Systematic Review and Meta-Analysis

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Efficacy and safety of vesatolimod in chronic hepatitis B

A systematic review and meta-analysis

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Abstract

Background: Vesatolimod is a toll-like receptor (TLR) agonist that is thought to suppress chronic hepatitis B (HBV) infection. This systematic review aimed to assess the safety and efficacy of vesatolimod in treating chronic hepatitis B.

Methods: We included randomized clinical trials (RCTs) that assessed vesatolimod in patients with hepatitis B infection without hepatocellular carcinoma or liver transplantation and with reported levels of hepatitis B surface antigen (HBsAg) or liver transaminases post-intervention. We searched MEDLINE, SCOPUS, Springer, Google Scholar, ClinicalTrials.gov, and Cochrane Central Register of Clinical Trials for all related articles during May 2022. Two independent authors screened articles for inclusion, and discrepancies were resolved by consensus and a third reviewer. Two independent reviewers assessed studies included in this systematic review using the Critical Appraisal Skills Programme checklist for RCTs.

Results and conclusion: Only 4 were considered eligible from 391 articles identified through our search. All eligible studies did not report any clinically significant outcomes following the use of vesatolimod, as evidenced by the persistence of HBsAg. However, vesatolimod was associated with induction of interferon-stimulated genes (ISGs) and only mild side effects, warranting further studies to evaluate its potential for future use as a safe, tolerable anti-HBV medication. No significant differences were noted amongst trials included in either of Vesatolimod doses (Vesatolimod 1 mg, RR = 0.99, 95% CI 0.76–1.30, $P = .95$, $I^2 = 0\%$; Vesatolimod 2 mg, RR = 1.06, 95% CI 0.82–1.37, $P = .66$, $I^2 = 0\%$; Vesatolimod 4 mg, RR = 1.06, 95% CI 0.82–1.37, $P = .66$, $I^2 = 0\%$;), further suggesting its comparable safety in comparison to oral antiviral agents.

Abbreviations: HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, IFNs = interferons, ISGs = interferon-stimulated genes, NK = natural killer cell(s), RCTs = randomized clinical trails, TLR = toll-like receptor.

Keywords: hepatitis B, toll-like receptors, vesatolimod

1. Introduction

The World Health Organization has estimated a high global health burden due to hepatitis B virus (HBV) infection, with 296 million individuals chronically infected and over 800,000 individuals predicted deaths due to the disease in 2019 alone.[1] The endemicity level of HBV varies between different countries. Thus, countries are generally categorized into areas of high (>8%), intermediate (2%–8%), or low prevalence (<2%). A previous epidemiological study has concluded that HBV infections appear to predominate in rural areas of low-income countries, prompting greater vaccination efforts to mitigate their spread.[2]

HBV is a double-stranded DNA virus that can confer acute and chronic states among those infected, albeit progression to the latter is more common amongst children. The virus has multiple antigens on its surface, including its hepatitis B surface antigen (HBsAg), hepatitis B core antigen, and hepatitis B e antigens. These antigens allow for proper diagnosis and tracing of the virus in its infected host, with the infection resolution corresponding to the surface antigen resolution.[3] HBV can be transmitted sexually, parenterally, and vertically through unprotected sexual practices, sharing intravenous needles, and mother-to-child transmission through the birth canal.[4]

Chronic hepatitis B, unlike hepatitis C, has no treatments that confer resolution of chronicity. Current treatment options include interferon (IFN) and nucelot(s)ide analogs. Treatment is only started upon evaluation of several indicators, including

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The datasets generated during and/or analyzed during the current study are publicly available.

Registration: PROSPERO - CRD42022325780.

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Table 1

Risk of bias assessment.

	1	2	3	4	5	6	7	8	9	10	11	12	13
Boni et al[10]	Yes	Yes	Yes	Yes	No	No	Can't tell	Yes	Yes	Yes	Yes	Yes	No
Agarwal et al[11]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Janssen et al[12]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Gane et al[13]	Yes	Yes	Yes	Yes	Yes	No	Can't tell	Yes	Yes	Yes	Yes	Yes	No

•Questions, CASP criteria for randomized clinical trials:
Section A: Is the basic study design valid for a randomized controlled trial?
1.Did the study address a clearly focused research question?
2.Was the assignment of participants to interventions randomized?
3.Were all participants who entered the study accounted for at its conclusion?
Section B: Was the study methodologically sound?
4.Were the participants "blind" to intervention they were given?
5.Were the investigators "blind" to the intervention they were giving to participants?
6.Were the people assessing/analyzing outcome/s "blinded?"
7.Were the study groups similar at the start of the randomized controlled trial?
8.Apart from the experimental intervention, did each study group receive the same level of care (that is, were they treated equally)?
Section C: What are the results?
9.Were the effects of intervention reported comprehensively?
10.Was the precision of the estimate of the intervention or treatment effect reported?
11.Do the benefits of the experimental intervention outweigh the harms and costs?
Section D: Will the results help locally?
12.Can the results be applied to your local population/in your context?
13.Would the experimental intervention provide greater value to the people in your care than any of the existing interventions?

