Studien zu FIP und Behandlungserfolge

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Kleintierklinik der LMU München

C·I·C·K. Coronaviruses in Cats & Kids

Inuvet-Seminar 1. April 2025

1

Studien zu FIP und Behandlungserfolge

Kleintierklinik der LMU München

- die tödliche Krankheit FIP
  - Entstehung der FIP
  - Gefahren durch neue FCoV-Varianten
- antivirale Medikamente gegen FIP
  - Ribavirin
  - Mefloquin
  - Itraconazol
  - GC376
  - Molnupiravir
  - Remdesivir und GS-441524
- derzeitig legale Therapieoptionen

2

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4

Prognose

Kleintierklinik der LMU München

bislang immer tödlich

- mittlere Überlebenszeit 8–9 Tage

ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

Veterinary Immunology and Immunopathology 123 (2008) 172–175

Veterinary immunology and immunopathology

www.elsevier.com/locate/vetimm

Short survey

Treatment of cats with feline infectious peritonitis

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5

Studien zu FIP und Behandlungserfolge

Kleintierklinik der LMU München

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6

In-vivo-Mutations-Hypothese

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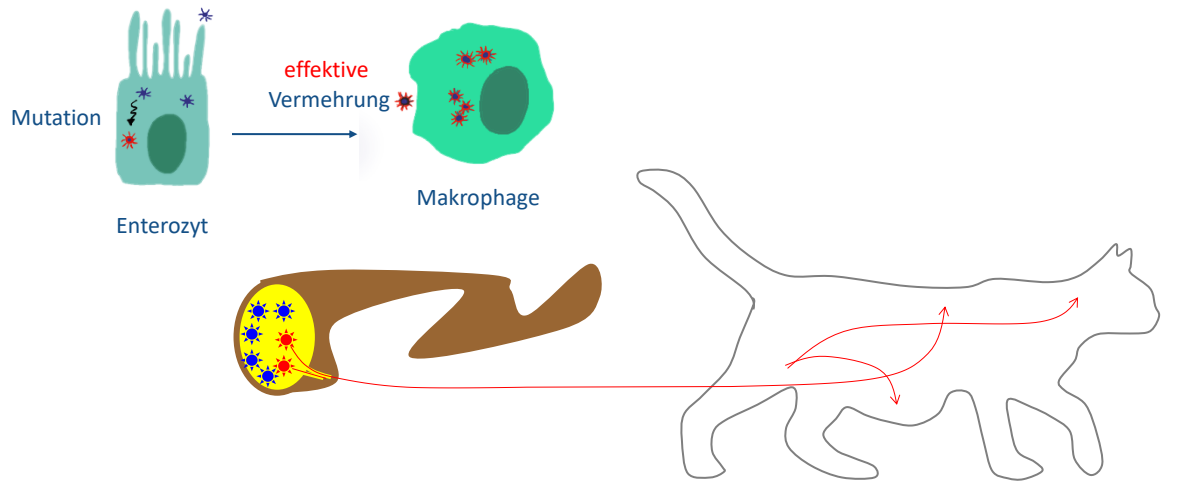

Mutation → Eintritt → Evasion → Dissemination → Immunpathologie → Tod

7

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8

FIP-Ausbruch auf Zypern

Kleintierklinik der LMU München

New Results

Follow this preprint

Emergence and spread of feline infectious peritonitis due to a highly pathogenic canine/feline recombinant coronavirus

Charalampos Attipa, Amanda S Warr, Demetris Epaminondas, Marie O'Shea, Sarah Fletcher, Alexandra Malbon, Maria Lyraki, Rachael Hammond, Alexandros Hardas, Antria Zanti, Stavroula Loukaidou, Michaela Gentil, Danielle Gunne-Moore, Stella Mazeri, Christine Tait-Burkard

doi: https://doi.org/10.1101/2023.11.08.566182

This article is a preprint and has not been certified by peer review [what does this mean?].

0 | 0 | 0 | 0 | 24 | 0 | 332

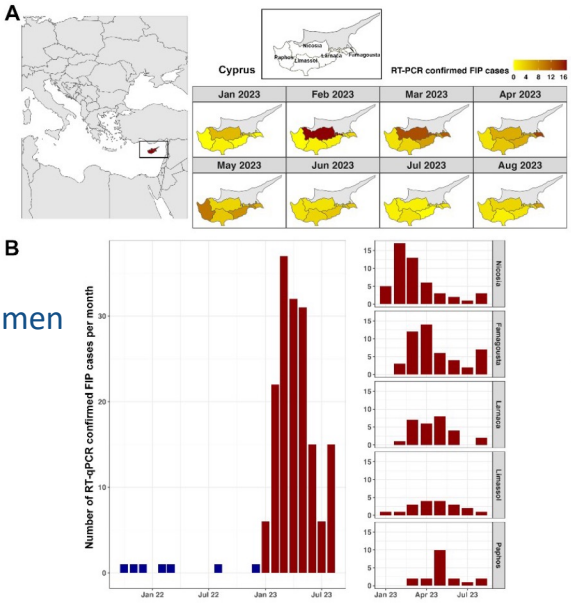
Abstract | **Full Text** | Info/History | Metrics | Preview PDF

9

FIP-Ausbruch auf Zypern

Januar – August 2023

- 165 bestätigte FIP-Fälle
  - → 69,7 % mit Ergüssen
  - → 27,9 % mit neurologischen Symptomen



- Schätzungen der Pancyprian Veterinary Association zufolge tatsächliche FIP-Todesrate sogar bei rund 8.000 Katzen

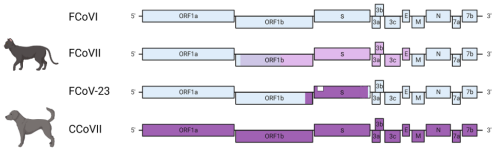
10

FIP-Ausbruch auf Zypern

Kleintierklinik der LMU München

FCoV-23-Sequenzierung

- neuartige, hoch pathogene Rekombination aus FCoV und dem hypervirulentem pantropischen caninen Coronavirus (pCCoV)



- hoch virulentes Virus
- FIP wird direkt und sehr schnell ausgelöst
  - → keine *in-vivo*-Mutation erforderlich
  - → rasanterer Krankheitsverlauf der FIP
- hohe Sequenz-Identität der Isolate von Katzen aus verschiedenen Bezirken
  - → starker Hinweis auf direkte Übertragbarkeit der FIP von Katze zu Katze

11

Vet Record

FELINE DISEASE

FCoV-23 causing FIP in a cat imported to the UK from Cyprus

Amanda Warr, Charalampos Attipa, Danielle Gunn-Moore, Christine Tait-Burkard

First published: 17 November 2023 | https://doi.org/10.1002/vetr.3696 | Citations: 1

FELINE DISEASE

FCoV-23 causing FIP in a cat imported to the UK from Cyprus

WE would like to report a case of feline infectious peritonitis (FIP) in a cat now in the UK having been imported from

ypрus at the end of August 2023. he imported cat is a nine-month- ld female that developed clinical igns (fever and ascites) compatible ith FIP a few weeks after being nported. The peritoneal fluid was a odified transudate with neutrophilic iflammation.

Subsequent viral sequencing of the eritoneal fluid revealed that the cat as infected with a feline coronavirus CoV) that we have recently identified be the cause of a large FIP outbreak Cyprus; provisionally, we have amed this virus FCoV-23. Unlike ases of classical FIP, which are not ansmissible from cat to cat, we have vidence suggesting that FCoV-23 is irectly transmissible from infected ats to other cats they are in contact with.[1]

Sequence analysis of the viral spike gene of the FCoVs from the outbreak in Cyprus and the imported cat indicate they are closely related and a part of the same outbreak. Analysis of the viral genome sequence from cats in the Cyprus outbreak reveals that the virus circulating in Cyprus is a novel recombination between FCoV type I (FCoVI) and a highly pathogenic canine coronavirus (pCCoV), with the spike gene of pCCoV replacing the spike of FCoVI.

Following confirmation of FIP due to FCoV-23 infection, treatment of the imported cat has been initiated under the supervision of the feline medical team of the Royal (Dick) School of Veterinary Studies, in collaboration with the local veterinary team.

Importantly, the imported cat is being kept strictly indoors and the owner has been advised to implement advanced hygiene measures to avoid further spread of the virus. The cat is being treated with high doses of GS-441524, and faecal samples are being monitored for viral shedding.

We ask that all veterinary surgeons who see cats showing signs suggestive of FIP ask the owners about potential importation from Cyprus. If this is identified, we advise that the cat should be isolated from other pets until antiviral treatment is started.

Currently, it is unclear how long cats infected with FCoV-23 remain infectious. As with classical FIP cases, if no treatment is initiated then the infection will result in the cat's death; euthanasia should be considered on welfare grounds.

We also ask that veterinarians identifying potential cases contact us about these cats.

Although there is no statutory requirement to do so, the APHA's Small Animal Expert Group (SAEG) has been informed about this case. The SAEG works collaboratively to gather, analyse and share information on new disease threats.

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for queries about the sequencing
email: danielle.gunn-moore@ed.ac.uk
for clinical and pet cat queries

Reference
1. Attipa C, Warr AS, Epaminondas D, et al. Emergence and spread of feline infectious peritonitis due to a highly pathogenic canine/feline recombinant coronavirus. *bioRxiv* 2023 doi: 10.1101/2023.11.08.566182

> **We have evidence suggesting that FCoV-23 is directly transmissible from infected cats to other cats they are in contact with**

Fallbericht aus UK

- importierte Katze aus Zypern
  - → 9 Monate, weiblich
  - → wenige Wochen nach Import klinische Anzeichen hinweisend auf FIP (Fieber, Aszites)
  - → Sequenzierung aus Erguss => neue FCoV-23-Variante
- Therapie mit GS-441524
- strenge Haltung im Haus (kein Freigang, Hygiene)
  - → keine Ausbreitung von FCoV-23

12

Studien zu FIP und Behandlungserfolge

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13

Diagnose vor der Therapie !!!

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viruses MDPI

Review

Diagnosis of Feline Infectious Peritonitis: A Review of the Current Literature

Sandra Felten * and Katrin Hartmann

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Received: 31 August 2019; Accepted: 13 November 2019; Published: 15 November 2019

check for updates

Abstract: Feline infectious peritonitis (FIP) is a fatal disease that poses several challenges for veterinarians: clinical signs and laboratory changes are non-specific, and there are two pathotypes of the etiologic agent feline coronavirus (FCoV), sometimes referred to as feline enteric coronavirus (FECV) and feline infectious peritonitis virus (FIPV) that vary fundamentally in their virulence, but are indistinguishable by a number of diagnostic methods. This review focuses on all important steps every veterinary practitioner has to deal with and new diagnostic tests that can be considered when encountering a cat with suspected FIP with the aim to establish a definitive diagnosis. It gives an overview on all available direct and indirect diagnostic tests and their sensitivity and specificity reported in the literature in different sample material. By providing summarized data for sensitivity and specificity of each diagnostic test and each sample material, which can easily be accessed in tables, this review can help to facilitate the interpretation of different diagnostic tests and raise awareness of their advantages and limitations. Additionally, diagnostic trees depict recommended diagnostic steps that should be performed in cats suspected of having FIP based on their clinical signs or clinicopathologic abnormalities. These steps can easily be followed in clinical practice.

Keywords: diagnosis; FIP; antibody; RT-PCR; immunohistochemistry; IHC; immunocytochemistry; ICC

Journal of Feline Medicine and Surgery (2022) **24**, 905–933

SPECIAL ARTICLE

2022 AAFP/EveryCat Feline Infectious Peritonitis Diagnosis Guidelines

Clinical importance: Feline infectious peritonitis (FIP) is one of the most important infectious diseases and causes of death in cats; young cats less than 2 years of age are especially vulnerable. FIP is caused by a feline coronavirus (FCoV). It has been estimated that around 0.3% to 1.4% of feline deaths at veterinary institutions are caused by FIP.

Scope: This document has been developed by a Task Force of experts in feline clinical medicine as the 2022 AAFP/EveryCat Feline Infectious Peritonitis Diagnosis Guidelines to provide veterinarians with essential information to aid their ability to recognize cats presenting with FIP.

Testing and interpretation: Nearly every small animal veterinary practitioner will see cases. FIP can be challenging to diagnose owing to the lack of pathognomonic clinical signs or laboratory changes, especially when no effusion is present. A good understanding of each diagnostic test's sensitivity, specificity, predictive value, likelihood ratio and diagnostic accuracy is important when building a case for FIP. Before proceeding with any diagnostic test or commercial laboratory profile, the clinician should be able to answer the questions of 'why this test?' and 'what do the results mean?' Ultimately, the approach to diagnosing FIP must be tailored to the specific presentation of the individual cat.

Relevance: Given that the disease is fatal when untreated, the ability to obtain a correct diagnosis is critical. The clinician must consider the individual patient's history, signalment and comprehensive physical examination findings when selecting diagnostic tests and sample types in order to build the index of suspicion 'brick by brick'. Research has demonstrated efficacy of new antivirals in FIP treatment, but these products are not legally available in many countries at this time. The Task Force encourages veterinarians to review the literature and stay informed on clinical trials and new drug approvals.

Keywords: Feline infectious peritonitis; FIP; FCoV; feline coronavirus; diagnosis; effusion; antibody; infection; fluid; blood test; analysis; cytology; Rivalta; AFAST; imaging; screening; laboratory sample; lesion; virus; RNA; RNA virus; polymerase chain reaction; PCR; PCR testing

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Introduction

Feline infectious peritonitis (FIP) was first described as a specific disease entity in 1963 challenging to diagnose owing to the lack of pathognomonic clinical signs or laboratory changes, especially when no effusion is present. However, given that the disease is

14

Journal of Feline Medicine and Surgery (2022) **24**, 905–933

SPECIAL ARTICLE

2022 AAFP/EveryCat Feline Infectious Peritonitis Diagnosis Guidelines

SUPPLEMENTAL FIGURE 8: Diagnostic Work-up for FIP 'Brick by Brick'
The veterinarian must consider the patient's history, signalment and physical examination findings, and then select diagnostic tests and sample types based on these, in order to build the index of suspicion 'brick by brick'. ADR = 'ain't doing right'. For explanation of other abbreviations, see box on page 906 of the Guidelines.

