CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3531979

Available online at: http://www.iajps.com *Research Article*

HEPATITIS REACTIVATION IN RHEUMATOLOGICAL PATIENTS AFTER BIOLOGICAL TREATMENT

Dr.Hana S Alahmari[1], Dr.Bayan H Alaqhatani[2], Dr. Majed Alsubaie[3], Dr. Hissah I ALMania[4], Dr. Hanady M Alhumaidi[5], Dr. Manal M AL-Qahtani[7] Dr. Mansour Somaily[6]

[1]Rheumatology Unit ,Department of Medicine ,King Khalid University,Abha,Saudi Arabia,[2, 3] Medical intern - collage of Medicine - king KHALID university - Abha - Saudi Arabia,[4,5,] [6]Internal medicine-departement of medicine –Asiri Central Hospital- Abha- Saudi Arabia, [7]Consultant Rheumatologist-collage of medicine-King Khalid university-Abha-Saudi Arabia.

Article Received: September 2019 **Accepted:** October 2019 **Published:** November 2019

Abstract:

Introduction: *Both Hepatitis B (HBV) and Hepatitis C (HCV) virus can cause chronic liver disease and hepatocellular carcinoma. Approximately 1 in every 3 individuals worldwide may have been exposed to hepatitis virus. The use of immunosuppressive and biological modifier agents for rheumatoid diseases which may result in reactivations among patients infected with HBV and HCV. Reactivation with its potential consequences is particularly a concern when these people are exposed to immunosuppressive therapies for the management of rheumatologic conditions.*

Objective: *To examine the incidence of reactivation or flare in chronic HBV and HCV patients who are at the same time treated for rheumatological disorder by immunosuppressant.*

Subjects &Methods: *This was a retrospective hospital record-based study. Study subjects include any patients who have follow up appointments in the rheumatology clinic in Aseer Central Hospital, Abha for rheumatological disease and has used immunosupp-ressive medications and labelled to have chronic hepatitis C or B. A structured and pretested proforma was used as study tool. SPSS was used for statistical analysis.*

Results: *78.8% of the cases having chronic hepatitis &receiving immunosuppressive drugs had HBV. Marked reduction of hepatic profile was noted in cases who received only one ISD as compared to two or three drugs consumption. On studding PCR change before and after receiving immunosuppressive drugs it was clear that 54.6% of the cases had no change. As for albumin, cases on combined therapy recorded 10.9% increase in its initial value compared to no change in the other cases (P>0.05).*

Conclusions: *There was marked reduction of hepatic profile in cases with only one ISD. Cases on combined therapy recorded significant change for albumin.*

Keywords: *Rheumatological disorder; Immunosuppressant drug (ISD), Hepatitis B & C, PCR.*

Corresponding author:

Dr. Hana S Alahmari,

Rheumatology Unit, Department of Medicine, King Khalid University, Abha,Saudi Arabia.

QR code

Please cite this article in press Hana S Alahmari et al., ***Hepatitis Reactivation in Rheumatological Patients after Biological Treatment.,*** *Indo Am. J. P. Sci, 2019; 06(11).*

INTRODUCTION:

Both Hepatitis B (HBV) and Hepatitis C (HCV) viruses can cause chronic liver disease and hepatocellular carcinoma. Reports show that an estimate of approximately 1 in every 3 individuals worldwide may have been exposed to hepatitis virus. [1-2] Given that viral hepatitis remnants endemic in Saudi Arabia [3-4], statistics of blood donors by Babanejad [5] show that the prevalence of HBsAg was found to be 1.5–2.6% in adult populations, and the prevalence rate of anti-HCV in Saudi nationals was assessed by Liakina et al. to be 0.74% [6]. A study reported the incidence of HBV, and HCV sero-positivity over eight years of surveillance in Saudi Arabia which showed that a total of 14224 seropositive cases were reported based on the records reported to the surveillance system. The study also showed that the average annual incidence of sero- positivity was100000 served population was highest for HBV & then HCV. [7]

Biological disease-modifying antirheumatic drugs (b-DMARDs) are a potent second-line treatment if the first-line immunosuppressive therapy is failed in several rheumatological, dermatological, and gastroenterological autoimmune diseases. Biological agents involve of proteins and protein fragments derived from living sources, such as humans, animals, or microorganisms [8] Though, as with almost all medications, these biological agents have a number of reported side effects ranging from minor (e.g., rash, myalgias, fever, and headache) to serious (e.g., worsening heart failure, demyelinating disorders, liver enzyme abnormalities, and increasing susceptibility to infections or reactivation of existing infections) [9-10-11]. Recently there were reports and published articles which theoretically discussed that the use of immunosuppressive and biological modifier agents for rheumatoid diseases which may result in reactivations among patients infected with HBV and HCV. (Reference)Reactivation with its potential consequences is particularly a concern when these people are exposed to immunosuppressive or biologic therapies for the management of rheumatologic conditions. [12-13]Up to this date, no studies investigated such incidence in Aseer Region in Saudi Arabia which the researcher aimed to scientifically investigate. Keeping this in mind, the current study was conducted with the objective to examine the incidence of reactivation or flare in chronic HBV and HCV patients who areat the same time treated for rheumatological disorder by immunosuppressantat several hospitals in Asir Region, Saudi Arabia during the period from2010 to 2017.

