Management konventionelle Immunosuppressiva bei chronisch entzündlichen Darmerkrankungen

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Mittwoch 16. Juni 2021; 15.30 – 16.00

History of IBD treatment

- 1954 – Steroiden

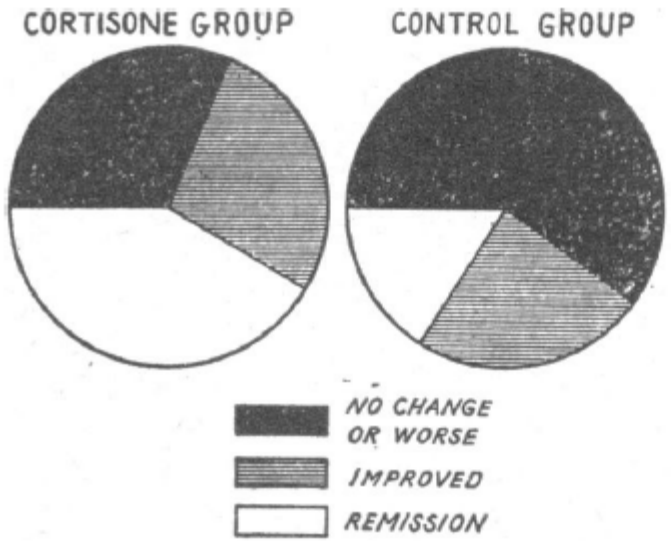

FIG. 1.—Effect of treatment — whole series.

cortisone enjoyed a clear-cut advantage over the patients on a dummy preparation. Thus about two out of every five patients on cortisone therapy were in clinical remission at the end of six weeks treatment, compared with less than one out of every six patients receiving the inert therapy.

TABLE I.—*Effect of Treatment on Whole Series*

Clinical State at End of Treatment	Cortisone Group	Control Group
Remission	45 (41·3%)	16 (15·8%)
Improved	30 (27·5%)	25 (24·8%)
No change or worse ..	34 (31·2%)	60 (59·4%)
Total	109 (100%)	101 (100%)

$\chi^2 = 21{\cdot}2$. n = 2. $P < 0{\cdot}001$.

BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 14 1954

CORTISONE IN ULCERATIVE COLITIS

PRELIMINARY REPORT ON A THERAPEUTIC TRIAL

BY

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Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford

With the co-operation of Professor R. E. TUNBRIDGE and Dr. G. WATKINSON (Leeds), Dr. F. AVERY JONES and Dr. RICHARD DOLL (North-west London), Professor T. L. HARDY and Dr. C. R. ST. JOHNSTON (Birmingham), Dr. W. I. CARD and Dr. MAXWELL WILSON (Edinburgh), and Sir JOHN TAYLOR (Medical Research Council)

History of IBD treatment

- 1955 - 75 – Steroiden, 5-ASA

Results

Forty-nine patients have been treated along these lines during the past 5 years.

TABLE I—RESPONSE TO THE 5-DAY INTENSIVE INTRAVENOUS REGIMEN (WHOLE SERIES)

Response	No.
Remission	36 (*73%*)
Improved	4 (*8%*)
No change or worse	9 (*18%*)
Total	49

Three-quarters of the patients showed a rapid response to the regimen and were entirely symptom-free after 5 days (table 1). A few showed improvement and about 1 in 5 were unchanged or worse.

History of IBD treatment

- 1955 - 75 – Steroiden, 5-ASA
- 1970 ’-1980’ AZA/ 6MP

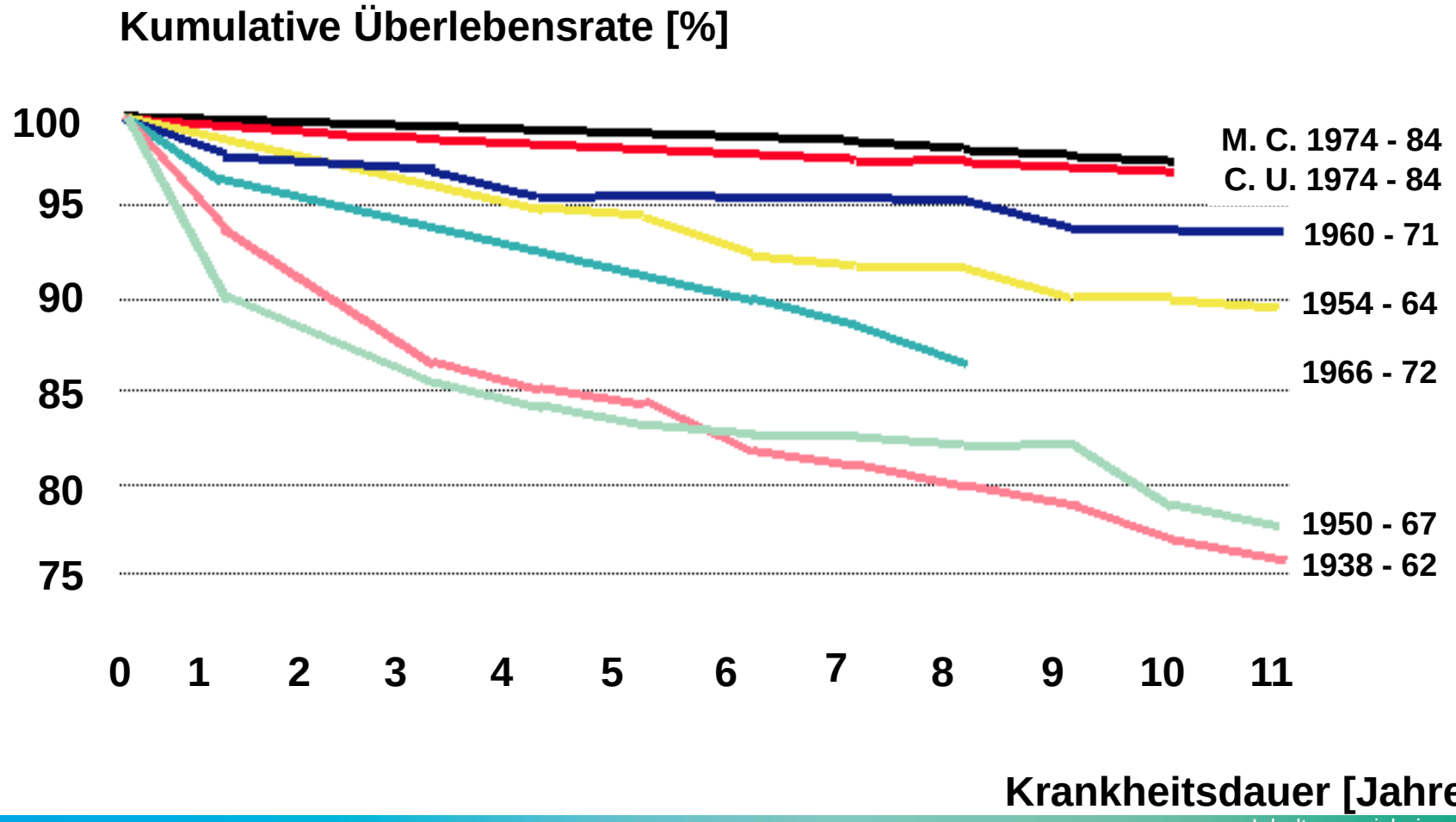
BRITISH MEDICAL JOURNAL 20 MARCH 1971

Reported Series of Patients with Ulcerative Colitis Treated by Immunosuppressive Drugs with Generally Favourable Responses.

	No. of Patients	Drug	Length of Treatment	Marrow Depression
Winkelman and Brown[52]	14	Nitrogen Mustard	Weeks	Common
Bean[53]	7	Busulphan 6MP 6TG	Months	Common
Caprilli *et al.*[54]	7	Aza	Months	Negligible
Bowen *et al.*[55]	10	Aza	Months	Common
MacKay *et al.*[56]	7	6MP Aza	Months	Negligible
Lal *et al.*[57]	16	6MP	Weeks–months	Negligible
Theodor *et al.*[58]	7	Aza	Weeks–months	Negligible
Jones[59]	10	Aza	Weeks–months	Common (large doses were deliberately used)
Brown *et al.*[60]	10	Aza	Weeks	Negligible

(6MP = 6-mercaptopurine; 6TG = Thioguanine; Aza = azathioprine).

Chronisch entzündliche Darmerkrankungen: Überlebensraten unter „konventioneller“ Therapie



