Response to Hepatitis A Vaccination in Immunocompromised Travelers

Hannah M. Garcia Garrido, Rosanne W. Wieten, Martin P. Grobusch, and Abraham Goorhuis

Center of Tropical Medicine and Travel Medicine, Department of Infectious Diseases, Division of Internal Medicine, Academic Medical Center, University of Amsterdam, The Netherlands

**Background.** Hepatitis A vaccines are highly immunogenic in healthy patients, but there is uncertainty about their immunogenicity in immunocompromised patients.

**Methods.** Our study included immunocompromised patients who received 1 or 2 hepatitis A vaccinations between January 2011 and June 2013. We assessed factors that influenced the serologic response to vaccination. We performed a literature review of previous studies on hepatitis A vaccination in immunocompromised patients.

**Results.** Of 85 immunocompromised patients, 65 used immunosuppressive drugs, 13 had received stem cell transplants, and 7 were infected with human immunodeficiency virus. After vaccination, 65 of 85 (76.5%) developed antibodies. Tumor necrosis factor α blocker use was associated with better serologic responses than other immunosuppressive drugs. Female patients were more compliant than male patients with postvaccination antibody titer measurements. In 11 relevant studies, antibody responses after the first and second vaccination averaged 37% and 82%, respectively. Factors that negatively influenced serologic response rates were high doses of immunosuppressive drugs, fewer hepatitis A vaccinations, and a short interval between vaccination and antibody measurement.

**Conclusions.** Immunocompromised patients showed moderate to good serologic responses to hepatitis A vaccination, but may need more time to develop immunity. Tumor necrosis factor α blocker use was associated with better antibody responses than other drugs. Specifically, male patients should be motivated to return for antibody titer measurements.

**Keywords.** hepatitis A vaccination; immunocompromised; serologic response; travelers.
in patients who use immunosuppressive medication or who are otherwise immunocompromised are scarce and heterogeneous.

Common immunosuppressive drugs include corticosteroids and classic disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX) and azathioprine. Other widely used immunosuppressive drugs include mycophenolate, and calcineurin inhibitors, such as cyclosporine A and tacrolimus, which are often prescribed in organ transplant recipients. These immunosuppressive drugs reduce the number of effector T and/ or B cells by blocking clonal expansion after stimulation by pathogens or vaccines, either by inhibition of DNA synthesis or by inhibition of intracellular signaling. The end result is an ineffective immune response. By contrast, tumor necrosis factor (TNF) α—blocking agents interfere with the immune response in more specific ways. By antagonizing the effects of TNF-α, they cause reduced migration and maturation of dendritic cells, inhibit activation of T cells, and reduce the survival of memory cells, but they do not induce extensive clonal deletion of activated T cells [27]. It would therefore be logical to hypothesize that TNF-α blockers cause less inhibition of the immune system, resulting in a better response to vaccination.

In this study, we investigated whether immunocompromised patients have an adequate antibody response to hepatitis A vaccination and whether there are predictive factors for an inadequate response, with specific interest to different immunosuppressive medication regimens. To that end, we analyzed our own data from patients who visited the travel clinic of the Academic Medical Center in Amsterdam. We also performed a literature review of previously published data on this subject.

METHODS

Original Data: Study Population

We included all immunocompromised patients who had visited the Academic Medical Center for travel advice between January 2011 and June 2013 and who received monovalent hepatitis A vaccination. We collected data on demographics, medical conditions, medication type and dose, travel destination and duration, travel vaccinations, and postvaccination antibody titers. We excluded patients with positive prevaccination antibody titers for hepatitis A or presumed naturally acquired immunity and patients expected to have a normal immune response according to the Dutch guidelines for travel medicine (national coordinating center for travel advice) [28]. Live vaccines are considered safe for those who received the last chemotherapy >3 months before vaccination and those who received a stem cell transplant >2 years before vaccination.