METHODOLOGY:

A descriptive retrospective hospital record-based approach was used targeting all HCV and HBV patients with rheumatological diseaseattended to rheumatology clinic in Aseer Central Hospital, Abha to receive biological treatment as a medical plan for their rheumatological diseases during the period starting from 2010 to 2017. Data were extracted using a previously structured and pretested data sheet to avoid data extraction error. Extracted data included patients' demographic and clinical characteristics like age, sex, type rheuma HX, Rheuma disease (RA, SLE, seronegative, vasculitis, rhnpus, Siogren syndrome, DM, PM, sarcodosis, behgat, others…), duration (less than 5 year, 5 to 10 years, more than 10 years), hepatitis type (B or C), duration of hepatitis, serology of (HBsAg, Anti-HBs, Anti-HBc IgM, Anti- HBc IgG, HCV antibody) whether are these positive or negative, dose of the patient having liver cirrhosis or not, the level of PCR before and after the immunosuppressant medications, drug HX (antiviral, immune- supperion drugs), liver enzymes (AST, ALT, LFT, PT, ALP, Albumin, Bilirubin) before and after the treatment.

Data analysis:

After data were extracted, were revised, coded and fed to statistical software IBM SPSS version

All statistical analysis was done using two tailed tests and alpha error of 0.05. P value less than or equal to 0.05 considered to be statistically significant. Descriptive analysis based on frequency and percent distribution was done for patient's demographic and clinical data. Patent's seroconversion before and after receiving immunosuppressive therapy was tested using Mc0Nemar test for related variables. Difference between groups who had treatment with and without antiviral therapy at liver profile was tested using Mann-Whitney test.

RESULTS:

The study included 33 patients, 33% of them were less than 50 years while 30.3% aged above 60 years with mean age of 54.2 ± 10.6 years. About 81.8% of the study subjects/ participants were females. A total of 84.8% of the study subjects had history of RA with duration of illness less than 5 years & 10 years among 48.5% & 12.1% of the study subjects respectively.

Regarding chronic hepatitis profile of the subjects receiving immunosuppressive drugs, 78.8% of such cases had HBV. The diagnosis was made < 5 years before and between 5 – 10 years before among 72.7% & 27.3% of cases respectively. HBSA was positive among 72.7%

of the studtsubjects while Anti HBs was positive among 9.1% of cases. A total of 36.4% of the cases had positive Anti-HBc IgM and 39.4% were positive for Anti-HBc IgG. HCV Ab was positive among 21.2% of the cases while liver cirrhosis was recorded only in one case. (Table 1)

As for the use of immunosuppressive drugs by the cases, corticosteroids were given for 87.9% of the cases followed with MTX (33.3%), leflunamide and etomercept (15.2% each) and only 3% received adalimumab or abatacept.

The distribution of patients with chronic hepatitis according to number of immunosuppressive drugs received showed clearly that majority of cases (54.5%) received only one type of immunosuppressive drugs while 33.3% of cases received 2 drug and only 12.1% received >2 drugs.

On studding PCR change before and after receiving immunosuppressive drugs, it was clear that 54.6% of the cases had no change (either undetected or detectable status). About 6% were of undetectable level changed to detectable while 39.4% of the cases were detectable became undetectable with recorded statistical significance (P=0.004). PCR based viral load was significantly reduced among cases who either received only one or two ISDs, but minimal reduction was recorded among who received three drugs (Figure 1).

As for hepatic profile, figure **(2)** depicts marked reductions in cases who received only one ISD while some increased level was noted for those who received two or three drugs. Regarding AST, a marked reduction was noticed among cases who were on one ISD but others recorded some increase in AST specially who were on three ISDs (Figure 3).

With regard to combining ISDs with antiviral therapy and its effect on PCR based viral load cases who received combined therapy (ISD with antiviral drug) recorded marked reduction in viral load (Figure 4). Also change in bilirubin level showed that cases that received two ISDs had marked reduction while others recorded nearly stationary level. Albumin level was slightly high among cases that received two or three ISDs but not for cases that were on one drug only (Figure 5). As for ALP, cases on one or three ISDs recorded some reduction in its value while those who received two drugs showed marked increase in its level (Figure 6).

Finally**, table (2)** shows that PCR, bilirubin, and albumin change % from before to after receiving immunosuppressive drugs for viral hepatitis patients. As for viral load, patients who were on combined therapy recorded on average 100% reduction rate in its initial value compared to 90.3% reduction rate for those who were on ISD only with recorded statistical significance (P=.048). Considering bilirubin, cases who received combined therapy recorded 3.3% reduction rate compared to no change for other cases without significant change. As for albumin, cases on combined therapy recorded 10.9% increase in its initial value compared to no change in the other cases (P>0.05).

DISCUSSION:

Hepatitis B and HCV infections are considered serious worldwide public health problems. According to the World Health Organization (WHO), as of 2010 around 1 million annual deaths occurred due to viral hepatitis infections. HBV and HCV reactivation are a critical challenge in patients with rheumatological diseases receiving immunosuppressive therapy. [14]

This descriptive, cross sectional study illustrates the prevalence of chronic hepatitis among our patient in the rheumatology department at a tertiary hospital serving the majority of the southern sector in Saudi Arabia. Up to our knowledge, this is the only paper studying this topic in the country. We found 33 of rheumatology patients are defined to have chronic hepatitis B or C (26-7 respectively). 85% of the infected cohorts are RA patients, as it is the commonest rheumatological disease among our patients.