IBD therapies over time

1950s
Steroide

1970s
Thiopurines

1990s
Methotrexate

2000s
Anti-TNFs

2015
Anti-Integrines

2016

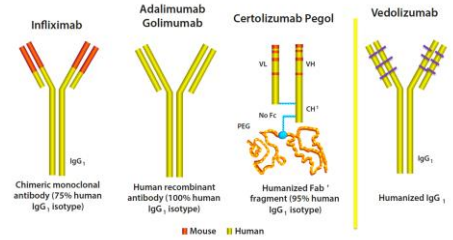
2017
Ustekinumab

Biosimilars

2019
Tofacitinib – JAK inhibitors

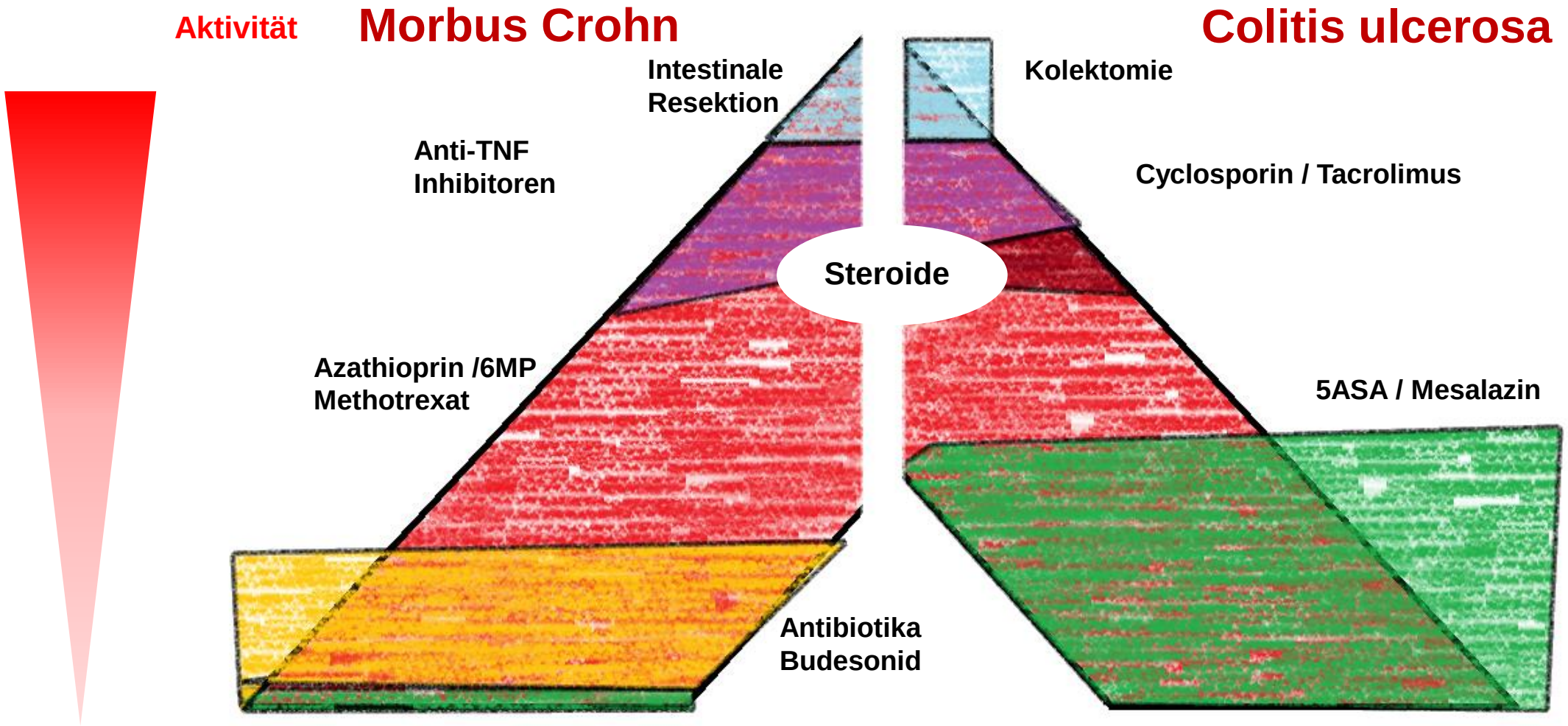
2019

Crowded pipeline, including multiple new mechanisms of action

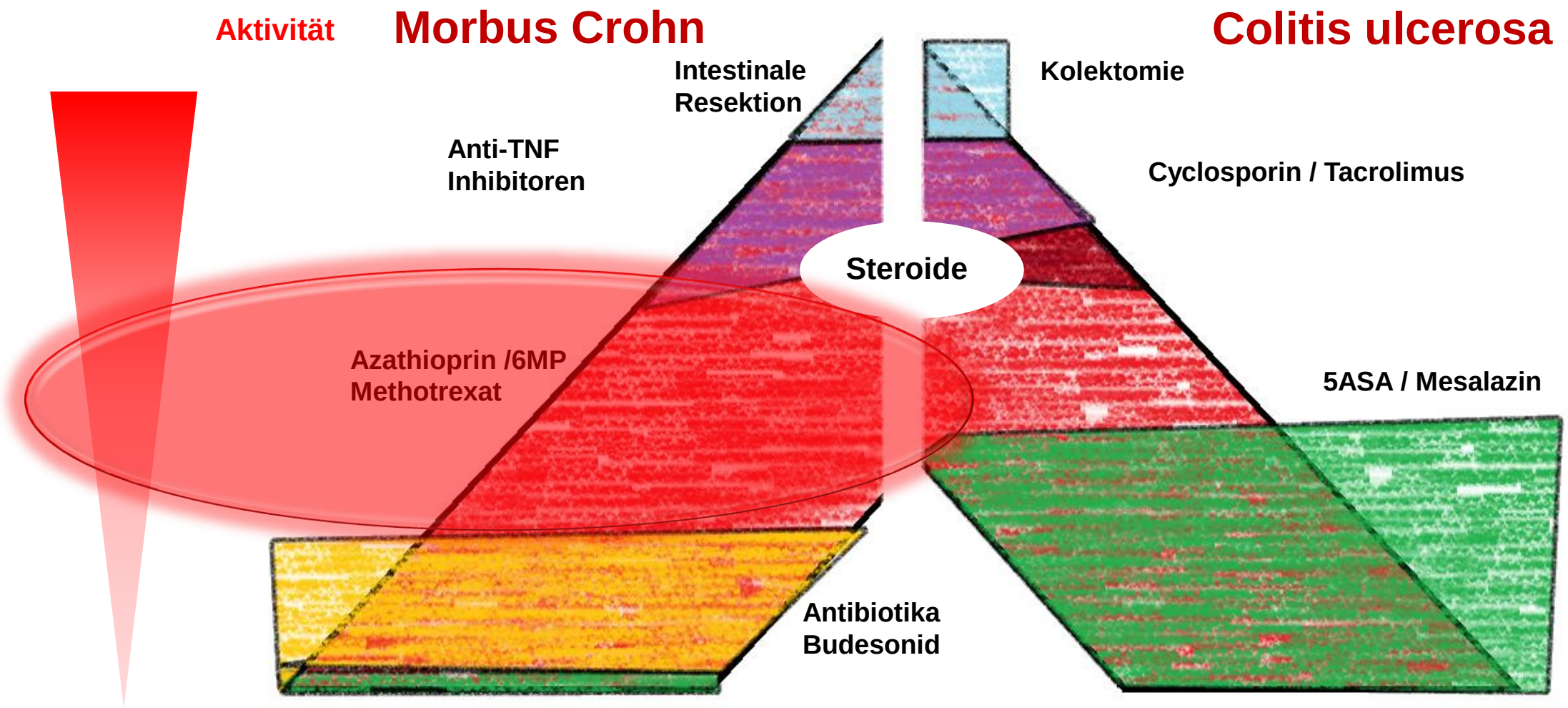


JAK, Janus kinase; MoA, mechanism of action; MTX, methotrexate; TNF, tumour necrosis factor; UC, ulcerative colitis.

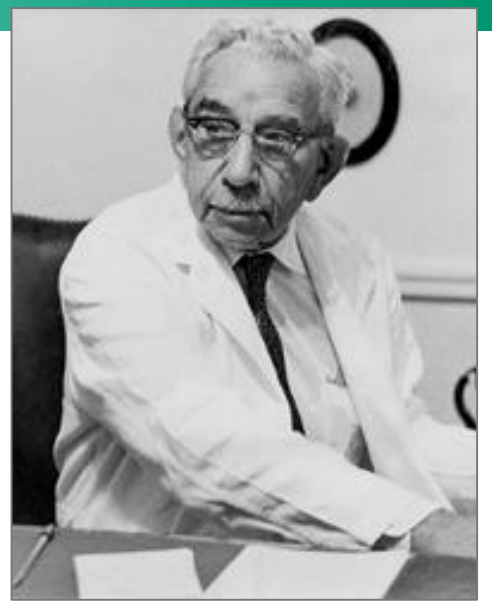
Therapie : IBD «Pyramide»



Therapie : IBD «Pyramide»



Burrill B. Crohn Mount Sinai Hospital New York City



An old drug for an old disease ?

5. Methotrexate

important in making the intestinal incision for any ureteral transplantation. The intestine should be held by four traction loops, which, when possible, should include any visible vessel in the intestinal wall that may cross the proposed line of incision. With a very sharp lance pointed knife, the peritoneum and part of the muscular coat are cut. The knife is now turned flatwise and with the point of the knife the remaining muscle fibers are teased through with gentle strokes, which cause the muscle ends to separate without damage to the submucosal vessels or membrane. With the handle of the knife, the muscle coat is pushed back, exposing the outer surface of the intestinal mucous membrane. This part of the operation must be done very delicately.

Technic 3, because of its simplicity, seems destined to assume an important rôle. Based on experimental surgery on animals and the very limited experience that it is

REGIONAL ILEITIS

A PATHOLOGIC AND CLINICAL ENTITY

BURRILL B. CROHN, M.D.
LEON GINZBURG, M.D.
AND
GORDON D. OPPENHEIMER, M.D.
NEW YORK

We propose to describe, in its pathologic and clinical details, a disease of the terminal ileum, affecting mainly young adults, characterized by a subacute or chronic necrotizing and cicatrizing inflammation. The ulceration of the mucosa is accompanied by a disproportionate connective tissue reaction of the remaining walls of the involved intestine, a process which frequently leads to stenosis of the lumen of the intestine, associated with the formation of multiple fistulas.

Clinical case

68 yo male patients, with **ileal Crohn's disease** (Montréal A2 L1 B2), currently *postoperative remission* after IC resection.

Previous therapies:

- Steroids / Budesonide, successfully – no longer needed
- Azathioprine – AE pancreatitis
- Infliximab, not successful – short before surgery

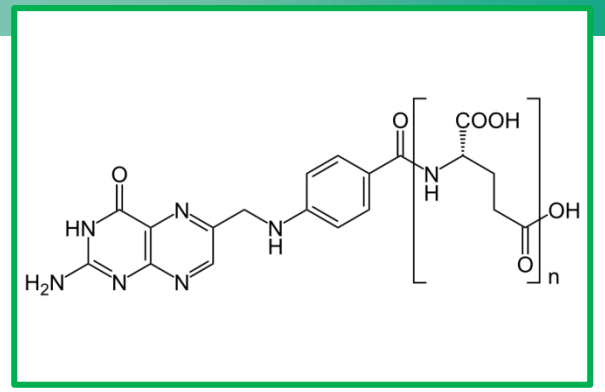
Comorbidites: newly diagnosed prostatic high grade dysplasia !

→ *What will be my **next Maintenance treatment** ?*

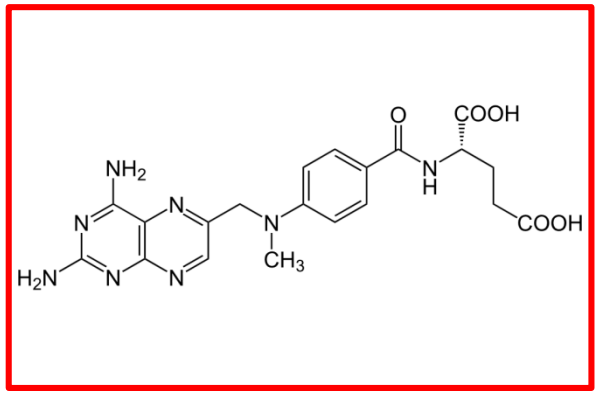
MTX ($C_{20}H_{22}N_8O_5$)

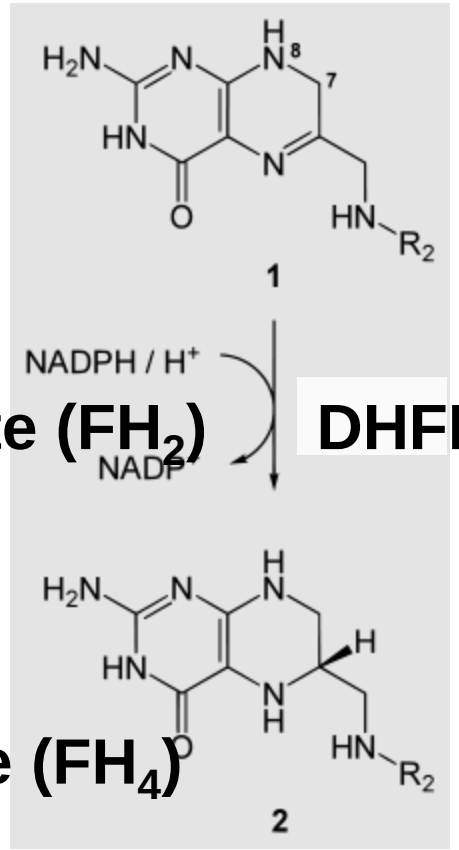
Analog to **Folic acid (VitaminB_9)**

(same structure as N-10-Methyl-aminopterin)



Inhibition of **Dihydrofolate-Reductase** (DHFR).





