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Resolved hepatitis B infection in patients receiving immunosuppressive therapy

Monitor versus prophylaxis against viral reactivation

Mohamed A. Elsebaey, MD[a], Tamer A. Elbedewy, MD[a], Heba Elashry, MD[b], Waleed Elrefaey, MD[a], Samah A. Elshweikh, MD[a], Ahmed A. Elhadidy, MD[a,*], Neveen A. Shalaby, MD[a], Assem Mohamed Elsokkary, MD[c], Hossam Eldin A. Elashtokhy, MD[d], Yousry Esam-Eldin Abo-Amer, MD[e], Ashraf Rafat Abo-Elfetoh, MD[e], Sharaf Elsayed Ali Hassanien, MD[f], Amina Fouad, MD[g], Raghda Samir Abdellatif, MD[g], Amro Abdelaziz Mohammed Ismail, MD[h]

Abstract

Risk of hepatitis B virus reactivation (HBVr) in patients with resolved HBV infection receiving immunosuppressive therapy has been a growing concern, particularly in the era of biological and targeted therapies. HBV monitoring versus antiviral prophylaxis against HBVr in those patients remains controversial. The aim of the study was to determine the incidence of HBVr and HBV-related hepatitis in resolved HBV patients who received immunosuppressive therapy with or without antiviral prophylaxis. This retrospective study included 64 patients with resolved HBV infection who received different regimens of immunosuppressive medications, with moderate risk of HBVr, for variable underlying diseases. Patients who had chronic HBV infection or other viral infections were excluded. Patients who received B-cell depleting therapies were ruled out. They were divided into 2 groups: group 1 included 31 patients who received immunosuppressive therapy without antiviral prophylaxis, and group 2 included 33 patients who received antiviral prophylaxis (entecavir) within 2 weeks of commencing the immunosuppressive therapy. HBVr, HBV-related hepatitis, and HBV-unrelated hepatitis were assessed along a 1-year duration. The overall HBVr incidence was 1.56% (1/64). This patient who had HBVr was seen in group 1. There were no significant differences between the 2 groups regarding the incidence of HBVr, HBV-related hepatitis, HBV-unrelated hepatitis, and immunosuppressive therapy interruption along a 1-year duration. Based on this retrospective study, close monitoring was equal to antiviral prophylaxis regarding the outcome of resolved HBV patients who received moderate risk immunosuppressive therapy. HBV treatment should commence once HBVr is confirmed.

Abbreviations: ALT = alanine aminotransferase, anti-HBc = hepatitis B core antibody, anti-HBs = hepatitis B surface antibody, DNA = deoxyribonucleic acid, eGFR = estimated glomerular filtration rate, HBsAg = hepatitis B surface antigen, HBVr = hepatitis B virus reactivation, HCV = hepatitis C virus, HDV = hepatitis D virus, HIV = human immunodeficiency virus.

Keywords: antiviral prophylaxis, hepatitis B virus reactivation, immunosuppressive therapy, resolved hepatitis B virus, viral monitoring

1. Introduction

Hepatitis B virus reactivation (HBVr) following immunosuppressive therapy is a well-known serious complication not only in hepatitis B surface antigen (HBsAg) positive patients but also in patients with resolved HBV infection.[1] It's preventable if at-risk individuals are early identified through screening and started on antiviral prophylaxis when indicated.[2–4]

Recently, there has been a great effort to stratify HBVr risk according to the patient's serological status and the type and duration of the immunosuppressive drugs used. The American Gastroenterological Association (AGA) classified HBVr risk

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Our study was approved by the research ethical committee of faculty of medicine, Tanta University (approval code: 35467/5/22). Institutional Review Board (IRB) for human studies. This study conforms to provisions of the Declaration of Helsinki. Informed written consent was taken from enrolled patients before the starting of data collection.