We defined HBV reactivation as "An increase in serum HBV DNA levels by greater than 1 to 2 $\log_{10}$ IU/mL (if HBV DNA was detectable at baseline) or the detection of serum HBV DNA (>100 IU/mL, if HBV DNA was negative at baseline)". We also defined HCV reactivation as "An increase in HCV RNA viral load >1 $\log_{10}$ IU/mL (virologic breakthrough) plus a ≥threefold increase in serum ALT or AST that could be explained by no other cause. [15]

By using these figures, no reactivation has been detected in all infected patients included in this study. This finding could be attributed to that all subjects or included patients are on antiviral medications which start concomitantly or prior to immunosuppressive drugs regardless of viral load or the group of the immunosuppressant.

The data studying the viral reactivation with steroid as a monotherapy are limited. 16 In addition, there is no agreed cut-off value to define high and low dose of corticosteroid and most of the patients are not on fixed dose. However, Bae et al reported a case of fatal hepatitis B, and it was a reactivation of infection during long-term, low-dose treatment with GKS of inactive carrier

of HBV. [16-17] Both were not on antiviral drug. The majority of patients in this study received oral corticosteroid 87% as a potent anti-inflammatory drug which is used mostly in the rheumatology field.

Methotrexate is well known for its hepatotoxic side effect and it has been prescribed to about one third of our studied patients. In a recent retrospective cohort study of 358 Taiwanese RA patients with untreated chronic HBV infection who were taking MTX, no evidence of an increased rate of liver cirrhosis was documented, providing indirect evidence of its safety in this population. [18]

In a recent analysis of all adverse events reported in the Food and Drug Administration's Adverse Event Reporting System database among 92 HBV-infected patients with RA receiving antirheumatic drugs, there were 27 fatalities and in 20 of them MTX was used (4 patients with fulminant hepatitis). In a recent case-control study from Japan, among 92 patients with HBVr with rheumatic disease, 12 cases of disease-modifying antirheumatic drugs (DMARDs) other than MTX (4 hydroxychloroquine, 4 LEF, 4 sulfasalazine) were reported. Thus, these agents can be categorized as low-risk treatments too. [19]

The association between TNF inhibitors (TNFi) use and HBVr has been well. It is believed that inhibition of TNF-α decreases the inflammatory cell response against a viral infection, and viral replication is extended and prevents the destruction of infected cell. [20] As found in most of the previous studies, etanercept is the commonest anti TNF prescribed to the patients in this study.In a review of all published cases until 2011, Pe´rez-Alvarez and colleagues reported a 64% reactivation rate among 33 HBs Ag positive patients (21 of 33) treated with TNFi without antiviral prophylaxis, [21] whereas in three recent studies from East Asia the respective rate was 29% (17 of 61). [22,23]

The risk for HBVr in untreated HBsAg positive rheumatic patients has been explored in 2 retrospective studies. In the first, all 4 inactive HBV carriers who had received intravenous ABA developed HBVr at a mean time of 10 months. [24] On the contrary, none of the 38 inactive HBV carriers treated with ABA for 24 months developed HBVr in a recent Italian study. [25] Altogether, these data indicate that MTX, anti TNF alfa, ABA are safe in rheumatic patients with chronic or past HBV infection (low risk: <1% according to the AGA). [20]

RTX is considered a high-risk agent (>10%) for HBsAg positive patients although there is a paucity of data for rheumatic patients (except from rare case reports). [26]

Data on the risk factors, prevalence and clinical outcomes of HCV reactivation with anti-inflammatory and immunomodulatory medications are insufficient and the prophylaxis use have not been illustrated. We prescribed seven patients with chronic hepatitis C with rheumatic disorder were the viral load remain stable most of the disease course.

Adverse hepatic outcomes of TNF-α inhibitors in HCV-infected RA patients have been reported in the literature. [27-28] In a study, the safety profiles of TNF-α inhibitors in HCV-infected patients appeared to be acceptable, irrespective of agent or underlying chronic inflammatory condition. [27] Safety signals of etanercept plus methotrexate in a prospective, multicenter study concluded that TNF-α inhibitors can be used in daily clinical practice without increased risk of hepatotoxicity or viral replication in HCV carriers. [29] Eshbaugh and Zito described four cases of abatacept treated RA patients with hepatitis C; the authors observed no adverse event of hepatic function deterioration or increased viral load and suggested that abatacept could be used in patients with HCV infection. [30]

CONCLUSION:

There was marked reduction of hepatic profile in cases with only one ISD. Cases on combined therapy recorded significant change for albumin.

Ethics Committee Approval:

Ethics committee approval was received for this study from the ethics committee of medical research studies department, *Department of Medicine, King Khalid University, Abha*, Saudi Arabia.

ACKNOELEDGEMENT:

We thank our study subject & the Director of Aseer Central Hospital, Abha for consenting the conduction of the current study.

Consent for Publication:

Written informed consent was not obtained due to the retrospective nature of the study.

CONTRIBUTION OF AUTHORS:

Responsible for overall design & concept of the study.

Responsible of Data Collection
Responsible for compilation of collected data and entry in the software.
Responsible for write up of the manuscript.
Responsible for statistical analysis and interpretation.

Responsible for overseeing, correction & finalizing the final manuscript.

