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Autoimmune DILI recognition and management

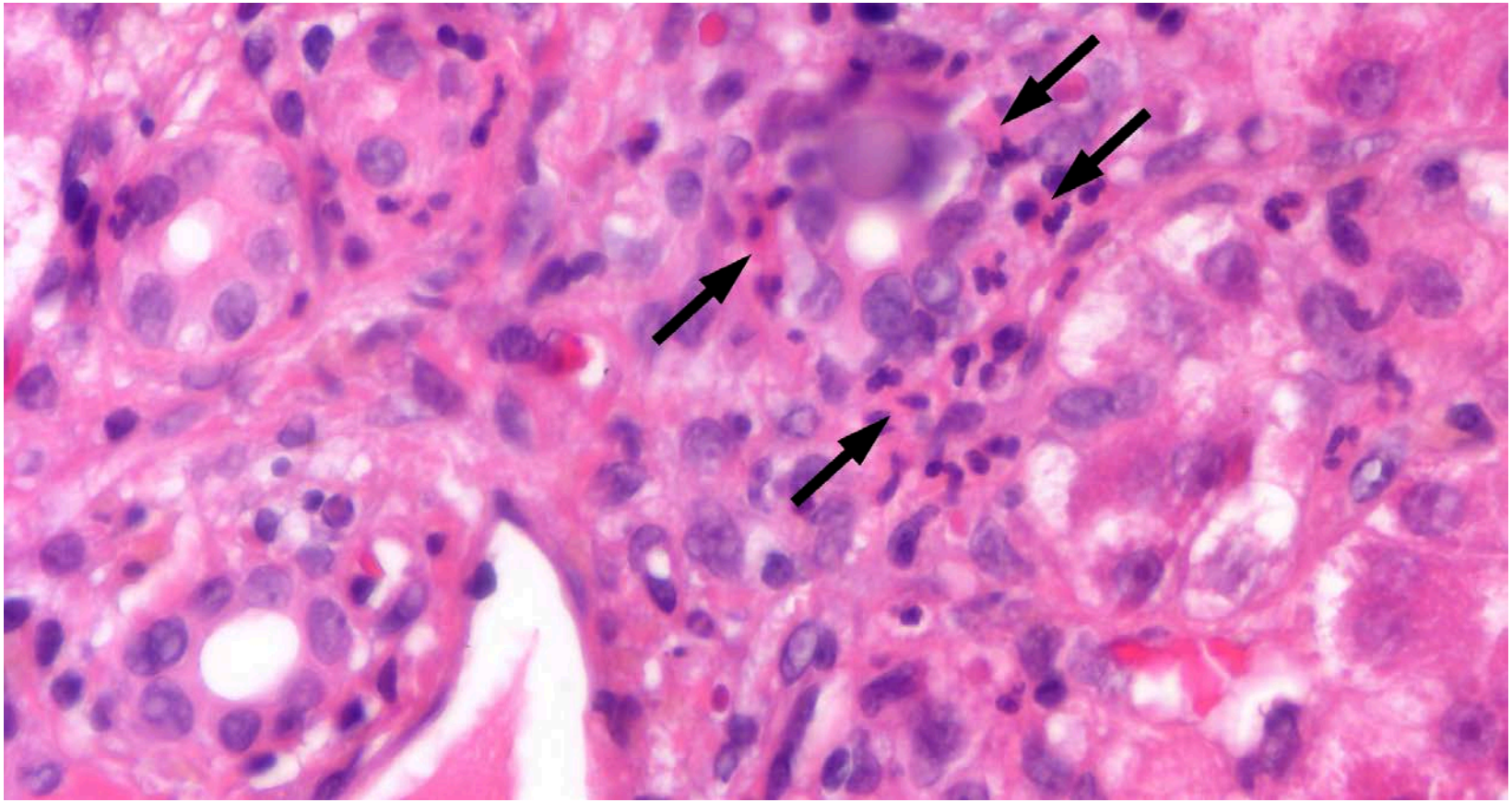
Einar S. Björnsson MD PhD

Disulfiram associated DILI
(Björnsson, Nordlinder, Olsson J Hepatol 2006)

