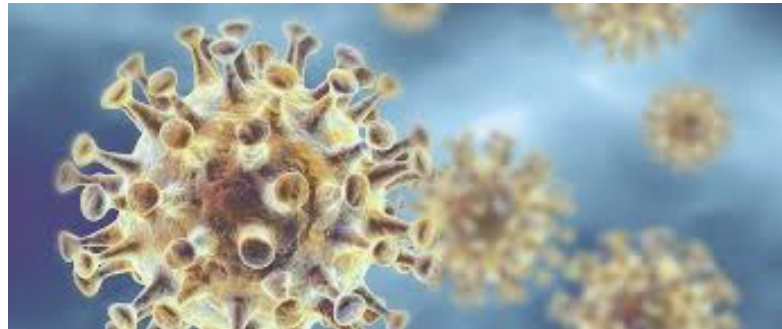


Viruses and drug allergies

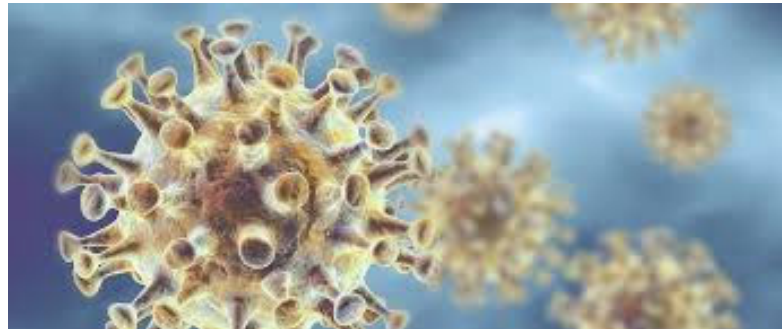
ADR-AC Symposium, 12th of May 2022



Prof. Marie-Charlotte Brüggemann, MD PhD
USZ, UZH, Hochgebirgsklinik Davos

Outline

- I. «Global» aspects: the interplay between viruses and drug allergies
- II. SARS-CoV2 and drug allergies

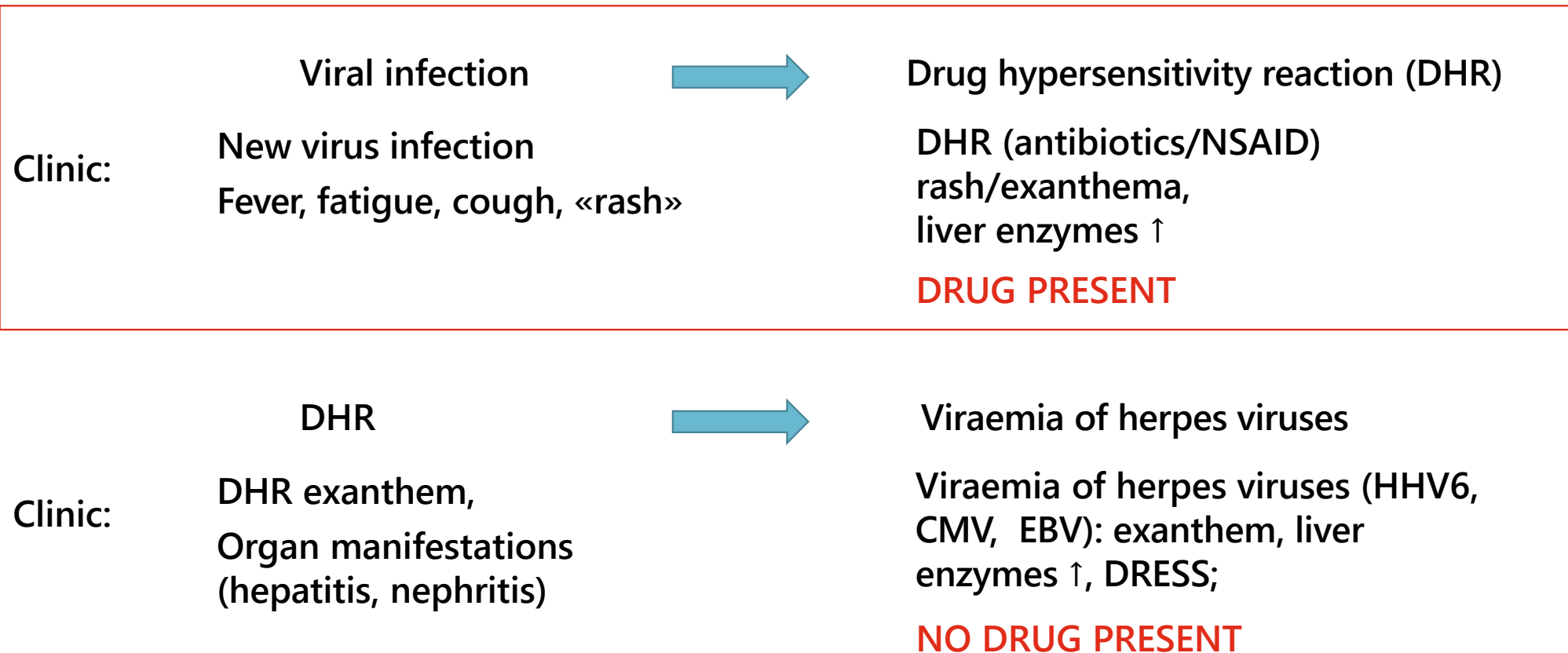


Viruses and drug allergies...

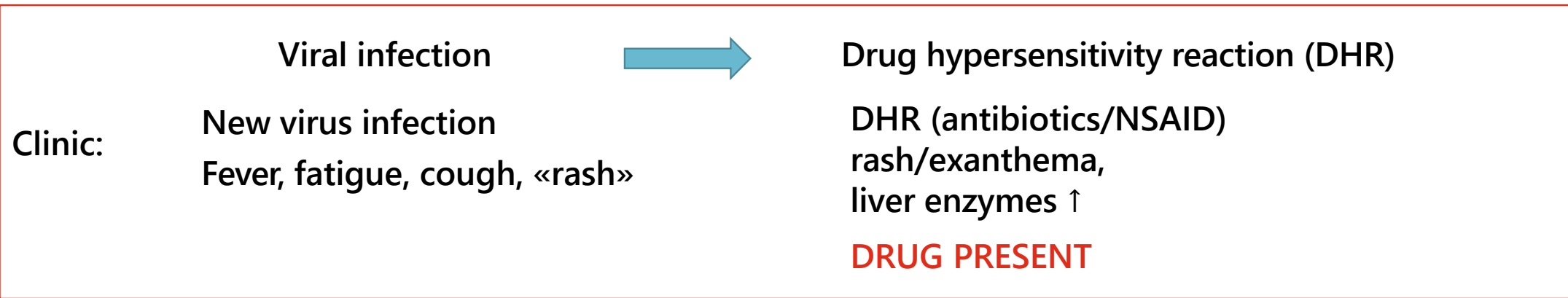


... Chicken or egg?

