EFFICACY OF VETERINARY ANTIVIRALS IN SMALL ANIMALS

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SARAH CADDY MA, VetMB, MRCVS reviews the use of various antiviral medicines in cats and dogs to determine their usefulness in treatment of viral infections presenting in these patients

Summary

Virus infections in small animals are common, yet very few antiviral drugs are available to treat patients. The only licensed antiviral drug in the UK is recombinant feline interferon, which has proven efficacy in clinical trials against feline retroviruses and canine parvoviruses. However, dosing protocols and expense often preclude its use. Numerous studies have deemed off-licence antivirals effective, including famciclovir for feline herpesvirus infections and off-license use of feline interferon against feline calicivirus. Studies on other products suggested to have antiviral properties have shown questionable efficacy – for example, oseltamivir and immune plasma for canine parvovirus, and lysine for feline herpesvirus infections. Despite this, continued antiviral research ensures progress is being made – polyprenyl immunostimulant is the latest antiviral drug to be approved in the US and it is hoped more will follow.

Key words

virus, **antiviral**, **interferon**, **parvovirus**, **retrovirus**

VIRALLY infected small animal patients will present at most practices fairly regular ly. From feline immunodeficiency virus (FIV) or feline leukaemia virus (FeLV)- infected cats to

parvovirus-infected pups and cat 'flu-ridden kittens, there is high demand for drugs that can help treat viral infections.

Despite this, the veterinary antiviral arsenal is minimal. Of the few antiviral drugs available – and even fewer that are licensed – most are expensive and have complicated dosing protocols. But if these issues can be overcome, are any of the veterinary antivirals worth using?

Many studies have sought to determine the efficacy of the antiviral drugs. Although some often-used drugs have shown no effect at all, others have had encouraging results. Research is striving to find new antivirals for the veterinary viruses, and some promising results are being published.

Although supportive therapy must remain the cornerstone of treating virally infected dogs and cats, this article aims to provide an overview of the drugs available to manage different viral diseases in our small animal population.

Feline retroviruses

Recombinant feline interferon omega: maybe yes, with committed owners

Only one drug is licensed for use against viral disease in dogs and cats – recombinant feline interferon omega (rFelFN-?; Figure 1). This is marketed by Virbac as Virbagen Omega.

This drug does not target any virus specifically; it instead works to enhance the antiviral immune response. IFN-? is naturally produced by virally infected cells to induce an antiviral state in neighbouring cells (Figure 2). The recombinant rFelFN-?, therefore, acts on many cell types to upregulate genes that can protect against viral invasion.

Virbagen Omega is specifically licensed for treatment against FeLV and FIV in cats more than nine weeks old. The recommended treatment protocol involves three cycles of injections at day 0, day 14 and day 60, with each treatment cycle consisting of five subcutaneous injections of 1MU/ kg once per day for five days.

In Virbac's seminal study investigating the efficacy of rFelFN-?, 81 cats naturally infected with FIV or FeLV were treated and monitored for one year[1]. During the initial fourmonth period, rFelFN-?-treated cats had improved clinical scores compared to controls, which was taken as evidence rFelFN-? could improve quality of life. However, there was no significant difference in mortality rates between treated and untreated cats one year after starting treatment.

In the most recently published study, 16 cats naturally infected with retroviruses were given rFelFN-? and clinically evaluated after each round of treatment[2]. After day 65, the majority of cats had improved clinical scores, which agrees with both the Virbac trial and also a separate 2011 study involving 11 cats[3]. The latter report also investigated levels of viraemia in treated cats. Despite

improving clinical signs, not a single cat became negative for FIV or FeLV during treatment.

This is an important point to emphasise to owners – rFelFN-? has not been shown to cure FIV/FeLV, but the improved quality of life still means rFelFN-? is a drug worth considering.

Human antiretrovirals: still unproven

For humans infected with HIV, a minimum of three different antiretroviral drugs are used as combination therapy. If a 20-year-old is infected today, these drugs can give them a life expectancy of 71 years. FIV is a remarkably similar virus to HIV, which has raised the question: “Can these drugs treat FIV in cats?”