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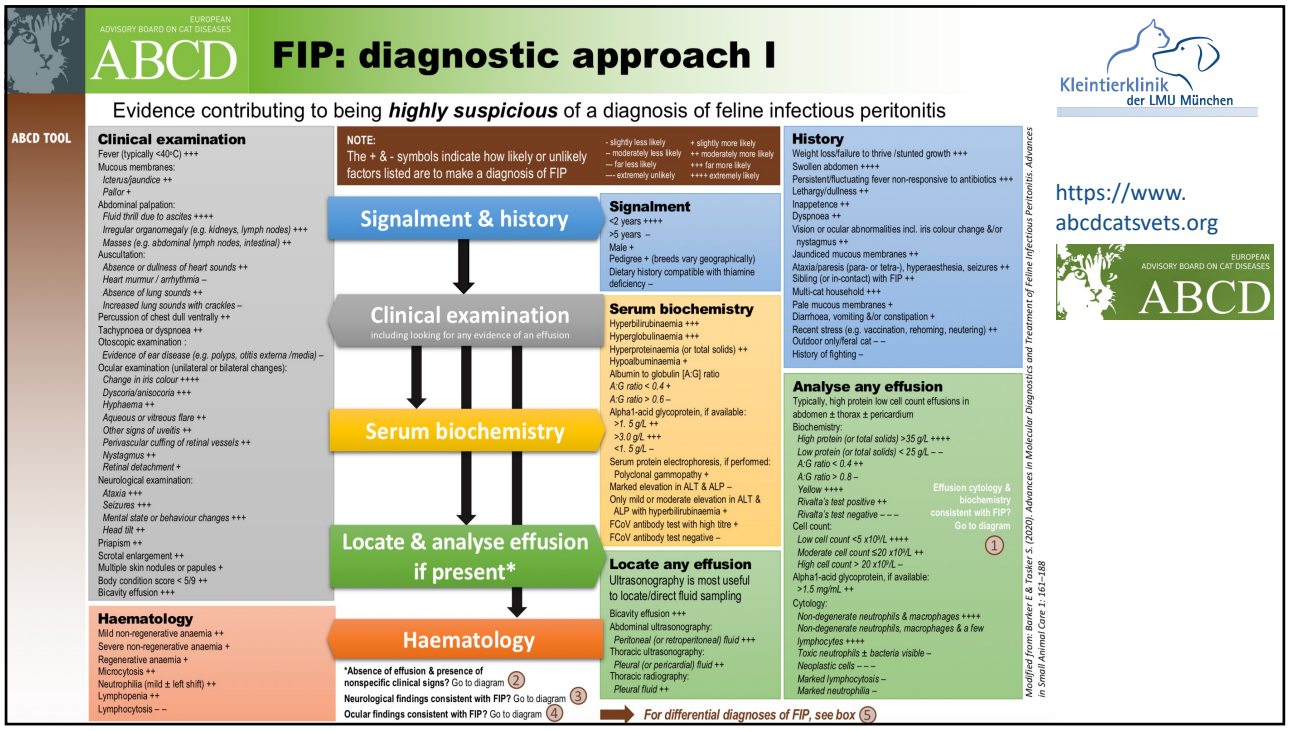
15


EUROPEAN ADVISORY BOARD ON CAT DISEASES
ABCD
FIP: diagnostic approach I
Evidence contributing to being ***highly suspicious*** of a diagnosis of feline infectious peritonitis
ABCD TOOL
Clinical examination
Fever (typically <40ºC) +++
Mucous membranes:
Icterus/jaundice ++
Pallor +
Abdominal palpation:
Fluid thrill due to ascites ++++
Irregular organomegaly (e.g. kidneys, lymph nodes) +++
Masses (e.g. abdominal lymph nodes, intestinal) ++
Auscultation:
Absence or dullness of heart sounds ++
Heart murmur / arrhythmia –
Absence of lung sounds ++
Increased lung sounds with crackles –
Percussion of chest dull ventrally ++
Tachypnoea or dyspnoea ++
Otoscopic examination :
Evidence of ear disease (e.g. polyps, otitis externa /media) –
Ocular examination (unilateral or bilateral changes):
Change in iris colour ++++
Dyscoria/anisocoria +++
Hyphaema ++
Aqueous or vitreous flare ++
Other signs of uveitis ++
Perivascular cuffing of retinal vessels ++
Nystagmus ++
Retinal detachment +
Neurological examination:
Ataxia +++
Seizures +++
Mental state or behaviour changes +++
Head tilt ++
Priapism ++
Scrotal enlargement ++
Multiple skin nodules or papules +
Body condition score < 5/9 ++
Bicavity effusion +++
Haematology
Mild non-regenerative anaemia ++
Severe non-regenerative anaemia +
Regenerative anaemia +
Microcytosis ++
Neutrophilia (mild ± left shift) ++
Lymphopenia ++
Lymphocytosis – –
NOTE:
The + & - symbols indicate how likely or unlikely factors listed are to make a diagnosis of FIP
- slightly less likely
– moderately less likely
— far less likely
—— extremely unlikely
+ slightly more likely
++ moderately more likely
+++ far more likely
++++ extremely likely
Signalment & history
Clinical examination
including looking for any evidence of an effusion
Serum biochemistry
Locate & analyse effusion if present*
Haematology
Signalment
<2 years ++++
>5 years –
Male +
Pedigree + (breeds vary geographically)
Dietary history compatible with thiamine deficiency –
Serum biochemistry
Hyperbilirubinaemia +++
Hyperglobulinaemia +++
Hyperproteinaemia (or total solids) ++
Hypoalbuminaemia +
Albumin to globulin [A:G] ratio
A:G ratio < 0.4 +
A:G ratio > 0.6 –
Alpha1-acid glycoprotein, if available:
>1. 5 g/L ++
>3.0 g/L +++
<1. 5 g/L –
Serum protein electrophoresis, if performed:
Polyclonal gammopathy +
Marked elevation in ALT & ALP –
Only mild or moderate elevation in ALT & ALP with hyperbilirubinaemia +
FCoV antibody test with high titre +
FCoV antibody test negative –
Locate any effusion
Ultrasonography is most useful to locate/direct fluid sampling
Bicavity effusion +++
Abdominal ultrasonography:
Peritoneal (or retroperitoneal) fluid +++
Thoracic ultrasonography:
Pleural (or pericardial) fluid ++
Thoracic radiography:
Pleural fluid ++
*Absence of effusion & presence of nonspecific clinical signs? Go to diagram 2
Neurological findings consistent with FIP? Go to diagram 3
Ocular findings consistent with FIP? Go to diagram 4
History
Weight loss/failure to thrive /stunted growth +++
Swollen abdomen ++++
Persistent/fluctuating fever non-responsive to antibiotics +++
Lethargy/dullness ++
Inappetence ++
Dyspnoea ++
Vision or ocular abnormalities incl. iris colour change &/or nystagmus ++
Jaundiced mucous membranes ++
Ataxia/paresis (para- or tetra-), hyperaesthesia, seizures ++
Sibling (or in-contact) with FIP ++
Multi-cat household +++
Pale mucous membranes +
Diarrhoea, vomiting &/or constipation +
Recent stress (e.g. vaccination, rehoming, neutering) ++
Outdoor only/feral cat – –
History of fighting –
Analyse any effusion
Typically, high protein low cell count effusions in abdomen ± thorax ± pericardium
Biochemistry:
High protein (or total solids) >35 g/L ++++
Low protein (or total solids) < 25 g/L – –
A:G ratio < 0.4 ++
A:G ratio > 0.8 –
Yellow ++++
Rivalta's test positive ++
Rivalta's test negative – – –
Effusion cytology & biochemistry consistent with FIP? Go to diagram 1
Cell count:
Low cell count <5 x10⁹/L ++++
Moderate cell count ≤20 x10⁹/L ++
High cell count > 20 x10⁹/L –
Alpha1-acid glycoprotein, if available:
>1.5 mg/mL ++
Cytology:
Non-degenerate neutrophils & macrophages ++++
Non-degenerate neutrophils, macrophages & a few lymphocytes ++++
Toxic neutrophils ± bacteria visible –
Neoplastic cells – – –
Marked lymphocytosis –
Marked neutrophilia –
For differential diagnoses of FIP, see box 5
Modified from: Barker E & Tasker S. (2020). Advances in Molecular Diagnostics and Treatment of Feline Infectious Peritonitis. Advances in Small Animal Care 1: 161–188
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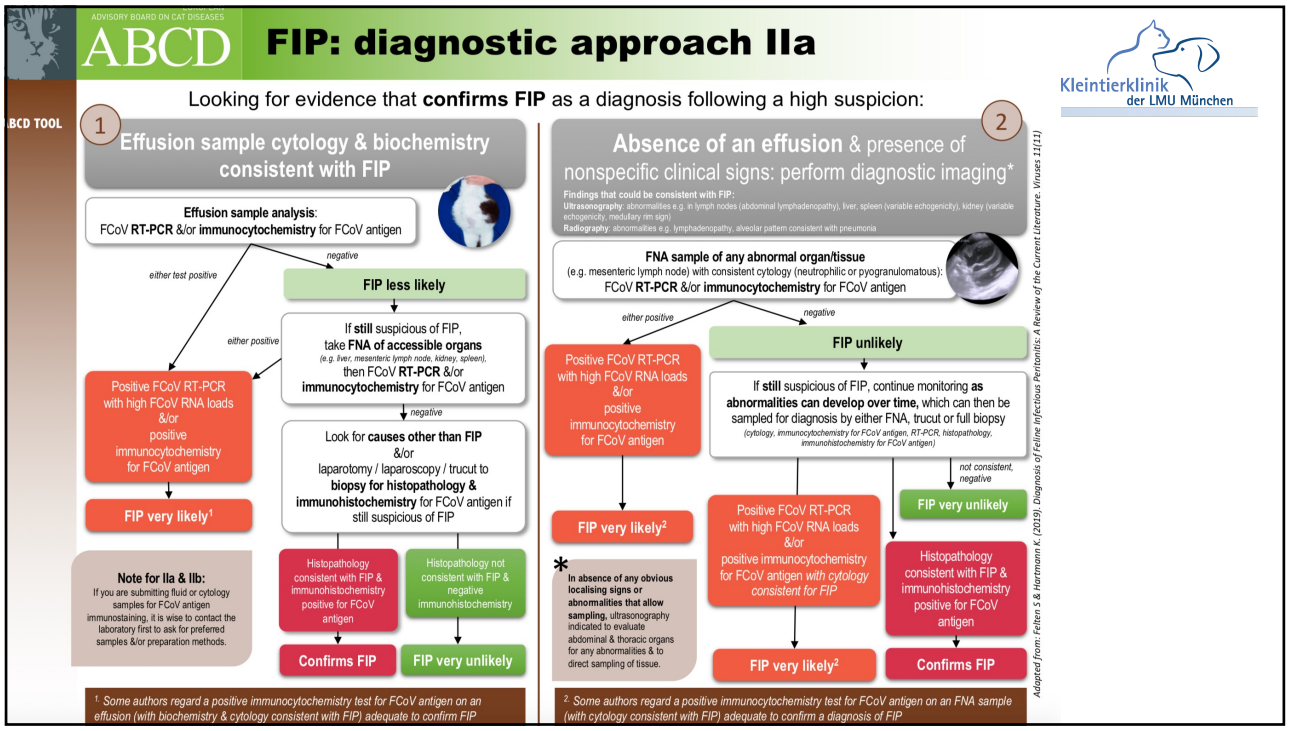
https://www.abcdcatsvets.org
EUROPEAN ADVISORY BOARD ON CAT DISEASES ABCD

16


ADVISORY BOARD ON CAT DISEASES
ABCD
FIP: diagnostic approach IIa
Looking for evidence that **confirms FIP** as a diagnosis following a high suspicion:
ABCD TOOL
1
Effusion sample cytology & biochemistry consistent with FIP
Effusion sample analysis:
FCoV **RT-PCR** &/or **immunocytochemistry** for FCoV antigen
negative
either test positive
FIP less likely
either positive
If **still** suspicious of FIP, take **FNA of accessible organs**
(e.g. liver, mesenteric lymph node, kidney, spleen),
then FCoV **RT-PCR** &/or **immunocytochemistry** for FCoV antigen
Positive FCoV RT-PCR with high FCoV RNA loads &/or positive immunocytochemistry for FCoV antigen
negative
Look for **causes other than FIP** &/or laparotomy / laparoscopy / trucut to **biopsy for histopathology & immunohistochemistry** for FCoV antigen if still suspicious of FIP
FIP very likely[1]
Histopathology consistent with FIP & immunohistochemistry positive for FCoV antigen
Histopathology not consistent with FIP & negative immunohistochemistry
Confirms FIP
FIP very unlikely
Note for IIa & IIb:
If you are submitting fluid or cytology samples for FCoV antigen immunostaining, it is wise to contact the laboratory first to ask for preferred samples &/or preparation methods.
2
Absence of an effusion & presence of nonspecific clinical signs: perform diagnostic imaging*
Findings that could be consistent with FIP:
Ultrasonography: abnormalities e.g. in lymph nodes (abdominal lymphadenopathy), liver, spleen (variable echogenicity), kidney (variable echogenicity, medullary rim sign)
Radiography: abnormalities e.g. lymphadenopathy, alveolar pattern consistent with pneumonia
FNA sample of any abnormal organ/tissue
(e.g. mesenteric lymph node) with consistent cytology (neutrophilic or pyogranulomatous):
FCoV **RT-PCR** &/or **immunocytochemistry** for FCoV antigen
either positive
negative
FIP unlikely
Positive FCoV RT-PCR with high FCoV RNA loads &/or positive immunocytochemistry for FCoV antigen
If **still** suspicious of FIP, continue monitoring **as abnormalities can develop over time,** which can then be sampled for diagnosis by either FNA, trucut or full biopsy
(cytology, immunocytochemistry for FCoV antigen, RT-PCR, histopathology, immunohistochemistry for FCoV antigen)
not consistent, negative
FIP very unlikely
FIP very likely[2]
Positive FCoV RT-PCR with high FCoV RNA loads &/or positive immunocytochemistry for FCoV antigen *with cytology consistent for FIP*
Histopathology consistent with FIP & immunohistochemistry positive for FCoV antigen
FIP very likely[2]
Confirms FIP
* In absence of any obvious localising signs or abnormalities that allow sampling, ultrasonography indicated to evaluate abdominal & thoracic organs for any abnormalities & to direct sampling of tissue.
1. Some authors regard a positive immunocytochemistry test for FCoV antigen on an effusion (with biochemistry & cytology consistent with FIP) adequate to confirm FIP
2. Some authors regard a positive immunocytochemistry test for FCoV antigen on an FNA sample (with cytology consistent with FIP) adequate to confirm a diagnosis of FIP
Adapted from: Felten S & Hartmann K. (2019). Diagnosis of Feline Infectious Peritonitis: A Review of the Current Literature. Viruses 11(11)
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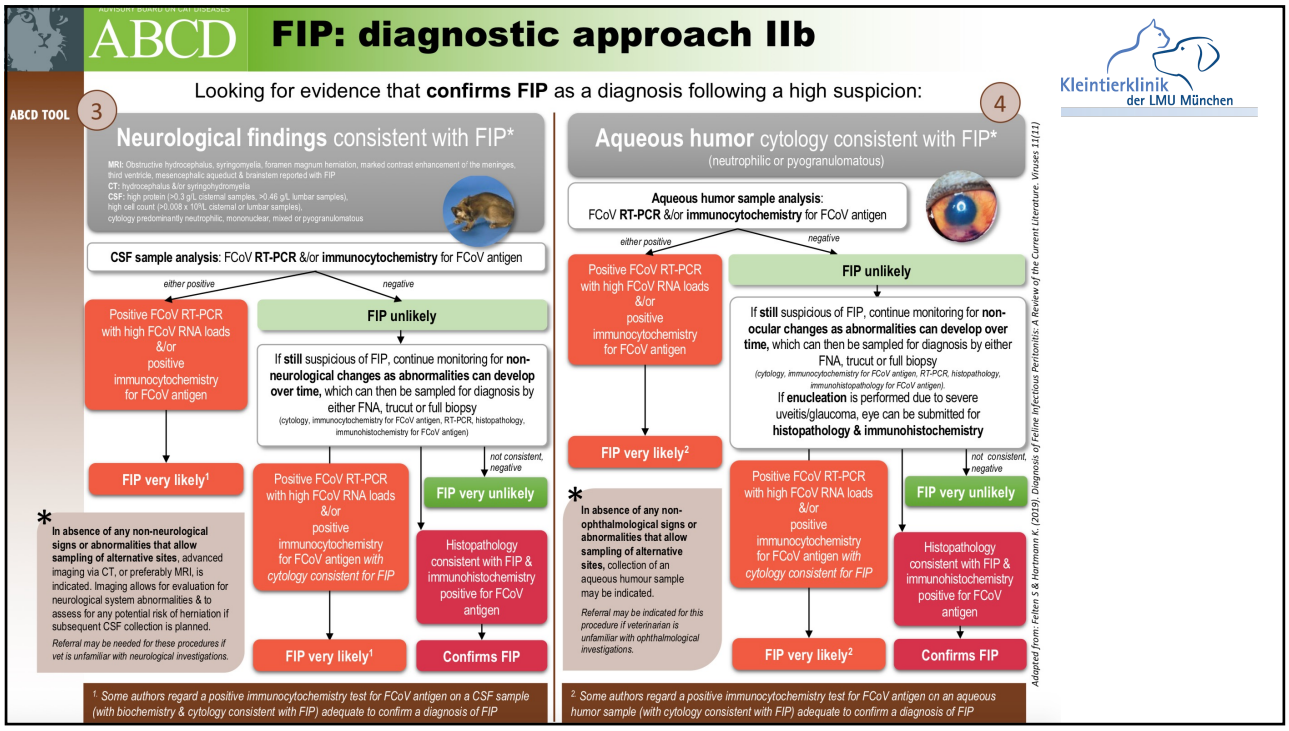
17



18

Diagnose der FIP

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- derzeit beste diagnostische Option
  - → Nachweis hoher Mengen viraler RNA durch quantitative RT-PCR
- diagnostische Therapie?