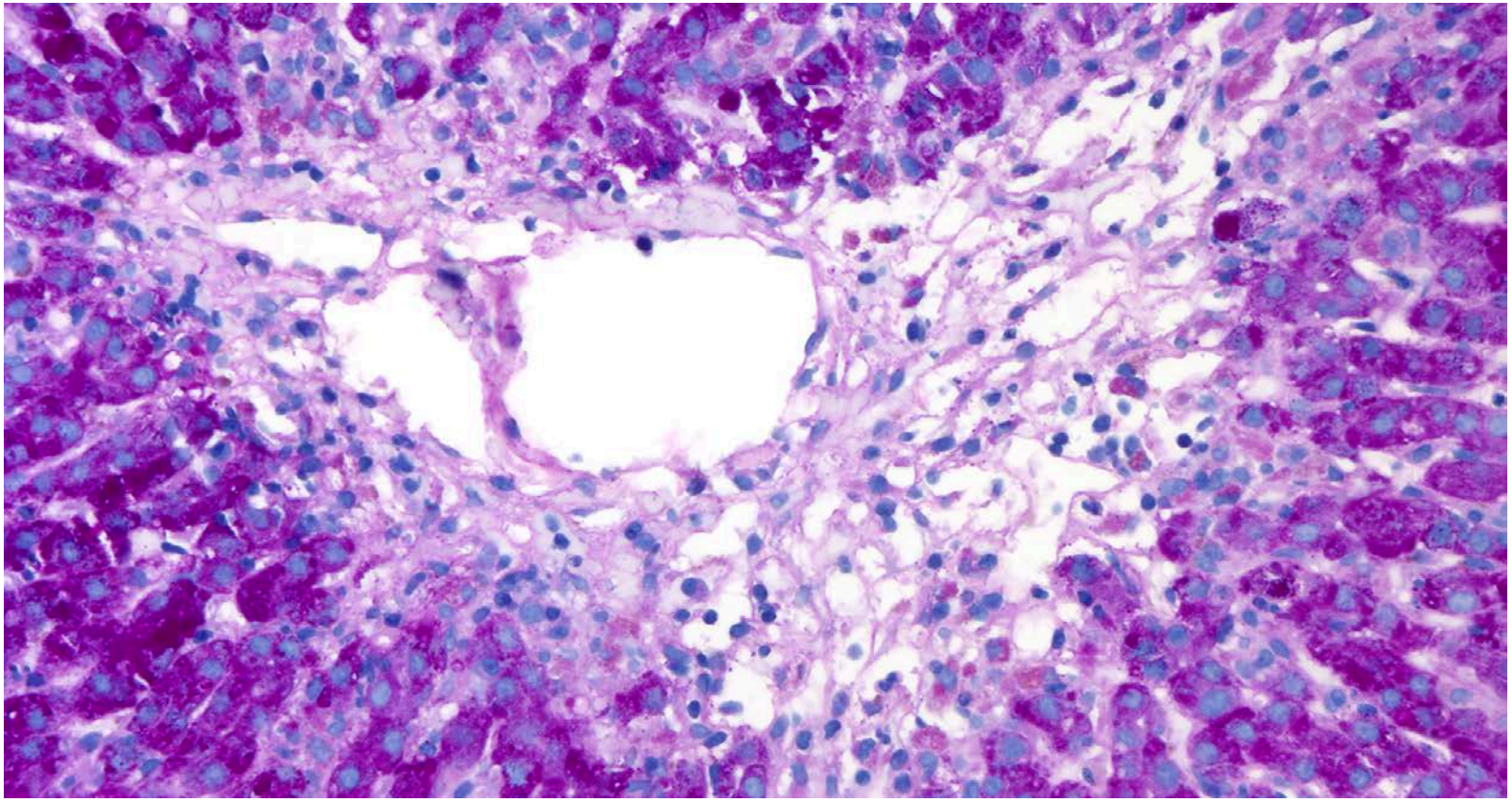
Among 88 cases of disulfiram associated DILI; 82 cases were considered to have at least possible relationship

Among these 8 either died or underwent a liver transplantation

Hepatic eosinophilia



Centrilobular hepatocyt drop-out



Liver histology in DILI outcome

Eosinophilic infiltration was associated with a favourable outcome, hepatocyte drop-out with a poor outcome

The impact of eosinophilia and hepatic necrosis on prognosis in DILI (Björnsson et al. APT 2007)

An electronic database research of MEDLINE for case reports on DILI associated with:

Amoxicillin/clavulanic acid

Carbamazepine

Diclofenac

Disulfiram

Erythromycin

Flucloxacillin

Halothane

Isoniazid

Phenytoin

Devarbhavi et al. Drug-Induced Liver Injury with Hypersensitivity Features Has a Better Outcome. Hepatology 2011.