Data Extraction and Antibody Measurement

All data were retrieved from the electronic hospital database. Hepatitis A antibody titers were measured using the immune fluorescence technique: AxSYM microparticle enzyme immunoassay (Abbott). A sample cutoff between 0 and 1 was considered a positive serologic outcome or “seroconversion.” This is a qualitative measure of the ratio between the fluorescence of the serum of the patient compared with the background and measures both immunoglobulin M and immunoglobulin G. According to the manufacturer’s brochure, the specificity of the assay is 98.96% (as tested in 384 patient samples). The test uses a positive control, which contains 20–34 mIU/mL of anti-hepatitis A virus (standardized against the World Health Organization reference standard). Therefore, at a minimum, patient specimens containing 20–34 mIU/mL are positive.

Study Groups

To evaluate determinants of serologic response to hepatitis A vaccination, we included patients in whom postvaccination antibody measurements were performed in study group A. To explore predictive factors for not receiving an antibody titer measurement after vaccination, we included patients without antibody titer measurement after vaccination in study group B.

Variable Definitions

Our primary outcome was serologic response after hepatitis A vaccination defined as a positive or negative result at microparticle enzyme immunoassay, as described above. Because TNF-α—blocking agents have a different mode of action compared with classic DMARDs, we hypothesized that this translates into differences in immune response. Therefore, we evaluated differences in serologic response by dividing the study population in the following medication groups: (1) patients using TNF-α—blocking agents, with or without other immunosuppressive medication; (2) patients using only classic DMARDs (MTX or azathioprine), with or without systemic corticosteroids; and (3) patients using transplantation rejection therapy (tacrolimus, systemic corticosteroids, or mycophenolate) and double- or triple-DMARD therapy. Patients using both DMARDs and TNF-α blockers were included in group 1, because these drugs are often used concomitantly either to prevent drug breakdown or because of insufficient clinical response [27].

To assess the effect of both dose and number of immunosuppressive drugs on hepatitis A protection, we established a categorical variable “degree of immunosuppression,” ranging from 1 (low) to 3 (high) and based on increasing dose and number of immunosuppressive drugs. If a dose was not registered in our databases (eg, because the patient originated from another hospital), we assumed treatment according to disease-specific treatment guidelines (Appendix).

The categories were defined as follows: (1) low: prednisone monotherapy ≤20 mg/d, MTX = 15 mg/ wk with or without prednisone ≤ 20 mg/ d, infliximab < 5 mg/kg/ every 8 weeks, adalimumab < 80 mg/2 wk, or azathioprine < 1 mg/kg/ d; (2) medium: MTX ≥ 15 mg/ wk with or without prednisone, MTX < 15 mg/ wk plus infliximab, prednisone > 20 mg/ d, infliximab ≥ 5 mg/kg/ every...
8 weeks, adalimumab ≥80 mg/2 wk, or azathioprine 1–3 mg/kg/d; and (3) high: MTX ≥15 mg/wk plus infliximab, infliximab plus azathioprine, double and triple therapies for organ transplant recipients, azathioprine 3–4 mg/kg/d with or without prednisone, or etanercept >50 mg/wk [29].

**Statistical Analysis**

The effects of age and interval between vaccination and antibody titer measurement on hepatitis A protection were analyzed using the nonparametric Mann–Whitney U test. We used the 2-sided \( \chi^2 \) test to examine the associations between hepatitis A protection and sex, type of medication, underlying disease, number of vaccinations, and degree of immunosuppression. In our multivariable model, factors with a \( P \) value < .05 in univariable analysis were included. We adjusted for the degree of immunosuppression and all variables that were associated with both our primary outcome and the covariate at \( P \leq .1 \). All analyses were conducted using IBM SPSS statistics software, version 21.

**Literature Review**

We performed a PubMed search on 31 August 2014 (search strategy in Appendix). We screened all titles and abstracts for relevance. We calculated the overall response rates after primary and second vaccination in patients using immunosuppressive medication by dividing the number of responding patients in each study by the total number of patients.

**RESULTS**

**Original Data**

Of 938 patients with chronic underlying conditions who visited the Academic Medical Center travel clinic during the study period, 109 met our inclusion criteria. Of these, 85 (78%) had received antibody titer measurements (group A), and 24 (22%) patients had not (group B). In group A, 22 of 85 (26%) had received prevaccination serologic examination, and all tested negative for hepatitis A antibodies.

**Study Group A: Hepatitis A Protection Rate**

Of 85 patients included in study group A, 65 used immunosuppressive drugs, 7 were HIV infected, and 13 had received a stem cell transplant. The overall response rate was 76.5% (Table 1), and no association with sex or age and the seroconversion rate was found.

