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Askling, H. H.

2014

Askling , H H , Rombo , L , van Vollenhoven , R , Hallen , I , Thörner , Å , Nordin , M , Herzog , C & Kantele , A 2014 , ' Hepatitis A vaccine for immunosuppressed patients with rheumatoid arthritis: a prospective, open-label, multi-centre study ' , Journal of Travel Medicine , vol. 12 , no. 2 , pp. 134-142 . https://doi.org/10.1016/j.tmaid.2014.01.005

http://hdl.handle.net/10138/224254
https://doi.org/10.1016/j.tmaid.2014.01.005

Travel Medicine and Infectious Disease (2014) 12, 134–142

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevierhealth.com/journals/tmid

Hepatitis A vaccine for immunosuppressed patients with rheumatoid arthritis: A prospective, open-label, multi-centre study ☆☆

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Received 12 November 2013; received in revised form 8 January 2014; accepted 13 January 2014
Available online 29 January 2014

☆☆The first preliminary report of this data was presented as a late breaker poster at the CISTM 12, Boston May 2011.

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http://dx.doi.org/10.1016/j.tmaid.2014.01.005

KEYWORDS
Hepatitis A;
Vaccination;
Immunosuppression;
Rheumatoid arthritis;
TNF-inhibitors

Summary *Background:* Hepatitis A vaccine is the most frequently used travel vaccine, yet data are scarce about its ability to induce protection in patients with concurrent immunosuppressive treatment. We assessed the immunogenicity of this vaccine in rheumatoid arthritis (RA) patients treated with tumour necrosis factor-inhibitors (TNFi) and/or methotrexate (MTX).
Methods: Hepatitis A vaccine was administered to non-immune RA patients at 0 and 6 months. Hepatitis A virus (HAV) antibodies were assessed at 0, 1, 6, 7, 12, and 24 months with a quantitative Chemiluminescent Microparticle Immuno Assay (CMIA) for HAV-IgG. Samples from month 1, 6, and 7 were, in addition, analysed with a microparticle EIA (MEIA) for anti-HAV IgM + IgG.
Results: The final study population consisted of 53 patients treated with TNFi ($n = 15$), TNFi + MTX ($n = 21$) or MTX ($n = 17$). One and six months after the *first* dose, 10% and 33% of the patients had attained seroprotection. One and six months after the *second* dose 83% and 72% were seroprotected. At month 24, 86% of the vaccinees showed protective levels.
Conclusions: Two doses of hepatitis A vaccine at a 6-month interval provided protection for most immunosuppressed RA patients. A single dose does not seem to afford sufficient protection to this group of patients.

Introduction

The outstanding anti-inflammatory effect of biological drugs has made them widely used in the treatment of many chronic inflammatory conditions. Tumour necrosis factor inhibitors (TNFi) are the most commonly prescribed biological drugs. Those suffering from rheumatic conditions constitute by far the largest group of patients given TNFi, often accompanied by methotrexate (MTX). Successful treatment improves the patients' physical condition, allowing them to travel more than was possible before. However, data about immunogenicity induced by travel vaccines in these patients are scarce.

Tumour Necrosis Factor alpha is a proinflammatory cytokine. The potent anti-inflammatory effect of TNFi drugs has proved beneficial in the treatment of various inflammatory conditions, such as rheumatoid arthritis (RA). MTX is a cytotoxic drug used for similar purposes due to its inhibitory capacity against T-cell activation and its ability to suppress adhesion molecule expression [1].

Data on vaccine-induced immunogenicity in adult patients treated with TNFi and/or MTX is mainly limited to influenza- and pneumococcal vaccinations [2–18]. These studies have shown that TNFi influences antibody responses only to a moderate degree, whereas a stronger negative effect is attributed to concomitant use of MTX [8,10,11,16,18].