Many of the human antiretrovirals have been tested in cats in the past 20 years, but no single drug – or drug combination – has proven to be ideal. Some antiretrovirals have shown some reduction in viral load initially, but longer term follow-up studies often report no prolonged effects[4]. In addition, the side effects reported in cats can be severe – anaemia and neutropaenia developed following azidothymidine/lamivudine therapy5 and nausea is common with several other drugs.

Feline calicivirus

Recombinant feline interferon omega: maybe yes, with committed owners

A number of studies focusing on the use of rFelFN-? for FIV/FeLV therapy have shown treated cats have an incidental reduction in the severity of gingivostomatitis. As this clinical condition is often associated with feline calicivirus (FCV), it has been suggested rFelFN-? could be helping to treat this virus as well

This theory is now supported by a clinical trial that specifically monitored the levels of FCV in cats being treated with rFelFN-? for FIV/FeLV infections. Before treatment, 81 per cent of cats were FCV positive, but after a month, all cats were FCV negative[2]. Although use of rFelFN-? for treatment of FCV is off licence, the clinical trial data suggests this may be a useful drug if owners consent to the involved treatment protocol.

Feline herpesvirus

Famciclovir: yes

Keratitis and keratoconjunctivitis are commonly induced by feline herpesvirus (FHV) infections. A wide number of antiviral drugs are available to treat herpesvirus infections in humans, and many of these have been tried in cats to assess their efficacy against FHV.

The single drug shown to be most effective is famciclovir. This has been confirmed in both

experimental and natural FHV infections[6,7]. Famciclovir is an oral drug, for which the recommended dose is 90mg/kg three times daily for three weeks. Although this use in cats is off licence, there is plenty of evidence to support offering this treatment option to owners.

Topical medications: can be effective

Aside from famciclovir, many of the human antiviral drugs used to treat herpesviruses have toxic effects if given systemically to cats. However, several of these are safe if administered topically and good results have been reported.

Trifluorothymidine (TFT) has proven efficacy against FHV in vitro, and is often recommended in the literature as the topical drug of choice. This is despite the lack of clinical trials that confirm the efficacy of TFT in cats. In addition, no standard pharmaceutical retailers in the UK supply this medication.

Other antiherpesvirus drugs that may be used to treat FHV include cidofovir, ganciclovir and aciclovir. These all are reported to be reasonably effective, but use of these topical medications requires multiple applications per day, with every four hours commonly suggested. This is demanding for the owner and cat alike.

Polyprenyl immunostimulant: a promising new product

This oral drug is new on the market in the United States as the first approved treatment for FHV. Polyprenyl immunostimulant (PI) is a plantbased drug shown to increase production of cytokines important in supporting the antiviral T cell response.

Studies of efficacy are ongoing, but it is known to be safe and well tolerated. Preliminary studies have also assessed the efficacy of PI in treatment of the dry form of feline infectious peritonitis (FIP). To date, these studies have shown questionable benefit for PI use, but interest has been raised and further trials are expected.

Lysine: no proven effect

The amino acid lysine is commonly sold as a dietary supplement for cats with clinical signs of FHV. There are conflicting reports of the benefits of lysine, with some studies suggesting efficacy in latently infected cats. However, the most up-to-date and comprehensive study involving more than 250 cats at a rehoming centre showed lysine supplementation provided no improvement in clinical signs compared to controls after four weeks of therapy[8].

Recombinant feline interferon omega: no proven effect

A trial published in early 2013 used rFelFN-? applied topically to the eyes of cats with naturally

occurring FHV keratoconjunctivitis, to determine whether this would be a useful therapy[9]. Of the 12 cats that received rFelFN-?, after two weeks none showed improvement compared to the cats that just received saline.

Canine parvovirus

Recombinant feline interferon omega: maybe, if finances allow?