The serologic response rate in HIV-infected patients was 57.1%. The mean CD4 cell count was \( 426 \times 10^6/L \) (standard deviation, \( 71.2 \times 10^6/L \)) and did not differ between responders and nonresponders (\( P = .21 \)). In the stem cell transplant recipients group (\( n = 12 \)) and the patient with a hematologic malignancy receiving chemotherapy <3 months before vaccination (\( n = 1 \)), the response rate was 76.9%. The median time between stem cell transplantation and vaccination was 2.20 years.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients/Total, No. (%)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protective immunity after vaccination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26/85 (30.6)</td>
<td>18/26 (69.2)</td>
</tr>
<tr>
<td>Female</td>
<td>59/85 (69.4)</td>
<td>47/69 (79.7)</td>
</tr>
<tr>
<td>No. of vaccinations before antibody titer measurement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vaccination</td>
<td>45/85 (52.9)</td>
<td>36/45 (80.0)</td>
</tr>
<tr>
<td>2 vaccinations</td>
<td>40/85 (47.1)</td>
<td>29/40 (72.5)</td>
</tr>
<tr>
<td>Use of immunosuppressive drugs(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-( \alpha ) blocker</td>
<td>25/65 (38.5)</td>
<td>23/25 (92.0)</td>
</tr>
<tr>
<td>Classic DMARD</td>
<td>29/65 (44.6)</td>
<td>20/29 (69.0)</td>
</tr>
<tr>
<td>Other</td>
<td>11/65 (16.9)</td>
<td>8/11 (72.7)</td>
</tr>
<tr>
<td>No. of immunosuppressive drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 drug</td>
<td>40/65 (61.5)</td>
<td>30/40 (75.0)</td>
</tr>
<tr>
<td>2 drugs</td>
<td>22/65 (33.8)</td>
<td>20/22 (90.9)</td>
</tr>
<tr>
<td>3 drugs</td>
<td>3/65 (4.6)</td>
<td>1/3 (33.3)</td>
</tr>
<tr>
<td>Degree of immunosuppression(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>14/65 (21.5)</td>
<td>12/14 (85.7)</td>
</tr>
<tr>
<td>Medium</td>
<td>31/65 (47.7)</td>
<td>23/31 (74.2)</td>
</tr>
<tr>
<td>High</td>
<td>20/65 (30.8)</td>
<td>16/20 (80.0)</td>
</tr>
<tr>
<td>Underlying condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV infection</td>
<td>7/85 (8.2)</td>
<td>4/3 (57.1)</td>
</tr>
<tr>
<td>HSCT</td>
<td>13/85 (15.3)</td>
<td>10/13 (76.9)</td>
</tr>
<tr>
<td>IBD</td>
<td>11/85 (12.9)</td>
<td>6/11 (54.4)</td>
</tr>
<tr>
<td>RA and other(^c)</td>
<td>44/85 (51.8)</td>
<td>39/44 (88.6)</td>
</tr>
<tr>
<td>Organ transplant</td>
<td>10/85 (9.2)</td>
<td>6/10 (60)</td>
</tr>
</tbody>
</table>

Abbreviations: DMARD, disease-modifying antirheumatic drugs; HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplant; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; TNF, tumor necrosis factor.

\(^a\) Of patients using TNF-\( \alpha \) blockers, 12 received monotherapy and 13 received a TNF-\( \alpha \) blocker in combination with another immunosuppressant (methotrexate [MTX], corticosteroids, or azathioprine). In the classic DMARD group, 16 patients received MTX and 13 azathioprine with or without corticosteroids. In the “other” group, 3 patients used mycophenolate with or without corticosteroids, 5 used corticosteroids >10 mg/d only, 6 used a combination therapy with tacrolimus, and 1 used cyclosporine A in combination with azathioprine.

\(^b\) Degree based on dose and number of drugs.

\(^c\) Including RA, vasculitis, spondyloarthritis, systemic lupus erythematosus, psoriasis, and psoriatic arthritis.

