Neues in der Therapie der CED

GOETHE UNIVERSITÄT FRANKFURT AM MAIN

AGAPLESION MARKUS KRANKENHAUS

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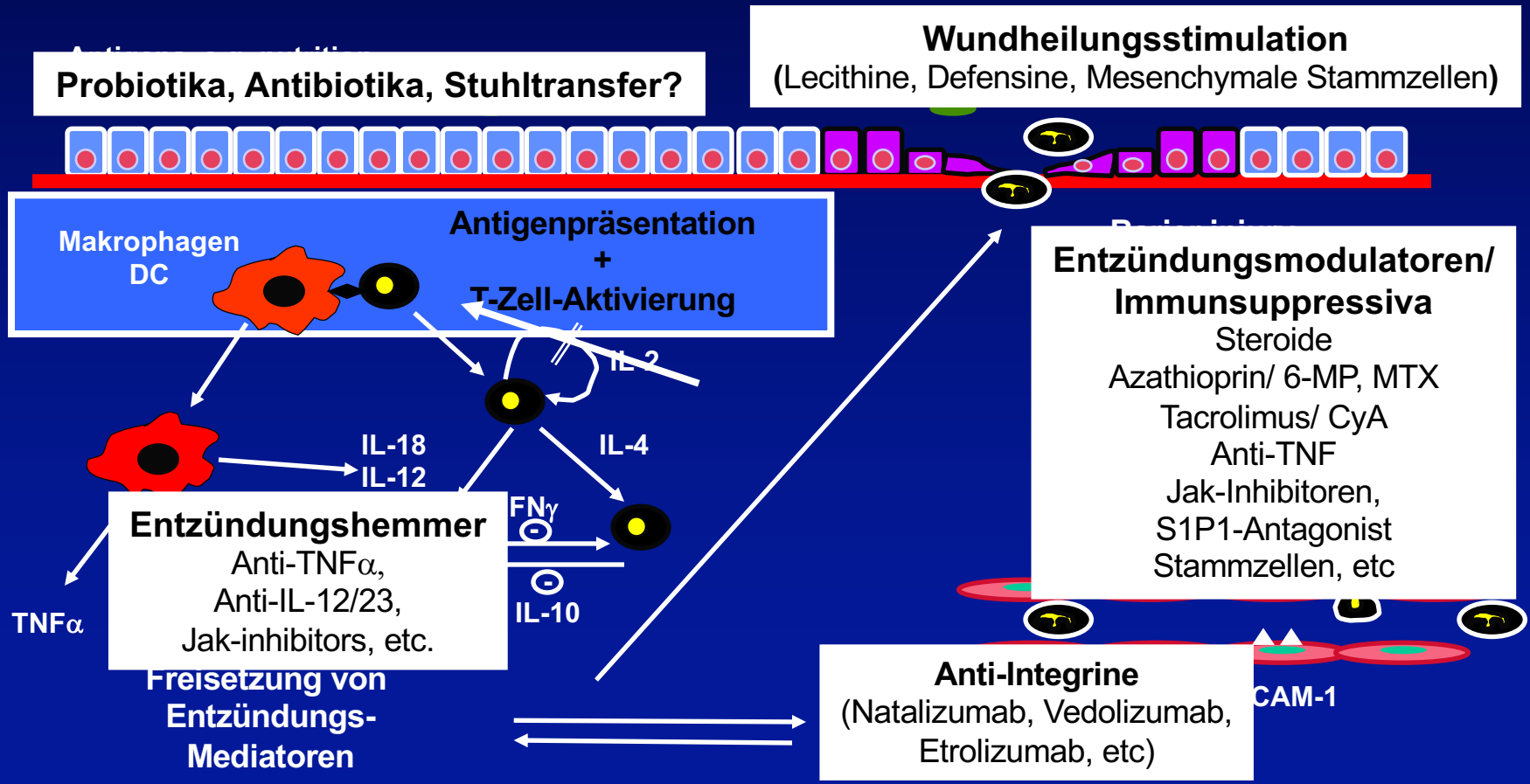
Therapieprinzipien bei CED



Medikamentöse Standardtherapie der CED

Probiotika
E. coli Nissle

Aminosalizylate
Mesalazin
Sulfasalazin
Olsalazin

Steroide
Prednisolon
Methylprednison
Budesonid
Hydrocortison
Beclomethason
u.a.

Supportiva
Loperamid
Ballaststoffe
Cholestyramin
Spasmolytika
Analgetika
Vitamine

Biologika
Infliximab
Adalimumab
Golimumab
Vedolizumab
Ustekinumab

Immunmodulatoren
Azathioprin/6-MP
MTX
Tacrolimus/Cyclosporin
Tofacitinib

Antibiotika
Ciprofloxacin
Metronidazol

Ernährung
parenteral
enteral

Chirurgie bei CED
z. B. bei narbigen Stenosen, Dysplasien/ Neoplasien, refraktäre Verläufe, Abszesse, lokalisierter Befall bei MC, Therapienebenwirkungen

Gomollon F, Dignass A et al. Journal of Crohn's and Colitis 2016,; Harbord M,..,Dignass A et al. J Crohns Colitis. 2017
Preiß J et al. Z Gastroenterol 2014; Kuckarzik T & Dignass A et al. Z Gastroenterol 2020

Warum wird der gewünschte Therapieerfolg nicht bei allen Patienten erreicht?

- Variabler Verlauf der CED
- Unzureichende Vorhersage des Erkrankungsverlaufes und Therapierfolges
- Diagnose und Behandlungsbeginn erfolgen häufig zu spät
- Therapien werden nicht optimal eingesetzt und adaptiert
- Neue Therapien benötigt

Mesenchymale Stammzellen
Darvadostrocel

Aminosalizylate
Neue Mesalazin-Galeniken
(MMX, Optocore, Granulate)

Steroide
Budesonid MMX

Immunmodulatoren
Jak-Hemmer
Filgotinib
Upadacitinib
etc
s1P1-Hemmer
Ozanimod
Etrasimod

Neue Therapieansätze der CED

Biologika
Biosimilars
IL-23-Blocker
Guselkumab
Risankizumab
Mirikizumab
Adhäsions-Blocker
Etrolizumab