Published studies have shown very promising data for rFelFN-? against canine parvovirus (CPV; Figure 3), with a 4.4 fold reduction in mortality noted in a trial involving 94 dogs given 2.5 million units/kg once daily for three consecutive days[10]. This data was generated by the pharmacological company that produces Virbagen Omega, and it stresses the dosing protocol should be closely adhered to in order to obtain similar effects. rFelFN-? is licensed for use against CPV in dogs more than one month old.

Oseltamivir: a likely no

Oseltamivir is better known as Tamiflu – the popular drug used to treat human influenza infections. Anecdotal evidence has reported a positive effect of using oseltamivir on CPV cases, despite the major differences between influenza and parvovirus pathology. It is thought oseltamivir's neuraminidase-blocking activity can limit bacterial movement through the mucin layer on gut epithelial cells.

Mortality from CPV infection is often believed to be due to sepsis following bacterial translocation from the gut, hence limiting bacterial movement may reduce this occurrence. To investigate this further, a trial with 35 dogs was designed to definitively establish whether oseltamivir might be beneficial in treating CPV[11]. All dogs received standard supportive therapy. No major advantage was noted in the treatment group, compared to the control group.

Immune plasma: minimal effect

Immune plasma has been suggested as another potentially useful therapy for treatment of CPV. The theory is that plasma from dogs vaccinated against CPV will contain sufficient anti-CPV antibody levels to block virus entry into cells.

A study from Colorado State University sought to establish the efficacy of this treatment by administering 12ml of immune plasma to seven dogs with naturally occurring CPV infection. A further seven CPV-infected dogs were given saline as a control group. There was no significant difference between the clinical course of disease in either group; therefore, the use of immune plasma for the treatment of CPV is not recommended.

Human recombinant granulocyte colony stimulating factor: no improvement

Human recombinant granulocyte colony stimulating factor (rhG-CSF) is a drug used in human medicine to treat neutropaenia by the stimulation of bone marrow to produce granulocytes. It has been theorised that rhG-CSF could be used to treat neutropaenia in dogs caused by CPV infection.

Eleven CPV-infected puppies were given rhG-CSF daily until their neutrophil count was normal, and a further 12 puppies were included as controls[12]. No differences were identified between the two groups regarding duration of hospitalisation, lowest neutrophil count or time until neutropaenia resolved. It was concluded that rhGCSF was not efficacious for treatment of CPV infection.

Soluble transferrin receptor for CPV: a future potential yes

The transferrin receptor is a cell surface molecule that facilitates transport of iron into cells. More importantly, in terms of viral pathogenesis, it has been identified as the receptor for CPV. It was proposed a soluble form of the transferrin receptor (sTfR) may have antiviral properties by binding to extracellular CPV particles and preventing entry into cells[13].

After promising in vitro studies, 24 dogs were enrolled in a treatment trial led by a research group in China and experimentally infected with CPV. A total of 75 per cent of the control dogs died, but of the dogs treated with sTfR, only 31 per cent died. Though the numbers of subjects used in this study were small, the positive data is encouraging. Future studies using this recombinant receptor protein are eagerly awaited.

Summary

Virbagen Omega rFelFN-? – the only licensed veterinary antiviral in the UK – remains the most effective drug available against FIV/FeLV and CPV. Clinical trials have also shown this drug may be valuable in treatment of gingivostomatitis associated with FCV, although this is an off-licence use.

Despite proven efficacy of rFelFN-? in multiple studies, use in general practice is limited. This is largely due to the involved and costly treatment regimes recommended for optimal effect. Committed owners and animals that do not mind repeated veterinary visits are essential for treating any of the viral conditions that can be controlled by this drug.

For treatment of FHV infections, human herpesvirus medications are known to be useful in cats. Oral famciclovir in particular has proven to be very effective, and topical TFT and aciclovir are additional off-licence drugs to try. In addition, it is predicted PI will become a commonly used antiviral once availability increases. The non-specific mechanism of action of PI may result in this drug proving useful against other viruses in the future.