19

Symptomatische FIP-Therapie

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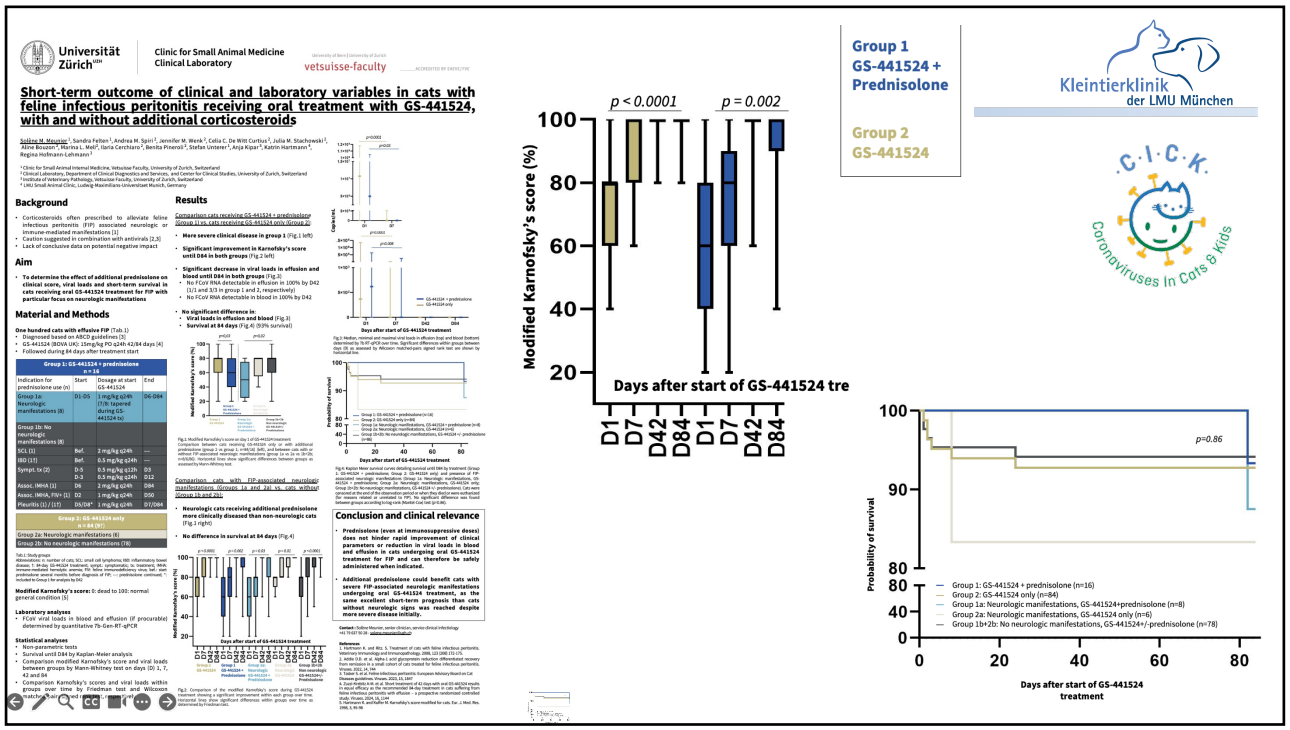
symptomatische Therapie (zusätzlich zur antiviralen Therapie)

- extrem wichtig
- intensive Betreuung der Katzen unter antiviraler Therapie
  - Flüssigkeits- und Energiezufuhr
  - Sauerstoff
  - Abziehen des Ergusses
  - fiebersenkende Medikamente
  - antiemetische Medikamente
  - Appetitanreger
  - Schmerztherapie
  - unterstützende Behandlung bei Lebertoxizität
  - Herz-Kreislauf-Medikamente
  - falls nötig, auch Glukokortikoide

20



21

Studien zu FIP und Behandlungserfolge

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22

Ribavirin

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experimentelle Studie

→ alle Katzen gestorben, behandelte Katzen

- stärkere klinische Symptome

- kürzere mittlere Überlebenszeit

massive Nebenwirkungen

- Hämolyse (Sequestration des Medikaments in roten Blutzellen)
- toxische Wirkung auf das Knochenmark
- Lebertoxizität

Versuch, die Toxizität zu verringern (Lecithin-enthaltende Liposomen)

→ ebenfalls nicht wirksam

Weiss et al., 1993

23

Studien zu FIP und Behandlungserfolge

Kleintierklinik der LMU München

- die tödliche Krankheit FIP
  - Entstehung der FIP
  - Gefahren durch neue FCoV-Varianten
- antivirale Medikamente gegen FIP
  - Ribavirin
  - Mefloquin
  - Itraconazol
  - GC376
  - Molnupiravir
  - Remdesivir und GS-441524
- derzeitig legale Therapieoptionen

24

Mefloquin

Kleintierklinik der LMU München

- Medikament zur Prophylaxe und Behandlung von Malaria beim Menschen
- *in-vitro*-Wirksamkeit gegen FCoV ohne zytotoxischen Effekt

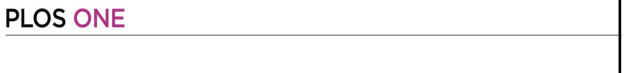
McDonagh et al., 2011

- 2 Studien zur Pharmakokinetik bei klinisch gesunden Katzen
- NW: Erbrechen nach Eingabe ohne Futter,
  Anstieg der Konzentration von SDMA (ohne Kreatinin)

Article

Pharmacokinetic Profile of Oral Administration of Mefloquine to Clinically Normal Cats: A Preliminary In-Vivo Study of a Potential Treatment for Feline Infectious Peritonitis (FIP)

Jane Yu *, Benjamin Kimble, Jacqueline M. Norris and Merran Govendir



RESEARCH ARTICLE

Assay validation and determination of in vitro binding of mefloquine to plasma proteins from clinically normal and FIP-affected cats

Aaron M. Izes, Benjamin Kimble, Jacqueline M. Norris, Merran Govendir

Sydney School of Veterinary Science, Faculty of Science, The University of Sydney, Sydney, Australia

25

Studien zu FIP und Behandlungserfolge

Kleintierklinik der LMU München

- die tödliche Krankheit FIP
  - Entstehung der FIP
  - Gefahren durch neue FCoV-Varianten
- antivirale Medikamente gegen FIP
  - Ribavirin
  - Mefloquin
  - Itraconazol
  - GC376
  - Molnupiravir
  - Remdesivir und GS-441524
- derzeitig legale Therapieoptionen

26

Itraconazol

Kleintierklinik der LMU München

- Antimykotikum und Inhibitor der Cholesterinsynthese und des Cholesterintransports → Hemmung der FCoV-Replikation

Takano et al., 2017
Takano et al., 2019
Takano et al., 2019


Contents lists available at ScienceDirect

Research in Veterinary Science

journal homepage: www.elsevier.com/locate/rvsc

In vitro antiviral effects of GS-441524 and itraconazole combination against feline infectious peritonitis virus

Tomoyoshi Doki, Ken Takahashi, Nobuhisa Hasegawa, Tomomi Takano *

Laboratory of Veterinary Infectious Disease, School of Veterinary Medicine, Kitasato University, Towada, Aomori 034-8628, Japan

- Kombination von GS-441524 mit Itraconazol *in vitro*
  - → synergistische antivirale Wirkung
  - → Verstärkung der antiviralen Wirkung von GS-441524 und der Hemmung der FCoV-Replikation

27

Studien zu FIP und Behandlungserfolge

Kleintierklinik der LMU München

- die tödliche Krankheit FIP
  - Entstehung der FIP
  - Gefahren durch neue FCoV-Varianten
- antivirale Medikamente gegen FIP
  - Ribavirin
  - Mefloquin
  - Itraconazol
  - GC376
  - Molnupiravir
  - Remdesivir und GS-441524
- derzeitig legale Therapieoptionen

28

Protease-Inhibitor GC376

Kleintierklinik der LMU München

Protease-Inhibitor
→ entwickelt von Gilead Sciences, USA
→ *in vitro* sehr wirksam, kaum zytotoxisch

RESEARCH ARTICLE 2016

Reversal of the Progression of Fatal Coronavirus Infection in Cats by a Broad-Spectrum Coronavirus Protease Inhibitor

Yunjeong Kim[1]*, Hongwei Liu[2], Anushka C. Galasiti Kankanamalage[3], Sahani Weerasekara[4], Duy H. Hua[4], William C. Groutas[3], Kyeong-Ok Chang[1], Niels C. Pedersen[2]

Compound	EC_{50} (μM)	CC_{50} (μM)
GC376	0.04±0.04	> 150
NPI64	0.04±0.03	61.91±0.2

***in-vitro*- und experimentelle Studie**
8 Katzen

- experimentell induzierte FIP
- alle Katzen mit klinischen Symptomen
  - 4 Katzen früh behandelt, 4 Katzen spät behandelt
  - 6 Katzen in Remission (2 euthanasiert)
  - 6 Katzen vollständig geheilt
    (keine Symptome oder Laborveränderungen über 8 Monate)
- Abnahme der Viruslast (bei den 2 euthanasierten Katzen)

29

Feldstudie GC376

Kleintierklinik der LMU München

Original Article

Efficacy of a 3C-like protease inhibitor in treating various forms of acquired feline infectious peritonitis

Niels C Pedersen[1], Yunjeong Kim[2], Hongwei Liu[1], Anushka C Galasiti Kankanamalage[3], Chrissy Eckstrand[4], William C Groutas[3], Michael Bannasch[1], Juliana M Meadows[5] and Kyeong-Ok Chang[2]

Journal of Feline Medicine and Surgery 1–15
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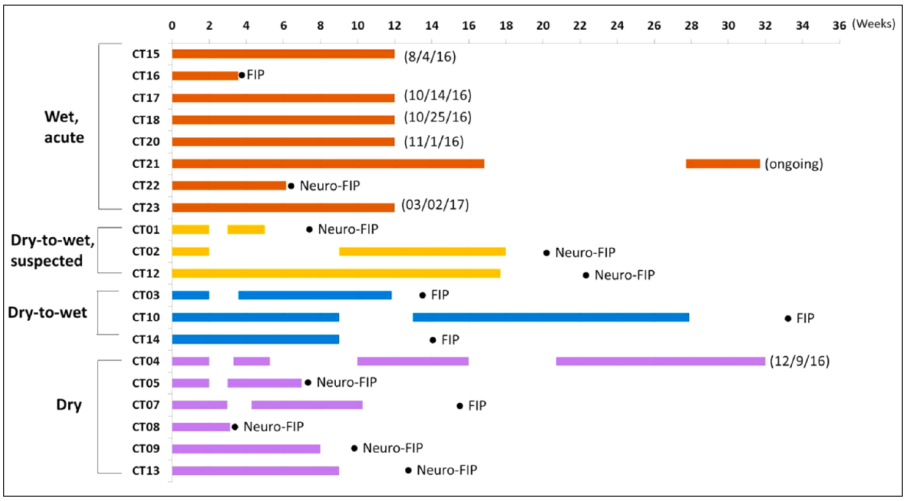
DOI: 10.1177/1098612X17729626
journals.sagepub.com/home/jfms
This paper was handled and processed by the American Editorial Office (AAFP) for publication in JFMS
SAGE

2017

- 19/20 Katzen in Remission innerhalb von 2 Wochen
- aber Rückfälle bei 13/19 Katzen

- **6/20 Katzen in Remission** 1 Jahr nach Therapie



30

Resistenz gegen GC376

Kleintierklinik der LMU München

- *in-vitro*-Passage des Wildtyp-FCoV (mutierter Stamm) in Anwesenheit von GC376
  → Entwicklung einer bis zu 3-fachen Resistenz gegen mehrere Protease-Inhibitoren
- GC376 unwirksam gegen diese resistenten Mutanten

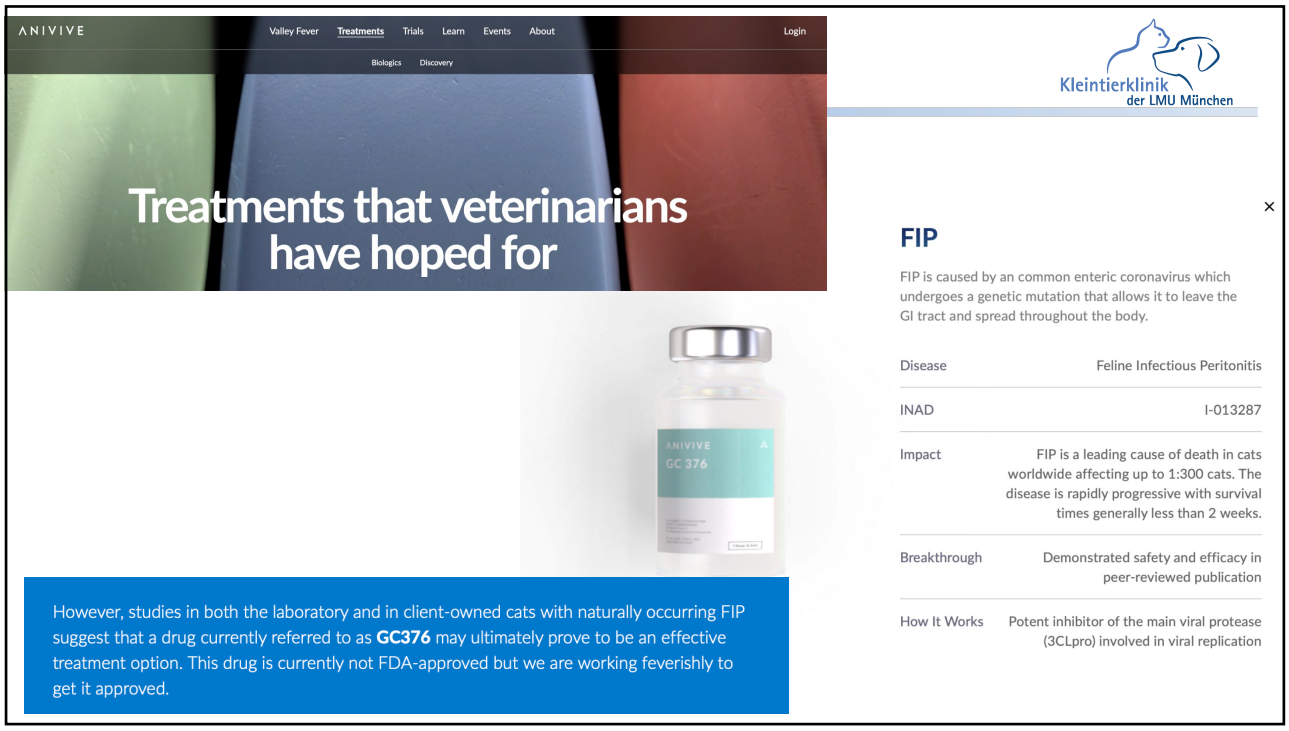
Veterinary Microbiology | Research Article | 24 August 2022

2022

Adaptive Mutation in the Main Protease Cleavage Site of Feline Coronavirus Renders the Virus More Resistant to Main Protease Inhibitors

Authors: Zhe Jiao, Yuanyuan Yan, Yixi Chen, Gang Wang, Xiaowei Wang, Lisha Li, Mengfang Yang, Xiaoshuai Hu, Yilin Guo, Yuejun Shi, Guiqing Peng | AUTHORS INFO & AFFILIATIONS

31



32

Studien zu FIP und Behandlungserfolge

Kleintierklinik der LMU München

- die tödliche Krankheit FIP
  - Entstehung der FIP
  - Gefahren durch neue FCoV-Varianten
- antivirale Medikamente gegen FIP
  - Ribavirin
  - Mefloquin
  - Itraconazol
  - GC376
  - Molnupiravir
  - Remdesivir und GS-441524
- derzeitig legale Therapieoptionen

33

Molnupiravir

Kleintierklinik der LMU München

- Molnupiravir (EIDD-2801) hergestellt als Lagevrio® von Merck (MSD)
- Notfallzulassung (EUA) für COVID-19 in USA
- orales Prodrug des Nukleosidanalogons B-D-N4-Hydroxycytidin
  → erhöht Mutationsraten mit Guanin zu Adenin, Zytosin zu Uracil über den akzeptierten Schwellenwert hinaus
  → inaktiviert Coronaviren

- EMA gegen die Zulassung von Molnupiravir
  → darf in der EU nicht beim Menschen verwendet werden
- in USA potenziell in der Tiermedizin anwendbar wegen Emergency Drug Release (EDR), wenn direkt vom Hersteller bezogen

34

Besitzerumfrage aus USA

Kleintierklinik der LMU München

pathogens 2022 MDPI

Article

Unlicensed Molnupiravir is an Effective Rescue Treatment Following Failure of Unlicensed GS-441524-like Therapy for Cats with Suspected Feline Infectious Peritonitis

Meagan Roy [1], Nicole Jacque [2], Wendy Novicoff [3], Emma Li [1], Rosa Negash [1] and Samantha J. M. Evans [1,*]

[1] Department of Veterinary Biosciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH 43210, USA
[2] Independent Researcher, San Jose, CA 95123, USA
[3] Departments of Orthopaedic Surgery and Public Health Sciences, School of Medicine, University of Virginia, Charlottesville, VA 22903, USA
* Correspondence: evans.2608@osu.edu

