (1 g, three times daily) was administered orally. No side effects of the drug in this patient were reported. The authors were of the opinion that a peripheral retinal examination must be done in cases with Kyrieleis' plaques to rule out retinitis and vasculitis [8A].

DRUGS ACTIVE AGAINST HERPES VIRUSES [SEDA-35, 507; SEDA-36, 407; SEDA-37, 332; SEDA-38, 263; SEDA-39, 271]

Acyclovir

Acyclovir (ACV) has been widely used to treat infections caused by herpes simplex virus (HSV) and varicella zoster virus (VZV). The common AEs of ACV included nausea, diarrhea, headache, dizziness and mental changes.

A randomized double-blind controlled trial compared the safety and efficacy of different strains of lactobacilli and ACV in female patients with recurrent genital HSV-2 infections. Patients were treated with multi-strain *Lactobacillus brevis* capsule every 12 h and oral ACV (400 mg, twice daily) for 6 months. Of the 53 patients treated, no differences were identified between ACV and probiotic for the primary and secondary efficacy end point, resolution of episode, lesion healing time, viral shedding, and percentage of pain. *L. brevis* was safe to treat patients compared to ACV. Some AEs were reported for ACV. The authors were of the opinion that multi-strain *L. brevis* could play an important role in suppression of recurrent genital HSV infection [9c].

A 67-year-old Chinese male who had VZV infection was on ACV (5 mg/kg, IV for 8 h) and developed severe thrombocytopenia within 10 days of starting ACV. ACV was stopped and the patient's condition improved. The

ACV-dependent platelet antibody test revealed that ACV was the causative agent for thrombocytopenia. This is the first case report of ACV-induced immune thrombocytopenia in VZV patients. The authors suggested that dentists should never overlook this rare AE of ACV, as rapid and appropriate treatment may prevent life-threatening complications [10A].

The effect of oral ACV administration in HSV-2-positive pregnant women on premature rupture of membranes (PROM) and risk of preterm delivery was reported in this study. A randomized, double-blind placebo-controlled trial among 200 HSV-2-positive pregnant women at 28 weeks of gestation was included in the study. Participants were assigned randomly to take ACV (400 mg orally, twice daily) for 28–36 weeks. Both control and treated patients were administered ACV after 36 weeks of pregnancy until delivery. One hundred women were randomized and received ACV and 100 were assigned to the placebo arm. There was a reduction of incidence of PROM at 36 weeks but this was not statistically significant in the ACV and placebo arms. A significant reduction occurred in the incidence of preterm delivery (11.1% vs 23.5%) in the ACV and placebo arms, respectively. The authors concluded that oral ACV treatment for HSV-2-positive pregnant women from 28 to 36 weeks reduced the incidence of preterm delivery but did not reduce the incidence of pre-PROM [11C].

Famciclovir

General adverse reactions reported for famciclovir treatment were headache, nausea, and diarrhea.

Neurological

A cross-sectional observational study by means of a quantitative survey in Ireland explored the frequency of diagnosis, methods of treatment and cost of acute herpes zoster and post-herpetic neuralgia (PHN). Famciclovir and valaciclovir were preferred for anti-viral therapy, and pregabalin for the treatment of increasing pain. Mild opioids (32%) were the most common analgesic agents used for first-line acute herpes zoster pain, and pregabalin (37%) for second-line acute herpes zoster pain. According to the authors, acute herpes zoster and its complication resulting herpetic neuralgia is a challenge in aging population of patients [12C].

One hundred and forty-three fibromyalgia patients were enrolled in a 16-week, double-blinded, multicenter, placebo-controlled study. This study evaluated a famciclovir + celecoxib drug combination (IMC-1), against suspected herpes virus reactivation and infection, and for the treatment of fibromyalgia. Patients received either IMC-1 or placebo in a 1:1 ratio. A significant decrease in fibromyalgia-related pain was observed in patients on IMC-1 treatment compared to the placebo group. Gastrointestinal and nervous system AEs were reported less in the IMC-1 group compared to the placebo group [13C].

Valaciclovir

A randomized, double-blind, valaciclovir-controlled Phase 3 study was conducted to evaluate the efficacy and safety of amenamevir. Seven hundred and fifty-one herpes zoster patients were randomly assigned to receive either amenamevir (400 or 200 mg) once daily or valaciclovir (1000 mg) three times daily for 7 days. The primary efficacy end point was the proportion of cessation of new lesion formation. The day 4 cessation proportions for amenamevir 400 and 200 mg and valaciclovir were 81.1% (197/243), 69.6% (172/247) and 75.1% (184/245), respectively. The study results revealed that amenamevir 400 mg was not inferior to valaciclovir. To the number of days taken for the cessation of new lesion formation, complete crusting, healing, pain resolution and virus disappearance were evaluated as secondary end points. There were no significant differences in secondary end points in any of the treatment groups. Amenamevir 400 and 200 mg and valaciclovir were all well tolerated. The proportions of patients who experienced drug-related AEs were 10.0% (25/249), 10.7% (27/252) and 12.0% (30/249) with amenamevir 400 mg, 200 mg, and valaciclovir, respectively. In conclusion, amenamevir 400 mg appears to be effective and well tolerated for treatment of herpes zoster in immunocompetent patients [14C].

A meta-analysis to examine the effectiveness and/or safety of nucleoside antiviral drugs for recurrent herpes labialis was reported. This study included 16 publications reporting 25 randomized controlled trials (8453 patients). The parameters used to measure efficacy were time to healing of classic and all lesions, time to resolution of pain, and percentage of aborted lesions. Nucleoside antiviral drugs decreased the time to healing of all lesions and also reduced the time to resolution of pain and increased the percentage of aborted lesions. Valaciclovir more effectively reduced the time to healing of all lesions and the time to resolution of pain than aciclovir. Both nucleoside antiviral drugs increased the percentage of aborted lesions, but penciclovir and famciclovir failed to improve curing the lesions. The authors were of the opinion that the nucleoside antiviral drugs are safe and beneficial for the treatment of recurrent herpes labialis; valaciclovir is more effective than ACV, especially in reducing the time to healing lesions [15R].

An overview of the clinical impact of alpha and beta herpes viruses was published that highlights the mechanisms of action, pharmacokinetics, clinical indications, and AEs of antiviral drugs for the management

of herpes simplex virus, VZV and CMV. The important AE, according to the authors, is the emergence of drug-resistant virus populations in organ transplant recipients [16R].