Those with hypersensitivity presented earlier (25 days vs. 35 days, p=0.24), had less severe disease (MELD 16 vs. 29, p=0.01)

Those with hypersensitivity features had no mortality (0/16 vs. 12/23, p<0.001)

Drug-induced AIH

* An adverse immune response to proteins within the liver initiated by a drug, clinically similar to autoimmune hepatitis

* Reactive metabolites created through hepatic metabolism of some drugs have been shown to bind to cellular proteins such as cytochrome P450. These can then be recognized by the immune system as neoantigens

* Nitrofurantoin, minocycline, α-methyl dopa, hydralazine have all been well documented as drug-induced AIH. More recently TNF-α antagonists and statins

Björnsson et al. Drug-Induced Autoimmune Hepatitis: Clinical Characteristics and Prognosis. Hepatology 2010;51:240

* Drug-induced autoimmune hepatitis (DIAIH) has been reported to be caused by several drugs.

* There is limited data comparing these patients with other patients with autoimmune hepatitis (AIH).

Methods

* A search was performed using the Mayo Clinic (Rochester Mn) diagnostic medical index for AIH patients and DIAIH patients identified over ten years.

* Individuals with overlap syndromes and decompensated liver disease were excluded.

Results

* Overall 261 patients (204 females, median age 52) were identified, and 24 (9.2%) were DIAIH cases with a median age of 53 years (IQR 24-61).

* Mostly Nitrofurantoin (n=11) and Minocycline (n=11)

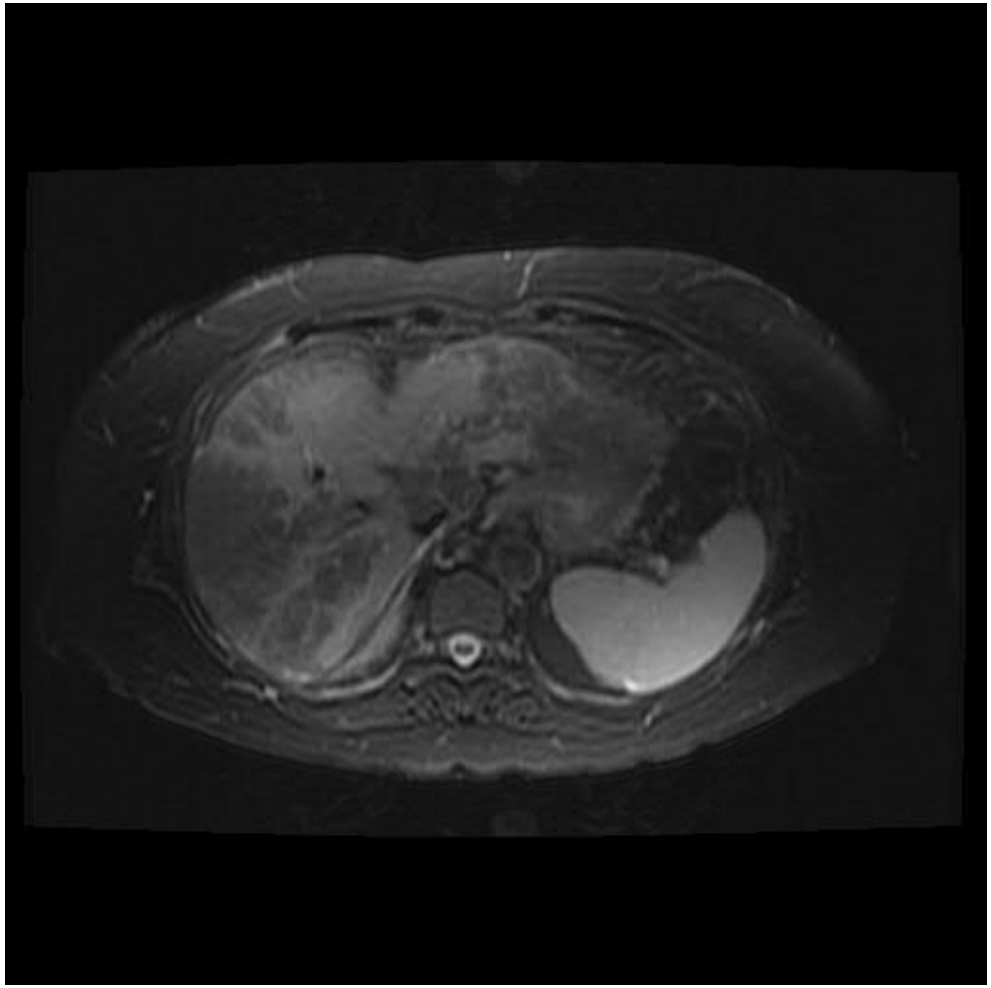
* A similar proportion of DIAIH patients had positive antinuclear antibodies (83% vs. 70%) and smooth muscle antibodies (50% vs. 45%) as compared to AIH patients.