REFERENCES:

1. Dienstag, J.L. (2008). Hepatitis B virus infection. New England Journal of Medicine, 359:1486–1500.
2. Liang, T.J., Block, T.M., &McMahon, B.J. (2015). Present and future therapies of hepatitis B: from discovery to cure. Hepatology, 62:1893–1908.
3. Abdo AA, Sanai FM, Al-Faleh FZ. Epidemiology of viral hepatitis in Saudi Arabia: are we off the hook? Saudi J Gastroenterol. 2012;18:349–57.
4. 11- Alfaleh FZ, Nugrahini N, Matičič M, Tolmane I, Alzaabi M, Hajarizadeh B, et al. Strategies to manage hepatitis C virus infection disease burden. JVH. 2015;22:42–65.
5. 12- Babanejad M, Izadi N, Najafi F, Alavian SM. The HBsAg Prevalence among blood donors from Eastern Mediterranean and Middle Eastern countries: a systematic review and meta-
6. Analysis. Hepat Mon. 2016;16:e35664.
7. Liakina V, Hamid S, Tanaka J, Olafsson S, Sharara AI, Alavian SM, et al. Historical epidemiology of hepatitis C virus (HCV) in select countries. JVH. 2015;22:4–20
8. Memish, Z., Al Knawy, B., &El-Saed, A. (2010). Incidence trends of viral hepatitis A, B, and Cseropositivity over eight years of surveillancein Saudi Arabia.International Journal of Infectious Diseases, 14, e115—e120.
9. Pucino F, Jr, Harbus PT, Goldbach-Mansky R. Use of biologics in rheumatoid arthritis: where are we going? Am J Health Syst Pharm. 2006;63(Suppl 4):S19–41.
10. 6- Toussaint NC, Maman Y, Kohlbacher O, Louzoun Y. Universal peptide vaccines - optimal peptide vaccine design based on viral sequence conservation. Vaccine.2011;29:8745–53.
11. 7- Calabrese LH, Zein NN, Vassilopoulos D. Hepatitis B virus (HBV) reactivation with immunosuppressive therapy in rheumatic diseases: assessment and preventive strategies. Ann Rheum Dis. 2006;65:983–9.
12. 8- Carlsen KM, Riis L, Madsen OR. Toxic hepatitis induced by infliximab in a patient with rheumatoid arthritis with no relapse after switching to etanercept. Clinical
13. rheumatol. 2009;28:1001–3.
14. Loombal, R., &Liang, J. (2017). Hepatitis B Reactivation Associated with Immune Suppressive and Biological Modifier Therapies: Current Concepts, Management Strategies, and Future Directions. Gastroenterology, 152:1297–130
15. Pompili M, Biolato M, Miele L, Grieco A. Tumor necrosis factor-alpha inhibitors and chronic hepatitis C: a comprehensive literature review. World J Gastroenterol. 2013;19:7867–73.
16. World Health Organization (WHO) Hepatitis: frequently asked questions. 2010. Availablé- from: http://www.who.int/csr/disease/hepatitis/world_hepatitis_day/question_answer/en/
17. Yazici O, Sendur MA, Aksoy S. Hepatitis C virus reactivation in cancer patients in the era of targeted therapies. World J Gastroenterol 2014;20:6716–6724.
18. Bae JH, Sohn JH, Lee HS, Park HS, Hyun YS, Kim TY, Eun CS, Jeon YC, Han DS. A fatal case of hepatitis B virus (HBV) reactivation during long-term, very-low-dose steroid treatment in an inactive HBV carrier. Clin Mol Hepatol. 2012;18(2):225–228. doi: 10.3350/cmh.2012.18.2.225.
19. Cheng J, Li JB, Sun QL, Li X. Reactivation of hepatitis B virus after steroid treatment in rheumatic diseases. J Rheumatol. 2011;38(1):181–182. doi: 10.3899/jrheum.100692.
20. Walker AM, Funch D, Dreyer NA, Tolman KG, Kremer JM, Alarcón GS, Lee RG, Weinblatt ME. Determinants of serious liver disease among patients receiving low-dose methotrexate for rheumatoid arthritis. Arthritis Rheum. 1993;36:329–335.
21. M. Toshihisa, E. Katsumi, N. Natsumi, T. Sousuke, A. Toshiyuki, T. Kaoru, I.Shinichi, T. Ikuko, K. Yasuhiro, O. Hidetoshi, K. Noboru, M. Hisamitsu, T.Naota, I.Tatsuki, K. Atsushi,N. Kazuhiko & U. Yukitaka (2018) Hepatitis B virus reactivation in patients with rheumatoid arthritis: A single- center study, Modern Rheumatology, 28:5, 808-813, DOI: 10.1080/14397595.2017.1419842
22. Uhl EW, Moldawer LL, Busse WW, et al. Increased tumor necrosis factor α (TNF-α) gene expression in parainfluenza type 1 (Sendai) virus-inducted bronchiolar fibrosis. Am J Pathol. 1998;152:513–522.
23. Perez-Alvarez R, Diaz-Lagares C, Garcia-Hernandez F, et al. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. Medicine (Baltimore) 2011;90(6):359–371. doi: 10.1097/MD.0b013e3182380a76
24. Tan J, Zhou J, Zhao P, Wei J. Prospective study of HBV reactivation risk in rheumatoid arthritis patients who received conventional disease-modifying antirheumatic drugs. Clin
25. Rheumatol. 2012;31(8):1169–1175. doi: 10.1007/s10067-012-1988-2. [PubMed]
26. [CrossRef] [Google Scholar]
27. Tamori A, Koike T, Goto H, Wakitani S, Tada M, Morikawa H, Enomoto M, Inaba M, Nakatani T, Hino M, Kawada N. Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: evaluation of both