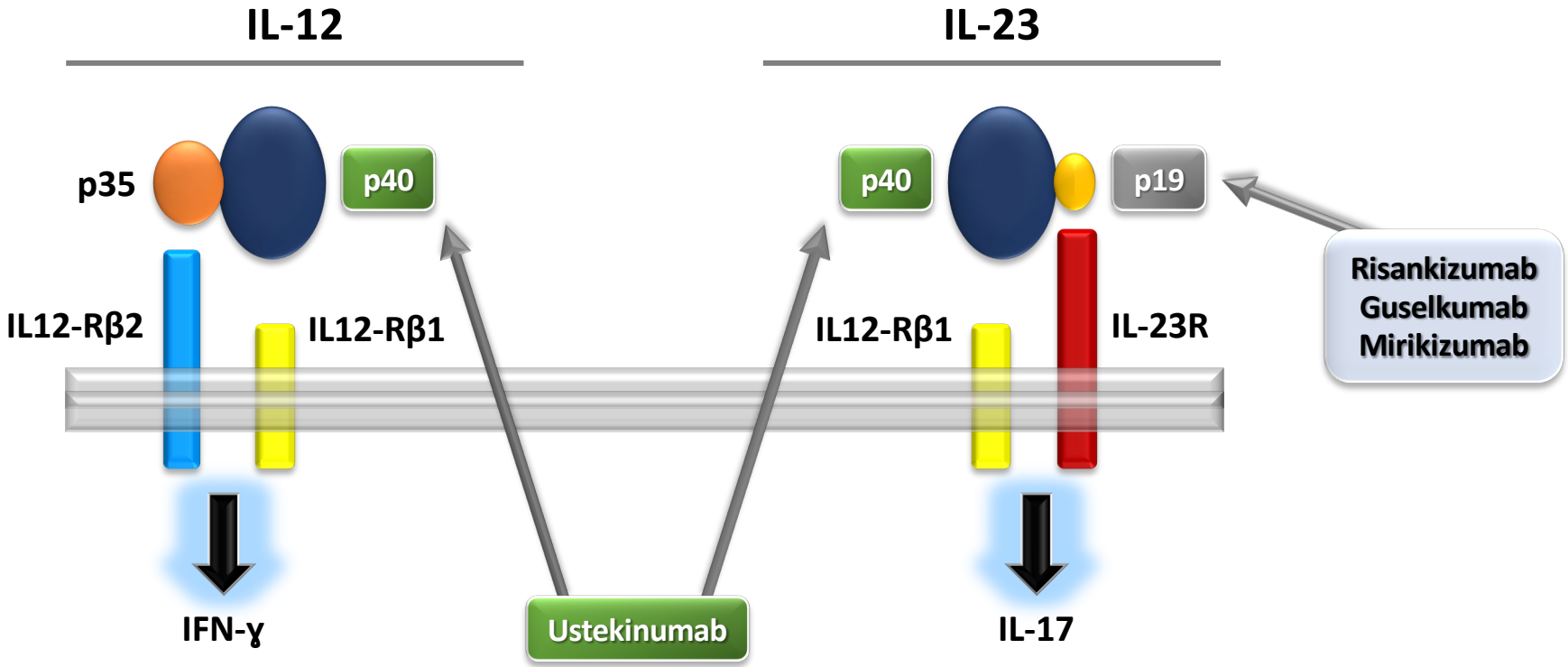
Probiotika
?
Mikrobiomtransfer

Ernährung
Levine Konzept
Ausschlußdiät + enterale Formeldiät

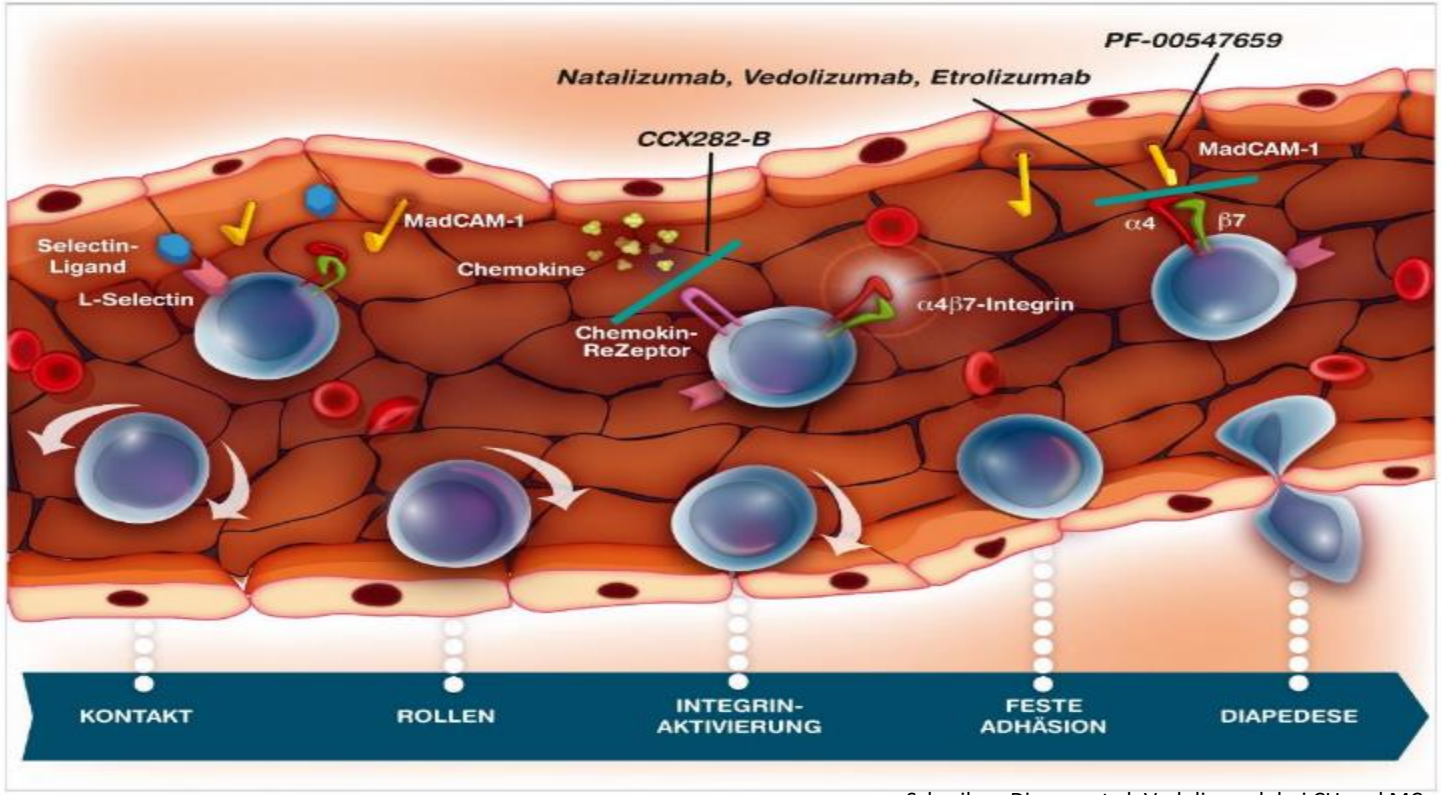
TNFα-Blocker

- Infliximab
  - Intravenös
  - Subkutan
  - Biosimilars
- Adalimumab
  - Subkutan
  - Biosimilars
- Golimumab

IL-12 und IL-23 bei CED



Adhäsionsblockade: Innovatives Wirkprinzip der Entzündungshemmung bei CED



Vedolizumab

Etrolizumab?