but not limited to liver enzyme levels, viral load, and hepatic fibrosis.[5]

Vesatolimod (GS-9620) is a newly developed oral drug that activates toll-like receptors (TLR-7). This activation induces responses in plasmacytoid dendritic cells and B lymphocytes,[6] resulting in the upregulation of type 1 IFNs[7] and immunoglobulin differentiation,[8] respectively. Herein, we conducted the first systematic review and meta-analysis to ever assess the efficacy and safety of vesatolimod among chronic hepatitis B patients as a potential therapeutic agent.

2. Methods

2.1. Ethical review

No ethical approval was necessary prior to this study as it is a meta-analysis.

2.2. Registration

This systematic review was registered on PROSPERO, which can be accessed using its ID CRD42022325780. We reported our findings according to the Preferred Reporting of Systematic Reviews and Meta-Analyses guidelines.

2.3. Eligibility criteria

Only randomized clinical trials (RCTs) were included in this systematic review. The inclusion criteria were patients with hepatitis B infection without hepatocellular carcinoma or liver transplantation and trials with reported levels of HBsAg or liver transaminases post-intervention. All articles that did not meet our inclusion criteria were excluded. No time or language restrictions were applied during the search process.

2.4. Study identification

We searched MEDLINE, SCOPUS, Springer, Google Scholar, ClinicalTrials.gov, and Cochrane Central Register of Clinical Trials in May 2022 using the MeSH terms (or keywords when applicable) "Vesatolimod" OR "GS-9620" AND "hepatitis" OR "HBV." Two independent reviewers screened the titles and abstracts of the articles for inclusion, and forward citation was done afterward to check for eligibility of further articles to be included in this systematic review. The 2 independent reviewers did a further full-manuscript screening of the screened articles. Discrepancies were resolved by consensus and a third independent reviewer.

2.5. Data extraction

Two independent reviewers conducted data extraction from the selected articles according to variables that included the setting, design, period, purpose, mean/median age of participants, sample size, inclusion/exclusion criteria, concomitant treatment(s), treatments stopped prior to the initiation of vestaolimod, overall conclusions, HBsAg levels, HBV DNA, interferon-stimulated genes (ISG)15/IFN pre- and post-administration of vesatolimod, natural killer cell(s) (NK) cell response, T cell response, and the top 3 reported adverse events.

2.6. Evaluation of study quality

Two independent reviewers assessed studies included in this systematic review using the Critical Appraisal Skills Programme checklist for RCTs, a tool that primarily focuses on research design, methodology, and results.[9] No points were allocated to screened articles, as recommended by the authors of the Critical Appraisal Skills Programme tool for RCTs. Discrepancies in the evaluation of study quality were resolved by consensus (Table 1).

3. Results

3.1. Study selection

A thorough search in targeted databases and registers yielded 391 studies. After removing duplicates (183), 208 studies remained. Two authors independently screened all the remaining 208 studies using the specified inclusion and exclusion criteria to assess eligibility further. By initially evaluating the title

and abstract, 192 articles were excluded due to being irrelevant to this topic, and 16 studies were selected for full-text review. Of those, only 4 were considered eligible after extensively reviewing the articles (Fig. 1).

3.2. Studies' characteristics

The 4 included articles[10–13] were all randomized control trials. All included studies were conducted between 2013 and 2018 and included 642 patients. The included studies were conducted in 77 centers in 9 different countries, the most common being Italy, South Korea, and New Zealand. Moreover, 2 studies were conducted over 48 weeks,[11,12] 1 study was conducted over 24 weeks,[10] and one did not report a specified duration. Almost all studies had similar exclusion criteria: cirrhosis, coinfection with Hepatitis C Virus (HCV), Delta virus, or Human Immunodeficiency Virus (HIV). Additionally, all patients in all 4 studies were taking the same concomitant medications that included different nucleoside analogs, such as Tenofovir, Fumarate, and Telbivudine (Table 2).

3.3. Purpose of the studies

The primary purpose behind the selected studies[10–13] was to assess the efficacy of vesatolimod in treating hepatitis B and its safety profile. Vesatolimod is a TLR-7 agonist that further activates immune cells and potentially helps to suppress chronic viral infections.

3.4. Overall conclusion

In order to assess the effectiveness of vesatolimod, HBsAg, HBV DNA, ISG15, natural killer response, and T cell response were all measured. All 4 studies[10–13] reported that vesatolimod is safe and well-tolerated in chronic hepatitis B patients; however, the medication did not result in any clinically significant decline in HBsAg or HBV DNA. Furthermore, the studies also stated that while T cell and natural killer response increased, the drug did not translate into meaningful changes in the patients' clinical status. Finally, 3 of the 4 studies reported that ISG-15 increased in a dose-dependent manner after the administration of vesatolimod and was consistent after repeated dosing. However, it normalized to baseline levels a week after stopping the medication[11–13] (Table 3).

