INSELGRUPPE

«Extraintestinal Manifestations in Inflammatory Bowel Disease»

Universitätsklinik für Viszerale Chirurgie und Medizin, Inselspital Bern

Bible Class, 20-APRIL-2022

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Overview:

1. «Rheumatism» as an EIM in IBD
2. EIM – Epidemiology and Pathogenesis
3. EIM - Therapy

1. «Rheumatism» as an EIM in IBD

Extraintestinal Manifestations = Disease patterns outside the intestinal tract that are or are suspected to be related to chronic inflammatory bowel disease *

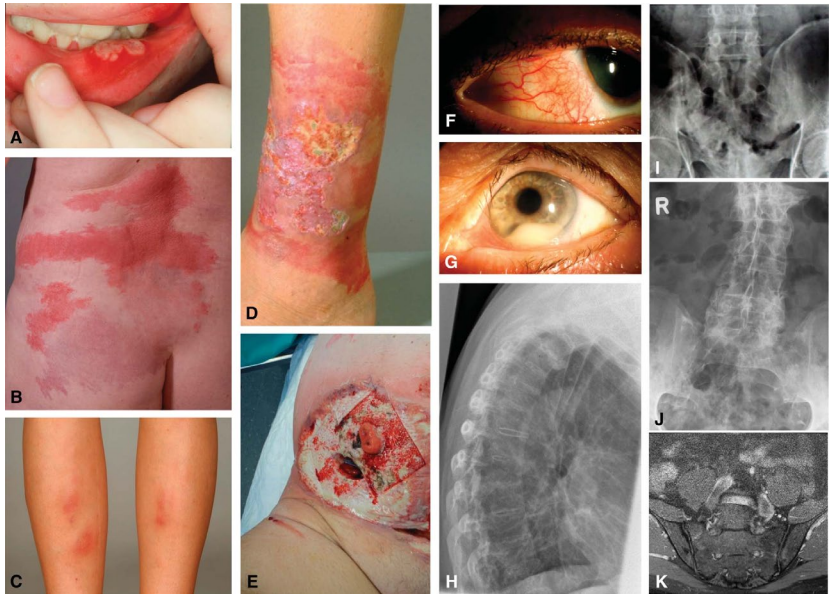


Table 1. Extraintestinal Manifestations of Inflammatory Bowel Diseases

Organ system	Manifestations	Prevalence
Gastrointestinal	PSC Autoimmune pancreatitis Autoimmune hepatitis	UC: up to 5%; CD: rare Rare Rare (< 1%)
Mucocutaneous	EN PG Oral aphthous ulcers Sweet syndrome Orofacial granulomatosis	5%–15% in CD; 2%–10% in UC 0.4%–2.6% in IBD 5%–50% in CD Rare Rare
Musculoskeletal	IBD-related arthritis Peripheral arthritis Axial arthritis Enthesitis	CD: 10%–20% ; UC: 4%–14% Up to 50% in CD (asymptomatic)
Ocular	Episcleritis and scleritis Anterior uveitis	Scleritis: up to 1%; CD: 5%–12%; UC: 3.5%–4.1%
Pulmonary	Pneumonitis	Rare
Vascular	Cardiovascular disease Thromboembolism Portal vein thrombosis	NA 3- to 4-fold increase Rare

* Krones E u. Fickert P., J Gastroenterol Hepatol Erkr 2013
Bildmaterial: links: Vavricka RS et al, Inflamm Bowel Dis 2015; rechts: Rogler G et al, Gastroenterology 2021, Article in press

EIM: demarcation difficulties

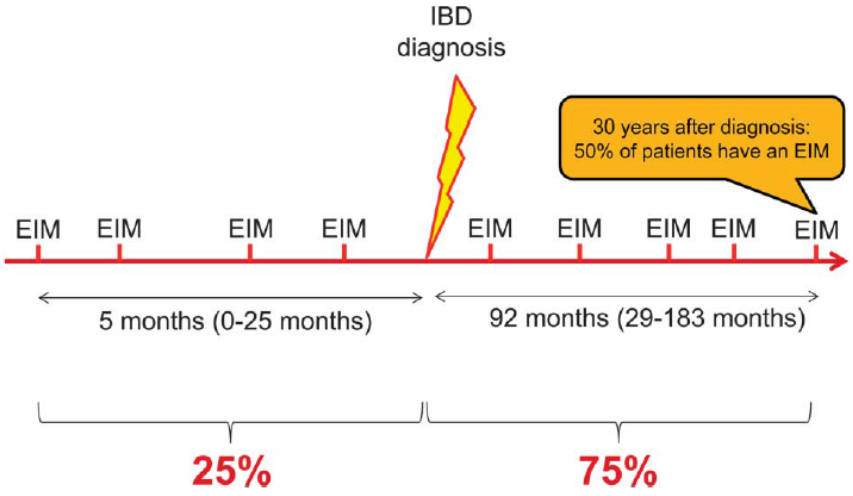
Extraintestinal Manifestations
vs.