[a] *Internal Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt,* [b] *Tropical Medicine Department, Faculty of Medicine, Tanta University, Tanta, Egypt,* [c] *Internal Medicine Department, Mansoura New General Hospital, Mansoura, Egypt,* [d] *Medical Oncology Department, Tanta Cancer Center, Tanta, Egypt,* [e] *Hepatology, Gastroenterology and Infectious Diseases Department, Mahala Hepatology Teaching Hospital, Gharbiya, Egypt,* [f] *Hepatology, Gastroenterology and Infectious Diseases Department, Faculty of Medicine, Benha University, Benha, Egypt,* [g] *Clinical Pathology Department, National Hepatology and Tropical Medicine Research Institute, Cairo, Egypt,* [h] *Internal Medicine Department, Faculty of Medicine, Cairo University, Cairo, Egypt.*

** Correspondence: Ahmed A Elhadidy, Department of Internal Medicine, Faculty of Medicine, Tanta University, Tanta 1111, Egypt (e-mail: Ahmed.elhadedy@med.tanta.edu.eg).*

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into low (<1%), moderate (1–10%), and high (>10%) risk groups.[5]

The issue of HBV monitoring versus antiviral prophylaxis against HBVr in patients with resolved HBV infection during immunosuppression remains currently the most controversial. There is more uncertainty over the treatment of this group than over HBsAg positive patients. This is because risk and incidence of HBVr in resolved HBV patients are variable depending upon host factors, the underlying disorders, and the type of immunosuppressive regimen applied.[6,7]

The guidance from international societies varies on the appropriate management of patients with resolved HBV undergoing immunosuppression. Anti-viral prophylaxis can be an effective approach to prevent HBVr and HBV-related hepatitis.[8,9] However, with this strategy, overexposure to antiviral medication may result in an increase in antiviral-related adverse events and drug resistance.[10,11] Moreover, it may not be economically viable to apply long-term antiviral prophylaxis for all patients. Regular HBV monitoring-guided preemptive antiviral treatment may be an alternative effective approach to prevent HBVr and also to reduce exposure to antiviral medications.[5]

The emergence of new immunosuppressive agents poses further controversy on HBVr management and monitoring guidance. Continuous expansion and application of more powerful immunosuppressive therapies for long durations have resulted in an increased rate of HBVr cases reported in the literature in the last decade.[12,13] However, despite these statistics, few studies have been conducted especially on resolved HBV patients. The aim of our study was to determine the incidence of HBVr and HBV-related hepatitis in resolved HBV patients who received immunosuppressive therapy with or without antiviral prophylaxis.

2. Patients and methods

This retrospective study was conducted between February 2018 and January 2021 at 4 medical centers in Egypt (Internal Medicine Department, Cairo University Hospital - Internal Medicine Department, Tanta University Hospital - Tanta Insurance Hospital - Tanta Oncology Institute). Sixty-four consecutive patients with resolved HBV were enrolled in our analysis.

Inclusion criteria were patients aged >18 years with resolved HBV infection, no prior use of antiviral therapy, and normal liver function tests. All eligible patients received different regimens of antineoplastic or immunosuppressive therapies, with moderate risk of HBVr, for variable underlying diseases. These medical conditions included hematological and non-hematological malignancies, rheumatic, renal, and inflammatory bowel diseases.

Patients who had chronic HBV infection (positive-HBsAg) or other viral infections (hepatitis C virus [HCV], hepatitis D virus [HDV], human immunodeficiency virus [HIV]) were excluded. Patients who received B-cell depleting therapies (e.g. rituximab) were excluded from the study. Patients with incomplete medical records or had a different management protocol from our study protocol were also ruled out.

The patients were divided into 2 groups. Group 1 (without antiviral prophylaxis) included 31 resolved HBV patients who received immunosuppressive therapy without antiviral prophylaxis. Group 2 (with antiviral prophylaxis) included 33 resolved HBV patients who received antiviral prophylaxis (entecavir) within 2 weeks of commencing the immunosuppressive therapy.

2.1.1. Data collection. Data which were collected from patients' records included: age, sex, underlying diseases, type of immunosuppressive regimens, routine laboratory investigations, viral serology (HBsAg, hepatitis B surface antibody [anti-HBs], hepatitis B core antibody [anti-HBc], anti-HCV, anti-HDV, and anti-HIV) and quantitative HBV-deoxyribonucleic acid (DNA) polymerase chain reaction (PCR). PCR was done by Taqman method, Q1A amp viral DNA, Mini Kit 50, Cat No 52904, Beckman Caulter, USA.

HBV DNA, HBsAg, and liver function tests were done every 3 months along a one-year duration. Viral markers for hepatitis A virus (HAV), HBV, HCV, HDV, and HIV were evaluated when hepatitis occurred.