3.5. Meta-analysis

Three-hundred-and-sixty-eight individuals from 2 studies were included in our meta-analysis for treatment-emergent adverse

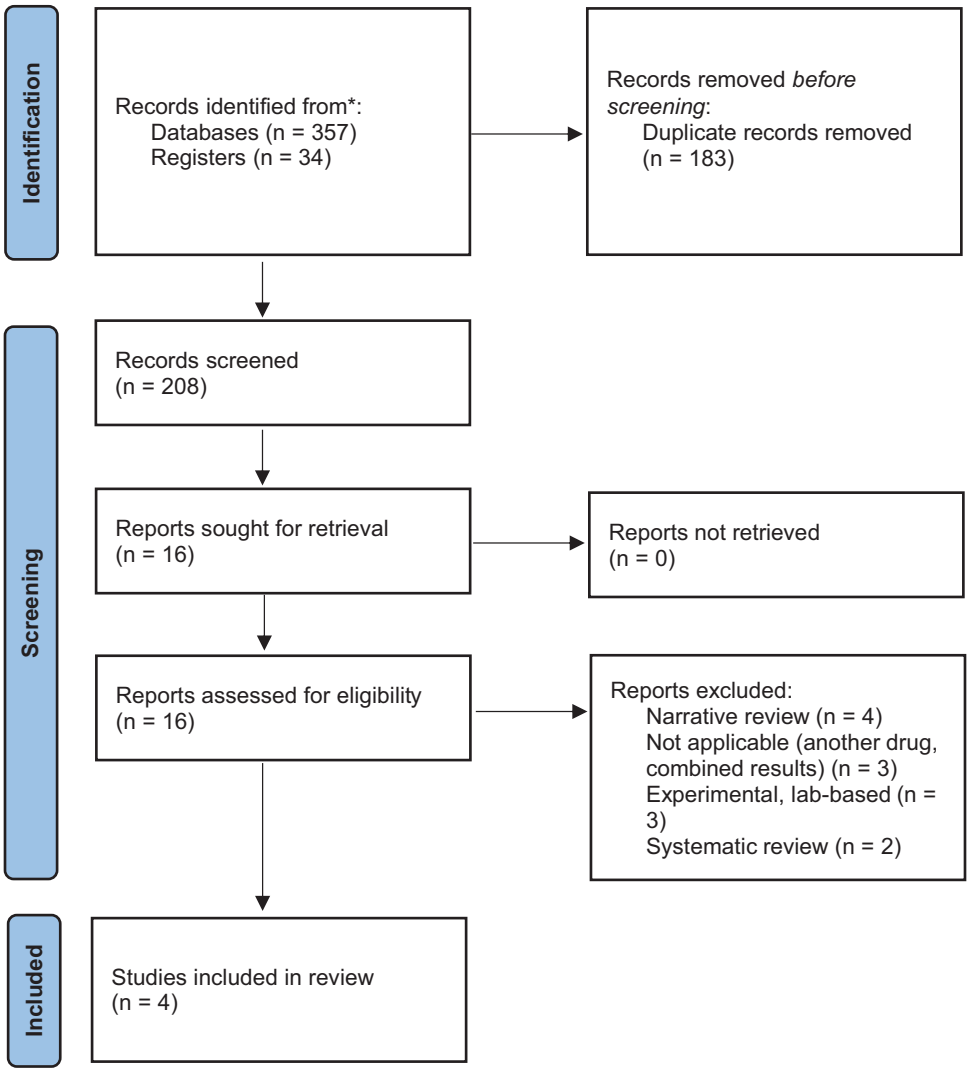

Figure 1. PRISMA flow diagram. PRISMA = Preferred Reporting of Systematic Reviews and Meta-Analyses.

Table 2

Studies' characteristics.

