Administration of Methotrexate in Rheumatoid Arthritis Patients with Chronic Hepatitis B

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ABSTRACT

Aim: *To identify if methotrexate (MTX) may be given to chronic hepatitis B patients and to evaluate the necessity of antiviral prophylaxis administration.*

Method: *Literature search procedure to answer this clinical problem was performed by exploring the literature online using PubMed, Highwire Stanford University, NUS Library, and MD Consult search engines. With this searching method, we found 20 articles in English. From those 20 articles, there were two articles relevant based on the title and abstract (studies by Tamori et al and Mori).*

Results: *From 45 patients without HbsAg from Tamori et al study, only one from 3 patients receiving disease-modifying antirheumatoid drug/DMARD (including MTX) experienced reactivation. Those three patients did not receive anti-TNF-α therapy. Study by Mori concluded that DMARD was relatively safe to be given to most RA patients with the history of HBV infection, although they were not given anti HBV prophylaxis therapy.*

Conclusion: *MTX is not recommended for patient in this case because it is contraindicated to be given in HBV infected patient with any given Child Pugh score. If MTX is still given, it is recommended to give antiviral prophylaxis therapy.*

Keywords: *methotrexate, chronic hepatitis B, antiviral prophylaxis*

ABSTRAK

Tujuan: *Untuk mengidentifikasi apakah methotrexate (MTX) dapat diberikan untuk pasien hepatitis B kronis dan untuk mengevaluasi kebutuhan administrasi profilaksis antivirus.*

Metode: *Prosedur pencarian literatur untuk menjawab masalah klinis ini dilakukan dengan menjelajahi literatur online menggunakan PubMed, Highwire Stanford University, NUS Perpustakaan, dan mesin pencari MD Consult. Dengan metode pencarian ini, ditemukan 20 artikel dalam bahasa Inggris. Dari 20 artikel, ada dua artikel yang relevan berdasarkan judul dan abstrak (penelitian oleh Tamori et al dan Mori)*

Hasil: *Dari 45 pasien tanpa HbsAg dari penelitian Tamori et al, hanya satu dari 3 pasien menerima disease-modifying antirheumatoid drug/DMARD (termasuk MTX) reaktivasi alami. Ketiga pasien tidak menerima terapi anti-TNF-α. Studi oleh Mori menyimpulkan bahwa DMARD relatif aman untuk diberikan kepada kebanyakan pasien RA dengan riwayat infeksi HBV, meskipun mereka tidak diberi terapi anti HBV profilaksis.*

Simpulan: *MTX tidak dianjurkan untuk pasien dalam kasus ini karena MTX berkontraindikasi apabila diberikan pada pasien yang terinfeksi virus hepatitis B dengan skor Child Pugh yang diberikan. Jika MTX masih diberikan, dianjurkan untuk memberikan terapi profilaksis antivirus.*

Kata kunci: *methotrexate, hepatitis B kronis, profilaksis antivirus*

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease that is marked by synovial proliferation in various joints. In most patients, if left untreated or treated inadequately, they would experience progressive polyarthritis which causes bone erosion, destruction, and joint deformation, and disability that ultimately would decrease patient's quality of life. In these several decades, RA therapy has developed, one of those is by the administration of disease-modifying antirheumatoid drug (DMARD).[1] American College of Rheumatology (ACR) recommends the use of methotrexate (MTX) or leflunomide as an initial monotherapy in RA patients with various duration or degree of disease activity.[2] These methotrexate (MTX) and leflunomide is categorized as non-biological DMARD group.