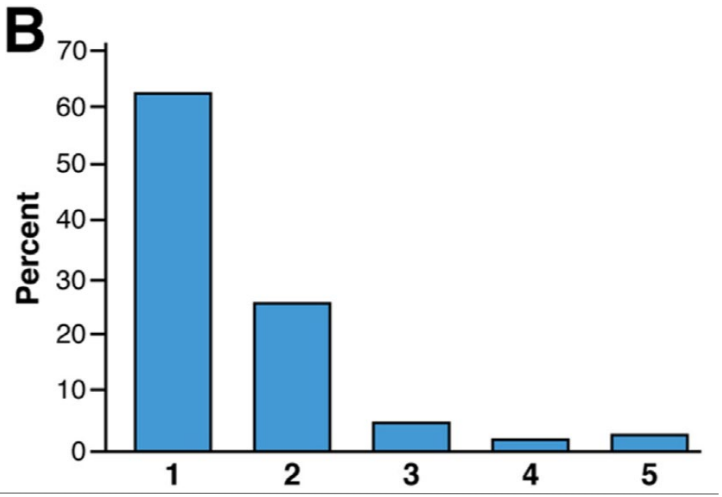
- Extraintestinal comorbidities (cholecysto-, nephrolithiasis)
- non-disease-specific complications (osteoporosis, thromboembolic complications)
- associated autoimmune diseases (e.g. thyroiditis, vitiligo)

2. EIM – Epidemiology and Pathogenesis

EIM – frequency in IBD patients*

- Up to 50% of all IBD patients develop at least one EIM
- More than 20% of all IBD patients with 2 EIMs
- Sometimes years before the onset of IBD!





2. EIM – Epidemiology and Pathogenesis

- **Musculoskeletal EIMs: most common EIMs in IBD patients***
- **Up to 70% of patients with AS or SpA with microscopic evidence of intestinal inflammation, 7% develop Crohn's disease** (macroscopic evidence of inflammation on ileocoloscopy in up to 37% of AS patients***)**
- **20 of 31 AS-associated genes (risk variants) also present in IBD (e.g. IL-23R, IL-12B, TYK-2, JAK-2, IL-27)******
- **50% of HLA-B27 positive IBD patients have AS*******

* Rogler G et al, Gastroenterology 2021, Article in press
** Harbord M et al, JCC 2016
*** Soo MA, Korean J Intern Med 2017
**** Pedersen SJ, Marksymowych WP, Drugs 2018
***** Colombo E et al World J Gastroenterol 2009

