Review Article

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Antiviral Drugs and Their Toxicities

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Abstract

Developments in antiviral agents have led to significant progress in the treatment of infections caused by herpes simplex virus 1-2, varicella-zoster virus (VZV), cytomegalovirus, influenza A and B, and human immunodeficiency virus (HIV). There are several antiviral drug therapies that are widely used today. These antiviral drugs are examined under four main headings: drugs effective against influenza viruses, drugs effective against herpes viruses, anti-HIV drugs and immunomodulators in antiviral therapy. Toxicities of these drugs are also examined in four main headings: toxicity of drugs that are effective against herpes viruses, toxicity of drugs effective against influenza viruses, toxicity of antiretroviral drugs and toxicity of other antiviral agents. Under these main headings, antiviral drugs and toxicities of these drugs will be analyzed in more detail. The side effects and toxicities of these drugs should be well known and if such a situation is encountered, it would be more appropriate to choose another antiviral treatment that may have less side effects and toxicity for the patient if necessary.

Key words: Antiviral drugs, side effects, toxicity

Özet

Antiviral ajanlardaki gelişmeler, herpes simpleks virüs 1-2, varisella-zoster virüs, sitomegalovirüs, influenza A ve B ve insan immün yetmezlik (HIV) virüsü kaynaklı enfeksiyonların tedavisinde önemli ilerleme sağlamıştır. Günümüzde yaygın olarak kullanılan çeşitli antiviral ilaç tedavileri vardır. Bu antiviral ilaçlar dört ana başlık altında incelenir: influenza virüslerine karşı etkili ilaçlar, herpes virüslerine karşı etkili ilaçlar, anti-HIV ilaçları ve antiviral tedavide kullanılan immünomodülatörler. Bu ilaçların toksisiteleri ayrıca dört ana başlıkta incelenmiştir: herpes virüslerine karşı etkili ilaçların toksisitesi, influenza virüslerine karşı etkili ilaçların toksisitesi, antiretroviral ilaçların toksisitesi ve diğer antiviral ajanların toksisitesi. Bu derlemerde, ana başlıklar altında, antiviral ilaçlar ve bu ilaçların toksisiteleri daha ayrıntılı olarak analiz edilecektir. Bu ilaçların yan etkileri ve toksisiteleri iyi bilinmeli ve eğer böyle bir durumla karşılaşılırsa, gerekirse hasta için daha az yan etkisi ve toksisitesi olabilecek başka bir antiviral tedavi seçmek daha uygun olacaktır.

Anahtar kelimeler: Antiviral ilaçlar, yan etki, toksisite

Introduction

Developments in antiviral agents have led to significant progress in the treatment of infections caused by herpes simplex virus 1-2, varicella-zoster virus (VZV), cytomegalovirus, influenza A and B, and human immunodeficiency virus (HIV).

The best drugs used against herpes simplex virus and cytomegalovirus infections are aciclovir, penciclovir and ganciclovir. The effects of these drugs are not optimal when administered orally. Higher oral drug doses may be required to provide the appropriate blood and tissue dose to inhibit viral replication. Three prodrugs have been produced for drug formulation and product development: valaciclovir, famciclovir and valganciclovir. Valine ester, which leads to increased gastrointestinal absorption of a drug, was added to aciclovir and ganciclovir to come up with valaciclovir and valganciclovir, respectively. When the drug reaches the liver, the valine is hydrolyzed and removed, which is followed by the formation of aciclovir and ganciclovir.

ANTIVIRAL DRUGS

1- Drugs Effective Against Influenza Viruses

Influenza is an acute and contagious disease caused by the influenza virus (usually A and sometimes B viruses) that affects the respiratory system, which is characteristically seen in the form of epidemics.

There are two main groups of drugs for influenza virus infections, which are used in prophylaxis or treatment. These two groups of drugs are amantans (amantadine and rimantadine), also known as M2 inhibitors, and the newer group of neuraminidase inhibitors (zanamivir and oseltamivir).