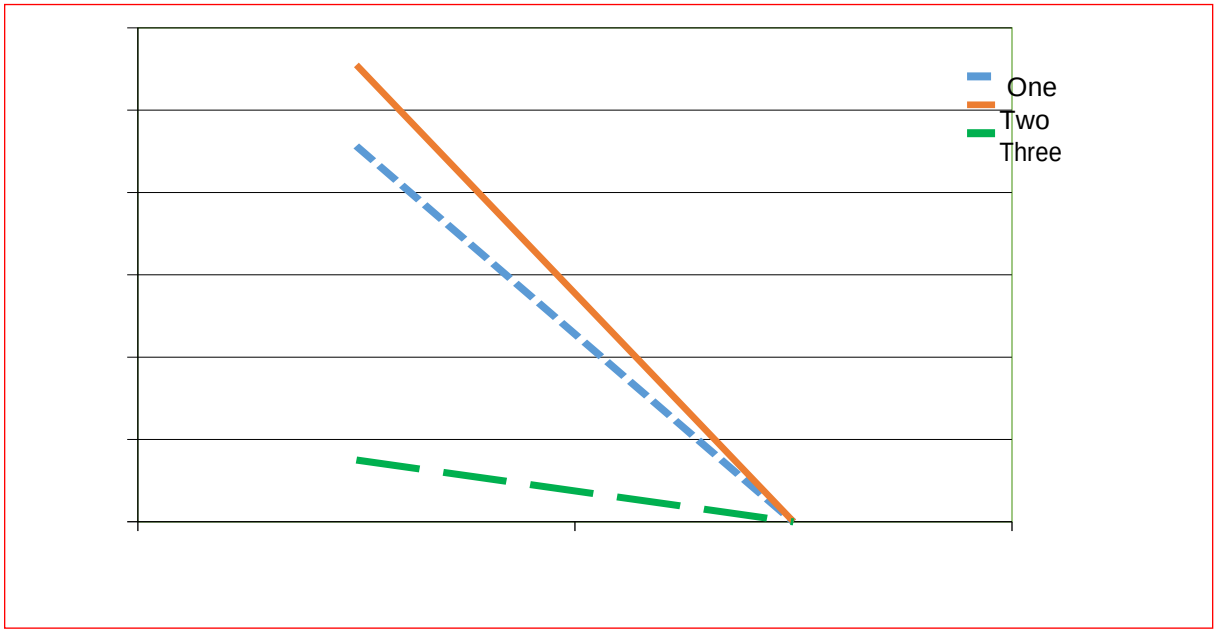
HBsAg- positive and HBsAg-negative cohorts. J Gastroenterol. 2011;46(4):556–564. doi: 10.1007/s00535-010-0367-5.

28. Koutsianas, C., Thomas, K. and Vassilopoulos, D. (2017). *Hepatitis B Reactivation in Rheumatic Diseases*. Rheumatic diseases clinical of north America. Volume 43, issue 1 pages 133-149.
29. Winthrop, K. and Calabrese, L. (2017). *Infection and Malignancy in Rheumatic Diseases, An Issue of Rheumatic Disease Clinics of North America, E-Book*. [online] Google Books.
30. Lu S, Xu Y, Mu Q, Cao L, Chen J, Zhu Z, Lou Y, Meng H, Qian W, Tong H, et al. The risk of hepatitis B virus reactivation and the role of antiviral prophylaxis in hepatitis B surface antigen negative/hepatitis B core antibody positive patients with diffuse large B-cell lymphoma receiving rituximab-based chemotherapy. Leuk Lymphoma. 2014:Aug 19; Epub ahead of print
31. Brunasso AM, Puntoni M, Gulia A, Massone C. Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review. Rheumatology (Oxford) 2011;50:1700–1711
32. Iannone F, Gremese E, Ferraccioli G, Lapadula G. GISEA. Comment on "Tumor necrosis factor-α antagonist therapy for concomitant rheumatoid arthritis and hepatitis C virus infection: a case series study". Clin Rheumatol 2016;35:839–840.
33. Iannone F, La Montagna G, Bagnato G, Gremese E, Giardina A, Lapadula G. Safety of etanercept and methotrexate in patients with rheumatoid arthritis and hepatitis C virus infection: a multicenter randomized clinical trial. J Rheumatol 2014;41:286–292.
34. Eshbaugh M, Zito S. Abatacept therapy for rheumatoid arthritis in patients with hepatitis C virus infection comorbidity: a series of four patients. Rheumatology(Sunnyvale)2014;S16:007.

TABLES & FIGURES

Table -1: Chronic hepatitis profile patients receiving immunosuppressive drugs, ACH, 2018

Hepatitis profile		No	%
Hepatitis type	HBV	26	78.8%
	HCV	7	21.2%
Duration of hepatitis	Less than 5 years	24	72.7%
	5-10	9	27.3%
HBSA	Negative	9	27.3%
	Positive	24	72.7%
AntiHBs	Negative	30	90.9%
	Positive	3	9.1%
Anti-HBcIgM	Negative	21	63.6%
	Positive	12	36.4%
Anti-HBcIgG	Negative	20	60.6%
	Positive	13	39.4%
HCVAb	Negative	26	78.8%
	Positive	7	21.2%
Liver cirrhosis	Yes	1	3.0%
	No	32	97.0%