Viral infections and drug allergies – sequence



Viral infections and drug allergies – sequence

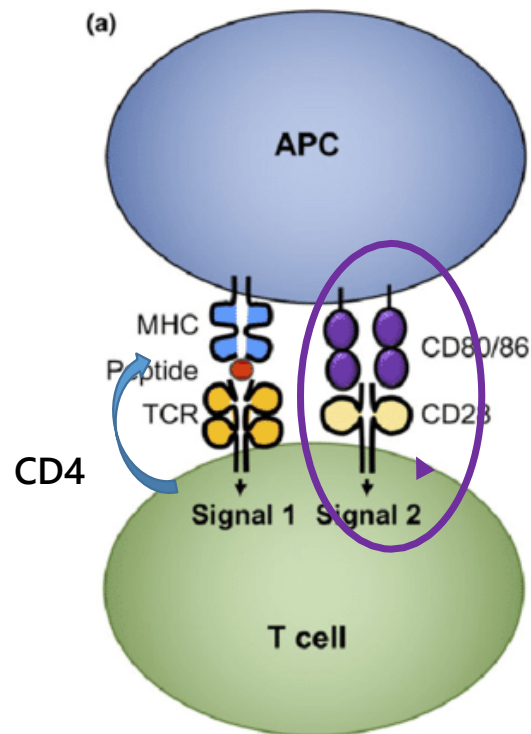


Virus PRIMING for T cell-mediated DHR

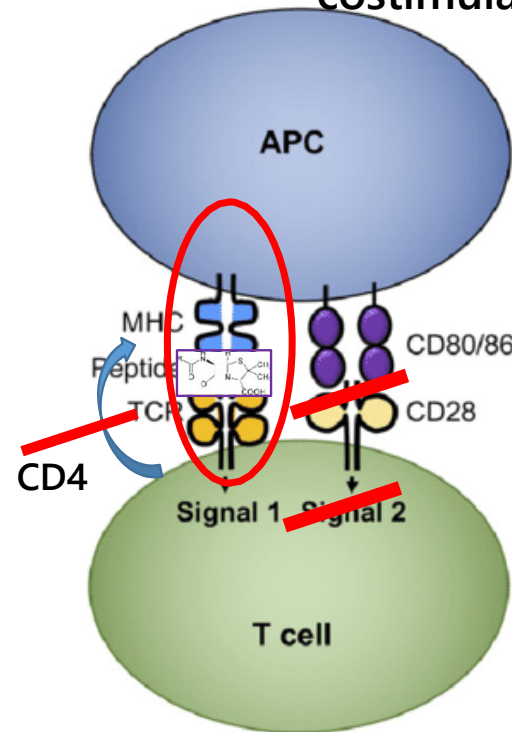
How does that work?

Virus facilitates / primes for T cell-mediated DHR

Peptide & Hapten-Antigen
T cell stimulation antigen & costimulation



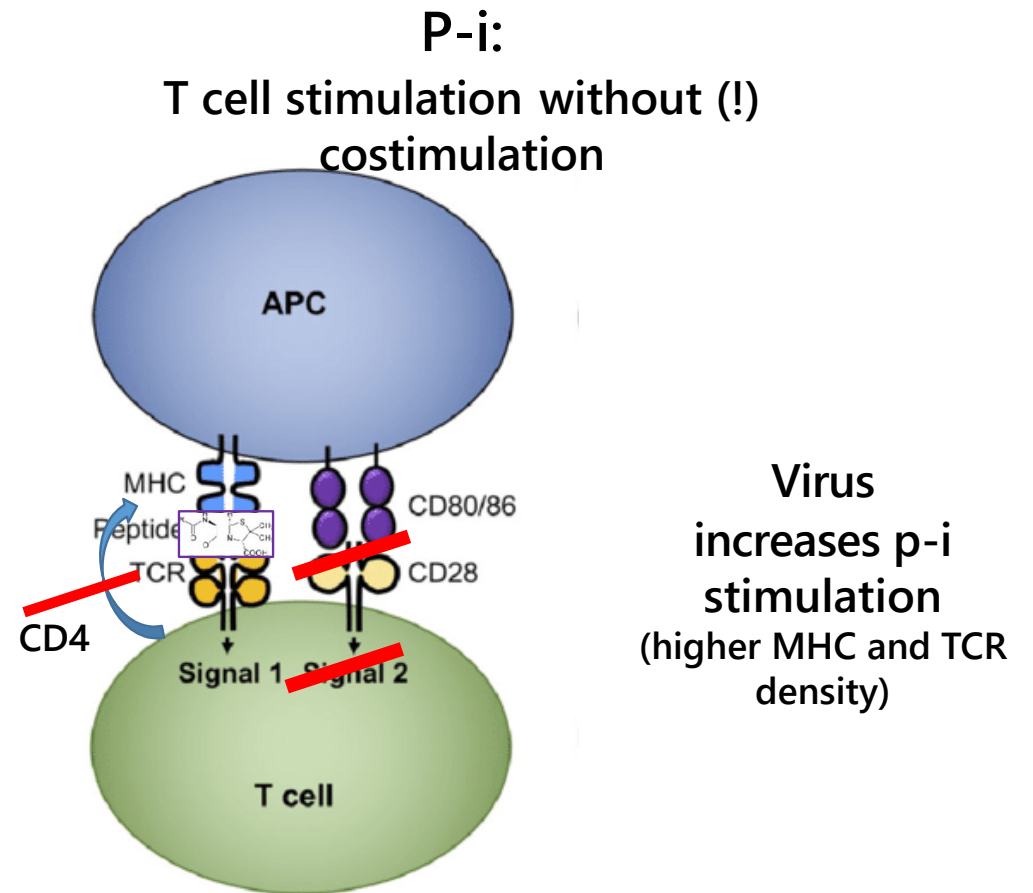
P-i:
T cell stimulation without (!)
costimulation



Virus
increases p-i
stimulation
(higher MHC and TCR
density)