Of 65 patients with immunosuppressive medication, 25 used a regimen containing a TNF-\( \alpha \) blocker. Of these, 12 (48%) had monotherapy and 13 (52%) used a TNF-\( \alpha \) blocker in combination with another immunosuppressive drug. Forty patients did not use a TNF-\( \alpha \) blocker. Of these, 28 (70%) used monotherapy and 12 (30%) used multiple immunosuppressive drugs.

Those who used a TNF-\( \alpha \) blocker, with or without other immunosuppressive drugs, had a higher serologic response rate than the rest of the population: 92% versus 76.5% (\( P = .04;\)
Table 2. Multivariable Analysis

<table>
<thead>
<tr>
<th>Immunosuppressive Drugs (n = 65)</th>
<th>Serologic Response Rate, %</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α blockers (n = 25)</td>
<td>92.0</td>
<td>5.21 (1.04–26.1)</td>
</tr>
<tr>
<td>Classic DMARD therapy (n = 29)</td>
<td>69.0</td>
<td>0.27 (0.07–1.10)</td>
</tr>
<tr>
<td>Other drugs (n = 11)</td>
<td>72.7</td>
<td>0.71 (0.15–3.36)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; DMARD, disease-modifying antirheumatic drug; OR, odds ratio; TNF, tumor necrosis factor.

a In this multivariable analysis of the association between serologic response rate after hepatitis A vaccination and type of immunosuppressive medication, each drug category was compared with the other 2 categories. Final ORs are adjusted for degree of immunosuppression, based on dose and number of drugs.

b Of patients using TNF-α blockers, 12 received monotherapy and 1 received a combination of anti-TNF with another immunosuppressant (methotrexate (MTX), corticosteroids, or azathioprine).

c In the classic DMARD group, 16 patients used MTX and 13 azathioprine with or without corticosteroids.

d All other drug regimens.

Table 1). In multivariable analysis, adjusted for degree of immunosuppression, this effect remained statistically significant (Table 2: odds ratio 5.21; confidence interval [CI], 1.04–26.1). A regimen with only classic DMARDs was associated with lower response rates (69.0% vs 76.5%) although this result did not reach statistical significance (Table 2). When we assessed the subgroup of patients who only used 1 immunosuppressive drug, 11 of 12 (91.7%) of those using a TNF-α blocker seroconverted, compared with 20 of 28 (71.4%, P = .16) using a DMARD and 2 of 3 (66.7%, P = .26) using other immunosuppressive drugs.

Patients with rheumatic disorders had significantly higher serologic response rates (88.6%) in univariable analysis (P = .006) than other patients (Table 1). TNF-α–blocking agents were used more often in this group: 84% in the group with rheumatic diseases versus 16% in the rest of the study population (P = .02).

Study Group B: Determinants of Adherence to Serologic Examination

Female patients were more likely to receive hepatitis A antibody titer measurement than male patients (59 of 68 [86.8%] vs 26 of 41 [63.4%]; odds ratio, 6.96; CI, 2.19–22.1). No associations were found with age, time to departure, underlying disease, or duration of travel.

Literature Review

The literature search resulted in 184 hits. After screening, 11 studies were included (Table 3), comprising 921 patients: 520 with IBD (4 studies), 175 with organ transplantation (5 studies), 53 with RA (1 study), and 173 other patients using immunosuppressive drugs (1 study). The overall serologic response rate after the first vaccination was 37%, but the majority of patients developed protective antibodies after 2 vaccinations; 527 of 642 (82%), with rates ranging from 0% to 100% [30–40].

Two studies assessed the effect of a single versus multiple immunosuppressive drugs on hepatitis A seroconversion. Both found that patients using multiple immunosuppressive drugs were less likely to respond to vaccination after 2 vaccinations [31, 38]. One study assessed response rate in renal transplant recipients using calcineurin inhibitors and found a lower response rate among patients using tacrolimus versus cyclosporine (20% vs 50%), among 52 patients after 2 vaccinations [40]. Three studies evaluated the development of seroconversion over time. All 3 found higher conversion rates 3–6 months after the first vaccination than 1 month after the first vaccination [33, 34, 39]. Four studies examined the effect of 1 versus 2 vaccinations and found that the response rates after 1 vaccination were lower than after 2 [31, 33, 34, 37].