DRUGS ACTIVE AGAINST HEPATITIS VIRUSES

Adefovir [SEDA-35, 507; SEDA-36, 409; SEDA-37, 333; SEDA-38, 264; SEDA-39, 272]

A comparative study on the benefits of using tenofovir disoproxil fumarate (TDF) in chronic hepatitis B virus (HBV) patients has been reported. Forty-six chronic HBV patients were evaluated after LAM monotherapy vs the combination of lamivudine (LAM) plus adefovir dipivoxil (ADV). No significant differences between the two groups were noted in identifying AEs (53.8%, TDF vs 37.5%, LAM + ADV), and none of the AEs were serious [17c].

Multidrug-resistant HBV is still a continuing problem. Another study reported that the use of TDF + LAM is an effective therapy in LAM-resistant patients. In this study, 59 patients were included and were on TDF + LAM (300 mg/day) for 5 years. At the end of 5-year treatment, 75% (45/59) of the patients had achieved complete viral suppression. Throughout the study, only two patients had dose reduction due to AEs, such as increased glomerular filtration rate (eGFR) and non-Hodgkin lymphoma. This study concluded that long-term TDF treatment is safe and effective in patients with prior failure to LAM treatment and a suboptimal response to ADV therapy [18c].

Tenofovir alafenamide (TAF) is a novel prodrug of tenofovir that showed significant suppression of drug resistant-HBV in vitro and in patients [19E,20A].

TDF in chronic hepatitis B patients with gastric ulcers showed improvement on host immune response. Sixty patients were included in this study. The control group was treated with ADV, and the observation group was treated with TDF. The incidence of AEs was 10.00% in the observation group and 13.33% in the control group. There was no significant difference in the incidence of adverse drug reactions between the two groups [21c].

Another study was reported from the Netherlands, using peg-interferon-alfa-2a (peg-IFN) and nucleotide analogue combination therapy in patients with chronic HBV and low viral load. Participants were randomly assigned (1:1:1) to receive peg-IFN (180 μg/week) plus ADV (10 mg/day), peg-IFN (180 μg/week) plus TDF (245 mg/day), or no treatment for 48 weeks. The most frequent AEs (>30%) were fatigue, headache, fever, and myalgia, which were attributed to peg-IFN treatment. Two (4%) serious AEs were reported in the peg-IFN plus adefovir group, and one was admitted to a hospital for alcohol-related pancreatitis and another with severe depression [22c].

Adverse effects of oral antiviral therapy in HBV patients were reviewed [23R].

DIRECT-ACTING ANTIVIRAL PROTEASE INHIBITORS [DAA-PI] [SEDA-35, 508; SEDA-36, 409; SEDA-37, 335; SEDA-38, 267, 334; SEDA-39, 273]

Entecavir [SEDA-35, 512; SEDA-36, 411; SEDA-37, 335; SEDA-39, 273]

Observational Study

The efficacy and safety of the combined therapy of LAM and ADV, as well as entecavir (ETV) monotherapy in patients with hepatitis B-induced decompensated cirrhosis have been reported. One hundred and twenty-seven patients with decompensated cirrhosis were divided into four groups, and each group received different doses of regimens: initial combination of LAM and ADV, ADV add-on therapies with previous 12-week LAM, ADV add-on therapies with previous 24-week LAM, and ETV monotherapy. No serious AEs were observed in each group at the end of the 96-week treatment. The authors concluded that combination therapy and early ADV addition were preferred in the antiviral treatment of hepatitis B-induced decompensated cirrhosis patients [24C].

Ribavirin [SEDA-35, 512; SEDA-36, 412; SEDA-37, 335; SEDA-38, 267; SEDA-39, 273]

HIV/HCV co-infected patients treated with all-oral DAA regimens were included in this study. They were on a combination antiretroviral therapy (cART). Among these 323 patients, 60% were cirrhotic; 68% had previously received anti-HCV treatment, but the treatment was not effective. In this study the cART used was a protease inhibitor (PI)-based in 23%, non-nucleoside reverse transcriptase inhibitors (NNRTI)-based in 15%, and integrase inhibitor (II)-based in 38%, while 24% of patients received other regimens. SOF + DCV ± RBV was prescribed to 56.0% of patients, followed by SOF + ledipasvir (LDV) ± RBV in 20.4% of cases, SOF + RBV in 15.8%, and SOF + SMV ± RBV in 5.9%. Of the 164 patients with cirrhosis receiving at least two DAAs, 26 patients (16%) received a RBV-containing regimen for 12 weeks ($n = 9$) or 24 weeks ($n = 17$). Fifteen non-cirrhotic patients (14%) received a dual-DAA + RBV regimen for 12 weeks ($n = 11$) or 24 weeks. The most common AEs reported were fatigue and digestive disorders. AEs related to HCV therapy were reported in 94 patients (30%). Anemia

occurred in 16 patients; of these, 11 patients received RBV. Eleven patients stopped their HCV therapy prematurely, two for intolerance and one for lack of virological response. HCV treatment modifications were reported for 36 patients, of whom 10 stopped RBV and one stopped DCV. Dose modifications were reported for 32 patients for the following drugs: DCV ($n=14$), RBV ($n=13$), SMV ($n=2$), asunaprevir ($n=1$), SOF ($n=1$) and LDV ($n=1$). The reasons for treatment modification were intolerance ($n=6$), under-dosing ($n=8$), and unknown reasons ($n=22$). The authors concluded that the new all-oral DAA regimens were well tolerated and had excellent viral clearance in HIV/HCV co-infected patients [25C].

Sofosbuvir [SEDA-37, 335; SEDA-38, 268; SEDA-39, 273]

Chronic hepatitis C is the leading problem in liver transplantation. A recent review analyzed DAAs that have advanced in treatment of HCV in terms of tolerability, and duration of therapy with significant increases in the rates of sustained virologic response (SVR) with low side effects [26c].

Another study reported certain AEs in chronic HCV patients after DAA therapy in Brazil. The most frequently reported AEs in these patients were fatigue (43%), headache (42%), neuropsychiatric symptoms (30%) and nausea (26%). The most frequent (38%) laboratory abnormality was the low levels of hemoglobin (<12 mg/dL). Neuropsychiatric symptoms were the only AEs significantly different in treatment-experienced group compared to naïve patients [27c].

Mild AEs were reported in HCV patients treated orally with SOF based DAAs [28c].

A retrospective chart review was conducted in 204 HCV patients on SOF, and the role of psychological factors was evaluated. Depression or generalized anxiety had no role in viral clearance, but the use of cocaine influenced the SVR12 [29M].

Observational Study

A retrospective cohort study reported on 213 HCV patients. Seventy percent of patients received both SOF + RBV, whereas the remaining patients received triple therapy (SOF + RBV + IFN). The overall rate of SVR at 12 weeks post treatment was 72.9%. Most patients reported anemia and fatigue. The authors suggested that patients with HCV genotype 1 and 3 infection are better off with triple therapy compared to dual therapy [30C].

