Autoimmune hepatitis

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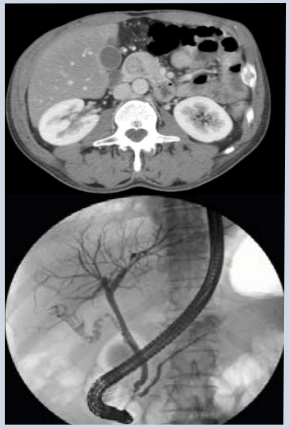


Dutch Autoimmune Hepatitis Group

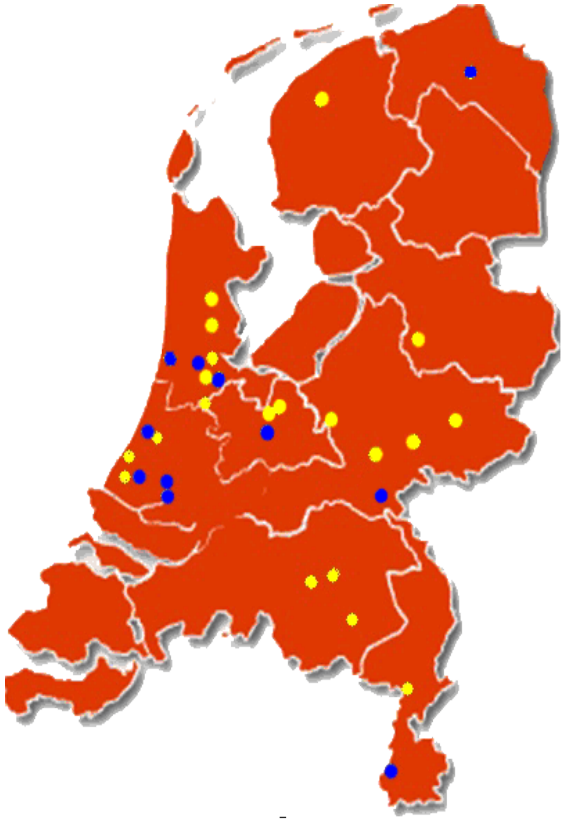
8 academic centers

24 general referral hospitals

Focus:

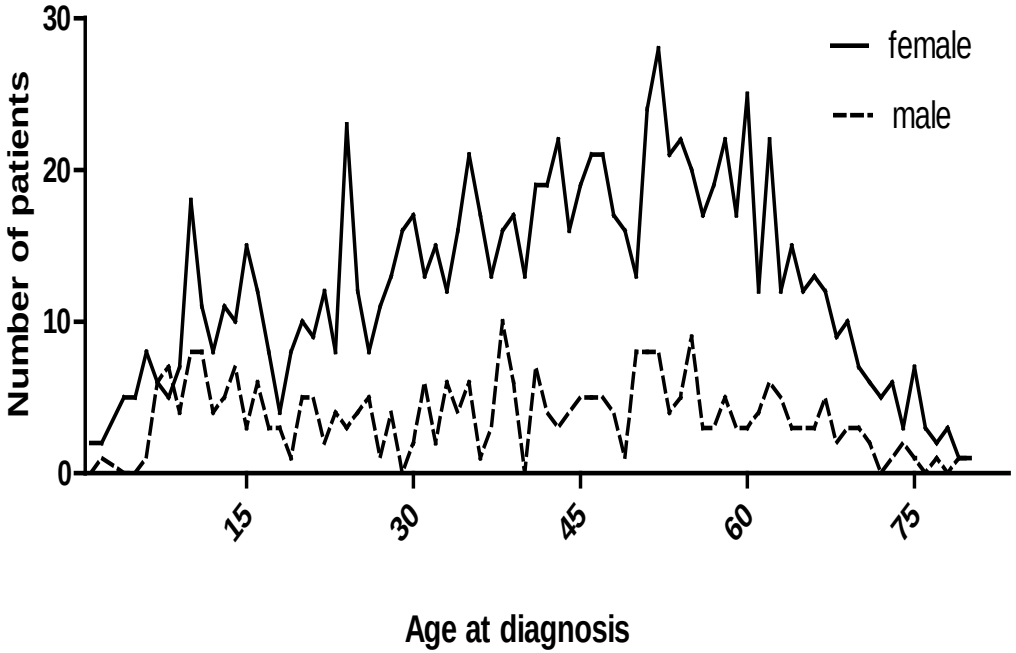
- Assessment of epidemiology and natural history in The Netherlands
- Understanding pathogenesis
- Evaluation of (novel) therapeutic strategies

Cohort of 1300 AIH patients



www.autoimmuunhepatitis.nl

Epidemiology in The Netherlands

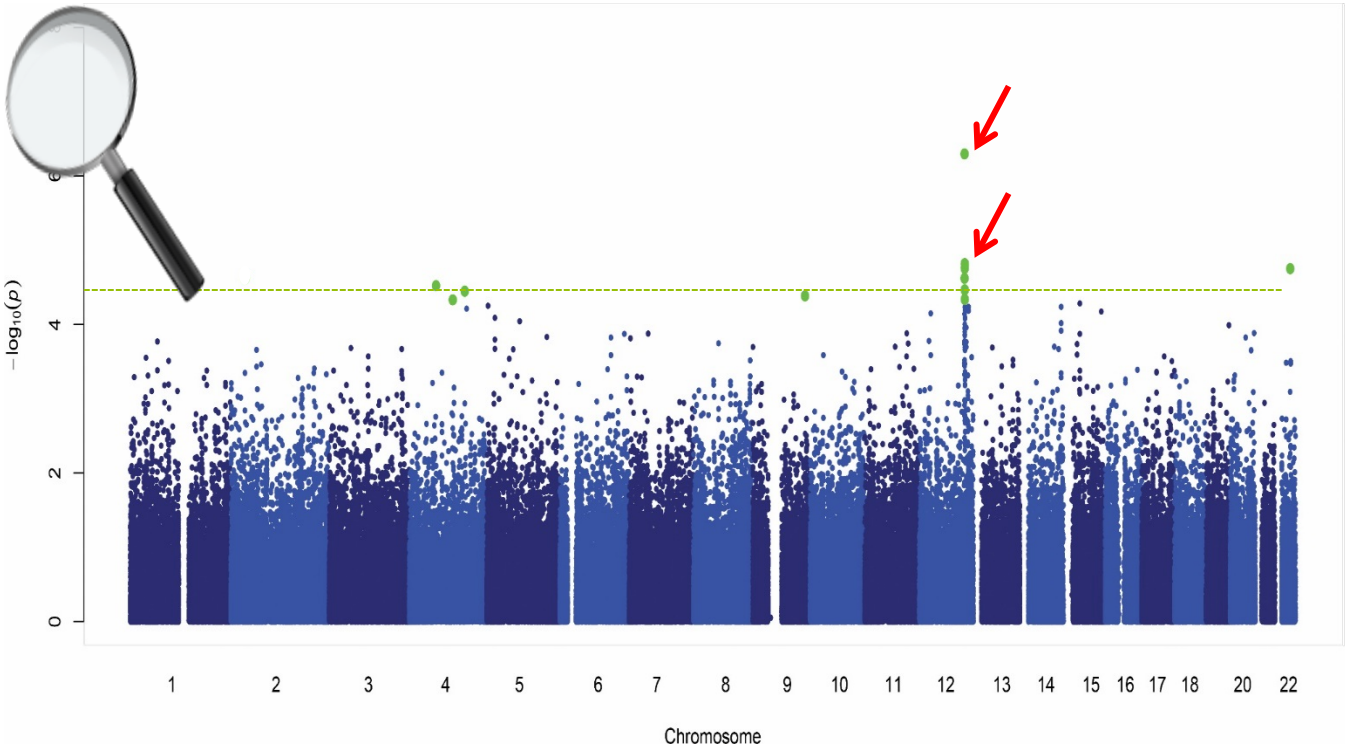


- Female predominance (F:M = 3:1)
- Average PSC and PBC (6 and 3%
- 56% fibrosis
- 12% cirrhosis
- 26% concomitant AID

- Female predominance (F:M = 3:1)
- Average PSC and PBC (6 and 3%
- 56% fibrosis 1.1/100.000/year
- 12% cirrhosis in liver biopsy
- 26% concomitant AID
- Prevalence: 18.3/100.000
- 3000 patients

Van Gerven et al., Scand J Gastro 2014

Genetics of AIH



De Boer YS et al. 2018, Gastroenterol 2014

Case (continued): Are the clinical, laboratory and histological findings compatible with the diagnosis AIH?

A. Yes

B. No

Feature/parameter	Discriminator	Score
ANA or SMA+	≥1:40	+1
ANA or SMA+	≥1:80	**+2**
Or LKM+	≥1:40	
Or SLA+	Any titre	
IgG or immunoglobulin level	>Upper limit of normal	+1
	>1.1× Upper limit	**+2**
Liver histology	Compatible with AIH	+1
	Typical of AIH	**+2**
Absence of viral hepatitis	No	0
	Yes	**+2**

≥6 points: probable AIH;

