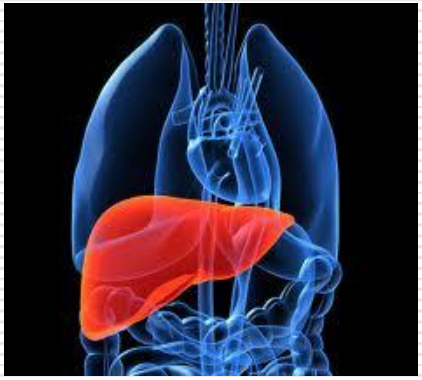


Ηπατικές ανεπιθύμητες ενέργειες των βιολογικών παραγόντων

Σπύρος Ν Νίκας

Ρευματολόγος

Ιωάννινα

snnikas@yahoo.com

www.rheumatologyUS.gr

ΕΠΕΜΥ - Επιστημονικό Ρευματολογικό Συμπόσιο

«Επικαιροποίηση των θεραπευτικών επιλογών στη ρευματολογία με προσαρμογές στην οικονομική κρίση»

ΠΟΡΤΑΡΙΑ ΠΗΛΙΟΥ (ΧΕΝΙΑ PALACE)

20 Οκτωβρίου 2012 09:15 - 14:00

drug-induced liver injury (DILI)

- with any agent
- the diagnosis is difficult to make
- may simply rely on an accurate patient history
  - establishment of the temporal relationship
  - improvement in liver enzymes after drug withdrawal

Hepatotoxicity

- a rise in transaminases 5 times above the upper limit of normal
- clinical jaundice
- acute hepatic failure
- cholestasis

mild hepatocellular injury

- defined as ALT/AST elevations >2× and <3× ULN

US FDA. Guidelines for Industry-drug Induced Liver Injury: Premarketing Clinical Evaluation. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf (accessed 24 Oct 2007).

Ηπατικές ανεπιθύμητες δράσεις

Σε ασθενείς με αυτοάνοσο ρευματικό νόσημα , υπό βιολογικό παράγοντα και:

- με Ηχ ηπατοπάθειας
- ΧΩΡΙΣ Ηχ ηπατοπάθειας

Ηπατικές ανεπιθύμητες ενέργειες βιολογικών παραγόντων

www.ncbi.nlm.nih.gov/pubmed

NCBI Resources How To My NCBI

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed | biologics liver side effects rheumatoid | Search

RSS Save search Advanced

Show additional filters

Clear all

Text availability
Abstract available
Free full text available
Full text available

Publication dates
5 years
10 years
Custom range...

Species
Humans
Other Animals

Article types clear
Meta-Analysis
✓ Review
Systematic Reviews
more ...

Languages
English
more ...

Clear all

Display Settings: Summary, 20 per page, Sorted by Recently Added

Send to:

Results: 13

Filters activated: Review Clear all

1. Co-morbidities in established rheumatoid arthritis.
Gullick NJ, Scott DL.
Best Pract Res Clin Rheumatol. 2011 Aug;25(4):469-83. doi: 10.1016/j.berh.2011.10.009. Review.
PMID: 22137918 [PubMed - indexed for MEDLINE]
Related citations

2. Liposomal drug formulations in the treatment of rheumatoid arthritis.
van den Hoven JM, Van Tomme SR, Metselaar JM, Nuijen B, Beijnen JH, Storm G.
Mol Pharm. 2011 Aug 1;8(4):1002-15. Epub 2011 Jun 17. Review.
PMID: 21634436 [PubMed - indexed for MEDLINE]
Related citations

3. Biological agents in kidney transplantation: belatacept is entering the field.
Węclawiak H, Kamar N, Ould-Mohamed A, Cardeau-Desangles I, Rostaing L.
Expert Opin Biol Ther. 2010 Oct;10(10):1501-8. Review.
PMID: 20726688 [PubMed - indexed for MEDLINE]
Related citations

4. Formulary review of 2 new biologic agents: tocilizumab for rheumatoid arthritis and ustekinumab for plaque psoriasis.
Schafer JA, Kjesbo MK, Gleason PP.
J Manag Care Pharm. 2010 Jul-Aug;16(6):402-16. Review.
PMID: 20635831 [PubMed - indexed for MEDLINE] Free Article
Related citations

Filters: Manage Filters

9 free full-text articles in PubMed Central

Markers of treatment response to methotrexate in il [Int J Rheumatol
Influence of polymorphisms within methotrexate [Br J Clin Pharmacol
Rare incidence of methotrexate-sp lesions in liver l [Arthritis Res The
Se