Four studies assessed hepatitis A vaccination in patients using TNF-α–blocking agents. One study found a lower response rate in patients using TNF-α blockers than in those using classic DMARDs after 2 vaccinations (79% vs 89%) [37]. Three studies found high conversion rates in patients using TNF-α blockers. The first of these reported a response rate of 92% (11 of 12) in pediatric patients with IBD after 2 vaccinations [35]. The second study also reported a rate of 92% (85 of 92) after 2 vaccinations, which was lower than in a control group of patients using no other immunosuppressive drugs or no medication at all [38]. The third found that 1 month after initial vaccination, patients using only TNF-α blockers were more likely to develop antibody titers of ≥20 mIU/L than patients using MTX or both MTX and TNF-α blockers (3 of 15 [20%] vs 1 of 17 [6%] and 1 of 20 [5%], respectively). After 2 vaccinations, these rates were 93% in patients using only TNF-α blockers and 71% in those using only MTX [39].

The duration of protection was assessed in 2 studies. One found a faster decline in protective immunity against hepatitis A in organ transplant recipients than in healthy persons; 2 years after 2 vaccinations, the protection rate had decreased from 37 of 38 (97%) to 16 of 27 (59%) in liver transplant recipients and from 28 of 39 (73%) to 6 of 23 (26%) in renal transplant recipients [32]. A second study reported that 4 of 29 initial responders to 2 vaccinations (14%) had lost their immunity at month 24 [39].

DISCUSSION

We investigated the serologic response rate after hepatitis A vaccination in immunocompromised patients, using our own data in combination with available data from the literature. The latter were scarce and heterogeneous, but some consistent observations could be made. In the literature, impaired serologic response rates in immunocompromised patients compared with historic healthy populations are described, especially after the
Table 3. Literature Overview

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Study Participants, No.</th>
<th>Underlying Patient Condition</th>
<th>Drug Regimena</th>
<th>Primary Outcome</th>
<th>Vaccine-Titer Interval</th>
<th>Protection Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dumot et al [30]</td>
<td>1999</td>
<td>Clinical trial</td>
<td>8</td>
<td>LTX</td>
<td>Cyclosporine A/tacrolimus/ prednisolone</td>
<td>Seroprotectionb</td>
<td>2 mo</td>
<td>0</td>
</tr>
<tr>
<td>Stark et al [31]</td>
<td>1999</td>
<td>Clinical trial</td>
<td>39 LTX, 29 Controls</td>
<td>LTX and RTX</td>
<td>LTX: cyclosporine A/tacrolimus; RTX: prednisolone + cyclosporine A +/azathioprine</td>
<td>Seroprotectionb</td>
<td>1 mo</td>
<td>LTX: 41; RTX: 24; Controls: 90</td>
</tr>
<tr>
<td>Günther et al [32]c</td>
<td>2001</td>
<td>Clinical trial</td>
<td>27 LTX, 23 RTX</td>
<td>LTX and RTX</td>
<td>LTX: cyclosporine A/tacrolimus; RTX: prednisolone + cyclosporine A +/azathioprine</td>
<td>Duration of protectiond</td>
<td>2 y</td>
<td>NR</td>
</tr>
<tr>
<td>Arslan et al [33]</td>
<td>2001</td>
<td>Clinical trial</td>
<td>37</td>
<td>LTX (matched)</td>
<td>Prednisolone + cyclosporine A + tacrolimus +/azathioprine</td>
<td>Seroprotection</td>
<td>1st dose: 1 and 6 mo; 2nd dose: 1 mo</td>
<td>1 mo: 8; 6 mo: 19</td>
</tr>
<tr>
<td>Radzikowski et al [34]</td>
<td>2011</td>
<td>Clinical trial</td>
<td>66</td>
<td>Pediatric IBD</td>
<td>A/6-MP +/prednisolone</td>
<td>Seroprotection</td>
<td>3 mo</td>
<td>Patients: 39; Controls: 64</td>
</tr>
<tr>
<td>Moses et al [35]</td>
<td>2011</td>
<td>Clinical trial</td>
<td>12</td>
<td>Pediatric IBD</td>
<td>Anti-TNF-α</td>
<td>Seroprotectione</td>
<td>1 mo</td>
<td>NR</td>
</tr>
<tr>
<td>Urganci et al [36]</td>
<td>2013</td>
<td>Clinical trial</td>
<td>23</td>
<td>Pediatric IBD</td>
<td>Mesalazine +/prednisolone +/azathioprine</td>
<td>Seroprotectione</td>
<td>1 mo</td>
<td>NR</td>
</tr>
<tr>
<td>van den Bijlaardt et al [37]</td>
<td>2013</td>
<td>Retrospective study</td>
<td>173</td>
<td>Underlying disease NR</td>
<td>Anti-TNF-α/DMARDs/other</td>
<td>Seroprotectione</td>
<td>Mean 73 wk (range, 19–430 wk)</td>
<td>Anti TNF-α: 46; DMARDs: 62; Overall: 60</td>
</tr>
<tr>
<td>Park et al [38]</td>
<td>2014</td>
<td>Clinical trial</td>
<td>419</td>
<td>IBD</td>
<td>Anti-TNF-α/azathioprine/6-MP +/prednisolone/none (39%)</td>
<td>Seroprotectione</td>
<td>1–3 mo</td>
<td>NR</td>
</tr>
<tr>
<td>Askling et al [39]</td>
<td>2014</td>
<td>Clinical trial</td>
<td>53</td>
<td>RA</td>
<td>Anti-TNF-α/anti-TNF-α + MTX/MTX</td>
<td>Seroprotectionf</td>
<td>1 and 6 mo</td>
<td>1 mo: 10; 6 mo: 33</td>
</tr>
<tr>
<td>Jeon et al [40]</td>
<td>2014</td>
<td>Clinical trial</td>
<td>52</td>
<td>RTX</td>
<td>Tacrolimus/cyclosporine A +/prednisolone</td>
<td>Seroprotectiong</td>
<td>1 mo</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: 6-MP, 6-mercaptopurine; anti-TNF-α, tumor necrosis factor α blocker; DMARDs, disease-modifying antirheumatic drugs (MTX and azathioprine); IBD, inflammatory bowel disease; LTX, liver transplant recipient; MTX, methotrexate; NR, not reported; RA, rheumatoid arthritis; RTX, renal transplant recipient.