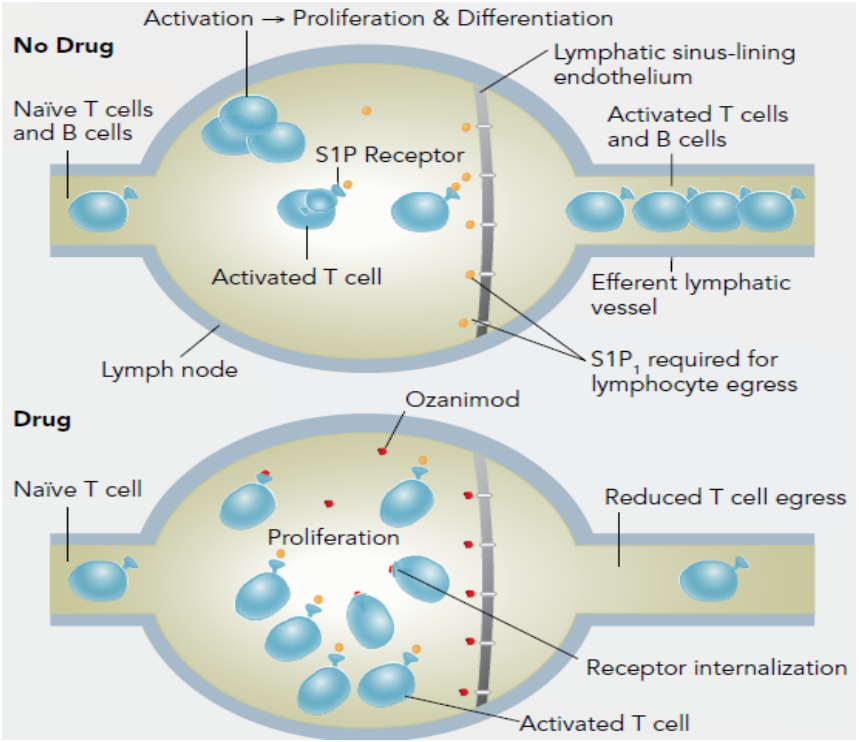
Schreiber, Dignass et al: Vedolizumab bei CU und MC – eine Standortbestimmung; ZfG 2014

Modulation der Lymphozyten-Migration durch Sphingosin-1-Phosphat (S1P)-Rezeptor Agonisten

Agonisten des S1P1 Rezeptor:

- Vermindern Lymphozytenmigration aus Lymphgewebe

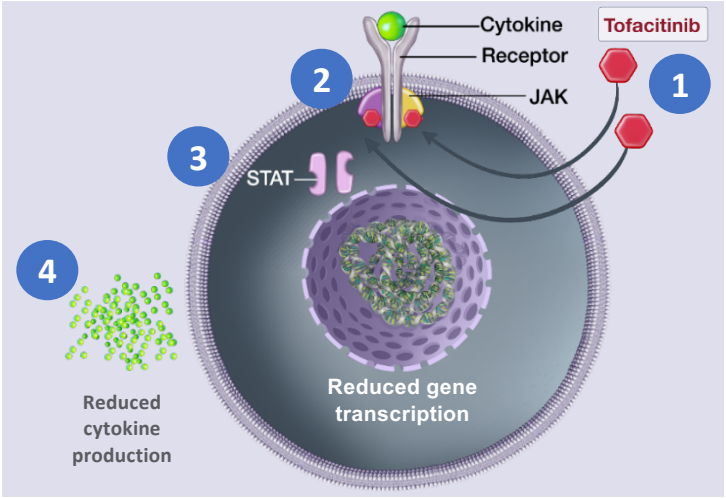
- Ozanimod
- Etrasimod
- weitere



Adapted from Horga A and Montalban X. *Expert Rev Neurother* 2008; 8(5):699–714.;Degagne E, Saba JD. *Clin Exp Gastroenterol* 2014;7:205–214; Gonzalez-Cabrera PJ, et al. *F1000Prime Rep* 2014;6:109.

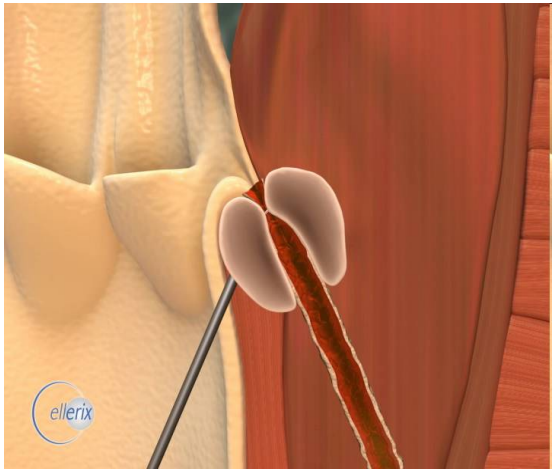
JAK Inhibitoren are oral, small-molecules that reduces cytokine signalling and production

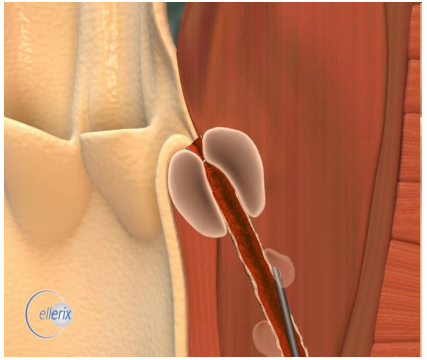
- Kleine Moleküle
- Reduzieren entzündungsfördernde Botenstoffe und Entzündungsvorgänge
- Tofacitinib zugelassen bei CU
- Filgotinib
- Upadacitinib

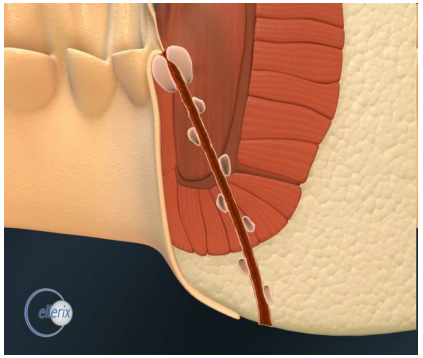


1. Hodge JA, et al. *Clin Exp Rheumatol*. 2016;34:318-328. 2. Clark JD, et al. *J Med Chem*. 2014;57:5023-5038.
3. Danese S, et al. *Am J Physiol Gastrointest Liver Physiol*. 2016;310:G155-162..

