Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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EDITORIAL

Is it safe to vaccinate rheumatic immunosuppressed patients? Yes, of course, but how?

Abbreviations

CDC	Center for Disease Control
COVID	coronavirus disease
DMARD	disease modifying antirheumatic drug
EULAR	European League Against Rheumatism
HSCP	*Haut Conseil de la santé publique*
IBD	inflammatory bowel diseases
MMR	measles, mumps & rubella vaccine

Adults and children with inflammatory rheumatism and systemic autoimmune diseases have a much higher risk of infection than healthy subjects. Bronchopneumopathies, whether viral or bacterial, are the most frequent infectious manifestations. The incidence and severity of infections are higher in patients with rheumatoid arthritis than in the general population [1]. Several infectious risk factors have been identified, such as age over 60 years, a history of severe infection, failure to respond to several disease modifying antirheumatic drug (DMARDs), systemic corticosteroid therapy, or biotherapy [2]. Vaccines are an effective means of preventing infections and necessary for managing rheumatic patients [3].

Inactivated vaccines can be administered without undue risk compared to the general population while retaining some or all of their immunogenicity [4]. In contrast, live vaccines are mostly contraindicated in patients undergoing immunosuppressive treatments, limiting their use in prevention. Therefore, it is essential to respect the vaccination schedule in early childhood, before hypothetical rheumatism occurs, and correct the situation before starting immunosuppressive treatment. As the review by Ben Nessib et al. [5] points out in this issue, the efficacy of vaccines remains real in these patients but varies according to the background treatment(s) used (alone or in combination) to treat inflammatory rheumatism, the type of vaccine used and the type of underlying disease. Besides, some immunization modalities require ''windows of opportunity'' particularly with rituximab [5], as highlighted in this review.

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Even in this coronavirus disease (COVID) pandemic context, vaccination coverage against pneumococcus and influenza remains modest [6], in about half in patients suffering from inflammatory rheumatism, mainly due to lack of the caregiver's vaccination proposal and fear of patient's adverse effects. The ''anti-vax'' widely relays this panic, via social networks, and even the hesitant of health authorities destabilize the population, despite the unanimous opinions of pharmacovigilance experts, contrasting with those of the self-proclaimed but mediatized ''knowers or influencers''. To improve vaccine acceptability and adherence, several simple principles are worth recalling [7]:

- annual reassessment of vaccine status by the health care team, if necessary, by computerized means (e.g. MyVaccines.net) [8];
- multidisciplinary explanation of the benefit-risk ratio to the patient in a shared decision;
- preferential administration of vaccines during a non-active period of the disease and ideally before initiation/switch of immunosuppressive therapy (especially those targeting B lymphocytes).

Most of the recent European League Against Rheumatism (EULAR) recommendations are consensual in these patients [7,9]:

- influenza and pneumococcal vaccination should be offered;
- tetanus vaccination should be under the vaccination schedule;
- hepatitis A and B vaccinations should be administered preventively in at-risk subjects (to prevent the risk of reactivation);
- vaccination against shingles may be offered, with the inactivated vaccine, in at-risk subjects;
- vaccination against yellow fever should be avoided, except in exceptional cases with caution (endemic areas);
- patients, especially those with lupus, should be vaccinated against HPV according to the standards of the general population;
- immunocompetent members of the patient's family should be up-to-date with their vaccinations;
- live attenuated vaccines should be avoided in infants under six months of age if the mother has received biotherapy in the second half of the pregnancy.

The consensus is less robust for live-attenuated vaccines [10], theoretically ''blacklisted''. For measles, mumps & rubella vacine (MMR), while the 2014 *Haut Conseil de la santé publique* (French High Council of Public Health [HSCP]) recommends stopping immunosuppressants for three months before primary immunization (6 months for rituximab), the new Center for Disease Control (CDC) recommendations allow for a customarily scheduled booster based on the immunosuppressant dosage [7]. Although pediatric data on primary immunization and booster doses are reassuring [11], given the small numbers of patients in the trials, these patients will be treated more often with multivalent immunoglobulins in the event of measles contact (see NB), and their families and friends will be vaccinated with MMR if necessary (except pregnant women for whom it remains contraindicated).