Until now, hepatitis B virus (HBV) is the most common chronic viral infection in the liver, also is the most common cause of cirrhosis and hepatocellular carcinoma. HBV reactivation is defined as the increase of serum HBV-DNA >1 $\log_{10}$ compared to the baseline value, or change of HBV-DNA into detected. Immunosuppressive agents, such as MTX, may cause HBV replication in the liver due to suppression of host immune response characterized by the increased number of HBV-DNA and HBV antigen in the hepatocytes. Later, immune-mediated liver inflammation and lysis of hepatocytes (hepatitis) occur as a consequence of immune response recovery after immunosuppressive therapy is ceased.[3,4]

From various studies to patients with neoplasm or haematological malignancy with hepatitis B infection, the risk of HBV reactivation ranges from 14-72% without antiviral prophylaxis and is associated with the high rate of mortality due to HBV infection liver disease (5-30%). However, only limited study evaluated HBV reactivation in patients with rheumatic diseases who received short-term or long-term immunosuppressive regiments, mostly in the form of case reports in patients who received low dose corticosteroid or DMARD (such as MTX). From various case reports, it is assumed that HBV reactivation risk is relatively lower in patients receiving corticosteroid or DMARD therapy compared to patients receiving chemotherapy or biological agents.[3]

CLINICAL QUESTION

A 63-year-old female was referred from the rheumatology polyclinic with the diagnosis of rheumatoid arthritis for consideration of MTX therapy administration. Patient was referred to the hepatology polyclinic due to the reactive HbsAg test results. Patient complained of joint stiffness in both of her hands since 1 year before hospital admission and worsened since the last 2 weeks. It was the first time she visited the rheumatology polyclinic in Cipto Mangunkusumo Hospital and was diagnosed with seronegative rheumatoid arthritis. For the last one week, she had been given methylprednisolone therapy 1 x 4 mg and was planned to also be given MTX 7.5 mg per week. There had been no previous history of hepatitis or jaundice. Patient had history of high cholesterol and was also receiving Actonel 35 mg per week. From physical examination, vital signs were within normal limits; generalized status including abdomen were also within normal limits. There was only tenderness on the finger joints of both hands. As an initial screening, routine blood count, liver and kidney function tests, random blood glucose, electrolytes, hepatitis serology, and abdominal plain x-rays were performed. Results obtained were reactive HBsAg, non-reactive anti HCV, AST 46 U/L and ALT 28 U/L. Further examination associated with hepatitis B and abdominal ultrasound had never been performed.

Currently, HBV-DNA examination was planned in the patient with the consideration as baseline data before MTX was administered. During the administration of MTX, AST and ALT examinations were planned to be performed every month in order to monitor MTX toxicity and/or acute exacerbation of patient's hepatitis. Based on the aforementioned clinical problem, we asked the following clinical question: may MTX be given in chronic hepatitis B patients and if there is necessity in administering antiviral prophylaxis.

METHOD

Literature searching procedure to answer this clinical problem was by exploring literature online by using PubMed, Highwire Stanford University, NUS Library, and MD Consult search engines. Keywords being used were: methotrexate, hepatitis B, rheumatoid arthritis, liver

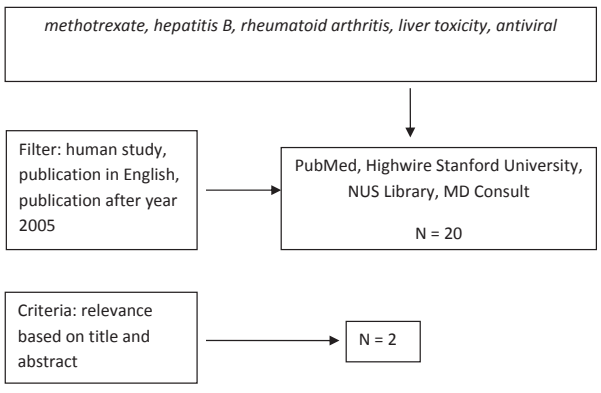

Figure 1. Flow chart of literature searching

toxicity, antiviral. Search was limited to human study, publication in English, and publication after year 2005.

With this searching method, we found 20 articles in English. From those 20 articles, we identified two articles to be relevant based on the title and abstract (study performed by Tamori et al and study conducted by Mori). These two articles were prospective studies without randomization and no control groups. We did not find studies with a level of evidence for this topic search. Further, in the discussion as an additional consideration, we would discuss several guidelines describing the use of MTX in HBV infected patients.