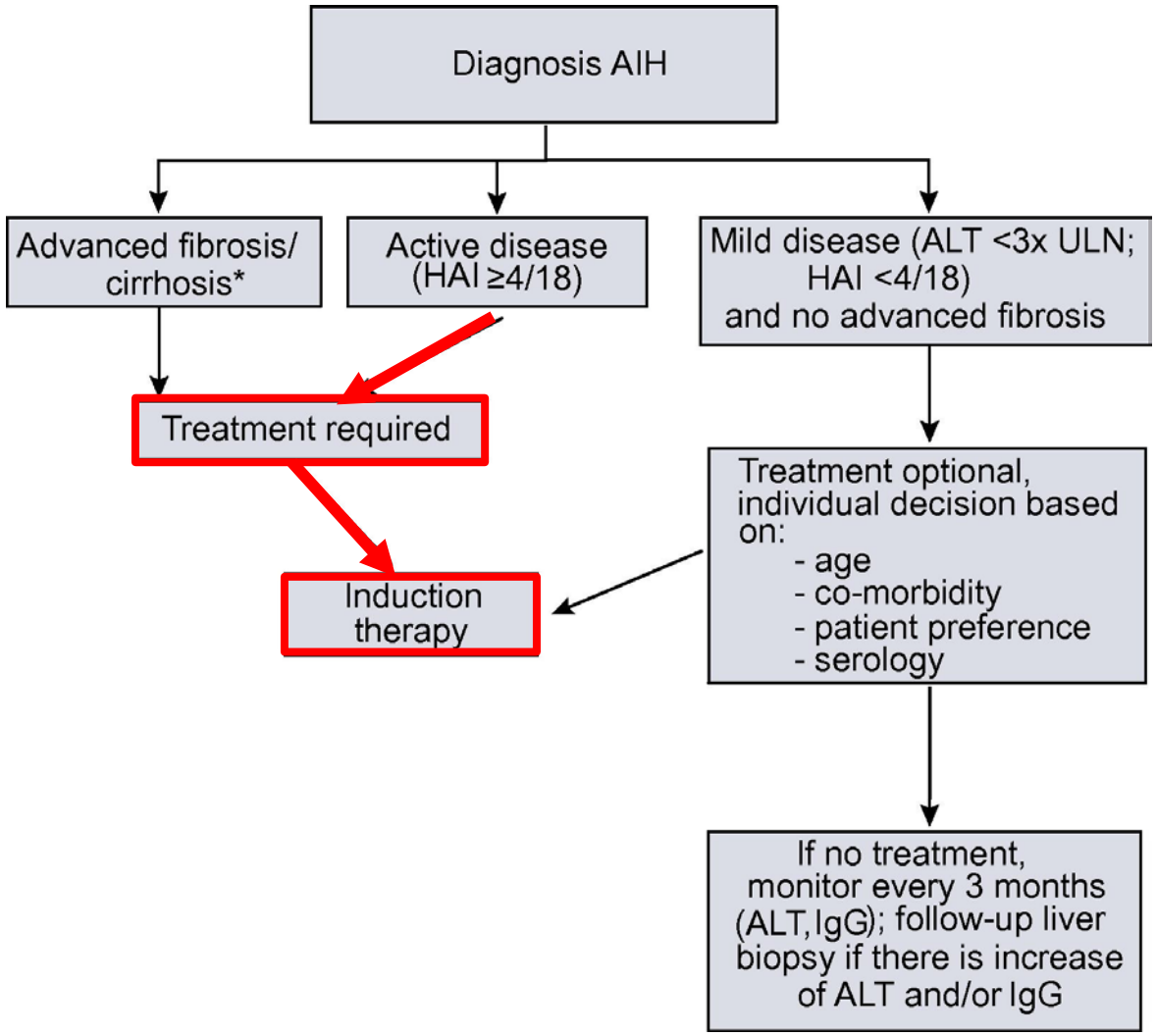
≥7 points: definite AIH

Is there always indication for treatment?

A. Yes

B. No

Indications for treatment



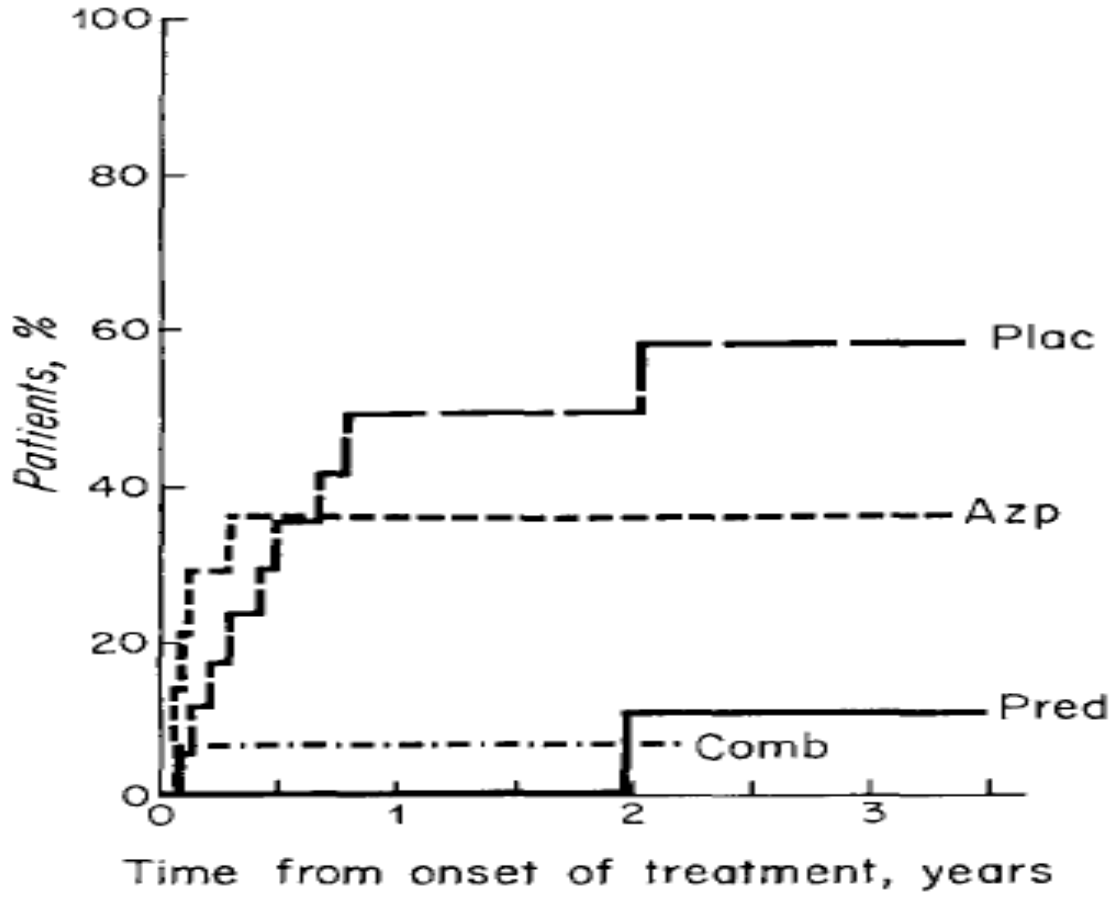
European Association for the Study of the Liver. *J Hepatol* 2015

What is the preferred medication for remission induction?

A. Steroid based induction scheme

B. Non-prednisone based induction scheme (e.g., Azathioprine)

Treatment of AIH



Soloway RD, et al. Gastroenterology 1972

What dose of azathioprine would you choose?

A. 50 mg/dag

B. 1 mg/kg

C. 2 mg/kg

Treatment scheme

EU 

Combination

- Prednisolone 0,5-1 mg/kg/d
- AZA 1-2 mg/kg/day
- Introduce AZA after 2 weeks

EASL. J Hepatol 2015

US 

Combination

- Prednisone 30 mg/day
- AZA 50 mg/day
- Introduce AZA and prednisone at start

Mono

- Prednisone 60 mg/day

AASLD. Hepatology 2010

Case (continued)

She was treated with prednisolone 40 mg/day, which led to initial strong reduction of ALT (255 IU/L) after 2 weeks. Azathioprine 75mg / day was then added.

Three months after initiation of therapy, symptoms have improved except from the arthralgia. At this moment the patient was on Prednisolone 10 mg/day plus Azathioprine 75 mg/day and weighed 70 Kg (+5 Kg).

Laboratory tests:

Bilirubin	19 µmol/l (normal < 20)
ALT	95 IU/L (normal < 30)
AST	73 IU/L (normal < 45)
IgG	18.1 g/L (normal <16.0)

Case

What do you tell your patient

A. The disease responds well to treatment. We continue current therapy and monitor over three months

B. Treatment response is unsatisfactory. We will need to switch to another therapeutic regimen

What can you expect?

- ✓ Majority of patients show improvement in biochemical parameters within two weeks
- ✓ Serum ALT < 2x ULN within 6 months in 80-90%
- ✓ Complete biochemical response at 6 months 60-70%
- ✓ In 5-10% of patients liver tests do not improve
- ✓ Histological normalization of the liver lags behind biochemical response for 6-12 months

Case

Six months after the start of treatment, liver tests and IgG have normalized on prednisolone 10 mg/day plus Azathioprine 75 mg/day. Her weight is 71 Kg (+6 Kg).

Patient is concerned about the side effects of treatment. She is aware of the side effects of steroid treatment but has also concerns about the side effects of azathioprine, in particular the risk of cancer.
What can you tell her?

A. The risk of malignancy is increased

B. Cancer risk due to thiopurines is neglectable

Side effects of Azathioprine: cancer risk

- Overall 41% to 68% excess risk of malignancy in patients exposed to thiopurines:
- Nonmelanoma skin cancers (risk persists after drug withdrawal): RR 2.3 (1.50 - 3.45)
- Association with cervical dysplasia and urinary tract cancers in organ transplant recipients, not clearly in IBD
- Lymphomas:

thiopurine monotherapy: HR 2.60 (1.96-3.44)
anti-TNF monotherapy HR 2.41 (1.60-3.64)
combination therapy HR 6.11 (3.46-10.8)
Absolute risk: 1 lymphoma per 1000 treatment years

Ariyaratnam J, Am J Gastroenterol 2014

Side effects of Azathioprine: cancer risk (AIH)

- ✓ 473 Swedish patients
- ✓ 44 malignancies after diagnosis
- ✓ 5 Non-Hodgkin lymphmomas
- ✓ Standardized Incidence Ratio NHL: 5.9 (1.9–13.8)

Journal of Hepatology

www.elsevier.com/locate/jhep

Characteristics of AIH patients with non-Hodgkin lymphoma and concomitant other autoimmune disorders.