Authors	Setting	Design	Period	Purpose (to determine):	Mean/ median age ± SD	Sample size	Inclusion criteria	Exclusion criteria	Concomitant treatments	Treatments stopped prior to initiation of vesatolimod	Groups	1. HBsAg levels, HBV DNA, and ISG15/IFN pre- and post-administration of vesatolimod 2. NK cell response 3. T cell response	Conclusion - overall	Top 3 reported adverse events
Boni et al[10]	Italy	RCT	24 wk	The capacity of GS-9620 to reconstitute protective immunity in virally-suppressed NUC-treated patients with chronic HBV infection.	Mean for GS-9620 treatment (yr) = 52.8 ± 9.31 Control mean (yr) = 58.1 ± 7.21	56 patients	1-HBeAg negative 2-Genotype D infected patient with CHB 3-treated with nucelos(t)ide analog(s) for 3 yr	NA	NUC (nucleos(t)ide analogues)	NA	4 groups: (1:3:3:3) ratio placebo GS-9620 at different doses (1 mg, 2 mg, 4 mg)	1-NA 2-enhanced NK cell activation and decreased NK cell inhibitory effect on HBV-specific T cells 3-increased T-cell response	No significant effect on HBsAg; however, it appears to increase T-cell and NK cell responses and reduce the ability of NK to suppress T cells	Two patients were hospitalized
Agarwal et al[11]	United States, Korea, Italy, United Kingdom, Canada, Taiwan, Hong Kong-China, and New Zealand from November 2015 to August 2017	Multicenter, double-blind, randomized, placebo-controlled study	48 wk	The safety and efficacy of vesatolimod was assessed in viremic CHB patients not on oral antiviral therapy.	Mean (yr) = 42	192 patients	1-CHB infection 2-not currently on oral antiviral treatment for ≥3 mo. 3-required to have HBV DNA ≥ 2000 IU/mL	Cirrhosis, coinfection with HCV, Delta virus or HIV.	All patients were co-administered TDF (tenofovir disoproxil fumarate)	NA	4 groups: (1:2:2:2) ratio placebo GS-9620 at different doses (1 mg, 2 mg, 4 mg)	1- TDF + PBO = 3.8 (0.8) IU/mL TDF + 1-mg Vesatolimod = 3.6 (0.8) IU/mL TDF + 2-mg Vesatolimod = 3.5 (0.9) IU/mL TDF + 4-mg Vesatolimod = 3.6 (0.7) IU/mL 2,3- NA	No significant effect on HBsAg. Vesatolimod was safe and well-tolerated in viremic patients with chronic HBV infection ISG15 response was dose-dependent	Mostly was influenza-like adverse events. (fatigue, pyrexia, chills, myalgia, joint pain, or headache)
Janssen et al[12]	United States,	Double-blind,	48 wk	The safety, efficacy and	Mean (yr) = 48.4 ± 15.6	162 patients	1-adults (18–65 yr) with CHB	Cirrhosis on liver biopsy	Tenofovir, disoproxil,	NA	Three cohorts A, B, C or 4, 8, 12 wk,	1-The mean declines in Cohort	No significant effect on HBsAg.	Headache, Fatigue, Influenza-like

(*Continued*)

Table 2

(*Continued*)

Authors	Setting	Design	Period	Purpose (to determine):	Mean/ median age ± SD	Sample size	Inclusion criteria	Exclusion criteria	Concomitant treatments	Treatments stopped prior to initiation of vesatolimod	Groups	1. HBsAg levels, HBV DNA, and ISG15/IFN pre- and post-administration of vesatolimod 2. NK cell response 3. T cell response	Conclusion - overall	Top 3 reported adverse events
	Canada, Italy, South	randomized, placebo		pharmacodynamics of vesatolimod in			infection 2-virally	within 5 yr of screening,	fumarate, Adefovir,		respectively, (1:3:3:3) ratio	A for the 1-, 2-, and	once-weekly	illness. Depending on the
	Korea, New Zealand, and the Netherlands from June 2014 to	(PBO)-controlled study,		patients with CHB, suppressed on oral antiviral (OAV) treatment with once-weekly administration			suppressed on an approved HBV OAV therapy (tenofovir disoproxil	coinfection with HCV, Delta virus or HIV.	lamivudine, telbivudine, or combination		placebo GS-9620 at different doses (1 mg, 2 mg, 4 mg)	4-mg groups were 0.005, +0.041, and 0.012 log10 IU/mL, respectively; for Cohort B, the	vesatolimod in virally suppressed patients with CHB is safe, well-tolerated and	numbers from the tables
	October 2016						fumarate [TDF], adefovir dipivoxil, entecavir, lamivudine, or telbivudine) for more than 1 yr 3-no change in the regimen in the last 3 mo 4-HBV DNA < 20 IU					mean declines for the 1-, 2-, and 4-mg groups were 0.086, 0.087, and 0.086 log10 IU/mL, respectively; for Cohort C, the mean declines for the 1-, 2-, and 4-mg groups were 0.047, 0.032, 0.033 log10 IU/mL, respectively. 2-	associated with consistent, transient peripheral ISG15 induction for up to 12 wk of treatment	
Gane et al[13]	United States, New Zealand, and South	Randomized, double-blind, placebo-	N/A	The safety, pharmacokinetics, and	Median (yr) = 41	232 patients	1-virally suppressed patients, who	Bridging fibroses or Cirrhosis on	Antiviral therapy (Tenofivir,	NA	Eight cohorts of 6 patients each and randomly	NA	Oral GS-9620 was safe, well tolerated, and associated	Headache, Myalgia, fatigue

(*Continued*)

Table 2
(*Continued*)