- Besitzerumfrage zur Verwendung von nicht zugelassenem Molnupiravir als Erst- oder Reservetherapie (hauptsächlich „Aura 2801“)
- 12–15 mg/kg q12h für 12 Wochen
- 24/26 noch am Leben zum Zeitpunkt des Artikels
- wenige Nebenwirkungen
  → Faltohren (1), abgebrochene Schnurrhaare (1), massive Leukopenie (1)

36

Prospektive Studie aus Japan

Kleintierklinik der LMU München

Received: 9 November 2022 | Accepted: 13 July 2023
DOI: 10.1111/jvim.16832

2022

CASE REPORT

Journal of Veterinary Internal Medicine ACVIM Open Access

Molnupiravir treatment of 18 cats with feline infectious peritonitis: A case series

Okihiro Sase

- Tabletten (20 mg) selbst hergestellt
- 18 Katzen mit FIP
  10–20 mg/kg PO q12h für 84 Tage
  - mit Erguss 10 mg/kg PO q12h
  - ohne Erguss 15 mg/kg PO q12h
  - neurologisch/okulär 20 mg/kg PO q12h

- **Outcome**
  - 4 Katzen tot/euthanasiert innerhalb von 7 Tagen nach Therapiebeginn
  - 14/18 in anhaltender Remission 139–206 Tage nach Therapiebeginn
  - Nebenwirkungen:
    ALT ↑ (3/18 Katzen zwischen Tag 7–9, keine Therapie notwendig)

38

Studien zu FIP und Behandlungserfolge

Kleintierklinik der LMU München

- die tödliche Krankheit FIP
  - Entstehung der FIP
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  - Itraconazol
  - GC376
  - Molnupiravir
  - Remdesivir und GS-441524
- derzeitig legale Therapieoptionen

39

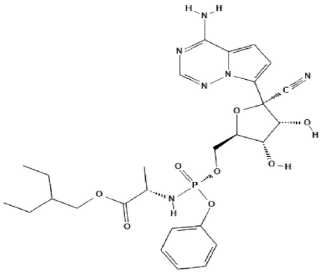
GS-441524 *versus* Remdesivir

Kleintierklinik der LMU München

Remdesivir
(GS-5734)

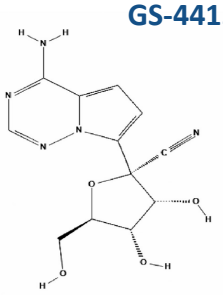
- Monophosphoramidat-Prodrug
- im Körper zur aktiven Form GS-441524 metabolisiert
- besser in Zellen transportiert durch Phosphorylierung (?)

A



B

GS-441524



One Health 9 (2020) 100128

Contents lists available at ScienceDirect

One Health

journal homepage: www.elsevier.com/locate/onehlt

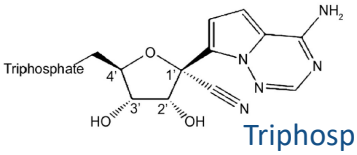
Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses

E. Susan Amirian[a,*], Julie K. Levy[b]

[a] Public Health & Healthcare Program, Texas Policy Lab, School of Social Sciences, Rice University, Houston, TX, USA
[b] Maddie's Shelter Medicine Program, College of Veterinary Medicine, University of Florida, Gainesville, FL, USA

2020

C



Triphosphat-Metabolit beider Substanzen

40

Remdesivir bei Katzen

Kleintierklinik der LMU München

- Breitspektrum-Virostatikum (ursprünglich für Ebola, dann COVID-19)
- entwickelt von der Firma Gilead Sciences, USA
- seit Mitte 2020 vertrieben unter dem Namen Veklury®
- angewendet bei Katzen in Australien und UK

Successful treatment of a South African cat with effusive feline infectious peritonitis with remdesivir 2022

J S Afr Vet Assoc, 2022

M Bohm

- **Fallbericht** aus Südafrika
- Therapie einer Katze mit FIP mit Remdesivir
  4,9–5,6 mg/kg q24h IV für 3 Tage und dann SC für 27 Tage
- nach 1 Woche klinische Verbesserung, nach 80 Tagen Remission
- 7 Monate nach Ende der Therapie weiterhin klinisch unauffällig

42

Vergleiche

viruses

MDPI

Article

2023

Efficacy of Oral Remdesivir Compared to GS-441524 for Treatment of Cats with Naturally Occurring Effusive Feline Infectious Peritonitis: A Blinded, Non-Inferiority Study

Emma Cosaro [1,*], Jully Pires [2], Diego Castillo [3], Brian G. Murphy [3] and Krystle L. Reagan [4]

[1] William R. Pritchard Veterinary Medical Teaching Hospital, School of Veterinary Medicine, University of California, Davis, CA 95616, USA
[2] Veterinary Center for Clinical Trials, School of Veterinary Medicine, University of California, Davis, CA 95616, USA; jypires@ucdavis.edu
[3] Department of Pathology, Microbiology, and Immunology, School of Veterinary Medicine, University of California, Davis, CA 95616, USA; ldcastillo@ucdavis.edu (D.C.); bmurphy@ucdavis.edu (B.G.M.)
[4] Department of Veterinary Medicine and Epidemiology, School of Veterinary Medicine, University of California, Davis, CA 95616, USA; kreagan@ucdavis.edu
* Correspondence: eccosaro@ucdavis.edu; Tel.: +1-(530)752-1393

- 18 Katzen aus USA
- Doppelblindstudie mit oralem chinesischen Präparaten
  - GS-442514 (12.5–15 mg/kg) für 12 Wochen PO
  - Remdesivir (25–30 mg/kg) für 12 Wochen PO
- kein signifikanter Unterschied in der Überlebensrate
  - GS-441524 5/9 (55 %)
  - Remdesivir 7/9 (77 %)

Original Article

jfms

Retrospective study and outcome of 307 cats with feline infectious peritonitis treated with legally sourced veterinary compounded preparations of remdesivir and GS-441524 (2020–2022)

Journal of Feline Medicine and Surgery 1–26
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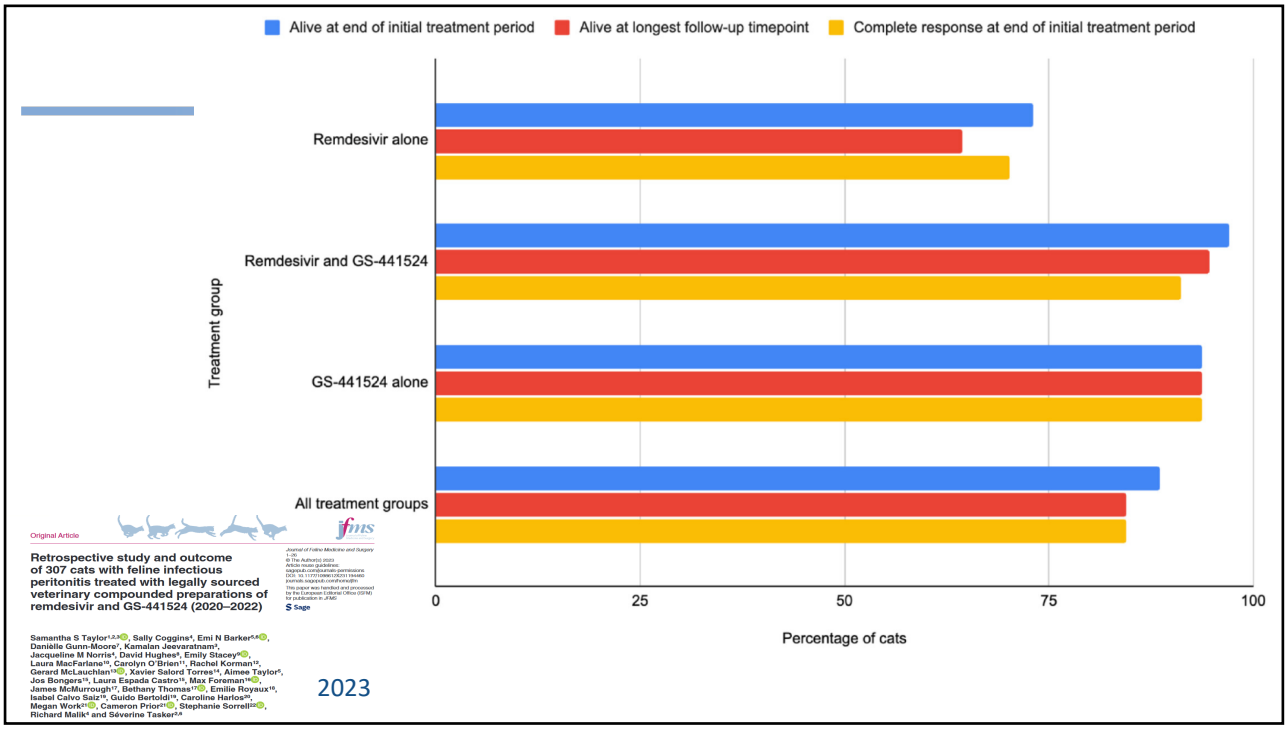
Sage

2023

Samantha S Taylor[1,2,3], Sally Coggins[4], Emi N Barker[5,6], Danièlle Gunn-Moore[7], Kamalan Jeevaratnam[3], Jacqueline M Norris[4], David Hughes[8], Emily Stacey[9], Laura MacFarlane[10], Carolyn O'Brien[11], Rachel Korman[12], Gerard McLauchlan[13], Xavier Salord Torres[14], Aimee Taylor[5], Jos Bongers[15], Laura Espada Castro[15], Max Foreman[16], James McMurrough[17], Bethany Thomas[17], Emilie Royaux[18], Isabel Calvo Saiz[19], Guido Bertoldi[19], Caroline Harlos[20], Megan Work[21], Cameron Prior[21], Stephanie Sorrell[22], Richard Malik[4] and Séverine Tasker[2,6]

- retrospektive Studie, versch. Länder vor allem UK, Australien, Japan
- 307 Katzen erhielten legale Produkte
  - 34 % nur Remdesivir SC
  - 56 % Remdesivir SC und GS-441524 PO
  - 10 % nur GS-441524 PO
- Überleben 89%
- Rückfall bei 33/307 (11 %)
  - 15 während Therapie
  - 18 nach Therapie

44



45

GS-441524 bei Katzen

Kleintierklinik der LMU München

- nicht auf dem Markt
- Patent gehört der Firma Gilead Sciences, USA
- von manchen Apotheken legal hergestellt

46

Veterinary Microbiology 219 (2018) 226–233

Contents lists available at ScienceDirect

Veterinary Microbiology

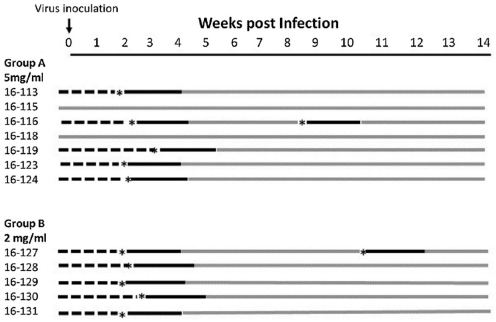
journal homepage: www.elsevier.com/locate/vetmic

2018

Kleintierklinik der LMU München

The nucleoside analog GS-441524 strongly inhibits feline infectious peritonitis (FIP) virus in tissue culture and experimental cat infection studies

B.G. Murphy[a], M. Perron[c], E. Murakami[c], K. Bauer[a], Y. Park[c], C. Eckstrand[a], M. Liepnieks[a], N.C. Pedersen[b,*]



- Nukleosid-Analogon GS-441524
- hoch effektiv *in vitro*

- 12 Katzen mit experimenteller FIP
- GS-441524 2 mg/kg oder 5 mg/kg SC q24h

- alle Katzen in anhaltender Remission 8 Monate nach der letzen Behandlung
- Nebenwirkungen: lokale Reaktionen auf SC-Injektion

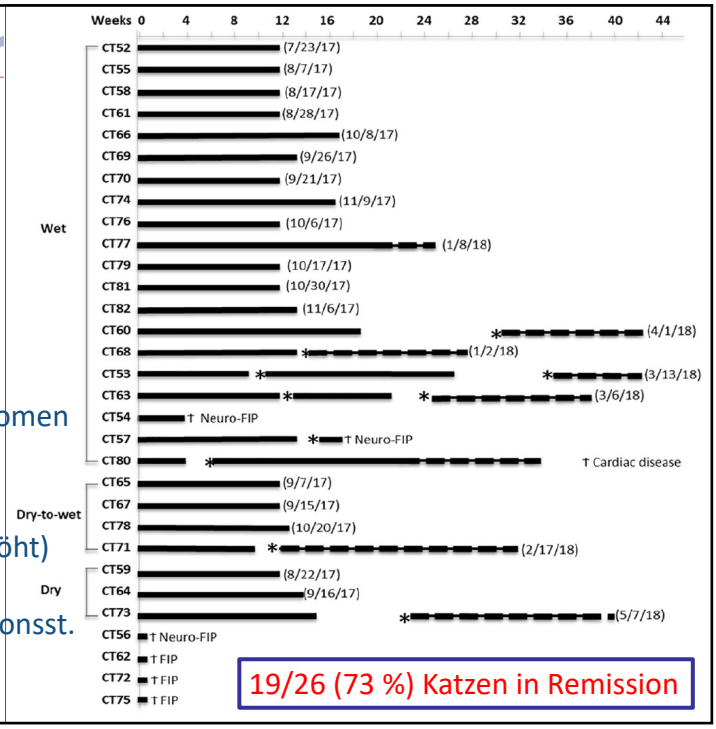
47

Original Article 2019

Efficacy and safety of the nucleoside analog GS-441524 for treatment of cats with naturally occurring feline infectious peritonitis

Niels C Pedersen[1], Michel Perron[2], Michael Bannasch[1], Elizabeth Montgomery[1], Eisuke Murakami[2], Molly Liepnieks[3] and Hongwei Liu[3]

- 31 Katzen im Feld mit FIP
- Katzen mit neurologischen Symptomen und/oder Uveitis ausgeschlossen
- GS-441524 2 mg/kg SC q24h über mindestens 12 Wochen (in einigen Fällen auf 4 mg/kg erhöht)
- 8/26 Katzen Rückfall
- Nebenwirkungen: Schmerz Injektionsst. 1 Katze ↑Hst und SDMA



19/26 (73 %) Katzen in Remission

48

Received: 20 December 2019 | Accepted: 26 March 2020
DOI: 10.1111/jvim.15780

CASE REPORT 2019 Journal of Veterinary Internal Medicine ACVIM

Kleintierklinik der LMU München

Antiviral treatment using the adenosine nucleoside analogue GS-441524 in cats with clinically diagnosed neurological feline infectious peritonitis

Peter J. Dickinson[1] | Michael Bannasch[2] | Sara M. Thomasy[1,3] | Vishal D. Murthy[2] | Karen M. Vernau[1] | Molly Liepnieks[4] | Elizabeth Montgomery[2] | Kelly E. Knickelbein[2] | Brian Murphy[4] | Niels C. Pedersen[5]

- 4 Katzen mit neurologischen Symptomen
- GS-441524 5 mg/kg SC q24h über mindestens 12 Wochen in einem Fall auf 10 mg/kg erhöht
- 3/4 Katzen (75 %) 528, 516 und 354 Tage nach Start unauffällig
- 1 Katze Euthanasie Tag 216 (nach 2x Therapie)

49

animals 2021 MDPI

Article

Unlicensed GS-441524-Like Antiviral Therapy Can Be Effective for at-Home Treatment of Feline Infectious Peritonitis

Sarah Jones [1], Wendy Novicoff [2], Julie Nadeau [3] and Samantha Evans [1,*]

[1] Department of Veterinary Biosciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH 43210, USA; Sarahejones79@yahoo.com
[2] Departments of Orthopaedic Surgery and Public Health Sciences, School of Medicine, University of Virginia, Charlottesville, VA 22903, USA; wmn2v@virginia.edu
[3] Hamilton Region Veterinary Emergency Clinic, Hamilton, ON L8P 4W3, Canada; julie.nadeau76@gmail.com
* Correspondence: evans.2608@osu.edu; Tel.: +1-614-292-9706

