CHAPTER

25

Antiviral Drugs

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Abbreviations

3TC lamivudine (dideoxythiacytidine)
AZT zidovudine (azidothymidine)
D4T stavudine (didehydrodideoxythymidine)
DDI didanosine (dideoxyinosine)
ETV etravirine
FTC emtricitabine
RPV rilpivirine
SIM simeprevir
SOF sofosbuvir

DRUGS ACTIVE AGAINST CYTOMEGALOVIRUS

Human cytomegalovirus (CMV) is a major cause of morbidity and mortality among immunocompromised individuals, especially those who have undergone allogeneic hematopoietic cell transplantation (HCT). Several available drugs induce significant side effects which deter their use for CMV; specifically, Ganciclovir (GCV), CDV, and Foscarnet (FOS). There are novel promising drugs without myelosuppressive properties or renal toxic effects, such as Maribavir (MBV), Letermovir (LMV) and Brincidofovir (BCV), which are very promising anti-CMV drugs that are in randomized phase II and III trials [1R].

Cidofovir [SED-15, 771; SEDA-32, 529; SEDA-33, 577; SEDA-34, 447; SEDA-35, 503; SEDA-36, 401; SEDA-37, 329; SEDA-38, 261]

See also Section Brincidofovir.

Cidofovir (CDV) was FDA approved in 1996 as an IV formulation for the treatment of a broad-range of DNA virus infections. CDV is a phosphonate (monophosphate analogue) and does not require initial viral phosphorylation. Cellular kinases add additional phosphates to produce CDV diphosphate, which could incorporate into the viral DNA by pUL54 leading to the termination of viral DNA replication. CDV has a very long intracellular half-life and is effective in the treatment of CMV retinitis in AIDS patients. CDV is also considered as a second-line antiviral drug for the treatment of CMV infection due to some concerns regarding its poor oral bioavailability, dose-related nephrotoxicity, and myelosuppression [2R].

Letermovir [SEDA-38, 261]

Letermovir (LMV) is a direct-acting antiviral that could lead to the emergence of LMV-resistant virus variants in CMV patients treated with LMV. Monitoring the emergence of resistant strains has been an integral part of the clinical studies. So far, only a small number of amino acid substitutions conferring LMV resistance have been identified. A suboptimal use of LMV leads to the emergence of LMV-resistant strains. The efficacy of different LMV (AIC246, MK8228) doses (60, 120, and 240 mg/day) against CMV was evaluated in a phase 2 dose-range-finding prophylaxis study in HSCT patients infected with CMV. The LMV resistance mutation emerged when a suboptimal prophylactic dose (60 mg/day) was used, but a higher dose of 240 mg/day achieved complete suppression of viremia [3c].

Three antiviral agents, GCV, FOS and CDV, are currently approved by Food and Drug Administration (USA) for the treatment of CMV infections. They all target the viral DNA polymerase and are associated with

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significant side effects. Combinations of novel antiviral compounds acting on different targets such as artesunate (ART) with currently approved drugs or eventually LMV or MBV may result in synergistic effects. The concentrations of GCV, FOS, CDV and ART that reduced the GLuc activity by 50% were 3.92 ± 1.64, 62.45 ± 8.39, 0.68 ± 0.19 and 3.86 ± 1.25 μM, respectively, whereas those of MBV and LMV were 64 ± 22 and 2.50 ± 0.83 nM, respectively. The combination of ART with GCV, CDV or MBV was associated with synergism, whereas combination of ART with FOS or LMV resulted in moderate synergism. These results suggest that the combination of ART with the antiviral agents could be an effective strategy for the treatment CMV [4c].

Brincidofovir

Brincidofovir (BCV), part of a new class of anti-viral drugs, is an oral nucleotide analog that has been a promising candidate against CMV. BCV is less nephrotoxic than CDV and could prevent CMV infection in HSCT patients. In a phase 2 clinical trials, BCV showed a dose–response relationship for the prevention of CMV infection in adult allogeneic HSCT recipients [5c].

A case study reported, a 68-year-old woman with stage III follicular lymphoma who underwent chemotherapy, showed complete remission. She developed CMV antigenemia during chemotherapy. The patient received IV of FOS for 19 days and was on valganciclovir (900 mg/day) for another 117 days. Later (249 days) she developed CMV reactivation and continued to receive FOS (60 mg/day). Although these treatments cleared the CMV, the patient developed acute kidney injury (AKI). FOS was discontinued and BCV was started (150 mg, twice weekly). In 4 days, the patient developed nausea and diarrhea. BCV was discontinued for next 5 days and on sixth onwards a mixture of BCV and FOS were given, in 2 weeks the CMV was cleared. However, the patient developed leukemia and sepsis that led to her death [6A].

A 59-year-old man underwent donor cell transplantation for acute lymphoblastic leukemia. The patient developed CMV infection and was on oral valganciclovir for a week. Side effects resulting from the treatment were vomiting, loose stools, and increase in CMV count. The patient's medication was changed to GCV for the next 44 days. CMV resistance to GCV was developed and the medication was replaced with FOS (90 mg/kg/day). The patient developed diarrhea and to overcome the side effect, BCV (100 mg twice daily) was added to FOS, and CMV became undetectable in 33 days. The patient died on day 419 due to other complications but not from CMV [6A].

Foscarnet [SED-15, 1447; SEDA-34, 448; SEDA-35, 504; SEDA-36, 403; SEDA-37, 329; SEDA-38, 262]

Observational Study

A 50-year-old woman who received double cord blood HSCT as part of her leukemia treatment showed CMV infection and treated with FOS. CMV was cleared in 2 weeks and the patient was subsequently kept on valaciclovir (900 mg/day). In about 152 days, the CMV count was elevated and valaciclovir was replaced with GCV. Resistant strains were again detected with a mutation in UL97, and FOS was given at 60 mg/kg/dose. CMV further increased and BDF 200 mg/kg/dose was started; this caused considerable decrease in CMV count within 2 weeks. Meanwhile, the patient developed abdominal discomfort and gastrointestinal disease involving stomach, duodenum and colon. Even after increasing the concentration of BCV, the side effects persisted. The patient died of gastrointestinal bleeding, septic shock and ongoing gastrointestinal CMV on the 342nd day of treatment [6A].