For the first time, a case was reported of an HCV infected patient treated for 12 weeks with the combination of SOF/ledipasvir plus RBV who developed a miliary tuberculosis (TB) infection. The authors are of the opinion that this case is relevant to increase the awareness of opportunistic infections such as TB during the treatment of HCV [31A].

One hundred patients with cirrhosis and infected with HCV genotypes 1 and 3 were included in a study that revealed the efficacy of SOF in combination with DCV and RBV. Patients were given 1 daily tablet of a combination pill (400 mg SOF and 60 mg DCV and weight-based RBV) for 12 weeks. One patient developed an increased creatinine level followed by severe diarrhea and gastroenteritis and was excluded from the study, one patient died due to unrelated reasons and four patients were lost to follow-up. Among the remaining 94 patients, 92 achieved SVR12 (98%). None of the patients reported any side effects [32C].

A case report showed two heart transplant recipients with HCV infection were treated with SOF + DCV and achieved SVR12 and neither patient showed any side effects [33A].

Twenty-four hundred cirrhotic patients with chronic HCV infection were treated with SOF and RBV for 24 weeks. The overall SVR12 rate was 71.2%. The most common AEs reported were fatigue, myalgia, headache, insomnia, and anemia. One hundred and thirty-five (5.63%) patients stopped treatment permanently due to the appearance of complications. The authors concluded that the use of SOF and RBV combination is safe and effective for treating HCV patients with liver cirrhosis [34C].

Combination Study

A multicenter, open-label, Phase 2 study evaluated the efficacy and safety of a fixed-dose combination of SOF-velpatasvir (400 mg/100 mg) plus weight-adjusted RBV administered for 24 weeks. Sixty-nine patients (HCV infected) did not achieve SVR by prior treatment with direct-acting antiviral regimens that included SOF plus the nonstructural protein 5A inhibitor, velpatasvir, with or without voxilaprevir. Most AEs were mild to moderate in severity. Other AEs reported were fatigue, nausea, headache, insomnia, and rash. One patient discontinued the study due to an AE (irritability) [35c].

SOF is not recommended for HCV patients with severe renal impairment. This study reported on 322 patients having renal dysfunction and infected with HCV. The patients received dual therapy of DCV and asunaprevir. Treatment discontinuation rates and AEs, including alanine aminotransferase elevation, anemia, and renal disorders, were not changed in dual therapy. According to the authors, the use of DCV and asunaprevir in combination therapy for HCV patients with renal dysfunction was safe and effective [36C].

Another study evaluated the use of ledipasvir/SOF without RBV for the treatment of recurrent HCV in post-liver transplant patients. There were no serious AEs and no discontinuation of treatment and 100% (60/60) SVR was achieved in 12 weeks of treatment.

This combination of ledipasvir/SOF was well tolerated without serious AEs or discontinuation [37C].

Sixty-three patients (median age 52 years; 80% males) with post-LT recurrent HCV were treated with SOF and RBV in a living donor liver transplant center in South Asia. Most (76.2%) were treatment experienced and predominantly HCV patients with either genotype 3 (77.7%) patients or genotype 1 (20.6%). AEs were noted in 34 patients; weakness and fatigue were the common side effects. Six patients showed a significant drop in hemoglobin (<8 g/dL). The authors concluded that SOF+ RBV combination therapy for 24 weeks was safe and effective in treatment for post-LT recurrent HCV patients [38C].

Chinese patients with kidney transplant (KT) having HCV infection were safely treated with SOF and DCV without any noticeable side effects or AEs [39c].

The emergence of drug resistance-associated variants (RAVs) in a combination of SOF plus ledipasvir therapy has been reported. One hundred and seventy-six patients with chronic HCV genotype 1 infection were treated with SOF/ledipasvir for 12 weeks. Serum lipid-related markers were measured. SVR was achieved in 94.9% (167 out of 176) of patients. Serum low-density lipoprotein cholesterol and apolipoprotein B levels were significantly elevated at week 4 in SOF/ledipasvir-treated patients. These elevations were greater than in ombitasvir/paritaprevir/ritonavir-treated patients. The authors concluded that NS5A multi-RAVs are likely to develop in patients who fail to respond to SOF/ledipasvir therapy [40c].

Co-Infection

The risk of HCV infection is six times higher for HIV-positive patients than for the HIV-negative population. HIV infection seems to accelerate HCV-associated liver fibrosis. This study was conducted in 669 HIV/HCV co-infected patients, who were treated with DCV (60 mg) plus SOF (400 mg) once daily, for 24 weeks. Fifty-five patients experienced one or more serious AEs, and 26 experienced one or more AEs of grade 3 or 4. There were 10 deaths, mostly due to advanced liver disease; one was considered possibly related to HCV or HIV treatment, and two were due to multi organ failure plus septic shock plus intestinal obstruction, and hepatic carcinoma. The remaining seven deaths were not related to treatment regimen. There were seven discontinuations or AEs, of which three were subsequently fatal (hepatic carcinoma, decompensated cirrhosis/multi organ failure, respiratory distress) and four were nonfatal (lymphopenia, renal insufficiency, attempted suicide, and anxiety/ascites/hepatocellular carcinoma pneumonia/encephalopathy). The authors concluded that treatment involving DCV+ SOF+RBV could achieve high SVR12 and was well tolerated in HIV/HCV co-infected patients having liver disease [41c].

Another study also showed a similar outcome when treated with DCV and SOF in HCV and HIV co-infected patients [42c].

Twenty-two adult liver transplant (LT) recipients with HCV (16 mono-infected and 6 co-infected with HIV) received a 24-week course of SOF+DCV treatment. Viral suppression was very rapid with undetectable HCV-RNA in all patients by 12 weeks. All patients completed the 24-week treatment course without any significant side effects except for one case of severe bradycardia [43c].

Multiple studies reported the use of SOF and DCV in combination or monotherapy to improve the liver function in chronic HCV patients [44c,45c,46c].

Simeprevir [SEDA-38, 269; SEDA-39, 274]

The efficacy and safety of simeprevir (SIM)/SOF in patients with chronic HCV genotype 4 infection were reported. A multicenter observational study conducted in Egypt included 583 patients with HCV genotype 4 infection and were treated with SOF/SIM for 12 weeks. Side effects reported included rash in 21 patients, photosensitivity in 18 patients, pruritus in 44 patients and hyperbilirubinemia in 42 patients [47C].