Hepatitis A is a highly contagious viral disease that is widely spread across the globe and, accordingly, hepatitis A vaccine is one of the most frequently used travel vaccines. The standard vaccination regimen of two doses administered from 6 to 12 months apart is known to provide long-standing immunity for at least 30 years [19]. Hepatitis A vaccines have been shown to induce protective levels of anti-hepatitis A virus (HAV) antibodies already 2–4 weeks after the first dose in ≥95–100% of adult healthy volunteers [20,21]. The well-established and reliable anti-HAV antibody response is widely exploited when vaccinating travellers: to take care of protection for trips with short notice, one injection is given before the journey [22,23] and the second only afterwards.

Gamma globulin with its efficacy of 80–90% one month after the injection [24,25] can be used as an alternative to hepatitis A vaccine for prophylaxis. Yet as gamma globulin only provides a short-lived protection of 4–8 weeks, it has generally been replaced by hepatitis A vaccines. Because of its limited use, gamma globulin may in fact no longer be available with short notice at travel clinics.

Immunosuppression and advanced age are risk factors for severe disease and increasing case fatality of hepatitis A [26]. Moreover, individuals aged 50 years or older have been shown to develop an impaired response to hepatitis A vaccine [27]. Apart from one recently published retrospective study [28], we are not aware of any other data about hepatitis A vaccination in adults with chronic inflammatory diseases and immunosuppressive treatment. Since there are no uniform accepted recommendations on how to protect this group, vaccination practices tend to vary. We therefore set out to prospectively evaluate immune responses to hepatitis A vaccine in patients with rheumatoid arthritis treated with TNFi and/or MTX.

Material and methods

Study population and design

This outpatient-based, uncontrolled and open-label multicentre study was carried out in a real-life setting. We enrolled adult patients (≥18 years) with rheumatoid arthritis (RA, ICD-10 code M59.0 or M06.0) having received regular treatment with TNFi (etanercept, infliximab, adalimumab) and/or methorexate (MTX) for at least one year and who had plans to travel to a hepatitis A endemic area in the near future. The exclusion criteria included the following: a history of hepatitis A disease or vaccination, allergy to eggs, treatment with rituximab within 9 months of enrolment or immunosuppressive treatment for diseases other than RA. The disease activity was estimated with the 28-joints Disease Activity Score (DAS-28, range 0–9) and C -

reactive protein (CRP). The daily function of the patient was validated with the Health Assessment Questionnaire (HAQ, range 0–3). Immunoglobulin G (IgG) in serum was checked at baseline. The inactivated hepatitis A vaccine regimen routinely used at the given study centre, either with Havrix® or Epaxal®, was given intramuscularly in the deltoid region with a two-dose (0, 6 month) schedule. Individuals with undetectable levels of anti-HAV at month 12 were offered a third dose. Written informed consent was obtained from all study participants. The study was conducted in accordance with the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines as well as local regulatory requirements. The study protocol was approved by the regional ethics committee in Stockholm, and registered with the Swedish Medicines Agency (EUDRACT EU 2009-016055-22) and in the Clinical trials register (Clin.gov.trials NCT01360970).

Aim of the study

The aim of this study was to explore the proportions of patients who had an antibody level of anti-HAV $\geq$ 20 mU/mL at months 1 and 7, after monovalent hepatitis A vaccine administered by the recommended two-dose schedule (at months 0 and 6).

Vaccine

One of the two adult hepatitis A vaccines, Havrix® given as a 1.0 ml dose or Epaxal® as a 0.5 ml dose, was used according to local preferences at the study centres. Havrix® contains 1440 enzyme-linked immunosorbent assay units (EU) of formalin-inactivated hepatitis A virus. Epaxal® contains at least 24 IE inactivated hepatitis A-viruses, produced in human diploid (MRC-5) cells, in which the virus particles are adsorbed to virosomes.