a In drug regimens, virgule (/) indicates “or”; plus sign (+), “combined with”; and both (+/), “and/or”.
b Defined as >33 mIU/mL.
c Follow-up to study by Stark et al [31].
d Defined as >33 mIU/mL after 2 years.
e Positive at immunoassay.
f Defined as >20 mIU/mL.
first vaccination (37.1%) [4–6]. However, the majority of patients in previous studies (82%) developed protective antibodies after 2 vaccinations [30–32, 37]. In our own data, the serologic protection rate in HIV-infected patients (57%) corresponded to the results of a meta-analysis by Shire et al [24]. The response rate we observed in SCT recipients was higher (77%) and consistent with described protection rates after influenza vaccination [41, 42]. This relatively good response could be explained by the fact that the mean interval between transplantation and vaccination was >2 years, when patients generally used little or no immunosuppressive medication.

The association in the literature between the use of multiple immunosuppressive drugs (vs a single drug) and lower serologic response rates could be explained by the fact that different steps in the immune response are simultaneously targeted [31, 38]. In our population, with relatively few patients using multiple immunosuppressive drugs (n = 25), we were not able to reproduce this result.

In contrast to previous studies [31, 33, 34, 37], we did not find a significantly higher response after 2 vaccinations compared with 1 vaccination, although trends were seen when patients were separated by medication group. A possible explanation is that in our study, antibody titer measurements were only performed once in each patient, so the patient group tested after 1 vaccination was different from that tested after 2 vaccinations. In the smaller subgroups, sample sizes may have been too small to reach statistical significance.

In the literature, reported serologic response rates were higher when the interval between vaccination and antibody titer measurement was 3–6 months, instead of 1 month [33, 34, 39]. Immunocompromised patients may need more time than healthy persons to develop protective antibodies. To reduce the risk of wrongly concluding that a patient did not respond to vaccination, an implication for clinical practice could be that patients using immunosuppressive drugs should be vaccinated at a longer interval before travel departure (3–6 months instead of 1 month).