Ganciclovir and Valganciclovir [SED-15, 1480; SEDA-34, 449; SEDA-35, 504; SEDA-36, 404; SEDA-37, 330; SEDA-38, 262]

Observational Study

GCV is a myelosuppressive drug, which is intracellularly phosphorylated to GCV monophosphate by a viral kinase encoded by CMV gene UL97. The most relevant side effect of GCV is bone marrow depression, particularly neutropenia, which has been associated with risk factors such as impaired renal function, high baseline viral load, and low-level neutrophil counts.

Combination Study

A comparative study in tissue transplant patients on the effect of GCV has been reported. In this study 22 solid organ transplant (SOT) and 17 HSCT patients were included. Of the 39 patients, 15 showed GCV resistance mutations and 11 had tissue-invasive CMV. Virological failure occurred in 33% and 31% showed relapses of viremia. HSCT patients showed higher mortality (31%). GCV resistance was higher in SOT patients compared to HSCT. The most common adverse event (AE) reported was renal dysfunction in 20 patients by the end of treatment and 7 patients after 6 months of treatments [7c].

CMV infection was studied using a murine model to understand the role of CMV in birth defects, mental retardation and non-genetic sensorineural hearing loss. The pharmacokinetics of GCV was assessed in adult mice and pups after 5 days of IP injection of GCV.

In adult rats, the intra-cochlear diffusion of GCV reached the same concentration as in blood. GCV was also capable of crossing the transplacenta in gestating mice and diffused into the brain and the perilymphatic space of the inner ear. High dose of GCV resulted in significant hematotoxicity in different blood cell populations of the mice [8E].

Valaciclovir

A study was conducted in 68 heart transplant patients, who were given 1000 mg/day valaciclovir to prevent CMV infection. The results from this study confirm that the daily use of low-dose valaciclovir (1000 mg/day) is sufficient for CMV prophylaxis without any significant AEs reported [9C].

Similarly, an open-label, phase II study showed that a high dosage of valaciclovir could prevent CMV in transplant patients. Oral administration of high-dosage valaciclovir to mothers significantly reduced the viral load and produced therapeutic concentrations in the blood of infected fetuses [10c].

Monoclonal Antibodies

The in vitro activities of two human monoclonal antibodies, LJP538 and LJP539, has been evaluated for CMV treatment in a study using a combination of these monoclonal antibodies (known as CSJ148) that is currently evaluated for safety and efficacy in clinical trials of CMV infection in HSCT patients. The antibodies target glycoproteins gB and the pentameric (gH/gL/UL128/UL130/UL131) complex. In vitro, LJP538 and LJP539 inhibited CMV infection in five epithelial and three endothelial cell lines; LJP538 also blocked the infection of fibroblasts. No loss of susceptibility to the combination of antibodies was observed for more than 400 days in culture and the binding regions of LJP538 and LJP539 are conserved among clinical isolates. These data provide a hope for the use of these monoclonal antibodies for clinical trials in CMV patients [11E].

DRUGS ACTIVE AGAINST HERPES VIRUSES [SEDA-32, 530; SEDA-33, 577; SEDA-34, 450; SEDA-35, 507; SEDA-36, 407; SEDA-37, 332; SEDA-38, 263]

Acyclovir

The most frequent AEs reported for acyclovir (ACV) are nausea, diarrhea, and headache. Another uncommon but serious side effect of ACV treatment is neurotoxicity that may lead to confusion, hallucinations, and seizures.

Observational Studies

Valacyclovir and ACV were used for the treatment of herpes zoster ophthalmicus in immunocompetent patients. Herpes zoster ophthalmicus affects the eye and vision and is caused by the varicella zoster virus. Patients treated with ACV and Valacyclovir showed side effects such as vomiting, eyelid or facial edema, and disseminated zoster [12R].

Herpes simplex virus-1 (HSV-1) and HSV-2 are closely related human herpesviruses. HSV-1 typically causes common cold sores, encephalitis, and over 400 000 cases of sight-threatening corneal disease annually. ACV is used to treat acute infections and reduces viral shedding and disease associated with HSV reactivations. The authors screened 26 synthetic α-hydroxytropolones, of which compound 118 showed significant inhibition of HSV. ACV resistant virus also failed to replicate in the presence of compound 118. The authors are of the opinion that troponoid drugs administered alone or in combination with existing nucleos(t)ide analogs could suppress the HSV replication without any significant side effects [13E].

Studies have been reported in predicting the risk factors for varicella zoster virus (VZV) infection and postherpetic neuralgia (PHN) after HSCT. This retrospective review was conducted in 163 patients who underwent HSCT between November 2004 and July 2014. Overall, the male/female (M/F) ratio was 80/83, median age at HSCT was 54 (range 15–69) years, and the autologous/allogeneic HCT (auto/allo-HCT) ratio was 71/92. Forty-four patients developed VZV infection after HSCT. All cases were successfully treated with ACV or valacyclovir, and there was no VZV-related death. Nine (20%) of the 44 patients developed PHN after resolution of zoster. The authors indicate that receiving immunosuppressive therapy at the cessation of ACV is a significant risk factor for allo-HSCT recipients [14C].

Famciclovir

The most common adverse experiences with the use of famciclovir were headache, nausea, and diarrhea.

Neurlogical

A 67-year-old man, who was on botulinum toxin A injections to control trigeminal neuralgia was infected with herpes labialis and herpes zoster. The patient was treated with famciclovir and showed significant improvement in pain and subsequent control of trigeminal neuralgia. No significant side effects of famciclovir was reported [15A].

Valacyclovir

Valacyclovir is an antiviral drug also used for the treatment of HSV. The most frequent ADRs reported for valacyclovir were headache, nausea, and abdominal pain.

Renal Toxicity

A female patient 35 years of age was hospitalized due to complaints of a hip blister, fever and kidney dysfunction. The patient was diagnosed with herpes simplex due to the hip blister with unknown causes accompanied by slight erythema. The patient was orally administered with valacyclovir hydrochloride tablets to treat herpes simplex. Subsequently, the patient experienced a significant reduction in quantity of urine produced, and an apparent elevation in serum creatinine levels. The patient was given the anti-inflammatory oral liquid combined with the iodophor solution. The patient's lumbar discomfort was not improved and the patient experienced dysuria and hypourocrinia. Serum creatinine was increased to 592.7 μmol/L and uric acid increased to 624 μmol/L. Renal tubular epithelial cell granule and vacuolar degeneration were also observed in the patient. The patient was given glutathione to alleviate renal tubular injury and sodium bicarbonate was given to induce the alkalized urine that could prevent the tubular formation. Compound polymyxin and topical use of iodophor were able to control HSV infection in this patient [16A].