Sample analysis

Blood-samples were drawn at month 0, 1, 6, 7, i.e. before each vaccination and one month after, as well as 12 and 24 months after the first vaccination dose and, if applicable, one month after a third dose. Hepatitis A virus (HAV) antibodies were analysed for anti-HAV IgG, using the HAVAb-IgG Architect System (Abbott) Chemiluminescent Immuno Assay (CMIA) at the Karolinska University Laboratory, Stockholm, Sweden. For quantification a standard curve was used by simultaneously analysing a set of standards (AxSYM HAVAB 2.0 Quantative Standard Calibrators, Abbott) with known concentrations of HAV antibodies. Initially we intended to exploit the newer HAVAb-IgG Architect System standardly used at the Karolinska Institutet. However, as the anti-HAV responses proved lower than expected, we also applied the older AxSYM test still employed by a few institutions in Europe. This assay measures total anti-HAV antibodies; i.e includes the early IgM response. Thus, samples from month 1, 6 and 7 were also analysed by HAV AB 2.0 quantitative Assay/AxSYM (Abbott) Microparticle EIA (MEIA) at the Institute of Virology, Technical University, Munich, Germany. The CMIA-method by the Architect system measures only anti HAV-IgG and thus misses the very early, mainly IgM-driven immune response, while the AxSYM method (MEIA) detects both anti-HAV IgM and IgG combined [29].

Definition of seroprotection

The protective level of antibodies against hepatitis A was defined as anti-HAV $\geq$ 20 mIU/mL. The lower limit of detection (LLD) was 10 mIU/mL. Geometric mean concentrations (GMC) were calculated, with corresponding 95% confident intervals (CI), using half of the LLD (5 mIU/mL) for negative sera. An "adjusted" GMC were calculated from the subgroup with anti-HAV $\geq$ 10 mIU/mL only, i.e. the negative sera were withdrawn so as to demonstrate better the anti-HAV antibody levels of those responding to the vaccine.

Anti-HAV $\geq$ 10 mIU/mL has been accepted as a measure of protection in recent years [24], therefore data were also presented in relation to this limit.

Safety

All participants were asked to report any kind of adverse event possibly related to the HAV-vaccination at every visit scheduled for vaccination or blood sampling. They were also carefully instructed to report any adverse events or contact with health care between these visits.

Statistics

GMCs with 95% CI were calculated using SAS Enterprise Guide version 5.1 version. Basic statistical analysis was performed with Excel. Differences were analysed with a two-sided test. The level of statistical significance was set at $p < 0.05$.

Results

Demographics

During the study period we included 68 patients (Fig. 1). Fifteen patients were found to be anti-HAV positive in pre-vaccination samples suggesting either a previous history of hepatitis A disease or a vaccination which they no longer remembered. These patients had been given one dose of vaccine at the time of inclusion but were then excluded from further analyses. The final study population consisted of 53 non-immune patients (73% women) with a median age of 60 years (mean 56; range 32–75). The median disease activity scores indicated a low disease activity and the daily function score a relatively physically active cohort of patients. Fifteen patients (28%) were treated with TNFi only (etanercept, infliximab or adalimumab), 21 (40%) with a combination of TNFi and MTX and 17 (32%) with MTX only (Fig. 1). None of the patients had been treated with rituximab ever before. Baseline characteristics, divided by treatment groups, are shown in Table 1.

Vaccines

Epaxal® was given to 32 patients at two different study centres, and Havrix® to 21 patients at one study centre.