As well as many successful clinical trials, it is important to be aware of the studies that have found no benefit from suggested antiviral drugs. These include the use of lysine and rFelFN-? in FHV

infection, and the use of immune plasma, oseltamivir and rhG-CSF against CPV.

Overall, it is clear there is a need to develop more antiviral drugs for the veterinary market. But as well as killing viruses, these drugs must be easy to administer and affordable for most clients. This is a very demanding set of criteria and it may be many years before the ideal set of veterinary antivirals are on the shelves.

• Please note some drugs mentioned in this article are not licensed for use in cats and dogs, and are used under the cascade.

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Figure 1. Recombinant feline interferon omega (rFelFN-?).

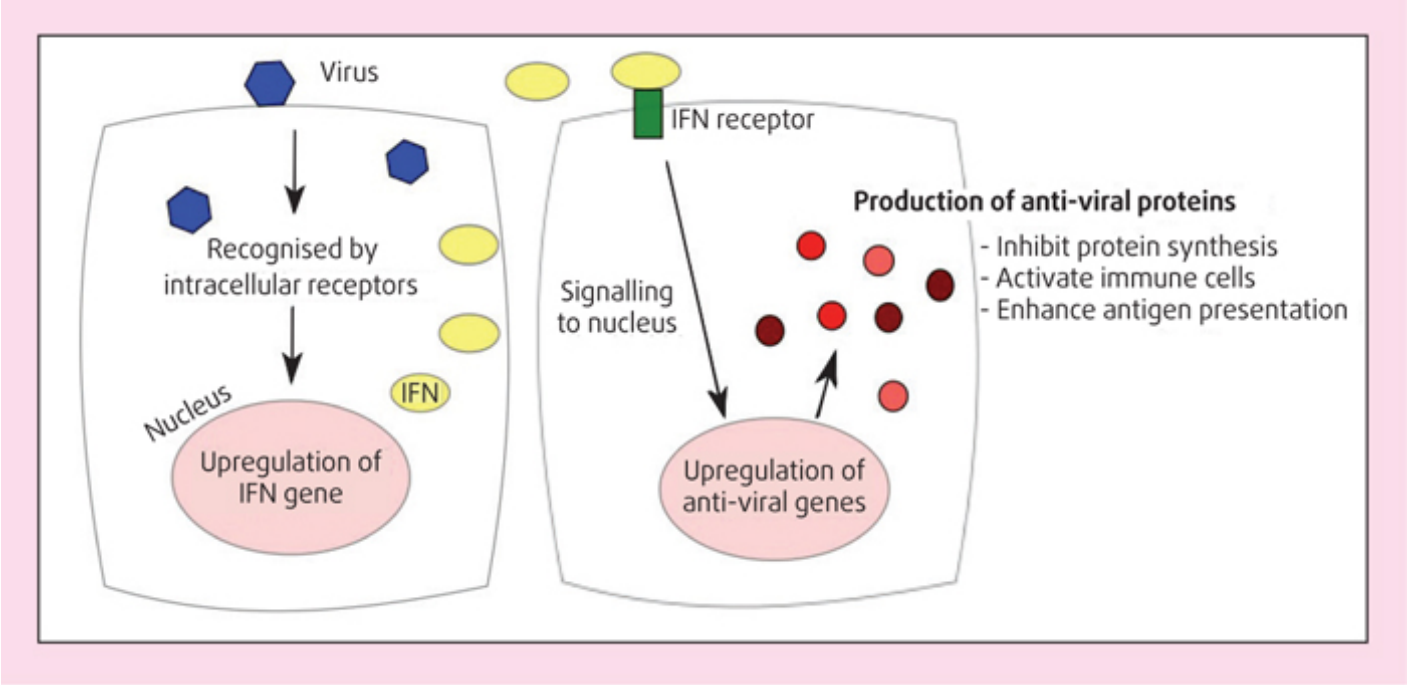

Figure 2. Interferon signalling pathways within a virally infected cell.