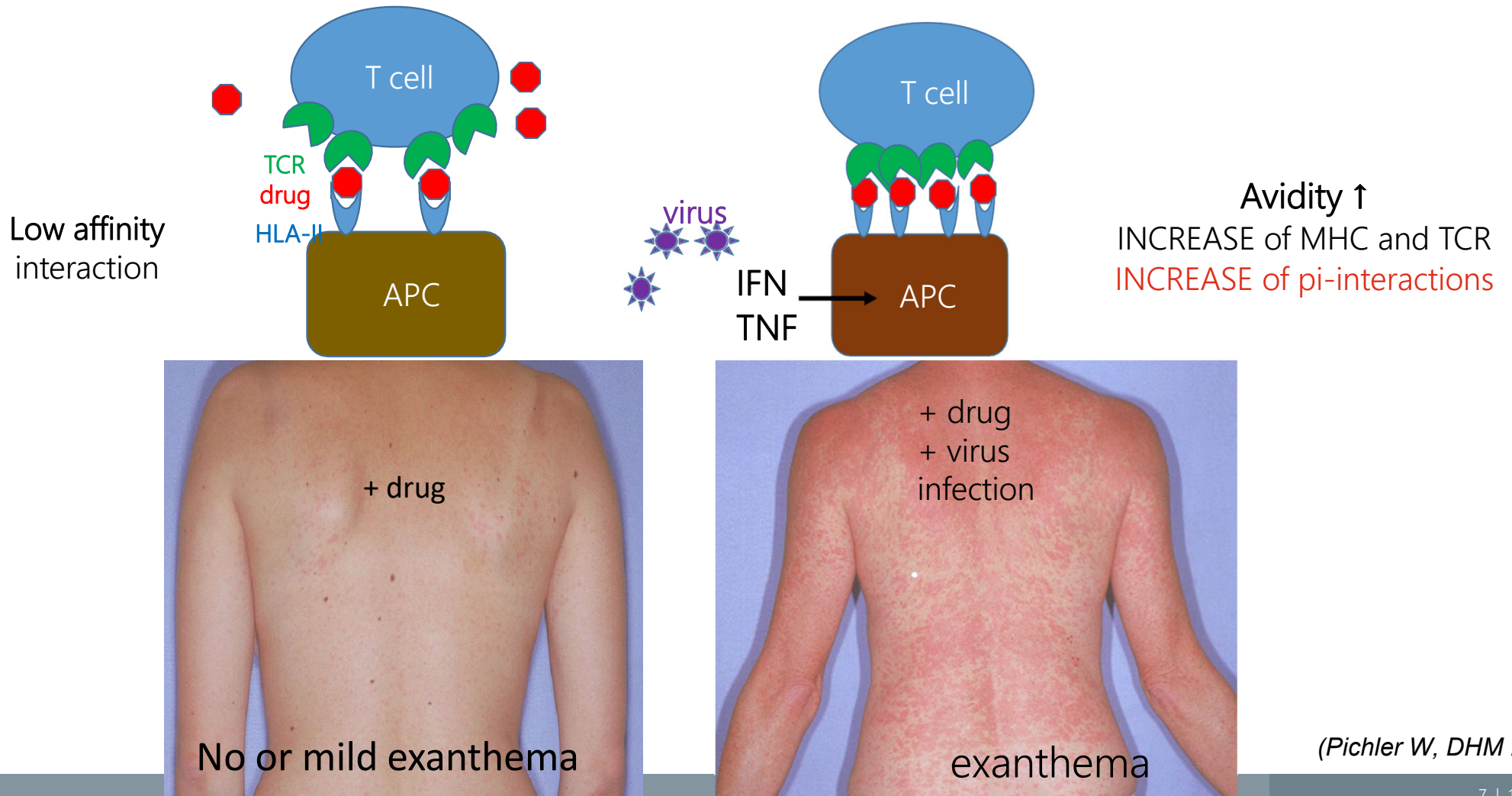
(Pichler W, DH; 2022)

Virus facilitates / primes for T cell-mediated DHR



(Pichler W, DHM 2022)

Virus facilitates / primes for T cell-mediated DHR



(Pichler W, DHM 2022)

Maculopapular drug exanthema

Picornavirus, coronavirus, hMPV, influenza A-B, parainfluenza, RSV

- „viral exanthema“/ drug exanthema?
- Most common in children; adults can also be affected

- **AND: Differential diagnosis challenge maculopapular drug reaction vs. Viral exanthema...**
- **So far: No reliable clinical / histological / serological marker identified to distinguish between them**

(Kaffenberger B et al, JAAD 2017)



Viral infections priming for DHR - examples

EBV
(infectious mononucleosis)

- „Ampicillin rash“; only in ca. 10% sensitization diagnosed
BUT also reported after other antibiotics



Expansion of CD8+ EBV-specific T cells;
Cross-reactivity with drug-reactive T cells

(Shiohara T, Dermat Sin 2013)

Viral infections priming for DHR - examples

HIV

- Up to 100x increased incidence of T cell-mediated DHR, eg, SJS
- Ca. 17x increased incidence of sulfonamide exanthema



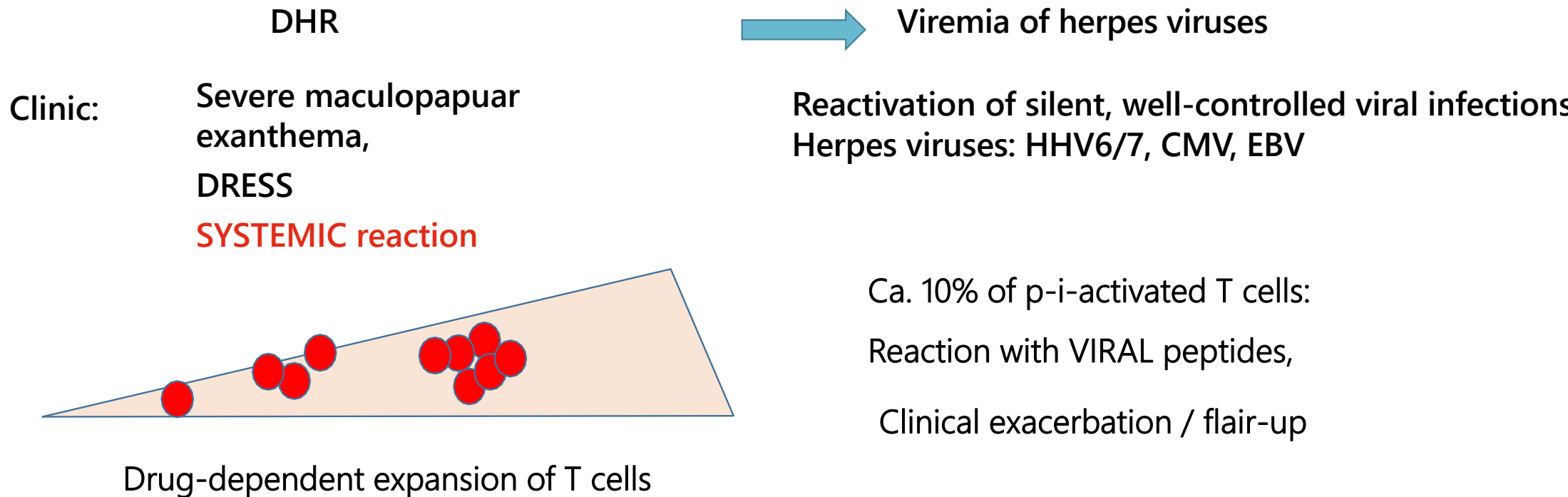
- Against NNRTI, anti-infectious agents (TB, fungal infections, etc.)
- Why this massive increase? MULTIFACTORIAL, not entirely clear; differences between early and advanced infection, Treg depletion, ...