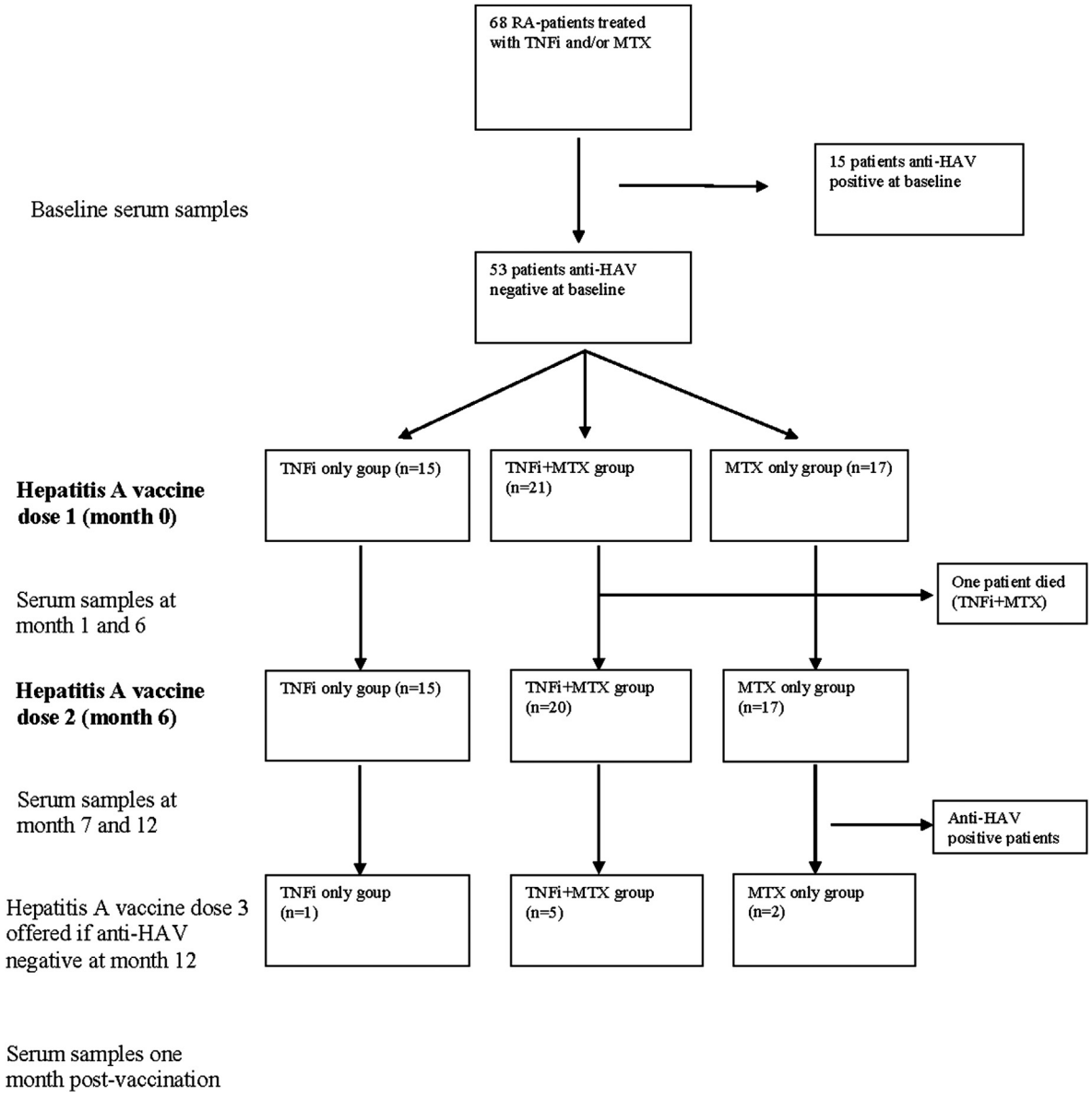

Fig. 1 Study schedule. TNFi = TNF-inhibitors. MTX = methotrexate.

Immunogenicity

Fifty-two patients were included in per protocol analysis and their samples were available for months 1, 7 and 12 (Fig. 1). Fifty-one samples were available for analysis of the post-vaccination titres at 6 months. Ten percent (5/52) reached the pre-defined immunity level of anti-HAV $\geq$ 20 mIU/mL one month after the first dose of vaccine. Thirty-three percent (17/51) reached protective levels after six months, before the second dose. At months 7 and 12, i.e. one and 6 months after the second vaccine dose, 83% (42/52) and 72% (37/52) of the patients were anti-HAV positive, respectively. The corresponding results when accepting the lower immunity level of $\geq$10 mIU/mL at month 1, 6, 7 and 12 were 29% (15/52), 45% (23/51), 84% (43/52) and 77% (40/52). Twenty-nine out of 37 patients with an anti-HAV $\geq$ 20 mIU/mL at month 12 provided a follow-up sample at month 24; the antibody level was $\geq$20 mIU/mL in 25/29 (86%) of these, between 10 and 20 mIU/mL in 2/29 (7%) and under the lower detection limit in 2/29 (7%, both patients had TNFi + MTX). Eight patients with anti-HAV levels below the detection limit at month 12 were given a third vaccine dose and 4/8 responded with an antibody titre above 20 mIU/mL (range 32–110) at one month post vaccination. With respect to the three different treatment groups, the proportion of patients with anti-HAV $\geq$20 mIU/mL at month 1 was higher in the TNFi (20%) than in the TNFi + MTX (5%) and MTX (6%) groups, yet the difference between groups did not prove statistically significant (Fig. 2a). Using the lower level of protection (anti-HAV 10 mIU/L), there was a significant difference between the TNFi group (73%) and others (15%, 6%) at month 1, indicating a potential for reaching protection after one vaccine dose only, in patients treated with TNFi only (Fig. 2b). The GMC values obtained with the two methods and corresponding 95% confidence intervals are displayed in Table 2.