Age/gender at diagnosis	Age at cancer diagnosis	Age when diseased	Azathioprine treatment
35/F [a]	47	48	2 Months
44/F [b]	64	64	Never
18/M [c]	38	39	8 Years
61/F [d]	69	75	Never
32/F [e]	50	50	8 Years

Per Sangfelt[10], Ola Weiland[11], Åke Danielsson[1]

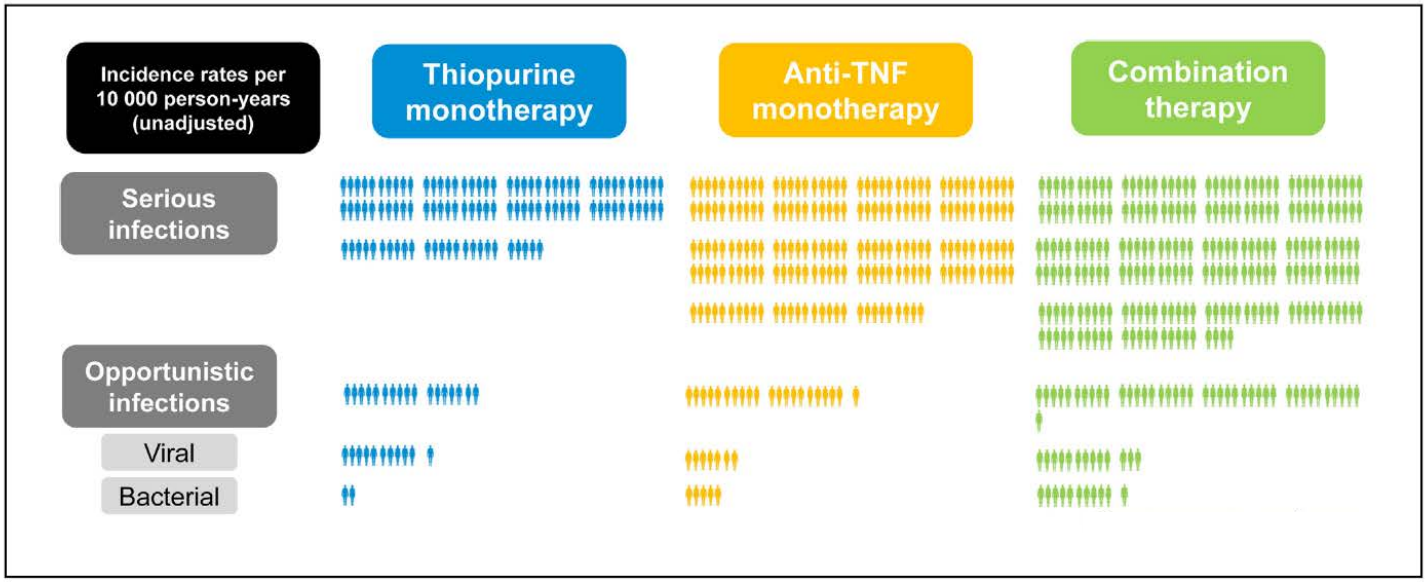
Azathioprine: infectious risk

Gastroenterology 2018;155:337–346

Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases

Julien Kirchgesner,[1,2,3] Magali Lemaitre,[1] Fabrice Carrat,[2] Mahmoud Zureik,[1,5] Franck Carbonnel,[4] and Rosemary Dray-Spira[1]

190.000 patients; 900.000 follow-up years



Annual risk severe infection:
0.8% (1 in 125) no immune suppression
1.1% (1 in 91) thiopurine monotherapy
1.9% (1 in 53) anti-TNF monotherapy
2.2% (1 in 45) combination therapy

Mortality: 3.9% in the first 3 months following serious infection
Risk for a serious infection is 20-50 times higher than lymphoma risk
Risk for fatal infection ~ as high as risk for developing lymphoma

Beware the elderly patient:
Annual risk of severe infection >65 years:
2.7% (1 in 37) thiopurine monotherapy

Case

Patient is concerned about the side effects of azathioprine, in particular the risk of cancer.

What can you tell her?

A. The risk of malignancy is increased

B. Cancer risk due to thiopurines is neglectable

Is this an indication for surveillance?

A. Yes

B. No

Case (continued)

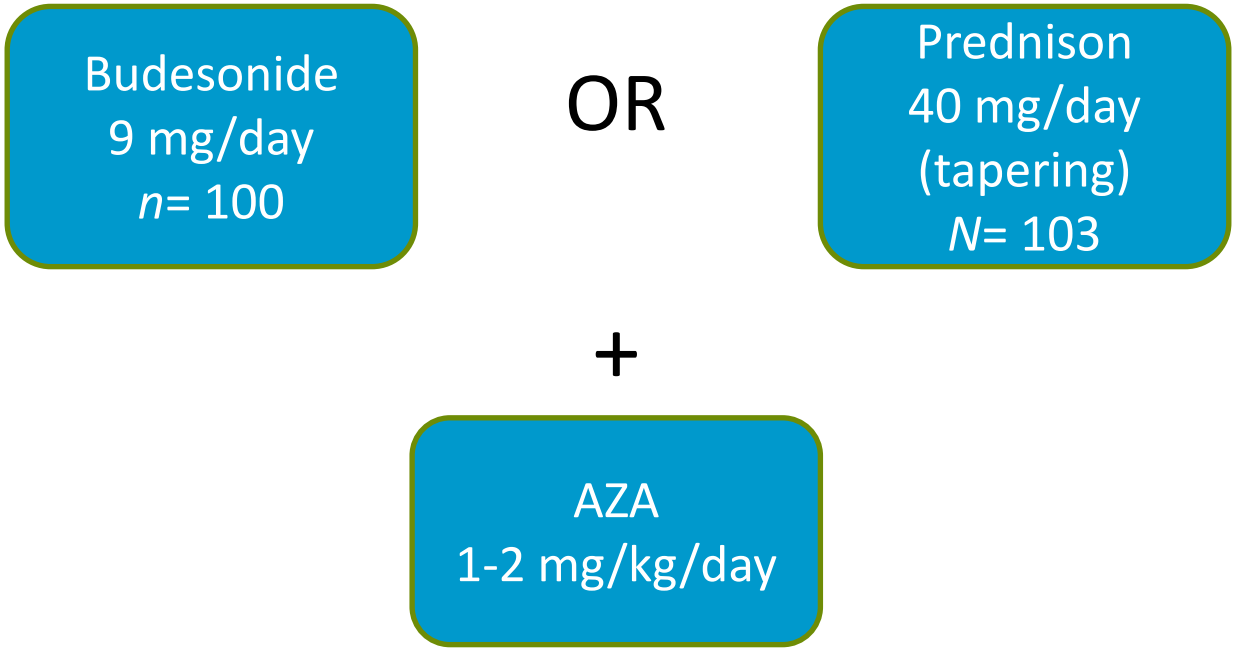
The patient has gained 10 kg of weight and has developed diabetes. What are the options?