Although 2 studies demonstrated impaired durability of protective immunity in immunocompromised patients after successful vaccination, precise time intervals need to be established in future studies [32, 39]. Two factors are of important in the loss of protective immunity: the reported faster decline of protective antibodies in immunocompromised patients and a lower postvaccination peak titer, described in 5 of the 11 included studies [28, 31, 34, 36, 37]. For now it is recommended that immunocompromised patients who initially responded to vaccination receive antibody titer measurements before travel, even if they still have a “valid” hepatitis A vaccination in their medication passport.

**TNF-α Blockers Versus DMARDs**

In our data, we found a higher protection rate in patients using TNF-α–blocking agents compared with DMARDs and other drugs, which was also observed in 3 other studies [36, 40, 41]. In contrast, 2 studies concluded the opposite. However, in the first study, patients who used TNF-α antagonists were compared with those who used no immunosuppressive drugs or only 1 [38]. In the second study, doses and number of drugs were not reported, nor did the authors mention the indications for using DMARDs and TNF-α–blocking agents [37]. We hypothesize that the replacement of a classic DMARD by a TNF-α antagonist results interfering with the immune response less than therapy with classic DMARDs only. This may be due to the more specific mechanism of action of TNF-α–blocking agent, as explained earlier.

**Medical Conditions**

The finding from our data that patients with rheumatic disorders showed better responses to hepatitis A vaccination than other patients probably reflects the doses and types of immunosuppressive medications used in this patient group. Patients with rheumatic diseases used significantly more TNF-α antagonists in relatively low doses. For example, according to national guidelines, patients with RA receive lower doses of infliximab than patients with IBD (3 vs 5 mg/kg) [33].

**Adherence to Antibody Titer Measurement**

Interestingly, we found from our data that female patients were more likely than male patients to return for a postvaccination antibody titer measurement. Earlier studies have reported that women are more likely to seek pretravel advice [43, 44] and show more concern about travel-related stressors than their male counterparts [45]. This may imply that healthcare professionals should more actively encourage immunocompromised male patients to return for postvaccination antibody titer measurement.

**Strengths and Limitations**

We combined a complete literature overview with an analysis of our own data, in which we accounted for the degree of immunosuppression in relation to the immune response. The first limitation was that not all patients were tested for hepatitis A antibodies before vaccination. However, hepatitis A endemicity is low in the Netherlands, and we excluded persons with presumed previous exposure to hepatitis A. Second, 52% of the patients who used TNF-α blockers also used another immunosuppressive drug, complicating the assessment of the effect of TNF-α blockers alone. However, among patients who did not use TNF-α blockers, only 30% used other immunosuppressive medication. Yet the immune response to hepatitis A vaccination was better in patients using a TNF-α–blocking regimen even after adjustment for the degree of immunosuppression. In the subgroup of patients using only 1 immunosuppressive drug, the results were similar, though not statistically significant owing to the smaller sample size. Third, we made some assumptions about the medication
dose when doses were not reported, but we cannot be certain that these patients were treated according to protocol for their conditions.

In conclusion, immunocompromised patients develop moderate to good serologic responses after hepatitis A vaccination. Patients using multiple immunosuppressive drugs have a higher risk of vaccination failure. Patients using a regimen with a TNF-α-blocking agent instead of other immunosuppressive drugs generally have better antibody responses. Because in the majority of cases protective immunity is not reached until after the second vaccination and because immunocompromised patients may need more time to develop protective immunity, postvaccination antibody titers measurements should always be performed. In this respect, male patients especially should be actively motivated. Furthermore, patients should be encouraged to seek travel advice as early as possible before travel departure. Because durability of protection after successful vaccination might be impaired, we recommend that pretravel antibody titers be checked in all immunocompromised patients, regardless of the validity of prior hepatitis A vaccinations.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


Appendix

We performed the following PubMed search:


When medication doses were not recorded, we assumed doses based on treatment guidelines: for patients with rheumatoid arthritis, infliximab 3 mg/kg every 8 weeks or subcutaneous adalimumab 40 mg/2 wk; for patients with IBD, psoriatic arthritis, or spondyloarthritis, infliximab 5 mg/kg every 8 weeks or subcutaneous adalimumab 80 mg/2 wk; for patients with IBD, azathioprine 1–3 mg/kg/d; and for organ transplant recipients, azathioprine 1–4 mg/kg/d [29].