RESULTS

Tamori et al conducted a non-randomized prospective study, without including controls, in 50 RA patients with positive antibody to hepatitis B core antigen (anti HBc) receiving DMARD therapy. Meanwhile, Mori performed a prospective study, also non-randomized, in 239 RA patients receiving biological/non-biological DMARD therapy, two of whom had positive HBsAg and 60 had positive anti HBc.[5,6]

Table 1. Comparison of study methodology between Tamori et al and Mori

Methods	Tamori et al	Mori
Design	Prospective	Prospective
Location	Osaka City University Hospital, Jepang	Rheumatology Clinic National Hospital, Kumamoto, Japan
Time	November 2007 – October 2009	October – November 2010
Inclusion criteria	RA patients with positiveHbsAg and/or anti-HBc	RA patients receiving DMARD
Exclusion criteria	Hepatitis C infection, alcoholic liver disease, primary biliary cirrhosis, liver autoimmune disease	-
Basic data	Anti HBs HBV-DNA every 2-3 months + genotype	HBsAg, Anti HBc HBV-DNA AST/ALT every 2-3 months
Intervention	HBV-DNA > 2.1 log copies/mL → entecavir	HBV-DNA > 2.1 log copies/mL → entecavir
Operational definition		
Reactivation	Increase of HBV-DNA > 1 log copy/ML	
Flare hepatitis	Increase of ALT ≥ 400 U/L or ≥ 10x upper cut-off normal value	-

Table 2. Comparison of study results between Tamori et al and Mori

	Tamori et al	Mori
Number of subjects	50 (9 males, 41 females)	239 (65 males, 172 females)
Age	59 (15-73)	62 (anti HBc -), 73 (anti HBc +) (56-78)
Observation time	23 months (12-32 months)	Not described
Results	5 HBsAg (+), anti HBc (+) 45 HBsAg (-), anti HBc (+): 9 anti HBs (+)	2 HBsAg (+) inactive HBV carrier → entecavir • MTX + tacrolimus • MTX + etanercept 60 HBsAg (-), anti HBc (+) → HBV-DNA (+) in 2 subjects (< 2.1 log copies/mL) → all did not receive prophylaxis
Reactivation	2 from HBsAg (+) subjects who initially did not receive entecavir 1 from HBsAg (-), anti HBc (+) subject → entecavir	None from the HBsAg (+) subjects 2 from 60 anti HBc (+) subjects • Tacrolimus + prednisolone + MTX → entecavir after 2 weeks detection • Adalimumab + prednisolone + MTX → HBV-DNA disappear spontaneously

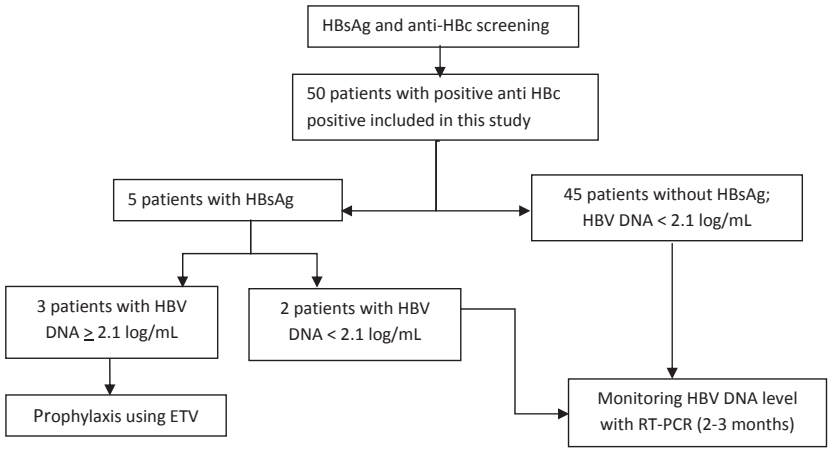

Figure 2. Screening of HBsAg and anti-HBc in patients who receive immunosuppressant therapy. Prophylaxis therapy with entecavir (ETV) is given in patients with HBV DNA > 2.1 log/mL. (5)

From the study by Tamori et al, from all positive HbsAg, negative HBeAg, and positive HBe patients, three of them received entecavir therapy. Two of them had HBV-DNA > 2.1 log copies/mL before the administration of anti-TNF-α therapy and one other patient before receiving MTX therapy. HBV-DNA decreases to < 2.1 log copies/mL 3 months after entecavir therapy and continued until RA therapy could be continued. In 2 positive HBsAg patients who did not receive entecavir prophylaxis therapy, HBV-DNA < 2.1 log copies/mL before MTX administration. Both then experienced increased of HBV-DNA in 14th and 19th month until entecavir therapy was then administered. After 2 months of entecavir therapy, HBV-DNA decreased to < 2.1 log copies/mL. Table 1 described 6 subjects who received entecavir therapy.