A. Switch prednisone to budesonide

B. Increase the dose of azathioprine and taper the dose of steroids

C. Both options can be effective

Steroid sparing strategies: Budesonide

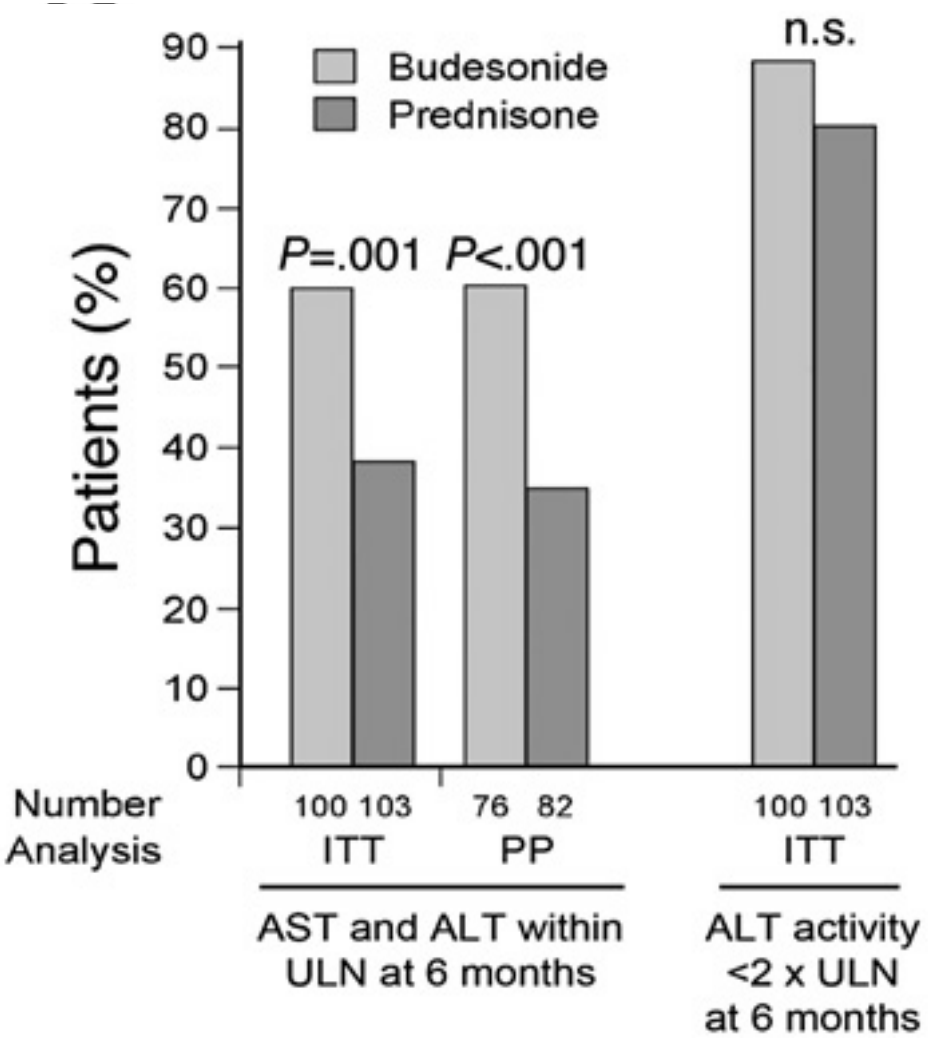


6 months prospective randomized, double-blind study

Open label phase 6 months AZA + Budesonide

Manns MP, *et al. Gastroenterology* 2010

Steroid sparing strategies: Budesonide



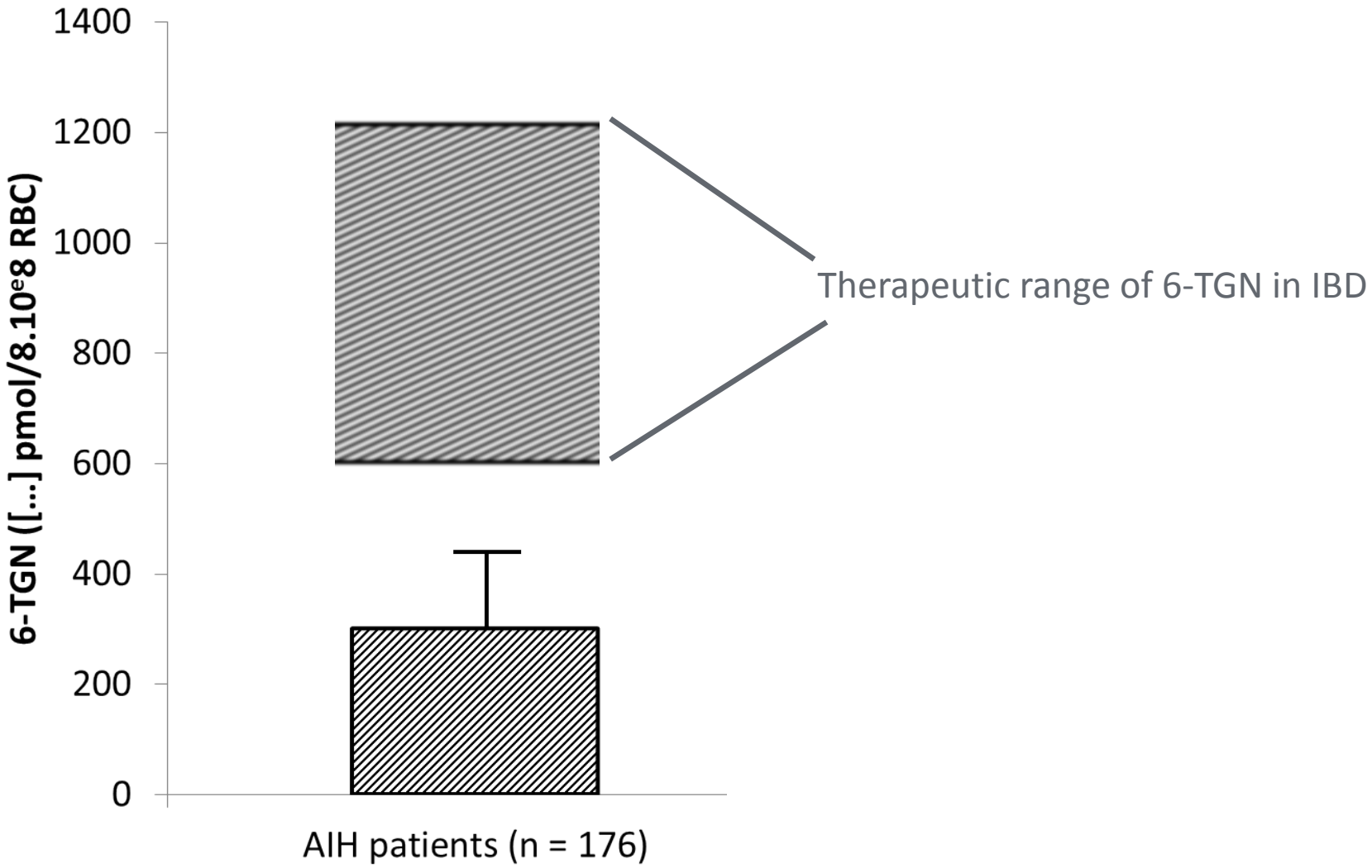
Complete biochemical response

Manns MP, *et al. Gastroenterology* 2010

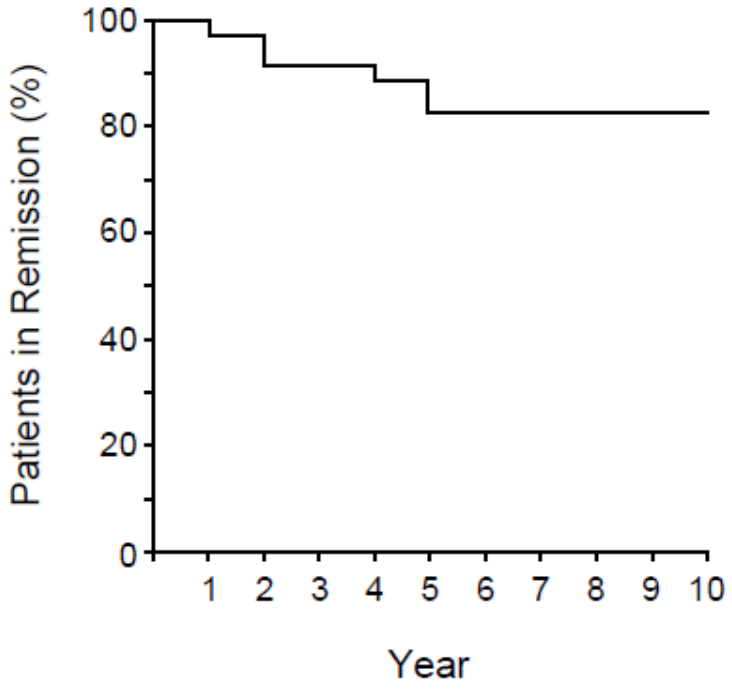
Budesonide - conclusion

- Budesonide (9 mg/day) plus azathioprine may be considered in treatment-naive non-cirrhotic patients with early stage disease
- Should not be used in cirrhotic patients or with concurrent extra-hepatic immune-mediated diseases
- Budesonide with azathioprine can both induce and maintain remission in paediatric patients with AIH but data are limited
- Long-term effects of this regimen on histological remission, bone growth and linear growth remain to be assessed

Optimizing thiopurine treatment



Optimizing thiopurine treatment



No. of Patients										
Total eligible for analysis	70	66	59	49	42	38	36	34	31	30
Cumulative total with relapses	2	5	5	6	7	7	7	7	7	7
Cumulative total excluded	2	6	13	23	30	34	36	38	41	42

72 patients in long-term remission

- steroids + AZA 1 mg/kg
- switch to mono AZA 2 mg/kg
- median f.u. > 5 years
- 38 arthralgia upon steroid withdrawal
- 9 deaths (1 lymphoma)
- 19 patients dose reduction: 5 relapse

Johnson *et al. NEJM* 1995

Case (continued)

The patient has gained 10 kg of weight and has developed diabetes. What are the options?

A. Switch prednisone to budesonide

B. Increase the dose of azathioprine and taper the dose of steroids

C. Both options can be effective, however

- Data are based on limited number of studies
- Budesonide data primarily based on treatment-naïve patients
- No histological follow-up in most studies
- Budesonide only in non-cirrhotic patients

Case (continued)

At six months the patient was switched to budesonide (9 mg/day) and Azathioprine 75 mg.

Six months later her biochemical results were:

IgG: 17 g/L
ALT: 200 U/L
AST: 130 U/L

What would you do now?

A. Switch back to prednisone

B. Increase the dose of Azathioprine

Case (continued)

At six months the patient was switched to budesonide (9 mg/day) and Azathioprine 75mg.

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AST 130 U/L

What would you do now?

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B. Increase the dose of Azathioprine

Case (continued)

Budesonide was replaced by prednisolone 20 mg / day which was subsequently tapered to 5 mg. Azathioprine dose was increased to 125 mg/day

Upon this treatment, IgG levels and serum transaminases normalized over the next three months.

However, she had persistent complaints of nausea and myalgia.

What is the most likely explanation for her ensuing complaints?

A. Azathioprine related side effects

B. Disease activity

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What is the most likely explanation for her ensuing complaints?

A. Azathioprine related side effects

B. Disease activity

Case (continued): Intolerant or difficult to treat patients

What would you do next?