Combination Study

A recurrent HCV study was reported in a cohort of 424 patients, treated for 24 weeks with SOF/RBV. In 55 patients, a treatment regimen with DCV or SIM was added. The outcome indicator SVR was 86.7% in patients treated with SOF/RBV and 98.3% (58/59) in patients who received a second antiviral (DCV/SIM). No significant AEs reported in all treatment groups and all patients tolerated the treatment [48c].

Twenty-three liver–kidney transplant recipients treated with DAAs were included in this study. Recipients had different HCV genotypes: genotype 1a in five cases, genotype 1b in nine cases, genotype 3 in five cases and genotype 4 in three cases. All the recipients received at least one NS5B inhibitor (SOF) in their antiviral regimen. Two patients received SOF+SIM, and other patients received SOF and ledipasvir or DCV or RBV or a combination of these two drugs. Mild to moderate AEs were reported in 20 recipients. The most common AE was anemia and was more common in RBV-treated patients. In recipients treated with RBV, the dose of RBV was reduced and then discontinued for 2 recipients. Serious AEs were reported in 9 recipients: severe infection in 3 recipients (CMV-induced colitis, pneumonia, septicemia related to urinary tract infection), and one case each of hematuria, basocellular carcinoma, stroke, acute leg ischemia, acute kidney failure, and anemia/leukopenia [49C].

Daclatasvir

Observational Study

A Phase 2, open-label, single-arm, multicenter study was conducted in 106 HCV patients on a dual therapy. Among the patients, 27% were aged >65 years, 39% had cirrhosis, 53% had an estimated GFR 30–89 mL/min, 14% had diabetes, and 38% had arterial hypertension. The patients were administered with SIM (150 mg) + DCV (60 mg) once daily for 12 or 24 weeks. Overall, 42/106 received 12 weeks of treatment and 64/106 received 24 weeks of treatment. Ninety-seven (92%) patients achieved SVR12 after the end of treatment. The reasons for failure were viral breakthrough ($n=7$) at weeks 4–16, early treatment discontinuation ($n=1$) and viral relapse ($n=1$). Seventy-four (70%) patients had more than one AE during treatment, including six (6%) patients with ≥1 serious AE. Three patients discontinued treatment due to AEs. SIM + DCV demonstrated strong antiviral activity and was well tolerated in patients with hepatitis C virus genotype 1b infection, but, viral breakthrough occurred in seven patients, making this treatment regimen unsatisfactory [50C].

Dual oral therapy with DCV and asunaprevir in real-life settings in Japan was well tolerated in HCV genotype 1b patients (651 patients) included in the study, with a similar safety profile and achieved similar SVR12. Of these, only 2.9% discontinued the therapy due to the elevation of alanine transaminase (ALT). Seven patients in clinical trial-met group and 20 in clinical trial-unmet group discontinued therapy because of AEs other than the ALT elevation [51C].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: COMBINATIONS

Abacavir/Lamivudine/DTG

A retrospective clinical audit was conducted on HIV-patients who switched treatment to DTG/ABC/3TC fixed-dose combination therapy. Data from 443 HIV patients (97% male and 45% ≥50 years) were included in the study. Four hundred and forty-three patients participated in the study, and two patients discontinued from DTG/ABC/3TC after the study period. The most common reason for patients to switch therapy to DTG/ABC/3TC was simplification, toxicity/intolerance and patient preference. Fourteen patients (3.2%) discontinued DTG/ABC/3TC; none of these were due to virologic failure. Discontinuations were mainly related to AEs in 2.5% of the patients. Less than 1% of patients discontinued the treatment due to a psychiatric event [52C].

A randomized, open-label, Phase 3b study was conducted in adults with HIV-1 RNA (<50 copies/mL) and on antiretroviral therapy (ART) at the time of enrollment. Subjects were randomly assigned to switch to ABC/DTG/3TC once daily for 48 weeks (early-switch group) or continue current ART for 24 weeks and then switch to ABC/DTG/3TC (late-switch group). The primary end point was the proportion of subjects with HIV-1 RNA <50 copies/mL at the end of 24 weeks treatment. 553 subjects were enrolled in the study and 275 were randomly assigned to switch immediately to ABC/DTG/3TC (early switch group), whereas 278 continued on current ART (late switch group). At week 24, subjects who switched to ABC/DTG/3TC (85%) or remained on current ART (88%) showed viral suppression, indicating that ABC/DTG/3TC was not inferior in virological suppression. AEs were reported more frequently with ABC/DTG/3TC (66%) than with current ART (47%) by week 24, and in the late-switch group 60% of the subjects reported AEs [53C].

Elvitegravir/Cobicistat/FTC/Tenofovir

Observational Studies

Weight gain has been reported in several HIV patients who switched from EFV/TDF/FTC to DTG/ABC/3TC [54c].

An observational study reported on 542 HIV-1-infected adult patients who were on ART with DTG or EVG/COBI. The combination of ABC/3TC/DTG in a single pill was given to 195 patients, TDF/FTC/EVG/COBI for 151 patients, TAF/FTC/EVG/COBI for 116 patients and DTG combined with other anti-retrovirals (i.e. NRTIs and NNRTIs) to 80 patients. The global incidence of discontinuation was 8.5%, with a 6.6% discontinuation rate due to DTG side effects. The neuropsychiatric disorders were the main AEs leading to discontinuation of the treatment. Other AEs were related to neuropsychiatric disturbances (70.4%), gastrointestinal discomfort (22.2%), alterations of renal function (3.7%) and hematology toxicity (3.7%). Most patients experienced more than one neuropsychiatric toxicity, which included abnormal dreams, insomnia, headache, dizziness, nervousness, irascibility, anxiety, depressive symptoms and suicidal ideation. In the case of EVG/COBI, 63.1% treatment discontinuations were due to AEs: 50% gastrointestinal discomfort, 33.3% related to neuropsychiatric disorders, and 16.7% because of alterations in renal function. The rest of discontinuations in EVG/COBI were 21.1% due to pharmacological interactions and 15.8% due to virological failure. In most cases, all reported side effects disappeared quickly once these drugs were discontinued or withdrawn from the treatment regimen. The authors concluded that DTG and EVG/COBI showed high efficacy in treatment-naïve and pre-treated patients. DTG especially in concomitant use with ABC was identified as a predictor for discontinuations due to neuropsychiatric AEs [55C].