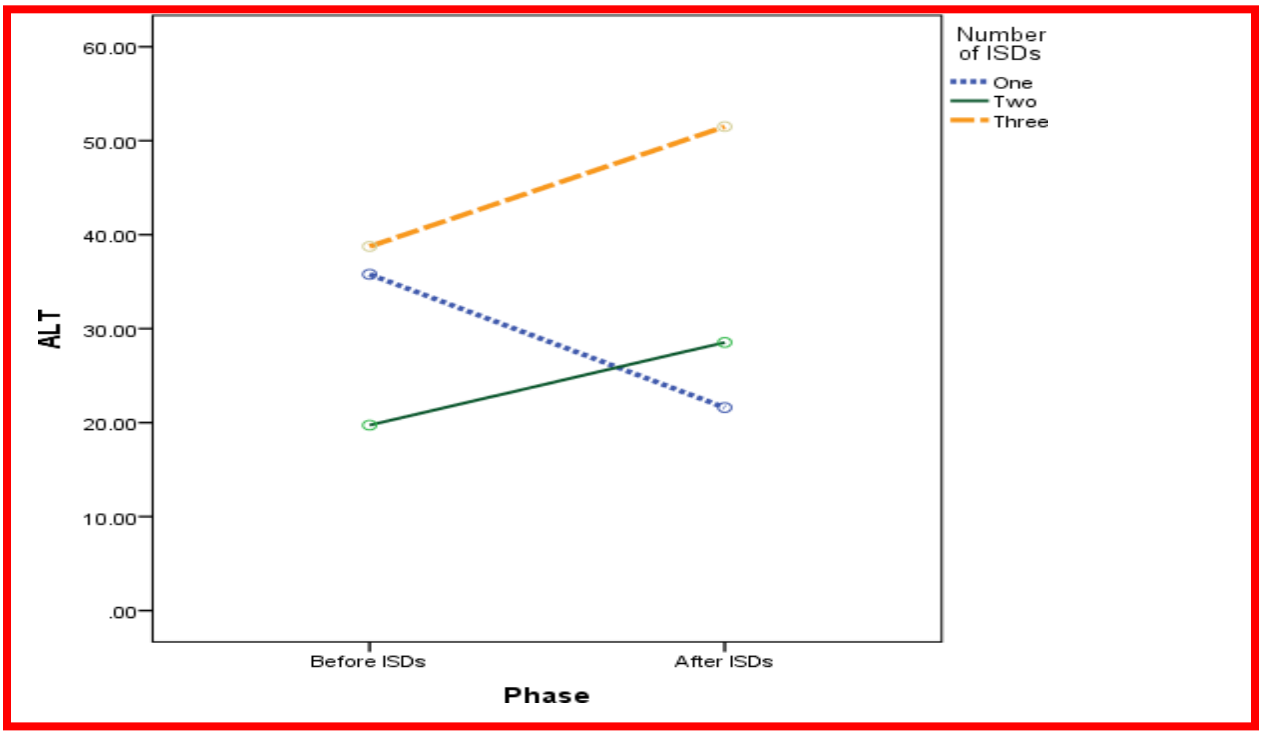


Figure -2: ALT level change before and after receiving immunosuppressive drugs, ACH, 2018 among patients with chronic hepatitis