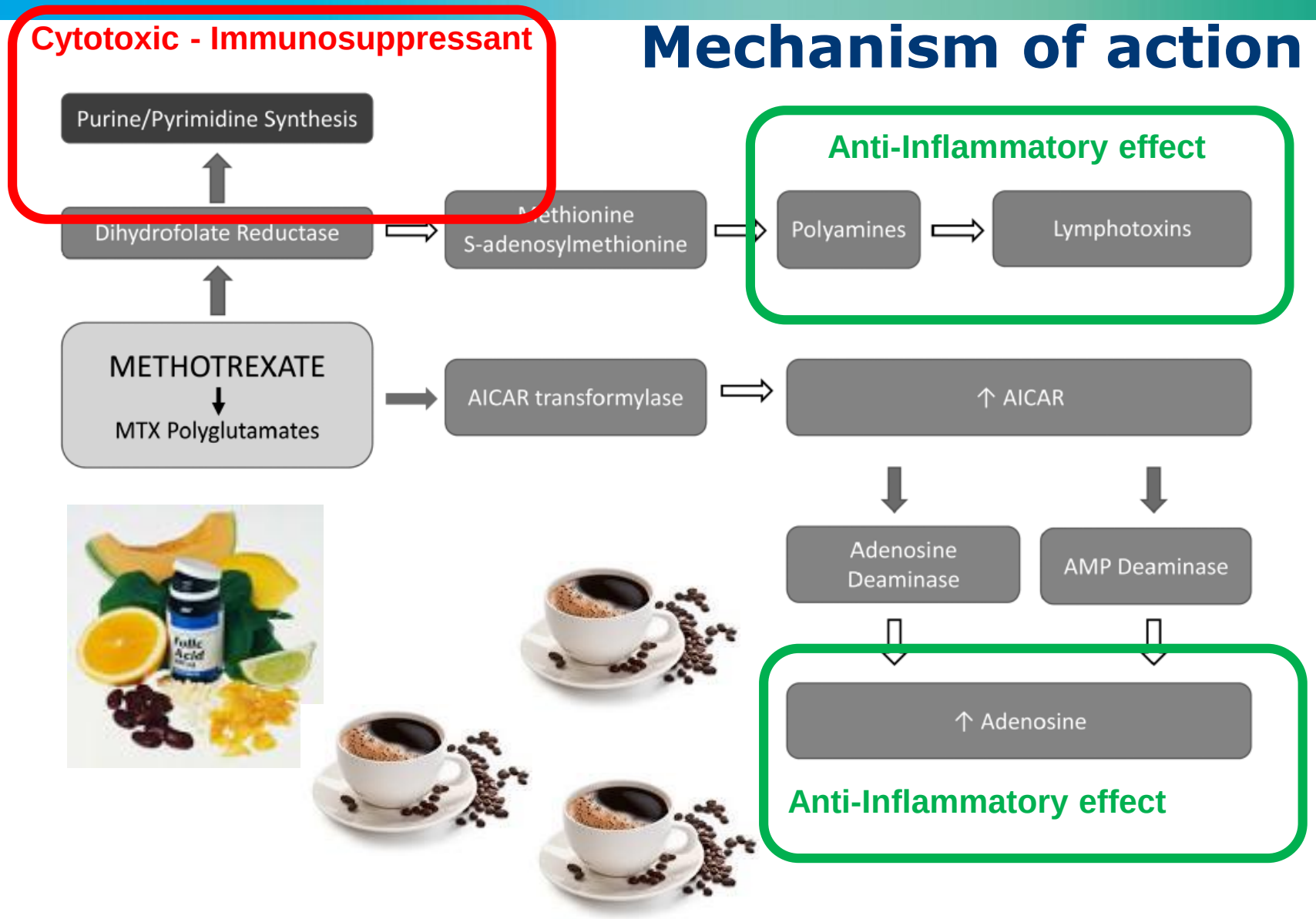
7,8-Dihydrofolate (FH_2) **DHFR**

Tetrahydrofolate (FH_4)

1940' Children's leucemia

Sources:
Feagan B. NEJM1995, Roblin X. APT2011, Wikipedia

Mechanism of action



Chan, E. and Cronstein, B. Bulletin of the Hospital for Joint Diseases 2013

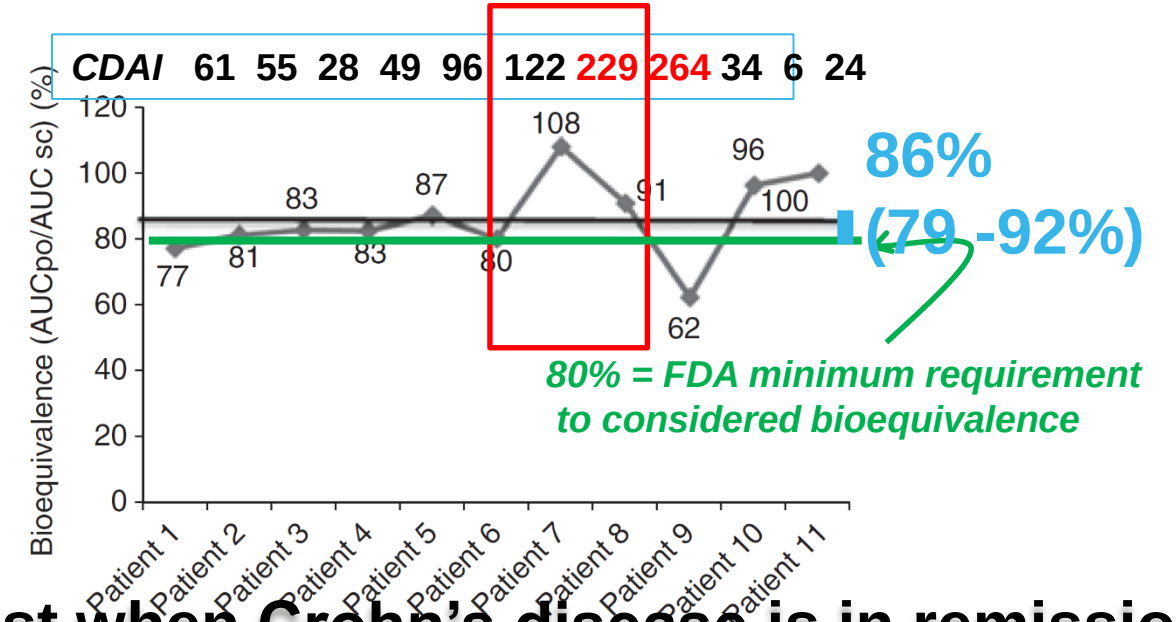
«Can I get oral treatment ?»

pharmacology / dynamics

CAVE: Bad Biodisponibility and highly variable ! (25-70%)

Crohn's disease patients : ***0.73*** *(CI 0.62- 0.86) -* ***vs.*** *RA, psoriasis :* **0.93 – 1.06**

11 Crohn's patients
Study in Ontario, Canada

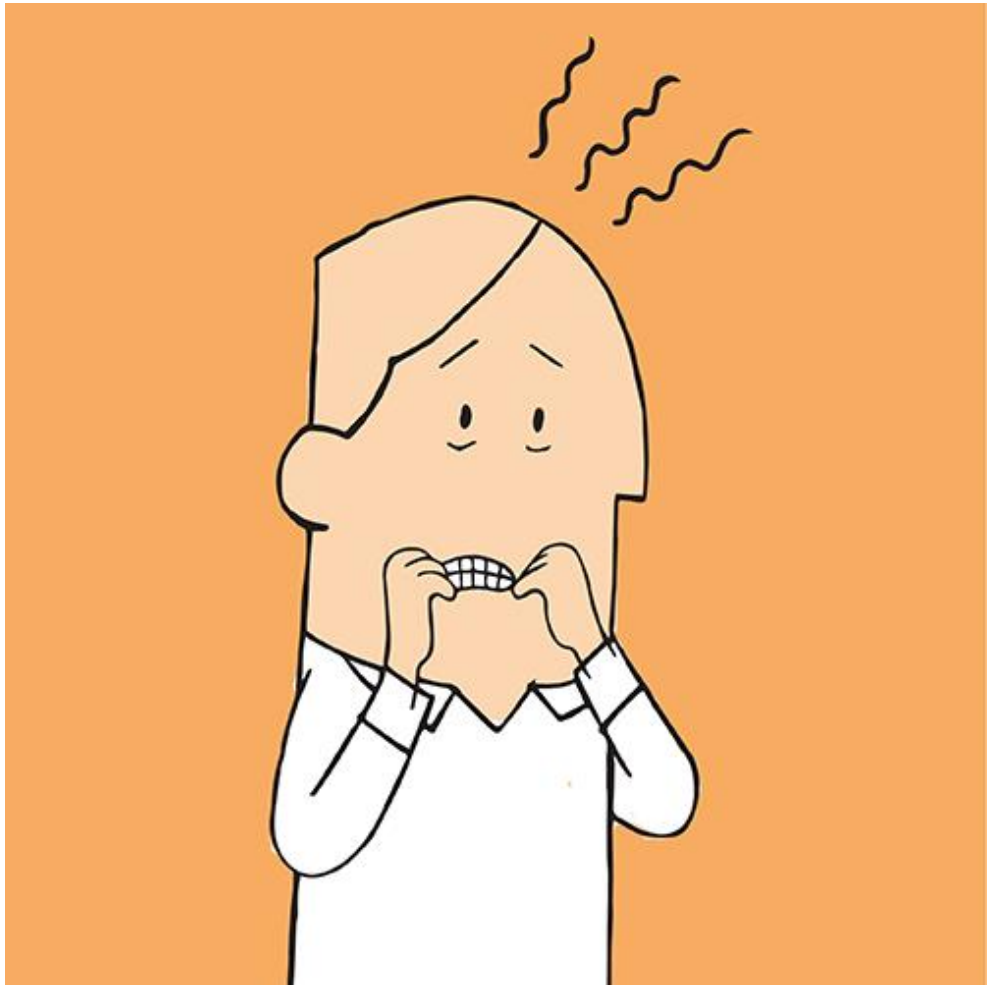


Kurnik D, et al. Aliment Pharmacol Ther 2003.
Chladek J, et al. Br J Clin Pharmacol 2002.
A. Wilson A. et al. Aliment Pharmacol Ther. 2013.

At least when Crohn's disease is in remission

→ reasonable to offer PO MTX *particularly in cases where compliance may be compromised by a parenteral route of administration.*

«How to start ?»



Low dose Methotrexate : use / dosage

Induction= 25 mg weekly subcutaneous (or intramuscular[1])

→ *(a) test for the tolerance : start a half dose ! (12.5mg – 1st injection)*

→ *(b) test the efficacy: it takes 6-8 weeks to work (min. 4 weeks)*

splitting (2-3x) the s.c dose (12-hour interval) improves tolerability and subcutaneous is better tolerated (less nausea, abd. pain) than oral [2]

Remission dose : 15 mg/week s.c. / oral 10 mg/week

splitting the oral dose (8-hour interval) improves bioavailabilty [3]

Storage : - at room temperature , protected from light . Once *opened*, vials of injectable can be safely stored at room temperature for 4 weeks.

1 Jundt JW, et al. A J Rheumatol 1993.
2 Weinstein GD, Arch Dermatol. 1971.
3 Hoekstra M,et al. J Rheumatol 2006;33:481–5.

INTOXICATION : *highest risk !*

→ ***this event is life threatening !***

MTX means **myelosuppression** (leukopenia, thrombopenia, and anemia).

MTX weekly ≠ MTX daily !

Moore TJ *et al.* Reported Medication Errors Associated With Methotrexate. Am J Health Syst Pharm.2004

Lomaestro BM, Lesar TS, Hager TP. Errors in prescribing methotrexate. *JAMA*. 1992.

Beware of erroneous daily oral methotrexate dosing. Institute for Safe Medication Practices; 2002.

Methotrexate overdose due to inadvertent administration daily instead of weekly. Institute for Safe Medication Practices; 2002.

Teratogenic !

Absolute

- Pregnancy or breastfeeding in women/conception in men
- Marked anemia, leukopenia, or thrombocytopenia
- Alcohol abuse
- Acute peptic ulcer
- Severe respiratory failure
- Immunodeficiency

- **Renal Failure !!**

Women of childbearing age taking MTX

must use at least **one or two effective methods of contraception**.

