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Editorial

Can patients on methotrexate receive live vaccines?

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The increased risk of serious infections associated with immune deficiencies and/or immunomodulating or immunosuppressive drug therapy results in high morbidity and mortality rates. Whether live vaccines can be administered to diminish this risk has long been a matter of lively debate. More specifically, the use of live vaccines in patients taking methotrexate is a complex and controversial issue about which recommendations are scarce and differ across countries.

Patients with rheumatic diseases exhibit increased susceptibility to infections and are therefore strong candidates for receiving preventive immunizations. In the past, one hypothesis of concern was that the administration of vaccines to patients with rheumatoid arthritis might trigger the production of autoantibodies, thereby inducing a disease flare. However, studies failed to detect any clinical or laboratory evidence of an increase in disease activity after immunizations. As always, immunizations should ideally be given at a time when the disease is stable and before initiating any immunosuppressive drugs.

The administration of vaccines to patients with immune deficiencies raises issues that have prompted the development of specific recommendations, which are updated regularly in France [1,2]. In theory, live vaccines are contraindicated due to the risk of clinical infection by the administered microorganism. Nevertheless, immunization with live vaccines deserves to be considered in specific situations, on a case-by-case basis, according to the balance between the vaccine-related risks and the risks related to the infectious disease targeted by the vaccine. In addition, the decreased immunogenicity of vaccines in patients with immune deficiencies can require specific immunization schedules.

1. Which live vaccines are used in France?

The live vaccines available in France are the BCG, MMR (measles, mumps, rubella), yellow fever vaccines, oral polio vaccine (rarely used since a combined diphtheria/tetanus/inactivated polio vaccine is available), rotavirus vaccine used in pediatric patients, and varicella and herpes zoster vaccines.

2. What are the risks of live vaccines in immunocompromised patients?

Before administering a live vaccine, the risk/benefit ratio must be evaluated. Risks consist of clinical infection by the administered microorganism, reactivation of the underlying disease, and primary viral infection. The expected benefit of immunization is a decrease in the risk of infection due to protection against the targeted infection.

In general, the best approach to minimizing patient selection, timing, and modality issues consists in updating all immunizations before initiating immunosuppressive therapy. Many studies have assessed the risks associated with more conventional vaccines such as those against influenza and pneumococcal infections. Unfortunately, no similar studies of live vaccines are available [2]. The options for each of these vaccines are discussed below.

2.1. BCG vaccine

Administration of the BCG vaccine is no longer mandatory in the general population in France. The BCG vaccine is contraindicated in patients taking biotherapies. Furthermore, the absence of evidence that immunization with the BCG is beneficial in adults makes this a moot issue.

2.2. MMR vaccine

In France, immunization with the MMR vaccine is recommended in all individuals born in or after 1980; in women of childbearing potential who have not already received two doses of the vaccine; and, during measles outbreaks, in individuals whose MMR immunization history is incomplete [1,2]. Administration of the MMR vaccine as recommended seems both crucially important and readily achievable at the diagnosis of a rheumatic disease. In all, two doses of the trivalent MMR vaccine should be given at an interval of at least 1 month, regardless of whether the patient has experienced any of the three diseases [1,2]. At least 2 weeks must be allowed to elapse between the last MMR dose and the first methotrexate dose.

2.3. Varicella and herpes zoster vaccines

Although varicella and herpes zoster are caused by a single virus, a specific vaccine exists for each. Administration of the vari-

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cella vaccine is not recommended as a routine procedure but is instead indicated only in healthy adults, in women of childbearing potential, and within 3 days after contact with a varicella patient. The varicella vaccine may also deserve consideration if the risk of varicella is increased or if varicella may induce complications, for instance in patients taking fingolimod to treat multiple sclerosis. No such complications exist with methotrexate. A few unusual situations may require a case-by-case discussion of the appropriateness of varicella immunization.

An increased risk of herpes zoster has been reported in patients with rheumatic diseases, notably rheumatoid arthritis, with incidence rates varying across studies from 0.55 to 12.1/1000 patient-years [3,4]. However, methotrexate therapy was not associated with an increased risk. In Canada and the US, herpes zoster immunization is recommended in adults aged 50 years or over who have chronic inflammatory rheumatic diseases requiring treatment with conventional or biologic disease-modifying anti-rheumatic drugs (DMARDs) or long-term glucocorticoids. Since 2008, the Advisory Committee on Immunization Practices of the Centers for Disease Control has recommended routine herpes zoster immunization of individuals aged 60 years or older [5]. The herpes zoster vaccine can be given 2 weeks before starting or 1 month after stopping a biologic agent (expert opinion) [5,6]. Herpes zoster immunization has been deemed appropriate in patients taking methotrexate dosages no greater than 0.4 mg/kg/week [7,8]. In France, herpes zoster immunization is recommended only in individuals aged 65 years or over, in whom its effectiveness is limited, with an about 61% decrease in the risk of herpes zoster and post-herpetic neuralgia. The herpes zoster vaccine is contraindicated in immunocompromised patients and should therefore not be given to patients taking methotrexate. A new, inactivated herpes zoster vaccine is scheduled for marketing in 2019. This vaccine will be suitable for patients taking immunosuppressive treatments and may prove particularly helpful in immunocompromised patients at high risk for infection with the varicella-herpes zoster virus [9]. It has been shown to diminish the risk of herpes zoster and of post-herpetic neuralgia by about 90%.