- online-Umfrage (393 Teilnehmer) unter Katzenbesitzern
  - Katzen mit Verdacht auf FIP
  - Therapie mit GS-441524 (über Schwarzmarkt)
- 380 Katzen (88 %) zum Zeitpunkt der Veröffentlichung am Leben

veterinary sciences 2021 MDPI

Article

Therapeutic Effects of Mutian® Xraphconn on 141 Client-Owned Cats with Feline Infectious Peritonitis Predicted by Total Bilirubin Levels

Masato Katayama * and Yukina Uemura

Bloom Animal Hospital, Kajiyama 1-10-32, Tsurumi, Yokohama City 230-0072, Kanagawa, Japan; marble1993.22@gmail.com
* Correspondence: bloom-animal@blue.plala.or.jp

- retrospektive Studie mit 141 Katzen mit FIP (mit Erguss) in Japan
- therapiert mit Mutian® Xraphconn
- 116 Katzen (Gruppe 1) am Leben, 25 Katzen (Gruppe 2) verstorben
- 78 % Überlebensrate
- Vergleich labordiagnostischer Parameter

→ Bilirubin als prognostischer Parameter
(> 4,0 mg/dl → geringere Überlebenschance)

50

OPEN ACCESS

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RECEIVED 26 January 2024
ACCEPTED 14 June 2024
PUBLISHED 26 June 2024

Owner experience and veterinary involvement with unlicensed GS-441524 treatment of feline infectious peritonitis: a prospective cohort study

Rosa Negash[1], Emma Li[1], Nicole Jacque[2], Wendy Novicoff[3] and Samantha J. M. Evans[1,4]*

[1]Department of Veterinary Biosciences, College of Veterinary Medicine, The Ohio State University, Columbus, OH, United States, [2]Independent Researcher, San Jose, CA, United States, [3]Department of Orthopedic Surgery and Public Health Sciences, School of Medicine, University of Virginia, Charlottesville, VA, United States, [4]Department of Microbiology, Immunology, and Pathology, Colorado State University, Fort Collins, CO, United States

frontiers Frontiers in Veterinary Science 2024

TYPE Original Research
PUBLISHED 26 June 2024
DOI 10.3389/fvets.2024.1377207

USA Besitzer (n = 141) Erfahrungen mit illegalem GS-441524

- negativer Effekt auf die Mensch-Katzen-Bindung
- Trend von SC- zu PO-Therapie

- Symptome, nach 12 Wochen GS-441524
  - keine Compliance während Injektionen 71 %
  - Vokalisieren während/nach Injektionen 69 %
  - erhöhtes Aktivitäts-Level 65 %
  - Schmerzen an Injektionsstellen 58 %
  - Wunde an der Injektionsstelle/offene Wunde 55 %
  - erhöhter Appetit 54 %
  - Blutungen an Injektionsstellen 35 %
  - Schwellungen an Injektionsstellen 32 %
  - allgemeine Verhaltensänderungen 20 %
  - Durchfall 15 %
  - Erbrechen 5 %

51

viruses 2021 MDPI

Kleintierklinik der LMU München

Article

Curing Cats with Feline Infectious Peritonitis with an Oral Multi-Component Drug Containing GS-441524

Daniela Krentz [1,*], Katharina Zenger [1], Martin Alberer [2], Sandra Felten [1], Michèle Bergmann [1], Roswitha Dorsch [1], Kaspar Matiasek [3], Laura Kolberg [2], Regina Hofmann-Lehmann [4], Marina L. Meli [4], Andrea M. Spiri [4], Jeannie Horak [5], Saskia Weber [6], Cora M. Holicki [6], Martin H. Groschup [6,7], Yury Zablotski [1], Eveline Lescrinier [8], Berthold Koletzko [5], Ulrich von Both [2,9,†] and Katrin Hartmann [1,†]

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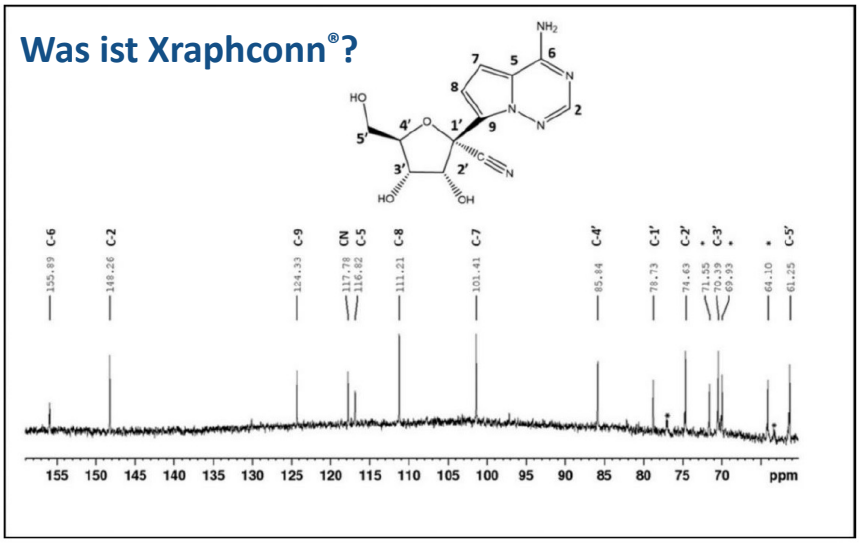
erste prospektive kontrollierte Studie mit oralem GS-441524

C·I·C·K Coronaviruses In Cats & Kids

52

Was ist Xraphconn®?



exzellente *in-vitro*-Wirksamkeit gegen FCoV

mittels Massenspektrometrie und Kernspintomographie

aktive Substanz → GS-441524

> 2-fach der angegebenen Konzentration

Figure 8. 13C spectrum of the analyzed sample. Labels refer to the assignment of carbons in the active component of Xraphconn® depicted above. All signals above 100 ppm belong to the cyano-group and nucleobase in the identified compound. Some additional signals of uncharacterized impurities were observed below 80 ppm (indicated with *). Ppm, parts per million.

viruses MDPI
Article
Curing Cats with Feline Infectious Peritonitis with an Oral Multi-Component Drug Containing GS-441524

53

JAVMA 2024 AVMA

Unlicensed antiviral products used for the at-home treatment of feline infectious peritonitis contain GS-441524 at significantly different amounts than advertised

Alycia M. Kent, MPH[1]*; Su Guan, PhD[2]; Nicole Jacque[3]; Wendy Novicoff, PhD[4,5]; Samantha J. M. Evans, DVM, PhD, DACVP[6]

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*Corresponding author: Alycia M. Kent (kent.342@buckeyemail.osu.edu)

Bewertung des Inhalts von nicht zugelassenen GS-441524-ähnlichen Produkten

- 87 injizierbare Formulierungen
  → 95 % **mehr** als erwartet
- 40 orale Formulierungen
  → 43 % **mehr** als erwartet
  → 58 % **weniger** als erwartet
- 1 injizierbare, 2 orale Proben **zusätzliches** Remdesivir

AJVR 2024 AVMA

Quality assessment and characterization of unregulated antiviral drugs for feline infectious peritonitis: implications for treatment, safety, and efficacy

Aidan J. Mulligan[1], and Megan E. Browning, PhD[2]*

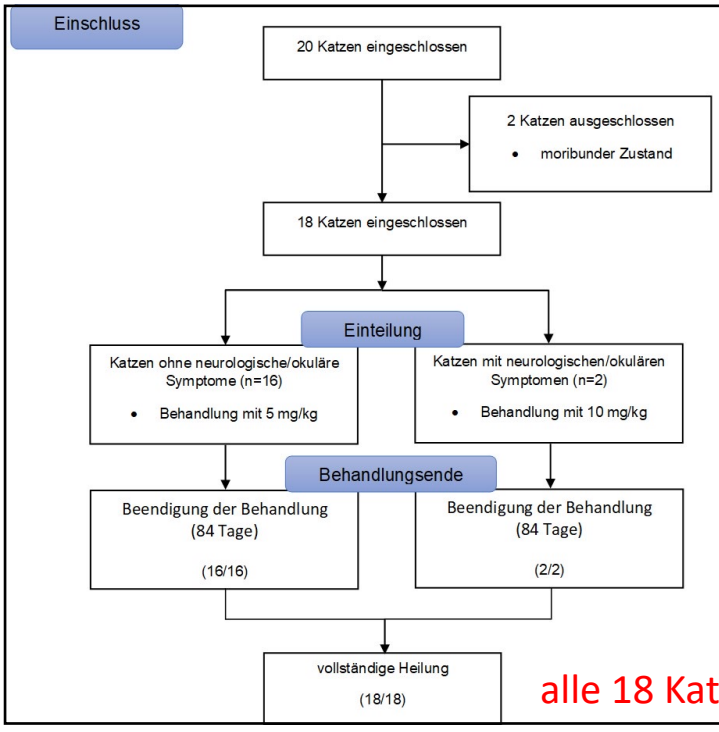
[1]Juan Diego Catholic High School, Draper, UT
[2]Department of Medicinal Chemistry, School of Pharmacy, University of Utah, Salt Lake City, UT

*Corresponding author: Dr. Browning (meganelizabethbrowning@gmail.com)

Bewertung der Sicherheit, Reinheit und Zusammensetzung von GS-441524 und GC376

- 5 Fläschchen von einer Marke GC376
- 30 Fläschchen von 17 Marken GS-441524
- GS-441524
  relativ konstant in Reinheit
  → aber 10–25 % höher konzentriert
- GC376
  keines der GC376-Fläschchen GC376
  (1/5 GS-441524, 4/5 Molnupiravir)

54



viruses MDPI

Article

Curing Cats with Feline Infectious Peritonitis with an Oral Multi-Component Drug Containing GS-441524

Daniela Krentz [1,*], Katharina Zenger [1], Martin Alberer [2], Sandra Felten [1], Michèle Bergmann [1], Roswitha Dorsch [1], Kaspar Matiasek [3], Laura Kolberg [2], Regina Hofmann-Lehmann [4], Marina L. Meli [4], Andrea M. Spiri [4], Jeannie Horak [5], Saskia Weber [6], Cora M. Holicki [6], Martin H. Groschup [6,7], Yury Zablotski [1], Eveline Lescrinier [8], Berthold Koletzko [5], Ulrich von Both [2,9,†] and Katrin Hartmann [1,†]

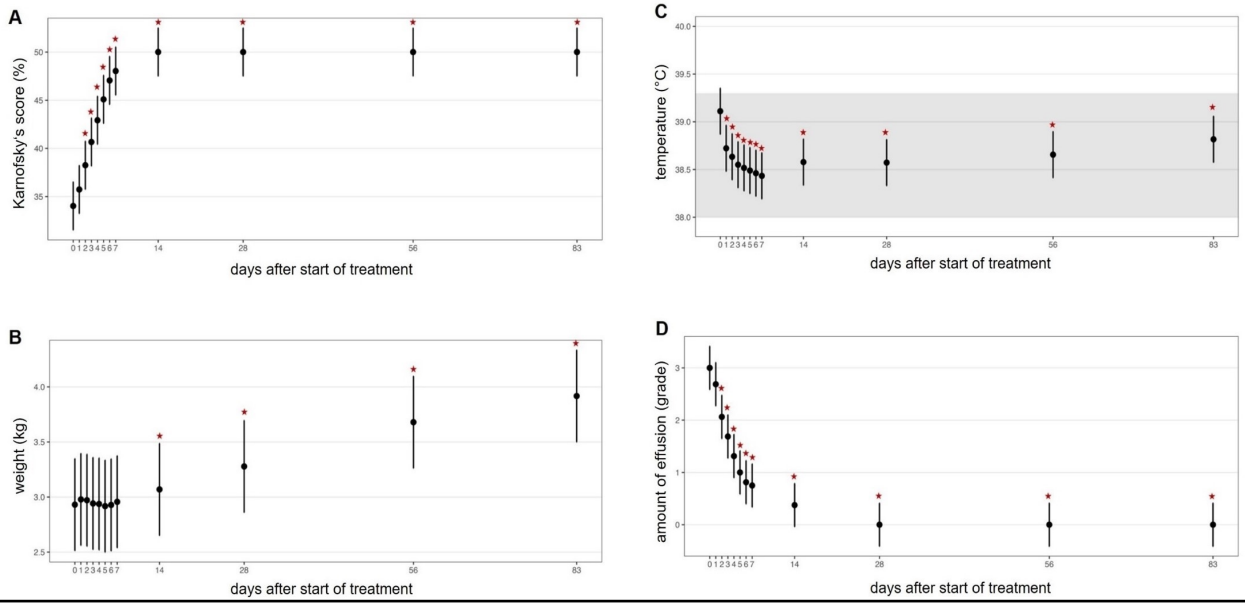
orale Behandlung mit Xraphconn® PO q24h über 84 Tage

alle 18 Katzen (100 %) vollständig geheilt

55

Klinische Parameter

Kleintierklinik der LMU München



56

Labordiagnostische Parameter (1)

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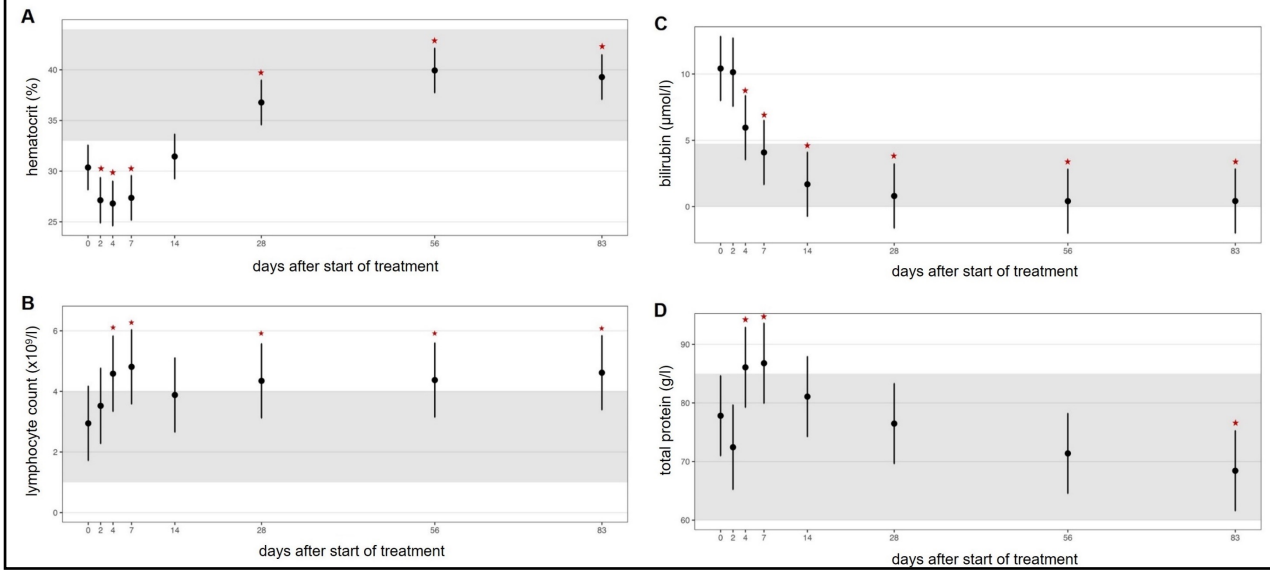

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Labordiagnostische Parameter (2)