→ If this however happened - Take into account that :
-1- the minimum teratogenic dose of MTX is 10 mg/wk
and
-2- the critical period for malformations is 6th to 8th week of pregnancy

Men: MTX also has a toxic effect on dividing cells, such as spermatocytes, and may produce **oligospermia**, which can be intense and persistent and affect male fertility.

68 yo male, at 3 Months after MTX start

- Oral stomatitis , Oesphageal candidosis and Nausea / vomiting

Fluconazol

Folate 5mg 1x/w to up to 3x/ week

30%-90%

= Dose <u>response-related toxic effects</u>, dyspepsia, abdominal pain, indigestion, diarrhea, anorexia and weight loss. as well as *bone marrow suppression*.

Other AE : Headache, paresthesia, alopecia, hepatotoxicity, and pulmonary toxicity.

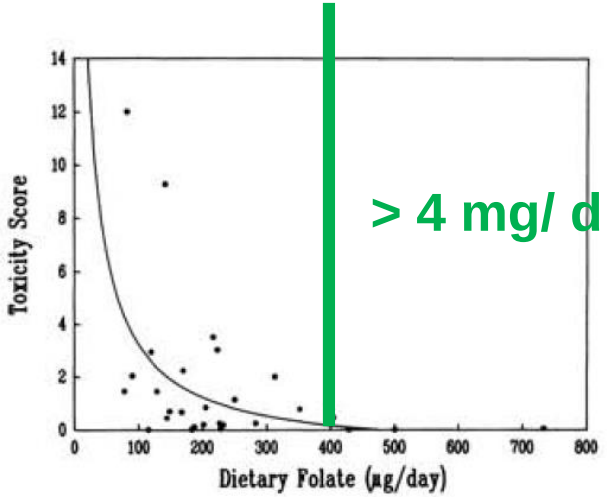


Figure 3. Toxicity score as a function of dietary folate intake in the placebo group. An exponential decay curve was fitted to the data. To convert micrograms to nanomoles, divide micrograms by 0.441 (the formula weight of folic acid is 441.4).

December 1994 • *Annals of Internal Medicine* •

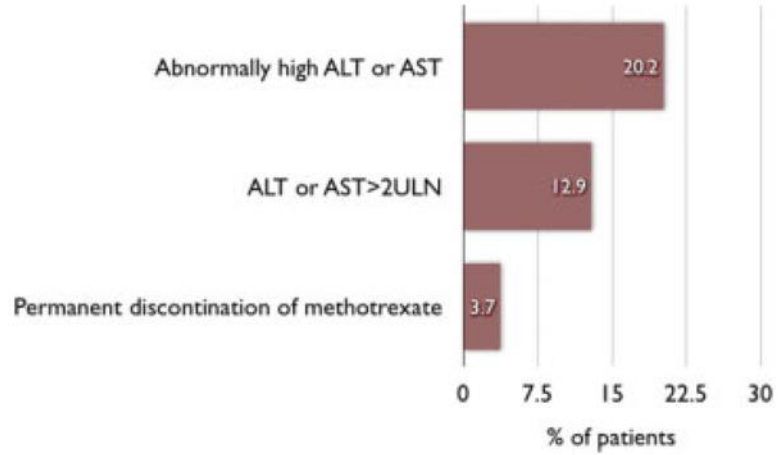
Blood monitoring with MTX

Routine blood labs

- basic chemistry panel, renal function.
- complete blood count.
- **Liver enzymes**

- *Frequency*:

1-2 week after initiation,
than every **2-3 months**



Pooled results of 27 RA studies (3808 patients)

H.Herfarth , Inflamm Bowel Dis 2010;16:1421–1430)

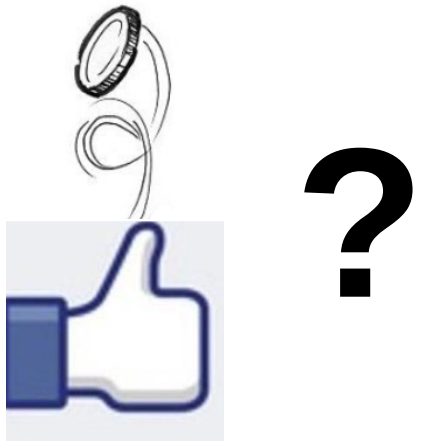
Liver biopsies not recommended,except w/ persistent LFT abnormalities
- however not always predictive of damages (Dufour, Kaplan NEJM 1996)-

→Alternativ : Fibroscan (> 9 Kpa) **(Laharie,et al. APT 2006 & Arena U et al. Dig. and Liv. Dis 2012)**

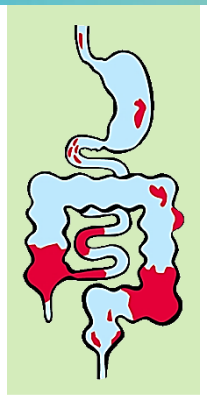
«Was it the right choice ?»

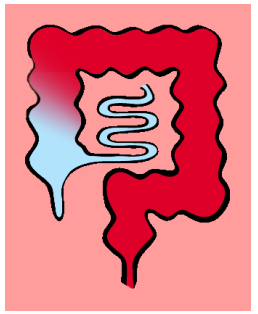
ECCO Guidelines / Indication / special situations

AND EFFICACY ?



Induction of remission





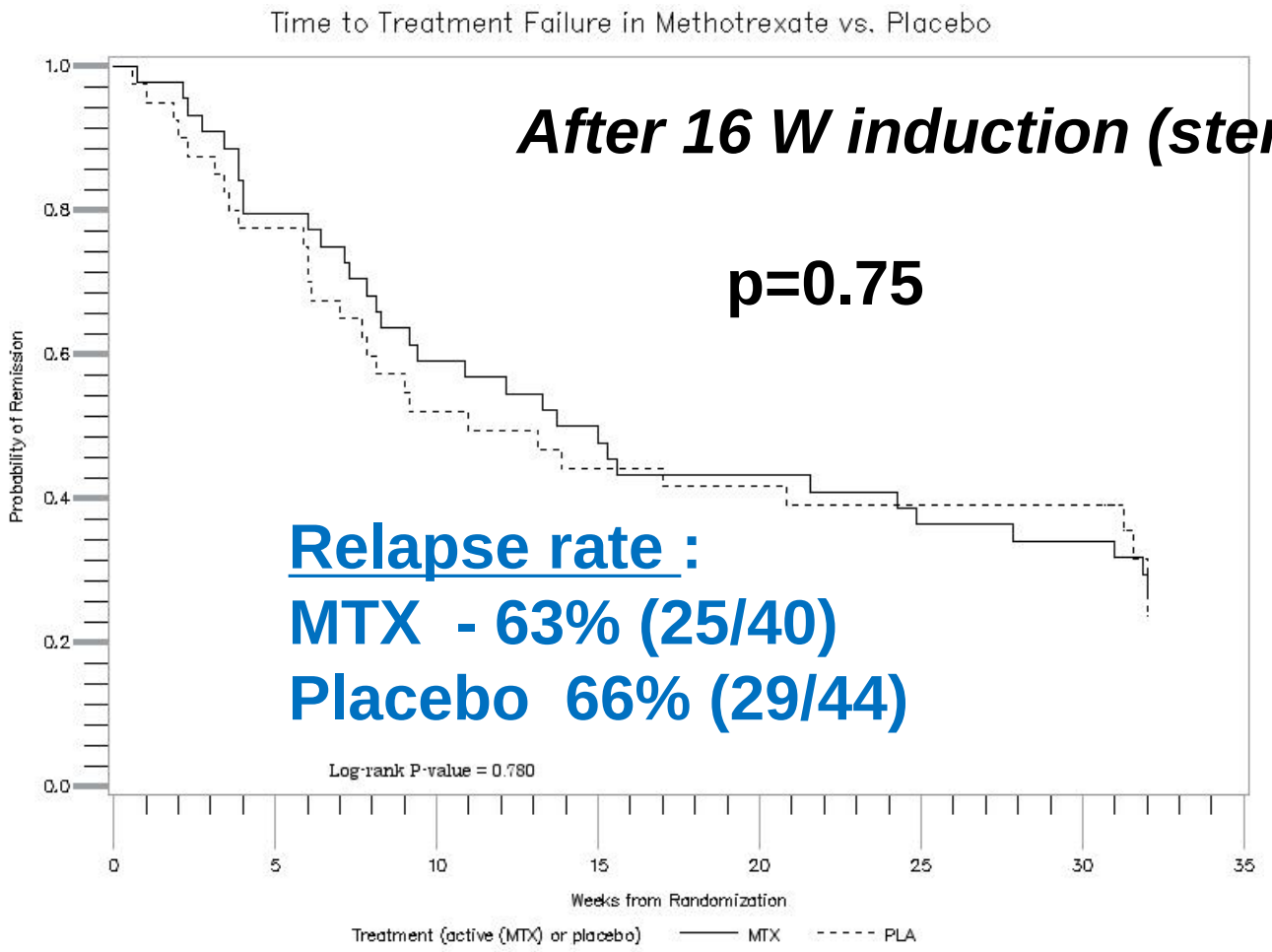
	Crohn's disease	Ulcerative colitis
Induction RCT **MTX 25 mg sc. 16 weeks** concomittant steroid (10-40mg) →**Steroid free remission** **clinical remission**	***NNT = 5*** ***(95%CI 3-19)*** **39% vs 19% (PBO) p=0.025** [1]	**METEORE Trial** [2] **32% vs. 20% (PBO) p=0.15** [2]
Cochrane Review	7 studies (495 pts) [3] - good evidence from 1 large RCT [1] - **oral : no benefit**	no benefit for methotrexate over placebo or active comparators [4] ***→ Higher DOSE !***

[1] **Feagan BG *et al.* Engl J Med 1995;332:292-7**
[2] **Carbonnel, *et al.* Gastroenterology 2016;150:380–388**

[2] **McDonald JWD, *et al.* Cochrane Database Syst Rev 2014;8:CD003459**
[4] **Chande, *et al.* Cochrane Database Syst Rev. 2014 Aug 27;(8):CD006618.**

MERIT UC - Maintenance of Steroid Free Remission in Ulcerative Colitis (Merit-UC) with MTX

Methotrexate is not superior to placebo in maintaining remission in UC patients.



After 16 W induction (steroids + MTX)

p=0.75

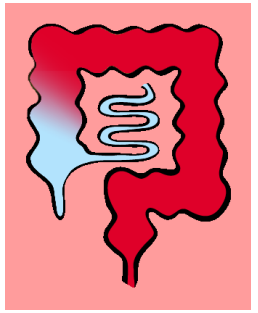
Relapse rate :
MTX - 63% (25/40)
Placebo 66% (29/44)

Enrollment: 179 patients – 37 sites across the US
Recruitement: February 2012 – May 2016
Study Completion Date: January 2018

MTX does not represent a therapeutic option for long term maintenance of remission in *patients with ulcerative colitis*.