In 45 patients without HbsAg from the study performed by Tamori et al, only one from 3 subjects receiving DMARD (including MTX) experienced reactivation. All three did not receive anti-TNF-α. One subject during initial therapy had detectable HBV-DNA although was only < 2.1 log copies/mL and actually had previous history of HBV infection.

Below is the characteristic of RA patients in the study conducted by Mori. In this table, we did not include 2 HBsAg (+) patients who immediately received entecavir as a prophylaxis from initial administration of DMARD and did not experienced reactivation.

DISCUSSION

Several case reports have reported liver failure associated with HBV in inactive HBV carrier who received DMARD or infliximab. From 3 case reports of HBV reactivation which was explored by the writer, 2 cases experienced improvements with antiviral therapy and cessation of DMARD, while 1 case passed away due to fulminant hepatitis.[7,8,9] Retrospective studies have recommended prophylaxis therapy using lamivudine to prevent HBV reactivation in RA patients who received immunosuppressive therapy. Prospective study by Tamori et al exhibited that HBV reactivation occurred in RA patients with positive HbsAg who received immunosuppressive therapy,

Table 2. Clinical results of subjects receiving entecavir therapy [5]

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	56	63	67	33	69	73
Sex	Male	Male	Male	Female	Female	Female
HBsAg	Positive	Positive	Positive	Positive	Positive	Negative
HbeAg	Negative	Negative	Negative	Negative	Negative	Negative
Anti Hbe	100	99	97	100	100	77
HBV DNA during inclusion	4.8 log/mL	Undetected	Undetected	3.6 log/mL	4.2 log/mL	< 2.1 log/mL
HBV DNA during reactivation	-	2,5	3	-	-	4,7
HBV DNA after ETV	Undetected	Undetected	< 2.1 log/mL	< 2.1 log/mL	Undetected	Undetected
HBV Genotype	B	C	C	A	C	C
ALT during inclusion	10	35	31	12	21	21
ALT after ETV	6	33	29	27	19	19
Therapy for RA	PSL, etanercept	PSL, MTX	PSL, MTX	MTX, infliximab	MTX	MTX
Duration of observation (months)	31	29	20	18	14	26
Duration of ETV therapy (months)	31	9	9	18	14	16

PSL: prednisolone; MTX: methotrexate; ETV: entecavir; 6 HbsAg patients become positive during reactivation

Table 3. Characteristics of RA patients during inclusion[6]

	Negative Anti-HBc (n=177)	Positive Anti-HBc (n=60)	p
Male/Female	43/134	22/38	0.06
Age, years old, median (25th, 75th percentile)	62 (56, 72)	73 (61, 78)	0.0002
RA duration, months, median (25th, 75th percentile)	23 (24, 113)	54 (33, 89)	0.36
AST, IU/l, median (25th, 75th percentile)	23 (19, 28)	24 (20, 28)	0.77
ALT, IU/l, median (25th, 75th percentile)	20 (15, 27)	18.5 (14, 27)	0.78
Positive HBsAg, number of patients (%)	0	0	-
Current and previous DMARD Total patients (%)/duration, months, median (25th, 75th percentile)			
Methotrexate (6-10 mg/week)	165 (93.2)/43 (17,57)	54 (90)/34 (11.5, 52)	-
Tacrolimus (1-2 mg/day)	41 (23.2)/19 (9, 37)	30 (50)/19.5 (6, 29)	-
Leflunomide (20 mg/day)	2 (1.1)/(20, 54)	0	-
anti-TNF-α agent	95 (53.7)/24 (5.5.42)	31 (51.7)/12 (6, 29.5)	-
Infliximab	63 (35.6)/19 (3.5, 30)	19 (31.7)/5 (3, 17)	-
Etanercept	55 (31.1)/17 (4, 32.5)	18 (30)/10 (6,25)	-
Adalimumab	4 (2.3)/3.5 (2.8, 6.5)	2 (3.3)/(15,15)	-
Tocilizumab	15 (8.5)/10 (2.5, 11)	5 (8.3)/6 (5, 7)	-
Prednisolone (5 mg/day)	99 (55.9)	38 (63.3)	-