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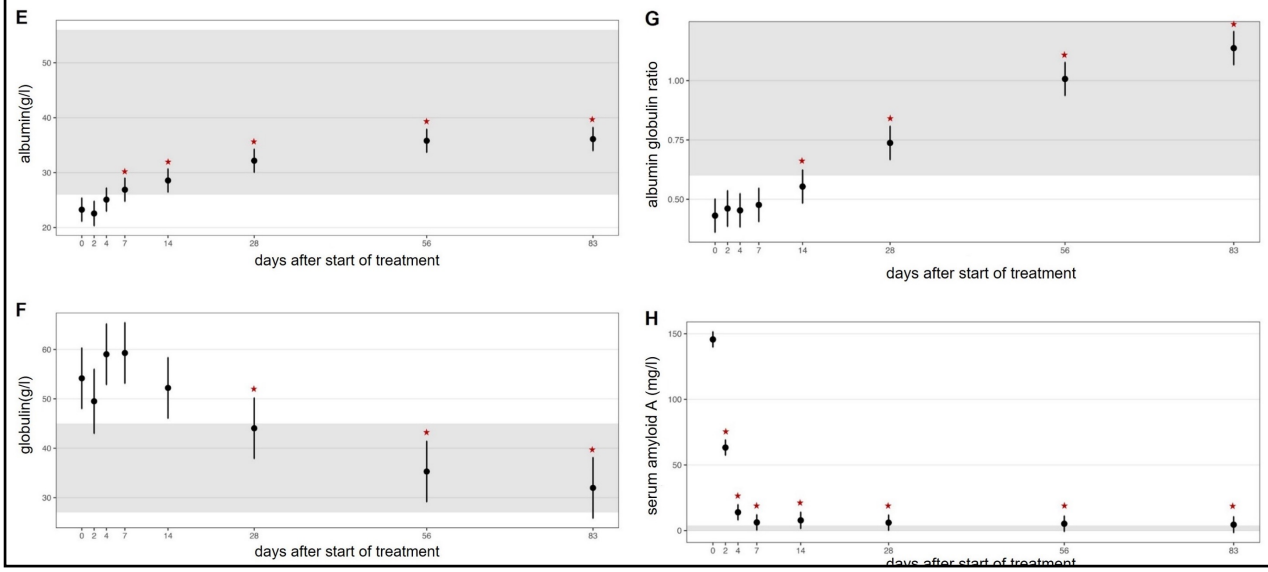
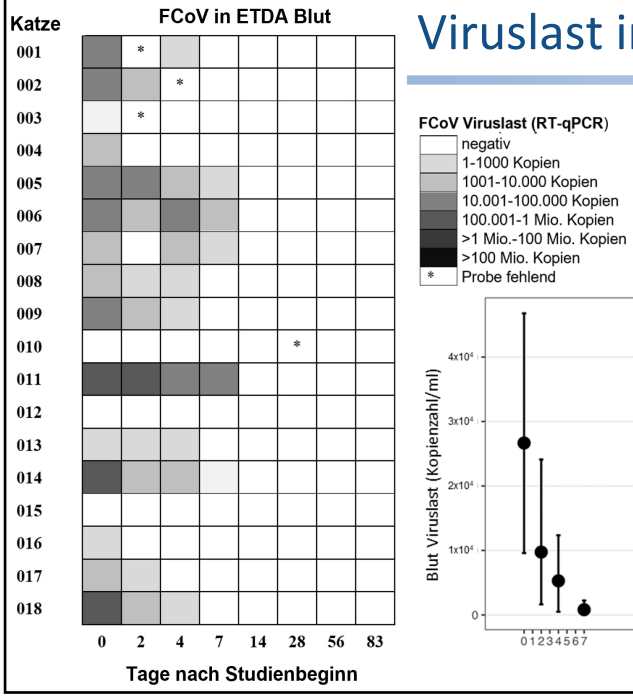
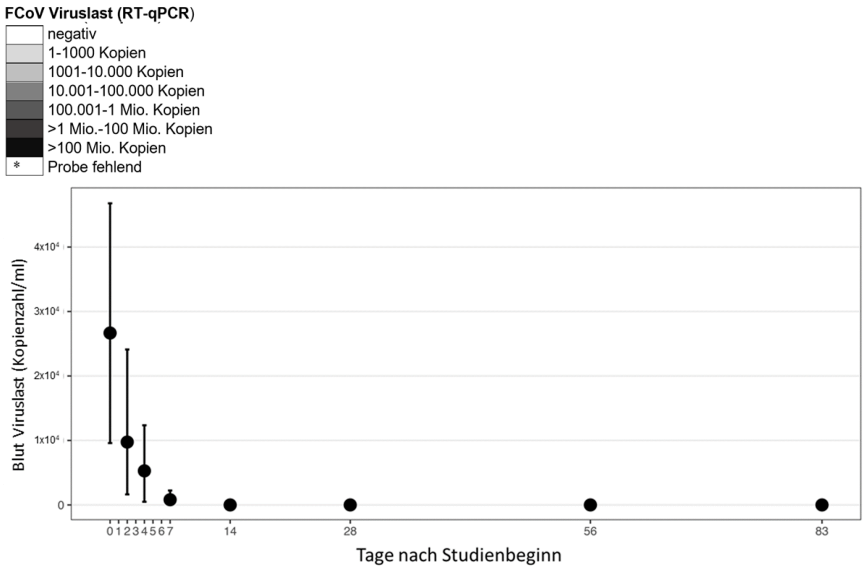


58

Viruslast im Blut

Kleintierklinik der LMU München





59

Nebenwirkung	Anteil der Katzen		Schweregrad	medianer Tag des ersten Auftretens (Bereich)	symptomatische Behandlung
Heinz-Body-Anämie	1/18		moderat	83	S-Adenosyl-Methionin
Lymphozytose	14/18	4/14	mild	4,5 (2 – 83)	keine
		6/14	moderat	1 (0 – 28)	
		4/14	schwerwiegend	1 (0 – 2)	
Eosinophilie	11/18	11/11	mild	14 (0 – 28)	keine
erhöhte Leberenzym-aktivitäten	11/18	8/11	mild	14 (0 – 28)	keine
		1/11	moderat	4	keine
		2/11	schwerwiegend	4	Silymarin

60

Gating-Strategie

frontiers | Frontiers in Veterinary Science 2024
TYPE Original Research
PUBLISHED 26 June 2024
DOI 10.3389/fvets.2024.1377414

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Adapting the SMART tube technology for flow cytometry in feline full blood samples

Katharina Zwicklbauer[1]*, Dominik von la Roche[2], Daniela Krentz[1], Laura Kolberg[3], Martin Alberer[3], Yury Zablotski[1], Katrin Hartmann[1], Ulrich von Both[3,4†] and Sonja Härtle[2†]

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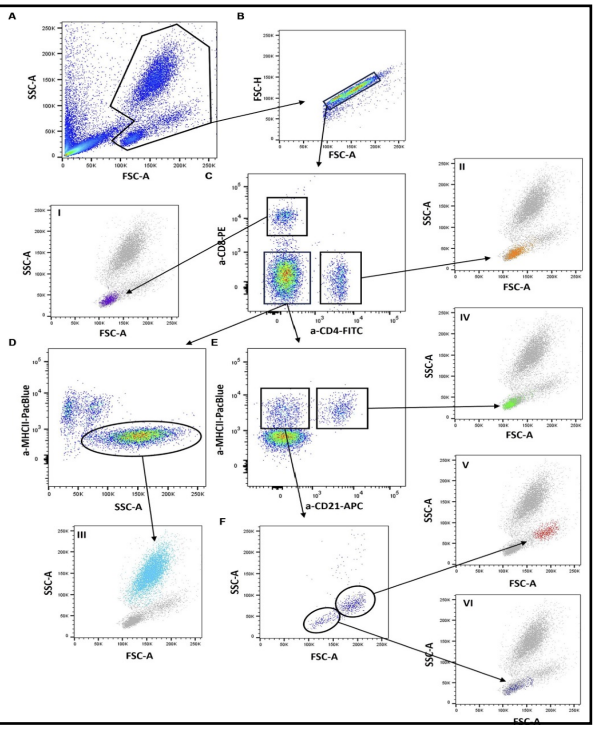
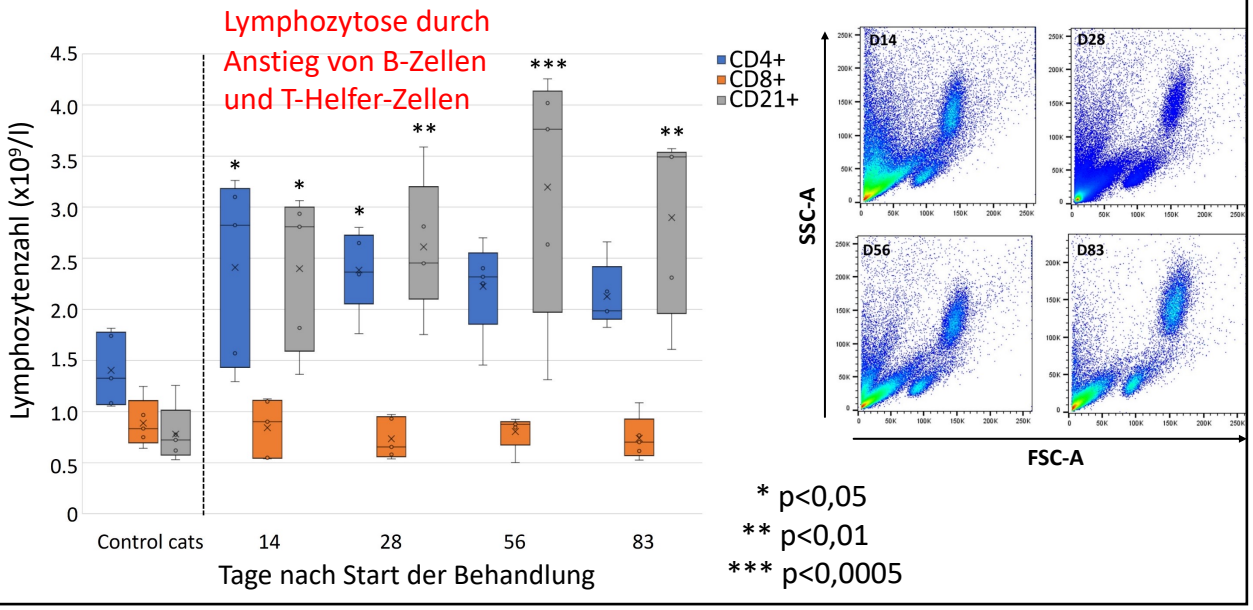
Antigene	Fluorochrome	Zielzellen
CD4	FITC	T-Helfer-Zellen
CD8	PE	zytotoxische T-Zellen
CD21	APC	B-Zellen
MHCII	CF405M	Monozyten, T-Zellen, B-Zellen



61

Charakterisierung der Lymphozytose

Kleintierklinik der LMU München

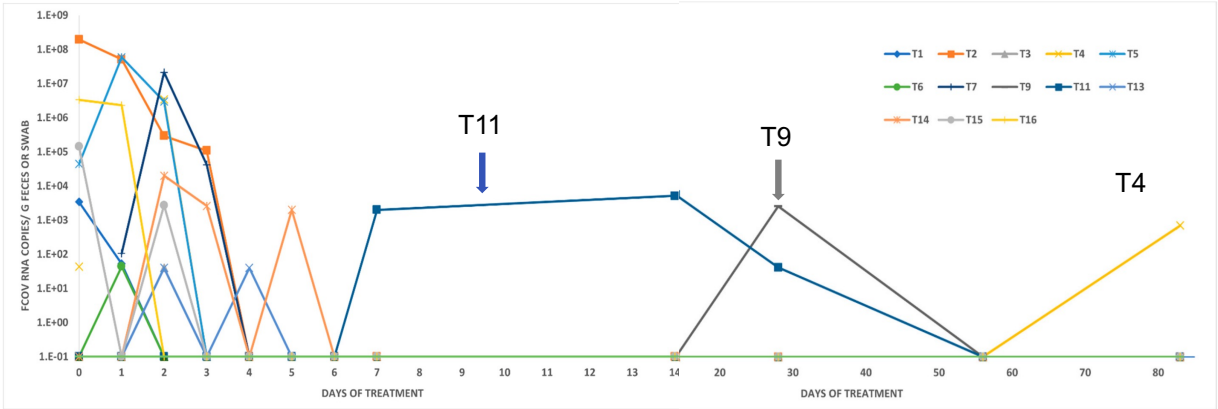


62

Virusausscheidung im Kot

viruses 2022 MDPI
Article
Fecal Feline Coronavirus RNA Shedding and Spike Gene Mutations in Cats with Feline Infectious Peritonitis Treated with GS-441524

- bei 61 % (11/18 Katzen) FCoV-RNA im Kot positiv in dem ersten 3 Tagen
- signifikanter Abfall der Viruslast ab Tag 4 (p = 0,040)
- alle Katzen negativ ab Tag 6, aber erneute Ausscheidung bei 3 Katzen



63

Long-term Follow-up der 18 Katzen

Kleintierklinik der LMU München

Original Article 2023

Long-term follow-up of cats in complete remission after treatment of feline infectious peritonitis with oral GS-441524

Journal of Feline Medicine and Surgery
1–14

DOI: 10.1177/1098612X231183250
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Sage

Katharina Zwicklbauer[1], Daniela Krentz[1], Michèle Bergmann[1], Sandra Felten[1], Roswitha Dorsch[1], Andrea Fischer[1], Regina Hofmann-Lehmann[2], Marina L Meli[2], Andrea M Spiri[2], Martin Alberer[3], Laura Kolberg[3], Kaspar Matiasek[4], Yury Zablotski[1], Ulrich von Both[3,5] and Katrin Hartmann[1]

klinische, labordiagnostische, virologische Parameter	Material	Hospitalisierung								Behandlung				Follow-ups		
		D0	D1	D2	D3	D4	D5	D6	D7	D14	D28	D56	D83	M6	M9	M12

64

	1. Follow-up (6 Monate)	2. Follow-up (9 Monate)	3. Follow-up (12 Monate)
Katzen	18/18	15/18	14/18
Tod	0/18	1/18 (tödlicher Autounfall)	1/18
Lymphadenopathie	**9/18**	**5/15**	**6/14**
neurologische Symptome (FHS)	0/18	1/15	2/14
FCoV in Blut	1/18 (CT 38,0)	0/15	0/14
FCoV in Erguss	0/18	0/15	0/14
FCoV in Kot	2/18	2/15	5/14
FCoV-Antikörper in Serum	18/18	14/15	13/14

65

„Gusti“

Kleintierklinik der LMU München

EKH, 6 Monate, männlich kastriert
- rezidivierendes Fieber
- Apathie, Inappetenz
- Uveitis links

Enukleation des linken Auges

- Immunhistochemie
  → FCoV-Antigen-positiv

C·I·C·K. Coronaviruses In Cats & Kids

viruses

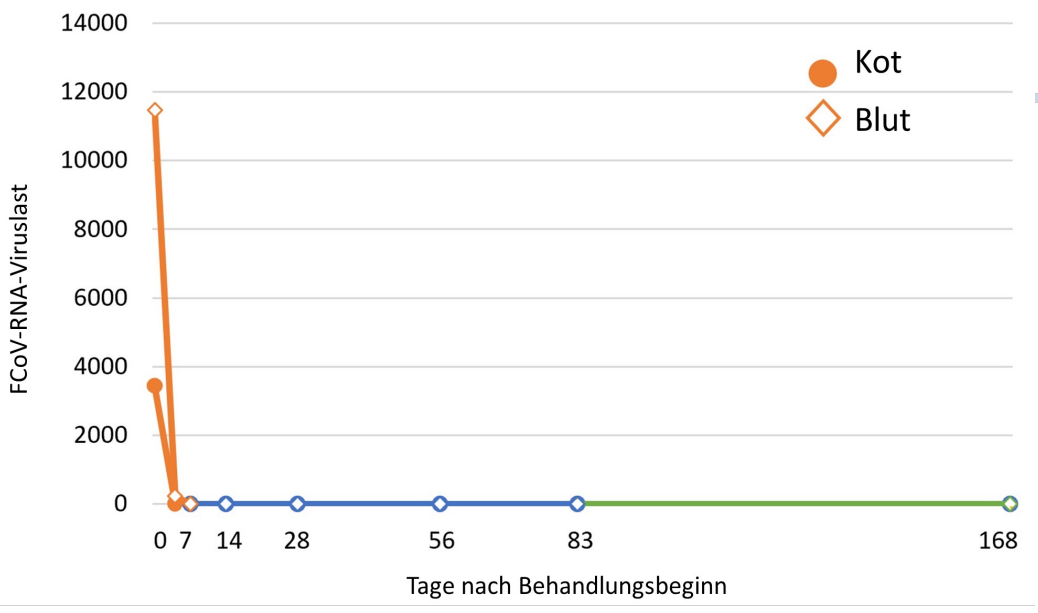
2022 MDPI

Case Report

Clinical Follow-Up and Postmortem Findings in a Cat That Was Cured of Feline Infectious Peritonitis with an Oral Antiviral Drug Containing GS-441524

Daniela Krentz [1,*,†], Katharina Zwicklbauer [1,†], Sandra Felten [1], Michèle Bergmann [1], Roswitha Dorsch [1], Regina Hofmann-Lehmann [2], Marina L. Meli [2], Andrea M. Spiri [2], Ulrich von Both [3], Martin Alberer [3], Anne Hönl [1,4], Kaspar Matiasek [4,†] and Katrin Hartmann [1,†]