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a) M2 inhibitors: Drugs developed in the early 1960s and used in infections caused by influenza A viruses are amantadine and rimantadine. M2 is found only in the influenza virus and is an acid-activated ion channel. It is a membrane protein necessary for the release of nucleocapsid after the fusion of the virus with the endosomal membrane. After this inhibition, they prevent the intake of the virus into the host cell through endocytosis, the uncoating of the virus, the coming together of viral products and the virion assembly. The second mechanism is associated with the fact that they reduce the lysosomal pH, following the concentration of amantadine and rimantadine in lysosomes[1–4].

b) Neuraminidase inhibitors: Influenza viruses all have two surface glycoproteins: hemagglutinin and neuraminidase. These antigens identify the specific type of the influenza. Zanamivir and oseltamivir are neuraminidase inhibitor drugs currently used in the clinic. Both of these drugs are sialic-acid analogues, but they potently and specifically inhibit neuraminidase found in both influenza A and influenza B viruses reversibly[5,6].

2- Drugs Effective Against Herpes Viruses

Antivirals are drugs that kill viruses or inhibit their reproduction. In order for an antiviral agent to be effective, it must prevent the virus from multiplying or kill the virus directly without affecting the host cell.

Viruses are made up of genetic materials in the structure of single or double-stranded DNA or RNA. On the outer side of the virus, there is a protein mantle called capsid. Some viruses have another structure called envelope other than capsid, which is composed of lipoproteins and has antigenic properties. Viruses can be described as intracellular parasites. They use the host cell (bacterial, plant or animal cell) that is more advanced than they are to produce their viral proteins and genetic materials[7].

The herpes virus family consists of morphologically similar enveloped and large viruses, containing large, double-helix DNAs. Following the primary infection, they remain latent in the host and can be reactivated, which are some of their most important characteristics[8].

Herpes virus family classification

A- Alpha herpes viruses:

1- Simplex viruses (HSV)
-Herpes Simplex Virus-Type 1 (HSV-1)
-Herpes Simplex Virus-Type 2 (HSV-2)

2- Varicella viruses
-Varicella-Zoster Virus (VSV)

B- Beta Herpes Viruses:
1- Cytomegalovirus (CMV)
2- Muromegalovirus
3- Roseolovirus

C- Gamma Herpes Viruses:
1- Epstein-Barr virus (EBV)
2- Rhadinoviruses

Drugs Effective Against Herpes Viruses

a) Aciclovir and Valaciclovir: These are drugs that block viral DNA synthesis[7]. The selectivity of their effect depends on their interaction with two viral proteins. Viral thymidine kinase is the first of these proteins. It is responsible for ensuring the entry of the drug into the cell and the initial phosphorylation of the drug. The interaction with the second protein is that aciclovir in the cell gets into competition with endogenous deoxyguanosine triphosphate (dGTP).

b) Famciclovir and Penciclovir: Penciclovir is an acyclic guanine nucleotide analogue. The diacetyl derivative manufactured to improve the oral bioavailability of penciclovir is famciclovir8. Penciclovir inhibits the viral DNA synthesis of HSV and VZV viruses. In infected cells, viral thymidine is phosphorylated by kinase and transformed into triphosphate, which is a competitive inhibitor of the DNA polymerase enzyme[9].

c) Ganciclovir and Valganciclovir: The prodrug of ganciclovir is valganciclovir. Ganciclovir inhibits viral DNA synthesis.

d) Cidofovir: Cidofovir is a nucleotide analogue of cytidine10. It inhibits viral DNA synthesis and subsequently slows or inhibits the lengthening of the DNA strand.

e) Foscarnet: Foscarnet is an inorganic pyrophosphate analogue (trisodium phosphonoformate). By inhibiting viral nucleic acid synthesis, foscarnet indirectly inhibits the DNA polymerase enzyme of the herpes virus and the HIV reverse transcriptase enzyme.

f) Docosanol: Docosanol prevents invitro replication of several viruses that carry lipid envelopes. It does not directly inactivate HSV but prevents the fusion between the cell membrane and the virus envelope, and it prevents the virus from entering the cell.

g) Fomivirsen: Its effect is on mRNA in the early protein synthesis process of CMV. Its effect on mRNA prevents replication of the virus and its binding to the cell.

h) Trifluridine: Thymidylate synthetase irreversibly inhibits trifluridine monophosphate, and trifluridine triphosphate is a competitive inhibitor of thymidine triphosphate.

i) Idoxuridine: It is an iodine thymidine analogue and inhibits the replication of the DNA virus.