Another study evaluated the effectiveness, safety and costs of switching to a RPV/FTC/TDF regimen in 146 treatment-experienced HIV-1-infected patients. Of the 146 patients 25.3% discontinued RPV/FTC/TDF (mainly due to renal impairment). Throughout the 96 weeks, there were significant decreases in total cholesterol (TC) (14.0 mg/dL), TC/HDL cholesterol ratio (0.4 mg/dL) and triglycerides. Moreover, switching to RPV/FTC/TDF reduced the annual per-patient anti-retroviral cost. According to the authors, this treatment regimen was less favorable compared to other treatments available due to high rates of virological failure and AEs [56C].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: NUCLEOSIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS (NRTI) [SEDA-35, 516; SEDA-36, 415; SEDA-37, 337; SEDA-38, 270; SEDA-39, 276]

Abacavir [SEDA-35, 516; SEDA-36, 415; SEDA-37, 337; SEDA-38, 270; SEDA-39, 276]

Observational Studies

A double-blinded, multicenter Phase 3 trial compared the initial treatment of HIV patients with bictegravir, emtricitabine, and TAF vs DTG, ABC, and LAM. Results from the study showed that the co-formulated bictegravir, emtricitabine, and TAF achieved virological suppression in 92% of previously untreated adults and were not inferior to co-formulated DTG, ABC, and LAM. Bictegravir, emtricitabine, and TAF were safe and well tolerated with better gastrointestinal tolerability than DTG, ABC, and LAM [57C].

Another study monitored the safety and evaluated the effectiveness of abacavir sulfate (300 mg) in a Korean population. A total of 669 patients were enrolled in this study. Of these, 196 (29.3%) patients reported 315 AEs, and four patients reported seven serious AEs. Among the 97 adverse drug reactions that were reported from 75 patients, the most frequent included diarrhea (12 events), dyspepsia (10 events), and rash (9 events) [58C].

Lamivudine [SEDA-35, 517; SEDA-36, 416; SEDA-37, 338; SEDA-39, 276]

Observational Studies

The applicability of dual treatments based on integrase inhibitors is less studied. 94 individuals were included in a study that used the combination of lamivudine + DTG as an option when switching from standard cART in virologically suppressed patients. All patients were switched to a dual combination of dolutegravir (50 mg once daily) plus lamivudine (300 mg once daily). The lipid profile slightly changed after switching to the dual regimen. Neither virological failure, nor viral failure above 50 copies/mL was detected. Nineteen percent of the patients reported AEs [59C].

Zidovudine [SEDA-35, 517; SEDA-36, 417; SEDA-37, 338; SEDA-38, 272; SEDA-39, 276]

Also see Tenofovir.

A retrospective cohort analysis was conducted within the International Epidemiologic Database to evaluate AIDS (IeDEA) collaboration in West Africa. The analysis examined adult patients (age ≥16 years) living with HIV and initiating a first-line ART regimen between 2002 and 2014 that contained three or more drugs. This study showed that the risk of developing severe neutropenia was associated with ZDV-containing ART regimen [60C].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: NUCLEOTIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

Tenofovir [SEDA-35, 518; SEDA-36, 418; SEDA-37, 338; SEDA-38, 272; SEDA-39, 276]

Relationship between adverse prenatal outcomes and prenatal TDF use has been reported. The most frequent ART regimens used were TDF/3TC/EFV (39%) and AZT/3TC/NVP (34%); 49% of pregnancies had prenatal TDF exposure and 6% used a protease inhibitor. AEs reported included neonatal death (2%), preterm birth (8%), and pregnancy loss (12%). There were no differences between pregnancies with and without exposure to TDF in the loss of pregnancy. Preterm birth occurred less frequently among pregnancies of patients administered with TDF. The authors concluded that maternal TDF use did not adversely affect perinatal outcomes [61c].

A cohort study was conducted in a South African population that included 15156 patients' data. Patients included antiretroviral-naïve ≥16 years old who started tenofovir-containing anti-retroviral therapy between 2002 and 2013. Overall, 292 (1.9%) patients developed EGFR <30 mL/min. Patients on tenofovir with baseline EGFR 90 mL/min experienced small, but significant declines in EGFR over time [62MC].

Bone mineral density reductions at the hip and spine after TDF initiation have also been reported, but there was no difference in phosphaturia after TDF and ABC treatment [63C].

Case reports showed that high creatinine levels occurred in HIV patients suggestive of nephrotoxicity due to TDF treatment. A 54-year-old patient with known HIV infection and on combined anti-retroviral treatment consisting of TDF, 3TC and EFV was admitted to the hospital. The patient was oliguric with a urine output of 55 mL in 24 h, with no evidence of hematuria and body swelling. He had no previous illnesses apart from HIV infection. His serum creatinine was 1361 μmol/L, urea concentration 30 mmol/L and the electrolyte concentrations were sodium 126 mmol/L, potassium 5.8 mmol/L, chloride 94 mmol/L, and calcium 1.91 mmol/L. He started hemodialysis and the cART regimen changed to ZDV, renal-dosed 3TC and EFV. His creatinine level decreased and he continued on the same cART. His creatinine levels dropped to normal in a few weeks [64A].

In another case study, a 53-year-old male having HIV infection was admitted to the hospital with symptoms of abdominal pains, nausea, and vomiting (the vomitus contained food, but not blood stained). He also complained of dizziness, some cough and his urine output was reduced without change in color. He had no history of diarrhea or fever. His treatment for HIV was initiated with ZDV, 3TC and EFV and cotrimoxazole prophylaxis (960 mg daily). Later, he was switched to a second line of treatment with ritonavir-boosted lopinavir, 3TC and TDF. His creatinine was 559 μmol/L, urea 55 mmol/L, potassium 4.5 mmol/L and sodium of 114 mmol/L. TDF was discontinued and replaced by ABC, and 3TC was renal dosed. In 3 days, his creatinine level was 541 μmol/L, urea 35 mmol/L, potassium 2.5 mmol/L, chloride 86 mmol/L and sodium122 mmol/L. The change in treatment regimen brought down his creatinine levels and renal function to normal levels [64A].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI) [SEDA-35, 519; SEDA-36, 420; SEDA-37, 339; SEDA-38, 273; SEDA-39, 277]

Efavirenz [SEDA-35, 519; SEDA-36, 420; SEDA-37, 339; SEDA-38, 273; SEDA-39, 277]