This excellent review by Ben Nessib et al. [5] identifies the benefit-risk ratio of vaccinations in children [12] or adults [11] immunocompromised by corticosteroids, conventional or targeted DMARds, or biotherapy. This framework can be extended to patients suffering from inflammatory bowel diseases (IBD), psoriasis, transplants, and those affected by certain immune deficiencies to be assessed in concert with the healthcare team. Patient-care provider collaboration is essential, aided by dedicated computer applications (such as an electronic vaccination record on a smartphone [8]) that also take into account any immunomodulated status. However, the tree must not hide the forest; let us not forget to regularly monitor and prevent adverse effects specific to each class of immunomodulator concomitantly prescribed.

However, this bibliographical watch must be continued, given the constant appearance of new original targeted treatments. Let us not forget that corticosteroid therapy, in its time, has seen an ''enchanted parenthesis'', more or less prolonged, followed by a ransom of hypercorticism. Other more recent examples should make us vigilant, such as anti-IL-17s favoring/aggravating IBD, specific paradoxical effects of dengue vaccination, and even unexpected off-target effects of specially targeted treatments. Moreover, as reported daily in the international press in the context of the COVID 19 pandemic, vaccination techniques are evolving. RNA-based vaccines and gene therapy will not necessarily react in the same way as current inactivated/attenuated vaccines in an immunocompromised organism.

Disclosure of interest

The author declares that he has no competing interest.

NB: Concerning MMR vaccination and immunosuppressants refer to Morel J's review. Vaccination contre la rougeole sous immunosuppresseurs. Lettre du Rhumatologue 2020 (465):25—7 (Edimark Editor, www, .edimark.fr, indexed in ICME. ISSN 0761-5027.

References

[1] Morel J, Czitrom SG, Mallick A, Sellam J, Sibilia J. Vaccinations in adults with chronic inflammatory joint disease: immunization schedule and recommendations for patients taking synthetic or biological disease-modifying antirheumatic drugs. Joint Bone Spine 2016;83(2):135—41.

[2] RABBIT - Rheumatoide Arthritis: Beobachtung der Biologika-Therapie; 2020 https://biologika-register.de/en/rabbit/rabbit-risk-score-of-infections/ [Accessed November26, 2020].

[3] McMahan ZH, Bingham 3rd CO. Effects of biological and non-biological immunomodulatory therapies on the immunogenicity of vaccines in patients with rheumatic diseases. Arthritis Res Ther 2014;16(6):506.

[4] Subesinghe S, Bechman K, Rutherford AI, Goldblatt D, Galloway JB. A systematic review and metaanalysis of antirheumatic drugs and vaccine immunogenicity in rheumatoid arthritis. J Rheumatol 2018;45(6):733—44.

[5] Ben Nessib D, Fazaa A, Miladi S, Sellami M, Ouenniche K, Souabni L, et al. Do immunosuppressive agents hamper the vaccination response in patients with rheumatic diseases? A review of the literature. Therapie 2020, http://dx.doi.org/10.1016/j.therap.2020.08.002 [in press].

[6] Friedman MA, Winthrop KL. Vaccines and disease-modifying antirheumatic drugs: practical implications for the rheumatologist. Rheum Dis Clin North Am 2017;43(1):1—13.
[7] Furer V, Rondaan C, Heijstek MW, Agmon-Levin N, van Assen S, Bijl M, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2020;79(1):39—52.
[8] MesVaccins net. Mon carnet de vaccination électronique; 2020 https://mesvaccins.net/web/recommendations [Accessed November 26, 2020].
[9] Rondaan C, Furer V, Heijstek MW, Agmon-Levin N, Bijl M, Breedveld FC, et al. Efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases: a systematic literature review for the 2019 update of EULAR recommendations. RMD Open 2019;5(2):e001035.
[10] Papadopoulou D, Tsoulas C, Tragiannidis A, Sipsas NV. Role of vaccinations and prophylaxis in rheumatic diseases. Best Pract Res Clin Rheumatol 2015;29(2):306—18.
[11] Buhler S, Eperon G, Ribi C, Kyburz D, van Gompel F, Visser LG, et al. Vaccination recommendations for adult patients with autoimmune inflammatory rheumatic diseases. Swiss Med Wkly 2015;145:w14159.
[12] Sousa S, Duarte AC, Cordeiro I, Ferreira J, Goncalves MJ, Meirinhos T, et al. Efficacy and safety of vaccination in pediatric patients with systemic inflammatory rheumatic diseases: a systematic review of the literature. Acta Reumatol Port 2017;42(1):8—16.

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