3- Anti-HIV Drugs

Acquired immune deficiency syndrome (AIDS) is a fatal, chronic, infectious disease that occurs as a result of the transmission of the human immunodeficiency virus (HIV), and the increasing suppression of the immune system. There is no cure yet to eliminate the virus in HIV infection, but there are drugs that control the proliferation of the virus. These drugs are called "Antiretroviral Drugs," and the treatment with these drugs is called "Antiretroviral Treatment." There is still no definitive solution for the treatment of the disease. With the drugs in use, it is possible to control the disease but not cure it. However, it is reported that life expectancy can be extended with intensive treatment11.

Today, antiretroviral drugs are examined in four groups: nucleoside reverse-transcriptase inhibitors (NRTIs), nonnucleoside reverse-transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and fusion inhibitors (FIs).

a) Nucleoside Reverse-Transcriptase Inhibitors (NRTIs): The phosphorylated active metabolites of the drugs in this group compete to bind to the viral DNA. They inhibit HIV's RT enzyme by competing and act as a strand that ends the DNA synthesis12. Drugs in this group include Zidovudine (ZDV, AZT) (Retrovir), Didanosine (ddl) (Videx), Zalcitabine (ddC) (HIVID), Stavudine (d4T) (Zerit), Lamivudine (3TC) (Epivir), Abacavir (ABC) (Ziagen), Emtricitabine (FTC) (Emtriva), and Tenofovir Disoproxil Fumarate (TDF) (Viread). Amdoxovir, Apricitabine and Elvucitabine are drugs whose experimental studies continue.

b) Nonnucleoside Reverse-Transcriptase Inhibitors (NNRTIs): These drugs bind directly to the parts of the RT enzyme that are different from the nucleoside-binding region of it. Resistance to these drugs develops rapidly in general. For this reason, they are not preferred in monotherapy except in special cases. Drugs in this group include Nevirapine (NVP) (Viramune), Delavirdine (DLV) (Rescriptor), and Efavirenz (EFV) (Sustiva). Calanolide A, Etravirine, and Rilpivirine are the drugs with continuing experimental studies.

c) Protease Inhibitors (PIs): Protease inhibitors constitute the most effective class among antiviral drugs. The viral protease enzyme is their main target. As a result of the inhibition of viral proteases, the division of gag-pol polyprotein is prevented, which results in the formation of non-infective viral particles. Drugs in this group include Saquinavir mesylate (SQV) (Invirase), Ritonavir (RTV) (Norvir), Lopinavir, Indinavir (IDV) (Crixivan), Nelfinavir mesylate (NFV) (Viracept), Amprenavir (APV) (Agenerase), Fosamprenavir Calcium (FOS-APV) (Lexiva), Atazanavir sulfate (ATV) (Reyatase), Tipranavir (TPV) (Aptivus), and Darunavir (Prezista).

d) Fusion Inhibitors: The effect of fusion inhibitors is to prevent the entry of HIV into healthy T cells in the body. Entry inhibitors take effect by binding to proteins on the surface of HIV or T cells. In order for HIV to bind to T cells, HIV's outer membrane proteins need to bind to the surface proteins of T cells. Entry inhibitors prevent this event. Some of the entry inhibitors target the gp120 or gp41 proteins on the surface of HIV. Drugs in this group include Enfuvirtide (ENF) (Fuzeon), Maraviroc, and Vicriviroc.

e) Combined Preparations: Atripla (Efavirenz + Emtricitabine + Tenofovir), Combivir (Retrovir + Epivir), Epzicom (Abacavir + Epivir), Trizivir (Abacavir + Zidovudine + Lamivudine), Truvada (Emtricitabine + Tenofovir), and Kaletra (Lopinavir + Ritonavir).

4- Immunomodulators in Antiviral Therapy

Immunomodulatory drugs have been used for years as a hope to treat cancer and infectious diseases.

Immunomodulators can be grouped under 6 groups:
a) Natural cytokines (colony stimulant factors, interleukins, interferons, chemokines and thymic hormones)
b) Monoclonal antibodies and receptor antagonists
c) Immunoglobulins
d) Steroids
e) Synthetic compounds (thalidomide, imiquimod, and so forth)
f) Anti-inflammatory anticoagulants (activated protein C).