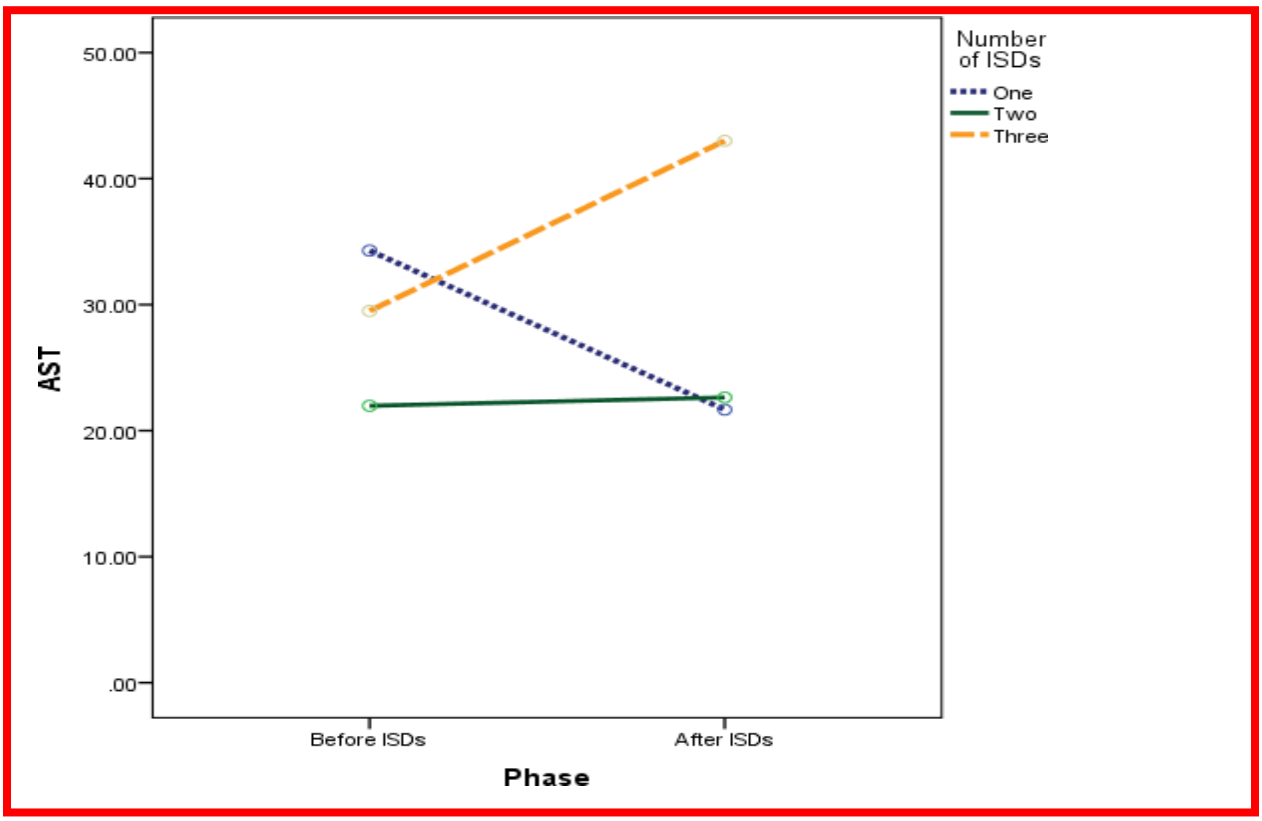
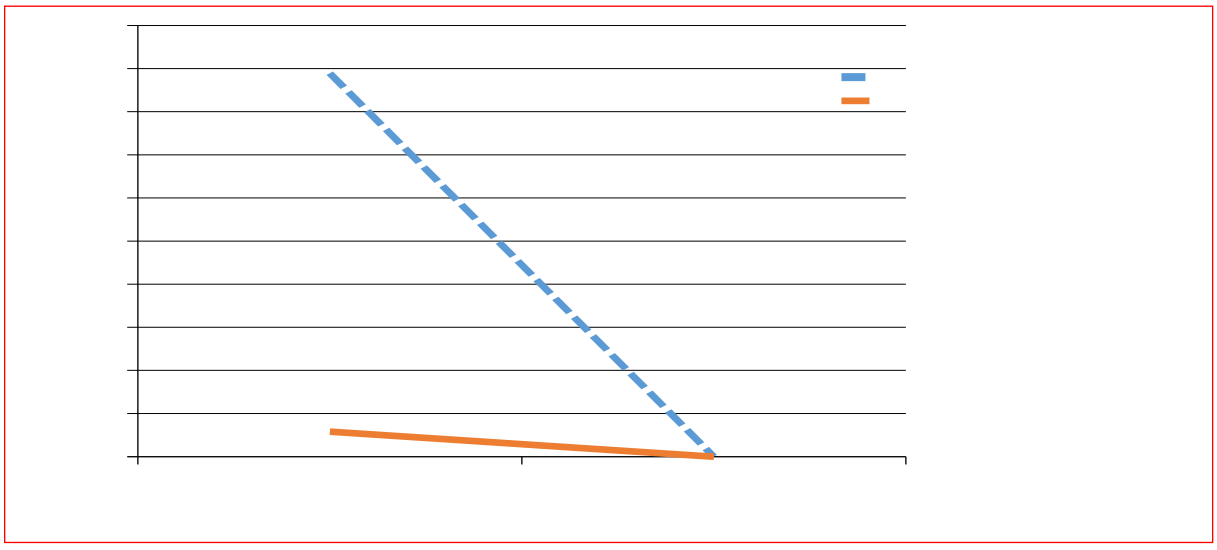


Figure -3: AST level change before and after receiving immunosuppressive drugs, ACH, 2018 among patients with chronic hepatitis