Authors	Setting	Design	Period	Purpose (to determine):	Mean/ median age ± SD	Sample size	Inclusion criteria	Exclusion criteria	Concomitant treatments	Treatments stopped prior to initiation of vesatolimod	Groups	1. HBsAg levels, HBV DNA, and ISG15/IFN pre- and post-administration of vesatolimod 2. NK cell response 3. T cell response	Conclusion - overall	Top 3 reported adverse events
	Korea from April 2012 to December 2013 and	controlled single ascending dose (SAD)		pharmacodynamics of GS-9620 in treatment-naïve and virally			were treated with any approved anti-HBV antiviral	liver biopsy within 3 yr of screening, coinfection with	Enticavir, Telbivudine)		assigned in a 5:1 ratio (active:placebo) to receive either active GS-9620 (0.3,		with induction of peripheral ISG15 production in the absence of	
	from June 2012 to October 2013, respectively	and multiple ascending dose (MAD) studies		suppressed CHB patients.			agent for at least 3 mo prior to screening 2-treatment-naive patients 3-18-65 yr with CHB 4-both treatment-naïve virally suppressed patients were required to have HBsAg level ≥ 250 IU/mL 5-virally suppressed patients were also required to have HBV DNA < LOQ (29	HCV, Delta virus or HIV. CYP3A inhibitors (e.g., clarithromycin) and inducers (e.g., carbamazepine) was not permitted.			1, 2, or 4 mg) or placebo. Patients in the single-ascending dose (SAD) cohorts received single doses of GS-9620 (at doses of 0.3 mg, 1 mg, 2 mg, 4 mg) or placebo. Patients in the multiple-ascending dose (MAD) cohorts received 2 doses of GS-9620 (at doses of 0.3 mg, 1 mg, 2 mg, 4 mg) or placebo 7 d apart.		significant systemic IFN-alpha levels or related symptomse; however, none of the treatment-naive or virally suppressed patients had clinically significant declines in HBsAg levels	

HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen.

events (Table 4). No significant differences were noted amongst trials included in either of Vesatolimod doses (Vesatolimod 1 mg, RR = 0.99, 95% CI 0.76–1.30, P = .95, I^2 = 0%; Vesatolimod 2 mg, RR = 1.06, 95% CI 0.82–1.37, P = .66, I2 = 0%; Vesatolimod 4 mg, RR = 1.06, 95% CI 0.82–1.37, P = .66, I^2 = 0%;) (Figs. 2–4), further suggesting its comparable safety in comparison to oral antiviral agents. All studies included were symmetrical upon inspection of the funnel plots, suggesting low heterogeneity (Figs. 5–7).

4. Discussion

Overall, as deduced by the included studies, vesatolimod is considered effective, safe, and well-tolerated once every week with minimal induction of IFNs-alpha. However, all studies agreed that regardless of the changes in lab results, vesatolimod revealed no significant change in patient outcomes clinically.

Of all studies included in this systematic review, a single study has shown an increase in NK levels in response to the administration of vesatolimod, partly due to the activation of a robust immune response.[10] In a Hepatitis B infection, there is a suboptimal activation of both innate and adaptive immune response and antigen-specific T cell exhaustion. Thus, initiating vesatolimod, a TLR agonist, will activate a robust immune response targeted against HBV by activating and secreting IFNs-alpha. As a result, this will transition the cells into an antiviral state by activating both NK cells and cytotoxic T lymphocyte(s), enhancing the clearance of HBsAg and inhibiting viral replication. Although NK cells can induce T-cell apoptosis, the increased expression of INF-alpha can exert a protective effect by inhibiting the interaction between T cells and NK cells. Therefore, NK cells may work synergistically with T-cells without inducing cytolysis as both are considerably improved simultaneously with the treatment course to have more robust and optimal quality control of the virus.

Another important finding reported in the included studies is the induction of ISG-15 upon administering vesatolimod. Type 1 IFNs are a host-defense mechanism that has a central role in the immune response elicited against viral infections resulting in the upregulation and induction of ISGs, which inhibit viral replication and invasion. Diversion in the normal pathway of ISG-15 might result in the upregulation and transformation of many genes that play a role in the replication and progression of HBV-related liver diseases. This can be explained by the nature of the sustained expression of ISG-15 that contributes to the chronicity of HBV. Hoan et al reported that variations and overexpression of ISG-15 are associated with an inferior outcome and further liver disease progression in chronic hepatitis B infections.[14] Nevertheless, in this systematic review, the utilization of vesatolimod contributed to an increase in the expression of ISG-15, which directly inhibits viral proliferation

Table 3

Summary of results.