Herfarth *et al.* Gastroenterology 2018

Maintenance of remission



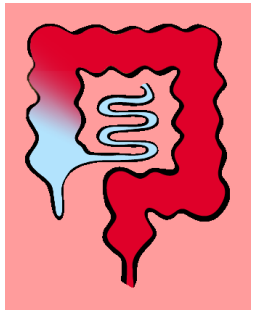
	Crohn's disease	Ulcerative colitis
Cochrane Review	5 trials (N= 333 patients): - vs. PBO (n=76) : **RR 1.67** (95% CI 1.05 to 2.67) [1]	2 Trials (N= 333 patients): - MTX vs. 6MP in cst –dep. : RR 0.74, (95% CI 0.43 to 1.29)
Results	- vs. 6MP (n=50) : **RR 1.36** (95% CI 0.92 to 2.00)	- Low dose MTX vs. PBO : RR 0.96 (95% CI 0.58 to 1.59)
Conclusion	- **15 mg/w s.c. superior to PBO**[2] **but not oral MTX**	**UNCERTAIN** [3] (HIGHER DOSE) **no evidence (MERIT UC)**.

[1] **Feagan BG, Fedorak RN, Irvine EJ, et al. N Engl J Med 2000;342:1627-32.**

[2] **Patel V., *et al.* Cochrane Database Syst Rev 2014;8: CD006884**

[3] **Chande, *et al.* Cochrane Database Syst Rev. 2014 Aug 27;(8):CD006618.**

Combination infliximab



	Crohn's disease	Ulcerative colitis
Cochrane Review **Results**	- Mono IFX vs. combi (n=145, including one RCT[1]) **RR 1.02**, (95% CI 0.76 to 1.38, P = 0.95).	**None**
Conclusion	[2] Combination therapy (methotrexate and infliximab) *not better than mono IF*	**None**

BUT:
- lower antibody formation with MTX combination (4% vs. 20%, P = 0.01)
- higher trough levels of infliximab (6.4 vs. 3.8, P = 0.08)

[1] **Feagan BG, *et al. Gastroenterology* 2014 – COMMIT trial**

[2] **Patel V., *et al.* Cochrane Database Syst Rev 2014: CD006884**

Special indications / categories of patients

- Methotrexate should be considered as a **valid option** in patients in whom thiopurines are not recommended.

- To diminish their risks by **avoiding long-term complications of thiopurines:**

Louis E. Gut 2014. Vol 63, No 11; 1695-9

- **a history of cancer**

Swoger JM, Regueiro M. Inflamm Bowel Dis. 2014;20:926–935.

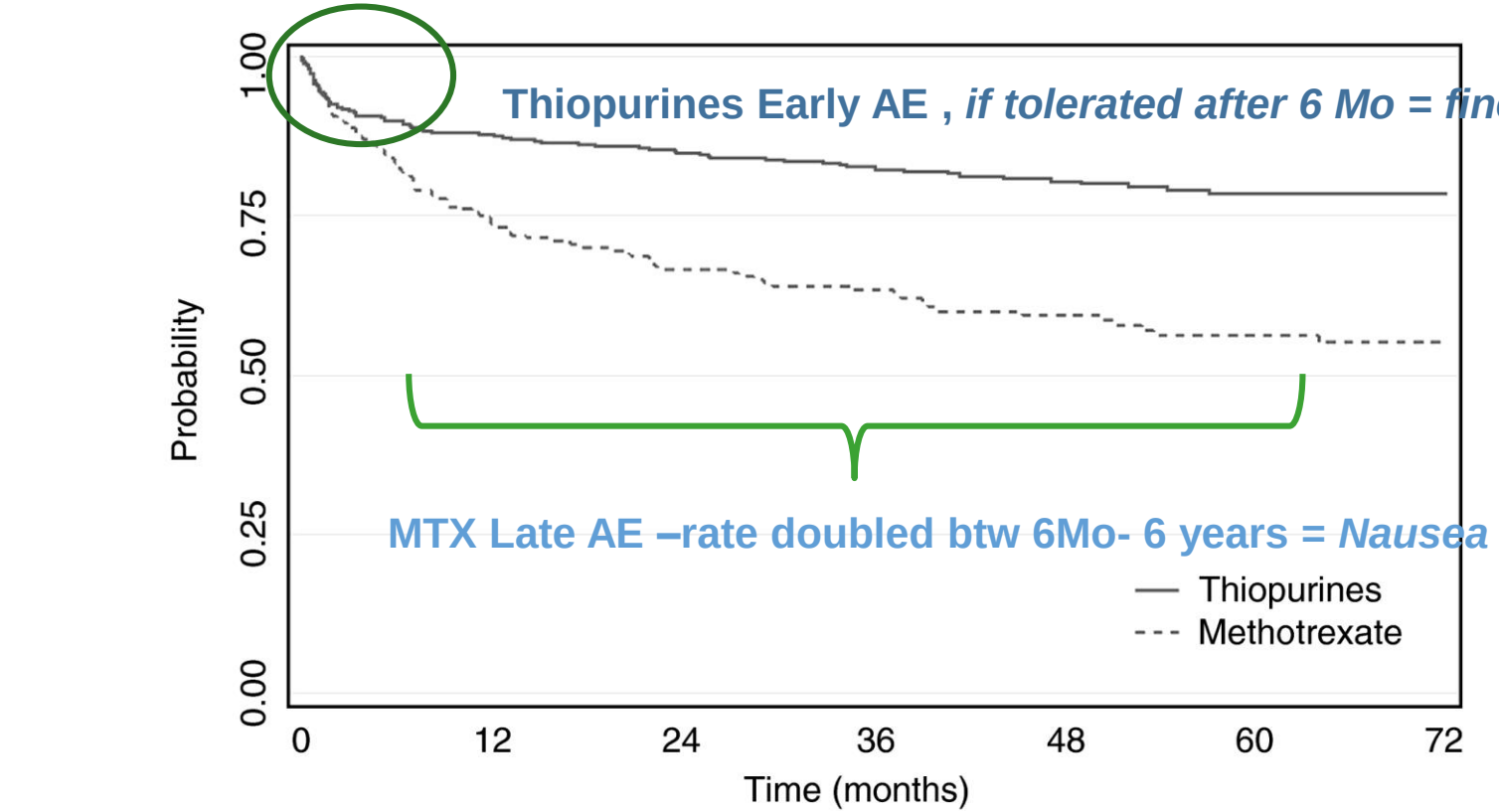
Jauregui-Amezaga A. & Vermeire S. *Annals of Gastro.* (2016) **29,** 127-136
Cesarini & Papi C. 2016, Expert Rev Gastroenterol Hepatol. 2016 May 13:1-10

When to avoid starting purine therapy:

- TMPT variant homozygotes (high risk of severe myelosuppression)
- Young EBV-seronegative patients (risk of fatal post-mononucleosis myeloproliferation of 3/1000 in males; risk of fatal hemophagocytic lymphohistiocytosis after primary EBV infection in both genders)

Stoping rate of Methotrexate vs Thiopurines

- In Australia (2004-2016): 782 pts, 244 MTX (31%), 538 Thiopurines



= 54% of previous int

Alimentary Pharmacology & Therapeutics, Volume: 52, Issue: 7, Pages: 1174-1184, First published: 14 August 2020, DOI: (10.1111/apt.16039)

Journal of Crohn's and Colitis, 2020, 4–22
doi:10.1093/ecco-jcc/jjz180
Advance Access publication November 11, 2019
ECCO Guideline/Consensus Paper

ECCO Guideline/Consensus Paper

ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment

Joana Torres,[a,*] Stefanos Bonovas,[b,c,*] Glen Doherty,[d] Torsten Kucharzik,[e] Javier P. Gisbert,[f] Tim Raine,[g] Michel Adamina,[h,i] Alessandro Armuzzi,[j] Oliver Bachmann,[k] Palle Bager,[l] Livia Biancone,[m] Bernd Bokemeyer,[n] Peter Bossuyt,[o] Johan Burisch,[p] Paul Collins,[q] Alaa El-Hussuna,[r] Pierre Ellul,[s] Cornelia Frei-Lanter,[t] Federica Furfaro,[c] Christian Gingert,[u] Paolo Gionchetti,[v] Fernando Gomollon,[w] Marien González-Lorenzo,[b,c] Hannah Gordon,[x] Tibor Hlavaty,[y] Pascal Juillerat,[z] Konstantinos Katsanos,[aa] Uri Kopylov,[ab] Eduards Krustins,[ac]

NEW GUIDELINES – Torres, et a

Introduction

Based on the current evidence, agreement on a recommendation for the use of MTX for inducing clinical remission in patients with CD could not be reached. However, MTX may be considered as an option for steroid-dependent patients with moderate-to-severe disease when alternative options [including surgery] cannot be used.

Methotrexate

maintenance

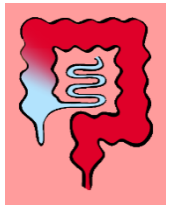
Recommendation 2.4. ECCO CD Treatment GL [2019]

We recommend methotrexate administered parenterally for the maintenance of remission in patients with steroid-dependent Crohn's disease [weak recommendation, moderate-quality evidence].

TAKE HOME MESSAGE

MTX : OLD DRUG = good safety profile !

>>



Cochrane Reviews Conclusions	Crohn's disease	Ulcerative colitis
Induction 25 mg/w s.c. or **maintenance** 15 mg/w s.c.	**superior to PBO** Not orally Probably equivalent to thiopurines in steroid- dependent cases	no evidence. UNCERTAIN → Should investigate higher dose

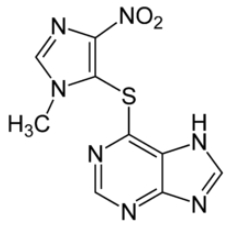
Conclusion : in CD same indication could apply as thiopurines, but in practice …

mostly in those refractory to or intolerant of thiopurines or anti-TNF agents .

Herfarth, *et al.* Dig Dis 2012;30(suppl 3):112–118
Fraser AG. Eur J Gastroenterol Hepatol 2003;15:225-31.

Immunosuppressiva

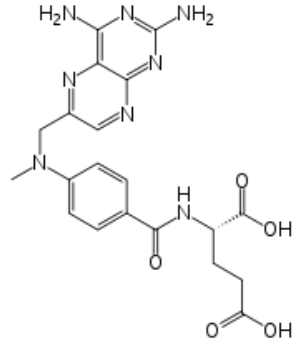
= Antimetaboliten (MTX=Thymidine; AZA/6MP=Guanine in DNA)



- Thiopurine: **Azathioprine**: 2-3 mg/kg/d

  6-Mercaptopurine: 1-1.5 mg/kg/d

  → *wirken nach 2-4 Mo (ca. 17 Wo).*



- **Methotrexate** : Induktion= 25 mg/Wo s.c. + Folsäure

  → *wirkt nach 6-8 Wo.*

  Remission = 15 mg/Wo s.c. (+Fol).

  CAVE: Schlechte Biodisponibilität, Teratogen

Feagan B. NEJM1995, Roblin X. APT2011

What is the biological effect of Thiopurines?

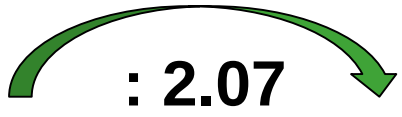
- Blocks NF-kB, and exerts a pro-apoptotic action on T-lymphocytes.
→ In particular activated T-lymphocytes, → decreases inflammation.

- inhibitor of purine de novo synthesis and seems to contribute, probably in a small manner, to the antiproliferative properties

31

What is the appropriate dosage of azathioprine and 6-mercaptopurine?

When should the effect of AZA evaluated?



- **AZA: 2-3 mg/kg - 6MP: 1-1.5 mg/kg**

-**For at least 2-3 months at optimal dosage**

What is the efficacy demonstrated in RCTs?