2.4. Yellow fever immunization

Yellow fever immunization is mandatory in individuals who live in French Guiana or plan to travel to an endemic area. The vaccine must be administered at least 10 days before the trip. However, the yellow fever vaccine is contraindicated in patients taking conventional or biological DMARDs. Although yellow fever is usually an asymptomatic disease that escapes diagnosis, severe symptoms may develop, and the risk of death is then 50% within 10 to 14 days. In March 2014, the World Health Organization stated that a single dose of the yellow fever vaccine conferred lifelong immunity. French health authorities have accepted this statement and, since February 2016, travelers to French Guiana must be immunized against yellow fever but are no longer required to obtain booster injections, provided they are free of immune deficiencies, since serological tests have established that protection persists far longer than previously thought. The yellow fever immunization certificate thus has lifelong validity. In the event of immunosuppressive treatment, the vaccine must be given at least 2 weeks before starting or at least 3 months after stopping the treatment. Administering more than two vaccine doses is not recommended, except in immunocompromised patients, whose neutralizing antibody titers should be monitored [1,10]. Consequently, yellow fever immunization should ideally be offered before starting methotrexate therapy if the patient is likely to visit endemic areas. Patients already on DMARD therapy should be discouraged from traveling to endemic areas. If an immediate trip to an endemic area is unavoidable, an accredited center can deliver a certificate stating that yellow fever immunization is contraindicated, after informing the patient of the risks inherent in not receiving the vaccine [11]. When evaluating an immunocompromised patient to determine whether repeat yellow fever immunization is in order, yellow fever antibody assays can be obtained to determine whether the titers are still protective. If a trip is unavoidable, a staff meeting is useful to evaluate the risk/benefit ratio of yellow fever immunization and more specifically of triggering a disease flare if the methotrexate must be stopped. In the few studies of yellow fever immunization in patients taking methotrexate, most of whom were receiving repeat immunization, no unexpected adverse events were recorded [12,13].

As a rule of thumb, methotrexate therapy must be discontinued before administering a live vaccine [11]. No consensus exists, however, regarding the duration of the drug-free window. There is no recommendation in the US to discontinue methotrexate, whereas the French health authorities require an at least 3 month-long methotrexate-free period before the administration of a live vaccine. After the immunization, at least 2 weeks must be allowed to elapse before restarting methotrexate, although a 3- to 4-week wait is probably optimal [11]. This strategy can be applied for all live vaccines. In practice, decisions depend chiefly on whether the immunization is absolutely necessary and on how long the patient can wait before receiving methotrexate. These data emphasize the usefulness of updating all immunizations as early as possible, ideally at the diagnosis of the inflammatory rheumatic disease, and of either anticipating the need for protection against diseases such as yellow fever or discouraging subsequent travel to endemic areas.

3. Immunogenicity of live vaccines

The immunogenicity of live vaccines in immunocompromised patients is an unsettled issue. Methotrexate may blunt certain antibody responses to vaccines, for instance the pneumococcal vaccine [14]. Since live vaccines are contraindicated in immunocompromised patients, their effectiveness in patients taking methotrexate cannot be investigated. Little information is available on the effects of methotrexate on vaccine immunogenicity or safety. For instance, the Centers for Diseases Control have stated that the herpes zoster vaccine is safe in patients with rheumatoid arthritis who take no more than 0.4 mg/kg/week of methotrexate. However, this statement is founded only on expert opinion, since no scientific evidence is available.

New recommendations issued by the EULAR indicate that an individually tailored immunization program should be developed in concertation with the patient [15]. Whenever possible, the necessary vaccines should be administered at a time when the rheumatic disease is stable and before starting immunosuppressive therapy. Attenuated live vaccines are best avoided in patients taking immunomodulating or immunosuppressive drugs. The BCG and MMR vaccines may constitute exceptions to this rule, although a comprehensive evaluation of the risk of infection should be performed at the diagnosis of the rheumatic disease. A pharmacovigilance report is recommended if a live vaccine is administered to a patient taking methotrexate. In the few reported cases of patients inadvertently given live vaccines, the adverse events were usually mild [12,16].

Disclosure of interest

The author declares that she has no competing interest.

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