A. **Stop Azathioprine and increase the dose of prednisone**

B. Replace Azathioprine with 6-mercaptopurine or 6 thioguanine

C. Replace Azathioprine with mycophenolate mofetil

D. Replace Azathioprine with tacrolimus or cyclosporin

E. Discontinue treatment

Case (continued)
Intolerant or difficult to treat patients

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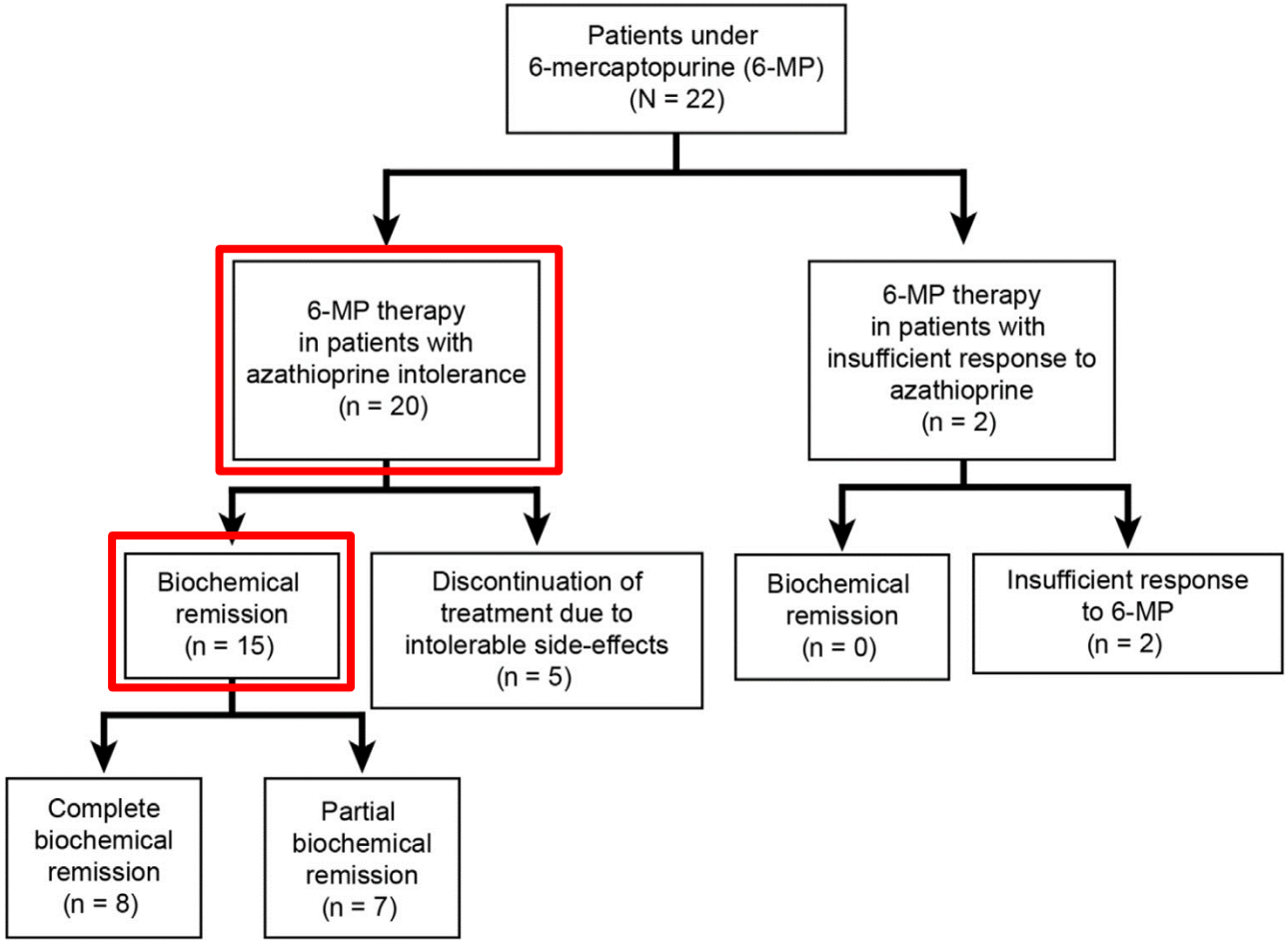
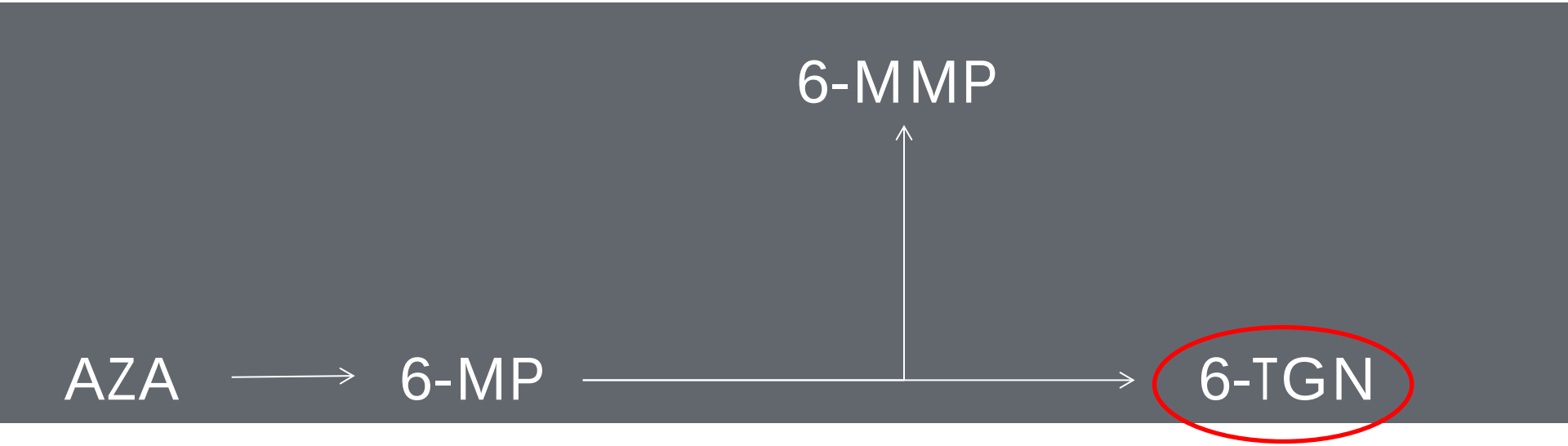
E. Discontinue treatment

Can we optimise thiopurine treatment? Switch to 6-mercaptopurine or 6-thioguanine

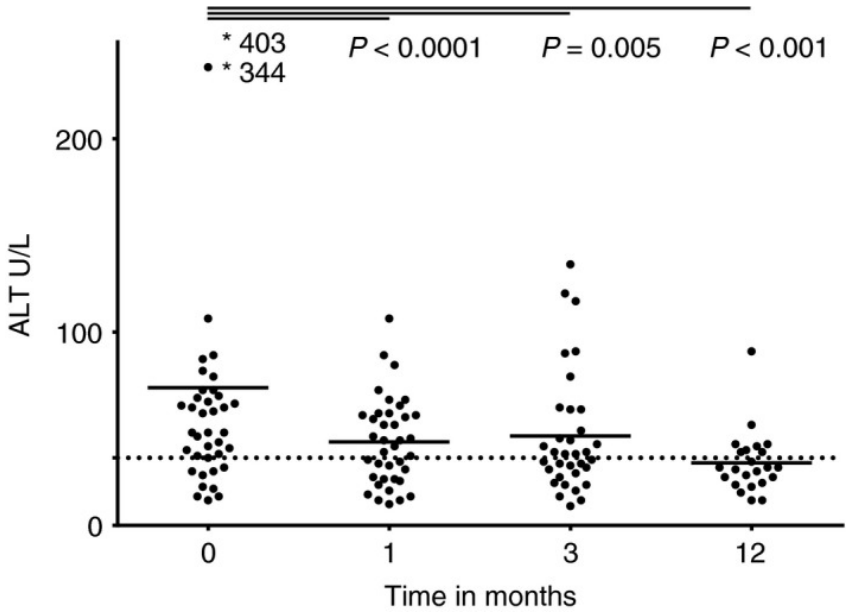


Hubener S et al, Clin Gastroenterol Hepatol. 2016

Can we optimise thiopurine treatment? Switch to 6-mercaptopurine or 6-thioguanine



Can we optimise thiopurine treatment? Switch to 6-mercaptopurine or 6-thioguanine



AZA/MP intolerant patients:

24/38 (63%) tolerant to TG and complete remission

van den Brand et al, AP&T 2018

Case (continued)
Intolerant or difficult to treat patients

What would you do next?

A. Stop Azathioprine and increase the dose of prednisone

B. Replace Azathioprine with 6-mercaptopurine or 6 thioguanine

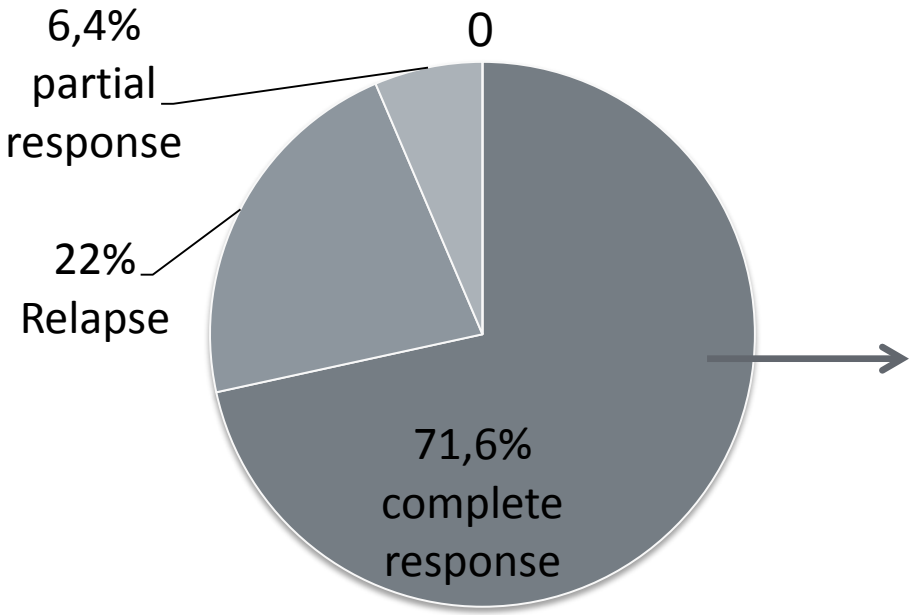
C. Replace Azathioprine with mycophenolate mofetil

D. Replace Azathioprine with tacrolimus or cyclosporin

E. Discontinue treatment

Mycophenolate Mofetil

Prednisolone + MMF 1,5-2 g/day
N= 109



78% remission without prednisone
(Median follow-up 5 years)

75% remission off treatment
(Median follow-up 2 years)

Efficacy in patients non-responding to azathioprine appears much lower!

Zachou, et al. Aliment Pharmacol Ther 2016

Case (continued)
Intolerant or difficult to treat patients

What would you do next?

A. Stop Azathioprine and increase the dose of prednisone

B. Replace Azathioprine with 6-mercaptopurine or 6 thioguanine

C. Replace Azathioprine with mycophenolate mofetil

D. Replace Azathioprine with tacrolimus or cyclosporin

E. Discontinue treatment

Cyclosporin

Experience mainly in severe disease or to prevent steroid side effects

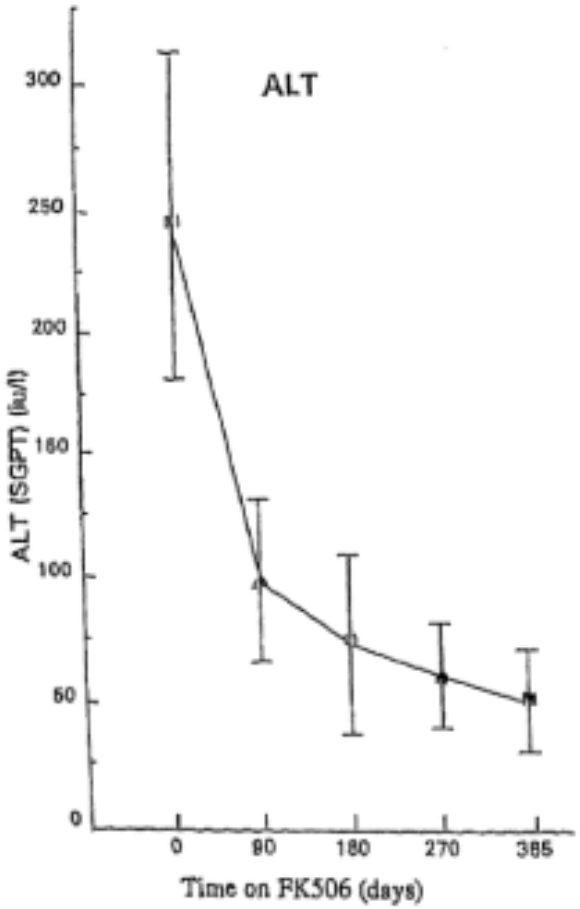
Biochemical response rate ranging from 80 to 100% in children and adults

Dose of 2–3mg/kg/day

Only data from small series

Malekzadeh, et al. Dig Dis Sci 2001;46:1321-7.