Observational Studies

HSV-2 infection may increase HIV-1 replication leading to greater infectivity and disease progression. A randomized clinical trial of valacyclovir for HSV-2 suppression in HIV co-infected patients was conducted between March and December 2005 in Peru. Women who were 18 years of age or older, HIV-1 and HIV-2 seropositive and not using antiretroviral or anti-HSV medications were selected for the study. Twenty HSV-2/HIV-1 co-infected women were enrolled in the study. The median age was 28 years and the median CD4 count was 372 cells/μL. The results from their study confirm that HSV-2 suppressive therapy with valacyclovir has little effect in reducing inflammation in the mucosal environment in HSV-2/HIV-1 coinfected women [17c].

A 52-year-old man with hypertension, diastolic congestive heart failure, end-stage renal disease and a remote history of a hemorrhagic stroke was admitted to the emergency department with a vesicular rash on his left arm. Diagnosis revealed that he had herpes zoster infection. The patient was discharged home on valacyclovir 1 g, three times a day for 7 days. The patient took two doses of valacyclovir, but reported with irritability and hallucinations. Over the next several days, the patient's neurologic status declined and he became disoriented and increasingly somnolent. Acyclovir was initiated intravenously at 600 mg (10 mg/kg) for every 12 hours. The patient subsequently had a seizure during dialysis and was felt to have status epilepticus due to ACV and valacyclovir neurotoxicity. The patient underwent daily hemodialysis for removal of the drug and eventually made a full neurologic recovery. ACV side effects resulted in status epilepticus, hallucinations, and altered consciousness [18A].

A case study of a 51-year-old woman was reported with recurrent, dusky and erythematous macules at fixed sites after taking valacyclovir for HSV infection. The patient had already reported similar adverse drug reactions (ADRs) after ACV. Patch and prick tests were performed for ACV, valacyclovir, and famciclovir at a concentration of 1% in petrolatum base, on normal and previous lesional skin. However, the patch and prick tests showed a negative response. The oral challenge test was done with valacyclovir 2 weeks after the patch test. Skin biopsy was performed on an erythematous patch on the lateral thigh, and histopathological findings were consistent with fixed drug eruption, an uncommon adverse drug reaction caused by delayed cell-mediated hypersensitivity. Famciclovir provoked the same ADR at previous lesion sites within 2 hours after administration. This study demonstrates concomitant sensitization to ACV, valacyclovir and famciclovir. Cross-reactions between ACV, valacyclovir and famciclovir in allergic contact dermatitis could be due to their close chemical structures, including a 2-aminopurine nucleus. This case study suggests that ACV, valacyclovir, and famciclovir could have cross-reactions and that could cause the macular drug eruptions, along with exanthematous drug eruptions [19A].

Vaccines

Herpes zoster (HZ), which is commonly referred to as shingles, is caused by reactivation of varicella zoster virus (VZV). The virus is reactivated when immunity to VZV declines mostly with aged or in immune compromised persons. Post-herpetic neuralgia, defined as pain persisting more than 3 months after the skin rash has healed, is a serious consequence of HZ. HZ vaccine reduces the incidence of HZ by 50%. The most common side effects of the vaccine are minor local injection site reactions and headache [20R].

DRUGS ACTIVE AGAINST HEPATITIS VIRUSES

Adefovir [SED-15, 35; SEDA-32, 530; SEDA-33, 578; SEDA-34, 452; SEDA-35, 507; SEDA-36, 409; SEDA-37, 333; SEDA-38, 264]

Urinary Tract

ADV has side effects in osteomalacia patients and could induce Fanconis's syndrome. A case report from

Japan showed altered urinary β-2 microglobulin (β2MG) levels in a patient receiving ADV therapy for HBV infection. A 66-year-old woman reported to have hypophosphatemia and a slightly elevated serum alkaline phosphatase (ALP) level was admitted to the hospital. She had a normal physical condition including normal muscle strength. She was previously diagnosed with chronic HBV infection and was on 3TC (100 mg/day) for 13 years and later on ADV (10 mg/day). Laboratory data showed she had elevated levels of urinary β2MG and *N*-acetyl-β-D-glucosaminidase levels. The ADV treatment induced temporary pain in her right ankle and hypophosphatemic osteomalacia was reported. ADV levels were reduced by prescribing ADV 10 mg on alternative days that resulted in reduced the β2MG levels. The authors suggest that β2MG could be used as a sensitive marker for drug-induced renal damage [21c].

Direct-Acting Antiviral Protease Inhibitors [SEDA-35, 508; SEDA-36, 409; SEDA-37, 334]

Entecavir [SEDA-33, 578; SEDA-34, 452; SEDA-35, 512; SEDA-36, 411; SEDA-37, 335]

Observational study: Entecavir (ETV) is a nucleoside analogue of 2-deoxyguanosine that inhibits the replication of the HBV. The role of ETV has been reviewed, where the authors shows the advantages of ETV in a combination therapy against HBV infections. A continuous therapy with ETV improves liver histology and reduces the risk of liver failure and hepatocellular carcinoma. Patients with 3TC/ADV resistance or baseline 3TC-resistant mutants should use the combination therapy with ETV in order to overcome the 3TC/ADV resistant HBV mutants [22R].

Another similar study conducted in 30 patients reported the efficacy of ETV in combination with ADV to eliminate the HBV mutants [23c].

Ribavirin [SEDA-33, 578; SEDA-34, 452; SEDA-35, 512; SEDA-36, 412; SEDA-37, 335; SEDA-38, 267]

Neurological

Ribavirin (RBV) is useful in cases like HCV genotype 1, treatment-experienced, cirrhotic patients, or patients with decompensated cirrhosis, and in HCV genotype 3, cirrhotic patients. In these cases RBV shorten the treatment period to 12 weeks. The need of RBV remains to be determined in cirrhotic patients with SOF plus SIM regimen. Generally, the addition of RBV to different combinations of direct-acting antivirals increases the risk of anemia [24R].