(Angamo MT et al, Clin Pharm Ther 2017; Peter J et al, Curr Opin Allerg 2019)

Viral infections priming for DHR - examples

Picornavirus, coronavirus, hMPV, influenza A-B, parainfluenza, RSV	<ul style="list-style-type: none">• „viral exanthema“/ drug exanthema?• Most common in children; adults can also be affected
EBV (infectious mononucleosis)	<ul style="list-style-type: none">• „Ampicillin rash“; only in ca. 10% sensitization diagnosed BUT also reported after other antibiotics
HIV	<ul style="list-style-type: none">• 100x increased incidence of T cell-mediated DHR, eg, SJS• Ca. 17x increased incidence of sulfonamide exanthema

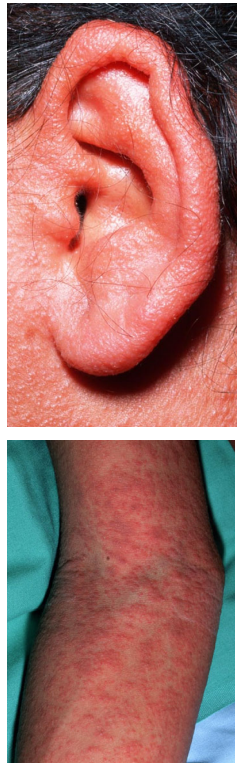
Viral infections and drug allergies – sequence



Drug reaction with eosinophilia and systemic symptoms (DRESS)



Facial edema



Maculopapular exanthema > 50% BSA

DRESS – Diagnosis

Clinical signs / symptoms	Blood values	Signs of organ damage
Fever	Eosinophilia	Liver
Maculopapular exanthema > 50% BSA	Atypical lymphocytes	Kidney
Facial edema		Heart
Lymphadenopathy		GI tract
		„Other“: SNC/PNC, pancreas, lung

+ exclusion of other causes
(depending on organ involvement)

(RegiSCAR diagnostic criteria)



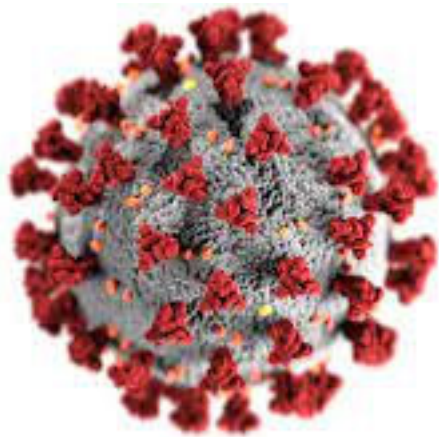
A maculopapular rash developing >3 weeks after drug initiation
Clinical symptoms continuing >2 weeks after stopping therapy
Fever >38°C
Liver abnormalities (ALT>100 IU/L) or other organ involvement
Haematological abnormalities:
Leucocytosis (>11*10 ⁹ /L)
Atypical lymphocytes (>5%)
Eosinophilia (>1.5*10 ⁹ /L)
Lymphadenopathy
HHV-6 reactivation
Total score: 7=Typical DRESS; 5=Atypical DRESS; <5=consider other diagnosis.

Japanese SCAR Diagnostic criteria

DRESS and viral reactivation – relevance for the clinic?

- More severe disease course (partly conflicting evidence), flair-ups / relapses
- Antiviral treatment (ganciclovir/valganciclovir) in the case of very high CMV viral load in blood
- Impact on diagnostic assessment of culprit drugs? No evidence supporting this

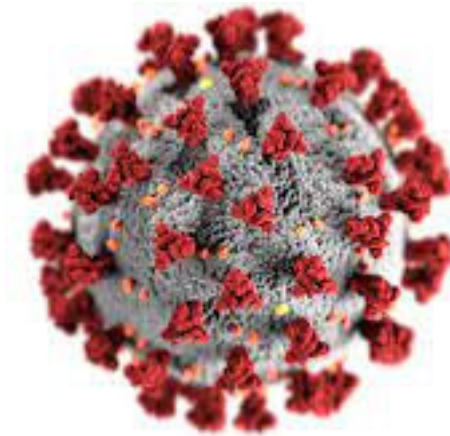
There is no way around it (yet)...



"You're not allowed to use
the sprinkler system to keep
your audience awake."

SARS-CoV2 and drug hypersensitivity reactions

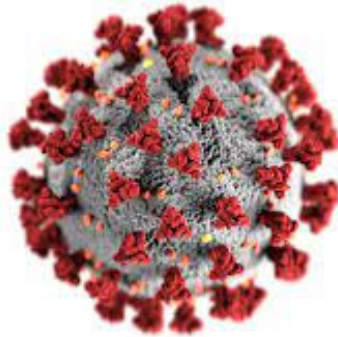
Interplay between
SARS-CoV2 and DHR



DHR following SARS-CoV2
mRNA vaccination

DHR against medications used
to treat SARS-CoV2

Interplay SARS-CoV2 and drug hypersensitivity reactions

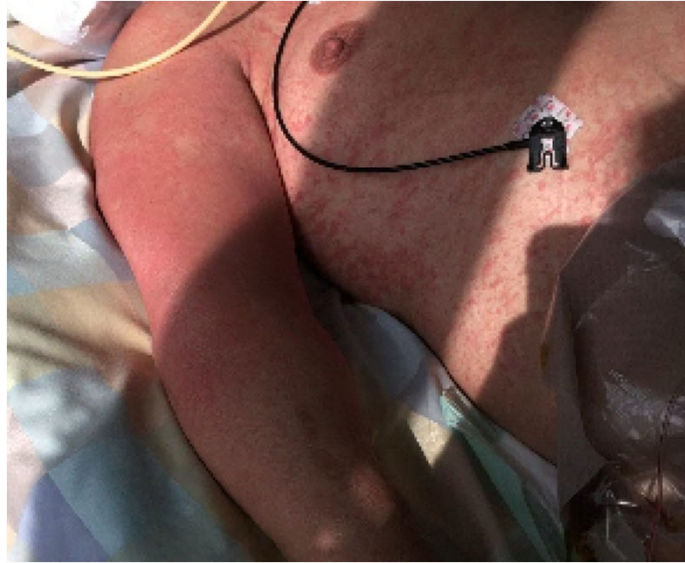


Does COVID-19 impact the course / development of DHR?