2.1.2. Dosage of prophylactic entecavir. In group 2, the dosage of prophylactic entecavir was 0.5 mg orally, daily. Dosage was adjusted in patients with renal impairment based on estimated glomerular filtration rate (eGFR; mL/min/1.73 m^2) measured by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[14]

2.1.3. Definitions. Resolved HBV was defined as seronegative HBsAg, seropositive anti-HBc, and undetectable HBV DNA. Reactivation of resolved HBV was defined by either the detection of HBV DNA in the blood and/or reappearance of HBsAg (reverse seroconversion). Time to HBV reactivation was defined as the time from first dose of immunosuppressive therapy given to the first occurrence of HBVr.[12]

Hepatitis was defined as an increase in serum alanine aminotransferase (ALT) to ≥3 times the baseline level and >100 IU/L. HBV-related hepatitis was defined as occurrence of hepatitis that associated with HBVr.[12]

2.1.4. Clinical outcome. Primary outcomes were the incidence of HBVr and HBV-related hepatitis. Secondary outcomes were the incidence of HBV-unrelated hepatitis and immunosuppressive therapy interruption within the 1-year follow up period.

2.1. Statistical analysis

Statistical analysis was carried by using Statistical Package for the Social Sciences (SPSS) software for Windows, version 22.0 (SPSS Inc., Chicago, IL). Data were expressed as absolute number and percentage for categorical variables, mean ± standard deviation for continuous parametric variables or median for continuous non-parametric variables. Chi-square tests were used for comparison between categorical variables. Comparison between 2 groups was made by using unpaired t test or Mann–Whitney test for continuous parametric and non-parametric variables, respectively. The accepted level of significance in this work was stated at 0.05 ($P < .05$ was considered significant).

3. Results

All the studied patients had seronegative HBsAg, seropositive anti-HBc, and undetectable HBV DNA. They were divided into 2 groups: group 1 (without antiviral prophylaxis group) and group 2 (with antiviral prophylaxis group). The baseline demographic and laboratory data of the studied patients were shown in Table 1.

Details of the underlying diseases and treatment regimens among the studied patients were shown in Table 2. Treatment regimens included antineoplastic, immunosuppressive and biological therapies.

It was noted that the dosage of entecavir was adjusted (in group 2) to be 0.5 mg every 48 hours in 2 patients with lupus nephritis; 1 patient had eGFR of 39 mL/min/m^2 and the other one had eGFR of 48 mL/min/m^2. No dosage adjustment required in the remaining patients of group 2 as their eGFRs were >50 mL/min/m^2.

To detect HBVr, laboratory investigations including ALT, HBsAg, and HBV DNA were done in both groups during clinic visit every 3 months along a 1-year duration. There were no significant differences between the 2 groups regarding these parameters as shown in Table 3. Also, there were no significant differences between the 2 groups regarding other investigations

Table 1

Baseline demographic and laboratory data of the studied patients.

Parameters			Without antiviral prophylaxis group (number: 31)	With antiviral prophylaxis group (number: 33)	*P* value
Age (yr)	Mean ± SD (range)		39.87 ± 13.70 (18–64)	42.18 ± 13.41 (19–69)	.4979
Gender	Male	Number	14	15	1.000
		%	45.16	45.45	
Serum creatinine (mg/dL)	Mean ± SD (range)		1.05 ± 0.24 (0.62–1.6)	1.06 ± 0.23 (0.71–1.7)	.7917
Estimated glomerular filtration rate (eGFR; mL/min/1.73 m^2)	Median (range)		77 (45–121)	76 (39–135)	.2855
Alanine transaminase (ALT) (IU/L)	Mean ± SD (Range)		32.26 ± 4.66 (24–42)	30.27 ± 4.87 (21–38)	.1011
Aspartate transaminase (AST) (IU/L)			28.58 ± 4.69 (20–36)	27.48 ± 4.83(19–36)	.3611
Serum albumin (mg/dL)	Median (range)		4 (2.7–5)	4 (2.9–4.9)	.4100
Serum total bilirubin (mg/dL)			0.9 (0.5–1)	0.9 (0.6–1.1)	.6322
International normalized ratio (INR)			0.98 (0.9–1.2)	0.99 (0.84–1.2)	.8453
Anti-HBs	Positive	Number	17	16	.6273
		%	54.84	48.48	

Anti-HBs = hepatitis B surface antibody, SD = standard deviation.

Table 2

Underlying diseases and treatment regimens in the studied patients.