Sofosbuvir (SEDA-37, 335; SEDA-38, 268)

Observational Study

A case study reported, a 72-year-old man infected with HCV genotype 1b admitted with cirrhosis and no prior history of inflammatory bowel disease. He developed drug-induced bloody diarrhea within 3 weeks of HCV antiviral therapy with SOF (400 mg/day), SIM (150 mg/day) and RBV (800 mg/day). During the third week of treatment, the patient complained of nausea, vomiting, abdominal pain and constipation [25A].

The use of direct-acting agents for HCV kidney transplant and kidney transplant recipient patients has been reviewed and was suggested to be safe in these particular patients [26R].

A prospective, open-label multicenter pilot study was reported in which adults with recent HCV infection received SOF, 400 mg daily and, weight-based RBV (<75 kg, 1000 mg/day; ≥75 kg, 1200 mg/day) for 6 weeks. Nineteen participants were enrolled between October 2014 and May 2015 through a network of tertiary hospitals in Australia and New Zealand. HCV RNA was below the limit of detection in 47%, 74%, and 79% of patients at weeks 1, 2, and 4 of treatment, respectively. At posttreatment week 12, 13 of 19 patients had treatment failure. One patient discontinued after 2 weeks of treatment. The remaining 12 participants demonstrated virological failure: 2 nonresponse, 9 posttreatment relapse, and 1 reinfection. Both participants with virological nonresponse had high HCV RNA. Another clinical ADRs were reported by 14 participants (74%), with most ADRs being of mild (68%) or moderate (29%) severity. In this, two serious ADRs were reported, one AKI requiring hospitalization and another *Escherichia coli* bloodstream infection; however, both were considered as unrelated to the study drug [27c].

Lung injury was reported in a liver transplant patients treated with SOF. Twenty-four liver transplant recipients with recurrent chronic HCV were treated: 8 received the SOF along with SIM, 6 with ledipasvir, 5 with daclatasvir, and 5 with RBV. At 8 weeks of direct-acting antiviral therapy all patients had achieved undetectable serum HCV-RNA. Moreover, all but one had reached serum virus recovery (SVR). Overall, SOF treatment was well tolerated in the study population with only mild degree of ADRs in 42% of patients. The most common ADRs were fatigue (25%), headache (13%), gastrointestinal disturbances (8%), and anemia (55%) in the RBV group. However, one patient who developed a serious ADE was a 52-year-old woman who had undergone a liver transplant 10 years ago. The patient was in the SOF-daclatasvir treatment group. Ten days after she was admitted in the hospital complaining of severe fatigue, nonproductive cough, dyspnea, and fever. She also developed respiratory failure. The patient was treated with high-dose

corticosteroids (60 mg methylprednisolone every 8 hours), and SOF was replaced with SIM. Patient was recoverd from the ADRs and in 24 weeks she achieved SVR. The authors concluded that the respiratory failure and SOF-associated lung injury are rare but potentially life-threatening conditions in patients that develop respiratory symptoms soon after beginning HCV therapy [28c].

A phase 2, multicenter, open-label study was conducted in 44 HCV genotype 4 patients in France from March to November 2014. Participants took a fixed-dose combination tablet of 90 mg of ledipasvir and 400 mg of SOF orally once daily for 12 weeks. The majority of the patients were white and male (64%). Of the 44 patients who were treated with ledipasvir/SOF, 41 (93%) reached the primary endpoint of SVR12. The most common AEs reported were asthenia, headache, and fatigue. All ADRs were mild or moderate in severity, and no patients experienced a serious AE or discontinued treatment because of an ADR. Authors conclude that the treatment with once-daily oral regimen of ledipasvir/SOF for 12 weeks resulted in a high rate of SVR among treatment-naïve and -experienced patients with HCV genotype 4 [29C].

A retrospective cohort study included 260 patients who were treated with a SOF-containing therapy between January 2014 and December 2015 in Germany. Patients were treated with SOF/DCV or SOF/LDV. Of the 256 patients, 240 patients achieved SVR12; 4 out of 256 lost follow-up and 12 patients suffered from relapse. One hundred and forty-seven patients reported side effects during treatment. In general, side effects were mild in intensity, thus, just one patient discontinued treatment prematurely due to back-pain. Overall, fatigue, headache, bone pain or joint pain, and myalgia were the most frequently reported side effects. Hospital admissions were required during treatment with SOF-based regimens in 22 (8.6%) patients. The reasons for hospitalization were infections ($n=8$); hepatic decompensation ($n=3$); cardiovascular disease ($n=3$); cholestatic hepatitis after liver transplantation ($n=2$); treatment of hepatocellular carcinoma ($n=2$); and lumbago, vomitus, diabetes insipidus and right upper quadrant pain ($n=1$, each). Of those hospitalized, two patients died from infectious complications (right-heart failure), and two patients died from cardiovascular disease (intracerebral bleeding) [30C].

A retrospective analysis with prospective follow-up was performed of post-kidney transplant patients with chronic HCV treated with DAAs in three academic centers in Boston, MA. Twenty-four kidney transplant recipients with chronic HCV infection received DAA during the study period. Patients were included irrespective of their liver fibrosis stage, genotype, or prior HCV treatment status. SOF was prescribed at 400 mg/day orally; SIM was prescribed at 150 mg/day orally; ledipasvir was prescribed at 90 mg/day administered orally in co-formulation with SOF 400 mg; RBV was prescribed according to body weight (1000 mg daily in patients who were <75 kg and 1200 mg daily in patients who were >75 kg). The treatment duration varied between 12 and 24 weeks based on HCV genotype, the stage of underlying liver fibrosis and prior treatment history. Twenty-three patients had SVR12 assessment; one patient had SVR4 assessment. Eleven patients (46%) reported AEs. Overall, there were three serious AEs. Of the seven patients that received RBV, two discontinued RBV due to side effects (fatigue, shortness of breath and gout flare), but they continued combined DAA treatment. Two of the seven patients developed anemia. The serious ADRs were gastrointestinal bleeding, portal vein thrombosis, and sinus bradycardia, and the common ADRs were shortness of breath, fatigue, headache, dizziness, diarrhea, pain in the lower extremity, photosensitivity, insomnia, and rashes [31C].

Antiviral treatment with a combination of SOF/LDV is highly effective, safe, and well tolerated in HCV patients who had orthotropic liver transplantation. The addition of RBV along with SOF often results in severe anemia and required dose reduction or discontinuation to avoid the side effects [32c].