Authors	1. HbsAg levels, HBV DNA, and ISG15/IFN pre- and post-administration of vesatolimod 2. NK cell response 3. T cell response	Overall effect
Boni et al[10]	1-NA 2-enhance NK cell activation, leading to an improved NK cell anti-viral potential, and decreased NK cell inhibitory effect on HBV-specific T cells 3-increased T-cell response	No significant effect on HBsAg; however, it appear to increase T-cell and NK cell responses and reduce the ability of NK to suppress T cells
Agarwal et al[11]	1-	No significant effect on HBsAg.
	TDF + PBO = 3.8 (0.8) IU/mL TDF + 1-mg Vesatolimod = 3.6 (0.8) IU/mL TDF + 2-mg Vesatolimod = 3.5 (0.9) IU/mL TDF + 4-mg Vesatolimod = 3.6 (0.7) IU/mL	vesatolimod was safe and well-tolerated in viremic patients with chronic HBV infection ISG15 response was dose-dependent
Janssen et al[12]	2,3- NA 1-The mean declines in Cohort A	No significant effect on HBsAg.
	for the 1-, 2-, and 4-mg groups were 0.005, +0.041, and 0.012 log10 IU/mL, respectively; for Cohort B, the mean declines for the 1-, 2-, and 4-mg groups were 0.086, 0.087, and 0.086 log10 IU/mL, respectively; for Cohort C, the mean declines for the 1-, 2-, and 4-mg groups were 0.047, 0.032, 0.033 log10 IU/mL, respectively.	once-weekly vesatolimod in virally suppressed patients with CHB is safe, well-tolerated and associated with consistent, transient peripheral ISG15 induction for up to 12 wk of treatment
Gane et al[13]	2- NA	Oral GS-9620 was safe, well tolerated, and associated with induction of peripheral
		ISG15 production in the absence of significant systemic IFN-alpha levels or related symptoms; however, none of the treatment-naive or virally suppressed patients had clinically significant declines in HBsAg levels

HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, ISGs = interferon-stimulated genes, NK = natural killer cell(s).

Table 4

Treatment-emergent adverse events (TEAEs).

Study	Placebo	Total	1-mg Vestaolimod	Total	2-mg Vesatolimod	Total	4-mg Vesatolimod	Total
Agarwal et al[11]	17	28	32	53	38	56	38	69
Janssen et al[12]	11	16	34	50	33	49	32	47

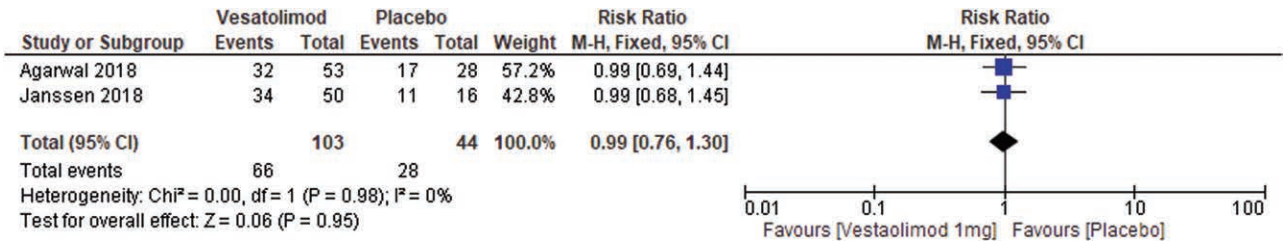

Figure 2. Treatment-emergent adverse events (TEAEs) for 1-mg Vesatolimod.

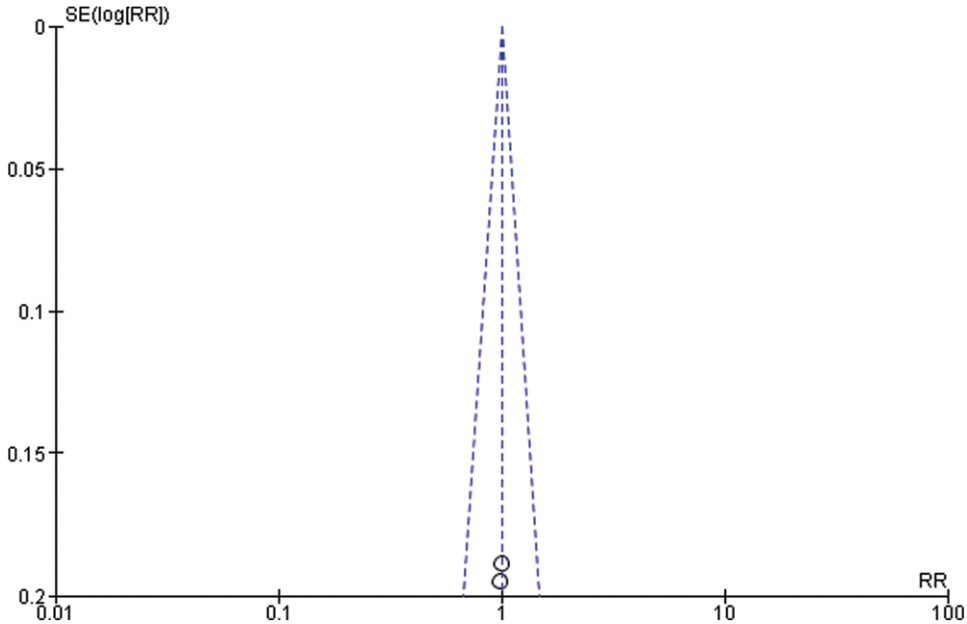

Figure 3. Treatment-emergent adverse events (TEAEs) for 2-mg Vesatolimod.