Fistelheilung durch mesenchymale Stammzelltransplantation







Long-term Efficacy and Safety of Stem Cell Therapy (Cx601) for Complex Perianal Fistulas in Patients With Crohn's Disease

Julián Panés,[1] Damián García-Olmo,[2] Gert Van Assche,[3] Jean Frederic Colombel,[4] Walter Reinisch,[5,6] Daniel C. Baumgart,[7] Axel Dignass,[8] Maria Nachury,[9] Marc Ferrante,[3] Lili Kazemi-Shirazi,[5] Jean C. Grimaud,[10] Fernando de la Portilla,[11] Eran Goldin,[12] Marie Paule Richard,[13] Mary Carmen Diez,[13] Ignacio Tagarro,[13] Anne Leselbaum,[13,14] and Silvio Danese,[15] for the ADMIRE CD Study Group Collaborators

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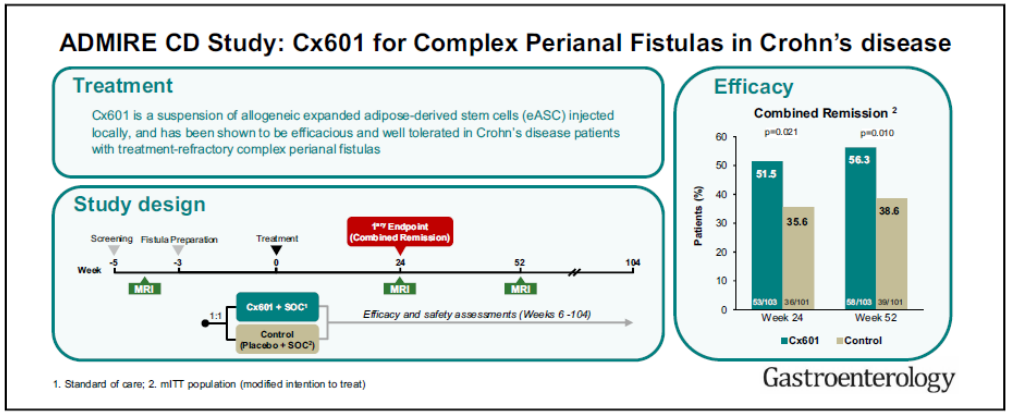
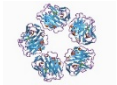


Evolution der Therapieziele – Haben wir das richtige Therapieziel und Untersuchungsmethode?

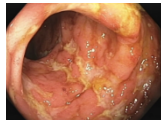
CDAI
Mayo Score

CRP

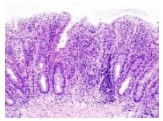


Calpro

Mayo-Score
SES-CD



Histologie



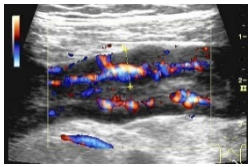
Klinische Remission

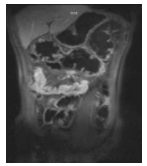
Biochemische Remission

Endoskopische Remission

**Histologische/
Transmurale Remission**

**PRO
+
CRP
+
Calpro
+
Endoskopie**





**IUS
MRI**

Zeitabhängige Erreichung von Therapiezielen bei M. Crohn - IOIBD

CD	Clinical response	Clinical remission	Norm of CRP/ESR	Decrease of fCal	EH
Oral steroids/EEN	2	4	5	8	13
Budesonide	3	6	8	10	15
Thiopurines	11	15	15	17	24
Methotrexate	9	14	14	15	24
Anti-TNF	2-4	4-6	9	11	17
Vedolizumab	11	17	15	17	24
Ustekinumab	7	13	11	14	19

Time in weeks

Turner D,… Dignass A, Gastroenterology. 2020 Dec 21 [Epub ahead of print].

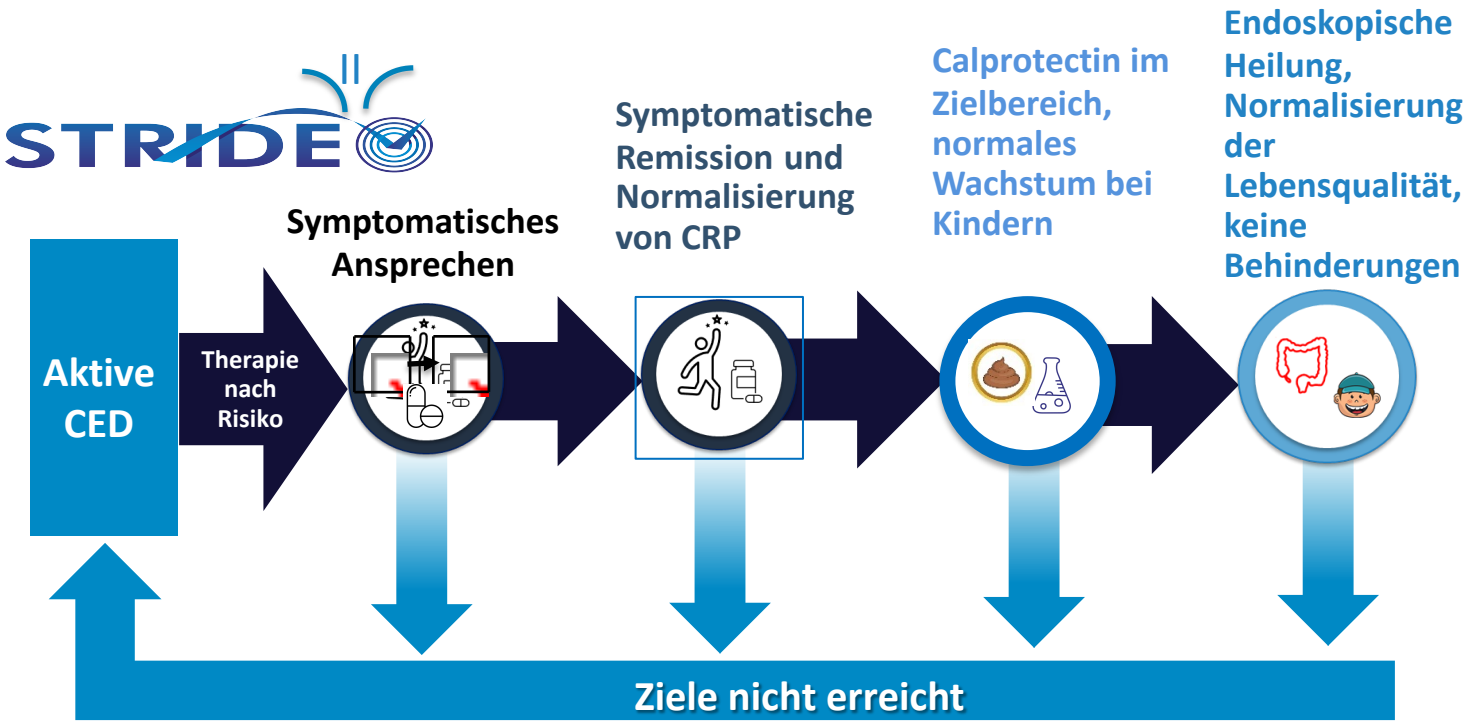
Zeitabhängige Erreichung von Therapiezielen bei Colitis ulcerosa - IOIBD