Find related data

Database: Select

Find items

Search details

```
||"biological agents"[Mesh Terms] OR |"biological"[All Fields] AND "agents"[All Fields]| OR "biological agents"[All Fields] OR
```

Search

Se

Ηπατικές ανεπιθύμητες ενέργειες βιολογικών παραγόντων

www.ncbi.nlm.nih.gov/pubmed?term=biologics%20hepatotoxicity%20rheumatoid

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed | biologics hepatotoxicity rheumatoid | Search

RSS | Save search | Advanced | Help

Show additional filters | Display Settings: Summary, 20 per page, Sorted by Recently Added | Send to: | Filters: Manage Filters

Clear all

Text availability
Abstract available
Free full text available
Full text available

Publication dates
5 years
10 years
Custom range...

Species
Humans

Article types clear
Review
Systematic Reviews
more ...

Languages
English
more ...

Clear all

Show additional filters

Results: 7

Filters activated: Review Clear all

1. The London position statement of the World Congress of Gastroenterology on **Biological** Therapy for IBD with the European Crohn's and Colitis Organisation: safety.
Van Assche G, Lewis JD, Lichtenstein GR, Loftus EV, Ouyang Q, Panes J, Siegel CA, Sandborn WJ, Travis SP, Colombel JF.
Am J Gastroenterol. 2011 Sep;106(9):1594-602; quiz 1593, 1603. doi: 10.1038/ajg.2011.211. Epub 2011 Aug 16. **Review**.
PMID: 21844919 [PubMed - indexed for MEDLINE]
Related citations

2. Methotrexate versus leflunomide in **rheumatoid** arthritis: what is new in 2011?
Singer O, Gibofsky A.
Curr Opin Rheumatol. 2011 May;23(3):288-92. **Review**.
PMID: 21378570 [PubMed - indexed for MEDLINE]
Related citations

3. Methotrexate: from its introduction to non-oncologic therapeutics to anti-TNF-α.
Benedek TG.
Clin Exp Rheumatol. 2010 Sep-Oct;28(5 Suppl 61):S3-8. Epub 2010 Oct 28. **Review**.
PMID: 21044425 [PubMed - indexed for MEDLINE]
Related citations

4. The use of low dose methotrexate in **rheumatoid** arthritis - are we entering a new era of therapeutic drug monitoring and pharmacogenomics?
Stamp L, Roberts R, Kennedy M, Barclay M, O'Donnell J, Chapman P.
Dec;60(10):678-87. Epub 2006 Oct 20. **Review**.

2 free full-text articles in PubMed Central
Hepatotoxicity due to tocilizumab and anakinra in **rheuma** [Int J Gen Med. 2011]
Elevated liver enzyme tests among patients with **rhe** [Ann Rheum Dis. 2010]
See all (2)...

Find related data
Database: Select
Find items

Search details
(("biological agents"[MeSH Terms] OR ("biological"[All Fields] AND "agents"[All Fields]) OR "biological agents"[All Fields] OR
Search
See more...

Recent activity
Turn Off | Clear
biologics hepatotoxicity rheumatoid
AND (Review[ptyp]) (7) PubMed

www.ncbi.nlm.nih.gov/pubmed?term=biologics hepatotoxicity rheumatoid#

Ηπατικές ανεπιθύμητες ενέργειες βιολογικών παραγόντων

Ηπατικές ανεπιθύμητες ενέργειες βιολογικών παραγόντων

- SPC
- Registries
- Studies
- Cases

Ηπατικές ανεπιθύμητες ενέργειες βιολογικών παραγόντων

- SPC
- Registries
- Studies
- Cases

Ηπατικές ανεπιθύμητες ενέργειες βιολογικών παραγόντων

SPC

- Anti-TNF-α
- CD-20
- IL-6
- CTLA-4
- IL-1

SPC

Respiratory, thoracic and mediastinal disorders	
Very common: Common:	Upper respiratory tract inection, sinusitis. Lower respiratory tract infection (e.g. bronchitis, pneumonia), dyspnoea, epistaxis.
Uncommon:	Pulmonary oedema, bronchospasm, pleurisy, pleural effusion.
Rare:	Interstitial lung disease (including rapidly progressive disease, lung fibrosis and pneumonitis).
Gastrointestinal disorders	
Very common: Common:	Abdominal pain, nausea. Gastrointestinal haemorrhage, diarrhoea, dyspepsia, gastroesophageal reflux, constipation.
Uncommon:	Intestinal perforation, intestinal stenosis, diverticulitis, pancreatitis, cheilitis.
Hepatobiliary disorders	
(≥ 1/100 to <1/10)	tic function abnormal, transaminases increased.
Uncommon:	Hepatitis, hepatocellular damage, cholecystitis.
Rare:	Autoimmune hepatitis, jaundice.
Not known:	Liver failure.