including MTX and prednisolone. In patients with HBV-DNA > 2.1 log copies/mL, prophylaxis therapy by entecavir succeeded to decrease the number of the HBV-DNA. Immunosuppressive therapy for RA also can be continued without hepatitis flare. Entecavir was chosen as a therapy in this study because in comparison with lamivudine, entecavir rapidly decrease HBV-DNA in patients with or without HBeAg. Besides, cumulative probability of HBV resistance was reported to be 57% in 3 years of lamivudine therapy, compared with only 1.2% in 5 years entecavir therapy. The disadvantage of entecavir was the higher cost compared to lamivudine. As a conclusion, prospective study by Tamori et al stated that screening of HBV-DNA and prophylaxis therapy with entecavir was effective in patients with positive HbsAg or HBcAg who received immunosuppressive therapy for RA.[5]

Meanwhile, study by Mori concluded that DMARD was relatively safe to be given in most RA patients with HBV infection history although anti HBV prophylaxis was not given. With the consideration of high prevalence of HBV infection history in RA patients and the high cost of prophylaxis therapy towards HBV reactivation, universal prophylaxis was considered as not efficient. The most efficient protocol was by regular monitoring of HBV-DNA.[6]

Table 3 below described 7 case reports of patients with rheumatic disease receiving immunosuppressive therapy who experienced HBV reactivation. Five from 7 case reports were rheumatoid arthritis in MTX therapy. From those 5 cases, 4 cases experienced reactivation in short duration (15-60 days) after decreased dose or cessation of immunosuppressive drugs, while one reactivation case happened while still under chronic therapy. All patients were positive HBsAg and negative HBeAg. Three from those 5 cases passed away, 1 case underwent liver transplant, and 1 case survived with antiviral therapy.[4]

ACR recommendation in 2008 about the administration of DMARD in RA discusses MTX administration in patients with liver function abnormalities, including patients with chronic hepatitis B. If transaminase increases more than two-fold the upper limit value, ACR contraindicates the administration of MTX. In patients with chronic hepatitis B, the decision of MTX administration needs to consider patients' compromised liver function. However, based on ACR guidelines, MTX is contraindicated in hepatitis B patients in all Child-Pugh classes, whether they have received hepatitis B antiviral therapy or not (table 4). Other non-biological DMARD have its own consideration, such as: minocycline and sulfasalazine which are contraindicated for Class C Child Pugh if patient has received antiviral therapy, while in untreated hepatitis B patients, like in our case, minocycline and sulfasalazine are contraindicated in all Child-Pugh classes. In chronic hepatitis B patients it is more recommended to use anti-tumour necrosis factor (TNF) α, but this agent is still contraindicated in patients with class B or C Child-Pugh.[2]

Figure 2 showed the algorhythm of prophylaxis management in HBV infected patients who will receive antiviral therapy. For positive HbsAg patient with blood malignancy or neoplasm who received chemotherapy, antiviral prophylaxis using lamivudine has been proven to decrease the rate of HBV reactivation and HBV-associated mortality up to > 80%. In patients with rheumatic diseases, the available data is still very limited. With regard that patients with rheumatic diseases will receive long-term treatment, it is more recommended to give antiviral with low-risk of resistance, such as: tenofovir or entecavir. Long-term lamivudine is dreaded to cause HBV strain that is resistant to lamivudine. Lamivudine, adefovir, or telbivudine can be given to inactive carrier or patients who will only receive short-term treatment (<1 year).