TOXICITY OF ANTIVIRAL DRUGS

1- Toxicity of Drugs Effective Against Herpes Viruses

a) Aciclovir (Hernovir): It has mutagenic characteristics because of its effects on the cell DNA. It does not have teratogenic and carcinogenic effects if used for a long time. Although its acute toxicities are relatively low in oral uses of less than 1 mg/kg, cases undergoing excessive intravenous therapy such as 80 mg/kg have been reported to experience excessive major toxic effects. It has also been reported that hallucinations occur in high dose use. Edema, arthralgia, sore throat, and weakness are some of the other common effects, in addition to CNS findings such as agitation, vertigo, confusion, and dizziness. From time to time, heavier clinical presentations can be seen, which include Stevens-Johnson syndrome, and toxic epidermal necrolysis. Coma, convulsions, neutropenia, leukopenia, crystalluria, anorexia, hepatitis and even anaphylactic reactions can be seen as rarer

side effects. In the urogenital system, a high level of urea and creatinine causes side effects that start with hematuria and then may lead to renal failure. Encephalopathy, and pain and irritation at the injection site may be seen in 1% of patients among additional side effects when they are given intravenous therapy[13–15].

b) Cidofovir (Vistide): Its effects are similar to those of ganciclovir and foscarnet, and renal insufficiency with proteinuria is its most important side effect. The effects cause rash, headaches, fever and even iritis and hypotonia[16].

c) Docosanol (Abreva 10%): It is well tolerated at the onset of treatment. Prodromal findings are also observed during the first 12 hours of treatment[17].

d) Famciclovir (Famvir): It inhibits DNA polymerase, and reduces recovery time and postherpetic neuralgia, especially in elderly patients[18].

e) Foscarnet (Foscavir): It reduces glomerular filtration rate in kidneys and increases serum creatinine. Its most important effect on the renal system is the fact that it causes acute and chronic renal insufficiency. It also causes frequent side effects of hypokalemia, hypocalcemia, hypomagnesemia, phosphatemia and CNS. Direct retinal toxicity, intravitreal bleeding, and endophthalmia are its potential side effects. Its safety in pregnant women and children is uncertain because it is mutagenic and can cause skeletal and dental anomalies[19].

f) Ganciclovir (Cytovene): It often and substantially causes hematologic reactions such as granulocytopenia, neutropenia, thrombocytopenia and anemia. Phlebitis accompanied by pain, redness, and itching may occur in parenteral use. Serum urea and creatinine may also be elevated. Ganciclovir has chronic toxic effects. These effects are thought to be carcinogenic, mutagenic and teratogenic, and inhibit spermatogenesis. For this reason, they are considered to be among cytotoxic drugs.

g) Idoxuridine (Herpes, Stoxil, Dendrite): It acts on viral and host cell DNAs and is highly toxic. Irritation, pain, pruritus, inflammation, eyelid edema, and photophobia are its rare allergic reactions[20].

h) Penciclovir (Denavir): It acts as a placebo in terms of side effects. Its cytotoxicity is negligible.

i) Trifluridine (Viroptic): Stinging in the eye, burning sensation, and palpebral edema are its common acute side effects. Less commonly, keratopathy and hypersensitivity reactions may occur.

j) Tromantadine (Viru-Merz)

k)Valaciclovir (Valtrex): It has side effects such as nausea, vomiting, diarrhea, and headaches. In 0.1% of patients, it causes CNS and hematopoietic side effects such as coma, convulsion, neutropenia, leukopenia, tremor, ataxia, and encephalopathy. It leads to thrombotic thrombocytopenic purpura and hemolytic uremic syndrome[13].

l) Valganciclovir (Valcyte): Neutropenia, anemia, and thrombocytopenia can occur. It may cause myelosuppression if used for a long time. Its side effects on GIS are diarrhea, nausea, vomiting, and abdominal pain. Fever, headache, insomnia, paresthesia, and peripheral neuropathy occur in the CNS, and especially retinal detachment occurs in the eye[21].

m) Vidarabine (Vira A, Ara A): Its toxic side effects are rare. Conditions such as vomiting, leukopenia, and thrombocytopenia may be seen, although rarely, in high dose intravenous therapy[22].