Results

* Histological grade and stage were similar in patients with DIAIH vs. AIH but none of the DIAIH patients had cirrhosis at baseline; this was present in 20% of matched AIH cases.

* Liver imaging was normal in all minocycline cases. 8/11 (73%) of nitrofurantoin patients had abnormalities on hepatic imaging (mainly liver atrophy) a finding seen in only 8/33 (24%) of a random sample of the rest of the AIH group (p=0.0089).

Confluent fibrosis centrally with general liver atrophy in a patient with nitrofurantoin induced AIH



Results

* Corticosteroid responsiveness was similar in DIAIH and the AIH patients.

* Discontinuation of immunosuppression was tried and successful in 14 DIAIH cases, with no relapses (0%) whereas 65% of the AIH patients had a relapse after discontinuation of immunosuppression ($p<0.0001$).

Conclusions

* A significant proportion of patients with AIH have drug-induced AIH, mainly due to nitrofurantoin and minocycline.

* These two groups had similar clinical and histological patterns.

* DIAIH patients do not seem to require long-term immunosuppressive therapy

TNF-α antagonists

* TNF-alpha antagonists have been found to be associated with drug-induced liver injury (DILI) with numerous case reports.

* The largest series included 6 patients (from the US) with additional 28 cases from the literature (Ghabril et al. Clin Gastro Hepatol 2013)

Background

* Little is known about the absolute risk of liver injury with these drugs.

* In a recent paper an absolute risk of DILI associated with Infliximab was 1: 148 of treated patients over a two year period (Bjornsson et al. Gastroenterology 2013; 144: 1419-25).

* It has not been well documented which kind of patients are at risk and population based studies are lacking.

Methods

* All patients with suspected DILI were identified who had been treated with TNF-alpha antagonists in Iceland (population 320, 000) during 5 years from 2009-2013.

* Data on the total use of these drugs was obtained.

* Clinical characteristics of these patients were analyzed, such as features of autoimmunity and causality assessment performed with the RUCAM method.

Results

* 11 patients, 8 females (73%), mean age 46 years (3) were found during the study period to have at least possible relationship according to RUCAM.

* A total of 9 patients (82%) had been treated with infliximab, one with etanercept and one with adalimumab.

* Two patients (18%) had Crohns disease or ulcerative colitis whereas seronegative rheumatoid arthritis (RA) (n=4), seropositive RA (n=2), spondylarthritis (n=1), psoriasis arthritis (n=1) and psoriasis (n=1).

Absolute risk of DILI associated with TNF-alpha antagonists

* During 2009-2013, overall 1076 patients had been started on infliximab leading to a DILI episode in:

* 1 /120 patients treated with Infliximab,

* 1/270 treated with adalimumab

* 1/430 treated with etanercept.

Results

* Overall 4/11 (36%) had jaundice at diagnosis

* 8 had hepatocellular, two cholestatic and one mixed pattern of liver injury.