Maculopapular exanthema associated with high eosinophilia



APHP Paris



University Hospital Zurich



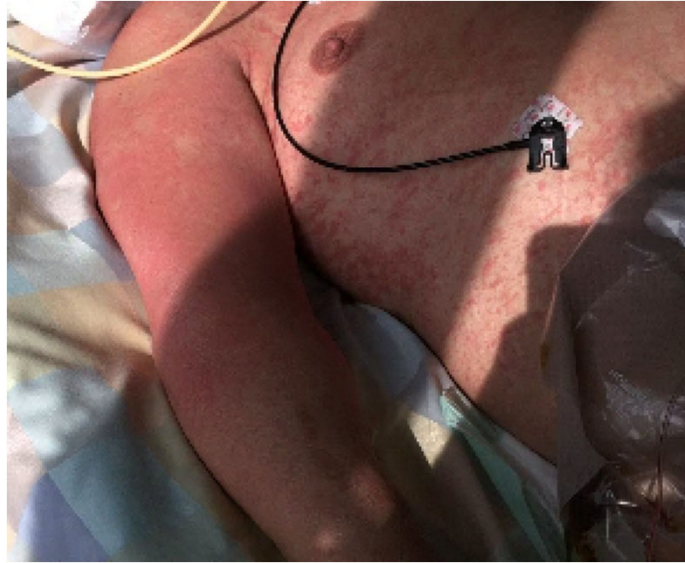
University Hospital Milano

01 - 07/2020: n=18

Maculopapular exanthema associated with high eosinophilia



APHP Paris



University Hospital Zurich



University Hospital Milano

01 - 07/2020: n=18

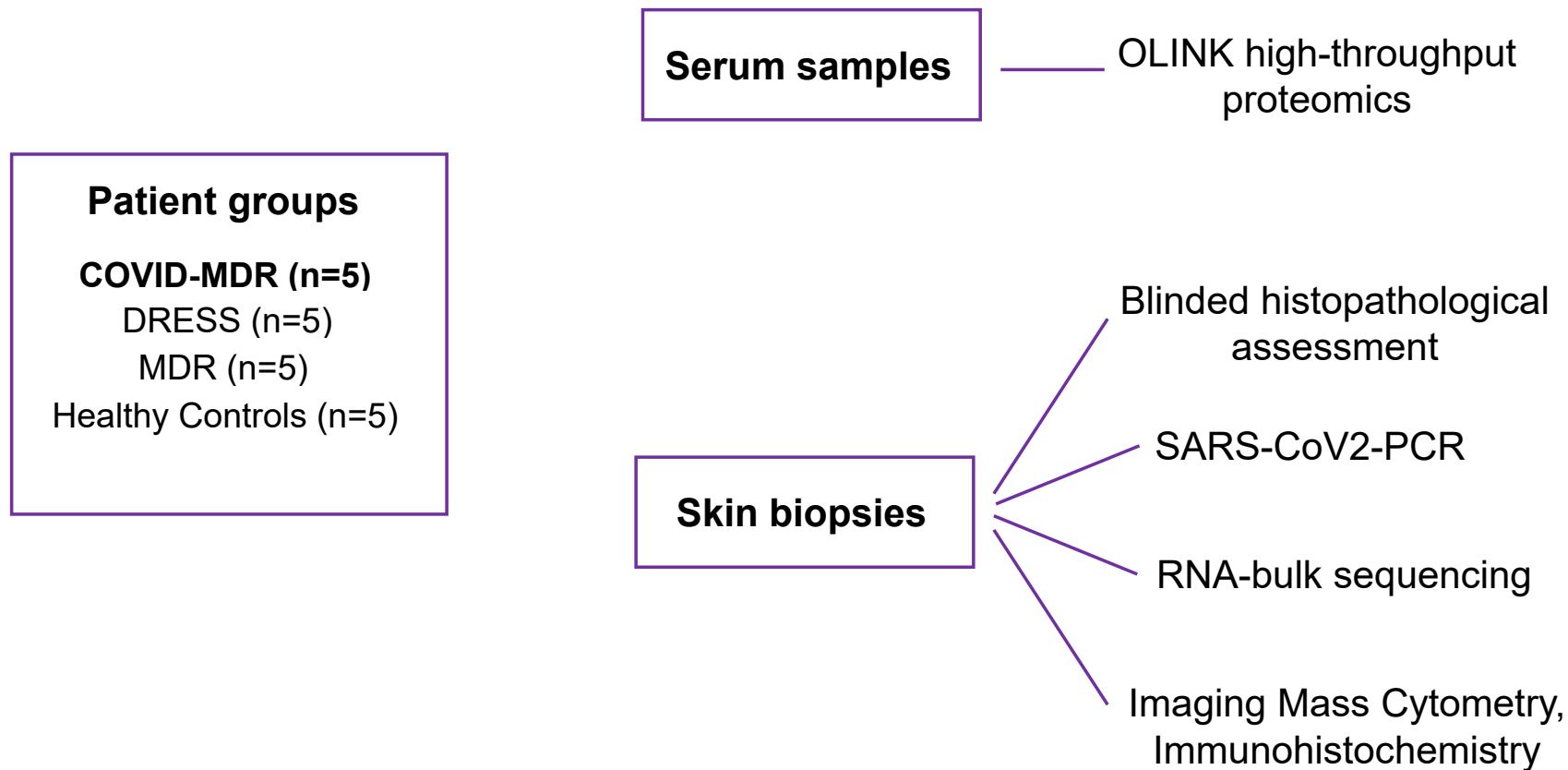
MPE associated with high eosinophilia in COVID-19 patients

MDR and COVID-19 characteristics	
COVID features	Very severe disease course (ICU), At time of onset: PCR not positive anymore
Clinical presentation	Maculopapula exanthema BSA affected: 50-80% Prominent eosinophilia (2.3 – 4.5 G/L)
Culprit drugs	Proton pump inhibitors: n=7 Antibiotics*: n=11
Mean time of onset	7 days (range: 5-30)
Treatment	Topical GCS (class III-IV): n=12 Systemic GCS (80mg daily): n=6
Time of resolution	Mean: 13 days (range: 6-18)

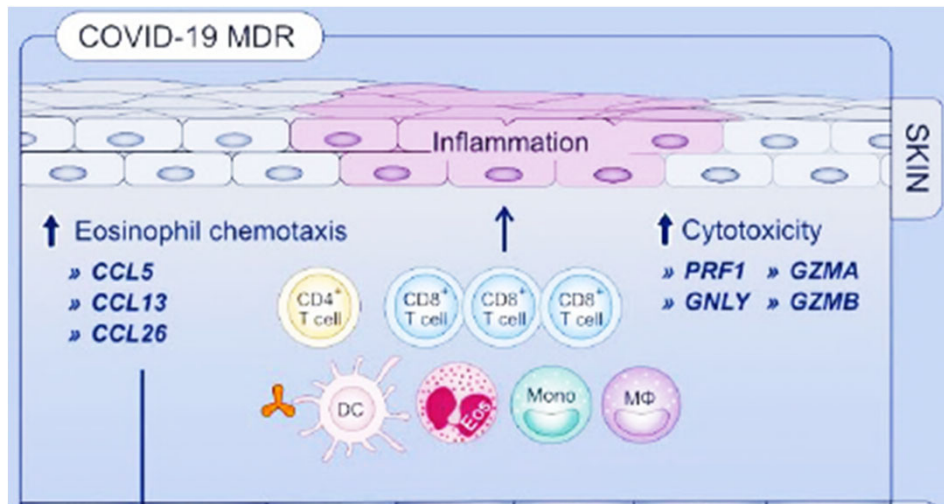
Does a severe course of COVID-19 favor the development of MDR?

And if so, is does Sars-CoV2 contribute to this directly or indirectly?