Observational Studies

A retrospective review reported in treatment-naive and treatment-experienced HIV-positive adult patients in a correctional facility. This study included 553 HIV patients. Patients were on either a single tablet regimen (STR) (efavirenz (EFV), rilpivirine, elvitegravir based) or multiple tablet regimen (MTR) (emtricitabine/tenofovir with ATV/ritonavir, darunavir/ritonavir, or RAL). No significant differences in virologic suppression were seen between the two groups (326 STR and 164 MTR patients). Similar proportions of patient-reported AEs, self-reported adherence, and discontinuation rates were found in both groups. Though there was no significant difference in the initial stages of treatment, at week 72, a significant difference in viral suppression was noted with MTR (97.5%) over STR (88.0%). Patients from both STR and MTR reported AEs (15.3% and 18.9%, respectively). The most common AEs found in STR patients were CNS symptoms (including difficulty concentrating, difficulty sleeping, or vivid/abnormal dreams; 7.7%), dizziness/lightheadedness (2.8%), psychiatric effects (depression/suicidal ideation; 1.5%), and gastrointestinal (GI)-related symptoms (nausea, vomiting, diarrhea; 1.5%). The AEs profile for patients on MTR included scleral icterus (9.1%), GI-related symptoms (8.5%), and rash (6.7%). Elevated total bilirubin was the most common lab-reported AE and occurred in 43.3% ($n=71$) of MTR patients. The overall rate of patients with at least one self- or laboratory-reported adverse reaction was significantly higher for MTR (53.6%) than STR (15.6%) [65C].

The drug–drug interactions that occurred in older HIV patients are reviewed in a study, which also provide the metabolic pathways of ART and highlight potential areas of concern for drug–drug interactions and suggest alternative approaches for treating HIV patients [66R,67R].

Among HIV-infected individuals, use of lopinavir/ritonavir compared with EFV was associated with lower cerebral vasoreactivity [68c].

Pediatric Patients

Data were collected from 51 children and adolescents aged ≤18 years who received EFV-based treatment from 1998 to 2014. Thirty patients (59%) subsequently stopped EFV—14 (29%) following virological failure, and 16 (30%) after reporting AEs. Most AEs reported for EFV were related to CNS (19.6%), including sleep disturbance, reduced concentration, headaches, mood change and psychosis. Four children developed gynaecomastia, two developed hypercholesterolemia, and one developed Stevens–Johnson syndrome. The authors concluded that pediatric patients may need an alternative treatment regimen and not EFV-based treatment [69c].

A prospective, Phase 1/2 open-label study was conducted of children with HIV infection (Cohort I) or HIV/TB co-infection (Cohort II). Participants were divided into two groups: 3 to less than 24 months (28 patients) and at least 24 to less than 36 months (19 patients) and were treated with an anti-retroviral regimen consisting of two nucleoside reverse transcriptase inhibitors and weight band-based EFV given as capsules opened into porridge, formula or expressed breast milk. An initial EFV [~1600 mg × (weight in kg/70)] was given to all participants. Fifteen of 47 participants (32%) experienced nonlife-threatening toxicities that were deemed at least related to anti-retroviral treatment

regardless of grade. Six patients (13%) reported neurologic toxicities of lethargy, sleepiness or sleep disturbances. There were no deaths, hospitalizations or other serious AEs. Among participants with evaluable virologic data, 89% at week 4 and 82% at week 8 achieved virologic success [70c].

Nevirapine [SEDA-33, 593; SEDA-34, 460; SEDA-35, 521; SEDA-36, 421; SEDA-37, 339; SEDA-38, 274; SEDA-39, 278]

Efavirenz- or Nevirapine-based antiretroviral therapy in HIV-infected children from Africa has been reported. Four hundred and forty-five (53%) children received efavirenz (EFV) and 391 children (47%) received nevirapine. The initial non-nucleoside reverse transcriptase inhibitor (NNRTI) was permanently discontinued due to AEs in 7 of 445 (2%) children initiating EFV and 9 of 391 (2%) initiating nevirapine [71C].

A study reported on 322 African children treated with nevirapine, LAM, and either ABC, stavudine, or AZT for HIV. The viral suppression increased with increasing nevirapine concentration, and there was no clear concentration threshold predictive of this suppression. AEs considered to be nevirapine-related were hypersensitivity reactions, elevated liver enzymes and acute hepatitis [72C].

Rilpivirine [SEDA-35, 521; SEDA-36, 423; SEDA-37, 340; SEDA-38, 274; SEDA-39, 278]

A prospective Swiss HIV cohort study was conducted in 644 HIV patients. 48 (7.5%) were cART-naïve at initiation of the RPV/TDF/FTC co-formulation. Five hundred and ninety-eight patients were switched to RPV/TDF/FTC during the study period. Treatment simplification (266/596; 44.6%) and CNS toxicity (143/596; 24.0%) were the two main reasons for switching to the co-formulation. CNS toxicity was the prime cause of switching 126 patients on an EFV-based regimen. AEs reported were insomnia/sleep disturbances (26.9%; 53/197); abnormal dreams (18.8%; 37/197); depression (17.3%; 34/197); dizziness (15.2%; 30/197); fatigue/tiredness (13.7%; 27/197); and other reasons (8.1%; 16/197). Six months after the switch from EFV to RPV, 74.8% (92/123) of patients reported an improvement of CNS symptoms, 14.6% (18/123) reported a stable condition and 3.2% (4/123) described worsening CNS side effects. Viral suppression in cART naive patients (HIV-RNA <50 copies/mL) was achieved in 24 months. According to the authors, use of RPV is a favorable option with most patients experiencing CNS side effects from EFV treatment showing improvement after switching to RPV [73C].

Low side effects and long-term use of RPV have been discussed here [74c].

A Phase 3b, randomized, double-blind, non-inferiority study was conducted in HIV-1 adult patients in 119 hospital sites in 11 countries in North America (Canada and the USA) and Europe (Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, and the UK). Participants were either switched to a single-tablet regimen of 25 mg RPV, 200 mg emtricitabine, and 25 mg TAF or remained on a single-tablet regimen of 25 mg RPV, 200 mg emtricitabine, and 300 mg TDF. Six hundred and thirty participants received at least one dose of study drug. Of these 630 participants, 316 were randomized to switch to the TAF regimen. The remaining 314 participants remained on their previous TDF regimen. Viral suppression was maintained in 296 (94%) out of 316 participants in the TAF group and in 294 (94%) of 314 participants in the TDF group. Both treatments were well tolerated, with most AEs reported as mild or moderate. AEs leading to study drug discontinuation were uncommon. Participants in the TAF group had a lower incidence of drug-related AEs than those in the TDF group. One participant (<1%) in each treatment group had a study drug-related AE leading to discontinuation; fatigue (in the TAF group) and hypersensitivity (in the TDF group). Two individuals died in the study, one in each treatment group: cardiac arrest in the TAF group and carbon monoxide poisoning in the TDF group. Forty participants (13%) out of 315 in the TAF group had grade 3 or 4 laboratory abnormalities compared with 19 (6%) out of 314 in the TDF group. Other AEs reported in both groups were upper respiratory tract infection, diarrhea, nasopharyngitis, headache, bronchitis, and sinusitis [75C].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: PROTEASE INHIBITORS [SEDA-35, 522; SEDA-36, 423; SEDA-37, 340; SEDA-38, 274; SEDA-39, 278]