SPC

Cardiac disorders:

Rare:	Worsening of congestive heart failure (see section 4.4)

Respiratory, thoracic and mediastinal disorders:

Uncommon:	Interstitial lung disease (including pneumonitis and pulmonary fibrosis)*

Hepatobiliary disorders:

≥1/10,000 - <1/1000	Elevated liver enzymes, autoimmune hepatitis

Skin and subcutaneous tissue disorders:

Common:	Pruritus
Uncommon:	Angioedema, urticaria, rash, psoriasiform rash, psoriasis (including new onset or worsening and pustular, primarily palms and soles)
Rare:	Cutaneous vasculitis (including leukocytoclastic vasculitis), Stevens-Johnson syndrome, erythema multiforme
Very rare:	Toxic epidermal necrolysis

Musculoskeletal and connective tissue disorders:

SPC

Gastrointestinal disorders	Very common	abdominal pain, nausea and vomiting
	Common	GI haemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	pancreatitis, dysphagia, face oedema
	Rare	intestinal perforation[1)]
Hepato-biliary disorders*	≥ 1/10	elevated liver enzymes
	Uncommon	cholecystitis and cholelithiasis, hepatic steatosis, bilirubin increased
	Rare	reactivation of hepatitis B[1)] autoimmune hepatitis[1)]

SPC

Respiratory, thoracic and mediastinal disorders	
Uncommon:	Asthma and related symptoms (such as wheezing and bronchial hyperactivity)
Rare:	Interstitial lung disease
Gastrointestinal disorders	
Common:	Constipation, dyspepsia, gastrointestinal and abdominal pain, nausea
Uncommon:	Gastrointestinal inflammatory disorders (such as gastritis and colitis), gastro-oesophageal reflux disease, stomatitis
Hepatobiliary disorders	
(≥ 1/100 to < 1/10)	Alanine aminotransferase increased, aspartate aminotransferase increased
Uncommon:	Cholelithiasis, hepatic disorders

SPC

Respiratory, thoracic and mediastinal disorders	Uncommon	asthma and related symptoms, pleural effusion and symptoms, respiratory tract congestion and inflammation, cough
	Rare	interstitial lung disease, pneumonitis
Gastrointestinal disorders	Common	nausea
	Uncommon	ascites, gastrointestinal ulceration and perforation, gastrointestinal tract inflammation (any site), stomatitis, dyspepsia, abdominal distension, oropharyngeal dryness
	Rare	odynophagia, hypermotility
Hepatobiliary disorders	Common	hepatitis (including hepatic enzyme increased)
	Uncommon	hepatopathy (including cirrhosis), cholestasis, blood bilirubin increased
	Rare	cholelithiasis
Skin and subcutaneous tissue disorders	Common	rash

SPC

Table 1 ADRs reported in clinical trials or during postmarketing surveillance in patients with NHL and CLL disease treated with MabThera monotherapy/maintenance or in combination with chemotherapy

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known[8]
Respiratory, thoracic and mediastinal disorders		Bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	asthma, bronchiolitis obliterans, lung disorder, hypoxia	interstitial lung disease[7]	respiratory failure[4],	lung infiltration,
Gastrointestinal disorders	nausea	vomiting , diarrhoea, abdominal pain, dysphagia, stomatitis, constipation, dyspepsia, anorexia, throat irritation	abdominal enlargement		gastrointestinal perforation[7]	
Skin and subcutaneous tissue disorders	pruritis, rash, +alopecia	urticaria, sweating, night sweats, +skin disorder			severe bullous skin reactions, toxic epidermal necrolysis[7]	

SPC

- The most commonly reported ADRs (occurring in ≥ 5% of patients treated with tocilizumab monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and **increased ALT**.