66



Kleintierklinik der LMU München

„Gusti“

Verlauf: tödlicher Autounfall 164 Tage nach Therapieende

67

Unfall 164 Tage nach Behandlungsende

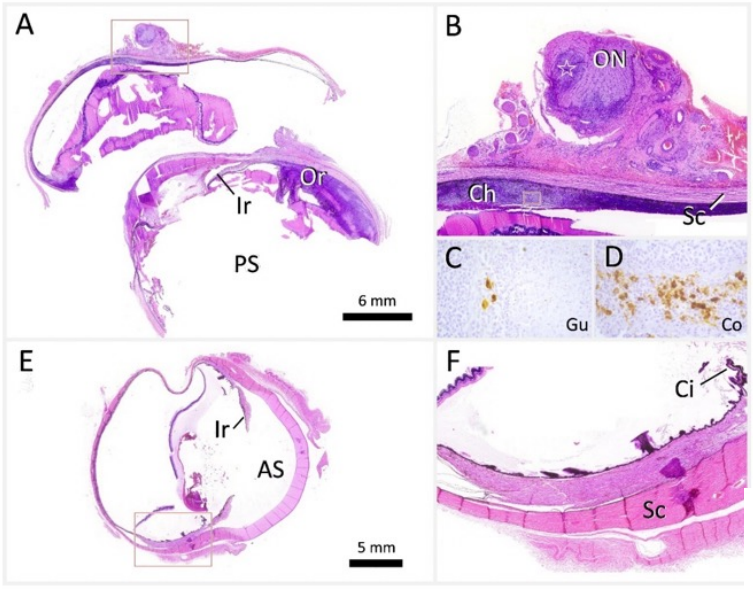
Kleintierklinik der LMU München

Immunhistochemie (IHC) und RT-PCR

aus verschiedenen Geweben

Gewebe	IHC FCoV-Antigen	FCoV RT-qPCR* (Viruslast)	18S rRNA RT-qPCR* (Kontroll-) CT-Wert
Lnn. mand.	negativ	negativ	15,09
Jejunum	negativ	negativ	15,86
Duodenum	negativ	negativ	14,08
Milz	negativ	negativ	14,18
Kolon	negativ	negativ	16,02
Lnn. mesent.	negativ	negativ	15,57
Nieren	negativ	negativ	20,62
Zäkum	negativ	negativ	14,28
Rektum	negativ	negativ	15,21
Leber	negativ	negativ	20,54
Gehirn	negativ	negativ	20,82

68



Kleintierklinik der LMU München

- vollständige Viruselimination
- keinerlei FIP-typischen Veränderungen (Ausnahme Lymphadenomegalie)

Figure 8. Comparison of the left eye (**A**, **B**, **C**), enucleated before antiviral treatment, and the right eye (**E**, **F**), harvested on necropsy. The feline infectious peritonitis (FIP)-affected left eye showed extensive pyogranulomatous and lymphocytic inflammation affecting mainly the optic nerve (ON) and choroid (Ch), thereby extending from the posterior pole to ora serrata (Or). Fibrin precipitates, proteinaceous fluid and free floating cells were abundantly present in both anterior and posterior segment (**A**: PS). On immunohistochemistry, there were scattered macrophages immunopositive for feline coronavirus (FCoV) antigen in the cat's eye (**C**: Gu). The signal was similar to that of polymerase chain reaction (PCR)-confirmed control tissue (**D**: Co). No such changes were seen in the right eye (**E**, **F**), taken on necropsy.

Landmarks: AS: anterior segment; Ch: choroid; Ci: ciliary body; Ir: iris; ON: optic nerve; Or: ora serrata; PS: posterior segment; Sc: sclera.

Stainings: **A**, **B**, **E**, **F**: haematoxylin-eosin; **C**, **D**: Diaminobenzidine tetrahydrochloride (brown), haematoxylin counterstain.

69

viruses 2024 MDPI

Article

Short Treatment of 42 Days with Oral GS-441524 Results in Equal Efficacy as the Recommended 84-Day Treatment in Cats Suffering from Feline Infectious Peritonitis with Effusion—A Prospective Randomized Controlled Study

Anna-M. Zuzzi-Krebitz [1,*], Katharina Buchta [1], Michèle Bergmann [1], Daniela Krentz [1], Katharina Zwicklbauer [1], Roswitha Dorsch [1], Gerhard Wess [1], Andrea Fischer [1], Kaspar Matiasek [2], Anne Hönl [1,2], Sonja Fiedler [2], Laura Kolberg [3], Regina Hofmann-Lehmann [4], Marina L. Meli [4], Andrea M. Spiri [4], A. Katrin Helfer-Hungerbuehler [4], Sandra Felten [5], Yury Zablotski [1], Martin Alberer [3], Ulrich von Both [3,6] and Katrin Hartmann [1]

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4 Clinical Laboratory, Department of Clinical Diagnostics and Services, and Center for Clinical Studies, Vetsuisse Faculty, University of Zurich, CH-8057 Zurich, Switzerland; regina.hofmann-lehmann@uzh.ch (R.H.-L.); mmeli@vetclinics.uzh.ch (M.L.M.); aspiri@vetclinics.uzh.ch (A.M.S.); khungerbuehler@vetclinics.uzh.ch (A.K.H.-H.)
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Citation: Zuzzi-Krebitz, A.-M.; Buchta, K.; Bergmann, M.; Krentz, D.; Zwicklbauer, K.; Dorsch, R.; Wess, G.; Fischer, A.; Matiasek, K.; Hönl, A.; et al. Short Treatment of 42 Days with Oral GS-441524 Results in Equal Efficacy as the Recommended 84-Day Treatment in Cats Suffering from

Kleintierklinik der LMU München

- Vergleich der Behandlungsdauer
  - 84 days (12 weeks) *versus*
  - 42 days (6 weeks)
- Effektivität von oralem GS-441524 (BOVA, UK)

71

viruses MDPI

Article

Short Treatment of 42 Days with Oral GS-441524 Results in Equal Efficacy as the Recommended 84-Day Treatment in Cats Suffering from Feline Infectious Peritonitis with Effusion—A Prospective Randomized Controlled Study

Anna-M. Zuzzi-Krebitz [1,*], Katharina Buchta [1], Michèle Bergmann [1], Daniela Krentz [1], Katharina Zwicklbauer [1], Roswitha Dorsch [1], Gerhard Wess [1], Andrea Fischer [1], Kaspar Matiasek [2], Anne Hönl [1,2], Sonja Fiedler [2], Laura Kolberg [3], Regina Hofmann-Lehmann [4], Marina L. Meli [4], Andrea M. Spiri [4], A. Katrin Helfer-Hungerbuehler [4], Sandra Felten [5], Yury Zablotski [1], Martin Alberer [3], Ulrich von Both [3,6] and Katrin Hartmann [1]

Kleintierklinik der LMU München

- prospektive randomisierte Studie
  - 40 Katzen mit diagnostizierter FIP (mit Erguss)

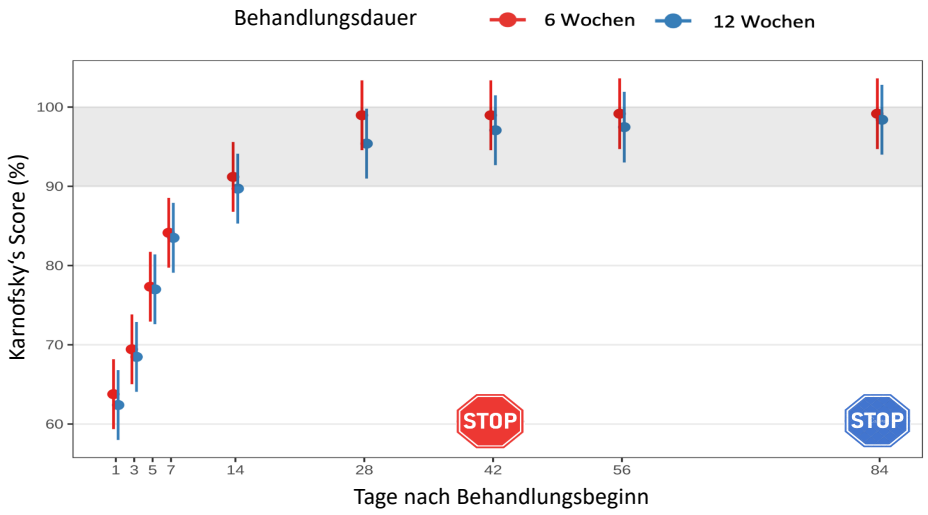
Ausschlusskriterien

- Katzen < 2 kg Körpergewicht
- FIV/FeLV-infizierte Katzen
- Katzen in moribundem Zustand
- Katzen mit Komorbiditäten

oral GS-441524 (BOVA, UK) 15 mg/kg q24h PO

- Tag 1–7 in Klinik mit intensiver Pflege
- dann zu Hause
- Untersuchungen bis Tag 168

72

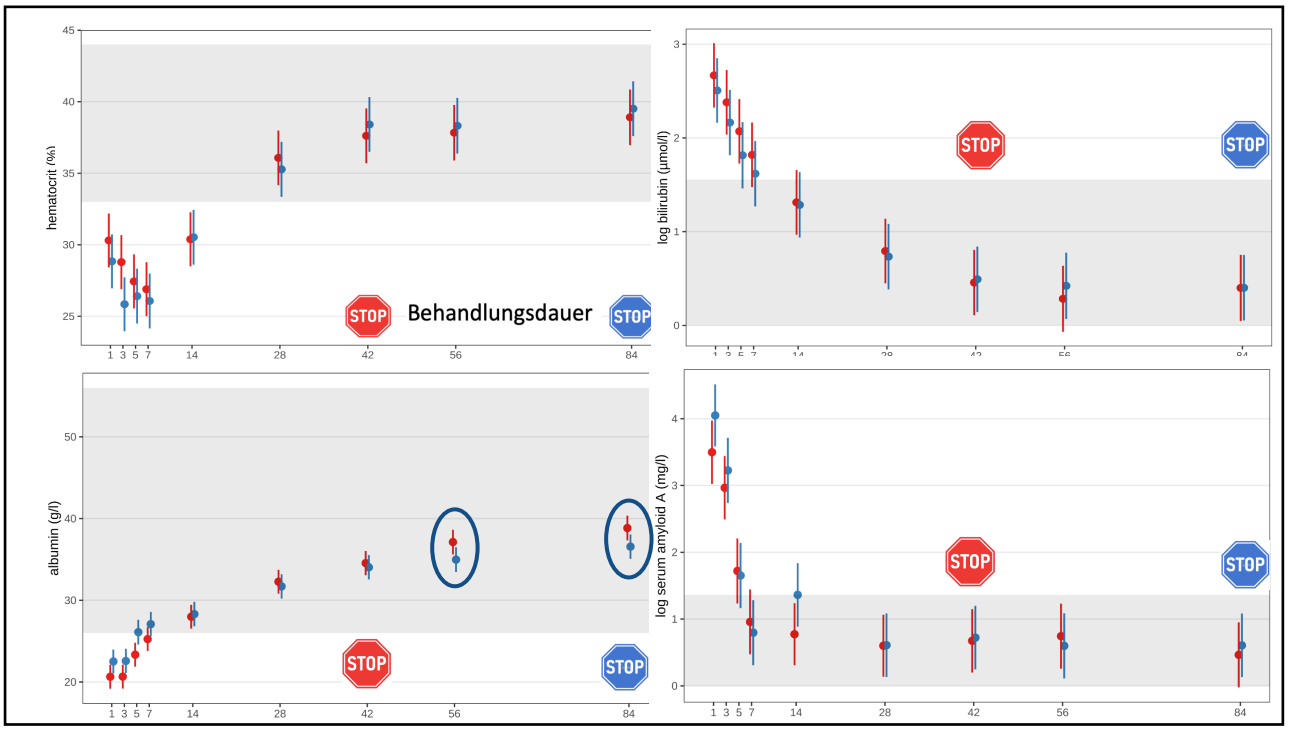


Outcome
38/40 Katzen
in vollständiger
Remission an Tag 168

2/40 Katzen euthanasiert
während Therapie
(Tag 3 und Tag 31)
→ in Sektion kein FCoV
mittels IHC nachweisbar

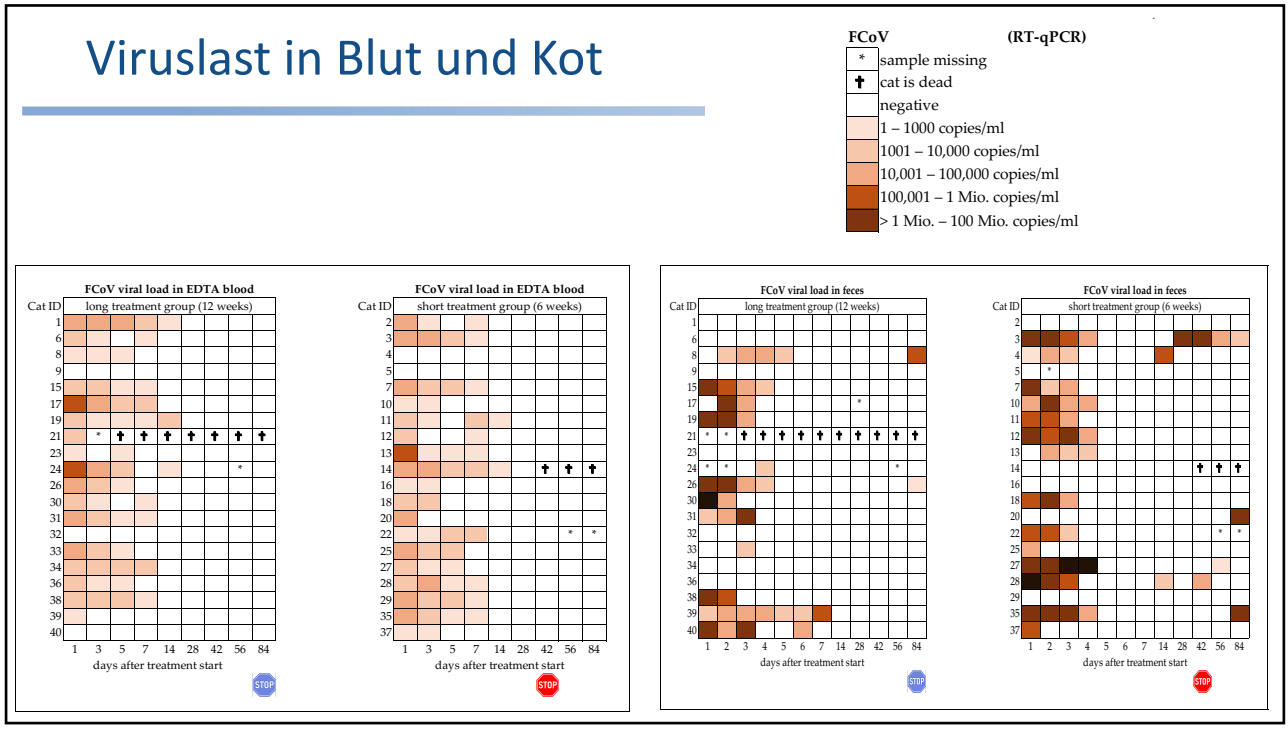
kein signifikanter Unterschied im Gruppenvergleich → an allen Tagen $p > 0,05$

73



74

Viruslast in Blut und Kot



75

Follow-up über 1 Jahr nach Therapiestart

Kleintierklinik der LMU München

- prospektive Studie
- 37/40 Katzen:
  - 2/40 Katzen euthanasiert
    „Kitty“: Tag 3
    „Gismo“: Tag 31
  - 1/40 Katzen
    lost to follow-up