* Max ALT 704 (102), range: 169-1658

* AST 503 (115), range: 91-1375

* ALP 261 (76), range 71-916

* Bilirubin 38 (11), range; 10-100

Patients treated with TNF-DILI vs. controls matched for age, gender and indication for therapy

Drugs Infliximab %	TNF-alpha DILI n=11	Controls n=22	p-value
Age	47(5) years	45 (3) years	NS
Female	73%	73%	NS
Drugs Infliximab %	82%	82%	NS
ANA positivity Prior to TNF therapy	**3/7 (43%)**	**5/9 (36%)**	NS
Methotrexate	1/11 (9%)	13/22 (59%)	0.01

Liver histology

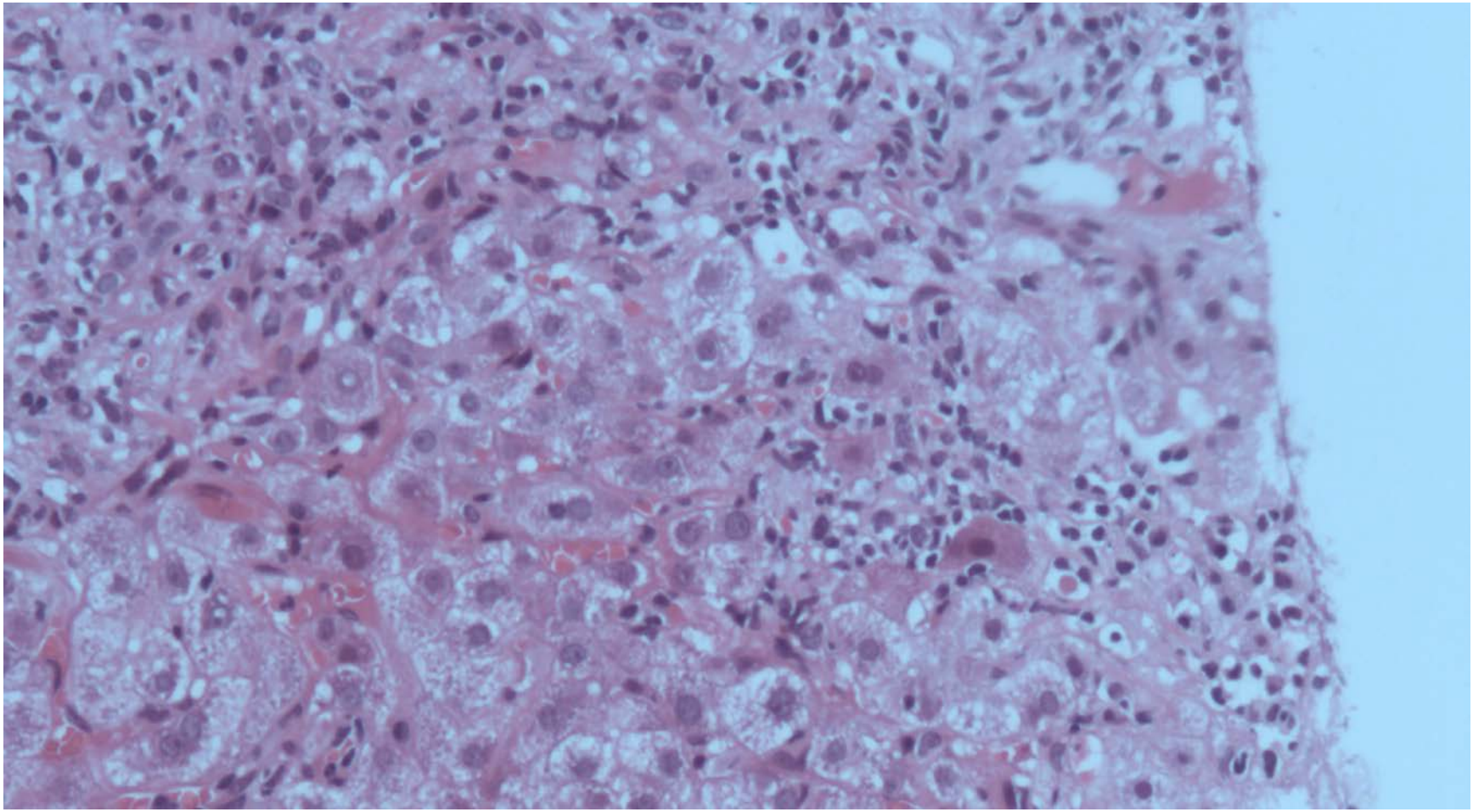
*** Liver biopsies were performed in 5/11 (46%)**