Table 4. Case reports of hepatitis B virus reactivation in rheumatoid arthritis receiving non-biological immunosuppressants[4]

Patients	No ref.	Diagnosis	Age/ Sex	Regiment of Immunosuppressant	Flare Time	Therapy and Result
1	31	AR	72/ F	MTX 4 mg/week, 2 years; PSL 5 mg/ day	60 days	IFN, GC, CsA Passed away
2	32	AR	75/ F	MTX 7.5 mg/week; PSL 5 mg/day	15 days	Plasmapheresis, IFN Passed away
3	34	AR	67/ M	MTX 7.5 mg/week; PSL 5 mg/day	21 days	GC Passed away
4	30	AR	57/ F	MTX 7,5-10 mg/ week; PSL 5 mg/day	41 days	Liver transplantation Survive
5	4	AR	58/ F	MTX 15 mg/week; PSL 7.5 mg/day	2 years chronic therapy	LAM Survive
6	33	PM	57/ F	PSL 40 mg/day	40 days chronic therapy	IFN, CsA Recover
7	29	Behcet	43/ M	Cyclo, IVMP	2 years chronic therapy, 10 days	GC Passed away

PM polymyositis; PSL prednisone/ prednisolone; IFN interferon; Cyclo cyclophosphamide; IVMP intravenous methylprednisolone; CsA cyclosporine A; LAM lamivudine

Table 5. Recommendation of immunosuppressant agents administration in RA patients [2]

Organ systems and contraindication	ABA	Anti-TNFa	HCQ	LEF	MTX	MIN	RIT	SSZ
Infectious disease and pneumonitis								
Serious bacterial infection, or current infection	X	X	-	X	X	-	X	-
Receiving antibiotics	X	X	-	-	-	-	X	-
URTI (viral) fever (>101^{o}C)								
Unhealing ulcer	X	X	-	-	-	-	X	-
Latent TB Infection or history, active TB, under TB treatment	X	X	-	X	X	-	X	-
Life-threatening severe fungal infection	X	X	-	X	X	-	X	-
Activated Herpes Zoster Infection	X	X	-	X	X	-	X	-
Interstitial Pneumonitis (due to RA/other etiologies), cystic fibrosis	-	-	-	-	X	-	-	-
Haematology-oncology								
Leucocytes < 3.000/mm^3	-	-	-	X	X	-	-	-
Thrombocytes < 50.000/mm^3	-	-	-	X	X	-	-	X
Myelodysplasia	-	-	-	X	X	-	-	-
Lymphoproliferative disease under therapy ≤ 5 years	-	X	-	X	X	-	-	-
Cardiac disease								
Severe Heart Failure (NYHA III/IV) and LVEF < 50%	-	X	-	-	-	-	-	-
Liver disease								
Liver transaminase enzymes > 2x UCNV	-	-	-	X	X	-	-	X
Active hepatitis B/C virus infection	X	X	-	X	X	X	X	X
Chronic hepatitis B, receiving therapy								
Child Pugh A	-	-	-	X	X	-	-	-
Child Pugh B/C	X	X	X	-	X	X**	X	X**
Chronic hepatitis B, not receiving therapy								
Child Pugh A	-	-	-	X	X	X	-	X
Child Pugh B/C	X	X	X**	X	X	X	X	X
Hepatitis C, receiving therapy								
Child Pugh A	-	-	-	X	X	-	-	-
Child Pugh B/C	X	X	-	X	X	X**	X	X
Hepatitis C, not receiving therapy								
Child Pugh A	-	-	-	X	X	X	-	-
Child Pugh B/C	X	X	X**	X	X	X	X	X
Kidney disease								
Creatinine clearance <30 ml/mnt	-	-	-	-	X	-	-	-
Neurological disease								
Multiple sclerosis or other demyelinating disease	-	X	-	-	-	-	-	-
Pregnancy and Lactation								
Planning or is pregnant	-	-	-	X	X	X	-	-
Breastfeeding	-	-	-	X	X	X	-	-

ABA : Abatacept; HCQ : hydroxichloroquine; LEF : Leflunomide; MTX : methotrexate; MIN : Minocycline; RIT : Rituximab; SSZ : Sulfasalazine; X : contraindicated; X** : contraindicated in patients SH CTP C