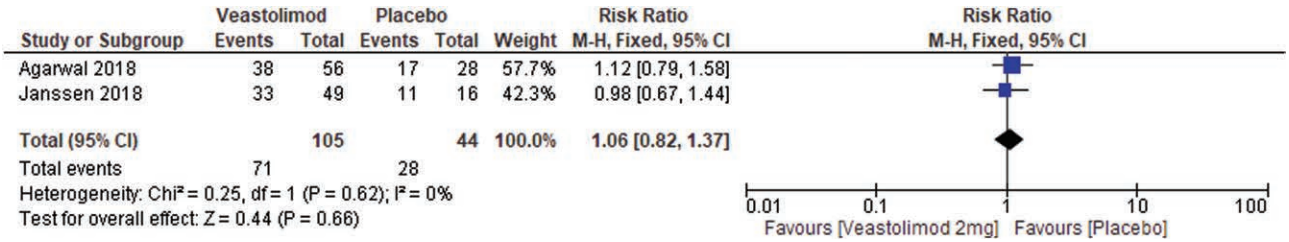

Figure 4. Treatment-emergent adverse events (TEAEs) for 4-mg Vesatolimod.

and reduces host damage by augmenting targeted adaptive and innate virus-specific immune response; therefore, eliminating HBsAg by enhancing HBV-specific cytotoxic T-cells. Moreover, this increase in ISG-15 levels is dose-dependent, where the most significant response was observed in patients receiving the highest doses of Vesatolimod during the peak of the first 24 to 48 hours of administration.[11]

Although no significant change in HBsAg and seroconversion has been detected in all included literature, the induction of a robust immune response by the administration of the TLR 7 agonist (vesatolimod) can satisfyingly enhance the antiviral state that is required to control HBV. The insufficient decline in HBsAg levels might be attributed to the differences in dose concentrations, frequencies, and duration of vesatolimod in humans

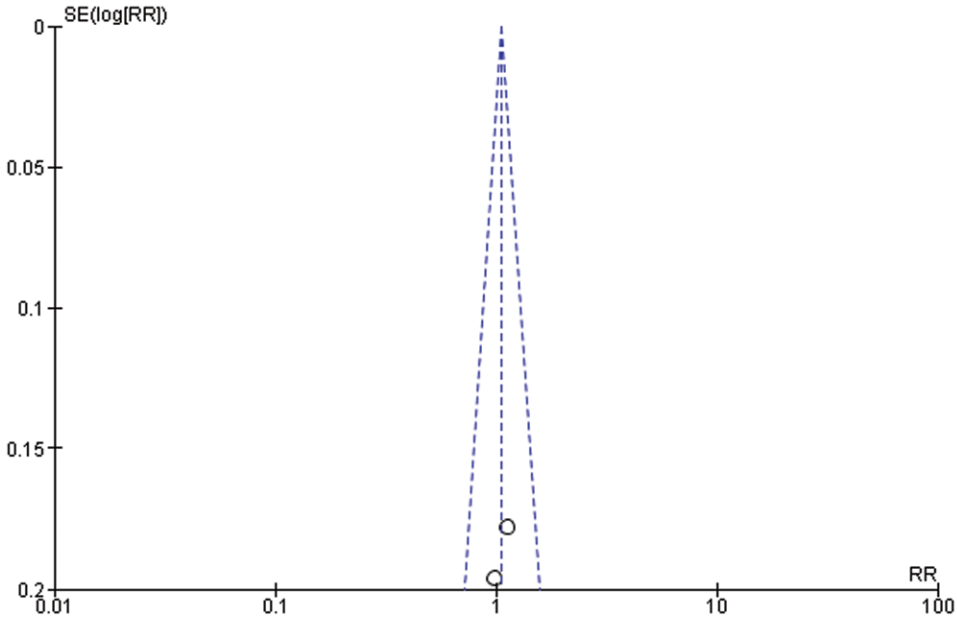

Figure 5. Treatment-emergent adverse events (TEAEs) for 1-mg Vesatolimod.

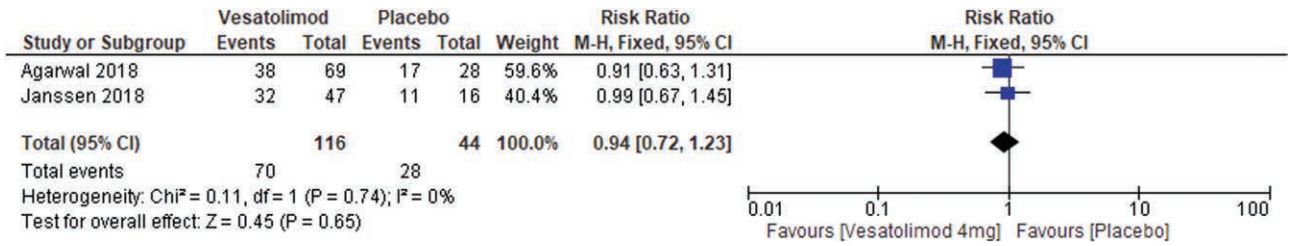

Figure 6. Treatment-emergent adverse events (TEAEs) for 2-mg Vesatolimod.