2. EIM – Epidemiology and Pathogenesis

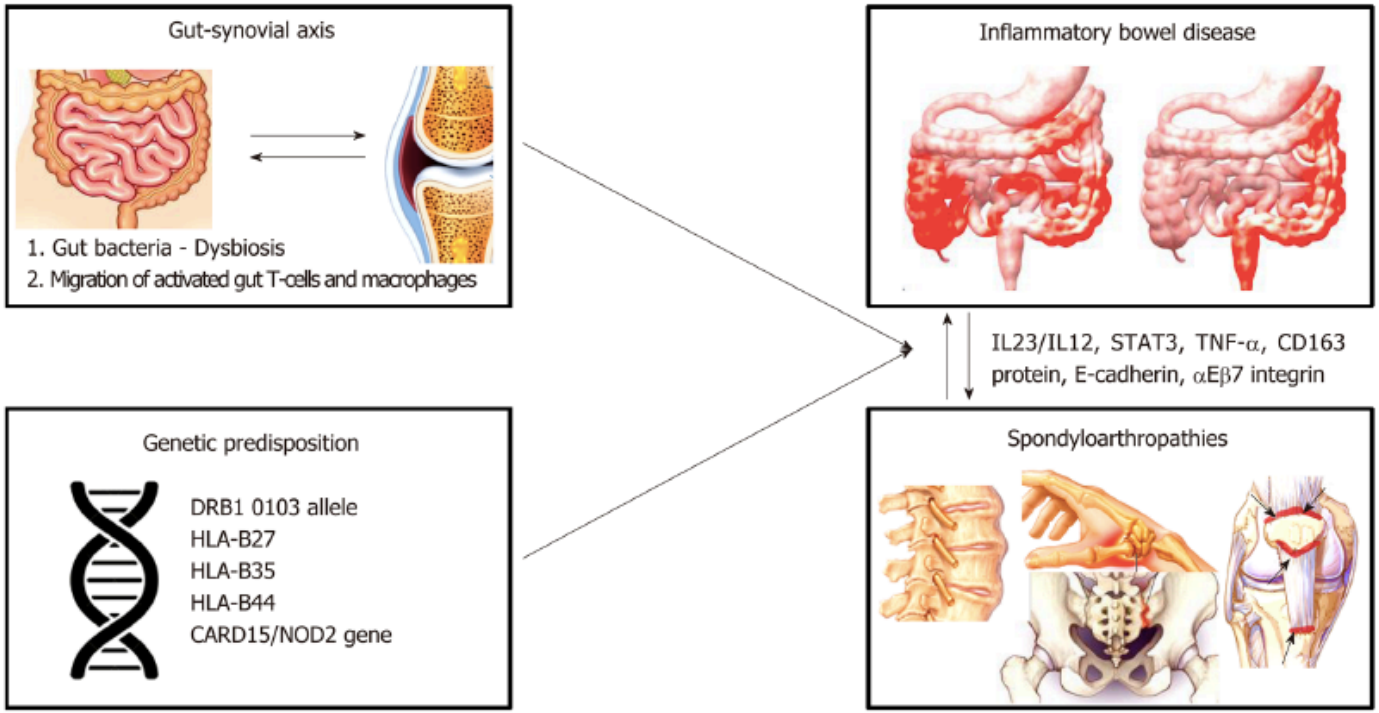
The pathogenesis of EIM in IBD has not yet been clearly elucidated *

- Influence of intestinal microbiome/microbial dysbiosis and environmental factors
- Genetic risk factors
- common epitopes of intestinal bacteria and extraintestinal organs (e.g. synovia)
- Migration of intestinal lymphocytes to the joints
- Immune response against common antigens of the gut and extraintestinal organs

* Rogler et al, Gastroenterology 2021, Article in press. Greuter T et Vavricka S R, Expert Rev Gastroenterol Hepatol 2019. Hedin CRH et al, DOP073, ECCO 2018 ; Ferreira SdC et al, J Gastroenterol Dig Dis 2018, Akshay ST, Phoebe L., Curr Opin Ophthalmol 2016; Gill T et al, Curr Opin Rheumatol 2015; Danese S et al, World Journal of Gastroenterology 2005; Peluso R et al, Clin Dev Immunol. 2013; Fragoulis GE et al, World J Gastroenterol 2019