Atazanavir

Observational Study

A large pool of HIV patients was screened to understand the effect of a protease inhibitor in HIV treatments. Seven hundred and five patients were screened for the study, and 499 were randomly assigned to receive study medication (250 in the DTG group vs 249 in the ATV group). Participants were randomly assigned (1:1) to receive either a fixed-dose combination single-tablet regimen of DTG (50 mg plus ABC 600 mg and lamivudine 300 mg) once a day or a three-tablet regimen (ATV 300 mg boosted with ritonavir 100 mg plus a fixed-dose combination of TDF 300 mg and emtricitabine 200 mg) once a day for 48 weeks. The overall rates of AEs were similar between treatment groups: 195 (79%) of 248 participants in the DTG group compared with 197 (80%) of 247 in the ATV group. Alanine aminotransferase

concentrations increased to at least three times the upper limit of normal in 4 (2%) of 248 participants assigned to DTG. Changes in serum creatinine concentrations were greater at week 48 in participants who were on DTG than ATV patients. Creatinine phosphokinase was increased in seven participants in each group. Three grade 3 creatinine phosphokinase toxic effects occurred in the DTG group, and one grade 4 toxic effect occurred in the ATV group. There were no significant differences between the two treatment groups in total cholesterol or HDL or triglycerides concentration [76C].

RAL-treated patients were compared for cost and safety with DRV/r and ATV/r, each used in combination with FTC/TDF, in adults with HIV-1 infection [77C].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: INHIBITORS OF HIV FUSION [SEDA-35, 525; SEDA-36, 428; SEDA-37, 341; SEDA-38, 275; SEDA-39, 278]

Enfuvirtide

Entry of HIV-1 virus into the target cell is initiated by binding of gp120, the surface subunit of HIV-1 envelope glycoprotein (Env), to the receptor CD4 and co-receptor CXCR4 or CCR5 on the target cell. This study demonstrated that the multivalent bispecific proteins 2Dm2m and 4Dm2m, which target both CD4bs and CoRbs in gp120, can effectively inactivate cell-free HIV-1 virions before attachment to the receptor CD4 and co-receptor, CCR5 or CXCR4, on the target cells. This study also provides information on the mechanism of fusion protein inhibitors functioning on HIV virus replication [78A].

Enfuvirtide (T20) is the only HIV viral fusion inhibitor used in combination therapy, but it has low antiviral activity and often develops resistant mutants. Recent studies showed that lipopeptide-based fusion inhibitors, such as LP-11 and LP-19, variants of LP-20, which target gp41, have greatly improved antiviral potency and in vivo stability [79A].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: INTEGRASE INHIBITORS [SEDA-35, 525; SEDA-36, 428; SEDA-37, 342; SEDA-38, 275; SEDA-38, 276; SEDA-39, 278]

Dolutegravir (DTG)

Observational Studies

Psychiatric symptoms (PSs) are reported in HIV patients and are common in DTG-treated patients. These events are reported with low frequency and rarely necessitate DTG discontinuation. Drug withdrawal rates for PSs were higher for RAL than DTG [80c].

A retrospective analysis in a cohort of HIV-infected patients from a German outpatient clinic between 2007 and 2016 has been reported. The estimated rates of any AE and of neuropsychiatric AEs leading to discontinuation within 12 months were 7.6% and 5.6% for DTG, respectively [81C].

A retrospective case chart analysis of HIV-1-positive adults on DTG between July 2014 and September 2015 has been reported. One hundred and fifty-seven DTG patients on ART were included in the study, of these 106 (68%) were switched to DTG from another regimen, and 51 (32%) were ART-naïve. Overall, 56 reported side effects; 40 patients reported either difficulty with low mood, anxiety or sleep disturbance. Sixteen discontinued DTG, with 13 due to intolerable side effects [82c].

Raltegravir

Observational Study

Dual therapy with raltegravir (RAL) plus LAM in selected patients could be safe, well tolerated and a proven effective strategy to reduce the long-term side effects and costs of combination ART. In this study of 14 patients, 4 being treated with ABC, 1 with AZT and 9 with TDF were switched to raltegravir once daily. Patients showed significant improvement in creatinine level, lipid profile and ALT after switching [83c].

A prospective cohort study compared the AEs between RAL and DTG. Neuropsychiatric complaints were the most common toxic AEs reported and were more frequent in the DTG treatment group than the RAL treatment group [84C].

Some ARV drugs have been shown to be nephrotoxic and associated with worsening renal function in HIV patients. This review describes the novel antiviral agents, such as DTG, RAL, elvitegravir, cobicistat, TAF and ATV, that have shown some issues with renal function, creatinine handling and potential nephrotoxicity [85R].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: CHEMOKINE RECEPTOR CCR5 ANTAGONISTS [SEDA-35, 528; SEDA-36, 430; SEDA-37, 343; SEDA-38, 276; SEDA-39, 279]

Maraviroc

Patients on 3-drug ART with stable HIV-1 RNA (<50 copies/mL) were randomized 1:1 to maraviroc (MVC) with darunavir/ritonavir per day (study arm) or

continued on the current ART (continuation arm). One hundred and fifteen patients were included in the study (56 in the study arm, 59 in the continuation arm). Two participants in the study arm and 10 in the continuation arm discontinued therapy due to significant AEs. Femoral bone mineral density was significantly improved in the study arm. Switching to MVC with darunavir/ritonavir showed improved tolerability but was virologically inferior to 3-drug therapy [86C].

A retrospective multicenter study (27 centers in Spain) evaluated the efficacy and safety of MVC administered once daily in HIV-1 patients. Data were collected from the records of patients starting a regimen with MVC. Laboratory and clinical data were recorded every 3 months the first year and every 6 months thereafter. Among the 667 patients treated with MVC, 142 (21.3%) received MVC once daily: 108 (76.1%) at a dose of 150 mg and 34 (23.9%) at a dose of 300 mg. Patients had baseline HIV-RNA <50 copies/mL. MVC was administered for the following reasons: salvage therapy (36.6%), drug toxicity (31.2%), simplification (16.9%), and immune discordant response (7.1%). Twenty-five (17.6%) patients discontinued MVC for the following reasons: virologic failure (6), medical decision (5), and other reasons (14). Two patients showed grade 3 AEs (hypertransaminasemia, hypertriglyceridemia) without the need for MVC withdrawal, whereas MVC was discontinued in two patients due to gastrointestinal toxicity. The authors were of the opinion that the use of MVC once-daily combined with at least PI/r was virologically effective in pretreated patients [87C].