76

Follow-up über 1 Jahr nach Therapiestart

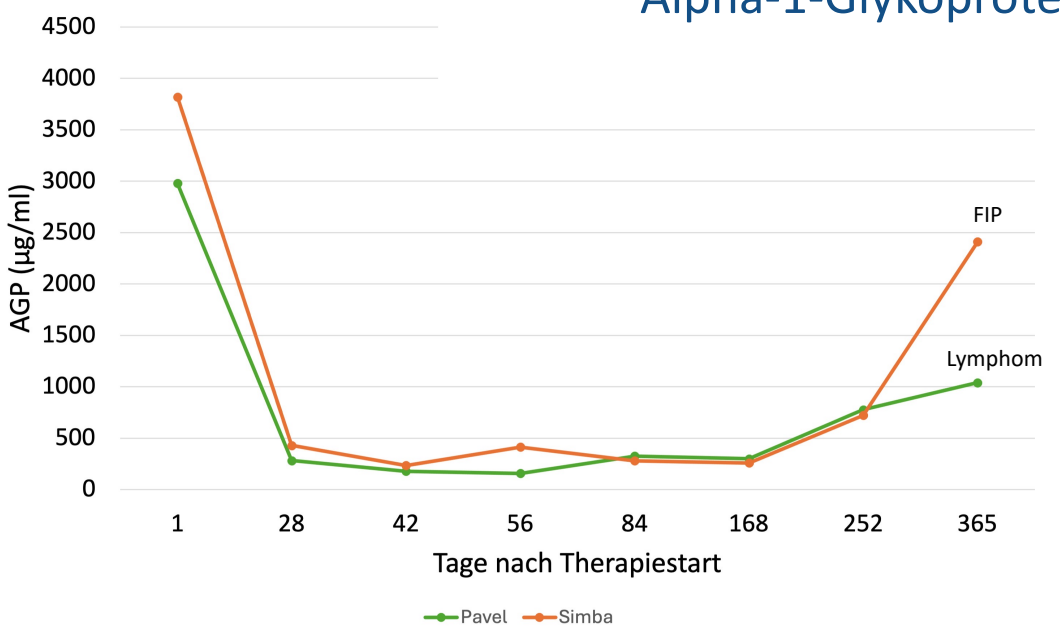
Kleintierklinik der LMU München

Langzeit-follow-up für 12 Monate nach Therapiestart

- **36/37 Katzen in Remission**
- 1/37 erneute FIP (Relapse vs. Reinfektion ?)
- 1/37 Lymphom

77

Alpha-1-Glykoprotein (AGP)



88

AGP-Konzentrationen während der Therapie

Kleintierklinik der LMU München

- leichter AGP-Anstieg von Tag 0 bis 2
- deutliche Abnahme in den ersten 7 Tage
- normale Werte (< 567 µg/ml) nach 14 Tagen
- **potenzielle Vorhersage eines Rückfalls**

viruses 2024 MDPI

Article

Alpha-1-Acid Glycoprotein Quantification via Spatial Proximity Analyte Reagent Capture Luminescence Assay: Application as Diagnostic and Prognostic Marker in Serum and Effusions of Cats with Feline Infectious Peritonitis Undergoing GS-441524 Therapy

A. Katrin Helfer-Hungerbuehler [1,*], Andrea M. Spiri [1], Theres Meili [1], Barbara Riond [1], Daniela Krentz [2], Katharina Zwicklbauer [2], Katharina Buchta [2], Anna-Maria Zuzzi-Krebitz [2], Katrin Hartmann [2], Regina Hofmann-Lehmann [1] and Marina L. Meli [1]

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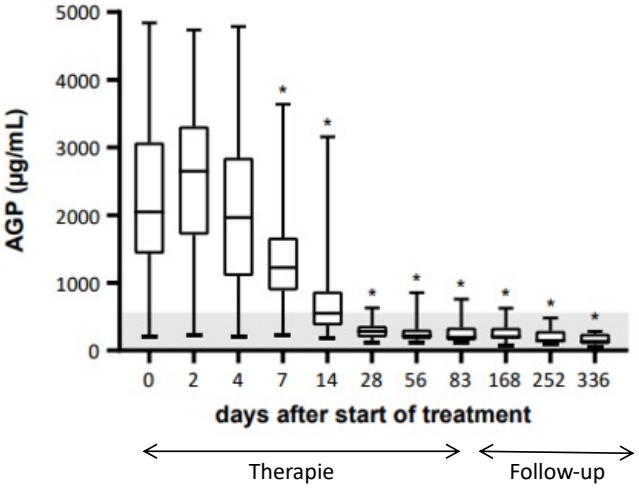

89

FIP-Myokarditis – ein neues Krankheitsbild

Kleintierklinik der LMU München

- 40 Katzen mit FIP
  - therapiert mit GS-441524 15 mg/kg q24h PO

→ 4/40 Katzen: Verdacht auf Myokarditis
  - cTnI-Messung
  - ausführliche kardiologische Untersuchung (Auskultation, EKG, Echokardiographie)

90

Myokarditis

Kleintierklinik der LMU München

Case Report

2019

jfms OPEN REPORTS

Feline coronavirus-associated myocarditis in a domestic longhair cat

Maria A Ernandes[1], Anna M Cantoni[2], Federico Armando[2], Attilio Corradi[2], Lorenzo Ressel[3] and Alice Tamborini[4]

Journal of Feline Medicine and Surgery Open Reports
1–5

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SAGE

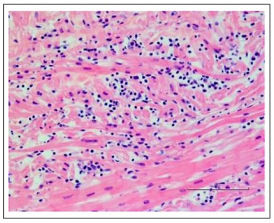

Figure 1 Histopathology of the heart. Myocardiocytes are mildly multifocally swollen and degenerated. The interstitium between myocardiocytes is diffusely expanded by oedema and focal infiltration by inflammatory aggregates characterised by a high number of lymphocytes, plasma cells and fewer macrophages. Haematoxylin eosin (×200)

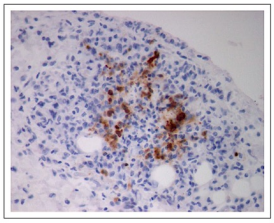

Figure 2 Immunohistochemistry of the myocardium. In an area close to the left atrioventricular valve, feline coronavirus (FCoV)-positive macrophages are evident (brown stain) in association with neutrophils and macrophages. Indirect immunoperoxidase (×400)

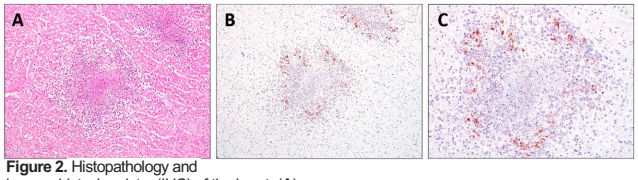

Figure 2. Histopathology and immunohistochemistry (IHC) of the heart. (**A**) Pyogranulomatous inflammation with a central core of necrosis (H&E, 200×); (**B**,**C**) FIPV-immunopositive macrophages were observed at the periphery of foci of myocardial necrosis (IHC, 200× and 400×, respectively).

Myocarditis in an FIP-Diseased Cat with FCoV M1058L Mutation: Clinical and Pathological Changes 2024

by Chiara Guarnieri [1,†], Luca Bertola [2,3,†], Luca Ferrari [1,*], Cecilia Quintavalla [1], Attilio Corradi [1,*,‡] and Rosanna Di Lecce [1,‡]

92

Zusammenfassung Myokarditis

Kleintierklinik der LMU München

- Myokarditis kann FIP-bedingt sein
- unterschiedliche kardiologische Präsentation

- **Diagnose:**
  ↑cTnI
  kardiologische Veränderungen
  (EKG, Echokardiographie)

→ Therapie der FIP-induzierte Myokarditis mit GS-441524 in Kombination mit symptomatischer kardiovaskulärer Therapie

98

Zusammenfassung Nebenwirkungen

Kleintierklinik der LMU München

Nebenwirkungen einer GS-441524-Therapie

- sofortige Nebenwirkungen
  - Lymphozytose und Eosinophilie
  - Abszesse nach Injektionen
  - GS-441524-Steine
- Langzeitfolgen
  - felines Hyperästhesie-Syndrom (FHS)?
  - Lymphom?
  - dermale Atrophie nach Injektionen?

99

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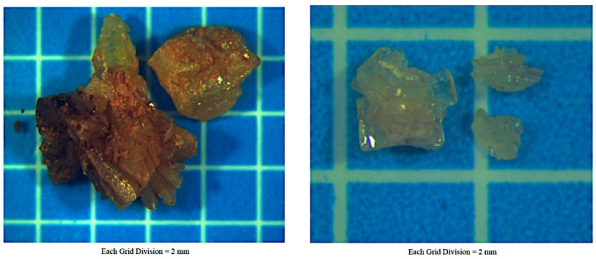
CASE REPORT 2023

Journal of Veterinary Internal Medicine ACVIM Open Access American College of Veterinary Internal Medicine

Uroliths composed of antiviral compound GS-441524 in 2 cats undergoing treatment for feline infectious peritonitis

Marissa Allinder[1] | Beth Tynan[2] | Cara Martin[3] | Amelia Furbish[4] | Glenn Austin[5] | Joe Bartges[3] | Bianca N. Lourenço[3]



Each Grid Division = 2 mm | Each Grid Division = 2 mm

2 Fälle
- multifokale Urolithiasis
- Steinanalyse: 98 % GS-441524

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journal homepage: www.journals.elsevier.com/journal-of-pharmaceutical-and-biomedical-analysis

First analytical confirmation of drug-induced crystal nephropathy in felines caused by GS-441524, the active metabolite of Remdesivir

Amelia Furbish[a], Marissa Allinder[b], Glenn Austin[c], Beth Tynan[b], Emilee Byrd[a], Ivette Pina Gomez[a], Yuri Peterson[a,*]
[a] Dept. of Drug Discovery and Biomedical Sciences, College of Pharmacy, Medical University of South Carolina, 70 President St, Charleston, SC 29425, USA
[b] Charleston Veterinary Referral Center, 3484 Shelby Bay Court, Charleston, SC, USA
[c] Louis C. Herring and Company, 1111 S. Orange Ave., Orlando, FL, USA

2024

2 Nierensteine
- aus GS-441524
- Tabletten-induzierte Kristall-Nephropathie

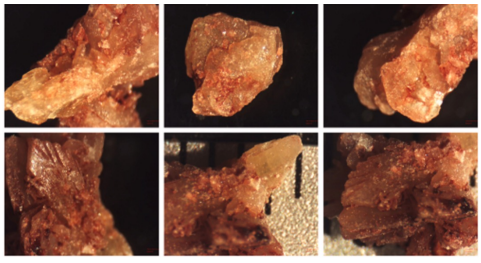


Fig. 1. Stereo microscopy images demonstrating compact crystallization pattern of feline renal stone #1, indicative of homogenous nucleation of GS-441524.

100

„Diego“ 3 Monate nach Ende der Therapie

Kleintierklinik der LMU München

ca. 2 Wochen nach Kastration
Durchfall,
sonst klinisch unauffällig,
kurz danach …

Symptome eines felinen Hyperästhesie-Syndroms (FHS)

101

„Pavel“, Somali, 23 Monate, m

Kleintierklinik der LMU München

Tag 365 nach Therapiestart => Lymphom
Therapie: Prednisolon, Cyclophosphamid, Lomustin
=> massive Verschlechterung => Euthanasie
in der Pathologie => multizentrisches B-Zell-Lymphom

102

Dermale Atrophie

Kleintierklinik der LMU München

Luna, Burma 3 Jahre wk

- aufgrund okulärer und neurologischer FIP vom Besitzer mit GS-441524-Injektionen über 84 Tage therapiert
- 6 Monate nach Therapieende
  - sehr große Zusammenhangstrennung der Haut an fast der Hälfte des Rumpfs
  - nach konservativem Management Besserung, aber nicht Abheilung

- Vorstellung an der TiHo Hannover
  - hochgradige dermale Atrophie am dorsalen und lateralen Rumpf genau da, wo die GS-Injektionen platziert wurden (nicht an anderen Körperbereichen)
  - Haut sehr stark vernarbt
  - offene Hautstelle palpatorisch nicht verschieblich von Subkutis

103

Studien zu FIP und Behandlungserfolge

Kleintierklinik der LMU München

- die tödliche Krankheit FIP
  - Entstehung der FIP
  - Gefahren durch neue FCoV-Varianten
- antivirale Medikamente gegen FIP
  - Ribavirin
  - Mefloquin
  - Itraconazol
  - GC376
  - Molnupiravir
  - Remdesivir und GS-441524
- derzeitig legale Therapieoptionen

104

Legale Therapieoptionen

Kleintierklinik der LMU München

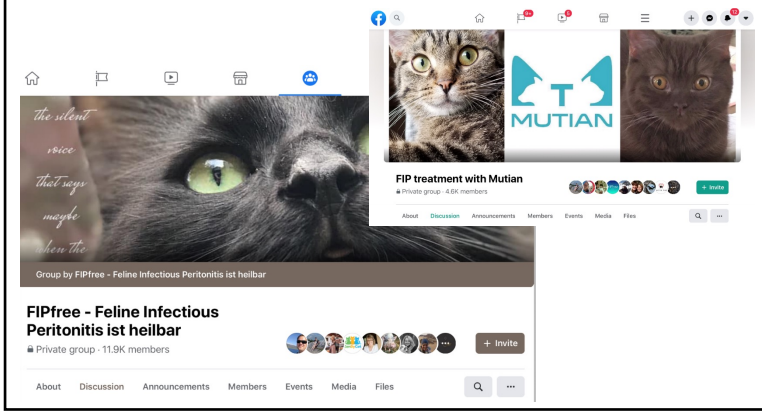
- aktuelle Optionen für eine Therapie
  - veterinärmedizinische „Betreuung" der GS-441524-Therapie durch Besitzer
  - humanes Remdesivir (oder Molnupiravir)
  - legale Herstellung durch Apotheken in manchen Ländern (z. B. BOVA, Depeche)
  - Arzneimittel-Notfall-Freigabe (EDR) für „FIP-Ausbrüche" (z. B. Zypern)
  - Teilnahme an einer genehmigten Studie
- Lizensierung von GS-441524
  - nach Ablauf des Gilead-Patents

105

Legale Therapieoptionen

Kleintierklinik der LMU München

- aktuelle Optionen für eine Therapie
  - veterinärmedizinische „Betreuung" der GS-441524-Therapie durch Besitzer



106

Legale Therapieoptionen

Kleintierklinik der LMU München

- aktuelle Optionen für eine Therapie
  - veterinärmedizinische „Betreuung" der GS-441524-Therapie durch Besitzer
  - humanes Remdesivir (oder Molnupiravir)
    - **Molnupiravir** nicht verfügbar in EU (EMA gegen Zulassung beim Menschen)
    - **Remdesivir**
      - schwer zu bekommen
      - extrem teuer (Dosierung 10-20 mg/kg IV oder SC q24h)
      - Kosten 330 Euro pro Ampulle mit 100 mg Remdesivir
      - maximale Haltbarkeitsdauer 48 Stunden nach dem Öffnen

107

Legale Therapieoptionen

Kleintierklinik der LMU München

- aktuelle Optionen für eine Therapie
  - veterinärmedizinische „Betreuung" der GS-441524-Therapie durch Besitzer
  - humanes Remdesivir (oder Molnupiravir)
  - legale Herstellung durch Apotheken in manchen Ländern (z. B. BOVA, Depeche)
    - hergestellt in Großbritannien und Australien (BOVA) oder Frankreich (Depeche)
    - kann per Rezept aus Frankreich eingeführt werden

108

Legale Therapieoptionen

Kleintierklinik der LMU München

- aktuelle Optionen für eine Therapie
  - veterinärmedizinische „Betreuung" der GS-441524-Therapie durch Besitzer
  - humanes Remdesivir (oder Molnupiravir)
  - legale Herstellung durch Apotheken in manchen Ländern (z. B. BOVA, Depeche)
  - Arzneimittel-Notfall-Freigabe (EDR) für „FIP-Ausbrüche" (z. B. Zypern)
    - GS-441524
    - Remdesivir
    - Molnupiravir

109

Legale Therapieoptionen

Kleintierklinik der LMU München

- aktuelle Optionen für eine Therapie
  - veterinärmedizinische „Betreuung" der GS-441524-Therapie durch Besitzer
  - humanes Remdesivir (oder Molnupiravir)
  - legale Herstellung durch Apotheken in manchen Ländern (z. B. BOVA, Depeche)
  - Arzneimittel-Notfall-Freigabe (EDR) für „FIP-Ausbrüche" (z. B. Zypern)
  - Teilnahme an einer genehmigten Studie

Studie in Deutschland (München) und Schweiz (Zürich)
mit 770 Katzen
Therapie mit GS-441524 (BOVA, UK)
fip@medizinische-kleintierklinik.de

110

Zusammenfassung legale Therapieoptionen

Kleintierklinik der LMU München

- aktuelle Optionen für eine Therapie
  - veterinärmedizinische „Betreuung" der GS-441524-Therapie durch Besitzer
  - humanes Remdesivir (oder Molnupiravir)
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  - Teilnahme an einer genehmigten Studie
- Lizensierung von GS-441524
  - nach Ablauf des Gilead-Patents

111

Kooperationen

Kleintierklinik der LMU München

Kleintierklink LMU München
Prof. Katrin Hartmann
PD Dr. Michèle Bergmann
PD Dr. Roswitha Dorsch
Dr. Daniela Krentz
Dr. Katharina Zwicklbauer
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Universität Sydney
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C·I·C·K
Coronaviruses In Cats & Kids

Institut für Veterinärmedizinische Pathologie
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112