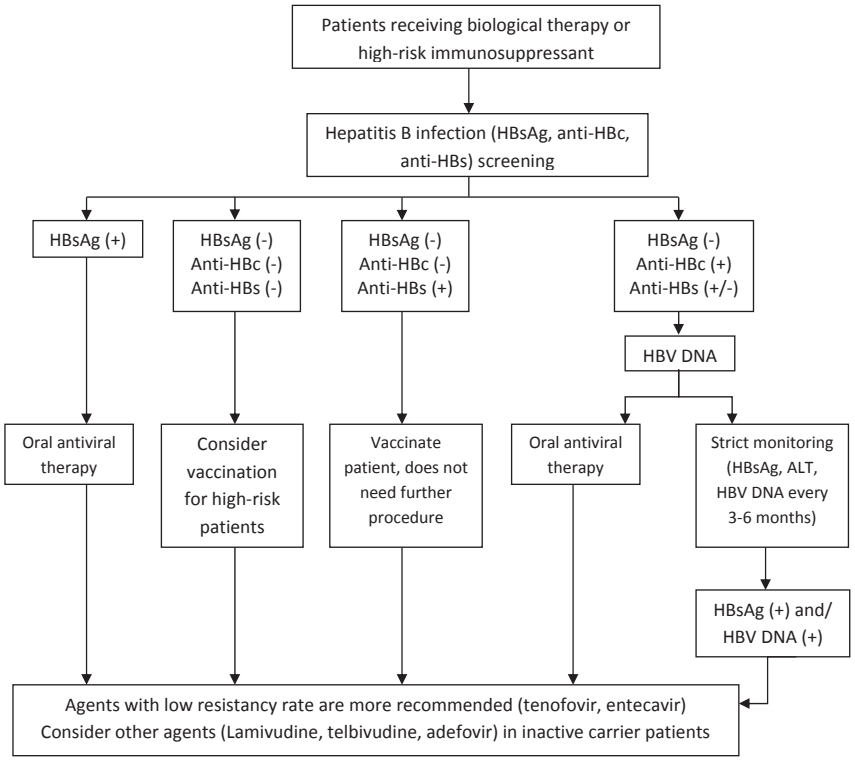

Figure 2. Algorithm on the approach of prophylaxis therapy in hepatitis B patients who received immunosuppressant

If immunosuppressive therapy is ceased, antiviral needs to be continued up to at least 6-12 months. Monitoring of ALT and HBV-DNA every 3-6 months is important for early detection and manage every reactivation due to resistant strain.[3] To this point, administration of adefovir dipifoxil showed lower resistancy rate compared to lamivudine (±15% after 4 years of therapy). [4] Prophylaxis is given 2-4 weeks before DMARD starts to be given.[10]

Increased transaminase enzymes are the second most common side effects during MTX administration, after gastrointestinal side effects. From a systematic literature search to 27 prospective studies which included 3808 RA patients receiving low-dose MTX (10,5 mg/ week) for the average of 55.8 months, 769 subjects (20.2%) experienced at least one episode of increased transaminase and in 3.7% subjects MTX administration was ceased due to liver toxicity.[11] Therefore, it is necessary that administration of MTX to be monitored in patients with underlying liver disease.

In addition to potential toxicity due to MTX, RA alone in several cases has liver involvement. Cases that have been reported to be found simultaneously with RA include liver congestion, steatosis, portal inflammation, primary biliary cirrhosis, autoimmune hepatitis, autoimmune cholangiopathy, nodular regenerative hyperplasia, spontaneous liver rupture due to vasculitis. Those incidences also need to be considered as differential diagnosis of HBV reactivation.[12]

CONCLUSION

MTX is not recommended in the patient in this case because it is contraindicated in HBV infected patients with any Child Pugh score. If MTX is still to be given, it is recommended to also give prophylaxis antiviral. Administration of antiviral starts from 2-4 weeks before MTX administration and is continued until at least 6-12 months after MTX administration is completed. Because MTX can be given all life long to RA patients, it is recommended to choose antiviral therapy with low rate of resistance, such as entecavir, adefovir, or tenofovir. Increased transaminase should be considered due to RA or MTX toxicity besides reactivation of hepatitis B infection.

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