DRUGS ACTIVE AGAINST INFLUENZA VIRUSES: NEURAMINIDASE INHIBITORS [SEDA-35, 528; SEDA-36, 431; SEDA-37, 344; SEDA-38, 277; SEDA-39, 279]

The M2 inhibitors, amantadine and rimantadine, were historically effective for the prevention and treatment of influenza A, but all circulating strains are currently resistant to these drugs [88R].

Oseltamivir (Tamiflu)

An open-label randomized study evaluated the difference in viral dynamics and influenza symptoms in patients aged 4–12 years to intravenous peramivir, oral oseltamivir, inhaled zanamivir, or inhaled laninamivir. The time to virus clearance was significantly shorter with peramivir than with oseltamivir [89c].

A retrospective cohort study reported on adult (≥18 years) patients with suspected influenza viral infection ($N=3743$). Adults hospitalized for seasonal influenza were enrolled as a comparison group ($n=312$). This study evaluated whether RSV infection is associated with higher mortality than seasonal influenza and on oseltamivir treatment. The outcome of the study showed that oseltamivir had no significant effect on mortality of patients with influenza [90C].

A retrospective cohort analysis was conducted in 57 patients admitted to the intensive care unit (ICU) with confirmed influenza infection. Patients receiving high-dose of oseltamivir were compared to those receiving standard dosing. As compared to the standard doses of oseltamivir, a higher-dose of oseltamivir was not associated with improvement in any clinical outcomes [91C].

Combination Study

A double-blind, randomized, Phase 2 study was conducted in 50 sites in the USA, Thailand, Mexico, Argentina, and Australia, on a combination of oseltamivir, amantadine, and RBV vs oseltamivir monotherapy with matching placebo for the treatment of influenza. Participants who were diagnosed with influenza and were at increased risk of complications were randomly assigned (1:1) to receive either oseltamivir (75 mg), amantadine (100 mg), and RBV (600 mg) combination therapy or oseltamivir monotherapy, twice daily for 5 days. Six hundred and thirty-three participants were randomly assigned to receive a combination of antiviral therapy ($n=316$) or monotherapy ($n=317$). The primary analysis included 394 participants, excluding 47 in the pilot phase, 172 without confirmed influenza, and 13 discontinued. Eighty participants in the combination group had detectable virus at day 3 compared with 97 participants in the monotherapy group. The most common AEs were gastrointestinal-related disorders, nausea (65 reported AEs in the combination group vs 63 reported AEs in the monotherapy group), diarrhea (56 vs 64), and vomiting (39 vs 23). Twenty-two serious AEs were also reported in 20 participants; 16 AEs in 14 participants in the combination group and 6 AEs in 6 participants in the monotherapy group. More than one participant showed asthma exacerbation, diarrhea, and pneumonia. There were four gastrointestinal serious AEs in the combination group and none in the monotherapy group. Only two of the serious AEs in the monotherapy group were related to study medication. One participant in the monotherapy group died from cardiovascular failure, and that was not drug related. Thirteen participants in the combination group and three participants in the monotherapy group were admitted to the hospital with other complications. This study showed that monotherapy is not inferior to the combination therapy in treating influenza patients [92C].

Peramivir

Peramivir is the first intravenously (IV) administered neuraminidase inhibitor for immediate delivery of an effective single-dose treatment in patients with influenza. A systematic meta-analysis compared the efficacy of IV peramivir with oral oseltamivir for treatment of patients with influenza. Seven trials (two randomized controlled trials and five non-randomized observational trials) involving 1676 patients were analyzed. The total numbers of peramivir- and oseltamivir-treated patients were 956 and 720, respectively. Overall, the time to alleviation of fever was lower in the peramivir-treated group compared with the oseltamivir-treated group. Mortality, length of hospital stay, change in virus titer, and the incidence of AEs were not significantly different between the two groups. IV peramivir therapy reduced the time to alleviation of fever compared with oral oseltamivir therapy in patients with influenza [93MC].

OTHER DRUGS

Imiquimod [SEDA-35, 530; SEDA-36, 431; SEDA-37, 344; SEDA-38, 277; SEDA-39, 280]

The most common AE reported for imiquimod (IM) is local skin irritation at the application site. Other AEs include headache, flu like symptoms and myalgia.

Dermatological Studies

Topical treatment with IM for penile cancer has been reported with very low AEs [94R].

A meta-analysis evaluated the efficacy and safety of photodynamic therapy (PDT), surgery excision (SE), cryotherapy (CT), IM, radiotherapy (RT), 5-fluorouracil (FU), and vehicle (VE) for non-melanoma skin cancer (NMSC) treatment. Data from 18 trials with 3706 patients showed IM were more likely to induce AEs than VE. The authors concluded that SE was the optimal regimen for NMSC with high efficacy considering CLR, CLC, and CRP [95MC].

Another study reported the use of IM to treat mycosis fungoides (MF) tumors. Two stage IIB MF patients, including one with large cell transformation, were treated with IM 5% cream after failing other therapies. One patient reported AE, such as application site irritation and flu-like symptoms [96c].

A recent review on the use of IM resulted in AEs as site reactions in patients with cutaneous molluscum contagiosum, caused by pox virus. Among the most common AEs of IM treatment in this patients were pain during application, erythema, and itching [97R].

Topical IM is sometimes used for lentigo maligna (LM) in situ melanoma instead of surgery, but frequency of cure is uncertain. A single-arm Phase 2 trial of 60 imiquimod applications over 12 weeks for LM was reported. Clinical evaluation showed that 13 of 28 patients had complete disappearance of the LM after IM treatment. Eleven of 29 patients (38%) had a severe local-site reaction over the study period; 10 (34%) had a moderate reaction and 8 (28%) had mild or no reaction [98c].

A Phase 2 prospective multicenter clinical trial assessed the safety and activity of TMX-101, a novel liquid formulation of IM. Enrolled patients in this study received six weekly intravesical administrations of 200 mg/50 mL TMX-101 0.4%. Overall, 75% of patients experienced treatment-related AEs, only one was >grade 2 (urinary tract infection). Two patients showed a negative cytology at 6 weeks of treatment. Significant increases in urinary cytokines, including IL-6 and IL-18, were also reported following IM treatment [99c].

Additional case studies on this topic can be found in these SEDA reviews [100R,101R,102R].

DISCLAIMER

The findings and conclusions in this review are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. Mention of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health, and Centers for Disease Control and Prevention.

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