Parameters		Without antiviral prophylaxis group (Number: 31)		With antiviral prophylaxis group (Number: 33)	
Underlying diseases	**Treatment regimens**	**Number**	**%**	**Number**	**%**
Hodgkin lymphoma	Doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD)	2	6.45	4	12.12
Chronic myeloid leukemia	Imatinib	5	16.13	3	9.09
Ulcerative colitis	Adalimumab	1	6.45	0	3.03
	Infliximab	1		1	
Rheumatoid arthritis	Adalimumab	4	22. 58	5	24.24
	Infliximab	2		1	
	Etanercept	0		1	
	Golimumab	1		1	
Lupus nephritis	Cyclophosphamide	4	19.35	2	12.12
	Mycophenolate mofetil	2		2	
Behcet disease	Adalimumab	1	3.23	0	0
Colon cancer	Folfox (oxaliplatin + leucovorin + fluorouracil)	2	12.90	3	18.18
	Folfox + bevacizumab	2		1	
	Folfox + cetuximab	0		2	
Breast cancer	Adriamycin + cyclophosphamide + docetaxel	4	12.90	4	18.18
	Navelbine	0		2	
Prostate cancer	Docetaxel	0	0	1	3.03

Table 3

Laboratory investigations during the 12 months follow up period in the studied patients.

Parameters	Time	Without antiviral prophylaxis group (Number: 31)	With antiviral prophylaxis group (Number: 33)	*P* value
Alanine transaminase (ALT) (IU/L) Median (range)	3 mo	39 (27–213)	37 (18–386)	.2477
	6 mo	37 (19–433)	40 (25–586)	.4847
	9 mo	36 (21–274)	37 (24–407)	.9946
	12 mo	35 (20–82)	37 (21–333)	.8824
Patients with non-reactive HBsAg Number (%)	3 mo	31 (100%)	33 (100%)	------
	6 mo	31 (100%)	33 (100%)	------
	9 mo	31 (100%)	33 (100%)	-----
	12 mo	31 (100%)	33 (100%)	-----
Patients with undetectable HBV-DNA Number (%)	3 mo	31 (100%)	33 (100%)	-----
	6 mo	30 (96.77%)	33 (100%)	.4844
	9 mo	30 (96.77%)	33 (100%)	.48.44
	12 mo	31 (100%)	33 (100%)	------

DNA = deoxyribonucleic acid, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus.

such as anti-HBs, creatinine, aspartate transaminase (AST), bilirubin, albumin, and international normalized ratio (INR) (not mentioned in the table).

Concerning clinical outcomes, there were no significant differences between the 2 groups regarding the incidence of HBVr, HBV-related hepatitis, and HBV-unrelated hepatitis as shown

in Table 4. Immunosuppressive therapy interruption was not observed in any patient along a 1-year duration.

The overall HBVr incidence was 1.56% (1/64). This patient who had HBVr was seen in group 1; this means that the incidence of reactivation among patients who did not receive antiviral prophylaxis was 3.23% (1/31) as demonstrated in Table 4.

The characteristic findings of the patient who experienced HBVr were as follows: elderly male aged 62 years, had Hodgkin's lymphoma and received doxorubicin-bleomycin-vinblastine-dacarbazine (ABVD) regimen. He was seronegative for anti-HBs. HBVr occurred at 6 months from commencing the first dose of chemotherapy and HBV DNA level at time of reactivation was 926 IU/mL. He was immediately managed by administering entecavir (0.5 mg orally every day) without anticancer therapy interruption.

4. Discussion

Risk of HBVr in patients with resolved HBV infection receiving immunosuppressive therapy has been a growing concern, particularly in the era of biological and targeted therapies. Currently in resolved HBV individuals who undergo moderate risk immunosuppression, it remains a controversial issue either to follow monitoring strategy or start antiviral prophylaxis.[15–17]

This retrospective study was done to determine the incidence of HBVr and HBV-related hepatitis in resolved HBV patients who received immunosuppressive therapy with or without antiviral prophylaxis along a 1-year duration.

The studied patients received different regimens of immunosuppressive medications with moderate risk of HBVr for variable underlying diseases such as hematological and non-hematological malignancies, rheumatic, renal and inflammatory bowel diseases. Patients who received B-cell depleting therapies were excluded from this study as they are at high risk for HBVr and antiviral prophylaxis is mandatory for these patients.