System Organ Class	Very Common	Common	Uncommon
Infections and infestations	Upper respiratory tract infections	Cellulitis, Pneumonia, Oral herpes simplex, Herpes zoster	Diverticulitis
Gastrointestinal disorders		Abdominal pain, Mouth ulceration, Gastritis	Stomatitis, Gastric ulcer
Skin and subcutaneous tissue disorders		Rash, Pruritus, Urticaria	
Nervous system disorders		Headache, Dizziness	
Investigations		Hepatic transaminases increased, Weight increased, Total bilirubin increased*	

SPC

Respiratory, thoracic and mediastinal disorders	Common	Cough
	Uncommon	Bronchospasm, wheezing, dyspnea
	Rare	Throat tightness
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, nausea, dyspepsia, mouth ulceration, aphthous stomatitis, vomiting
	Uncommon	Gastritis
Hepatobiliary disorders	Common	Liver function test abnormal (including transaminases increased)
Skin and subcutaneous tissue disorders	Common	Rash (including dermatitis), alopecia, pruritus
	Uncommon	Increased tendency to bruise, dry skin, urticaria, psoriasis
Musculoskeletal and connective tissue disorders	Common	Pain in extremity

SPC

4.8 Undesirable effects | Go to top of the page

In all placebo-controlled studies, the most frequently reported adverse reactionwith Kineret was injection site reaction (ISRs), which was mild to moderate in the majority of patients. The most common reason for withdrawal from study in Kineret-treated patients is injection site reaction. The subject incidence of serious adverse reactions at the recommended dose of Kineret (100 mg/day) is comparable with placebo (7.1% compared with 6.5% in the placebo group). The incidence of serious infection was higher in Kineret-treated patients compared with patients receiving placebo (1.8% vs. 0.7%). Neutrophil decreases occurred more frequently in patients receiving Kineret compared with placebo.

Adverse reactions are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

MedDRA Organ System	**Frequency**	**Undesirable Effect**
Infections and infestations	Common (≥ 1/100 to < 1/10)	Serious infections requiring hospitalisation
Blood and lymphatic system disorders	Common (≥ 1/100 to < 1/10)	Neutropenia
Immune system disorders	Uncommon (≥ 1/1,000 to < 1/100)	Allergic reactions including anaphylactic reactions, angioedema, urticaria and pruritus
Nervous system disorders	Very common (≥ 1/10)	Headache
Skin and subcutaneous tissue disorders	Very common (≥ 1/10)	Injection site reaction
	Uncommon (≥ 1/1,000 to < 1/100)	Rash

Βιολογικοί παράγοντες & ηπατικές SE

SPC –συμπεράσματα I

Δεν είναι μόνο η αύξηση των ηπατικών

- Χολερυθρίνη
- χολόσταση
- χολολιθίαση
- χολοκυστίτιδα
- αυτοάνοση ηπατίτιδα
- κίρρωση
- ίκτερος

Βιολογικοί παράγοντες & ηπατικές SE

SPC –συμπεράσματα II

Διαφορές μεταξύ φαρμάκων

- Καθόλου : rituximab , anakinra
- Σπάνια : etanercept
- Συχνά : cetrolizumab, golimumab, infliximab, orencia
- Πολύ συχνά: tocilizumab & adalimumab

Ηπατικές ανεπιθύμητες ενέργειες βιολογικών παραγόντων

- SPC
- Registries
- Studies
- Cases

Ηπατικές ανεπιθύμητες ενέργειες βιολογικών παραγόντων

- SPC
- Registries
- Studies
- Cases

Registries

Extended report

Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis

Jeremy Sokolove,[1] Vibeke Strand,[1] Jeffrey D Greenberg,[2] Jeffrey R Curtis,[3] Arthur Kavanaugh,[4] Joel M Kremer,[5] Alina Anofrei,[6] George Reed,[6] Leonard Calabrese,[7] Michele Hooper,[8] Scott Baumgartner,[8] Daniel E Furst[9]; on behalf of the CORRONA Investigators

Ann Rheum Dis 2010;**69**:1612–1617. doi:10.1136/ard.2009.112136

Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis

Ann Rheum Dis 2010;**69**:1612–1617. doi:10.1136/ard.2009.112136

- LFT elevations in patients with rheumatoid arthritis
- receiving adalimumab (ADA), etanercept (ETN) or infliximab (INF)
- enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA registry)
- October 2001 to March 2007

Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis

Ann Rheum Dis 2010;**69**:1612–1617. doi:10.1136/ard.2009.112136

- 6861 patients (ADA: 849; ETN: 1383; INF: 1449) with 22 522 determinations were analysed.