- **Meta-analysis from Kahn *et al* : no significant effect in inducing remission**
→ Prevention of relapse over 1-2 years : HR 0.64 (95%CI : 0.34-1.23)

- **Cochrane review : NNT = 5, NNH= 20** (Prefontaine *et al.*, 2009; CD 000067)

- **Mucosal healing rate (SONIC trial) = 16.5 % vs 30%(IFX) vs 44% (Combi)**

Induction of steroid free remission (at 6 Mo) was 30% vs 44% vs 57% (p<0.01)

Colombel *et al*, NEJM 2010; 362;1383-95

What to do in cases of thiopurine intolerance or resistance ?

9% of thiopurines resistance / 15-30% Intolerance **.**

→A) Optimisation of Thiopurine Therapy a) increase dose

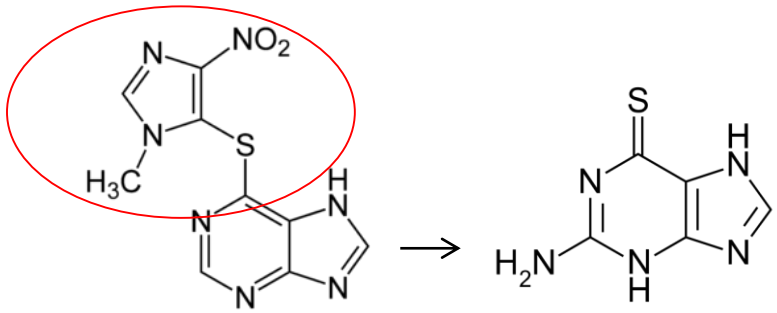
OR b) allopurinol combitherapy

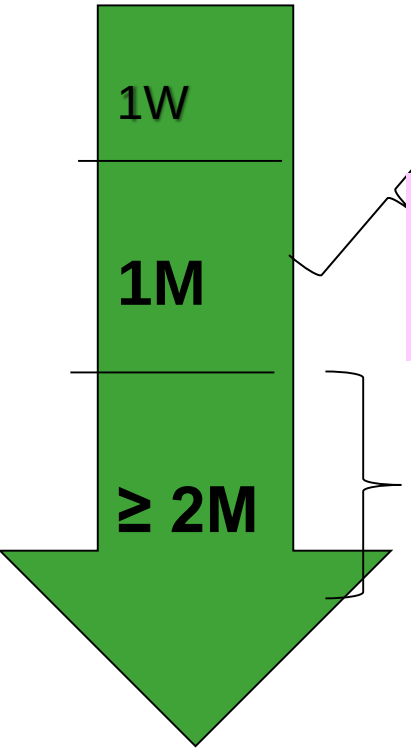
with some AE c) Switch AZA → 6MP

→ B) Anti-TNFs agents

Adverse events of thiopurines?

1) Global intolerance rate
2) Describe the most frequent AE





15% (to up tp 30%) of the patients are intolerant = experiencing AE
mostly GI AE (nausea, abdominal pain) → *possible switch AZA to 6MP*
But also → drug fever, arthralgies, rash, erythema

dose independent
VS

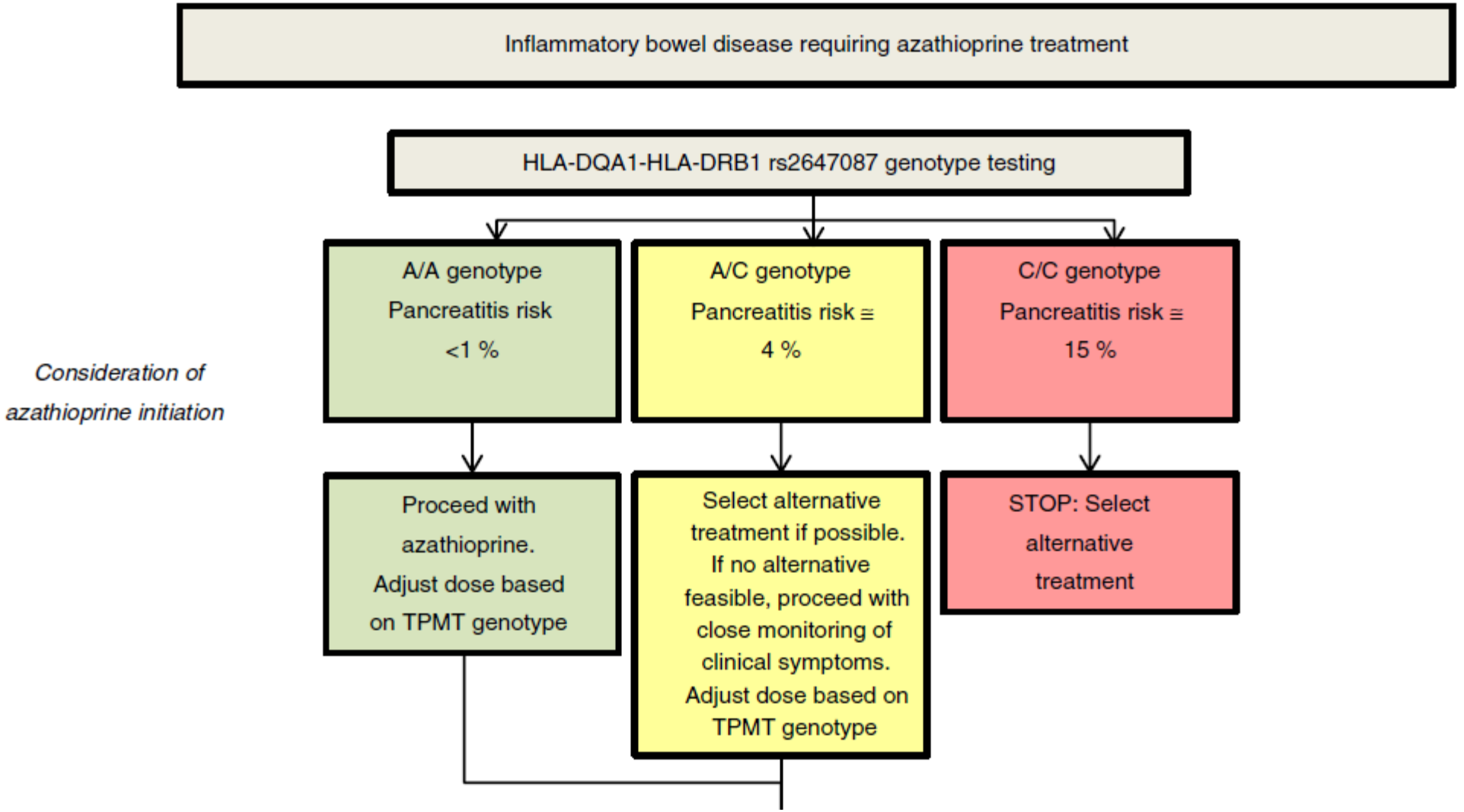
3 – 7% acute pancreatitis (allergic-like reaction)

dose-dependent AE

2 -10% Leucopenia / 1% pancytopenia

3% Hepatitis (cytolytic and cholestatic)

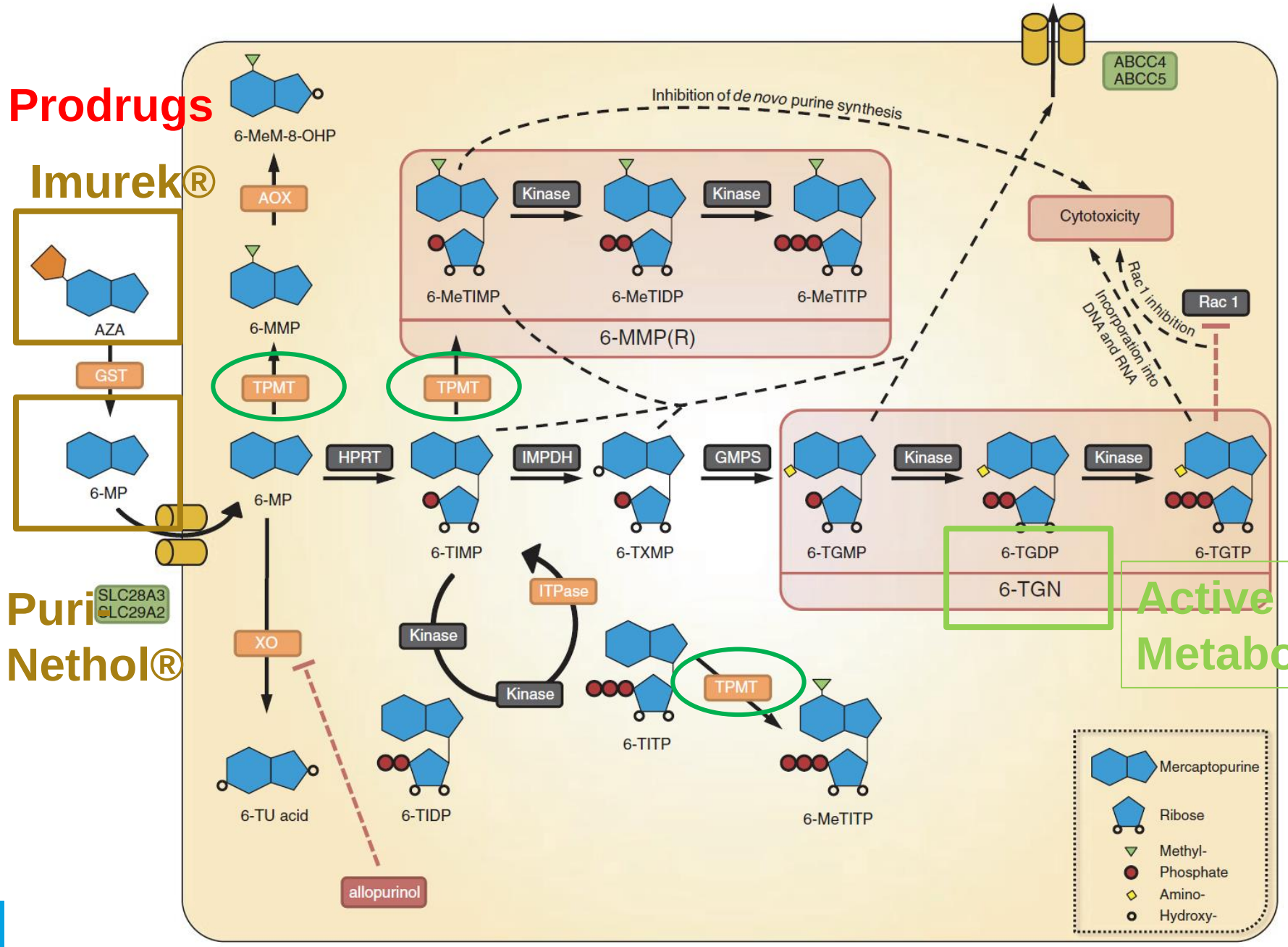
HLA - Allele assoziiert mit Thiopurin Pankreatitiden