In the present study, the overall HBVr incidence was 1.56% (1/64). This patient who had HBVr was seen in group 1; this means that the incidence of reactivation among patients who did not receive antiviral prophylaxis was 3.23% (1/31).

The incidence rate of HBVr in resolved HBV patients varied widely among different studies.[18,19] This could be related to the following factors: geographical area studied (higher in Asian than that in European regions),[20,21] underlying disease (higher in hematological than that in non-hematological disorders),[22] and type of immunosuppressive regimens used (higher with B-cell depleting therapy than with other medications).[23]

In our study, the characteristic findings of the patient who experienced HBVr were as follows: elderly male aged 62 years, had Hodgkin's lymphoma and received doxorubicin-bleomycin-vinblastine-dacarbazine (ABVD) regimen. He was seronegative for anti-HBs. HBVr occurred at 6 months from commencing the first dose of chemotherapy and HBV DNA level at time of reactivation was 926 IU/mL. He was immediately managed by administering entecavir (0.5 mg orally every day) and continued his anticancer therapy regimen.

Our results were in harmony with those of previous studies. Yeo et al reported that elderly males were more prone to undergoing HBVr when they were exposed to chemotherapy.[24] Cao et al demonstrated that lymphomas were the hematological malignancies most commonly associated with HBVr.[25] Paul et al showed that negative baseline anti-HBs was associated with a higher risk of viral reactivation among resolved HBV patients receiving chemotherapy.[26]

Because of its high potency and high resistance barrier, it was noted that all patients in group 2 who received entecavir didn't have HBVr. This was in accordance with multiple meta-analyses which had demonstrated reduced reactivation, hepatitis, mortality, and anticancer therapy interruption when entecavir was used.[27,28]

As comparing outcomes of the studied patients with or without receiving antiviral prophylaxis, the current study showed no significant differences between the 2 groups regarding the incidence of HBVr, HBV-related hepatitis, HBV-unrelated hepatitis, and immunosuppressive therapy interruption along a 1-year duration. Upon these results, regular viral monitoring could be an effective and considerable strategy in resolved HBV patients who were not on high-potency immunosuppressive regimens. In addition to that, antiviral treatment was only initiated upon HBVr occurrence.

Our results were in agreement with those of Koutsianas et al who concluded that in patients with resolved HBV infection treated with immunosuppressive therapy other than B-cell depleting agents, serial monitoring of serum aminotransferases, HBsAg, and HBV-DNA was a preferable alternative to receiving antiviral prophylaxis.[29]

Su et al found that HBVr was infrequent among resolved HBV patients who received immunosuppressive therapy and hence they should be monitored. Antiviral prophylaxis without evidence of HBVr should be discouraged.[30]

Koffas et al as well recommended initiating viral monitoring in resolved HBV patients who were at moderate risk of reactivation. However, in situations where monitoring could not be offered reliably, immunosuppressive therapy escalation, a prolonged duration of immunosuppression, or the underlying disease predisposed to more immune suppression, then antiviral prophylaxis might be a more appropriate and pragmatic approach.[31]

Liver fibrosis assessment was recommended by Asian-Pacific clinical practice guidelines on the management of HBV. Resolved HBV patients with a moderate risk of reactivation without advanced fibrosis or cirrhosis should be monitored with serum ALT (± HBV DNA) testing every 3 months. At the same time, patients with baseline advanced fibrosis or cirrhosis should receive antiviral prophylaxis.[32]

The limitations of the present study were retrospective design, relatively small number of patients and short follow-up period. Accordingly, HBVr that might appear during prolonged immunosuppression couldn't be evaluated in our study. Another limitation was the heterogeneity regarding the underlying diseases,

Table 4

Outcomes of the studied patients during the 12 months follow up periods.

	Without antiviral prophylaxis group (Number: 31)		With antiviral prophylaxis group (Number: 33)		
Parameters	**Number**	**%**	**Number**	**%**	***P* value**
HBV reactivation	1	3.23	0	0	.4844
HBV-related hepatitis	1	3.23	0	0	.4844
HBV-unrelated hepatitis	4	12.90	4	12.12	.000

HBV = hepatitis B virus.

type and durations of therapeutic immunosuppressive regimens, and serological status of anti-HBs.