UC	Clinical response	Clinical remission	Norm of CRP/ESR	Decrease of fCal	EH
Oral 5-ASA	4	8	8	10	13
Systemic steroids	2	2	5	8	11
Locally active steroids	3	8	8	9	13
Thiopurines	11	15	15	15	20
Adalimumab	6	11	10	12	14
Infliximab	5	10	9	11	13
Vedolizumab	9	14	14	15	18
Tofacitinib	6	11	9	11	14

Time in weeks

Turner D,… Dignass A, Gastroenterology. 2020 Dec 21 [Epub ahead of print].

Stride-2: Behandlungsziele bei CED



Turner D,…Dignass A, Gastroenterology 2020

Chronisch entzündliche Darmerkrankungen: Neue Therapiemöglichkeiten

- Grosses Spektrum therapeutischer Möglichkeiten
- Verbesserung der Therapie durch:
  - optimale Anwendung der Medikamente
  - Neue Therapiestrategien (früher, Therapiekontrollen und -anpassungen, etc)
  - Neue Medikamente

Aktuelle Studien

- Filgotinib
- Upadacitinib

- Risankizumab
- Guselkumab
- Ustekinumab

- Ozanimod
- Etrasimod

- Etrolizumab
- Liposomales CyA

COVID-19 Impfung bei CED

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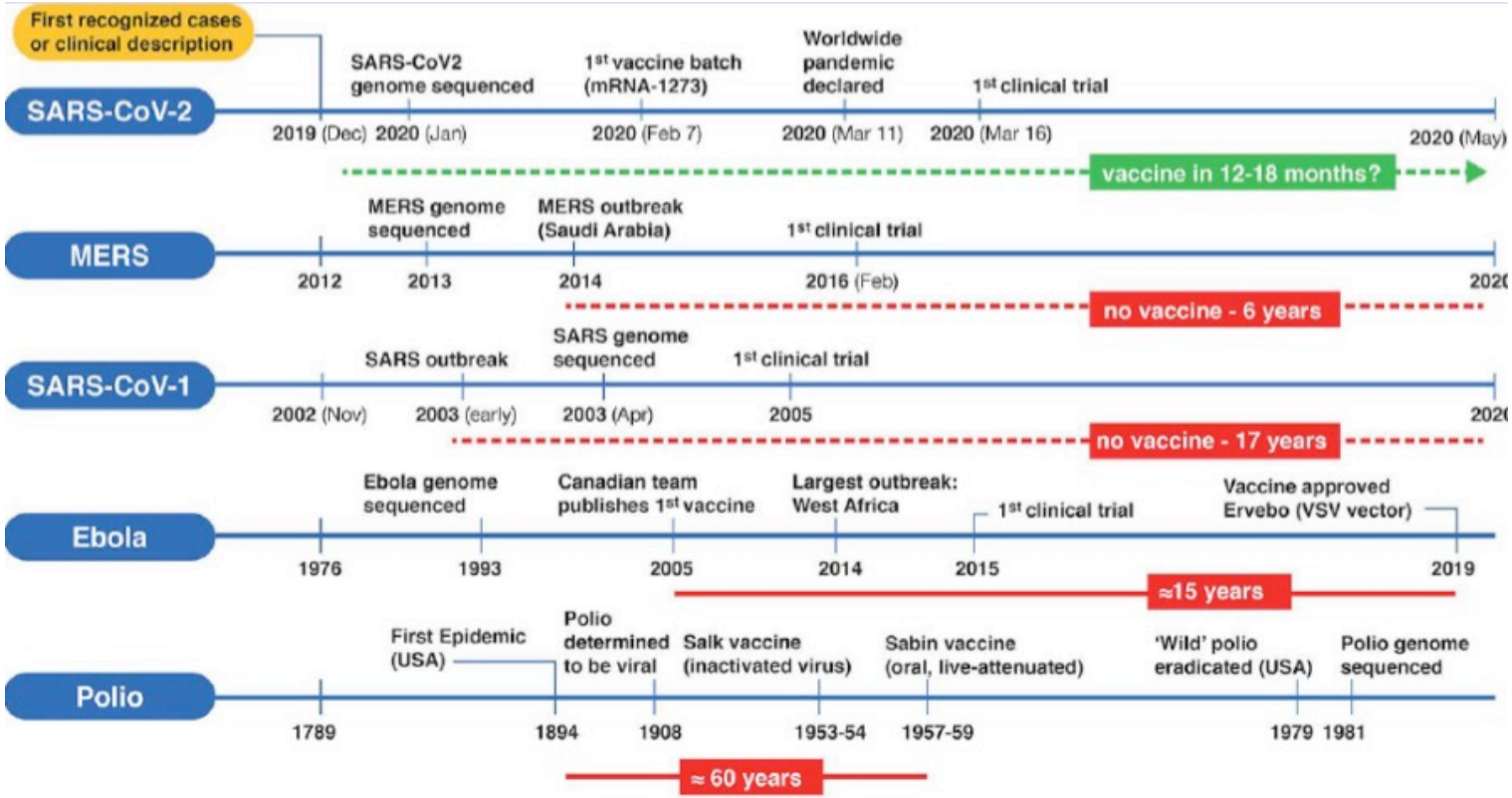
GOETHE UNIVERSITÄT FRANKFURT AM MAIN