2- Toxicity of Drugs Effective Against Influenza Viruses

a) Amantadine (Symmetrel): Irritability, anxiety, agitation, insomnia, concentration disorder, lisping, ataxia, depression, and hallucinations may often occur as CNS side effects. GIS findings such as nausea and constipation may also be observed. These effects are intensive within 48 hours of drug use and decreases over time. Its safety in pregnant women is not certain[23].

b) Rimantadine (Flumadine): Its side effects are mostly on GIS and CNS and are less common than those of other influenza drugs. Nausea, stomach pain, irritability, fatigue, sensitivity to light, sleep disturbance, and difficulty in concentration have been observed in 6% of patients using the drug[23].

c) Oseltamivir (Tamiflu): Nausea, vomiting, diarrhea, abdominal pain, and headaches are common, but less commonly, serious effects such as hepatitis, increased liver enzymes, allergic reactions leading up to anaphylaxis, and even Stevens-Johnson syndrome may also occur. Cases of toxic epidermal necrolysis, arrhythmia, convulsions, confusion, increased diabetes, and hemorrhagic colitis have also been reported in recent years. Abnormal behaviors and hallucinations have been added to its neurological effects in recent years. As a matter of fact, it was observed that oseltamivir-related deaths occurred between 2000 and 2004 for various reasons. Its pediatric safety is unclear and attention should be paid to behaviors such as delirium and hallucinations. Its safety in pregnant women is not certain, either[24].

d) Zanamivir (Relenza): Although generally well tolerated in children and adults, it has been reported to cause wheezing and bronchospasm. For this reason, it is not preferred to be

used in people with respiratory diseases. It is comfortable to use in terms of drug interactions, and there is no information as to whether it is mutagenic, teratogenic or carcinogenic[25].

3- Toxicity of Antiretroviral Drugs

If we are to generalize the side effects caused by retroviral drugs, they vary depending on the individual, the drug used with it, the ethnicity, and the amount of alcohol consumption. Their common side effects include abdominal pain, alopecia, anemia, asthenia, diarrhea, vertigo, fanconi syndrome, flatulence, headache, hepatitis, hyperbilirubinemia, hypercholesterolemia, hyperpigmentation in palms, soles and nails, insomnia, liver failure, weakness, mental confusion, myalgia, encephalomyelitis, myopathy, nausea, neutropenia, intraoral ulcers, pancreatitis, paresthesia, peripheral neuropathy, redness, renal insufficiency, somnolence, Stevens-Johnson syndrome, vomiting, dry mouth, dry skin, and deterioration in the sense of taste.

A- Nucleoside Analog Reverse-Transcriptase Inhibitors (NARTIs)

a) Zidovudine (Retrovir, Retrovis) (AZT, ZDV): Nausea, headaches, discoloration of the feet and fingernails are its common acute toxic effects. Bone marrow suppression and anemia are also its serious side effects. Its unexpected side effect is gamma DNA polymerase sensitivity in cell mitochondria. It has additive or synergistic interaction with many drugs for treating HIV. However, aciclovir and ribavirin reduce the effect of AZT. Its hepatic glucuronidation is inhibited and its toxic effects increase when used with aspirin, indomethacin and trimethoprim.

b) Didanosine (Videx, Videx EC): Diarrhea, nausea, vomiting, abdominal pain, fever, headache, and redness are its common side effects. In addition to these, peripheral neuropathy, pancreatitis, retinal changes, optic neuritis, and liver dysfunctions may also occur rarely. These conditions worsen even further if alcohol is used with it. The development of resistance to the drug is slower than that to zidovudine. It causes gene mutations[26].

c) Zalcitabine (Hivid): Nausea and headaches are frequently seen at the onset of treatment. Peripheral neuropathy, intraoral ulcers, esophageal ulcers and rarely pancreatitis are observed in more than 33% of patients with progression of the disease. It causes mutations.

d) Stavudine (Zerit, Zerit XR): Peripheral neuropathy is a serious side effect of it that also requires reducing the drug dose. In laboratory studies, it has been observed to be genotoxic but not carcinogenic at clinical doses. Lipodystrophy is one of the conditions frequently caused by antiviral drugs.