2. EIM – Epidemiology and Pathogenesis

Pathogenesis of SpA in IBD – the 'gut-synovial' axis*



2. EIM – Epidemiology and Pathogenesis

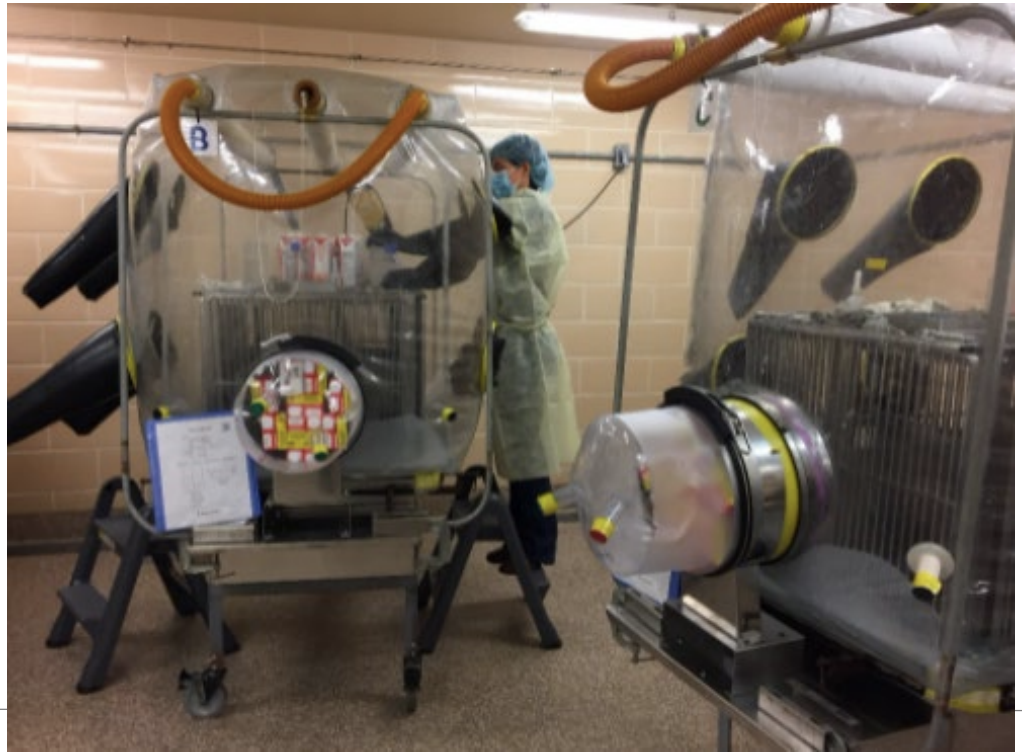
In the beginning there was the gut!?*

- Human HLA-B27 transgenic rat model: SpA and IBD-like disease (arthritis and EAM: psoriasiform skin, nail lesions, enterocolitis) when reared under normal conditions

- **Rats did not develop inflammation of peripheral joints and intestines under germ-free conditions!**
- **Recurrence of inflammation upon re-establishment of normal flora**

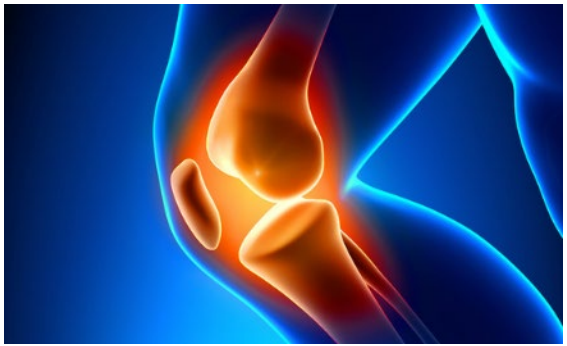
2. EIM – Epidemiology and Pathogenesis

Example: Gnotobiotic Facility for Pigs and Mice – The Ohio State University College of Veterinary Medicine



3. EIM – Therapie

IBD – therapy decision for joint involvement



- Differentiation: involvement of the axial skeleton vs. peripheral joint involvement*
- Classification: seronegative spondyloarthropathies (SpA)**
- DD: collagenosis/other rheumatological diseases (e.g. GPA, PsoA), steroid withdrawal/under steroid therapy, steroid-induced osteonecrosis/osteoporosis, drug-induced (lupus-like syndrome, Aza, MTX)

* Rogler G et al, Gastroenterology 2021, Article in press. Greuter et al, Gut 2021. Aktualisierte S3-Leitlinie Mb. Crohn DGVS (08/2021)
** Atenzi F et al, Autoimmun Rev. 2014

3. EIM – therapy for joint involvement*

- **<u>Peripheral joint involvement:</u>** Sulfasalazin, MTX, COX2-Inh., Anti-TNF-Ak
- **<u>Axial spondyloarthritis:</u>** Anti-TNF-Ak

Variable	Prevalence	Diagnosis	Therapy
Peripheral arthritis (peripheral SpA)	5%–14% in UC 10%–20% in CD	Clinical (and US or MRI)	Treatment of intestinal inflammation COX-2 inhibitors Corticosteroids (short term) Sulfasalazine (especially in UC) Methotrexate Anti-TNF
Axial arthritis/ axSpA	Up to 50 % in CD symptomatic in up to 8%	Clinical and MRI	Anti-TNF

MRI, magnetic resonance imaging; US, ultrasound.