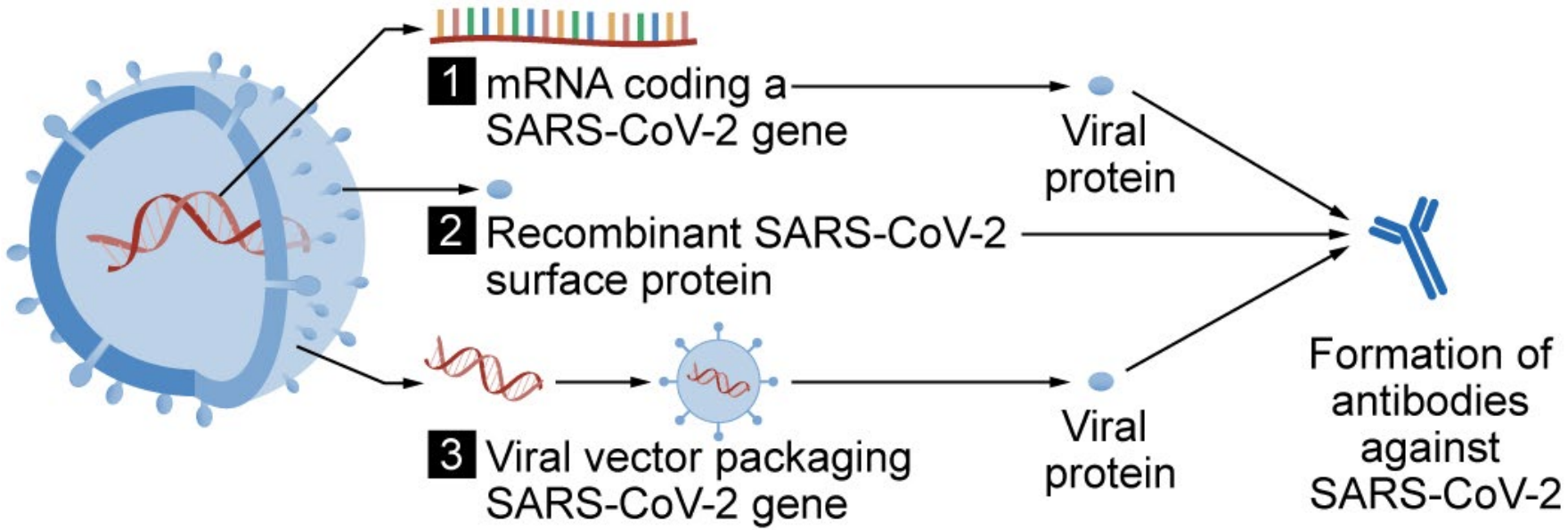
AGAPLESION MARKUS KRANKENHAUS

SARS-CoV-2 vaccination: A success story



Funk et al. Front Pharmacol 2020

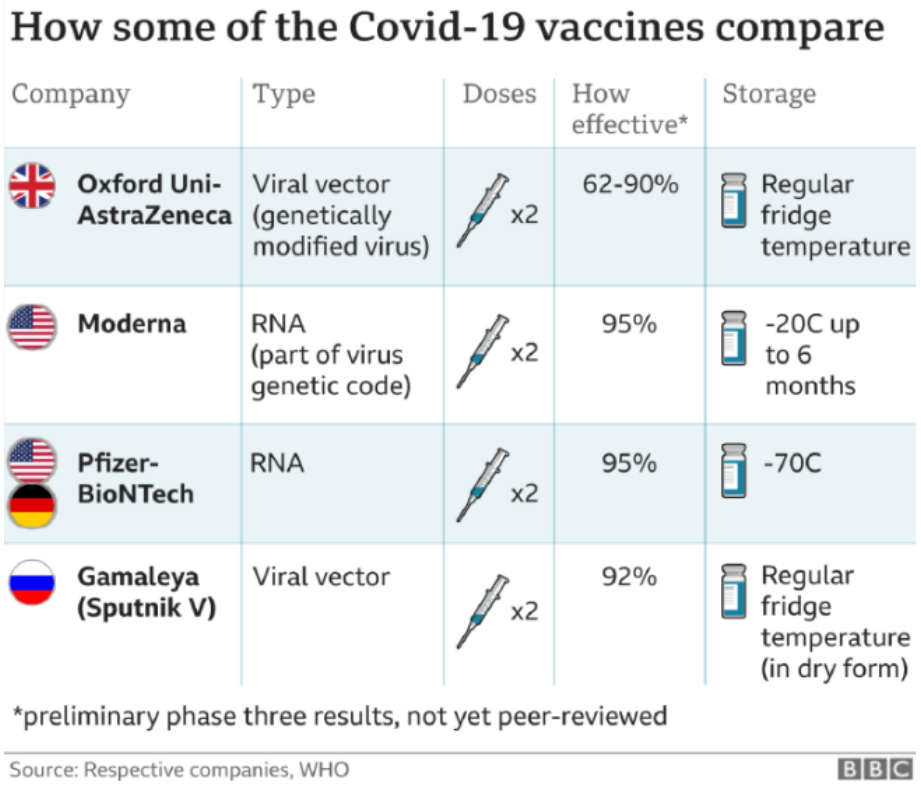
SARS-CoV-2 Impfung



Source: GAO. | GAO-20-583SP

Wikipedia 2021

SARS-CoV-2: in Europe zugelassene Impfungen



How some of the Covid-19 vaccines compare

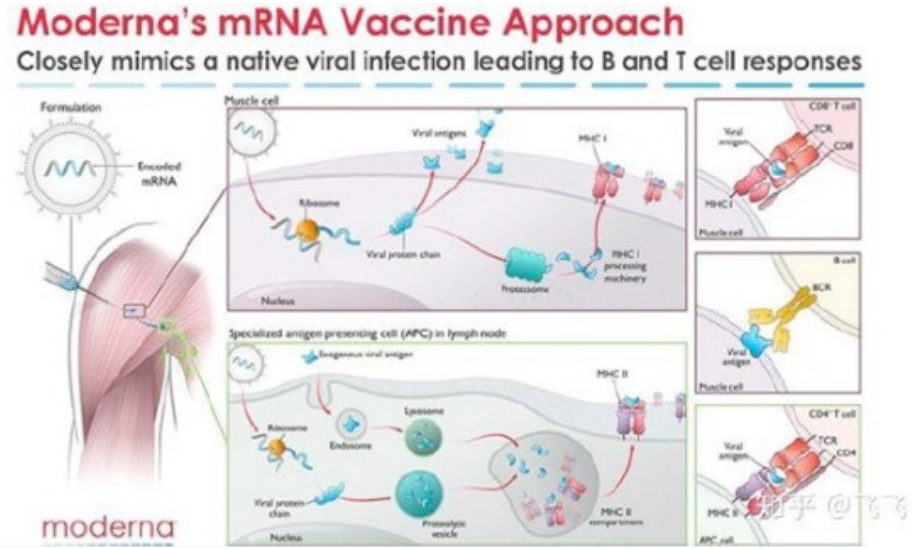
Company	Type	Doses	How effective*	Storage
Oxford Uni-AstraZeneca	Viral vector (genetically modified virus)	x2	62-90%	Regular fridge temperature
Moderna	RNA (part of virus genetic code)	x2	95%	-20C up to 6 months
Pfizer-BioNTech	RNA	x2	95%	-70C
Gamaleya (Sputnik V)	Viral vector	x2	92%	Regular fridge temperature (in dry form)

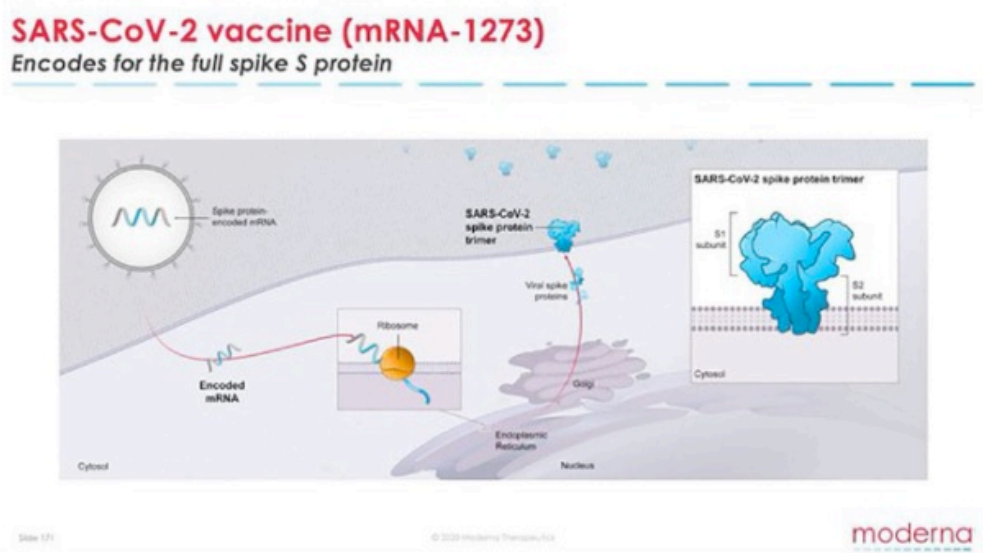
*preliminary phase three results, not yet peer-reviewed