Study Design



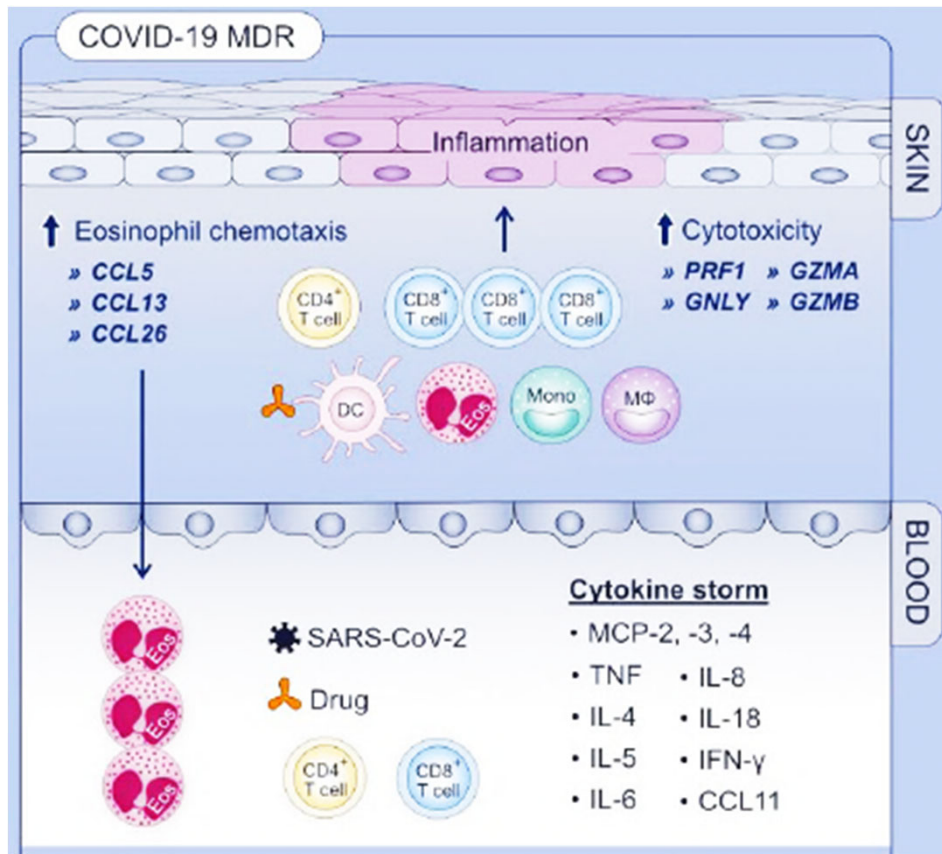
Summary: COVID-19 might indirectly favor COVID-MDR



- Highly cytotoxic CD8⁺ T cells, hyperactivated macrophages
- NO SARS-CoV2 in the skin!

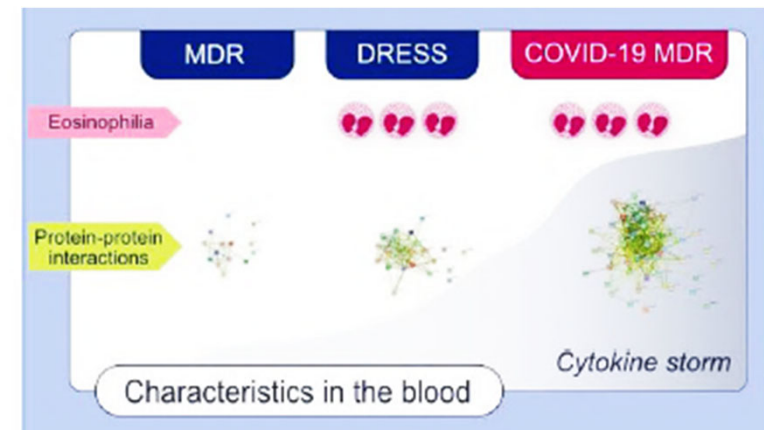
(Mitamura Y and Schulz D,Brüggen MC, Allergy 2021)

Summary: COVID-19 might indirectly favor COVID-MDR

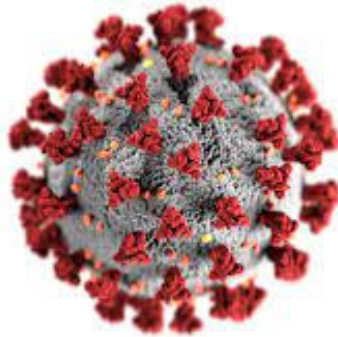


- Highly cytotoxic CD8⁺ T cells, hyperactivated macrophages
- NO SARS-CoV2 in the skin!

- **MASSIVE cytokine storm**
- High eosinophilia



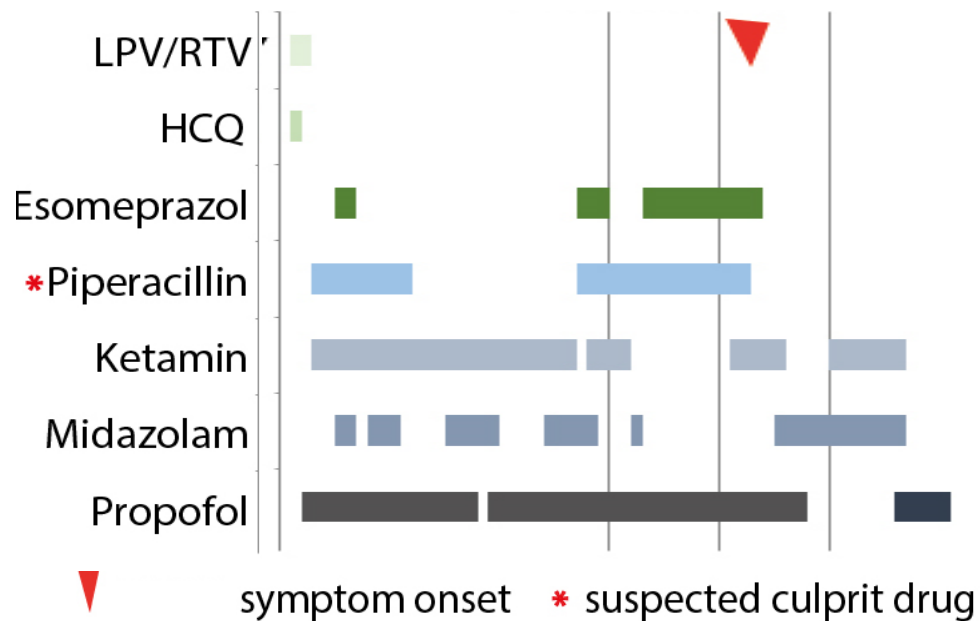
(Mitamura Y and Schulz D,Brüggen MC, Allergy 2021)



What about DRESS?