Prodrugs

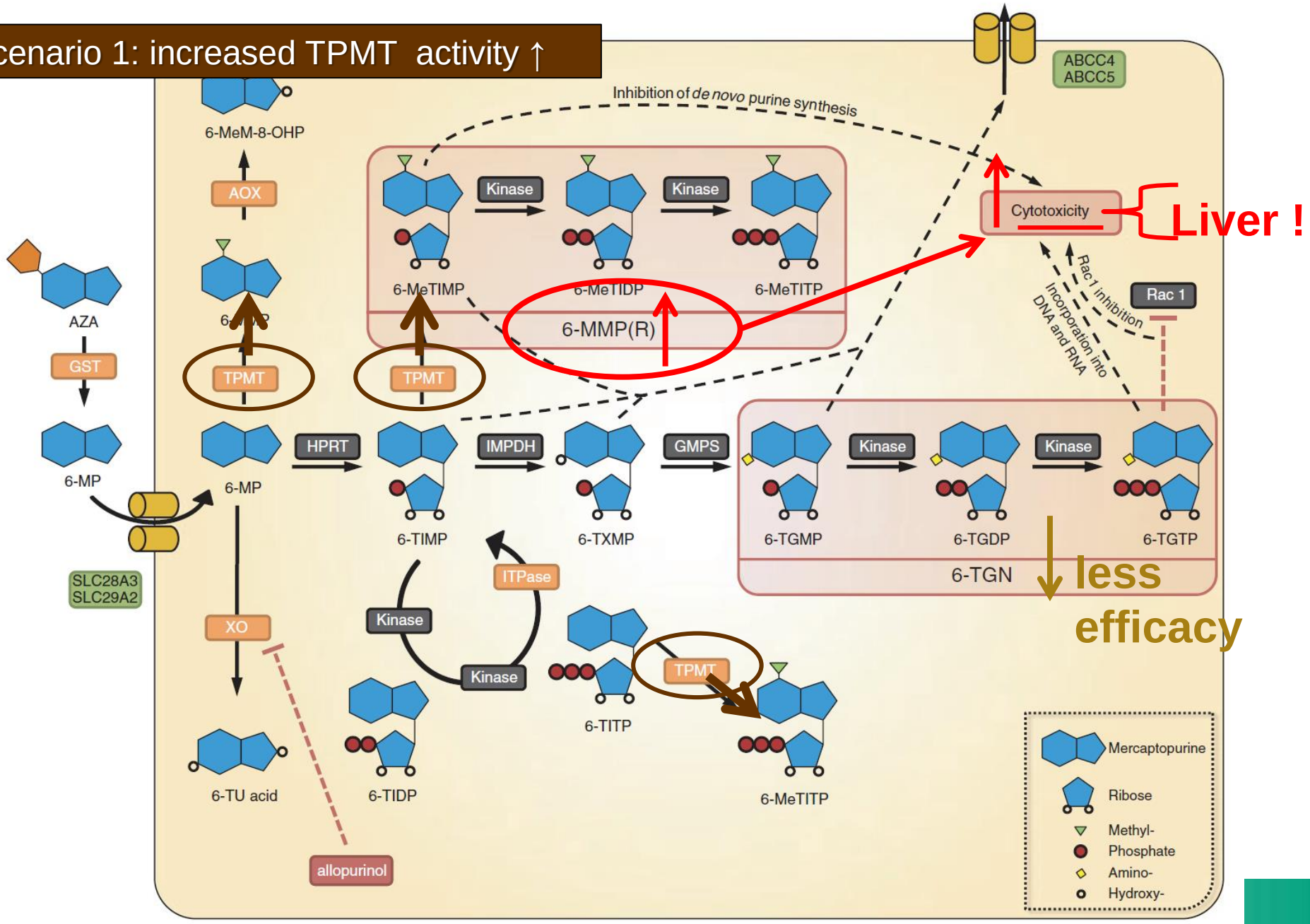
Imurek®

Puri Nethol®

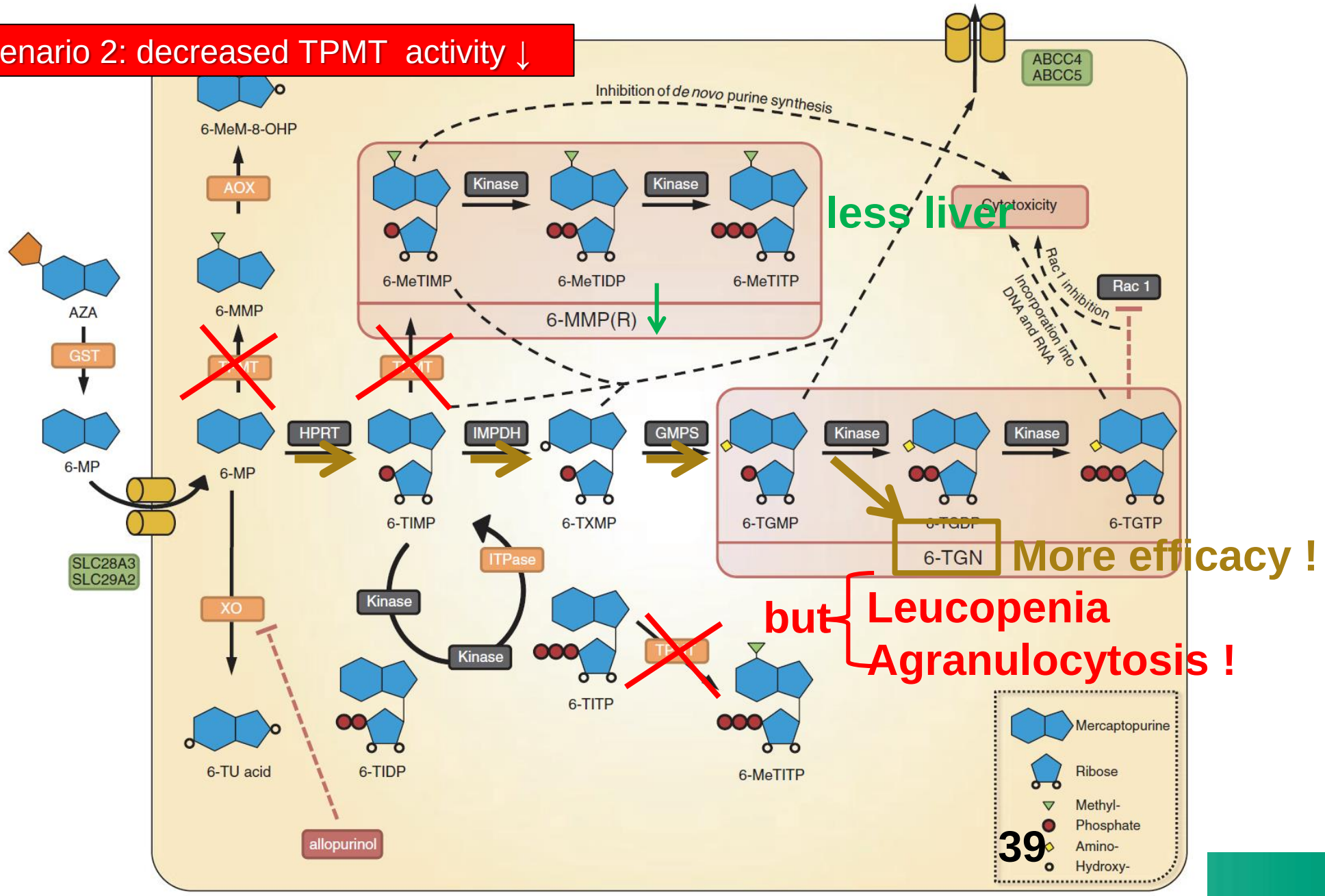


Active Metabolite !

Scenario 1: increased TPMT activity ↑



Scenario 2: decreased TPMT activity ↓



less liver

More efficacy !

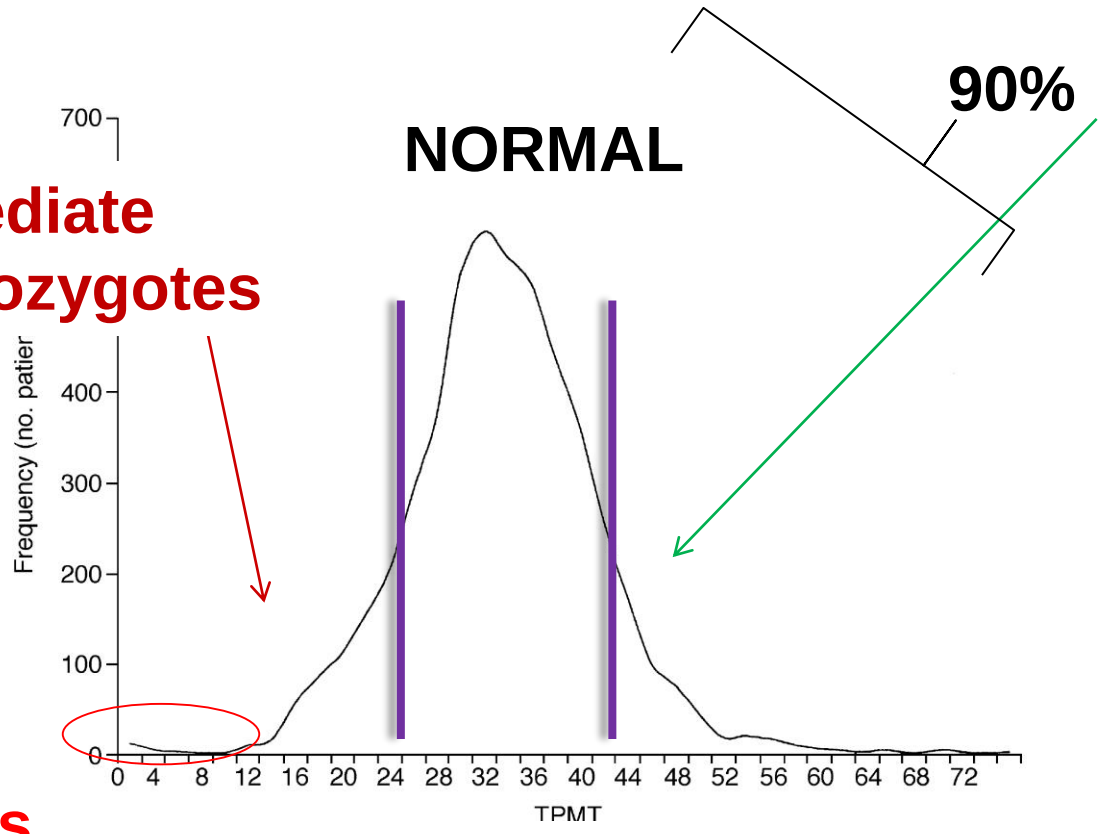
but
- Leucopenia
- Agranulocytosis !

39

Distribution of TPMT activity

10%
Caucasian
(2-5% Asia)

Intermediate
= heterozygotes



Hypermetabolisers (above the normal) = 11-12% →Risk of resistance up to 3mg/kg.