5. Conclusion

Based on this retrospective study, close monitoring was equal to antiviral prophylaxis regarding the outcome of resolved HBV patients who received moderate risk immunosuppressive therapy. HBV treatment should be commenced once HBVr is confirmed. Yet, further prospective long-term follow-up studies involving a larger number of patients are warranted to confirm these suggestions.

Author contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, took part in drafting the article or revising it critically for important intellectual content, agreed to submit to the current journal, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Conceptualization: Mohamed A Elsebaey, Tamer A Elbedewy, Heba Elashry, Waleed Elrefaey, Samah A Elshweikh, Ahmed Atta Elhadidy, Neveen A Shalaby, Assem Mohamed Elsokkary, Hossam Eldin A Elashtokhy, Yousry Esam-Eldin Abo-Amer, Ashraf Rafat Abo-Elfetoh, Sharaf Elsayed Ali Hassanien, Amina Fouad, Raghda Samir Abdellatif, Amro Abdelaziz Mohammed Ismail.

Data curation: Mohamed A Elsebaey, Tamer A Elbedewy, Heba Elashry, Waleed Elrefaey, Samah A Elshweikh, Ahmed Atta Elhadidy, Neveen A Shalaby, Assem Mohamed Elsokkary, Hossam Eldin A Elashtokhy, Yousry Esam-Eldin Abo-Amer, Ashraf Rafat Abo-Elfetoh, Sharaf Elsayed Ali Hassanien, Amina Fouad, Raghda Samir Abdellatif, Amro Abdelaziz Mohammed Ismail.

Formal analysis: Mohamed A Elsebaey, Tamer A Elbedewy, Heba Elashry, Neveen A Shalaby, Assem Mohamed Elsokkary, Ashraf Rafat Abo-Elfetoh, Sharaf Elsayed Ali Hassanien, Amina Fouad, Raghda Samir Abdellatif, Amro Abdelaziz Mohammed Ismail.

Funding acquisition: Amro Abdelaziz Mohammed Ismail.

Investigation: Heba Elashry, Hossam Eldin A Elashtokhy, Amina Fouad, Raghda Samir Abdellatif.

Methodology: Mohamed A Elsebaey, Tamer A Elbedewy, Heba Elashry, Waleed Elrefaey, Ahmed Atta Elhadidy, Neveen A Shalaby, Assem Mohamed Elsokkary, Yousry Esam-Eldin Abo-Amer, Amina Fouad, Raghda Samir Abdellatif, Amro Abdelaziz Mohammed Ismail.

Resources: Mohamed A Elsebaey, Tamer A Elbedewy, Samah A Elshweikh, Assem Mohamed Elsokkary, Hossam Eldin A Elashtokhy, Amina Fouad.

Software: Mohamed A Elsebaey, Tamer A Elbedewy, Heba Elashry, Waleed Elrefaey, Samah A Elshweikh, Assem Mohamed Elsokkary, Hossam Eldin A Elashtokhy, Yousry Esam-Eldin Abo-Amer, Sharaf Elsayed Ali Hassanien, Amina Fouad.

Supervision: Waleed Elrefaey, Ahmed Atta Elhadidy, Neveen A Shalaby, Yousry Esam-Eldin Abo-Amer, Sharaf Elsayed Ali Hassanien.

Validation: Neveen A Shalaby.

Visualization: Ashraf Rafat Abo-Elfetoh, Raghda Samir Abdellatif.

Writing – original draft: Mohamed A Elsebaey, Tamer A Elbedewy, Heba Elashry, Samah A Elshweikh, Neveen A Shalaby, Assem Mohamed Elsokkary, Hossam Eldin A Elashtokhy, Yousry Esam-Eldin Abo-Amer, Ashraf Rafat Abo-Elfetoh, Sharaf Elsayed Ali Hassanien, Amina Fouad, Raghda Samir Abdellatif, Amro Abdelaziz Mohammed Ismail.

Writing – review & editing: Mohamed A Elsebaey, Tamer A Elbedewy, Heba Elashry, Waleed Elrefaey, Ahmed Atta Elhadidy, Neveen A Shalaby, Assem Mohamed Elsokkary, Hossam Eldin A Elashtokhy, Yousry Esam-Eldin Abo-Amer, Ashraf Rafat Abo-Elfetoh, Sharaf Elsayed Ali Hassanien, Amina Fouad, Raghda Samir Abdellatif, Amro Abdelaziz Mohammed Ismail.

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