Case 1: Consult on the intensive care unit in May 2020

- 54 year-old female, intubated COVID-19 patient
- New-onset maculopapular exanthema, lymphadenopathy, facial swelling and fever

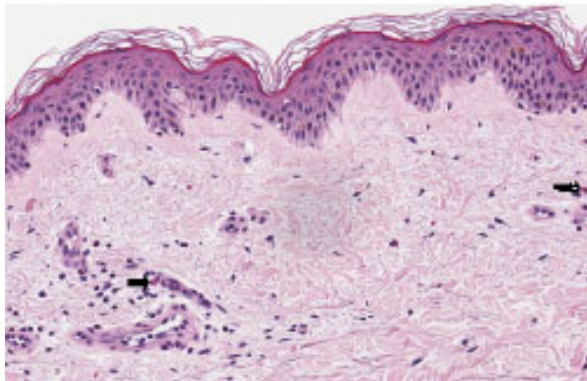


Case 1: Consult on the intensive care unit in May 2020

- COVID-19 diagnosis 42 days earlier; very severe disease course:
ARDS (intubated for 32 days), lung embolia and multiple venous thromboses
Treatment: lopinavir/ritonavir, hydroxychloroquine
- Pre-existing type II, diabetes no history of drug reactions

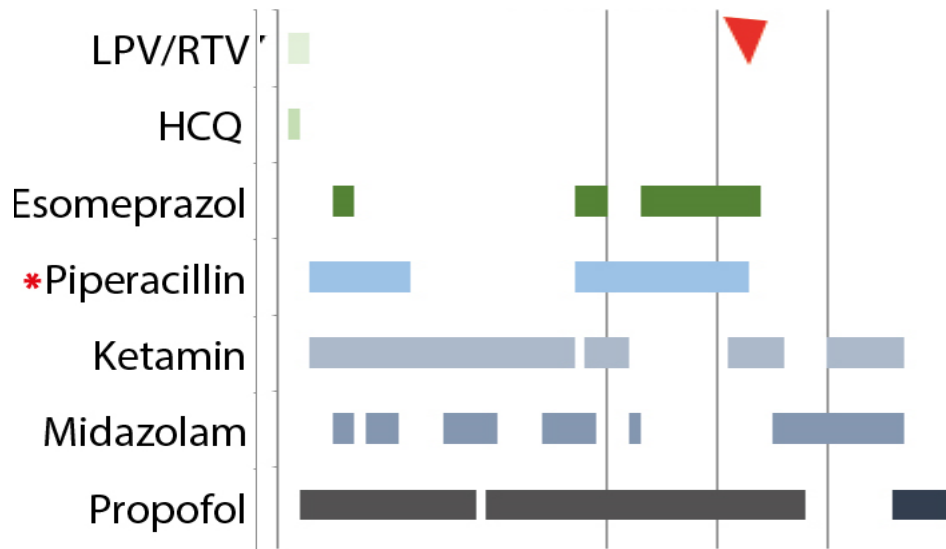
Case 1: DRESS in a COVID-19 patient

- Blood count: Eosinophilia (1.8 G/L), no atypical lymphocytes
- Laboratory:
 - 14xN increase of liver enzymes (ASAT/ALAT); 8xN increase of myoglobin
 - Viral PCR (HHV6, CMV, EBV, HSV1/2) negative
- Dermatohistopathology: compatible with DRESS



- RegiSCAR DRESS score: 7

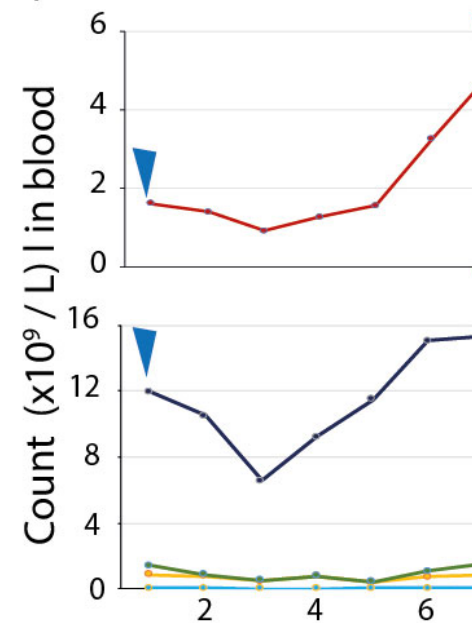
COVID-19 und GCS-refraktäres DRESS



▼ DRESS symptom onset * suspected culprit drug

— Eosinophils — Neutrophils — Lymphocytes — Basophils — Monocytes

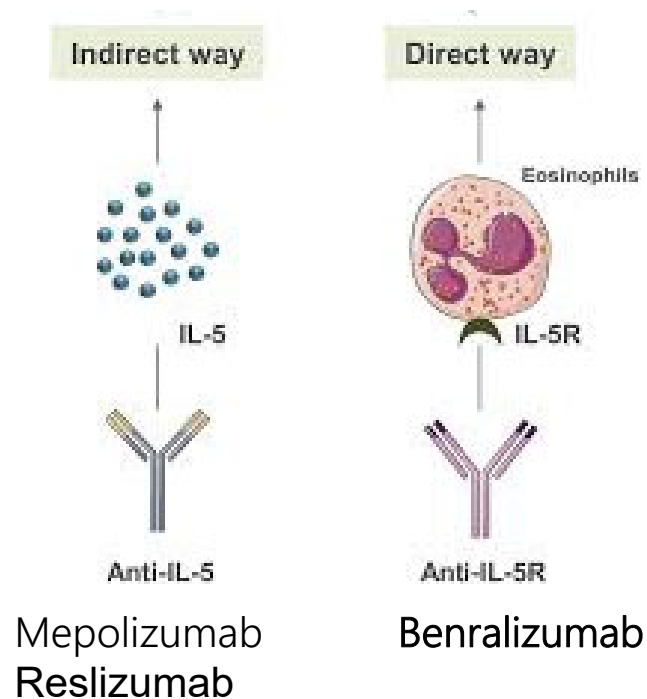
Normal: <0.7 (x10⁹/L)



No clinical response, eosinophils raising

▼ Methylprednisolone (125mg 4 days, then 70mg 3 days; intravenously)

Inhibition der IL-5 Achse



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Glucocorticoid–Sparing Effect of Benralizumab in Severe Asthma

Parameswaran Nair, M.D., Ph.D., Sally Wenzel, M.D., Klaus F. Rabe, M.D., Ph.D., Arnaud Bourdin, M.D., Ph.D., Njira L. Lugogo, M.D., Piotr Kuna, M.D., Ph.D., Peter Barker, Ph.D., Stephanie Sproule, M.Math., Sandhia Ponnarambil, M.D., and Mitchell Goldman, M.D., for the ZONDA Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