*** Severe acute hepatitis pattern (n=3),**

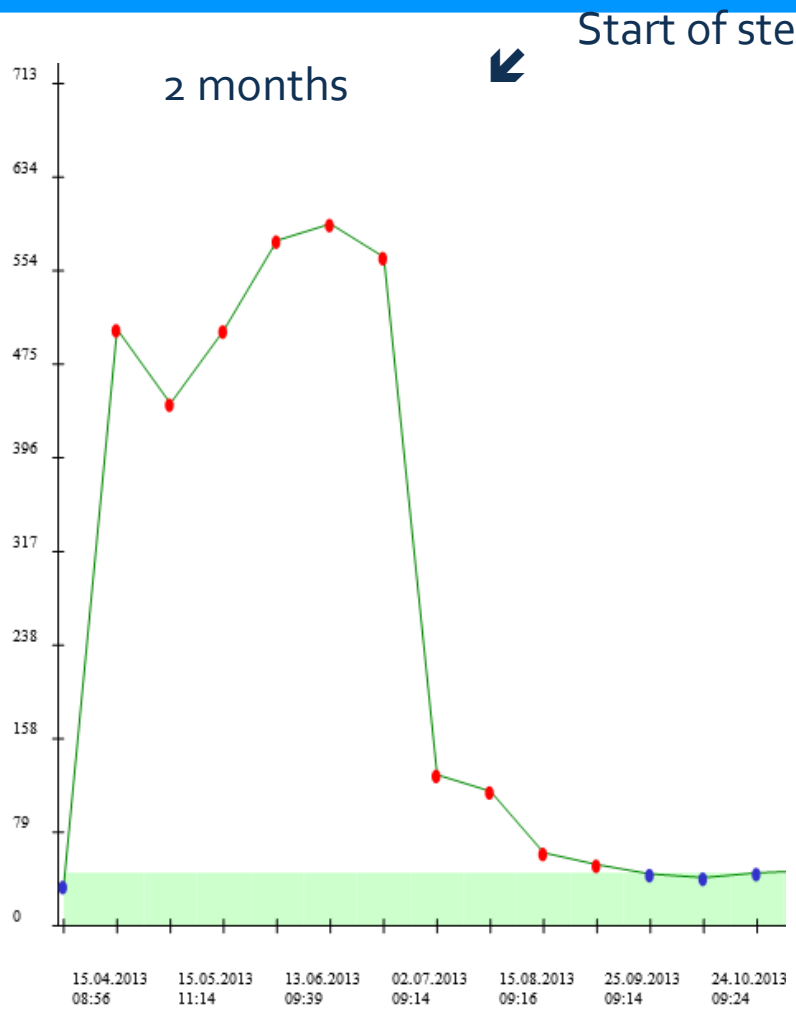
*** Acute and chronic hepatitis pattern (n=1)**