Table 1 Baseline characteristics of the 53 patients anti-HAV negative at inclusion as evaluated before vaccination, in the different treatment groups. TNFi = TNF-inhibitor. MTX = Methotrexate. All variables are medians unless other information given.

	All (range)	TNFi	TNFi + MTX	MTX
N	53	15(28%)	21(40%)	17(32%)
Age (yrs)	60 (32–75)	49	61	61
Female (%)	73%	80%	71%	70%
Duration of the disease (yrs)	12 (2–45)	12	14	6
Time span since last TNFi-infusion (days)	6 (0–49)	3	7	NA
MTX weekly dose (mg)	15 (7.5–22.5)	NA	15	15
DAS-28[a]	2.66 (0.49–5.89)	3.17	2.48	2.38
HAQ[b]	0.75 (0–1.88)	0.75	0.75	0.5
C- reactive protein mg/l	2 (0–46)	3	3	0
Immunoglobulin G g/l	11.2 (5.9–18.8)	12.6	11.3	9.7
Prednisone[c] (no of patients)	15	4	4	7
NSAID[d] (no of patients)	5	4	3	0
Salazopyrin (no of patients)	2	1	1	0
Anti-malarial drugs (no of patients)	3	0	0	3

[a] 28-joints Disease Activity Score (DAS-28, 0–9).
[b] Health Assessment Questionnaire (HAQ, 0–3).
[c] Prednisone dose (median 5 mg, range 1.25–10 mg).
[d] NSAID = Non Steroidal Anti Inflammatory Drugs.

HAV antibody response at month 1 after the first vaccine dose was consistent with the higher sensitivity reported with the AxSYM-method analysing also the early IgM-response: 10% of the patients reached a protective level of anti-HAV $\geq$ 20 IU/mL and 29% a level of $\geq$10 mIU/mL compared to 1% for both levels with the CMIA-method. There was no difference between the two methods, with respect to proportion of seroprotected patients, beyond month 1.

Non-responders at month 7

Ten out of 52 patients (19%) lacked a serological response (one of these had a level between 10 and 20 mIU/mL) after two doses of hepatitis A-vaccine at month 7. In this group the median age was 62 years, 5/10 were women and 1/10 were treated with TNFi, 4/10 with TNFi + MTX and 5/10 with MTX.

Safety

One patient died of a heart-attack 10 days after the first vaccine dose (Epaxal®). The study team in cooperation with the cardiologist considered the death to be due to known co-morbidities and an association with the vaccine was deemed unlikely. One female patient was hospitalized due to meningo-encephalitis 2.5 weeks after the second dose (Epaxal®). This patient recovered but TNF-inhibitor treatment was interrupted as the aetiology remained unknown. Two patients reported mild reversible adverse event of slight vertigo (Havrix®) and non-itching exanthema (Epaxal®), both of them 1–2 days after the second vaccine dose. There was no evidence suggesting increased disease activity of RA in the follow-up of any of the study patients.

Premature termination of the study due to lack of protective pre-travel immunity

Initial we planned to include 330 patients, as suggested by pre-study power calculation based on reports of one vaccine dose being non-inferior to gamma globulin in terms of seroprotection. However, we considered it unethical either to include immunosuppressed patients not needing the vaccine, or to carry on once the first interim results had revealed that the short-term immunity could not be guaranteed for patients receiving only one dose. These results were not only unexpected but also a strong signal that rendered the power calculation invalid. Patients having not reached protective levels of anti-HAV ($\geq$20 mIU/mL) in their last samples were informed that they should be given gamma globulin as a pre-travel prophylaxis.