- **LFT elevations >1×** ULN with TNF-I use were seen in 5.9% of AST/ALT determinations

- **abnormalities >2×** ULN in 0.77%

Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis

Ann Rheum Dis 2010;**69**:1612–1617. doi:10.1136/ard.2009.112136

In the primary model the adjusted ORs for LFT **elevations >1×** ULN were

- **INF** 1.58 (95% *CI* 1.35 to 1.86)
- **ADA** 1.35 (95% *CI* 1.09 to 1.66)
- **ETN** 1.00 (95% *CI* 0.83 to 1.21)

Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis

Ann Rheum Dis 2010;**69**:1612–1617. doi:10.1136/ard.2009.112136

For **elevations** 2× ULN, adjusted ORs were:

- **INF** 2.40 (95% CI 1.53 to 3.76)
- **ADA** 1.72 (95% CI 0.99 to 3.01)
- **ETN** 1.10 (95% CI 0.64 to 1.88)

Similar results were obtained in other models

Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis

Ann Rheum Dis 2010;**69**:1612–1617. doi:10.1136/ard.2009.112136

Conclusions:

- The overall incidence of LFT elevations >1× ULN with TNF-I use was uncommon

- abnormalities >2× ULN were rarely observed

- Significant differences were most consistently observed with
  - INF
  - less commonly with ADA
  - were not observed with ETN

compared with comparator DMARDs

Rheumatol Int
DOI 10.1007/s00296-012-2524-z

SHORT COMMUNICATION

Tumour necrosis factor-alpha inhibitor-induced hepatic injury in patients with rheumatoid arthritis: two case reports and an analysis of the laboratory data from the Slovenian national biologicals registry

Katja Perdan-Pirkmajer · Alojzija Hočevar · Žiga Rotar · Janez Žibert · Vera Ferlan Marolt · Filip Gučev · Matija Tomšič

Received: 10 March 2012 / Accepted: 23 August 2012

Tumour necrosis factor-alpha inhibitor-induced hepatic injury in patients with rheumatoid arthritis: two case reports and an analysis of the laboratory data from the Slovenian national biologicals registry

- RA patients are frequently treated with several potentially **hepatotoxic** drugs concomitantly
- causative link between TNF-a inhibitors and liver injury is usually **difficult** to establish

Perdan-Pirkmajer K, Tumour necrosis factor-alpha inhibitor-induced hepatic injury in patients with rheumatoid arthritis: two case reports and an analysis of the laboratory data from the Slovenian national biologicals registry. Rheumatol Int. 2012 Sep 7. [Epub ahead of print]

Tumour necrosis factor-alpha inhibitor-induced hepatic injury in patients with rheumatoid arthritis: two case reports and an analysis of the laboratory data from the Slovenian national biologicals registry

- 2 cases of RA patients who developed histologically manifest liver injury shortly after the introduction of treatment with 2 different TNF-a inhibitors
- elevated levels of serum aminotransferase **can be observed** in patients treated with TNF-a inhibitors
- no significant differences between the impact of adalimumab and etanercept on aminotransferase levels

Perdan-Pirkmajer K, Tumour necrosis factor-alpha inhibitor-induced hepatic injury in patients with rheumatoid arthritis: two case reports and an analysis of the laboratory data from the Slovenian national biologicals registry. Rheumatol Int. 2012 Sep 7. [Epub ahead of print]

Tumour necrosis factor-alpha inhibitor-induced hepatic injury in patients with rheumatoid arthritis: two case reports and an analysis of the laboratory data from the Slovenian national biologicals registry

- 256 (47 %) patients with AST and/or ALT elevations above the ULN in at least one measurement
- 238 patients (38.2 %) had aminotransferase levels between ULN and 2 times the ULN
- 36 patients (6.6 %) between 2 and 3 times the ULN
- 12 (2.2 %) patients had values between 3 and 5 times the ULN,
- 2 (0.4 %) had levels more than 5 times the ULN

Perdan-Pirkmajer K, Tumour necrosis factor-alpha inhibitor-induced hepatic injury in patients with rheumatoid arthritis: two case reports and an analysis of the laboratory data from the Slovenian national biologicals registry. Rheumatol Int. 2012 Sep 7. [Epub ahead of print]

