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

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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 -