Tacrolimus



Predominantly used as salvage therapy

Average dose 5 mg/day

Response rates 50-70% in small series

Van Thiel, et al. Am J Gastroenterol 1995

Than NN, et al. Scand J Gastroenterol 2016

Case (continued)

The azathioprine was replaced by 6-mercaptopurine 50 mg/day and prednisolone was subsequently successfully tapered out.

Over the next year she did not experience arthralgia and she was feeling well. Her liver enzymes and IgG tests remained consistently normal.

She became pregnant.

What can she expect?

Pregnancy outcomes in AIH

171 deliveries in 140 women with AIH

Women with AIH have an increased risk of:

Preterm births <37 wk	RR 3.12 (1.97–4.92)
Birthweight <2500 gr	RR 2.51 (1.51–4.19)
Gestational diabetes	RR 4.35 (CI 2.21–8.57)

No association was seen for neonatal mortality

No increased risk for congenital malformations

Stokkeland, et al. Liver Int 2016

Pregnancy in autoimmune hepatitis

- ✓ The patient should be in stable remission
- ✓ AIH usually subsides during pregnancy
- ✓ Post-partum exacerbations are common
- ✓ Continuation of thiopurines during pregnancy appears to be safe
- ✓ Azathioprine or 6-MP is considered safe for breastfeeding
- ✓ MMF is highly teratogenic!

EASL. *J Hepatol* 2015 Westbrook, et al. J Autoimmun 2012 Stokkeland, et al. Liver Int 2016

Case (continued)

Is there an indication for DEXA scan

A. Yes

B. No

When there are signs of osteoporosis, is there an indication for bisphosphonates (BPs)?

A. Yes

B. No

Bone health in AIH

Bone disease well known in liver disease

Few studies on osteoporosis in AIH

Recent cross sectional study from Germany (n=211):

15.6% osteoporosis

> 50 years: 19.2%.

42.9% osteopenia

Mean bone loss: 1.2% per year (normal: 0,7%/year)

Risk associated with: advanced age, lower BMI, high TE values, and long glucocorticoid treatment

Schmidt et al, CGH 2019 in press

Bone health in AIH

- ✓ A low BMD must be interpreted with caution in young individuals of small body size (constitutionally lean) and/or stunted growth
- ✓ Certain BPs reduce bone loss in glucocorticoid-induced osteoporosis
- ✓ Evidence of their effect on fracture risk reduction in premenopausal women and men is scarce.

- ✓ There is an important concern about the risk of congenital malformations
- ✓ affect fetal skeletal ossification in animal models

- ✓ BPs be appropriate in premenopausal women and younger men with a previous history of fracture or those receiving high doses of glucocorticoids

Ferrari et al, Osteoporosis Internat 2012
Cohen et al, Endocrinol Metab Clin North Am 2018

Case (continued)

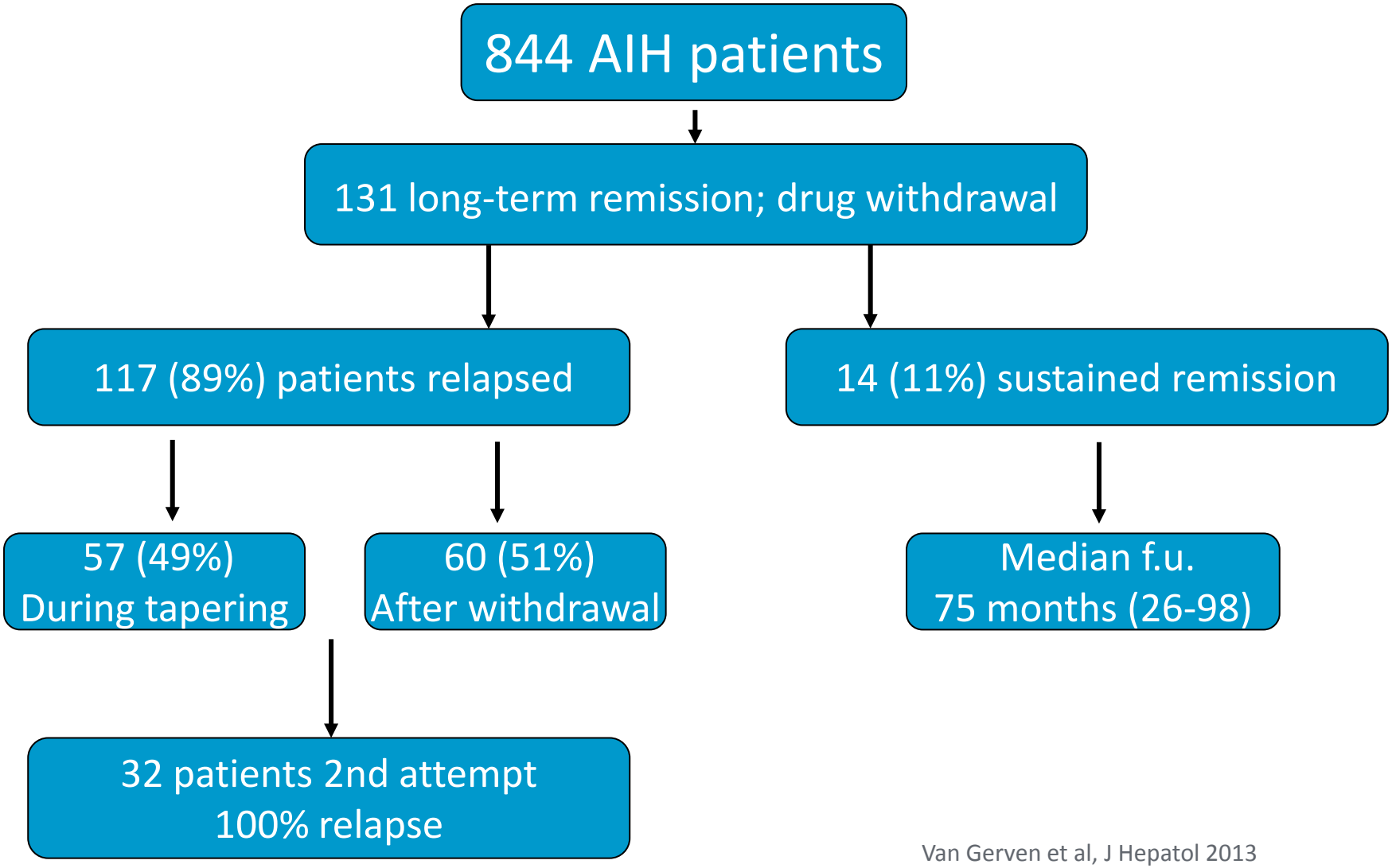
She remained asymptomatic with normal liver tests and IgG in the ensuing 2 years after delivery.

At this time, can she stop taking 6-mercaptopurine?