Ηπατικές ανεπιθύμητες ενέργειες βιολογικών παραγόντων

- SPC
- Registries
- Studies
- Cases

Ηπατικές ανεπιθύμητες ενέργειες βιολογικών παραγόντων

- SPC
- Registries
- Studies
- Cases

papers

ETA & AS

- 105 patients were included
- Elevated serum aminotransferases, probably or possibly related to etanercept treatment, were observed in **9 %** of the AS patients
- An increased risk for the elevation of liver enzymes was found in patients with a **higher body mass** index

van Denderen JC, Blom GJ, van der Horst-Bruinsma IE, Dijkmans BA, Nurmohamed MT. Elevated liver enzymes in patients with ankylosing spondylitis treated with etanercept.Clin Rheumatol. 2012 ***Sep 1****.*

Ηπατικές ανεπιθύμητες ενέργειες βιολογικών παραγόντων

- SPC
- Registries
- Studies
- Cases


Real Life
Patient Case
Series
Real Life
Patient Case
Series

Hepatitis with interface inflammation and IgG, IgM, and IgA anti–double-stranded DNA antibodies following infliximab therapy: comment on the article by Charles et al

Arthritis Rheum. 2001 Aug;44(8):1966-8.

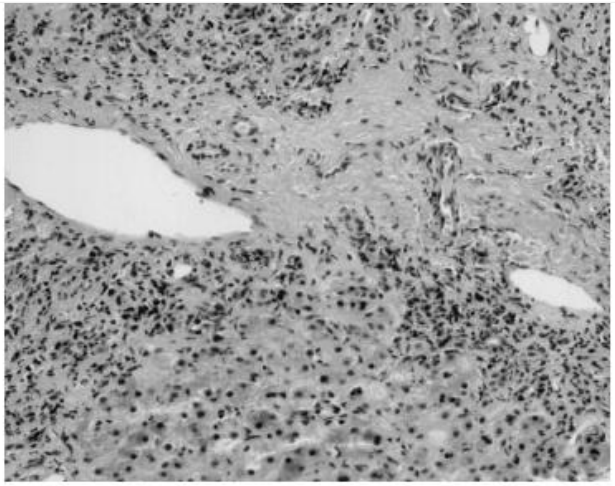


Figure 1. Liver biopsy section showing prominent portal interface inflammation (original magnification × 200).

- 36-year-old woman with seropositive RA
- developed **acute hepatic inflammation**
- IgG, IgM, and IgA anti-dsDNA antibodies
- after treatment with infliximab
- The patient's symptoms and liver function rapidly resolved with
  - the discontinuation of infliximab
  - the institution of methylprednisolone therapy

cases

A 39-year old RA patient was admitted with **cholestatic liver disease** after 8 months of treatment with infliximab

A 54-year old RA patient, was diagnosed with **autoimmune hepatitis** after 12 infliximab infusions

Tobon GJ, Cañas C, Jaller JJ, Restrepo JC, Anaya JM. Serious liver disease induced by infliximab. Clin Rheumatol. 2007 Apr;26(4):578-81. Epub 2006 Mar 18.

cases

a patient with rheumatoid arthritis who developed **granulomatous hepatitis** after taking **etanercept**

Infectious and metabolic causes of liver disease had been excluded and the liver biopsy was not typical of sarcoidosis.

Liver enzyme abnormalities improved after etanercept was discontinued

Farah M, Al Rashidi A, Owen DA, Yoshida EM, Reid GD. Granulomatous hepatitis associated with etanercept therapy. J Rheumatol. 2008 Feb;35(2):349-51.

Cases (switching)

- one patient with spondyloarthropathty who presented **severe liver dysfunction** related to infliximab
- 10 weeks after infliximab discontinuation serum concentrations of liver blood tests were normal
- ankylosing spondylitis symptoms had relapsed
- he was treated with etanercept with a rapid and sustained improvement

.

García Aparicio AM, Rey JR, Sanz AH, Alvarez JS. Successful treatment with etanercept in a patient with hepatotoxicity closely related to infliximabClin Rheumatol. 2007 May;26(5):811-3. Epub 2006 Jul 7.

Cases (switching)

a patient presenting with acute hepatitis while receiving **infliximab** for ankylosing spondylitis

The treatment was stopped after the 6th infusion when laboratory work-up revealed a **10-fold** increase in serum levels of aminotransferases.

A liver biopsy showed interportovenular bridging necrosis with macrophage accumulation consistent with the diagnosis of **acute toxic hepatitis**.

After infliximab discontinuation, hepatic abnormalities resolved and the patient was treated with **etanercept** for more than 2 years without recurrence of hepatitis

.