Early treatment of HCV infection with IF-α is highly effective. A prospective, open-label, multicenter, single-arm pilot study in adults having acute HCV genotype 1 monoinfection was reported from 10 centers in Germany. Patients were administered ledipasvir (90 mg) plus SOF (400 mg) as a fixed-dose combination tablet once daily for 6 weeks. The primary efficacy outcome was the proportion of patients with SVR 12 weeks after the end of treatment. All patients achieved a SVR 12 weeks after the end of treatment (20 out of 20 patients). Treatment was well tolerated, and up to 12 weeks after treatment, 22 possible drug-related adverse drug events (ADRs) were reported but none of them was a serious ADRs. There was one serious ADE, which was judged as unrelated to the study drug [33C].

Simeprevir [SEDA-38, 269]

A SIM plus SOF regimen was recommended for certain patients with HCV genotype 1 infection. A multicenter observational study reported included 583 patients with HCV genotype 4 infection were treated with SIM plus SOF for 12 weeks. The overall SVR rate was 95.7% (558 out of 583 patients). Side effects included rash in 21 patients, photosensitivity in 18 patients, pruritus in 44 patients and hyperbilirubinemia in 42 patients [34C].

Dermatological reactions caused by SIM+SOF treatment in HCV patients has been reported [35c].

SOF and SIM combination therapy early after allo-HSCT was also reported to clear the HCV without any significant ADRs [36c].

Sixty-two patients with HCV cirrhosis underwent organ liver transplant (OLT) at a transplant center. Five patients developed recurrence HCV in the form of severe FCH and were treated with SOF and SIM for 24 weeks. All patients achieved significant improvement in HCV viral load. One patient developed refractory pruritus and acute pancreatitis. The third patient showed hepatic artery thrombosis and developed sepsis and renal failure [37C].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: COMBINATIONS

Abacavir/Lamivudine/DTG

Dolutegravir (DTG) in combination with abacavir (ABC)/3TC is one of the preferred regimens in multiple clinical scenarios, including treatment-naive and treatment-experienced patients. Triple combination therapy with ABC/3TC/DTG should be considered among the initial options for treatment-naïve HIV patients, being effective, well tolerated, with a high genetic barrier to resistance along with a convenient once-daily administration. DTG inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration into host cell DNA. ABC and 3TC are both metabolized sequentially by intracellular kinases to the respective 5′-triphosphates, which are the active moieties with extended intracellular half-lives. The main antiviral activity of ABC and 3TC is through the incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination.

DTG has relatively fewer side effects and is generally better tolerated than most other available ARVs. Common AEs reported for DTG included headache, insomnia, nausea, and diarrhea, but the proportion of patients reporting severe reactions never exceeded 1%. Hypersensitivity reactions were reported in <1% of trial participants, despite the fact that ABC has been associated with serious and sometimes fatal multiple-organ hypersensitivity reactions. Creatinine elevation is the most frequently observed biochemical alteration due to DTG use. Transaminase elevation might occur in 5% of subjects receiving DTG but were mild [38M].

Elvitegravir/Cobicistat/FTC/Tenofovir

Observational Studies

An open-label, non-comparative switch study evaluated the efficacy and safety of ETV/COB/FTC/TAF in HIV/HBV-coinfected adults. At 48 weeks, 91.7% of the 72 participants maintained or achieved virologic suppression. ETV/COB/FTC/TAF was associated with improved renal function and reduced bone turnover. These data support the use of ETV/COB/FTC/TAF in treating HIV/HBV coinfection without significant AEs [39c].

Acute kidney injury (AKI) was reported in children treated with highly active antiretroviral therapy (HRRT). Sixty-three children were included in the study with a mean age of 5.3 ± 4.27 years (range 1–14 years); 44 (69.8%) were younger than 7 years; and 35 (55.6%) were females. Forty-three (68.3%) patients were using HRRT prior to admission, but 20 were not on HRRT. Among all patients using HRRT, 37 were using 3TC; 31 on AZT; 16 on LPV; and 5 were treated with TDF. One patient needed hemodialysis and one patient died. One patient showed microscopic hematuria and three had proteinuria. Among all patients, the most frequent opportunistic infections (OIs) were pneumonia (44.4%), pulmonary tuberculosis (9.5%), and varicella zoster/chickenpox (6.3%). AKI was observed in 33 children, of which 19 children were classified as risk, 13 children were classified as injury, and 1 child considered as failure. Prevalence of AKI was lower in those on HRRT than those not on HRRT [40c].

A 47-year-old black man with a solitary kidney who was infected with HIV was treated with EFV 600 mg/ETV 200 mg/TDF 300 mg, daily for 19 months. The patient showed no evidence of nephrotoxicity over the course of 19 months on ART. He maintained adequate renal function, comparable to his baseline renal function. The authors suggest that, for patients with solitary kidneys, ART containing TDF maybe a better choice [41c].

An open-label, non-comparative switch study evaluated the efficacy and safety of coformulated ETV, COB, FTC, and tenofovir alafenamide (TAF) in HIV/HBV-coinfected adults. Of the 100 adults screened, 74 received at least one dose of ETV/COB/FTC/TAF. The participants were predominantly male. At 48 weeks, 72 participants maintained or achieved virologic suppression. ETV/COB/FTC/TAF was associated with improved renal function and reduced bone turnover. There was no proximal tubulopathy or drug discontinuation because of renal AEs. The most frequently reported study drug-related AEs were diarrhea (4.1%) and increased appetite (2.7%). One participant (1.4%) discontinued ETV/COB/FTC/TAF because of AEs of increased weight and appetite. Serious AEs were infrequent (8.1%) and there was no death reported by the treatment. There were small increases in total cholesterol, direct LDL cholesterol and HDL cholesterol, but not affecting the total cholesterol-to-HDL ratio [39c].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: NUCLEOSIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS (NRTI) [SEDA-15, 2586; SEDA-32, 534; SEDA-33, 585; SEDA-34, 456; SEDA-35, 516; SEDA-36, 415; SEDA-37, 337; SEDA-38, 270]

Abacavir [SEDA-15, 3; SEDA-32, 534; SEDA-33, 585; SEDA-34, 456; SEDA-35, 516; SEDA-36, 415; SEDA-37, 337; SEDA-38, 270]

Observational Studies

The efficacy and safety data from phase 2 and 3 clinical study on a combination of ABC/3TC/DTG, particularly on the results of both SPRING (1 and 2) and SINGLE studies suggest that the use of these combination compounds reduced the side effects. The authors are of the opinion that the triple combination therapy with ABC/3TC/DTG should be considered among the initial options for treatment-naive HIV patients, being effective, well tolerated, with a high genetic barrier to resistance along with a convenient once-daily administration [38c].