Discussion

The present study is the first to prospectively investigate the immune response to hepatitis A vaccine in adult patients treated with TNF-inhibitors and/or methotrexate. The results reveal an insufficient antibody response one month after the first dose of inactivated hepatitis A vaccine.

Current practices of using HAV vaccines and reasons for terminating the study

Several studies have shown that in healthy individuals one dose of hepatitis A vaccine renders seroprotection [20,21,30]. Accordingly, it is a common practice to take care of short-term protection for a pending trip by giving only one dose to naive travellers. This would also appear to

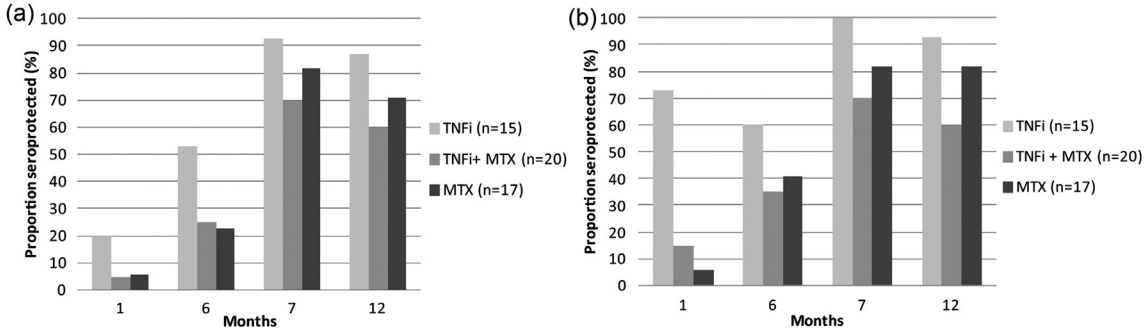

Fig. 2 Proportion of RA patients (%) with (a) anti-HAV $\geq$ 20 mIU/mL and (b) anti-HAV $\geq$ 10 mIU/mL divided by treatment group (TNFi = TNF-inhibitors, MTX = methotrexate). $N = 52$. Hepatitis A vaccine was given as single doses at months 0 and 6. For month 1 anti-HAV IgG + IgM data (analysed with HAV AB 2.0 quantitative Assay/AxSYM Mikropartikel EIA, MEIA) and for months 6, 7 and 12 anti-HAV IgG data (analysed with HAV Ab Architect System Chemiluminescent Microparticle Immuno Assay, CMIA) are presented.

be a logical approach to the pretravel care of RA patients taking immunosuppressive drugs, since other types of vaccines have been shown to induce protective levels of antibodies in this group [2,8–14,16]. Advanced age is a factor related to an impaired antibody response [27], and the median age of our population of RA patients was 60 years. However, the age-group was similar to studies with pneumococcal and influenza vaccinations showing adequate immune-response [2,8–14,16]. Therefore inadequate antibody responses observed in the present study one month after vaccinations were unforeseen. As the patients were planning to travel soon, it was considered unethical to continue the study when the protocol could not grant them protection against hepatitis A. Premature termination of the study resulted in inclusion of fewer subjects than intended.

Comparison with other studies

We know of only one recently published paper dealing with seroprotection after Hepatitis A vaccination in patients with drug-induced immunosuppression [28]. It was concluded in that retrospective study that one dose of vaccine does not provide seroprotection. This is consistent with our findings, yet the data of that study should be compared with caution, since the underlying inflammatory diseases and seroprotective level were not defined, and the pre-vaccination anti-HAV status of the patients was unknown. This illustrates the difficulties of a retrospective design and motivates our prospective outline of a homogenous patient group.