Thiéfin G, Morelet A, Heurgué A, Diebold MD, Eschard JP. Infliximab-induced hepatitis: absence of cross-toxicity with etanercept Joint Bone Spine. 2008 Dec;75(6):737-9. Epub 2008 Aug 6.

Cases (switching)

- After 7 infusions, progressive elevations of the transaminases up to five times the upper normal limit were noted and treatment with infliximab was terminated
- Liver biopsy showed late signs of **acute toxic hepatitis**
- the patient continued with etanercept without new episodes of liver dysfunction

.

Carlsen KM, Riis L, Madsen OR. Toxic hepatitis induced by infliximab in a patient with rheumatoid arthritis with no relapse after switching to etanercept. Clin Rheumatol. 2009 Aug;28(8):1001-3. Epub 2009 Apr 16.

Cases (switching)

- a patient with PsA who presented liver dysfunction during adalimumab, subsequently successfully treated with etanercept

Massarotti M, Marasini B. Successful treatment with etanercept of a patient with psoriatic arthritis after adalimumab-related hepatotoxicity. Int J Immunopathol Pharmacol. 2009 Apr-Jun;22(2):547-9.

Cases - IBD

44-year-old woman with Crohn disease who developed **jaundice** after an infusion of infliximab

Menghini VV, Arora AS. Infliximab-associated reversible cholestatic liver disease. Mayo Clin Proc. 2001 Jan;76(1):84-6

Inflamm Bowel Dis • Volume 13, Number 12, December 2007

Occurrence of Hepatoxicicty and Elevated Liver Enzymes in a Crohn's Disease Patient Treated with Infliximab

Of additional interest, the patient had previously been treated with certolizumab pegol for 19 month in a clinical trial and was withdrawn due to loss of response. During this treatment no changes in transaminases were observed. The patient received 3 infusions with infliximab (5 mg/kg) at weeks 0, 2,

- We report a case of acute liver injury potentially related to infliximab
- in a 45-year-old female patient
- with a history of CD for more than 15 years

Liver damage / IBD

- Ierardi E, Valle ND, Nacchiero MC, et al. Onset of liver damage after a single administration of infliximab in a patient with refractory ulcerative colitis. *Clin Drug Investig.* 2006;26:673– 676

- Menghini VV, Arora AS. Infliximab-associated reversible cholestatic liver disease. *Mayo Clin Proc.* 2001;76:84–86

- Data on file (Module 2.7.4, p 321–323; August 2005), Centocor

- Lichtenstein GR, Cohen RD, Feagan BG, et al. Safety of infliximab in Crohn's disease: data from the 5000-patient TREAT Registry [Abstract]. *Digest Dis Week.* 2004, May 15– 20. New Orleans, LA. Abstract 439

Case TSZ

Clinical Pharmacology: Advances and Applications

Dovepress

open access to scientific and medical research

Open Access Full Text Article

CASE SERIES

Hepatotoxicity of tocilizumab and anakinra in rheumatoid arthritis: management decisions

Clinical Pharmacology: Advances and Applications 2011:3 39–43

Clinical Pharmacology: Advances and Applications
Dovepress
open access to scientific and medical research
Open Access Full Text Article
CASE SERIES

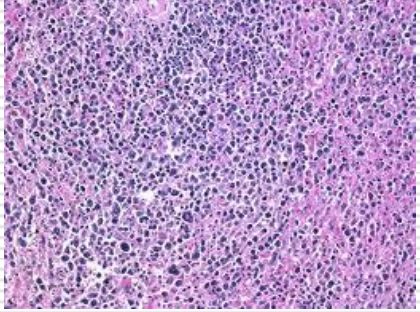
Hepatotoxicity of tocilizumab and anakinra in rheumatoid arthritis: management decisions

Clinical Pharmacology: Advances and Applications 2011:3 39–43

- toxic liver effects
- Liver biopsy in both cases showed **focal necrosis of hepatocytes** – a hallmark of drug toxicity – with steatosis and early fibrosis
- Discontinuation of anakinra led to rapid normalization of liver enzymes

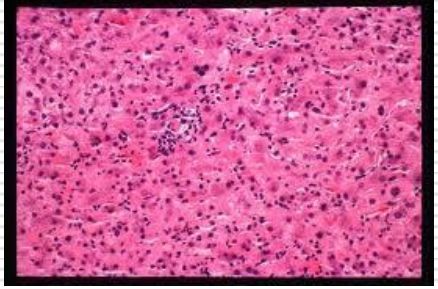
- The patient receiving tocilizumab developed hepatosplenomegaly
- but had normal liver enzymes
- the tocilizumab treatment was continued
  since the patient had not responded to other drugs
  There was a good response to the tocilizumab treatment
  and the liver biopsy showed only insignificant, reversible liver injury