e) Lamivudine (Epivir): It has been found, according to the results of many mutagenic tests, that it does not cause any mutagenic activity at the dose of treatment. Cases requiring to see a doctor are redness, stomach pain, burning and numbness in toes and fingers[27].

f) Abacavir (Ziagen): During treatment, fatal hypersensitivity reactions, GIS findings such as fever, redness, weakness, nausea, vomiting, diarrhea and abdominal pain, and respiratory system findings such as pharyngitis, dyspnea and cough occur. Hypersensitivity reactions strongly correlate with HLA-B 5701, and this relationship is stronger in western countries. Hepatomegaly and lactic acidosis are also common serious side effects[28].

g) Emtricitabine (Emtriva): Toxicity of this drug is not usual in clinical studies. It does not cause a mutagenic effect. Diarrhea, headache, nausea and redness are its side effects related to treatment. These symptoms are usually mild or moderate. These conditions increase as the treatment is continued. It has severe side effects such as pancreatitis, hepatitis and lactic acidosis, while it causes hyperpigmentation on soles and palms.

B- Nucleotide Analog Reverse-Transcriptase Inhibitors (NTARTIs)

Nucleoside analogues are transformed into nucleotide analogues in the body, and this group of drugs have been shown to cause less toxicity.

a) Tenofovir (Viread): Although it causes unease in the stomach, diarrhea, vomiting, decreased appetite and gas complaints, these effects are not serious. It causes effects similar to those of adefovir and cidofovir. It has been reported in in vitro studies16 that it does not cause renal tubular damage in humans, but acute renal failure and Fanconi Syndrome have been reported in rare cases with tenofovir[29].

C- Nonnucleoside Reverse-Transcriptase Inhibitors (NNRTIs)

a) Neviparine (Viramune): Approximately 13% of patients have mild or moderate redness, and 1.5% have been observed to have severe and life-threatening skin reactions. These are Stevens-Johnson syndrome, toxic epidermal necrolysis and hypersensitivity30. Moreover, severe liver toxicity is observed in the first six months of the use of neviparine.

b) Delavirdine (Rescriptor): Moderate and severe redness is a common side effect in 20% of patients. Moreover, nausea, weakness, headache, and liver toxicity findings have been reported, but it does not cause fatal hepatitis. Severe skin lesions such as erythema multiforme and Stevens-Johnson syndrome may be seen, although rarely.

c) Efavirenz (Sustiva, Stacrin): Psychiatric findings such as insomnia, confusion, loss of memory and depression may occur. In addition to these, redness in the skin, nausea, headache, and dizziness may also occur. It can cause fetal anomaly and therefore should not be used in pregnant women. It is also a drug that is not completely safe for children.

D- Protease Inhibitors

a) Saquinavir (Fortavase): Acute effects are mostly findings of GIS irritation such as moderate diarrhea, nausea and abdominal uneasiness. Its oral bioavailability is low when used alone. It interacts with drugs that interact with the cytochrome P450 3A4 enzyme. It causes lipodystrophy.

b) Tipranavir (Aptivus): Its causes quite a high number of side effects[31].

c) Ritonavir (Norvir): It interacts with drugs that interact especially with the cytochrome P450 3A4 enzyme. Its frequently seen acute effects are weakness, fatigue, vomiting, stomach uneasiness, diarrhea, headache, and vertigo. It may also cause increased blood sugar, increased cholesterol, frequent urination, and thirst[32].

d) Nelfinavir (Viracept): It causes diarrhea, abdominal pain and gas complaints in more than 1% of patients, and weakness, frequent urination, mouth ulcers and hepatitis in 0.01–0.1% of patients. Nephrolithiasis, arthralgia, leukopenia, pancreatitis and severe allergic reactions may occur less commonly. It increases cholesterol and triglycerides.

e) Lopinavir (Kaletra): Severe diarrhea and nausea are seen in more than 27% of patients. Moreover, frequently observed acute effects are abdominal pain, asthenia, headache, vomiting, redness (mostly in children), high liver enzymes, and hyperlipidemia[32]. Lopinavir is used in combination with ritonavir.