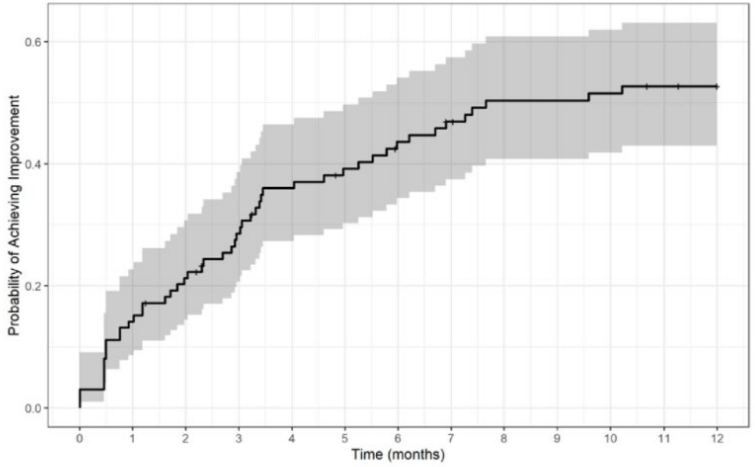
 * Aktualisierte S3-Leitlinie Mb. Crohn DGVS (08/2021). Rogler G et al, Gastroenterology 2021, Article in press. Greuter et al, Gut 2021. Greuter T et Vavricka S R, Expert Rev Gastroenterol Hepatol 2019. Tabelle: Rogler et al, Gastroenterology 2021, Article in press

3. EIM – therapy for joint involvement

Data on other drug therapies: Vedolizumab

- ECCO 2021: Kopylov U et al (P406): A retrospective analysis of the efficacy of vedolizumab on extra-intestinal manifestations in patients with inflammatory bowel disease across five European countries
- Conclusion: VDZ treatment associated with an improvement in 37% and 50% of EIM at 6 and 12 months, respectively, in a real-world IBD cohort.

Figure 1. Time between vedolizumab initiation and first EIM improvement



*Improvement defined as resolution of symptoms or partial response.

3. EIM – therapy for joint involvement

Data on other drug therapies: Vedolizumab

Possible explanations for the positive effects of VDZ*:

- Better control of the intestinal disease → positive influence of parallel occurring EIMs
- Lymphocytes require α4β7 – MAdCAM1 interaction for access to the intestine (site of activation, subsequent α4β7-independent entry into extraintestinal locations)

Post hoc analysis of the GEMINI studies and meta-analyses** without clear evidence for the effectiveness of VDZ in EIM

→ Currently NO recommendation for VDZ for the treatment of EIM*

3. EIM – therapy for joint involvement

Data on other drug therapies: ustekinumab*

- Potential efficacy in IBD-related peripheral arthritis and skin EIMs, but not in axial SpA

- Efficacy in psoriatic arthritis (approval!)

- Ankylosing spondylitis: Discontinuation of the phase III program due to lack of efficacy

 * Rogler G et al, Gastroenterology 2021, Article in press. Greuter T et al, Gut 2021

3. EIM – therapy for joint involvement

Data on other drug therapies: vedolizumab vs. ustekinumab

- ECCO 2022: P450 Ustekinumab and vedolizumab for extraintestinal manifestations in inflammatory bowel disease (Livne-Margolin, M. Ling, D. Attia Konyo, S. Haj, O. Abitbol, C.M. Ben-Horin, S. Kopylov, U.)
- 112 IBD patients with active EIM at the start of treatment with VDZ or UST followed in the gastroenterology department of Sheba medical center (Israel) between 2015 and 2021
- 53 patients (47%) treated with UST, 59 (53%) with VDZ. 55% women, **88% had CD**. 21% naive to anti-TNF inhibitors. Most common EIM was arthralgia (84%). **Patients treated with UST more likely to be anti TNF experienced (96%** compared with 58%, p<0.0001)

3. EIM – therapy for joint involvement

Data on other drug therapies: vedolizumab vs. ustekinumab*

- Results: Clinical response of EIM at week 52 achieved in 42% of patients treated with UST (vs. 25% of patients treated with VDZ, difference not statistically significant (p =0.08)). No difference between UST and VDZ regarding their effect on EIM at earlier timepoints. No difference observed for specific types of EIMs

- **Conclusion:** no difference was found between VDZ and UST regarding their effect on EIM in IBD patients for up to 52 weeks of follow-up

3. EIM – therapy for joint involvement

Data on other drug therapies: upadacitinib

- ECCO 2022: OP33 Effect of upadacitinib (UPA) treatment on extraintestinal manifestations (EIMs) in patients with moderate-to-severe Ulcerative Colitis (UC): Results from the UPA Phase 3 programme (Colombel, J.F.; Cao, Q.; Ghosh, S.; Reinisch, W.; Zhou, W.; Ilo, D.; Shu, L.; Yao, X.; Rubin, D.T.)

- Patients with moderate-to-severe UC randomised 2:1 to 8 weeks' induction treatment with UPA 45 mg once daily (QD) or placebo. Patients with a clinical response to induction were re-randomised (1:1:1) to 52 weeks' maintenance treatment with UPA 15 mg or 30 mg QD, or placebo.