A. Yes

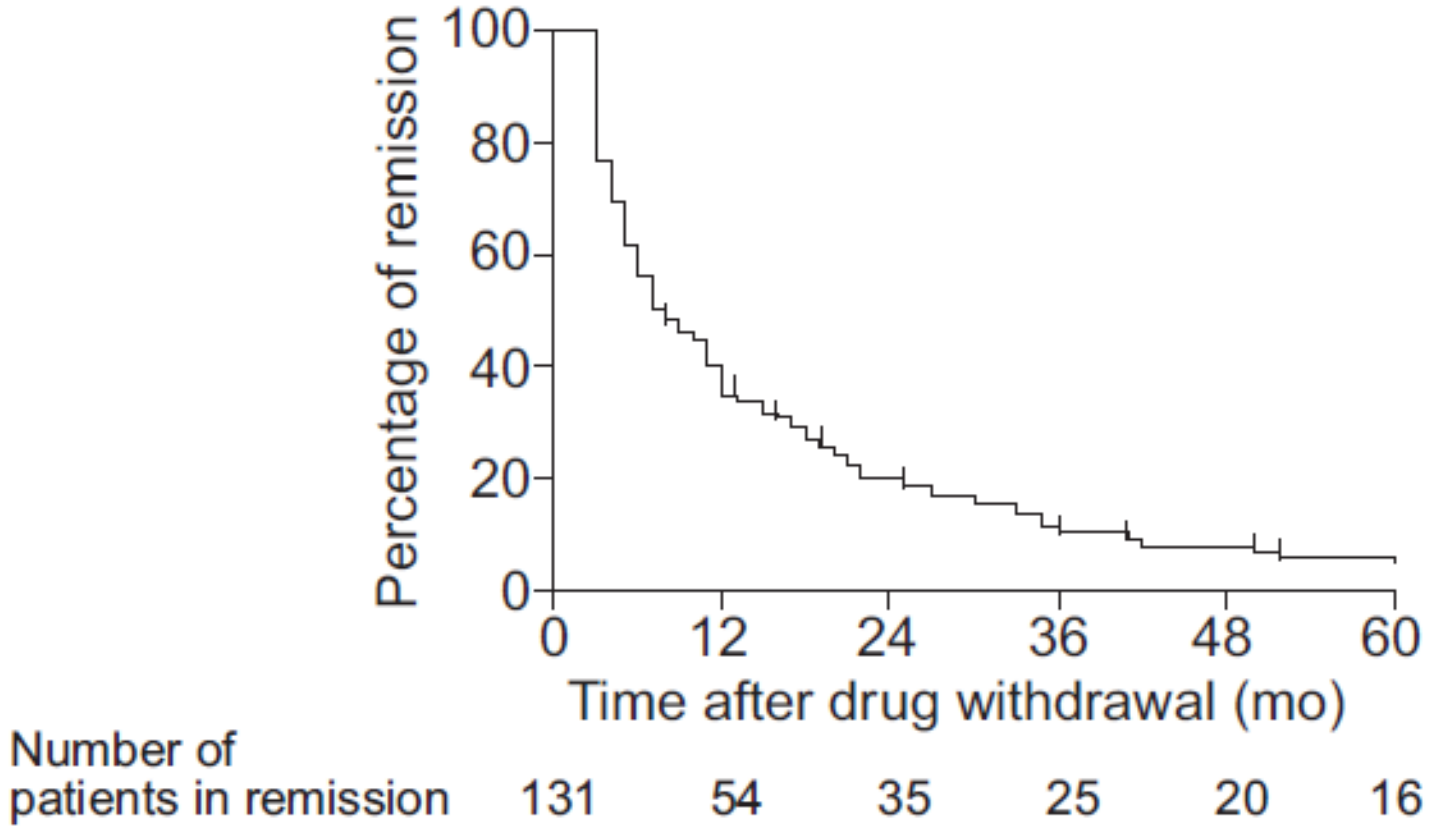
B. No

Drug withdrawal in AIH



Van Gerven et al, J Hepatol 2013

Drug withdrawal in AIH

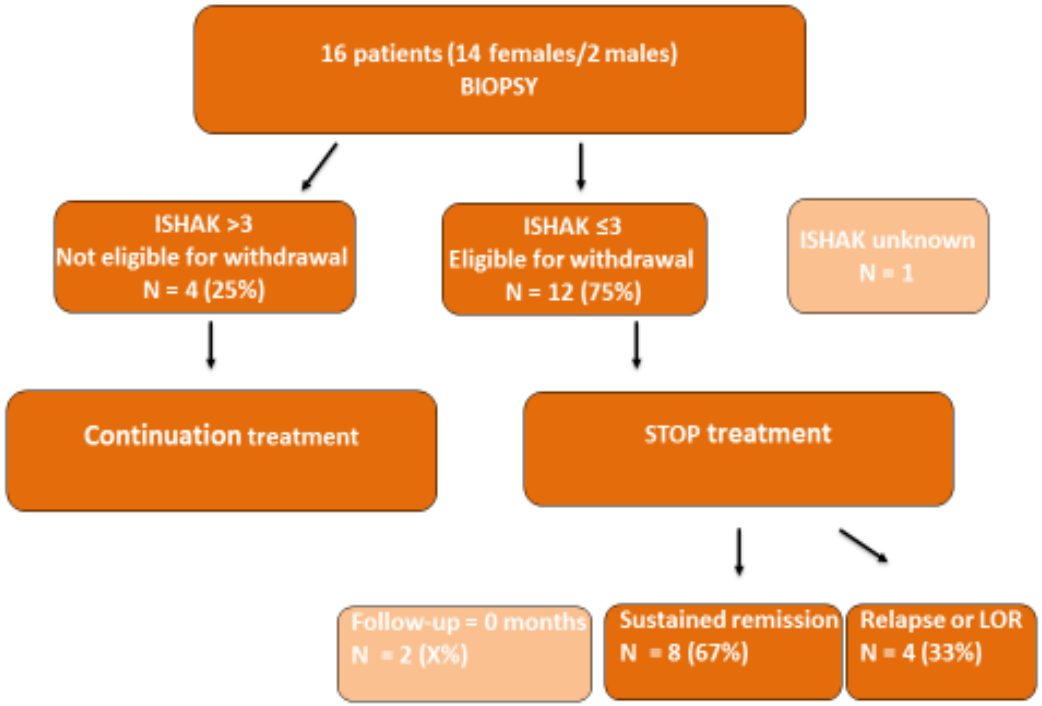


Van Gerven et al, J Hepatol 2013

Drug withdrawal in AIH: role of biopsy

Sustained remission **67%**

25% histological features of active AIH even with biochemical remission >2 years



Case (continued)

At this time, can she stop taking 6-mercaptopurine?

A. **Yes,** *after 3 years of treatment and 2 years of biochemical remission, in the absence of histological inflammatory activity, at a high risk of relapse*

B. No

EASL. *J Hepatol* 2015

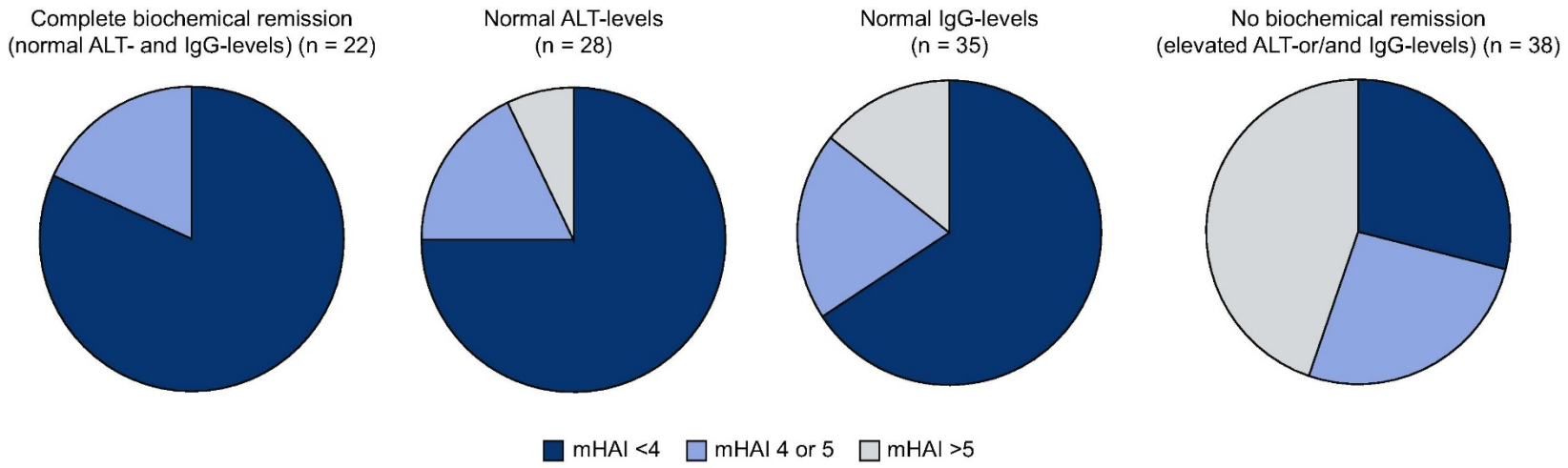
Would you otherwise perform a follow-up biopsy?

A. Yes

B. No

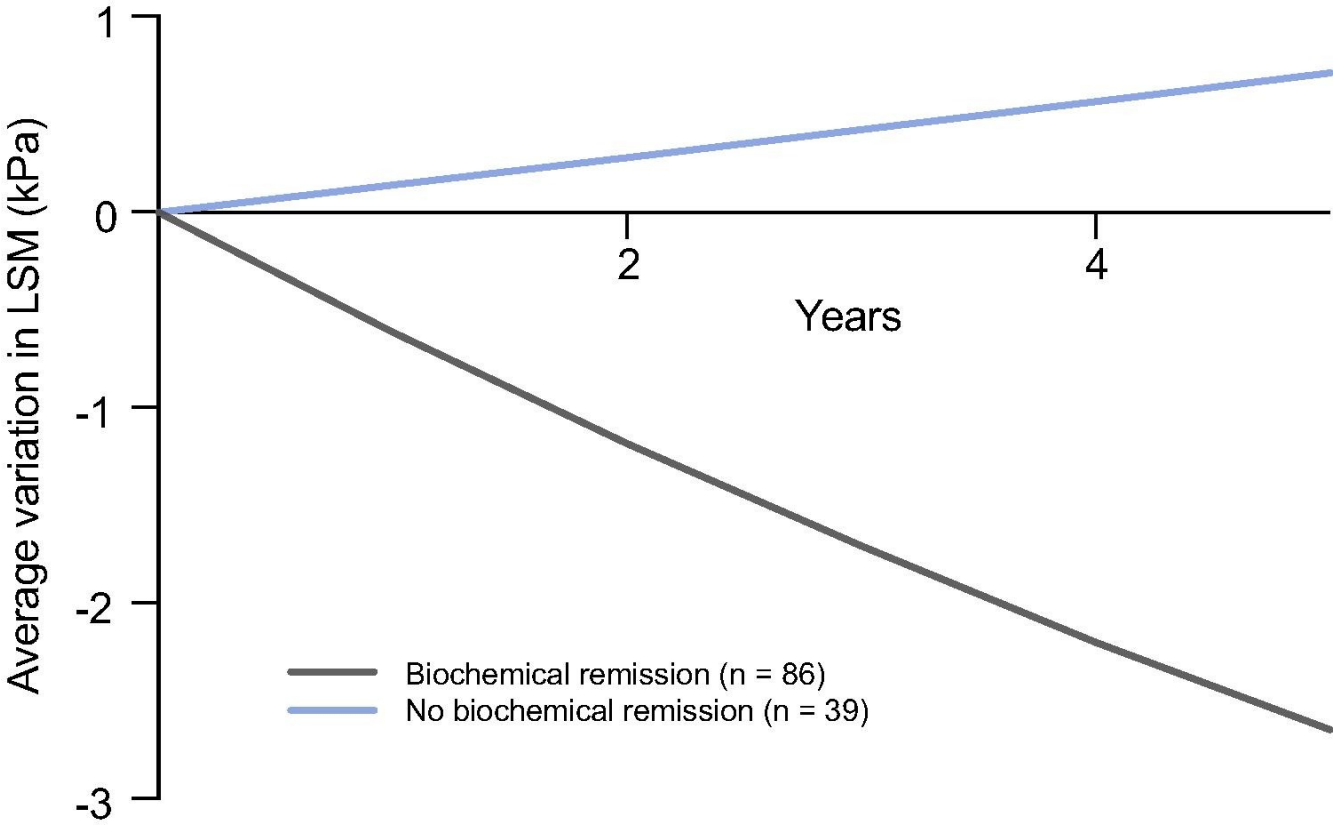
EASL. *J Hepatol* 2015

Follow-up: biopsy required?