Hepatosplenic T-cell lymphoma



- all cases of HSTCL reported to the FDA in patients receiving TNF-a inhibitors
- **25 cases** of HSTCL were identified
- Twenty-two (88%) patients had inflammatory bowel disease and **3 had rheumatoid arthritis**
- 4 cases (16%) were in women
- 4 patients were above 65 years of age
- 24 cases (96%) also received an immunomodulator (azathioprine, 6-mercaptopurine, or methotrexate).
- 2 patients received adalimumab alone

Parakkal D, Sifuentes H, Semer R, Ehrenpreis ED. Hepatosplenic T-cell lymphoma in patients receiving TNF-a inhibitor therapy: expanding the groups at risk. Eur J Gastroenterol Hepatol. ***2011*** *Nov;23(12):1150-6.*



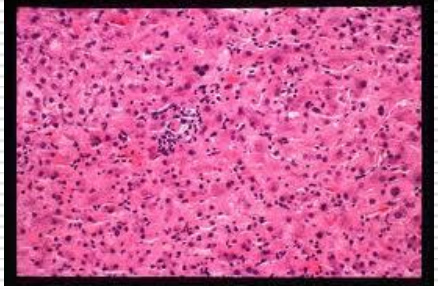
Αυτοάνοση ηπατίτιδα

The latest update of our registry (15 July 2009) included more than **800** cases of autoimmune **diseases** secondary to biological therapies, including a wide variety of both

- systemic (lupus, vasculitis, sarcoidosis and antiphospholipid syndrome)
- organ-specific (interstitial lung disease, uveitis, optic neuritis, peripheral neuropathies, multiple sclerosis and **autoimmune hepatitis**) autoimmune processes

Ramos-Casals M, Roberto-Perez-Alvarez, Diaz-Lagares C, Cuadrado MJ, Khamashta MA; BIOGEAS Study Group. Autoimmune diseases induced by biological agents: a double-edged sword? Autoimmun Rev. 2010 Jan;9(3):188-93. Epub 2009 Oct 23.

Αυτοάνοση ηπατίτιδα



- one month and one year after initiation of the biological agent
- complete resolution was observed in nearly 75% of cases after cessation of therapy

Ramos-Casals M, Roberto-Perez-Alvarez, Diaz-Lagares C, Cuadrado MJ, Khamashta MA; BIOGEAS Study Group. Autoimmune diseases induced by biological agents: a double-edged sword? Autoimmun Rev. 2010 Jan;9(3):188-93. Epub 2009 Oct 23.

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Drug induced autoimmune hepatitis and TNF-α blocking agents: Is there a real relationship?

Cumali Efe *

Hacettepe University, Department of Gastroenterology, Turkey

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Drug induced autoimmune hepatitis and TNF-α blocking agents: Is there a real relationship?

Cumali Efe *

Hacettepe University, Department of Gastroenterology, Turkey

Take-home messages

- TNF-α blockers are commonly used drugs in the treatment of autoimmune disorders and drug induced liver injury or drug induced-AIH has been reported in only few cases.
- Therefore, it is difficult to draw a definitive conclusion as TNF-α blockers are strong potential causative agents for the development of AIH or DILI.
- In the light of views, it seems some of these patients have indolent AIH that become overt after drug usage rather than de novo disease onset.
- Anti-TNF-α induced AIH or DILI shows good response to short term immunosuppressive therapy.

Κάτι να...μείνει

- Οι ανεπιθύμητες δράσεις στο ήπαρ ΔΕΝ είναι συχνές
- Δεδομένα (μελέτες, registries) δεν υπάρχουν πολλά
- Ανεπιθύμητες δράσεις από το ήπαρ ΔΕΝ είναι μόνο η αύξηση των ηπατικών
- Υπάρχουν διαφορές μεταξύ των βιολογικών παραγόντων

Κάτι να...μείνει

- Μηχανισμός ?
- Η αλλαγή βιολογικού δεν υποχρεώνει σε νέα ηπατική δυσλειτουργία
- Ρευματολογικός ασθενής
  - Φάρμακα (MTX, ΜΣΑΦ, IEF)
  - Συνοσηρότητα (φάρμακα πχ στατίνες)
  - ΣΒ

Νικολής 6 ετών, 13-10-12