1/300
= 0.3%

Deficient
= homozygotes

Ansari *et al.* *APT 2008*
Cara *et al.* Med sci Monit 2004

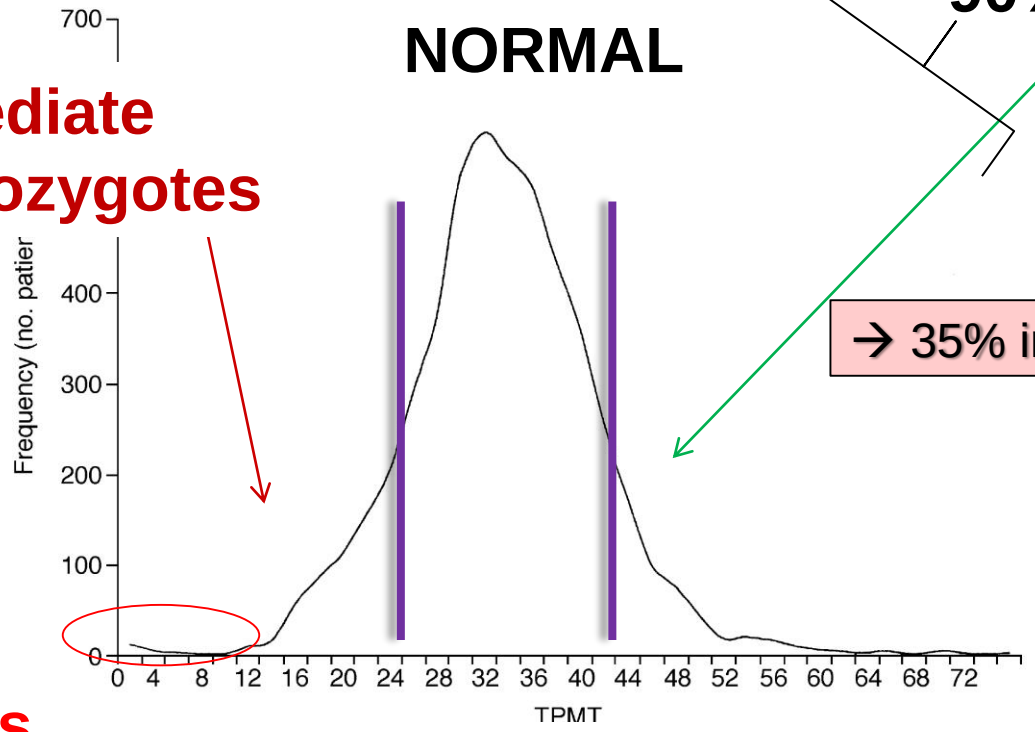
(pmol 6MMP/h/mg Hb)

Sanderson J *et al.* Ann Clin Biochem 2004; 41: 294

Wt allele: TPMT*1
mutant allele → loss of activity
Most common by the caucasian: TPMT*3A
NB: (double mutation = deficient → 3%)
- also TPMT*2 & TPMT*3C and TPMT*8 -

10%
Caucasian
(2-5% Asia)

Intermediate
= heterozygotes



Hypermetabolisers
(above the normal)
= 11-12%
→Risk of resistance up to 3mg/kg.

→ 35% increased risk of toxicity

Ansari *et al.*
APT 2008
Cara *et al.*
Med sci Monit
2004

1/300
= 0.3%

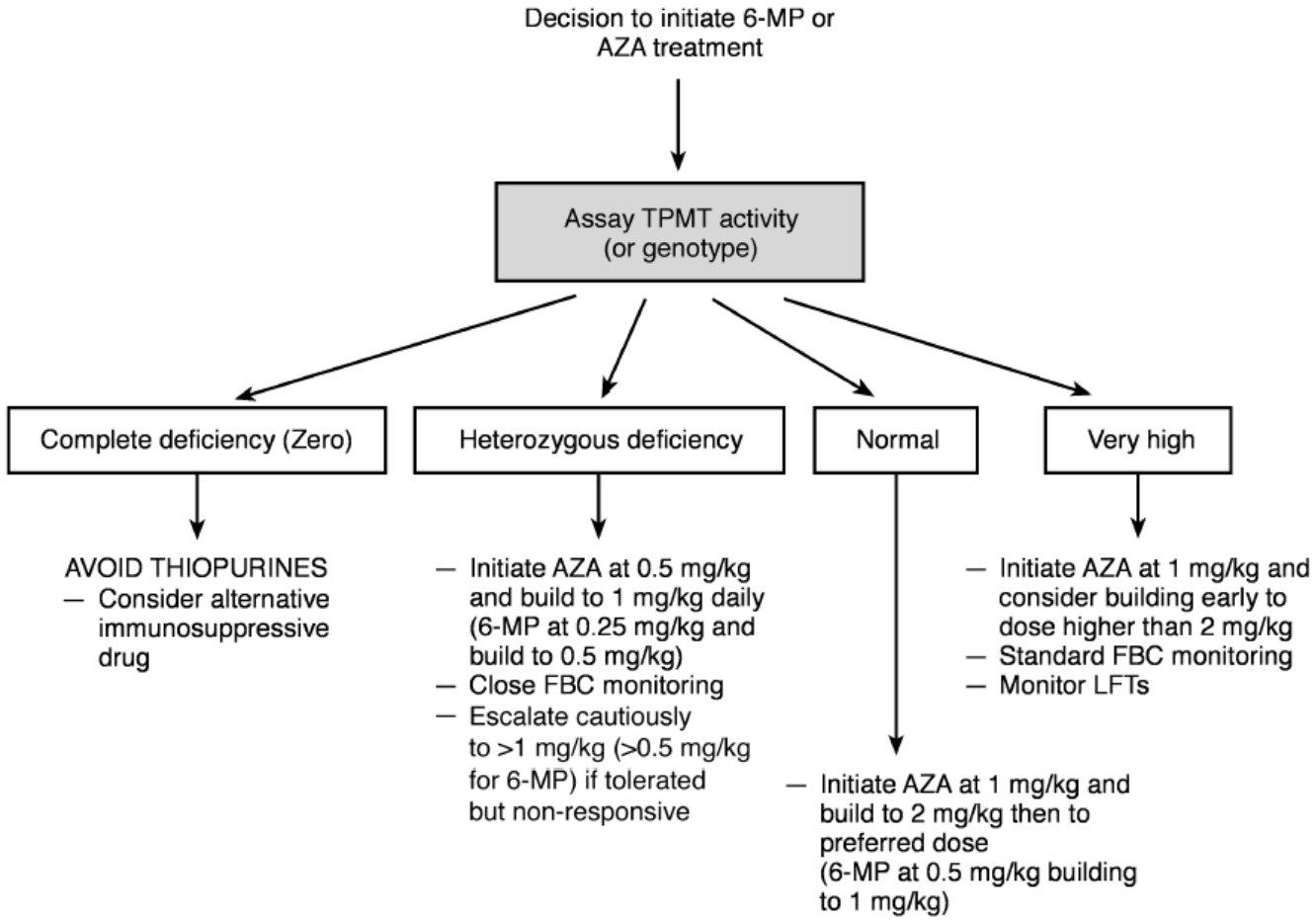
Deficient
= homozygotes

(pmol 6MMP/h/mg Hb)

Sanderson J *et al.* Ann Clin Biochem 2004; 41: 294

Management according to TPMT activity ?

Sanderson *et al.*



How to optimise Therapy ?

Das ist Dosis abhängig !!

OR= 5.0 (95% CI 2.6-9.7)

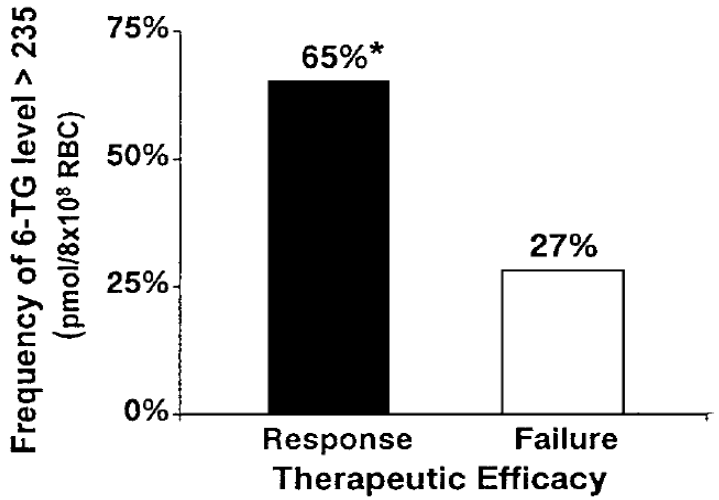


Figure 3. Frequency of 6-TG levels > 235 (pmol/8 × 10^8 RBC) at clinical evaluation points corresponding to therapeutic response, compared with points of therapeutic failure. *$P < 0.001$.

-**Messung der 6TG/ 6MMP**

→ **Ziel &TG > 235 pmol/8*10^8 Erythrocytes**

and 6MMP : > 5000 – 5700 pmol/8*10^8 Erythrozyten – Lebertoxizität.

Dubinsky *et al.*, Gastroenterology 2000
Seidman *et al.*, Rev. gastroenterol disorders 2003

Lab monitoring of thiopurines?

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL

Bern, January 2013

AZATHIOPRINE (Imurek ®) for Inflammatory Bowel Disease patients (Crohn's disease, ulcerative colitis) – Immunosuppressive treatment – Information for Patients

Therapy plan: In most cases, a gradual reduction of steroids with simultaneous start of an azathioprine treatment (maintenance therapy). In the beginning, the azathioprine dose will be at 50 mg for 2 weeks, after that with normal laboratory values a slow increase of the dose up to a target dose between 150 and 200 mg (2-2.5 mg/kg) daily. We thank you for a weekly (or at least every 2 weeks) check-up of the laboratory values, blood count and the liver values in the first month and then according to the protocol below by your general practitioner.

44

Tabelle – Ambulatorium Poliklinik

Therapie Schema / Überwachung :

	Dosis	**Dauer**	**Blutkontrolle beim Hausarzt**
1.	50mg /Tag (1 Tablette)	2 Wochen	➔ nach 2 Wochen, *wenn gut, dann*
2.	100mg /Tag (2 Tabletten)	2 Wochen	➔ nach 2 Wochen, *wenn gut, dann*
3.	Erhöhung der Dosis (jedes Mal 1-2 Tabletten)	2 Wochen	➔ nach 2 Wochen
➔	Bis Ziel: ……mg (vom Gastroenterologen auszufüllen)	Gewicht : ……kg	➔ Zyklus (3.) wiederholen bis zur Zieldosis
4.	Stabile Dosis	Langdauernde Therapie	➔ Ein Mal pro Monat für 2 Monate
			➔ alle 2 Monate für 1 Jahr
5.	Regelmässige Kontrollen		➔ alle 3 Monate

NB: an active Hepatitis B or an inactive carrier of the Hepatitis B virus should have been already excluded.

Please fax the results to Dr ……., fax # **031 632 07 99**.

! Caution: dose may not be increased without the consent of the physician!

With **strong epigastric abdominal pain** +/- radiating to the back (suspicion of drug-induced pancreatitis) stop taking the drug and have pancreatic enzymes measured by your family practitioner.

With **fever**, shivering – family practitioner / emergency consultation

- ➔ Most frequent side effects: increased liver values (hepatitis), decreased white blood cells count (leukopenia) and red blood cells count (anemia), pancreatitis, nausea, vomiting, rash, joint pain, diarrhea.
- ➔ INFECTIONS (bronchitis, pneumonia, pharyngitis, condyloma, herpes and other viral infections) – yearly flu vaccination. Avoid contact with persons with a cold.

Drug interaction (please inform the physician) with:
ACE inhibitors (e.g. Lisinopril, Zestoretic), Allopurinol (Allopur), Cyclosporine (Sandimmun) Methotrexate, anticoagulant (Coumadin - Marcoumar, Heparin, Plavix) and Bactrim.

Inselspital, Universitätsklinik für Viszerale Chirurgie und Medizin, CH-3010 Bern. www.viszerale.ch
Policlinic registration: Phone +41 (0)31 632 93 04, fax +41 (0)31 632 07 99

Azathioprin/ 6MP Therapie - NEBENWIRKUNGEN

- **INFEKTIONEN**

→ v.a. von den oberen Atemwegen: Bronchitis, Pneumonie, Pharyngitis,

→ Virale infektionen: Warzen, Condylomen, Herpes labialis

- Am häufigsten:
  - Hepatitis
  - Leukopenie oder Bizytopenie mit Anämie
  - Pankreatitis
  - Gastrointestinal : Nausea, Diarrhö
  - Haut: Ausschlag
  - Rheuma: Arthralgien
  - Lymphomen…

General population – Risk :

1/12'000

IBD – Thiopurine : 5-6/12'000