3. EIM – therapy for joint involvement

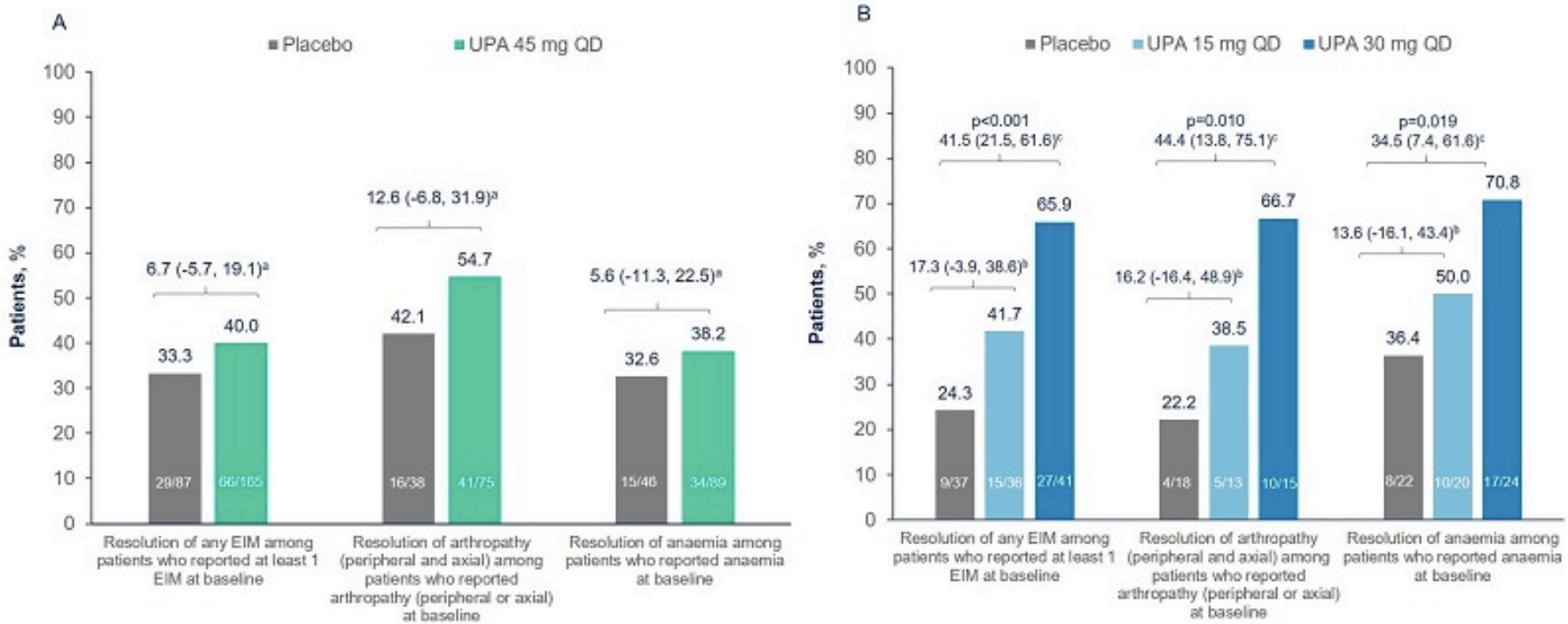
Data on other drug therapies: upadacitinib (ECCO 2022: OP33)

- presence of EIMs (peripheral arthropathy, axial arthropathy, episcleritis, uveitis, iritis, erythema nodosum, pyoderma gangrenosum, Sweet's syndrome, oral aphthous ulcers, primary sclerosing cholangitis, autoimmune hepatitis, venous thromboembolism, chronic obstructive pulmonary disease, bronchiectasis, nephrolithiasis and anaemia) captured in the EIM form at the start of induction (baseline) and at every visit up to Week 52.

3. EIM – therapy for joint involvement

Data on other drug therapies: upadacitinib (ECCO 2022: OP33)

Figure 1. Proportion of patients achieving resolution of any EIM, arthropathy, and anaemia at (A) Week 8 in the induction studies and (B) Week 52 in the maintenance study



3. EIM – therapy for joint involvement

Data on other drug therapies: upadacitinib (ECCO 2022: OP33)

- Results: most common EIMs at baseline were anaemia, peripheral arthropathy and axial arthropathy; all other EIMs were reported in <2% of patients. Resolution at Week 52 of any EIM in patients with ≥1 EIM at baseline significantly increased with UPA 30 mg QD ($p<0.001$), and numerically greater with UPA 15 mg QD, versus placebo. The same was true for arthropathy and anaemia

- **Conclusion: UPA treatment effective in resolving EIMs in patients with UC**

3. EIM – therapy for joint involvement

Data on other drug therapies:

- Tofacitinib*: post hoc analysis (OCTAVE): possible improvement in IBD-associated peripheral arthritis (but: small number of patients). Possible positive effects in EN, PG, uveitis, scleritis. But: side effects!