Lamivudine [SED-15, 1989; SEDA-32, 531; SEDA-33, 587; SEDA-34, 456; SEDA-35, 517; SEDA-36, 416; SEDA-37, 338]

Observational Studies

An observational study was conducted in the antiretroviral treatment center in North India from February 2009 to December 2013 to record the effects of 3TC-induced rashes. 3TC-induced skin rash occurred in 23 HIV-infected individuals out of 3213 HIV-infected patients who were on ZDV/TDF+3TC+NVP/EFV during the study period. 3TC-induced rash was more common in women than men [42c].

A 54-year-old white woman diagnosed with HIV infection started treatment with FTC/TDF in combination with NVP. An itchy rash on the neckline, abdomen and limbs appeared 8 hours after the first dose. The symptoms improved with antihistamine treatment. However, 24 hours after this reaction, the patient took another dose and a new rash with extensive skin scaling appeared, accompanied by oral and genital ulceration, fever, hepatitis, diarrhea, and loss of consciousness. Nine months later, the patient resumed HAART, and subsequently suffered from three milder episodes after FTC/TDF with etravirine, ABC/3TC with RAL, and FTC/TDF with RAL. However, the patient continued to have the rashes. The patient started an alternative treatment plan with TDF, RAL and ritonavir/lopinavir for a year without having any episode of rashes [43A].

Zidovudine [SED-15, 3713; SEDA-32, 536; SEDA-33, 588; SEDA-34, 458; SEDA-35, 517; SEDA-36, 417; SEDA-37, 338]

HIV-infected pediatric patients, aged <18 years from 14 cohorts participating in EPPICC's pharmacovigilance program who were on AZT/3TC tablets between 2008 and 2012, were included in this study. Data from 541 patients on AZT/3TC were taken for the study. Five patients aged <10 years and six ≥10 years at start of AZT/3TC tablets had grade ≥3 neutropenia. Two patients aged <10 years had a grade ≥3 ALT event. One patient aged <10 years had a grade ≥3 AST event 12–24 months after starting AZT/3TC. Five patients aged <10 years had grade ≥3 hyperbilirubinemia. Five patients aged <10 years had grade ≥3 anemia. Two patients aged <10 years had grade ≥3 platelet results (both <12 months after starting AZT/3TC). There was only 1 grade ≥3 WBC event among patients aged ≥10 years [44C].

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

Tenofovir [SED-15, 3314; SEDA-32, 537; SEDA-33, 588; SEDA-34, 458; SEDA-35, 518; SEDA-36, 418; SEDA-37, 338; SEDA-38, 272]

Renal Toxicity

Combination therapy including nucleoside and nucleotide analogues for the treatment of chronic HBV with multidrug resistance has been recommended as an effective treatment, but it has shown side effects. A study was conducted from December 2012 to June 2014 in patients exhibiting antiviral drug resistance who were treated with TDF for more than 6 months. The patients were categorized into three groups: 3TC-resistance (LAM-R) group ($n=290$), and LAM-R+ADV-resistance (ADV-R) group ($n=43$), and LAM-R+ETV-resistance (ETV-R) group ($n=113$). TDF mono-rescue therapy in the entire cohort was well tolerated, and no clinically significant side effects were reported. Thirteen patients had a low eGFR

($\leq$50 mL/min/1.73 m^2) at the onset of TDF initiation and were treated with a reduced dose of TDF, which normalized the eGFR level [45C].

Bone Density

When treated with TDF, HIV-infected patients showed a decrease in the bone mineral density (BMD). This study compared the effects of EFV/FTC/TDF with the effects of RAL/DRV/r on BMD on antiretroviral treatment-naïve African American subjects. Thirty-five HIV patients were randomized to receive either EFV/FTC/TDF or RAL/DRV/r. All of the subjects received supplemental vitamin D-3 and calcium. CD4 counts, HIV RNA, parathyroid hormone, osteocalcin, *N*-telopeptide, and 25-hydroxyvitamin D levels were obtained at baseline and at 8, 24, 36, and 48 weeks, but the 25-hydroxyvitamin D levels were decreased in both groups. By week 48, the levels of 25-hydroxyvitamin D in the RAL/DRV/r group increased but not in the EFV/FTC/TDF group [46c].

A review article also discusses the bone safety of TDF in HIV patients [47R].

A phase 1, single-dose, pharmacokinetic (PK) investigation of TDF and FTC treatment in 49 healthy female volunteers participated in the clinical trial between April 2012 and August 2013 included in the study. A mathematical modeling was also used to determine the number of doses required for effective HIV pre-exposure prophylaxis (PrEP). A PK/pharmacodynamic (PD) model was developed by measuring mucosal tissue concentrations of TAF, FTC, and their active metabolites (tenofovir diphosphate and FTC triphosphate, respectively), and competing endogenous nucleotides (dATP and dCTP) in all participants. This model is predictive of PrEP trial results in which 2–3 doses/week were 75%–90% effective in men but not effective in women [48C].

A single-arm, open-label study recruited 242 patients with mean age of 58 years. Tenofovir alafenamide (TAF) is a novel tenofovir pro-drug with improved renal and bone safety. A 48-week safety and efficacy study on a once-daily single tablet regimen of ETV 150 mg, COB 150 mg, FTC 200 mg, and TAF 10 mg (ETV/COB/FTC/TAF) was conducted in HIV-1-infected patients. The primary endpoint was the change from baseline in eGFR. Through week 48, no significant change in estimated CrCl was observed. Two patients (0.8%) discontinued the study drug due to decreased creatinine clearance. Subjects had significant improvements in proteinuria, albuminuria, and tubular proteinuria. Hip and spine bone mineral density significantly increased from baseline to week 48. Ninety-two percent of the patients maintained less than 50 copies of HIV-1 RNA at week 48 [49C].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI) [SEDA-15, 2553; SEDA-31, 486; SEDA-32, 537; SEDA-33, 590; SED-34, 459; SEDA-35, 519; SEDA-36, 420; SEDA-37, 339; SEDA-38, 273]

Efavirenz [SEDA-15, 1204; SEDA-32, 537; SEDA-33, 590; SEDA-34, 459; SEDA-35, 519; SEDA-36, 420; SEDA-37, 339; SEDA-38, 273]

The impact of Efavirenz (EFV), Etravirine, RPV and NVP on the integrity of the blood–brain barrier, and their impact on severity of stroke, was studied in an animal model. EFV altered claudin-5 expression, increased endothelial permeability, and disrupted the blood–brain barrier integrity and also increased the severity of stroke in the middle cerebral artery occlusion in mice [50E].