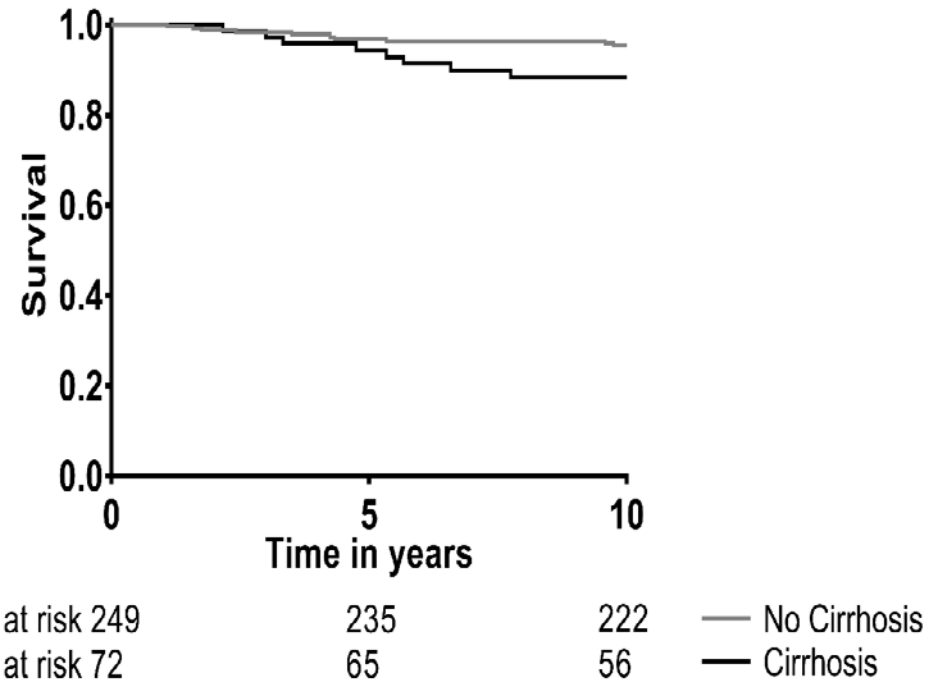
Hartl et al, J Hepatol 2018

Is biochemical remission clinically relevant?

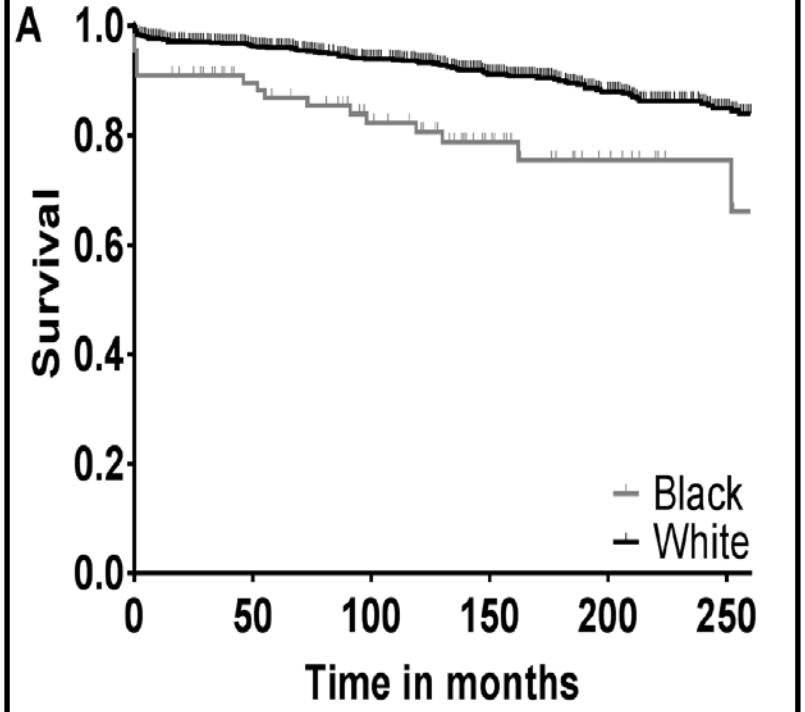


Hartl et al, J Hepatol 2018

Natural history of AIH in The Netherlands



Van den Brand et al. CGH 2018



Black (n=88) and White (n=897) pts

De Boer YS et al. 2018

Variant syndromes

Primary biliary cholangitis
Combined therapy with UDCA and immunosuppressants is recommended.

Primary sclerosing cholangitis
Addition of UDCA to immunosuppressant can be considered.

In patients with dominant AIH features, an alternative approach is to start with immunosuppressants only and then add UDCA if response is insufficient

EASL. *J Hepatol* 2015

Conclusions

- ✓ Most AIH patients require immunosuppressive medication
  - Prednisolone induction and azathioprine maintenance remains the standard of care
  - Budesonide can be considered in those patients without cirrhosis
  - Azathioprine escalation is effective in preventing steroid related side effects
- ✓ Virtually all patients in stable remission do relapse after drug withdrawal, requiring life-long immunosuppressive treatment

Conclusions

- ✓ Patients should be monitored regularly for early relapse detection (both on *and* off treatment)
- ✓ Pregnancy is not contra-indicated in AIH patients with and without azathioprine therapy
- ✓ 6-mercaptopurine, mycophenolate mofetil, cyclosporin, tacrolimus and 6-TG can be used as second-line agents in patients with intolerance or non-response to standard therapy (15-20%)
- ✓ Management of overlap with PBC or PSC should focus on treatment of both conditions

Monitoring: Transient Elastography

Long-term non-invasive fibrosis assessment by Fibroscan is possible.

Accurate detection of severe fibrosis after 6 months of therapy

Caveats:
Inflammation and oedema give higher scores

Table 4. Diagnostic performance of TE according to the time interval between TE measurement and initiation of immunosuppressive treatment.

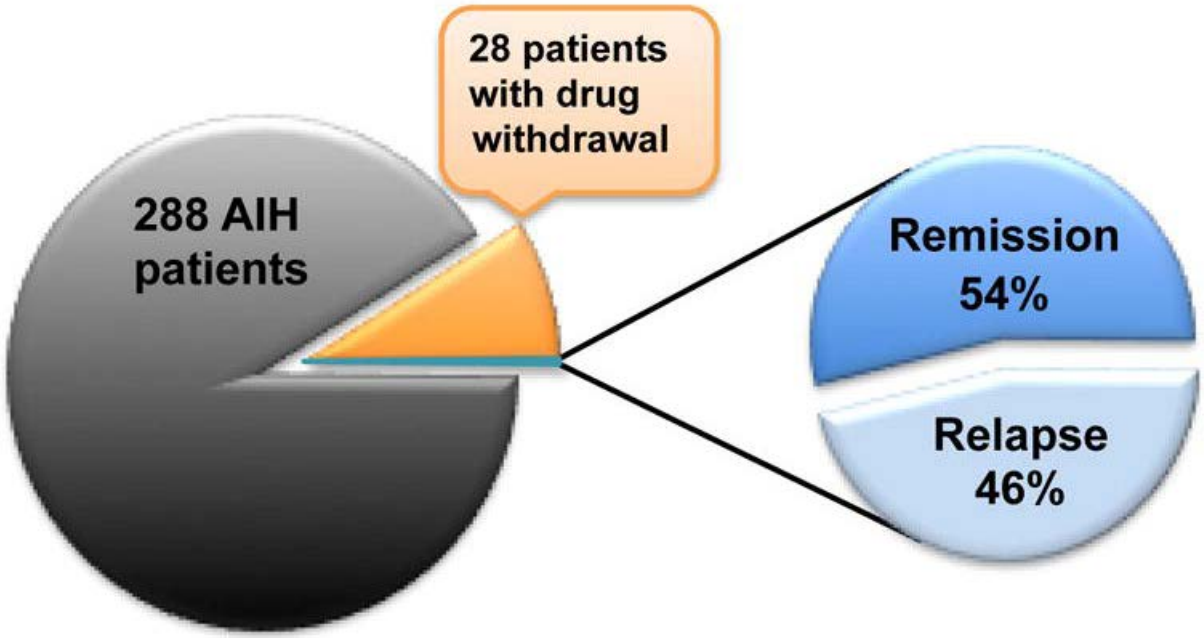
	Histological fibrosis stage		
	F ≥2 (≥5.8 kPa)	F ≥3 (≥10.5 kPa)	F = 4 (≥16.0 kPa)
<3 months (n = 34) Group 1			
AUROC	0.68	0.80	0.71
Sensitivity	0.71	0.60	0.60
Specificity	0.66	0.88	0.93
Positive predictive value	0.65	0.75	0.60
Negative predictive value	0.58	0.85	0.93
6-12 months (n = 25) Group 2			
AUROC	0.97	1.00	1.00
Sensitivity	0.94	1.00	1.00
Specificity	0.88	1.00	1.00
Positive predictive value	0.94	1.00	1.00
Negative predictive value	0.88	1.00	1.00
>4 years (n = 27) Group 3			
AUROC	0.94	0.96	1.00
Sensitivity	1.00	0.95	1.00
Specificity	0.77	0.94	1.00
Positive predictive value	0.80	0.80	1.00
Negative predictive value	0.88	0.94	1.00

Comparison of AUROCs: F ⩾ 2: group 1 *vs.* group 2: $p = 0.027$, group 1 *vs.* group 3: $p = 0.012$; F ⩾3: group 1 *vs.* group 2: $p = 0.029$, group 1 *vs.* group 3: $p = 0.12$; F ⩾ 4: group 1 *vs.* group 2: $p = 0.036$, group 1 *vs.* group 3: $p = 0.036$.

EASL. *J Hepatol* 2015 Hartl J, et al. *J Hepatol* 2016;65:769-75.

History of drug withdrawal in AIH: deep sustained remission?

28 patients (out of 288) 45 months (range: 24–111) in biochemical remission on thiopurine monotherapy



Hartl J et al, J Hepatol 2015

Potential adverse events

Calcineurin inhibitors

Hypertension
Nefrotoxicity
Neurotoxicity
Hepatotoxicity
Hyperkalemia
Pancreatitis
Myelosuppression
Progressive multifocal leukoencephalopathy

MMF

Hyperglycemia
Malignancies
Myelosuppression
Hypertension
Progressive multifocal leukoencephalopathy
Diarrhea

Second-line maintenance therapy

When	How
AZA intolerance	Modify thiopurine treatment; e.g., 6-MP, 6-TG, Allopurinol, Mycophenolate mofetil (MMF)
Insufficient response to standard therapy:	Modify thiopurine treatment; e.g., 6-MP, 6-TG, Allopurinol Calcineurin inhibitors *Consider referral tertiary centre*
MMF intolerance or non-response:	Calcineurin inhibitors *Consider referral tertiary centre*

Some key facts about AIH

Incidence: 1.1/ 100.000

Prevalence: 18/ 100.000

~3000 patients in the Netherlands

Presentation:

30-40% fulminant hepatitis

50% chronic

25% asymptomatic

30% already cirrhosis at diagnosis

Other autoimmune diseases in 30-50% of patients:

PBC, PSC, hypo- or hyperthyreodie, IBD, celiac disease, Sjogren, DM, RA

Drug-induced Liver Injury can mimic autoimmune hepatitis:

nitrofurantoin or minocycline

methyldopa and hydralazine