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Tick-borne encephalitis (TBE) vaccine to medically immunosuppressed patients with rheumatoid arthritis: A prospective, open-label, multi-centre study

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ABSTRACT

Background: Tick-borne Encephalitis (TBE) is endemic in south-eastern Sweden as well as in the Baltic regions, Central Europe and Russia. Ageing and immunosuppressed individuals are more prone to severe disease and neurological complications. We assessed the immunogenicity of TBE-vaccine in rheumatoid arthritis (RA) patients treated with tumor necrosis factor-inhibitors (TNFi) and/or methotrexate (MTX).
Methods: TBE vaccine, FSME-Immune® or Encepur®, was administered to non-immune RA patients as well as age and gender matched healthy controls. Individuals <60 years of age were given three doses at month 0, 1, 12. Individuals ≥60 years old were given an additional priming dose at month 3, i.e. a total of four doses. Tick-borne encephalitis neutralizing antibodies were assessed by a rapid fluorescent focus inhibition test.
Results: The study population consisted of 66 patients and 56 age and gender matched healthy controls. Median age was 58.5 years. The patients were either treated with TNFi ($n = 16$), TNFi + MTX ($n = 36$) or MTX ($n = 14$). After the last TBE-vaccine dose, given one year after the first, 39% of the patients compared to 79% of the healthy controls had seroprotective levels ($p = <0.05$).
Conclusions: Standard TBE-vaccine schedule does not confer enough immunogenicity in this group of immunosuppressed patients, who should be carefully informed about a higher risk for vaccination failure and risk of infection when exposed in high-endemic areas.

1. Introduction

TBE (tick-borne encephalitis) is a notifiable disease according to the Swedish Act of Communicable Diseases. The incidence trend in Sweden has been slowly increasing during the last decades, despite a growing number of distributed doses of TBE-vaccine [1]. TBE-virus (TBEV) is a flavivirus, in Sweden dominated by the European subtype. The clinical symptoms range from asymptomatic to mild fever and headache, as well as neurological symptoms and fulminant encephalitis in severe cases, which is more common in the older age-group. Sequele occur in 30–40% of the patients [2,3]. The case-fatality rate for the European subtype of the TBEV is 1–2% and severe sequele occur more frequently with increasing patient age [4]. Two different TBE-vaccines are available in northern and central Europe, FSME-Immune® and Encepur®. Both are inactivated and considered to exhibit more than 95% seroprotectivity after the first three doses of vaccine, which are all given during one year [4]. A Swedish study has shown that vaccine-failures occur, predominately in the older age groups and in cases with documented immunosuppression [5]. These results, as well as the continuous case-surveillance, are the basis for the current regional TBE-vaccine recommendations that include an extra priming vaccine-dose to individuals >60 years old exposed to outdoor risk-areas.

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The success story with immunomodulating biological drugs for patients with chronic inflammatory diseases renders a growing cohort of active individuals with very low diseases activity, but with an ongoing immunosuppression that increases risk of a more severe course of several infections. Tumor Necrosis Factor-inhibitors (TNFi) are the most widely used biological drugs. Those suffering from rheumatic conditions constitute by far the largest group of patients given TNFi, often accompanied by methotrexate (MTX), and patients with rheumatoid arthritis (RA) dominate this group. In patients with RA, infectious diseases in general cause significant morbidity, probably due to a combination of a dysfunctional immune system and immunosuppressive therapy [6]. Data on vaccine-induced immunogenicity in adult patients treated with TNFi and/or MTX are mainly limited to influenza- and pneumococcal vaccinations [7–23]. These studies have shown that TNFi only moderately influences antibody responses, whereas a stronger negative effect is attributed to concomitant use of MTX [13,15,16,21,23]. One study concerning Hepatitis A vaccine to patients with RA and TNFi and/or MTX treatment showed failure to reach seroprotective antibody levels after one dose [24]. Concomitant prednisolone treatment had no significant impact on the serological response after polysaccharide vaccination [11] or influenza vaccination [15].