Observational Studies

The efficacy, safety, and anti-inflammatory effects of cenicriviroc (CVC) with EFV in treatment-naive, HIV-1-infected adults were studied. In this study, a randomized, double-blind, double-dummy phase 2b trial at 43 institutions (USA and Puerto Rico) was conducted in 143 HIV-1-infected adults for 48 weeks. Study participants were randomized to receive CVC 100 mg (59 patients), CVC 200 mg (56 patients), or EFV 600 mg (28 patients), each administered with FTC/TDF. Virologic success was obtained at week 24 and at week 48. Resistance mutations emerged in five CVC-treated participants. Treatment-related AEs of at least grade 2 and discontinuations due to AEs were less frequent in CVC-treated study participants. Total and low-density lipoprotein cholesterol decreased with CVC, but increased with EFV. The authors suggest that CVC showed better efficacy and favorable safety in treatment-naive HIV-1-infected patients and that the drug could go on to phase 3 trials [51C].

Neurological

The first case of complex partial seizures arising due to EFV treatment in HIV patient was reported. A 33-year-old Nigerian man was treated with an EFV-based antiretroviral regimen for HIV infection. He reported with seizures soon after starting the antiretroviral drugs. His blood levels of sodium, glucose, urea, and creatinine were within normal limits. His electroencephalogram showed intermittent bursts of sharp waves and spikes bilaterally

over front temporoparietal regions. His seizures stopped following a switch to a non-EFV-based regimen [52A].

Four black African children, between the ages of 4 and 8 years and between 1 and 20 months post-EFV initiation, developed cerebellar dysfunction and generalized seizures. Plasma EFV levels ranged from 20 to 60 mg/L, 5–15 times the upper limit. All abnormal central nervous system manifestations abated after EFV discontinuation. This study suggests that CYP2B6 single-nucleotide polymorphisms should be analyzed before starting the antiviral treatment to avoid the neurological side effects [53A].

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

See also Section Efavirenz.

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

PAINT is a phase II, open-label, single-arm, 2-part study, with an 8-week screening period, an initial 48-week treatment period and an ongoing post-week 48-treatment extension period. The study was conducted between December 2010 and June 2014 for 48 weeks. Thirty-six patients were enrolled and treated in the study, and at the end of 48 weeks, 8 patients (22%) discontinued for various reasons. In Cohort 1 of the study, the PK, safety, efficacy and virology of RPV taken in combination with an investigator-selected dual NTRTI background regimen was evaluated. The median time to virologic response was 11.4 weeks. Study demonstrated that RPV 25 mg combined with two NTRTI was effective and generally well tolerated over 48 weeks in HIV-1-infected patients. AEs considered to be at least related to RPV were somnolence (14%), nausea (6%), dizziness, headache, abdominal pain, blurred vision, pyrexia, drug hypersensitivity, skin papilloma, and rash in 3% of the patients [54C].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: PROTEASE INHIBITORS [SED-15, 2586; SEDA-32, 541; SEDA-33, 593; SEDA-34, 461; SEDA-35, 522; SEDA-36, 423; SEDA-37, 340; SEDA-38, 274]

Atazanavir

Observational Study

Ritonavir-boosted atazanavir (ATV/r) is the preferred treatment for HIV patients in resource-limited settings and with ADRs for other drugs. Data analyzed on the ATV/r-associated ADRs in Southern India. In this prospective study, 111 HIV patients treated with ATV/r for at least 2 years who followed a follow-up visits for the emergence of hyperbilirubinemia, hypertransaminasemia, and serum creatinine elevation were included in the study. The incidence of severe hyperbilirubinemia, hypertransaminasemia, and creatinine elevation was 28.6, 0.76, and 1.62 cases/100 person years, respectively. 3TC/FTC+TDF were found to be significantly associated with hypertransaminasemia and creatinine elevation [55C].

Cardiovascular risk among HIV-infected patients treated with ATV has been reviewed [56R]. In this systematic review of cardiovascular disease in HIV-infected patients receiving ATV, there was no increase in the risk or occurrence of adverse clinical outcome with boosted and unboosted ATV compared to other antiviral agents.

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: INHIBITORS OF HIV FUSION [SEDA-33, 598; SEDA-34, 464; SEDA-35, 525; SEDA-36, 428; SEDA-37, 341; SEDA-38, 275]

Enfuvirtide

Fusion inhibitors are a class of molecules designed to disrupts the HIV-1 fusion protein equipment at the final stage of fusion with the host cell. HIV binds to the host CD4+ cell receptor via the viral protein gp120 and gp41, and then undergoes a conformational change that assists in the fusion of the viral membrane with the host cell membrane. Enfuvirtide binds to gp41 and thus preventing the formation of an entry pore for the capsid of the HIV-virus. Enfuvirtide has side effects include diarrhea, fatigue, nausea, and reactions at the site injection [57R].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: INTEGRASE INHIBITORS [SEDA-33, 599; SEDA-34, 465; SEDA-35, 525; SEDA-36, 428; SEDA-37, 342; SEDA-38, 275; SEDA-38, 276]

Dolutegravir

Observational studies: DTG is one of the preferred antiretroviral agents in cART. A cohort study including all patients who started DTG in two HIV treatment centers in the Netherlands. All cART-naïve and cART-experienced patients who had started DTG were identified from the institutional HIV databases. In total, 556 patients were included, of whom 102 (18.4%) were cART-naïve at initiation of DTG. Median follow-up time was 225 days. Overall, in 85 patients (15.3%), DTG was stopped. In 76 patients (13.7%), this was due to intolerability. Insomnia and sleep disturbance (5.6%), gastrointestinal complaints (4.3%) and

neuropsychiatric symptoms such as anxiety, psychosis and depression (4.3%) were the predominant reasons for switching from DTG. In regimens that included ABV, DTG was switched more frequently. In particular, DTG was stopped more frequently if the regimen included ABV [58c].