Studies of other vaccines

Studies of inactivated trivalent influenza vaccines have shown that although TNFi treatment moderately decreases humoural responses, the patients still develop protective antibody levels [2,3,12–14], and the response can even equal that in healthy controls [11]. The aforementioned studies were conducted in RA patients, yet one study also included patients with other chronic illnesses [3]. Pneumococcal polysaccharide and conjugate vaccines have been reported to elicit an equal [8,10,11,16], or only slightly impaired [9] antibody response in TNFi-treated RA patients compared to healthy controls. A moderate decrease in antibody levels has been found in inflammatory bowel disease (IBD) patients on TNFi [6]. Notably, several studies of pneumococcal and influenza vaccines have demonstrated the immunosuppressive effect to be reinforced by concomitant use of MTX [2,8,11,15,16,18]. These findings are consistent with our data showing that 9/10 non-responders, after two hepatitis A vaccine doses, belonged to groups treated with MTX alone or in combination with TNFi. The proportion of patients who attained protective levels at month one appeared significantly higher in the group treated solely with TNFi compared to the other two groups, yet a statistical significance could only be verified when using anti-HAV antibodies $\geq$10 mIU/mL as a limit of protection (Fig. 2a and b).

Our data, like most of the studies quoted above, strictly applies only to patients with RA which is the largest group of patients treated with biological drugs such as TNFi. Other inflammatory conditions elicit diverse inflammatory responses and patients may be prescribed other drug combinations, which might interfere with the serological response in a different way. Further studies are needed to investigate those other patients groups.

Methodological considerations

In studies of healthy individuals, estimates of the minimum levels of serum anti-HAV antibodies required for protection have varied between 10 and 33 mIU/mL, yet the lowest level providing protection against HAV remains undetermined [31]. Due to these differences, we present our results with the cut-off $\geq$20 mIU/mL used in the CMIA method, and in addition also with $\geq$10 mIU/mL to allow comparison with studies using this cut-off. Difference in the results obtained by the two methods at month one did not influence our decision to terminate the study, since the proportion of patients protected with one dose remained too low altogether. The use of two methods strengthens our findings, demonstrating also the advantages of anti-HAV IgM measurements in this population. It is noteworthy that even though cell-mediated immunity in healthy individuals may contribute significantly to protection against disease, in immunosuppressed older patients the risk of getting

Table 2 Geometric Mean Concentrations (GMC) anti-HAV antibody responses in 52 RA patients receiving hepatitis A vaccine at 0 and 6 months. The protective level of anti-HAV antibodies was defined as ≥20 mIU/mL. The lower limit of detection (LLD) was 10 mIU/mL. The results are shown with the two different serological assays; HAV Ab Architect System Chemiluminescent Microparticle Immuno Assay (CMIA) and HAV AB 2.0 quantitative Assay/AxSYM Mikropartikel EIA (MEIA) (the latter not tested at 12 and 24 months). The results are given as a) Geometric Mean Concentrations (GMC) of anti-HAV antibodies (mIU/mL) with 95% confidence intervals (CI) at 1,6,7,12 and 24 months. GMC was calculated using half of the LLD (5 mIU/mL) for negative sera. b) "Adjusted" Geometric Mean Concentrations (GMC), including only the subpopulation with antibody levels anti-HAV ≥ 10 mIU/mL, i.e withdrawing all the negative sera to better demonstrate the anti-HAV antibody levels of those who responded to the vaccine. This is shown with 95% confidence intervals (CI) at 1,6,7,12 and 24 months.

Method	Month 1	Month 6	Month 7	Month 12	Month 24
a					
HAV Ab Architect System Chemiluminescent Microparticle Immuno Assay (CMIA)	5.2 (4.8—5.6)	11.8 (8.7—16)	45.4 (32.8—62.8)	35.7 (25.3—50.3)	43.1 (30.6—60.8)
HAV AB 2.0 Assay/AxSYM (Abbott) Mikropartikel EIA (MEIA)	7.5 (6.3—8.9)	12.6 (8.8—17.9)	109.3 (60.8—196.5)	NA	NA
b					
HAV Ab Architect System Chemiluminescent Microparticle Immuno Assay (CMIA)	NA[a]	36.6 (27.3—48.9)	71.9 (59.5—87.1)	64.3 (51.8—79.8)	49.6 (37.4—65.6)
HAV AB 2.0 Assay/AxSYM (Abbott) Mikropartikel EIA (MEIA)	16.3 (13.5—19.8)	42.3 (26.5—67.6)	182.7 (106.6—313.3)	NA	NA

[a] Only one observation with anti-HAV ≥ 10 mIU/mL.

seriously ill from hepatitis A is increased, which is why it should not be relied on, if the antibody level is below 10—20 mIU/mL.