*** Canalicular cholestasis (n=1)**

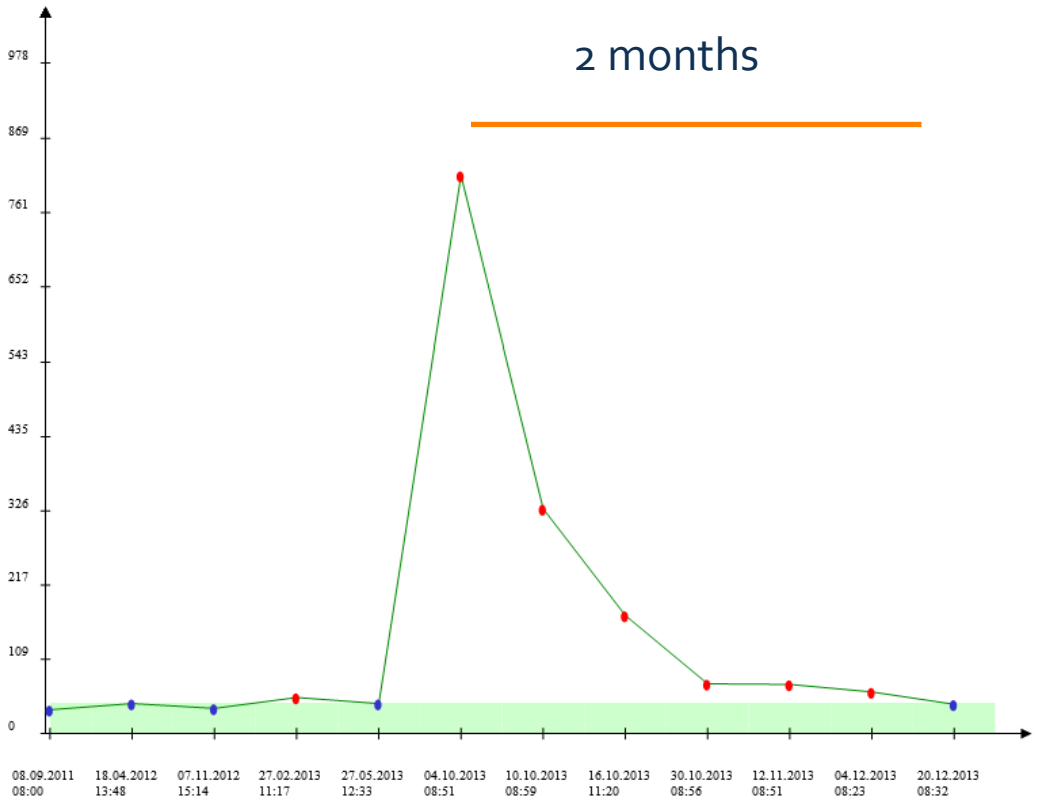
Severe Acute hepatitis in 40 year old female with Infliximab DILI



ALT before and after steroids in a 40 year old female with Infliximab DILI



ALT development in a 55 year old female- Infliximab DILI-spontaneous recovery



Treatment

* Overall 5 patients were treated with steroids (46%) that could be discontinued without relapse in 4 when tried whereas one is still on treatment.

* In all 8/11 when another TNF alpha inhibitor was tried this was successful without DILI, adalimumab (n=4), etanercept (n=2), etanercept and adalimumab (n=2), Infliximab (n=1)

Conclusions

* Infliximab was more often associated with DILI than other TNF-alpha antagonists with 1/120 treated at risk

* Autoimmune features were frequent requiring steroids in approximately 50% of patients.

* The overall prognosis is favorable and the vast majority do not need steroids long-term for the treatment of liver injury.

* Other TNF-alpha antagonists were safe and this does not seem to be a class effect

DILI and AIH

In a long-term follow-up of patients with DILI with concomitant jaundice leading to hospitalisation, AIH developed in 5/23 (22 %) patients (all females) after the initial event over a mean period of 6 years (Bjornsson and Davidsdottir. J Hepatology 2009)

DILI and AIH

*** In a Japanese study, ANA was detected after DILI in 6 patients and 5/6 (83 %) were females** (Ohmoto K, et al. Drug-induced liver injury associated with antinuclear antibodies. Scand J Gastroenterol. 2002;37:1345–6.)

*** In another study, 7 cases diagnosed as DILI, but features of AIH became apparent later despite discontinuation of the drug. Interestingly, ANA titers and immunoglobulin (Ig) G levels increased during the course.** (Sugimoto K,. Seven cases of autoimmune hepatitis that developed after drug-induced liver injury. Hepatology. 2011;54:1892–3.

DILI and AIH

*** In the Spanish DILI registry 9/742 463 (1.2 %), patients had evidence of two DILI episodes caused by different drugs .**

*** An interesting finding was 4/9 cases (44 %) developed DIAIH in the second episode during follow-up. This clearly exceeds the chance of association of this liver injury phenotype in the Spanish DILI registry's general patient cohort**

Lucena MI, et al. Recurrent drug-induced liver injury (DILI) with different drugs in the Spanish Registry: the dilemma of the relationship to autoimmune hepatitis. J Hepatol. 2011;55:820–7.