Source: Respective companies, WHO

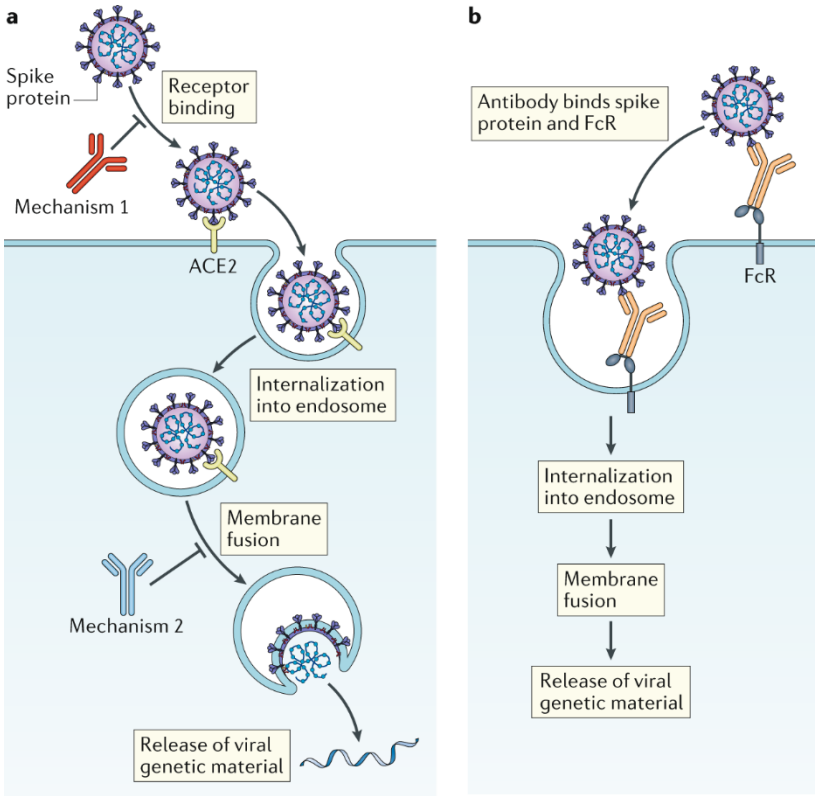
BBC

SARS-CoV-2 mRNA vaccination





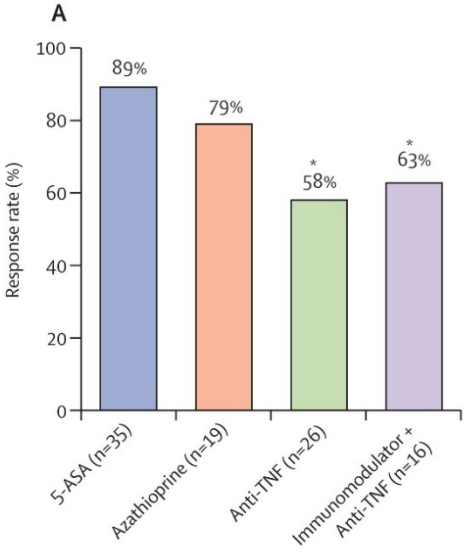
Passive Sars-CoV-2 Immunisierung



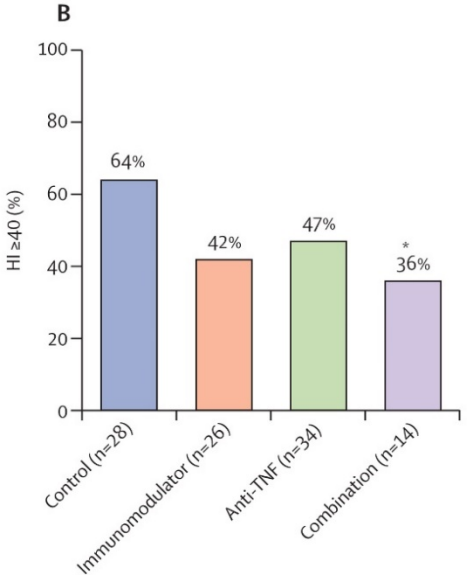
- **convalescent plasma** from recovered patients
- Recombinant **monoclonal antibodies**
  - **Bamlanivimab**
    - mild to moderate symptoms for < 10 d, at high risk to get very sick from COVID-19, not for people who are already in the hospital because COVID-19 symptoms
    - age 65 or older, obesity, with a body mass index (BMI) of 35 or higher, diabetes, chronic kidney disease, or a condition that weakens the immune system, take medication that weakens the immune system; age 55 or older and Heart disease, High blood pressure, Long-term lung disease

Abraham J, Nature Reviews Immunology 2020

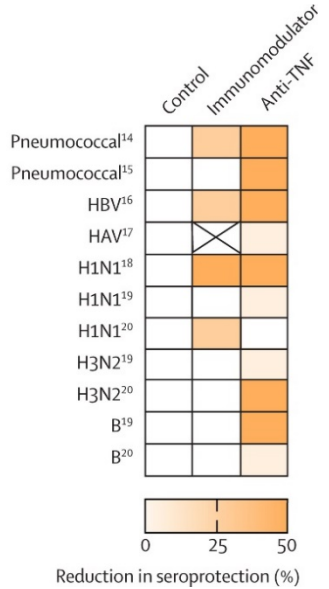
Immunogenicity of vaccines in patients taking immunosuppressive therapies



Pneumococcus Vaccine



H1N1 Influenza Vaccine



Alexander JL et al., Lancet Gastroenterology & Hepatology2021 DOI: (10.1016/S2468-1253(21)00024-8)

Wichtige Infos zur Covid-19 Impfung bei CED

- SARS-CoV-2 Impfungen werden bei CED unbedingt empfohlen
- Risiken einer SARS-CoV-2 Impfung bei CED-Patienten werden als sehr gering eingeschätzt
- Bei CED-Patienten mit immunosuppressiver Therapie (auch Biologika) werden keine erhöhten Nebenwirkungen sondern allenfalls verringerte Impferfolge erwartet
- Alle derzeit verfügbaren SARS-CoV-2 Impfstoffe werden bei CED-Patienten empfohlen
- Wiederholungsimpfungen gegen SARS-CoV-2 werden bei Patienten unter Immunsuppression bei unzureichendem Impferfolg möglicherweise nötig und von Experten auch empfohlen
- Andere wichtige Impfungen (Virusgrippe, etc) sollten nicht vergessen werden

IOIBD Recommendations on Sars-CoV-2 vaccination in IBD

Accepted statements	Proportion agreement	Strength of agreement (Mean)	SD
Timing of when to receive SARS-CoV-2 vaccination			
The best time to administer SARS-CoV-2 vaccination in patients with IBD is at the earliest opportunity to do so.	95.3%	8.91	1.27
Disease activity of IBD should not impact the timing of SARS-CoV-2 vaccination.	90.0%	8.50	1.55
Vaccination against SARS-CoV-2 is unlikely to cause a flare of IBD.	89.1%	8.31	1.38