- Further therapeutic options (IBD/EIM) in the pipeline: Filgotinib, (‚selective' JAK-1 inhibitor), IL23 (p19)-antibodies (Tildrakizumab, Guselkumab, Risankizumab, Mirikizumab), …

 * Greuter T et al, Gut 2021. Rubin DT et al, Ther Adv Gastroenterol 2021.

3. EIM – therapy for joint involvement

Data on other drug therapies: tofacitinib*

Berlin, 24.03.2021

▼ XELJANZ (TOFACITINIB):

Erste Ergebnisse einer klinischen Studie deuten auf ein erhöhtes Risiko für schwerwiegende unerwünschte kardiovaskuläre Ereignisse und maligne Erkrankungen (ohne NMSC) bei der Verwendung von Tofacitinib im Vergleich zu TNF-alpha-Inhibitoren

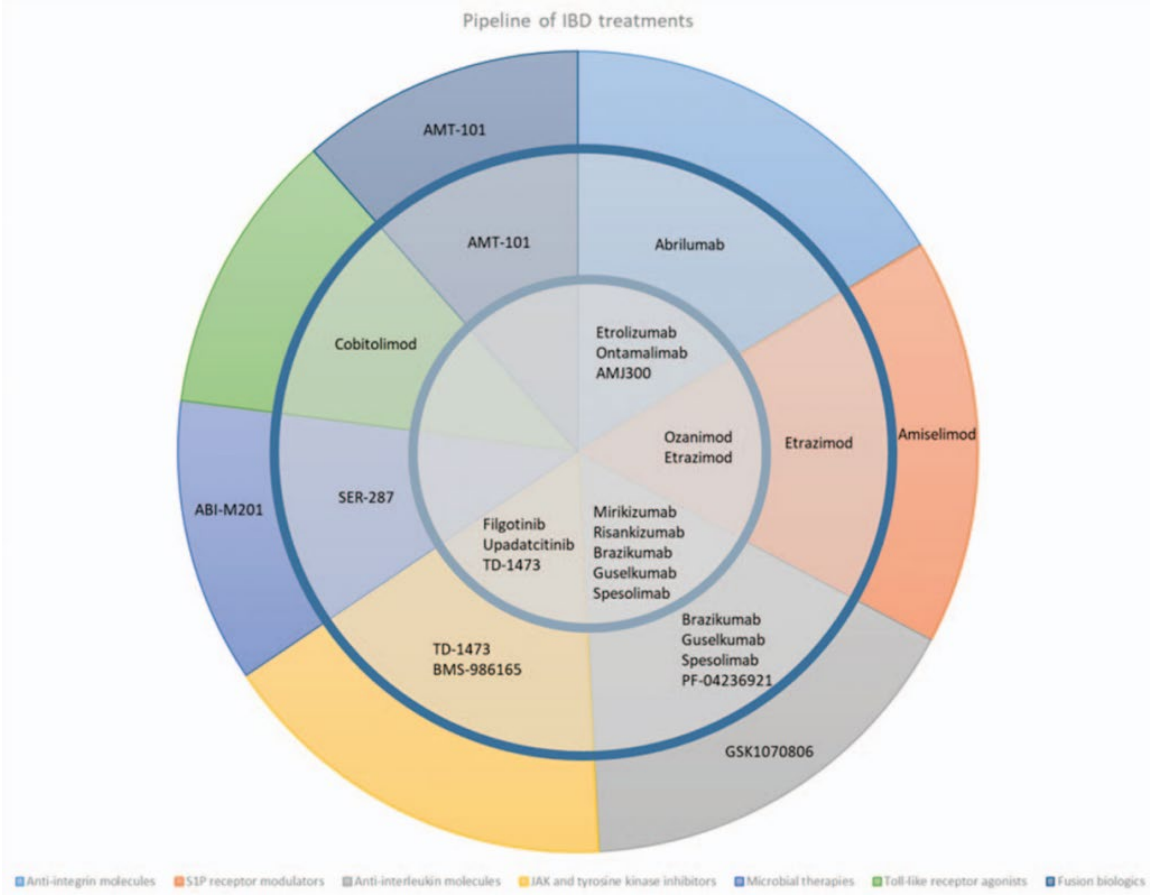
Sehr geehrte Damen und Herren,

in Abstimmung mit der Europäischen Arzneimittelagentur (EMA) und dem Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) möchte Sie Pfizer über Folgendes informieren:

Zusammenfassung

- **Vorläufige Daten aus einer abgeschlossenen klinischen Studie bei Patienten mit rheumatoider Arthritis (A3921133) deuten auf ein höheres Risiko für schwerwiegende unerwünschte kardiovaskuläre Ereignisse (MACE) und maligne Erkrankungen (mit Ausnahme von nicht melanozytärem Hautkrebs [NMSC]) unter der Behandlung mit Tofacitinib im Vergleich zu Patienten, die mit einem TNF-Alpha-Inhibitor behandelt wurden.**

3. EIM - Pipeline of IBD therapies*



3. EIM – therapy for joint involvement

Future therapeutic approaches: microbiome modulation!?

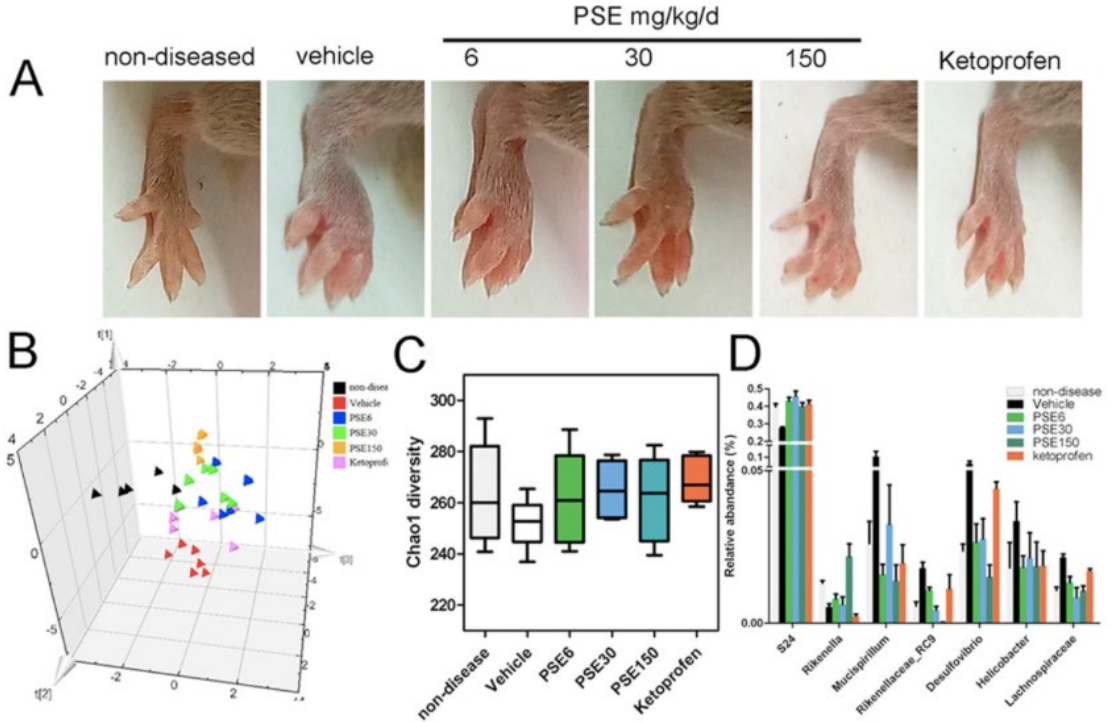
Influence of Paederia scandens (foetida) in the RA mouse model by microbiome modulation*

- → P. scandens extract p.o. in mice with collagen-induced arthritis over 24d
- → Significant reduction in paw swelling and arthritis score. Histological inhibition of tissue fibrosis and inflammatory cell infiltration
- → Significant suppression of elevated serum levels of TNF-α, IL-1β, IL-6, IL-7, IL-23
- → Decrease in inflammation-associated microorganisms

 * Xiao M at al, J Ethnopharmacol 2018

3. EIM – Zukünftiger Therapieansatz!?

Microbiome modulation in the arthritis model*



PSE significantly inhibited paw swelling and help restore gut microbial ecosystem altered in RA mice.

* Xiao M at al, J Ethnopharmacol 2018

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Thank you very much for your attention!
Questions?