Recommendations for practical use

As one dose does not seem to suffice to provide short-term protection in these patients, the only reasonable choice at the moment is to use gamma globulin. Another option would be to give the vaccine and gamma globulin at the same time or, as suggested before [32] but not yet studied, two vaccine doses at one-month intervals. A different solution can be applied to patients not travelling in the six-month period post initial vaccination, since a sufficient serological response was seen in 83% of the patients one month after the second dose. Importantly, in the group on TNFi only, 73% had attained seroprotection by anti-HAV ≥10 mIU/mL after one vaccine dose, while in the TNFi + MTX and MTX group, only 15% and 6% were protected after one month. This implies that for patients treated solely with TNFi and travelling with short notice, one dose of hepatitis A vaccine might be considered, although this needs to be confirmed in a larger study. Our data indicate that patients with inflammatory conditions should preferably be given the first dose of hepatitis A vaccine upon diagnosis, or at least prior to immunosuppressive treatment. This approach has in fact also been recommended for other inactivated vaccines e.g. pneumococcal and hepatitis B as well as for live vaccines, if a future need for these vaccines is anticipated [33,34].

Limitations of the study

The main limitation of this study is the lack of a relevant control group. However, we considered the robust and repeated data on serological hepatitis A vaccine response in healthy individuals so well established [35] that any deviation from that will be an important signal and lead to quick reporting. The latter appears imperative, also, from the perspective that the reports on adequate overall serological response in RA-patients of the same age-group after influenza- and pneumococcal vaccination made us expect the same for hepatitis A vaccine. Another limitation of the study is the small sample size, a consequence of the premature termination due to ethical concern of travellers unprotected to hepatitis A. The small sample size limits the external validity of the study. It also renders any conclusions on subgroups, such as age, gender, TNFi group, difficult to interpret.

Strength of the study

The findings indicate an important signal that should be studied further in a prospective study with a larger number of volunteers, and in patients with other immunosuppressive conditions. In lack of data, health care professionals might unintentionally send their patients off unprotected to hepatitis A risk areas. Our results are also consistent with studies in the same patient group on influenza and pneumococcal vaccination concerning the fact that

monotherapy with TNFi is not influencing serological vaccine response significantly. Moreover our results proved consistent by two different serological methods. These data also attested to the importance of measurement of anti-HAV IgM in early post-vaccination response.

Conclusions

Two doses of hepatitis A vaccine given six months apart can be considered to provide protective immunity to most travellers having RA treated with TNFi and/or MTX. In contrast to recommendations for healthy travellers, a single of hepatitis A vaccine dose does not suffice as pre-exposure prophylaxis for these patients, except may be patients treated with TNFi only. Larger studies are required to confirm this, and to determine if increased dosage or a second priming dose of the vaccine could provide adequate protection. Until then, for journeys with a time span of six months or shorter, travellers should be protected with gamma globulin.

Funding source

The research was partly funded by Crucell (part of the vaccines, costs of the MEIA-analyses) but they did not have any input in collection, analysis and interpretation of data; the writing of the manuscript or the decision to submit the manuscript for publication.

Conflict of interest statement

HHA has received honoraria from Abbott. LR has participated in an advisory board for Crucell. AK has acted as a consultant on vaccination immunology and received research funds from Crucell. LR and AK have participated as members in an advisory board for and received honoraria from Novartis and received honoraria for lectures from Crucell, GlaxoSmithKline, and Pfizer. RvV has received research grants and/or honoraria from: Abbott, BMS, GSK, MSD, Pfizer, Roche, and UCB. CH was formerly employed by Crucell. IH, ÅT and MN declare no conflicts of interest.

Acknowledgement

Professor Gert Frösner for the MEIA-analysis. Åsa Lagergren, Berit Schmidt, Ingrid Andrén for administration, vaccination and blood sampling. Dr.Tommy Wingren for including patients.

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