SARS-CoV-2 vaccination can be administered to patients with IBD during induction with biologic therapies irrespective of timing within the treatment cycle.	97.5%	8.33	1.14
SARS-CoV-2 vaccination can be administered to patients with IBD on maintenance biologic therapies irrespective of timing within the treatment cycle.	100%	8.93	1.00

IOIBD: Siegel C et al. Gut 2021

IOIBD Recommendations on Sars-CoV-2 vaccination in IBD

Accepted statements	Proportion agreement	Strength of agreement (Mean)	SD
The prioritisation of patients with IBD for SARS-CoV-2 vaccination			
Healthcare/essential workers with IBD should be vaccinated in the same prioritisation tier as healthcare/essential workers without IBD.	92.2%	8.84	2.00
Individuals who are not healthcare/essential workers and have no risk factors for complications of COVID-19 but have IBD should be vaccinated in the same prioritisation tier as those who are non-healthcare/essential workers and have no risk factors for SARS-COV2.	82.5%	8.02	2.03
Individuals at increased risk for complications of COVID-19 based on age or comorbidities who also have IBD should be vaccinated in the same prioritisation tier as individuals at increased risk for complications of COVID-19 without IBD.	96.8%	9.13	1.07
Individuals with IBD who are on immune-modifying therapies but are not otherwise at risk for complications of COVID-19 should be vaccinated in the same prioritisation tier as those who are 'immunocompromised'.	81.3%	8.09	1.80
Once SARS-CoV-2 vaccinations are authorised for children, guidance for vaccination of children with IBD will be the same as for children without IBD.	100%	8.90	1.03
Household contacts of patients with IBD are encouraged to receive SARS-CoV-2 vaccination.	97.4%	9.08	1.34
Household contacts of patients with IBD should avoid live, replication-competent SARS-CoV-2 vaccination.	81.6%	7.71	2.04
Women with IBD planning pregnancy should be encouraged to receive the SARS-CoV-2 vaccine prior to attempting conception, but not delay conception solely to wait for vaccination.	100%	8.87	1.03
SARS-CoV-2 vaccines should be offered to pregnant women with IBD in accordance with regional recommendations for pregnant women without IBD.	100%	8.97	1.07
SARS-CoV-2 vaccines should be offered to lactating women with IBD in accordance with regional recommendations for lactating women without IBD.	100%	8.81	1.08

IOIBD: Siegel C et al. Gut 2021