

Potential serious immunomodulatory complications of hepatitis C therapies

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Introduction:

- Chronic hepatitis C (HCV) is associated with many systemic manifestations (including fatigue, myalgia, weight loss, cryoglobulinaemia, vasculitis, lymphoproliferative disorders, membranoproliferative glomerulonephritis and porphyria cutanea tarda)
- Recently treatment has changed from interferon-based regimens to use of direct acting antiviral (DAA) agents.
- Interferon-free treatments produce higher rates of sustained virological response at week 12 (SVR12) as well as fewer reported side effects. (PEG-IFN/ribavirin-based regimes can cause bone marrow suppression, depression, psychosis, myalgias, arthralgias, optic neuritis, retinal thrombosis, rheumatoid arthritis, hyper/hypothyroidism, hyperglycaemia and sarcoidosis)
- We report 2 causes of serious and unusual complications from patients receiving treatment for HCV

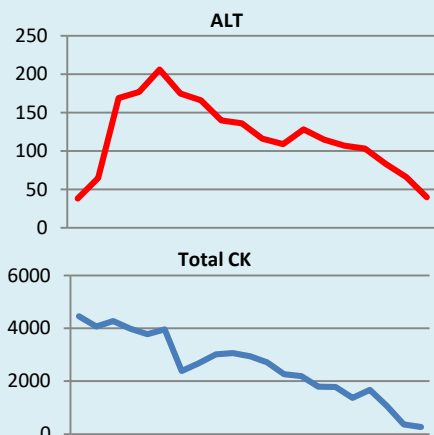
Case 1

A 54 year old male non-cirrhotic co-infected HIV and HCV genotype 3 was treated with PEG-IFN and ribavirin. After 12 weeks of treatment he developed severe progressive muscular weakness over 4 weeks leaving him bedbound and unable to swallow. Examination revealed peripheral neuropathy with LMN signs and dysphagia.

Investigations

HIV	20 copies/ml
WCC	5.5x10 ⁹ /L
Hb	122g/L
MCV	103.1fL
Plts	158x10 ⁹ /L
ALT	691iU/L
ALP	62iU/L
Bil	10umol/L
GGT	220iU/l
INR	1.1
UEG	normal
CK	4453 u/L
ESR	46mm/h

(Bloods on admission)



(Total CK and ALT decreased over several weeks in response to treatment)

Imaging including MRI head and spine, CT TAP were all normal.

ANA was 1:12560 and anti-Ro 52 was positive. The remaining auto-immune screen was negative.

EMG was suggestive of myositis.

Muscle biopsy showed non-specific inflammatory changes.

Management:

Rheumatology and neurology opinions were sought. NG feeding with regular SALT and physio assessments were required. Steroids were started for a diagnosis of myositis and interferon was stopped prematurely at week 22. HCV PCR remained undetectable and he achieved SVR12.

Outcome:

Full recovery.

Conclusion:

- Case 1 reports a significant temporal association between initiation of PEG-IFN/ribavirin and development of severe life-threatening myositis. Myositis has rarely been reported as a side effect of PEG-IFN in hepatitis C. We postulate that the immunomodulatory effect of PEG-IFN was responsible for the initiation of myositis.
- Case 2 reports cryptococcal disease developing on a PEG-sparing regimen. Very rarely an association of cryptococcal peritonitis and cirrhosis has been reported and malignancy may have played a role here too but the temporal association between these events the subsequent severity of disease is noteworthy.
- It is difficult at this stage in our understanding of these drugs to postulate a mechanism of action.

Case 2

A 56 year old female known cirrhotic with HCV genotype 3 was treated with daclastavir/sofosbuvir/ribavirin for 12 weeks. During treatment she was noted to have focal lung lesions leading to a left thoracotomy. Cryptococcal antigen on blood was negative but histology and PCR confirmed these lesions to be *Cryptococcus neoformans*.

4 months after completing her HCV treatment she developed headaches and was admitted to hospital with reduced GCS and seizures.

Investigations

WCC	5.3x10 ⁹ /L
Hb	150g/L
Plts	35x10 ⁹ /L
ALT	191iU/L
ALP	120iU/L
Bil	19umol/L
INR	1
UEG	normal
Adj Ca	3.8mmol/L
Phos	1.21 mmol/L
TSH	1.3miu/L
CRP	5mg/L
PTH	13.2ng/L



(CT TAP: total collapse left lower lobe with multiple areas of consolidation. Diffuse sclerosis of dorsal spine)

(Bloods on admission)

CSF: Day 1

Appearance	Clear
Protein	0.92g/L
Lactate	3.0 mmol/L
CSF gluc	2.4mmol/L
Serum gluc	5.6mmol/L
RCC	<5
WCC	16
polys	5%
Gram film	NOS
CrAg	negative
Pressure	

CSF: Day 7

Appearance	Clear
Protein	0.89g/L
Lactate	4.0 mmol/L
CSF gluc	3.0mmol/L
Serum gluc	6.3mmol/L
RCC	7
WCC	75
polys	0%
Gram film	yeasts
CrAg	positive
Pressure	24.5cm/H2O

Management:

Hypercalcaemia was treated medically and she was transferred to ITU for refractory seizures despite anti-convulsants.

Initially expert opinion from neurology, endocrinology, respiratory and Infectious Diseases consultants supported a paraneoplastic cause for her seizures so anti-fungals withheld. Meropenem started for pneumonia. CRP continued to rise and she developed fevers so an LP was repeated which confirmed cryptococcal meningitis.

Despite ITU support and aggressive treatment for cryptococcal meningitis she died from the complications of this infection.

Post-mortem:

- Extensive malignancy either a carcinoma or a lymphoma.
- Brain features are consistent with **cryptococcal meningitis**.
- Histology revealed widely **disseminated small cell carcinoma**.