f) Indinavir (Crixiva): It causes side effects such as calculous formation, crystalluria, hyperlipidemia, hyperbilirubinemia, hyperglycemia, and lipodystrophy. It has also been reported to cause dry skin, lip dryness and rarely GIS findings.
g) Fosamprenavir (Lexia): It changes hyperglycemia and lipid profile, as well as causing symptoms such as nausea, vomiting, diarrhea, weakness, paresthesia, and headache. It causes the same effects as those of amprenavir[33].

h) Darunavir (Prezista): It is used in combination with ritonavir. Its effects are like those of ritonavir[32].

i) Atazanavir (Reyataz): Lipodystrophy, high cholesterol and triglyceride, and hyperbilirubinemia are the side effects that it causes frequently. Its effect on blood sugar is not clearly known[34].

j) Amprenavir (Agenerase): It causes mild diarrhea and self-limiting skin rashes[33].

E- Fusion Inhibitors

a) Enfuvirtide (Fuzean): In rare cases, pain, erythema, cysts, nodules, itching are seen at the injection site. Especially in the first week of use, peripheral neuropathy, insomnia, depression, cough, dysphonia, anorexia, arthralgia, bacterial infection and eosinophilia are seen in almost all patients. Hypersensitivity reactions such as skin redness, fever, nausea, vomiting, shivering, hypotension and elevated liver transaminases have been observed; and anaphylaxis has been observed, which involve these findings accompanied by respiratory distress and glomerulonephritis[35].

4- Toxicity of Other Antiviral Agents

a) Adefovir dipivoxil (Preveon, Hepsore): The drug, which is used to treat hepatitis B, has not been approved for HIV by the FDA. It causes unease in the stomach, diarrhea, vomiting, decreased appetite and gas complaints, but these are not serious effects. It causes effects similar to those of tenofovir and cidofovir16. It causes proteinuria, glucosuria, hypophosphatemia, acidosis and azotemia and even cause tubular dysfunction. It should not be used in pregnant women because it can cause anomalies[36].

b) Fomivirsen (Vitravene): It is used locally in the treatment of CMV retinitis. Its side effects are mostly ocular, and it may cause iritis, cataracts and elevated intraocular pressure in 25% of patients.

c) Imiquimod (Aldara): Irritation, burning and redness in the skin are its common side effects during treatment.
d) Inosine: It has been reported to cause moderate GIS findings, such as abdominal uneasiness and nausea. It has been observed to increase the production of uric acid, a natural antioxidant, and prevent axon degeneration by binding peroxynitrite that occurs in multiple sclerosis[37].

e) Interferon (Intron A, Roferon A, Infergen, Alferon N): The risks and side effects of this drug are almost nonexis-

tent. Successful results are obtained in preventing malignant cells from spreading and in persistent infections. Its known side effects are hypertension, dyslipidemia, hyperglycemia, proteinuria, azotemia, interstitial nephritis, hepatotoxicity, pneumonia, and peptic ulcers. This immune-suppressive drug reacts with other drugs. Fever, shivering, weakness and myalgia, which occurs 7–12 hours after the first injection, lasting up to 12 hours, are seen[38].

f) Podophyllotoxin (Etoposide): It lowers blood pressure. Hair loss, pain and redness at the intravenous therapy site, constipation or diarrhea, metallic taste in the mouth, and bone suppression may be seen. As a result, it can cause leukopenia, anemia and thrombocytopenia and consequent bleeding in the bone marrow[39].

g) Ribavirin (Virazole, Rebetol, Copegus): Its serious side effect is hemolytic anemia. It has also been observed to worsen cardiac diseases, but the mechanism of this is not yet known. Although it does not interact with DNA, it has been reported to inhibit DNA synthesis depending on the dose and cause a serious teratogenic effect. There are also clinical studies claiming that it facilitates tumor formation, that it probably has genotoxic effects and that it causes breathing difficulties due to its use.

In conclusion, there are several antiviral drug therapies that are widely used. Although each of the agents we use in antiviral therapies has many different side effects, sometimes these therapies can lead to many different toxic clinical presentations. The side effects and toxicities of these drugs should be well known and if such a situation is encountered, it would be more appropriate to choose another antiviral treatment that may have less side effects and toxicity for the patient if necessary.

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