Diagnosis

* In most case reports of DIAIH patients have developed liver injury associated with drug intake considered responsible for the liver injury and concomitant elevation in antinuclear (ANA) and/or smooth muscle antibodies (SMA) and/or elevation of IgG.

* This is probably not an adequate for making this diagnosis. Some drugs can lead to development of autoantibodies and/or IgG levels, in the absence of liver disease

* History: Did drug intake precede the symptoms of liver injury? In other words, was the drug taken for symptoms of liver injury?

Diagnosis

*** HISTOLOGY: A subgroup analysis demonstrated that severity of inflammation and fibrosis and the frequency of what have been considered AIH-specific findings were comparable between DIAH and AIH**

*** Marked fibrosis (Ishak score >4) was however only seen in patients with classical AIH and not in DIAIH cases**

(Suzuki A, et al. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis vs. drug-induced liver injury. Hepatology 2011;54: 931–9.)

Management

* Identification of the role of the drug

* In one study 2/11 (18%) minocyline induced AIH achieved clinical and biochemical resolution without any immunosuppression (Bjornsson et al. 2010)

* Out of 4/9 (30 %) with DIAIH developing after a second exposure of drugs leading to DILI in the Spanish registry liver tests normalised in two patients without requiring immunosuppression, and smooth muscle antibody became negative after drug discontinuation (Lucena et al. 2011)

Management

* Steroids in those who do not normalise liver tests with cessation of the implicated agent

* How long the immunosuppression should be continued is unknown?

* Successful withdrawal of therapy in most cases of DIAIH when it has been tried.

* Only 3 case reports when this has not been possible (Alla et al. 2006; Ramakrishna 2009; Hergue-Berlot 2011)

Question about a patient in Turkey

"I am a pediatric surgeon. I have a 17 year old daughter. She has been diagnosed with type II AIH. I have doubts about the diagnosis, the treatment protocol and duration of treatment. Read your article: Drug-induced AIH etc. we need your suggestion and advice"

My daughter has not any complaints. Physical examination signs are normal. Weight is 46/kg. Past medical history was significant for chronic urticaria for 18 months and acne vulgaris. August 5, 2014. She was prescribed Isotretinoin (Roaccutane) 30 mg/day by dermatologist for acne vulgaris.

Lab tests and follow-up

August 5, 2014. Before treatment, AST 36 (normal range 5-40 U/L), ALT 43 (normal range 5-40 U/L).

September 5, 2014. AST 72, ALT 91. Isotretinoin was discontinued.
September 14, 2014. AST 98 , ALT 141

October 5, 2014. AST 152, ALT 221, GGT 23(7-49 U/L), ALP 69 (30-128 U/L) Bilirubin (total) 0,76 (0,2-1,2 mg/dl),

ANA Positive 1:100 , ASMA < 1:100, Anti LKM 1:100, IgG 2320 (550-1900).

Imaging normal, hepatitis serologies negative and other etiologies excluded.

17 year old girl

January 29, 2015. Histopathological examination showed portal and periportal plasma cell-rich inflammation and marked lobular necro inflammatory activity. Staging: Fibrosis 1/6

January 29, 2015. The diagnosis of tip II Autoimmune Hepatitis was made and treatment with prednisone 60 mg daily was begun. Azathioprine 50 mg daily will be added one week later and prednisone will be gradually decreased to 15 mg daily. The treatment will be continued for two years.

What to do?

"What do you think about the diagnosis? Is the diagnosis Type II Autoimmune Hepatitis or Drug-Induced Autoimmune Hepatitis?

Is the treatment protocol suitable for seventeen years old girl?

How long should be the duration of the treatment?

What could you suggest for treatment and duration of treatment?"

Conclusions

* In a patient with a high clinical suspicion of DILI with positive autoantibodies and/or with the syndrome of DIAH, immunosuppression is indicated if aminotransferases remain elevated despite discontinuation of the suspected drug.

* Discontinuation of immunosuppression in patients with DIAIH when attempted is usually successful and immunosuppression is rarely required long-term in these patients.