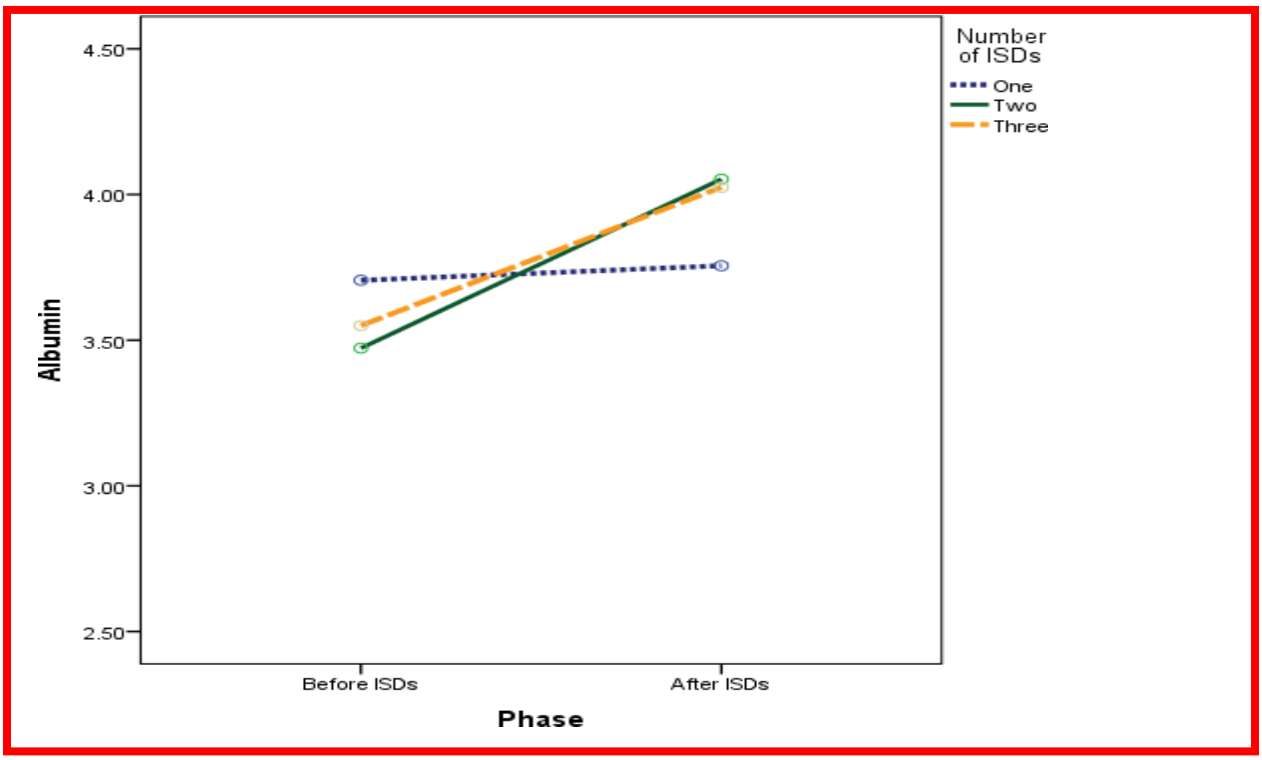


Figure -5: Albumin level change before and after receiving immunosuppressive drugs, ACH, 2018 among patients with chronic hepatitis

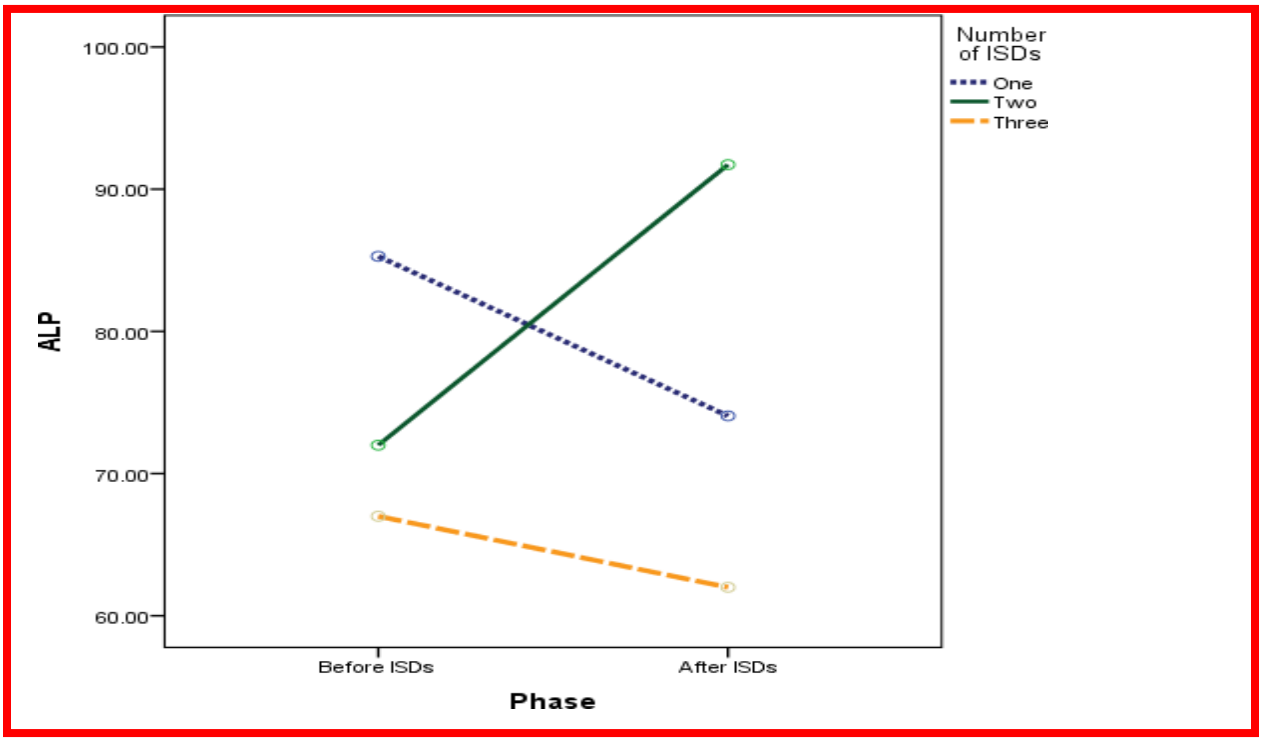


Figure -6: ALP level change before and after receiving immunosuppressive drugs, ACH, 2018 among patients with chronic hepatitis

Table -2: PCR, bilirubin, and albumin change % from before to after receiving immunosuppressive drugs for viral hepatitis patients according to antiviral receiving status, ACH, 2018

Parameter	Group						P
	ISD with antiviral			ISD without antiviral			
	Minimum	Maximum	Median	Minimum	Maximum	Median	
PCR	-100.0%	-76.0%	-100.0%	-100.0%	375.0%	-90.3%	.048*
Bilirubin	-80.0%	600.0%	-3.3%	-95.7%	166.7%	0.0%	.682
Albumin	- 17.9%	36.4%	10.9	-13.0%	39.3%	0.0%	.290

P: Mann-Whitney test * P < 0.05 (significant)