Raltegravir

The use of RAL in clinical practice raised new hopes in the achievement of HIV eradication, since its mechanism of action based on the inhibition of HIV integration in uninfected cells.

Observational Study

A prospective cohort study was conducted of HIV-1-infected adult patients from January 2011 through December 2012 receiving a stable antiretroviral regimen for at least 12 months including a ritonavir-boosted PI plus two NRTIs for at least 6 months. All patients who switched to a dual antiretroviral regimen constituting RAL (400 mg twice daily) and darunavir/ritonavir (800/100 mg daily) were enrolled in the study and followed for 48 weeks. This study enrolled 82 patients with a mean age of 45.2 years, of which 60 patients were male. The reasons for switch to RAL plus darunavir/ritonavir were renal toxicity (increased creatinine, hypophosphoremia, or tubular proteinuria), reduced BMD, hyperlipidemia, gastrointestinal symptoms, or resistance to nucleoside/nucleotide analogues. After 48 weeks from the switch to RAL plus darunavir/ritonavir, 6 discontinued, 2 due to virological failure and 4 due to non-serious AEs. The four discontinuations for non-serious AEs were due to diarrhea with abdominal discomfort in three cases and nausea with lack of appetite in one. The authors concluded that the dual therapy containing RAL and darunavir/ritonavir was well tolerated after a 48-week follow-up as a strategy in persistently suppressed HIV-infected patients [59c].

DRUGS ACTIVE AGAINST HUMAN IMMUNODEFICIENCY VIRUS: CHEMOKINE RECEPTOR CCR5 ANTAGONISTS [SEDA-33, 600; SEDA-34, 465; SEDA-35, 528; SEDA-36, 430; SEDA-37, 343; SEDA-38, 276]

Maraviroc

Observational study: Maraviroc is an entry inhibitor registered for the treatment of HIV. Binding of MVC to CCR5 prevents interaction with the third hypervariable loop (V3 loop) of the viral envelope protein gp120 and thereby prevents HIV entry into the cell. A retrospective cohort study was reported in patients with an HIV-1 diagnosis who were ≥18 years of age. Sixty-two patients were included in the study. In 40 patients, plasma HIV-RNA was detectable (≥50 copies/mL) at the start of MVC, whereas in 22 patients MVC was started when plasma HIV-RNA was undetectable. Thirty-four patients (54.8%) started MVC because of virological failure of their previous regimen, whereas 15 patients (24.2%) switched to MVC-containing regimen because of toxicity problems. MVC-containing regimens were well tolerated. Twelve patients (19.4%) discontinued MVC therapy. Of these patients, three re-started MVC treatment after 6 months. Three patients discontinued MVC due to side effects. Out the remaining patients, four developed increased ALT levels, but was not related to MVC therapy. Increased plasma creatinine level was found in five patients. However, all five patients were known to have renal insufficiency before the start of MVC. Five patients (8.1%) died during follow-up. Causes of death were pneumonia (two cases), B-cell lymphoma, squamous cell carcinoma, and cardiomyopathy in combination with pulmonary hypertension (3 cases). There appeared to be no direct correlation between MVC therapy and any of the deaths [60C].

A multicenter, randomized, open-label, 96-week noninferiority switch study of MVC was reported. Participants were included if they were HIV-1-infected adults aged ≥18 years. Seven hundred ninety-five participants were screened from sites in 13 countries (Argentina, Australia, Canada, Chile, France, Germany, Ireland, Japan, Mexico, Poland, Spain, Thailand, and United Kingdom). Twenty-three percent of participants were women. Sixty-eight percent were on tenofovir-based N(t)RTI backbones; 35%, 28%, and 17% were on ritonavir-boosted ATV, lopinavir (LPV/r), or darunavir, respectively. Eight hundred and eighty-four AEs were reported; 86% were determined as not related or probably not related to study drugs. During the 48 weeks of follow-up, 1 patient died, 1 patient in the MVC+PI/r arm developed an AIDS-defining illness, and 9 had serious non-AIDS-defining events (2 and 7 in the control and MVC arms, respectively). One myocardial infarction event was reported as a safety alert in a patient on MVC [61c].

DRUGS ACTIVE AGAINST INFLUENZA VIRUSES: NEURAMINIDASE INHIBITORS [SED-15, 2436; SEDA-32, 544; SEDA-33, 601; SEDA-34, 466; SEDA-35, 528; SEDA-36, 431; SEDA-37, 344; SEDA-38, 277]

Oseltamivir (Tamiflu)

Oseltamivir is well tolerated in influenza patients and the most commonly reported side effect is associated with the gastrointestinal system [62R].

A survey was conducted in a cross-sectional, multiple-choice, adult patients and adult caregivers of pediatric patients who were admitted to the emergency department with flu-like symptoms. The survey asked about the use of oseltamivir in flu-like symptoms. The survey responders were of the opinion that they were not willing to take the medication since it may have adverse effects on kidney and liver [63c].

A novel cyclopentane neuraminidase inhibitor of influenza virus, Peramivir, was active against both A and B strains of influenza virus, and was approved by the Food and Drug Administration in December 2014. Common side effects of peramivir were gastrointestinal disorders and decreased neutrophil counts [64R].

OTHER DRUGS

Imiquimod [SED-15, 1718; SEDA-35, 530; SEDA-36, 431; SEDA-37, 344; SEDA-38, 277]

Imiquimod is an immune response modifier. The mechanism of action of imiquimod has been detailed [65R].

Cervical intraepithelial neoplasia (CIN) is the premalignant condition of cervical cancer and is caused by cervical human papillomavirus (HPV) infection. Imiquimod has been employed to treat CIN [66C].

A 67-year-old male patient presenting with infiltrating basal cell carcinoma above the left eyebrow was treated with Imiquimod. The reported side effects of imiquimod were multiple eruptive milia, erythema, irritation and crusting [67c].

Dermatological studies: Periocular melanoma was treated with 5% Imiquimod cream and showed no systemic side effects [68c].

A recent survey of case studies pertaining to antivirals was published in 2015 [69].

Disclaimer

The findings and the conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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