We know from previous studies that older age reduces the TBE antibody titers post vaccination [25–28]. Data about immunogenicity induced by TBE-vaccines in immunosuppressed patients are, as far as we know, not available. Given the spread of the tick *Ixodes ricinus* [29], the increasing incidence of TBE despite high vaccination coverage, and the expanding cohort of patients treated with immunomodulating drugs, the aim of our study was to prospectively evaluate immune responses to TBE-vaccine in patients living in a high-endemic area with rheumatoid arthritis treated with TNFi and/or MTX.

2. Material and methods

2.1. Study population and design

This outpatient-based open-label multicentre study was carried out in a real-life setting during two years 2010–2012. We aimed to enroll 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 methotrexate (MTX) for at least one year. They were all living in a TBE-endemic area and were invited to participate in the study if they were considered to need TBE-vaccine. The exclusion

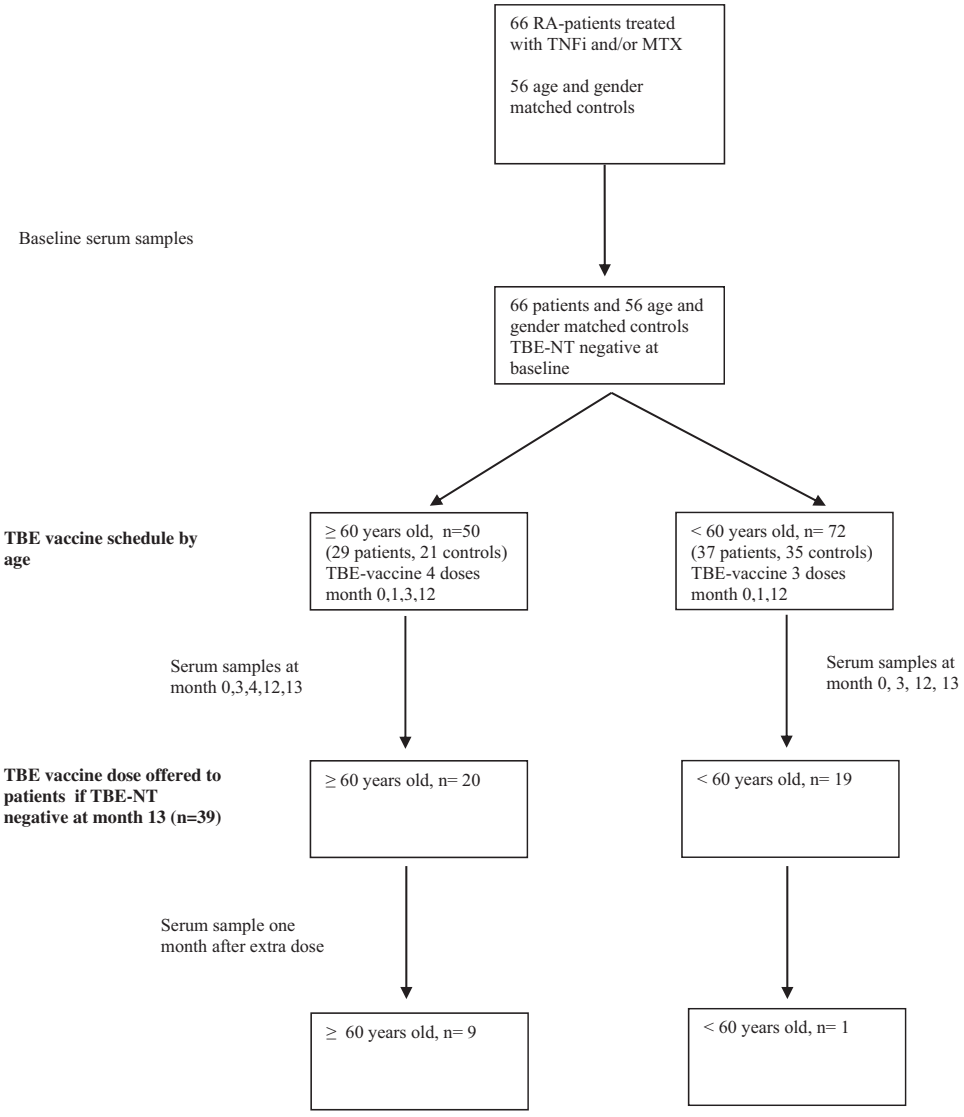

Fig. 1. Study schedule.