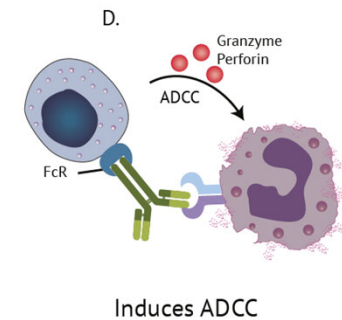
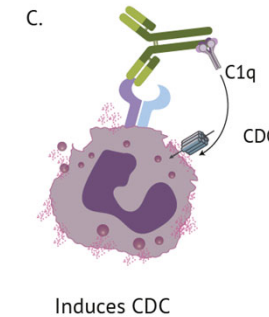
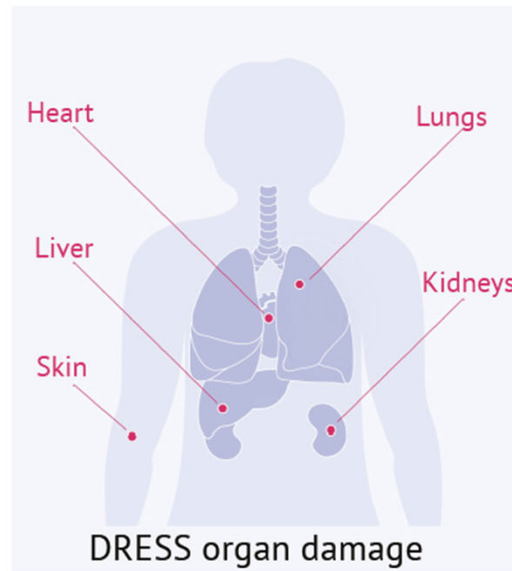
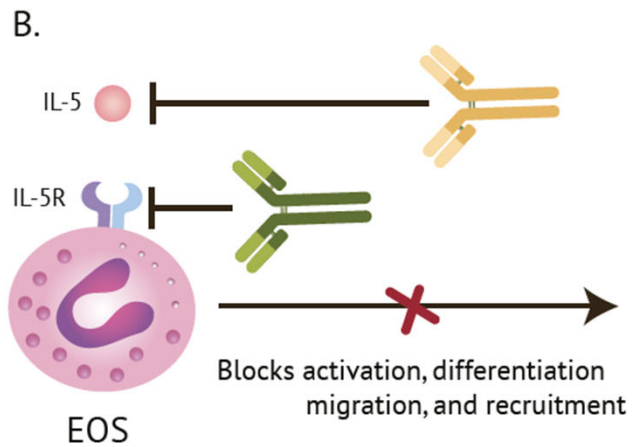
ORIGINAL ARTICLE

Benralizumab for *PDGFRA*-Negative Hypereosinophilic Syndrome

F.L. Kuang, F. Legrand, M. Makiya, J.A. Ware, L. Wetzler, T. Brown, T. Magee, B. Piligian, P. Yoon, J.H. Ellis, X. Sun, S.R. Panch, A. Powers, H. Alao, S. Kumar, M. Quezado, L. Yan, N. Lee, R. Kolbeck, P. Newbold, M. Goldman, M.P. Fay, P. Khoury, I. Maric, and A.D. Klion

(Matucci A et al, Resp Med 11/2019)

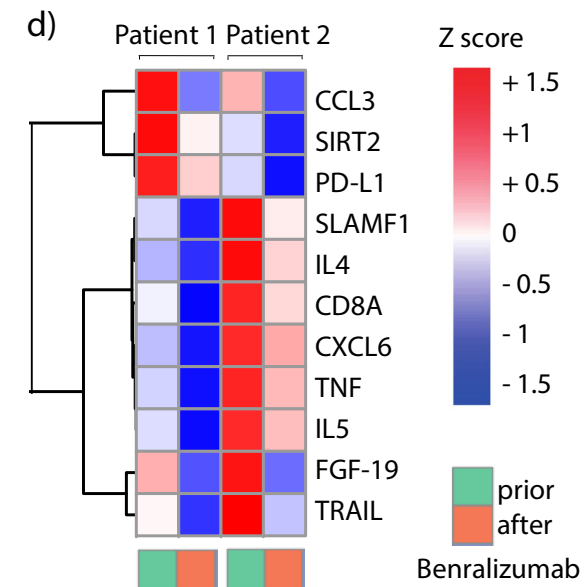
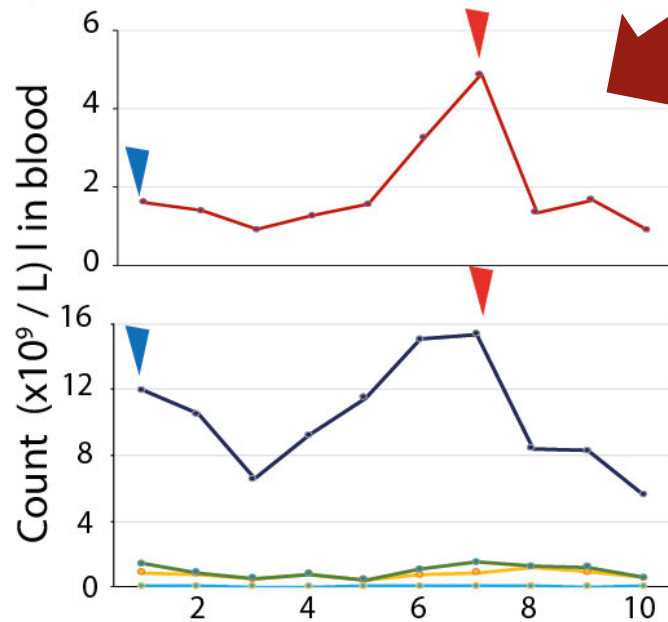
Inhibition of the IL-5 / IL-5R axis in DRESS



(Maverakis E, Xiu A, Brüggemann MC; Allergy 2022)

GCS-refractory DRESS in a COVID-19 patient with severe disease course

And clinical response



(Schmid-Grendelmeier P, Lang C, ... Brüggemann MC, JACI Practice 2021)

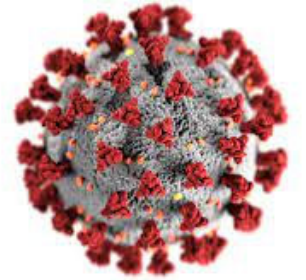
— Eosinophils — Neutrophils — Lymphocytes — Basophils — Monocytes

Normal: <0.7 (x10⁹/L) 1.4-8.0 1.5-4.0 <0.15 0.16-0.95

▼ Benralizumab (1x 30mg; subcutaneously)

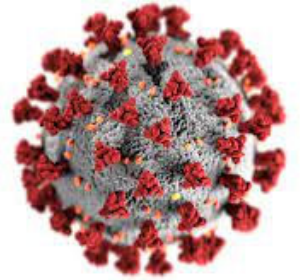
▼ Methylprednisolone (125mg 4 days, then 70mg 3 days; intravenously)

Conclusions so far



- A severe COVID-19 disease course might via the associated cytokine storm indirectly impact and favor the development of DHR
- This might result in a more severe DRESS phenotype and possibly impact the responsiveness of DRESS to systemic glucocorticoids

Take-aways for the Clinics: COVID-19 and drug allergies



- Careful monitoring of DRESS cases in patients with (severe) COVID-19
- Monoclonal antibodies against IL5 / IL5R a possibility in steroid-refractory DRESS

Many open questions...

- Is this phenomenon related to certain SARS-CoV2 strains?

What will come next?

Viruses and drug allergies...



Many more discoveries ahead!

Thank you very much for your attention!



Charlotte Brüggen: marie-charlotte.brueggen@usz.ch