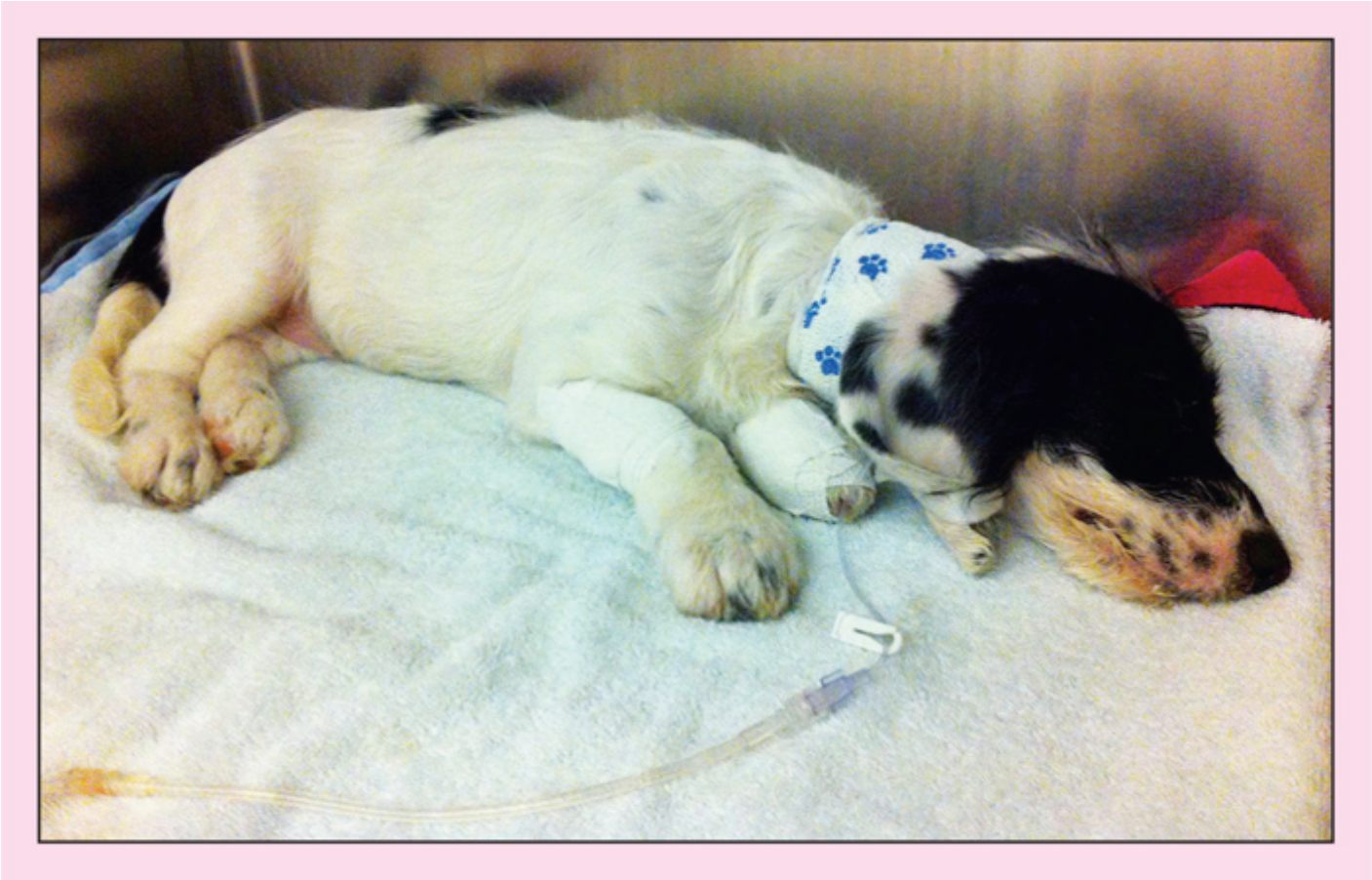

Figure 3. Canine parvovirus infection in an eight-week-old cross breed dog.