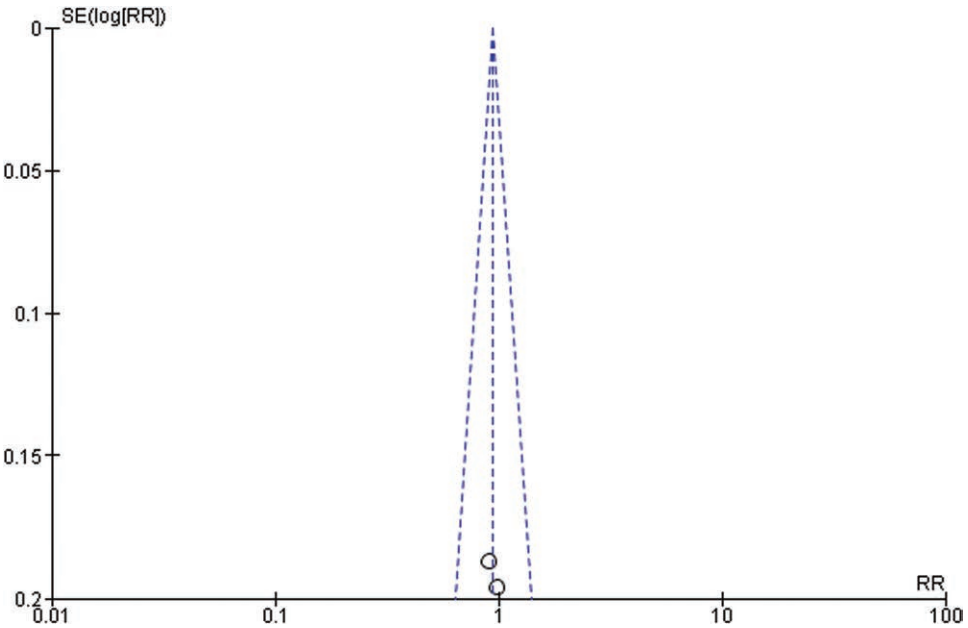

Figure 7. Treatment-emergent adverse events (TEAEs) for 4-mg Vesatolimod.

due to safety concerns and tolerability compared to chronically-infected animals.[11]

Even though there is no dose-dependent relation between the treatment course with adverse effects, a strong induction of immune response resulting in a high expression rate of ISG-15 might be associated with a higher likelihood of mild to moderate influenza-like symptoms, including headaches and chills that are in most cases resolved within 48 hours.[12] These adverse reactions are consistent with the systemic effects of IFN-alpha levels, which can be used clinically as a predictor of overdosing. Compared to other current nucleoside analog treatment regimens, low doses of vesatolimod can achieve similar efficacy with minimal systemic adverse effects due to low plasma levels of IFN-alpha.

Although all studies included in this systematic review have not revealed a significant difference in HBsAg, this might be attributed to the short duration of the TLK17 intervention. Thus, more studies assessing the effectiveness of vesatolimod with a more comprehensive treatment course are needed to assess the immune response accurately exerted and measure the variation of HBsAg, anticipate its decline, and determine its efficacy. Another limitation is that all included studies are at risk of performance bias, reflecting the poor methodological quality and jeopardizing the accuracy and validity of the results reported.

In conclusion, the administration of TLK17 agonist, Vesatolimod, once weekly is considered safe and uneventful and results in strong induction of NK cells, cytokine production, and enhancement of the cytotoxic function of cytotoxic T lymphocyte(s). Also, the treatment course is significantly correlated with a consistent short-term induction of ISG15 with minimal side effects reported.

Limitations of this study included that none of its randomized clinical trials were carried out in South America or Africa, which limits the generalizability of its results. In addition, only 4 randomized controlled trials were included in this systematic review, with multiple not reporting HBV DNA nor ISG15/IFN levels pre- and post-administration of vesatolimod, which limits the quantification of results deduced.

5. Conclusion

While vesatolimod did not appear to resolve the chronicity of hepatitis B infection, as evidenced by the persistence of HBsAg across all 4 RCTs included in this systematic review, its stimulatory effect on ISGs should be taken into account, mainly because vetastolimod appears to be associated with only mild influenza-like side effects, as evidenced by the data we extracted from 3 of the 4 included RCTs. Further studies focusing on the molecular basis to further potentiate the effect of vesatolimod are in dire need at the moment.

Author contributions

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